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Oral iron supplements for children in malaria-endemic areas (Review)

Neuberger A, Okebe J, Yahav D, Paul M

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[Intervention Review]

Oral iron supplements for children in malaria-endemic areas

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ABSTRACT

Background

Iron-deficiency anaemia is common during childhood. Iron administration has been claimed to increase the risk of malaria.

Objectives

To evaluate the effects and safety of iron supplementation, with or without folic acid, in children living in areas with hyperendemic or holoendemic malaria transmission.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library, MEDLINE (up to August 2015) and LILACS (up to February 2015). We also checked the *meta*Register of Controlled Trials (*m*RCT) and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) up to February 2015. We contacted the primary investigators of all included trials, ongoing trials, and those awaiting assessment to ask for unpublished data and further trials. We scanned references of included trials, pertinent reviews, and previous meta-analyses for additional references.

Selection criteria

We included individually randomized controlled trials (RCTs) and cluster RCTs conducted in hyperendemic and holoendemic malaria regions or that reported on any malaria-related outcomes that included children younger than 18 years of age. We included trials that compared orally administered iron, iron with folic acid, and iron with antimalarial treatment versus placebo or no treatment. We included trials of iron supplementation or fortification interventions if they provided at least 80% of the Recommended Dietary Allowance (RDA) for prevention of anaemia by age. Antihelminthics could be administered to either group, and micronutrients had to be administered equally to both groups.

Data collection and analysis

The primary outcomes were clinical malaria, severe malaria, and death from any cause. We assessed the risk of bias in included trials with domain-based evaluation and assessed the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. We performed a fixed-effect meta-analysis for all outcomes and random-effects meta-analysis for hematological outcomes, and adjusted analyses for cluster RCTs. We based the subgroup analyses for anaemia at baseline, age, and malaria prevention or management services on trial-level data.

Main results

Thirty-five trials (31,955 children) met the inclusion criteria. Overall, iron does not cause an excess of clinical malaria (risk ratio (RR) 0.93, 95% confidence intervals (CI) 0.87 to 1.00; 14 trials, 7168 children, *high quality evidence*). Iron probably does not cause an excess of clinical malaria in both populations where anaemia is common and those in which anaemia is uncommon. In areas where there are prevention and management services for malaria, iron (with or without folic acid) may reduce clinical malaria (RR 0.91, 95% CI 0.84 to 0.97; seven trials, 5586 participants, *low quality evidence*), while in areas where such services are unavailable, iron (with or without folic acid) may increase the incidence of malaria, although the lower CIs indicate no difference (RR 1.16, 95% CI 1.02 to 1.31; nine trials, 19,086 participants, *low quality evidence*). Iron supplementation does not cause an excess of severe malaria (RR 0.90, 95% CI 0.81 to 0.98; 6 trials, 3421 children, *high quality evidence).* We did not observe any differences for deaths (control event rate 1%, *low quality evidence*). Iron and antimalarial treatment reduced clinical malaria (RR 0.54, 95% CI 0.43 to 0.67; three trials, 728 children, *high quality evidence*). Overall, iron resulted in fewer anaemic children at follow up, and the end average change in haemoglobin from base line was higher with iron.

Authors' conclusions

Iron treatment does not increase the risk of clinical malaria when regular malaria prevention or management services are provided. Where resources are limited, iron can be administered without screening for anaemia or for iron deficiency, as long as malaria prevention or management services are provided efficiently.

12 April 2019

No update planned

Other

There is high-certainty evidence that oral iron supplements do not adversely affect children living in malaria-endemic areas, meaning further research is unlikely to change our confidence in the estimate of effect. All eligible published studies found in the last search (30 Aug, 2015) were included.

PLAIN LANGUAGE SUMMARY

Iron supplements for children living in malaria-endemic countries

Why the review is important

Children living in malarial areas commonly develop anaemia. Long-term anaemia is thought to delay a child's development and make children more likely to get infections. In areas where anaemia is common, health providers may give iron to prevent anaemia, but there is a concern amongst researchers that this may increase the risk of malaria. It is thought that the iron tablets will increase iron levels in the blood, and this will promote the growth of the *Plasmodium* parasite that causes malaria. We aimed to assess the effects of oral iron supplementation in children living in countries where malaria is common.

Main findings of the review

Cochrane researchers searched the available evidence up to 30 August 2015 and included 35 trials (31,955 children). Iron did not increase the risk of malaria, indicated by fever and the presence of parasites in the blood (*high quality evidence*). There was no increased risk of death among children treated with iron, although the quality of the evidence for this was low. Among children treated with iron, there was no increased risk of severe malaria (*high quality evidence*). Although it is hypothesized that iron supplementation might harm children who do not have anaemia living in malarial areas, there is probably no increased risk for malaria in these children (*moderate quality evidence*). In areas where health services are sufficient to help prevent and treat malaria, giving iron supplements (with or without folic acid) may reduce clinical malaria. In areas where these services are not available, iron supplementation (with or without folic acid) may increase the number of children with clinical malaria (*low quality evidence*). Overall, iron resulted in fewer anaemic children at follow up, and the end average change in haemoglobin from base line was higher with iron.

Conclusions

Our conclusions are that iron supplementation does not adversely affect children living in malaria-endemic areas. Based on our review, routine iron supplementation should not be withheld from children living in countries where malaria is prevalent and malaria management services are available.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Oral iron versus placebo or no treatment for children in malaria-endemic areas

Does iron supplementation or fortification increase malaria and related morbidity and mortality among children in malaria-endemic areas?

Participant or population: children in malaria-endemic areas
Setting: areas which are malaria-endemic, and where children may benefit from iron treatment.
Intervention: iron
Comparison: placebo or no treatment

Subgroup	Anticipated absolute effects* (95% CI)		Relative effect results (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with iron supplementation				
Clinical malaria	27/100	25/100 (23 to 27)	RR 0.93 (0.87 to 1.00)	7168 (14 RCTs)	⊕⊕⊕⊕ High[1]	Overall, among anaemic or non-anaemic children, iron does not cause an excess of clinical malaria
Clinical malaria Subgrouped by population anaemia (trial level)	**Anaemic at baseline**		RR 0.92 (0.84 to 1.00)	7168 (14 RCTs)	⊕⊕⊕⊖ Moderate[2]	In populations where anaemia is common, iron probably does not cause an excess of clinical malaria
	256 per 1000	236 per 1000 (256 to 216)				
	Not anaemic at baseline		RR 0.97 (0.86 to 1.09)	2112 (5 RCTs)	⊕⊕⊕⊖ Moderate[3]	In populations where anaemia is uncommon, iron probably does not cause an excess of clinical malaria
	326 per 1000	316 per 1000 (280 to 355)				
Severe malaria Defined as clinical malaria with high-grade parasitaemia or requiring admission	397 per 1000	357 per 1000 (389 to 321)	RR 0.90 (0.81 to 0.98)	3421 (6 RCTs)	⊕⊕⊕⊕ High	Iron supplementation does not cause an excess of severe malaria
Death	10 per 10000	10 per 1000 (10 to 10)	Not estimated	7576 (18 RCTs)	⊕⊕⊖⊖ Low[4]	Iron may have no effect on mortality

Hospitalization plus clinic visits	295 per 1000	295 per 1000 (294 to 296)	RR 0.99 (0.95 to 1.04)	12,578 (6 RCTs)	⊕⊖⊖⊖ Very low[5,6]	It is uncertain whether iron affects hospitalizations or clinic visits

*__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; **RR:** risk ratio; **OR:** odds ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[1]Funnel plot asymmetry favouring the control arm, publication bias not suspected. The CIs range from important benefits of iron supplementation in reducing clinical malaria to no excess of clinical malaria.
[2]Downgraded by 1 for inconsistency. The CIs range from important benefits of iron supplementation in reducing clinical malaria to no excess of clinical malaria.
[3]Downgraded by 1 for imprecision. The upper CI of 9% could be regarded as representing clinically important harms.
[4]Downgraded by 1 for imprecision and by 1 for suspected publication bias.
[5]Study population and number of participants expressed as children-months.
[6]Downgraded by 1 for inconsistency and 2 for indirectness of the outcome. Hospitalizations and clinic visits do not necessarily reflect the burden of malaria.

Summary of findings 2. Effects of oral iron with or without folic acid on malaria among children in malaria-endemic areas

Does iron with or without folic acid increase malaria among children in malaria-endemic areas?

Participant or population: children in malaria-endemic areas
Setting: areas which are malaria-endemic, and where children may benefit from iron treatment.
Intervention: Iron ± folic acid
Comparison: placebo or no treatment

Subgroup	Anticipated absolute effects* (95% CI)		Relative effect results (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with iron supplementation				
Clinical malaria Subgrouped by presence of malaria prevention or management services	**Malaria prevention or management services present**		RR 0.91 (0.84 to 0.97)	5586 (7 RCTs)	⊕⊕⊖⊖ Low[1]	In areas where there are prevention and management services for malaria, iron supplementation may reduce clinical malaria
	24 per 100	22 per 1000 (20 to 23)				

	Malaria prevention or management services not present		RR 1.16 (1.02 to 1.31)	19,086 (9 RCTs)	⊕⊕⊖⊖ Low[2]	In areas where there are no prevention and management services for malaria, iron may increase the number of children with clinical malaria
	6 per 100	7 per 1000 (6 to 8)				

*__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; **RR:** risk ratio; **OR:** odds ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded by 1 for inconsistency and 1 for funnel plot asymmetry and suspected publication bias.
[2]Downgraded by 1 for indirectness, since the analysis is dominated by Sazawal 2006 (C)a that assessed only admissions for malaria resulting a spuriously low event rate and 1 for funnel plot asymmetry and suspected publication bias.

Summary of findings 3. Oral iron with antimalarial prophylaxis versus placebo or no treatment for children in malaria-endemic areas

Is iron supplementation with antimalarial treatment safe and beneficial for children living in malaria-endemic areas?

Participant or population: children with or without anaemia at baseline
Settings: hyper- or holoendemic areas for malaria
Intervention: oral iron supplement plus antimalarial

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (trials)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Iron supplementation plus antimalarial**				
Clinical malaria	41 per 100	22 per 100 (18 to 28)	RR 0.54 (0.43 to 0.67)	728 (3 (RCTs)	⊕⊕⊕⊕ High[1,2]	Iron given together with antimalarial antimicrobials reduce malaria
All-cause mortality	42 per 1000	44 per 1000 (23 to 85)	RR 1.05 (0.52 to 2.11)	728 (3 (RCTs)	⊕⊕⊖⊖ Low [3]	Iron given together with antimalarial antimicrobials may have no effect on mortality

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in the footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **RR:** risk ratio.

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

[1]All trials were individually randomized, with adequate concealment, double-blinded, and no loss to follow-up.
[2]We measured heterogeneity as P = 0.08, I^2 statistic = 60%, but all trials point in the same direction.
[3]We downgraded by 2 for imprecision.

BACKGROUND

Description of the condition

Childhood anaemia and iron deficiency

Childhood anaemia is a major, widespread public health problem in sub-Saharan Africa and other low-income areas (WHO 2008a; Kassebaum 2014). The highest prevalence of anaemia is found among children younger than five years of age who are living in low-income countries (Kassebaum 2014). Causes of anaemia in developing countries are numerous and often multifactorial, and include iron deficiency, infectious diseases (such as malaria, intestinal helminths, and schistosomiasis), haemoglobinopathies, and chronic kidney disease (WHO 2011a; Kassebaum 2014).

Iron is an important mineral needed to produce haemoglobin. It is also a component of many enzymes that are essential for proper cell development and cell growth of the brain, muscle, and the immune system (Beard 2001). It is a component of the peroxidase and nitrous oxide-generating enzymes that participate in the immune response to infections and is probably involved in regulating the production and action of cytokines (mediators of immune function released during early stages of infection). Since free iron is toxic to cells, it is stored as ferritin, an intracellular protein.

A relatively large amount of iron is required to produce red blood cells (erythropoiesis) in the first few months after birth. This is usually derived from the iron stored by the foetus in the last months of pregnancy. However, by the time a child is four to six months old, these stores become marginal or depleted. A child whose diet does not provide enough iron risks development of iron-deficiency anaemia. Infants with low total body iron at birth are particularly prone to iron deficiency; this is often exacerbated by the early introduction of cereal-based weaning food from which iron absorption can be as low as 5% (FAO/WHO 2005). Iron deficiency may be worsened by chronic blood loss from the intestines that results from intestinal parasitic infections (Stoltzfus 1997).

Iron deficiency is common and affects approximately two billion people worldwide, which results in over 500 million cases of anaemia (WHO 2004). In most areas, and specifically in all low- and middle-income regions, the most significant contributor to the onset of anaemia is iron deficiency (WHO 2008a; Kassebaum 2014). In sub-Saharan Africa, the prevalence of iron-deficiency anaemia is estimated to be around 60% overall (WHO 2004), with 40% to 50% of all children under five years in developing countries being iron-deficient (UNICEF 1998).

Based on estimates of iron-deficiency anaemia as a risk factor for death, iron deficiency has been estimated to cause 726,000 deaths in the perinatal and childhood periods globally, with the greatest toll in Southeast Asia and in Africa (WHO 2004; FAO/WHO 2005). Experimental and observational studies have linked iron deficiency to adverse effects on child development, including impairments of cognitive, emotional, and motor development (Pollitt 1993; Grantham-McGregor 2001; Gewa 2009), growth (Lawless 1994), immune function, and increased risk of infection (Berger 2000; Beard 2001). The relative risk for mental retardation associated with a 1 g/dL increase in population mean haemoglobin level has been estimated at 0.78 (95% confidence interval (CI) 0.70 to 0.86) (WHO 2004). However, these studies have been criticized for their inability to fully adjust for confounders and to establish causality (Oppenheimer 2001). Systematic reviews of randomized controlled trials (RCTs) on iron supplementation's effect on mental development, intelligence scores, motor development, and growth reported conflicting results (Bhandari 2001; Ramakrishnan 2004; Sachdev 2005; Iannotti 2006; Sachdev 2006; Low 2013; Thompson 2013; Wang 2013). Notably the time frame of many RCTs may not have allowed for a full evaluation of developmental outcomes.

The diagnosis of iron deficiency and iron deficiency anaemia relies mainly on the measurement of a person's haemoglobin, iron, and ferritin (Pasricha 2013). The measurement of haemoglobin alone is not sufficiently sensitive (due to overlapping values in iron-replete and iron-deficient individuals) and is not specific because of the numerous causes of anaemia in developing countries. Ferritin is the most commonly accepted measure of iron status (Mei 2005). However, there is a complex interaction between infection, inflammation (even when subclinical), and ferritin. Infection and inflammation increase ferritin, which is an acute phase reactant. The increase is proportional to the baseline ferritin levels and available iron stores (Thurnham 2010). It decreases only slowly after the resolution of infection and remains elevated in the convalescent phases of infection. Thus, in developing countries it is difficult to interpret ferritin levels and their use as a biomarker of iron deficiency may underestimate the true prevalence of iron deficiency (Nyakeriga 2004; Zimmermann 2005). Other biomarkers or combinations of biomarkers have been suggested for the assessment of iron deficiency in locations with a high prevalence of infection. These include the serum transferrin receptor, zinc protoporphyrin, transferrin saturation, and the ratio of serum transferrin receptor to serum ferritin (Lynch 2011), as well as the adjustment of ferritin to C-reactive protein or alpha1-acid glycoprotein levels, or both (Mburu 2008; Thurnham 2010). The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) recommend the use of concurrent measurements of haemoglobin, ferritin, and transferrin receptor to assess the iron status of a group (WHO/CDC 2004; WHO 2011b). The concurrent measurement of the inflammatory markers C-reactive protein and alpha1-acid glycoprotein facilitates the interpretation of ferritin levels. However, the exclusion of children with elevated markers of inflammation from iron deficiency assessment is not reasonable, since up to 69% of children in malaria-endemic areas may have elevated markers of inflammation (Darboe 2007).

Malaria and iron deficiency

Malaria is a leading cause of morbidity and mortality in children in sub-Saharan Africa (Breman 2001; WHO 2008b). Most infections are caused by the most virulent parasite species, *Plasmodium falciparum (* WHO 2008b), which is transmitted to humans by the bite of an infected female *Anopheles* mosquito. Trends and general patterns of malaria transmission vary greatly geographically. Children are vulnerable to malaria from the age of approximately three months, when immunity acquired from the mother wanes. Malaria is an important contributor to anaemia in endemic regions through the destruction of parasitized red blood cells (haemolysis), increased clearance of infected and uninfected red blood cells by the spleen, cytokine-induced dyserythropoiesis (abnormal production of red blood cells), and probably also decreased absorption of dietary iron (Menendez 2000; Ekvall 2003; Glinz 2015).

There is an ongoing debate on whether iron deficiency offers protection from malaria and whether an excess of iron increases the risk of malaria or severe malaria (Oppenheimer 2001; Stoltzfus 2010; Suchdev 2010; Oppenheimer 2012). Iron is required by many pathogens for their survival and pathogenicity (killing ability) (Beard 2001). Removal of free circulating iron seems to be an important part of the host (human) response to infection. The theory that iron deficiency may be an important defence mechanism has been termed "nutritional immunity" (Kochan 1973). The erythrocytic form of the *Plasmodium* parasite requires free iron (which is lacking in an iron-deficient person). In one observational study iron deficiency was associated with a small, albeit significant, degree of protection from episodes of clinical malaria in a cohort of young children living on the Kenyan coast (Nyakeriga 2004).

Description of the intervention

In areas where the prevalence of anaemia is 40% or more in young children, guidelines generally recommend that children of normal birthweight receive oral iron (2 mg/kg/day of elemental iron, daily, for three months) between the ages of six months and two years, and that children with a low birthweight receive the same amount of iron starting at two months (Stoltzfus 1998; INACG 1999).

Several meta-analyses have previously examined the benefits and risks of iron supplementation in children (INACG 1999; Oppenheimer 2001; Gera 2002; Iannotti 2006; Gera 2007). These have shown that iron treatment increases haemoglobin and prevents anaemia. The absolute effects on haemoglobin were larger among children who were anaemic at baseline and smaller in malarial hyperendemic regions compared with non-endemic regions, and with iron-fortified food compared with oral medicinal iron (Gera 2007). An increased risk of malaria has been highlighted by several meta-analyses. Most studies reported parasitaemia (being slide-positive for *P. falciparum* at the end of supplementation) rather than clinical malaria (INACG 1999; Oppenheimer 2001; Gera 2002; Iannotti 2006). The effects on parasitaemia were associated with baseline rates of parasitaemia (Gera 2002). In Gera 2002 other infections were also assessed. Overall there was no difference in the incidence rate ratio for all recorded infections. Diarrhoea was more frequent in the iron-supplemented group.

Why it is important to do this review

In 2006, the results of a large RCT that evaluated the effect of iron and folate supplements in a malaria-endemic area of Zanzibar (Pemba Island) were published (Sazawal 2006 (C)a). The study was terminated prematurely on the recommendation of the study data safety and management board following the higher proportion of hospitalization or death among participants randomized to treatment with iron and folic acid. A subgroup analysis revealed that the risk was limited to children who were iron-replete when iron supplementation was started. This trial heightened global concern about the routine, non-selective iron supplementation policy in areas where malaria is highly prevalent. Before this trial, the WHO guidelines for children living in malaria-endemic areas were no different than the general recommendations (WHO 2003). In 2007 a consultation convened to consider the recommendations for children living in malaria-endemic areas (WHO 2007). The trial's subgroup analysis suggested that it might be necessary to screen for iron deficiency and treat only iron-deficient children. However, such a recommendation is difficult or impossible to implement. There is no consensus on the most appropriate biomarker to assess iron deficiency or monitor iron status during supplementation in regions with a high prevalence of infection (Mburu 2008; Thurnham 2010; Lynch 2011; Pasricha 2013). Furthermore, as a public health intervention, screening of all children before iron supplementation is impractical in most malaria-endemic areas. Thus, it has become critical to examine the safety and effects of iron supplementation in malaria-endemic areas considering all the available evidence. In 2013 another large RCT that evaluated the effect of iron added to micronutrient powder was conducted in Ghana. Insecticide-treated bed nets were provided to all participants and antimalarial treatment was systematically administered when indicated (Zlotkin 2013 (C)). The use of iron in this trial did not result in an increased incidence of malaria among participants.

In view of the newly available data we set to examine the complete evidence in all RCTs that assessed iron supplementation for children in malaria-endemic areas. In a previous version of the review, we did not observe an increased risk of malaria with iron supplementation overall nor was iron harmful in the treatment of malaria (Ojukwu 2007; Ojukwu 2009; Okebe 2011). Since any theoretical harm of iron administration would be expected to occur in the setting of intense malaria transmission, in the current review version we limited our analysis to areas with hyperendemic or holoendemic transmission of malaria or to trials conducted in other areas, but reported malaria-related outcomes. We specifically searched for outcomes related to malaria and data for all-cause mortality, which ultimately combines benefit and harm. Due to the conflicting results of the studies conducted in Pemba Island, Sazawal 2006 (C)a, and in Ghana, Zlotkin 2013 (C), we compared the effect of iron administration on the incidence of clinical malaria in studies in which prevention or management of malaria were offered as an integral part of the study design, with studies in which neither malaria prevention nor malaria management were systematically administered.

OBJECTIVES

To evaluate the effects and safety of iron supplementation, with or without folic acid, in children living in areas with hyperendemic or holoendemic malaria transmission.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) that randomized individuals or clusters, and were conducted in countries defined as hyperendemic or holoendemic for malaria (Hay 2004; Table 1) or reported on any malaria-related outcome. We excluded studies if the publication specifically stated, or we obtained information from the study authors, that the study was conducted in an area or period without malaria activity. We considered cluster RCTs eligible only if they included at least two units per trial arm. We excluded trials conducted in hypoendemic and mesoendemic areas, unless they reported malaria-reported outcomes. In addition, we excluded studies that did not report at least one of the review-defined primary or secondary outcomes.

Types of participants

Children (less than 18 years of age), with or without anaemia, and with or without malaria or parasitaemia at baseline. We excluded pregnant women.

Types of interventions

Intervention

- Iron.
- Iron plus folic acid.
- Iron plus antimalarial treatment.

Control

- Placebo.
- No treatment.
- Antimalarial (only when the intervention is iron plus antimalarial).

We only included trials that allocated antiparasitics or other micronutrients (for example, zinc, vitamin A, vitamin C) if both trial arms received the same dose and schedule. Iron could be administered orally in any form of tablet, elixir, supplementation, or fortification (including fortification of food, drink, sprinkles, or other modes of iron administration as long as it provided at least 80% of the Recommended Dietary Allowance (RDA) recommended by the World Health Organization (WHO) for prevention of anaemia by age (Table 2; Stoltzfus 1998). Eighty per cent of the RDA would approximate the Estimated Average Requirement (EAR), which is the daily intake value of a nutrient that is estimated to meet the nutrient requirement of half the healthy population, by age (Institute of Medicine 1998). Iron could be administered for any duration or interval of administration.

We constructed the following comparisons:

- Iron versus placebo or no treatment.
- Iron plus folic acid versus placebo or no treatment.
- Iron either with or without folic acid versus placebo or no treatment

Types of outcome measures

Primary outcomes

- Clinical malaria: uncomplicated malaria, defined as a history of fever with parasitological confirmation (WHO 2010). We included cases of severe malaria if they were not reported separately.
- Severe malaria: cerebral malaria or acute *Plasmodium falciparum* malaria with signs of severity, or evidence of vital organ dysfunction, or both (WHO 2010). If it had been defined differently, we extracted the outcome as reported in the trial and used the trial authors' definitions.
- Death from any cause.

Secondary outcomes

- Malaria parasitaemia; any level of parasitaemia, and above a specific threshold as used in the study to define high-grade parasitaemia.
- Malaria parasite density, as reported in the included trial.
- Hospitalizations for any cause.
- Clinic visits.
- Haemoglobin levels.
- Prevalence of anaemia, as defined in the trial.
- Infections other than malaria (including diarrhoea, pneumonia, sepsis, meningitis, measles, and pertussis), expressed as episodes per child-month.
- Weight, absolute values.
- Height, absolute values.

We excluded studies that did not report at least one of the review-defined primary or secondary outcomes.

Search methods for identification of studies

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

Electronic searches

Databases

The Information Specialist of the Cochrane Infectious Diseases Group (CIDG) editorial base, Vittoria Lutje, searched the following databases and used the search terms and strategy described in Table 3: the CIDG Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (February 2015); MEDLINE (1966 to August 2015); EMBASE (1980 to February 2015); and LILACS (1982 to February 2015). We also searched the *meta*Register of Controlled Trials (*m*RCT) and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) using 'iron' and 'malaria' as search terms.

Searching other resources

Researchers, organizations, and pharmaceutical companies

We contacted the primary investigators of all included trials, ongoing trials, and those awaiting assessment to ask for unpublished data and further trials.

Reference lists

We scanned the bibliographies of all included trials, pertinent reviews, and previous meta-analyses for additional references.

Data collection and analysis

Selection of studies

Several review authors (Juliana Ojukwu, Dafna Yahav (DY), Joseph Okebe (JO), and Mical Paul (MP) for first version of this Cochrane review (Ojukwu 2009); Rana Shbita (RS), DY, JO, and MP for the second version (Okebe 2011); and Ami Neuberger (AN), JO, and MP for this review update) independently inspected the abstract of each identified reference and obtained the full text of relevant articles. Two review authors independently reviewed the articles and applied the inclusion criteria. If needed, we contacted the study authors to clarify study eligibility. We resolved any areas of disagreement by discussion with a third review author. Each trial was scrutinized to identify multiple publications from the same data set. We documented the justification for exclusion of studies from the review. We named studies by the first author and year of publication (with the addition of a, and b, for different studies from the same author and year of publication). The addition of (C) to the trial's identification denotes that the trial was cluster randomized.

Data extraction and management

Two review authors independently extracted data into a prepiloted data-extraction spreadsheet which detailed relevant epidemiologic and clinical data. We resolved any differences in the data extracted by discussion. One review author entered data into Review Manager (RevMan) (RevMan 2014).

For individually RCTs, we recorded the number of participants that experienced the event and the number of participants analysed in each treatment group or the effect estimate reported (for example, risk ratio (RR)) for dichotomous outcome measures. For count data, we recorded the number of events and the number of child-months of follow-up in each group. Whenever a trial did not report the number of child-months, we used the product of the duration of follow-up and the number of children evaluated to estimate this figure. For continuous data, we extracted means (arithmetic or geometric) and a measure of variance (standard deviation (SD), standard error (SE), or confidence interval (CI)) and the numbers analysed in each group. We calculated haemoglobin values in g/dL by multiplying hematocrit or packed cell volume values by 0.34, when a trial did not report haemoglobin values.

In cluster RCTs, we recorded the unit of randomization (for example, household, compound, sector, or village), the number of clusters in the trial, and the average cluster size. We documented the statistical methods used to analyse the trial alongside details that described whether these methods adjusted for clustering or other covariates. We extracted estimates of the intracluster correlation coefficient (ICC) for each outcome whenever possible. Where results had been adjusted for clustering, we extracted the treatment effect estimate and the SD or CI. If we did not adjust the results for clustering, we extracted the data reported (see adjustment below).

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias. For all included trials we assessed the following.

- Generation of randomization sequence.
- Allocation concealment.
- Blinding: participants, investigators, or outcome assessors.
- Incomplete outcome data: we recorded the number of participants randomized and number of participants evaluated per outcome.
- Selective reporting bias.
- Other biases: premature discontinuation or other biases.

We graded the generation of randomization sequence and allocation concealment as at either low, high, or unclear risk of bias, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

For cluster RCTs we also assessed the following.

- Recruitment bias.
- Baseline imbalance.
- Loss of clusters.
- Incorrect analysis.
- Comparability with individually RCTs.

Measures of treatment effect

For dichotomous data we calculated RRs and for continuous data absolute mean differences, with 95% CIs. We computed SDs from SEs or 95% CIs, and assumed a normal distribution of the values. We calculated risk difference for the outcome of all-cause mortality to allow the inclusion of the large number of trials with no deaths in both trial arms in the analysis. For count data, we calculated the rate ratio and SE for each study. We replaced zero events by 0.5. When the original included trials reported covariate-adjusted incidence rate ratios, we used these data with SEs. We analysed infectious episodes, hospitalizations, and clinic visits as count data, and reported rate ratios per child-months. We calculated standardized mean differences for the outcomes of weight and height, since we combined absolute values with weight/height for age Z scores.

Unit of analysis issues

- When cluster RCTs reported results as if they were individually randomized, we extracted the data reported in the trial and used estimated ICCs and design effects (DE) to adjust for clustering (Higgins 2011). When one or more of the cluster RCTs reported RRs adjusted for clustering, we computed cluster-adjusted SEs for the other trials (unadjusted SE of the log RR [SE(lnRR)] * $DE^{0.5}$ = adjusted SE(lnRR)). When none of the cluster RCTs provided cluster-adjusted RRs, we adjusted the sample size for clustering. We divided by the estimated DE the number of events and number evaluated for dichotomous outcomes and the number evaluated for continuous outcomes, where DE = 1 + [(average cluster size - 1) * ICC]. We have provided the derivation of the estimated ICCs and DEs in Appendix 1.
- In several outcomes a child might have experienced more than one outcome event during the trial period. For all outcomes we extracted the number of children with at least one event, except for infectious episodes other than malaria, hospitalizations, and clinic visits where repeated episodes were counted.
- Trials with several trial arms could be included more than once for different comparisons. We did not include a trial arm more than once in the same meta-analysis. In trials with an even number of arms, we included the trial for each pair of arms, as relevant. For trials with an odd number of arms, we summed up arms with the same intervention, as relevant.

Dealing with missing data

We contacted the trial authors if the available data were unclear, missing, or reported in a format that was different from the one required.

We aimed to perform an intention-to-treat analysis, where the trial authors accounted for all randomized participants; otherwise we performed a complete case analysis.

Assessment of heterogeneity

We assessed heterogeneity in the included trials by visual examination of the forest plot to detect non-overlapping CIs, using the Chi^2 test of heterogeneity ($P < 0.1$ indicating statistical significance) and the I^2 statistic of inconsistency (with a value > 50% denoting moderate levels of heterogeneity). When statistical heterogeneity was present, we investigated the reasons for it using subgroup analysis.

Assessment of reporting biases

We constructed a funnel plot to assess the effect of small trials on the main outcome (when we included more than 10 trials).

Data synthesis

We conducted analyses using RevMan (RevMan 2014). We included cluster RCTs in the main analysis after adjustment for clustering (see above). We performed the meta-analysis using the Mantel Haenszel (M-H) fixed-effect model or the generic inverse variance method (when adjustment for clustering was performed by adjusting SEs). Regarding the outcomes of haemoglobin and anaemia, we used a random-effects model where we expected a priori heterogeneity to be displayed due to different mean baseline haemoglobin values and definitions of anaemia in different studies.

We assessed the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and constructed 'Summary of findings' tables using GRADEpro Guideline Development Tool (GDT) (www.gradepro.org). We presented 'Summary of findings' tables for the primary outcomes and hospital admissions.

Subgroup analysis and investigation of heterogeneity

When we detected heterogeneity, we attempted the following subgroup analyses. We defined subgroups by trial (or trial arm) level and not at the level of individual participants, since most trials targeted the participant subgroup of interest as the main study (for example, trials were conducted on anaemic or non-anaemic children, and recruited children within a narrow age range). Moreover, trials most commonly did not present all outcomes for children subgroups.

- Anaemia at baseline (representing prevention versus treatment of anaemia): mean haemoglobin of children in trial at baseline below 10 g/dL or 10 g/dL and above. If the trial did not report mean haemoglobin we used the hematinic values reported or the local population's prevalence of anaemia to subgroup the trial.
- Age groups: children under two years of age; children aged two to five years old; and children aged over five years old. We classified trials that recruited children whose ages spanned more than one subgroup into the age group of most children.
- Malaria management strategy: trials in which at least one of the following were reported as being in place. This was in comparison to other trials where such infrastructure was not available:
  - treated bed nets were supplied to all participants;
  - prophylactic antimalarials were administered to all trial groups;
  - standardized diagnosis of malaria among febrile children was performed;
  - standardized treatment offered to children diagnosed with malaria as an integral part of the study intervention.

We primarily stratified analyses by the presence of anaemia at baseline or malaria endemicity (selected by relevance to the outcome assessed), regardless of the presence or absence of heterogeneity to address clinically relevant populations. Similarly, for the outcomes related to malaria we assessed the effects of age. We performed comparisons between subgroups with RevMan (RevMan 2014).

Sensitivity analysis

We conducted sensitivity analyses by methods of allocation concealment to assess the effect of risk of bias on primary outcomes. We restricted the analysis of malaria-related outcomes to *P. falciparum*. When we assessed all malaria species together, we included in this analysis trials where over 85% of malaria spp. diagnosed were *P. falciparum*. We excluded trials that counted multiple episodes of the outcome in individuals and trials whose outcome assessment occurred at a different point in time from that used in other included trials.

RESULTS

Description of studies

Results of the search

After the filtration of publications that were irrelevant or clearly incompatible with the inclusion criteria, we initially considered in full 120 studies that were conducted in hyperendemic or holoendemic malaria areas or that reported on malaria. Of these we excluded 83 publications for the reasons we have detailed in the 'Characteristics of excluded studies' tables. Overall, we included 52 publications, which represent 35 individual RCTs. Eleven trials were multi-armed, which led to 51 comparisons included in the review. We added five new trials in this current review update (Hop 2005; Giovannini 2006; Thi 2006; Esan 2013; Zlotkin 2013 (C)). We excluded 17 trials that assessed iron for the prevention or treatment of anaemia, which were included in the previous review version (Okebe 2011) from the current review update since they were conducted in hypoendemic or mesoendemic areas for malaria or provided an insufficient iron dose. Similarly, we excluded four trials that assessed iron as part of the treatment of malaria, as we dropped this analysis from the current version of this review.

Where the full publication did not provide enough information, we attempted to contact the authors of included and potentially relevant trials. We requested data primarily on malaria and all-cause mortality. We established correspondence with 26 trial authors, of whom 21 supplied further information.

Included studies

We have provided a description of the included trials in the 'Characteristics of included studies' tables. The trials were published between the years 1973 and 2013. Overall the included trials recruited 31,955 children: 7953 in 26 individually RCTs and 24,002 (73%) in nine cluster RCTs. The largest cluster RCT included two separate, independent cohorts: the main trial, Sazawal 2006 (C)a, and an independent substudy, Sazawal 2006 (C)b. We only included two arms of this trial in the review (iron, folic acid, and vitamin A versus vitamin A alone), totaling 15,956 children in the main study and 1619 children in the substudy (analysed as separate trials in the review). We included unpublished data supplied by the trial authors on the outcomes of malaria and death from the substudy. Our attempts to obtain data on the two trial arms that compared iron and folic acid and vitamin A and zinc versus zinc and vitamin A (Sazawal 2007) at the time the iron trial arm had been stopped (August 2014) were unsuccessful. This analysis could have been a major contribution to the evidence. Twenty trials reported

adherence, and the average overall adherence to all trial drugs was good (89%).

All trials assessed the administration of iron or iron plus folic acid for the prevention or treatment of anaemia among children without an acute illness. The mean iron supplementation dose was 2 mg/kg/day, and the mean duration of treatment was 4.5 months (one to 12 months). Twenty-seven trials added the antimalarial treatment to the iron arm or both trial arms, 12 trials added anthelminthics to both trial arms, and eight trials added micronutrients to both trial arms. Twenty-three trials reported one or more of the review-defined malaria-related outcomes (65.7% of trials included in the review. We have described the types of outcomes and their definitions in Table 4. Severe malaria, as defined per protocol, was reported in a single trial and its substudy that reported on cerebral malaria (Sazawal 2006 (C)a; Sazawal 2006 (C)b). Five trials reported clinical malaria with high-grade parasitaemia (Smith 1989 (C); Adam 1997 (C); Massaga 2003; Ayoya 2009; Zlotkin 2013 (C)). Twelve trials reported only or mostly (over 80%) on *P. falciparum* malaria (Table 4). Most trials that reported malaria-related outcomes performed regular surveillance for malaria using blood smears at baseline and during treatment (either at regular intervals or whenever children were febrile), and offered trial participants treatment when they were symptomatic (Table 4). Notably, no surveillance or treatment outside the hospital was offered in the main trial (Sazawal 2006 (C)a , unlike its substudy (Sazawal 2006 (C)b), where monitoring was performed and treatment was offered to children at their home. The baseline rate of malaria parasitaemia (reported in 11 of 19 trials) ranged from 0% to 70% of children (mean 45%). The mean baseline haemoglobin was lower than 10 g/dL in 17 trials (when iron was most commonly administered for the treatment of anaemia) and 10 g/dL or higher in 22 (when iron was administered for the prevention of anaemia). The trial population consisted of children aged less than two years of age in 12 trials, two to five years of age in 11 trials, and over five years of age in 16 trials. The respective number of trials that reported on malaria-related outcomes in the three age groups were eight, nine, and six trials.

Excluded studies

We have detailed the specific reasons for exclusion in the 'Characteristics of excluded studies' tables. The major reasons for exclusion of studies were the following.

- The trials were conducted in non-malaria-endemic, mesoendemic, or hypoendemic areas, including studies in which it was explicitly stated or the study authors confirmed that there was no malaria activity in the study location at the time of the trial.
- The administration of iron fortification in a dose lower than at 80% of the Recommended Dietary Allowance (RDA) recommended by the World Health Organization (WHO) for prevention of anaemia by age (Types of interventions; Table 2).
- The interventions were incompatible with the inclusion criteria, such as the administration of iron together with other micronutrients or the administration of iron to both trial arms.
- Four trials assessed the intervention of iron during an acute attack of malaria (van Hensbroek 1995; Nwanyanwu 1996; van den Hombergh 1996; Gara 2010) among children under five years of age, all of whom were anaemic at baseline (haemoglobin range 4.1 to 9.6 g/dL).

Risk of bias in included studies

We have detailed the risk of bias in the included trials in the 'Risk of bias' tables and presented these assessments overall in Figure 1 and by study in Figure 2.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included trials. The unclear category for incomplete outcome data represents trials that did not report this outcome.

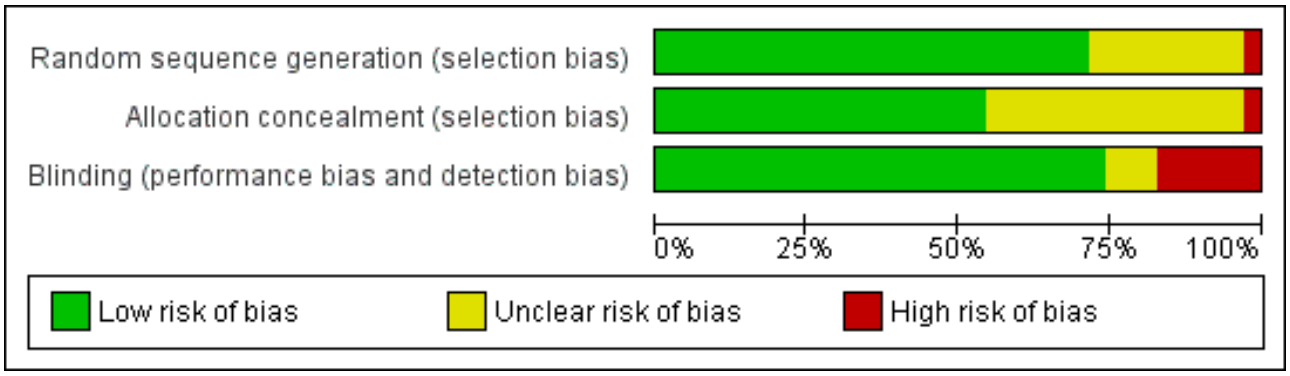


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included trial.

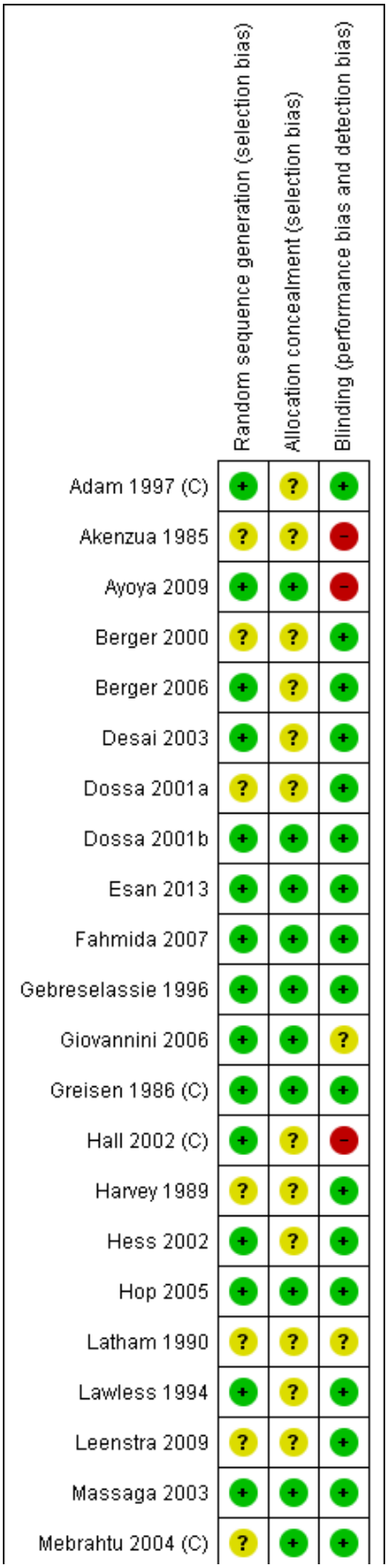
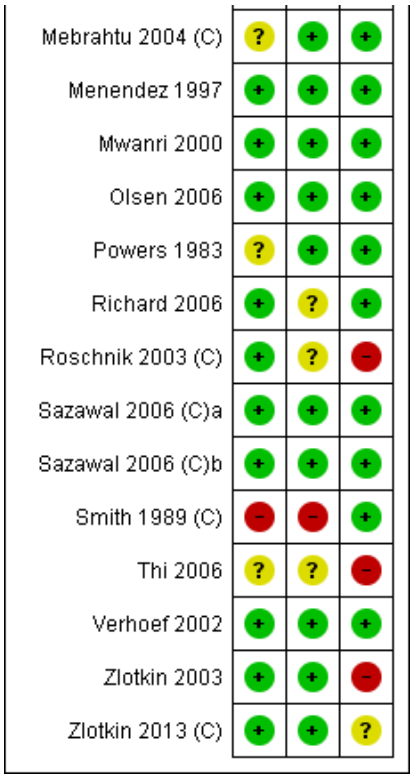


Figure 2. (Continued)



Allocation

We judged 20 of the 35 trials (57.1%) as at low risk of bias related to allocation concealment. One trial was at a high risk of bias (Smith 1989 (C)). All the remaining trials either did not describe their methods clearly or did not provide a description of them. We judged the generation of randomization sequence to be at low risk of bias in 26/35 (74.3%) trials, at a high risk for bias in the one trial using alternation, and at unclear risk in all the others. Overall, we considered the allocation procedure (both allocation concealment and generation) as at low risk of bias in 18 (51.4%) trials.

Blinding

Twenty-seven trials out of 35 trials (77.1%) described double-blinding or stated that the trial was double-blind, but gave no description of the blinding techniques; we considered all of these trials to be at low risk of bias (see the 'Risk of bias' tables). We considered six trials to be at high risk, and three trials at an unclear risk of bias.

Incomplete outcome data

The included trials explained the reasons for exclusion of participants from malaria-related and haemoglobin outcome reporting and related it to an inability to obtain blood samples from the participants. The reasons for the exclusion of randomized children from mortality assessments were unclear and we considered this to be a serious risk for bias since deaths could have occurred among the excluded children. We have provided the details of the number of participants randomized and evaluated in the 'Risk of bias' tables.

Selective reporting

We did not have access to protocols to compare planned outcomes with those reported in the final publication.

One trial specified methods for assessment of malaria throughout the trial (without defining these as study outcomes), but did not report the results per trial arm (Olsen 2006). We could not contact the authors of this trial. We contacted authors of trials that did not report on malaria in their methods or result sections; the authors of one trial reported that data had been collected in the trial but were no longer available (Powers 1983), while the authors of seven trials replied that malaria-related outcomes were not collected in their trials (Greisen 1986 (C); Latham 1990; Dossa 2001a; Dossa 2001b; Hall 2002 (C); Hess 2002; Zlotkin 2003). Thus, selective reporting bias is unlikely with regard to the outcomes related to malaria.

Only one trial defined death as an outcome (Sazawal 2006 (C)a; Sazawal 2006 (C)b), although 16 trials reported these results and we obtained these results from authors of another 14 trials. Thus, it is not possible to discuss reporting bias in relation to the outcome of mortality.

Cluster RCTs

Nine of the included RCTs were cluster randomized.

- Recruitment bias: one trial randomized households. It was clear that children could be born and added to the cluster after randomization (Sazawal 2006 (C)a; Sazawal 2006 (C)b), one trial was at low risk of bias, and none of the other trials described clearly whether children could be recruited into the trial after the clusters had been randomized.

- Basline imbalance: no differences in main baseline characteristics of different trial groups existed in any included trial.
- Loss of clusters: none of the included trials provided data on the loss of clusters.
- Incorrect analysis: only Sazawal 2006 (C)a, its substudy (Sazawal 2006 (C)b), and Zlotkin 2013 (C) adjusted the main outcomes for clustering. The other trials reported results per individual only and did not provide data regarding the ICC. We could usually calculate the average cluster size from the number of clusters and individuals included in the trial. We have provided the crude results reported in the publication, the DE used for adjustment, and the adjusted results used in the meta-analyses for the main outcomes in Table 5 (for outcomes pooled with the use of adjusted SEs) and Table 6 (for outcomes pooled using effective sample size).
- Comparability with individually RCTs: cluster RCTs were larger than individually RCTs (see above); the percentage of children excluded from outcome assessment was higher (10.2% versus 5.9% respectively), and adherence to study medications was lower (84.2% versus 91.3% respectively). The average dose of iron used was lower in cluster RCTs (1.6 versus 2.7 mg/kg/day), and the median treatment duration was longer (4.3 versus 3.3 months), both without statistical significance. Baseline haemoglobin levels were similar (10.5 versus 10.2 g/dL, but fewer children were defined as anaemic at baseline (median 55% versus 84.5%).

Other potential sources of bias

One trial was discontinued prematurely on the recommendation of the data- and safety-monitoring board, when it reached a predefined difference in mortality of P = 0.2 (Sazawal 2006 (C)a; Sazawal 2006 (C)b).

Effects of interventions

See: **Summary of findings for the main comparison** Oral iron versus placebo or no treatment for children in malaria-endemic areas; **Summary of findings 2** Effects of oral iron with or without folic acid on malaria among children in malaria-endemic areas; **Summary of findings 3** Oral iron with antimalarial prophylaxis versus placebo or no treatment for children in malaria-endemic areas

1. Iron versus placebo/no treatment for the treatment or prevention of anaemia (31 trials, 12,963 children)

We included trials or trial arms that compared iron plus antimalarial versus antimalarial alone in this comparison. We did not separate the comparisons of iron versus placebo/no treatment and iron plus antimalarial versus antimalarial, unless there was significant heterogeneity in results explained by this factor. Four-armed trials including both comparisons appear twice in the analyses (Menendez 1997; Verhoef 2002; Massaga 2003), once for the comparison of iron versus placebo/no treatment and once for the comparison of iron plus antimalarial versus antimalarial (each arm included different children).

Primary outcomes

Clinical and severe malaria

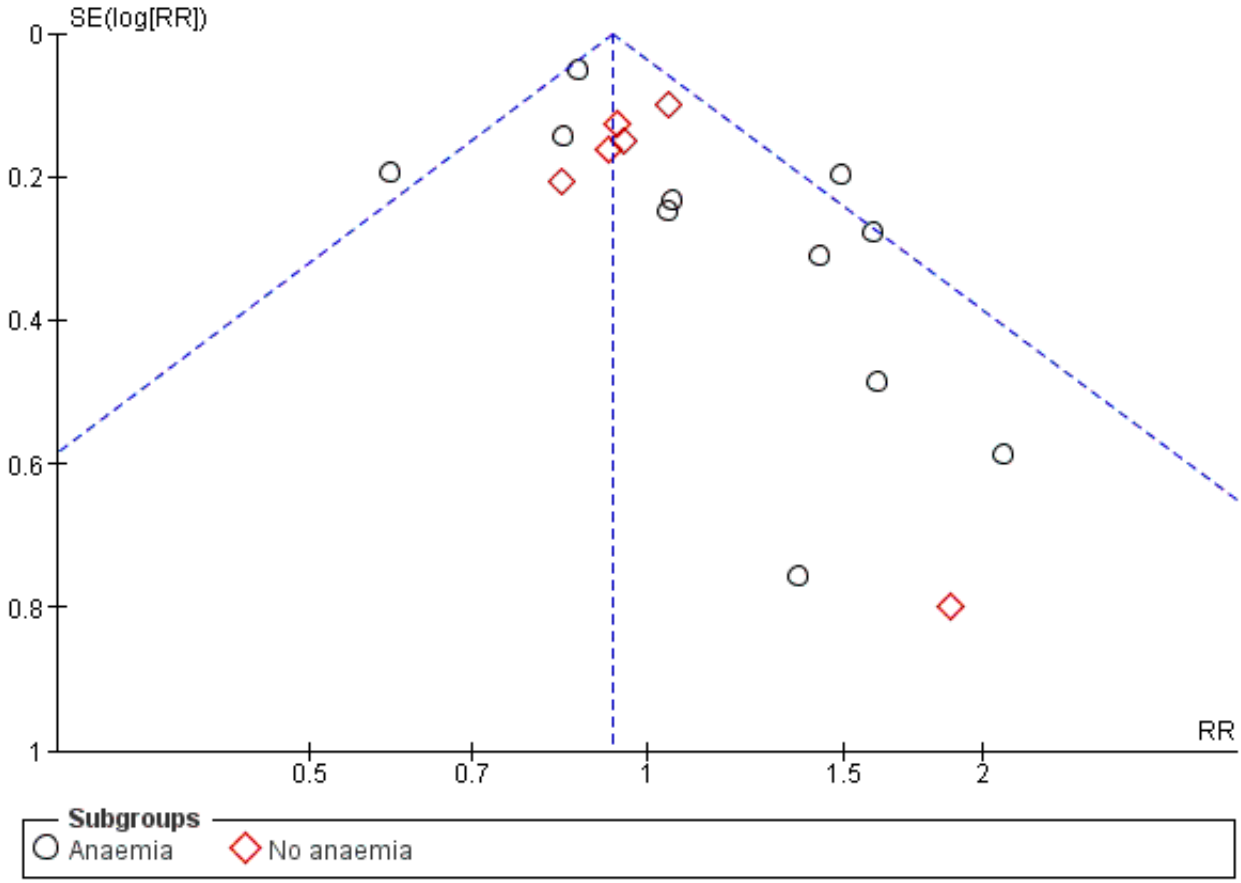
All trials defined clinical malaria as fever (usually greater than 37.5°C) and parasitaemia (any density). Overall, there was no significant difference in the risk ratio (RR) for clinical malaria between iron treatment and placebo or no treatment, with a trend in favour of iron treatment (RR 0.93, 95% CI 0.87 to 1.00; 14 trials, 7168 children). Specifically, there was no difference in the risk for clinical malaria between iron treatment versus placebo or no treatment in the subgroup of trials including non-anaemic children (RR 0.97, 95% CI 0.86 to 1.09; five trials, 2112 children) without heterogeneity, Analysis 1.1). Significant heterogeneity was present in the subgroup analysis with anaemia (P = 0.01, I^2 statistic = 56%) and in the overall analysis. We rated the quality of the evidence as high for the overall analysis and moderate for the subgroups of anaemic and non-anaemic children (Summary of findings for the main comparison).

The RR of malaria was lower for children younger than two years of age (RR 0.89, 95% CI 0.82 to 0.97), and this result was largely driven by the recent study conducted in Ghana (Zlotkin 2013 (C)). In children aged between two and five years, and among children older than five years, we did not observe any effect of iron treatment on the relative risk of clinical malaria (Analysis 1.2).

The results favoured iron treatment when we only included trials that described malaria caused solely or primarily by *P. falciparum* (RR 0.91, 95% CI 0.84 to 0.99; nine trials, 5503 children, Analysis 1.3). Similarly, in six trials that reported malaria with high-grade parasitaemia as an outcome, the RR was lower among children treated with iron when compared to children receiving placebo or no treatment (RR 0.90, 95% CI 0.81 to 0.98; Analysis 1.6) and we rated the quality of this evidence as high (Summary of findings for the main comparison).

Ten of the 17 trials included in the analysis were at low risk of bias with respect to allocation concealment, and all but two of the trials were double blinded. Sensitivity analysis restricted to trials at low risk of bias for allocation concealment did not affect results. The funnel plot was asymmetrical, which indicated that small studies that favour iron could be missing (Figure 3). Three trials reported either on episodes of malaria (Richard 2006; Leenstra 2009) or clinic visits for malaria (Smith 1989 (C)) rather than participants with their first or only episode. The exclusion of these trials did not affect the pooled RR for this comparison. One trial reported on children with clinical malaria only at end of follow-up, which was six months after completion of iron supplementation (Menendez 1997). Its exclusion did not affect the results.

Figure 3. Funnel plot of comparison: 1. Iron versus placebo or no treatment, outcome: 1.1 Clinical malaria (grouped by presence of anaemia).



Deaths

15/17 trials reported mortality, and in most trials no deaths occurred among the evaluable children (control event rate 1%). Overall, there was no difference between the iron and placebo/no treatment groups, without heterogeneity (Analysis 1.5). We assessed the quality of the evidence for this outcome as low due to imprecision (very low event rate) and incomplete outcome assessment in most of the trials (a drop-out range of 2% to 62% of participants), as deaths might have occurred among the people lost to follow up (Summary of findings for the main comparison).

Secondary outcomes

Parasite prevalence and density

There was no statistically significant difference in the prevalence of parasitaemia of any level, with a trend favouring placebo or no treatment (RR 1.11, 95% CI 1.0 to 1.23; nine trials, 3393 children, without significant heterogeneity;Analysis 1.4). We converted odds ratios to RRs to allow for the use of data on parasitaemia from one trial (Mebrahtu 2004 (C)). This outcome was not affected by age, anaemia at baseline, or *Plasmodium* species assessed (Analysis 1.4; Analysis 1.7; Analysis 1.8). Despite the lack of heterogeneity overall, there was a significant difference between trials that described adequate allocation concealment (RR 0.98, 95% CI 0.83 to 1.15, four trials, 1727 children, Analysis 1.9) and trials with unclear or inadequate methods that showed significantly higher rate of parasitaemia with iron treatment (RR 1.22, 95% CI 1.06 to 1.40, five trials, 1666 children; P = 0.04 for the difference between subgroups; Analysis 1.9). All of the trials included in the comparison of parasitaemia were double blinded. There was no statistically significant difference in the occurrence of high-grade asymptomatic parasitaemia, most commonly defined as > 5000 parasites/µL (RR 1.13, 95% CI 0.93 to 1.37; five trials, 2565 children Analysis 1.10). In trials that continued follow-up after the cessation of iron administration, there was a higher prevalence of any level of parasitaemia at the end of follow-up among participants treated with iron (RR 1.23, 95% CI 1.09 to 1.40; five trials, 1150 children; Analysis 1.11).

It was difficult to establish whether the trials reported on children with parasitaemia or on parasitaemia episodes. Gebreselassie 1996 clearly reported on cumulative incidence and Leenstra 2009 included repeated episodes. Leenstra 2009 reported incidence rate ratios with 95% CIs adjusted for age, baseline parasitaemia, and school. We used these in our analysis as relative risks. The exclusion of these trials did not affect the results.

The trials reported parasite density differently, with differences that referred both to the unit of measurement and the denominator (Table 7). A meta-analysis was therefore not possible; we have shown the results in Table 7 for each trial. Qualitatively, parasite density was higher in the iron supplemented group in four trials,

lower in one, and similar in one of the six trials that reported on parasite density at the end of treatment.

Admissions to hospital and clinic visits

Six trials reported hospitalizations or clinic visits. Overall, there was no difference between iron and placebo or no treatment (Analysis 1.12); these results were not affected by the administration of antimalarial medications. We assessed the quality of the evidence as very low due to inconsistency and indirectness of this outcome ('Summary of findings' table 1).

Haemoglobin and anaemia

Analyses for haemoglobin were highly heterogeneous, since the absolute magnitude of treatment effect in trials differed, and the 95% CIs were narrow. However, the heterogeneity stemmed from different magnitudes of increase in haemoglobin with iron supplementation and not in the direction of the result. Overall, at the end of treatment there was a mean difference of haemoglobin level of 0.75 g/dL (95% CI 0.48 to 1.01; 16 trials, 5261 children; I^2 statistic = 93%; Analysis 1.13). In trials with anaemic children at baseline, the children gained 0.95 g/dL haemoglobin (95% CI 0.38 to 1.51; seven trials, 2481 participants) with iron supplementation, while in trials including mostly children without anaemia the end haemoglobin was higher than control by 0.61 g/dL (95% CI 0.38 to 0.85; nine trials, 2780 participants; P = 0.28 for subgroup difference). The mean change of haemoglobin from the baseline at end of treatment was 0.67 g/dL (95% CI 0.42 to 0.92; 12 trials, 2462 children; I^2 statistic = 82%; Analysis 1.19).

The RR for anaemia at the end of treatment, as defined in the trial, was 0.63 (95% CI 0.49 to 0.82; 15 trials, 3784 children; Analysis 1.15), with similar substantial heterogeneity mainly in the magnitude of benefit.

We did not observe any differences when we analysed the effect of iron on haemoglobin by age groups, or by the addition of antimalarial medications or multinutrients to both study arms (analyses not shown). Heterogeneity was maintained in all these subgroup analyses.

Other outcomes

Six studies provided data on respiratory infections. There was no difference between iron and placebo overall (rate ratio 0.99, 95% CI 0.85 to 1.15; six trials, 21,767 child-months; I^2 statistic = 0%; Analysis 1.20). Trials usually reported diarrhoea as 'infectious diarrhoea', although we could not clearly differentiate the symptoms from diarrhoea related to iron or iron/zinc supplementation. We stratified this analysis by zinc co-administration (Analysis 1.17). Overall, treatment was associated with an increased risk of diarrhoea (rate ratio 1.15, 95% CI 1.06 to 1.26; eight trials, 23,912 child-months; I^2 statistic = 40%). This association was driven by the effect of the iron-zinc combination (rate ratio 1.29, 95% CI 1.15 to 1.44; three trials, 6346 children), and not by iron treatment alone (rate ratio 0.99, 95% CI 0.87 to 1.13; seven trials, 17566 children). Six trials reported the number of febrile episodes; there was no difference between iron treatment and control arm (RR 1.03, 95% CI 0.93 to 1.14; 15531 children). One trial reported more days with fever among iron-treated participants, and one trial reported more infectious episodes among participants randomized to the iron treatment arm. Definitions and reporting methods were highly variable; results are shown per outcome (Analysis 1.18).

Results for height and weight were inconsistently reported as end values or as the change from baseline and absolute values or z-scores matched for age, height, or weight. The analyses shown are based on absolute weight in kg and height in cm at the end of treatment or weight/height for age z-scores. For end of treatment weight, there was no statistically significant difference between iron and placebo/no treatment study arms (Analysis 1.14), while the change from baseline favoured iron (Analysis 1.16). The latter analysis was heterogenous and the heterogeneity was not explained by the review-defined subgroups. There were no significant differences in end values or change from baseline of height, with similar heterogeneity in the change from baseline analysis (Analysis 1.21; Analysis 1.22).

2. Iron plus folic acid versus placebo for treatment or prevention of anaemia (6 trials, 19,456 children)

Primary outcomes

Clinical and severe malaria

The only trial that reported on malaria-related outcomes was the Pemba study (Sazawal 2006 (C)a; Sazawal 2006 (C)b). Malaria-related outcomes reported were admissions for malaria (Analysis 2.1) and cerebral malaria (Analysis 2.2). The results for the main study and the substudy were significantly different, and the main study showed a higher risk for severe malaria with iron plus folic acid and the substudy showed a lower risk. Therefore we did not pool the results. Children in the substudy were older than children in the main trial (mean age of 22.5 versus 18.3 months) and the baseline haemoglobin for the substudy cohort was probably higher than that of the main trial, because children with severe anaemia (haemoglobin < 7 g/dL) were excluded only from the substudy. However the main difference, as described by the trial authors, was that children in the substudy were monitored and offered treatment for malaria at home throughout the trial period. In the main trial, Sazawal 2006 (C)a, there was no organized infrastructure for the diagnosis and treatment of uncomplicated malaria.

Deaths

The pooled risk difference for mortality was 0.00 per 1000 children (95% CI −0.00 to 0.01; five trials, 18,034 children, Analysis 2.3), and Sazawal 2006 (C)a contributed 88.4% of the weight of this analysis.

Secondary outcomes

Hospital admissions were reported only in Sazawal 2006 (C)a (RR 1.08, 95% CI 0.96 to 1.22; 22,959 children). Haemoglobin at end of treatment was similarly reported in a single study, Giovannini 2006, and was higher with iron and folate, mean difference 0.90 g/dL (95% CI 0.51 to 1.29; 124 children Analysis 2.5). The RR for anaemia at end of treatment was 0.49 (0.25 to 0.99; three trials, 633 children, Analysis 2.6). No consistent data were reported for respiratory infections, other febrile episodes, and diarrhoea. There were no significant differences in the absolute end values of weight (Analysis 2.7) and height (Analysis 2.8).

We did not create any 'Summary of findings' tables for this comparison, as malaria-related outcome were based on a single trial. The risk of bias for the trial was low, except for the fact that it was discontinued for harm (Sazawal 2006 (C)a; Sazawal 2006 (C)b).

3. Iron with or without folic acid versus placebo for treatment or prevention of anaemia (15 trials, 24,743 children for the outcome of malaria)

We analysed a single outcome for this comparison to enable the compilation of malaria in all trials that administered iron versus placebo or no treatment. We subgrouped the analysis by the presence of malaria prevention and management services in the trial setting and showed a significant lower risk of malaria with iron with or without folic acid when services were present (RR 0.91, 95% CI 0.84 to 0.97; seven trials, 5586 children), and a significantly higher risk of malaria when such services were absent (RR 1.16, 95% CI 1.02 to 1.31; nine trials, 19,086 children, analysis 3.1, P < 0.001 for subgroup difference). We assessed the quality of the evidence as low for both subgroups, due to inconsistency and suspected publication bias when malaria prevention and management services were present and indirectness in the analysis without malaria prevention and management services, as the latter was dominated was the Sazawal 2006 (C)a study that assessed only admissions due to malaria rather than all events of malaria ('Summary of findings' table 2).

4. Iron plus antimalarial versus placebo for treatment or prevention of anaemia (four trials, 1915 children)

Primary outcomes

Clinical malaria

Three trials reported on clinical malaria and all were individually RCTs. The trials uniformly showed that the intervention was protective for clinical malaria (pooled RR 0.54, 95% CI 0.43 to 0.67; three trials, 728 children, I^2 statistic = 0%; Analysis 4.1), high quality evidence ('Summary of findings' table 3). These trials did not assess severe malaria.

Deaths

There was no difference in the risk of death for the three trials combined (RR 1.05, 95% CI 0.52 to 2.11; three trials, 728 participants, Analysis 4.2). The quality of the evidence was low due to imprecision ('Summary of findings' table 3).

Secondary outcomes

Both the number of hospitalizations and the number of clinic visits were significantly reduced in two trials (Analysis 4.3). Iron plus antimalarial significantly improved haemoglobin in one trial and decreased the prevalence of anaemia in two trials (Analysis 4.4; Analysis 4.5). Respiratory infections, diarrhoea, and other infections were not reported in these studies.

The trials included in this comparison were four-armed trials that assessed iron, placebo, iron with an antimalarial, and an antimalarial alone. The comparison of antimalarial treatment alone versus placebo showed identical results to the comparison of iron plus antimalarial versus placebo, except for the outcomes of haemoglobin/anaemia where the addition of iron conferred a higher benefit (analysis not shown). This observation strengthens the lack of effect of iron on malaria or other adverse outcome.

DISCUSSION

Summary of main results

Oral iron supplementation alone did not increase the risk for clinical malaria, and the upper level of the 95% CI indicated no harm (risk ratio (RR) 0.93, 95% CI 0.87 to 1.00). The risk was probably not increased in trials that recruited children who were not anaemic at baseline (RR 0.97, 95% CI 0.86 to 1.09). There was no increased risk of *P. falciparum* malaria or malaria with high-grade parasitaemia, and pooled results favoured iron treatment. The combination of iron and folate resulted in a higher rate of admissions for malaria and cerebral malaria in one large trial, Sazawal 2006 (C)a, but a substudy pointed at the opposite direction. The difference in malaria surveillance and management strategies in the two parts of this trial led to an analysis of all iron supplementation trials by malaria management infrastructure. Overall, iron treatment, with or without folate, was safe and may be protective in settings where malaria prevention or management programmes were implemented (RR 0.91, 95% CI 0.84 to 0.97). Conversley, it might be associated with an increased risk of clinical malaria when neither prevention nor antimalarial treatment were available (RR 1.16, 95% CI 1.02 to 1.31; P < 0.001 for the difference between subgroups). This finding agrees with the analysis of iron with an antimalarial drug as the intervention, which significantly decreased the occurrence of clinical malaria compared to placebo or no treatment. In all analyses, mortality was low in general and not different between iron-treated participants, and those that received placebo or no treatment.

There were no effects of iron administration alone on infections, hospitalizations and clinic visits, and parasitaemia at the end of treatment. Iron treatment alone resulted in higher rates of parasitaemia at the end of follow-up in trials with unclear allocation concealment methods. The combination of iron and antimalarial medication resulted in fewer clinic visits and hospitalizations, which probably reflected the effect of the antimalarial drug. The combination of zinc and iron was associated with more episodes of diarrhoea, while iron monotherapy was not. In all comparisons, iron supplementation increased haemoglobin and decreased anaemia. All analyses were highly heterogenous, which precluded a precise pooled estimate of effect, but the increase in haemoglobin was substantial in most individual trials and the prevalence of anaemia was reduced by 40% to 50% in most comparisons. We did not observe a clear beneficial or adverse effect of iron supplementation on weight or height.

In this current review update we applied more stringent inclusion criteria to focus on the question of iron's safety and beneficial effect in areas where these are doubtful. Firstly, since the debate that concerned iron administration centred around its effect in areas with significant burden of malaria, we chose to include only trials conducted in hyperendemic or holoendemic areas for malaria transmission, or trials that reported malaria outcomes. Secondly, we included trials of iron fortification and for all included trials we excluded trials that administered low-dose iron that is not expected to result in iron repletion. Of the five trials that we added to the current review update, one large trial had a large impact on the pooled malaria outcome results (Zlotkin 2013 (C)). Thirdly, we omitted from this update an analysis of iron administration during proven malaria episodes. We included four trials in the 2011 version of this review, Okebe 2011, that assessed this intervention and no new trials have been published in recent years.

In the 2011 version of this review, Okebe 2011, we deemed that iron treatment not harmful regarding clinical malaria. In the current analysis, we found a trend towards a favourable effect of iron treatment on clinical malaria, with a statistically significant benefit in several subgroup analyses: children younger than two years of age, children infected primarily or exclusively by *P. falciparum*, and children included in trials in which malaria prevention or management strategies were implemented as an integral part of the trial's design. These results strengthen our conclusions from the previous versions of this Cochrane review (Ojukwu 2009; Okebe 2011); iron administration for the prevention or treatment of anaemia is safe in malaria-endemic areas if malaria is adequately prevented, diagnosed, and treated.

Overall completeness and applicability of evidence

We have provided the results and the quality of evidence assessments in the 'Summary of findings' tables. There were several main reasons that led to downgrading of the evidence. We downgraded the quality of the evidence for imprecision whenever the 95% confidence intervals (CIs) showed possible harm with iron. Some of the important patient-relevant outcomes assessed, including hospital admissions, clinical visits, and deaths, can obviously be triggered by causes other than malaria and the difference between arms is probably not only explained by malaria. Thus, we downgraded these outcomes for indirectness. For deaths, a serious concern of missing data with or without publication bias led to downgrading of the evidence; mortality data were reported in 26/39 of the trials included in the analyses and most of the trials that reported on mortality referred only to children available for analysis at the end of treatment or follow-up. Deaths should be assessed among all children randomized, mainly those lost to follow-up. Inconsistency was apparent in the outcome definitions, mainly with the large Pemba trial that reported only on malaria requiring hospital admission, while all other trials reported on fever with parasitaemia (Sazawal 2006 (C)a; Sazawal 2006 (C)b). Some degree of imprecision might exist in the latter outcome, as asymptomatic parasitaemia is common in malaria-endemic regions and fever with parasitaemia may be caused by infections other than malaria. Funnel plot asymmetry was present in the analyses of iron versus placebo or no treatment, with an excess of small trials that favoured the control arm. However, we did not consider this as a reflection of publication bias since malaria was not the primary outcome assessed in most trials (specifically, it was not the primary outcome in all small trials) and the direction of the small trials' effect was against the safety of iron.

For the intervention of iron with folic acid, the large Pemba trial reported a significantly increased risk for death or hospital admission (Sazawal 2006 (C)a; Sazawal 2006 (C)b), but the relative contributions of the addition of folic acid and the poor infrastructure for diagnosis and surveillance of malaria to the adverse effects of iron in this trial are unclear. Thus, data on the safety of iron and folate supplementation are unclear.

Potential biases in the review process

There is an interest in the assessment of the effect of iron supplementation on malaria by iron status and iron-deficiency anaemia at baseline. We could not conduct a subgroup analysis by individual children's iron status or haemoglobin at baseline due to the lack of subgroup data reported in the included trials for the outcomes of deaths and malaria. Our analyses stratified by anaemia are based on the study groups' mean haemoglobin level. Most of the trials recruited a uniform population of anaemic or non-anaemic children, and thus enabled this stratification in the meta-analysis. Although this analysis could mask an adverse effect in individual iron-replete, non-anaemic children compensated by benefit in iron-deplete, anaemic children, the lack of heterogeneity in the analyses for malaria and deaths makes this possibility unlikely. This possibility is not supported by a trial-level stratified analysis restricted to trials that recruited only anaemic or non-anaemic children (data not shown). However, we could not conduct an analysis by true iron status or iron-deficiency anaemia at baseline. Since all trials of non-anaemic children had malaria prevention and management services, we could not assess iron supplementation in non-anaemic populations where malaria prevention and management services were not present.

There was heterogeneity regarding the management of children identified as anaemic during the trial and after its conclusion. Some trials supplied iron to all children identified as anaemic below a certain threshold during the trial. After treatment, during a follow-up period, children who remained anaemic were all given iron per protocol, were offered the possibility of treatment, or the issue was not addressed specifically. We could not assess the effects of this variable due to the large heterogeneity in trial protocols and poor reporting. This factor could underlie some of the unexplained heterogeneity observed in our analyses for haemoglobin and anaemia.

Much of the evidence relies on cluster RCTs. Naturally, these were the largest trials and thus carried a large weight in the meta-analysis. However, the major outcomes assessed in these trials are probably correlated within clusters, including anaemia, iron status, malaria, and other infectious complications. In classes or schools, the correlation between individuals may be smaller than among families, but the large cluster size increases the cluster effect. Ideally, we would want these trials to be planned and analyzed accordingly. The trial should report on the unit of randomization, the average cluster size (number of children in household or class), the number of clusters and individuals randomized, the intracluster correlation coefficient (ICC) value for each outcome (denoting the degree of similarity between individuals in the same cluster) and an effect estimate adjusted for clustering. Unadjusted effect estimates, calculated as if the trial was individually randomized, may result in an exaggerated precision of the effect estimate, thus inflating the weight of the trial in the meta-analysis. Out of the nine cluster RCTs included in our review, only Sazawal 2006 (C)a, Sazawal 2006 (C)b, and Zlotkin 2013 (C) reported adjusted analyses for the primary outcomes. In our analyses we used estimated ICCs to adjust the weight of the cluster RCTs in the meta-analysis. We cannot be sure that the contribution of these trials to the compiled analysis is correct.

Other analyses or outcomes lacking from our Cochrane review include an assessment of the effect of children's nutritional status at baseline on the results; analyses stratified by the schedule of iron supplementation (daily versus weekly); psychomotor and cognitive outcomes assessed in another Cochrane review (Wang 2013); tuberculosis, and age/weight/height-adjusted Z scores for growth. Finally, we do not have the data from Sazawal 2006 (C)a on malaria-related events, hospital admissions, and deaths for the two trial arms: iron plus folic acid plus vitamin A plus zinc versus zinc plus vitamin A. These data could add 16,196 more children to the

analyses of iron plus folic acid versus placebo treatment. Similarly, we cannot exclude the existence of more unpublished RCTs that could contribute to the evidence on iron supplementation and malaria, such as those identified in PhD theses (Gebreselassie 1996; Adam 1997 (C)) or others (Roschnik 2003 (C)).

Agreements and disagreements with other studies or reviews

Sazawal 2006 (C)a is by far the largest trial to date, and probably the only trial to date, powered to assess the effect of iron supplementation on severe malaria. It showed a significantly increased risk for the composite outcome of death or hospitalization among children, most of whom who were younger than two years of age. The risk of death was increased, but without statistical significance. In a stratified analysis of an independent substudy, we observed adverse effects of iron supplementation among children who were iron-replete and non-anaemic at baseline, while among children who were iron-deficient and anaemic there were fewer adverse events. At the time there was no malaria control programme in Zanzibar, and the main trial's protocol did not offer children special malaria prevention or management services. In the substudy, Sazawal 2006 (C)b, surveillance for parasitaemia was performed and children received treatment according to the study protocol in their homes. The main trial showed that iron is harmful, while the substudy showed that iron supplementation is protective for severe malaria. Our analysis, which included all trials that assessed iron supplementation, concords with this conclusion (Analysis 3.1).

In 2007, based on Sazawal 2006 (C)a, the World Health Organization (WHO) released a statement that recommended that iron supplementation should be prescribed only after screening for iron deficiency (WHO 2007). Universal screening for anaemia and iron status places a significant burden on healthcare systems in low-income countries. This Cochrane review was originally published in 2009, Ojukwu 2009, and added further debate into the conundrum of iron supplementation for children in malaria-endemic areas (Roth 2010; Stoltzfus 2010; Suchdev 2010; Oppenheimer 2012). The previous versions of this systematic review, Ojukwu 2009 and Okebe 2011, challenged the recommendations for universal screening, and placed the Sazawal 2006 (C)a trial in the context of the complete evidence. In 2011 the WHO amended its recommendation to state that “In malaria-endemic areas, the provision of iron should be implemented in conjunction with measures to prevent, diagnose and treat malaria" (WHO 2011c). In 2013 the results of the Zlotkin 2013 (C) trial became available, with no harm observed for iron-treated children. Children included in the latter trial underwent initial screening for malaria, received insecticide-treated bed nets, and were provided with first-line antimalarial treatment if ill. The results of the Zlotkin 2013 (C) trial and this current analysis further shift the emphasis of decision making prior to iron supplementation on malaria prevention and management rather than on the assessment of iron status.

AUTHORS' CONCLUSIONS

Implications for practice

We did not find an increased risk of clinical malaria and parasitaemia, all-cause mortality, or other infectious complications with iron supplementation alone for children living in areas with intense malaria transmission. Subgroup analyses did not point at an increased risk for these outcomes in children that were non-anaemic at baseline and in children younger than two years of age. Overall, iron supplementation may be associated with an increased risk of malaria in settings with no access to malaria prevention or management services, but is safe when such services are available. In such circumstances, administration of iron with an antimalarial drug confers significant protection from malaria, and probably reflects the effect of the antimalarial drugs.

Iron supplementation significantly improves haemoglobin levels and reduces the prevalence of anaemia in highly malaria-endemic areas. Universal screening for iron deficiency and anaemia can select the population most likely to benefit from iron administration, but such screening programmes are not currently feasible in most areas with intense malaria transmission.

Based on our Cochrane review, iron supplementation should not be withheld from children that live in malaria-endemic countries. The new data added to this meta-analysis since 2011 significantly strengthen this recommendation. Malaria prevention and management should be offered to children regardless of iron supplementation, since these interventions reduce malaria, mortality, and anaemia (Meremikwu 2008). Improvements in prevention and management of malaria have occurred in the last decade in sub-Saharan Africa, allowing for iron supplementation in safer settings than ever before (WHO GMP 2010; MDG 2011; Murray 2014).

There are not enough data to draw conclusions on the intervention of iron with folic acid. Folic acid may interfere with the efficacy of sulphadoxine-pyrimethamine, an antimalarial drug used for intermittent preventive treatment or treatment of clinical episodes of malaria (Mulenga 2006; Metz 2007). Furthermore, there is no evidence of folate deficiency among children under two years old in malaria-endemic areas (Metz 2007).

Implications for research

There is perhaps a remaining uncertainty whether iron supplementation alone results in an increased risk of malaria in a subset of iron-replete, non-anaemic children living in highly malaria-endemic areas. To address this question, an individual patient data (IPD) meta-analysis of existing trials might be of value. Such an analysis will allow a better assessment of the covariates of interest than the trial-level analysis presented herein. These include participants' iron and haemoglobin status at baseline (most trials reported baseline assessment of one or measures of iron status and haemoglobin), and more precise age stratification to address the main group of interest, that of children between six months and two years of age.

Well-conducted observational studies that assess the effects of iron supplementation and fortification (Stoltzfus 2011) are important since RCTs measure only a limited duration of iron supplementation and may not represent the child population in need of iron supplementation. Growth and developmental outcomes would probably be better assessed in such long-term studies.

Further studies should establish optimal malaria prevention and management programmes to prevent harm during iron administration.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adam 1997 (C)

Methods	Cluster randomized controlled trial (RCT) Trial years: May 1993 to October 1995 Unit of randomization: household Number of units randomized: not stated Average cluster size: not stated Adjustment for clustering: none Methods of adjustment: not stated
Participants	Number of children: 841 randomized, 738 evaluated Age: mean 45.2 months (range 6 to 84 months) Setting: school, rural Mean haemoglobin (Hb) (standard deviation (SD)) at baseline: iron arm: 8.27 (1.2) g/dL; placebo: 8.27 (1.3) g/dL Subgroup classification: anaemia % parasitaemia at baseline: 12.35%
Interventions	Ferrous sulfate elixir, about 3 mg/kg/day elemental iron versus placebo elixir Duration of treatment: 12 weeks Duration of follow-up: 12 months
Outcomes	Main objective/outcome: effect of iron supplementation on malaria Review outcomes reported in the trial. • Clinical malaria, parasitaemia, severe malaria, parasite density. • Anaemia. • Hospitalization. • Hb (end and change). • All infections, diarrhoea.
Notes	Trial location: north-western Ethiopia, Shehdi town, and Aftit village Malaria endemicity: mesoendemic (trial included the rainy season) Language of publication: English

Adam 1997 (C) *(Continued)*

	Exclusion criteria: Hb < 6 g/dL and Hb > 11 g/dL, debilitating chronic disease or acute infection, new residents or about to leave the region PhD dissertation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables. Done in random permuted blocks of four households.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	Low risk	Same bottles as intervention used for placebo elixir. Participants and those who supplied the medications were blinded to the intervention.

Akenzua 1985

Methods	Individually RCT Trial years: not stated
Participants	112 randomized, 97 evaluated Age: range 1 to 14 years Setting: community, rural Mean Hb: 10 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: not stated
Interventions	Trial arms. • Unsupervised administration of: ferrous fumarate tablets, about 2 mg/kg/day plus folic acid tablets 5 mg/day plus antimalarial drug (single dose of 5 mg/kg chloroquine orally). • Unsupervised administration of ferrous fumarate syrup, about 1.5 mg/kg/day plus folic acid tablets 5 mg/day plus antimalarial drug (single dose of 5 mg/kg chloroquine orally). • Supervised administration of ferrous fumarate tablets, about 2 mg/kg/day plus folic acid tablets 5 mg/day plus antimalarial drug (single dose of 5 mg/kg chloroquine orally). • Proguanil hydrochloride tablets, 50 mg daily. • Folic acid plus chloroquine. • Iron intramuscularly plus chloroquine. • Iron intramuscularly plus chloroquine plus folic acid Duration of treatment: 6 weeks Duration of follow-up: 6 weeks
Outcomes	Main objective/outcome: to determine more accurately the extent to which folate deficiency contributes to the anaemia of childhood in the community; to find out how the prevalence of anaemia in children can be reduced by 50 % or more; to decide on a cheap and effective supplementation programme as a public health measure applicable in the community

Akenzua 1985 *(Continued)*

	Review outcomes reported in the trial. • Anaemia. • Hb packed cell volume change (not used in analyses).
Notes	Trial location: Nigeria Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: haemoglobinopathies; refusal of consent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prepared set of random numbers.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Open.

Ayoya 2009

Methods	Individually RCT Trial years: not stated
Participants	218 randomized (to 2 arms included in review), 202 evaluated Age: 7 to 12 years. Mean age per study arm: iron: 8.40 (SD 1.55), no iron: 8.82 (SD 1.51) Setting: school, urban Mean Hb: (SD) at baseline: iron arm: 10.4 (1.2) g/dL; no iron arm: 10.4 (1.0) g/dL Subgroup classification: no anaemia % parasitaemia at baseline: not stated
Interventions	Trial arms. • Iron plus praziquantel: ferrous sulfate tablets, 60 mg elemental iron per day 5 days/week, estimated 2 mg/kg/day elemental iron plus praziquantel tablet 40 mg at enrolment and at 4 weeks. • Praziquantel tablet 40 mg at enrolment and at 4 weeks. Two additional trial arms that we excluded from this Cochrane review compared praziquantel plus multiple micronutrients (including iron); and praziquantel plus multiple micronutrients plus iron Duration of treatment: 12 weeks Duration of follow-up: 12 weeks
Outcomes	Main objective/outcome: effect of iron supplementation on haematological status

Ayoya 2009 *(Continued)*

	Review outcomes reported in the trial. • Deaths. • Clinical malaria, severe malaria (clinical malaria and high-grade parasitaemia), parasite density. • Anaemia. • Hb (end). • Ferritin. • Admissions.
Notes	Trial location: Bamako, Mali Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: Hb < 7 g/dL or > 12 g/dL, hookworm infection

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized individual randomization within strata of Hb and parasite load in blocks of 4.
Allocation concealment (selection bias)	Low risk	The investigator that recruited participants was unaware of allocation assignment.
Blinding (performance bias and detection bias) All outcomes	High risk	Only laboratory personnel who performed hematological and biochemical determinations were blinded.

Berger 2000

Methods	Individually RCT Trial years: not stated
Participants	197 randomized, 163 evaluated Age: 6 to 36 months. Mean age per study arm: intervention: 22.8, SD 8.42 months, placebo: 24.9, SD 8.3 months Setting: community Mean Hb: iron arm: 9.89 SD 1.16 g/dL, placebo arm: 10.04 SD 1.06 g/dL Subgroup classification: anaemia % parasitaemia at baseline: iron arm: 59.3, placebo arm: 63.6
Interventions	Iron betainate tablet 2 to 3 mg/kg/day elemental iron versus placebo Duration of treatment: 3 months Duration of follow-up: 9 months
Outcomes	Main objective/outcome: impact of iron supplementation on haematological status, cell-mediated immunity and susceptibility to infections

Berger 2000 *(Continued)*

	Review outcomes reported in the trial: • Parasitaemia (% plasmodial index), parasitaemia > 3000, malaria density. • Anaemia. • Diarrhoea. • Respiratory infections. • Hb (end and change). • Ferritin, total iron binding capacity (TIBC), protoporphyrin.
Notes	Trial location: sea region, Togo Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: Hb < 8 g/dL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized assignment of children into an intervention and placebo groups.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated as double blind.

Berger 2006

Methods	Individually RCT Trial duration: March 1998 to November 1998
Participants	988 randomized. 760 to 780 (depending on outcome assessed) evaluated Age: mean 5.9 months (range: 4 to 7 months) Setting: community, rural Mean Hb: 10.9 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: not stated
Interventions	Ferrous sulphate syrup 10 mg/day (about 1.5 mg/kg/day elemental iron) versus zinc versus ferrous sulphate plus zinc versus placebo. 100,000 IU of vitamin A was given to all infants at the start of the study. Duration of treatment: 6 months Duration of follow-up: 6 months
Outcomes	Main objective/outcome: to evaluate the effect of combined iron–zinc supplementation on micronutrient status, growth and morbidity

Berger 2006 *(Continued)*

	Review outcomes reported in the trial. • Anaemia. • Any infection. • Respiratory infections. • Diarrhoea • Hb (end and change). • Ferritin, zinc, TIBC. • Weight and height.
Notes	Location: district of Que Vo, 50 km northwest of Hanoi in the Red River Delta in Vietnam Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: chronic or acute illness, severe malnutrition or congenital abnormality, Hb < 7 g/dL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated as double blind.

Desai 2003

Methods	Individually RCT Trial duration: April to November 1999
Participants	546 randomized, 491 evaluated Age range: 2 to 36 months, mean for all groups = 11.6 months Setting: community Mean Hb: 9.5 g/dL. Subgroup classification: anaemia 20% to 28% malaria prevalence at baseline
Interventions	Ferrous sulfate suspension (40 mg/mL) 3 to 6 mg/kg/day elemental iron plus sulfadoxine-pyrimethamine 25/2.25 mg as a single dose at baseline, week 4 and 8 (intermittent preventive therapy (IPT)) versus IPT versus ferrous sulfate plus sulfadoxine-pyrimethamine 25/2.25 mg as a single dose at baseline versus placebo plus sulfadoxine-pyrimethamine 25/2.25 mg as a single dose at baseline Duration of treatment: 8 weeks Duration of follow-up: 24 weeks

Desai 2003 *(Continued)*

Outcomes	Main objective/outcome: the efficacy of single and combined therapy with iron supplementation and IPT with SP in improving Hb concentrations among anaemic preschool children Review outcomes reported in the trial. • Deaths. • Clinical malaria, parasitaemia, malaria density. • Anaemia. • Hb (end). • Clinic visits.
Notes	Trial location: 15 villages in Asembo, Bondo district, Western Kenya Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: parasite count > 20,000/ µL, sickle cell disease

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number listing generated independently before the study
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated as double-blind

Dossa 2001a

Methods	Individually RCT Trial duration: not stated
Participants	177 participants randomized Age range: 3 to 5 years. Mean 46 months Setting: community, rural Mean Hb: 10.5 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: not stated
Interventions	Ferrous sulphate 60 mg/day elemental iron (about 4.6 mg/kg/day) plus albendazole 200 mg/day for 3 days; 1 month later same dose versus ferrous sulphate plus placebo plus albendazole plus placebo versus placebo plus placebo Duration of treatment: 3 months Duration of follow-up: 10 months

Dossa 2001a *(Continued)*

Outcomes	Main objective/outcome: the effects of iron and deworming treatments on appetite and physical growth performance in preschool children Review outcomes reported in the trial. • Deaths. • Hb (end and change). • Weight and height.
Notes	Trial location: Agblangandan, south Benin 10 km from Cotonou, Benin Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Children were selected and randomly assigned to 4 treatment groups.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind.

Dossa 2001b

Methods	Individually RCT Trial duration: not stated
Participants	154 participants randomized, but only 76 in the relevant intervention groups, 74 were evaluated Age range: 3 to 30 months, mean 22 months Setting: community Mean Hb: 9.5 g/dL Subgroup classification: anaemia % parasitaemia at baseline: not stated
Interventions	Ferrous fumarate 66 mg/day elemental iron (about 7.3 mg/kg/day) versus placebo (Seresta forte). Both arms received mebendazole 200 mg/day for 3 days Duration of treatment duration: 6 weeks Duration of follow-up: 5.5 months
Outcomes	Main objective/outcome: the effects of iron and deworming treatments on physical growth performance, Hb level, and intestinal helminth egg loads in preschool children Review outcomes reported in the trial.

Dossa 2001b *(Continued)*

1. Deaths.
2. Hb (end and change).
3. Fever, diarrhoea.
4. Weight and height change.

Notes	Trial location: Ze, south Benin 50 km from Cotonou, Benin Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Low risk	A researcher not involved in the trial allocated children by the randomization code.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo used.

Esan 2013

Methods	Individually RCT Trial duration: January 2009 to August 2010
Participants	209 participants randomized, 209 evaluated Age range: 6 to 59 months, mean 25.8 months Setting: community (through HIV clinics) Mean Hb: 9.4 g/dL Subgroup classification: anaemia % parasitaemia at baseline: 6% in iron arm, 3.9% in control
Interventions	3 mg/kg/day elemental iron + multivitamins+ malaria chemoprophylaxis versus multivitamins + malaria chemoprophylaxis. Duration of treatment duration: 3 months Duration of follow-up: 6 months
Outcomes	Main objective/outcome: determine the effect of iron supplementation on Hb level, HIV disease progression, and morbidity among HIV-infected children with anaemia Review outcomes reported in the trial. • Any clinical malaria. • Anaemia. • Hb change.

Esan 2013 *(Continued)*

- Deaths.
- Hospitalizations.
- Clinic visits.
- Pneumonia.

Notes	Trial location: Thyolo District, Malawi Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: Hb < 7 Hb > 9.9, non-human immunodeficiency virus (HIV), severe malnutrition, already receiving micronutrient supplements/fortified diets, gross congenital, cognitive, or neurodevelopmental anomaly

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.

Fahmida 2007

Methods	Individually RCT Trial duration: July 1998 until March 1999
Participants	800 participants randomized, but only 392 in the relevant intervention groups. All were evaluated Age range: 3 to 6 months, mean 5.1 ± 1.1 months Setting: community Mean Hb: 9.6 g/dL Subgroup classification: anaemia % parasitaemia at baseline: not stated
Interventions	Iron sulfate syrup 10 mg/day (about 2 mg/kg/day elemental iron) plus zinc sulfate versus zinc sulfate versus iron plus zinc plus vitamin (not used in review) versus placebo (not used in review) Duration of treatment duration: 6 months Duration of follow-up: 12 months
Outcomes	Main objective/outcome: to investigate the effect of supplementation on improving infants' micronutrient status and linear growth Review outcomes reported in the trial. • Clinical malaria.

Fahmida 2007 *(Continued)*

- Deaths.
- Anaemia.
- Fever, diarrhoea, pneumonia.
- Hb (end and change).
- Ferritin, TIBC.
- Weight and height (end).

Notes	Trial location: East Lombok, West Nusa Tenggara, Indonesia Malaria endemicity: mesoendemic Language of publication: English Exclusion criteria: congenital abnormalities, Hb < 6 g/dL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation to supplementation groups was conducted using systematic random sampling in each sex group. The randomization of the subjects in the study was done, firstly, by assigning to each intervention group codes A to D (randomly assigned to placebo; zinc; zinc plus iron; and zinc plus iron plus vitamin A groups, respectively), then each child was randomly assigned to each A to D category using systematic random sampling.
Allocation concealment (selection bias)	Low risk	Central.
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated as double-blind.

Gebreselassie 1996

Methods	Individually RCT Trial duration: February 1994 to July 1994
Participants	500 participants randomized, 480 evaluated Age range: 5 to 14 years, mean 10.3 years Setting: school Mean Hb: 9.5 g/dL Subgroup classification: anaemia % parasitaemia at baseline: 98% with ≥1 episodes) of malaria attack in the past 14 days; negative malaria smears on initial screening for all
Interventions	Ferrous sulphate 60 mg/day elemental iron (about 2.5 mg/kg/day) versus placebo Duration of treatment duration: 3 months Duration of follow-up: 6 months

Gebreselassie 1996 *(Continued)*

Outcomes	Main objective/outcome: To assess the effect of oral iron on host susceptibility to malaria infection in children with mild to moderate iron deficiency anaemia Review outcomes reported in the trial. • Clinical malaria, cumulative incidence of parasitaemia, parasite density, parasitaemia > 5000/µL • Deaths • Anaemia • Hb (end) • Ferritin
Notes	Trial location: Northwest Ethiopia, Beles Valley (Pawe), Ethiopia Malaria endemicity: mesoendemic Language of publication: English Exclusion criteria: Hb > 12 or < 5, serum ferritin > 12, positive malaria smears on initial screening, concurrent major illnesses; no iron supplementation past 6 m, < 12 m residence in the area

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated list of random numbers.
Allocation concealment (selection bias)	Low risk	Central procedure.
Blinding (performance bias and detection bias) All outcomes	Low risk	Field workers, technicians, parents and children blinded. Placebo used in coded bottles.

Giovannini 2006

Methods	Cluster RCT Trial duration: 6 months (dates not stated)
Participants	204 participants randomized, 204 evaluated Age range: 6 months (± 7 days) Setting: community Mean Hb: 10.1 g/dL. Subgroup classification: no anaemia % parasitaemia at baseline: NS
Interventions	Iron fumarate as sprinkles 12.5 mg/day versus placebo (zinc arm not included) Duration of treatment duration: 12 months Duration of follow-up: 12 months

Giovannini 2006 *(Continued)*

Outcomes	Main objective/outcome: compare efficacy of two micronutrient sprinkle supplementation on growth, anaemia, and iron deficiency Review outcomes reported in the trial. • Hb. • Anaemia. • Infections. • Diarrhoea/ pneumonia/ meningitis. • Weight, height.
Notes	Trial location: Cambodia, Chhnang Province Malaria endemicity: holoendemic Language of publication: English Exclusion criteria: Hb > 7

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Field workers, parents and children.

Greisen 1986 (C)

Methods	Cluster RCT Trial duration: May to June 1981 Unit of randomization: 12 school classes Average cluster size: 38.7 Adjustment for clustering: none Methods of adjustment: none
Participants	12 school classes were divided in 2 equal groups according to their listing on the class registers yielding 24 groups, overall 464 children Age range: 5 to 15 years Setting: school, rural Mean Hb: 12.4 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: not stated

Greisen 1986 (C) *(Continued)*

Interventions	Iron-fumarate 66 mg/day on school days (about 2 mg/kd/day elemental iron) plus placebo versus iron-fumarate plus chloroquine 300 mg at baseline and 28 days plus tetrachlorethylene liquid 2.5 mL at baseline versus iron-fumarate plus chloroquine versus iron-fumarate plus tetrachloroethylene Duration of treatment: 6 weeks Duration of follow-up: 6 weeks
Outcomes	Main objective/outcome: to evaluate association between anaemia and running distance Review outcomes reported in the trial. • Deaths. • Hb (end and change).
Notes	Trial location: Namwala township in the great plains of the Kafue river, Zambia Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: acute illness, increased reticulocyte count

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers (12 school classes were divided in 2 equal groups according to their listing on the class registers, yielding 24 groups).
Allocation concealment (selection bias)	Low risk	Central procedure (at the pharmacy).
Blinding (performance bias and detection bias) All outcomes	Low risk	Open.

Hall 2002 (C)

Methods	Cluster RCT Trial duration: started January 2000 Unit of randomization: school Number of units randomized: 60 schools Average cluster size: authors' statement: "We did not look at size of school or sub-district. But since they were all community schools, they were all small rural schools". Adjustment for clustering: not mentioned Methods of adjustment: no adjustment method was used
Participants	Number of children: 1201 randomized, 1113 evaluated Age range: mean 11.4 years range (6 to 19 years) Setting: school; rural

Hall 2002 (C) *(Continued)*

	Mean Hb: 10.5 g/dL. Subgroup classification: no anaemia % parasitaemia at baseline: not stated
Interventions	Trial arms. • Iron: ferrous sulphate tablets, about 0.25 mg/kg/day elemental iron plus folic acid plus albendazole. • Control: albendazole only. All children received vitamin A before intervention Duration of treatment: 10 weeks Duration of follow-up: 2 weeks after end of treatment, 14 to 16 weeks from baseline survey weeks
Outcomes	Main objective/outcome: to assess the effect of weekly iron on Hb status Review outcomes reported in the trial. • Deaths. • Prevalence of anaemia. • Hb (end and change). • Growth parameters. • Adverse events.
Notes	Trial location: Kolondieba district in Sikasso region of south eastern Mali Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: severe anaemia (Hb < 8 g/dL)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Unclear risk	Nor reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Open.

Harvey 1989

Methods	Individually RCT Trial duration: started June 1985
Participants	318 randomized, up to 298 evaluated for malaria outcomes, 318 evaluated for Hb Age: mean 9.7 years (range 8 to 12 years) Setting: school, rural

Harvey 1989 *(Continued)*

	Mean Hb: 10.7 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: 70.5%
Interventions	Trial arms. • Iron: ferrous sulphate tablets, about 3.8 mg/kg/day elemental iron • Placebo: 75% cellulose, 25% lactose tablets Duration of treatment: 16 weeks Duration of follow-up: 24 weeks
Outcomes	Main objective/outcome: to investigate the effects of iron therapy and changes in iron status on malarial infection in children with mild to moderate iron deficiency and some immunity to malaria Review outcomes reported in the trial. • Malaria (clinical and uncomplicated). • Hb (end and change). • Adherence.
Notes	Trial location: north coast,, Madang, Papua New Guinea Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: Hb < 8 g/dL or > 12 g/dL, signs of puberty

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Of 318 participants authors formed 156 matched pairs based on Hb, age and oval-shaped RBC. Members of each pair were randomized to either iron or placebo.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind.

Hess 2002

Methods	Individually RCT Trial duration: 1999 to 2000
Participants	169 randomized, 166 evaluated Age: mean 8.5 years (range 5 to 14 years) Setting: school, rural % anaemic at baseline: 85%

Hess 2002 *(Continued)*

	Mean Hb: 10.9 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: not stated
Interventions	Trial arms. • Iron: ferrous sulphate tablets, about 1 mg/kg/day elemental iron plus albendazole single dose (400 mg) at baseline. • Placebo: identical looking tablets plus albendazole single dose (400 mg) at baseline. Half received a single dose of iodinized poppy seed oil containing 200 mg Duration of treatment: 16 weeks Duration of follow-up: 20 weeks
Outcomes	Main objective/outcome: to investigate change in response to iodine after iron supplementation Review outcomes reported in the trial. • Prevalence of anaemia. • Hb (end and change). • Ferritin (end). • Zinc (end). • TIBC. • Growth parameters.
Notes	Trial location: Danané health district, an area of endemic goitre in the mountains of western Côte d'Ivoire Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: Hb < 8 g/dL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	No description
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind

Hop 2005

Methods	Individually RCT Trial duration: June 2000 to January 2001

Hop 2005 *(Continued)*

Participants	169 randomized, 166 evaluated Age: 6 to 12 months Setting: rural, community % anaemic at baseline: Mean Hb: 9.9 g/dL Subgroup classification: anaemia % parasitaemia at baseline: not stated
Interventions	Trial arms. • Iron: 10 mg/day. • Placebo. • Daily micronutrients- not included in analysis. • Weekly micronutrients - not included in analysis. Duration of treatment: 6 months Duration of follow-up: 6 months
Outcomes	Main objective/outcome: effect of iron on anaemia and growth. Review outcomes reported in the trial. • Prevalence of anaemia. • Hb (end and change). • Weight. • Height.
Notes	Trial location: Soscon District, Vietnam Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: severe wasting, fever (> 39°C), premature birth (< 37 weeks) or low birth weight (< 2500 g), and severe anaemia (Hb < 8 g/dL)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number selection.
Allocation concealment (selection bias)	Low risk	Central code not on study site.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind.

Latham 1990

Methods	Individually RCT Trial duration: April to November 1986
Participants	55 randomized, 54 evaluated Age: mean 8 years Setting: school Mean Hb (SE): iron arm: 11.6 (0.18) g/dL; placebo arm: 11.5 (0.18) g/dL Subgroup classification: no anaemia % parasitaemia at baseline: iron arm: 76%, placebo arm: 46%
Interventions	Trial arms. • Iron: ferrous sulphate tablets, about 2.85 mg/kg/day elemental iron. • Placebo: saccharin tablets. All groups received albendazole tablets 400 mg single dose once after 32 weeks Duration of treatment: 15 weeks Duration of follow-up: 32 weeks
Outcomes	Main objective/outcome: to determine whether iron given to school children in Kenya improves growth Review outcomes reported in the trial. • Uncomplicated malaria. • Death. • Malaria density. • Hb (end and change). • Growth parameters (end and change).
Notes	Trial location: Kwale district, Coast Province, south of Mombasa, Kenya Malaria endemicity: holoendemic, undertaken during rainy season Language of publication: English Exclusion criteria: haematuria and proteinuria (indicative of *Schistosoma haematobium*), absence on the day of first examination, serious disease or malnutrition, Hb < 8 g/dL, heavy infections with hookworms (> 10,000 eggs/g stool), and refusal to participate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Children were paired by gender within the Hb rankings, from each pair one was randomly assigned to placebo and the other to iron.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Saccharin used as placebo.

Lawless 1994

Methods	Individually randomized Trial duration: March to July 1990
Participants	87 randomized, 86 evaluated Age: mean 8.7 years (range 6 to 11 years) Setting: school, rural Mean Hb: 11.1 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: not stated
Interventions	Trial arms. • Iron: ferrous sulphate sustained release capsules, about 1.4 mg/kg/day elemental iron. • Placebo: identical placebo capsules. Duration of treatment: 14 weeks Duration of follow-up: 14 weeks
Outcomes	Main objective/outcome: to determine effects of iron given to school children in Kenya on appetite and growth Review outcomes reported in the trial. • Clinical malaria. • Diarrhoea. • Hb (end and change). • Ferritin (end). • Growth parameters (change).
Notes	Trial location: Coast Province, Shamu village, Kenya Malaria endemicity: holoendemic Language of publication: English Exclusion criteria: Hb < 8 g/dL, heavy hookworm infection (> 10,000 eggs/g faeces), hematuria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.

Leenstra 2009

Methods	Individually randomized Trial duration: April to November 1998
Participants	279 randomized, 279 evaluated Age: mean 13.8 years (range 12 to 18 years) Setting: school, urban Mean Hb: 12.8 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: 25.4%
Interventions	Trial arms. • Iron plus vitamin A: ferrous sulphate tablets weekly, about 0.4 mg/kg/day elemental iron + vitamin A capsule 25,000 U per week. • Iron only: same as above. • Vitamin A only: same dosage as above. • Placebo. Duration of treatment: 5 months Duration of follow-up: 5 months
Outcomes	Main objective/outcome: to determine effects of iron and vitamin A on Hb, iron status, malaria, and other morbidities in schoolgirls Review outcomes reported in the trial. • Clinical malaria. • Severe malaria. • Infections. • Adverse events.
Notes	Trial location: Kisumu City, on shores of lake Victoria, Nyanza province, western Kenya Malaria endemicity: mesoendemic, undertaken during rainy season Language of publication: English Exclusion criteria: Hb < 7 g/dL, severe vitamin A deficiency (xerophthalmia), pregnancy, concomitant disease requiring hospitalization

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias)	Low risk	Double-blind.

Leenstra 2009 *(Continued)*

All outcomes

Massaga 2003

Methods	Individually RCT Trial duration: June 1999 to May 2000
Participants	291 randomized, 291 evaluated Age: mean 14.3 weeks Setting: community, rural Mean Hb: 9.9 g/dL. Subgroup classification: anaemia % parasitaemia at baseline: mean 31.5%
Interventions	Trial arms. • Iron: ferric ammonium citrate suspension daily, about 7.5 mg/kg/day elemental iron. • Placebo oral suspension. • Iron as described above + amodiaquine oral suspension 25 mg/kg once every 2 months (overall three doses). • Amodiaquine only as described above. Duration of treatment: 6 months Duration of follow-up: 10 months
Outcomes	Main objective/outcome: infections Review outcomes reported in the trial. • Malaria. • Anaemia. • Death.
Notes	Trial location: Muheza district, north-eastern Tanzania Malaria endemicity: holoendemic Language of publication: English Exclusion criteria: infants with congenital malformation, conditions that needed hospital treatment, fever within preceding 2 weeks, packed cell volume < 24%, participants on chemoprophylaxis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Central.
Blinding (performance bias and detection bias)	Low risk	Double-blind.

Massaga 2003 *(Continued)*
All outcomes

Mebrahtu 2004 (C)

Methods	Cluster RCT Trial duration: 1996 to 1997 Unit of randomization: household Number of units randomized: 451 households Average cluster size: 1.5 children per household Adjustment for clustering: yes Methods of adjustment: generalized estimating equation approach was used to account for repeated measurements in children
Participants	684 children randomized, 684 evaluated for mortality, 614 evaluated for malaria, 459 evaluated for anaemia Age: mean 33.4 months (range 4 to 71 months) Setting: community, rural Mean Hb: 8.7 g/dL Subgroup classification: anaemia % parasitaemia at baseline: not stated
Interventions	Trial arms. • Iron: ferrous sulphate syrup daily, about 1 mg/kg/day elemental iron. • Placebo syrup. Randomization was also done by child to oral mebendazole 500 mg every 3 months; versus placebo Duration of treatment: 12 months Duration of follow-up: 12 months
Outcomes	Main objective/outcome: to assess the effect of low-dose, long-term iron supplementation on malaria infection Review outcomes reported in the trial. • Malaria (any malaria, severe malaria). • Mortality. • Hb (end). • Ferritin (end).
Notes	Trial location: Pemba Island, Tanzania Malaria endemicity: holoendemic Language of publication: English Exclusion criteria: severe anaemia (Hb < 7 g/dL)

Mebrahtu 2004 (C) *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Low risk	Pharmacy, sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.

Menendez 1997

Methods	Individually RCT Trial duration: 1995
Participants	832 randomized, 832 evaluated Age: range 8 to 48 weeks Setting: community, rural Subgroup classification: anaemia (based on population incidence of anaemia in region and age group) % parasitaemia at baseline: not stated
Interventions	Trial arms. • Iron: ferrous glycine sulphate syrup daily, about 2 mg/kg/day elemental iron. • Placebo syrup. • Iron (same as above) plus pyrimethamine plus dapsone (Deltaprim) syrup 3.125 mg plus 25 mg once weekly. • Pyrimethamine plus dapsone (Deltaprim) alone, as described above. Duration of treatment: iron; 16 weeks, antimalarial; 40 weeks Duration of follow-up: 1 year
Outcomes	Main objective/outcome: Hb, anaemia and iron-related outcomes Review outcomes reported in the trial: • Malaria. • Mortality. • Anaemia. • Hospitalizations.
Notes	Trial location: Ifakara, Kilombero District, Morogoro Region, south-eastern Tanzania Malaria endemicity: hyperendemic Language of publication: English

Menendez 1997 *(Continued)*

	Exclusion criteria: packed cell volume < 25%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequential numbers of a randomization code.
Allocation concealment (selection bias)	Low risk	Randomization code kept by an independent monitor - central.
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated as double blind.

Mwanri 2000

Methods	Individually RCT Trial duration: not stated
Participants	136 randomized, 135 evaluated Age: mean 10.8 (range 9 to 12 years) Setting: school, rural Mean Hb: 10.5 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: not stated
Interventions	Trial arms. • Iron: ferrous sulphate tablets thrice weekly, about 0.65 mg/kg/day elemental iron. • Vitamin A (retinyl acetate) 5000 IU thrice weekly. • Iron plus vitamin A (both as described above). • Placebo tablets. All subjects were dewormed for helminthiasis 2 weeks before baseline survey Duration of treatment: 3 months Duration of follow-up: 3 months
Outcomes	Main objective/outcome: effects of dietary supplements on anaemia and growth Review outcomes reported in the trial. • Anaemia. • Hb (change). • Weight and height changes.
Notes	Trial location: Bagamoyo District, coastal area of Tanzania Malaria endemicity: hyperendemic

Mwanri 2000 *(Continued)*

	Language of publication: English
	Exclusion criteria: chronic illnesses, physical impairments, severe anaemia (Hb < 8 g/dL)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The RAND function of Excel was used to implement randomization.
Allocation concealment (selection bias)	Low risk	Pharmacy.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.

Olsen 2006

Methods	Individually RCT Trial duration: November 1994 to January 1996
Participants	231 children randomized, 231 evaluated for mortality, 200 for Hb end and change Age: mean 8.7 years Setting: community Mean Hb: 11.5 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: 60.6%
Interventions	Trial arms. • Iron: ferrous dextran tablets twice weekly, about 0.7 mg/kg/day elemental iron. • Placebo tablets twice weekly. Duration of treatment: 12 months Duration of follow-up: 12 months
Outcomes	Main objective/outcome: effect of 12 months of twice weekly iron supplementation on Hb and ferritin Review outcomes reported in the trial. • Death. • End and change in Hb.
Notes	Trial location: Kisumu district of Nyanza province, Kenya Malaria endemicity: mesoendemic Language of publication: English Exclusion criteria: Hb < 8 g/dL, pregnancy and refusal to participate

Olsen 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Sealed envelopes kept in a central location.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.

Powers 1983

Methods	Individually randomized Trial duration: not stated
Participants	80 randomized, 40 evaluated Age: range 4 to 12 years Setting: community, rural Mean Hb: 11.1 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: not stated
Interventions	Trial arms. • Iron: ferrous sulphate syrup daily, about 2 mg/kg/day elemental iron plus chloroquine tablets 6 days before the supplementation and thereafter weekly. • Iron (as described above) plus riboflavin. • Placebo (lactose tablets) plus chloroquine tablets 6 days before the supplementation and thereafter weekly. Duration of treatment: 6 weeks Duration of follow-up: 6 weeks
Outcomes	Main objective/outcome: haematological status Review outcomes reported in the trial. • Mortality. • Hb end and change. • End iron level.
Notes	Trial location: Keneba village, Gambia Malaria endemicity: hyperendemic Language of publication: English

Powers 1983 *(Continued)*

	Exclusion criteria: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.

Richard 2006

Methods	Individually RCT Trial duration: February to September 1998
Participants	855 randomized, 836 evaluated for malaria, 748 evaluated for mortality and Hb Age: range 0.5 to 15 years Setting: school, rural Mean Hb: 11.4 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: 5%
Interventions	Trial arms. • Iron: iron sulphate syrup daily, about 0.75 mg/kg/day elemental iron. • Iron (as described above) plus zinc 20 mg/day. • Zinc only (20 mg/day). • Placebo syrup. Duration of treatment: 7 months Duration of follow-up: 7 months
Outcomes	Main objective/outcome: effect of daily iron or zinc or both on morbidity - malaria, diarrhoea, and respiratory infections Review outcomes reported in the trial. • Mortality. • Malaria. • End Hb.
Notes	Trial location: Santa Clara Village, Peru Malaria endemicity: mesoendemic Language of publication: English

Richard 2006 *(Continued)*

	Exclusion criteria: chronic illness (congenital diseases or major illness requiring medical care or medication, or both, determined by the physician at baseline evaluation) or severe malnutrition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Triple blinded: participants, study personnel, and data analyst were all blinded.

Roschnik 2003 (C)

Methods	Cluster RCT Trial duration: February to September 2002 Unit of randomization: schools Number of units randomized: 40 schools Average cluster size: 29 Adjustment for clustering: none Methods of adjustment: not stated
Participants	Number of children: 40 schools, 1160 were tested for Hb at baseline. Number randomized not stated Age: 7 to 8 years and 10 to 12 years Setting: school, rural Mean Hb: 11.8 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: no or little malaria, not reported further
Interventions	Ferrous sulfate tablets 65 mg/week elemental iron (about 0.3 mg/kd/day) + folic acid 0.25 mg / week versus no treatment. In addition all children received praziquantel 600 mg once, 1 week before the beginning of the trial Duration of treatment: 3.5 months Duration of follow-up: 4.5 months
Outcomes	Main objective/outcome: to evaluate the effectiveness of weekly school-based iron supplementation: its impact on mean Hb concentration and anaemia prevalence, on school attendance, performance, drop-out, and repetition rates Review outcomes reported in the trial: • Anaemia

Roschnik 2003 (C) *(Continued)*

- Hb (end)

Notes	Trial location: Mangochi District in Malawi, upland and coastal areas Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table (inside each class 33% of children were selected for the trial - started from a random number and taking every third trial from this number on).
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Open.

Sazawal 2006 (C)a

Methods	Cluster RCT Unit of randomization: households Number of units randomized: 22,959 Average cluster size: 1.4 Adjustment for clustering: was performed for adverse events (episodes of infection) and admissions. For mortality and cause-specific mortality adjustment for clustering is not reported Methods of adjustment: for analysis of adverse events and admissions, Anderson Gill time-to-event survival methods in Cox regression with robust estimation of standard error to account for multiple events per child or within household were used (SAS version 9.0, STATA version 8.2). For total mortality and cause-specific mortality, Cox regression with exact handling for ties was used Trial duration: January 2002 to August 2003
Participants	22,959 units and 32,155 individuals; 15,956 in the 2 arms relevant for this review Age: 1 to 35 months, mean about 18 months Setting: community Hb levels: not reported % parasitaemia at baseline: not stated
Interventions	Iron tablets (preparation not stated) dissolved in water or breast milk 12.5 mg/day plus folic acid 50 µg/day plus vitamin A; versus placebo plus vitamin A; versus iron plus folic acid plus zinc 10 mg/day plus vitamin A (not used in this review); versus zinc plus vitamin A. Children aged 1 to 11 months received a half dose of iron

Sazawal 2006 (C)a *(Continued)*

	Duration of treatment: not fixed; from < 3 months to maximum of 18 months of age (until the age of 48 months or the discontinuation of the study). Most participants received the intervention for about 12 months Duration of follow-up: not fixed. Maximum of 18 months (until age 48 months or study discontinuation)
Outcomes	Main objective/outcome: composite of death or hospital admission (looking very specifically at malaria) Review outcomes reported in the trial. • Clinical malaria, severe malaria. • Deaths. • Hospitalization. • Any infection, diarrhoea.
Notes	Trial location: Tanzania Malaria endemicity: holoendemic Language of publication: English Exclusion criteria: none Comparison relevant to this review (iron + folic) stopped at interim analysis based on recommendation from the data and safety monitoring board. The board received data from the main trial every month and established at the beginning of the trial that it would do further analysis of the data when the difference in mortality between any 2 groups reached a P value of 0.2 or less. Stopping rules not defined in publication. No statement on sample size and analysis adjustment for interim monthly monitoring and truncation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation sequence generated at the World Health Organization (WHO) controlled by computer (page 136). Permuted in blocks of 16.
Allocation concealment (selection bias)	Low risk	Labelled the strips of supplements with 16 letter codes- 4 for each of the groups. This letter code was hidden in the batch number on each strip of tablets.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. Strips of supplements coded with 16 letter codes.

Sazawal 2006 (C)b

Methods	Cluster RCT (independent substudy of Sazawal 2006 (C)a Unit of randomization: households Number of units randomized: 2818 before exclusion of anaemic children Average cluster size: 1.2 Adjustment for clustering was performed for adverse events (episodes of infection) and admissions. For mortality and cause-specific mortality, adjustment for clustering is not reported.

Sazawal 2006 (C)b *(Continued)*

	Methods of adjustment for the analysis of adverse events and admissions, Anderson Gill time-to-event survival methods in Cox regression with robust estimation of SE to account for multiple events per child or within household were used (SAS version 9.0, STATA version 8.2). For total mortality and cause-specific mortality, Cox regression with exact handling for ties was used. Trial duration: March to November 2002
Participants	3171 individuals; 1619 in the 2 arms relevant for this review Age: 1 to 35 months, mean about 22.5 months Setting: community Mean Hb: 9.7 g/dL Subgroup classification: anaemia % parasitaemia at baseline: not stated
Interventions	Iron tablets (preparation not stated) dissolved in water or breast milk 12.5 mg/day plus folic acid 50 µg/day plus vitamin A; versus placebo plus vitamin A; versus iron plus folic acid plus zinc 10 mg/day plus vitamin A (not used in review); versus zinc plus vitamin A. Children aged 1 to 11 months received a half dose of iron. Duration of treatment: not fixed from < 3 months to a maximum of 18 months (until the participants were aged 48 months or the discontinuation of the study). Most received the intervention for about 12 months. Duration of follow-up: not fixed. Maximum 18 months (until the participants were aged 48 months or the discontinuation of the study).
Outcomes	Main objective/outcome: to make a composite of death or hospital admission (looking very specifically at malaria) Review outcomes reported in the trial. • Clinical malaria, severe malaria. • Deaths. • Anaemia.
Notes	Trial location: Tanzania Malaria endemicity: holoendemic Language of publication: English Exclusion criteria: Hb < 7 g/dL This was a separate, independent, substudy of the bigger Sazawal 2006 (C)a trial. Separate households were randomized to the substudy, where children had baseline blood samples, anaemic children excluded (Hb < 7 g/dL), half-yearly surveillance for malaria and clinical infections performed, and treatment for malaria offered throughout the trial. Comparison relevant to this review (iron plus folic) stopped at interim analysis based on recommendation from the data and safety monitoring board. The board received data from the main trial every month and established at the beginning of the trial that it would do further analysis of the data when the difference in mortality between any 2 groups reached a P value of 0.2 or less. Stopping rules not defined in publication. No statement on sample size and analysis adjustment for interim monthly monitoring and truncation.
Risk of bias	

Sazawal 2006 (C)b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation sequence generated at the WHO controlled by computer (page 136). Permuted in blocks of 16.
Allocation concealment (selection bias)	Low risk	Labelled the strips of supplements with 16 letter codes- 4 for each of the groups. This letter code was hidden in the batch number on each strip of tablets.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. Strips of supplements coded with 16 letter codes.

Smith 1989 (C)

Methods	Cluster RCT Trial duration: July to August 1983 Unit of randomization: household Number of units randomized: not stated Average cluster size: not stated Adjustment for clustering: none Methods of adjustment: not stated
Participants	Number of participants: 213 children Age: 6 months to 5 years, mean about 2.7 years Setting: community Mean Hb: 9.3 g/dL Subgroup classification: anaemia % parasitaemia at baseline: not stated
Interventions	Ferrous sulphate elixir of crushed tablets in orange juice 3 to 6 mg/kg/day elemental iron versus orange juice (placebo) Duration of treatment: 12 weeks Duration of follow-up: 13 weeks
Outcomes	Main objective/outcome: Hb/iron + malaria status Review outcomes reported in the trial. • Clinical malaria, parasitaemia, parasitaemia > 5000/µL. • Deaths. • Febrile disease.
Notes	Trial location: Gambia Malaria endemicity: hyperendemic

Smith 1989 (C) *(Continued)*

	Language of publication: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The first compound on the compound list for each village was randomly assigned and compounds were assigned alternately thereafter.
Allocation concealment (selection bias)	High risk	Alternation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Parents, field workers, and study investigator blinded.

Thi 2006

Methods	Individually RCT Trial duration: November 2004 to May 2005.
Participants	Number of participants: 168 children Age: mean 87 months Setting: community Mean Hb: 10.8 g/dL. Subgroup classification: no anaemia % parasitaemia at baseline: not stated
Interventions	Iron fumarate tablets 200 mg and mebendazole versus placebo and mebendazole Duration of treatment: 6 months Duration of follow-up: 6 months
Outcomes	Main objective/outcome: Hb Review outcomes reported in the trial. • Hb change. • Prevalence of anaemia.
Notes	Trial location: Phu Tho Province, Vietnam. Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: Hb < 7 g/dL

Risk of bias

Bias	Authors' judgement	Support for judgement

Thi 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"carried out by a researcher" - method not described.
Allocation concealment (selection bias)	Unclear risk	Methods not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Not described.

Verhoef 2002

Methods	Individually RCT Trial duration: 1998 to 2000
Participants	In total 328 randomized Age: 2 to 36 months, mean about 18 months Setting: community Mean Hb: 9.6 g/dL Subgroup classification: anaemia % parasitaemia at baseline: as indicated by a dipstick test result, 31% in this age group from an earlier survey
Interventions	Ferrous fumarate suspension 6 mg/kg/week elemental iron (about 0.86 mg/kg/day) given in two doses (twice a week) plus sulfadoxine/pyrimethamine 25/1.25 mg/kg once every 4 weeks versus ferrous fumarate plus placebo; versus sulfadoxine-pyrimethamine plus placebo versus placebo Duration of treatment: 3 months Duration of follow-up: 3 months
Outcomes	Main objective/outcome: effect of intermittent iron and sulfadoxine-pyrimethamine on Hb in symptom-free children Review outcomes reported in the trial. • Clinical malaria • Anaemia • Hb (end)
Notes	Trial location: Kenya Malaria endemicity: mesoendemic Language of publication: English Exclusion criteria: Hb < 6 or >11 g/dL, axillary temp > 37.5 °C, symptoms suggestive of malaria or anaemia, or any systemic illness occurring in combination with a blood dipstick test result indicating current or recent malaria infection
Risk of bias	

Verhoef 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Tables with randomized permutations.
Allocation concealment (selection bias)	Low risk	The order of children listed was concealed from the person generating the allocation schedule.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind: field investigators, participants.

Zlotkin 2003

Methods	Individually RCT Trial duration: October 1999 to March 2000
Participants	437 randomized, 165 evaluated Age: mean 16.5 ± 3.9 months for iron drops versus 15.4 ± 4.4 for iron sprinkles versus 15.2 ± 4.1 for placebo Setting: community Mean Hb: 12.7 g/dL. Subgroup classification: no anaemia % parasitaemia at baseline: 62.3% (202/324 children who completed the intervention)
Interventions	Ferrous sulphate drops 12.5 mg/day elemental iron (about 1.25 mg/kd/day) versus iron fumarate sprinkles 40 mg/day versus placebo versus iron fumarate sprinkles (not used in this review as could not compare two iron treatment group to one placebo group) plus vitamin A (not used in this review) Duration of treatment: 6 months Duration of follow-up: 18 months (only children who were not anaemic at the end of supplementation were followed-up for the additional period of time)
Outcomes	Main objective/outcome: to compare the efficacy of microencapsulated iron fumarate sprinkles ± Vit A with iron sulphate drops with placebo in preventing recurrent anaemia and to determine the long-term haematological outcome Review outcomes reported in the trial. • Anaemia. • Deaths. • Hb (end and change). • Ferritin.
Notes	Trial location: Ghana Malaria endemicity: hyperendemic Language of publication: English Exclusion criteria: Hb < 10 g/dL, age 8 to 20 months, only breast feeding children

Risk of bias

Zlotkin 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial, intervention and control arms different.

Zlotkin 2013 (C)

Methods	Cluster RCT Trial duration: March 2010 to September 2010
Participants	1958 randomized, 1958 evaluated Age: mean 19.5 ± 8.6 months and 19.4 ± 8.6 months for iron versus placebo Setting: community Mean Hb: 10.3 g/dL Subgroup classification: no anaemia % parasitaemia at baseline: 31%
Interventions	Microencapsulated ferrous fumarate 12.5 mg and micronutrients versus micronutrients alone Duration of treatment: 5 months Duration of follow-up: 6 months
Outcomes	Main objective/outcome: malaria Review outcomes reported in the trial. • Any malaria. • Uncomplicated/ severe malaria. • Deaths. • Hospitalizations. • Diarrhea, pneumonia, meningitis.
Notes	Trial location: Ghana Malaria endemicity: hyperendemic. Bed nets and antimalarials available. Language of publication: English Exclusion criteria: Hb < 7, severe malnutrition, receipt of iron supplements within the past 6 months, or chronic illness

Risk of bias

Bias	Authors' judgement	Support for judgement

Zlotkin 2013 (C) *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Central.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Trial team, caregivers, and data analysts blinded but packages marked with A/B for fortification/no fortification.

Abbreviations: RCT: randomized controlled trial; Hb: haemoglobin; SD: standard deviation; HIV: human immunodeficiency virus; TIBC: total iron binding capacity; WHO: World Health Organization.

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

Study	Reason for exclusion
Abdelrazik 2007	Not a randomized controlled trial (RCT).
Adu-Afarwuah 2008	I ncompatible intervention.
Ahmed 2001	Study not in children (participants' age 14 to 19 years and results for children not separated).
Angeles-Agdeppa 1997	Incompatible intervention (iron + other micronutrients).
Anonymous 2006	Editorial (not a RCT).
Asibey-Berko 2007	incompatible intervention, insufficient dose.
Baird 1997	Not a RCT.
Bates 1987	Incompatible intervention (iron + other micronutrients) iron + vitamin C + riboflavin versus placebo.
Bates 1994	Incompatible intervention (i ron + other micronutrients) iron + multivitamin tablet.
Beasley 2000	Incompatible intervention (iron + other micronutrients: iron versus B12).
Bender-Götze 1980	RCT conducted in non-endemic area: Germany.
Berger 1992	Not a RCT.
Boivin 1993	None of the reported outcomes relevant/usable for the review.
Bojang 1997	RCT, blood transfusion versus iron (parenteral administration of iron).
Bradfield 1968	Not a RCT.
Brunser 1993	Non-endemic area (Chile); iron administered as fortification of milk.
Carter 2005	RCT, all groups received iron.
Chandramohan 2005	RCT, all groups received iron.

Study	Reason for exclusion
CIGNIS 2010	Incompatible intervention (i ron + other micronutrients). Comparison between basal and rich fortification including multiple vitamins + iron.
Cusick 2005	RCT, all groups received iron.
Desai 2004	Dose comparison, all groups given iron.
Dijkhuizen 2001	Stated specifically in study that the area wa s malaria-free.
Diouf 2002	Not a RCT (correspondence).
Ekvall 2000	Incompatible intervention (iron + other micronutrients: multivitamins versus promethazine hydrochloride).
Fuerth 1972	Not a malaria- endemic area: California.
Gara 2010	RCT that assessed iron as part of a treatment for malaria.
Gomber 1998	All children were given iron supplementation.
Greisen 1986	Not a RCT.
Hathirat 1992	Stated specifically in study that the area wa s malaria-free.
Heywood 1989	RCT, parenteral iron.
Honig 1978	RCT with intramuscular iron.
Isager 1974	Not a RCT (review article).
ISRCTN85737357	No relevant outcome. In correspondence with study author, who stated that the study was not adequately completed, therefore results will not be analysed.
ISRCTN88523834	Randomization to antimalaria treatment. All children received iron.
Jacobi 1972	Not a RCT.
Kanani 2000	Cluster-RCT with less than 2 units per arm.
Kleinschmidt 1965	Not a RCT.
Kurz 1985	Not a RCT.
le Cessie 2002	Not a RCT.
Lima 2006	Not a RCT.
Liu 1995	Comparison of different iron administration schedules. No placebo group.
Liu 1996	Dose comparison, all groups given iron.
Lozoff 1982	Incompatible intervention (iron + other micronutrients).
Lozoff 1996	None of the reported outcomes relevant/usable for the review.

Study	Reason for exclusion
Mamiro 2001	Not a RCT (cross-sectional survey).
Migasena 1972	Stated specifically in study that the area wa s malaria-free.
Mitra 1997	Stated specifically in study that the area wa s malaria-free.
Mosha 2014	No placebo group.
Mozaffari-Khosravi 2010	Incompatible intervention (dose of iron administered was 0.08 mg/kg/day, too low for consideration as supplementation.
Murray 1978	RCT that included adults.
Mwanakasale 2009	Incompatible intervention (iron versus vitamin C).
Nchito 2004	No relevant outcome (study assessed geophagy as outcome),
NCT00301054	No relevant outcome. The pharmaceutical company that supplied the drugs, placebo, and drug blinding codes did not provide the investigators with the codes (author correspondence). The authors stated that "Should the drug company come forth with the codes we will certainly share the results with you".
Nguyen 2002	Incompatible interventions: group 1 placebo, group 2 iron, group 3 daily iron, group 4 weekly iron. Only groups 3 and 4 were assigned randomly.
Nwanyanwu 1996	RCT that assessed iron as part of treatment for malaria.
Oppenheimer 1986	RCT, parenteral iron.
Oski 1978	RCT, parenteral iron.
Oski 1983	Not a RCT.
Ouédraogo 2010	Incompatible intervention (i ron + other micronutrients). Intervention included iron, zinc, vitamin A, vitamin C and iodinedes MM . (TO AUTHORS: please write in full at first mention)
Pereira 1978	Not a RCT.
Rahimy 2007	Not a RCT.
Rahman 1999	Stated specifically in study that the area wa s malaria-free.
Rico 2006	None of the reported outcomes were relevant/usable for the review.
Rohner 2010	Insufficient iron dose.
Roschnik 2004 (C)	Stated by the author: specific area wa s hypoendemic.
Schellenberg 2001	RCT, all groups received iron.
Schellenberg 2004	Dose comparison, all groups given iron.
Schultink 1995	All groups given iron (dose, schedule, or other comparisons).
Schumann 2009	I nsufficient iron dose.

Study	Reason for exclusion
Schumann 2009a	Insuficient iron dose. Non-endemic areas. Author stated in correspondence that area not endemic for malaria.
Seshadri 1982	None of the reported outcomes relevant/usable for the review.
Sharma 2000	All groups given iron (dose, schedule, or other comparisons).
Singla 1982	Incompatible intervention (iron + other micronutrients: iron + FA + B12 versus placebo).
Sungthong 2002	Stated specifically in study that the area wa s malaria-free.
Tee 1999	Stated specifically in study that the area wa s malaria-free.
Thu 1999	Incompatible intervention (iron + other micronutrients: iron + zinc + retinol + vitamin C versus placebo).
Tielsch 2006	Non-endemic area, according to correspondence with the author.
Tomashek 2001	RCT, all groups received iron.
Troesch 2011	Non-endemic areas. Stated specifically that the area is malaria-free. Intervention consisted of multiple micronutrients.
van den Hombergh 1996	RCT that assessed iron as part of treatment for malaria.
van Hensbroek 1995	RCT that assessed iron as part of treatment for malaria.
Vaughan 1977	None of the reported outcomes were relevant/usable for this review.
Walter 1986	Not a RCT.
Wegmüller 2006	I nsufficient iron dose.
Zimmermann 2010	I nsufficient iron dose.

Abbreviations : RCT: randomized controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Sazawal 2006 (C)c

Methods	Cluster RCT, double-blind, placebo controlled
Participants	Children aged 1 to 35 months living in Pemba, Zanzibar
Interventions	In the current version of the review we included two arms of this trial: iron- folic acid-vitamin A versus placebo-vitamin A, up until the time the iron arms were stopped based on the safety committee decision. Depending on data availability, we plan to add results from the iron-folic acid plus vitamin A and zinc; versus zinc-vitamin A arms at the time the iron arms were stopped (and the children receiving iron were transferred to the respective study arms without iron supplementation).
Outcomes	Admissions for malaria Cerebral malaria Hospital admissions

Sazawal 2006 (C)c *(Continued)*	
	Mortality
Notes	Data correspondence with Professor Sazawal. FInal study published as Sazawal 2007

DATA AND ANALYSES

Comparison 1. Iron versus placebo or no treatment

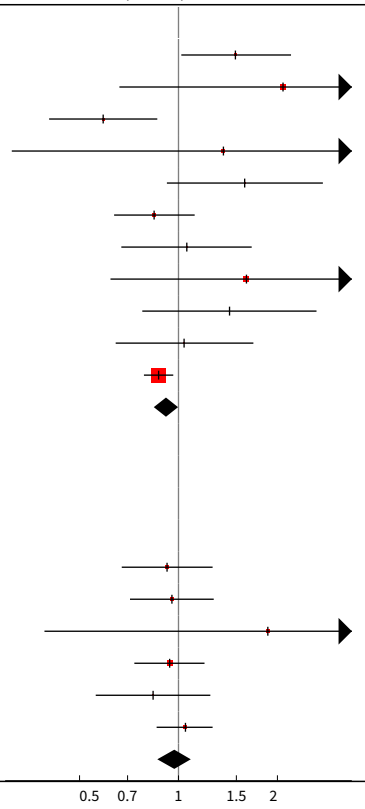
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical malaria (grouped by presence of anaemia)	14		Risk Ratio (Fixed, 95% CI)	0.93 [0.87, 1.00]
1.1 Anaemia	9		Risk Ratio (Fixed, 95% CI)	0.92 [0.84, 1.00]
1.2 No anaemia	5		Risk Ratio (Fixed, 95% CI)	0.97 [0.86, 1.09]
2 Clinical malaria (grouped by age)	14		Risk Ratio (Fixed, 95% CI)	0.93 [0.87, 1.00]
2.1 < 2 years	5		Risk Ratio (Fixed, 95% CI)	0.89 [0.82, 0.97]
2.2 2 to 5 years	3		Risk Ratio (Fixed, 95% CI)	0.97 [0.75, 1.26]
2.3 > 5 years	6		Risk Ratio (Fixed, 95% CI)	1.04 [0.91, 1.20]
3 Clinical malaria (*P. falciparum* only)	9		Risk Ratio (Fixed, 95% CI)	0.91 [0.84, 0.99]
4 Any parasitaemia, end of treatment (by anaemia at baseline)	9		Risk Ratio (Fixed, 95% CI)	1.11 [1.00, 1.23]
4.1 Anaemia	6		Risk Ratio (Fixed, 95% CI)	1.07 [0.94, 1.23]
4.2 No anaemia	3		Risk Ratio (Fixed, 95% CI)	1.17 [0.99, 1.40]
5 All-cause mortality	18	7576	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.01]
6 Clinical malaria with high-grade parasitaemia or requiring admission	5		Risk Ratio (Fixed, 95% CI)	0.90 [0.81, 0.98]
7 Any parasitaemia, end of treatment (by age)	9		Risk Ratio (Fixed, 95% CI)	1.11 [1.00, 1.23]
7.1 < 2 years	2		Risk Ratio (Fixed, 95% CI)	1.28 [0.98, 1.68]
7.2 2 to 5 years	4		Risk Ratio (Fixed, 95% CI)	1.06 [0.91, 1.23]
7.3 > 5 years	3		Risk Ratio (Fixed, 95% CI)	1.12 [0.93, 1.34]
8 Any parasitaemia, end of treatment (*P. falciparum* only)	7		Risk Ratio (Fixed, 95% CI)	1.09 [0.97, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Iron versus placebo/no treatment	5		Risk Ratio (Fixed, 95% CI)	1.09 [0.96, 1.24]
8.2 Iron + antimalarial versus antimalarial	2		Risk Ratio (Fixed, 95% CI)	1.10 [0.76, 1.59]
9 Any parasitaemia, end of treatment (by allocation concealment)	9		Risk Ratio (Fixed, 95% CI)	1.11 [1.00, 1.23]
9.1 Adequate	4		Risk Ratio (Fixed, 95% CI)	0.98 [0.83, 1.15]
9.2 Unclear	5		Risk Ratio (Fixed, 95% CI)	1.22 [1.06, 1.40]
10 High-grade parasitaemia	5		Risk Ratio (Fixed, 95% CI)	1.13 [0.93, 1.37]
11 Any parasitaemia, end of follow-up	5	1150	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.09, 1.40]
12 Hospitalizations and clinic visits	7		Risk Ratio (Fixed, 95% CI)	0.99 [0.95, 1.04]
12.1 Hospitalization, iron versus placebo	5		Risk Ratio (Fixed, 95% CI)	0.94 [0.82, 1.08]
12.2 Hospitalization, iron + antimalarial versus antimalarial	3		Risk Ratio (Fixed, 95% CI)	1.23 [0.97, 1.56]
12.3 Clinic visit, iron versus placebo	2		Risk Ratio (Fixed, 95% CI)	0.95 [0.88, 1.02]
12.4 Clinic visit, iron + antimalarial versus antimalarial	4		Risk Ratio (Fixed, 95% CI)	1.03 [0.96, 1.10]
13 Haemoglobin, end of treatment (by anaemia at baseline)	16	5261	Mean Difference (IV, Random, 95% CI)	0.75 [0.48, 1.01]
13.1 Anaemia	7	2481	Mean Difference (IV, Random, 95% CI)	0.95 [0.38, 1.51]
13.2 No anaemia	9	2780	Mean Difference (IV, Random, 95% CI)	0.61 [0.38, 0.85]
14 Weight, end value	5	1830	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.12, 0.06]
15 Anaemia, end of treatment	15	3784	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.49, 0.82]
16 Weight, change from baseline	4	486	Std. Mean Difference (IV, Fixed, 95% CI)	0.31 [0.13, 0.49]
17 Diarrhoeal episodes per patient-month (by zinc administration)	8	23912	Risk Ratio (Fixed, 95% CI)	1.15 [1.06, 1.26]
17.1 Without zinc	7	17566	Risk Ratio (Fixed, 95% CI)	0.99 [0.87, 1.13]
17.2 With zinc	3	6346	Risk Ratio (Fixed, 95% CI)	1.29 [1.15, 1.44]

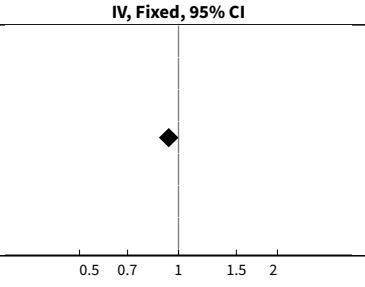
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18 Infections per patient-month	8		Risk Ratio (Fixed, 95% CI)	Subtotals only
18.1 Febrile episodes	6	15531	Risk Ratio (Fixed, 95% CI)	1.03 [0.93, 1.14]
18.2 Days with fever	1	110	Risk Ratio (Fixed, 95% CI)	8.37 [1.91, 36.58]
18.3 All disease episodes	1	1395	Risk Ratio (Fixed, 95% CI)	1.15 [0.91, 1.46]
19 Haemoglobin, change from baseline, end of treatment	12	2462	Mean Difference (IV, Random, 95% CI)	0.67 [0.42, 0.92]
20 URTI/pneumonia episodes per patient-month	6	21767	Risk Ratio (Fixed, 95% CI)	0.99 [0.85, 1.15]
21 Height, end value	5	2102	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.08, 0.10]
22 Height, change from baseline	4	486	Std. Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.09, 0.27]

Analysis 1.1. Comparison 1 Iron versus placebo or no treatment, Outcome 1 Clinical malaria (grouped by presence of anaemia).

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.1.1 Anaemia						
Adam 1997 (C)	366	372	0.4 (0.197)		3.21%	1.49[1.02,2.2]
Ayoya 2009	105	97	0.7 (0.585)		0.36%	2.08[0.66,6.54]
Desai 2003	256	235	-0.5 (0.194)		3.33%	0.59[0.4,0.86]
Fahmida 2007	155	159	0.3 (0.755)		0.22%	1.37[0.31,6.01]
Gebreselassie 1996	239	241	0.5 (0.279)		1.61%	1.59[0.92,2.75]
Massaga 2003	74	72	-0.2 (0.143)		6.09%	0.84[0.64,1.12]
Massaga 2003	72	73	0.1 (0.233)		2.3%	1.06[0.67,1.67]
Smith 1989 (C)	97	89	0.5 (0.485)		0.53%	1.61[0.62,4.15]
Verhoef 2002	82	82	0.4 (0.312)		1.28%	1.43[0.78,2.63]
Verhoef 2002	82	82	0 (0.246)		2.05%	1.04[0.64,1.69]
Zlotkin 2013 (C)	0	0	-0.1 (0.052)		45.45%	0.87[0.79,0.96]
Subtotal (95% CI)					**66.43%**	**0.92[0.84,1]**
Heterogeneity: Tau²=0; Chi²=22.83, df=10(P=0.01); I²=56.2%						
Test for overall effect: Z=2.03(P=0.04)						
1.1.2 No anaemia						
Harvey 1989	144	144	-0.1 (0.162)		4.76%	0.92[0.67,1.27]
Lawless 1994	44	42	-0 (0.15)		5.56%	0.95[0.71,1.28]
Leenstra 2009	138	141	0.6 (0.798)		0.2%	1.87[0.39,8.93]
Menendez 1997	204	207	-0.1 (0.126)		7.81%	0.94[0.73,1.2]
Menendez 1997	213	208	-0.2 (0.205)		2.96%	0.84[0.56,1.25]
Richard 2006	418	418	0 (0.101)		12.28%	1.05[0.86,1.27]
Subtotal (95% CI)					**33.57%**	**0.97[0.86,1.09]**

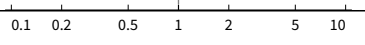


Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=1.92, df=5(P=0.86); I²=0%						
Test for overall effect: Z=0.48(P=0.63)						
Total (95% CI)					**100%**	**0.93[0.87,1]**
Heterogeneity: Tau²=0; Chi²=25.37, df=16(P=0.06); I²=36.92%						
Test for overall effect: Z=1.93(P=0.05)						
Test for subgroup differences: Chi²=0.61, df=1 (P=0.43), I²=0%						

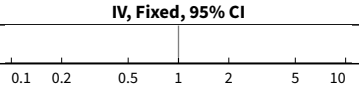


Analysis 1.2. Comparison 1 Iron versus placebo or no treatment, Outcome 2 Clinical malaria (grouped by age).

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.2.1 < 2 years						
Fahmida 2007	155	159	0.3 (0.755)		0.22%	1.37[0.31,6.01]
Massaga 2003	72	73	0.1 (0.233)		2.3%	1.06[0.67,1.67]
Massaga 2003	74	72	-0.2 (0.143)		6.09%	0.84[0.64,1.12]
Menendez 1997	213	208	-0.2 (0.205)		2.96%	0.84[0.56,1.25]
Menendez 1997	204	207	-0.1 (0.126)		7.81%	0.94[0.73,1.2]
Verhoef 2002	82	82	0.4 (0.312)		1.28%	1.43[0.78,2.63]
Verhoef 2002	82	82	0 (0.246)		2.05%	1.04[0.64,1.69]
Zlotkin 2013 (C)	0	0	-0.1 (0.052)		45.45%	0.87[0.79,0.96]
Subtotal (95% CI)					**68.17%**	**0.89[0.82,0.97]**
Heterogeneity: Tau²=0; Chi²=4.18, df=7(P=0.76); I²=0%						
Test for overall effect: Z=2.62(P=0.01)						
1.2.2 2 to 5 years						
Adam 1997 (C)	366	372	0.4 (0.197)		3.21%	1.49[1.02,2.2]
Desai 2003	256	235	-0.5 (0.194)		3.33%	0.59[0.4,0.86]
Smith 1989 (C)	97	89	0.5 (0.485)		0.53%	1.61[0.62,4.15]
Subtotal (95% CI)					**7.07%**	**0.97[0.75,1.26]**
Heterogeneity: Tau²=0; Chi²=12.47, df=2(P=0); I²=83.96%						
Test for overall effect: Z=0.23(P=0.82)						
1.2.3 > 5 years						
Ayoya 2009	105	97	0.7 (0.585)		0.36%	2.08[0.66,6.54]
Gebreselassie 1996	239	241	0.5 (0.279)		1.61%	1.59[0.92,2.75]
Harvey 1989	144	144	-0.1 (0.162)		4.76%	0.92[0.67,1.27]
Lawless 1994	44	42	-0 (0.15)		5.56%	0.95[0.71,1.28]
Leenstra 2009	138	141	0.6 (0.798)		0.2%	1.87[0.39,8.93]
Richard 2006	418	418	0 (0.101)		12.28%	1.05[0.86,1.27]
Subtotal (95% CI)					**24.76%**	**1.04[0.91,1.2]**
Heterogeneity: Tau²=0; Chi²=5.15, df=5(P=0.4); I²=3.01%						
Test for overall effect: Z=0.6(P=0.55)						
Total (95% CI)					**100%**	**0.93[0.87,1]**
Heterogeneity: Tau²=0; Chi²=25.37, df=16(P=0.06); I²=36.92%						
Test for overall effect: Z=1.93(P=0.05)						

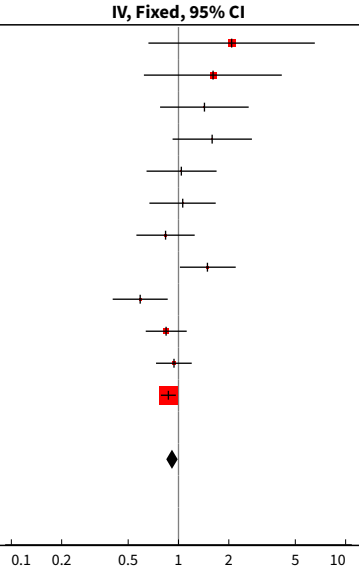


Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Test for subgroup differences: Chi²=3.56, df=1 (P=0.17), I²=43.81%						



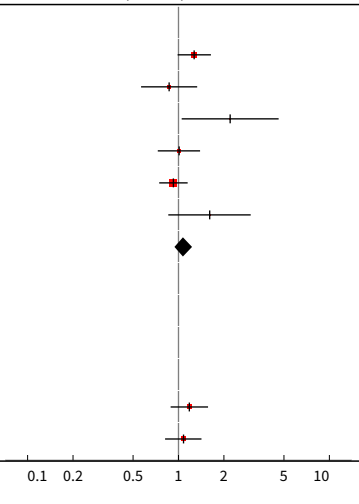
Analysis 1.3. Comparison 1 Iron versus placebo or no treatment, Outcome 3 Clinical malaria (*P. falciparum* only).

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Ayoya 2009	105	97	0.7 (0.585)		0.47%	2.08[0.66,6.54]
Smith 1989 (C)	97	89	0.5 (0.485)		0.69%	1.61[0.62,4.15]
Verhoef 2002	82	82	0.4 (0.312)		1.67%	1.43[0.78,2.63]
Gebreselassie 1996	239	241	0.5 (0.279)		2.09%	1.59[0.92,2.75]
Verhoef 2002	82	82	0 (0.246)		2.66%	1.04[0.64,1.69]
Massaga 2003	72	73	0.1 (0.233)		2.99%	1.06[0.67,1.67]
Menendez 1997	213	208	-0.2 (0.205)		3.85%	0.84[0.56,1.25]
Adam 1997 (C)	366	372	0.4 (0.197)		4.17%	1.49[1.02,2.2]
Desai 2003	256	235	-0.5 (0.194)		4.32%	0.59[0.4,0.86]
Massaga 2003	74	72	-0.2 (0.143)		7.91%	0.84[0.64,1.12]
Menendez 1997	204	207	-0.1 (0.126)		10.15%	0.94[0.73,1.2]
Zlotkin 2013 (C)	0	0	-0.1 (0.052)		59.03%	0.87[0.79,0.96]
Total (95% CI)					**100%**	**0.91[0.84,0.99]**
Heterogeneity: Tau²=0; Chi²=22.78, df=11(P=0.02); I²=51.72%						
Test for overall effect: Z=2.23(P=0.03)						

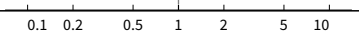


Analysis 1.4. Comparison 1 Iron versus placebo or no treatment, Outcome 4 Any parasitaemia, end of treatment (by anaemia at baseline).

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.4.1 Anaemia						
Adam 1997 (C)	368	372	0.2 (0.129)		17.47%	1.27[0.99,1.64]
Desai 2003	215	209	-0.1 (0.219)		6.06%	0.87[0.56,1.33]
Esan 2013	0	0	0.8 (0.377)		2.04%	2.2[1.05,4.61]
Gebreselassie 1996	239	241	0 (0.165)		10.61%	1.01[0.73,1.39]
Mebrahtu 2004 (C)	307	307	-0.1 (0.111)		23.76%	0.92[0.74,1.15]
Smith 1989 (C)	97	89	0.5 (0.321)		2.82%	1.61[0.86,3.01]
Subtotal (95% CI)					**62.75%**	**1.07[0.94,1.23]**
Heterogeneity: Tau²=0; Chi²=9.81, df=5(P=0.08); I²=49.05%						
Test for overall effect: Z=1.05(P=0.29)						
1.4.2 No anaemia						
Berger 2000	84	79	0.2 (0.147)		13.52%	1.18[0.89,1.57]
Harvey 1989	156	142	0.1 (0.142)		14.44%	1.08[0.81,1.42]



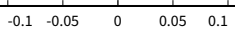
Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Leenstra 2009	138	141	0.3 (0.177)		9.29%	1.33[0.94,1.88]
Subtotal (95% CI)					**37.25%**	**1.17[0.99,1.4]**
Heterogeneity: Tau²=0; Chi²=0.88, df=2(P=0.64); I²=0%						
Test for overall effect: Z=1.81(P=0.07)						
Total (95% CI)					**100%**	**1.11[1,1.23]**
Heterogeneity: Tau²=0; Chi²=11.32, df=8(P=0.18); I²=29.33%						
Test for overall effect: Z=1.94(P=0.05)						
Test for subgroup differences: Chi²=0.63, df=1 (P=0.43), I²=0%						



Favours iron — Favours control

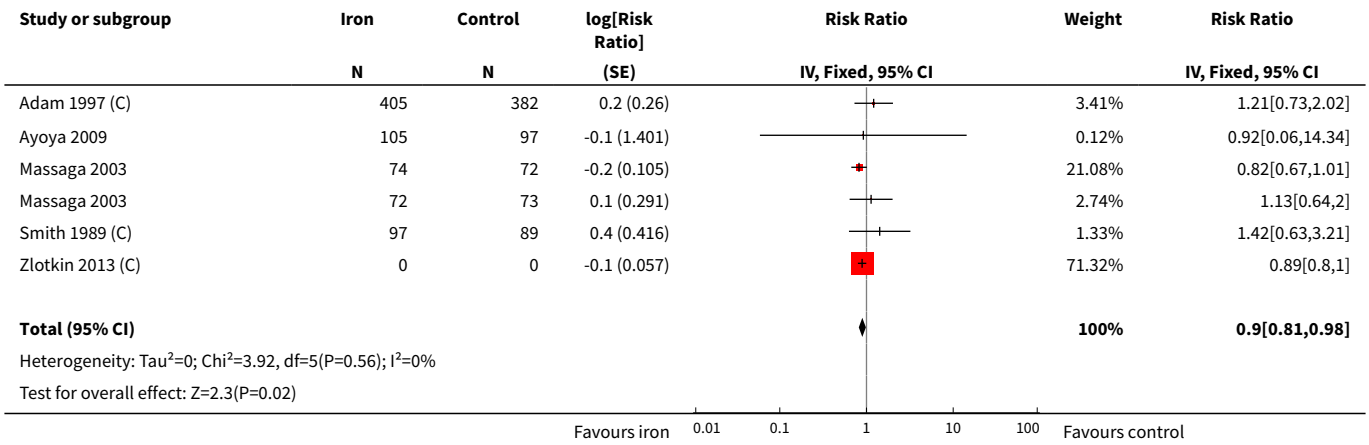
Analysis 1.5. Comparison 1 Iron versus placebo or no treatment, Outcome 5 All-cause mortality.

Study or subgroup	Iron n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Ayoya 2009	0/105	0/97		2.66%	0[-0.02,0.02]
Desai 2003	5/256	2/235		6.47%	0.01[-0.01,0.03]
Dossa 2001a	0/68	0/70		1.82%	0[-0.03,0.03]
Dossa 2001b	0/35	0/39		0.97%	0[-0.05,0.05]
Esan 2013	3/103	3/99		2.67%	-0[-0.05,0.05]
Fahmida 2007	2/196	2/196		5.18%	0[-0.02,0.02]
Gebreselassie 1996	0/239	0/241		6.34%	0[-0.01,0.01]
Latham 1990	0/28	0/26		0.71%	0[-0.07,0.07]
Massaga 2003	4/72	4/73		1.91%	0[-0.07,0.08]
Massaga 2003	4/74	3/72		1.93%	0.01[-0.06,0.08]
Mebrahtu 2004 (C)	0/340	2/344		9.03%	-0.01[-0.02,0]
Menendez 1997	11/213	9/208		5.56%	0.01[-0.03,0.05]
Menendez 1997	12/204	10/207		5.43%	0.01[-0.03,0.05]
Olsen 2006	0/121	0/110		3.04%	0[-0.02,0.02]
Powers 1983	0/19	0/21		0.53%	0[-0.09,0.09]
Richard 2006	0/368	0/380		9.87%	0[-0.01,0.01]
Smith 1989 (C)	0/106	0/107		2.81%	0[-0.02,0.02]
Verhoef 2002	0/82	1/82		2.17%	-0.01[-0.05,0.02]
Verhoef 2002	0/82	0/82		2.17%	0[-0.02,0.02]
Zlotkin 2003	0/112	0/108		2.9%	0[-0.02,0.02]
Zlotkin 2013 (C)	3/966	2/990		25.82%	0[-0,0.01]
Total (95% CI)	**3789**	**3787**		**100%**	**0[-0,0.01]**
Total events: 44 (Iron), 38 (Control)					
Heterogeneity: Tau²=0; Chi²=4.58, df=20(P=1); I²=0%					
Test for overall effect: Z=0.58(P=0.56)					

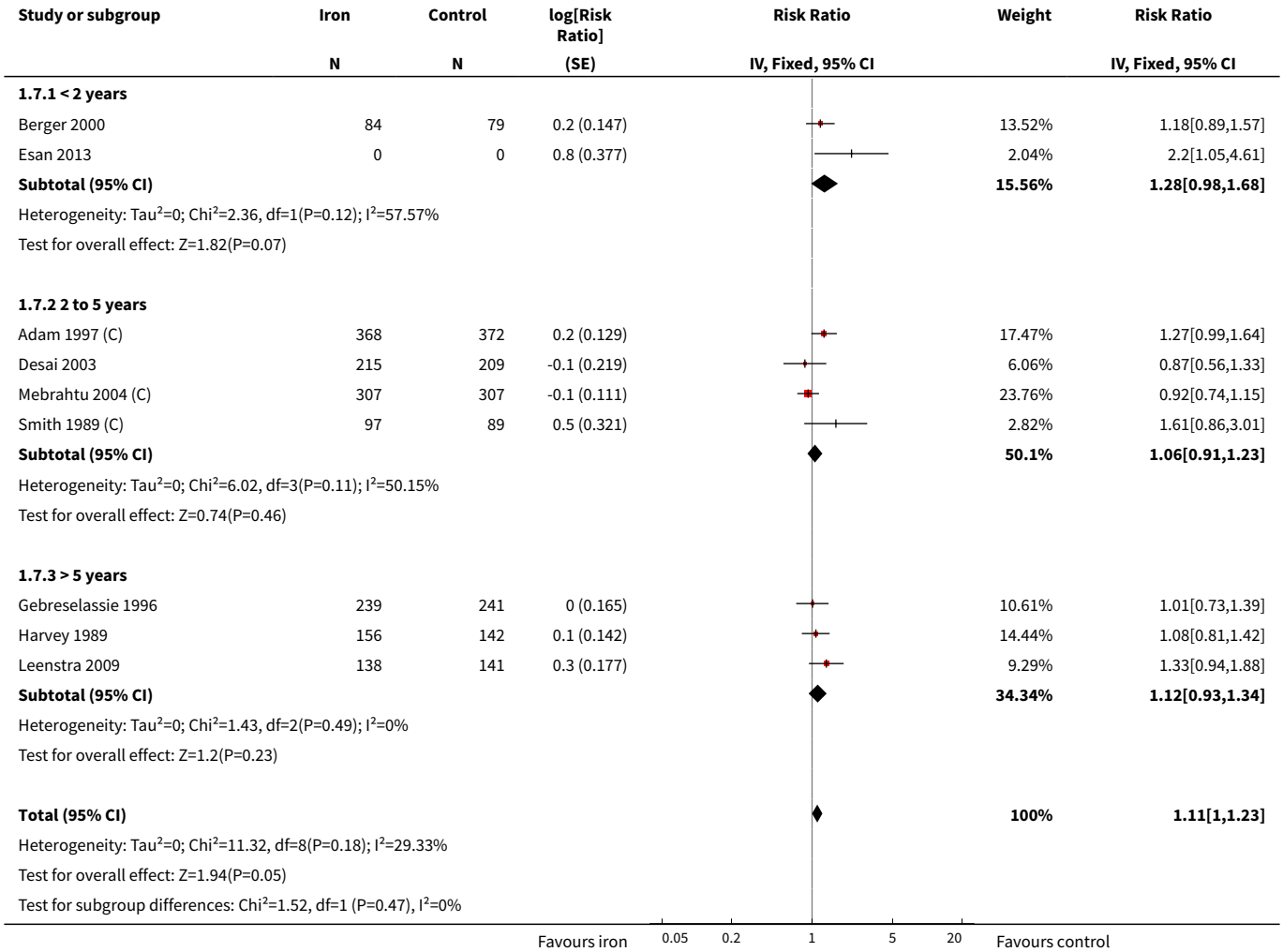


Favours iron — Favours control

Analysis 1.6. Comparison 1 Iron versus placebo or no treatment, Outcome 6 Clinical malaria with high-grade parasitaemia or requiring admission.

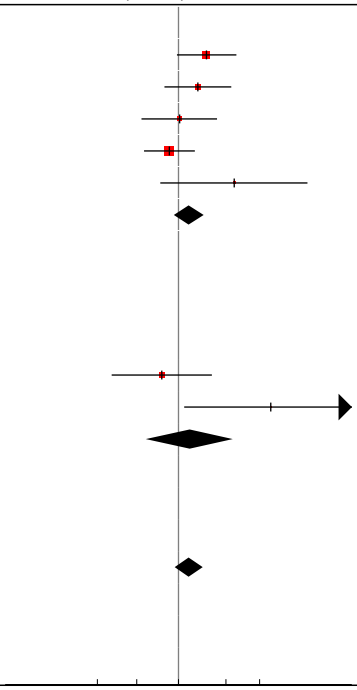


Analysis 1.7. Comparison 1 Iron versus placebo or no treatment, Outcome 7 Any parasitaemia, end of treatment (by age).



Analysis 1.8. Comparison 1 Iron versus placebo or no treatment, Outcome 8 Any parasitaemia, end of treatment (*P. falciparum* only).

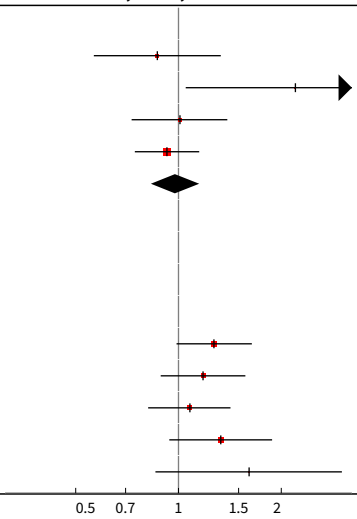
Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.8.1 Iron versus placebo/no treatment						
Adam 1997 (C)	368	372	0.2 (0.129)		22.9%	1.27[0.99,1.64]
Berger 2000	84	79	0.2 (0.147)		17.72%	1.18[0.89,1.57]
Gebreselassie 1996	239	241	0 (0.165)		13.91%	1.01[0.73,1.39]
Mebrahtu 2004 (C)	307	307	-0.1 (0.111)		31.15%	0.92[0.74,1.15]
Smith 1989 (C)	97	89	0.5 (0.321)		3.69%	1.61[0.86,3.01]
Subtotal (95% CI)					**89.38%**	**1.09[0.96,1.24]**
Heterogeneity: Tau²=0; Chi²=5.6, df=4(P=0.23); I²=28.63%						
Test for overall effect: Z=1.35(P=0.18)						
1.8.2 Iron + antimalarial versus antimalarial						
Desai 2003	215	209	-0.1 (0.219)		7.95%	0.87[0.56,1.33]
Esan 2013	0	0	0.8 (0.377)		2.67%	2.2[1.05,4.61]
Subtotal (95% CI)					**10.62%**	**1.1[0.76,1.59]**
Heterogeneity: Tau²=0; Chi²=4.56, df=1(P=0.03); I²=78.05%						
Test for overall effect: Z=0.48(P=0.63)						
Total (95% CI)					**100%**	**1.09[0.97,1.23]**
Heterogeneity: Tau²=0; Chi²=10.16, df=6(P=0.12); I²=40.95%						
Test for overall effect: Z=1.44(P=0.15)						
Test for subgroup differences: Chi²=0, df=1 (P=0.99), I²=0%						



Favours iron — Favours control

Analysis 1.9. Comparison 1 Iron versus placebo or no treatment, Outcome 9 Any parasitaemia, end of treatment (by allocation concealment).

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.9.1 Adequate						
Desai 2003	215	209	-0.1 (0.219)		6.06%	0.87[0.56,1.33]
Esan 2013	0	0	0.8 (0.377)		2.04%	2.2[1.05,4.61]
Gebreselassie 1996	239	241	0 (0.165)		10.61%	1.01[0.73,1.39]
Mebrahtu 2004 (C)	307	307	-0.1 (0.111)		23.76%	0.92[0.74,1.15]
Subtotal (95% CI)					**42.47%**	**0.98[0.83,1.15]**
Heterogeneity: Tau²=0; Chi²=5.21, df=3(P=0.16); I²=42.36%						
Test for overall effect: Z=0.29(P=0.77)						
1.9.2 Unclear						
Adam 1997 (C)	368	372	0.2 (0.129)		17.47%	1.27[0.99,1.64]
Berger 2000	84	79	0.2 (0.147)		13.52%	1.18[0.89,1.57]
Harvey 1989	156	142	0.1 (0.142)		14.44%	1.08[0.81,1.42]
Leenstra 2009	138	141	0.3 (0.177)		9.29%	1.33[0.94,1.88]
Smith 1989 (C)	97	89	0.5 (0.321)		2.82%	1.61[0.86,3.01]



Favours iron — Favours control

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Subtotal (95% CI)					**57.53%**	**1.22[1.06,1.4]**
Heterogeneity: Tau²=0; Chi²=1.91, df=4(P=0.75); I²=0%						
Test for overall effect: Z=2.81(P=0)						
Total (95% CI)					**100%**	**1.11[1,1.23]**
Heterogeneity: Tau²=0; Chi²=11.32, df=8(P=0.18); I²=29.33%						
Test for overall effect: Z=1.94(P=0.05)						
Test for subgroup differences: Chi²=4.21, df=1 (P=0.04), I²=76.24%						

Favours iron 0.5 0.7 1 1.5 2 Favours control

Analysis 1.10. Comparison 1 Iron versus placebo or no treatment, Outcome 10 High-grade parasitaemia.

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Berger 2000	84	79	0.5 (0.482)		4.26%	1.72[0.67,4.43]
Gebreselassie 1996	113	94	0.2 (0.256)		15.16%	1.21[0.73,2]
Leenstra 2009	138	141	0.3 (0.338)		8.7%	1.36[0.7,2.64]
Mebrahtu 2004 (C)	307	307	0 (0.122)		66.15%	1.03[0.81,1.31]
Smith 1989 (C)	97	89	0.4 (0.416)		5.72%	1.42[0.63,3.21]
Total (95% CI)					**100%**	**1.13[0.93,1.37]**
Heterogeneity: Tau²=0; Chi²=1.96, df=4(P=0.74); I²=0%						
Test for overall effect: Z=1.21(P=0.23)						

Favours iron 0.2 0.5 1 2 5 Favours control

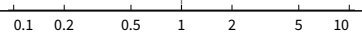
Analysis 1.11. Comparison 1 Iron versus placebo or no treatment, Outcome 11 Any parasitaemia, end of follow-up.

Study or subgroup	Iron n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Berger 2000	40/84	42/79		18.19%	0.9[0.66,1.22]
Esan 2013	52/105	33/104		13.94%	1.56[1.11,2.2]
Gebreselassie 1996	104/223	85/222		35.81%	1.22[0.98,1.52]
Harvey 1989	78/141	57/138		24.22%	1.34[1.05,1.72]
Latham 1990	23/28	18/26		7.85%	1.19[0.87,1.62]
Total (95% CI)	**581**	**569**		**100%**	**1.23[1.09,1.4]**
Total events: 297 (Iron), 235 (Control)					
Heterogeneity: Tau²=0; Chi²=6.54, df=4(P=0.16); I²=38.88%					
Test for overall effect: Z=3.3(P=0)					

Favours iron 0.01 0.1 1 10 100 Favours control

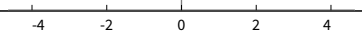
Analysis 1.12. Comparison 1 Iron versus placebo or no treatment, Outcome 12 Hospitalizations and clinic visits.

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.12.1 Hospitalization, iron versus placebo						
Adam 1997 (C)	1215	1146	0.2 (0.236)		0.97%	1.21[0.76,1.92]
Ayoya 2009	315	291	0 (2)		0.01%	1[0.02,50.4]
Massaga 2003	444	432	-0.4 (0.285)		0.67%	0.68[0.39,1.19]
Menendez 1997	2448	2484	-0.3 (0.107)		4.72%	0.77[0.62,0.95]
Zlotkin 2013 (C)	0	0	0.2 (0.111)		4.35%	1.17[0.94,1.46]
Subtotal (95% CI)					**10.72%**	**0.94[0.82,1.08]**
Heterogeneity: Tau²=0; Chi²=9.77, df=4(P=0.04); I²=59.06%						
Test for overall effect: Z=0.82(P=0.41)						
1.12.2 Hospitalization, iron + antimalarial versus antimalarial						
Esan 2013	0	0	0.3 (0.54)		0.18%	1.32[0.46,3.81]
Massaga 2003	432	438	0.2 (0.379)		0.38%	1.17[0.56,2.46]
Menendez 1997	2556	2496	0.2 (0.134)		3.01%	1.23[0.95,1.6]
Subtotal (95% CI)					**3.57%**	**1.23[0.97,1.56]**
Heterogeneity: Tau²=0; Chi²=0.03, df=2(P=0.98); I²=0%						
Test for overall effect: Z=1.67(P=0.09)						
1.12.3 Clinic visit, iron versus placebo						
Massaga 2003	444	432	-0.1 (0.133)		3.03%	0.93[0.72,1.21]
Menendez 1997	2448	2484	-0 (0.038)		37.86%	0.95[0.88,1.02]
Subtotal (95% CI)					**40.9%**	**0.95[0.88,1.02]**
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.87); I²=0%						
Test for overall effect: Z=1.41(P=0.16)						
1.12.4 Clinic visit, iron + antimalarial versus antimalarial						
Desai 2003	768	705	-0 (0.093)		6.24%	0.95[0.8,1.15]
Esan 2013	0	0	0.2 (0.193)		1.45%	1.17[0.8,1.71]
Massaga 2003	432	438	-0 (0.158)		2.16%	0.99[0.73,1.35]
Menendez 1997	2556	2496	0 (0.039)		34.96%	1.04[0.96,1.12]
Subtotal (95% CI)					**44.81%**	**1.03[0.96,1.1]**
Heterogeneity: Tau²=0; Chi²=1.18, df=3(P=0.76); I²=0%						
Test for overall effect: Z=0.73(P=0.47)						
Total (95% CI)					**100%**	**0.99[0.95,1.04]**
Heterogeneity: Tau²=0; Chi²=16.86, df=13(P=0.21); I²=22.91%						
Test for overall effect: Z=0.37(P=0.71)						
Test for subgroup differences: Chi²=5.85, df=1 (P=0.12), I²=48.75%						

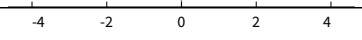


Analysis 1.13. Comparison 1 Iron versus placebo or no treatment, Outcome 13 Haemoglobin, end of treatment (by anaemia at baseline).

Study or subgroup	Iron N	Iron Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.13.1 Anaemia							
Adam 1997 (C)	368	9.7 (1.2)	374	8.5 (1.3)		5.45%	1.16[0.98,1.34]

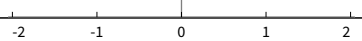


Study or subgroup	Iron N	Iron Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Dossa 2001b	35	10.1 (1.1)	39	9.1 (1.5)		4.37%	1[0.4,1.6]
Fahmida 2007	155	9.6 (1.6)	153	9 (1.5)		5.1%	0.61[0.26,0.96]
Gebreselassie 1996	239	11.6 (1.4)	241	9 (2.1)		5.17%	2.6[2.28,2.92]
Hop 2005	55	11.3 (1.5)	56	10.8 (1.4)		4.55%	0.44[-0.1,0.98]
Mebrahtu 2004 (C)	232	10 (1.5)	227	9.9 (1.8)		5.21%	0.1[-0.2,0.4]
Verhoef 2002	79	10.6 (1.8)	76	9.8 (0.9)		4.84%	0.85[0.41,1.29]
Verhoef 2002	75	10.7 (1.7)	77	9.9 (1.7)		4.51%	0.76[0.21,1.31]
Subtotal * **	**1238**		**1243**			**39.23%**	**0.95[0.38,1.51]**
Heterogeneity: Tau²=0.62; Chi²=142.28, df=7(P<0.0001); I²=95.08%							
Test for overall effect: Z=3.29(P=0)							
1.13.2 No anaemia							
Ayoya 2009	105	11.5 (0.9)	97	10.8 (0.8)		5.35%	0.73[0.49,0.97]
Berger 2000	84	10.8 (1.3)	79	10.4 (1.2)		5.03%	0.36[-0.02,0.74]
Berger 2006	184	12.9 (1.6)	190	11.8 (1.6)		5.16%	1.15[0.83,1.47]
Berger 2006	195	13.2 (1.7)	191	11.8 (1.6)		5.17%	1.35[1.03,1.67]
Dossa 2001a	34	10.8 (1.2)	32	10.5 (0.9)		4.64%	0.3[-0.21,0.81]
Dossa 2001a	34	10.9 (1.1)	38	10.1 (1.2)		4.58%	0.8[0.27,1.33]
Harvey 1989	159	11.1 (0.9)	159	10.5 (1.1)		5.39%	0.6[0.38,0.82]
Lawless 1994	44	11.4 (1.1)	42	11 (1.2)		4.76%	0.38[-0.09,0.85]
Olsen 2006	108	11.9 (1.3)	92	11.8 (1.2)		5.11%	0.07[-0.28,0.42]
Richard 2006	183	11.9 (1.1)	189	11.7 (1.2)		5.35%	0.21[-0.03,0.45]
Richard 2006	185	11.9 (1)	191	11.7 (1.2)		5.37%	0.25[0.02,0.47]
Zlotkin 2003	85	12.5 (1.5)	80	11.3 (1.4)		4.87%	1.17[0.74,1.6]
Subtotal * **	**1400**		**1380**			**60.77%**	**0.61[0.38,0.85]**
Heterogeneity: Tau²=0.14; Chi²=71.89, df=11(P<0.0001); I²=84.7%							
Test for overall effect: Z=5.08(P<0.0001)							
Total * **	**2638**		**2623**			**100%**	**0.75[0.48,1.01]**
Heterogeneity: Tau²=0.33; Chi²=256.35, df=19(P<0.0001); I²=92.59%							
Test for overall effect: Z=5.48(P<0.0001)							
Test for subgroup differences: Chi²=1.16, df=1 (P=0.28), I²=13.65%							



Analysis 1.14. Comparison 1 Iron versus placebo or no treatment, Outcome 14 Weight, end value.

Study or subgroup	Iron N	Iron Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Berger 2006	197	8 (0.9)	195	8.1 (0.8)		21.44%	-0.08[-0.28,0.12]
Berger 2006	187	8.1 (0.9)	191	8.2 (0.9)		20.63%	-0.15[-0.36,0.05]
Fahmida 2007	185	-1.6 (0.9)	189	-1.7 (0.9)		20.45%	0.09[-0.11,0.29]
Hop 2005	75	-1.5 (0.9)	73	-1.6 (0.9)		8.09%	0.1[-0.22,0.43]
Latham 1990	28	22.4 (3.7)	26	21.9 (3.2)		2.94%	0.14[-0.39,0.68]
Richard 2006	119	0 (1)	119	0 (0.9)		13.03%	-0.01[-0.26,0.24]
Richard 2006	117	-0.1 (0.9)	129	-0 (0.9)		13.43%	-0.06[-0.31,0.19]
Total * **	**908**		**922**			**100%**	**-0.03[-0.12,0.06]**
Heterogeneity: Tau²=0; Chi²=4.15, df=6(P=0.66); I²=0%							
Test for overall effect: Z=0.61(P=0.54)							

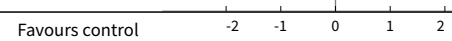


Analysis 1.15. Comparison 1 Iron versus placebo or no treatment, Outcome 15 Anaemia, end of treatment.

Study or subgroup	Iron n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adam 1997 (C)	260/263	255/267		7.37%	1.04[1.01,1.07]
Akenzua 1985	13/40	15/15		6.02%	0.34[0.22,0.53]
Ayoya 2009	64/105	88/97		7.16%	0.67[0.57,0.79]
Berger 2000	46/84	50/79		6.86%	0.87[0.67,1.12]
Berger 2006	16/195	58/191		5.66%	0.27[0.16,0.45]
Esan 2013	41/105	60/104		6.73%	0.68[0.51,0.9]
Fahmida 2007	130/155	140/153		7.32%	0.92[0.84,1]
Gebreselassie 1996	121/239	228/241		7.24%	0.54[0.47,0.61]
Hop 2005	20/55	29/56		6.09%	0.7[0.46,1.08]
Massaga 2003	20/146	35/145		5.75%	0.57[0.34,0.93]
Mebrahtu 2004 (C)	129/166	123/194		7.23%	1.23[1.07,1.4]
Mwanri 2000	7/34	33/34		4.92%	0.21[0.11,0.41]
Thi 2006	5/76	11/73		3.43%	0.44[0.16,1.2]
Verhoef 2002	42/79	58/76		6.92%	0.7[0.55,0.89]
Verhoef 2002	30/75	60/77		6.69%	0.51[0.38,0.69]
Zlotkin 2003	14/85	11/80		4.6%	1.2[0.58,2.48]
Total (95% CI)	**1902**	**1882**		**100%**	**0.63[0.49,0.82]**
Total events: 958 (Iron), 1254 (Control)					
Heterogeneity: Tau^2=0.23; Chi^2=574.11, df=15(P<0.0001); I^2=97.39%					
Test for overall effect: Z=3.53(P=0)					

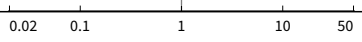
Analysis 1.16. Comparison 1 Iron versus placebo or no treatment, Outcome 16 Weight, change from baseline.

Study or subgroup	Iron N	Iron Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Dossa 2001a	36	0.3 (0.4)	32	0.5 (0.6)		14.34%	-0.39[-0.87,0.09]
Dossa 2001a	34	0.4 (0.4)	38	0.4 (0.4)		15.5%	0[-0.46,0.46]
Hop 2005	75	-0.6 (0.4)	73	-0.7 (0.4)		31.95%	0.05[-0.28,0.37]
Latham 1990	28	2.1 (0.9)	26	1.2 (0.6)		9.93%	1.13[0.56,1.71]
Mwanri 2000	36	0.7 (0.5)	36	0.2 (0.5)		13.53%	1.06[0.57,1.56]
Mwanri 2000	36	0.9 (0.5)	36	0.6 (0.5)		14.75%	0.64[0.16,1.11]
Total ***	**245**		**241**			**100%**	**0.31[0.13,0.49]**
Heterogeneity: Tau^2=0; Chi^2=31.03, df=5(P<0.0001); I^2=83.89%							
Test for overall effect: Z=3.33(P=0)							



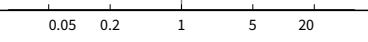
Analysis 1.17. Comparison 1 Iron versus placebo or no treatment, Outcome 17 Diarrhoeal episodes per patient-month (by zinc administration).

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.17.1 Without zinc						
Adam 1997 (C)	1215	1146	0 (0.175)		6.41%	1.03[0.73,1.45]
Berger 2000	252	237	-0.6 (0.365)		1.47%	0.56[0.28,1.15]
Berger 2006	1200	1182	-0.1 (0.203)		4.73%	0.89[0.6,1.32]
Dossa 2001b	52	58	0.3 (0.606)		0.53%	1.34[0.41,4.39]
Lawless 1994	154	147	-0.2 (0.518)		0.73%	0.84[0.3,2.3]
Richard 2006	1060	1073	-0 (0.1)		19.55%	0.99[0.81,1.2]
Zlotkin 2013 (C)	4835	4955	0.1 (0.145)		9.25%	1.13[0.85,1.5]
Subtotal (95% CI)					**42.67%**	**0.99[0.87,1.13]**
Heterogeneity: Tau²=0; Chi²=3.88, df=6(P=0.69); I²=0%						
Test for overall effect: Z=0.09(P=0.93)						
1.17.2 With zinc						
Berger 2006	1134	1170	-0 (0.198)		4.98%	0.99[0.67,1.46]
Fahmida 2007	930	954	0.2 (0.123)		12.89%	1.18[0.93,1.51]
Richard 2006	1071	1087	0.3 (0.07)		39.46%	1.36[1.19,1.57]
Subtotal (95% CI)					**57.33%**	**1.29[1.15,1.44]**
Heterogeneity: Tau²=0; Chi²=2.86, df=2(P=0.24); I²=30.09%						
Test for overall effect: Z=4.3(P<0.0001)						
Total (95% CI)					**100%**	**1.15[1.06,1.26]**
Heterogeneity: Tau²=0; Chi²=15.01, df=9(P=0.09); I²=40.05%						
Test for overall effect: Z=3.19(P=0)						
Test for subgroup differences: Chi²=8.27, df=1 (P=0), I²=87.91%						

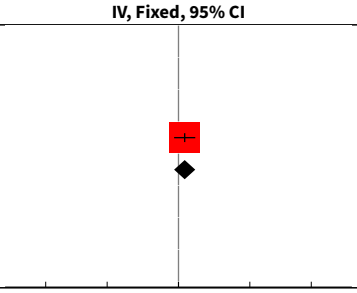


Analysis 1.18. Comparison 1 Iron versus placebo or no treatment, Outcome 18 Infections per patient-month.

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.18.1 Febrile episodes						
Adam 1997 (C)	1215	1146	0.1 (0.064)		62.27%	1.09[0.96,1.24]
Berger 2000	252	237	0 (0.309)		2.7%	1.03[0.56,1.9]
Berger 2006	2334	2351	0.1 (0.192)		7%	1.1[0.76,1.61]
Fahmida 2007	930	954	-0.1 (0.12)		17.99%	0.94[0.74,1.19]
Mebrahtu 2004 (C)	2784	2724	-0.3 (0.194)		6.87%	0.73[0.5,1.06]
Smith 1989 (C)	315	289	0 (0.285)		3.17%	1[0.57,1.75]
Subtotal (95% CI)					**100%**	**1.03[0.93,1.14]**
Heterogeneity: Tau²=0; Chi²=4.84, df=5(P=0.44); I²=0%						
Test for overall effect: Z=0.6(P=0.55)						
1.18.2 Days with fever						
Dossa 2001b	52	58	2.1 (0.753)		100%	8.37[1.91,36.58]
Subtotal (95% CI)					**100%**	**8.37[1.91,36.58]**
Heterogeneity: Not applicable						

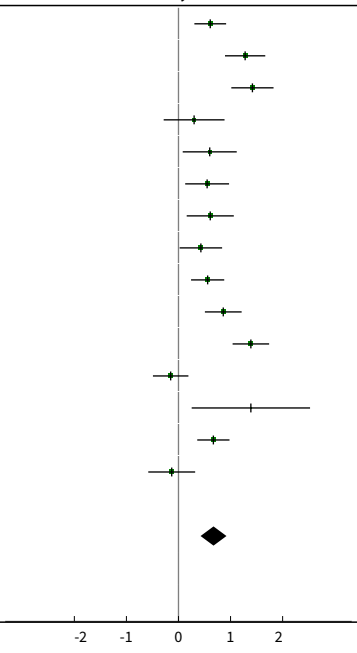


Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Test for overall effect: Z=2.82(P=0)						
1.18.3 All disease episodes						
Leenstra 2009	690	705	0.1 (0.122)		100%	1.15[0.91,1.46]
Subtotal (95% CI)					**100%**	**1.15[0.91,1.46]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.15(P=0.25)						
Test for subgroup differences: Chi^2=8.28, df=1 (P=0.02), I^2=75.84%						



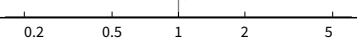
Analysis 1.19. Comparison 1 Iron versus placebo or no treatment, Outcome 19 Haemoglobin, change from baseline, end of treatment.

Study or subgroup	Iron N	Iron Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Berger 2000	84	0.9 (1.4)	79	0.3 (0.1)		7.5%	0.61[0.31,0.91]
Berger 2006	194	2.3 (1.9)	191	1 (1.9)		7.02%	1.28[0.89,1.67]
Berger 2006	184	2.1 (1.9)	190	0.6 (2.1)		6.9%	1.42[1.01,1.83]
Dossa 2001a	34	0.7 (1.4)	32	0.4 (1)		5.77%	0.3[-0.28,0.88]
Dossa 2001a	34	0.8 (0.3)	38	0.2 (1.6)		6.18%	0.6[0.08,1.12]
Esan 2013	102	2.1 (1.4)	97	1.5 (1.6)		6.8%	0.55[0.13,0.97]
Fahmida 2007	155	-0 (2)	153	-0.6 (2)		6.61%	0.61[0.16,1.06]
Hop 2005	55	1.3 (1.2)	56	0.9 (1)		6.89%	0.43[0.02,0.84]
Lawless 1994	44	0.3 (0.8)	42	-0.2 (0.7)		7.42%	0.56[0.24,0.88]
Mwanri 2000	36	2.2 (0.8)	36	1.4 (0.8)		7.22%	0.86[0.51,1.21]
Mwanri 2000	36	1.8 (0.8)	36	0.4 (0.8)		7.24%	1.39[1.04,1.74]
Olsen 2006	108	0.2 (1.2)	92	0.3 (1.3)		7.3%	-0.15[-0.49,0.19]
Powers 1983	19	1.5 (2.1)	21	0.1 (1.4)		3.06%	1.39[0.25,2.53]
Thi 2006	76	2.1 (1.1)	73	1.5 (0.9)		7.47%	0.67[0.36,0.98]
Zlotkin 2003	85	-0.1 (1.5)	80	0.1 (1.4)		6.62%	-0.13[-0.58,0.32]
Total ***	**1246**		**1216**			**100%**	**0.67[0.42,0.92]**
Heterogeneity: Tau^2=0.19; Chi^2=79.9, df=14(P<0.0001); I^2=82.48%							
Test for overall effect: Z=5.3(P<0.0001)							

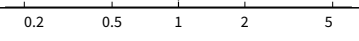


Analysis 1.20. Comparison 1 Iron versus placebo or no treatment, Outcome 20 URTI/pneumonia episodes per patient-month.

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Berger 2000	252	237	-0.3 (0.474)		2.74%	0.75[0.3,1.91]
Berger 2006	1134	1170	0.1 (0.139)		31.73%	1.05[0.8,1.38]
Berger 2006	1200	1182	0 (0.136)		33.4%	1.05[0.81,1.37]
Esan 2013	315	312	0.1 (0.385)		4.15%	1.07[0.5,2.27]

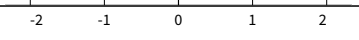


Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Fahmida 2007	930	954	0.4 (0.913)		0.74%	1.54[0.26,9.21]
Richard 2006	1071	1087	-0.2 (0.239)		10.83%	0.83[0.52,1.33]
Richard 2006	1060	1073	-0.2 (0.22)		12.73%	0.8[0.52,1.23]
Zlotkin 2013 (C)	4835	4955	0.2 (0.41)		3.67%	1.21[0.54,2.7]
Total (95% CI)					**100%**	**0.99[0.85,1.15]**
Heterogeneity: Tau²=0; Chi²=2.69, df=7(P=0.91); I²=0%						
Test for overall effect: Z=0.13(P=0.89)						



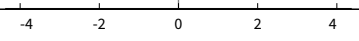
Analysis 1.21. Comparison 1 Iron versus placebo or no treatment, Outcome 21 Height, end value.

Study or subgroup	Iron N	Iron Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Berger 2006	197	71 (2.5)	195	71 (2.4)		18.68%	-0.01[-0.21,0.19]
Berger 2006	187	70.8 (2.5)	191	71.2 (2.5)		17.98%	-0.12[-0.33,0.08]
Fahmida 2007	185	-1.4 (0.9)	189	-1.4 (1)		17.82%	-0.04[-0.25,0.16]
Hop 2005	75	-1.4 (0.8)	73	-1.4 (0.8)		7.05%	-0.03[-0.35,0.3]
Latham 1990	28	124.5 (6.9)	26	125.9 (7.4)		2.56%	-0.19[-0.73,0.34]
Richard 2006	182	-2 (0.9)	189	-2.2 (0.9)		17.59%	0.19[-0.01,0.39]
Richard 2006	195	-2 (0.9)	190	-2.1 (0.9)		18.33%	0.08[-0.12,0.28]
Total ***	**1049**		**1053**			**100%**	**0.01[-0.08,0.1]**
Heterogeneity: Tau²=0; Chi²=6.07, df=6(P=0.42); I²=1.14%							
Test for overall effect: Z=0.24(P=0.81)							



Analysis 1.22. Comparison 1 Iron versus placebo or no treatment, Outcome 22 Height, change from baseline.

Study or subgroup	Iron N	Iron Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Dossa 2001a	34	1.9 (0.6)	38	2.3 (0.8)		14.53%	-0.56[-1.03,-0.08]
Dossa 2001a	36	1.9 (0.6)	32	2.1 (0.9)		14.15%	-0.26[-0.74,0.22]
Hop 2005	75	-0.4 (0.4)	73	-0.5 (0.4)		31.1%	0.14[-0.18,0.46]
Latham 1990	28	3.2 (0.9)	26	3.2 (0.8)		11.36%	0[-0.53,0.53]
Mwanri 2000	36	0.4 (0.4)	36	0.1 (0.4)		13.85%	0.85[0.36,1.33]
Mwanri 2000	36	0.5 (0.4)	36	0.4 (0.4)		15.01%	0.28[-0.18,0.75]
Total ***	**245**		**241**			**100%**	**0.09[-0.09,0.27]**
Heterogeneity: Tau²=0; Chi²=19.55, df=5(P=0); I²=74.43%							
Test for overall effect: Z=0.93(P=0.35)							

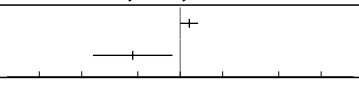


Comparison 2. Iron plus folic acid versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe malaria (malaria requiring admission)	2		Risk Ratio (Fixed, 95% CI)	Totals not selected
2 Severe malaria (cerebral malaria)	2		Risk Ratio (Fixed, 95% CI)	Totals not selected
3 All-cause mortality	5	18034	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.01]
4 Any hospitalization	1		Risk Ratio (Fixed, 95% CI)	Subtotals only
5 Haemoglobin, end of treatment	1	124	Mean Difference (IV, Random, 95% CI)	0.90 [0.51, 1.29]
6 Anaemia, end of treatment	3	633	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.25, 0.99]
7 Weight, end value	2	1080	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.18, 0.06]
8 Height, end value	2	1082	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.12, 0.12]

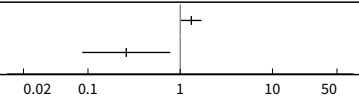
Analysis 2.1. Comparison 2 Iron plus folic acid versus placebo or no treatment, Outcome 1 Severe malaria (malaria requiring admission).

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Sazawal 2006 (C)a	7950	8006	0.1 (0.075)		1.16[1,1.34]
Sazawal 2006 (C)b	815	804	-0.8 (0.331)		0.46[0.24,0.88]



Analysis 2.2. Comparison 2 Iron plus folic acid versus placebo or no treatment, Outcome 2 Severe malaria (cerebral malaria).

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Sazawal 2006 (C)a	7950	8006	0.3 (0.13)		1.32[1.02,1.7]
Sazawal 2006 (C)b	815	804	-1.3 (0.561)		0.26[0.09,0.78]

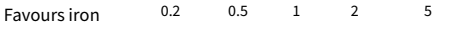


Analysis 2.3. Comparison 2 Iron plus folic acid versus placebo or no treatment, Outcome 3 All-cause mortality.

Study or subgroup	Iron n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Giovannini 2006	0/68	0/68		0.75%	0[-0.03,0.03]
Greisen 1986 (C)	0/114	0/111		1.25%	0[-0.02,0.02]
Hall 2002 (C)	0/551	0/562		6.17%	0[-0,0]
Sazawal 2006 (C)a	149/7941	130/7996		88.38%	0[-0,0.01]
Sazawal 2006 (C)b	4/302	7/321		3.45%	-0.01[-0.03,0.01]
Total (95% CI)	**8976**	**9058**		**100%**	**0[-0,0.01]**
Total events: 153 (Iron), 137 (Control)					
Heterogeneity: Tau²=0; Chi²=2.29, df=4(P=0.68); I²=0%					
Test for overall effect: Z=1.02(P=0.31)					

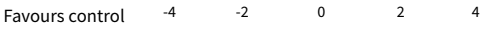
Analysis 2.4. Comparison 2 Iron plus folic acid versus placebo or no treatment, Outcome 4 Any hospitalization.

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Sazawal 2006 (C)a	95400	96072	0.1 (0.061)		0%	1.08[0.96,1.22]



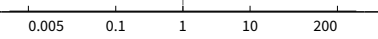
Analysis 2.5. Comparison 2 Iron plus folic acid versus placebo or no treatment, Outcome 5 Haemoglobin, end of treatment.

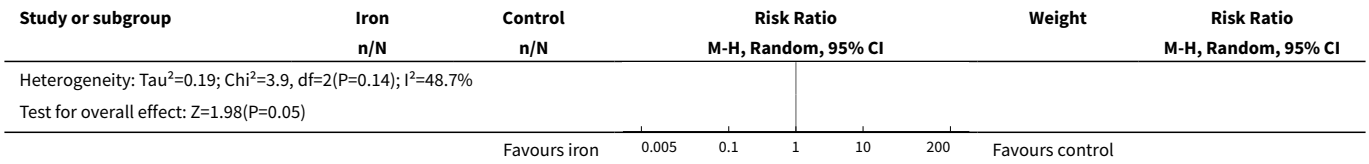
Study or subgroup	Iron N	Iron Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Giovannini 2006	64	10.9 (1.2)	60	10 (1)		100%	0.9[0.51,1.29]
Total ***	**64**		**60**			**100%**	**0.9[0.51,1.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.55(P<0.0001)							



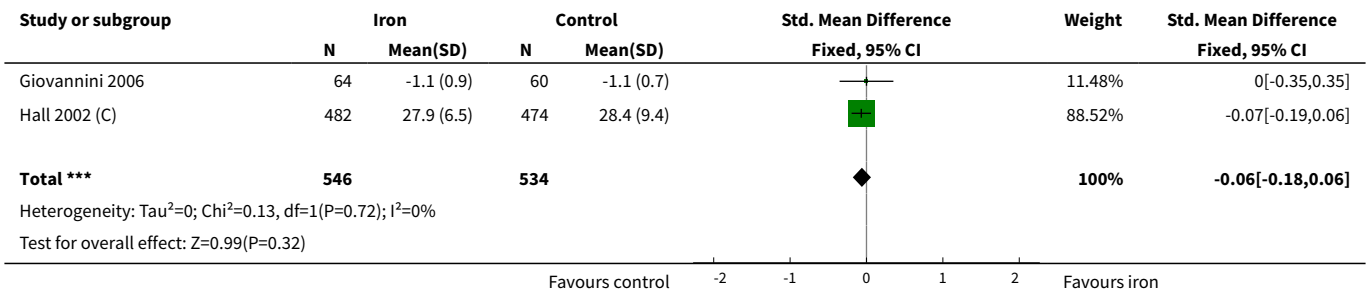
Analysis 2.6. Comparison 2 Iron plus folic acid versus placebo or no treatment, Outcome 6 Anaemia, end of treatment.

Study or subgroup	Iron n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Akenzua 1985	13/40	15/15		52.44%	0.34[0.22,0.53]
Giovannini 2006	7/64	8/60		29.8%	0.82[0.32,2.12]
Sazawal 2006 (C)b	3/220	5/234		17.76%	0.64[0.15,2.64]
Total (95% CI)	**324**	**309**		**100%**	**0.49[0.25,0.99]**
Total events: 23 (Iron), 28 (Control)					

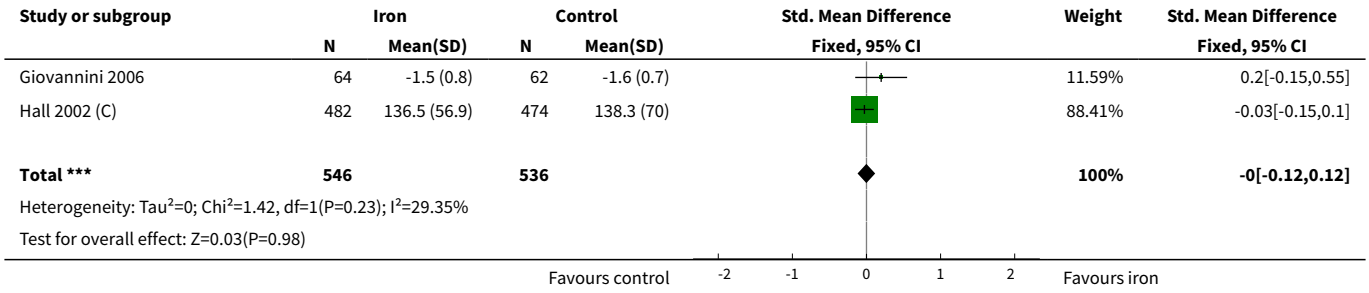




Analysis 2.7. Comparison 2 Iron plus folic acid versus placebo or no treatment, Outcome 7 Weight, end value.



Analysis 2.8. Comparison 2 Iron plus folic acid versus placebo or no treatment, Outcome 8 Height, end value.

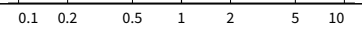


Comparison 3. Iron with or without folic acid versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical malaria (grouped by presence of malaria prevention or management)	16		Risk Ratio (Fixed, 95% CI)	0.97 [0.91, 1.03]
1.1 Services present	11		Risk Ratio (Fixed, 95% CI)	0.91 [0.84, 0.97]
1.2 Services absent	5		Risk Ratio (Fixed, 95% CI)	1.16 [1.02, 1.31]

Analysis 3.1. Comparison 3 Iron with or without folic acid versus placebo or no treatment, Outcome 1 Clinical malaria (grouped by presence of malaria prevention or management).

Study or subgroup	Iron N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
3.1.1 Services present						
Ayoya 2009	105	97	0.7 (0.585)		0.3%	2.08[0.66,6.54]
Desai 2003	256	235	-0.5 (0.194)		2.69%	0.59[0.4,0.86]
Gebreselassie 1996	239	241	0.5 (0.279)		1.3%	1.59[0.92,2.75]
Harvey 1989	144	144	-0.1 (0.162)		3.86%	0.92[0.67,1.27]
Leenstra 2009	138	141	0.6 (0.798)		0.16%	1.87[0.39,8.93]
Massaga 2003	74	72	-0.2 (0.143)		4.93%	0.84[0.64,1.12]
Massaga 2003	72	73	0.1 (0.233)		1.87%	1.06[0.67,1.67]
Menendez 1997	204	207	-0.1 (0.126)		6.33%	0.94[0.73,1.2]
Menendez 1997	213	208	-0.2 (0.205)		2.4%	0.84[0.56,1.25]
Richard 2006	418	418	0 (0.101)		9.94%	1.05[0.86,1.27]
Sazawal 2006 (C)b	815	804	-0.8 (0.331)		0.92%	0.46[0.24,0.88]
Verhoef 2002	82	82	0 (0.246)		1.66%	1.04[0.64,1.69]
Verhoef 2002	82	82	0.4 (0.312)		1.04%	1.43[0.78,2.63]
Zlotkin 2013 (C)	0	0	-0.1 (0.052)		36.8%	0.87[0.79,0.96]
Subtotal (95% CI)					**74.19%**	**0.91[0.84,0.97]**
Heterogeneity: Tau²=0; Chi²=22.05, df=13(P=0.05); I²=41.05%						
Test for overall effect: Z=2.68(P=0.01)						
3.1.2 Services absent						
Adam 1997 (C)	366	372	0.4 (0.197)		2.6%	1.49[1.02,2.2]
Fahmida 2007	155	159	0.3 (0.755)		0.18%	1.37[0.31,6.01]
Lawless 1994	44	42	-0 (0.15)		4.5%	0.95[0.71,1.28]
Sazawal 2006 (C)a	7950	8006	0.1 (0.075)		18.1%	1.16[1,1.34]
Smith 1989 (C)	97	89	0.5 (0.485)		0.43%	1.61[0.62,4.15]
Subtotal (95% CI)					**25.81%**	**1.16[1.02,1.31]**
Heterogeneity: Tau²=0; Chi²=3.84, df=4(P=0.43); I²=0%						
Test for overall effect: Z=2.34(P=0.02)						
Total (95% CI)					**100%**	**0.97[0.91,1.03]**
Heterogeneity: Tau²=0; Chi²=37.29, df=18(P=0); I²=51.73%						
Test for overall effect: Z=1.11(P=0.26)						
Test for subgroup differences: Chi²=11.4, df=1 (P=0), I²=91.23%						



Favours iron — Favours control

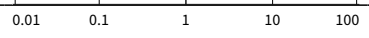
Comparison 4. Iron plus antimalarial versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical malaria	3	728	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.43, 0.67]
2 All-cause mortality	3	728	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.52, 2.11]
3 Hospitalizations and clinic visits	2		Risk Ratio (Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Hospitalization, iron + antimalarial versus placebo	2	5904	Risk Ratio (Fixed, 95% CI)	0.59 [0.48, 0.73]
3.2 Clinic visit, iron + antimalarial versus placebo	2	5904	Risk Ratio (Fixed, 95% CI)	0.88 [0.82, 0.95]
4 Haemoglobin at end of treatment	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Anaemia	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Iron + antimalarial versus placebo, end of treatment	2	295	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.28, 0.70]
5.2 Iron + antimalarial versus placebo, end of follow-up	1	420	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.26, 0.54]

Analysis 4.1. Comparison 4 Iron plus antimalarial versus placebo, Outcome 1 Clinical malaria.

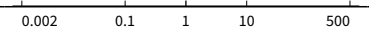
Study or subgroup	Antimalarial + iron n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Massaga 2003	25/72	45/72		29.97%	0.56[0.39,0.8]
Menendez 1997	36/213	81/207		54.71%	0.43[0.31,0.61]
Verhoef 2002	20/82	23/82		15.32%	0.87[0.52,1.46]
Total (95% CI)	**367**	**361**		**100%**	**0.54[0.43,0.67]**
Total events: 81 (Antimalarial + iron), 149 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.95, df=2(P=0.08); I^2=59.59%					
Test for overall effect: Z=5.42(P<0.0001)					



Favours iron+antimalarial — Favours control

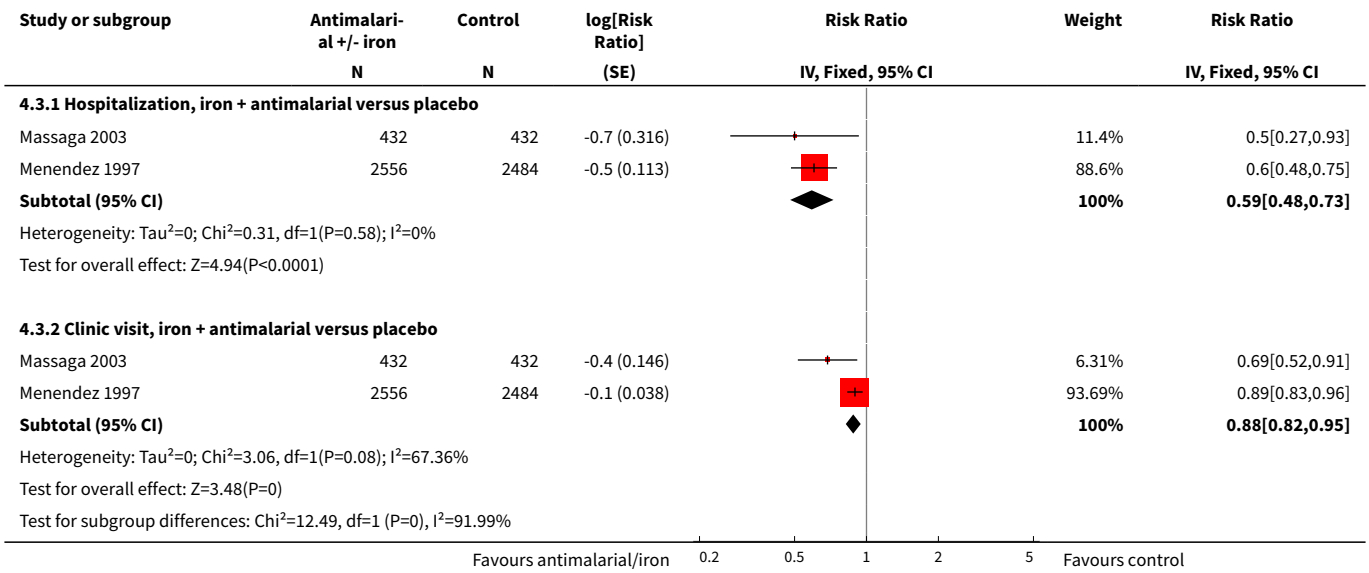
Analysis 4.2. Comparison 4 Iron plus antimalarial versus placebo, Outcome 2 All-cause mortality.

Study or subgroup	Antimalarial +/- iron n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Massaga 2003	4/72	3/72		20.49%	1.33[0.31,5.75]
Menendez 1997	11/213	10/207		69.27%	1.07[0.46,2.46]
Verhoef 2002	0/82	1/82		10.24%	0.33[0.01,8.06]
Total (95% CI)	**367**	**361**		**100%**	**1.05[0.52,2.11]**
Total events: 15 (Antimalarial +/- iron), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.6, df=2(P=0.74); I^2=0%					
Test for overall effect: Z=0.13(P=0.9)					

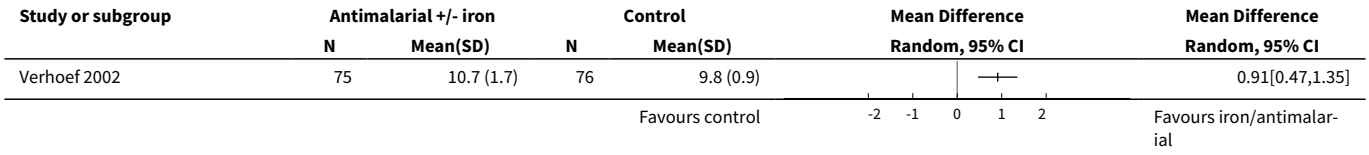


Favours antimalarial/iron — Favours control

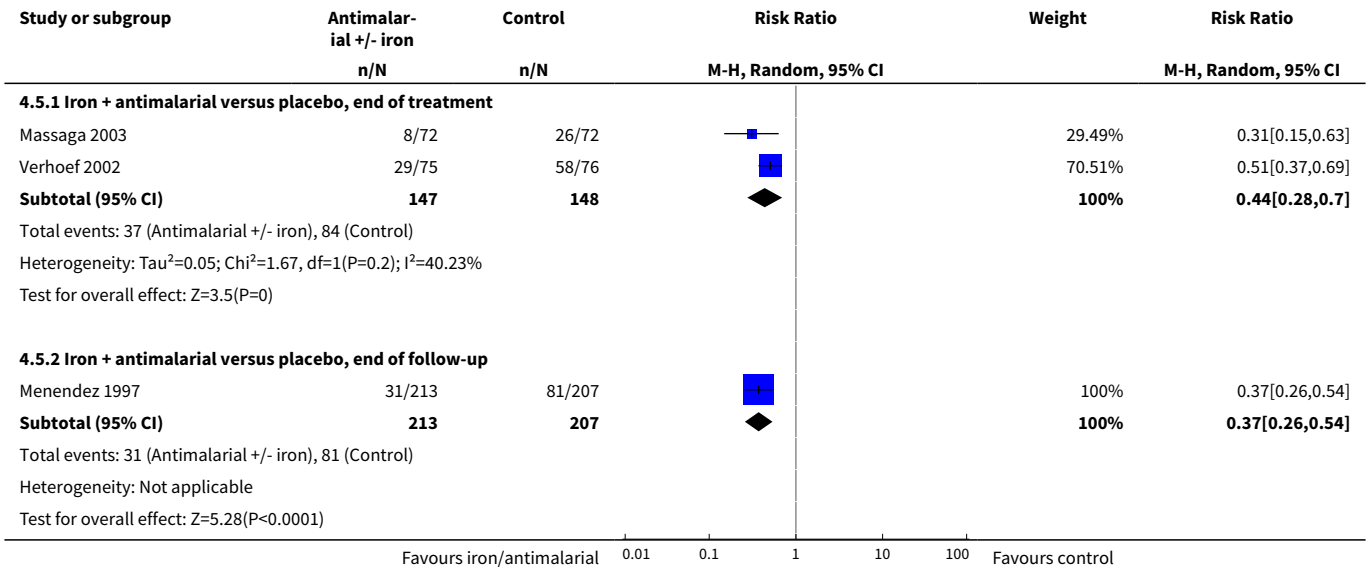
Analysis 4.3. Comparison 4 Iron plus antimalarial versus placebo, Outcome 3 Hospitalizations and clinic visits.



Analysis 4.4. Comparison 4 Iron plus antimalarial versus placebo, Outcome 4 Haemoglobin at end of treatment.



Analysis 4.5. Comparison 4 Iron plus antimalarial versus placebo, Outcome 5 Anaemia.



ADDITIONAL TABLES

Table 1. Description and location of malaria-endemic areas

Area definition	Parasite rates	Description	Geographical location
Hypoendemicity (also called designated unstable malaria)	10% or fewer children aged 2 to 9 years, but may be higher for part of the year	Areas where there is little transmission and during the average year the effects upon the general population are unimportant	AFRO: Chad AMRO: Belize, Bolivia, El Salvador, Guatemala, Mexico, Nicaragua, Costa Rica, Paraguay EMRO: Afghanistan, Iraq, Oman EURO: Armenia, Azerbaijan, Georgia, Kyrgyzstan, Tajikistan SEARO: Nepal WPRO: China
Mesoendemicity (also called unstable and stable malaria)	11 to 50% of children aged 2 to 9 years	Typically found among rural communities in subtropical zones where wide geographical variations in transmission exist	AFRO: Angola, Botswana, Cape Verde, Chad, Eritrea, Ethiopia, Kenya (considered hyper- or holoendemic in review, as indicated in most of the trials), Mauritania, Namibia, Niger, Zambia, Zimbabwe AMRO: Brazil, Colombia, Ecuador, Guyana, Panama, Peru, Venezuela EMRO: Iran, Pakistan, Saudi Arabia SEARO: Bangladesh, Bhutan, India, Indonesia, Sri Lanka, Thailand WPRO: Malaysia
Hyperendemicity (also called stable malaria)	Consistently > 50% among children aged 2 to 9 years	Areas where transmission is intense but seasonal; immunity is insufficient in all age groups	AFRO: Angola, Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Malawi, Mali, Mozambique, Nigeria, Sao Tome and Principe, Senegal, Sierra Leone, Togo, Uganda,Tanzania, Zambia SEARO: Timor-Leste WPRO: Papua New Guinea, Philippines, Solomon Islands, Vanuatu, Vietnam
Holoendemicity (also called stable malaria)	Consistently > 75% among infants aged 0 to 11 months	Intense transmission resulting in a considerable degree of immunity after early childhood	AFRO: Central African Republic, Democratic Republic of Congo, Tanzania, Uganda, Burundi, Madagascar, Malawi, Mozambique AMRO: Dominican Republic, Suriname EMRO: Djibouti, Somalia, Sudan, Yemen SEARO: Myanmar WPRO: Cambodia, Lao People's Democratic Republic

Abbreviations: AFRO: WHO African Regional Office; AMRO: WHO Americas Regional Office; EMRO: WHO Eastern Mediterranean Regional Office; EURO: WHO Europe Regional Office; SEARO: WHO South East Asian Regional Office; WPRO: WHO Western Pacific Regional Office.

Table 2. WHO RDA of iron by age group

Age group	Minimal daily dose
< 6 months	2 mg/kg
6 to 24 months	12.5 mg or 2 mg/kg
2 to 5 years	20 mg

Table 2. WHO RDA of iron by age group *(Continued)*

6 to 11 years	30 mg
11 to 18 years	60 mg

Abbreviations: WHO: World Health Organization; RDA: recommended dietary allowance.

Table 3. Detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	iron	iron	iron	iron	iron
2	ferrous	ferrous	ferrous	FERROUS-SULPHATE	ferrous
3	1 or 2	IRON COMPOUNDS	IRON COMPOUNDS	1 or 2	1 or 2
4	malaria	1 or 2 or 3	1 or 2 or 3	supplem$	malaria
5	anaemia	supplem*	supplem*	3 and 4	anaemia
6	anaemia	4 and 5	4 and 5	malaria	anaemia
7	4 or 5 or 6	malaria	malaria	anaemia	4 or 5 or 6
8	3 and 7	anaemia	anaemia	6 or 7	3 and 7
9	—	anaemia	anaemia	5 and 8	—
10	—	7 or 8 or 9	7 or 8 or 9	child$	—
11	—	6 and 10	6 and 10	infant$	—
12	—	—	child*	10 or 11	—
13	—	—	infant*	9 and 12	—
14	—	—	12 or 13	—	—
15	—	—	11 and 14	—	—

[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 (Cochrane 2011).

Table 4. Studies reporting malaria as an outcome: malaria definitions, types of outcomes and methods of surveillance and treatment in the trial

Trial ID	Clinical definition	Laboratory definition	Malaria-related outcomes reported	Time of assessment	Malaria prevention or management strategies	Malaria prevention or management
Adam 1997 (C)	Physician's diagnosis of malaria	Any parasitaemia (all malaria	Clinical malaria; any parasitaemia; malaria necessitating hospital-	3 months to end of treatment	Blood smears for malaria obtained before, during and after treatment. Chil-	No

Table 4. Studies reporting malaria as an outcome: malaria definitions, types of outcomes and methods of surveillance and treatment in the trial *(Continued)*

		species, assumed most *Plasmodium falciparum* since trial conducted in same region as Gebreselassie 1996)	ization (used as severe malaria); parasite density (all N events/N individuals, unadjusted for clustering)		dren with clinical malaria referred to local hospital and treated	
Ayoya 2009	Fever > 37.5°C (axillary)	Any parasitaemia (*P. falciparum*)	Clinical malaria; clinical malaria with parasitaemia ≥ 5000/µL (used as severe malaria); parasite density	3 months to end of treatment	Malaria screening was done at baseline for all children and repeated throughout the study in children who had fever. Children infected with *P. falciparum* also were treated with sulfadoxine-pyrimethamine	Yes
Berger 2000	Isolated fever	Parasite density > 3000 (*P. falciparum*, *Plasmodium malariae* and *Plasmodium ovale* assessed. Over 97% were *P. falciparum*)	Parasite index (%, used as parasitaemia); parasitaemia above 3000 / µL (used as severe malaria) and 10,000 / µL (%); parasite density	3 months to end of treatment 9 months to end of follow-up (FU)	Blood smears for malaria obtained at baseline, end of treatment (3 months) and end of FU (6 months). Chloroquine treatment given for all isolated fevers	Yes
Desai 2003	Fever ≥37.5°C	Any parasitaemia (*P. falciparum)* with fever or parasitaemia > 5000/mm^3 alone	Clinical malaria; any parasitaemia; hazard ratios for these; parasite density	3 months to end of treatment	Blood smears at baseline and every 4 weeks. Oral quinine given for any fever with parasitaemia and cases of severe malaria referred for further treatment	Yes
Esan 2013	No clinical definition	Any parasitaemia	All cause sick visits (including malaria),	3 months to end of treatment 6 months to end of FU	Routine trimethoprim - sulfamethoxazole prophylaxis	Yes
Fahmida 2007	Not stated	Not stated	Participants with "malaria" (used primarily as clinical malaria)	6 months to end of treatment	Not stated	No
Gebreselassie 1996	Fever ≥ 37.5°C with signs and symptoms suggestive of malaria and other	Presence of parasites in blood (all species, *P. falciparum* 88.9%)	Children with at least one episode of clinical malaria; cumulative incidence of parasitaemia; parasite density > 5000 µL (used as severe malaria); parasite density	3 months to end of treatment 6 months to end of FU	Blood smears negative at baseline and repeated weekly. Chloroquine with or without primaquine given for any positive smear	Yes

Table 4. Studies reporting malaria as an outcome: malaria definitions, types of outcomes and methods of surveillance and treatment in the trial *(Continued)*

	diagnoses ruled out					
Harvey 1989	Fever and headache at the same time	Any parasitaemia (*P. falciparum* 67%, *P. vivax* 26.4%, *P. malariae* 6.6%)	First episodes of clinically suspected malaria (used primarily as clinical malaria); any parasitaemia	4 months to end of treatment 6 months to end of FU	Blood smears for malaria obtained at 0, 6, 16, and 24 weeks. Chloroquine given for any illness reported as fever or headache, or both	Yes
Latham 1990	Not assessed	Any positive smear (malaria species not stated)	Any positive smear; parasite density	8 months to end of FU	Blood smears for malaria obtained at baseline and end of treatment. Treatment not stated	Yes
Lawless 1994	Child's recall of clinical illness	Any positive blood smear (malaria species not stated)	Malaria is not defined (used as clinical malaria)	3.5 months to end of treatment	No blood smears at baseline or during the trial (only at end of treatment). Treatment not stated	No
Leenstra 2009	Fever ≥ 37.5°C	Positive blood smear (malaria species not stated)	Episodes of clinical malaria and RRs adjusted for school; episodes of malaria parasitaemia and parasitaemia > 500 parasites/mm^3 (used as severe malaria) and RRs adjusted for school, age, and baseline parasitaemia	5 months to end of treatment	Blood smears for malaria at baseline (1/4 of participants positive) and monthly during the trial. No treatment offered for positive smears; symptomatic cases referred to physician	Yes
Massaga 2003	History of fever in the previous 24 to 72 hours or measured temperature of ≥ 37.5°C	Any level of parasitaemia (*P. falciparum* only)	Clinical malaria as first or only episode per participant (used as clinical malaria) and episodes of clinical malaria; episodes of clinical malaria associated with parasitaemia > 5000 parasites/µL (used as severe malaria)	6 months to end of treatment	Blood smears for malaria at baseline and every 2 weeks. Sulfadoxine-pyrimethamine treatment given for uncomplicated cases; complicated and severe malaria referred to the hospital	Yes
Mebrahtu 2004 (C)	Not assessed	Any positive smear (*P. falciparum* only)	Parasitaemia as OR (95% CI) adjusted for repeated measurements in each child	12 months to end of treatment	Blood smears for malaria at baseline and end of treatment. In addition, monthly smears from a random sample (50% of randomized). Treatment not stated	Yes
Menendez 1997	Fever ≥ 37.5°C	Parasitaemia of any density (*P. falciparum* only)	First or only episode of clinical malaria	1 year (6 months after end of treatment)	Blood smears for malaria at baseline, week 8 and for any fever. Chloroquine treatment given for clinical malaria	Yes

Table 4. Studies reporting malaria as an outcome: malaria definitions, types of outcomes and methods of surveillance and treatment in the trial *(Continued)*

Richard 2006	Any fever within the previous 72 hours	*P. falciparum* (29%) or *P. vivax* (71%), any density	Episodes of falciparum or vivax malaria, or both (used primarily as clinical malaria)	7 months to end of treatment	Blood smears for malaria at baseline and whenever febrile. Treatment given for all clinical cases	Yes
Sazawal 2006 (C)a	Fever > 38°C and	Parasitaemia > 1000 or history of fever and parasitaemia > 3000 or parasitaemia > 10,000 parasites/mm^3 regardless of fever (mostly *P. falciparum*)	Malaria-related adverse events, defined as hospital admission or death due to malaria (used primarily as clinical malaria). RRs with 95% CI adjusted for multiple events per child and clustering; cerebral malaria (used as severe malaria)	Not fixed. End of treatment about 1 year and end of FU about 18 months	No baseline or routine surveillance for malaria during the trial. Treatment given only if admitted to the hospital and malaria diagnosed	No
Sazawal 2006 (C)b	Fever > 38°C	Parasitaemia > 1000 or history of fever and parasitaemia > 3000 or parasitaemia > 10,000 parasites/mm^3 regardless of fever (mostly *P. falciparum*)	Malaria-related adverse events, defined as hospital admission or death due to malaria (used primarily as clinical malaria). RRs with 95% CI adjusted for multiple events per child and clustering; cerebral malaria (used as severe malaria)	Not fixed. End of treatment about 1 year and end of FU about 18 months	Blood smear for malaria at baseline, and at 6 and 12 months. Sulfadoxine-pyrimethamine treatment delivered to home to all slide-confirmed malaria participants or clinical disease presenting during the study	Yes
Smith 1989 (C)	Fever > 37.5°C	> 500 parasites/mm^3 (mostly *P. falciparum*)	Visits for clinical malaria; parasitaemia > 500/µL; fever with parasitaemia > 5000 parasites/mm^3 (used as severe malaria (all N events/N individuals, unadjusted for clustering)	3 months to end of treatment	Blood smear for malaria at baseline, 2 weeks and end of treatment. No treatment at baseline; clinical malaria referred to local healthcare services	No
Verhoef 2002	Axillary temperature ≥ 37.5°C	Dipstick test for *P. falciparum*	Number of children with malaria infection (used primarily as clinical malaria)	3 months to end of treatment	Dipstick for *P. falciparum* tested at baseline, 4, 8, and 12 weeks. Confirmed with blood smear if febrile and treated with sulfadoxine-pyrimethamine, amodiaquine or halofantrine	Yes
Zlotkin 2013 (C)	Axillary temperature ≥ 37.5°C	Parasitaemia of any density (mostly *P. falciparum)*	Incidence of clinical malaria, malaria with parasite density > 5000/µL, cerebral malaria	5 months to end of treatment 6 months to end of FU	Insecticide-treated bed nets supplied with instructions for use. Children with malaria treated with artemisinin combination therapy	Yes

Time of assessment: refers to time from randomization.
Abbreviations: FU, follow-up.

Table 5. Analysis of cluster randomized trials adjusting standard errors

Trial ID	Outcome	n Int reported	N Int reported	n Cont reported	N Cont reported	Average cluster size	DE	Unadjusted RR (95% CI)	ln(RR)	Unadjusted SE(lnRR)	Adjusted SE(lnRR)/ sample size
Adam 1997 (C)	Clinical malaria	72	366	49	372	Household (used 1.5)	1.34	1.49 (1.07 to 2.08)	0.40	0.17	0.20
Adam 1997 (C)	Parasitaemia	127	368	101	372	Household (used 1.5)	1.34	1.27 (1.02 to 1.58)	0.24	0.11	0.13
Adam 1997 (C)	Clinical malaria necessitating hospitalization	41	405	32	382	Household (used 1.5)	1.34	1.21 (0.78 to 1.88)	0.19	0.22	0.26
Mebrahtu 2004 (C)	Parasitaemia	—	307	—	307	1.5	1.34	OR 0.9 (0.72 to 1.19) Converted to RR 0.98	0.47	0.28	0.32
Mebrahtu 2004 (C)	High-grade parasitaemia	—	307	—	307	1.5	1.34	OR 1.04 (0.82 to 1.34) Converted to RR 1.03	0.03	0.12	0.14
Sazawal 2006 (C)a	Clinical malaria	467	7950	411	8006	1.4	—	**1.16 (1.00** to **1.34)**	**0.15**	—	**0.07**
Sazawal 2006 (C)a	Severe malaria (cerebral)	—	7950	—	8006	1.4	—	**1.32 (1.02** to **1.70)**	**0.28**	—	**0.13**
Sazawal 2006 (C)b	Clinical malaria	14	815	30	804	1.2	—	**0.46 (0.24 to 0.88)**	**-0.78**	—	**0.33**
Sazawal 2006 (C)b	Severe malaria (cerebral)	4	815	15	804	1.2	—	**0.26 (0.09** to **0.81)**	**-1.35**	—	**0.56**
Smith 1989 (C)	Clinical malaria	14	97	8	89	Household (used 1.5)	1.34	1.60 (0.42 to 0.71)	0.47	0.42	0.48
Smith 1989 (C)	Parasitaemia	28	97	16	89	Household (used 1.5)	1.34	1.61 (0.93 to 2.76)	0.47	0.28	0.32

Table 5. Analysis of cluster randomized trials adjusting standard errors *(Continued)*

Smith 1989 (C)	High-grade parasitaemia	17	97	11	89	Household (used 1.5)	1.34	1.42 (0.70 to 2.86)	0.35	0.13	0.15
Zlotkin 2013 (C)	Clinical malaria	338	966	392	989	Compounds	—	**0.87 (0.79 to 0.97)**	**-0.14**	—	**0.05**
Zlotkin 2013 (C)	Clinical malaria with high grade parasitaemia	273	966	308	989	Compounds	—	**0.89 (0.80 to 1.00)**	**-0.12**	—	**0.06**

Text in bold;results provided in publication or from authors adjusted for clustering.
Abbreviations: cont: control; DE: design effect used for adjustment (see methods for derivation of design effect and ICC used per outcome); Int: intervention; n: number of outcomes; N: number evaluated; OR: odds ratio; RR: risk ratio.

Table 6. Analysis of cluster randomized trials adjusting sample size

Study ID	Outcome	n Int reported	N Int reported	n Cont reported	N Cont reported	Average cluster size	DE	n Int adjusted	N Int adjusted	n Cont adjusted	N Cont adjusted
Adam 1997 (C)	Anaemia	364	368	357	374	Household (used 1.5)	1.4	260	263	255	267
Hall 2002 (C)	Anaemia	273	551	356	562	20	2.77	99	199	129	203
Mebrahtu 2004 (C)	All-cause mortality	0	340	2	344	1.5	1.001	0	340	2	344
Mebrahtu 2004 (C)	Anaemia	180	232	172	272	1.5	1.4	129	166	123	194
Roschnik 2003 (C)	Anaemia	133	224	110	203	30	3.70	36	61	30	55
Sazawal 2006 (C)a	All-cause mortality	149	7950	130	8006	1.4	1.001	149	7941	130	7996
Sazawal 2006 (C)b	All-cause mortality	8	815	9	804	1.2	1.0004	8	815	9	804
Sazawal 2006 (C)b	Anaemia	4	308	7	327	1.2	1.4	3	220	5	234
Zlotkin 2013 (C)	All-cause mortality	3	967	2	991	Compound	1.001	3	966	2	990

None of the trials provided results adjusted for clustering for the outcomes reported in the table.

Abbreviations: cont: control; DE: design effect used for adjustment (see methods for derivation of design effect and ICC used per outcome); Int: intervention; n: number of outcomes; N: number evaluated.

Table 7. Comparative malaria parasitaemia rates

Trial ID	Intervention	Unit of measurement	Iron	Control	No. iron	No. control	Favours
For prevention or treatment of anaemia							
Adam 1997 (C)	Iron versus placebo	Geometric mean, parasites/μL	15,059	8225	368 slides	372 slides	Control
Ayoya 2009	Iron versus placebo	Geometric mean, parasites/μL ± SD	2733 ± 1459	2648 ± 1562	105 children	97 children	Control
Berger 2000	Iron versus placebo	Geometric mean, RBC/mm^3	61.2	25.7	49 children with malarial index	39 children with malarial index	Controlor similar
Desai 2003	Iron plus antimalaria versus antimalaria Iron versus placebo (with single-dose antimalarial treatment)	Geometric mean, parasites/mm^3	1705 2569	2485 3778	129 children 127 children	127 children 108 children	Iron
Gebreselassie 1996	Iron versus placebo	Average parasite density class (parasite density classified in ascending order from 1 to 10)	5.2	5.0	239 children	241 children	Control or similar
Latham 1990	Iron versus placebo	Geometric mean, infected RBCs/100 WBC	4.8	1.9	28 children	26 children	Control
Mebrahtu 2004 (C)	Iron versus placebo	Geometric mean, parasites/μL (counting against 200 to 500 WBC, assuming 8000 WBC/μL	Age < 30 months 3402 Age > 30 months 2188	Age < 30 months 3422 Age > 30 months 2046	273 children (225 households)	265 children (225 households)	Similar
For treatment of malaria							
Nwanyanwu 1996	Iron daily plus antimalarial versus iron weekly plus antimalarial versus antimalarial	Mean, parasites/μL (counting against 300 WBC, assuming 6000 WBC/μL	4927 (daily) 2207 (weekly)	1812	77 (daily) 63 (weekly) children	75 children	Control

Table 7. Comparative malaria parasitaemia rates *(Continued)*

van den Hombergh 1996	Iron plus antimalarial plus folic acid versus antimalarial plus folic acid	Geometric mean, parasites/μL	5308	9302	48 children	47 children	Iron (at baseline groups unbalanced favouring placebo)

Abbreviations: RBC: red blood cell; WBC: white blood cell.

APPENDICES

Appendix 1. Analysis of cluster randomized controlled trials

Based on other trials included in this Cochrane review we assumed an average cluster size of 1.5 for households and 32 for classes, when the average cluster size or number of clusters and individuals were not reported (see 'Characteristics of included studies' tables, Table 5 and Table 6 for reported and assumed cluster sizes). The design effects (DEs) or intracluster correlation coefficients (ICCs) used for the different outcomes were the following.

- Malaria (Sazawal 2006 (C)a): unadjusted risk ratio (RR) 1.14 (confidence interval (CI) 1.01 to 1.30) (using number of events reported and number evaluated for clinical malaria), SE (ln RR) = 0.064391; adjusted RR 1.16 (CI 1.00 to 1.34) (reported in the publication for the same outcome), SE (ln RR) = 0.074661. DE = $(0.074661/0.064391)^2$ = 1.3444 for an average cluster size of 1.4 (households). All trials reporting on malaria-related outcomes used households as the unit of randomization and the same DE of 1.34 was used for all trials and all malaria-related outcomes.
- Deaths (Tielsch 2006): unadjusted RR 1.04 (0.80 to 1.34), SE (ln RR) = 0.131585; adjusted RR 1.03 (0.78 to 1.37), SE (ln RR) = 0.143692. DE = $(0.143692/0.131585)^2$ = 1.192481 for an average cluster size of 82 (sectors), ICC = 0.002. The DE adjusted for a cluster size of 1.5 (household) was 1.001.
- Anaemia (Kaiser 2006). We expected a significant ICC between children in the same household (given their similar nutritional status and infection incidences) and a lower degree of clustering at the community level. However, we did not find ICC estimates in the literature for these units and the cluster RCTs included in the review did not provide data that allowed us to calculate DE or ICC. Ngnie-Teta 2007 reported that the degree of community-level clustering with regard to moderate to severe anaemia among Beninese and Malian children was 0.14 to 0.19. Assuncao 2007 reported an ICC of 0.07 and a DE of 2.5 in a cluster survey of all children under six years of age, where clusters of about 30 children comprised several households each. Kaiser 2006 reported the design effects (DE) between 1.4 and 2.4 for anaemia < 11 g/dL in three cluster surveys in Afghanistan and Mongolia (DEs between 1.4 and 2.4), which allowed us to calculate ICCs of between 0.093 and 0.100. We used a DE of 1.4 for trials that used households as the unit of randomization and an ICC value of 0.093 to calculate the DE of trials using larger units of randomization (DE range 2.8 to 3.9). The ICC for haemoglobin, though measuring the same thing, is much smaller because it is a more precise measure. We used an ICC of 0.000 for households and 0.00271 for large clusters (school or class) based on values reported for households and the district health authority level, respectively, although these values refer to adults in England (Gulliford 1999).
- Diarrhoea (Kaiser 2006). The pooled design effect from five observational studies in Kaiser 2006 was 3.1, for an average cluster size of 17, the ICC value was 0.131. The DE adjusted for a cluster size of 1.5 was 1.065.
- Infectious episodes: we calculated a DE of 1.36 from the Sazawal 2006 (C)a study that reported both raw numbers and adjusted RR/SE.

WHAT'S NEW

Date	Event	Description
30 August 2015	New search has been performed	We updated the literature search.
30 August 2015	New citation required but conclusions have not changed	New author team; we amended the inclusion and exclusion criteria; and significantly restructured the analyses.

HISTORY

Protocol first published: Issue 3, 2007
Review first published: Issue 3, 2009

Date	Event	Description
6 August 2009	Amended	**Error in data for graph corrected for Issue 4, 2009:** thanks to an observant reader, we identified a log conversion error for the analysis of hospitalizations and clinic visits in comparison 1. This has been corrected in Issue 4, 2009.

CONTRIBUTIONS OF AUTHORS

First edition

JUO conceived the idea for the review, wrote the protocol, identified studies for inclusion and exclusion, extracted the data, entered the data in RevMan (RevMan 2014), participated in the data analysis, and reviewed all the drafts of the first edition of this review.

Joseph Okebe (JO) wrote the protocol, identified studies for inclusion and exclusion, extracted the data, entered data in RevMan (RevMan 2014), participated in the data analysis, and reviewed all the drafts and the final review.

DY extracted the data from all included studies, entered data in RevMan (RevMan 2014), participated in the data analysis, and reviewed all drafts and the final review.

Mical Paul (MP) planned the data extraction, extracted the data, entered data in RevMan (RevMan 2014), participated in the data analysis, and wrote the review.

All review authors approved the final publication.

2011 edition

MP updated the RevMan file (RevMan 2014), reorganized previous data, carried out the subgroup analyses, performed the GRADE classifications, wrote the final version of the update, and revised the final manuscript.

Rana Shbita (RS) performed the search for the 2011 update and identified studies for inclusion and exclusion, extracted the data for the new studies, participated in the data analysis, and reviewed all the drafts and the final review. This work was performed in partial fulfilment of RS Master in Epidemiology,

DY performed the search for the 2011 update, extracted the data for the new studies, performed the GRADE classifications, and revised the final manuscript.

2015 edition

AM identified studies for inclusion and exclusion, extracted the data for the new studies, entered data in RevMan (RevMan 2014), performed data analysis, and wrote the final version of the update.

MP updated the RevMan file (RevMan 2014), reorganized previous data, carried out the subgroup analyses, performed the GRADE classifications, co-wrote the final version of the update, and revised the final manuscript.

DY and JO performed the search for the 2015 update, and revised the final manuscript.

All review authors listed approved the revised publication.

DECLARATIONS OF INTEREST

AM has no known conflicts of interest.
JO has no known conflicts of interest.
DY has no known conflicts of interest.
MP has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department of Nutrition for Health and Development, World Health Organization, Switzerland.
- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the original protocol and review

- We moved parasitaemia was moved from the primary to secondary outcomes.
- We removed protocol-defined secondary outcomes on iron levels, ferritin levels, total iron binding capacity (TIBC), zinc protoporphyrin concentration and zinc. We extracted these outcomes but reporting was sparse

- We conducted post hoc subgroup analyses by malaria surveillance and treatment.

Differences between previous review versions and 2011 update

- We completely separated comparisons of iron versus placebo/no treatment and iron plus folic acid versus placebo/no treatment.
- We separated analyses of severe malaria by definition of this outcome.
- Trials that did not report any of the review-defined outcomes were excluded.
- We added new trials and reclassified trials awaiting assessment.
- We added stratification for anaemia at baseline based on mean haemoglobin in the control group rather than on the percentage of children with anaemia in the trial and subgroup analyses by anaemia at baseline.
- Sensitivity analyses that considered only *P. falciparum* in malaria-related outcomes were added.
- Juliana Okwuru stepped down from her role as a review author.

Differences between the 2011 update and the current update

- We limited our analyses to areas with hyperendemic or holoendemic transmission of malaria.
- We included studies that reported iron fortification as well as iron supplementation, as long as it provided at least 80% of the Recommended Dietary Allowance (RDA) recommended by the WHO for prevention of anaemia by age (Types of interventions).

INDEX TERMS

Medical Subject Headings (MeSH)

*Endemic Diseases; Anemia, Iron-Deficiency [etiology] [*prevention & control]; Antimalarials [administration & dosage]; Dietary Supplements [adverse effects]; Folic Acid [adverse effects]; Iron [*administration & dosage] [adverse effects]; Malaria [chemically induced] [*complications]; Parasitemia [chemically induced] [complications]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Humans