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

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[Intervention Review]

Oral iron supplements for children in malaria-endemic areas

Michael Itzkovich[1,2], Ami Neuberger[3], Itai Harris[4,5], Dafna Yahav[1,5], Mical Paul[3], Mayan Gilboa[5,6a]

[1]Infectious Diseases Unit, Sheba Medical Center, Ramat Gan, Israel. [2]First Faculty of Medicine, Charles University, Prague, Czech Republic. [3]Division of Infectious Diseases, Rambam Health Care Campus and The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel. [4]Internal Medicine C, Sheba Medical Center, Ramat Gan, Israel. [5]Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel. [6]Infection Prevention and Control Unit, Sheba Medical Center, Ramat Gan, Israel

[a]ORCID iD: https://orcid.org/0000-0003-1754-7750

Contact: Mical Paul, paulm@technion.ac.il.

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ABSTRACT

Rationale

Iron deficiency anaemia is a common nutritional disorder among children in malaria-endemic regions and is associated with adverse developmental and health outcomes. However, concerns have been raised that iron supplementation might increase the risk of malaria by enhancing parasite growth, particularly in areas lacking adequate malaria prevention and treatment services.

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, where malaria is intense and occurs year-round.

Search methods

We searched CENTRAL (Wiley), MEDLINE (Ovid), Embase (Ovid), and Global Index Medicus (WHO) up to 30 April 2024. We also searched two trial registries, ClinicalTrials.gov and WHO ICTRP, to 30 April 2024. We conducted a top-up search on 20 May 2025. We contacted trial investigators and scanned references of included trials and reviews for relevant studies.

Eligibility criteria

We included individual and cluster-randomised controlled trials (RCTs) conducted in malaria-endemic regions that enrolled children under 18 years of age. We included trials that compared: (1) oral iron alone versus placebo or no treatment; (2) oral iron plus folic acid versus placebo or no treatment; (3) oral iron (with or without folic acid) versus placebo or no treatment, grouped by malaria prevention and management services for the outcome of clinical malaria only; and (4) oral iron plus antimalarial treatment versus placebo or no treatment. Iron or fortified interventions had to provide ≥ 80% of age-appropriate Recommended Dietary Allowance (RDA). Antihelminthics and micronutrients other than iron and folic acid had to be administered equally to both groups.

Outcomes

The critical outcomes were clinical malaria, severe malaria, and death from any cause. Important outcomes included hospitalisations and clinic visits.

Risk of bias

We assessed risk of bias in the included trials using the Cochrane RoB 1 tool.

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Synthesis methods

We used fixed-effect meta-analysis (Mantel-Haenszel or generic inverse variance) and adjusted for clustering in cluster-RCTs. For haemoglobin and anaemia outcomes, we applied a random-effects model due to anticipated heterogeneity. We assessed the certainty of evidence using GRADE and explored heterogeneity through subgroup analysis.

Included studies

Forty trials (33,785 children) met the inclusion criteria.

Synthesis of results

Iron versus placebo/no treatment

Iron results in little or no difference in the risk of clinical malaria (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.87 to 1.00; 16 trials, 7843 children; high-certainty evidence) and reduces the risk of severe malaria slightly (RR 0.90, 95% CI 0.81 to 0.98; 5 trials, 3421 children; high-certainty evidence). Iron may result in little or no difference in mortality (RR 1.15, 95% CI 0.76 to 1.74; 20 trials, 8809 children; low-certainty evidence) and hospitalisations or clinic visits (RR 0.99, 95% CI 0.95 to 1.04; 10 trials, 14,011 children; low-certainty evidence).

Iron plus folic acid versus placebo/no treatment

The evidence for this comparison comes largely from one large trial (Pemba) plus four smaller trials (19,456 children). Clinical malaria was not reported. Iron plus folic acid may result in little to no difference in severe malaria requiring admission (RR 1.11, 95% CI 0.96 to 1.28; 2 trials, 17,575 children; low-certainty evidence); all-cause mortality (RR 1.13, 95% CI 0.90 to 1.42; 5 trials, 18,034 children; low-certainty evidence); and hospitalisations (RR 1.08, 95% CI 0.96 to 1.22; 1 trial, 15,956 children; low-certainty evidence).

Iron (with or without folic acid) versus placebo/no treatment; grouped by presence or absence of malaria prevention and management services

We also grouped trials by the presence of malaria prevention and management services, analysing 19 trials (25,531 children). In areas with services, iron (with or without folic acid) may reduce clinical malaria slightly (RR 0.91, 95% CI 0.84 to 0.97; 12 trials, 5777 children; low-certainty evidence). In areas without services, iron (with or without folic acid) may increase clinical malaria slightly (RR 1.15, 95% CI 1.02 to 1.30; 7 trials, 19,754 children; low-certainty evidence). Overall, when not grouping by presence of malaria prevention and management services, iron supplementation (with or without folic acid) may have little to no effect on clinical malaria (RR 0.96, 95% CI 0.91 to 1.03; 19 trials, 25,531 children; low-certainty evidence).

Iron plus antimalarial prophylaxis versus placebo/no treatment

Adding iron to antimalarial prophylaxis results in a large reduction in clinical malaria (RR 0.54, 95% CI 0.43 to 0.67; 3 trials, 728 children; high-certainty evidence); likely results in a large reduction in hospitalisations and clinic visits (RR 0.85, 95% CI 0.81 to 0.89; 2 trials, 5976 child-months; moderate-certainty evidence); and may not reduce all-cause mortality (RR 1.05, 95% CI 0.52 to 2.11; 3 trials, 728 children; low-certainty evidence). Severe malaria was not reported for this comparison.

Authors' conclusions

Iron treatment results in little to no difference in the risk of clinical malaria (high-certainty evidence). Where resources are limited, iron can be administered without screening for anaemia or iron deficiency, as long as malaria prevention or management services are provided efficiently. Where resources for the prevention and treatment of malaria are limited, iron may increase the risk of clinical malaria (low-certainty evidence). These conclusions are consistent with those reported in the previous version of this review (2016).

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Registration

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PLAIN LANGUAGE SUMMARY

What are the benefits and risks of iron supplements for children living in malaria-endemic areas?

Key messages

- Iron supplements do not increase the risk of malaria in children when malaria prevention and management services are available.
- Iron supplements may slightly increase the risk of malaria in areas without malaria prevention and management services, but the increased risk is small.
- Future studies are needed to better understand which groups of children benefit most, whether folic acid changes the effects of iron, and how to safely deliver iron in settings with limited malaria services.

What are anaemia and malaria?

Anaemia is a condition where the body does not have enough healthy red blood cells to carry oxygen to its tissues. It is often caused by a lack of iron in the diet, leading to symptoms like tiredness, weakness, and poor growth and development in children.

Malaria is a serious disease caused by parasites transmitted to people through the bites of infected mosquitoes. It is common in many tropical and subtropical regions. Symptoms include fever, chills, and flu-like illness, and it can be life-threatening if not treated promptly.

In areas where malaria is endemic, meaning it is constantly present and occurs at a relatively stable and predictable rate throughout the year, there has been concern that giving iron supplements to children might increase their risk of getting malaria. This is because the malaria parasite needs iron to grow, so higher iron levels in the blood could potentially help the parasite. However, anaemia can weaken the immune system, making children more susceptible to infections, including malaria.

What did we want to find out?

We wanted to find out whether giving iron supplements to children living in malaria-endemic areas is safe and effective. Specifically, we aimed to determine whether providing iron supplements to children in malaria-endemic areas affects the risk of:

- clinical malaria (defined as fever and malaria parasites in the blood);
- severe malaria (a more dangerous form of the disease that may cause coma, severe anaemia, or organ failure);
- death; and
- hospitalisations or clinic visits.

What did we do?

We searched for studies that looked at giving iron supplements (with or without folic acid) to children under 18 years old living in areas with high malaria transmission. This included all studies from the 2016 version of the review as well as newly identified studies. We included studies that compared iron supplements to a placebo (dummy pill) or no treatment. We also included studies looking at giving iron along with antimalarial treatment.

We found 40 studies involving 33,785 children. We compared and summarised the results of the studies and rated our confidence in the evidence based on study methods and sizes.

What did we find?

- Iron treatment results in little to no difference in clinical malaria; slightly reduces the risk of severe malaria; and may result in little to no difference in death or hospitalisations and clinic visits.
- Iron with folic acid may result in little to no difference in severe malaria, death, and hospitalisations.
- In areas with good malaria prevention and management that includes mosquito nets, spraying to reduce mosquito populations, and access to testing and treatment, iron may reduce the risk of clinical malaria. In areas where such resources are not available, iron may increase the risk of clinical malaria.
- Iron combined with malaria prophylaxis greatly reduces clinical malaria; may not reduce the risk of death; and probably reduces hospitalisations and clinic visits.

What are the limitations of the evidence?

Our confidence in the evidence varied. We are confident that oral iron supplements do not increase the risk of clinical or severe malaria. In cases where our confidence was limited, studies did not provide detailed information about how they were conducted, making it hard to know if their findings are reliable. In areas without malaria prevention and management services, the evidence is less certain because it is based mainly on a single large study. Finally, we have limited information about the effects of combining iron with folic acid.

How up-to-date is the evidence?

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The evidence is current to 20 May 2025.

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Summary of findings 1. Oral iron versus placebo or no treatment for children in malaria-endemic areas; malaria prevention either present or absent in all arms

Oral iron versus placebo or no treatment for children in malaria-endemic areas; malaria prevention either present or absent in all arms

Participant or population: children in malaria-endemic areas; malaria prevention either present or absent in all arms
Setting: areas which are malaria-endemic, and where children may benefit from iron treatment
Intervention: iron
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect results (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with iron supplementation				
Clinical malaria	349 per 1000	325 per 1000 (304 to 349)	RR 0.93 (0.87 to 1.00)	7843 (16 RCTs)	⊕⊕⊕⊕ High[a]	Iron results in little to no difference in risk of clinical malaria.
Severe malaria Defined as clinical malaria with high-grade parasitaemia or requiring admission	311 per 1000	280 per 1000 (252 to 305)	RR 0.90 (0.81 to 0.98)	3421 (5 RCTs)	⊕⊕⊕⊕ High	Iron supplementation slightly reduces the risk of severe malaria.
All-cause mortality	9 per 1000	9 per 1000 (9 to 9)	RR 1.15 (0.76 to 1.74)	8809 (20 RCTs)	⊕⊕⊖⊖ Low[b]	Iron may result in little to no difference in all-cause mortality.
Hospitalisation and clinic visits	60 per 1000	59 per 1000 (57 to 62)	RR 0.99 (0.95 to 1.04)	14,011 (10 RCTs)	⊕⊕⊖⊖ Low[c,d]	Iron may result in little to no difference in hospitalisations and 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).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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

[a]Funnel plot asymmetry favouring the control arm, publication bias not suspected, as the asymmetry is in the opposite direction to that expected with positive-result publication bias. The CIs range from important benefits of iron supplementation in reducing clinical malaria to no excess of clinical malaria.
[b]Downgraded by one level for imprecision: although the CI is narrow, the total number of events is low. Downgraded by one level for suspected publication bias due to lack of publication of negative trials.
[c]Study population and number of participants expressed as child-months.
[d]Downgraded by one level for inconsistency and one level for indirectness of the outcome. Hospitalisations and clinic visits do not necessarily reflect the burden of malaria.

Summary of findings 2. Summary of findings table - Oral iron with folic acid compared to placebo or no treatment for children in malaria-endemic areas; malaria prevention either present or absent in all arms

Oral iron with folic acid compared to placebo or no treatment for children in malaria-endemic areas; malaria prevention either present or absent in all arms

Patient or population: children in malaria-endemic areas; malaria prevention either present or absent in all arms
Setting: areas which are malaria-endemic, and where children may benefit from iron treatment
Intervention: oral iron with folic acid
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with oral iron with folic acid				
Clinical malaria - not reported	-	-	-	-	-	None of the studies included in the comparison assessed this outcome.
Severe malaria (malaria requiring admission)	50 per 1000	**56 per 1000** (64 to 48)	**RR 1.11** (0.96 to 1.28)	17575 (2 RCTs)[a]	⊕⊕⊖⊖ Low[b]	The evidence suggests that oral iron with folic acid may result in little to no difference in severe malaria.
All-cause mortality	15 per 1000	**15 per 1000** (from 15 to 5)	**RR 1.13** (0.90 to 1.42)	18034 (5 RCTs)	⊕⊕⊖⊖ Low[c]	The evidence suggests that oral iron with folic acid may result in little to no difference in all-cause mortality.
Hospitalisations and clinic visits	104 per 1000	**113 per 1000** (127 to 100)	**RR 1.08** (0.96 to 1.22)	15956 (1 RCT)	⊕⊕⊖⊖ Low[d]	The evidence suggests that oral iron with folic acid may result in little to no difference in hospitalisations.

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

CI: confidence interval; **RR:** risk ratio

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_459703790847773165.

[a] Malaria-related outcomes were based on a single cluster trial (Sazawal 2006a; Sazawal 2006b). The trial was discontinued early for harm, and it was at high risk of recruitment bias because participants could be added after randomisation (post-randomisation recruitment).
[b] Downgraded by one level for inconsistency: substantial heterogeneity (I^2 = 87%) with opposing directions of effect between the included studies. Downgraded by one level for imprecision: the CI crosses the line of no effect and includes the possibility of an important increase in risk.
[c] Downgraded by one level for imprecision due to the low total number of events. Downgraded by one level for risk of bias.
[d] Downgraded by one level for imprecision: single study with CI crossing no effect and including the possibility of a potentially important increase in risk. Downgraded by one level for indirectness, as hospitalisations and clinic visits do not necessarily reflect the burden of malaria.

Summary of findings 3. Oral iron with or without folic acid versus placebo for children in malaria-endemic areas; grouped by presence or absence of malaria prevention in both arms

Oral iron with or without folic acid versus placebo for children in malaria-endemic areas; grouped by presence or absence of malaria prevention in both arms

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect results (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with iron supplementation				
Clinical malaria	10 per 1000	10 per 1000 (9 to 10)	RR 0.96 (0.91 to 1.03)	25,531 (19 RCTs)	⊕⊕⊖⊖ Low[a]	Overall, iron supplementation may have little to no effect on clinical malaria.

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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)	5777 (12 RCTs)	⊕⊕⊖⊖ Low[b]	In areas where there are prevention and management services for malaria, iron supplementation may slightly reduce the risk of clinical malaria.
	24 per 1000	22 per 1000 (20 to 23)				
	Malaria prevention or management services not present		RR 1.15 (1.02 to 1.30)	19,754 (7 RCTs)	⊕⊕⊖⊖ Low[c]	In areas where there are no prevention and management services for malaria, iron may slightly increase the risk of clinical malaria.
	6 per 1000	7 per 1000 (6 to 8)				
Severe malaria	-	-	-	-	-	There are no data for this outcome in this comparison.
All-cause mortality	-	-	-	-	-	There are no data for this outcome in this comparison.
Hospitalisations and clinic visits	-	-	-	-	-	There are no data for this outcome in this comparison.

*__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).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

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

[a]Downgraded by one level for inconsistency (statistically significant subgroup differences; $I^2 = 47\%$), and one level for funnel plot asymmetry and suspected publication bias.
[b]Downgraded by one level for inconsistency and one level for suspected publication bias (fewer than 10 trials contributed to some subgroup analyses, so small-study effects and reporting bias could not be ruled out).
[c]Downgraded by one level for indirectness, since the analysis is dominated by Sazawal 2006a (C), which assessed only admissions for malaria resulting in a spuriously low event rate, and one level for funnel plot asymmetry and suspected publication bias.

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Summary of findings 4. Oral iron with antimalarial prophylaxis versus placebo or no treatment for children in malaria-endemic areas; malaria prevention present in the intervention arm only

Oral iron with antimalarial prophylaxis versus placebo or no treatment for children in malaria-endemic areas; malaria prevention present in the intervention arm only

Participant or population: children in malaria-endemic areas; malaria prevention present in the intervention arm only
Settings: areas which are malaria-endemic, and where children may benefit from iron treatment
Intervention: oral iron supplement plus antimalarial

Comparison: placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no treatment	**Iron supplementation** plus **antimalarial**				
Clinical malaria	410 per 1000	220 per 1000 (180 to 280)	RR 0.54 (0.43 to 0.67)	728 (3 RCTs)	⊕⊕⊕⊕ High[a,b]	Iron given together with antimalarial antimicrobials results in a large reduction in clinical malaria.
Severe malaria - not reported	-	-	-	-	-	None of the studies included in the comparison assessed this outcome.
All-cause mortality	42 per 1000	44 per 1000 (23 to 85)	RR 1.05 (0.52 to 2.11)	728 (3 RCTs)	⊕⊕⊖⊖ Low[c]	Iron given together with antimalarial antimicrobials may not reduce mortality.
Hospitalisations and clinic visits	665 per 1000[d]	572 per 1000 (330 to 580)	RR 0.85 (0.81 to 0.89)	5976 child-months (2 RCTs)	⊕⊕⊕⊖ Moderate [d,e]	Iron given together with antimalarial antimicrobials likely results in a large reduction in hospitalisations and clinic visits.

*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).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

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

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

[a]All trials were individually randomised, with adequate concealment, double-blind, and no loss to follow-up.
[b]We measured heterogeneity as P = 0.08, I^2 = 60%, but all trials point in the same direction.
[c]We downgraded by two levels for imprecision: very small number of events (29 total across 3 trials) and wide CI including important benefit and important harm (RR 1.05, 95% CI 0.52 to 2.11).
[d]Study population and number of participants expressed as child-months.
[e]Downgraded by one level for indirectness. Hospitalisations and clinic visits do not necessarily reflect the burden of malaria.

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BACKGROUND

Description of the condition

Childhood anaemia and iron deficiency

Iron deficiency anaemia is widespread in low-income settings, especially sub-Saharan Africa, affecting about 60% of children aged nine months to three years [1, 2, 3]. Major causes include nutritional inadequacy, infections (notably malaria), helminths, and genetic conditions [2, 4]. Iron is essential for haemoglobin and neurological development [5, 6, 7], but only ~1 to 2 mg/day is absorbed from the diet, while ~20 to 25 mg/day is required for erythropoiesis [7, 8, 9]. Globally, ~1900 million people had anaemia in 2021, causing ~52 million years lived with disability; ~85% of this burden is iron-related [10, 11]. Iron deficiency has been associated with impaired growth, cognition, immunity, and increased infection risk [[5], [6], [7], [8]].

Diagnosing iron deficiency is complex in malaria-endemic regions. Ferritin is elevated in inflammation, which is common in such settings, leading many experts and the World Health Organization (WHO) to recommend measuring ferritin alongside inflammatory markers or using alternative biomarkers [12, 13, 14]. Given the overlapping burden of anaemia and malaria in many low-income regions, concerns have been raised that iron supplementation might increase malaria risk in children. These concerns, which form the basis of this review, are discussed in detail below.

Malaria and iron deficiency

Malaria is a leading cause of morbidity and mortality in children in sub-Saharan Africa [15, 16]. In 2022, an estimated 249 million malaria cases occurred globally, with ~608,000 deaths, more than 90% of them in Africa, mostly in children under five years of age [16], with *Plasmodium falciparum* being the predominant species [17]. Malaria is an important contributor to anaemia in endemic regions through the destruction of parasitised 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 likely also decreased absorption of dietary iron [18, 19, 20].

There is an ongoing debate about whether iron deficiency offers protection from malaria, and whether an excess of iron increases the risk of malaria or severe malaria [21, 22, 23, 24, 25]. Iron is required by many pathogens for their survival and pathogenicity [8]. 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' [26]. The erythrocytic form of the *Plasmodium* parasite requires free iron (which is lacking in an iron-deficient person) [27]. In one observational study, iron deficiency was associated with a 50% protection from clinical malaria in a cohort of preschool children in Malawi [28], and in another observational study, asymptomatic malaria was attributed to 61% of anaemia in schoolchildren in a hyperendemic region [29].

Description of the intervention and how it might work

In areas where the prevalence of anaemia is 40% or more in young children, international guidelines such as those issued by the WHO 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 [30, 31].

Several meta-analyses have previously examined the benefits and risks of iron supplementation in children [21, 32, 33, 34, 35, 36, 37]. 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 [35, 36]. While oral iron supplementation is generally well-tolerated, it may cause gastrointestinal side effects such as nausea, abdominal discomfort, constipation, or diarrhoea [38].

In populations living in malaria-endemic regions, there have been concerns that increased iron availability could enhance susceptibility to infections such as malaria, due to the role of iron in parasite growth. Several meta-analyses have highlighted a possible increased risk of malaria. Most studies reported parasitaemia (defined as the presence of *P falciparum* on a blood slide at the end of supplementation) rather than clinical malaria [21, 32, 33, 34]. The effect of iron on parasitaemia appeared to be influenced by the baseline prevalence of parasitaemia [33]. In the same analysis [33], other infections were also assessed. Overall, there was no difference in the incidence rate ratio for all recorded infections, although diarrhoea was more frequently reported in the iron-supplemented group.

Why it is important to do this review

In 2006, the results of a large randomised controlled trial (RCT) that evaluated the effect of iron and folate supplements in a malaria-endemic area of Zanzibar (Pemba Island) were published (Sazawal 2006a (C) [39, 40]). The study was terminated prematurely on the recommendation of the study data safety and management board following the higher proportion of hospitalisation or death among participants randomised 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 from the general recommendations [41]. In 2007, a consultation was convened to consider the recommendations for children living in malaria-endemic areas [42]. 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 [12, 13, 43, 44]. Furthermore, as a public health intervention, screening of all children before iron supplementation is impractical in most malaria-endemic areas. It has thus 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 for all participants, and antimalarial treatment was systematically administered when indicated (Zlotkin 2013 (C) [45, 46, 47, 48]). The

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use of iron in this trial did not result in an increased incidence of malaria among participants. These conflicting findings highlighted the need for further synthesis of the evidence.

This is an update of a Cochrane review first published in 2009 [49] and previously updated in 2016 [50]. In the 2016 update, we found high-certainty evidence that oral iron supplements do not adversely affect children living in malaria-endemic areas, and that further research was unlikely to change our confidence in this conclusion. Nonetheless, several new trials have been published since then, and previously included studies have had new data released or reclassified. As a result, this update aimed to incorporate the most complete and current evidence available.

As in the 2016 update [50], the current version of the review focuses on trials conducted in areas with hyperendemic or holoendemic malaria transmission – settings where malaria occurs intensely and year-round. We specifically sought to compare the effects of iron supplementation on clinical malaria and all-cause mortality, stratified by the presence or absence of malaria prevention and treatment services within the trial design.

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, where malaria is intense and occurs year-round.

METHODS

We followed the Methodological Expectations of Cochrane Intervention Reviews (MECIR) [51] for conducting the review and adhered to the PRISMA 2020 [52] guidelines for reporting.

Differences between the original protocol and review

- We moved parasitaemia from the critical to important outcomes.
- We removed protocol-defined secondary outcomes for 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 using malaria surveillance and treatment.

Differences between previous review versions and the 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 the definition of this outcome.
- We excluded trials that did not report any of the review-defined outcomes.
- We added new trials and recategorised trials awaiting classification.
- 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.
- We added sensitivity analyses that considered only *P falciparum* in malaria-related outcomes.
- Juliana Okwuru stepped down from her role as a review author.

Differences between the 2011 update and 2016 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).

Differences between the 2016 update and the current update

- We added new trials and recategorised trials awaiting classification.
- We introduced the use of the GRADE approach to assess the certainty of the evidence.
- For the main outcomes of the analysis, comparing oral iron versus placebo or no treatment for children in malaria-endemic areas, we used the largest study (Zlotkin 2013 (C)), which had a weight of 45.4% in this analysis, for calculating the anticipated absolute effect. This approach was adopted to provide a more precise estimation of the absolute effect size based on the most substantial available evidence. The method for calculating relative effect results remained unchanged.
- We combined the clinical visits and hospitalisations into one outcome.
- Joseph Okebe stepped down from his role as a review author.

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that randomised individuals or clusters, and were conducted in countries defined as hyperendemic or holoendemic for malaria ([53]; Table 1). 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. Cluster-RCTs were eligible only if they included at least two units per trial arm. We excluded trials conducted in hypoendemic and mesoendemic areas. In addition, we excluded studies that did not report at least one of the review-defined critical or important 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.

If a study included a mixed population (e.g. adults or pregnant women), we included the study only if data for eligible participants (i.e. non-pregnant children under 18) were reported separately or could be obtained from the authors. If separate data were not available, the study was excluded.

Types of interventions

Intervention

- Iron
- Iron plus folic acid

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- Iron plus antimalarial treatment

Control

- Placebo
- No treatment

We only included trials that allocated antiparasitics or other micronutrients (e.g. 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 is provided at least 80% of the RDA recommended by the WHO for prevention of anaemia by age (Table 2; [30]). 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 [54]. 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 with or without folic acid versus placebo or no treatment grouped by malaria prevention services
- Iron plus antimalaria versus placebo or no treatment

Outcome measures

We included studies that reported one or more of the review-defined outcomes at the end of treatment or at the latest follow-up point, as specified by the trial authors. When outcomes were reported at multiple time points, we extracted data from the longest follow-up available, unless otherwise justified.

To count outcomes such as infectious episodes, clinic visits, or hospitalisations, we extracted or calculated rates per child-months, defined as the total number of months each child was under observation, summing across all children in the study. This allows for the normalisation of event counts over differing follow-up durations across trials.

Critical outcomes

- Clinical malaria: uncomplicated malaria, defined as a history of fever with parasitological confirmation [55]. We included cases of severe malaria if they were not reported separately.
- Severe malaria: cerebral malaria or acute *P falciparum* malaria with signs of severity, or evidence of vital organ dysfunction, or both [55]. If defined differently, we extracted the outcome as reported in the trial and used the trial authors' definitions.
- Death from any cause.

Important outcomes

- Hospitalisations and clinic visits for any cause.
- Malaria parasitaemia: any level of parasitaemia, and above a specific threshold as used in the study to define high-grade parasitaemia.
- Malaria parasite density.
- Haemoglobin levels and change in haemoglobin from baseline.
- 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-months.
- Weight, absolute values.
- Height, absolute values.

We excluded studies that did not report at least one of the review-defined critical or important 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). We contacted six primary investigators of included, ongoing, or awaiting-classification trials; all responded, but no additional data were obtained [56]. Supplementary material 1, Table 3

Electronic searches

Databases

The Information Specialist of the Cochrane Infectious Diseases Group (CIDG) editorial base, Vittoria Lutje, conducted the searches. We searched the following databases using the detailed search terms and strategies described in Supplementary material 1 and Table 3.

- Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Library (Wiley), Issue 4 of 12, searched on 30 April 2024, and updated on 20 May 2025.
- MEDLINE, via Ovid (1946 to 30 April 2024; updated on 20 May 2025).
- Embase, via Ovid (1947 to 30 April 2024; updated on 20 May 2025).
- Global Index Medicus (searched on 30 April 2024; not updated in May 2025).
- ClinicalTrials.gov (clinicaltrials.gov) (searched on 30 April 2024; updated on 20 May 2025).
- WHO International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int) (searched on 30 April 2024; updated on 20 May 2025).

Searching other resources

Researchers, organisations, and pharmaceutical companies

We contacted the primary investigators of the included trials, ongoing trials, and those awaiting classification to enquire about 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

We extracted the following data for each included study: study design, setting, inclusion and exclusion criteria, participant characteristics (age, sex, baseline haemoglobin and iron status), intervention details (formulation, dosage, frequency, duration, and whether co-supplementation with folic acid or antimalarial drugs was given), comparison group details, malaria transmission intensity in the study setting, outcomes reported (including

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definitions and measurement time points), methods of outcome assessment, number of participants randomised and analysed per outcome, length of follow-up, losses to follow-up, and funding sources.

Selection of studies

Several review authors (JO, DY, JO, and MP for the first version of this Cochrane review [49]; RS, DY, JO, and MP for the second version [57]; AN, JO, and MP for the third version; and MG, MI, IH, DY, and MP for this review update) independently inspected the abstract of each identified reference and obtained the full-text reports of relevant articles. At least two review authors independently reviewed each article and applied the inclusion criteria. If needed, we contacted the study authors to clarify study eligibility. Any disagreements were resolved by discussion with a third review author (MP, DY). Each trial was scrutinised to identify multiple publications from the same data set. We documented the reasons for exclusion of excluded studies. We named studies by the first author and year of publication (with the addition of a and b, for different studies by the same author and year of publication). The addition of (C) to the trial's identification denotes that the trial was cluster randomised.

We used Rayyan [58], a web-based tool, to manage and screen search results exported from MEDLINE (Ovid), Embase (Ovid), CENTRAL, and WHO Global Index Medicus. We used Rayyan's de-duplication feature to identify and remove duplicate records. Two review authors independently screened titles and abstracts using Rayyan's blinding feature and categorised studies as included, excluded, or unresolved. Any disagreements were resolved through discussion among review authors.

Data extraction and management

Two review authors (MG and MI) independently extracted data into a piloted data extraction spreadsheet that detailed relevant epidemiological and clinical data. Any differences in the data extraction were resolved by discussion with a third review author (MP or DY). Two review authors (MG and MI) entered data into RevMan [59].

For individual 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 (e.g. 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. When 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 haematocrit or packed cell volume values by 0.34, when a trial did not report haemoglobin values.

For cluster-RCTs, we recorded the unit of randomisation (e.g. 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 in Unit of analysis issues).

All extracted data, including subgroup variables and outcomes, and the full analytic dataset, including subgroup comparisons and sensitivity analyses, are provided in Supplementary material 6.

Risk of bias assessment in included studies

Three review authors (MG, MI, and IH) independently assessed the risk of bias using the Cochrane RoB 1 tool [60, 61]. Any disagreements were resolved by discussion with a third review author (MP or DY). We assessed the following risk of bias domains for all included studies.

- Generation of randomisation sequence
- Allocation concealment
- Blinding: participants, investigators, or outcome assessors
- Incomplete outcome data: we recorded the number of participants randomised and the number of participants evaluated per outcome
- Selective reporting bias

In this update, we added formal assessments of incomplete outcome data and selective reporting bias, which had not been evaluated in previous versions of this review. For selective reporting bias, when a prospectively dated protocol/registration/statistics analysis plan existed, we compared the prespecified outcomes with the final report; when this was unavailable (common in older trials), we judged selective reporting by internal consistency (whether 'clinical malaria' was stated in the methods and reported in the results). Any mismatch between prespecification and reporting in the final report led to a judgement of high risk of bias.

We graded all risk of bias domains as either low, high, or unclear risk of bias, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* [62].

For cluster-RCTs, we also assessed the following.

- Recruitment bias
- Baseline imbalance
- Loss of clusters
- Incorrect analysis
- Comparability with individual RCTs [63]

Measures of treatment effect

For dichotomous data, we calculated RRs, and for continuous data, absolute mean differences (MDs), with 95% CIs. We computed SDs from SEs or 95% CIs, and assumed a normal distribution of the values. We calculated risk differences for the outcome of all-cause mortality to allow for 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 with 0.5. When the included trials reported covariate-adjusted incidence rate ratios, we used these data with SEs. We analysed infectious episodes, hospitalisations, and clinic visits as count data, and reported rate ratios per child-months. We calculated standardised mean differences (SMDs) for the outcomes

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of weight and height, since we combined absolute values with weight/height for age z-scores.

Note: For the main outcomes of the analysis comparing oral iron versus placebo or no treatment for children in malaria-endemic areas, we used the largest study (Zlotkin 2013 (C)), which had a weight of 45.4% in this analysis, for calculating the anticipated absolute effect. We adopted this approach to provide a more precise estimation of the absolute effect size based on the most substantial available evidence. The method for calculating relative effect results remained unchanged.

For trials with multiple intervention arms, we ensured that the same control group was not included in more than one comparison in the same meta-analysis. For example, in Verhoef 2002 [64, 65] and Massaga 2003 [66], the comparisons of iron versus placebo and iron plus antimalarial versus placebo were conducted on independent groups of children with separate control arms, therefore no unit of analysis adjustment (e.g. halving the shared control group) was required.

Unit of analysis issues

- When cluster-RCTs reported results as if they were individually randomised, we extracted the data reported in the trial and used estimated ICCs and design effects (DE) to adjust for clustering [62]. 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 Supplementary material 7.
- For outcomes that could occur more than once per participant (e.g. infectious episodes other than malaria, hospitalisations, and clinic visits), we treated the data as count data and calculated rate ratios per child-months of follow-up. This approach accounts for multiple events per individual and follows Cochrane guidance per Section 6.7.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* [62].
- 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 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 randomised participants; otherwise, we performed a complete-case analysis.

Reporting bias assessment

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

Synthesis methods

We conducted analyses using RevMan [59]. We included cluster-RCTs in the main analysis after adjustment for clustering (see above). We performed meta-analysis using the Mantel-Haenszel fixed-effect model or the generic inverse variance method (when adjustment for clustering was performed by adjusting SEs). For the outcomes haemoglobin and anaemia, we used a random-effects model where we expected a priori heterogeneity to occur due to different mean baseline haemoglobin values and definitions of anaemia in different studies.

We assessed heterogeneity among the included trials using both statistical and descriptive approaches. We examined forest plots for consistency in the direction and magnitude of effects, and applied the Chi^2 test (with $P < 0.10$ considered evidence of heterogeneity) together with the I^2 statistic to quantify the degree of inconsistency (with values above 50% indicating moderate or substantial heterogeneity). Where important heterogeneity was detected, we explored possible explanations through prespecified subgroup analyses (e.g. presence of malaria prevention and management services, type of intervention) and sensitivity analyses (e.g. excluding trials at high risk of bias or not meeting review-defined criteria).

Investigation of heterogeneity and subgroup analysis

We attempted the following subgroup analyses in the presence of heterogeneity. 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 (e.g. 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 haematinic 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 was reported as being in place. This was in comparison to other trials where such infrastructure was not available:
  - treated bed nets were supplied for all participants;
  - prophylactic antimalarials were administered to all trial groups;
  - standardised diagnosis of malaria among febrile children was performed;
  - standardised treatment was offered to children diagnosed with malaria as an integral part of the study intervention.

The analysis presented in the third comparison in the Results (iron with or without folic acid versus placebo, stratified by availability of malaria prevention and management services) corresponds to the third subgroup. Although the studies overlap with those in the primary intervention comparisons, they were regrouped by malaria management setting to explore whether contextual infrastructure

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influenced the effect of iron on clinical malaria. No studies were double-counted in the pooled effect estimates.

We primarily stratified analyses using 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 using RevMan [59]. Supplementary material 7 provides a breakdown of findings from cluster-RCTs relevant to subgroup effects and heterogeneity.

Equity-related assessment

Malaria-endemic areas are inherently disadvantaged populations. This review focuses on these populations, and no further subgroup analyses based on equity factors were conducted.

Sensitivity analysis

We conducted sensitivity analyses by methods of allocation concealment to assess the effect of risk of bias on our critical outcomes. We restricted the analysis of malaria-related outcomes to *P falciparum*. When assessing all malaria species together, we included in the analysis trials in which over 85% of malaria infections were attributed to *P falciparum*. We had planned a sensitivity analysis excluding trials that counted multiple episodes of the same outcome per individual; however, this analysis could not be performed because none of the included trials reported sufficient disaggregated data to separate single-episode from recurrent event.

Certainty of the evidence assessment

We assessed the certainty of the evidence using the GRADE approach. We constructed summary of findings tables using GRADEpro GDT [67] and presented them for our critical outcomes as well as the important outcome of hospitalisation and clinic visits.

The GRADE assessment considers the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Two review authors (MG and MI) independently assessed the certainty of the evidence for each outcome. Any discrepancies were resolved through discussion or with input from a third review author (MP) as needed. We assessed the certainty of the evidence as high, moderate, low, or very low, and summarised our judgements in the summary of findings tables.

Consumer involvement

Consumers (patients or caregivers) were not directly involved in this review. The original article was published in 2006, a time when consumer involvement was not routinely required in Cochrane reviews. However, the outcomes and conclusions were developed with consideration of patient-relevant outcomes, ensuring relevance to the target population.

RESULTS

Description of studies

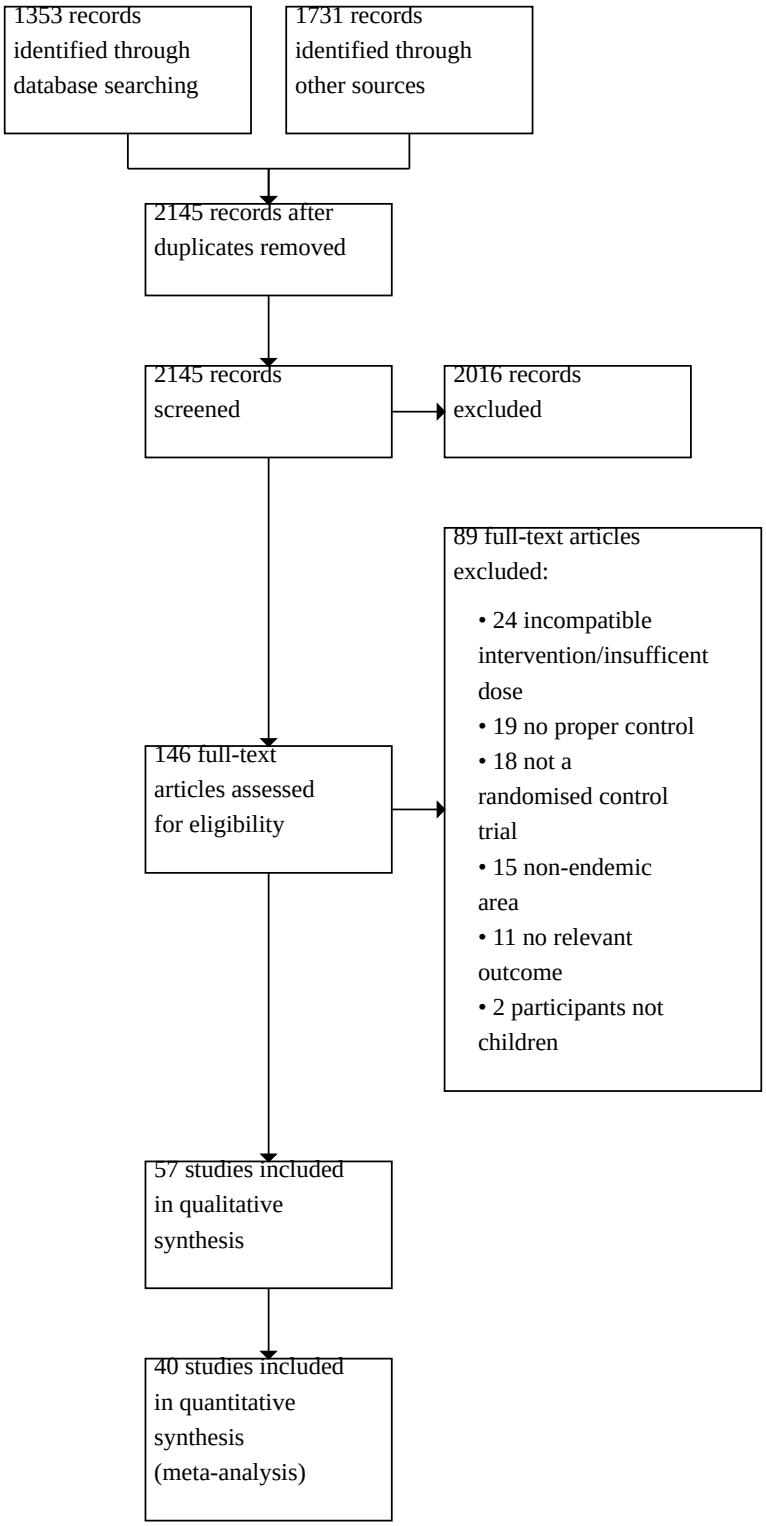
Results of the search

After the filtration of publications that were irrelevant or clearly incompatible with the inclusion criteria, we assessed the full-text reports of 146 studies that were conducted in hyperendemic or holoendemic malaria areas or that reported on malaria. Of these, we excluded 89 publications for the reasons detailed in Supplementary material 3. We included a total of 57 publications representing 40 individual RCTs. Eleven trials were multi-armed. We added five new trials in the current update (Frosch 2024 [68]; Mohammed 2023 [69]; Prasetyani 2017 [70]; Tang 2017 [71]; Teshome 2017 [72]).

Where the full publication did not provide enough information to determine study eligibility, we attempted to contact the authors of the included and potentially relevant trials. We requested data primarily on malaria and all-cause mortality. We established correspondence with 29 trial authors, of whom 21 supplied further information. A study flow diagram is presented in Figure 1.

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Figure 1. Study flow diagram.



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Included studies

A description of the included trials is provided in Table 4 and Supplementary material 2. The trials were published between the years 1985 and 2024.

Participants

The included trials recruited a total of 33,785 children: 9783 in 31 individually randomised controlled trials and 24,002 (71%) in nine cluster-RCTs. The trial populations included children under two years of age (17 trials), two to five years of age (15 trials), and over five years of age (19 trials). The mean baseline haemoglobin was below 10 g/dL in 18 trials and 10 g/dL or higher in 24 trials. Baseline malaria parasitaemia, reported in 14 of 24 trials, ranged from 0% to 70% (mean: 45%).

Interventions

All trials assessed the administration of oral iron or iron plus folic acid for the prevention or treatment of anaemia in children without acute illness. The average iron dose was 2 mg/kg/day, and the mean duration of treatment was 4.5 months (range: 1 to 12 months).

- 29 trials added antimalarial treatment to the iron arm or both trial arms.
- 14 trials added anthelminthics to both arms.
- 9 trials added other micronutrients to both arms.

Adherence was reported in 24 trials, with an average overall adherence rate of 86%.

Comparisons

Control groups included placebo, no treatment, or active comparators such as vitamin A, zinc, or micronutrients. In the Sazawal 2006 trial, two independent cohorts were included (Sazawal 2006a (C) and Sazawal 2006b (C) [73, 74]); we analysed only the relevant trial arms. Data from Sazawal 2006b (C) were obtained directly from the authors.

Outcomes

- 28 trials (70%) reported malaria-related outcomes (e.g. clinical malaria, severe malaria, and high-grade parasitaemia).
- 5 trials assessed anaemia and growth but did not report malaria outcomes (Akenzua 1985 [75]; Berger 2006 [76]; Hop 2005 [77, 78, 79, 80]; Mwanri 2000 [81]; Thi 2006 [82, 83]).
- Severe malaria, including cerebral malaria, was reported in Teshome 2017, Sazawal 2006a (C), Sazawal 2006b (C), and Frosch 2024.
- 5 trials reported clinical malaria with high-grade parasitaemia (Adam 1997 (C) [84]; Ayoya 2009 [85]; Massaga 2003; Smith 1989 (C) [86]; Zlotkin 2013 (C)).
- 12 trials reported mostly *P falciparum* malaria.

Most trials that reported malaria outcomes conducted regular surveillance (e.g. blood smears, rapid diagnostic testing (RDT), or polymerase chain reaction (PCR) testing) either routinely or when children were febrile, and offered treatment when appropriate. The types of outcomes and their definitions are detailed in Table 5.

Settings

The trials were conducted in malaria-endemic regions across sub-Saharan Africa and Asia, in both rural and urban settings. Surveillance and treatment protocols varied. For example, Sazawal 2006a (C) did not provide treatment outside the hospital, whereas Sazawal 2006b (C) implemented home-based monitoring and treatment.

Ongoing studies

We identified one ongoing study that meets the inclusion criteria and is described in detail in Supplementary material 4. This study is still in progress, with no results available at the time of this review update.

Excluded studies

The reasons for exclusion of 89 trials are detailed in Supplementary material 3. The major reasons for the exclusion of studies are as follows.

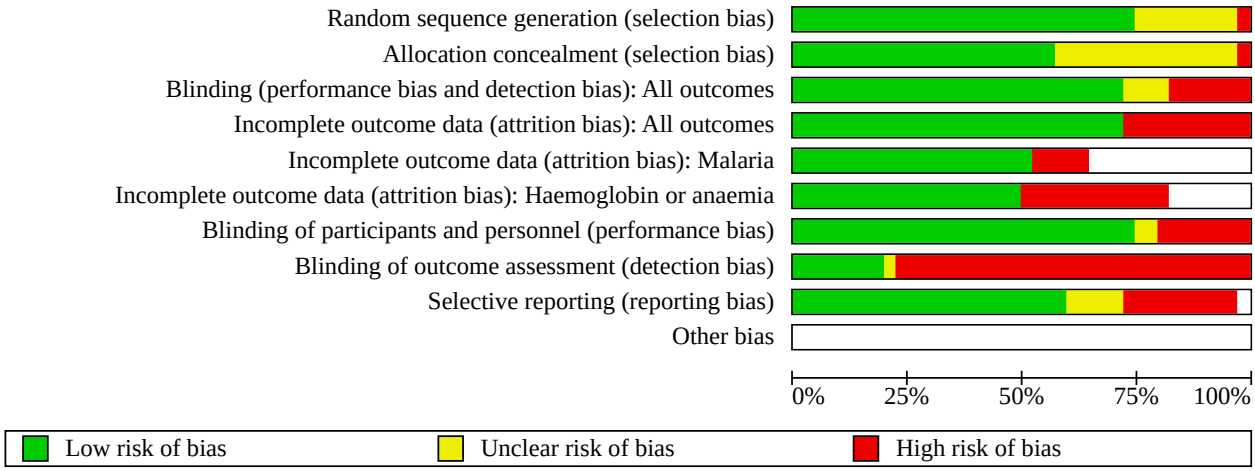
- The trials were conducted in non-malaria-endemic, mesoendemic, or hypoendemic areas, including studies in which it was explicitly stated, or the study authors confirmed that there was no malaria activity in the study location at the time of the trial.
- The administration of iron fortification was at a dose lower than 80% of the RDA recommended by the WHO for the 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 to only one arm or the administration of iron to both trial arms.
- We excluded 11 studies because they did not report any of the review-defined critical or important outcomes prespecified in the protocol (e.g. clinical malaria, severe malaria, mortality, hospitalisations or clinic visits, parasitaemia, haemoglobin, or anaemia).
- Four trials assessed the intervention of iron during an acute attack of malaria among children under five years of age (Gara 2010 [87]; Nwanyanwu 1996 [88, 89]; van den Hombergh 1996 [90]; van Hensbroek 1995 [91]), 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 (Supplementary material 2). Risk of bias assessments overall and by study are presented in Figure 2 and Figure 3, respectively.

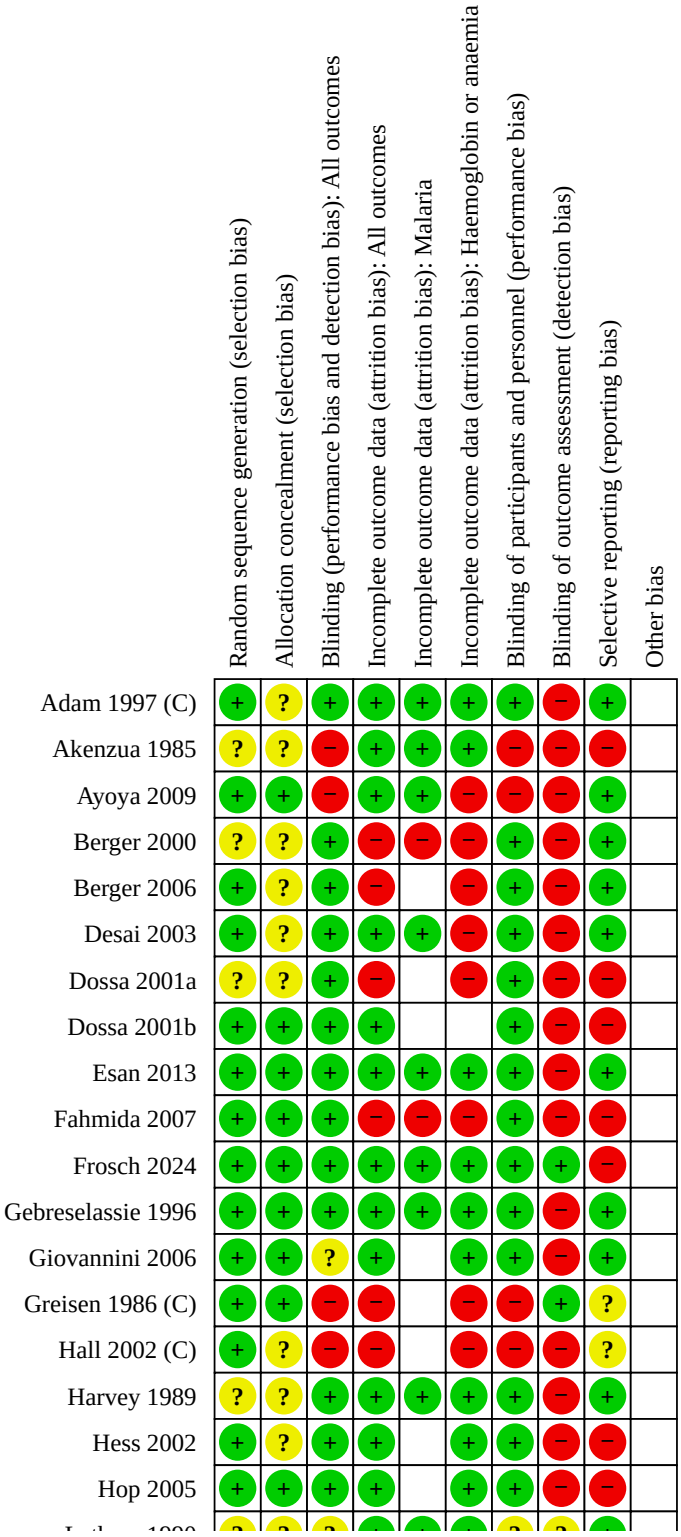
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Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included trials. The unclear category for incomplete outcome data represents trials that did not report this outcome.



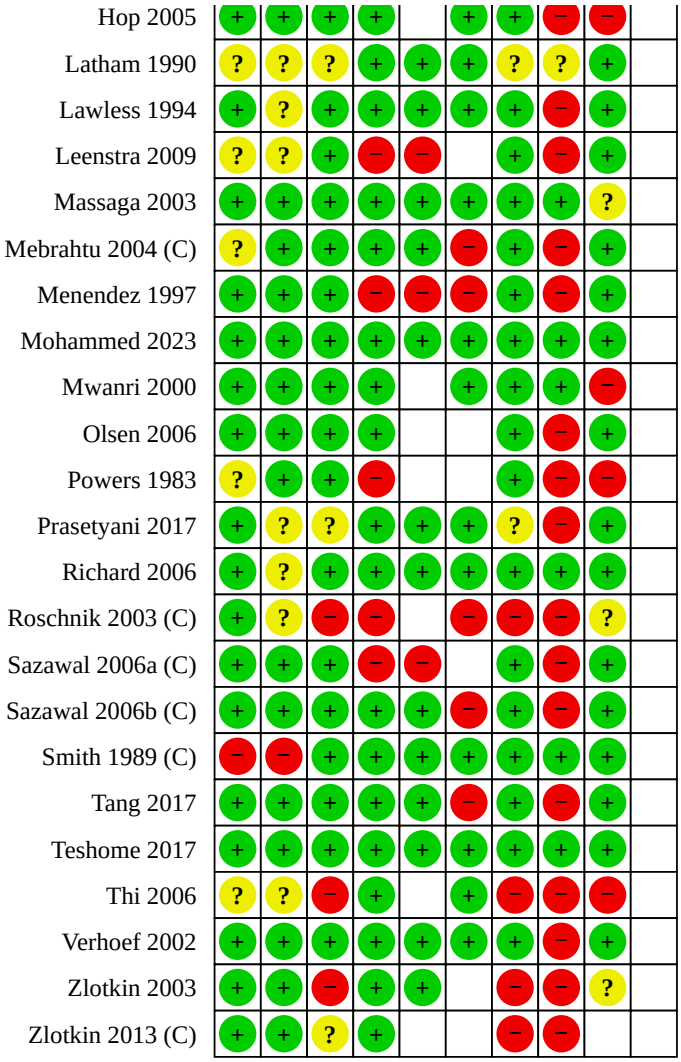
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Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included trial.



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Figure 3. (Continued)



We judged the generation of the randomisation sequence to be at low risk of bias in 30/40 (75%) trials, high risk for bias in the one trial using alternation, and unclear risk of bias in the remaining trials. We judged 23 of the 40 trials (58%) as at low risk of bias related to allocation concealment. One trial was at a high risk of bias (Smith 1989 (C)). The remaining trials either did not describe their methods clearly or did not provide a description of them. Overall, we considered the allocation procedure (both random sequence generation and allocation concealment) as at low risk of bias in 23 (58%) trials.

Thirty out of 40 trials (75%) described double-blinding or stated that the trial was double-blind, but gave no description of the blinding techniques used; we considered all of these trials to be at low risk of bias (see the risk of bias tables in Supplementary material 2). Eight trials lacked blinding or used single-blind methods for outcomes susceptible to bias and were therefore judged at high risk for performance or detection bias, or both. Two trials provided insufficient information to determine whether blinding was implemented effectively and were judged at unclear risk of bias.

The included trials explained the reasons for the 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 randomised children from mortality assessments were unclear, and we considered this to be high risk of bias, since deaths could have occurred among the excluded children. We have provided the details of the number of participants randomised and evaluated in the risk of bias tables (Supplementary material 2).

We judged 24 of the 40 trials (60%) to be at low risk of selective reporting bias, based on whether clinical malaria was prespecified in the methods and reported consistently in the results.

One trial specified methods for the assessment of malaria throughout the trial (without defining these as study outcomes), but did not report the results per trial arm (Olsen 2006 [92]). We could not contact the authors of this trial. We contacted the authors of trials that did not report on malaria in their methods or results sections; the authors of one trial reported that data had been collected in the trial but were no longer available (Powers 1983

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[93]), while the authors of seven trials replied that malaria-related outcomes were not collected in their trials (Dossa 2001a [94]; Dossa 2001b [95]; Greisen 1986 (C) [96]; Hall 2002 (C) [97]; Hess 2002 [98]; Latham 1990 [99]; Zlotkin 2003 [100]).

Only one trial prespecified death as an outcome (Sazawal 2006a (C); Sazawal 2006b (C)), although 18 trials reported this information in their results, and we obtained mortality data from the authors of another 14 trials. It is thus not possible to discuss reporting bias in relation to the outcome of mortality.

Cluster-RCTs

Nine of the included RCTs were cluster-randomised.

- Recruitment bias: in the Sazawal 2006a (C) and Sazawal 2006b (C) cluster-RCTs, children could be born and added to the household after randomisation; these trials were therefore judged at high risk of recruitment bias. For all other cluster-RCTs, the reports did not describe whether new participants could join after randomisation, and therefore we judged the risk of recruitment bias as unclear.
- Baseline imbalance: there were no differences in the main baseline characteristics of different trial groups in any of the included trials.
- Loss of clusters: none of the included trials provided data on the loss of clusters.
- Incorrect analysis: only Sazawal 2006a (C), its substudy (Sazawal 2006b (C)), 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 6 (for outcomes pooled with the use of adjusted SEs) and Table 7 (for outcomes pooled using effective sample size).
- Comparability with individual RCTs: cluster-RCTs were larger than individual RCTs (see above); the percentage of children excluded from outcome assessment was higher (10.2% versus 5.9%); and adherence to study medications was lower (84.2% versus 91.3%). 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), showing no evidence of a difference. 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%).

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 2006a (C); Sazawal 2006b (C)).

Synthesis of results

1. Iron versus placebo/no treatment for the treatment or prevention of anaemia (32 trials, 14,429 children); malaria prevention either present or absent in all arms

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 evidence of heterogeneity in results explained by this factor. Four-armed trials including both comparisons appear twice in the analyses (Massaga 2003; Menendez 1997 [101, 102, 103, 104]; Verhoef 2002), 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).

Critical outcomes

Clinical malaria

All trials defined clinical malaria as fever (usually greater than 37.5 °C) and parasitaemia (any density). Overall, iron results in little to no difference in clinical malaria when compared to placebo or no treatment (RR 0.93, 95% CI 0.87 to 1.00; I^2 = 35%; 16 trials, 7843 children; high-certainty evidence; Analysis 1.1). We conducted a subgroup analysis based on baseline anaemia, which yielded no evidence of subgroup differences (P = 0.41). Therefore, no interpretation of subgroup-specific treatment effects is provided, in accordance with Cochrane guidance. (Summary of findings 1; Supplementary material 5). We also conducted a subgroup analysis based on age (Analysis 1.2), which yielded no evidence of subgroup differences (P = 0.17). Therefore, no interpretation of subgroup-specific treatment effects is provided.

When we only included trials that described clinical malaria caused solely or primarily by *P falciparum,* iron was associated with a lower risk of clinical malaria when compared to placebo or no treatment (RR 0.91, 95% CI 0.84 to 0.99; I^2 = 52%; 9 trials, 5503 children; Analysis 1.3).

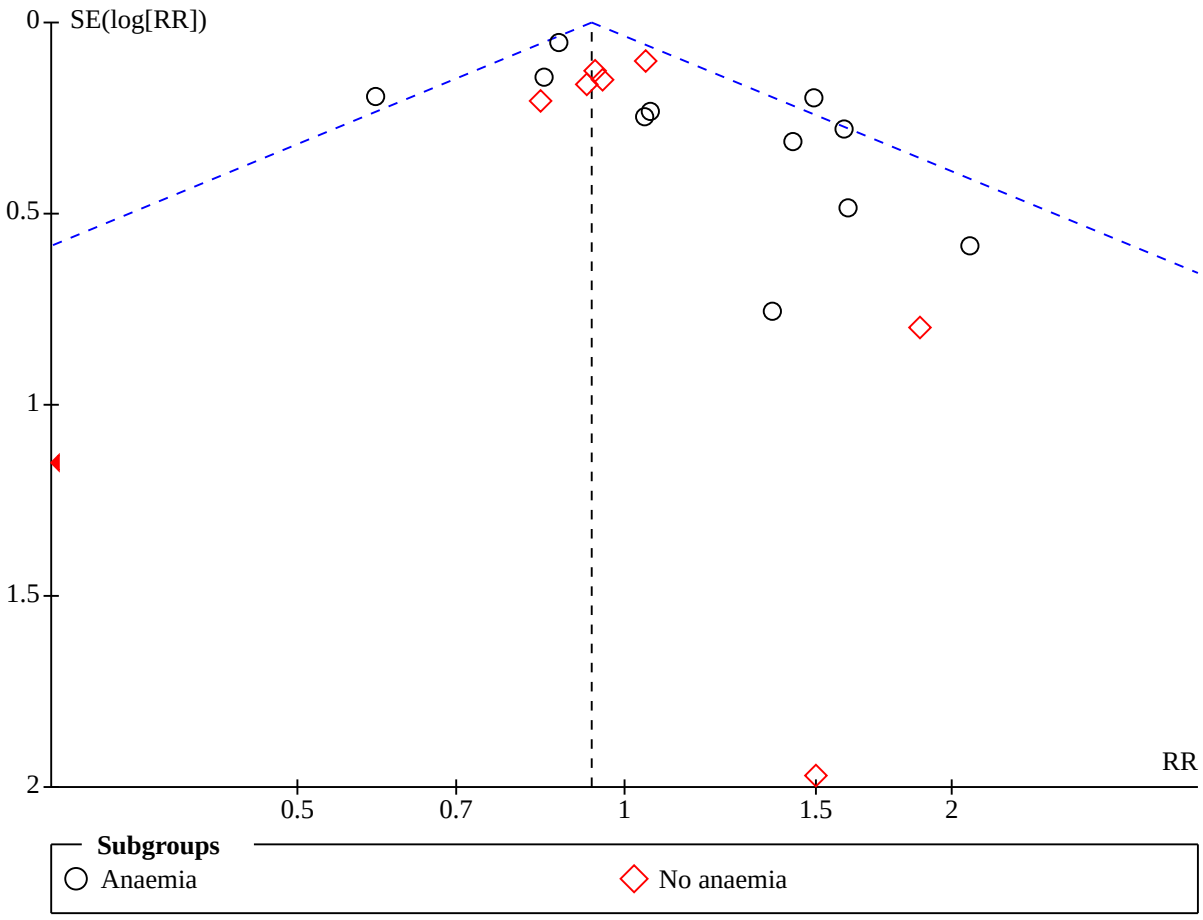
Severe malaria

In this comparison, we defined severe malaria as clinical malaria with high-grade parasitaemia or requiring admission. Iron reduces the risk of severe malaria slightly when compared to placebo or no treatment (RR 0.90, 95% CI 0.81 to 0.98; I^2 = 0%; 5 trials, 3421 children; high-certainty evidence; Analysis 1.4) (Summary of findings 1).

Sensitivity analysis restricted to trials at low risk of bias for allocation concealment did not affect the results. The funnel plot was asymmetrical, indicating that small studies that favour iron could be missing (Figure 4). Three trials reported either on episodes of malaria (Leenstra 2009 [105]; Richard 2006 [106]) 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 the end of follow-up, which was six months after completion of iron supplementation (Menendez 1997). Its exclusion did not affect the results.

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Figure 4. Funnel plot of comparison: 1. Iron versus placebo or no treatment, outcome: 1.1 Clinical malaria (grouped by presence of anaemia).



All-cause mortality

Twenty trials reported mortality, and in most trials no deaths occurred among the evaluable children (control event rate 1%). Overall, the evidence suggests that iron may result in little to no difference in mortality compared to placebo or no treatment (RR 1.15, 95% CI 0.76 to 1.74; 20 trials, 8809 children; low-certainty evidence; Analysis 1.5). We assessed the certainty 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 dropout range of 2% to 62% of participants), as deaths might have occurred among children lost to follow-up (Summary of findings 1).

Important outcomes

Hospitalisations and clinic visits for any cause

Ten trials reported hospitalisations or clinic visits. Overall, the evidence suggests that iron may result in little to no difference in hospitalisations and clinic visits when compared to placebo or no treatment (RR 0.99, 95% CI 0.95 to 1.04; I^2 = 25%; 10 trials, 14,011 children; low-certainty evidence; Analysis 1.6); these results were not affected by the administration of antimalarial medications. We assessed the certainty of the evidence as low due to the inconsistency and indirectness of this outcome (Summary of findings 1). There was no evidence of subgroup differences when hospitalisations and clinic visits were examined separately, or when comparing trials with and without concurrent antimalarial therapy (test for subgroup differences across all four subgroups: P = 0.15). Therefore, no interpretation of subgroup-specific treatment effects is provided.

Malaria parasite prevalence and density

Twenty-four trials reported the prevalence of parasitaemia at any level at the end of treatment, and iron was associated with an increased risk of parasitaemia when compared to placebo or no treatment (RR 1.13, 95% CI 1.01 to 1.25; I^2 = 39%; 24 trials, 4659 children; Analysis 1.7). The certainty of evidence was not assessed, as this was not a critical outcome. We converted odds ratios to RRs to allow for the use of data on parasitaemia from one trial (Mebrahtu 2004 (C) [107, 108, 109, 110]). We conducted a subgroup analysis based on baseline anaemia, which yielded no evidence of subgroup differences (P = 0.56). Therefore, no interpretation of subgroup-specific treatment effects is provided, in accordance with Cochrane guidance. The outcome of any parasitaemia at the end of treatment was also not affected by age or *Plasmodium* species assessed (Analysis 1.8; Analysis 1.9). Nine trials reported any parasitaemia at the end of treatment and described allocation concealment. Overall, there was no evidence of a difference in risk of any parasitaemia at the end of treatment (RR 1.11, 95% CI

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1.00 to 1.23; I^2 = 29%; 9 trials, 3393 children; Analysis 1.10). We performed a subgroup analysis based on allocation concealment, with evidence of a difference between the subgroup of trials that described adequate allocation concealment and the trials with unclear or inadequate methods (P = 0.04). Four trials described adequate allocation concealment, with no evidence of a difference in the risk of any parasitaemia at the end of treatment between iron and placebo or no treatment (RR 0.98, 95% CI 0.83 to 1.15; I^2 = 42%; 4 trials, 1727 children; Analysis 1.10). Five trials had unclear or inadequate allocation methods, with iron being associated with an increased risk of parasitaemia when compared to placebo or no treatment (RR 1.22, 95% CI 1.06 to 1.40; I^2 = 0%; 5 trials, 1666 children; Analysis 1.10). All trials evaluating this outcome were double-blinded. Five trials reported the outcome of asymptomatic high-grade parasitaemia, most commonly defined as > 5000 parasites/µL, with no evidence of a difference in risk between groups (RR 1.13, 95% CI 0.93 to 1.37; I^2 = 0%; 5 trials, 2565 children; Analysis 1.12). Seven trials reported the outcome of any level of parasitaemia at the end of follow-up, after the cessation of iron administration, with iron being associated with an increased risk of parasitaemia at the end of follow-up compared to placebo or no treatment (RR 1.29, 95% CI 1.14 to 1.46; I^2 = 38%; 7 trials, 1952 children; Analysis 1.11).

It was difficult to establish whether the trials reported on children with parasitaemia or on parasitaemia episodes. Gebreselassie 1996 [111] clearly reported on cumulative incidence, and Leenstra 2009 included repeated episodes. Leenstra 2009 reported incidence rate ratios of 95% CIs adjusted for age, baseline parasitaemia, and school. We used these in our analysis as RRs. The exclusion of these trials did not affect the results.

The trials reported parasite density differently with regard to both the unit of measurement and the denominator (Table 8). A meta-analysis was therefore not possible; the results for each trial are presented in Table 8. 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.

Haemoglobin levels and anaemia prevalence

Analyses of 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. Nineteen trials reported haemoglobin levels at the end of treatment, with the mean level being higher in the iron group compared to the placebo or no-treatment group (MD 0.67 g/dL, 95% CI 0.41 to 0.92; I^2 = 94%; 19 trials, 6499 children; Analysis 1.13).

We conducted a subgroup analysis based on baseline anaemia (mean haemoglobin < 10 g/dL versus ≥ 10 g/dL), which yielded no evidence of subgroup differences (P = 0.17). Therefore, no interpretation of subgroup-specific treatment effects is provided, in accordance with Cochrane guidance. Thirteen trials reported haemoglobin change from baseline at the end of treatment, and the pooled analysis showed the mean change was higher in the iron group compared to the placebo or no-treatment group (MD 0.63 g/dL, 95% CI 0.36 to 0.89; I^2 = 89%; 13 trials, 3040 children; Analysis 1.14).

Nineteen trials reported anaemia at the end of treatment, as defined in the trial, with iron being associated with a reduced risk for end-of-treatment anaemia when compared to placebo or no treatment (RR 0.66, 95% CI 0.53 to 0.83; I^2 = 97%; 19 trials, 5404 children; Analysis 1.15). Similar to the analyses of haemoglobin, there was a substantial heterogeneity that stemmed mainly from the magnitude of the effect, and not the direction of the effect.

Infections other than malaria (including diarrhoea, pneumonia, sepsis, meningitis, measles, and pertussis)

Six studies provided data on respiratory infections, with no evidence of a difference in the risk for respiratory infections between iron and placebo or no treatment (RR 0.99, 95% CI 0.85 to 1.15; I^2 = 0%; 6 trials, 21,767 child-months; Analysis 1.18). Ten trials reported diarrhoeal episodes. Overall, iron treatment was associated with an increased risk of diarrhoea compared with placebo or no treatment (RR 1.15, 95% CI 1.06 to 1.25; I^2 = 31%; 10 trials, 27,005 child-months; Analysis 1.17). Trials usually reported diarrhoea as 'infectious diarrhoea', although we could not clearly differentiate the symptoms from diarrhoea related to iron or iron/zinc supplementation, and therefore performed a subgroup analysis based on zinc co-administration. The test for subgroup differences indicated evidence of an interaction between zinc supplementation and the effect of iron (Chi^2 = 7.98, df = 1, P = 0.005; I^2 = 87.5%). In the subgroup without concurrent zinc supplementation, there was no evidence of a difference between iron and placebo or no treatment (RR 1.01, 95% CI 0.89 to 1.14; I^2 = 0%; 9 trials, 20,659 child-months; Analysis 1.17). In the subgroup with concurrent zinc supplementation, iron was associated with an increased risk of diarrhoea when compared to placebo or no treatment (RR 1.29, 95% CI 1.15 to 1.44; I^2 = 30%; 3 trials, 6346 child-months; Analysis 1.17). Seven trials reported the number of febrile episodes, and there was no evidence of a difference between iron treatment and placebo or no treatment (RR 1.03, 95% CI 0.94 to 1.14; I^2 = 0%; 7 trials, 16,713 child-months; Analysis 1.16). In one trial, iron was associated with more days of fever when compared to placebo or no treatment (RR 8.37, 95% CI 1.91 to 36.58; 1 trial, 110 child-months; Analysis 1.16). Two trials reported on infectious episodes, with no evidence of a difference between iron and placebo or no treatment (RR 1.01, 95% CI 0.89 to 1.16; I^2 = 33%; 2 trials, 3321 child-months, Analysis 1.16). Definitions and reporting methods were highly variable; results are shown per outcome (Analysis 1.16).

Weight, absolute values, and height, absolute values

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. There was no evidence of a difference in end-of-treatment weight between iron supplementation and placebo or no treatment (SMD –0.03, 95% CI –0.12 to 0.06; I^2 = 0%; 6 trials, 1849 children; Analysis 1.19). However, iron was associated with a greater weight gain from baseline when compared with placebo or no treatment (SMD 0.31, 95% CI 0.13 to 0.49; I^2 = 84%; 4 trials, 486 children; Analysis 1.20). Six trials reported end-of-treatment height, and there was no evidence of a difference between iron and placebo or no treatment (SMD 0.00, 95% CI –0.08 to 0.09; I^2 = 29%; 6 trials, 2121 children; Analysis 1.21). There was also no evidence of a difference in change in height from baseline

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between iron and placebo or no treatment (SMD 0.09, 95% CI −0.09 to 0.27; I^2 = 74%; 4 trials, 486 children; Analysis 1.22).

2. Iron plus folic acid versus placebo/no treatment for the treatment or prevention of anaemia (5 trials, 19,456 children); malaria prevention either present or absent in all arms

Critical outcomes

Clinical malaria

None of the studies included in the comparison reported this outcome.

Severe malaria

The only trial that reported malaria-related outcomes was the Pemba study (Sazawal 2006a (C); Sazawal 2006b (C)). The risk of bias in the trial was low, except for the fact that it was discontinued for harm. Malaria-related outcomes reported were those of severe malaria: malaria requiring admission and cerebral malaria. The evidence suggests that oral iron with folic acid may result in little to no difference in severe malaria requiring admission (RR 1.11, 95% CI 0.96 to 1.28; 2 trials, 17,575 children; low-certainty evidence; Analysis 2.1). We assessed the certainty of evidence for this outcome as low due to inconsistency and imprecision. For the outcome cerebral malaria, there was evidence of a difference between the results of the main study and those of the substudy. The main study showed that iron plus folic acid was associated with a higher risk of severe malaria when compared to placebo (RR 1.32, 95% CI 1.02 to 1.70; 1 trial, 15,956 children; Sazawal 2006a (C)), while the substudy showed that iron plus folic acid was associated with a lower risk of severe malaria (RR 0.26, 95% CI 0.09 to 0.78; 1 trial, 1619 children; Analysis 2.2, Sazawal 2006b (C)). Therefore, we did not pool the results for this outcome. 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 only excluded 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 2006a (C), there was no organised infrastructure for the diagnosis and treatment of uncomplicated malaria.

All-cause mortality

The evidence suggests that oral iron with folic acid may result in little to no difference in all-cause mortality (RR 1.13, 95% CI 0.90 to 1.42; 5 trials, 18,034 children; low-certainty evidence; Analysis 2.3). Sazawal 2006a (C) contributed 88.4% of the weight of this analysis (Summary of findings 2). We assessed the certainty of evidence for this outcome as low due to risk of bias and imprecision.

Important outcomes

Hospitalisations and clinic visits for any cause

Only Sazawal 2006a (C) reported hospital admissions. The evidence suggests that oral iron with folic acid may result in little to no difference in hospitalisations when compared to placebo (RR 1.08, 95% CI 0.96 to 1.22; 1 trial, 15,956 children; low-certainty evidence; Analysis 2.4). We assessed the certainty of evidence for this outcome as low due to imprecision and indirectness.

No included studies reported the number of clinic visits during the study period.

Malaria parasite prevalence and density

No trials in this comparison reported on parasitaemia (any level or high-grade) or malaria parasite density.

Haemoglobin levels and anaemia prevalence

Only Giovannini 2006 [112] reported haemoglobin at the end of treatment. Iron plus folic acid was associated with a higher haemoglobin at the end of treatment (MD 0.90 g/dL, 95% CI 0.51 to 1.29; 1 trial, 124 children; Analysis 2.5).

Three trials reported anaemia as a binary outcome at the end of treatment, with iron plus folic acid associated with a lower risk for end-of-treatment anaemia when compared to placebo (RR 0.49, 95% CI 0.25 to 0.99; I^2 = 49%; 3 trials, 633 children; Analysis 2.6).

Infections other than malaria (including diarrhoea, pneumonia, sepsis, meningitis, measles, and pertussis)

No consistent data was reported for respiratory infections, other febrile episodes, or diarrhoea.

Weight, absolute values, and height, absolute values

Two trials reported end-of-treatment weight. There was no evidence of a difference in end-of-treatment weight between iron plus folic acid and placebo (SMD −0.06, 95% CI −0.18 to 0.06; I^2 = 0%; 2 trials, 1080 children; Analysis 2.7). Two trials also reported height at the end of treatment, with no evidence of a difference observed between groups (SMD −0.00, 95% CI −0.12 to 0.12; I^2 = 29%; 2 trials, 1082 children; Analysis 2.8). No trials reported a change from baseline in either weight or height.

3. Iron with or without folic acid versus placebo/no treatment for the treatment or prevention of anaemia (19 trials, 25,531 children for the outcome of malaria); grouped by presence or absence of malaria prevention in both arms

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. Overall, when not grouping by presence of malaria prevention and management services, iron supplementation with or without folic acid may have little to no effect on clinical malaria (RR 0.96, 95% CI 0.91 to 1.03; I^2 = 47%; 19 trials, 25,531 children; low-certainty evidence; Analysis 3.1). We assessed the certainty of evidence for this clinical malaria outcome in comparison 3 as low due to inconsistency. The funnel plot for this meta-analysis appeared approximately symmetric with no clear evidence of small-study effects, but we could not exclude the possibility of reporting bias because fewer than 10 trials contributed to some of the subgroup analyses. We subgrouped the analysis by the presence of malaria prevention and management services in the trial setting, with evidence of a difference between the subgroup of trials where malaria prevention services were present and the subgroup of trials without malaria prevention services (test for subgroup differences: P = 0.001). In areas where there are prevention and management services for malaria, iron supplementation with or without folic acid may reduce the risk of clinical malaria slightly (RR 0.91, 95% CI 0.84 to 0.97; I^2 = 37%; 12 trials, 5777 children; low-certainty evidence; Analysis 3.1). In areas where there are no prevention and management services for malaria, iron with or without folic acid may increase the risk

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of clinical malaria slightly (RR 1.15, 95% CI 1.02 to 1.30; I^2 = 10%; 7 trials, 19,754 children; low-certainty evidence; Analysis 3.1) (Summary of findings 3).

4. Iron plus antimalarial versus placebo/no treatment for the treatment or prevention of anaemia (3 trials, 1915 children); malaria prevention present in the intervention arm only

Critical outcomes

Clinical malaria

Three trials reported on clinical malaria, all of which were individual RCTs. Iron plus antimalarial results in a large reduction in clinical malaria (RR 0.54, 95% CI 0.43 to 0.67; I^2 = 60%; 3 trials, 728 children; high-certainty evidence; Analysis 4.1) (Summary of findings 4).

Severe malaria

None of the studies included in this comparison reported on severe malaria.

All-cause mortality

The evidence suggests that iron plus antimalarial may not reduce mortality (RR 1.05, 95% CI 0.52 to 2.11; I^2 = 0%; 3 trials, 728 children; low-certainty evidence; Analysis 4.2). We assessed the certainty of evidence as low due to imprecision (Summary of findings 4).

Important outcomes

Hospitalisations and clinic visits for any cause

Iron plus antimalarial probably results in a large reduction in hospitalisations and clinic visits (RR 0.85, 95% CI 0.81 to 0.89; 2 trials, 5976 child-months; moderate-certainty evidence; Analysis 4.3). We assessed the certainty of evidence as moderate due to indirectness.

Malaria parasite prevalence and density

No trials in this comparison reported on parasitaemia (any level or high-grade) or malaria parasite density.

Haemoglobin levels and anaemia prevalence

Iron plus antimalarial was associated with higher haemoglobin at the end of treatment when compared to placebo in one trial (MD 0.91 g/dL, 95% CI 0.47 to 1.35; 1 trial, 151 children; Analysis 4.4).

In two trials, iron plus antimalarial was associated with a lower risk of end-of-treatment anaemia when compared to placebo (RR 0.44, 95% CI 0.28 to 0.70; I^2 = 40%; 2 trials, 295 children; Analysis 4.5) and a lower risk of end-of-follow-up anaemia when compared to placebo in another trial (RR 0.37, 95% CI 0.26 to 0.54; 1 trial, 420 children; Analysis 4.5).

Infections other than malaria (including diarrhoea, pneumonia, sepsis, meningitis, measles, and pertussis)

No trials in this comparison reported on infections other than malaria.

Weight, absolute values, and height, absolute values

No trials in this comparison reported on weight or height at the end of treatment or change from baseline.

Reporting biases

We generated a funnel plot (Figure 4) for the critical outcome of clinical malaria, based on 17 included studies, to assess potential reporting bias. Visual inspection suggested approximate symmetry, with no clear evidence of small-study effects. However, as several comparisons included fewer than 10 studies, the power to detect publication bias is limited. We therefore cannot exclude the possibility of reporting bias.

DISCUSSION

Summary of main results

This updated review examined the effects of oral iron supplementation in children living in malaria-endemic areas, across four main comparisons.

1. Iron versus placebo or no treatment

Iron results in little to no difference in the risk of clinical malaria and reduces the risk of severe malaria slightly when provided in the context of malaria-endemic settings. It may result in little to no difference in mortality or hospitalisations and clinic visits. The certainty of evidence for all-cause mortality and hospitalisations and clinic visits was low due to imprecision, suspected publication bias, inconsistency, and indirectness. See Summary of findings 1.

2. Iron plus folic acid versus placebo or no treatment

The evidence for this comparison was limited and came mainly from a single large trial and a related substudy. Clinical malaria was not assessed, but iron plus folic acid may result in little to no difference in severe malaria requiring admission, all-cause mortality, and hospitalisations. The certainty of evidence for all the main outcomes was low. We downgraded clinical malaria for inconsistency and imprecision; severe malaria and anaemia for imprecision; mortality for imprecision and suspected publication bias; hospitalisations and clinic visits for inconsistency and indirectness; and parasitaemia for indirectness. See Summary of findings 2.

3. Iron (with or without folic acid), stratified by malaria control availability

In areas with adequate malaria prevention or treatment services, iron supplementation appears to be safe and may reduce clinical malaria risk. In contrast, in settings without such services, iron may increase clinical malaria risk. These findings were primarily influenced by one large trial. The certainty of evidence was low due to inconsistency, indirectness, and suspected publication bias. See Summary of findings 3.

4. Iron combined with antimalarial treatment versus placebo or no treatment

Iron administered alongside effective antimalarial drugs considerably reduces the risk of clinical malaria, and likely results in a large reduction in hospitalisation and clinic visits, but may not reduce all-cause mortality. Severe malaria was not assessed for this comparison. These findings suggest a clear benefit of integrated nutritional and malaria control interventions. The certainty of evidence was high for clinical malaria, moderate for hospitalisations and clinic visits due to indirectness, and low for all-cause mortality due to significant imprecision. See Summary of findings 4.

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The safety of supplementation depends on the availability of malaria prevention and treatment services. This review identified areas of uncertainty, particularly for less common outcomes like mortality and hospitalisations and clinic visits, where evidence was limited and often of low certainty. The risk of bias varied across trials, with some studies showing concerns due to lack of blinding or incomplete data.

This review update applied stricter inclusion criteria than previous versions to better reflect current clinical questions. It excluded trials with low or intermittent iron dosing and those conducted during acute malaria illness. The addition of five new trials did not substantially change the overall conclusions, but reinforced the importance of contextual factors, especially the presence of malaria control services.

Overall, oral iron supplementation is safe and effective for reducing anaemia in malaria-endemic regions when provided in settings with adequate malaria control. The certainty of these findings, as detailed in the summary of findings tables, supports the continued use of iron in public health programmes, tailored to local infrastructure and disease burden.

Limitations of the evidence included in the review

The results and the certainty of the evidence assessments are provided in the summary of findings tables. We downgraded the certainty of evidence for several main reasons. We downgraded for imprecision whenever the 95% CIs included the possibility of harm or no benefit from iron supplementation. 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 study arms is probably not only explained by malaria, resulting in downgrading due to indirectness. We downgraded the certainty of evidence for deaths due to a serious concern about missing data with or without publication bias; mortality data were reported in 23/40 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 randomised, including those lost to follow-up. Inconsistency was apparent in the outcome definitions, primarily with the large Pemba trial, which reported only on malaria requiring hospital admission, while all other trials reported on fever with parasitaemia (Sazawal 2006a (C); Sazawal 2006b (C)). 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 do 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.

Many of the included trials pre-date routine registration/protocol availability, so prospectively dated sources were often unavailable. Consequently, our selective-reporting assessment relied mainly on internal consistency of the final report, which may under-detect selective omission of outcomes in the trials. This constraint was prespecified in our methods and should be considered when interpreting the certainty of evidence.

For the intervention of iron with folic acid, the large Pemba trial reported a probable increased risk of death or hospital admission (Sazawal 2006a (C); Sazawal 2006b (C)), 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, evidence on the safety of iron and folate supplementation is unclear.

Additionally, subgroup analysis on the presence of malaria prevention or management services was only available for the comparison of oral iron with or without folic acid versus placebo/no treatment, but not for the other comparisons due to insufficient data, limiting the ability to assess the impact of these services across all analyses. Ongoing studies may provide further insights into the effects of iron supplementation, particularly in areas where malaria prevention and management services are limited (Supplementary material 4).

We were also unable to examine the effect of geographic location, as several trials reported combined data from multiple countries without stratifying results by setting. Instead, we used malaria transmission intensity (hyperendemic or holoendemic) as a proxy for geographic variation.

This updated meta-analysis, while including five new studies, only increased the total number of children recruited for the included trials by 1830, from 31,955 in the previous analysis to 33,785, which may limit the ability to detect evidence of differences or changes in outcomes.

Limitations of the review processes

In this review, malaria outcomes, iron status, and iron deficiency anaemia were all outcomes of particular interest when evaluating the effects of iron supplementation. We could not conduct a subgroup analysis on 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, thus enabling this stratification in the meta-analysis. Although this analysis could mask an adverse effect on individual iron-replete, non-anaemic children compensated by benefit in iron-depleted, anaemic children, the lack of heterogeneity in the analyses for malaria and deaths makes this possibility unlikely. However, we could not conduct an analysis on 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 trials and after their 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 of haemoglobin and anaemia.

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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 analysed accordingly. The trial should report on the unit of randomisation, the average cluster size (number of children in household or class), the number of clusters and individuals randomised, the 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 randomised, may result in an exaggerated precision of the effect estimate, thus inflating the weight of the trial in the meta-analysis. Of the nine cluster-RCTs included in our review, only Sazawal 2006a (C), Sazawal 2006b (C), and Zlotkin 2013 (C) reported adjusted analyses for our critical 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 in 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 [113]; tuberculosis, and age/weight/height-adjusted z-scores for growth. Finally, we do not have data from Sazawal 2006a (C) on malaria-related events, hospital admissions, and deaths for the two trial arms: iron plus folic acid plus vitamin A plus zinc versus vitamin A plus zinc. These data could add 16,196 more children to the analyses of iron plus folic acid versus placebo/no 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 (Adam 1997 (C); Gebreselassie 1996) or others (Roschnik 2003 (C) [114]).

Agreements and disagreements with other studies or reviews

Sazawal 2006a (C) 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 probable increased risk for the composite outcome of death or hospitalisation among children, most of whom were younger than two years of age. Mortality appeared to be higher, but the evidence is insufficient to confirm an effect. 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 there were fewer adverse events among children who were iron-deficient and anaemic. 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 2006b (C), 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, is in agreement with this conclusion (Analysis 3.1).

In 2007, based on Sazawal 2006a (C), the WHO released a statement that recommended that iron supplementation should be prescribed only after screening for iron deficiency [42]. Universal screening for anaemia and iron status places a substantial burden on healthcare systems in low-income countries. This Cochrane review was originally published in 2009 [49] and added further debate to the conundrum of iron supplementation for children in malaria-endemic areas [22, 23, 24, 115]. The previous versions of this systematic review, [49], [57], and [50], challenged the recommendations for universal screening, and placed the Sazawal 2006a (C) 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" [116]. These recommendations remained unchanged in both 2016 [31] and 2023 [117, 118]. In 2013, the results of the Zlotkin 2013 (C) trial became available, with no harm observed to 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.

Although this update included five additional trials with 1830 participants, our overall conclusions remain unchanged from the 2016 review. The direction and certainty of effect estimates are largely unchanged across outcomes, suggesting no increase in clinical malaria risk with iron supplementation when malaria prevention and case management are in place, reinforcing previous findings regarding the benefits and safety of iron supplementation in malaria-endemic areas when malaria control measures are in place.

AUTHORS' CONCLUSIONS

Implications for practice

This review did not find clear evidence of 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 also did not indicate an increased risk for these outcomes in children who were non-anaemic at baseline and in children younger than two years of age. Overall, iron supplementation may not be associated with harm when malaria prevention or management services services were available, but may be associated with an increased risk of malaria in settings with no access to such services. In trials where iron was administered with antimalarial drugs, a reduction in malaria was observed, likely reflecting the protective effect of the antimalarials themselves.

The findings of this updated review are consistent with the 2016 version. The new data added to this meta-analysis since 2016 strengthens the overall certainty of some outcomes and reinforces the importance of considering malaria control context when interpreting the safety of iron supplementation. As previous studies have suggested, malaria prevention and management should be offered to children regardless of iron supplementation, since these interventions reduce malaria, mortality, and anaemia [119]. Improvements in the prevention and management of malaria have occurred in recent decades in sub-Saharan Africa, along with

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the implementation of novel malaria vaccines. This may allow for iron supplementation in safer settings than ever before [120, 121, 122, 123, 124].

There is currently insufficient data to permit any conclusions on the intervention of iron with folic acid. Folic acid may interfere with the efficacy of sulfadoxine-pyrimethamine, an antimalarial drug used for intermittent preventive treatment or treatment of clinical episodes of malaria [125, 126]. Furthermore, there is no consistent evidence of folate deficiency among children under two years old in malaria-endemic areas [126].

Implications for research

Uncertainty remains about whether iron supplementation alone increases malaria risk in iron-replete, non-anaemic children, particularly in areas lacking malaria control. An individual participant data meta-analysis of existing trials could help clarify this by enabling more detailed analyses of baseline iron status and age, especially in children aged six months to two years.

Well-designed observational studies are also needed to assess long-term outcomes such as growth and neurodevelopment, which are not adequately captured in short-term trials. Further trials should evaluate how best to integrate iron supplementation with malaria prevention strategies across different epidemiological settings. Trials should prioritise reporting key effect modifiers: site-level malaria transmission intensity, seasonality (months of enrolment and follow-up), baseline anaemia and iron status, and malaria-control co-interventions such as insecticide-treated bed nets, chemoprevention, and deworming. In multi-country trials, disaggregated site estimates should be provided or individual participant data shared to enable geography-stratified and moderator analyses.

The evidence for iron combined with folic acid remains limited and of low certainty. Additional studies are required to clarify safety, especially where antifolate antimalarials are used.

As this update reinforces previous conclusions without major changes in effect estimates, future updates may not be warranted unless new, high-quality trials become available.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD006589.pub5.

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Characteristics of ongoing studies

Supplementary material 5 Analyses

Supplementary material 6 Data package

Supplementary material 7 Analysis of cluster randomized controlled trials

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Zohra Lassi, University of Adelaide;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Pricivel Carrera, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Cynthia Stafford, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Lisa Winer, Cochrane Central Production Service;
- Peer reviewers (provided comments and recommended an editorial decision): Alejandro González-Garay, Research Methodology Unit Instituto Nacional de Pediatría, Mexico (clinical review), Clare Miles, Cochrane (methods review), Ina Monsef, Cochrane Evidence Synthesis Unit (ESU) Germany/UK, Institute of Public Health, Faculty of Medicine and University Hospital Cologne, University of Cologne (search review), Ibrahim Atia, Sudan (consumer reviewer). One additional peer reviewer provided clinical/content peer review but chose not to be publicly acknowledged.

Contributions of authors

First edition

Juliana U Ojukwu (JUO) conceived the idea for the review, wrote the protocol, identified studies for inclusion and exclusion, extracted data, entered data into RevMan [59], participated in the data analysis, and reviewed all drafts of the first edition of this review.

Joseph Okebe (JO) wrote the protocol, identified studies for inclusion and exclusion, extracted data, entered data into RevMan [59], participated in the data analysis, and reviewed all drafts and the final review.

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Dafna Yahav (DY) extracted data, entered data into RevMan [59], participated in the data analysis, and reviewed all drafts and the final review.

Mical Paul (MP) planned the data extraction, extracted data, entered data into RevMan [59], participated in the data analysis, and wrote the review.

All review authors approved the final publication.

2011 edition

MP updated the RevMan file [59], reorganised previous data, carried out subgroup analyses, performed the GRADE assessment, 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 data for the newly included studies, participated in the data analysis, and reviewed all drafts and the final review. This work was done in partial fulfilment of RS Master's in Epidemiology.

DY performed the search for the 2011 update, extracted data for the newly included studies, performed the GRADE assessment, and revised the final manuscript.

2015 edition

Ami Neuberger (AN) identified studies for inclusion and exclusion, extracted data for the newly included studies, entered data into RevMan [59], performed the data analysis, and wrote the final version of the update.

MP updated the RevMan file [59], reorganised previous data, performed the subgroup analyses and GRADE assessment, 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 approved the revised publication.

2024 edition

Michael Itzkovich (MI) identified studies for inclusion and exclusion, extracted data for the newly included studies, entered data into RevMan [59], performed the data analysis and GRADE assessment, and assisted in writing the final version of the update.

AN revised the final manuscript.

Itai Harris (IH) identified studies for inclusion and exclusion and performed the risk of bias assessment.

DY identified studies for inclusion and exclusion, contacted authors for additional information, resolved disagreements in study selection and data extraction, and revised the final manuscript.

MP identified studies for inclusion and exclusion, updated the RevMan file [59] (reorganised previous data, structural adjustments), performed the subgroup analyses and GRADE assessment, resolved disagreements in study selection and data extraction, co-wrote the final version of the update, and revised the final manuscript.

Mayan Gilboa (MG) identified studies for inclusion and exclusion, extracted data for the newly included studies, entered data into RevMan [59], performed the data analysis and GRADE assessment, and wrote the final version of the update.

All review authors approved the revised publication.

What's new

Declarations of interest

MI has no known conflicts of interest.

AN has no known conflicts of interest.

IH has no known conflicts of interest.

DY has a collaborative retrospective study (Pfizer) and received funding for an investigator-initiated clinical study (Shionogi).

MP has no known conflicts of interest.

MG has no known conflicts of interest.

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External sources

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  Project number 300342-104

Registration and protocol

This review follows the protocol originally registered with the Cochrane Infectious Diseases Group and published in the Cochrane Database of Systematic Reviews (2016, Issue 2, DOI: 10.1002/14651858.CD006589.pub4).

Data, code and other materials

As part of the published Cochrane review, the following materials are available for download via the Cochrane Library data package (see Supplementary material 2): full search strategies for each database; full citations of each unique report for all studies (included, ongoing, awaiting classification or excluded at the `full-text` screen); `study-level` data, including study information, study arms and outcomes; consensus risk of bias assessments; and analysis datasets, including overall estimates, subgroup estimates and individual data rows. Analyses and data management were conducted within RevMan Web using the inbuilt computation methods. No additional code was used outside RevMan. Template `data-extraction` forms (Excel) are available from the authors on reasonable request.

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Date	Event	Description
9 January 2026	New search has been performed	This is an update of the 2016 version of the review. Five additional trials (1830 participants) were included, increasing the total number of studies from 35 to 40 and participants from 31,955 to 33,785. We applied stricter inclusion criteria, excluding trials with low-dose or intermittent iron regimens and those assessing supplementation during acute malaria. We reassessed the risk of bias for all included studies and updated the certainty of the evidence for the main outcomes using the GRADE approach. These updates are reflected in the summary of findings tables, which report the prespecified critical outcomes (clinical malaria, severe malaria, all-cause mortality) and the important outcome hospitalisations/clinic visits. For most outcomes, the direction and certainty of the effect estimates remained consistent with the 2016 review. The author team has also changed in this version.
9 January 2026	New citation required but conclusions have not changed	This is an update of the 2016 version of the review. Five additional trials (1830 participants) were included, increasing the total number of studies from 35 to 40 and participants from 31,955 to 33,785. We applied stricter inclusion criteria, excluding trials with low-dose or intermittent iron regimens and those assessing supplementation during acute malaria. We reassessed risk of bias and updated the certainty of the evidence using the GRADE approach. For most outcomes, the direction and certainty of effect estimates remained consistent with the 2016 review. The author team has also changed in this version.

History

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

Date	Event	Description
27 July 2025	New citation required but conclusions have not changed	New author team. We conducted a new search and updated the analyses. We reassessed risk of bias using the Cochrane RoB 1 tool and updated the certainty of the evidence using GRADE. The summary of findings tables have been updated accordingly and present the prespecified critical outcomes (clinical malaria, severe malaria, all-cause mortality) and the important outcome hospitalisations/clinic visits.
20 May 2025	New search has been performed	We updated the literature search.
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 hospitalisations and clinic visits in comparison 1. This has been corrected in Issue 4, 2009.

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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 amongst rural communities in subtropical zones where wide geographical variations in transmission exist	AFRO: Angola, Botswana, Cape Verde, Chad, Eritrea, Ethiopia, Kenya[1], 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% amongst 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, Kenya[1], Liberia, Madagascar, Malawi, Mali, Mozambique, Nigeria, São Tomé and Príncipe, 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% amongst 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, Kenya[1], Madagascar, Malawi, Mozambique AMRO: Dominican Republic, Suriname EMRO: Djibouti, Somalia, Sudan, Yemen SEARO: Myanmar WPRO: Cambodia, Lao People's Democratic Republic

[1]Kenya is listed under meso-, hyper-, and holoendemic categories, reflecting regional and temporal variation in transmission intensity as defined in the individual studies.
Abbreviations: WHO: World Health Organization; 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

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

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

Abbreviations: RDA: Recommended Dietary Allowance; WHO: World Health Organization

Table 3. Detailed search strategies

Search strategy used for MEDLINE (OVID) and Embase (OVID)

1 Iron/ or Iron, Dietary/

2 iron supplement*.mp.

3 Iron Compounds/

4 Ferrous Compounds/ or ferrous.mp.

5 1 or 2, or 3 or 4

6 Malaria/ or malaria*.mp.

7 (Chad or Belize or Bolivia or El Salvador or Guatemala or Mexico or Nicaragua or Costa Rica or Paraguay or Afghanistan or Iraq or Oman).mp

8 (Armenia or Azerbaijan or Georgia or Kyrgyzstan or Tajikistan or Nepal or China or Angola or Botswana or Cape Verde or Eritrea or Ethiopia or Kenya or Mauritania or Namibia or Niger or Zambia or Zimbabwe).mp.

9 (Brazil or Colombia or Ecuador or Guyana or Panama or Peru or Venezuela).mp.

10 (Iran or Pakistan or Saudi Arabia or Bangladesh or Bhutan or India or Indonesia or Sri Lanka or Thailand).mp.

11 (((Malaysia or Angola or Benin or Burkina Faso or Cameroon or Central African Republic or Congo or Côte d'Ivoire or Equatorial Guinea or Gabon or Gambia or Ghana or Guinea or Guinea-Bissau or Liberia or Madagascar or Malawi or Mali or Mozambique or Nigeria or São Tomé) and Principe) or Senegal or Sierra Leone or Togo or Uganda or Tanzania or Zambia).mp.

12 (Timor-Leste or Papua New Guinea or Philippines or Solomon Islands or Vanuatu or Vietnam).mp.

13 (Burundi or Dominican Republic or Suriname or Djibouti or Somalia or Sudan or Yemen).mp.

14 (Myanmar or Cambodia or Lao or Laos).mp.

15, 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14,

16, 5 and 15

17 Child, Preschool/ or Child/ or child*.mp.

18 infant*.mp. or Infant/

19 (baby or babies or toddler* or preschool* or pre-school* or schoolchild* or adolescent* or teenager*).mp.

20 Adolescent/

21, 17 or 18 or 19 or 20

22, 16 and 21

23 randomised controlled trial.mp. or Randomised Controlled Trial/

24 controlled clinical trial.mp. or Controlled Clinical Trial/

25 (randomi?ed or randomly).ab. or (randomi?ed or randomly).ti.

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Table 3. Detailed search strategies

26 (placebo* or double-blind*).ab. or (placebo* or double-blind*).ti.

27, 23 or 24, or 25 or 26.

28, 22 and 27

Global Index Medicus

tw:((tw:(iron OR ferrous)) AND (tw:(baby OR babies OR toddler* OR preschool* OR pre-school* OR schoolchild* OR adolescent* OR teenager* OR infant*))) AND (tw: Chad or Belize or Bolivia or El Salvador or Guatemala or Mexico or Nicaragua or Costa Rica or Paraguay or Afghanistan or Iraq or Oman or Armenia or Azerbaijan or Georgia or Kyrgyzstan or Tajikistan or Nepal or China or Angola or Botswana or Cape Verde or Eritrea or Ethiopia or Kenya or Mauritania or Namibia or Niger or Zambia or Zimbabwe or Brazil or Colombia or Ecuador or Guyana or Panama or Peru or Venezuela or Iran or Pakistan or Saudi Arabia or Bangladesh or Bhutan or India or Indonesia or Sri Lanka or Thailand or Malaysia or Angola or Benin or Burkina Faso or Cameroon or Central African Republic or Congo or Côte d'Ivoire or Equatorial Guinea or Gabon or Gambia or Ghana or Guinea or Guinea-Bissau or Liberia or Madagascar or Malawi or Mali or Mozambique or Nigeria or São Tomé) and Principe) or Senegal or Sierra Leone or Togo or Uganda or Tanzania or Zambia or Timor-Leste or Papua New Guinea or Philippines or Solomon Islands or Vanuatu or Vietnam or Burundi or Dominican Republic or Suriname or Djibouti or Somalia or Sudan or Yemen or Myanmar or Cambodia or Lao or Laos) Filter: Clinical trials.

Cochrane Library

ID Search

#1 MeSH descriptor: [Iron, Dietary] this term only

#2 MeSH descriptor: [Iron Compounds] this term only

#3 MeSH descriptor: [Ferrous Compounds] this term only

#4 iron supplement* or ferrous:ti,ab,kw (Word variations have been searched)

#5 MeSH descriptor: [Iron] this term only

#6, #1 or #2 or #3 or #4 or #5

#7 MeSH descriptor: [Malaria] explode all trees

#8 malaria*:ti,ab,kw (Word variations have been searched)

#9 Chad or Belize or Bolivia or El Salvador or Guatemala or Mexico or Nicaragua or Costa Rica or Paraguay or Afghanistan or Iraq or Oman:ti,ab,kw (Word variations have been searched)

#10 Armenia or Azerbaijan or Georgia or Kyrgyzstan or Tajikistan or Nepal or China or Angola or Botswana or Cape Verde or Eritrea or Ethiopia or Kenya or Mauritania or Namibia or Niger or Zambia or Zimbabwe:ti,ab,kw (Word variations have been searched)

#11 Brazil or Colombia or Ecuador or Guyana or Panama or Peru or Venezuela or Iran or Pakistan or Saudi Arabia or Bangladesh or Bhutan or India or Indonesia or Sri Lanka or Thailand or Malaysia or Angola or Benin or Burkina Faso or Cameroon or Central African Republic or Congo or Côte d'Ivoire or Equatorial Guinea or Gabon or Gambia or Ghana or Guinea or Guinea-Bissau or Liberia or Madagascar or Malawi or Mali or Mozambique or Nigeria or São Tomé and Príncipe or Senegal or Sierra Leone or Togo or Uganda or Tanzania or Zambia or Timor-Leste or Papua New Guinea or Philippines or Solomon Islands or Vanuatu or Vietnam or Burundi or Dominican Republic or Suriname or Djibouti or Somalia or Sudan or Yemen or Myanmar or Cambodia or Lao or Laos:ti,ab,kw (Word variations have been searched)

#12, #8 or #9 or #10 or #11

#13, #6 and #12

#14 MeSH descriptor: [Child] explode all trees

#15 MeSH descriptor: [Infant] explode all trees

#16 baby or babies or toddler* or preschool* or pre-school* or schoolchild* or adolescent* or teenager* or infant*:ti,ab,kw (Word variations have been searched)

#17, #14 or #15 or #16

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Table 3. Detailed search strategies

#18, #13 and #17
WHO ICTRP trials register, Clinicaltrials.gov
Iron or ferrous
And
Baby or babies or toddler* or preschool* or pre-school* or schoolchild* or adolescent* or teenager* or infant*

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Table 4. Overview of Included Studies and Synthesis Table (OSIS)

Study ID, country, (year)	Study design	Population size (age/setting/subgroup)	Intervention	Comparator	Key outcome	Duration of treatment and follow-up	Malaria endemicity
Adam, Ethiopia (1997)	Cluster RCT	841 children (mean 45.2 months, rural schools, anaemia subgroup)	Ferrous sulphate elixir, about 3 mg/kg/day elemental iron	Placebo elixir	Effect of iron supplementation on malaria	Duration of treatment: 12 weeks Duration of follow-up: 12 months	Mesoendemic
Akenzua, Nigeria (1985)	Individually RCT	112 children (1-14 years, community-rural, no-anaemia subgroup)	Unsupervised or supervised administration of ferrous fumarate tablets 1.5 or 2 mg/kg/day with 5 mg/day folic acid and antimalarial drug	Folic acid plus chloroquine	Anaemia	Duration of treatment: 6 weeks Duration of follow-up: 6 weeks	Hyperendemic
Ayoya, Mali (2009)	Individually RCT	218 children (7-12 years, school-urban, no anaemia subgroup)	Iron plus praziquantel: ferrous sulphate tablets, 60 mg elemental iron per day 5 days/week, plus praziquantel tablet 40 mg at enrolment and at 4 weeks	Praziquantel tablet 40 mg at enrolment and for 4 weeks	Effect of iron supplementation on haematological status	Duration of treatment: 12 weeks Duration of follow-up: 12 weeks	Hyperendemic
Berger, Togo (2000)	Individually RCT	197 children (6-36 months, community, anaemia subgroup)	Iron betainate tablet, 2-3 mg/kg/day	Placebo	Impact of iron supplementation on haematological status, cell-mediated immunity and susceptibility to infections	3 months treatment, 9 months follow-up	Hyperendemic
Berger, Vietnam (2006)	Individually RCT	988 children (mean 5.9 months, community, rural, no anaemia subgroup)	Ferrous sulphate syrup 10 mg/day ± zinc ± vitamin A	Placebo	To evaluate the effect of combined iron–zinc supplementation on micronutrient status, growth and morbidity	6 months treatment, 6 months follow-up	Hyperendemic
Desai, Kenya (2003)	Individually RCT	546 children (2-36 months, community, anaemia subgroup)	Ferrous sulphate 3-6 mg/kg/day + sulfadoxine-pyrimethamine	Placebo + sulfadoxine-pyrimethamine	Hb concentrations	8 weeks treatment, 24 weeks follow-up	Hyperendemic

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Table 4. Overview of Included Studies and Synthesis Table (OSIS) *(Continued)*

Dossa, Benin (2001)	Individually RCT	177 children (3-5 years, community, rural, no anaemia subgroup)	Ferrous sulphate 60 mg/day + albendazole	Placebo	Appetite and physical growth performance in preschool children	3 months treatment, 10 months follow-up	Hyperendemic
Dossa, Benin (2001)	Individually RCT	154 children (3-30 months)	Ferrous fumarate 66 mg/day+ mebendazole	Placebo + mebendazole	Physical growth performance, Hb level, and intestinal helminth egg loads in preschool children	6 weeks treatment, 5.5 months follow-up	Hyperendemic
Esan, Malawi (2013)	Individually RCT	209 children (6-59 months, HIV clinic, anaemia subgroup)	3 mg/kg/day elemental iron + multivitamins + malaria chemoprophylaxis	Multivitamins+ malaria chemoprophylaxis	Hb level, HIV disease progression, and morbidity	3 months treatment, 6 months follow-up	Hyperendemic
Fahmida, Indonesia (2007)	Individually RCT	800 children (3-6 months, community, anaemia subgroup)	Iron sulphate syrup 10 mg/day ± zinc ± vitamin A	Placebo	Infants' micronutrient status and linear growth	6 months treatment, 12 months follow-up	Mesoendemic
Frosch, Uganda (2024)	Individually RCT	200 children (6 months-12 years, community, no anaemia subgroup)	Ferrous sulfate (6-23 months 12.5 mg; >24 months received 30 mg)	Placebo	Mean Hb concentration at day 84	84 days treatment, 84 days follow-up	Holoendemic
Gebreselassie, Ethiopia (1996)	Individually RCT	500 children (5-14 years, school, anaemia subgroup)	Ferrous sulphate 60 mg/day	Placebo	Host susceptibility to malaria infection	3 months treatment, 6 months follow-up	Mesoendemic
Giovannini, Cambodia (2006)	Cluster RCT	204 children (6 months, community, no anaemia subgroup)	Iron fumarate 12.5 mg/day	Placebo	Growth, anaemia, and iron deficiency	12 months treatment, 12 months follow-up	Holoendemic
Greisen, Zambia (1986)	Cluster RCT	464 children (5-15 years, school, rural, no anaemia subgroup)	Iron-fumarate 66 mg/day ± chloroquine ± tetrachloroethylene	Placebo	Association between anaemia and running distance	6 weeks treatment, 6 weeks follow-up	Hyperendemic
Hall, Mali (2002)	Cluster RCT	1201 children (mean 11.4 years, school, rural, no anaemia subgroup)	Ferrous sulphate tablets 0.25 mg/kg/day + folic acid + albendazole	Albendazole only	Hb status	10 weeks treatment, 14–16 weeks follow-up	Hyperendemic

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Table 4. Overview of Included Studies and Synthesis Table (OSIS) *(Continued)*

Harvey, Papua New Guinea (1989)	Individually RCT	318 children (mean 9.7 years, school, rural, no anaemia subgroup)	Ferrous sulphate tablets 3.8 mg/kg/day	Placebo (cellulose/lactose tablets)	Malaria (clinical/uncomplicated)	16 weeks of treatment, 24 weeks follow-up	Hyperendemic
Hess, Côte d'Ivoire (2002)	Individually RCT	169 children (mean 8.5 years, school, rural, no anaemia subgroup)	Ferrous sulphate tablets 1 mg/kg/day + albendazole	Albendazole	Anaemia prevalence	16 weeks of treatment, 20 weeks follow-up	Hyperendemic
Hop, Vietnam (2005)	Individually RCT	169 children (6-12 months, rural, anaemia subgroup)	Iron 10 mg/day	Placebo	Anaemia prevalence and growth	6 months treatment, 6 months follow-up	Hyperendemic
Latham, Kenya (1990)	Individually RCT	55 children (mean 8 years, school, no anaemia subgroup)	Ferrous sulphate tablets 2.85 mg/kg/day	Placebo	Growth parameters	15 weeks of treatment, 32 weeks follow-up	Holoendemic
Lawless, Kenya (1994)	Individually RCT	87 children (mean 8.7 years, school, rural, no anaemia subgroup)	Ferrous sulphate sustained release capsules of 1.4 mg/kg/day	Placebo	Appetite and growth	14 weeks treatment, 14 weeks follow-up	Holoendemic
Leenstra, Kenya (2009)	Individually RCT	279 girls (12–18 years, school, urban, no anaemia subgroup)	Ferrous sulphate tablets 0.4 mg/kg/day + vitamin A	Placebo	Clinical malaria	5 months treatment, 5 months follow-up	Mesoendemic
Massaga, Tanzania (2003)	Individually RCT	291 children (mean 14.3 weeks, rural, anaemia subgroup)	Ferric ammonium citrate suspension 7.5 mg/kg/day Â± amodiaquine	Placebo ± amodiaquine	Infections	6 months treatment, 10 months follow-up	Holoendemic
Mebrahtu, Tanzania (2004)	Cluster RCT	684 children (mean 33.4 months, community, rural, anaemia subgroup)	Ferrous sulphate syrup 1 mg/kg/day	Placebo	Malaria infection	12 months treatment, 12 months follow-up	Holoendemic
Menendez, Tanzania (1997)	Individually RCT	832 children (8-48 weeks, rural, anaemia subgroup)	Ferrous glycine sulphate syrup 2 mg/kg/day ± pyrimethamine + dapsone	Placebo	Hb, anaemia and iron-related outcomes	16 weeks treatment, 1 year follow-up	Hyperendemic
Mohammed Gambia (2023)	Individually RCT	642 children (6-35 months, rural, anaemia subgroup)	IHAT (iron hydroxide adipate tartrate) (20 mg/day) or ferrous sulphate (12.5 mg/day)	Placebo	Anaemia	12 weeks treatment, 16 weeks follow-up	Hyperendemic

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Table 4. Overview of Included Studies and Synthesis Table (OSIS) *(Continued)*

Mwanri, Tanzania (2000)	Individually RCT	136 children (mean 10.8 years, school, rural, no anaemia subgroup)	Ferrous sulphate tablets thrice weekly, 0.65 mg/kg/day	Placebo	Anaemia and growth	3 months treatment, 3 months follow-up	Hyperendemic
Olsen, Kenya (2006)	Individually RCT	231 children (mean 8.7 years, community, no anaemia subgroup)	Ferrous dextran tablets 0.7 mg/kg/day	Placebo	Hb and ferritin	12 months treatment, 12 months follow-up	Mesoendemic
Powers, Gambia (1983)	Individually RCT	80 children (4–12 years, community, rural, no anaemia subgroup)	Ferrous sulphate 2 mg/kg/day plus chloroquine	Placebo plus chloroquine	Haematological status	6 weeks treatment, 6 weeks follow-up	Hyperendemic
Prasetyani, Indonesia (2017)	Individually RCT	605 children (5-18 years, schools, semi-urban, anaemia subgroup)	Iron(III)-hydroxide polymaltose complex 6 mg/kg	Placebo	Malaria	8 weeks treatment, 16 weeks follow-up	Mesoendemic
Richard, Peru (2006)	Individually RCT	855 children (0.5-15 years, school, rural, no anaemia subgroup)	Ferrous sulphate syrup 0.75 mg/kg/day ± zinc	Placebo	Morbidity - malaria, diarrhoea, and respiratory infections	7 months treatment, 7 months follow-up	Mesoendemic
Roschnik, Malawi (2003)	Cluster RCT	1160 children (7–12 years, school, rural, no anaemia subgroup)	Ferrous sulphate 65 mg/week + folic acid + praziquantel	Placebo + praziquantel	Mean Hb concentration and anaemia prevalence, on school attendance, performance, drop-out, and repetition rates	3.5 months treatment, 3.5 months follow-up	Hyperendemic
Sazawal, Tanzania (2006)a	Cluster RCT	15,956 children (1-35 months, community)	Iron tablets 12.5 mg/day + vitamin A	Placebo + vitamin A	Composite of death or hospital admission due to malaria	12 months treatment, 18 months follow-up	Holoendemic
Sazawal, Tanzania (2006)b	Cluster RCT	1691 children (1-35 months, community)	Iron tablets 12.5 mg/day + vitamin A	Placebo + vitamin A	Composite of death or hospital admission due to malaria	12 months treatment, 18 months follow-up	Holoendemic
Sazawal, Tanzania (2006)c	Cluster RCT	3171 children (1-35 months, community)	Iron tablets 12.5 mg/day + vitamin A	Placebo + vitamin A	Composite of death or hospital admission due to malaria	12 months treatment, 18 months follow-up	Holoendemic

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Table 4. Overview of Included Studies and Synthesis Table (OSIS) *(Continued)*

Smith, Gambia (1989)	Cluster RCT	213 children (6 months–5 years, community, anaemia subgroup)	Ferrous sulphate 3-6 mg/kg	Orange juice	Hb/iron + malaria status	12 weeks treatment, 13 weeks follow-up	Hyperendemic
Tang, Kenya (2017)	Individually RCT	45 children (6 months, community, rural no anaemia subgroup)	Micronutrient powder containing 12.5 mg/day iron	Micronutrient powder	Composition of the gut microbiome and inflammation status	3 months treatment, 3 months follow-up	Holoendemic
Teshome, Kenya (2017)	Individually RCT	338 children (12–36 months, rural, no subgroup analysis)	Home fortification with 12.5 mg iron as ferrous fumarate	Placebo	Hb response	30 days treatment, 100 days follow-up	Hyperendemic
Thi, Vietnam (2006)	Individually RCT	168 children (mean 87 months, community, no subgroup analysis)	Iron fumarate tablets 200 mg and mebendazole	Placebo and mebendazole	Hb response	6 months treatment, 6 months follow-up	Hyperendemic
Verhoef, Kenya (2002)	Individually RCT	328 children (mean 18 months	Ferrous fumarate 6 mg/kg/week and sulfadoxine/pyrimethamine	Sulfadoxine-pyrimethamine plus placebo	Hb response	3 months treatment, 3 months follow-up	Mesoendemic
Zlotkin, Ghana (2003)	Individually RCT	437 children (mean 16.5 months, community, no anaemia subgroup)	Ferrous sulphate drops 12.5 mg/day	Placebo	Long-term haematological outcome	6 months treatment, 18 months follow-up	Hyperendemic

Hb: haemoglobin; RCT: randomised controlled trial

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Table 5. Studies reporting malaria as an outcome: malaria definitions, types of outcomes and methods of surveillance and treatment in the trial

Study ID	**Clinical definition**	**Laboratory definition**	**Malaria-related outcomes reported**	**Time of assessment***	**Malaria prevention** and management strategies	Malaria prevention or management
Adam 1997 (C)	Physician's diagnosis of malaria	Any parasitaemia (all malaria species, assumed most *Plasmodium falciparum* since trial conducted in same region as Gebreselassie 1996)	Clinical malaria; any parasitaemia; malaria necessitating hospitalisation (used as severe malaria); parasite density (all N events/N individuals, unadjusted for clustering)	3 months to end of treatment	Blood smears for malaria are obtained before, during and after treatment. Children with clinical malaria are referred to a local hospital and treated.	No
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* were also treated with sulfadoxine-pyrimethamine.	Yes
Berger 2000 [128, 129, 130]	Isolated fever	Parasite density of > 3000 (*P falciparum*, *P malariae* and *P ovale* were 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 FU	Blood smears for malaria are obtained at baseline, end of treatment (3 months) and end of FU (6 months). Chloroquine treatment given for all isolated fevers	Yes
Desai 2003 [131, 132]	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 is referred for further treatment.	Yes
Esan 2013 [133]	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 [134]	Not stated	Not stated	Participants with "malaria" (used primarily as clinical malaria)	6 months to end of treatment	Not stated	No

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Table 5. Studies reporting malaria as an outcome: malaria definitions, types of outcomes and methods of surveillance and treatment in the trial *(Continued)*

Gebreselassie 1996	Fever ≥ 37.5 °C with signs and symptoms suggestive of malaria and other diagnoses ruled out	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 are negative at baseline and repeated weekly. Chloroquine with or without primaquine given for any positive smear.	Yes
Harvey 1989 [135]	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 were 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 are obtained at baseline and the end of treatment. Treatment not stated	Yes
Lawless 1994 [136]	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 were positive) and monthly during the trial. No treatment offered for positive smears; symptomatic cases referred to a 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% randomised). Treatment not stated	Yes

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Table 5. Studies reporting malaria as an outcome: malaria definitions, types of outcomes and methods of surveillance and treatment in the trial *(Continued)*

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
Mohammed 2023	Fever ≥ 37.5 °C	RDT testing and conformation with bloodfilm	Episodes of clinical malaria-defined as fever and parasitaemia), as well as uncomplicated malaria and severe malaria	113 days (4 weeks after end of treatment)	Capillary blood collection for malaria RDT testing at baseline and weekly	No
Prasetyani 2017	Fever ≥ 38 °C	Any positive smear or positive RT-PCR	Detection of microscopically positive malarial parasitaemia at one of the four time points and the number of RT-PCR positive children at week 16.	16 weeks (8 weeks after the end of treatment)	Measurement of body temperature and collection of blood for malaria slide and RT-PCR malaria detection every 4 weeks	No
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 2006a (C)	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 is about 1 year and the end of FU is 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 2006b (C)	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 is about 1 year and the end of FU is about 18 months.	Blood smears for malaria at baseline, and at 6 and 12 months. Sulfadoxine-pyrimethamine treatment delivered to home to all slide-confirmed malaria participants or clinical diseases 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	3 months to end of treatment	Blood smears for malaria at baseline, 2 weeks and end of treatment. No treatment at baseline; clinical malaria referred to local healthcare services	No

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Table 5. Studies reporting malaria as an outcome: malaria definitions, types of outcomes and methods of surveillance and treatment in the trial *(Continued)*

			events/N individuals, unadjusted for clustering)			
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	Dipsticks for *P falciparum* were 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 are supplied with instructions for use. Children with malaria treated with artemisinin combination therapy.	Yes

*Time of assessment: refers to time from randomisation.
Abbreviations: CI: confidence interval; FU: follow-up; OR: odds ratio; RDT: rapid diagnostic test; RR: risk ratio; RT-PCR: reverse transcription-polymerase chain reaction

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Table 6. Analysis of cluster randomised trials adjusting standard errors

Study 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 hospitalisation	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 2006a (C)	Clinical malaria	467	7950	411	8006	1.4	—	**1.16 (1.00** to **1.34)**	**0.15**	—	**0.07**
Sazawal 2006a (C)	Severe malaria (cerebral)	—	7950	—	8006	1.4	—	**1.32 (1.02** to **1.70)**	**0.28**	—	**0.13**
Sazawal 2006b (C)	Clinical malaria	14	815	30	804	1.2	—	**0.46 (0.24 to 0.88)**	**-0.78**	—	**0.33**
Sazawal 2006b (C)	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
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

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Table 6. Analysis of cluster randomised trials adjusting standard errors *(Continued)*

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: CI: confidence interval; cont: control; DE: design effect used for adjustment (see methods for derivation of design effect and ICC used per outcome); ICC: intracluster correlation coefficient; Int: intervention; n: number of outcomes; N: number evaluated; OR: odds ratio; RR: risk ratio; SE: standard error

Table 7. Analysis of cluster randomised 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 2006a (C)	All-cause mortality	149	7950	130	8006	1.4	1.001	149	7941	130	7996
Sazawal 2006b (C)	All-cause mortality	8	815	9	804	1.2	1.0004	8	815	9	804
Sazawal 2006b (C)	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); ICC: intracluster correlation coefficient; Int: intervention; n: number of outcomes; N: number evaluated.

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Table 8. Comparative malaria parasitaemia rates

Study ID	Intervention	Unit of measurement	Parasitaemia intervention	Parasitaemia control	N Intervention	N 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	Control or 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

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Table 8. 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: N: number evaluated; RBC: red blood cell; SD: standard deviation; WBC: white blood cell

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