Effect of iron supplementation on incidence of infectious illness in children: systematic review

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Abstract

Objective To evaluate the effect of iron supplementation on the incidence of infections in children.

Design Systematic review of randomised controlled trials.

Data sources 28 randomised controlled trials (six unpublished and 22 published) on 7892 children.

Interventions Oral or parenteral iron supplementation or fortified formula milk or cereals.

Outcomes Incidence of all recorded infectious illnesses, and individual illnesses, including respiratory tract infection, diarrhoea, malaria, other infections, and prevalence of positive smear results for malaria.

Results The pooled estimate (random effects model) of the incidence rate ratio (iron *v* placebo) was 1.02 (95% confidence interval 0.96 to 1.08, P=0.54; P < 0.0001 for heterogeneity). The incidence rate difference (iron minus placebo) for all recorded illnesses was 0.06 episodes/child year (– 0.06 to 0.18, P=0.34; P < 0.0001 for heterogeneity). However, there was an increase in the risk of developing diarrhoea (incidence rate ratio 1.11, 1.01 to 1.23, P=0.04), but this would not have an overall important on public health (incidence rate difference 0.05 episodes/child year, –0.03 to 0.13; P=0.21). The occurrence of other illnesses and positive results on malaria smears (adjusted for positive smears at baseline) were not significantly affected by iron administration. On meta-regression, the statistical heterogeneity could not be explained by the variables studied.

Conclusion Iron supplementation has no apparent harmful effect on the overall incidence of infectious illnesses in children, though it slightly increases the risk of developing diarrhoea.

Introduction

Anaemia caused by iron deficiency is a major public health problem, affecting 46% of school children globally.[1] Iron deficiency has adverse effects on psychomotor development[2] and on the capacity to work. The reversible consequences in childhood have prompted recommendations for early intervention. The proposed interventions rely primarily on enhancing iron intake either through supplementation or fortification of food.[3 4]

Because of these proposed interventions their safety needs to be unequivocally established. The role of iron in resistance to disease remains controversial. Iron deficiency may be an important defence mechanism, and the term "nutritional immunity" was coined to highlight the importance of hypoferraemia in preventing bacterial growth.[5] Conversely, data suggest that iron deficiency is associated with impairment of cell mediated immunity and the bactericidal activity of neutrophils, thus increasing susceptibility to infection.[6 7] Iron supplementation may also cause damage to cells mediated through free radicals.[8] Objective safety data from longitudinal studies of iron supplementation are conflicting; trials have shown either beneficial effects,[9] no effect,[10] or an increase in infectious illnesses.[11 12] Children, particularly infants and those living in developing countries, are vulnerable to infectious diseases. It is thus important to establish the safety of iron supplementation in children on a public health scale. We conducted a systematic review to determine the effect of iron supplementation on infectious illnesses.

Methods

Inclusion criteria

To be included trials had to be randomised placebo controlled trials—except for those in which iron was given parenterally, in which case trials could be non-placebo controlled because it would be difficult to administer a similar placebo; had to investigate iron supplementation through the oral or the parenteral route or as formula milk or cereals fortified with iron; and evaluate one or more infectious illnesses as an outcome measure. We also included studies in which other micronutrients and drugs were simultaneously administered if the only difference between the study and the control groups was iron supplementation.

Data collection

We searched computerised bibliographic medical databases, including Medline, Cochrane controlled trials register, Embase, IBIDS, and Healthstar. We also reviewed reference lists of identified articles and hand searched reviews, bibliographies of books, and abstracts and proceedings of international conferences or meetings. Donor agencies, "experts," and authors of recent iron supplementation trials were contacted to identify any additional or ongoing trials. The title and

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abstract of the studies identified in the computerised search were scanned to exclude studies that were obviously irrelevant. We retrieved the full text of the remaining studies and identified studies that fulfilled the inclusion criteria. To avoid publication bias we included published and unpublished trials.

Quality of methods

We assessed the quality of trials using recommended criteria.[13 14] Concealment of allocation was classed as adequate, unclear, inadequate, or not used. To assess completeness of follow up we classified studies by percentage of participants excluded (<3%, 3-9.9%, 10-19.9%, and ≥20%). Blinding was classified as double blinding, single blinding, no blinding, and unclear. TG Abstracted all data.

Data abstraction

We used preformed questionnaires to abstract data. The data included in this review were derived from the published papers or were provided by the authors. Illnesses and the outcomes included were as defined by the authors. Whenever possible we contacted the authors for clarifications.

Statistical analysis

The presence of bias in the extracted data was evaluated by funnel plots.[15] We used the metabias command in Stata software to perform the statistical tests for funnel plot asymmetry.[16] The pooled estimates of incidence rate ratio and incidence rate difference were calculated by StatsDirect statistical software (version 1.9.5; StatsDirect, Cambridge) with fixed effects and random effects model assumptions.[17] This program also computes the formal test of heterogeneity (Q statistic). We primarily report random effects estimates because most of the pooled results obtained were statistically heterogeneous. We chose incidence rate summary to account for the differences in duration of follow up in the various extracted studies. The data were recorded in the form of the total number of episodes of illness and the person time exposed (in child years). For trials in which the results were available in this format we recorded the figures directly from the publication, and this category of studies was labelled as the "actual" group. In the "computed" group of trials, the person time of follow up was not provided, and we calculated estimates from the product of the duration of follow up and the sample sizes available at the beginning and the end of the study. In some trials data were obtained by quantitative analysis of published graphs.

Some studies had reported only on the prevalence of malaria parasitaemia confirmed from smears at the beginning and the end of the supplementation period. Pooled estimates of the odds ratio of positive smears at the end of the supplementation period were computed by the "meta" command in Stata software.[16] We also performed a meta-regression (restricted maximum likelihood iteration) through the "metareg" command in Stata software to determine the pooled log odds ratio of developing malaria in the group with iron supplementation compared with the placebo group. The covariate in the meta-regression equation was the log odds ratio at the beginning of the trial to adjust for the baseline differences in the prevalence of malaria.

We carried out stratified analyses for quality of methods; case detection (active field based or passive facility based); specificity of case definition; route of iron administration (parenteral, oral supplement, or fortified food); dose—this was initially planned but could not be performed as it could not be extracted for each study; duration of supplementation; type of illness (gastrointestinal, respiratory, malaria, non-diarrhoeal, or others); and baseline haemoglobin concentration in the supplemented group. The contribution of these variables to heterogeneity was also explored by meta-regression.[16 17]

Table 1 Characteristics of excluded trials

	Reason for exclusion
Andelman[18]	Information not extractable
Burman[19]	Information not extractable
Damodaran[20]	Supplemented folic acid with iron
Oppenheimer[21]	Same study group in included trial
Bates[22]	Supplemented other micronutrients
Heresi[23]	Supplemented other micronutrients
Chwang[9]	Information not extractable
Heywood[24]	Subset of an included trial
Angeles-Agdeppa[25]	Supplemented other micronutrients
Heresi[26]	Supplemented other micronutrients
Van Hensbroek[27]	Supplemented multiple antimalarials in crossover manner
Beck[28]	Same study group in an included trial
Von Stujvenberg[29]	Supplemented other micronutrients
Picaud[30]	Erythropoietin given with iron supplementation
Allen, Lonnerdal, Ninh, Zimmermann, Quyen	Unpublished, full text not available from authors

Results

We identified 47 randomised controlled trials that were potentially eligible. Of these, 38 trials were published in medical journals or were theses[9–52] and 9 were unpublished (box 1). Nineteen studies were ineligible (table 1). We therefore evaluated 28 studies (22 published[10 11 31–44 47–52] two theses,[45 46] and six unpublished) in this systematic review.

Baseline characteristics of the studies

Table 2 depicts the baseline characteristics of the included trials. Thirteen trials were in children aged <1 year, 10 studies included preschool children (≤ 5 years), and five trials included children aged >5 years. Eleven trials were from Africa, eight from Asia, five from the Americas, two from Europe, and two from Australia and New Zealand. The eligibility and exclusion criteria varied. Most of the studies used oral iron supplementation (20/28; 71%). Three trials used parenteral administration, and five studies used iron fortified foods.

Differences in the mode of administration may have implications for bioavailability of iron and its possible effect on the immune function. The supplementation dose used could influence the degree to which illness was affected. As a crude generalisation, the fortified formulas had the lowest dosage and the parenteral route had the highest. The duration of supplementation and follow up for oral intake varied from 2 months to 30 months.

The specificity of the definition used for illness was variable. Specificity of diagnosis has the potential to bias the observed effect of supplementation on illness. For example, low specificity definitions could underestimate the effect of iron supplementation on malaria

Unpublished studies

Papers presented at International Nutritional Anaemia Consultative Group (INACG) Symposium, Hanoi, Vietnam, 2001

Allen LH, Lopez P, Galvaz IA, Garcia DP, Isoard F, Rosado JL. Does multiple micronutrient supplementation increase haemoglobin and iron status more than iron alone?

Lonnerdal B, Domellof M, Dewey KG, Cohen R, Rivera LL, Hernell O. Effects of iron supplementation of breastfed infants in Honduras and Sweden from 4-9 or 6-9 months of age.

Ninh NX, Berger J, Tolvanen M, Trung NQ, Nhien NV, Lien DK, et al. Control of iron deficiency anaemia in Vietnamese infants by efficacy of iron and zinc supplementation to reduce anaemia and growth faltering in Vietnamese infants.

Zimmermann M, Hess S, Adou P, Torresani T, Cook J, Hurrell R. Treatment of iron deficiency in goitrous children improves the efficacy of iodized salt.

Quyen DT, Berger J, Ninh NX, Khan NC, Khoi HH. Control of iron deficiency anaemia in Vietnamese infants by weekly and daily iron supplementation: efficacy and effectiveness.

Atukorala S, de Silva A, Ahluwalia N. Evaluation of iron status of children in the presence of infections: effect of iron supplementation on iron status, infection and morbidity.*

Other unpublished papers

Rice AL, Stoltzfus RJ, Tielsch JM, Savioli L, Montresor A, Albonico M, et al. Iron supplementation and mebendazole treatment do not affect respiratory or diarrhoeal morbidity incidence rates in Tanzanian preschoolers. 1999.*

Agarwal D, Sachdev HPS, Mallika V, Singh T. Iron supplementation in breast fed, full term, low birth weight infants. 1999.*

Nagpal J, Sachdev HPS, Mallika V, Singh T. Iron supplementation with complementary feeding in predominantly breastfed infants. 2000.*

*Included in the review

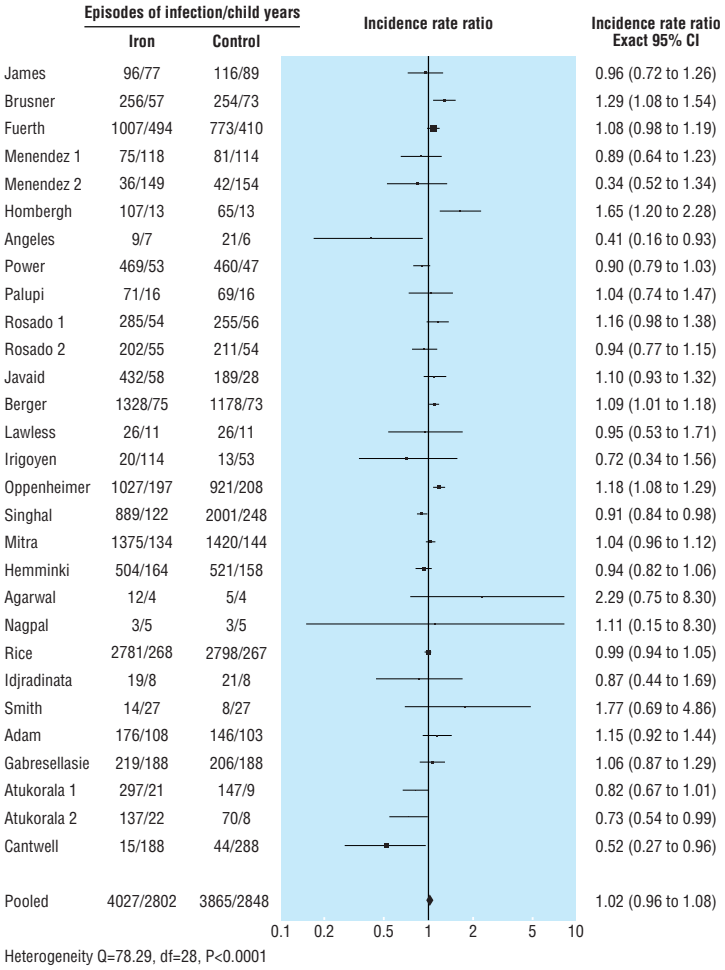

Fig 2 Forest plot for incidence rate ratio for all recorded illnesses

due to a high rate of misclassification of non-malarial fevers as malaria. In some studies, fever was recorded as an additional infectious illness because fever in children is mostly attributed to infectious diseases.[41 51] Inclusion of fever as a separate infection may lead to duplication of data because fever may accompany malaria, respiratory tract infection, and diarrhoea. However, we have included it on the assumption that an equal distribution of fever in both groups would eliminate any bias and also prevent non-inclusion of any observed infection.

The methods of surveillance varied: 15 were clinic based whereas 13 were field trials with active surveillance for cases. If iron supplementation has selective effects on mild rather than more severe episodes of illness then differences in methods of case detection may influence the observed effects of iron supplementation.

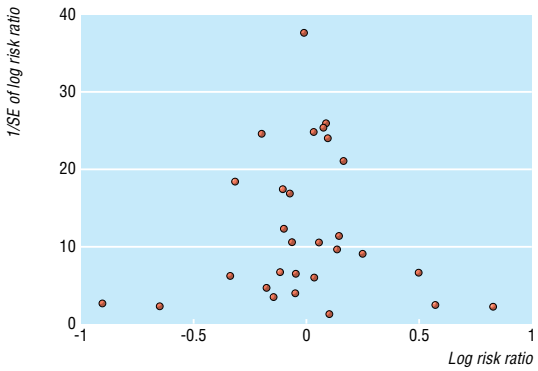

Fig 1 Funnel plot of extracted studies

Bias detection for included studies

The funnel plot (fig 1) seems symmetrical, and we found no evidence of bias using the Egger (weighted regression) method (P=0.663 for bias) or the Begg (rank correlation) method (continuity corrected P=0.488).

Pooled and stratified estimates

We collected data on 7892 children followed up for 5650 child years—4027 children and 2802 child years in the iron supplemented group and 3865 children and 2848 child years in the placebo group (table 3). The pooled estimate of the incidence rate ratio (iron versus placebo) for all the recorded morbidities was 1.02 (95% confidence interval 0.96 to 1.08; P=0.54; test for heterogeneity Q=78.29, P < 0.0001, fig 2). Calculations of incidence rate ratio based on "actual" data

Table 2 Baseline characteristics of included trials (posted as supplied by author)

	Location	Age group	Sample size (total, iron, control)	Method of randomisation, allocation concealment, follow up, blinding*	Eligibility and exclusion criteria	Iron supplementation (route, dose, duration of supplementation, duration of follow up, intervention in treatment group, control group)	Case detection	Morbidities studied	Case definition
James, 1960[31]	USA	1 month	181, 84, 97	Unclear, B, D, C	Birth weight ≤2000 g, survival for more than 24 hours, weight >2000 g	Parenteral, 50 mg X 5, -, 11 months; T/t: Iron dextran C: No placebo	Clinic	URTI, LRTI, Diarrhoea	Hospital diagnosis
Cantwell, 1972[32]	New Zealand	2 days	238, 94, 144	By alternate days of birth, D, A, C	Maori babies (at least 25% Maori blood) delivered at Hawkes Bay	Parenteral, 50mg X 5, -, 30 months; T/t: Iron dextran C: No placebo	Clinic	Pneumonia, URTI, skin infections, gastroenteritis	Hospital diagnosis
Fuerth, 1974[33]	USA	1 month	602, 329, 273	Alternate allocation, D, D, A	Full term *Exclusion:* On iron medication, vitamins, received blood transfusion, received less than 50% supplements between two visits, Hb dropped to <80 g/l during study	Oral, 30mg/day, 18 months, 18 months; T/t: Ferrous sulphate C: Placebo containing bismuth	Clinic	Infectious illness	Not mentioned
Oppenheimer, 1986[34]	Papua New Guinea	2 months	486, 236, 250	Matched pairs randomised into treatment and control groups, B, C, B	Resident of Madang	Parenteral, 150 mg, 10 mo T/t: Iron dextran C: Saline	Field and clinic	URTI, LRTI, TB, lung abscess, malaria, gastroenteritis, etc.	RTI- WHO classification Malaria: symptomatic Rest: not mentioned
Harvey, 1989[35]	Papua New Guinea	8-12 years	312, 156, 156	Matched pairs randomised into treatment and control groups, C, C, D	Hb = 80-120 g/l	Oral, 130 mg/day, 4 months, 6 months; T/t: Ferrous sulphate C: Identical placebo (75% cellulose, 25% lactose)	Field	Malaria prevalence	PS for malaria +
Smith, 1989[11]	Gambia	6 months-5 years	213, 106, 107	Unclear, B, C, A	Hb, MCV <3rd centile of reference population *Exclusion:* Hb <50 g/l	Oral, 3-6 mg/kg/day, 3 months, 3 months T/t: Ferrous sulphate in orange juice C: Orange juice	Field	Malaria	Axillary temp >37.5°C with *P. falciparum* +
Power, 1991[36]	South Africa	3-12 months	149, 75, 74	Stratified randomisation by purpose written computer program, B, C, A	Birth weight ≥3000 g, Weight at 3 months = 5 kg in females and 5.5 kg in males, Hb >90 g/l at 3 months *Exclusion:* Blood transfusion received, serious illness before enrolment	Fortified, 40 mg/100 mg, 9 months, 9 months; T/t: Iron enriched formula C: Standard cow's milk formula	Clinic	RTI, GI infection, oral thrush, eye infection, others.	Not mentioned
Javaid, 1991[37]	Pakistan	4 months	129, 87, 42	Unclear, B, D, D	Birth weight >2500 g	Fortified, 7.5 mg/100 mg, 8 months, 8 months; T/t: Iron fortified milk cereal C: Milk cereal	Field	URTI, LRTI, diarrhoea	LRTI: significant complaint with +ve physical examination; Diarrhoea: >4 loose stools/day
Irigoyen, 1991[38]	USA	6 months	334, 228, 106	Unclear, B, D, A	Hb ≤115 g/l *Exclusion: Prematurity, milk allergy, failure to thrive, HIV+, recent H influenzae* type b meningitis, fed low iron formula, exclusively breastfed, primary physician refusal	Oral, 3, 6 mg/kg/day, 3 months, 3 months; T/t: Ferrous sulphate C: Identical placebo†	Clinic	Diarrhoea	Not mentioned
Chippaux, 1991[39]	Togo	6-36 months	190, 95, 95	Unclear, B, D, A	Hb ≥80 g/l	Oral, 2.5 mg/kg/day, 3 months, 9 months; T/t: Iron Betainate C: Identical placebo†	Clinic	Malaria	Smear positive
Brunser, 1993[40]	Chile	3 months	400, 200, 200	Random numbers table, A, D, A	Birth weight ≥2500 g, W/A ≥80% or 50th centile, Hb ≥105 g/l	Fortified, 12 mg/l, 6 months, 6 monthsl; T/t: Iron enriched milk C: Control milk	Field	Diarrhoea	>3 liquid stools/day or maternal report
Angeles, 1993[41]	Indonesia	2-5 years	80, 40, 40	Unclear, B, B, A	W/A z score between –2 and –3, Hb = 80-110 g/l, ferritin <120μg/l	Oral, 30 mg/day, 2 months, 2 months; T/t: Ferrous sulphate, Vitamin C C: Vitamin C	Field	Fever, RTI, Diarrhoea	Fever: Temp >37°C, Diarrhoea: >4 watery stools/d, RTI: not mentioned

Table 2 Baseline characteristics of included trials (posted as supplied by author) *contd*

	Location	Age group	Sample size (total, iron, control)	Method of randomisation, allocation concealment, follow up, blinding*	Eligibility and exclusion criteria	Iron supplementation (route, dose, duration of supplementation, duration of follow up, intervention in treatment group, control group)	Case detection	Morbidities studied	Case definition
Lawless, 1994[42]	Kenya	6-11 years	86, 44, 42	Stratified randomisation (by gender and initial Hb value), C, A, A	Hb ⩾80 g/l *Exclusion*; Heavy hookworm infection, Blood in the urine indicative of *S haematobium,* dislike of uji, absence at the time of interval exams	Oral, 150 mg/day, 3 months, 3 months; T/t: Ferrous sulphate C: Identical placebo†	School	Diarrhoea, cough, malaria	PS for MP+; diarrhoea, cough—not mentioned
Idjradinata, 1994[10]	Indonesia	12-18 months	47, 24, 23	Random numbers table, B, B, D	Birth weight >2.5 kg, singleton pregnancy, Hb ⩾8g/dL, wt, length and head circumference within 2 SD of NCHS standards. *Exclusion:* Congenital malformation, major perinatal complication, jaundice treated with phototherapy, hospital admission, supplementation with micronutreints before enrolment, chronic illness, folic acid deficiency, haemoglobinopathy or thalassaemia	Oral, 3 mg/kg/day, 4 months, 4 months; T/t: Ferrous sulphate C: Identical placebo†	Clinic	URTI, LRTI, gastroenteritis	Paediatrician's diagnosis
Hemminki, 1995[43]	Hungary	<45 days	322, 164, 158	Unclear, A, B, D	Birth weight ⩾2500 g *Exclusion:* Critically ill, malformations, child cared for outside home, consultation with private physician	Fortified, 6.5 mg/l, 10.5 months, 10.5 months; T/t: Iron fortified formula C: Non-fortified formula	Clinic	URTI, fever	Not mentioned
Van den Hombergh, 1996[44]	Tanzania	<30 months	100, 50, 50	Unclear, B, B, D	Hb ⩽50 g/l, PS for MP +. *Exclusion:* Cerebral malaria, Non-falciparum malaria, sickle cell anaemia, other significant illness	Oral, 200 mg/day, 3 months, 3 months; T/t: Ferrous sulphate, folic acid C: Folic acid	Clinic	Malaria, pneumonia, other infections	Malaria: smear positive Pneumonia, other infections: not mentioned
Adam, 1996[45]	Ethiopia	6 months-7 years	841, 431, 410	Unclear, B, B, A	Hb = 60-110 g/l	Oral, 3mg/kg/day, 3 months, 3 months; T/t: Ferrous sulphate C: Identical placebo†	Active	Malaria	Fever
Gebresellassie, 1996[46]	Ethiopia	5-14 years	500, 250, 250	Unclear, B, C, A	Hb = 50-120 g/l, *P falciparum* –ve	Oral, 60mg/day, 3 months, 6 months T/t: Ferrous sulphate C: Identical placebo†	Active	Malaria	Temp >37.5°C, *P. falciparum* +ve
Mitra, 1997[47]	Bangladesh	2-48 months	349, 172, 177	Block randomisation of 4 homogeneous clusters, A, C, A	*Exclusion:* Critically ill, congenital malformations, metabolic disorders	Oral, 15mg/day, 15 months, 15 months T/t: Ferrous gluconate, vitamins‡ C: Vitamins‡	Field	Diarrhoea, dysentery, ARI	Diarrhoea: >2 liquid stools/d and maternal report; Dysentery: blood in stools; ARI: >50 bpm in child <1 yr, >40 bpm in child 12-15 months
Palupi, 1997[48]	Indonesia	2-5 years	194, 96, 98	Unclear, B, B, A	Registered at village health centre	Oral, 15mg/week, 2 months, 2 months T/t: Ferrous sulphate C: Identical placebo†	Clinic	Worm infestation	Stool microscopy +
Rosado, 1997[49]	Mexico	1.5-3 years	219, 109, 110	Stratified randomisation (by age and sex), B, C, A	Age as stated	Oral, 20 mg/day, 12 months, 12 months Group 1 T/t: Ferrous sulphate C: Placebo† Group 2 T/t: Ferrous sulphate, zinc methionine C: Zinc methionine	Field	RTI, diarrhoea, fever	RTI: runny nose, common cold, sore throat, cough; Diarrhoea, Fever: maternal reporting

Table 2 Baseline characteristics of included trials (posted as supplied by author) *contd*

	Location	Age group	Sample size (total, iron, control)	Method of randomisation, allocation concealment, follow up, blinding*	Eligibility and exclusion criteria	Iron supplementation (route, dose, duration of supplementation, duration of follow up, intervention in treatment group, control group)	Case detection	Morbidities studied	Case definition
Menendez, 1997[50]	Tanzania	2 months	832, 417, 415	Block randomisation, A, D, A	Birth weight >1500 g, PCV >25% at 8 weeks. *Exclusion:* Congenital malformation, congenital or neonatal infection.	Oral, 2 mg/kg/day, 4 months, 10 months Group 1 T/t: Ferrous glycine sulphate, placebo syrup‡ C: Placebo syrups‡ Group 2 T/t: Iron syrup, Deltaprim C: Deltaprim, placebo syrup‡	Clinic	Malaria	Axillary temp >37.5°C with *P falciparum* +ve
Rice, 1999 (unpublished)	Tanzania	3-56 months	614, 307, 307	Randomisation of households of the study area into two groups, B, A, B	Age as stated	Oral, 10mg/day, 12 months, 12 months T/t: Iron sulphate C: Identical placebo†	Field	Diarrhoea, dysentery, RTI, malaria, fever	RTI: cough with difficult breathing; Diarrhoea: >3 liquid stools/ day; Dysentery: blood in stools
Agarwal, 1999 (unpublished)	India	50-80 days	73, 37, 36	Computer generated random numbers, A, C, A	Gestation ⩾37 weeks, birth weight <2500 g. *Exclusion:* Twins, congenital malformations, received blood, adverse neonatal event requiring admission in nursery, sampling before recruitment >10 ml, significant current morbidity, maternal APH	Oral, 3 mg/kg/day, 2 months, 2 months T/t: Ferric ammonium citrate C: Identical placebo†	Clinic	RTI	Maternal report as interpreted by paediatrician
Nagpal, 2000 (unpublished)	India	4-6 months	100, 49, 51	Computer generated random numbers, A, D, A	Gestation ⩾37 weeks, birth weight ⩾2500 g, breast fed *Exclusion:* Twins, congenital malformations, received blood or iron, adverse neonatal event requiring admission in nursery, sampling before recruitment >10 ml, significant current morbidity	Oral, 2.5mg/kg/day, 2 months, 2 months T/t: Ferric ammonium citrate C: Identical placebo†	Clinic	RTI, diarrhoea, others	Maternal report as interpreted by paediatrician
Berger, 2000[51]	Togo	6-36 months	197, 100, 97	Unclear, B, C, B	Hb ⩾80 g/l	Oral, 2-3mg/kg/day, 3 months, 9 months T/t: Iron Betainate C: Identical placebo†	Field	URTI, LRTI, malaria, diarrhoea, cutaneous infection, fever, worms	Not mentioned
Singhal, 2000[52]	UK	9 months	493, 162, 331	Separate randomisation for Asians and non-Asians, A, C, A	Birth weight >2500 g, gestation >36 weeks. *Exclusion:* Severe chronic disease, congenital anomalies, haematologic disorders, previously received iron or blood	Fortified, 12mg/L, 9 months, 9 months; T/t: Iron fortified formula C: Cows' milk or standard formula	Clinic	Chest infection, URTI, others	URTI, diarrhoea: maternal report; chest infection: treatment with antibiotics
Atukorala, 2001 (unpublished)	Sri Lanka	5-10 years	364, 262, 102	Unclear, B, C, A	Outpatients at children's hospital	Oral, 60mg/day, 2 months, 2 months T/t: Ferrous sulphate C: Lactose	Field	URTI, diarrhoea	URTI: clinical evidence with inflammatory parameters; diarrhoea: >2 semisolid watery stools/day

ARI=acute respiratory illness; bpm=breaths per minute; C=intervention in the control group; GI=gastrointestinal; Hb=haemoglobin, LRTI=lower respiratory tract infection; MCV=mean corpuscular volume; MP=malarial parasite; *P falciparum*=*Plasmodium falciparum*; PS=peripheral smear; RTI=respiratory tract infection; TB=tuberculosis; URTI=upper respiratory tract infection; T/t=intervention in the treatment group;
*Allocation concealment: (A) adequate; (B) unclear; (C) inadequate; (D) not used. Completeness of follow up: (A) <3% of participants excluded; (B) 3% to 9.9% of participants excluded; (C) 10% to 19.9% of participants excluded; (D) 20% or more of participants excluded. Blinding: (A) double blinding; (B) single blinding; (C) no blinding; (D) unclear.
†Mentioned by the authors as being identical in appearance and/or taste; exact composition not mentioned.
‡Exact composition not mentioned.

(when available) and computations from sample size at the end of the study (1.03, 0.97 to 1.08, P=0.21; test for heterogeneity Q=72.19, $P<0.0001$) were virtually identical with computations based on sample sizes at the beginning of the study. Besides the incidence rate ratio, from the public health perspective the incidence rate difference is considered to be more informative. The incidence rate difference (iron minus placebo) for all the recorded illnesses was 0.06 episodes per child

Table 3 Extracted data from included studies. Episodes of infection and exposure time (in child years) (posted as supplied by author)

	Total infections				Diarrhoea				Respiratory tract infection				Malaria				Other infections			
	Iron		Control		Iron		Control		Iron		Control		Iron		Control		Iron		Control	
Study	Epi	Obs	Epi	Obs	Epi	Obs	Epi	Obs	Epi	Obs	Epi	Obs	Epi	Obs	Epi	Obs	Epi	Obs	Epi	Obs
James[31]	96	77	116	88.91	16	77	25	88.91	80	77	91	88.91								
Cantwell[32]	15	188	44	288	1	188	6	288	7	188	30	288					7	188	8	288
Fuerth[33]	1007	493.5	773	409.5													1007	493.5	773	409.5
Oppenheimer[34]	1027	196.66	921	208.33	44	196.66	37	208.33	498	196.66	435	208.33	82	196.66	66	208.33	403	196.66	383	208.33
Smith[11]	14	26.5	8	26.75									14	26.5	8	26.75				
Power[36]	469	52.5	460	46.5	84	52.5	91	46.5	105	52.5	88	46.5					280	52.5	281	46.5
Javaid[37]	432	58	189	28	250	58	105	28	182	58	84	28								
Irigoyen[38]	20	114	13	53	20	114	13	53												
Brunser[40]	256	56.88	254	72.57	256	56.88	254	72.57												
Angeles[41]	9	6.5	21	6.16	2	6.5	6	6.16	4	6.5	10	6.16					3	6.5	5	6.16
Lawless[42]	26	11	26	10.5	7	11	8	10.5	19	11	18	10.5								
Idjradinata[10]	19	8	21	7.66													19	8	21	7.66
Hemminki[43]	504	164	521	158					288	164	305	158					216	164	216	158
Van den Hombergh[44]	107	12.5	65	12.5					26	12.5	5	12.5					81	12.5	60	12.5
Adam[45]	176	107.75	146	102.5	73	107.75	67	102.5	40	107.75	32	102.5	41	107.75	32	102.5	22	107.75	15	102.5
Gabresellasie[46]	219	187.5	206	187.5									219	187.5	206	187.5				
Mitra[47]	1375	134	1420	143.5	670	127	695	139	705	141	725	148								
Palupi[48]	71	15.5	69	15.66													71	15.5	69	15.66
Rosado 1[49]	285	54	255	56	76	54	62	56	192	54	179	56					17	54	14	56
Rosado 2[49]	202	55	211	54	46	55	40	54	139	55	163	54					17	55	8	54
Menendez 1[50]	75	118.4	81	113.8									75	118.4	81	113.8				
Menendez 2[50]	36	148.5	42	145.4									36	148.5	42	145.4				
Rice (unpublished)	2781	267.97	2798	267.39	388	267.98	376	267.37	1006	267.98	995	267.37					1387	267.97	1427	267.39
Agarwal (unpublished)	12	3.75	5	3.58					12	3.75	5	3.58								
Nagpal (unpublished)	3	4.5	3	5	2	4.5	2	5	1	4.5	0	5					0	4.5	1	5
Berger[51]	1328	75	1178	72.75	211	75	127	72.75	623	75	627	72.75					494	75	424	72.75
Singhal[52]	889	121.5	2001	248.25	66	121.5	132	248.25	823	121.5	1869	248.25								
Atukorala 1 (unpublished)	297	21.33	147	8.66	23	21.33	5	8.66	274	21.33	142	8.66								
Atukorala 2 (unpublished)	137	22.33	70	8.33	8	22.33	2	8.33	129	22.33	68	8.33								
Totals	11 887	2802.07	12 064	2848.7	2243	1616.93	2053	1763.83	5153	1840.3	5871	1821.34	467	785.31	435	784.28	4024	1701.38	3705	1709.95

Epi=no of episodes of infections observed. Obs=observation/exposure time in child years. RTI=respiratory tract infections.

year (−0.06 to 0.18, P=0.34; test for heterogeneity Q= 80.01, P<0.0001).

Stratified analysis for the effect on individual infectious illnesses showed that children in the iron supplementation group had an 11% (1% to 23%) higher risk (incidence rate ratio) of developing diarrhoea (P=0.04; test for heterogeneity Q= 30.24, P= 0.04, table 4). The effect on other individual illnesses was not significant. However, the incidence rate difference (public health impact) for diarrhoea was 0.05 episodes per child year (−0.03 to 0.13, P=0.21; test for heterogeneity Q= 42.03, P=0.001). Further stratification showed that the significantly increased risk of diarrhoea associated with iron supplementation was restricted to oral supplementation (nine studies; incidence rate ratio 1.15, 1.01 to 1.32, P=0.04; incidence rate difference 0.18 episodes per child year, −0.01 to 0.37; P=0.07). The individual studies had not determined the cause of the diarrhoea, though dysentery indicates severe infectious diarrhoea. Only two studies provided information on dysentery; they showed no difference in the incidence between the two groups. Meta-regression showed that the route of iron administration (oral versus other) was not significantly associated with incidence rate ratio for diarrhoea (risk ratio 1.06, 0.85 to 1.32, P=0.59).

From the available data we found no increased risk of severe illness associated with iron supplementation (analysis possible only for lower respiratory tract infection and dysentery).

Malarial parasitaemia

Table 5 shows the data extracted on malarial parasitaemia. The pooled odds ratio for positive smear tests for malaria at the end of the supplementation period (random effects model) was 1.43 (1.08 to 1.91, P=0.014; test for heterogeneity Q=11.611, P=0.114, fig 3. Meta-regression analysis of trials with relevant data (excluding the study by Oppenheimer et al[34]) indicated that this treatment effect was significantly associated with the baseline positivity of smear tests (for a unit increase in log odds ratio of baseline positivity, the treatment effect increased by 2.89; 1.37 to 6.10; P=0.005) but not iron supplementation (1.24; 0.98 to 1.57; P=0.076).

Table 4 Pooled estimates (incidence rate ratio) of effect of iron supplementation on total and individual infections

Infection type	No of trials	Random effects model (95% CI)	P value	Tests for heterogeneity (P value)
Diarrhoea	17	1.11 (1.01 to 1.23)	0.04	30.24 (0.04)
Non-diarrhoeal	24	0.97 (0.95 to 1.06)	0.99	63.05 (<0.0001)
Respiratory tract	17	0.98 (0.90 to 1.06)	0.54	53.18 (<0.0001)
Malaria	5	1.07 (0.94 to 1.24)	0.35	5.58 (0.35)
Other infections*	13	1.04 (0.98 to 1.11)	0.20	18.15 (0.15)
Lower respiratory tract†	8	0.97 (0.83 to 1.23)	0.93	21.91 (0.003)
Dysentery†	2	1.00 (0.87 to 1.15)	0.99	0.02 (0.90)

*Other infections included septicaemia, urinary tract infections, tuberculosis, unspecified fever, pyoderma, and infectious morbidities not classifiable under respiratory tract infections, diarrhoea, or malaria.
†Included as component of respiratory tract infection or diarrhoea (as relevant). Separate stratification done to assess possible differential effects on more severe infection.

Table 5 Extracted data from trials depicting prevalence of smears positive for malaria

Study	Baseline		End	
	Iron	Control	Iron	Control
Hombergh[44]	50/50	50/50	13/47	13/47
Berger et al[51]	59/100	62/97	40/84	42/79
Rice (unpublished)	258/316	253/295	233/279	221/256
Chippaux[39]	72/120	74/120	59/120	66/120
Smith[11]	23/106	19/107	28/97	16/90
Harvey[35]	119/159	103/159	78/141	57/138
Gebresellassie[46]	30/239	31/241	23/239	17/241
Oppenheimer[34]	—	—	37/200	24/212

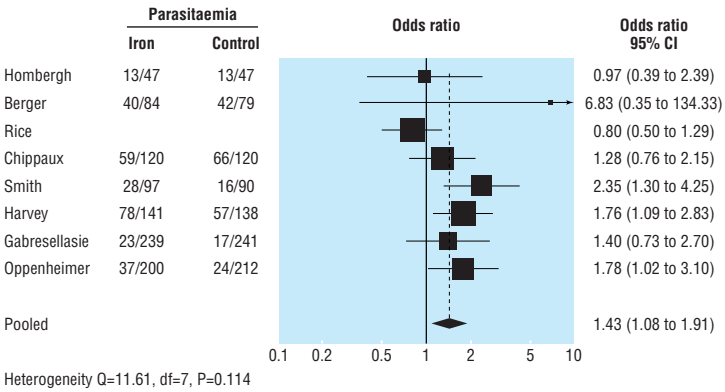

Fig 3 Forest plot for odds ratio of malarial parasitaemia (positive results on blood smear test) at end of supplementation period

Meta-regression analyses to explore heterogeneity

Stratified estimates indicated that iron supplementation did not significantly ($P>0.05$) increase the incidence of infections (incidence rate ratio and incidence rate difference), irrespective of the quality of methods, methods of surveillance, route of iron supplementation, duration of supplementation, geographic location of the study population, or the basal haemoglobin concentration of the iron supplemented group (data not presented). Meta-regression analysis showed that the treatment effect (incidence rate ratio) was not significantly associated with any of these study characteristics (table 6).

Discussion

The results from our analysis of these studies show that iron supplementation does not significantly increase the risk of overall infection. However, there was an increase in the risk of developing diarrhoea, but this would not have an important overall impact on public health. The occurrence of other illnesses and malarial parasitaemia (adjusted for positive smear results at baseline) was not significantly affected by iron administration ($P>0.05$).

Strengths and limitations of analysis

Despite wide clinical and methodological heterogeneity in the various trials, the main inference remained stable for the various sensitivity analyses that we performed. An important caveat is the lack of uniform definitions for the individual clinical morbidities. Uniform definitions and active surveillance would have provided greater weight to the conclusions. Furthermore, not all the included trials were of high quality. We could not explain the statistical heterogeneity by various study characteristics.

There are still some questions unanswered and some new issues raised. We could not determine whether the higher risk of diarrhoea was a result of increased gastrointestinal infections or a consequence of the irritant effect of iron on the gut motility, a known effect.[53] Dysentery is invariably infective in origin, and the two trials that provided information found no evidence of an increase in dysentery in children receiving iron supplements.

We could not analyse the effect of dose on the incidence of infections. However, the near absence of any important adverse effects, particularly diarrhoea, in children receiving fortified foods (compared with medicinal iron) raises the possibility of a dose related effect. Interestingly, there was also a similar significant protective effect against the development of respiratory tract infections (four studies; incidence rate ratio=0.92; 0.86 to 0.98; P=0.02). However, our meta-regression analysis showed that the route of administration was not significantly associated with incidence rate ratio. Fortification with low doses of iron is closest to the physiological situation and could theoretically be considered the safest public health intervention. There is thus a case for concomitant evaluation of the possible beneficial effects of iron fortified foods on the haematological response and infections.

Meta-regression analysis suggested that the risk of acquiring infectious illnesses is inversely associated with the baseline haemoglobin concentration. Stratified analysis also suggested increased risk of infections in children who had a mean baseline concentration below 100 g/l. Iron supplementation promotes production of free radicals, and this may have a deleterious effect on the immunity of a child. Ironically, defences against free radicals are compromised the

Table 6 Meta-regression analyses for incidence rate ratio (IRR)

Characteristic	Univariate analysis IRR (95% CI), P value	Controlled for all variables IRR (95% CI), P value
Quality of study:		
Allocation concealment (not adequate *v* adequate)	1.02 (0.90 to 1.16), 0.716	0.94 (0.72 to 1.22), 0.624
Completeness of follow up (≥10% participants excluded *v* <10% excluded)	1.01 (0.89 to 1.16), 0.839	1.17 (0.92 to 1.50), 0.202
Blinding (not double blind *v* double blind)	1.06 (0.95 to 1.19), 0.298	1.11 (0.91 to 1.36), 0.287
Morbidity surveillance (passive *v* active)	0.94 (0.84 to 1.05), 0.266	1.03 (0.83 to 1.27), 0.809
Route of supplementation (oral or parenteral *v* fortified)	1.04 (0.92 to 1.17), 0.555	1.03 (0.82 to 1.30), 0.815
Geographic location (developed* *v* Asian or African countries)	0.98 (0.87 to 1.11), 0.759	1.05 (0.81 to 1.36), 0.723
Unit increase in baseline haemoglobin status of iron supplemented group (g/l)	0.97 (0.94 to 1.01), 0.151	0.95 (0.90 to 1.00), 0.059
Unit increase in duration of supplementation (months)	1.00 (0.99 to 1.02), 0.864	0.99 (0.97 to 1.03), 0.921

*Europe, North America, South America, and Australia and New Zealand.

What is already known on this topic

Iron supplementation is recommended to prevent iron deficiency, which is a major health problem, especially in the developing countries

Conflicting data exist regarding the possibility of an increase in the incidence of infections with iron supplementation, resulting in concern about the safety of this intervention

What this study adds

Iron supplementation has no apparent harmful effect on the overall incidence of infectious illnesses in children

Iron administration increases the risk of developing diarrhoea

Fortification of foods may be the safest and most beneficial mode of supplementation in relation to infectious illnesses

most in iron deficiency and malnutrition,[54 55] which are conditions likely to benefit the most from iron supplementation. Interestingly, all the studies included in this stratified subset were from regions of the African continent where malaria is endemic. Some data suggest indirectly that iron deficiency in such regions decreases the susceptibility to disease related to malaria, HIV, and tuberculosis.[56] The safety of iron supplementation in people with anaemia, particularly in regions where malaria is endemic, may be difficult to determine because of the ethical problem of withholding treatment in a control group.

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Contributors: TG prepared the protocol, applied the search strategy, performed the retrieval of articles, and extracted the data from the included studies. HPSS developed the idea for the review, finalised the protocol and search strategy, and performed the statistical analysis. Both the authors contributed to the drafting of the final version of the paper. HPSS is guarantor.

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