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

Tarun Gera, H P S Sachdev

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Data sources 28 randomised controlled trials (six unpublished and 22 published) on 7892 children.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 vs 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. Iron deficiency has adverse effects on psychomotor development 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. 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. 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. Iron supplementation may also cause damage to cells mediated through free radicals. Objective safety data from longitudinal studies of iron supplementation are conflicting; trials have shown either beneficial effects, no effect, or an increase in infectious illnesses. 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
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.5,14 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 metafit command in Stata software to perform the statistical tests for funnel plot asymmetry.15 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

Results
We identified 47 randomised controlled trials that were potentially eligible. Of these, 38 trials were published in medical journals or were theses and 9 were unpublished (box 1). Nineteen studies were ineligible (table 1). We therefore evaluated 28 studies (22 published and 6 theses, and 2 theses, 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


Other unpublished papers


*Included in the review.

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. 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.

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 2848 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)

<table>
<thead>
<tr>
<th>Location</th>
<th>Age group</th>
<th>Sample size (total, iron, controls)</th>
<th>Method of randomisation, allocation concealment, follow up, blindinga</th>
<th>Eligibility and exclusion criteria</th>
<th>Iron supplementation (route, dose, duration of supplementation, duration of follow up, intervention in treatment group, control group)</th>
<th>Case detection</th>
<th>Morbidities studied</th>
<th>Case definition</th>
</tr>
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<tbody>
<tr>
<td>James, 1960b</td>
<td>USA</td>
<td>1 month 181, 84, 97</td>
<td>Unclear, B, D, C</td>
<td>Birth weight &gt;2000 g, survival for more than 24 hours, weight &gt;2000 g</td>
<td>Parenteral: 50 mg X 5, 11 months; T/t: Iron dextran C: No placebo</td>
<td>Clinic</td>
<td>URTI, LRTI, Diarrhoea</td>
<td>Hospital diagnosis</td>
</tr>
<tr>
<td>Cantwell, 1972a</td>
<td>New Zealand</td>
<td>2 days 238, 94, 144</td>
<td>By alternate days of birth, D, A, C</td>
<td></td>
<td>Parenteral: 50mg X 5, 30 months; T/t: Iron dextran C: Placebo containing bismuth</td>
<td>Clinic</td>
<td>Pneumonia, URTI, skin infections, gastroenteritis</td>
<td>Hospital diagnosis</td>
</tr>
<tr>
<td>Fuerth, 1974a</td>
<td>USA</td>
<td>1 month 602, 259, 273</td>
<td>Alternate allocation, D, A, C</td>
<td>Full term Exclusion: On iron mediation, vitamins, received blood transfusion, received less than 50% of iron between two visits; Hb dropped to &lt;80 g/l during study</td>
<td>Oral, 30mg/day, 18 months, 18 months; T/t: Ferrous sulphate C: Placebo</td>
<td>Clinic</td>
<td>Infectious illness</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Oppenheimer, 1986a</td>
<td>Papua New Guinea</td>
<td>2 months 466, 256, 250</td>
<td>Matched pairs randomised into treatment and control groups, B, C, D</td>
<td>Resident of Madang</td>
<td>Parenteral: 150 mg, 10 mo; T/t: Iron dextran C: Saline</td>
<td>Field and clinic</td>
<td>URTI, LRTI, TB, lung abscess, malaria, gastroenteritis, etc</td>
<td>Malaria prevalence</td>
</tr>
<tr>
<td>Harvey, 1989a</td>
<td>Papua New Guinea</td>
<td>8-12 years 312, 156, 156</td>
<td>Matched pairs randomised into treatment and control groups, C, C, D</td>
<td>Hb = 80-120 g/l</td>
<td>Oral, 130mg/day, 4 months, 6 months; T/t: Ferrous sulphate C: Identical placebo (75% cellulose, 25% lactose)</td>
<td>Field</td>
<td>URTI, LRTI</td>
<td>PS for malaria +</td>
</tr>
<tr>
<td>Smith, 1989a</td>
<td>Gambia</td>
<td>6 months-5 years 213, 106, 107</td>
<td>Unclear, B, C, A</td>
<td>Hb, MCV &lt;3rd centile of reference population Exclusion: Hb &lt;50 g/l</td>
<td>Oral, 3-6 mg/kg/day, 3 months, 3 months; T/t: Ferrous sulphate in orange juice C: Orange juice</td>
<td>Field</td>
<td>Malaria</td>
<td>Auxiliary temp &gt;37.5°C with P. falciparum +</td>
</tr>
<tr>
<td>Power, 1991b</td>
<td>South Africa</td>
<td>3-12 months 149, 75, 74</td>
<td>Stratified randomisation by purpose written computer program, B, C, A</td>
<td>Birth weight &gt;3000 g, Weight at 3 months = 5 kg in females and 5.5 kg in males, Hb &gt;80 g/l at 3 months Exclusion: Blood transfusion received, serious illness before enrolment</td>
<td>Fortified, 40 mg/100 mg, 9 months, 9 months; T/t: Iron enriched formula C: Standard cow’s milk formula</td>
<td>Clinic</td>
<td>URTI, LRTI, RTI</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Javaid, 1991b</td>
<td>Pakistan</td>
<td>4 months 129, 87, 42</td>
<td>Unclear, B, D, D</td>
<td>Birth weight &gt;2500 g</td>
<td>Fortified, 7.5 mg/100 mg, 8 months, 8 months; T/t: Iron fortified milk cereal C: Milk cereal</td>
<td>Field</td>
<td>URTI, LRTI, diarrhoea</td>
<td>Malaria</td>
</tr>
<tr>
<td>Irigoyen, 1991b</td>
<td>USA</td>
<td>6 months 334, 228, 106</td>
<td>Unclear, B, D, A</td>
<td>Hb &lt;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</td>
<td>Oral, 3, 6 mg/kg/day, 3 months, 3 months; T/t: Ferrous sulphate C: Identical placebo†</td>
<td>Clinic</td>
<td>Diarrhoea</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Chippaux, 1991b</td>
<td>Togo</td>
<td>6-36 months 190, 95, 95</td>
<td>Unclear, B, D, A</td>
<td>Hb &gt;80 g/l</td>
<td>Oral, 2.5 mg/kg/day, 3 months, 9 months; T/t: Iron Betalaine C: Identical placebo†</td>
<td>Clinic</td>
<td>Malaria</td>
<td>Smear positive</td>
</tr>
<tr>
<td>Brunser, 1993d</td>
<td>Chile</td>
<td>3 months 400, 200, 200</td>
<td>Random numbers table, A, D, A</td>
<td>Birth weight &gt;2500 g, WFA &gt;80% or 50th centile, Hb &gt;105 g/l</td>
<td>Fortified, 12 mg/l, 6 months, 8 months; T/t: Iron enriched milk C: Control milk</td>
<td>Field</td>
<td>Diarrhoea</td>
<td>&gt;3 liquid stools/day or maternal report</td>
</tr>
<tr>
<td>Angeles, 1993a</td>
<td>Indonesia</td>
<td>2-5 years 80, 40, 40</td>
<td>Unclear, B, A, WA score between –2 and –3, Hb = 80-110 g/l, ferritin &lt;120µg/l</td>
<td></td>
<td>Oral, 30 mg/day, 2 months; T/t: Ferrous sulphate, Vitamin C C: Vitamin C</td>
<td>Field</td>
<td>Fever, RTI, Diarrhoea</td>
<td>Fever: Temp &gt;37°C; Diarrhoea: &gt;4 watery stools/d, RTI: not mentioned</td>
</tr>
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Table 2 Baseline characteristics of included trials (posted as supplied by author) contd

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<th>Morbidities studied</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Lawless, 1994**</td>
<td>Kenya</td>
<td>6-11 years</td>
<td>Stratified randomisation (by gender and initial Hb value), C, A, A</td>
<td>Hb &gt;80 g/l</td>
<td>Oral, 150 mg/day, 3 months, 3 months; T/t: Ferrous sulphate C: Identical placebo†</td>
<td>School</td>
<td>Diarrhoea, cough, malaria</td>
<td>PS for MP+, diarrhoea, cough—not mentioned</td>
</tr>
<tr>
<td>Adam, 1996*</td>
<td>Ethiopia</td>
<td>6-14 years</td>
<td>Random numbers table, B, B, D</td>
<td>Birth weight &gt;2.5 kg, singleton pregnancy, Hb &gt;80 g/l, wt, length and head circumference within 2 SD of NCHS standards.</td>
<td>Birth weight &gt;2500 g</td>
<td>Clinic</td>
<td>URTI, LRTI, gastronenteritis</td>
<td>Paediatrician’s diagnosis</td>
</tr>
<tr>
<td>Rosado, 1997**</td>
<td>Mexico</td>
<td>1.5-3 years</td>
<td>Stratified randomisation (by age and sex), B, C, A</td>
<td></td>
<td>Oral, 3 mg/kg/day, 4 months, 4 months; T/t: Ferrous sulphate C: Identical placebo†</td>
<td>Clinic</td>
<td>URTI, fever</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Idjradinata, 1994**</td>
<td>Indonesia</td>
<td>12-18 months</td>
<td>Random numbers table, B, B, D</td>
<td>Birth weight &gt;2.5 kg, singleton pregnancy, Hb &gt;80 g/l, wt, length and head circumference within 2 SD of NCHS standards.</td>
<td>Birth weight &gt;2500 g</td>
<td>Clinic</td>
<td>Malaria, pneumonia, other infections</td>
<td>Malaria: smear positive Pneumonia, other infections: not mentioned</td>
</tr>
<tr>
<td>von der Hontergh, 1996*</td>
<td>Tanzania</td>
<td>&lt;30 months</td>
<td>Unclear, B, B, D</td>
<td>Hb &lt;50 g/l, PS for MP +, Exclusion: Cerebral malaria, Non-falciparum malaria, sickle cell anemia, other significant illness</td>
<td>Hb &lt;50 g/l</td>
<td>Clinic</td>
<td>Malaria, pneumonia, other infections</td>
<td>Malaria: smear positive Pneumonia, other infections: not mentioned</td>
</tr>
<tr>
<td>Gebresellassie, 1996*</td>
<td>Ethiopia</td>
<td>5-14 years</td>
<td>Unclear, B, C, A</td>
<td>Hb &lt;50-120 g/l, P falciparum –ve</td>
<td>Hb &lt;50-120 g/l</td>
<td>Active</td>
<td>Malaria</td>
<td>Fever</td>
</tr>
<tr>
<td>Mitra, 1997**</td>
<td>Bangladesh</td>
<td>2-48 months</td>
<td>Block randomisation of 4 homogeneous clusters, A, C, A</td>
<td>Exclusion: Critical Ill, congenital malformations, metabolic disorders</td>
<td>Oral, 15mg/day, 15 months, 15 months T/t: Ferrous gluconate, vitamins§ C: Vitamins§</td>
<td>Field</td>
<td>Diarrhoea, dysentery, ARI</td>
<td>Diarrhoea: &gt;2 liquid stools/d and maternal report; Dysentery: blood in stools, ARI; &gt;50 bpm in child &lt;1 yr, &gt;40 bpm in child 12-15 months</td>
</tr>
<tr>
<td>Palupi, 1997**</td>
<td>Indonesia</td>
<td>2-5 years</td>
<td>Registered at village health centre</td>
<td></td>
<td>Oral, 15mg/week, 2 months, 2 months T/t: Ferrous sulphate C: Identical placebo†</td>
<td>Clinic</td>
<td>Worm infestation</td>
<td>Stool microscopy +</td>
</tr>
<tr>
<td>Rosado, 1997**</td>
<td>Mexico</td>
<td>1.5-3 years</td>
<td>Age as stated</td>
<td></td>
<td>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</td>
<td>Field</td>
<td>RTI, diarrhoea, fever</td>
<td>RTI: runny nose, common cold, sore throat, cough; Diarrhoea, Fever: maternal reporting</td>
</tr>
</tbody>
</table>

*Sample size includes follow up. **Sample size includes follow up and control group.
Table 2 Baseline characteristics of included trials (posted as supplied by author) contd

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<th>Case detection</th>
<th>Morbidities studied</th>
<th>Case definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menendez, 1997†‡</td>
<td>Tanzania</td>
<td>2 months 832, 417, 415</td>
<td>Block randomisation, A, D, A</td>
<td>Birth weight &gt;1500 g, PCV &gt;25% at 6 weeks. Exclusion: Congenital malformation, congenital or neonatal infection.</td>
<td>Oral, 2 mg/kg/day, 4 months, 10 months Group 1 T/t: Ferrous glycine sulphate, placebo syrup‡ C: Placebo syrup‡ Group 2 T/t: Iron sulphate, Deltaprim C: Deltaprim, placebo syrup‡</td>
<td>Clinic</td>
<td>Malaria</td>
<td>Axillary temp &gt;37.5°C with P falciparum +ve</td>
</tr>
<tr>
<td>Rice, 1999</td>
<td>Tanzania</td>
<td>3-56 months 614, 307, 307</td>
<td>Randomisation of households of the study area into two groups, B, A, B</td>
<td>Age as stated</td>
<td>Oral, 10mg/day, 12 months, 12 months T/t: Iron sulphate C: Identical placebo†</td>
<td>Field</td>
<td>Diarrhoea, dysentery, RTI, malaria, fever</td>
<td>RTI: cough with difficult breathing; Diarrhoea: &gt;3 liquid stools/ day; Dysentery: blood in stools</td>
</tr>
<tr>
<td>Agarwal, 1999</td>
<td>India</td>
<td>50-80 days 73, 37, 36</td>
<td>Computer generated random numbers, A, C, A</td>
<td>Gestation &gt;37 weeks, birth weight &lt;2500 g. Exclusion: Twins, congenital malformations, received blood, adverse neonatal event requiring admission in nursery, sampling before recruitment &gt;10 ml. Significant current morbidity, maternal APH</td>
<td>Oral, 3 mg/kg/day, 2 months, 2 months T/t: Ferric ammonium citrate C: Identical placebo†</td>
<td>Clinic</td>
<td>RTI</td>
<td>Maternal report as interpreted by paediatrician</td>
</tr>
<tr>
<td>Nagpal, 2000†‡</td>
<td>India</td>
<td>4-6 months 100, 49, 51</td>
<td>Computer generated random numbers, A, D, A</td>
<td>Gestation &gt;37 weeks, birth weight &gt;2500 g. Breast fed Exclusion: Twins, congenital malformations, received blood or iron, adverse neonatal event requiring admission in nursery, sampling before recruitment &gt;10 ml. Significant current morbidity</td>
<td>Oral, 2.5mg/kg/day, 2 months, 2 months T/t: Ferric ammonium citrate C: Identical placebo†</td>
<td>Clinic</td>
<td>RTI, diarrhoea, others</td>
<td>Maternal report as interpreted by paediatrician</td>
</tr>
<tr>
<td>Berger, 2000†‡</td>
<td>Togo</td>
<td>6-36 months 197, 100, 97</td>
<td>Unclear, B, C, B</td>
<td>Hb &gt;80 g/l</td>
<td>Oral, 2-3mg/kg/day, 3 months, 9 months T/t: Iron Bialate C: Identical placebo</td>
<td>Field</td>
<td>URTI, LRTI, malaria, diarrhoea, cutaneous infection</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Singhal, 2000†‡</td>
<td>UK</td>
<td>9 months 493, 162, 331</td>
<td>Separate randomisation for Asians and non-Asians, A, C, A</td>
<td>Birth weight &gt;2500 g, gestation &gt;36 weeks. Exclusion: Severe chronic disease, congenital anomalies, haematologic disorders, previously received iron or blood</td>
<td>Fortified, 12mg/L, 9 months, 9 months T/t: Iron fortified formula C: Cocoa milk or standard formula</td>
<td>Clinic</td>
<td>Chest infection, URTI, others</td>
<td>URTI, diarrhoea: maternal report; chest infection: treatment with antibiotics</td>
</tr>
<tr>
<td>Atukorala, 2001</td>
<td>Sri Lanka</td>
<td>5-10 years 384, 282, 102</td>
<td>Unclear, B, C, A</td>
<td>Outpatients at children’s hospital</td>
<td>Oral, 60mg/day, 2 months, 2 months T/t: Ferrous sulphate C: Lactose</td>
<td>Field</td>
<td>URTI, diarrhoea</td>
<td>URTI: clinical evidence with inflammatory parameters; diarrhoea: &gt;2 semisolid watery stools/day</td>
</tr>
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**Table notes:**
- 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; P=peripheral smear; RTI=respiratory tract infection; TB=tuberculosis; URTI=upper respiratory tract infection; VOLUME 325 16 NOVEMBER 2002 bmj.com
- *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.
- †Exact composition not mentioned.
- ‡Exact composition not mentioned.

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).

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<thead>
<tr>
<th>Study</th>
<th>Total infections</th>
<th>Diarrhoea</th>
<th>Respiratory tract infection</th>
<th>Malaria</th>
<th>Other infections</th>
</tr>
</thead>
</table>
|       | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi | Obs | Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi | Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Obs |Epi |Observations: 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=50.24, 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, and the incidence rate difference (public health effect) for diarrhoea was 0.04 episodes per child year, 1.32, 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 1.51, 1.51 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=11.61, P=0.114, fig 3. Meta-regression analysis of trials with relevant data (excluding the study by Oppenheimer et al14) 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.

<table>
<thead>
<tr>
<th>Infection type</th>
<th>No of trials</th>
<th>Random effects model (95% CI)</th>
<th>P value</th>
<th>Tests for heterogeneity (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>17</td>
<td>1.11 (1.01 to 1.23)</td>
<td>0.04</td>
<td>0.30 (0.04)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>27</td>
<td>0.98 (0.90 to 1.06)</td>
<td>0.54</td>
<td>0.53 (0.19)</td>
</tr>
<tr>
<td>Malaria</td>
<td>5</td>
<td>1.07 (0.94 to 1.24)</td>
<td>0.35</td>
<td>0.55 (0.35)</td>
</tr>
<tr>
<td>Other infections*</td>
<td>13</td>
<td>1.04 (0.98 to 1.11)</td>
<td>0.20</td>
<td>0.18 (0.15)</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>8</td>
<td>0.97 (0.83 to 1.23)</td>
<td>0.93</td>
<td>0.21 (0.03)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iron</td>
<td>Control</td>
</tr>
<tr>
<td>Hombergh</td>
<td>50/50</td>
<td>13/47</td>
</tr>
<tr>
<td>Berger et al</td>
<td>59/100</td>
<td>62/97</td>
</tr>
<tr>
<td>Rice (unpublished)</td>
<td>253/296</td>
<td>233/219</td>
</tr>
<tr>
<td>Chippaux</td>
<td>72/120</td>
<td>14/120</td>
</tr>
<tr>
<td>Smith</td>
<td>23/106</td>
<td>19/107</td>
</tr>
<tr>
<td>Chippaux</td>
<td>72/120</td>
<td>14/120</td>
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<td>23/106</td>
<td>19/107</td>
</tr>
<tr>
<td>Smith</td>
<td>23/106</td>
<td>19/107</td>
</tr>
</tbody>
</table>

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 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. Dysentery is invariably infective in origin, and 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 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...
most in iron deficiency and malnutrition, 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. 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.

We thank Sunil Sinha for facilitating access to Embase and two PhD dissertations. We also thank L. Satyanaryana for help in conducting the meta-regression analysis. Part of this paper was presented as a poster at the International Nutritional Anaemia Consultative Group symposium 2001, held at Hanoi, Vietnam. 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. Funding: None. Competing interests: International Life Science Institute (ILSI) sponsored TG for travel to Hanoi, Vietnam for the purpose of attending the International Nutritional Anaemia Consultative Group symposium and presenting part of the analysis as a poster.

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.


(Accepted 28 June 2002)