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

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Authors' objectives
To evaluate the effect of iron supplementation on the incidence of infections in children.

Searching
MEDLINE, the Cochrane Controlled Trials Register, EMBASE, IBIDS and HealthSTAR were searched. In addition, the reference lists of identified articles were checked and reviews, bibliographies of books, and abstracts and proceedings of international conferences or meetings were handsearched. Experts in the field and authors of recent trials were also contacted. Both published and unpublished trials were eligible for inclusion in the review.

Study selection
Study designs of evaluations included in the review
To be eligible for inclusion, the trials generally had to be randomised and placebo-controlled. The exception was trials in which iron was given parenterally, in which case they could be non placebo-controlled due to difficulties in administering a similar placebo.

Specific interventions included in the review
The included trials needed to investigate iron supplementation through oral or parenteral routes, or as formula milk or through cereal fortification. Studies in which other micronutrients and drugs were simultaneously administered were included if the only difference between the intervention and control group was iron supplementation. Twenty of the 28 studies used oral iron supplementation, 3 used parenteral administration and 5 used iron-fortified foods. The duration of supplementation and follow-up for the oral intake route ranged from 2 to 30 months.

Participants included in the review
Thirteen trials were conducted in children less than 1 year of age, 10 were in pre-school children (age 5 or younger) and 5 included children older than 5 years. Eleven trials were from Africa, 8 from Asia, 5 from the Americas, 2 from Europe and 2 from Australia and New Zealand.

Outcomes assessed in the review
The included trials needed to evaluate one or more infectious illnesses as an outcome measure.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The reviewers assessed the quality of the included trials using published checklists. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
One reviewer extracted data that were derived from published papers or were provided by the study authors. The illnesses and outcomes considered were as defined by the individual study authors, but clarification was sought where possible. The reviewers chose to use incidence rate summary to account for differences in the duration of follow-up in the extracted studies. Data were recorded as 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, the reviewers recorded the figures directly; this category of studies was labelled the 'actual' group. In the 'computed' group of trials, the person time of follow-up was
not provided and estimates were calculated from the product of the duration of follow-up and the sample sizes at the beginning and end of the study. In some trials data were obtained from published graphs.

**Methods of synthesis**

How were the studies combined?
The reviewers used statistical methods to investigate the presence of publication bias. Pooled incidence rate ratios and incidence rate differences were calculated using fixed-effect and random-effects models.

How were differences between studies investigated?
The reviewers conducted a formal test of statistical heterogeneity. They reported random-effects estimates due to the statistically heterogeneous nature of the results. The contribution of a variety of clinical and quality variables to heterogeneity was explored in stratified analyses. Differences between the studies were further explored using meta-regression analyses.

**Results of the review**

Twenty-eight randomised controlled trials (7,892 children) were included.

The reviewers found no evidence of publication bias. The pooled estimate of the incidence rate ratio (iron supplementation versus placebo) for all recorded morbidities was 1.02 (95% confidence interval, CI: 0.96, 1.08, P=0.54; heterogeneity test, Q=78.29, P<0.0001). The incidence rate difference (iron versus placebo) for all recorded illnesses was 0.06 episodes/child-year (95% CI: -0.06, 0.18, P=0.34; Q=80.01, P<0.0001). A stratified analysis for the effect on individual diseases showed that children in the iron supplementation group had an increase in the risk of developing diarrhoea, with an incidence rate ratio of 1.11 (95% CI 1.01, 1.23, P=0.04), but the incidence rate difference was 0.05 episodes/child-year (95% CI: -0.03, 0.13, P=0.21; Q=42.03, P=0.001). The occurrence of other illnesses and positive results on malaria smears was not significantly affected by iron supplementation. The results of the meta-regression analyses, which investigated a range of clinical and study quality variables, could not explain the statistical heterogeneity of the trials.

**Authors’ conclusions**

Iron supplementation had no apparent harmful effect on the overall incidence of infectious illnesses in children. However it slightly increased the risk of developing diarrhoea, although this would not have an important overall impact on public health.

**CRD commentary**

This review had a clear objective with defined inclusion criteria for the study design, interventions and outcomes. The search was comprehensive, using a range of databases and information sources. The reviewers attempted to find unpublished material and also tested for possible publication bias. The trials were quality assessed and this variable was explored as a possible source of statistical heterogeneity. It was unclear whether more than one reviewer was involved throughout the review process, which would serve to minimise bias. The reviewers presented a pooled incidence rate ratio and an incidence rate difference for all types of infectious illnesses. They also carried out a series of meta-regression analyses to explore the observed heterogeneity and pooled by subtype of infection. This allows the reader to judge how the incidence of different infectious diseases varies with iron supplementation. However, given the international nature of the evidence, it may be difficult to draw general conclusions about the effectiveness of iron supplementation in the UK.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The reviewers identified a need to evaluate the possible benefits of foods fortified with iron on haematological response and infections.
Bibliographic details

PubMedID
12433763

Original Paper URL
http://bmj.bmjjournals.com/cgi/content/full/325/7373/1142

Other publications of related interest
This additional published commentary may also be of interest. Kolsteren P, Roberfroid D. Iron supplementation is unlikely to increase the incidence of infectious disease in children. Evidence-based Healthcare 2003;7:104-5.

Indexing Status
Subject indexing assigned by NLM

MeSH
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.