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Editorial by Tomkins

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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Data sources 28 randomised controlled trials (six unpublished and 22 published) on 7892 children.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 The reversible consequences in childhood have prompted recommendations for early intervention. The proposed interventions rely primarily on enhancing iron intake through supplementation or fortification of food.^{3,4}

Objective safety data from longitudinal studies of iron supplementation are conflicting; trials have shown either beneficial effects,⁵ no effect,⁶ or an increase in infectious illnesses.^{7,8} 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; 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.

Data collection

We searched 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. We included published and unpublished trials and assessed quality using recommended criteria.^{9,10}

Statistical analysis

The presence of bias in the extracted data was evaluated by funnel plots.¹¹ We primarily report random effects estimates because most of the pooled results obtained were statistically heterogeneous (*Q* statistic). The data were recorded in the form of the total number of episodes of illness and the person time exposed (in child years).

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. We also performed a meta-regression 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); 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.

Results

We identified 47 randomised controlled trials that were potentially eligible. We finally included 28 studies (22 published, and six unpublished) in this systematic review (see also bmj.com).

Baseline characteristics of the studies

The detailed baseline characteristics of the included trials can be found with the full version of this paper (see bmj.com). 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. Most of the studies used oral iron supplementation (20/28; 71%). Three trials used parenteral administration, and five studies used iron fortified foods.

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. The methods of surveillance also 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.

We found no evidence of bias (see bmj.com).

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. 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; $P=0.54$; $Q=78.3$, $P<0.0001$, fig 1). From the public health perspective the incidence rate difference is considered to be more informative. The incidence rate difference for all the recorded illnesses was 0.06 episodes per child year (-0.06 to 0.18 , $P=0.34$).

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 ($P=0.04$; $Q=30.24$, $P=0.04$, table). 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 , $P=0.21$). 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 ; $P=0.07$). Meta-regression showed that the route of iron administration (oral versus other) was not significantly associated with incidence rate ratio for diarrhoea.

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

The pooled odds ratio for positive smear tests for malaria at the end of the supplementation period was 1.43 (1.08 to 1.91, $P=0.014$; $Q=11.6$, $P=0.11$, fig 2).

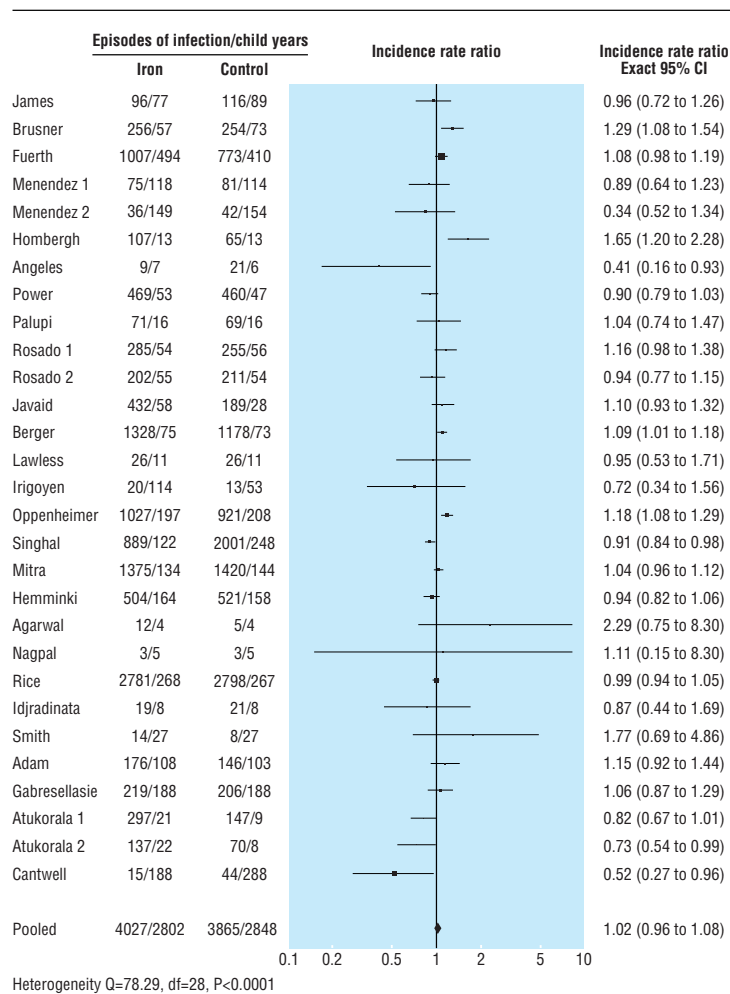


Fig 1 Forest plot for incidence rate ratio for all recorded illnesses

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.

Meta-regression analysis 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; $P=0.076$).

Exploring 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,

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

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. Meta-regression analysis showed that the treatment effect was not significantly associated with any of these study characteristics (see bmj.com).

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 (after adjustment for positive smear results at baseline) was not significantly affected by iron administration.

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 (see bmj.com). 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 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. 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.

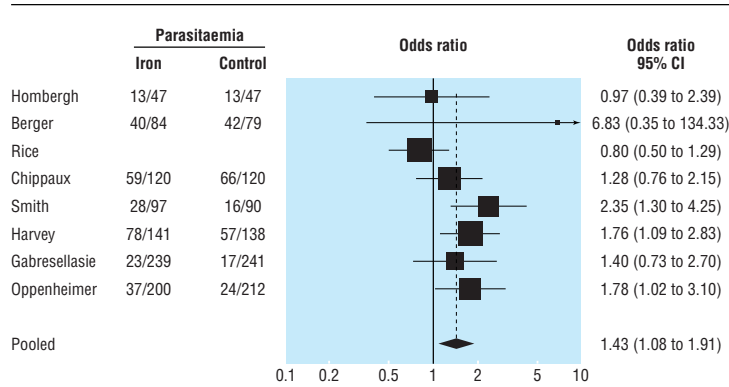
Meta-regression analysis suggested that the risk of acquiring infectious illnesses might be inversely associated with the baseline haemoglobin concentration (incidence rate ratio 0.95 (0.90 to 1.00), $P=0.059$). Interestingly, all the studies included in this stratified subset were from regions of the 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.¹² 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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Heterogeneity $Q=11.61$, $df=7$, $P=0.114$

Fig 2 Forest plot for odds ratio of malarial parasitaemia (positive results on blood smear test) at end of supplementation period

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