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Increased risk of pyrexial illness with higher doses of iron supplementation

Dear Editor,

The study conducted by da Silva et al. sets out to investigate the relative advantages and disadvantages of three different iron prophylactic regimens.[1] The authors claim that the findings about an association of iron supplementation and enhanced vulnerability to infections are controversial, and they also claim that the groups of their study did not show differences in morbidity. A close look at the data provided by the authors reveals that, if one compares the group with 2 mg/kg/day of iron supplementation with the other groups, who had 1 mg/kg/day iron or less, pooled into one group, the incidence of fever was significantly greater in the group with higher iron intake (28/36), compared to the incidence in the pooled group with half or less of this iron intake (42/77) (p = 0.03, chi-square test). The majority of comparisons (seven out of 10) in incidence of infectious diseases between the three groups reveals an (albeit not statistically significant) increased incidence in the group with 2 mg/kg/day of iron. Larger sample sizes may have revealed a statistically significant difference for each comparison. Such a difference became evident in the largest randomized, controlled trial of iron supplementation by Sazawal et al. involving 24,076 children.[2] That study, the largest to date, concluded that, in areas with high rates of malaria, iron and folic acid supplementation can result in a 12% increased risk of severe illness and death. Analysis of results for infection-related causes included confirmed febrile illness not meeting definitions for malaria (e.g., pneumonia, sepsis, meningitis, measles, pertussis) and revealed that, compared with placebo, the iron supplemented groups had a significantly higher risk for serious adverse events (1.32, 1.10-1.59), deaths (1.61, 1.03-2.52), and admissions to hospital (1.28, 1.05-1.55) due to these causes. The findings were significant enough for the data and safety monitoring board to stop the trial of iron and folic acid supplementation prematurely. Subgroup analysis of this trial showed that these effects are mainly due to increased risk of infectious complications in children who were not iron-deficient at the beginning of the trial. Based on this trial, it is possible to conclude that prophylactic iron supplementation in children who are not iron-deficient in areas with high incidence of infectious diseases cannot be justified.

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Authors' reply

Dear Editor,

We appreciate the comment made by researchers on our paper.[1] However, we admit that the differences in morbidity between iron-supplemented groups should be interpreted with caution, because possible confounding variables were not controlled. It should also be underscored that, unlike the study cited by the researchers,[2] whose region is endemic to malaria, the investigated population belongs to a non-endemic area. Therefore, we believe other studies are necessary to look into the relationship between morbidity and prophylactic iron supplementation in similar populations. Some authors have observed that iron supplementation does not seem to increase the general risk for infection in non-endemic areas of malaria, as opposed to endemic areas, where such risk apparently exists.[3,4] The debates about this issue are of great importance as they stress the need to identify the actual risks and benefits of using prophylactic iron supplementation as a preventive measure against iron deficiency in the first years of life. In addition, based on these data, one should also assess whether the confirmation of specific risks justifies keeping the general population from receiving the benefits of this supplementation.

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