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Iron Fortification and Malaria Risk in Children

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Iron deficiency, with its consequent effects on anemia, immune function, cognitive development, and physical capacity, is estimated to be one of the most prevalent nutritional problems worldwide.[1] Yet iron is the second most abundant element on the earth's crust. How can this be? The answer is an intriguing one that has important implications for the understanding of iron biology and may point toward safer ways of administering iron. In brief, the useful oxidoreductive characteristics of iron have made it the element of choice in many biochemical pathways for both the human host and its legions of pathogens, leading to a highly evolved metabolic competition for this element.[2]

Almost all bacteria, protozoa, and viruses are heavily dependent on iron, and bacteria, in particular, have evolved myriad exquisite mechanisms for maintaining iron supply even in low-iron environments. In response, humans have evolved mechanisms for chaperoning iron by using high-affinity chelators of both iron (transferrin, ferritin, lactoferrin) and heme (haptoglobin, hemopexin). The production of these defensive proteins is modulated in response to infectious threats (via toll-like receptors and cytokine-mediated pathways) and coordinated with an additional lock-out and lock-down defense mechanism; namely, the exclusion of dietary iron and the blocking of iron recycling by macrophages. This defense is regulated by hepcidin (the main regulator of iron metabolism), which downregulates ferroportin, the iron efflux transporter on enterocytes and macrophages.[2] Together, these mechanisms lead to the well-known reduction in iron levels during the acute phase response that is a major component of first-line, innate immune defenses.

Why is all this biology important to the interpretation of the iron fortification intervention trial among Ghanaian children reported by Zlotkin et al[3] in this issue of *JAMA*? First, the new biological insights reverse the previous nutritional view that young children in developing countries are constitutionally ill-equipped to absorb dietary iron and require administration of large doses of iron. To minimize the risk of infection, the physiology of these children has adapted to actively exclude iron much of the time, which is validated by the fact that rare genetic variants in the hepcidin-ferroportin pathway lead to iron overload

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even in people on low-iron diets. Second, because so much evolutionary experience has been distilled into extensive genomic investment in mechanisms mediating the host-pathogen competition for iron, it may be hazardous to intentionally override such processes by administration of excess iron.[2]

Good evidence supports this contention and forms the background of the new trial reported by Zlotkin el at.[3] In brief, a large micronutrient supplementation trial in young children on Pemba Island, Zanzibar, Tanzania, was prematurely terminated in 2003 by its data and safety monitoring board (DSMB) due to an excess of serious adverse events in the 2 groups receiving iron.[4] Another micronutrient trial in Tanzania found an excess of malaria cases in the early phase of supplementation with a multiple micronutrient formulation containing iron.[5] A more recent randomized trial of multiple micronutrient powders (MNPs) conducted in 2008–2011 among Pakistani children also reported significant excesses of diarrhea, severe diarrhea, and respiratory infections,[6] which may be related to the iron in the MNP.

The trial by Zlotkin and colleagues was conducted in a highly malaria-endemic area of Ghana to test whether iron administered in aMNP would increase the risk of clinical malaria.[3] Nearly 2000 children aged 6 to 35 months were randomized to receive a MNP with or without 12.5 mg/d iron and were closely monitored by field staff for 5 months of intervention and an additional 1 month postintervention. Each participant was visited weekly for a health check (including axillary temperature), recall by the caregivers of the child's morbidity since last being seen, adherence to the supplementation regimen (by packet counts), and administration of the next week's MNP supply. Study identity cards were used to track visits to health facilities in which malaria diagnosis was confirmed by a rapid diagnostic test and blood smear.

In the intention-to-treat analyses, malaria incidence was significantly lower in the iron group compared with the no iron group during the intervention period (risk ratio [RR], 0.87; 95% CI, 0.78–0.96). In secondary analyses, these differences were no longer statistically significant after adjusting for baseline iron deficiency and anemia status overall (RR, 0.87; 95% CI, 0.75–1.01) and during the 5-month intervention period (RR, 0.86; 95% CI, 0.74–1.00), but there was nonetheless no suggestion that iron contributed to an increased risk of malaria.

This apparently reassuring result runs counter to a large body of other data and therefore requires some discussion. First, there is now evidence that moderate iron deficiency and anemia are associated with reduced risk of malaria among children[7] and pregnant women.[8] If iron deficiency is protective, reversing such deficiency would be expected to enhance malaria susceptibility as previously demonstrated.[4,5,9] In a secondary exploratory analysis of the Ghana trial results, Zlotkin et al found that the marginal protective association of iron administration in the iron group as a whole appeared significant within the subset of children with iron deficiency and moderate anemia (RR, 0.67; 95%CI, 0.50–0.88) for all malaria cases, and for malaria with parasite count greater than 5000/μL (RR, 0.62; 95% CI, 0.45–0.84). This is consistent with a sub-analysis from the Pembatrial,[4] but contrary to the results from the other Tanzanian trial.[5]

A resolution to this paradox might be found by separating the effects of iron deficiency from anemia. The Ghana data emphasize that these 2 conditions have only partial overlap. After exclusion of children with inflammation, which confounds the assessment of iron deficiency, 20% of children had anemia and iron deficiency, 20% had anemia and were iron replete, and 25% had iron deficiency and no anemia. Iron deficiency impairs several aspects of immune function,[2] and its resolution would be expected to be protective if achieved without encouraging pathogen growth during iron supplementation.

Another possibility is that anemia exerts some protection against plasmodial infections. A key virulence factor of *Plasmodium falciparum* is the ability of the erythrocytic stage of the parasite to invade and grow in red blood cells (RBCs).[10] Although *P falciparum* is capable of invading RBCs of all ages, the merozoites preferentially infect and grow better in reticulocytes and large, young RBCs.[11] The more limited invasion of *P falciparum* and replication in older and microcytic RBCs may in part explain how anemia might protect against malaria. Resolution of anemia necessarily requires an enhanced reticulocytosis and a shift in the age distribution and size of RBCs toward younger larger erythrocytes until a new less anemic steady state had been achieved. Emerging data suggest that this may cause an unavoidable “transient malarial susceptibility”[12] that would fit well with the observations of transiently increased malaria risk in the Tanzanian trial by Veenemans et al[5] and with the explanation proposed by Zlotkin and colleagues.[3]

So why was there no increase in malaria risk in the Ghana trial?[3] The answer may be that contrary to previous MNP trials, the iron-containing MNP was not as efficacious in resolving anemia as intended. In a subgroup analysis of 704 children who had anemia at baseline and for whom additional blood samples were obtained at the end of the intervention period, Zlotkin et al report a small mean increase in hemoglobin in the iron group (mean change of 0.08 g/dL, much of which might be attributable to regression to the mean or, as the authors note, a lack of sufficient statistical precision for this subgroup analysis). Thus, the conclusion that iron did not increase the risk of malaria may offer limited reassurance and may be related to a lack of desired efficacy of the iron-containing MNP in respect to anemia resolution.

Furthermore, the children in the Ghana trial who received MNP with iron showed a significantly higher number of hospital admissions during the 5 months of active intervention compared with those who received the MNP without iron (156 vs 128 admissions, respectively; RR, 1.23 [95% CI, 1.02–1.49]). The data on disease categories suggest that diarrhea episodes were a common reason for hospital admissions and visits to health care facilities, second only to diagnoses of malaria. This increase in hospital admissions, which by definition constitutes a potentially serious adverse event, was twice as large as that reported for the Pemba trial,[4] and adds further to the concerns about the safety of iron administration in highly malaria-endemic environments.

Participants in an expert panel convened by the World Health Organization in 2007[13] speculated that iron given with foods, either by centralized or point-of-use fortification, would be safe. However, the Ghanaian trial reported by Zlotkin et al in this issue of *JAMA*

now becomes the fourth trial to question this suggestion,[5,6,14] and leaves global health policy makers with an unresolved dilemma.

Until a means of safely administering iron in infectious environments has been developed, there remains an imperative to reduce the infectious burden as a prerequisite to moving poor populations from their current state of widespread iron deficiency and anemia.

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