Safety of Iron Fortification and Supplementation in Malaria-Endemic Areas

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This review considers the safety of iron supplementation and fortification for the prevention and correction of iron deficiency in malaria-endemic areas, with a focus on potential means whereby provision of additional iron might heighten the risks of malaria and other infections. Iron deficiency itself may increase the risk of morbidity and mortality from malaria and other infections [1]. The available evidence indicates that iron interventions are safe in settings without endemic malaria [2], and, with adequate health care, in regions with high transmission of malaria and other infections [3]. Without regular surveillance and treatment of malaria and other infections, iron supplementation of individuals who are iron deficient seems safe but, as shown in figure 1, individuals who are iron replete may have an increased risk of adverse outcomes [1]. Iron fortification appears to be generally safe, although more data from malaria-endemic areas are needed.

The mechanisms responsible for harmful effects with iron supplementation have not been established but almost certainly involve a complex interaction between iron status, the specific iron intervention, and malaria and other infections. Broadly, underlying potential mechanisms for adverse effects with iron supplementation or fortification may be considered as those resulting from (a) the increased amounts of iron absorbed, (b) the increased amounts of iron in the gastrointestinal tract, and (c) the immune effects of iron interventions. While a single mechanism might underlie the harmful effects of iron administration reported in the Pemba and other trials, a variety of mechanisms acting in concert is more likely to be responsible.
Mechanisms for Adverse Effects of Iron Interventions Involving Increased Iron Absorption

A WHO Consultation [4] identified plasma non-transferrin-bound iron as a probable cause of the adverse events in the Pemba trial. For non-malarial infections, the most likely explanation for an increased risk would seem to be plasma non-transferrin-bound iron being available to pathogens reaching the blood stream and enhancing their growth. With respect to the potential adverse effects of plasma non-transferrin-bound iron on malarial infection, direct donation of iron to *Plasmodium falciparum* seems unlikely. Plasma non-transferrin-bound iron has been reported to increase the expression of vascular endothelial adhesion molecules involved in sequestration of *P. falciparum*, providing a potential explanation for the more severe clinical course in children in the Pemba trial [1] given iron and folic acid. Increased sequestration of infected erythrocytes would increase the risk of more severe forms of malaria, especially of cerebral malaria, by worsening microvascular obstruction.

Mechanisms for Adverse Effects of Iron Interventions Involving Increased Amounts of Iron in the Gastrointestinal Tract

Because only a fraction of supplementation and fortification iron is absorbed, most of the dose given passes into the lower small intestine and colon. Iron and iron status affect the structural and immunological integrity of the gastrointestinal tract as well as the gastrointestinal microflora, potentially promoting invasion by pathogenic enteric bacteria.

Mechanisms for Adverse Effects of Iron Interventions Involving Immune Effects of Iron Interventions

Both malaria and iron modify host immune responses in complex and still poorly characterized fashions. Malaria-induced dysregulation of innate and adaptive immune responses interferes with protection against a variety of microorganisms. The withholding of iron from pathogens is a central component of host defense [5]. Supplemental and fortification iron, by compromising iron withholding and interfering with the regulation and coordination of innate and adaptive immune defenses both systemically and within the gastrointestinal tract, might impair defenses against a variety of pathogens.
Further research is needed to provide an improved understanding of the mechanisms underlying the adverse effects of iron interventions [2].

**References**

4. WHO Secretariat on behalf of the participants to the Consultation: Conclusions and recommendations of the WHO consultation on prevention and control of iron deficiency in infants and young children in malaria-endemic areas. Food Nutr Bull 2007;28:S621–S627.