Considerations for the Safe and Effective Use of Iron Interventions in Areas of Malaria Burden – Executive Summary

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Abstract: In 2006, the World Health Organization and the United Nations Children’s Fund released a joint statement advising that, in regions where the prevalence of malaria and other infectious diseases is high, iron and folic acid supplementation should be limited to those who are identified as iron-deficient. Although precipitated, in large part, by a recent report of adverse events associated with iron supplementation in children, questions about the risk/benefit of iron deficiency and mechanisms underlying potential adverse effects of iron in the context of infection are long-standing. Moreover, the implementation of this revised policy is compromised in most settings by the lack of consensus on the best methods to screen for iron deficiency. In response to these concerns a comprehensive review was conducted by a Technical Working Group (TWG), constituted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the U.S. National Institutes of Health, in partnership with the Bill and Melinda Gates Foundation. The review included an evaluation of the putative mechanisms associated with adverse effects of iron in the context of malaria; applicability of available biomarkers for assessing iron status in the context of infections; and evaluation of evidence with regard to the safety and effectiveness of available interventions to prevent iron deficiency, particularly in areas of endemic malaria.

The aim of this paper is to summarize the technical details of the larger TWG review conclusion that the occurrence and mechanism(s) of adverse effects associated with providing iron supplements (i.e.,

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Introduction

Nutritional iron deficiency remains an intractable global health concern. According to the most recent assessment by the World Health Organization (WHO), anemia affects 1.62 billion people globally, corresponding to 24.8% of the population, with the highest prevalence in preschool-age children (47.4%) [1]. Of that burden, it is estimated that approximately 50% is due to nutritional iron deficiency [2].

Previous estimates rank iron deficiency ninth among 26 risk factors included in the Global Burden of Disease [3]; it accounts for 841,000 deaths and more than 35 million disability-adjusted life years (DALYs) lost per year [3–4]. According to the recent Lancet series, nutritional iron deficiency accounts for 20,854 deaths in under-fives and 115,000 maternal deaths with an estimated 2.2 million and 3.4 million DALYs lost per year, respectively [5]. Irrespective of which estimate is used, nutritional iron deficiency undoubtedly continues to present major challenges to the global health community.

In addition to the magnitude of the problem and the operational challenges associated with prevention and treatment of iron deficiency, iron presents an added challenge because of its inherent nature (e.g., its potential to act as a pro-oxidant) [6], and the complexity of the iron homeostatic systems designed to manage its impact [7]. Because of iron’s chemical properties, it has the potential to affect health both positively and, under certain circumstances, adversely. In view of this dichotomy, there is a need for evidence-based policies and programs that take into account the risk versus benefit of iron interventions in different settings. A specific concern is the influence of iron and iron deficiency states on the immune response to infection.

The anemia of infection is a well-described clinical condition [8–9]. An evolutionary explanation for this response is that it confers protection against the acquisition of iron by invading organisms [10]. Recently, Wander et al. described the biology of iron deprivation as a component of an innate immune response whereby “microbial invasion stimulates an ‘iron withholding defense’ in which acute phase reactants sequester circulating iron and decrease iron absorption, restricting availability of growth-essential iron to pathogens and inhibiting pathogen proliferation” [11].

In settings where infectious diseases such as malaria or HIV infection are endemic, a fundamental biological question is whether this innate immune, iron-withholding defense is impaired or enhanced by nutritional iron deficiency. Is a lack of iron in the host detrimental by way of weakening the host immune response, beneficial by further limiting the availability of this essential nutrient to infectious organisms, or both? A corollary to this question is whether providing iron to the host via any of the currently available intervention vehicles (e.g., supplements, fortified foods, etc.) is harmful by abruptly increasing iron availability to invading organisms, or possibly beneficial by correcting iron deficiency and restoring immune function. The clinical relevance and programmatic implications of these scenarios are discussed in this paper.

The role of iron and iron deficiency in infection has been a long-standing clinical concern [12]. Adverse effects of iron reported in earlier and much smaller trials have been reinforced by findings from a large, randomized controlled trial that reported detrimental effects of iron-folic acid supplementation in children in Pemba, Tanzania [13], referred to hereafter as the “Pemba trial”. In the Pemba trial, children who received iron and folic acid supplements were more likely to die or to be treated in hospital for an adverse event. In a sub-study of the main Pemba trial, the investigators observed that iron-deficient children had a greater risk of adverse events compared to iron-replete children, and that, in the iron-deficient and anemic subgroup, iron-folic acid supplementation reduced the rate of
adverse events. Although much of this finding would seem intuitive (i.e., treating iron deficiency is a good thing), a closer evaluation of the data in the sub-study, which involved a smaller sample size, revealed a disconcerting but non-significant increase in adverse effects among children who were not deficient prior to receiving iron/folic acid supplements. It was this sub-study analysis that raised further concerns and prompted a global discussion about the safety of iron supplements.

In January of 2006, the WHO and United Nations Children’s Fund (UNICEF) released a joint statement [14] advising that, “in settings where the prevalence of malaria and other infectious diseases is high, iron and folic acid supplementation should only be administered to those who are anemic and at risk of iron deficiency. They should receive concurrent protection from malaria and other infectious diseases through prevention and effective case management.” This recommendation did not apply to the delivery of fortification or food-based iron interventions, or to regions that did not have a high malaria burden. However, these recommendations were difficult, if not impossible, to implement in the field due to concerns about safety related to infection risk.

A consultation commissioned by the WHO in Lyon, France, June 12–14, 2006, aimed to develop evidence-based recommendations on iron administration in malaria-endemic regions [15]. Using the WHO/UNICEF statement as a starting point, the consultation concluded that, “Universal iron supplementation (i.e., use of medicinal iron as tablets or syrups) should not be implemented without the screening of individuals for iron deficiency, because this mode of iron administration may cause severe adverse events in iron-sufficient children [16].” The consultation highlighted three main areas requiring investigation: (1) identifying plausible mechanisms to explain altered infection risk with iron supplementation; (2) assessment of biomarkers of iron status in areas of endemic infections, including malaria; and (3) evaluation of the safety and effectiveness of the full range of available interventions to improve iron status.

In October 2007, a collaboration was initiated involving the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH), the Bill & Melinda Gates Foundation (BMGF), and the WHO, which was designed to address the issues raised by the Pemba trial and the subsequent global response. The initiative was designed with two arms: the first is translational, intended to review and continuously update the extant data; the other is a research arm intended to generate new data through solicitation and support of targeted research projects.

This Executive Summary reflects the review and conclusions of the Technical Working Group (TWG) constituted by the NICHD in support of the larger collaboration (see the Appendix for a list of TWG members). The expanded presentation of the TWG’s review is available in the TWG Iron and Malaria Technical Report [17]. The Iron and Malaria Technical Report provides the community with a full assessment of the science and strength of evidence to support those involved in the development of evidence-based programs and policies related to the use of iron interventions. It is not intended to serve as a set of recommendations for public policy, nor does it represent the views of the NICHD/NIH, the WHO, or the BMGF.

This Executive Summary follows the same structure as the Iron and Malaria Technical Report, addressing the safe and effective use of iron interventions, particularly in areas of malaria burden in the following categories:

- **Mechanisms**: evidence to support potential mechanisms underlying adverse effects of iron in the context of malaria;
- **Biomarkers**: specificity, sensitivity, and applicability of available biomarkers for assessing iron status in the context of infections, including malaria;
- **Interventions**: safety and effectiveness of interventions to prevent iron deficiency, particularly in areas of endemic malaria.

Each section draws conclusions and identifies research priorities relevant to current practice.

### Mechanisms

The TWG explored three core hypotheses within the mechanisms category that might explain adverse effects of iron in the context of malaria: (1) increased non-transferrin bound iron (NTBI) enhances growth and pathogenesis of malaria parasites and other infectious agents and has a potential negative impact on host tissues; (2) iron supplements have direct effects on immune function; and (3) other factors militate against the protection imparted by the “anemia of infection.”

#### Hypothesis 1: NTBI

Plasma NTBI is accessible to and can enhance the growth of pathogenic microorganisms [18] and could
act to abrogate the critical iron-withholding component of innate immunity. Such a scenario could create advantageous conditions for malaria parasites and other pathogens. The presence of co-morbid pathogens has been reported and further confounds the clinical prognosis in patients with malaria [19].

Other plausible mechanisms for adverse effects of increased plasma NTBI include: (i) potential interactions at various stages of the malaria parasite’s life cycle (e.g., erythrocyte, hepatic stages); (ii) indirect effects on immune function via alterations in macrophage iron metabolism [20–21]; (iii) increased expression of vascular endothelial adhesion molecules involved in sequestration of *Plasmodium falciparum*, increasing risk for severe forms of malaria, especially cerebral malaria [22–23], the pathogenesis of which may be implicated [24]; and (iv) direct toxic effects mediated by harmful oxidative free-radical reactions [19].

The evidence to support the enhancement of parasite growth by direct donation of iron to *P. falciparum* from plasma NTBI is not convincing. It appears that the growth of *P. falciparum* in infected red blood cells is independent of host iron status [22–23], although there are stages in the malaria parasite life cycle in which NTBI could play a role. For example, during the erythrocytic phase of infection, plasma NTBI might increase the amount of iron in the intra-erythrocytic cytosolic pool, thus intensifying infection. Alternatively, plasma NTBI is rapidly removed from the portal circulation by hepatocytes, and iron availability within hepatocytes might enhance merozoite production during the hepatic phase, resulting in higher parasitemia during the erythrocytic phase of the infection.

**Hypothesis 3: Iron and Gastrointestinal Function**

An important interplay exists among iron, gastrointestinal ecology/physiology, and immunity. Iron supplementation could conceivably impact infection through a couple of plausible mechanisms. Increased gut iron concentrations could increase growth of pathogenic enteric microorganisms in the gut lumen; or, these increased concentrations could impact mucosal defenses possibly through increased oxidative stress and free-radical formation. Studies are now being conducted to determine if such scenarios are plausible in non-typhi *Salmonella* bacteremia, which has been frequently identified in children with severe malaria [29]. Moreover, because *P. falciparum* locates in the gastrointestinal microvasculature, effects of iron supplements on the gut wall could interact with the inflammatory effects of malaria, predisposing the host to systemic bacterial invasion, bacteremia, and septicemia.

**Hypothesis 4: Overriding the Protection Imparted by the “Anemia of Infection”**

Protective mechanisms against infection resulting from iron deficiency and iron sequestration may be overridden with supplemental iron, or through its effects on either erythrocytic or hepatic zinc protoporphyrin. Current evidence for the former scenario is not compelling. During states of iron deficiency, zinc replaces iron to form zinc protoporphyrin. The significance of this in malaria is that, in iron-deficient parasitized red blood cells, the increased zinc protoporphyrin could bind to heme crystals, inhibiting the formation of hemozoin in a manner analogous to the antimalarial quinolines. While plausible, this scenario warrants further research for validation.

**Other Issues Considered by the TWG Regarding Mechanisms**

Because the design of the Pemba trial [13] did not include a group that received iron supplementation without folic acid, the observed increase in serious adverse events cannot be ascribed unequivocally to iron alone, to folic acid alone, or to the combination of the two [30]. Further, for pregnant women in malarial areas, there is evidence that folic acid supplementation in high, but not low, doses compromises the efficacy of sulfadoxine-pyrimethamine (Fansidar®), the most commonly used antifolate antimalarial [31]. Current
public health approaches recognize that the benefits of folic acid supplementation for pregnant women in malaria-endemic areas outweigh the potential risks, although high doses should be avoided [32].

An additional and critical consideration is the role of iron biochemistry in some of the major co-morbidities common in regions where malaria is endemic. One of the more prominent would be the interaction between iron status, malaria, and HIV infection. Iron metabolism and status are clearly altered by both HIV infection and its treatments [33–34]. Although the details of the HIV-malaria interaction have not been fully described, studies to date indicate an additive and adverse effect from co-infection [35]. Several clinical studies have provided evidence that iron excess has adverse effects in patients with HIV disease [36]. Attempts to more systematically evaluate the effect of iron status on HIV progression in women have led to conflicting results [37–39], discussed in further detail in the Iron and Malaria Technical Report. The TWG recognized that other co-morbidities, such as tuberculosis and enteric diseases, warrant additional attention in this context but are beyond the scope of this report. Further research is needed to more fully appreciate the potential interactions among iron status, malaria, co-morbidities, and their treatments in children and in women of child-bearing age.

Research Priorities: Mechanisms

Many of the biological mechanisms controlling iron homeostasis in the host and in pathogens have been well characterized. However, a number of questions remain about factors that could influence iron metabolism and that have important clinical implications. Specific research priorities include:

- The functional significance of NTBI in health and disease, including:
  - Enhancement of growth of *P. falciparum* malaria, the growth of other pathogens, or both
  - Possible increased sequestration of parasitized red blood cells
  - Immune effects of plasma NTBI
  - Direct toxic oxidant effects of plasma NTBI
- The role of hepcidin in diseases, specifically infections and inflammation
- Factors that can reduce iron-deficiency protection against malaria and other infections, including protection by zinc protoporphyrin and non-specific protection
- Alterations in balance between pro- and anti-inflammatory cytokines
- Effects of iron on gut microflora when delivered through different means and formulations
- Extent to which iron in the gut lumen favors growth of enteric microorganisms with pathogenic potential
- Functional impact of malnutrition (e.g., iron deficiency, protein/calorie, multiple micronutrient deficiencies) on gut ecology
- Role of age-dependent development on gut ecology in the context of health and disease
- Extent to which iron intake affects the innate immune response of the small intestine
- Functional impact of infection, including malaria, on gastrointestinal integrity

Conclusions

Clearly, much is known about iron metabolism in the host and in pathogens such as *P. falciparum*. A more concerted effort is required to determine the exact nature of the interactions among iron, immune function, infection, and inflammation, particularly as these interactions pertain to infections such as malaria. Such effort will help to expand existing knowledge about this essential nutrient and provide the underpinnings for developing better assessment approaches and interventions.

At this time, the available evidence is insufficient to definitively determine the mechanism(s) that explain potential adverse effects of iron interventions in regions with malaria. The Pemba trial [13] and other studies illustrated the need to study the potential for adverse effects of iron supplementation given to infants and children, as well as pregnant women, in areas where malaria and other infectious diseases are endemic. Neither the Pemba trial [13] nor other clinical studies have been designed to comprehensively examine the mechanisms responsible for adverse outcomes.

Biomarkers

Paramount among the conclusions reached in response to the Pemba trial, and implicit in the recommendations outlined by the WHO/UNICEF, is the need to assess iron status before giving an iron supplement to infants and children living in areas with a high burden of malaria [15–16]. Serum ferritin is generally recognized as the best single biomarker for evaluating the response to iron interventions [40], but the interpretation of serum ferritin is complicated by its role as an
acute phase protein in infection or inflammation [41]. There is a need to identify biomarkers of iron status that can be used by the public health community to ascertain the prevalence of iron deficiency, guide the use of iron supplements, and assess the response to intervention programs in regions where malaria and other chronic infections are endemic. The following section is a review of the evidence regarding iron assessment in this context.

Specific iron biomarkers should be used to establish the prevalence of iron deficiency and the impact of intervention strategies. The choice of biomarker will depend on the setting and available resources, as well as on the relationship among iron status and the susceptibility to and severity of infections. Table I contains a description of the stages of iron deficiency that lead to anemia and the utility of available biomarkers at each stage.

In developing countries, hemoglobin concentration remains a widely utilized screening test for iron deficiency. The TWG, however, emphasized that hemoglobin screening is neither sensitive nor specific enough to detect nutritional iron deficiency, and highlighted the fact that nutritional iron deficiency accounts for only about 50% of anemia globally. Other causes of anemia include infections and red blood cell polymorphisms, which are common in developing countries.

The utility of serum ferritin for identifying iron-deficiency anemia in the U.S. population was examined in a forerunner of the first National Health and Nutrition Examination Survey (NHANES). When one abnormal measure of iron was used (transferrin saturation, erythrocyte protoporphyrin, or serum ferritin) the prevalence of anemia was 11% compared to 28% when two abnormal parameters were used, and increased to 63% when all three parameters were evaluated [42]. The observation led to the use of all three measurements for identifying iron deficiency, referred to as the “ferritin model,” in subsequent NHANES [43].

The TWG expressed reservations about the reliability of using the ferritin model for surveys conducted in many developing countries. The primary concern was that the anemia of inflammation influenced all three parameters. This fluctuation, along with the high cost and complexity of measuring several parameters in large surveys, provided support for the recent WHO recommendation that prevalence surveys of iron status include only serum ferritin with the hemoglobin determination. The WHO also suggested that, to assist in the interpretation of serum ferritin, assessments should include inflammatory markers such as C-reactive protein (CRP), among others, in areas where the prevalence of chronic inflammatory disease is high [44].

Because of the influence inflammation and infection have on iron assessment, several inflammatory markers, including CRP, α1-antichymotrypsin, and α1-acid glycoprotein, have been used to adjust serum ferritin [45–46]. The success of these efforts in controlling for the effect of inflammation and/or infection has been disappointing, in part because these markers vary with the type of inflammation and the stages of a particular disease. A more practical approach may be to exclude serum ferritin determinations when CRP is increased. However, this approach may exclude a large proportion of the population, leading to biased prevalence estimates. Thurnam et al. have proposed that adjusting for acute-phase protein responses provides the most accurate correction of serum ferritin [41].

Another iron indicator that has received attention is serum transferrin receptor (sTfR). The utility of sTfR for identifying iron deficiency in areas where malaria is common has been evaluated extensively, but studies have led to varying conclusions. Some have found that sTfR levels decrease in acute malaria [47–48].

<table>
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<tr>
<th>Table I: Anemia and Iron Biomarkers</th>
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<tr>
<td><strong>Biomarker Stage</strong></td>
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<tr>
<td>Storage Iron Depletion</td>
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<tr>
<td>Early Functional Iron Deficiency</td>
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<td>Established Functional Iron Deficiency</td>
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while others have reported that levels increase in acute malaria [49–50].

The calculation of body iron stores, based on the serum transferrin receptor/serum ferritin (sTfR/serum ferritin) ratio, has been proposed for estimating iron status and responses to nutritional interventions in adult men and non-pregnant women of childbearing age in populations in which infectious disorders are not prevalent. The utility of this approach in adults has been validated experimentally. Recognizing that a similar validation in children would be difficult, the TWG found the report by Cook et al. to be useful. The researchers found a highly significant correlation between the iron stores of preschool children and their mothers, indicating that results derived from sTfR/serum ferritin can be applied to children after the first year of life [51]. Further examination of the utility of the sTfR/serum ferritin ratio as the biomarker of choice for iron status is required. Particular priority areas of use would include population surveys comprising preschool and school-age children, non-pregnant women of childbearing age, postmenopausal women, and men, as would assessment of interventional strategies in these groups.

Information on the utility of the sTfR/serum ferritin ratio for assessing iron status in areas where malaria infection is prevalent is limited. However, in a landmark study conducted in such a region, bone marrow examination was used to validate a battery of peripheral markers of iron deficiency in children with severe anemia [52]. The sTfR/serum ferritin ratio proved the best predictor for the recognition of iron deficiency as defined by absent marrow iron irrespective of the presence of infection [50] in this study.

Zinc protoporphyrin increases in the anemia of inflammation because iron delivery to the bone marrow is restricted. However, the impact of inflammation on zinc protoporphyrin levels is smaller than that of iron deficiency on zinc protoporphyrin levels. In the presence of inflammation, zinc protoporphyrin/heme (ZPP/H) is reported to be a better indicator of iron deficiency than is serum ferritin [53]. However, zinc protoporphyrin levels are elevated in beta-thalassemia trait, alpha-thalassemia trait, hemoglobin E disease, and in some sickle-cell carriers [54–61]. The results from the Pemba trial indicated that zinc protoporphyrin may have an important application in regions where malaria is common, but improved instrumentation would be required to detect this biomarker.

NTBI may be an important proxy measure of potential harm that could be useful for testing the safety of iron interventions. Currently, measurement of NTBI has limited application due to lack of a definitive, valid, and reliable assay. Other limitations include the negative values for NTBI obtained with currently available assays, the difficulty in avoiding iron contamination, and uncertainty about the nature of iron complexes that constitute NTBI.

To provide additional context, the evaluation of available methodologies for malaria diagnosis is useful. Clinical diagnosis of malaria remains imprecise, leading to both under- and overdiagnosis [62]. The magnitude and consequences of misdiagnosis have not been adequately investigated, but misdiagnoses have an impact on malaria treatment decisions, case classification in treatment studies and intervention trials, and monitoring epidemiologic trends [63]. Despite its demands, light microscopy by an experienced technician, using thick films, remains the gold standard for detecting parasitemia in suspected malaria infection [64].

Conclusions

The reliance on serum ferritin as the sole indicator of iron status in individuals suffering from infectious or inflammatory disorders may be misleading because: (1) serum ferritin values could increase as a result of increases in storage iron; and (2) the influence of the inflammatory response alters iron status results. The utility of serum ferritin assays for identifying iron deficiency is also greatly reduced in areas with high malaria prevalence. The measurement cannot be used when there is significant parasitemia, regardless of patient age, nor in acutely ill or severely anemic children younger than 3 years of age who have reduced parasite immunity. Of the currently available approaches (i.e., hemoglobin, ferritin, sTfR, or sTfR/serum ferritin ratio) for assessing iron status at a population level, and with due consideration for resource and capacity needs, the sTfR/serum ferritin ratio emerges as the best biomarker.

Based on biomarkers, the definition of “optimal iron status” developed primarily in western countries should be applied universally. The calculation of body iron store based on the sTfR/serum ferritin ratio provides the best estimates of iron status and response to nutritional interventions for adult men and non-pregnant women of childbearing age among populations in which infectious disorders are not prevalent. More research is needed on the utility of the sTfR/serum ferritin ratio in settings with high malaria prevalence.

For individual assessment, the less-invasive ZPP/H assay seems to be the most promising biomarker at this time, but requires improved instrumentation for broad implementation in low-resource settings.
Research Priorities: Biomarkers

The need exists to stratify populations by iron status before providing iron supplements in large intervention trials, particularly trials involving infants, children, or women. To do so, development of a field-friendly, non-invasive, cost-effective biomarker for detecting iron status (sufficiency or deficiency) is required.

Specific research priorities include:
- Identifying the optimal biomarker to evaluate iron status in children younger than one year of age and in women during pregnancy; studies in pregnant women should include evaluations of fetal and infant development and of the iron status of children during early childhood
- Establishing an optimal approach to laboratory evaluation of iron status in the presence of infectious and inflammatory disorders and clarifying the relative utility of correction factors
- Developing a field-friendly zinc protoporphyrin assessment method and instrumentation that does not require frequent recalibration, and determining whether this is a preferred method in areas where infections are endemic; an instrument could likely be designed to make direct measurements, perhaps through the mucosal surface in the mouth
- Streamlining TIR/serum ferritin methodology and making low-cost tests available for field studies in developing countries
- Determining the utility of NTBI as a clinical or research tool for assessing iron status, particularly in areas where infections, such as malaria, are endemic

Interventions

Despite the attention raised in response to the Pemba Trial results and the conclusions of the subsequent international meetings, significant questions remain about the safety of currently available strategies to improve iron status. To address these questions, the TWG reviewed the evidence for those interventions (Table II) and examined the recent Cochrane Review on the safety of iron supplementation in children younger than 18 years old in regions with high malaria burden.

Table II: Iron Interventions

<table>
<thead>
<tr>
<th>Food-Based</th>
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<tbody>
<tr>
<td>Direct Dietary Diversification</td>
<td>Increases the iron bioavailability of traditional foods or the consumption of iron-rich foods</td>
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<tr>
<td>Indirect Diet Modification</td>
<td>Includes the use of iron cooking pots</td>
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<tr>
<th>Food Fortification</th>
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<tbody>
<tr>
<td>Centrally Processed</td>
<td>Adds iron to commonly consumed staple foods, beverages, or condiments Aims to provide the amount of daily iron lacking in the diet relative to the daily iron requirement For staple foods, often adds less than would be consumed from a supplement</td>
</tr>
<tr>
<td>Home- or Point-of-Use Fortification</td>
<td>Adds iron directly to meals at the time of consumption May also be considered a form of supplementation, depending on the amount of iron provided per meal, but for this report was reviewed in the context of fortification because of its direct use with food</td>
</tr>
<tr>
<td>Biofortification</td>
<td>Increases iron concentration of staple foods by plant breeding or genetic engineering techniques Is not discussed in this report</td>
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<tr>
<th>Supplementation</th>
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<tr>
<td>Oral iron in the form of pills or liquids</td>
<td>Represents the most common intervention Is relatively simple to implement within existing health care systems</td>
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<tr>
<th>Non-Dietary Intervention</th>
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<tbody>
<tr>
<td>Delayed cord clamping</td>
<td>Increases the amount of placental blood transferred to the infant by delaying clamping of the umbilical cord by two to three minutes</td>
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</table>
Food-Based Interventions

The TWG recognized that dietary modification would be the ideal way to improve iron status, but recognized certain limitations within that paradigm. For example, the inclusion of iron-rich animal source foods in the diet is expensive and may not be culturally appropriate in all settings. Similarly, strategies to increase iron availability from plant-based diets using iron pots or food-processing strategies, such as phytate reduction, are difficult to control and have had limited success in improving iron status.

Fortified foods may be a viable option for improving iron status. By careful choice of the iron compound and the amount added, iron-fortified foods can be designed to improve or maintain the iron status of at-risk populations. Options include iron-fortified complementary foods for infants younger than 6 months of age and young children, and iron-fortified staple foods and condiments for women and older children. Despite the promise of such approaches, operational challenges remain. Furthermore, some trials have had very limited success with fortification, and few examples exist of widespread programmatic application of this approach in developing countries. The recent WHO Food Fortification Guidelines represent an important step toward improving these situations, but difficulties continue [65].

The TWG endorsed the use of home-use fortification mixtures with appropriate amounts of absorbable iron compounds because the mixtures can be formulated to improve or maintain the iron status of infants, children, and pregnant and non-pregnant women. These mixtures are added to the food at the point of consumption and may be an alternative intervention to iron supplementation.

With specific regard to the safety of centrally processed iron-fortified complementary foods or iron-containing home-use fortification mixtures, little evidence was found to suggest that they are not safe; however, it should be noted that, to date, no published studies exist that were specifically designed to examine safety of these interventions in malaria-endemic areas. Furthermore, because malaria and other infections can potentially reduce iron absorption, the efficacy of fortified, home-fortified, or centrally processed fortified foods might be compromised in areas with high disease prevalence. The TWG expected that iron-fortified foods would be safe for use in such areas, assuming that the iron from these food-based approaches is absorbed more slowly and would lead to little or no increase in NTBI-associated harmful effects.

Medicinal Iron Supplements (Liquid/Pill)

Iron supplementation remains the safest, most efficacious, and cost-effective intervention for the treatment of anemia and other manifestations of iron deficiency in children and pregnant women. Most safety concerns are obviated by the knowledge that the target groups have already been identified as being iron-deficient, and there are no compelling data to support the contention that iron deficiency conveys some benefit in the context of infection. Large-scale community-based supplementation programs aimed at improving the iron status of populations and, hence, preventing iron-deficiency anemia are recognized as a necessary interim step, although one often viewed as less desirable than food fortification or dietary diversification programs in the long-term [66–67].

However, there is evidence that iron supplements, in liquid or tablet form and usually in combination with folic acid, may increase the incidence, and possibly the severity, of malaria in children, when given without malarial prophylaxis and in the absence of universal access to treatment [68]. There is also evidence of an adverse effect of iron supplementation in pregnant women, but the few reported studies are strongly confounded [69]. For example, increased placental malaria has been demonstrated with intravenous iron infusions. The TWG hypothesized that modifying the way supplements are provided could make supplementation safer in malaria-endemic areas, although research on this approach is lacking. The TWG offered three suggestions in this context:

- Supplement distribution programs should instruct recipients to take their supplements with food.
- Distribution should target only iron-deficient individuals, but this approach would depend on the availability, affordability, and feasibility of a suitable method to screen for iron deficiency in such populations.
- The use of a slow-release supplement may also help overcome harmful effects, assuming that the increase in adverse effects results from a mechanism related to increased NTBI, and that NTBI would be greatly reduced by slow iron absorption.

Cochrane Review

Since the TWG concluded its original review of the literature, the Cochrane Research Group published a meta-analysis, Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas (Review) [70]. The meta-analysis makes
important contributions to the global discussion on safety of iron supplementation; therefore the TWG conducted an extended review of this important paper, available as an appendix to the Iron and Malaria Technical Report. The following is a summary of the TWG’s conclusions.

In the meta-analysis, 68 trials (42,981 children) met the inclusion criteria. Iron supplementation did not increase the risk of clinical malaria (RR 1.00, 95% CI 0.88 to 1.13; 22,724 children, 14 trials, random-effects model). The risk was similar among children who were non-anemic at baseline (RR 0.96, 95% CI 0.85 to 1.09). Iron supplementation was associated with increased risk of malaria only in trials that did not provide malaria surveillance and treatment. The risk of malaria parasitemia was higher with iron (RR 1.13, 95% CI 1.01 to 1.26), but there was no difference in risk in adequately controlled trials. The combination of iron plus anti-malarial drugs was protective for malaria (four trials). Iron did not increase the risk of parasitological failure when given during malaria (three trials). No increased mortality risk was found across all trials comparing iron versus placebo (RR 1.11, 95% CI 0.91 to 1.36; 21,272 children, 12 trials). Iron supplementation increased hemoglobin, with significant heterogeneity, and malaria endemicity did not affect this outcome. Growth and other infections were mostly not affected by iron supplementation [70].

The Cochrane authors concluded that “iron does not increase the risk of clinical malaria or death, when regular malaria surveillance and treatment services are provided. There is no need to screen for anemia prior to iron supplementation.”

This review is the most comprehensive meta-analysis of iron supplementation to date. The conclusions are consistent with the findings of the Pemba trial, the joint recommendation statement by the WHO/UNICEF, previously published reviews, and the conclusions of the TWG as outlined in the Iron and Malaria Technical Report.

Specifically, these resources agree that insufficient health care services are associated with an increased risk of malaria when iron supplementation is given (Cochrane review, RR= 1.16, 95% CI: 1.03 to 1.31, no heterogeneity). Further, in the presence of comprehensive surveillance and prompt malaria diagnosis and treatment, there was no compelling evidence of increased risk of adverse events from iron supplementation (Cochrane review, RR=0.93, 95% CI: 0.84 to 1.04, with heterogeneity). However, the TWG noted that the meaning of “adequate malaria surveillance” was not defined and was unlikely to be practiced in many settings. Moreover, inequalities may exist between communities and within families, meaning the safety of iron supplementation (pills/liquids) in relation to infection risk under such conditions remains a concern.

Other Potential Interventions

Research also suggests that delayed cord clamping may effectively provide the newborn infant with a greater endowment of body iron at birth, which could help the infant maintain satisfactory iron status during early life. Guidelines currently exist for implementation and uptake of this strategy to prevent iron deficiency during the first six months of life in low-resource settings [71–72]. Specific information is still needed on the safety and efficacy of delayed cord clamping in malaria-endemic areas, and how this might impact malarial disease in infants.

Research Priorities: Interventions

A better understanding of the mechanism(s) by which supplementary iron might increase the incidence of malaria and other infections is needed to ensure the safe and effective delivery of iron interventions in malaria-prone areas. Other priorities include the development of novel approaches for enhancing iron status and reliable proxy measures of potential harm that can be used to test the safety of iron interventions at clinical and population levels. Until these steps have been achieved, the research topics suggested below will have to rely on presumed indicators of harm, a less-than-optimal strategy.

The TWG recognizes that future large-scale randomized trials with serious adverse events or mortality as outcomes will be challenging both ethically and logistically. The TWG understands that, to ethically conduct a fresh trial, would require implementation of comprehensive clinical care for participants, thus reducing the outcomes of interest and increasing the required sample size to an extent that would make the trial unfeasible. One possible solution to this dilemma would be to stratify subjects of future research subjects according to their baseline iron status (cf. the Pemba trial sub-study) [13]. Such studies should be conducted in infants, children, adolescents, and women (before, during, and after pregnancy).

The TWG identified the following specific research priorities:

- Definition of the conditions under which direct dietary modification and use of iron pots can be
effective and safe interventions to prevent iron deficiency, particularly in malaria-endemic areas
- Studies in malaria-endemic areas to establish the safety of iron administration through food fortification (both centrally processed fortified foods and home fortification); at present, such studies will have to rely on proxy measures of presumed risk and measures of impact
- Determination of whether the safety of iron supplements is only a concern for iron-replete subjects in malaria-endemic areas, particularly where malaria treatment facilities are limited
- Evaluation of the safety and efficacy of administering iron supplements with food rather than the usual current practice of administering it between meals; stratification of subjects according to their baseline iron status will be critical to these efforts
- Revisiting the viability and feasibility of novel approaches to developing safe and efficacious vehicles for iron supplementation in malaria-endemic areas, such as the Gastric Delivery System
- Evaluate the impact of iron supplementation timing relative to a malaria attack, and the need for iron-absorption studies, with assessment of the risks from acute diarrhea, in children who have acute malaria
- Conducting meta-analysis of studies using individual patient data to evaluate the impact of oral-iron supplementation in children (those younger than 18 years of age) living in malaria endemic areas
- Studies of iron absorption in children with acute malaria, including evaluations of the role of comorbidities, such as acute diarrhea, in outcomes
- Evaluation of the safety and efficacy of delayed cord clamping in malaria-endemic areas, including the impact of the mother’s iron status on the outcomes in infants
- Evaluation of the risk for jaundice as a result of delayed cord clamping in populations with a high prevalence of glucose-6-phosphate dehydrogenase deficiency

Conclusion

The TWG conducted a comprehensive review of the key issues associated with the role of iron in immune function and infection and its safe and effective uses, particularly in malaria-endemic areas. As noted at the outset, the core issues addressed were whether:

1) In environments where malaria and other infectious diseases are endemic, the innate immune

iron-withholding defense of the host is impaired or enhanced by nutritional iron deficiency; and
2) Providing supplemental iron by any of the currently available iron intervention vehicles (i.e., supplements, fortified foods, etc.) has a harmful effect on the host by abruptly increasing iron availability to invading organisms, and/or whether correcting iron deficiency is helpful to the host by improving immune function.

The evidence for an overall protective effect of nutritional iron deficiency against malaria and other infections is inconclusive and limited, while the negative impact of iron deficiency on immunocompetence, growth, development, and health is well established. However, the role of the metabolic response to infection and its importance to the immune response remains an important consideration for improving outcomes. The unknown role of, and potential advantages or disadvantages associated with, genetic disorders of iron metabolism in the context of infections, including malaria, is another consideration. Although nutritional iron deficiency does not seem to be protective generally and should be prevented and ameliorated, research to ascertain optimal treatment strategies in the context of infection is also needed. Fundamentally, there is a critical need to better understand the relative risk/benefit relationship between the contributions of iron status to risk of infection and the potential for acute adverse effects of iron interventions, especially when compared to the expected longer-term benefits gained by ensuring adequate iron stores.

Questions about the specific impact of providing iron under conditions of malaria and high infection exposure remain unanswered, especially in settings where care and treatment are not readily available or accessible, and warrant further focused research efforts. At this time, the provision of iron via tablets or liquids requires caution and may be the least desirable approach in malaria-endemic areas, particularly in areas with poor clinical care provision. Efforts should continue to ensure adequate iron status for infants, children, and women. To accomplish this, fortified foods may be the most viable alternative intervention for accomplishing this goal. Such strategies could include iron fortification of complementary foods for infants and young children, and iron-fortification of staple foods and condiments for women and older children. The TWG’s review emphasizes the need for careful selection of the type and amount of iron compound. If done correctly, iron-fortified foods can be designed as a sustainable intervention to improve or maintain the iron status of all at-risk population groups.
Finally, the TWG recognizes that a “one size fits all” public health approach is likely to be inappropriate in the absence of clinical data on the health of individuals. The questions raised in response to this global health concern reinforce the need for improved approaches to the management of health and disease at community and population levels.

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Disclaimer

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