Pediatric Nutrition: Challenges and Approaches to Address Them

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Balancing Safety and Potential for Impact in Universal Iron Interventions

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Abstract

Almost 300 million children under 5 years of age are anemic worldwide. International policymakers recommend universal distribution of iron-based interventions – either iron supplements or iron-containing multiple micronutrient powders – to alleviate the burden of anemia in young children. When considering whether to implement universal iron interventions, it is essential to balance the putative benefits with possible risks. The key rationale for deploying universal iron interventions to reduce anemia in young children is to improve development, growth, and well-being. While plausible, few randomized controlled trials (RCTs) of iron interventions have carefully assessed these outcomes and there is currently inadequate evidence to support the hypothesis that universal iron interventions provide benefits on functional child health outcomes. Conversely, several important RCTs have found that when iron interventions are given to all children in a population, they may increase infection risk. Other possible risks of iron interventions have not yet been extensively described but include a risk of iron overdose and long-term iron loading in high-risk individuals. Identifying whether these interventions provide a net benefit or harm to populations is challenging. Until the quality of evidence for benefits improves, implementation of universal iron interventions in young children should be undertaken with caution.
Introduction

Anemia represents a significant health burden globally. In its recent review, the World Health Organization (WHO) estimated that around 41% of children under 5 years of age were anemic worldwide in 2016 [1]. Anemia peaks in children under 2 years of age and generally improves as they reach pre-school age. In children, it is linked to rapid growth and increased demand for iron in erythropoiesis, as well as a potential reduction in iron intake due to reliance on complementary foods low in iron. Anemia risk is also influenced by factors including other micronutrient deficiencies, inflammation, infection, and the onset of disorders affecting red blood cell production or survival, such as hemoglobinopathies or thalassemia syndromes.

Iron interventions used to control anemia in large-scale programs in low- and middle-income countries (LMICs) may be given as iron salts (e.g., ferrous sulfate iron drops) but are increasingly being incorporated into multiple micronutrient powders (MNPs), which contain lipid microencapsulated iron (usually as ferrous fumarate or iron-EDTA) together with other micronutrients such as zinc, vitamin A, and ascorbate and enable home fortification of complementary foods.

The WHO recommends that such iron interventions be administered to all children in areas of high anemia prevalence [2, 3] (Table 1). The universal approach to iron interventions, using either iron drops or MNPs, is aimed at maximizing the benefits to children at a population level and avoiding the logistic and financial challenges of individual screening prior to supplementation. However, there is evidence of risk for young children, including significant associations with infection, and these must be included in the evaluation of these universal intervention programs.

This review will discuss some of the challenges relating to universal delivery of iron interventions, focusing on children under 2 years of age; it specifically does not pertain to clinical therapy for iron deficiency in diagnosed cases.

Determinants of Anemia

Anemia disproportionately affects children in LMICs in Asia and sub-Saharan Africa [4]. In these regions, there is an intersection between malnutrition, endemic infections including malaria, and genetic disorders of red cells, all of which contribute to the disease [5, 6] (Table 2).

Anemia has been previously proposed as a surrogate for low iron status in assessments of population nutrition status [7]; however, this fails to account for other causes of anemia and inevitably misses cases of iron deficiency in
### Table 1. WHO guidelines for universal iron interventions in children aged 6–23 months [2, 3]

<table>
<thead>
<tr>
<th></th>
<th>Iron syrup/drops</th>
<th>Micronutrient powders containing iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron dose</td>
<td>10–12.5 mg elemental iron</td>
<td>10–12.5 mg elemental iron</td>
</tr>
<tr>
<td>Intervention schedule</td>
<td>Daily for 3 consecutive months in a year</td>
<td>90 sachets or doses over 6 months</td>
</tr>
<tr>
<td>Target regions</td>
<td>Regions where anemia prevalence is 40% or higher*</td>
<td>Regions where anemia prevalence is 20% or higher*</td>
</tr>
</tbody>
</table>

Reprinted from WHO Guideline: Daily iron supplementation in infants and children, Table A, Page 2, Geneva: World Health Organization; 2016 and WHO guideline: Use of multiple micronutrient powders for point-of-use fortification of foods consumed by infants and young children aged 6–23 months and children aged 2–12 years, Table 1, Page 4, Geneva: World Health Organization; 2016.* From WHO guidelines: in malaria-endemic areas, these iron interventions should only be made together with “(public health) measures to prevent, diagnose, and treat malaria” [2, 3]. WHO, World Health Organization.

### Table 2. Global prevalence of conditions known to contribute to anemia at the population level (excluding dietary iron deficiency)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence in 2013 (all age groups) [5]</th>
<th>Prevalence of related anemia in 2013 (all age groups) [5]</th>
<th>Mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria*</td>
<td>351 million</td>
<td>80 million</td>
<td>Multifactorial: intravascular hemolysis, chronic inflammation leading to reduced iron absorption/ increased iron sequestration</td>
</tr>
<tr>
<td>Hookworm infection</td>
<td>472 million</td>
<td>35 million</td>
<td>Chronic blood loss</td>
</tr>
<tr>
<td>Thalassemias including thalassemia traits</td>
<td>208 million</td>
<td>105 million</td>
<td>Ineffective erythropoiesis</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>3 million</td>
<td>3 million</td>
<td>Altered oxygen binding properties of hemoglobin S</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>338 million</td>
<td>743,000</td>
<td>Intravascular hemolysis</td>
</tr>
<tr>
<td>Other micronutrient deficiency (folate, vitamin B12)</td>
<td>–</td>
<td>–</td>
<td>Reduced erythropoiesis</td>
</tr>
<tr>
<td>Anemia of inflammation</td>
<td>–</td>
<td>–</td>
<td>Reduced iron absorption and increased iron sequestration mediated by hepcidin</td>
</tr>
</tbody>
</table>

* 219 million cases in 2017 [6].

G6PD, glucose-6-phosphate dehydrogenase.
which the hemoglobin remains within the reference range [8]. Although iron deficiency has historically been considered the primary cause of anemia, accounting for 50% of cases [9], the WHO now estimates that 42% of cases of anemia in children globally can be corrected by iron supplementation, and in Africa, this figure falls to 32% due to the contribution by malaria [4]. The global estimated prevalence of iron deficiency among pre-school children is around 17% and of iron deficiency anemia is 10% [10]. It is thus almost certain that the contribution of iron deficiency to the overall prevalence of anemia is much lower than previously thought, making precise estimates difficult.

There are key limitations to assessing the true prevalence of iron deficiency and hence the number of children worldwide who would benefit from iron interventions. Given iron deficiency can exist separately to anemia and that iron deficiency can occur concurrent with other factors in an individual with anemia, devising population-level estimates of anemia determinants requires a sensitive and specific biomarker for iron status beyond relying on hemoglobin alone. Biomarkers for the estimation of iron status include ferritin, soluble transferrin receptor (sTfR), and hepcidin. Low ferritin is specific for iron deficiency and is commonly used in regions of the world where individual screening and treatment are employed. However, as ferritin is a positive acute-phase reactant, it may be elevated (or falsely normal) in inflammatory states [11]. Relying on hypoferritinemia alone for the diagnosis of iron deficiency, particularly in populations with a relatively high incidence of infection and inflammation, may underestimate true prevalence of iron deficiency. Furthermore, thresholds for defining iron deficiency remain uncertain, differ between different laboratories and expert agencies, and are not based on high-quality primary studies [12].

It may be feasible to use ferritin for population-level estimates of iron deficiency in areas of high infection prevalence by raising the usual cutoff level or correcting individual ferritin concentration for inflammation [11–13]. In an effort to account for inflammation, the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia Project developed a model for interpreting serum ferritin concentrations in populations with inflammation, adjusting for inflammatory markers C-reactive protein and alpha 1-acid glycoprotein [14]. External validation of this approach is needed before this approach can be widely recommended. Implementation of direct iron status measurement for population estimates of iron deficiency will require utilization of a well-validated and reproducible approach that enables integration and adjustment of ferritin levels with inflammatory biomarkers and infection prevalence data.
Other biomarkers of iron status are available and may be useful in the future. The sTfR is raised in iron deficiency and is less influenced by inflammation, rendering it potentially more sensitive to iron deficiency [15]. However, its widespread implementation is limited due to several factors. First, it is also raised in increased erythropoiesis (e.g., hemolysis) and dyserythropoiesis (e.g., thalassemia syndromes) [16, 17], reducing its specificity [18]. Second, the assay is not commonly used, even in higher-income countries. Finally, there is variation between assays and therefore no standard reference range. Hepcidin is another promising biomarker of iron status. Studies in children have shown it to be diagnostic of iron deficiency, predictive of iron absorption, and capable of distinguishing anemia of inflammation from iron deficiency [19, 20]. However, like sTfR, hepcidin assays are largely ELISA-based and have substantial variation in values (although close correlation) between kits.

Even though researchers recognize the complexity of assessing iron deficiency, the case for screening of individuals is becoming more compelling. While WHO guidelines recommend universal intervention in areas of high prevalence, if only 30–40% of children are likely to respond and there are potential risks of delivering iron- to non-iron-deficient individuals, a more efficient approach may be to incorporate a more direct measure of iron status to screen at the level of the individual prior to administering iron. Individual screening, however, presents a significant logistical challenge, as iron measures need to be individually interpreted, and multiple encounters may be required for screening, commencing treatment, and evaluating response. Furthermore, given that the assays that most directly measure iron status are less widely available than other measures that use point-of-care instruments, their routine use would be problematic. Nevertheless, ambitious clinical trials are currently testing a “screen-and-treat” approach in the field and will provide important insights into the efficacy and feasibility of this method [21].

Due to the limitations of screen-and-treat approaches, iron interventions are universally distributed. It is therefore critical to define the net benefits and risks associated with universal iron interventions to justify this practice.

**Evidence of Benefits from Universal Iron Interventions**

Iron is an essential micronutrient required not only primarily for the synthesis of hemoglobin but also for other biological processes including neural development [22, 23]. Anemia, including iron deficiency anemia, has been associated in observational studies with adverse cognitive development in children and with reduced productivity in adults, resulting in significant economic consequences for LMICs [2].
Improvement of Anemia and Iron Deficiency

Iron supplementation improves anemia and iron deficiency. A systematic review and meta-analysis of randomized controlled trials (RCTs) found that daily iron reduced anemia by 39% and iron deficiency by 70% in children aged 4–23 months [24]. A similar review of MNP trials in young children showed a 31% reduction in anemia and a 51% reduction in iron deficiency [25].

Iron and Cognitive Development

There is limited quality evidence for functional benefits on child health from iron interventions. An important rationale for iron supplementation in infants and young children is to improve cognitive development. Observational studies consistently indicate that non-anemic children perform better on developmental assessments than their anemic peers [26]. However, few high-quality, double-blinded, well-powered RCTs exist that show benefits of iron supplementation on functional outcomes in children. Further, there is a lack of uniformity with regard to baseline population characteristics, iron dose, treatment age and duration, reporting of adherence to the iron intervention, and tools used to assess functional outcomes, particularly child development [23, 27, 28].

The most common developmental assessment tool used in iron trials is the Bayley Scales of Infant Development including the Mental Development Index (MDI) and the Psychomotor Development Index. Of the iron RCTs in children aged under 2 years living in settings with high prevalence of anemia, several show a modest benefit on child development. For example, Yousafzai et al. [29] showed that an “enhanced nutrition” intervention (MNP containing iron and other micronutrients) among 742 children aged 6–24 months was associated with higher MDI at 12 months and improved language at 12 and 24 months compared with the control group. However, as an effectiveness trial, this study was not placebo-controlled, and the intervention group received additional micronutrients aside from iron which likely contributed to the benefits observed [29]. An RCT in Indonesia randomized 680 infants aged 6 months to daily supplementation with iron, iron plus zinc, or placebo for 6 months. Following intervention, children in the iron group had significantly higher Psychomotor Development Index scores than did those in the placebo group. There were no significant differences in the other Bayley domains – including MDI – and the positive effect was not seen in the iron plus zinc group [30]. The lack of other evidence of positive effects on cognition may be in part due to many trials being underpowered to detect small changes on the assessment scales. A meta-analysis of children 4–23 months of age found no evidence of improvement in mental or
psychomotor development scores following iron supplementation [24]. Current trials underway are recruiting larger cohorts with longer follow-up to better quantify the effects on cognitive development in children under 2 years of age [31].

**Iron and Growth**

Iron interventions do not benefit weight or linear growth in children in this age group [24, 25, 32]. Importantly, several trials have shown negative association between iron interventions and gains in weight and length [24]. Recent studies have found that more rapid child growth is associated with depletion of iron meaning children gaining the most weight have lower iron stores [33].

**Evidence of Risk**

While children in LMICs have a high theoretical potential to benefit from iron interventions, they also bear a large burden of infectious diseases including malaria, respiratory tract, and diarrheal infections.

**Iron and Malaria**

Malaria was estimated to be responsible for around 435,000 deaths worldwide in 2017 and 61% of these deaths were in children [6]. Endemic areas also show a high burden of anemia in addition to morbidity and mortality caused by *Plasmodium falciparum* malaria. In an anemic individual, iron supplementation, if effective, leads to a reticulocytosis, and these immature red blood cells are more prone to invasion by Plasmodium parasites [34]. An iron-deficient state appears relatively protective against malarial parasitemia and clinical infection [35].

The Pemba trial [36] was a major pediatric RCT of iron supplementation in a malaria-endemic region powered to assess adverse effects of universal intervention. It recruited 24,076 children aged 1–35 months from the Tanzanian island of Pemba and randomized children to receive one of iron and folic acid, iron and folic acid with zinc, or placebo. The 2 intervention arms containing iron were closed early due to an increased incidence of serious adverse events: a 12% increase in death or serious morbidity leading to hospital admission. Children in the iron-containing arms also had a 16% increased risk of serious adverse events due to clinical malaria compared to the placebo arm. The findings from this trial have had an ongoing impact on the landscape of global anemia control policy, prompting reconsideration of the universal intervention model as well as further study to determine how to deploy iron interventions safely in malaria-endemic areas [2, 3]. By contrast, a study of 1,958 children in
Ghana aged 6–35 months randomized to either an iron-containing MNP or an MNP without iron for 5 months showed no increase in malaria. These participants were given insecticide-treated bed nets at enrollment and cases of malaria were promptly treated [37]. There was, however, a 23% increased rate of hospital admission during the intervention period among those in the iron MNP group. Subsequent and current recommendations for children in malaria-endemic regions recognize the importance of the risks. A 2016 systematic review of 35 trials of iron interventions in children in malaria-endemic regions found that overall, iron interventions were not associated with increased clinical malaria. However, comparison between trials conducted in sites in which malaria prevention and management were present or absent showed that iron was associated with reduced clinical malaria where these facilities were present and with a higher risk of clinical malaria where they were absent, though quality of this evidence was evaluated as poor [38]. Recommendations from this review and from the WHO state that universal interventions should be implemented “in conjunction with public health measures to prevent, diagnose and treat malaria” [2, 3].

Iron and Diarrhea
Iron has been shown to reprofile the intestinal microbiota and increase markers of intestinal inflammation. Several studies of the intestinal microbiota in humans have shown an increased abundance of potentially pathogenic taxa and a reduction in commensal groups such as Bifidobacterium. This was evident in a study involving 2 RCTs of 115 six-month-old infants in Kenya receiving MNPs with and without iron. The infants who received iron had increased carriage of gut enteropathogens including Escherichia, Shigella, and Clostridium species. They also had significant increases in the intestinal inflammatory marker calprotectin by the end of the iron interventions [39].

Beyond changes in pathogen carriage and inflammation, large trials have also shown an increase in the incidence of diarrhea. A key study of 6-month-old infants conducted in Pakistan showed increased diarrhea with oral iron supplementation. These children were randomized to receive (1) an iron-containing MNP with zinc, (2) an iron-containing MNP without zinc, or (3) no intervention (control). Children in the arms receiving iron had a significantly increased proportion of days with diarrhea during the 12-month intervention, as well as increased bloody diarrhea [40]. A large non-placebo-controlled trial in Pakistan of iron-containing MNPs together with nutrition education and responsive stimulation showed a significantly higher maternal-reported diarrhea incidence in children who received iron compared to those who did not [29]. As these studies did not use a placebo, interpreting these adverse events must be done with caution.
Potentially pathogenic changes to the intestinal microbiota from iron may be influenced by the presence of environmental contaminants and therefore baseline pathogen carriage in the gut. Two similar iron intervention trials – one of children in Côte d'Ivoire and the other in South Africa – showed that higher enteropathogen carriage at baseline (Côte d'Ivoire) led to increases in these taxa at the end of the intervention, whereas in the South African cohort, there was lower enteropathogen abundance and no significant change with iron [41, 42]. There remains a paucity of evidence linking changes to the intestinal microbiota and the clinical outcome of diarrhea.

**Iron and Respiratory Tract Infections**

Iron supplementation has also been linked to respiratory tract infection. Soofi et al. [40] showed increased incidence of these infections among children receiving iron-containing MNPs. More recently, a double-blind RCT of 155 infants in Kenya showed a significantly higher incidence of treated respiratory tract infections in those receiving an iron-containing MNP (87%) versus those receiving no iron (75% – \( p = 0.024\% \)) [43]. However, the previously discussed meta-analysis of trials of children aged 4–23 months found no evidence of significant increase in the overall risk of acute respiratory infection or incidence of lower respiratory tract infection [24].

**Risks in Iron-Replete Individuals**

Additionally, the assumption that anemia is due to low iron stores fails to consider diseases causing anemia in which iron may not be required or is even contraindicated, such as thalassemia and hemoglobinopathies, which have high prevalence in several studies and whose distribution often corresponds to areas with current or previous malaria burden. For example, a case-control study in Mozambique performed thalassemia testing on participant samples and found an incidence of alpha thalassemia of 53% (including heterozygous and homozygous single-gene deletions). Participants with alpha thalassemia trait were overrepresented in anemic compared with non-anemic children [44].

Iron overload is a life-threatening disease that can lead to organ dysfunction including liver, heart, and endocrine failure [45]. While it is possible for children with thalassemia traits or syndromes to be iron deficient, in some conditions (e.g., HbE-beta thalassemia, beta thalassemia intermedia, hemoglobin H disease), there is a risk of iron overload brought about by ineffective hematopoiesis and increased intestinal iron absorption [46]. In South-East Asia, 2003 data showed that 44% of the population carried an alpha thalassemia mutation and there are also high rates of carriage of beta globin mutations and clinical syn-
dromes of deletional and non-deletional HbH disease (such as hemoglobin H-Constant Spring) [47]. In the case of hemoglobin H-Constant Spring, iron overload can manifest in childhood [48].

Iron Toxicity

Finally, acute iron toxicity may result from ingestion of excess iron and lead to multiorgan dysfunction and, if severe and left untreated, death. This is a potential issue for programs that distribute iron in large quantities – for example, providing the total amount of iron syrup or tablets at a single initial time point – and where safety information is not provided to or understood by parents or guardians.

Conclusions

Anemia remains common in children living in LMICs. Universal iron intervention programs that aim to deliver iron to all members of a particular group assume that treating individuals with iron deficiency – and preventing iron deficiency in some of the others – makes this approach worthwhile. They also assume that the net benefit to the population is high because the benefits in the deficient group are high, the preventive effects in the non-deficient group are beneficial, and the possible risks in both deficient and non-deficient people are sufficiently low that supplementing them is inconsequential. While iron interventions in children have potential for enormous benefit, there is an urgent need to strengthen the evidence for the role of iron in improving child growth and development based on longer-term assessments and to clarify the risks associated with iron supplementation including infectious morbidity and risk of iron overload. Policymakers must consider risk-benefit when looking to open, continue, or expand universal iron intervention programs in children.

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