Prevention of Iron Deficiency in Infancy, Childhood and Adolescence

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Introduction

Iron is an essential nutrient for the functioning of nearly all cells of the human body, with particularly high dietary requirements during growth [1]. Iron deficiency (ID) in childhood, as in adults, results mainly from low dietary iron intake and low bioavailability [2]. The amount of dietary iron needed to meet the physiological iron requirements depends on the iron bioavailability of the diet, which may vary from approximately 5 to 18% [1, 3] (table 1). The lower the bioavailability, the more dietary iron needed and the higher the risk of ID. Imbalance between iron requirements and iron intake gradually depletes the iron stores, and exhausted iron stores eventually lead to iron deficiency anemia (IDA) [4]. ID is the most common nutritional deficiency in children worldwide [5], with a high prevalence in both low- and high-income countries. Although the risk of ID is higher during periods of rapid body growth, in infancy and again at
puberty, the prevalence rates in developing countries are often generally high throughout childhood due to overall poor iron bioavailability diet. Menstruating adolescent girls are at further risk as they need additional iron to cover menstrual iron losses [3]. Additional risk factors and negative health consequences of ID and IDA throughout childhood are described in another article in this issue [6].

ID during childhood can be prevented by improving the iron intake [2, 7]. Adverse effects may be reversed by improved iron status in early childhood or before ID becomes severe or chronic [8]. The goal of all population-based iron prevention approaches is to improve iron status, reduce the prevalence of ID and eliminate the negative functional consequences of ID [9]. In this overview, we outline the main ID prevention strategies during infancy, childhood and adolescence, relevant to both low- and high-income countries.

**Special Foods for Young Children**

**Breast Milk**

Term, normal birth weight infants of iron-sufficient mothers are born with sufficient iron stores supplying them with iron during the first months of life [10]. Despite its low iron content (0.2–0.4 mg/l), breast milk supplies sufficient iron to meet the infants’ modest iron requirements [1, 11]. The universal recommendation for ID prevention in infants is exclusive breast-feeding for 6 months [12, 13]. When newborn iron stores are suboptimal, particularly in preterm infants, low-birth-weight infants and infants of iron-deficient mothers, exclusive breast-feeding should be complemented with iron supplementation [11]. Continued breast-feeding is recommended along with the introduction of iron-rich complementary food for at least the 1st year of life and beyond [12–14]. In situations when breast milk is not an option, iron-fortified infant formulas should be given to infants during their first 6 months [11, 15, 16].

**Complementary Food**

The innate iron stores are exhausted at about 4–6 months of age and the daily dietary iron requirements rapidly increase [10, 11]. Sufficient amount of highly bioavailable iron (approx. 1 mg/kg per day) in complementary foods is critical for the prevention of ID in infants 6–24 months of age [17–19]. The total amount of iron required depends on the age of the child, the quantity of breast milk intake and the dietary bioavailability.

<table>
<thead>
<tr>
<th>Population group</th>
<th>Recommended iron intake for different dietary iron bioavailability, mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WHO&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infants</td>
<td></td>
</tr>
<tr>
<td>0–6 months</td>
<td>––</td>
</tr>
<tr>
<td>7–12 months</td>
<td>18.6</td>
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<tr>
<td>Children</td>
<td></td>
</tr>
<tr>
<td>1–3 years</td>
<td>11.6</td>
</tr>
<tr>
<td>4–6 years</td>
<td>12.6</td>
</tr>
<tr>
<td>7–10 years</td>
<td>17.8</td>
</tr>
<tr>
<td>Adolescents</td>
<td></td>
</tr>
<tr>
<td>11–14 years (males)</td>
<td>29.2</td>
</tr>
<tr>
<td>15–17 years (males)</td>
<td>37.6</td>
</tr>
<tr>
<td>11–14 years (females)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>28.0</td>
</tr>
<tr>
<td>15–17 years (females)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>62.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> World Health Organization. Adapted from the World Health Organization [3].
<sup>b</sup> Institute of Medicine, United States. Adapted from the National Academy of Sciences, Institute of Medicine [1].
<sup>c</sup> Age range: 4–8 years.
<sup>d</sup> Age range: 9–13 years.
<sup>e</sup> Premenarche.
<sup>f</sup> Menstruating adolescent girls need additional iron to cover menstrual iron losses.

Cereal-based gruels or porridges, fruits and vegetables are usually the first semisolid complementary foods introduced into the infant’s diet. However, home-prepared complementary foods generally have low iron content and low iron bioavailability and are unlikely to meet the iron requirements [19, 20]. Increased dietary diversification and traditional food-processing techniques may improve the iron content and bioavailability of home-based complementary foods, but are hardly ever sufficient (see below) [19, 21].

Iron-fortified formulas or cereals are therefore recommended as first complementary foods [22–24]. In settings where commercial products are not available, home fortification [using micronutrient powders (MNPs), crushable tablets, or fat-based products] or iron supplements in the form of iron drops will be required (see below) [9].

The timing of the introduction of complementary foods may be critical for iron. Although international WHO guidelines recommend complementary foods to be introduced at 6 months of age [12], recent studies in-
dicate that breast milk alone may not meet the full iron requirements of all infants at 6 months of age \[25–28\]. Pediatric guidelines in the United States \[13, 23, 24\] and Europe \[14, 29\] promote exclusive breast-feeding for 6 months, but recommend introduction of complementary foods between 4 and 6 months. The argument against introducing other liquid or solid foods than breast milk during the first 6 months of life is mainly hygienic to prevent food-borne infections \[30, 31\]. When safe hygiene conditions can be assured, introduction of iron-rich complementary foods into the diet of healthy term infants between the age of 4 and 6 months is safe and does not pose a risk for adverse health effects and may be beneficial for the prevention of ID in some young children \[29\].

**Food-Based Strategies to Prevent ID**

*Dietary Diversification*

Food-based strategies to improve iron status involve increased dietary diversity and traditional food-processing techniques aiming at increasing the total iron content and improving the dietary absorption of non-heme iron in complementary food and/or in the diet of older children. Food-based approaches are sustainable ways to improve iron status in childhood and should always be the first priority. Such strategies can be implemented at the household level, are safe and do not require universal screening for ID.

*Dietary Iron and Its Bioavailability*

Dietary iron is present in 2 different forms: heme iron from hemoglobin and myoglobin in animal source foods and non-heme iron [inorganic, ferrous (Fe\(^{2+}\)) and ferric (Fe\(^{3+}\)) iron] present mainly in plant-based foods such as vegetables and grains \[2, 32\]. Heme iron has high bioavailability, is well absorbed (estimated at 15–35%) and is therefore the preferred source of dietary iron \[32\]. However, the proportion of heme iron in the overall dietary iron is often low, approximately 10% in children in meat-eating populations but commonly lower in low-income countries or vegetarian populations. The major part of iron in children’s diet is therefore non-heme iron. The absorbed amount of non-heme is highly variable and depends both on the child’s iron status and on the other components of the diet which may interact with non-heme iron to either enhance or inhibit non-heme iron bioavailability \[32\]. In subjects with no iron stores, the bioavailability of non-heme iron is estimated to be in the range of 14–18% for mixed diets and 5–12% for vegetarian diets \[32\]. Regulatory mechanisms strictly control iron absorption \[33\], and individuals with sufficient iron stores absorb dietary iron to a lower degree.

Enhancers of non-heme iron absorption are ascorbic acid, organic acids and muscle tissues in meat, fish and poultry \[32\]. While ascorbic acid and some amino acids, such as cysteine, promote iron absorption by reducing ferric iron to the more soluble and absorbable ferrous form, large amounts of organic acids like citric acid enhance non-heme iron absorption by chelating iron to keep it in solution. Inhibitors of non-heme iron absorption are phytate in plant-based diets and cereals, polyphenol compounds in vegetables, legumes, fruits, berries and beverages such as tea and chocolate, calcium in dairy products, plus milk and egg proteins \[32\]. These inhibitors typically bind either ferrous or ferric iron in a tight complex in the gut lumen and make iron unavailable for absorption. The negative effect of phytate on iron absorption can start at very low concentrations of 2–10 mg/meal and is dose dependent \[34, 35\]. A diet that contains large amounts of inhibitors, particularly vegetarian diets, unrefined grains and cereal-based complementary foods generally has poor iron bioavailability \[36\].

**Improving Non-Heme Iron Absorption**

The most powerful dietary strategy to improve non-heme iron absorption is to add fresh fruits (e.g. citrus fruits, guava fruits) or vegetables (e.g. tomatoes, green leaves) rich in ascorbic acid and animal foods to a meal \[32, 37, 38\]. Ascorbic acid (when present in a molar ratio from 2:1 to 4:1 to iron) overcomes the negative effects on iron absorption from phytate and polyphenols in cereals and legumes, calcium and proteins in milk products and increases the absorption of both native and fortification iron \[32\]. Even a small amount of ascorbic acid is beneficial, and increasing the consumption of foods rich in ascorbic acid is usually economically feasible and can be adapted to local conditions. A mixed, balanced diet including meat, fruits and vegetables thus has the potential to meet requirements in children, except perhaps for weaning infants \[19\].

Reducing the amount of inhibitors in the diet is another simple dietary approach to improve iron bioavailability. Foods with a high amount of inhibitors can be replaced with foods containing lower amounts; for example, whole-grain flour with high phytate content versus milled refined flour with lower content, or red beans with high polyphenol content versus white beans with...
lower content. The amount of phytate in foods can be reduced by soaking or by enzymatic degradation during food processing and food preparation. Traditional household methods such as fermentation and germination can be used to activate native phytase enzymes which degrade phytates [32, 39]. Phytate content has been reported to be reduced by up to 90% by fermentation and up to 64% by germination [37]. Alternatively, exogenous phytases can be added to degrade phytate during food production [40] or after consumption during digestion [41]. Lastly, the consumption of coffee and tea together with meals should be avoided as they strongly negatively influence the non-heme iron absorption and iron status [32]. It should be noted, however, that efficacy studies evaluating the influence of dietary approaches reducing the amount of iron absorption inhibitors on children’s iron status are largely lacking, or have failed to demonstrate effect [42].

Cow’s Milk
Cow’s milk has about the same low iron concentration as human milk (approx. 0.5 mg/l), but its bioavailability is lower, possibly due to the high amounts of calcium and casein inhibiting non-heme iron absorption [32]. The amount of bioavailable iron contributes little to the iron requirements of infants and young children. Furthermore, cow’s milk consumption during the first year of life may also cause occult intestinal blood loss in infants, likely due to an intolerance reaction, which may cause and/or aggravate ID [43, 44]. Whole cow’s milk should therefore be avoided during the first year of life [23, 24, 45]. However, modification of cow’s milk protein in the preparation of commercial infant formula or evaporated milk alters the protein structure and prevents the allergic reaction which leads to intestinal bleeding [44]. Iron-fortified infant formulas containing processed cow’s milk can therefore be given to infants weaned before 12 months [15] or can replace breast milk when his is not available. Although cow’s milk can be consumed by children older than 12 months, it is a generally poor iron source and consumption has been shown to be negatively associated with iron status [46, 47].

Meat, Poultry and Fish
Meat, poultry and fish (MPF) are good sources of iron in both complementary foods [22, 48, 49] and in the diet of older children [50]. MPF have two advantages: they provide highly bioavailable heme iron and also increase the absorption of non-heme iron through an unknown ‘meat factor’ [32]. The heme iron content is highest in beef and red meat (approx. 60%), followed by pork (approx. 40%), poultry (approx. 30%) and fish (approx. 25%) [51].

MPF can be introduced as small pieces or as puréed meat in complementary foods already at 6 months of age when the child is able to chew and swallow well and daily consumption of MPF is recommended [17, 49]. Increased meat intake during the weaning period is associated with a better iron nutrition as shown in both observational studies [52, 53] and intervention studies [54, 55]. The trend is the same in older children, and the prevalence of ID is generally high in populations consuming low amounts of MPF.

Despite recommendations to include meat in children’s diet, meat is often introduced late [56, 57] and strategies to promote meat intake have been poorly implemented in both high- and low-income countries [27, 58]. Such strategies have long been considered unrealistic due to limited access to meat, particularly in low-income settings. However, there are numerous recent examples on feasible programs promoting animal source foods to improve overall nutrition [58] and innovative approaches include adding dried meat powder to complementary foods [59, 60]. Dietary studies of school children in Kenya estimate that the addition of 100 g meat plus 150 mg ascorbic acid would be necessary to reduce the prevalence of inadequate iron intake from 88% to below 5% [61]. Still, relatively few intervention trials have assessed the benefits of increasing MPF intake in older children in populations where the usual intake is low [50].

Iron Pots
Cooking foods in iron pots and thereby increasing the iron of the food has been suggested as a simple strategy to improve the dietary iron intake in children. Iron from the pot dissolving into a slightly acid food matrix such as tomatoes would be expected to be as bioavailable as the food iron, whereas iron still in the elemental form would be absorbed only if dissolved during digestion. However, although some studies investigating the impact of the use of iron pots on iron status have shown positive results [62], the data are inconclusive [63, 64]. The amount dissolved will vary with the type of pot used and the acidity of the food prepared and will ultimately determine the impact on iron status.

Biofortification
Biofortification is an iron intervention strategy aiming at increasing the content of select micronutrients, including iron, in staple food crops such as rice, wheat, maize, pearl millet, and others by agricultural breeding
or genetic engineering [65]. Increasing the iron content by genetic engineering can be achieved by introducing ferritin into grains such as rice [66]. Although there was some concern about bioavailability, ferritin iron seems to be readily released during food preparation and digestion [67]. Biofortification can also be used to improve the iron bioavailability in crops by increasing concentrations of enhancers such as ascorbic acid and cysteine-rich polypeptides and/or reducing concentrations of inhibitors such as polyphenols or phytate. Research and breeding programs of biofortified crops are underway, but efficacy studies evaluating the impact of biofortified crops on iron status in children are still lacking.

**Food Fortification**

**Main Principles**

Iron fortification by means of adding iron to regularly consumed foods is now generally considered the most cost-effective and sustainable public health approach to improve iron status and prevent ID during childhood [68–70]. Iron fortification is recommended for infant formulas, infant cereals and complementary foods, and for staple foods reaching the general population [70, 71]. The cost of iron fortification varies depending on the iron compound, the food vehicle used and packing, but is estimated to be approximately 0.10–0.12 USD per person/year [69].

Iron fortification can be aimed at all individuals (mass fortification), aimed at particular population groups (targeted fortification), or be market driven allowing food producers to add iron to food products in response to market demand [70]. Mass fortification is generally aimed at households, while targeted fortification to children can be provided through special food products, school meal programs, ration shops or health care programs. Market-driven iron fortification may have the disadvantage of only reaching well-informed consumer groups or only middle- and high-income groups [72], but has been shown to be feasible for low-price products like flour and salt in both low- and high-income countries, and is also useful for targeted iron fortification in industrialized countries. An iron fortification strategy can be mandatory, for example the food vehicle selected as target for the iron fortification is only available in fortified form, or voluntary, for example the food vehicle for fortification is available in both fortified and non-fortified form, giving the consumer a free choice. Both strategies are regulated by legislation. The type of fortification strategy depends on the iron status of the population and should ensure that the fortified foods are consumed by the most vulnerable children. Many developing countries have made it mandatory for staple foods to be fortified with iron [71].

**Food Vehicle**

The vehicle used for iron fortification is a food regularly consumed by the majority of children in the target population and is selected depending on the geographic region. Infant formulas, infant cereals and complementary foods are widely fortified in most industrialized countries. Staple foods such as flour, rice, pasta, noodles or daily consumed condiments such as salt, sugar, soy and fish sauce are vehicles commonly used for mass fortification [70, 73, 74]. Flour is the most commonly used vehicle for iron, and mass fortification of flour is implemented in 78 countries [71]. Further vehicles specifically aimed at children and adolescents are breakfast cereals, dried cow’s milk powder, yoghurt, biscuits and fruit drinks [70, 73].

**Iron Fortificants**

An array of iron compounds is available for food fortification, but their bioavailability and sensory stability vary considerably [70, 71, 73]. One of the main challenges for successful iron fortification is to select an iron fortificant with high bioavailability, but with stable sensory characteristics which do not change taste, texture and smell of the food vehicle. Water-soluble iron compounds such as ferrous sulfate are highly bioavailable, but may cause adverse organoleptic changes and rancidity in dry foods like flour when stored for longer periods [73]. Water-insoluble iron compounds, such as electrolytic iron (elemental iron powder) and ferric pyrophosphate, are more stable in cereals. However, water-insoluble iron compounds are absorbed to a lower degree and usually require double the amount of iron to be efficacious [71, 73]. Ferrous fumarate is an alternative compound with low solubility in water, but soluble in dilute acid in the stomach. Ferrous fumarate does not cause fat oxidation in sensitive foods and is therefore recommended for cereal-based complementary foods [70, 71, 73], but may cause color changes during food preparation [75] and in the presence of fruits [73]. Chelated iron compounds, i.e. sodium iron EDTA and ferrous bisglycinate, have generally the highest bioavailability [73], but the cost is relatively high compared to other fortificants [76]. Encapsulation of compounds such as ferrous sulfate and ferrous fumarate is one way of reducing potential sensory changes by protecting iron from reacting with the food (and food with iron) [77]. The coating dissolves in the stomach.
and releases iron to be absorbed as dietary iron. Encapsulated compounds are particularly useful in dry and/or light-colored foods and products, such as flour, cereals and salt.

The level of fortification for products used in national programs should be specifically defined for each target population depending on the dietary requirements, dietary iron intake, consumption patterns, sensory characteristics of the food vehicle, bioavailability of the iron compound and characteristics of the fortification program [70]. This is, however, not usually the case in commercial iron-fortified products for which the level of fortification may be restricted to maximally 30% of the recommended daily allowance. The absorption of soluble iron compounds is influenced more by an individual’s iron status and the presence of inhibitors and enhancers in the food than is the absorption of nonsoluble iron compounds [71].

Most large-scale flour fortification programs and many commercially available cereal products are unfortunately still using elemental iron compounds which are not recommended [71]. Foods fortified with such iron compounds have only limited or no impact on iron status. In the 78 countries with flour fortification, only 9 countries use appropriate compounds at sufficient levels likely to be effective [71]. This is an important consideration when recommending fortified foods to prevent ID in children.

Efficacy
Iron fortification has been implemented as a prevention strategy for ID for over 60 years, but well-designed randomized controlled studies evaluating various iron compounds have largely become available only during the last decade. Efficacy studies have been carried out in infants, in preschool children, school-aged children and adolescents, the majority of them performed in populations with a high prevalence of ID and anemia [71, 79–81]. The evidence of efficacy is generally consistent, and with only a few exceptions, most studies of the recommended iron compounds [70] demonstrate improved iron status and reduced prevalence of ID in all age groups. However, the degree of the impact depends on the iron compound, the level of fortification, the iron status in the population, the amount lacking in the diet and the iron bioavailability of the overall diet. Lack of other micronutrients and infection or inflammatory anemia may also hinder iron utilization and blunt efficacy [80].

In-Home Fortification
Micronutrient Powders
MNPs, also known as ‘sprinkles’, are tasteless powders that can be added easily to any foods or meal [19, 82, 83]. MNPs commonly provide iron plus a blend of other micronutrients such as zinc and vitamin C and are usually supplied in individual sachets containing the recommended daily intake of vitamins and minerals for 1 person [83, 84]. MNPs can be sprinkled into home-prepared food after food preparation before serving the food and thus provide additional dietary iron at the household level. The iron compounds presently used in MNPs are ferrous fumarate (encapsulated), micronized ground ferric pyrophosphate and NaFeEDTA. A recent meta-analysis of efficacy trials in infants shows that home fortification with MNPs reduces the risk of anemia in infants by half [83]. The amount of iron added to the sachet depends on the bioavailability of the iron compound and should provide the child with the amount of iron lacking in the diet while not adding extra iron which could aggravate infection. There is no evidence that iron fortification can cause negative health effects when given to children with an infection as has been reported for iron supplements consumed without food, although this still remains to be confirmed [85]. Home fortification may, however, have higher levels of iron compared to mass fortification. Efficacy studies in infants testing different doses of encapsulated ferrous fumarate conclude that 12.5 mg is as efficacious as higher daily doses and is thus now the standard dose [86, 87]. However, an advantage with sachets is that the doses can be adapted to specific local needs. MNPs have mainly been used for infants and children [83, 88], but can theoretically also be used for other individuals in the family requiring extra iron. The acceptability of home fortification with MNPs among young children and their caregivers is high [83]. The cost of 1 sachet is approximately 0.014 USD, and although data on cost-effectiveness are limited, the few data available indicate that MNPs are at least as cost-effective as other approaches [83].

Complementary Food Supplements
Complementary food supplements with iron are used for prevention and treatment of moderate malnutrition and micronutrient deficiencies in infants [89, 90] or for high-risk groups in an emergency setting [91]. They are used as ‘in home’ fortificants and can be added to other foods or eaten alone to improve both macronutrient and micronutrient intake [83]. Complementary food supplements commonly provide higher fat content than the...
normal diet, plus additional essential fatty acids, milk, micronutrients, minerals, and high-quality protein. Examples are lipid-based nutrient supplements (e.g., fortified peanut spread) and fortified full-fat soy flour. The products may be flavored to mask the off-taste from soluble iron compounds. A recent meta-analysis shows that consumption of complementary food supplements containing a mix of micronutrients improves general nutrition status, iron status, growth and child development [83].

Iron Supplementation

Prevention of ID through routine oral supplementation with higher doses of iron may be required in populations where the iron intake and iron bioavailability of the diet is poor and the risk of ID is high [9, 92]. Iron supplementation has repeatedly been demonstrated to be highly effective in maintaining iron status in early infancy, improving iron status and reducing the prevalence of ID and IDA in older children [93, 94]. The recommended daily iron doses vary with age (table 2) [9, 92, 95]. The daily doses apply to otherwise healthy children and are based on the content of ‘elemental’ iron available for absorption. In infants aged 6–12 months, iron supplementation is recommended when iron-fortified complementary foods are not widely available or affordable. In settings where the prevalence of anemia in young children (6–24 months) is 40% or more, supplementation is recommended through the 2nd year of life [92]. For infants and young children up to 5 years, the recommended iron dosage is based on 2 mg iron/kg per day. In populations where the prevalence of ID and IDA is high, iron supplements at a dose of 20–30 mg/day may be provided to children aged 2–5 years, 30–60 mg/day to 6- to 11-year-olds and 60 mg/day to adolescents. Iron supplementation in preterm infants and infants born with low birth weight is covered by Lönnderdal and Hernell in this issue [11].

Supplemental iron is supplied as medical iron drops for infants and younger children, and as iron tablets for older children and adolescents. Ferrous salts (ferrous sulfate and ferrous gluconate) are the preferred iron compounds for oral iron supplementation because of their low cost and high bioavailability [2]. The daily dose can be given as 1 or more oral doses of medicinal drops or tablets, preferably on an empty stomach to enhance iron absorption. If side effects like nausea and epigastric pain develop, lower doses between meals should be attempted, or iron should be provided with meals [2]. However, food reduces absorption of medicinal iron by about two thirds [4].

Weekly oral iron supplementation supplied in larger weekly doses instead of daily iron doses has been suggested to increase fractional iron absorption [96, 97], to reduce side effects and improve compliance and ultimately to improve the cost-effectiveness compared to lower daily doses. Although weekly iron supplementation has been shown to be effective in improving iron status in women of reproductive age [96, 97] and in adolescent girls [98, 99], daily iron supplementation is more efficacious in infants [100, 101] and in school children [102].

Iron supplements have a long shelf life and can be provided commercially and distributed for free or at a subsidized price through commercial health centers, national immunization days, schools and community centers [92]. The price of iron supplements is low, and with effective logistics and distribution channels iron supplementation is cost effective [68].

The concerns with iron supplementation in early infancy and the interactions between iron and infection are reviewed elsewhere in this issue [11, 103]. The WHO recommends avoidance of large doses of iron supplementation in populations with a low prevalence of ID [85]. In malaria-endemic areas, iron supplementation should only be given to children who are anemic or iron deficient and concurrent protection from malaria should be provided [85, 95].

Prevention of ID as Part of Integrated Maternal and Child Health Programs

While low dietary iron intake is the primary cause of ID and anemia in infants and children, ID and anemia may also have other causes such as infections and other nutritional deficiencies. ID prevention strategies should therefore be integrated and incorporated into the primary health care system and other existing programs for maternal, child and adolescent health. Recommended prevention strategies include, for example, malaria, antihelminth and *Helicobacter pylori* treatment [7, 104]. In low-income countries or in high-risk children in industrialized countries, ID commonly occurs in combination with other deficiencies. ID impairs vitamin A and iodine metabolism and may reduce the efficacy of vitamin A and iodine interventions [105, 106]. Iron prevention strategies may therefore also be part of vitamin A and iodine interventions, multiple micronutrient fortifica-
Prevention of Iron Deficiency in Infancy, Childhood and Adolescence

... or multiple micronutrient supplementation [107, 108] or multiple micronutrient supplementation [109, 110].

ID during pregnancy is a risk factor for low iron status of the infants [111]. Prevention strategies should therefore ideally start in adolescent girls and women of reproductive age before conception and in women during pregnancy. National iron food fortification programs or specific school feeding programs targeting adolescent girls should be considered. In areas with a high prevalence of ID and IDA in women, weekly iron supplementation is recommended to women of reproductive age [97]. There is solid evidence that iron supplementation during pregnancy in low-income countries improves maternal iron status both during pregnancy and post-partum [112]. Infants born from mothers taking iron supplements during pregnancy are prevented from IDA at birth and at 3, 6 and 12 months of age [113, 114]. The impact on preterm delivery and low-birth-weight infants is less clear. Iron supplementation with 60 mg iron/day and 400 μg folic acid/day during pregnancy is recommended in developing countries where women often enter pregnancy with low iron stores [9, 115, 116]. Most industrialized countries also recommend routine iron supplementation during pregnancy, although little evidence exists that it improves maternal or fetal outcomes [117, 118]. Recent studies suggest that lower doses with 30 mg iron/day may be as effective as the currently recommended dose of 60 mg/day for both maternal and infant iron status [116, 119, 120]. In low-income countries, multiple micronutrient supplementation during pregnancy has been demonstrated to be as effective as iron/folic acid alone in reducing anemia in pregnant women [116, 121]. Multiple micronutrient supplementation of pregnant mothers may also further reduce the risk of low birth weight [122, 123] and improve growth in infancy and childhood [109, 124]. Delaying clamping of the cord until the cord has stopped pulsing (approximately 2–3 min) also improves infants’ iron status during the first 6 months of life [18, 125] and is recommended by the WHO [126].

### Table 2. Guidelines for iron supplementation to infants, children, adolescents, women of reproductive age and pregnant women

<table>
<thead>
<tr>
<th>Indications for supplementation</th>
<th>Daily dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preterm infants</strong></td>
<td>2 mg/kg body weight/day</td>
<td>From age 1 to 12 months (varies)</td>
</tr>
<tr>
<td><strong>Low-birth-weight infants</strong></td>
<td>2 mg/kg body weight/day</td>
<td>From age 2 (varies) to 23 months</td>
</tr>
<tr>
<td><strong>Children 6–24 months</strong></td>
<td>12.5 mg iron (2 mg/kg body weight/day)</td>
<td>From age 6 to 12 months</td>
</tr>
<tr>
<td><strong>Children 6–24 months</strong></td>
<td>12.5 mg iron (2 mg/kg body weight/day)</td>
<td>From age 6 to 24 months</td>
</tr>
<tr>
<td><strong>Children 2–5 years</strong></td>
<td>20–30 mg iron (2 mg/kg body weight/day)</td>
<td>3 months</td>
</tr>
<tr>
<td><strong>Children 6–11 years</strong></td>
<td>30–60 mg iron</td>
<td>–</td>
</tr>
<tr>
<td><strong>Adolescents</strong></td>
<td>60 mg iron</td>
<td>–</td>
</tr>
<tr>
<td><strong>Women of reproductive age</strong></td>
<td>60 mg iron</td>
<td>–</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>60 mg iron</td>
<td>As soon as possible after gestation starts; no later than the 3rd month and continuing for the rest of pregnancy</td>
</tr>
</tbody>
</table>

Adapted from the World Health Organization [9, 85, 95, 97], Stoltzfus and Dreyfus [92] and Iannotti et al. [93].

ID = Iron deficiency; IDA = iron deficiency anemia.

a For children aged from 6 months to 5 years, iron dosage is based on 2 mg iron/kg body weight/day.

b In settings where malaria is endemic, iron supplements should only be given to infants and young children detected with ID and in combination with malaria treatment.

c Weekly iron supplementation.
For iron prevention strategies to be effective, involvement from all relevant sectors is necessary [104]. Education strategies communicating the benefits of adequate iron nutrition, causes of ID and its prevention strategies as well as effective supply mechanisms to attain access to fortified foods and iron supplements are critical.

Monitoring Impact

The impact of iron interventions should be monitored and evaluated by measuring iron status, the prevalence of ID and IDA in the population over time in cross-sectional or longitudinal studies. The recommended iron status indicators for population assessment and evaluation are hemoglobin, serum ferritin, serum transferrin receptor, erythrocyte zinc protoporphyrin and mean corpuscular volume, plus a marker for infection, for example C-reactive protein [127]. A combination of indicators is generally used to identify the different stages of ID. The selection of appropriate indicators depends on the severity of ID and the presence of infection/inflammation or chronic disease [127].

Conclusions

There is solid evidence that effective ID interventions will improve iron status in children and will have large effects on preventing adverse health outcomes attributable to ID in children. Prevention requires a range of multiple combined strategies, starting with prenatal iron supplementation of pregnant women, delayed cord clamping at birth and exclusive breast-feeding during the first 6 months of life. Dietary interventions increasing the iron content and iron bioavailability of the diet, iron-fortified foods and iron supplementation are strategies in weaning infants, children and adolescents. Iron fortification is the most cost-effective iron intervention strategy, but only iron compounds with high bioavailability should be used. In-home iron fortification is efficacious in infants and young children and may be expanded in low-income countries. Iron supplementation is recommended in areas with a high prevalence of ID, but low rate of malaria. In malaria-endemic areas, iron supplementation should be targeted to iron-deficient children only or be provided in combination with malaria treatment. All intervention strategies should be incorporated as a routine part of children’s health care programs and integrated into other health strategies.

References

Prevention of Iron Deficiency in Infancy, Childhood and Adolescence


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Prevention of Iron Deficiency in Infancy, Childhood and Adolescence


