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Food Fortification as a Strategy to Combat Iron Deficiency / Iron Deficiency Anaemia in Developing Countries

by

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KEYWORDS. — Anaemia; Iron Deficiency; Iron Fortification; Iron Sulfate; Ferrous Fumarate; Iron Phosphate.

SUMMARY. — Iron deficiency anaemia is the most widespread public health problem affecting millions of people, primarily infants, children and women in developing countries. The negative impact of anaemia on health, which includes reduced growth and increased morbidity, is well known, and is in fact an important issue to resolve as indicated by the United Nations and their different agencies. However, there was virtually no progress achieving successful intervention programmes for infants and children. Fe food fortification is currently considered the most cost-effective approach to combat Fe deficiency. Different potential fortificant compounds including ferrous sulfate, ferrous fumarate, ferric pyrophosphate, elemental iron, and Na_2 EDTA, have been investigated. However, while Fe fortification programmes have been relatively successful in industrialized countries, little development has been made in developing countries. It is assumed that the success of food fortification programmes may be limited because of high prevalence of low gastric acid output, high phytate content in diet and low intake of ascorbic acid in those populations. Therefore, there is a need to find out suitable iron compounds that would be well absorbable in populations with low gastric acid output without causing unwanted sensory changes in selected food. There would be the need also to overcome the barriers of inhibitor of Fe absorption, *i.e.* phytic acid in the food vehicle, or in the diet with which such fortified compounds would be consumed. Effective and sustainable iron fortification programmes could contribute in achieving the goal of reducing by one third the prevalence of anaemia by 2010, which the United Nations General Assembly adopted at its special session on children in 2002.

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Introduction

Anaemia is one of the most widespread public health problems of both developing and developed countries in the world. It has important health and welfare, and social and economic consequences. Review of the prevalence of anaemia globally reveals large variations among regions; however, its prevalence is the highest in developing countries. With the exception of Japan, Korea, and perhaps Singapore and Malaysia, the prevalence of anaemia is relatively higher in most other Asian countries (FLORENTINO *et al.* 1984). Nutrition Surveys in Bangladesh (1995-1996) noted prevalence of anaemia (Hb <11.0 g/dl) in 78 % of children aged 6-11 months, and 64 % among children aged 12-23 months (HKI/IPHN 1999). A National Family Health Survey in India (1998-1999) also reported somewhat similar prevalence of anaemia (72 %) in children aged 6-35 months (NFHS 2000). The proportion of anaemic children in Indonesia and in the Philippines was reported to be 37-73 % and 42-47 % respectively (FLORENTINO *et al.* 1984). Prevalences of anaemia have, however, decreased in developed countries during the last two decades indicating that the problem can be reduced substantially. A nationally representative UK sample suggests current anaemia prevalence of 12 % among children aged 1.5 to 2 years (GREGORY *et al.* 1995). However, in socio-economically disadvantaged populations in UK, the prevalence of anaemia varies from 25 to 40 %. Iron deficiency (ID) is by far the most common single cause of nutritional anaemia in the world that affects over 3.5 billion people (United Nations 1992, WHO 1997). Differences in consumption of meat, availability of iron supplements, iron-fortified foods, health care, and the frequencies of infections and gastrointestinal parasites are likely to contribute to the differences observed in the prevalence of anaemia in developed and less developed countries. In general, anaemia appears to be more common in young children (0-5 years) compared to older children (6-12 years) (LONNERDAT & DEWEY 1995).

The most vulnerable groups for iron deficiency are infants, children, women and adolescent girls (DE MAEYER & ADIELS-TEGMEN 1985) who also have higher iron requirements. The consequences of Iron Deficiency Anaemia (IDA) are particularly severe in these vulnerable groups, which include increased perinatal morbidity, mortality among mother and child, and impaired immune functions, increased susceptibility to infections, decreased work performance, poor growth and poor cognitive functions. According to KWIATKOWSKI *et al.*, iron deficiency is a multisystem disorder, with profound effects on the central nervous system or brain development. Numerous studies over the past twenty years have clearly defined an effect of iron deficiency on mental development

and often on motor function (LOZOFF *et al.* 1987, 1991; SCRIMSAW 1984; PALTI *et al.* 1985). The reduced activity of iron-containing enzymes observed in the central nervous system, based on animal studies and a number of observations in young children, appears to be irreversible, *i.e.* non-responsive to iron therapy (COOK & LYNCH 1986, LOZOFF *et al.* 1996).

Aetiology of Iron Deficiency / IDA

The high prevalence of IDA observed in infants in developing countries is accounted for by several overlapping factors. However, Fe bioavailability from poor-quality diets is undoubtedly the most important among them (TAYLOR *et al.* 1995). Diets consumed in many developing countries are cereal-based and thus high in phytic acid, a potent inhibitor of Fe absorption (HALLBERG *et al.* 1987, HURRELL *et al.* 1992, DAVIDSSON *et al.* 1994) and low in major promoters of Fe absorption such as ascorbic acid and animal tissue (LAYRISSE *et al.* 1984, HALLBERG *et al.* 1989, TAYLOR *et al.* 1986). The overall Fe bioavailability from these diets can thus be expected to be low or very low, resulting in inadequate Fe absorption to meet the relatively high requirements of infants, children and women of child-bearing age. As iron is very sensitive to total energy intake, inadequate or lowered energy intakes, prevalent in most developing countries (PATTERSON *et al.* 1998), coupled with low Fe bioavailability, put the population at increased risk of micronutrient deficiencies including iron. Early introduction of unmodified cows' milk at around six months of age is also considered a cause of iron deficiency at one year (SADOWITZ & OSKI 1983).

Iron stores at birth is a major factor influencing growth and occurrence of IDA in infancy. Maternal iron deficiency results in large placental size and small babies (low birth weight) with iron stores inadequate to sustain their rapid early growth (HINDMARSH *et al.* 2000). Low birth weight, which is highly prevalent in developing countries (MA LACHLAN 1999), is therefore an important cause for iron deficiency in infants. A recent Indian study observed early cord clumping is a risk factor for IDA in infants (GUPTA & RAMJI 2002). Apart from low bioavailability from the diets, the high prevalence of infections and other nutritional deficiencies in developing countries can also contribute to the development of IDA. Early introduction of unmodified cows' milk at around six months of age was found to be the most common dietary characteristic of infants, which leads to development of IDA at one year. Gastrointestinal parasites such as hookworm (STOLTZFUS *et al.* 1997), malaria (STOLTZFUS *et al.* 1997) and vitamin A deficiency (WEST 1996) are also important contributors to anaemia and IDA.

Helicobacter pylori Infection and Iron Deficiency Anaemia

Helicobacter pylori infection rate is very high in children in developing countries and in many of them it occurs in early infancy (Sarker *et al.* 1997). The vast majority of the population does not present with any overt symptoms and signs attributable to this infection. It is known that this kind of infection can cause gastritis and has been found to be associated with altered gastric acid secretion in a study performed in Bangladesh (Sarker *et al.* 2000, 2002). The infection has been found to be associated with iron deficiency and IDA; however, the mechanism of causality is poorly defined (Kostaki *et al.* 2003, Marignani *et al.* 1997). It has been proposed that *H. pylori* may have an iron acquisition mechanism *in vivo* by forming a parasitic relationship and competing with host for iron. It is well known that microorganisms need host's iron to grow (Otto *et al.* 1992). Furthermore, the possibility of *H. pylori*-associated hypochlorhydria as observed in children and women in Bangladesh (Sarker *et al.* 2000, 2002), leading to impairment of non-heme iron absorption, may be linked to anaemia in this population. However, our recently concluded study with a double iron isotope technique indicates that *H. pylori* infection does not influence iron absorption from water soluble and non-water soluble iron compound. Eradication of *H. pylori* however did result in an improvement in haemoglobin concentration indicating an important role of *H. pylori* infection in the aetiology of anaemia (Sarker *et al.* 2004).

Prevention

Given the magnitude of the problem, prevention and treatment of anaemia and IDA have been identified as important goals of nutritional intervention programmes by the United Nations and various international agencies. However, much to the dismay of policy-makers and paediatricians, little progress has been made during the last decade towards achieving successful intervention programmes for infants and children in the developing world. There are numerous strategies to address iron deficiency. For the first six months breast feeding is suggested to be the best strategy. Although human breast milk contains little iron (< 1.0 mg/l), its bioavailability is considered to be high with 50 % absorption of breast milk iron. By six months of age iron stores are depleted in exclusively breast-fed children, and by nine to twelve months of age they exhibit frank IDA. This needs provision of additional sources of iron to infants.

There are three possible approaches for the prevention of anaemia in infants older than six months: dietary diversification, individual supplementation and food fortification. Dietary diversification involves promotion of foods with a wider variety of iron content, especially meat or fish. This intervention needs education to change feeding practices, and is often not affordable to poor populations of developing countries due to the high cost of foods rich in higher amounts of bioavailable iron.

Oral supplementation of ferrous sulfate drops or elixir has been the primary source of iron for the treatment and prevention of IDA for the past hundred and fifty years (ANDREWS 1999). When a soluble form of elemental iron (such as ferrous sulfate) is ingested in adequate dose (3-6 mg/kg.d in two divided doses), this inexpensive intervention is effective in most cases. However, compliance to long-term ingestion of oral iron is often poor because of the unpleasant metallic taste of such formulations. Moreover, iron drops can stain teeth unless wiped out immediately after administration, and administration of a higher dose might lead to abdominal discomfort or vomiting in infants. To date, there is little evidence for large-scale effectiveness drops or elixir formulation of iron supplementation. In order to enhance or ensure the compliance, avoid change in colour, texture or taste, UNICEF consultants suggested developing a potentially viable new method of delivery of micronutrient including iron supplement (NESTEL & AINWICK 1996, PISACANE 1996). Responding to the UNICEF directives, the Metabolic Research Group at the Hospital for Sick Children, University of Toronto, Canada, developed the microencapsulated ferrous fumarate in powder form (plus ascorbic acid), which can be sprinkled over any complementary food at the table of the caregiver. Recent studies in Ghana demonstrated that the sprinkles are as efficacious in preventing and treating iron deficiency anaemia in infants as the standard drops (ZLOTKINS *et al.* 2001).

As ferrous fumarate needs dissolution by gastric acid before absorption (HURRELL *et al.* 1989), its efficacy is likely to be uncertain in populations with compromised gastric acid output. Large-scale clinical trials along with evaluation of safety and cost effectiveness are necessary before this could be considered as useful strategy for treating and preventing iron deficiency anaemia in infants.

Food Fortification as a Strategy to Combat Fe Deficiency

Food fortification is often suggested as the best sustainable and cost-effective approach to increase iron intake and thus combat iron deficiency in children.

The success of Fe fortification programmes largely depends on careful choice of the Fe compound (HURRELL 1998). There were few common iron fortificant compounds investigated for their bioavailabilty during the last few decades. They differ both in their relative bioavailability (RBV) and potential to cause unacceptable sensory changes in the fortification matrix. Their RBV depends on their solubility in the gastric juice during digestion. Water-soluble compounds, such as ferrous sulfate, dissolve readily and have the highest RBV. Being water soluble, they do not require gastric acid for digestion. Water-insoluble compounds, such as ferrous fumarate, may be as well absorbed as ferrous sulfate, but they require dilute acid of gastric juice for complete dissolution. The other groups of compounds are poorly soluble in dilute acid; they have lower bioavailability since they never dissolve completely in the gastric juice.

FERROUS SULFATE

Being water-soluble compound, ferrous sulfate has the highest bioavailability (HURRELL 2002). It has been successfully used to fortify infant formula, bread and pasta (HURRELL *et al.* 1991) and can be added to wheat flour stored for shorter periods. It may, however, cause fat oxidation and rancidity in cereal flours stored for longer periods, and has been reported to cause unwanted colour change in infant cereals with fruit and salt. Encapsulated ferrous sulfate may exhibit excellent potential for overcoming unwanted sensory changes while maintaining high RBV. Encapsulated ferrous sulfate sprinkle supplement has already been reported to be effective in treating and preventing iron deficiency anaemia in children in Ghana. Fortification of cereals with microencapsulated ferrous sulfate would be an interesting programme in combating iron deficiency in the near future. The bioavailability of encapsulated ferrous sulfate has been found to be similar to ferrous sulfate in rat assays (HURRELL 1989), but still requires confirmation in human studies.

FERROUS FUMARATE

This compound is often used to fortify infant cereals and chocolate powder drinks. Being poorly soluble in water it causes less organoleptic changes in the food vehicle than water-soluble compounds like ferrous sulfate do. Ferrous fumarate requires dissolution in gastric acid before absorption from the intestine can occur. Although this appears to occur in healthy adults, it has not been demonstrated in children or population from developing countries where gastric acid secretion may be less efficient due to infections or nutrient deficiencies. If gastric acid output is compromised in a large proportion of

the target population, the effect of food fortification with fumarate might be less than expected as a result of reduced capacity to absorb iron from fortified foods. We have recently conducted studies to measure gastric acid secretion and iron absorption from ferrous fumarate and ferrous sulfate in children with and without *Helicobacter pylori* infection (SARKER *et al.* 2004). Gastric acid secretion was significantly lower in *H. pylori* infected children compared to non-infected children (tab. 1). Contrary to observations in healthy western adults, it was found that iron absorption from ferrous fumarate was significantly lower than that of ferrous sulfate in both *H. pylori* infected and non-infected children. The geometric mean relative absorption of ferrous fumarate (absorption of ferrous fumarate compared to that of ferrous sulfate) was approximately 25 % by these young children (SARKER *et al.* 2004) (tab. 2), indicating that the effect of iron fortification programmes that use fumarate or other non-water soluble iron compounds to prevent iron deficiency in similar population needs to be defined.

IRON PHOSPHATE COMPOUNDS

European companies use ferric pyrophosphate and ferric orthophosphate to fortify infant cereals and chocolate drink powder. In a recent study using stable isotope, the absorption of ferric pyrophosphate was reported to be only a third of that of ferrous fumarate from wheat-soy infant formula (DAVIDSSON *et al.* 2000). Although consumption of fortified cereals with ferric pyrophosphate or ferrous fumarate in Pakistani infants resulted in an increase in haemoglobin and ferritin level in both groups compared to those receiving non-fortified cereals, both groups remained iron deficient, indicating the possible need for higher level of fortification. Further investigations are needed

Table 1

Gastric acid output before (BAO) and after stimulation (SAO) with pentagastrin in *Helicobacter pylori* infected and uninfected children with iron deficiency anaemia*

	BAO (mmol/h)	SAO (mmol/h)
H. pylori infected children before anti-*H. pylori* treatment (n = 12)	0.2 ± 0.2	1.6 ± 0.9
H. pylori infected children after anti-*H. pylori* treatment (n = 12)	0.8 ± 1.3[2]	3.3 ± 2.4[2]
Uninfected children (n = 11)	0.9 ± 0.7[2]	3.1 ± 0.9[2]

* Adapted from SARKER *et al.* 2004.

Table 2
Iron absorption from ferrous fumarate and ferrous sulfate in uninfected children with iron deficiency anaemia (IDA) and in *Helicobacter pylori* infected children with IDA before and after treatment*

	H. pylori infected children before treatment (n = 12)		*H. pylori* infected children after treatment (n = 12)		*H. pylori* non-infected children (n = 11)	
	Ferrous fumarate (%)	Ferrous sulfate (%)	Ferrous fumarate (%)	Ferrous sulfate (%)	Ferrous fumarate (%)	Ferrous sulfate (%)
Geometric mean	5.3	19.7	6.4	22.5	5.4	5.4
+1 SD	13.5	32.9	12.9	33.0	12.7	12.7
–1 SD	2.1	11.8	3.2	15.4	2.3	2.3
P	< 0.0001		< 0.0001		< 0.0001	

* Adapted and modified from SARKER *et al.* 2004.

to define its role and optimal dose for its possible use in fortification programmes.

BARRIER FOR EFFECTIVE IRON FORTIFICATION

Apart from bioavailability of fortification by Fe compounds, the composition of meal, *i.e.* presence of promoters and inhibitors of Fe absorption, needs to be considered for successful food fortification programmes. Phytic acid, phenolic compounds, calcium, and certain milk and soy proteins are common dietary inhibitors of iron absorption. They can significantly reduce the absorption of both native food iron and fortification iron by forming unabsorbable complexes in the gastrointestinal tract. Phytic acid is present in cereal and legume-based foods, which are often used as vehicles of iron fortification. As cereals contain phytate and constitute staple food in most of the developing countries, the Fe added to such diets could also be poorly absorbed unless protected from the inhibitors of Fe absorption.

COUNTERACTING BARRIER OF FE ABSORPTION

There are three different ways to counteract inhibitors of iron absorption: addition of Na_2EDTA or ascorbic acid together with iron compound, addition

of fortification iron in a form that is protected from combining with dietary inhibitor (Na_2Fe EDTA, ferrous bisglycinate, heme iron), or degradation or removal of phytic acid from fortified food products.

The action mechanism of Na_2EDTA is not known; however, it is thought that EDTA binds iron in a soluble complex in the gastrointestinal tract, preventing it from forming insoluble non-absorbable complex with dietary inhibitors or hydroxyl ions. Sodium EDTA has been observed to increase iron absorption in adults from ferrous sulfate-fortified rice meal (MAC PHALL *et al.* 1994). EDTA is also capable of preventing sensory changes. Therefore, there is a potential for use of Na_2EDTA in ferrous sulfate-fortified rice for longer storage in the developing world. In the presence of phytic acid, iron is two to three times better absorbed from NaFeEDTA than from ferrous sulfate (HURRELL *et al.* 2000). There are a number of studies demonstrating an improvement of the iron status of the target population consuming NaFeEDTA-fortified fish sauce (THUY *et al.* 2003) or NaFeEDTA-fortified sugar (VITERI *et al.* 1995).

The use of NaFeEDTA for fortification exhibits less lipid oxidation during the storage of cereal flours, further it does not cause peptide precipitation. These properties offer more potential for long-term storage stability. However, its higher cost could limit its use in food fortification programmes in developing countries.

Enzymatic degradation of phytic acid in cereals and legumes could improve iron absorption, which is likely to be suitable for manufacturing low-cost complementary foods. Commercial phytase can completely degrade phytic acid within one-two hours, when added in an aqueous slurry of cereal, held at the optimum temperature and pH for phytase activity. Phytate degradation with phytase is technologically possible and should be considered especially for low-cost complementary food for the developing world.

Ascorbic acid appears to act as both solubilizing and reducing agent. It reduces ferric to ferrous state and preserves its solubility as the pH rises in the duodenum. Ascorbic acid has been reported to increase the absorption of many iron compounds including ferrous sulfate and ferric pyrophosphate from fortified cereal (DAVIDSSON *et al.* 1997), breakfast meal (DAVIDSSON *et al.* 2001) and drink (DAVIDSSON *et al.* 1998, NESTEL & AINWICK 1997). Few studies, however, observed that ascorbic acid might have little or no effect on absorption of ferrous fumarate (HURRELL *et al.* 1991). Moreover, ascorbic acid added to fortified foods might not remain stable during storage in hot and humid climates. Further studies are, therefore, required to define its role on absorption of ferrous fumarate and other iron compounds.

Role of Breast Milk as a Source of Ascorbic Acid on Iron Bioavailability

Although ascorbic acid rich foods are readily available in many communities, the intake of fruit and fruit juice by infants and young children might not be encouraged according to traditional feeding practice. Moreover, in resource-poor countries, it has been observed that the intake of fruit juice by young infants is virtually nil (Daneel 2003). Therefore, we have recently evaluated human milk as an alternative source of ascorbic acid for enhancing iron bioavailability from *khichuri*, a traditional Bangladeshi complementary food based on rice and lentils. Erythrocyte incorporation of stable iron isotopes 14d after administration was used as a proxy for iron bioavailability. A cross-over design was used to compare iron bioavailability from labelled test meals followed by either breast feeding or water intake in thirty-one infants and young children. Although human milk contributed significant quantities of ascorbic acid, no significant difference in iron bioavailability was found between *khichuri* consumed with water and that consumed with human milk (6.5 % vs 6.2 % respectively, $p = 0.76$, paired t-test) (Davidsson *et al.* 2004). These results indicate either that the molar ratio of ascorbic acid to iron was not sufficiently high to overcome the inhibitory effect of phytic acid in *khichuri* or that components of human milk modified the influence of ascorbic acid on iron bioavailability.

Challenges and Recommendations

The tragedy related to iron deficiency anaemia is well recognized in developing countries and should not occur. Traditionally, iron deficiency anaemia is prevented by increasing the use of iron-rich food, iron supplementation and targeted food fortification for infants and children. Unfortunately, none of these interventions have yet been proven to be successful in developing countries. Therefore, programme strategy will have to be redefined to be more comprehensive and include strategies for reproductive women, infants, and young children.

Food fortification is a promising strategy and should be an important component in forging effective strategies to combat IDA.

There are multiple challenges in the delivering and selection of suitable iron compounds for fortification of foods in a population with a high prevalence of infection and low gastric acid output. These compounds should provide meaningful levels of bioavailable iron without altering the acceptability and stability of the enriched food vehicle.

In the areas of food processing and product formulation, multiple issues like overcoming the barrier of Fe absorption inhibitors like phytic acid in both the food vehicle and diet need to be addressed.

Eradication of iron deficiency anaemia can be feasible by implementing an effective and sustainable iron fortification programme based on local conditions overcoming technical and practical barriers. Accompanied with a political commitment and strong partnerships involving all relevant sectors, such a programme could achieve, by 2010, the goal of reducing by one third the prevalence of anaemia that the United Nations' General Assembly adopted at its special session on children (May 2002).

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