



GAP ANALYSIS

Information Needed for Consensus on Policies and Programs to Improve Iron Nutrition

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BACKGROUND

Despite over 50 years of research, nutritional iron deficiency remains the most prevalent micronutrient deficiency disorder worldwide. As stated in a recent UNICEF/UNU/WHO publication (2001): “Iron deficiency affects a significant part, and often a majority, of the population in nearly every country in the world. Programs for the prevention of iron deficiency, particularly iron supplementation for pregnant women, are under way in 90 of 112 countries as reported to WHO in 1992 (WHO, 1992). Most of these programs, however, are neither systematically implemented nor well monitored or evaluated.” Nevertheless, significant advances in addressing iron deficiency anemia have been made in the last 10-15 years, by applying established scientific observations to the design, implementation, and evaluation of interventions. At the same time, the increased emphasis on outcome analysis has uncovered new problems that require more rigorous scientific evaluation, the most urgent being the possible risks of delivering iron in regions where malaria is endemic. There is also a pressing need to find safe and effective mechanisms for providing iron to infants and young children.

This paper seeks to identify the key gaps in information that must be filled to move towards consensus on policies and programs to improve iron nutrition.

SCIENTIFIC BASIS AND OPERATIONAL FEASIBILITY OF CURRENT APPROACHES

Programs and interventions should consider the following issues during planning stages:

- Methods for evaluating iron status, iron deficiency prevalence, and responses to interventions
- Evidence for efficacy and effectiveness of intervention strategies
- Evidence for improved functional outcomes from iron intervention programs
- Interactions between micronutrient deficiency states and intervention strategies
- Risks of iron supplementation
- Future opportunities for intervention in populations consuming little or no processed foods

METHODS FOR EVALUATING IRON STATUS, IRON DEFICIENCY PREVALENCE, AND RESPONSE TO INTERVENTIONS

It is now generally recognized that anemia assessed by hemoglobin concentration is a poor indicator for determining the prevalence of nutritional iron deficiency. Estimates of iron deficiency prevalence based only on anemia prevalence fail to recognize the importance of other factors, particularly ethnic

variations in hemoglobin distribution, the high prevalence of globin polymorphisms in some populations, infections such as malaria, and deficiencies of other nutrients such as vitamin A. As a result, one or more iron status indicators are now reported in most of the published surveys and intervention trials.

There is a current consensus that serum ferritin concentration in combination, where possible, with transferrin receptor concentration (adjusted ratio) (Cook et al., 2006) is the best method for determining the distribution of iron stores in population samples drawn from regions in which infections are not widespread. However significant barriers to the immediate implementation of this recommendation include cost, the absence of readily available, inexpensive field-based methodology, and standardization of the transferrin receptor reagents. The utility of these measures in young infants is also unclear, since iron regulation may not be fully mature.

Serum ferritin is much less satisfactory for determining the prevalence of iron deficiency in populations that commonly suffer from infectious or inflammatory disorders, because ferritin is an acute phase reactant. Values are increased in the presence of inflammation by pathophysiological mechanisms that are not related to iron status. Serum transferrin receptor results may also be misleading if bone marrow function is affected by infections such as malaria. There is an urgent need for additional research to identify the best practical method for recognizing iron deficiency in regions where malaria and/or other infections are prevalent. This is particularly critical at the present time because recommendations being considered by WHO and UNICEF advocate the delivery of iron supplementation only to children who have been shown to be iron deficient (see below). Studies carried out in Zanzibar (Sazawal et al., 2006) suggest that the zinc protoporphyrin/hemoglobin (ZPP/H) ratio may be the best indicator. If confirmed, there would be a strong impetus for developing technology to allow ZPP/H measurements to be made in the field at minimal cost. However the potential utility of other possible indicators including hepcidin should be evaluated.

Serum ferritin does have another important role. It is considered to be adequate for determining whether an intervention has been effective in increasing iron stores, even in the presence of infectious disease. It should therefore be employed in combination with hemoglobin measurements in all efficacy evaluations.

In summary, there is a continued need for better implementation of methodology for detecting and monitoring iron deficiency prevalence. Suitable tools are available for regions where infections, particularly malaria, are not prevalent, but there is a need for standardization and streamlining the methodology. In regions where infections are prevalent, more basic research is required to identify the best indicator(s). The latter is an urgent priority.

EVIDENCE FOR EFFICACY AND POTENTIAL EFFECTIVENESS OF INTERVENTION STRATEGIES

Infants and Young Children

The **efficacy** of supplementation and home fortification products (complementary food supplements, sprinkles, spreads, etc.) for improving iron status and reducing the prevalence of anemia has been confirmed in several recent trials (Zlotkin et al., 2004; Ruel et al., 2004).

On the other hand, there is very limited evidence to show **effectiveness** for iron supplementation when administered in liquid form through the public health service. The lack of effectiveness of this form of supplementation has led three South American countries (Bolivia, Guyana, and Nicaragua) to introduce sprinkles, another (Peru) to promote the consumption of animal foods starting at six months, and others (Bolivia, Ecuador, Chile, Argentina, Paraguay, and Uruguay) to provide fortified complementary foods or fortified milk.

Recent studies in Ecuador and Mexico have confirmed the effectiveness of fortified complementary foods that use an appropriate iron compound and that are precooked to ensure the preservation of ascorbic acid (to promote iron absorption) (Rivera et al., 2004). Fortification of powdered milk with ferrous sulfate and ascorbic acid for children less than 18 months of age has been shown to be effective in markedly reducing the prevalence of iron deficiency in Chile (Olivares, 1989).

In summary, there is an established scientific basis for the effectiveness of several methods of delivering iron to infants and young children. Cost (e.g. the estimated cost of Sprinkles in Latin America is US\$0.04 per single dose sachet), technical considerations, and the lack of access to processed foods for those who would benefit most from such interventions are obstacles to large-scale implementation. In the case of supplementation in regions where malaria transmission is year round, the risk to iron sufficient children (discussed below) is another major obstacle to scaling-up appropriate interventions. The greatest need is for the identification of formulations that have the strongest impact on both linear growth and anemia reduction. In addition, there is a need for research on the most cost-effective distribution mechanisms.

Women of Childbearing Age and Older Children

Fortification and intermittent supplementation are the primary strategies for improving iron status in these groups. Mass fortification of staple foods or condiments is considered to be the best approach to reducing the prevalence of iron deficiency

for older children, adolescents, and women of childbearing age. Wheat flour and maize meal are considered prime vehicles for iron as well as other micronutrients. However, technical problems still limit the implementation and effectiveness of this strategy.

Regardless of these difficulties, some 50 countries currently fortify flour. The Flour Fortification Initiative, a consortium of organizations involved in the promotion of flour fortification around the world, estimates that about 20 percent of wheat flour is currently fortified with iron and other micronutrients. Their goal is to see fortification of 70 percent of all white, roller-milled flour by 2008.

The major technical obstacles remaining include:

- *Fortification in small mills (milling capacity less than 20 metric tonnes per day)*—These present technical, logistical, and economic barriers to establishing adequate quality and economic viability of the interventions. Pilot studies designed to address the technical problems related to small mill fortification are underway in Central Asia, Mongolia, Pakistan, and China. Resolving these difficulties is important because small mills provide an attractive option to serve high-need populations in geographically inaccessible areas that are generally poor and usually have a high prevalence of iron deficiency.
- *Type and levels of iron to add*—Ferrous sulfate is the preferred fortificant (better bioavailability than elemental iron or ferric pyrophosphate), but it may not be acceptable where the product experiences a long shelf life because it is reactive, increasing the rate of spoilage due to fat rancidity. Elemental iron is generally preferred by millers because it is inert. Guidelines for the use of elemental iron powders have been published by SUSTAIN, CDC, and WHO. These recommendations state that only the electrolytic form of elemental iron should be used and that the fortification level should be twice that recommended for ferrous sulfate. There remain, however, several questions about the potential effectiveness of this approach:

The terminology for elemental iron powders is not applied consistently or rigorously.

The term “reduced iron” is often employed for any elemental iron powder. There is therefore inadequate specification of powder type in country regulations.

Studies by SUSTAIN (submitted for publication) indicate that the potential bioavailability of different powder types varies considerably.

The Food Chemical Codex guidelines include particle size definition for elemental iron powders, but this may be insufficient to ensure adequate bioavailability.

There are only two published studies that indicate that an elemental iron powder (electrolytic iron) is potentially efficacious for mass fortification (Zimmermann et al., 2005; Swain et al., 2007). In both of these studies the other (non-electrolytic) elemental iron powder studied was far less efficacious.

Finally it should be noted that several publications suggest that micronized ferric pyrophosphate could be used because it is also inert, but high fortification levels appear to be necessary and the cost of micronization has not been addressed adequately.

- *Inhibitory components in flour* — High extraction wheat flours (not highly refined) inhibit iron absorption primarily because of high phytic acid (PA) levels. Current experimental evidence suggests that the PA:Fe ratio should be <1 for meals with little vitamin C and/or meat and < 6 for those that have ample quantities of these promoters of iron absorption to ensure fortificant efficacy. It appears that the ratio is <1.0 in leavened bread made from low extraction wheat flours. However the ratios are likely to be much higher in non-leavened products (chappatis, noodles, pasta, steamed bread, cooked maize meal), atta and whole wheat flour. Several trials have addressed this bioavailability inhibition issue. Vitamin C is ineffective if added to flour because it is inactivated by cooking. However, the use of NaFeEDTA has now been shown to be very efficacious in several studies with wheat and maize flour (unpublished) and when added to condiments (curry powder, soy sauce, fish sauce) eaten with the meals.
- *Monitoring and quality assurance for fortified products*—Methods for monitoring both additional levels and type of iron compound used in fortification need to be refined.
- *High cost of using bioavailable forms of iron*—Fortification can increase the cost of fortified products and this is a major barrier in open market situations. At present this applies primarily to NaFeEDTA.

Fortification of wheat flour is being scaled-up rapidly and the technical problems related to fortification in small mills are being addressed. However, in the scaling-up process, insufficient attention is being paid to flour consumption rates and fortification compounds used. Moreover, if poorly bioavailable elemental iron powders are selected and/or high phytate products fortified without any attempt to improve bioavailability, successful reduction of iron deficiency rates is unlikely to occur. Efforts to standardize recommendations for elemental iron powders that include criteria for adequate bioavailability are needed urgently.

NaFeEDTA continues to be the most effective fortificant for poor bioavailability diets. Obstacles to scaling-up its use (although this is occurring in parts of China and Vietnam) include cost and lingering doubts about its safety (the Joint FAO/WHO Expert Committee on Food Additives restricts total daily EDTA consumption from all sources to 2.5 mg/Kg. Fortification levels in young children may exceed this amount because the 67 mg EDTA is consumed with each 10 mg iron)

Finally it is important to note that at this time, there is only circumstantial evidence to suggest that wheat fortification has been effective in one developing country - Chile, where wheat consumption is high and shelf life of the product is short. In that case, ferrous sulfate is the fortificant used.

The implementation of maize flour fortification is in general less advanced than that for wheat flour. Technical problems for maize flour are the same as those for high extraction wheat flour. Rice fortification remains a technical challenge. However several limited trials have demonstrated the effectiveness of fortifying simulated rice grains or rice flour. Ferric pyrophosphate has been used in some of them.

Mass fortification of condiments appears to be an attractive option, especially in Asia. Fortification of soy sauce and fish sauce in China and Vietnam with NaFeEDTA has been very successful in several trials. This approach is being scaled-up in China and Vietnam.

Salt fortification with encapsulated ferrous sulfate and vitamin C or ferric pyrophosphate has been shown to be efficacious in trials in children, but the high costs involved in this process make the approach more practical in social programs than in open market situations.

Intermittent (e.g. weekly) supplementation with iron for women of reproductive age and adolescents is expanding and appears to be promising in some settings (Beaton and McCabe, 1999; Cavalli-Sforza, 2005). While health services are a potential delivery mechanism, other channels (e.g. schools, factories, communities, religious groups) probably are more realistic. In populations with small or no consumption of processed foods, intermittent supplementation approaches are likely to be more practical than fortification.

Pregnancy

Supplementation in some form remains the only practical approach to ensuring optimal iron status in pregnancy. Adequate maternal iron status for fetal development and an adequate iron endowment at birth is very important. However, the problems of assuring that supplies are available, inadequate health provider motivation, and finally the failure of women

to adhere to recommended protocols, continue to be the major obstacles for these strategies. The promotion of delayed cord clamping also appears to be valuable in addressing iron deficiency in infancy.

EVIDENCE FOR IMPROVED FUNCTIONAL OUTCOMES FROM IRON INTERVENTION PROGRAMS

Effect of iron deficiency on infant development — A major issue here is the effect of iron deficiency on infant development and the permanence of the putative consequences. With over two dozen studies from countries around the world, there is conclusive evidence that infants with iron deficiency anemia are developmentally at risk in the short term (see review, Lozoff, 2006). Fifteen studies assessed overall functioning in otherwise healthy full-term infants in the 6- to 24-month age range, and all but one found poorer outcomes when infants were iron-deficient. Standardized cognitive development test scores of iron-deficient anemic infants averaged 6-15 points lower than infants with better iron status (effect sizes 0.5-1.3 SD). Language was also affected. Among 12 studies that included a standardized assessment of motor development, nine observed that infants with iron deficiency anemia received lower motor scores, averaging 9-15 points lower (effect sizes 0.7-1.1 SD). Virtually every study that examined social-emotional behavior found differences in iron-deficient anemic infants (e.g., more wary, hesitant, solemn, unhappy, closer to their mothers, less social interaction, etc.). Recent studies of infants at risk for stunting also reported poorer pretreatment motor development in those with iron deficiency anemia.

Of the few studies that assessed brain functioning more directly (Lozoff, 2006), all but one found iron-related differences. Compared to non-anemic infants, those with iron deficiency anemia showed slower neural transmission using evoked potentials (Roncagliolo et al., 1998), altered sleep assessed by polysomnography, poorer recognition memory with event related potentials, and altered spontaneous motor activity assessed actigraphically.

Many of the above studies included assessments before and immediately after iron therapy. Of studies with a full course of iron treatment (three to six months), seven used standardized tests. In four of them, lower developmental test scores persisted in iron-deficient anemic infants after treatment, whereas they improved in three studies. With respect to neurophysiologic outcomes, differences in auditory system transmission, activity, and sleep state organization persisted even after a full year of iron treatment. Thus, the majority of studies find that developmental deficits are not corrected with iron therapy in infancy (Lozoff, 2006).

Nine studies – from Costa Rica, Israel, France, the United States, and Yugoslavia – assessed overall developmental outcomes years after iron deficiency anemia in infancy, with a follow-up period ranging from preschool age to young adulthood. All show that children who had anemia, presumably due to iron deficiency, or other evidence of chronic, severe iron deficiency in infancy, do worse on tests of overall mental, motor, and social/emotional functioning, despite iron therapy. They also show that poorer iron status in infancy correlates with poorer outcome later on (Lozoff, 2006). A recent meta-analysis estimates the long-term effects on IQ to be 1.73 points lower for each 10 g/l decrease in hemoglobin (Stoltzfus et al., 2004). Brain-based measures come from follow-up studies in Chile and Costa Rica. Despite correction of anemia, former iron-deficient anemic children (through 10-19 years) show poorer neurocognitive function, slower transmission in the auditory and visual pathways (Algarin et al., 2003), altered sleep-wake cycle organization, and disrupted neuroendocrine responses (Felt et al., 2006).

In contrast to studies of therapeutic iron for iron deficiency anemia, supplementation trials in populations at risk for iron deficiency – with random assignment to supplemental iron or placebo regardless of initial iron status – show quite consistent benefits, especially in the motor and social-emotional domains. There are 11 such studies, five involving healthy full-term infants and six involving infants at risk for stunting and infectious diseases (Lozoff, 2006). The design of these studies is the most powerful way to address the issue that iron deficiency typically goes together with environmental disadvantage in humans. Among preventive trials with healthy full-term infants in the 6- to 24-month range, only a large study in Chile (n = 1657) showed benefits of iron supplementation on cognitive functioning (visual recognition memory); two showed motor benefits, and two of the three trials that assessed the affective domain reported benefits as well. A small randomized controlled trial involving breast-fed infants in Canada showed a benefit of even earlier iron supplementation on grading visual acuity and motor scores at 12 months, compared to those receiving placebo.

In addition to the Chile study, there are five large, recent supplementation trials in developing countries (Zanzibar, Indonesia, Bangladesh, and India, ns 220 - 650), some of which assessed iron with or without other micronutrients. All showed benefits of iron for motor development, and three of four that assessed the social-emotional domain showed benefits as well. The magnitude of effects at the conclusion of the trials ranged from 0.27 to 0.39 SD for motor outcomes and 0.30 to 0.41 SD for social-emotional ones. One randomized control trial of food iron fortification included a developmental outcome and found a similar benefit on motor outcome (Faber et al., 2005). Although no long-term follow-ups have been reported, these results suggest that poorer developmental outcomes can be prevented if iron is provided before infants have chronic, severe

iron deficiency and hold the promise that long-term effects can be prevented with supplementation.

Effect of iron deficiency on malarial morbidity—The second important issue is related to the Pemba substudy (Sazawal et al., 2006) which indicates that iron deficiency is a significant risk factor for increased morbidity from malaria and malaria related infections in children under age three living in a region where malaria transmission is year round. This is an important functional outcome that is getting insufficient attention because it has been overshadowed by the increase in adverse events in the overall trial. If confirmed, this could be a functional outcome that is as important as the developmental one.

INTERACTIONS BETWEEN MICRONUTRIENT DEFICIENCY STATES AND INTERVENTION STRATEGIES

There are urgent issues related to the concurrent delivery of micronutrients, especially when considering the potential competition for absorption between iron and zinc. Clarification is needed with respect to the functional importance of such interactions, the conditions under which they occur, and the programmatic changes that should be made to avoid them.

There are other possible interactions that may not have received enough attention as yet. Examples include the effects of vitamin A deficiency in combination with iodine deficiency (Zimmermann et al., 2004) and the interaction between vitamin A deficiency, anemia, and iron (Majia et al., 1977; Jang et al., 2000). These interactions may complicate the interpretation of trial data. More importantly, they emphasize the importance of multiple micronutrient interventions.

RISKS OF IRON SUPPLEMENTATION

The iron, zinc, and folic acid supplementation trial conducted in Pemba is likely to have a very significant impact on iron intervention strategies in regions where malaria is prevalent and might significantly handicap both program implementation and further research. The findings will need to be interpreted carefully. The Micronutrient Forum provides an opportunity to develop a rational way forward. The following is our interpretation of the salient facts:

- Iron supplementation with readily soluble ferrous sulfate and folic acid following the INACG/WHO/UNICEF guidelines caused an increased risk for serious infection-related morbidity in children less than three years of age.

- It is likely, that the mortality risk might also have been higher in these children.
- The trial design makes it impossible to exclude folic acid as the factor responsible for the increased morbidity, but other scientific evidence suggests that an iron effect is more likely.
- The substudy, which is a statistically adequate sample, indicates somewhat paradoxically, that iron deficiency is a risk factor for increased serious morbidity (significantly more adverse events among iron deficient children in the placebo group) and that iron and folic acid administration to iron deficient children reduces their risk of serious morbid events substantially. It must be noted that this was in the context of more readily available access to medical care and malaria treatment than was the case for the overall study.
- It has been postulated that the adverse effect of iron could be related to periods of increased plasma iron following its administration, because ready access to iron increases the virulence of many pathogens. It has been suggested that another mode of delivery such as the use of fortified complementary foods or home fortification of meals could be safer. However, research is needed to determine the safety of home fortification in malarial settings.

These observations, taken in their entirety, strongly suggest that an effort should be made to integrate iron interventions with malaria programs (to improve the outcome of treating malaria and promote normal infant development), but there are significant obstacles. If universal screening for iron deficiency were needed in malarial areas, an appropriate method would have to be developed. A more likely practical approach might be the identification of a risk-free, effective way of giving the iron. The latter option probably constitutes the more urgent current research priority.

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FUTURE OPPORTUNITIES FOR INTERVENTION IN POPULATIONS WHO DO NOT CONSUME PROCESSED FOODS

In the longer term, there is a need for strategies to improve the diet. They include traditional approaches, that have been attempted in the past – greater meal variability (more meat or fish), but also new initiatives to increase iron content and bioavailability in staple foods. The initial work in this area suggests that it is possible to grow vegetable foods that contain significantly more iron and there is encouraging preliminary information to suggest that this iron may be in a form that is highly bioavailable and perhaps less affected by dietary inhibitors. These findings need to be confirmed and refined. Efficacy should be evaluated in a well controlled trial in human volunteers. This work is very important, but the time frame for program implementation is undoubtedly much longer than that for the other approaches discussed above.

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