

Iron Supplements: Scientific Issues Concerning Efficacy and Implications for Research and Programs

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Forging Effective Strategies to Combat Iron Deficiency

Iron Supplements: Scientific Issues Concerning Efficacy and Implications for Research and Programs^{1,2}

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ABSTRACT Iron supplementation remains an important strategy for the prevention and treatment of iron deficiency anemia and can produce substantial improvements in the functional performance of iron deficient individuals and populations. Many potential benefits of iron supplementation require further exploration, including its effect on vitamin A and iodine metabolism. There is strong evidence that vitamin A and riboflavin deficiencies affect iron utilization from supplements and are important on a global scale, but little evidence that folate and vitamin B-12 deficiencies play a major causal role in the global burden of anemia. The efficacy of multiple micronutrient supplements for the prevention and treatment of anemia must be further evaluated. Because weekly supplementation with iron is effective at improving iron status, this option should be thoroughly explored and evaluated in the context of programs for the prevention and the treatment of iron deficiency and anemia. More conformation is warranted concerning the number of tablets that must be consumed in different situations, and the efficacy of supplying other micronutrients weekly with iron. Weekly supplementation programs may improve the logistical and economic constraints that currently limit the provision of supplements to the many target population groups for whom they are recommended, but usually fail to reach. Further work is required to clarify the purpose, delivery and outcomes of iron supplementation programs. *J. Nutr.* 132: 813S–819S, 2002.

KEY WORDS: • *iron deficiency* • *iron deficiency anemia* • *iron supplements* • *micronutrient deficiencies*

Supplementation with iron tablets is the most widely used approach to controlling the global problem of iron deficiency/anemia. Much has been learned from our experiences with iron supplementation, but many scientific and logistical issues remain to be resolved. The objectives of this article are to present an overview of these issues, to propose logical supplementation strategies based on current information and to identify some unresolved questions that should be addressed by further research and evaluation in the context of new and ongoing programs. This review focuses on factors that affect the efficacy of iron supplements for improving iron status in the program context. Other authors in this conference have addressed program delivery issues in more detail, and other publications describe how iron supplementation fits within the range of program options available for controlling iron deficiency anemia (1).

Benefits from iron supplementation

A recent consensus meeting, organized to review what is known about the adverse effects of iron deficiency/anemia on human function, arrived at the following conclusions (2). Sufficient evidence is available to show that severe anemia increases the risk of both child and maternal mortality, and that iron deficiency anemia impairs work productivity and child development. In contrast, causal evidence is contradictory or lacking to show that iron deficiency anemia increases risk of low birth weight or preterm delivery, or that it has either adverse or protective effects on infectious disease. There is insufficient evidence to prove that mild-to-moderate anemia affects either maternal or child mortality.

It is important to appreciate that many of the relevant studies were not designed adequately to demonstrate the potential effects of iron deficiency anemia, or of iron supplementation, on human function. A common problem is that potential participants who are found to have severe (or sometimes moderate) anemia are often treated immediately with iron for ethical reasons and dropped from the study, leaving only mildly iron-deficient participants in the intervention. Randomized, placebo-controlled iron supplementation studies are often not deemed to be possible in pregnant women due to the fact that the WHO and many other advisory groups recommend universal iron supplementation for all pregnant women, regardless of their baseline hemoglobin or iron status. Our methods for detecting changes in function are relatively crude (such as birth weight or scores on the Bayley scales of child development). Some outcomes of iron supplementation

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trials have rarely been evaluated (such as preterm delivery, infant cognitive function and development or adult cognitive performance and behavior), and little attention has been paid to measuring the effects of iron supplements on underlying metabolic and hormonal changes that could detect, predict and explain functional responses (3,4). Evidence is accumulating to show that iron supplementation of iron-deficient pregnant women improves both maternal and infant iron stores postpartum (5,6), but the functional consequences of this improvement have not been documented adequately (6,7).

An additional consideration is that most research to date has focused on the effects of *anemia* on function. Little work has been done to investigate whether function is affected at the earlier stage of *iron deficiency*. There is some evidence that supports the need to assess this possibility more carefully. Animal experiments have established the principle that endurance performance is adversely affected by tissue iron depletion and is relatively independent of hemoglobin concentration until it falls below 100 g/L (3,8); a limited number of studies support an adverse effect of iron deficiency on VO_2^{max} and endurance in humans (9). In a recent study of iron-deficient, nonanemic women in the United States, the subjects were provided with an iron supplement (50 mg of iron, twice daily for 6 wk) vs. a placebo. All women received aerobic training during the intervention. The iron supplements significantly improved VO_2^{max} compared with the placebo group (10). In another recent study, iron supplements (10 mg/d for 12 mo) improved the language development of both anemic and nonanemic preschoolers in Zanzibar (11). The supplements improved iron status but not hemoglobin, an observation probably explained by the high prevalence of malaria in this group.

Iron supplementation may have other important benefits that are not yet generally recognized. These should be investigated further and, if confirmed, used as additional support of the importance of iron intervention programs. The two following examples are based on the fact that iron deficiency impairs both vitamin A and iodine metabolism, and can therefore limit the effectiveness of vitamin A and iodine intervention programs. In rat models, iron deficiency lowers serum retinol, and vitamin A accumulates in the liver as retinyl esters, probably due to impaired activity of hepatic acid retinyl ester hydrolase, an iron dependent enzyme (12). Consistent with the data from these animal studies, long-term supplementation with iron caused large increases in serum retinol in Mexican children (13). Preschoolers ($n = 219$) were provided with zinc (20 mg/d), iron (20 mg/d) or zinc + iron supplements (20 mg of both minerals) for 12 mo. As illustrated in the *left panel* of **Figure 1**, in zinc deficient children (plasma zinc $<10.7 \mu\text{mol/L}$), zinc supplements significantly increased plasma retinol, whereas iron supplements did not, but providing zinc plus iron increased plasma retinol even more than zinc alone. Thus, predictably, in children with no evidence of zinc deficiency, iron supplements alone improved plasma retinol. Supplements containing iron alone increased plasma retinol in iron deficient children (plasma ferritin $<12 \mu\text{g/L}$), but not in those with adequate iron stores (Fig. 1, *middle panel*). Finally, for children with low plasma retinol ($<0.70 \mu\text{mol/L}$) at baseline, but not normal values, plasma retinol concentrations were increased by either zinc or iron supplements. These observations strongly support the hypothesis that the low plasma retinol concentrations seen in 29% of these children at baseline were in fact caused by iron deficiency and/or zinc deficiency, rather than vitamin A deficiency. Iron supplements increased plasma retinol by $\sim 0.65 \mu\text{mol/L}$, which is a remark-

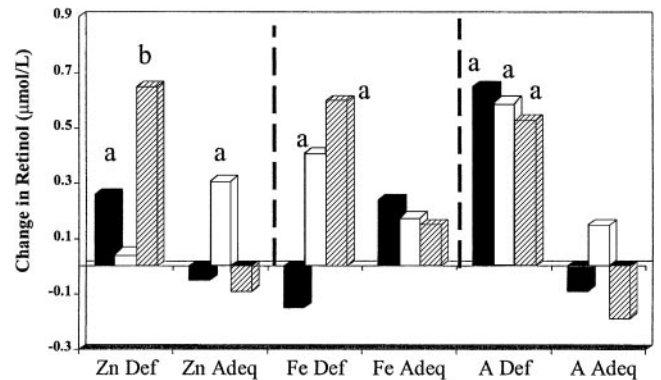


FIGURE 1 Change in plasma retinol concentrations after providing 212 Mexican preschoolers with 20 mg/d zinc (shaded bars), iron (clear bars) or zinc + iron (hatched bars) for 12 mo. The *left panel* shows data for children with deficient (Zn Def, $<10.7 \mu\text{mol/L}$) vs. adequate (Zn Adeq, $\geq 10.7 \mu\text{mol/L}$) plasma zinc at baseline. The *middle panel* shows data for children with deficient (Fe Def, $<12 \mu\text{g/L}$) vs. adequate (Fe Adeq, $\geq 12 \mu\text{g/L}$) plasma ferritin at baseline. The *right panel* shows data for children with deficient (A Def, $<0.7 \mu\text{mol/L}$) vs. adequate (A Adeq, $\geq 0.7 \mu\text{mol/L}$) plasma retinol at baseline. Values with letters are significantly different from baseline, and bars with different letters are significantly different from each other [modified from Munoz et al. (13)].

ably large increase considering that the cut-off values for vitamin A deficiency are $<0.35 \mu\text{mol/L}$ (severe) and $<0.7 \mu\text{mol/L}$ (mild). If similar results are found in other locations, they may reveal that we have overestimated the global prevalence of vitamin A deficiency and underestimated the benefits of iron supplementation.

Iron deficiency anemia may limit the effectiveness of iodine supplementation programs. In Cote d'Ivoire, a high dose iodine supplement was given to children with goiter (14). Ten weeks after the iodine treatment, the prevalence of goiter fell from 51 to 6% in nonanemic children, but only from 53 to 34% in those with anemia. Among children, the reduction in goiter was inversely correlated with initial hemoglobin concentrations. Although studies are required that test the effects of providing iodine with and without iron supplements in different populations, these results suggest another important reason for iron supplementation programs that has not been recognized adequately.

Benefits of supplementation with other micronutrients in addition to iron

Not infrequently, iron supplements are reported as failing to restore hemoglobin concentrations to normal (15). A common reason for this observation is that inadequate amounts of iron have been supplied, due to problems such as low compliance, short duration of the intervention or high iron requirements during periods such as pregnancy (15,16). In these situations, there should be evidence of persistent iron deficiency such as low serum ferritin. In other situations, however, iron stores normalize, whereas low hemoglobin concentrations persist (17,18). In these cases, it is possible that other micronutrient deficiencies are limiting hemoglobin response to iron supplements.

One of these limiting micronutrients might be folic acid, which for decades has been included in the iron supplements provided by UNICEF, for example. Originally, folic acid was included on the assumption that folic acid deficiency is a common cause of nutritional anemia. However, the global

prevalence of folic acid deficiency, especially of a severity high enough to cause anemia, is uncertain (19). This deficiency is possibly more common in Africa and Asia (20,21) although few data exist on this question. In an older WHO collaborative study in Burma and Thailand, there was no additional increase in hemoglobin concentrations when folic acid was added to iron supplements for pregnant women (22). Small, nonsignificant increases in hemoglobin, usually compared with iron alone, were observed in pregnant women in Australia (23), Burma (24), India (25,26), Liberia (27), Nigeria (28) and Thailand (29). A meta-analysis of 22 studies evaluated the effect of folic acid supplementation with and without iron on the progression of anemia in pregnant women who were non-anemic at baseline (30). Inclusion of folic acid produced a 40% lower risk of anemia in late pregnancy and a 35% reduction in megaloblastosis. Most of the benefit was seen in African countries. Unfortunately, half of the studies took place in the United Kingdom >30 y ago and only four occurred in the last 20 y.

More recently, the inclusion of folic acid in iron supplements for women of fertile age has been justified on the basis of reducing the risk of neural tube defects, and the amount of the vitamin increased from 250 to 400 $\mu\text{g}/\text{tablet}$ for this reason. Folic acid taken later in pregnancy may also reduce risk of preterm delivery (31,32) and thereby increase birth weight. Elevated plasma homocysteine has been associated with preterm delivery, preeclampsia and several fetal abnormalities (33) and is often lowered by supplemental folic acid. Thus the continued inclusion of folic acid in iron supplements is justified on the basis of improving fetal outcomes, but there is a lack of evidence that it can reduce the global burden of anemia substantially.

Vitamin A deficiency definitely impairs hemoglobin synthesis. This was most clearly demonstrated in a clinical experiment in which adults were depleted of vitamin A. Hemoglobin levels fell markedly, causing an anemia that was responsive to vitamin A supplementation, but not to iron supplementation (34). Weekly retinol supplements reduced anemia in pregnant Nepali women by 45% (35). Vitamin A supplements also improved hemoglobin response to iron supplements in Indonesian pregnant women (36) and Mexican children (37). The addition of weekly vitamin A to weekly iron supplements increased hemoglobin and reduced serum ferritin and transferrin in Indonesian pregnant women; the reduction in serum ferritin was ascribed to improved iron utilization (38). In general, experience shows that vitamin A supplementation of individuals deficient in the vitamin increases hemoglobin by $\sim 10 \text{ g/L}$ (39) and improves their hemoglobin response to iron supplementation.

The global prevalence of vitamin B-12 deficiency is uncertain, although it is common in areas in which the intake of animal products is low (19,40,41) or in which meat is avoided (42,43). However, vitamin B-12 deficiency has to be severe to cause anemia (44), which probably does not occur until plasma levels of the vitamin fall below $\sim 150 \text{ pmol/L}$. In Indian adults, even plasma cobalamin concentrations $< 100 \text{ pmol/L}$ were not associated with an increased risk of anemia (41).

There is little information concerning whether vitamin B-12 supplements improve the effects of iron supplements on hemoglobin synthesis. In a group of Mexican preschoolers (30% had B-12 deficiency and 50% had anemia), oral supplementation with 1 mg/d vitamin B-12 eliminated low serum concentrations of the vitamin but had no effect on hemoglobin, mean cell volume or mean corpuscular hemoglobin concentration (45). Thus, there is little evidence at present to

show that vitamin B-12 deficiency explains an important proportion of the global prevalence of anemia.

There is somewhat stronger evidence that riboflavin deficiency limits the efficacy of iron supplements. Riboflavin and iron deficiencies often coexist when animal product intake is low. Riboflavin deficiency increases the intestinal loss of iron and impairs iron absorption and the mobilization of intracellular iron (46–48). It may also impair globin synthesis and the activity of NADH-FMN oxidoreductase so that iron is trapped in ferritin and thus unavailable for erythropoiesis. Riboflavin supplements increased hemoglobin response to iron supplementation in adult men, children, and pregnant and lactating women in The Gambia (49,50). In lactating women in rural Guatemala, supplementation with riboflavin plus iron for 2 mo caused serum ferritin to increase more than iron alone (51). Although the prevalence of riboflavin deficiency is uncertain, values in the relatively few studies in which it has been investigated include 77% of lactating women (51) and 50% of elderly (52) in Guatemala, >90% of adults in a region of China (53) and almost 100% of pregnant and lactating women in The Gambia (54).

Multiple micronutrient supplements

Because several micronutrients can improve the hemoglobin response to iron, it is reasonable to assume that multiple micronutrient supplements would be more effective in reducing anemia than iron alone. Surprisingly, few trials of this assumption have been conducted. Preliminary results of two separate trials in rural Mexico, however, indicate that supplements containing multiple vitamins and minerals actually resulted in lower postintervention hemoglobin and ferritin concentrations in preschoolers (45) and pregnant women (55) compared with iron alone. Iron absorption may be inhibited by nutrients such as calcium, magnesium and zinc. Additional studies of the effect of multiple micronutrient supplements on anemia are in progress. Even if they also show that hemoglobin response is less than with iron alone, the other benefits of multiple micronutrient supplements must be considered.

Frequency of iron supplementation

One important reason for the relative lack of programmatic success with iron supplements has been the perceived need for these supplements to be taken daily, over relatively long periods of time. This contrasts markedly with the efficacy of vitamin A capsules for which a high dose can improve status for $\sim 4 \text{ mo}$, or iodized oil, for which a single dose can improve status over an even longer period.

For this reason, and because of concern about the potential toxicity and intolerance to daily supplementation, there has been interest in the relative efficacy of weekly compared with daily iron supplementation. A statistical analysis of data from studies examining this issue concluded that both daily and weekly iron supplementation reduced the prevalence of iron deficiency and anemia (15). Daily supplementation was found to be more effective than weekly for increasing hemoglobin and ferritin. Although daily supplementation produced only a 2 g/L greater increase in hemoglobin across studies on average, it caused a 34% greater reduction in the risk of anemia. This apparent inconsistency is explained by the fact that the daily dose was more effective at increasing low hemoglobin concentrations, thereby eliminating anemia in the most anemic individuals. The relative efficacy was greatest across studies in the case of pregnant women, adolescents and school-age children. Logically this would be due to the relatively high iron

demands of pregnancy and adolescence. The report concluded that weekly supplementation might be more effective when weekly supervision is feasible, but daily supervision is not.

These findings are consistent with the important observation by Ekstrom (56) that the magnitude of the hemoglobin response to iron depends on the amount of iron consumed. For example, in pregnant women in rural Bangladesh, the number of 120-mg iron tablets consumed was monitored carefully by providing the pills in a bottle with a computer chip that recorded how many times the bottle was opened (56). In that study, the hemoglobin response *per tablet* was similar no matter whether the dose was given weekly or daily. Another important observation is that most of the hemoglobin response was produced by the first 20 tablets, with no further response after 40 tablets. Similar results were found in Indonesian pregnant women, for whom increases in hemoglobin and improvements in iron status indicators were greater in women consuming ≥ 50 tablets/d (120 mg iron) compared with < 50 tablets/d (38). Additional studies of this type in various situations that include assessment of serum ferritin response would be extremely valuable to guide programs that provide advice on the need to ingest a fixed number of tablets over specified periods of time, while allowing flexibility on the interval over which they should be consumed.

Logically, the evidence available currently suggests that iron supplements should be taken daily to *treat* anemia, especially by pregnant women who are consuming low amounts of available iron. Because daily supplementation does improve iron status, weekly supplementation should be an effective way to *prevent* iron deficiency. Weekly supplements would reduce side effects (57,58) and lower cost, might improve compliance and reduce oxidative stress (59), and would maintain iron stores for a longer period when supplementation is stopped (57). More information is required to test the relative effectiveness of daily and weekly supplementation in the program context, but at least we now know that *both* strategies are effective. The decision to use one vs. the other must depend primarily on the local situation.

Dose and type of iron

Global guidelines for iron supplementation have been published by the International Nutritional Anemia Consultative Group/World Health Organization/UNICEF (60). The recommendations are as follows: for age 6 to 24 mo, 12.5 mg/d plus 50 μg /d folic acid until 12 mo of age, with supplementation from 2 to 12 mo for low birth weight cases; for age 2 to 5 y, 20 to 30 mg/d (2 mg iron/kg body); for age 6 to 11 y, 30 to 60 mg/d; for adolescents and adults, 60 mg/d (plus 400 μg folic acid for women of reproductive age); and for pregnant women, 60 mg/d plus 400 μg folic acid for 6 mo, continuing for 3 mo of lactation where the prevalence of anemia is high ($> 40\%$). These doses are doubled for the first 3 mo in cases of severe anemia (Hb < 70 g/L).

In setting the Lowest Observed Adverse Effect Level (LOAEL) for iron, the Institute of Medicine in the United States reviewed existing information on the side effects of iron supplements (61). The limited amount of available information showed that high dose supplements (120 mg or more) were associated with more constipation, nausea, vomiting and diarrhea in several studies. The effect of lower doses is much less severe if the supplements are taken with food, or if they are manufactured in a slow-release form. The selection of a LOAEL of 60 mg/d was based on a relatively well-designed study that found a significantly higher risk of constipation, higher rates of gastric pain and diarrhea, and significantly more

total gastrointestinal effects (nausea, gastric pain, constipation and diarrhea) than a placebo (62). It is important to point out, however, that there is little evidence that adverse side effects are the major cause of noncompliance in iron supplementation programs (63). High doses of iron given once per week are better tolerated than when given once per day (58).

The most common form of iron in iron tablets is ferrous sulfate (20% iron in the hydrated form), although fumarate (33% iron) and gluconate (12% iron) are sometimes used. Infants are usually supplemented with a liquid formulation, which is more expensive, but tablets that can be crushed or mixed with food, or that dissolve readily in the mouth have now been developed. Although iron absorption from these compounds is reasonable, improvements in the amount of iron absorbed from supplements are possible. Formulation of 50 mg iron into a "gastric delivery system," in which the iron becomes suspended in a colloidal matrix in the stomach, produced the same hemoglobin and ferritin response as providing 50 mg iron twice daily as ferrous sulfate (64). Unfortunately, production of the gastric delivery system iron has been discontinued. More work must be done on the relative bioavailability of other forms of iron supplements including amino acid chelates. Little is known about iron bioavailability from multiple micronutrient supplements, but at least one study showed that iron absorption from some such supplements can be poor, especially when they contain calcium or magnesium (65). Absorption from different formulations is also affected differentially by consumption with a meal vs. in the fasted state (66). Given the low cost of iron supplements compared with the expense of the delivery system, it is clearly important to verify that the iron is as bioavailable as possible and provides the recommended amounts of absorbable iron.

Targeting iron supplements

A summary of the prevalence of anemia shows that this condition affects infants, children and women of all ages, and adult men in whom parasite-induced blood losses or malaria are endemic (67). From one third to more than one half of infants, children, women and the elderly are affected on average in developing countries, and a substantial number in these groups in industrialized regions. This implies that iron supplements are needed across the life span, and not just by pregnant women, the most commonly targeted group. In fact, it is difficult to prioritize target groups because there are arguments to support the need for adequate iron at any age. Low-birth-weight infants become iron depleted shortly after birth and anemia becomes common in most infants who do not receive supplements or fortified foods after ~ 6 mo of age. Anemia and/or iron deficiency may have especially adverse effects on the development of infants although more research is warranted on this question (7). The adverse effects of iron deficiency anemia and benefits of supplementation on pre-schoolers and school-age children have been documented (7).

Adolescent females become more susceptible to iron deficiency during the growth spurt and the onset of menstruation and have been suggested as a logical target group for supplementation to replete iron stores before pregnancy. However, the benefits of supplementation do not last long in this group once supplementation is stopped. For example, at the end of an iron supplementation study in 273 adolescents, daily (60 mg/d) iron supplements increased serum ferritin concentrations from 35 $\mu\text{g}/\text{L}$ at baseline to 63 $\mu\text{g}/\text{L}$ after 12 wk; weekly 60-mg doses increased ferritin from 27 to 42 $\mu\text{g}/\text{L}$, and weekly 120-mg doses, from 29 to 45 $\mu\text{g}/\text{L}$ (68). However, 6 mo after supplementation was stopped, the increases in ferritin over

baseline were small in all groups ($\sim 6 \mu\text{g/L}$), although those in the placebo group had fallen by $5 \mu\text{g/L}$. Sean Lynch made the following comments concerning the durability of improving the iron status of adolescent women through supplementation (69); when supplements are stopped, there will be a period of negative iron balance because iron absorption has been down-regulated; the benefits of supplementation will be temporary if diets are low in available iron; and importantly, iron balance in pregnancy depends more on the adequacy of current intakes of iron than on iron stores at conception, so that regardless of prepregnancy supplementation, iron supplements will be required during pregnancy by women consuming low amounts of absorbable dietary iron.

Pregnant women are an obvious target group due to the high iron demands of pregnancy and the potential for anemia to cause adverse pregnancy outcomes (4,6,70). Supplementation during pregnancy does increase the iron stores of the infant and of the mother postpartum (5). The higher hemoglobin and serum ferritin concentrations of postpartum women typically fall again by ~ 3 mo postpartum when the mother could benefit from supplementation to prepare her for a subsequent pregnancy. In cases in which blood loss during delivery has been high, women will require additional iron immediately postpartum. Finally, iron deficiency in the elderly in developing countries has been virtually ignored even though the average prevalence of anemia in these groups is $\sim 50\%$ (67). Men will need supplementation if they are anemic due to high parasite-induced blood losses or malaria.

Is it feasible to provide or consume supplements throughout the life span? Probably not, using current programmatic strategies. A review of iron supplementation programs in UNICEF field offices revealed that by far the majority of effort was on programs for pregnant women; of 57 country programs reporting, 49 stated that iron supplements were routinely provided for pregnant women, whereas 8 stated that only anemic pregnant women were supplemented. Most programs recommended daily supplementation although five recommended weekly supplementation both prepregnancy and during pregnancy, and three recommended weekly during pregnancy alone. Other groups were rarely targeted; supplementation was recommended for postpartum women in 4 of the 57 countries, and for preschoolers and school-age children in 23 of 57 countries. The reported (maximum) coverage in the majority of pregnancy programs was $>50\%$. It is likely that coverage is very much lower for children. Thus, ongoing programs fall far short of supplying or even recommending iron supplements for many of the groups that theoretically should benefit.

Supplementation in regions with endemic malaria

Malaria is one of the major causes of severe and moderate anemia. Current opinion, based on a review of 13 randomized, controlled clinical trials, is that the known benefits of iron supplementation are likely to outweigh the risk of adverse effects in regions with endemic malaria (71). It is difficult, however, to know who is iron deficient on an individual basis, because indicators of iron status such as ferritin and transferrin receptors are altered by the malarial infection (72). On a population basis, the need for iron intervention programs is therefore best assessed after eliminating samples from individuals with evidence of parasitic infection using blood smears or antigen tests, or the presence of fever.

Conclusions and unresolved programmatic issues

Iron supplements do improve hemoglobin and iron status in efficacy trials. There is substantial evidence that treatment of

iron deficiency anemia improves several important human functions. Unfortunately iron supplementation trials are often inadequately designed to detect functional improvements, and some potential benefits have not been assessed adequately. There appear to be important interactions between iron status and vitamin A utilization, and iron status and recovery from goiter. Overall, the existing data show that although iron deficiency is by far the most important cause of nutritional anemia, vitamin A deficiency and probably riboflavin deficiency can be substantial risk factors in many countries. Evidence is less strong that folate and vitamin B-12 deficiencies are important contributors to the global prevalence of anemia, although these deficiencies certainly have other adverse effects. Taken together, the facts support a need to compare the relative efficacy of multiple micronutrient supplements against iron alone. Although such trials are ongoing at present, two such trials in Mexico actually showed poorer hemoglobin response to multiple micronutrients compared with iron.

A question of critical importance is whether weekly iron supplementation can improve compliance and coverage compared with daily supplementation, both within and across population groups. The ideal programmatic approach might be to provide weekly supplements as a *preventive* measure to a large proportion of individuals in iron deficient populations. This might reduce anemia, improve compliance, minimize side effects, lower costs and therefore enable greater coverage. Daily supplementation does not appear to be a logical strategy for all potential target groups, and might be best used for pregnant women and those diagnosed with anemia on testing. Trials to test these options and outcomes are required at the field level in the context of current programs, including the optimum number of tablets that must be consumed in different situations.

From a policy perspective, there is a serious lack of clarity about the goals of iron supplementation programs. For example, should iron supplementation be recommended for individuals or population groups who are iron deficient as well as those with anemia? Should iron supplementation programs remain focused on the *treatment* of anemia, or can we use them effectively to *prevent* anemia and iron deficiency? What type of anemia, i.e., mild, moderate or severe? How long should daily or weekly supplements be taken? Should recommended duration be based on the prevalence of anemia in the population (as at present), or on the severity of the anemia? Is weekly supplementation with iron tablets containing multiple micronutrients also effective for rectifying deficiencies of these micronutrients, and what levels of the other micronutrients are required? Can we suggest that treatment consists of a specified number of tablets in some situations? Which population groups should be priorities for supplementation? Finally, what approaches best improve adherence to iron supplementation programs? Scientists and program implementation professionals should join forces to answer these questions.

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