Iron Interventions for Child Survival

Edited by Penelope Nestel, Ph.D.

May 17-18, 1995
London, United Kingdom
PROCEEDINGS
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INTRODUCTION

Background

After pregnant women, children under 5 years old are at greatest risk of being iron deficient when anemia is used as the major clinical manifestation; however, few countries have good prevalence data, which means that the problem often goes unrecognized and unaddressed. To the extent that data exist, the World Health Organization (WHO) estimates that 51 percent or 183 million children from birth to 4 years old in developing countries, excluding China, are anemic. Among this age group, anemia is more prevalent in Africa (56 percent) and South and Southeast Asia (56 percent) than in Latin America (26 percent) and East Asia (20 percent).

The physiologic demand for iron varies throughout the life cycle and is particularly high during infancy and pregnancy. In infancy, iron is needed for tissue synthesis, especially skeletal muscle and red blood cell synthesis, and in pregnancy for tissue synthesis in the mother, the placenta, and the fetus, as well as for blood loss at parturition.

Healthy iron nutriture throughout the life cycle depends on an individual having sufficient iron stores that can be mobilized during the periods of high demand. During pregnancy, maternal iron metabolism is self-adjusting so that the fetus is provided with sufficient iron stores to protect it through infancy. Women of reproductive age must protect themselves against iron deficiency by accumulating iron stores before the onset of menses and replenishing their iron stores between pregnancies.

Left uncorrected, the severity of anemia increases; this has serious implications in terms of diminished learning capacity and growth in children, increased susceptibility to infection, greater risk of death associated with pregnancy and childbirth, and reduced work capacity. The causes of anemia are many. In addition to iron deficiency, deficiencies of folate and vitamin B₁₂ also result in anemia. Other micronutrients, such as vitamin A, impact on iron status. The most important cause of iron deficiency is the low bioavailability of dietary iron, particularly in plant foods, but chronic infections and inflammations are also significant factors. The latter include parasitic infections, such as hookworm and malaria.

Improving the bioavailability of dietary iron and, to a much lesser extent, increasing the quantity of iron consumed are possible but tenuous means to improve iron status. The former can be achieved through increasing the consumption of heme iron and/or iron bioavailability enhancers, such as vitamin C, as well as reducing the consumption of iron bioavailability inhibitors such as phytates, polyphenols, and tannins. The programmatic means to do the above include nutrition education, social marketing, and horticultural/agricultural interventions. Few of these interventions, however, appear to have been evaluated; their impact on reducing iron deficiency in infants and young children appears to be largely unknown.

Iron fortification of infant foods has been in place in developed countries for a great many years. The challenge in developing countries is to make culturally acceptable, processed, complementary food(s) available throughout the country at an affordable price for the most vulnerable socioeconomic strata of the population. Few developing countries have achieved this.
The easiest way to improve iron status is to provide a pharmacological iron supplement through the health care delivery system; however, because iron metabolism is highly regulated, supplements are only effective if they are taken on a regular basis and in a relatively low dose, that is, three to ten times the daily dietary level. This means that iron supplement programs tend not to be sustainable over a long period of time, but they can be effectively used in programs of 3 to 4 months duration. Because of this, iron supplement programs are used primarily for pregnant women, who are not only the most vulnerable group but who are reachable through antenatal care services. Very few programs appear to have taken on the challenge of providing an iron supplement to children under 5 years old who may not visit health facilities on a regular basis.

**Purpose**

The purpose of the workshop was to bring together program managers who have worked on or are presently working on iron interventions targeted at infants and young children. In addition to giving an overview on why these children are so vulnerable to iron deficiency, the workshop did the following:

- Identified and described pilot and subnational- and national-level programs that have addressed iron deficiency in children under 5 years old
- Identified the constraints to these programs and, where applicable, how they have been overcome
- Identified key research questions that must be addressed for iron interventions to be more effective for these children

The discussions were directed to help resolve issues critical to the implementation of iron interventions for young children and to guide the choice and design of interventions.

**Outcomes**

Program managers and policymakers would be brought together to discuss both interventions to eliminate iron deficiency in preschool children and known information that could guide and prioritize program agendas for the future.

The plenary presentations and discussions would be compiled and distributed to the wider program community, researchers, and donors who are concerned with programs to eliminate iron deficiency. Representatives of donor agencies that support field programs and research in developing countries would also participate to consider collaborative support and coordination for field programs and research as formulated by the workshop.

Representatives from the food and pharmaceutical industries would also attend to promote greater cooperation between the private and public sectors regarding iron intervention programs.
OPENING REMARKS

Frances Davidson, Ph.D.
U.S. Agency for International Development
Washington, D.C.

Andrew Tomkins, M.D.
Institute for Child Health
London

Dr. Davidson opened the meeting by welcoming everyone on behalf of the U.S. Agency for International Development (USAID), the USAID-funded Opportunities for Micronutrient Interventions (OMNI) project, and the Institute for Child Health, which organized the meeting.

Dr. Davidson briefly described the genesis of the meeting by stating that the organizers, with input from other colleagues, reviewed micronutrient issues still in need of consensus before programs could be put in place. Various issues were identified; those of particular relevance to micronutrients included the role of carotenoids in vitamin A deficiency, iron deficiency anemia in early childhood, and micronutrient interactions. The role of carotenoids in vitamin A deficiency was recently discussed at a meeting in Washington, D.C.; a report of the meeting would be available in the summer. Micronutrient interactions are much more complicated and difficult subjects to tackle and are currently being reviewed. This leaves the issue of iron deficiency anemia in early childhood. This subject is important because it has implications for both cognitive and physical development. Despite this, conventional notions continue to exist; for example, developmental delays can be reversed, which means that programmers have deluded themselves into thinking that it is possible to make up for the early insults of iron deficiency on child development more so than appears really possible. A need clearly exists to know more about the consequences of iron deficiency anemia for child survival and development. Agencies such as USAID and others represented at this workshop need to know what the important information is and what needs to be done to support programs to help countries reduce the prevalence of and eventually eliminate iron deficiency. Dr. Davidson emphasized that USAID is interested in interventions as they relate to iron status. She noted that anemia involves many issues including diet, breastfeeding, and parasite infections, and experts in each of these areas are present at this meeting; however, rather than focus on specific interventions, it is important to concentrate on integrated interventions as they relate to iron status to determine what can be done to eliminate iron deficiency.

Dr. Tomkins described the workshop agenda and expected outcomes. He started out by reminding everyone that although anemia in preschool children is a major problem, many causes of anemia exist. Iron deficiency, the focus of this workshop, is obviously very important. But other factors such as helminths, malaria, and other systemic infections have to be considered. Dr. Tomkins pointed out that a number of ways exist to intervene to improve iron status and the workshop was fortunate to have people with expertise in issues ranging from disease prevention, pharmaceutical supplements, dietary diversification, and food fortification. He reminded participants the outcome was not to produce global recommendations, because there are other organizations whose role it is to produce global recommendations for nutrition, but to look carefully at the different ways in which strategies for improving iron status can be applied in different situations. What might be suitable for a country with complete destruction of its infrastructure and horrific economic and environmental challenges, such as
Burundi, is not going to be suitable for a more stable country such as Tanzania, a more industrialized country such as Thailand, one that has an Eastern European tradition such as Romania, or a European country such as Great Britain. Each of the different countries obviously has its own specific needs; thus, the purpose of this meeting is to identify state-of-the-art knowledge of what interventions can offer, particularly in the context of different scenarios, in which a combination of integrated programs can together provide more than any individual program.
1. IRON NUTRITION IN CHILDREN UNDER FIVE YEARS OLD: REQUIREMENTS AND ASSESSMENT

Suzanne Filteau, Ph.D.
Institute of Child Health
London, United Kingdom

Factors determining dietary iron requirements and measures of iron status

Dietary allowance tables from different countries show wide variations in the recommended daily intake of iron for young children. This variation does not appear to be based on real differences in iron needs in different parts of the world. Instead, it is influenced by the different weights given to various factors affecting iron absorption that are used in the calculations. There are good reasons why expert committees often have had trouble defining recommended daily intakes for iron. First, dietary iron absorption differs markedly depending on other components of the diet and on the iron status and needs of the individual. Second, iron losses from infections or bleeding can be as important as iron intake in determining status and can complicate estimates of dietary requirements because of a feedback mechanism that is able to trigger increased intestinal iron absorption. Third, to determine dietary requirements, it is necessary to be able to determine iron intakes that result in adequate status. Unfortunately, no good functional measures exist of iron status; paleness or tiredness are too crude and subjective and there are no enzymes whose activities correlate well with iron status; therefore, biochemical measures of iron parameters in blood are used. The advantages and constraints of these for assessing iron status in field situations are the subject of this presentation.

For any nutritional assessment, the best techniques to use depend on the purpose of the assessment. This purpose may be surveying a population to determine the extent of a problem, monitoring a program that has been implemented, measuring the status of an individual in a clinic, or conducting research. In the last two cases, the number of subjects is likely to be smaller and the financial and material resources available for the work are frequently larger, making the choice of assessment techniques broader than for population-based surveys and program monitoring.

An additional consideration when choosing a method to assess iron status is the degree of deficiency expected. For example, a successful intervention will improve iron status and will require more sensitive techniques for monitoring as it progresses. During iron depletion, storage forms of iron (ferritin and hemosiderin), which represent about one-third of total body iron, decrease first. Heme iron, which composes about two-thirds of total body iron, is the next most sensitive measure of iron depletion. The final 1 to 2 percent of total body iron, including the iron-dependent enzymes, seems fairly resistant to iron deficiency.
Methods of assessment

Iron assessment methods can be grouped into those directed toward red blood cells (RBC) and those that are not. The simplest and most common measures used in blood are hematocrit and hemoglobin. Both lack sensitivity, but both are simple and cheap to perform and thus widely used. If an automated cell counter is available, additional measurements can be made of mean RBC volume, RBC hemoglobin, or RBC size distribution width. Although these may add information under some circumstances, in general, the added sensitivity or specificity over and above that provided by hematocrit and hemoglobin measurements do not appear sufficient to justify the expense of purchasing an automated cell counter where one is not present and where budgets are limited.

The most popular non-RBC measure of iron status is serum ferritin. It has advantages in that it is the most sensitive measure of iron status, because it reflects iron stores rather than heme synthesis and is easy and relatively cheap to measure, for example, by enzyme-linked immuno-sorbent assay (ELISA), using very small amounts of serum. A low serum ferritin is diagnostic of iron deficiency. Unfortunately, a normal or high serum ferritin cannot be so unambiguously interpreted. Ferritin is a positive acute phase protein, and plasma levels increase dramatically after infection or trauma. Infection can be a serious confounder, not only in subjects who are clinically ill but also in preschool children from poor communities who suffer frequent, often subclinical, infections. This problem is illustrated by data from the Ghana Vitamin A Supplementation Trials in which there was a high prevalence of anemia, particularly among children 6 to 11 months old, who also had the highest prevalence of malaria parasitemia (Binka et al., 1994). When children were subdivided according to whether they had normal or raised serum levels of another acute phase protein, alphal-acid glycoprotein (AGP), some interesting results were observed (Filteau, unpublished). First, about twice as many children had raised levels of AGP as had normal levels, indicating that infection was extremely common in this population. Second, whereas in both groups many children had serum ferritin levels less than or equal to 10 g/l, confirming that this was an iron-deficient population, even more children in the high AGP group had a serum ferritin concentration of 50 g/l or higher, which has been used as a cutoff value to indicate iron deficiency in the presence of inflammation or infection (Kuvibidila et al., 1994a). Among Ghanaian children, a cutoff value beyond 50 g/l did not improve interpretation of the serum ferritin data because most of the children with raised AGP had serum ferritin levels in the 100–200 g/l range. Another example of the need to interpret cautiously serum ferritin data from children in poor communities comes from recent work by the Institute of Child Health, which has shown that mean serum ferritin levels of Tanzanian school children were decreased after deworming (Beasley, unpublished). This is more likely to reflect the decrease in acute phase proteins, including ferritin, in children given antihelminths rather than a worsening of iron status after deworming.

Another frequently used measure of iron status is transferrin saturation; however, this exhibits the same problem as serum ferritin in that it is affected by infection. It also has the added disadvantages of being somewhat more difficult to measure because two measures, serum iron and total iron-binding capacity, are needed and it is influenced by the high intra-individual variation in serum iron levels (Beaton, Corey, and Steele, 1989).

A third measure is erythrocyte protoporphyrin (EP) level, which rises when iron deficiency prevents iron being added to protoporphyrin during heme synthesis. EP is more sensitive to iron deficiency than are measurements of heme (anemia), because small changes are seen against a low background.
protoporphyrin level rather than against the high levels of heme present in RBC (Beaton, Corey, and Steele, 1989). Protoporphyrin can be measured using a hematofluorometer, but this equipment may be unavailable when resources are limited. The Institute of Child Health has evaluated a solvent extraction method for protoporphyrin (Piomelli, 1977) but is unsatisfied with the technique because of fluorescence quenching by RBC, which results in poor recovery of the protoporphyrin added to samples. RBC protoporphyrin is also affected by infection (Gibson, 1990).

The most recent addition to the battery of techniques available for assessing iron status is the measurement of serum transferrin receptors (Cook, Skikne, and Baynes, 1993). This, after serum ferritin, appears to be the most sensitive measure of iron status and reflects cell receptor levels, which rise as cells sense an increased need or decreased availability of iron. The technique used is a simple ELISA assay, requiring only small amounts of serum. The greatest advantage of this method over virtually all the other measures of iron status is that serum transferrin receptor levels are not affected by infection and inflammation, as illustrated by recent work on Zairian women (Kuvibidila et al., 1994b).

**Methods of assessment to use when resources are limited**

Frequently, lack of funds, facilities, and personnel preclude the measurement of any indicators of iron status other than anemia, but it is debatable whether this is a serious constraint. In many instances, for example, in population-based surveys, assessing the prevalence and severity of anemia may suffice. This is because anemia is physiologically the most relevant measure of iron deficiency and the evidence that iron deficiency without anemia has adverse effects on functional outcomes such as cognitive functions, which are sensitive to anemia, is inconclusive (Pollitt, 1993). Second, epidemiological evidence also shows that anemia can be used as a proxy measure of iron deficiency, because iron deficiency is the major cause of anemia in most populations (Dallman, Yip, and Johnson, 1984). Finally, evidence exists that the prevalence of iron deficiency is several times higher than the prevalence of anemia (Yip, 1994); thus, if anemia affects more than about 40 percent of a population, virtually the entire population is likely to be iron deficient.

It is important, however, to pay some attention to other causes of anemia besides iron deficiency. Deficiencies of folate and vitamin B₁₂ can result in anemia, and vitamin A deficiency inhibits bone marrow uptake of iron and thus heme syntheses (Sijtsma et al., 1993). Various components of the diet can enhance (e.g., ascorbic acid) or inhibit (e.g., phytates) iron absorption. Nondietary causes of anemia include infections such as helminths or malaria, which influence iron metabolism. Other causes of anemia, for example, chronic diseases, are less relevant to pediatric populations. Finally, it must be remembered that hemoglobin levels are influenced by race (Johnson-Spear and Yip, 1994) and altitude.

Several techniques exist for assessing anemia; the choice depends on available funds and either the availability of equipment on site or a reliable system for transporting samples to a nearby laboratory. Hematocrit measurements only require a centrifuge; given that inexpensive robust models are available, this is often a good method to use. The gold standard for hemoglobin measurements is the cyanmethemoglobin assay, but this method is difficult under field conditions and requires a trained technician. The problem of doing measurements in the field may be overcome by drying samples of blood spots on filter papers. There can be problems with the quality of filter paper and the blood spot samples, which often result in them having lower hemoglobin readings than fresh blood samples. The
advent of the portable photocell HemoCue has greatly facilitated hemoglobin measurements under field conditions. The instrument is accurate and robust and can be used by workers without laboratory training. An additional advantage is that results are available immediately. The main limitation is the relatively high cost of the disposable cuvettes.

Use of anemia prevalence to monitor programs

Most programs are implemented in areas where anemia prevalence is moderately high, so the need for sensitive assessment tools is not a priority at the outset and reductions in prevalence or severity of anemia would be good indicators of success. In situations in which there is no change in the prevalence or severity of anemia, other measures of iron status, for example, serum ferritin or serum transferrin receptors, may be needed to determine whether iron deficiency is an important cause of anemia and whether more sensitive measures of status are being affected. It may also be important to consider measuring other potential dietary contributors to anemia, such as folate deficiency. Specific indicators of infections, for example, malaria parasitemia, or general ones, such as acute phase protein levels, could be used to determine to what extent anemia is secondary to infection. Finally, program indicators, such as compliance, availability of iron supplements, or delivery of these to the target group, and effectiveness of nutrition education interventions need to be considered.

References


**Discussion**

*Dr. Fleming* commented that he had no experience with serum transferrin receptors and wanted to know their specificity as an indicator of iron deficiency, because serum levels depend on the number of receptors per normoblast, which are raised in iron deficiency and erythrocyte hyperplasia, for example, in megaloblastic anemia. This form of hyperplasia may be what is being seen in Ghanaian children who have recurrent malaria and who are also raised with sickle cell anemia. *Dr. Fleming* also reported that he did not find serum ferritin a useful indicator. For example, extremely high serum ferritin levels of 900 g/l, were observed in Cameroon when there was absolutely no iron in the bone marrow. In South Africa, serum ferritin was related to anemia among elite Johannesburg preschool children but had no relation to anemia in Soweto. *Dr. Fleming* also questioned the assumption that iron deficiency is the most common cause of anemia. For example, in malaria-endemic areas, anemia is most common among primigravidae pregnant women and declines with parity, whereas iron deficiency increases with parity.

*Dr. Filteau* responded by saying that it is important to look at anemia in the context of the “setting,” which makes it particularly interesting that Soweto and Johannesburg, which are relatively close, should differ so dramatically. She added that iron deficiency is the most common cause of anemia globally but not necessarily in specific populations.

*Dr. Svanberg* questioned the rationale for ruling out erythrocyte protoporphyrin as a measure of iron deficiency because of problems in its estimation and asked what the experience had been in using portable machines, which he considered appropriate. *Dr. Filteau* replied that she had no personal experience with portable machines, but people at the Centers for Disease Control (CDC) in Atlanta indicated that the results obtained do not justify the expense incurred.

*Dr. Fairweather-Tait* noted that when serum ferritin was first proposed as a good measure of iron status, everybody did the assays even though no international standards were available; thus, the data were not comparable between different centers. The same situation is now happening with serum transferrin receptors; there are no international standards. A group in Sweden looked at serum transferrin receptor levels in adolescents and showed they were not at all predictive of iron status, which they presumed to be related to this age group being in a period of rapid growth, as with young children. *Dr. Fairweather-Tait* suggested that there has been a ballooning in serum transferrin receptor research, which some hematologists claim to be the answer; but many people are beginning to wonder whether transferrin receptors do indeed reflect iron status.
Dr. Filteau pointed out that aside from determining bone marrow iron, which is not possible, no gold standard exists for determining iron status; thus, one inadequate measure, which is probably showing a different stage of iron deficiency or a different level of depletion, is being compared with another. It is not surprising that the different indicators do not correlate very well.

Dr. Stoltzfus made three comments based on work in Zanzibar using different indicators. First, the semiportable hematofluorometer used to measure erythrocyte protoporphyrin was found to be rugged enough to put in a Land Rover day after day and bounced around back and forth to schools. It also has the tremendous advantage of giving immediate data, which is not a trivial matter in large field surveys. Second, serum ferritin, serum transferrin receptors, and other iron status indicators require good management of blood samples, including a good storage and transport system, a good laboratory, and a way to link those data to the original data. A hematofluorometer gives an immediate digital number that can be written on the form and automatically entered into the computer. Third, the machine costs about US$5,000 but with very few recurrent costs. In the Zanzibar study, the hematofluorometer ended up being cheaper than the HemoCue used to measure hemoglobin because, even though the HemoCue machine costs less, the recurrent costs of the cuvettes are high. She added that Dr. Savioli did have to repair a part once in the hematofluorometer, so it would not be accurate to represent it as flawless.

Dr. Brabin noted that it is important to clarify that serum transferrin receptors are in fact cell surface components in serum that have lost their membrane sections. This may be important to know, for instance, when antibody levels are high or low because antibodies may mobilize serum transferrin receptors, thereby affecting transferrin receptor concentration. How the human immune response affects serum transferrin receptor levels in serum is unknown; this has not been examined in malaria-endemic areas.

Dr. Tomkins asked for comments on the sensitivity and specificity of erythrocyte protoporphyrin measurements, because data on British children show a very poor correlation between erythrocyte protoporphyrin and other indices. Dr. Stoltzfus responded by saying hemoglobin, erythrocyte protoporphyrin, and serum ferritin were the three indicators used to define iron status in the baseline survey in Zanzibar, which is a malaria-endemic area. The results showed a strong relationship in the expected direction between serum ferritin and erythrocyte protoporphyrin, and serum ferritin and hemoglobin across different levels of malaria parasitemia in Zanzibari school children. These results might be somewhat less skewed than the high value seen in preschool children and may reflect different immunological responses.

Dr. Menéndez commented that it is expensive to determine red blood cell indicators using a coulter counter; however, blood slides can be made for morphological examination on iron deficiency in the field and require only a trained laboratory technician.

Dr. Trumbo mentioned that a relatively new method exists for determining iron status that only looks at the ferritin bound to iron as opposed to total ferritin. This method seems to be fairly sensitive to total iron body stores and is not affected by infections and so on. The method requires an additional step to that currently used for serum ferritin.
Dr. Jalal asked how anemia can be monitored in populations, such as Indonesia, where the prevalence of thalassemia is high. Dr. Filteau replied that in such situations it is important to use indicators that will pick this out. The red blood cell distribution width is probably the easiest way to do this; however, in many areas of the world, thalassemia is not a major concern. Dr. Fleming noted that red blood cell width has no value for measuring iron deficiency but is truly valuable in measuring the response to iron deficiency.

Dr. Fairweather-Tait made a comment on the U.K. dietary reference values, which the committee determined using basal losses and requirements for growth, interpolated according to age and body weight. Dr. Fairweather-Tait also suggested that the conventional Hb cutoff points need to be reconsidered in terms of the population being studied, because they may vary among population groups. For this reason, some other index of iron status is needed to back up Hb levels in an adult population. Dr. Filteau noted that there are confounding factors such as race and altitude.

Dr. Liang pointed out that in pediatric intervention studies, measures other than Hb should be explored with respect to a child’s functional development. Dr. Filteau noted that Dr. MacGregor and her colleagues in Jamaica have looked at cognitive function and school performance in school children who were dewormed and given iron supplements. They did find improvement in cognitive function measures, but these were unrelated to improvement in Hb levels.

Dr. Tomkins concluded the discussion by pointing out the danger of saying that unless iron status can be actually measured, programs cannot go forward. Obviously, programs will go forward because there are many things that are being done in the way of interventions that do change iron status as measured by a number of indicators.
The body's capacity to excrete iron is extremely limited (McCance and Widdowson, 1937), therefore, the absorptive process plays a key role in maintaining iron homeostasis. In general, only a small proportion of dietary iron is absorbed and the amount absorbed varies both between and within individuals (Kuhn et al., 1968). Iron absorption is greatly influenced by a number of dietary and host-related factors.

Measurements of iron intake are of limited value in assessing the nutritional value of a diet without some indication of iron bioavailability, which is defined as the proportion of the total dietary intake that is utilized for normal body function (U.K. Department of Health and Social Services, 1991). Eighty to 100 percent of absorbed iron is incorporated into red blood cells, the amount depending on the iron status and erythropoietic activity of the individual.

Assessment of iron availability

Various techniques have been developed to predict the availability of iron for absorption (Fairweather-Tait, 1992a) and are shown in table 2.1. These can be broadly subdivided into in vitro and in vivo techniques, the most useful of which are discussed below. The method adopted for any study must be chosen after taking into account the resources available (financial, skill base, and equipment), question(s) to be answered (e.g., iron bioavailability from specific foods, whole diets, or effects of processing techniques), and ethical considerations (e.g., use of radioisotopes in subject group(s) under investigation).

A very important aspect of iron bioavailability studies, which should be considered is the extent to which a single meal approach (i.e., the measurement of iron absorption from a labeled single meal in a previously fasted subject) represents absorption from the diet as a whole. Cook, Dassenko, and Lynch (1991) found that when subjects consumed their normal diets, there was good agreement between dietary absorption (6.4 percent) and representative single meals fed in the laboratory (6.1 percent). When the diet was modified to promote iron absorption maximally, dietary absorption increased only slightly (8.0 percent) and remained significantly lower than it was from single meals (13.5 percent). With an iron inhibitory diet, the decrease in absorption from single meals was similarly exaggerated. These results indicate the presence of short-term compensatory adaptive mechanisms, whereby bioavailability data obtained from single test meals may perhaps be an overestimate or underestimate for the same meals when taken in the context of the whole diet.
### Table 2.1: Techniques used to study iron bioavailability

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</table>

**In vitro methods**

Simple in vitro screening methods have been used to predict the proportion of iron that is available for absorption, including ionizable iron (Narasinga Rao and Prabhavathi, 1978) or dialyzable iron, using equilibrium dialysis (Miller et al., 1981) or continuous flow dialysis (Minihane, Fox, and Fairweather-Tait, 1993). These methods avoid the need to understand and control all the physiological factors that affect the efficiency with which iron is absorbed and, in theory, should provide a consistent and reproducible means of assessing the effect of dietary variables on absorbable iron. Clearly, it is not possible to simulate the physiological factors that account for major variations in the absorption of iron; thus, the objective of an in vitro method is to rank individual foods in order of available iron content and to predict the relative effects of enhancers and inhibitors on iron absorption. In vitro methods are less expensive and generally require fewer resources than in vivo techniques, thus, they are worthy of further development; however, caution must be applied in the interpretation of results from such studies (Miller and Berner, 1989; Valdez et al., 1992).

**In vivo isotopic iron incorporation into hemoglobin**

Hemoglobin incorporation is probably the only true method of determining bioavailability of any trace element/mineral because it is a direct measure of actual utilization, in this case, of iron. Iron repletion studies are useful when considering the value of iron sources in treating iron deficiency anemia, but they are lengthy and require strict dietary control. Furthermore, they are not necessarily appropriate for studying iron-replete individuals, whose efficiency of absorption is much lower than that in iron-deficient subjects. The method of choice is to use radio isotopes ($^{55}$Fe and $^{59}$Fe) to label extrinsically the iron in foods or meals and to determine the percentage of the dose that is incorporated into hemoglobin 14 days post-dosing, as described by Bothwell et al. (1979).

Because of the marked effect of the size of body iron stores on iron absorption, a method that corrects for individual absorption values using a common reference point is needed. The most widely applied technique is to use one isotope to label the food iron and a different one to label a reference dose (3 mg of iron as ferrous ascorbate). Absorption, or hemoglobin incorporation of both isotopes, is measured and food absorption corrected to a mean reference value of 40 percent in each subject by multiplying by
Bioavailability of Iron

40/R, where R is the reference dose absorption. The value of 40 percent is taken to represent the amount of iron that is absorbed by someone with virtually zero iron stores but with "normal" hemoglobin concentration (Magnusson et al., 1981).

An alternative approach suggested by Cook, Dassenko, and Lynch (1991) is based on the inverse relationship between serum ferritin concentrations and iron absorption (Cook et al., 1974; Walters et al., 1975; Magnusson et al., 1981). Dietary iron absorption is corrected to a value corresponding to a serum ferritin of 40 μg/l (the overall mean of all the volunteers in the study) from the equation Log A_c = Log A_o + Log F_o - Log 40, where A_c is corrected dietary absorption, A_o is observed absorption, and F_o is observed serum ferritin. Iron absorption can be predicted in groups of subjects with different levels of body stores (i.e., different serum ferritin values) but, if this technique is to be employed, the determination of serum ferritin must be carried out very carefully and preferably more than once during the course of a study.

When measuring isotopic incorporation into hemoglobin to determine iron absorption, an assumption has to be made about the percent of absorbed iron that is incorporated into the red blood cells. This is usually taken to be 80 percent (Bothwell et al., 1979), but it is possible to measure it accurately by directly injecting a known (small) dose of radio-labeled iron into the blood at the same time as giving the oral dose of iron labeled with a different isotope (Brise and Hallberg, 1962).

In iron absorption studies, a multiple dose design is preferred because it overcomes, to some extent, the problem of intrasubject variability (Khun et al., 1968).

Where there are ethical constraints regarding the use of radio isotopes, alternative methods have been developed using stable isotopes (Janghorbani, Ting, and Fomon, 1986). These are more appropriate for work on infants (Fairweather-Tait and Minski, 1986; Fomon et al., 1989), in which case the doses needed to achieve a measurable enrichment in the blood are much lower than in adults (Barrett et al., 1992); however, a very important consideration when employing stable isotopes of iron for bioavailability studies is the validity of extrinsic labels and the effects of adding nonnegligible quantities of iron to produce labeled foods/meals (as discussed by Sandstrom et al., 1993).

**Whole body counting/fecal monitoring**

Other in vivo techniques involve the measurement of iron absorption and/or retention in the body. The method of choice is to administer a meal labeled with the radio isotope ^{59}Fe and then measure body retention by means of whole body counting. Where there is no access to a suitable counter, isotopic retention can be determined from fecal monitoring and, unlike whole body counting, this approach is also suitable for use with other radio and stable isotopes of iron. As with the hemoglobin incorporation techniques, the use of stable isotopes to label native (endogenous) food iron requires critical evaluation.

**Plasma appearance**

Plasma appearance of an orally administered or stable radio isotope can be used to quantify iron absorption (Whittaker, Lind, and Williams, 1991). An intravenous dose of a different iron isotope is given at the same time as the oral dose, and the area under the curve (AUC) of the plasma enrichment of
both isotopes is measured by the trapezoidal rule for at least six hours post-administration. For practical reasons, blood sampling is usually discontinued before isotopic enrichment has returned to baseline values; therefore, an extrapolation area is calculated from the enrichment of the last sample time and an estimate of the elimination rate content. The smaller the contribution of the extrapolation area to the total area, the more accurate the estimation of total area. Absorption from the oral dose is calculated as follows: percent absorption = AUC (oral)/AUC (i.v.) x dose (i.v.)/dose (oral) x 100.

Dietary factors affecting iron bioavailability

Four characteristics of food influence iron bioavailability. These include the physicochemical form of the food, other dietary constituents, the way in which the food is processed, and the quantity of iron in the food. Each of these as well as examples of diets in which the bioavailability of iron is low, medium, or high is discussed below.

Physicochemical form

Iron in foods exists in two main forms: heme iron found in meat as part of hemoglobin and myoglobin, and nonheme iron naturally present in cereals, vegetables, and other foods. Iron compounds can be added deliberately to fortify staple foods or processed food products or adventitiously via contamination from metal objects or soil. Iron supplements are another source of dietary iron but, as with iron fortificants, the efficiency with which the iron is absorbed depends to a great extent on the physicochemical form of the iron. The homeostatic control of iron absorption mediated via the intestinal mucosal cells is of special importance when considering the efficiency of absorption of high intakes of iron, such as from supplements or fortified foods.

Heme and nonheme iron are absorbed by different pathways with different degrees of efficiency depending on the chemical form, other dietary constituents, and level of iron stores in the individual (Hallberg, 1981). It is generally agreed that between 20 and 30 percent of heme iron is absorbed and that this is a constant figure, being relatively unaffected by other dietary or physiological variables such as body iron stores (FAO, 1988). On the other hand, a large number of dietary variables that enhance (see table 2.2) or inhibit (see table 2.3) nonheme iron absorption have been identified (see reviews by Hallberg [1981] and Fairweather-Tait [1992b]). The various mechanisms whereby different dietary substances affect iron absorption include chemical reactions in the digesta, such as chelation and changes in iron valency, effects on intestinal or mucosal function, and competition with other minerals for transport protein.

Other dietary constituents

1. Ligands, such as citric and ascorbic acid, fructose, amino acids, and peptides form soluble complexes with iron, thus preventing precipitation and polymerization and thereby promoting absorption. Claims have also been made that amino acid-bound iron is actively taken up into the mucosal cell.
### Table 2.2: Dietary constituents that enhance the absorption of nonheme iron

<table>
<thead>
<tr>
<th>Enhancing Food</th>
<th>Degree of Effect</th>
<th>Active substance(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guava and pawpaw</td>
<td>+++</td>
<td>Ascorbic and citric acids</td>
<td>Ballot et al. (1987)</td>
</tr>
<tr>
<td>Beef, lamb, pork, liver, chicken, and fish</td>
<td>+++</td>
<td>Cysteine-containing peptides</td>
<td>Cook and Monsen (1976); Taylor et al. (1986)</td>
</tr>
<tr>
<td>Orange, pear, apple, and pineapple juices</td>
<td>+++/+</td>
<td>Ascorbic and citric acids</td>
<td>Rossander, Hallberg, and Björn-Rasmussen (1979); Hallberg, Brune, and Rossander (1986); Ballot et al. (1987)</td>
</tr>
<tr>
<td>Cauliflower</td>
<td>++</td>
<td>Ascorbic acid</td>
<td>Hallberg, Brune, and Rossander (1986)</td>
</tr>
<tr>
<td>Beer</td>
<td>++</td>
<td>Ethanol, lactic acid</td>
<td>Derman et al. (1980)</td>
</tr>
<tr>
<td>Sauerkraut</td>
<td>++</td>
<td>Lactic acid</td>
<td>Gillooly et al. (1983)</td>
</tr>
<tr>
<td>Plums, rhubarb, banana, mango, pear, and cantaloupe</td>
<td>+++/+</td>
<td>Ascorbic and citric acids</td>
<td>Ballot et al. (1987)</td>
</tr>
<tr>
<td>Carrots, potato, beet root, pumpkin, broccoli, cauliflower, tomato, cabbage, and turnip</td>
<td>+++/+</td>
<td>Citric, malic, and tartaric acids</td>
<td>Gillooly et al. (1983)</td>
</tr>
<tr>
<td>Salad (lettuce, tomatoes, green pepper, and cucumber)</td>
<td>+</td>
<td>Ascorbic acid</td>
<td>Hallberg, Brune, and Rossander (1986)</td>
</tr>
<tr>
<td>Red wine</td>
<td>+</td>
<td>Ethanol</td>
<td>Hallberg and Rossander (1982)</td>
</tr>
<tr>
<td>Rice miso</td>
<td>+</td>
<td></td>
<td>Macfarlane et al. (1990)</td>
</tr>
<tr>
<td>Soy sauce</td>
<td>+</td>
<td>Fermentation products</td>
<td>Baynes et al. (1990)</td>
</tr>
<tr>
<td>Cysteine</td>
<td>+</td>
<td></td>
<td>Martinez-Torres, Ramano, and Layrisse (1981)</td>
</tr>
<tr>
<td>Glutathione</td>
<td>+</td>
<td></td>
<td>Layrisse et al. (1984)</td>
</tr>
</tbody>
</table>

1. The number of plus (+) signs indicates the incremental degree of enhancing effect
### Table 2.3: Dietary constituents that inhibit the absorption of nonheme iron

<table>
<thead>
<tr>
<th>Inhibitory food</th>
<th>Degree of effect</th>
<th>Active substance(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat bran</td>
<td>---</td>
<td>Phytate</td>
<td>Björn-Rasmussen (1974)</td>
</tr>
<tr>
<td>Tea</td>
<td>---</td>
<td>Polyphenols</td>
<td>Disler et al. (1975); Hallberg and Rossander (1982)</td>
</tr>
<tr>
<td>Nuts</td>
<td>---</td>
<td>Phytate and polyphenols</td>
<td>Macfarlane et al. (1988)</td>
</tr>
<tr>
<td>Legumes</td>
<td>---</td>
<td>Phytate and polyphenols</td>
<td>Lynch et al. (1984)</td>
</tr>
<tr>
<td>Soy protein</td>
<td>---</td>
<td>Phytate</td>
<td>Cook, Morck, and Lynch (1981); Lynch et al. (1985)</td>
</tr>
<tr>
<td>Oats</td>
<td>---</td>
<td>Phytate</td>
<td>Rossander-Hulthen, Gleerup, and Hallberg (1990)</td>
</tr>
<tr>
<td>Oregano</td>
<td>---</td>
<td>Polyphenols</td>
<td>Brune, Rossander, and Hallberg (1989)</td>
</tr>
<tr>
<td>Leafy vegetable</td>
<td>---</td>
<td>Polyphenols</td>
<td>Tuntawiroon et al. (1991)</td>
</tr>
<tr>
<td>(Leucaema glauca)</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coffee</td>
<td>---/---</td>
<td>Polyphenols</td>
<td>Hallberg and Rossander (1982); Morck, Lynch, and Cook (1983)</td>
</tr>
<tr>
<td>Maize (tortilla, corn meal, and bran)</td>
<td>---/---</td>
<td>Phytate</td>
<td>Acosta et al. (1984); Hurrell et al. (1988); Siegenberg et al. (1991)</td>
</tr>
<tr>
<td>Milk chocolate</td>
<td>---</td>
<td>Phytate, calcium, and polyphenols</td>
<td>Rossander, Hallberg, and Björn-Rasmussen (1979)</td>
</tr>
<tr>
<td>Milk and cheese</td>
<td>---</td>
<td>Calcium plus phosphate</td>
<td>Deehr et al. (1990); Gleerup et al. (1995); Monsen and Cook (1976)</td>
</tr>
<tr>
<td>Rice</td>
<td>---/---</td>
<td>Phytate</td>
<td>Tuntawiroon et al. (1990)</td>
</tr>
<tr>
<td>Eggs</td>
<td>---</td>
<td>Phosphoprotein and albumin</td>
<td>Rossander, Hallberg, and Björn-Rasmussen (1979); Monsen and Cook (1979); Hurrell et al. (1988)</td>
</tr>
<tr>
<td>Spinach</td>
<td>---</td>
<td>Polyphenols and oxalic acid</td>
<td>Brune, Rossander, and Hallberg (1989)</td>
</tr>
<tr>
<td>Oxalic acid</td>
<td>---</td>
<td></td>
<td>Gillooly et al. (1983)</td>
</tr>
<tr>
<td>EDTA</td>
<td>---</td>
<td></td>
<td>Monsen and Cook (1976)</td>
</tr>
</tbody>
</table>

---

2. The number of minus (−) signs indicates the incremental degree of inhibiting effect.
2. Other chelating compounds, including polyphenols containing galloyl groups, phosphates, carbonates, and oxalates have an adverse effect on iron bioavailability. Their inhibitory effect is usually due to the formation of large insoluble polymers.

3. Ligands, such as citric and ascorbic acid, fructose, amino acids, and peptides form soluble complexes with iron, thus preventing precipitation and polymerization and thereby promoting absorption. Claims have also been made that amino acid-bound iron is actively taken up into the mucosal cell.

4. Ligands, such as citric and ascorbic acid, fructose, amino acids, and peptides form soluble complexes with iron, thus preventing precipitation and polymerization and thereby promoting absorption. Claims have also been made that amino acid-bound iron is actively taken up into the mucosal cell.

5. Ligands, such as citric and ascorbic acid, fructose, amino acids, and peptides form soluble complexes with iron, thus preventing precipitation and polymerization and thereby promoting absorption. Claims have also been made that amino acid-bound iron is actively taken up into the mucosal cell.

6. Other chelating compounds, including polyphenols containing galloyl groups, phosphates, carbonates, and oxalates have an adverse effect on iron bioavailability. Their inhibitory effect is usually due to the formation of large insoluble polymers.

7. Meat, fish, and poultry have a promoting effect on nonheme iron absorption. The mechanism is not yet known, but these substances probably counteract luminal absorption inhibition through the formation of iron complexes with amino acids such as cysteine or peptides.

8. Reducing agents such as ascorbic acid will change the valency of iron from Fe$^{3+}$ to Fe$^{2+}$, which increases its absorption because Fe$^{2+}$ is more soluble than Fe$^{3+}$ at pH values greater than 3, as found in the duodenum and small intestine.

9. Associated anions affect iron absorption, for example, ferric chloride is more soluble than ferric phosphate (an important constituent of vegetables), even at low pH.

10. Competition among similar cations for uptake into the intestinal mucosal cells has been described between copper, zinc, manganese, and cobalt. The mechanism(s) for these interactions have not yet been established.

11. Dietary constituents that alter gut secretions and transit time may affect iron bioavailability. For example, alcohol and meat promote gastric acid production; the lower the pH of the stomach contents, the more the iron in the stomach will be solubilized from the food.

12. Calcium inhibits iron absorption from meals (Hallberg et al., 1992).
Effect of processing on iron bioavailability

A number of studies have shown changes in iron bioavailability as a result of various forms of food processing. These can be attributed to changes in the chemistry of iron (valency, solubility, and type of chelation) and/or the nature of food constituents that modify iron absorption (e.g., proteins and phytates).

Food processing encompasses a wide range of treatments, including heating, cooling, freezing, curing, pickling, dehydration, homogenization, fermentation, and various forms of cooking. The effect of heat processing on the bioavailability of native and added (fortification) iron is reviewed in detail by Lee (1982). In some cases, heating has an inhibitory effect and in others it increases the bioavailability of iron; the observed effect depends on the food matrix and the physicochemical form of any added iron. With added iron, wet-heat processing usually appears to increase iron bioavailability, whereas dry-heat processing has little effect. The addition of ascorbic acid to an aqueous food before heating enhances iron bioavailability.

Iron bioavailability is increased with processes that add organic acids to food, for example, in the preparation of sauerkraut (see table 2.2). Any increase in ascorbic acid, as occurs when beans are allowed to germinate, may well improve iron bioavailability. In general, fermentation (e.g., leavening bread with yeast) or gentle heat treatment of foods has a beneficial effect on the bioavailability of iron from high phytate foods, because it causes hydrolysis of the myo-inositol hexaphosphate (phytate) to lower inositol phosphates that do not reduce iron absorption; however, more severe heating may have the opposite effect. Oats are often subjected to autoclaving or steam treatment to destroy their relatively high content of lipase enzyme, which causes rancidity of lipids on storage, but this also inactivates endogenous phytase. Consequently, processed oat products have a relatively high phytate content that inhibits iron absorption (Rossander-Hulthen, Gleerup, and Hallberg, 1990).

There has been a major expansion in the quantity and type of processed foods available in developed countries, which has necessitated the use of semipurified proteins to formulate new products. Animal proteins enhance iron absorption irrespective of the source (Cook and Monsen, 1976). The mechanism is unclear, but it is possible that the cysteine-containing peptides produced during digestion facilitate iron absorption. Protein may also act on food constituents that influence iron absorption. For example, polyphenols and phytate form stable complexes with protein, which could render them less reactive with iron and, hence, blunt their inhibitory effect on iron absorption. On the other hand, soy products (Cook, Morck, and Lynch, 1981) and semipurified protein fractions (casein, whey, wheat gluten, soy protein isolate) all have a pronounced inhibitory effect on iron absorption, but when they are hydrolyzed before consumption, the inhibitory effect is reduced, probably in relation to the extent of hydrolysis and perhaps the enzyme used (Lynch et al., 1989); however, milk has been reported to have no effect on iron absorption from a cereal-based diet (Turnlund et al., 1990) and calcium supplements do not appear to affect iron nutrition adversely in the long term (Sokoll and Dawson-Hughes, 1992).
Iron dose

Not only does the physicochemical form of the iron affect its bioavailability, but the quantity of iron also has an effect. There is a negative relationship between the iron dose and percent absorbed but, provided the iron is in an assimilable form, there is a progressive rise in the actual amount absorbed because there is no defined upper limit to iron absorption. Acute iron poisoning is not uncommon, but it is usually only seen in infants or children whose mucosal regulation mechanism is not fully developed. Chronic iron overload may be produced by several mechanisms, including high oral intake over a prolonged period. The classic example of this is the iron overload, which resulted in “bronze diabetes,” observed in South Africa some years ago in people consuming large quantities of local beer that was brewed in iron pots. There are other documented cases of iron overload in subjects taking medical iron over many years, but it is not known whether or not the subjects also carried the gene for hemochromatosis.

Examples of diets containing iron of low, medium, and high bioavailability

Typical diets can be separated into three broad categories of “low,” “intermediate,” and “high” bioavailability, with mean absorption from the mixture of heme and nonheme iron of approximately 5, 10, and 15 percent respectively by individuals with very low iron stores but normal hemoglobin concentrations (FAO, 1988).

A low bioavailability diet (5 percent of iron absorbed) is a simple, monotonous diet containing cereals and root vegetables with negligible quantities of meat, fish, or ascorbic acid-rich foods. This diet contains a preponderance of foods that inhibit iron absorption (maize, beans, and whole wheat flour) and is common in many developing countries, particularly among lower socioeconomic groups.

An intermediate bioavailability diet (10 percent of iron absorbed) consists mainly of cereals and root vegetables, but contains some ascorbic acid-rich foods and meat. A high bioavailability diet can be reduced to this intermediate level by regular consumption of inhibitors of iron absorption, such as tea, coffee, cereal fiber, beans, and high calcium foods with main meals.

A high bioavailability diet (15 percent of iron absorbed) is a diversified diet containing generous quantities of meat, poultry, fish, and/or foods containing high amounts of ascorbic acid. This is the type of diet generally consumed by people in developed countries.
Physiological factors affecting absorption

The size of body iron stores, physiological state of the individual, and other physiological factors all affect absorption.

**Body iron content**

The amount of iron absorbed is markedly influenced by the size of body iron stores (see table 2.4). The efficiency of absorption is affected by the following:

- The level of iron to which the intestinal mucosal cells have been previously exposed (short-term control) (Fairweather-Tait, 1986; O’Neil-Cutting and Crosby, 1987).
- Body iron stores, as measured by serum ferritin concentrations (long-term control) (Cook et al., 1974).
- The rate of erythropoiesis (Bothwell et al., 1979).

**Table 2.4: Host-related factors that affect nonheme iron absorption**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect on absorption</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of body iron stores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Low</td>
<td>Marked effect (inverse relationship)</td>
<td>Baynes et al. (1987)</td>
</tr>
<tr>
<td>(b) Normal, high</td>
<td>Minor effect (inverse relationship)</td>
<td></td>
</tr>
<tr>
<td>Rate of erythropoiesis</td>
<td>Positively correlated</td>
<td>Skikne and Cook (1992)</td>
</tr>
<tr>
<td>Physiological state</td>
<td>Increased absorption in pregnancy</td>
<td>Whittaker, Lind, and Williams (1991)</td>
</tr>
<tr>
<td>Iron content of mucosal cells</td>
<td>Exposure to iron reduces subsequent absorption</td>
<td>Fairweather-Tait and Minski (1986); O’Neil-Cutting and Crosby (1987)</td>
</tr>
<tr>
<td>High altitude and hypoxia</td>
<td>Increased absorption</td>
<td>Skikne and Baynes (1994)</td>
</tr>
<tr>
<td>Secretion of gastric juice</td>
<td>Positively correlated</td>
<td>Bezwoda et al. (1978)</td>
</tr>
<tr>
<td>GI secretions (bile, pancreatic</td>
<td>Increased absorption in presence of amino acids, peptides,</td>
<td>Bothwell et al. (1979)</td>
</tr>
<tr>
<td>secretsions, and mucus)</td>
<td>ascorbic acid, and mucoprotein</td>
<td></td>
</tr>
</tbody>
</table>

**Physiological state**

The absorption of iron is known to increase in conditions in which tissue iron is reduced, including anabolic states, such as periods of growth and in pregnancy. During the latter half of pregnancy, the efficiency of iron absorption is increased from both the diet (Apte and Iyengar, 1970) and inorganic iron (Whittaker, Lind, and Williams, 1991). Reports concerning the size of the increase vary, depending on
the test conditions (including quantity and form of iron administered, iron status of the individual, method of measuring absorption, and stage of pregnancy). Recently, Whittaker, Lind, and Williams (1991) used stable, isotopically labeled iron to measure iron absorption in pregnant women from 5 mg iron as ferrous sulphate. They observed increases between 12, 24, and 36 weeks gestation from a mean of 7.6 percent to 21.1 percent and 37.4 percent respectively. Absorption was still elevated (26.3 percent) 12 weeks post-delivery.

**Other physiological factors**

A number of other physiological factors affect iron absorption and utilization (see table 2.4), including the following:

- **Gastric juice.** Hydrochloric acid plays a key role in the release of iron from food during peptic digestion. Achlorhydria results in a reduced absorption of nonheme iron, although heme iron is unaffected. Gastric acid output is affected by dietary constituents as well as factors unrelated to diet such as genetic predisposition and stress.

- **Stomach emptying.** The longer the food stays in the acidic environment of the stomach, the greater the proportion of iron that is solubilized from it. Patients who have undergone partial gastrectomy have impaired iron absorption; this may be due to the partial loss of the reservoir function of the stomach and consequent accelerated progress of the food bolus through the upper gastrointestinal tract. As yet, no evidence exists that small intestinal transit time has any effect on the efficiency of iron absorption (Fairweather-Tait and Wright, 1991).

- **Pancreatic secretions.** Pancreatin per se has no effect on iron absorption, but bicarbonate will promote the formation of unavailable iron hydroxide polymers; however, the overall effect of pancreatic juice may be to enhance iron absorption by releasing amino acids and polypeptides from foods, which can then act as absorption-promoting ligands.

- **Biliary and other intestinal secretions.** Animal studies indicate an enhancing effect of bile on iron absorption (Wheby et al., 1962). It has been suggested that this is due to the ascorbic acid in bile, but in vitro studies have demonstrated the formation of mucoprotein ligands rather than iron-ascorbic acid complexes (Jacobs and Miles, 1970). Studies in rats have shown that fasting increases the quality and iron-binding properties of the mucus layer (via a change in sialic acid content), which results in increased iron transport (Quarterman, 1987).

**Relationship between dietary and physiological factors**

Although there are very wide variations in nonheme iron absorption both between and within individuals, depending on the dietary source of iron and accompanying dietary constituents, mean figures have been agreed on for the purposes of deriving dietary reference values/recommended allowances. In diets containing generous levels of meat, poultry, fish, and/or foods containing high amounts of ascorbic acid (promoters of iron absorption), as found in the United Kingdom, mean absorption from the whole diet
Iron Interventions for Child Survival

(heme and nonheme iron) by individuals with low iron stores is taken to be 15 percent (FAO, 1988; U.K. Department of Health and Social Services, 1991). Monotonous diets consisting mainly of cereals, roots and/or tubers, and negligible quantities of foods of animal origin and/or ascorbic acid typical of many developing countries contain iron that is of low bioavailability and usually assumed to be 5 percent. Mean iron absorption in this type of diet can be improved to 10 percent by increasing the intake of foods rich in ascorbic acid and/or meat or fish and decreasing the intake of inhibitors such as phytate and tannins (FAO, 1988).

Recently, Cook, Dassenko, and Lynch (1991) examined the nutritional relevance of absorption studies that investigated dietary factors believed to modify iron absorption. Iron absorption is generally higher from meals than the diet as a whole because of the experimental conditions used (e.g., fasting of subjects). The conclusion from the study was that for mixed Western diets, nonheme iron bioavailability is less important than absorption studies with single meals would suggest. The three-way relationship between absorbability of iron (as determined by dietary factors), level of iron stores (the major physiological determinate), and iron absorption is illustrated in figure 2.1. Individual data have been plotted from a series of iron absorption studies (Morck, Lynch, and Cook, 1983; Lynch et al., 1984; Beard et al., 1988; Guindi, Lynch, and Cook, 1988), in which the absorption of iron is expressed as the ratio of iron absorbed from food to the reference iron salt (3 mg ferrous ascorbate), and iron stores are expressed as plasma ferritin concentration. Although a greater number of data points would undoubtedly have smoothed out the surface plot, it is quite clear from figure 2.1 that dietary factors are only important in subjects with low iron stores. When serum ferritin values exceed 25 mg/ml, there is no difference in absorption of iron from foods containing iron with very different absorbability.

Figure 2.1: Effect of dietary and physiological factors on iron absorption

![Figure 2.1: Effect of dietary and physiological factors on iron absorption](image-url)
Acknowledgments

Part of this paper is published in the Report of the British Nutrition Foundation Task Force on Iron.

References


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**Discussion**

*Dr. Henry* asked Dr. Fairweather-Tait to comment on whether geophagia is an important factor in iron absorption, because it seems to be quite common among preschool children in many different countries. *Dr. Fairweather-Tait* replied by saying that, as with piglets, geophagia seems to be a response to iron deficiency. Dr. Hallberg has shown that some of the iron from soil can be absorbed. *Mr. Alnwick* noted that in parts of East Africa, the practice of buying soils for deliberate consumption during pregnancy is widespread. Nobody has ever looked at this seriously or postulated whether this has a positive or negative effect on iron status. *Dr. Savioli* stated that geophagia is usually associated with a highly intense transmission of geohelminths.

*Dr. Solon* asked about the timing of eating foods that contain iron absorption inhibitors. *Dr. Fairweather-Tait* replied that the inhibitors have to be together in the gut and the inhibitory effects depends on the rate of gastric emptying. People should be advised not to drink tea for two hours after a meal and one hour before, but it will vary from person to person. The inhibitory effect of calcium has been shown when calcium is taken about an hour within the mealtime, otherwise there is no effect. A two-hour margin can be generally assumed to prevent iron-absorption inhibition.
Dr. Schultink commented on the relative importance of inhibitors and enhancers. At the population level, for example, in Holland, everybody drinks milk with their meal. In England, tea is taken in the morning and it would not be possible to convince everyone in the United Kingdom to drink coffee instead of tea. Despite the high intake of iron inhibitors in Holland and England, anemias are not very important at the population level, and it is difficult to fathom whether these inhibitors are important in populations that have sufficient iron in their diet. At the same time, it is questionable whether these inhibitors are important in an iron-deficient population. The fact that people have low iron status probably overrules the importance of inhibitors in the diet. Dr. Fairweather-Tait responded by saying that if inhibitors are present, the iron is not available for absorption: it is bound up. Even though an individual is iron deficient and requires iron, the inhibitors do have a dramatic effect. In an iron-deficient population, bioavailability is going to be the critical factor and the inhibitors are very, very important.

Dr. Gopaldas noted that the typical diet in India is highly cereal based and Indians are a tea-drinking nation. Preschool children get the same diet once they are off the breast. Most of the enhancers being discussed are not affordable for many people in India. Dr. Tomkins suggested that Indians drink less tea because one of the most striking findings from studies in India and Gaza is the close association between tea drinking and anemia.

Dr. Blum asked about the link between studies on single meals versus long-term, or regular, diets because there are differences in the findings. The question is how can the results of Dr. Hallberg and others on single meals be extrapolated to Indian diets; how does this literature relate to these practical situations because there are studies that show the contrary of what was shown 20 years ago? For example, one study shows that the enhancing effect of ascorbic acid may not be that great. Dr. Fairweather-Tait replied that, in terms of inhibitors, the work of Dr. Cook shows that if inhibitors are there, they have both short- and long-term inhibitory effects. In single-meal studies, the standard protocol is that meals are eaten after a night’s fast, which exaggerates the effect of enhancers. If there is high absorption from a meal, there will be down regulation the next time that same meal is eaten; thus, there is no discrepancy in what has been found, but the magnitude of the effects that have been shown in the past may differ in terms of whole diets, that is, it may not be as great. In a multidose study on 9-month-old babies fed an ascorbic acid (juice) drink or a placebo with a meal for six meals, iron absorption doubled.

Dr. Blum asked if data exist showing the long-term homeostatic effect of giving different types of foods and what kind of effect the enhancers or inhibitors have on iron status. Dr. Fairweather-Tait replied that these data do not exist and that the U.K. Committee on Nutrition Additives has asked for this information. Dr. Yeung offered an answer to this question. He said that there was a complaint a few years ago about the lack of bioavailability of iron in infant cereals. Since then, a study was done in Chile, where infants were fed approximately 25 g of cereal/day fortified with small particle-size iron. In a three-month study, they showed that the iron was bioavailable. In the double-iron-labeled studies, the absorption was only about 4 percent, which is not good enough for children. But in long-term studies, it is very clear that the amount of iron is sufficient for babies. This study has been repeated with normal iron-status infants and toddlers in Canada by Dr. Beaton.
Iron deficiency occurs when an insufficient amount of dietary iron is absorbed to meet body requirements. Individual iron requirements are determined by the needs for growth and iron losses. The highest prevalences of iron deficiency are found in infants, young children, adolescents, and pregnant women, reflecting the demands from growth and the concurrent expanding red blood cell volume and periods of increased physiological need. The situation is further aggravated when there are pathological losses, for example, hookworm infestation and when absorption is impaired during acute periods of illness, such as malaria. It is, therefore, possible to influence the onset of iron deficiency by reducing iron losses and/or by increasing iron absorption from the diet.

Dietary iron intake is closely related to energy intake. A cereal-based diet in developing countries may contain about 7 mg Fe/1,000 Kcal (FAO, 1980). Relative differences in iron and energy requirements between adult men and children are reflected in the variation in the percent of dietary iron that must be absorbed to meet physiological needs (see table 3.1). Adult men with high energy intakes and relatively low iron requirements are least likely to suffer from iron deficiency; a mere 5 percent absorption of ingested iron would be enough to satisfy their needs. Children ages 1 to 2 and 2 to 6 years old require slightly more iron to be absorbed (about 7 percent), while women with high physiological losses require up to 16 percent of dietary iron to be absorbed. The latter group is, therefore, at a much greater risk of iron deficiency when the availability of dietary iron is low.

It is also clear from table 3.1 that the daily intake of iron is considerably higher than requirements; however, even when a diet with meat and vitamin C–rich foods is eaten, only about 30 percent of total dietary iron will be absorbed (Cook, 1990), whereas between 1 and 8 percent of the nonheme iron from a solely vegetable-based diet will be absorbed. When physiological needs for iron are high, indicated by low iron stores, and a higher proportion of the available iron is absorbed, most dietary iron is wasted due to the body’s inability to extract the needed iron; thus, the bioavailability of dietary iron is as important, or even more important, in maintaining iron balance than the total amount of iron ingested.

The balance between the amount of iron required and absorbed is affected by three factors: changed physiological requirements, extensive iron losses, and inadequate iron in the diet. Iron deficiency anemia (IDA) will develop if an imbalance exists among these factors and more rapidly so in the absence of adequate iron stores. In addressing the problem of IDA in developing countries, the emphasis has generally been directed toward preventing excessive blood loss through parasite infestation and less so toward improving the dietary factors; however, with an increasing awareness of the wide variation in the bioavailability of iron in food, it has become apparent that it is the poor bioavailability of iron in cereal/vegetable-based diets that is the major cause of IDA in developing countries.
Table 3.1: Relationship between iron requirement and dietary iron supply

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–2 years</td>
<td>2–6 years</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Food intake (Kcal)</td>
<td>1,140</td>
<td>1,450</td>
</tr>
<tr>
<td>Iron intake (mg)</td>
<td>8.0</td>
<td>10.2</td>
</tr>
<tr>
<td>Iron requirement (mg)</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Absorption requirement (%)</td>
<td>7.5</td>
<td>6.9</td>
</tr>
</tbody>
</table>


Food-based strategies constitute the most desirable and sustainable methods for preventing and controlling IDA. These include dietary modification and food fortification. Both strategies aim to make available a continuous supply of foods that will result in an increased intake and absorption of dietary iron. To have a significant impact, the diet should provide sufficient amounts of iron and the bioavailability of the iron should be high.

In developing countries, dietary iron intake can be increased in two ways. The first is to ensure that individuals consume larger amounts of their habitual foods to meet their energy needs and includes increasing the household availability of iron-rich foods, for example, animal foods, fruits, vegetables, pulses, as well as iron-fortified foods. The amount of additional iron ingested will depend on the extent to which the energy gap is bridged. The second approach is to enhance the bioavailability of the iron ingested rather than its total amount. There are a number of ways to do this, each with its advantages and drawbacks, but all are based either on promoting the intake of iron absorption enhancers, including heme iron, or on reducing the ingestion of absorption inhibitors such as polyphenols (tannin) and phytic acid. Food-based approaches, thus, should address issues of food production, preservation, processing, marketing, and preparation.

This paper discusses different measures to improve the availability of dietary iron for absorption and the potential and expected effects of dietary modifications on iron status with special reference to preschool children. The need for further food-based research in relation to iron nutrition will also be discussed.

Types of dietary iron and absorption

Heme iron

Heme iron, derived primarily from hemoglobin and myoglobin in meat, is transferred to intestinal cells as an intact porphyrin complex. Between 20 and 25 percent of the heme iron consumed is absorbed. Absorption is little affected by other components of the meal and only slightly influenced by the

---

1. Assuming a cereal-based diet.
individual's iron status; however, only 10 percent or less of dietary iron is in the heme form, even in Western diets where meat intake is high. The diet of most individuals in developing countries contains very little or no meat at all.

**Nonheme iron**

The majority of dietary iron is in an inorganic form. This nonheme iron has a heterogeneous origin, being derived from vegetable foods, inorganic contaminant iron, meat iron that is not in the form of heme, and inorganic iron fortificants added to the diet. The iron from all these sources needs to be in a soluble form before absorption is believed to occur. A common nonheme iron pool containing this soluble iron is formed in the lumen of the upper gastrointestinal tract, and absorptive mechanisms extract iron from this pool. The amount of iron absorbed depends not only on mucosal behavior in the intestinal wall but also on the presence of ligands in the meal, which either promote or depress iron absorption from the pool. Because nonheme iron absorption occurs before food has been exposed to digestive enzymes in the intestines, it is not surprising that the ligands present in undigested or partially digested foods play a major role in absorption. Several of these enhancers and inhibitors of nonheme iron absorption have been identified and are listed in table 3.2. Their central role in modifying the proportion of nonheme iron absorbed from a meal (including any added fortification iron) is well established. Vitamin C and, to some extent, organic acids such as lactic (Derman et al., 1980b), citric, and malic acids (Gillooly et al., 1983) have a profound enhancing effect on iron absorption; these acids are found in various combinations in fruits and vegetables. Phytate, polyphenols (including tannins), calcium, and soy proteins are food components that inhibit iron absorption; these are found mainly in the bran of cereals and pulses, some vegetables and spices, tea, coffee, and milk. The actual effect, however, of these enhancing and inhibiting factors depends on the balance of these in the meal. For example, a glass of orange juice may counteract the inhibiting effect of a cup of tea. Also, drinking tea or milk, which contains calcium, with the meal inhibits iron absorption more so than if taken in between meals.

**Insoluble iron**

A variable proportion of ingested iron is in forms that are not readily solubilized in the upper gastrointestinal tract. This iron does not enter the common nonheme pool and is essentially unavailable for absorption. Such iron may be in meals as a result of contamination during food preparation from water or cooking pots and storage (dust and soil particles); it may occur naturally in certain foods, such as intact rice grains; or it may be added to the food as an insoluble iron fortificant. In many developing countries, evidence exists that a large proportion of iron intake emanates from contamination iron (Sufian and Pittwell, 1968; Charlton, Bothwell, and Seftel, 1973; Derman et al., 1980b; Hallberg et al., 1983; Hercberg et al., 1987), which can exceed that naturally found in the staple food. The bioavailability of this contamination iron is poorly documented, although Hercberg et al. (1987) and Guiro et al. (1991) have shown that a significant proportion of this iron is available for absorption. Iron III hydroxide, which belongs to the group of iron compounds most commonly found in soil, as well as river and well water, was found to be about one-half as well absorbed as the intrinsic iron in a maize meal (Derman et al., 1977). Other studies have shown that iron solubilized from cooking utensils has
about the same bioavailability as food iron (Charlton, Bothwell, and Seftel, 1973; Derman et al., 1980b; WHO, 1989).

**Table 3.2: Enhancers and inhibitors of nonheme iron absorption**

<table>
<thead>
<tr>
<th>Food Factor</th>
<th>Food Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enhancers</strong></td>
<td></td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Fruits and vegetables</td>
</tr>
<tr>
<td>Animal tissue</td>
<td>Meat, fish, and poultry</td>
</tr>
<tr>
<td><strong>Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Polyphenols</td>
<td>Tea, coffee, some vegetables (e.g., eggplant and spinach), sorghum, and lentils</td>
</tr>
<tr>
<td>Phytate</td>
<td>Cereals (e.g., wheat, maize, and rice), legumes (e.g. soybean products)</td>
</tr>
<tr>
<td>Calcium</td>
<td>Milk</td>
</tr>
<tr>
<td>Protein</td>
<td>Soybean products, milk</td>
</tr>
</tbody>
</table>

**Dietary iron content and intake**

Iron is present in many foodstuffs. Table 3.3 shows the iron content of different African foods (FAO, 1968). The iron contents of sorghum and millet are high and probably reflect a high content of contamination iron. Data on dietary iron intakes in Africa are scanty, but, as table 3.4 shows, variations in intake are wide among countries. Nevertheless, caution must be exercised in comparing published estimates, because much of the iron in some foods is probably of extrinsic origin, either from soil dust or from surfaces or containers or cooking utensils. Table 3.4 suggests that per capita iron intakes are on the order of 10 to 20 mg/day, which is consistent with an analysis of food balance sheets (FAO, 1980), showing that total per capita iron intake in developing countries varies from 14 to 21 mg/day. Staple cereals such as maize, millet, and sorghum supply, on average, over 60 percent of dietary iron while staple roots and tubers only supply about 24 percent. This most likely reflects the lower intrinsic iron content of these staples (see table 3.3) and that these staples are less likely to become contaminated with iron during processing. The latter is because cereal and pulses have a larger surface area compared with their volume than roots and tubers; thus, they contain relatively more contamination iron. Furthermore, cereals and pulses are usually prepared as gruels, which means that a lot of water (with its contaminated iron) is added. In contrast, roots and tubers are more often boiled in pieces, thus, relatively less water is taken up. Average per capita iron supply, calculated from food production data (FAO, 1990) confirm the data on iron intake. Daily per capita iron intake in Asia and South America is lower than in African countries, but intakes from animal sources are higher in certain regions (see figure 3.1).
Table 3.3: Iron content of different vegetable foods from Africa

<table>
<thead>
<tr>
<th>Food</th>
<th>Fe content (mg/100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maize</td>
<td>3.6–4.9</td>
</tr>
<tr>
<td>Sorghum</td>
<td>5.0–15.6</td>
</tr>
<tr>
<td>Millet</td>
<td>39.0</td>
</tr>
<tr>
<td>Teff</td>
<td>20.9–75.5</td>
</tr>
<tr>
<td>Rice</td>
<td>1.7–2.0</td>
</tr>
<tr>
<td>Cassava</td>
<td>1.9</td>
</tr>
<tr>
<td>Yam</td>
<td>0.8</td>
</tr>
<tr>
<td>Gari</td>
<td>1.6</td>
</tr>
<tr>
<td>Lentils</td>
<td>7.0</td>
</tr>
<tr>
<td>Chickpea</td>
<td>11.1</td>
</tr>
<tr>
<td>Cowpea</td>
<td>7.6</td>
</tr>
<tr>
<td>Soybean</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Source: FAO (1968)

Table 3.4: Dietary intake of iron

<table>
<thead>
<tr>
<th>Country</th>
<th>mg/day</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>8.8–14.5</td>
<td>Prata (1978)</td>
</tr>
<tr>
<td>Cameroon</td>
<td>10.0</td>
<td>WHO (1970)</td>
</tr>
<tr>
<td>Mali</td>
<td>27.8–31.1</td>
<td>Mondot-Bernard (1980)</td>
</tr>
<tr>
<td>Senegal</td>
<td>12.6–36.4</td>
<td>WHO (1970)</td>
</tr>
<tr>
<td>Togo</td>
<td>11.5–18.0</td>
<td>Pollitt and Leibel (1976)</td>
</tr>
<tr>
<td>Kenya</td>
<td>16.8</td>
<td>WHO (1970)</td>
</tr>
<tr>
<td>Tanzania</td>
<td>10.0–16.2</td>
<td>Maletnelma and Bavu (1974)</td>
</tr>
<tr>
<td>South Africa (local beer)</td>
<td>15.0–100.0</td>
<td>Charlton, Bothwell, and Seftel (1973)</td>
</tr>
<tr>
<td>Cameroon</td>
<td>10.0</td>
<td>WHO (1970)</td>
</tr>
<tr>
<td>Mali</td>
<td>27.8–31.1</td>
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</tr>
<tr>
<td>South Africa (local beer)</td>
<td>15.0–100.0</td>
<td>Charlton, Bothwell, and Seftel (1973)</td>
</tr>
</tbody>
</table>

The critical question is to what extent dietary levels of iron can support adequate iron nutriture. It is clear from table 3.1 that the absorption requirement for preschool children should exceed absorption from a diet categorized as being a “low bioavailability diet” (iron absorption about 5 percent). In fact, iron absorption from diets consisting almost entirely of cereals may be as low as 1 to 2 percent. This means that for many people the supply of iron probably does not reach even the minimum average requirement, which is in line with these regions having the highest prevalences of IDA; however, a diet with low iron bioavailability can be converted to a diet with “intermediate bioavailability,” that is, about 10 percent
absorption, by increasing the intake of foods that enhance iron absorption such as meat, fish, and ascorbic acid–rich foods, or by reducing the amounts of iron absorption inhibitors in the diet.

**Figure 3.1:** Dietary iron supply, haem and non-haem iron, in different regions 1989 (mg per caput and day).

![Bar chart showing dietary iron supply in different regions](chart)

*Source: FAO (1990)*

**Effects of dietary modifications on iron availability**

*Increased intake of iron absorption enhancers*

The two major enhancers of iron bioavailability are ascorbic acid and meat. The enhancing effect of ascorbic acid on nonheme iron absorption has been well documented (Sayers et al., 1973; Hallberg et al., 1986). Ascorbic acid as a reducing agent maintains the food iron in its more soluble ferrous form. It also forms a soluble iron-ascorbate chelate, which remains soluble as the pH increases in the duodenum. The effect of ascorbic acid is dose related (semi-log-dose relationship) (see figure 3.2) and is significant in all kinds of diets (Sayers et al., 1973; Derman et al., 1980a). This relationship implies that the main effect is obtained with the first 25 to 50 mg ascorbic acid in the meal and that the effect of adding more ascorbate is relatively less effective (Hallberg et al., 1986). The ascorbic acid content of a variety of different ascorbic acid–rich foods also implies that, if added in amounts of 100 g to a meal, about 25 to 50 mg ascorbic acid will be provided (FAO, 1968; Paul and Southgate, 1976). In many rural households, however, vegetables and fruits are eaten only infrequently, in small amounts, and the expected impact from promoting the frequent use of these foods may be considerable.
Dietary Interventions to Prevent Iron Deficiency in Preschool Children

Figure 3.2: Effects on increasing quantities of ascorbic acid on absorption of non-haem iron in a meal

![Graph showing effects of ascorbic acid on non-haem iron absorption]

Source: Derman et al. (1980), Sayers et al. (1973)

The enhancing effect of meat and fish on iron absorption is well documented. Meat has a twofold beneficial effect on iron nutrition. Its content of heme iron has a uniformly high bioavailability independent of the diet composition. Meat proteins also promote the uptake of nonheme iron from the diet (Cook and Monsen, 1976; Hallberg and Rossander, 1984; Layrisse et al., 1984), and it has been calculated that 1 g meat (about 20 percent protein) has an enhancing effect on nonheme iron absorption equivalent to that of 1 mg ascorbic acid (Monsen et al., 1978). A Latin American-type meal (maize, rice, and black beans) with a low iron bioavailability had the same improved bioavailability when either 75 g meat or 50 mg of ascorbic acid was added (Hallberg and Rossander, 1984). It will, however, be unrealistic to assume that meat consumption by poor rural people and especially preschool children, among whom iron deficiency is most prevalent, will increase significantly in the near future.

Reducing the amount of iron absorption inhibitors

Several methods are available to reduce the level of iron absorption inhibitors in foods. These include physical removal (extraction and dehulling) and a number of traditional household-level processing methods, such as soaking, germination/malting, and lactic acid fermentation that activate endogenous enzymes, which can degrade phytate, and to some extent polyphenols.

- Dehulling. In local settings in developing countries, abrasive dehullers that remove the outer layers of cereals (sorghum, millet, and rice) are becoming increasingly available. In tannin-rich cereals, the polyphenols are located mainly in the outer layers of the grains and the phytate in layers just below this; thus, it is possible to remove most of the polyphenols and a large proportion of the phytate by
Removing the outer layers of the grain. Gillooly et al. (1984) studied the effect of abrasive dehulling of tannin-rich (brown) sorghum and nontannin (white) sorghum grains on iron absorption in humans. By removing 55 percent of the high tannin grain through dehulling, only 4 percent and 8 percent of the initial polyphenol and phytate content respectively remained. Similarly, removing 40 percent of the nontannin grain through dehulling resulted in a grain containing 14 percent of the original phytate. Absorption studies showed that iron uptake increased from 2.4 to 6.3 percent after dehulling brown sorghum, when 10 mg of ascorbic acid was also added to the meals. A similar increase was obtained after dehulling white sorghum. The percentage of iron absorbed was still comparatively low after the dehulling process and the actual uptake of iron was not improved, because more than 50 percent of the iron content was also removed in the dehulling process. Later findings by Brune et al. (1992) also demonstrated that the phytate content needs to be even further decreased to have a more significant enhancing effect on iron absorption.

Enzymatic processes. Soaking, germination, sour dough leavening, and lactic acid fermentation may create optimal conditions for endogenous phytase in cereals. Recent absorption studies in humans have demonstrated that even low levels of phytate (about 5 percent of the amounts in cereal whole flours) have a strongly inhibitory effect on iron absorption (Hallberg et al., 1989; Brune et al., 1992). It is, therefore, important to find the optimal conditions for phytate degradation using traditional food techniques. Phytases that hydrolyze phytate into lower inositol phosphates are present in most cereals and are believed to be activated during fermentation (Svanberg and Sandberg, 1988; Svanberg, Lorri, and Sandberg, 1993) and germination (Bartnik and Szafranska, 1987). Phytate levels are reduced during yeast fermentation in rye, white, and whole wheat breads (Harland and Harland, 1980) and sour dough leavening results in an almost complete degradation of phytate (Bartnik and Ceglinska, 1981; Bartnik and Florysiak, 1988; Larsson and Sandberg, 1991).

Lactic fermentation of sorghum and maize gruels also seems to have a high potential in reducing phytate content (Svanberg and Sandberg, 1988). Figure 3.3 shows the effect of lactic acid fermentation on iron solubility, which is an index of iron bioavailability as measured by an in vitro method. The fermentation process can provide optimal pH conditions for degradation of phytate. The pH of the unfermented gruel is about 6.5 and reaches pH 3.6 after complete fermentation. A pH interval of 5.0 to 4.5, believed to be optimal for cereal phytases, is thus achieved during the fermentation process. To completely degrade the phytate, sufficient time is needed in the optimum pH range. This is obtained by initial soaking of the flour in water for about 24 hours. This modification of the traditional method, that is, the soaking, increases the amount of soluble iron up to ten-fold (Svanberg, Lorri, and Sandberg, 1993). Soaking wheat and rye flour for 2 hours under optimal pH conditions results in complete phytate hydrolysis (Sandberg and Svanberg, 1991). In a household-level study in Tanzania (Svanberg and Lorri, unpublished data), the modified fermentation technique that included soaking was tested in ten households. Table 3.5 shows that the amount of soluble iron was 0.37 mg/100 g dry matter in traditionally fermented maize gruels and was not significantly different from that in the nonfermented gruels. The amount of soluble meals from having "low iron bioavailability" into a meal having "intermediate to high iron, however, increased to 1.43 mg/100 g dry matter when a soaking step was included in the process.
Dietary Interventions to Prevent Iron Deficiency in Preschool Children

Figure 3.3: In vitro iron solubility in traditionally processed non-tannin cereals

\[ y = 40.0 \times (1 + x)^2 - 0.789 \]

\[ r^2 = 0.91 \]

\[ p < 0.001 \]

The total amount of iron in these gruels is significantly higher than the amount of intrinsic iron from the cereals, indicating a large portion of contamination iron.

In quantitative terms, this means that lactic fermentation of maize or sorghum gruels can change such bioavailability,\(^1\) which otherwise could only be achieved by including generous quantities of iron absorption promoters, such as meat or foods containing large amounts of ascorbic acid.

Potential effects on iron status of dietary modifications

It is clear from table 3.1 that preschool children need an iron absorption of at least 7 to 8 percent from a cereal-based diet to maintain iron balance. Such diets are possible to achieve with realistic modifications of the traditional diet in developing countries, especially if the diet also contains large amounts of contamination iron that is available for absorption. Simple measures include eating foods with iron inhibitors at different times from the main meals, for example, to drink tea or coffee in between meals and to include vitamin C-rich foods with the main meals, for example, eating fresh fruits and vegetables with the meals; however, this entails behavior changes that may not be readily done. Some of the traditional food-processing techniques may be relatively easily modified to have an optimal effect on iron bioavailability.
Iron Interventions for Child Survival

Table 3.5: In vitro iron solubility of nonfermented and fermented maize gruels prepared in village households (traditional and modified method with soaking)

<table>
<thead>
<tr>
<th>Gruel</th>
<th>Total Fe (mg/100g)</th>
<th>Soluble Fe (mg/100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfermented ((n = 10))</td>
<td>16.8±5.9</td>
<td>0.35±0.12</td>
</tr>
<tr>
<td>Fermented ((togwa))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) /traditional method ((n = 9))</td>
<td>33.2±12.2</td>
<td>0.37±0.06</td>
</tr>
<tr>
<td>(b) /+soaking ((n = 10))</td>
<td>32.1±14.0</td>
<td>1.43±1.05</td>
</tr>
</tbody>
</table>

The effect of vitamin C supplementation on iron stores is the only dietary modification that has been tested in long-term studies. Table 3.6 summarizes five studies in which the diet was supplemented with different amounts of ascorbic acid, but only two have been on preschool children. One study in China (Xu and Gushi, 1992) showed a significant improvement in iron stores measured by serum ferritin (SF) and erythrocyte protoporphyrin (EP); however, the supplemented drink also contained large amounts of citric acid that is also known to enhance iron absorption. In an unpublished study in Tanzania, vitamin C tablets (50 mg) were given once daily with the main maize meal to preschool children, but no improvement in hemoglobin (Hb) was detected over 12 weeks compared with a placebo group.

Table 3.6: Effect of ascorbic acid supplementation on body iron stores

<table>
<thead>
<tr>
<th>Dose</th>
<th>Subjects</th>
<th>Iron store</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g/day for 16 wks</td>
<td>17 adults (iron replete)</td>
<td>No effect (SF(^a))</td>
<td>Cook et al. (1984)</td>
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<tr>
<td>300 mg/day for 8 wks</td>
<td>25 nurses (iron replete)</td>
<td>No effect (SF)</td>
<td>Malone et al. (1986)</td>
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<tr>
<td>25 to 150 mg/day for 8 wks (+citric acid)</td>
<td>65 preschool children (mild IDA)</td>
<td>Significant improvement (SF, EP(^b), Hb(^c))</td>
<td>Xu and Gushi (1992)</td>
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<tr>
<td>1.5 g/day for 10 wks</td>
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<td>No effect (SF)</td>
<td>Hunt et al. (1994)</td>
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<td>50 mg/day for 12 wks</td>
<td>26 preschool children</td>
<td>No effect (low Hb)</td>
<td>Tatala and Svanberg (unpublished)</td>
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</tbody>
</table>

| a. SF = serum ferritin | b. EP = erythrocyte protoporphyrin | c. Hb = hemoglobin |

References


Dietary Interventions to Prevent Iron Deficiency in Preschool Children


Discussion

*Dr. Fairweather-Tait* mentioned it is important that ascorbic acid is given with meals to iron-deficient subjects in sufficient amounts and for a sufficiently long period, because both these are confounding variables; thus, every study needs to look at this in detail before ascorbic acid is dismissed. *Dr. Svanberg* agreed and noted that there are no reliable studies in which vitamin C has been given to an iron-deficient population in a daily diet for a sufficiently long period of time.

*Dr. Schultink* asked about the relationship between soluble iron and bioavailable iron and how the solubility of iron is determined. He also asked whether any intervention studies have been done on the modified gruels to see if there is any change in hemoglobin levels. *Dr. Svanberg* replied that a modification of the Miller technique was used to estimate iron solubility in twenty single meal diets provided by Dr. Hallberg, who has determined their bioavailability in human studies. *Dr. Svanberg* commented that about 20 percent of the iron was soluble and about 10 percent was absorbed using the in vitro technique. No intervention studies have been started.

*Mr. Alnwick* asked about the importance of milling techniques and the potential effects of milling on phytates and, thus, iron absorption. He noted that milling techniques are changing rapidly in parts of Africa. For example, 2 years ago between 70 and 80 percent of the Zambian population bought breakfast maize, which was 70 percent extracted using large mechanical roller mills. As a result of the current economic situation, 60 to 70 percent of the population now procure maize, which is 90 percent extracted, from small hammer mills; thus, phytate intake has increased two to three times in the course of 2 years and the impact on iron status is unknown. *Mr. Alnwick* also asked about the role of yeast in bread making. *Dr. Svanberg* replied that phytate needs to be reduced by at least 95 percent to have any effect on iron status and this will not be achieved through decontecification. High extraction milling of wheat flour, for example, 55 to 60 percent, will remove this amount of phytate, but many other important nutrients will also be lost. With the current milling techniques available in Africa, 40 to 50 percent of the phytate will be present after milling and there will be no effect on iron availability. In other words,
milling makes no difference on iron absorption, but it may affect the degradation of phytate, for example, in the soaking process. Dr. Svanberg also commented that although milling reduces a small amount of the intrinsic iron, it reduces a large proportion of the contamination iron.

Dr. Tomkins asked what proportion of total iron comes from contamination iron to which Dr. Svanberg replied that it can be as high as 90 percent. Dr. Henry pointed out that part of the contamination iron comes from the hammer mill process itself. Dr. Blum added that iron cooking pots can also be an important source of contamination iron. Dr. Svanberg noted that iron in clay pots may be dissolved into gruels when stored, for example, during fermentation, and can contribute significantly to total iron content. A few studies have been done on the bioavailability of contamination iron. In one study, iron hydroxide, which is the major form of iron in soil, was added to food; at least 50 percent of this iron may be available for absorption.

Dr. Fleming pointed out that the size of the grain is important. Small grains with a large surface area such as teff, which is the staple food in Ethiopia, carry the dirt. Dr. Svanberg noted that the type of soil is also important. Dr. Fairweather-Tait said the iron matrix in soil is very important because some are insoluble.

Dr. Svanberg commented that in sour dough fermentation, the pH is very important. To degrade the phytate by 96 to 97 percent, a pH of 5.0 is needed. The yeast and lactic acid bacteria together provide this pH.

Dr. Luo asked about soya protein, because in Zambia soya porridge is being promoted for babies as a nutritious food and has been shown to have a positive impact on growth. Dr. Svanberg replied that soya proteins inhibit iron absorption. Dr. Fairweather-Tait added that all soya products, not just the protein, are inhibitory. Dr. Blum commented that there are many studies on infant formulae and the use of soya. Where soya is used as a substitute for milk, many countries have regulations in place to correct the nutritional profile of soya-based foods to avoid nutritional deficiencies.
4. OVERVIEW OF IRON FORTIFICATION OF FOODS

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Foods have been fortified with iron for over 50 years. In the 1930s and 1940s, iron was first added to cereal flour to restore the iron lost in milling. Today, many foods, including infant formulae and weaning foods, are fortified according to standards and principles defined by established bodies, including FAO/WHO (1976), the ESPGAN Committee on Nutrition (1982), and the National Research Council (1989). This presentation reviews food vehicles suitable for iron fortification, iron requirements, iron fortificants, and the technological and nutritional criteria required for food fortification. Examples of successful applications are also presented.

A considerable amount of data is available on the bioavailability of iron from standardized diets and single meals (Monsen et al., 1978; Cook, 1983; Cook and Reusser, 1983; Hallberg, Brune, and Rossander, 1989a; Hallberg, 1985; Stekel et al., 1985; Monsen, 1988; Hallberg, Brune, and Rossander, 1989b; Hurrell, 1989; Hurrell et al., 1989); however, it is beyond the scope of this presentation to review this data.

Criteria for selecting food vehicles

Four criteria exist for selecting an appropriate food vehicle for iron. First, it is essential that frequency and average consumption of the food by the target group is both known and predictable, especially for young children, adolescents, and pregnant women. Second, there should be no risk of overconsumption. Third, the addition of iron should not affect the organoleptic qualities of the food: iron in its ionized form is an aggressive compound that interacts with vitamins, minerals, and other nutrients. Finally, the cost of the fortified product should not be beyond the reach of those for whom it is intended. Cost will be influenced by the type of iron compound added to the food vehicle, which depends on the nature of the food and its shelf life. Some iron compounds cost as much as a complete vitamin/mineral premix; this needs to be considered in designing micronutrient concepts and priorities.

Iron requirements

Net iron losses from the body through the skin, urine, and blood are about 2 mg/day for women, 1 mg/day for men, and 0.8 mg/day for children, reflecting that net iron requirements are indeed very low. The Recommended Dietary Allowances (RDA) are 15 mg/day for women and 12 mg/day for men, which
Iron interventions for child survival is 7.5 and 12 times higher than net iron requirements; therefore, the RDAs take into account the low bioavailability of dietary iron (Herbert, 1987; National Research Council, 1989).

The bioavailability, or more specifically the relative bioavailability (RBV), of iron in foods is measured as the incremental absorption of that iron in a standardized diet or test meal. Ferrous sulfate has been used as a reference and has an RBV of 100 percent, against which other iron compounds are compared. For example ferrous fumarate, which is used in infant foods, has an RBV that is equal to ferrous sulfate, while ferric pyrophosphate, ferric orthophosphate, and reduced iron have an RBV of one-half to one-third of ferrous sulfate (Hurrell, 1989; Hurrell et al., 1989; Hurrell and Cook, 1990).

**Food vehicles for iron fortification**

Suitable food vehicles for iron fortification include cereal flours, such as wheat and corn. These foods already contain iron, although most of it has been removed during milling to white flour. Suitable technologies to fortify flour with reduced iron or iron pyrophosphate have been developed. In general, the quality of bread, fine bakery products, and pasta is not negatively affected by reduced iron or iron pyrophosphate.

In the process of cooking cereal, free iron binds to proteins and amino acids, resulting in a rearrangement of the iron in food. Because of a low interaction with other food components, flour, ready-to-eat cereals, and extruded cereals are suitable vehicles for iron. Cocoa beverages, such as chocolate breakfast drinks, are suitable, even though they contain tannins that reduce iron absorption, because iron can be added to compensate for this. UHT milk, liquid diets, infant formulae, and powdered skim milk lend themselves very well technologically and nutritionally as a vehicle for iron.

Foods not recommended as vehicles for iron fortification include soft drinks and isotonic beverages. This is because consumption is poorly controlled and people may drink as much as 2 or 3 liters per day, thereby exceeding the maximum recommended daily intake for iron. Fat-based foods are also not suitable for fortification, because iron catalyzes oxidation and degradation of fat, making the food rancid; thus, fresh dairy products are not suitable vehicles for iron fortification. Salt and sugar are not good vehicles because they are hygroscopic and, in a moist environment, the addition of iron causes color changes and adverse iron-nutrient interactions. Salt poses another problem, because it is used in food preservation. For example, iron-fortified salt may cause severe quality problems when used for curing vegetables, meat, and cheese. A special iron-vitamin A, double-fortified salt has been developed, which may be suitable for fortification of powdered weaning foods (The Micronutrient Initiative, pers. com.).

**Iron fortificants**

A number of iron compounds are listed as "generally recognized as safe" (GRAS) by the U.S. Food and Drug Administration (Code of Federal Regulations, 1994). Iron fortificants listed as GRAS are reduced iron, ferric phosphate, ferric pyrophosphate, ferric-sodium-pyrophosphate, ferrous gluconate, ferrous lactate, and ferrous sulfate; however, some non-GRAS iron fortificants are also being recommended and used. These compounds may be safe, but in some cases more data are needed to corroborate their safety. Examples of these include carbonyl iron, iron amino acid chelates, and sodium iron EDTA (MacPhail et al., 1990).
al., 1994). As of today, sodium iron EDTA is not manufactured on a commercial scale. Furthermore, the compound is expensive to produce and its superior bioavailability has only been shown in diets high in phytate (MacPhail et al., 1994).

**Food technology criteria**

The most frequent problems encountered in adding iron compounds to food are discoloration, appearance of specks, segregation, sedimentation, and sandy texture. Other quality problems that may occur are lipid oxidation, off-flavor development, and vitamin degradation.

From a technical point of view, solid or liquid foods present different challenges for successful fortification. In liquid foods, solubility and dispersibility of the iron fortificant are important factors.

**Nutritional criteria**

Bioavailability and safety are the most important nutritional criteria. The main dietary factors affecting iron bioavailability are vitamin C and the presence of iron inhibitors such as phytate and tannin. Iron compounds added to foods should be safe and not cause gastric irritation. The iron should not interact with vitamins and minerals, and it should be of high purity. The purity of some of the non-GRAS iron compounds may not be defined, and they may contain traces of other metals. For this reason iron fortificants should comply with quality standards outlined in the U.S. Pharmacopoeia or Food Chemical Codex (FCC). Finally, the safety of the iron compound should be recognized by the U.S. Food and Drug Administration or other regulatory agencies. To date, no “accepted daily intake” (ADI) values for iron fortificants have been established.

**Successful applications of iron fortification**

A number of iron compounds can be successfully added to foods on a large scale. Reduced iron is used to fortify wheat added to flour and ready-to-eat cereals in combination with vitamins B₁, B₂, B₆, and niacin. The amount of reduced iron actually absorbed from fortified flours has been investigated and depends on the type of diet (Hallberg, 1985; Hallberg, Brune, and Rossander, 1989a and 1989b).

Desiccated ferrous sulfate is used to fortify low acid foods and infant formulae. For prevention of color changes, the food has to be slightly acid because ferrous sulfate turns food brown above pH 6.3.

Ferric pyrophosphate has a low solubility. The compound can be dispersed and suspended in a liquid food. It is used to fortify cereals, pasta products, milk powder, liquid diets, infant formulae, and cocoa drinks. Ferric pyrophosphate interacts least with food components, and its bioavailability is considered to be good. In the acid environment of the stomach, its solubility and, thus, bioavailability is increased.

In extensive tests, ferrous fumarate was found to be suitable for fortification of cereal-based weaning foods, biscuits, and wafers; however, because of its brown color and insolubility, it is not appropriate for fortification of milk and white or off-white foods (Hurrell, 1989; Hurrell et al., 1989; Hurrell and Cook, 1990).
Iron Interventions for Child Survival

Ferrous lactate is highly hygroscopic and cannot, therefore, be used in dry foods. It is the preferred iron source for liquid foods such as UHT milk and liquid formulae diets.

**Technical measures to enhance iron bioavailability**

Phytate is a powerful inhibitor of iron absorption. Its inhibitory effect can be neutralized by yeast fermentation through activation of the enzyme phytase (Cook, 1983; Cook and Reusseur, 1983; Acosta et al., 1984; Beard, 1986).

Acidification of foods represents another strategy to increase iron bioavailability. Lactic acid may be used to acidify vegetables and other foods. Vitamin C fortification and lactic acid fermentation have been shown to increase iron bioavailability (Hallberg, Brune, and Rossander, 1989a; Borch-Iohnsen et al., 1994).

**Impact of iron fortification on anemia**

Few studies show the efficacy of iron fortification on anemia prevention. One such study was conducted in Chile (Stekel et al., 1985), in which the prevalence of anemia in children between 3 and 15 months old supplemented with iron-fortified milk was reduced from 36 percent to 13 percent. Anemia prevalence was reduced from 28 percent to 2 percent in children supplemented with both iron- and vitamin C–fortified milk. The data show that vitamin C and iron together were more effective in reducing anemia than iron supplementation alone (see figure 4.1).

**Figure 4.1: Prevalence of anemia in children age 3 to 15 months fed iron and iron/vitamin C-fortified milk**

![Prevalence of anemia in children age 3 to 15 months fed iron and iron/vitamin C-fortified milk](image)

*Source: Stekel et al. (1985)*
The effect of vitamin C on increasing nonheme iron absorption in a synthetic test diet and in a standard meal was investigated by Monsen (1988). By taking 50 mg, 100 mg, and 500 mg of vitamin C with a semisynthetic test meal, absorption of nonheme iron was increased 1.9, 3.2, and 4.7 times, respectively. In the same study, nonheme iron absorption increased 1.7 times when 100 mg of vitamin C was included in a standard diet (see figure 4.2).

**Figure 4.2: Effect of vitamin C on non-heme iron absorption**

![Figure 4.2: Effect of vitamin C on non-heme iron absorption](image)

Source: Monsen (1989)

The inhibitory effect of phytate on iron absorption from bread rolls has been studied by Hallberg et al. (1989b). Increasing the amount of phytate in bread rolls was found to decrease the ratio of iron absorbed from 80 to 20 percent. The inhibitory effect of phytate (25 mg) was neutralized by taking 100 mg vitamin C as a beverage with the bread roll (see figure 4.3).

In the process of establishing strategies for anemia prevention, it is important to realize that micronutrients other than iron are important in anemia prevention. In addition to iron, copper, vitamins A, B₂, B₁₂, C, and folate are essential for hemoglobin formation; thus, it is important to look at the total diet and not just iron when discussing anemia prevention. The premise of any fortification program should be to design a diet to increase the availability of nutrients needed to maintain good iron status.
Figure 4.3: Effect of sodium phytate and vitamin C on iron absorption

Source: Modified from Hallberg et al. (1989)

Summary

Iron fortification is a widely used public health measure for prevention of iron deficiency anemia. The selection of iron fortificants should be based on technological suitability, bioavailability, efficacy in reducing anemia, safety, and low cost. There is no point in fortifying a food with iron alone if the cost of the compound is higher than the cost of a vitamin-mineral mix that includes iron. Alternative strategies to increase iron bioavailability in foods must continue to be sought.

References


Discussion

Dr. Lorri commented that most of the nonrecommended food vehicles are those commonly consumed in developing countries; thus, it is questionable whether fortification is a viable solution for developing countries. Dr. Blum replied that different criteria have to be applied depending on the country, because of unique dietary characteristics. Mr. Mannar added that because of the limited number of foods that can be fortified with iron in developing countries, the University of Toronto is developing a stable formulation of doubly fortified salt with iron (ferrous fumarate) and iodine (potassium iodate) using a special encapsulation technique, in which dextrin encapsulates the compounds. The formula is stable for up to six months. In vivo and in vitro trials are needed before carrying out a community-based trial.

Dr. Henry asked about the use of bovine blood for iron fortification. Dr. Blum replied that studies in Chile have shown that bovine hemoglobin can be successfully used in fortification; however, disease problems in blood mean that governments have strict regulations about shipping blood products. Ethical considerations also exist because there are groups, for example, Muslims, who could not accept such products for religious reasons.
5. ANEMIA AND INTESTINAL PARASITES

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During the last 10 years, scientists working on helminths have been looking at the impact of antihelminthic treatment on nutrition, both in terms of child growth and micronutrient status. This interest stemmed from pioneering work conducted mostly in East Africa by Stephenson (1987). An inherent assumption in the ongoing research on the impact of helminths on morbidity is that the latter is related to the intensity of intestinal nematode infections and treatment, which reduces helminth intensity, and would have an impact on growth, nutritional status, and school performance; thus, the consequences of helminth disease may be controlled using regular antihelminthic treatment. The challenge for WHO is to find a low-cost generic antihelminthic drug that can be produced in developing countries.

This paper describes the use of antihelminthic chemotherapy as a tool to control anemia and draws on work in Zanzibar, supported by both USAID and WHO. Specifically, the research is looking at the long-term effect of a regular single dose, 500 mg mebendazole tablet on morbidity in school children. Initially, some 3,600 primary school children were followed for one year, during which fecal blood loss and hookworm egg counts were monitored. The dominant hookworm species in the area is Necator americanus.

Preliminary results showed a highly significant intensity-related effect of infection on fecal blood loss, iron stores, and severe anemia. This suggests that if the intensity of infection could be reduced to a level that is not associated with blood loss and morbidity, regular deworming would probably be the appropriate approach for morbidity control. In other words, the first objective of regular antihelminthic chemotherapy would be to reduce morbidity by reducing the intensity of infection, even though individuals may not be completely cured and will continue to be exposed to reinfection. The latter is because none of the antihelminthic drugs available are 100 percent effective, especially against hookworms and Trichuris trichiura (Albonico et al., 1994; Albonico et al., 1995).

In the late 1960s, the Belgian pharmaceutical company Janssen developed mebendazole as the drug of choice for treating worm infections. The initial recommended regimen against T. trichiura and hookworm infection was 100 mg twice a day for 3 days. In the late 1970s, Janssen developed the 500 mg preparation for use in large-scale interventions against intestinal nematodes and for long-term treatment against alveolar echinococcosis, a relatively rare infection that requires high-dose, long-term therapy with antihelminthics. Two small studies, one in Thailand (Johgsuksuntigul, pers. com.) and the other in Sri Lanka (Ismail, Premaratne, and Suraweera, 1991) have compared the effect of a single dose of 500 mg mebendazole on the intensity of intestinal nematodes with other drugs, such as the commonly used and inexpensive pyrantel.
Iron Interventions for Child Survival

Because mebendazole is a generic drug that can be purchased for about US$0.02 per single 500 mg dose, it is important to know whether it is as efficacious as a single dose of albendazole, a commonly used single-dose antihelminthic, which is significantly more expensive.

A trial was designed to compare the efficacy of Janssen’s original 500 mg mebendazole, a generic 500 mg mebendazole produced in Malta by Pharmamed, and the original 400 mg albendazole produced in the United Kingdom by SmithKline Beecham. The results showed that both the albendazole and mebendazole were very effective in eliminating *Ascaris lumbricoides* eggs after 21 days of treatment (see figure 5.1), but this was expected because most antihelmintics are very effective against *A. lumbricoides*. In contrast, the effect of albendazole treatment on *T. trichiura* was much less significant (see figure 5.2). Indeed, the number of children that had no *T. trichiura* eggs was quite small but, more interesting, most of the children had egg counts below 500 eggs/g feces. In other words, the intensity of infection was significantly reduced. Mebendazole, both the original and cheap generic product, was found to be slightly more effective against *T. trichiura* than albendazole. Although albendazole was significantly more effective than mebendazole in curing hookworms (see figure 5.3), the majority of children treated with mebendazole had egg counts below 500 eggs/g feces and many were cured.

The results of this study have important program implications for public health planners. The question is whether to use a drug that is more expensive, that is, albendazole, which has a greater effect on hookworm infection and a similar effect for the other two parasites (*Ascaris* and *Trichuris*), or a drug that is twenty times less expensive, that is, mebendazole, that also has a very significant impact on reducing the intensity of infection. Given that the amount of blood lost from the gut is similar in a child whose worm intensity is very low and a noninfected child, it seems logical that a more sustainable program would be one that uses mebendazole, which has a more frequent retreatment interval, than one that uses albendazole.

The efficacy trial was continued, and the same children were followed up again at four and six months. The results of the follow-up study showed that, regardless of whether a child was cured of helminths or not, most got reinfected after treatment; thus, the post treatment reinfection rate is an important aspect of large-scale, chemotherapy-based helminth control programs. The results also showed that after four months, the difference in the efficacy of the two drugs on hookworm egg counts was less evident than at 21 days; at 6 months the intensity of hookworm infection was exactly the same as before the intervention (see figure 5.4).

A similar pattern to that for curing hookworm infection was observed for *T. trichiura*, but neither mebendazole or albendazole were as effective (see figure 5.4). Because both drugs are highly effective against *A. lumbricoides*, egg count levels fell close to zero, but reinfection took place and preintervention levels were reached after six months. These results show that even if a more effective drug is used, in this area of very high transmission, egg counts revert to pretreatment levels six months after treatment. This means that in areas of high transmission, the retreatment schedule has to be quite frequent.

A large-scale trial, which includes an untreated control group, is currently under way to look at the impact of retreatment schedules on egg count intensities at 4- versus 6-month intervals, using all three chemotherapies. Several issues are being monitored, including differences in worm intensities and the impact this has on iron stores, vitamin A status, and undernutrition.
Figure 5.1: Efficacy of Albendazole and Mebendazole treatment on eliminating Ascaris eggs.

Ascaris

Albendazole

Eggs per gram

Mebendazole

Eggs per gram
Figure 5.2: Efficacy of Albendazole and Mebendazole treatment on eliminating Trichuris eggs

Trichuris

Albendazole

Mebendazole

Eggs per gram

% pretreatment and post-treatment.
Figure 5.3: Efficacy of Albendazole and Mebendazole treatment on eliminating hookworm eggs
Figure 5.4: Egg count distributions in Mebendazole and Albendazole groups before treatment, and after 21 days, 4 months, and 6 months of treatment

**Ascaris**

<table>
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<tr>
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**Trichuris**

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<tr>
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**Hookworm**

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<td>Albendazole</td>
<td>5.942</td>
<td>2.352</td>
<td>3.354</td>
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In summary, a single dose of 400 mg albendazole is more effective against hookworm than a single 500 mg dose of mebendazole; the difference attenuates at four months. Both drugs are similarly and extremely effective against *Ascaris*. Mebendazole is more effective than albendazole against *Trichuris*, although the cure rates are low for both drugs. Both the egg production rate and intensity of infection may be sufficient for disease control in endemic areas; at four months, efficacy is similar for both drugs. Although data comparing the generic with the original mebendazole are not shown, the results indicate that both formulations had similar efficacy against hookworms *Ascaris* and *Trichuris*.

The recommendations arising from the above studies were that in areas where hookworms are the main parasites, albendazole may be recommended, whereas in *Trichuris* and *Ascaris* transmission areas, mebendazole is the drug of choice. Where mixed infections are prevalent, the dose should be based on the local epidemiological and financial situation, given that the efficaciousness of the drugs is similar at four months. In high transmission areas, the prevalence and transmission of *Trichuris* and hookworms return to pretreatment levels after six months.

Both drugs are very safe for school children; a one-half tablet mebendazole (i.e., 250 mg) is safe for children under two years old. This means that a tablet must be manufactured in a form in which it can be broken into two. Albendazole is not recommended for children under two years old. Another advantage of both albendazole and mebendazole is that the recipient’s weight does not need to be known when prescribing the drug—unlike for levantisoled and pyrantel, which are two commonly used antihelminths.

**References**


**Discussion**

*Dr. Tomkins* asked if the use of albendazole and mebendazole had any impact on iron status. *Dr. Savioli* replied that this is not yet known. Small-scale studies, conducted over the last fifteen years in East Africa using a single dose of albendazole in school children, have shown a significant impact on iron status after six months. Other studies have shown an improved school performance. *Dr. Stoltzfus* commented that the purpose of the ongoing Zanzibar study is to look at the long-term effect on the shift of the hemoglobin distribution in a population of school children that were hookworm endemic and who were then dewormed. The baseline data show that iron requirements are doubled because of blood loss due to
hookworm infestation, which has implications for iron balance in children; however, hookworm loads will be lower in preschool children, but at the same time, their iron needs are relatively high and a smaller hookworm load could have a similarly dramatic effect on iron requirement.

Dr. Brabin asked if there are any hematologic criteria or prevalence figures for anemia that could be used as guidelines for initiating an antihelminthic program. Dr. Savioli replied that the priority setting for deworming programs has never been based on scientific criteria. Indeed, the purpose of the Zanzibar trial is to develop tools for setting priorities.

Dr. Nestel asked Dr. Savioli to comment on the safety of antihelminths for children under two years old, for example, albendazole is not recommended. Dr. Savioli responded that 250 mg mebendazole, piperazine, pyrantel, and levamisole are safe and have been widely used. The Sick Child Initiative recommends mebendazole treatment in a single 250 mg dose for all ages in areas where helminths are widespread for all ages.

Dr. Mascie-Taylor asked about the consequences of bilharzia on blood loss. Dr. Savioli responded that the overriding factor for blood loss is hookworm. The Zanzibar study in school children has not shown an association between Schistosoma infection and anemia, but this may be due to the long-term positive effect of Schistosoma treatment. Nevertheless, Schistosoma haematobium is unlikely to be a big problem in children under five years old.

Dr. Schultink commented on a Brazilian study in children heavily infected with Ascaris and Trichuris. Serum retinol levels of children given a vitamin A supplement did not increase, unlike in the control group who were dewormed but not given vitamin A at the outset. Dr. Schultink asked whether there is an increase in acute-phase response indicators in children infected with Ascaris and Trichuris, because several studies on the effect of deworming on iron status show no effect on hemoglobin status. The acute phase response may play a role in vitamin A metabolism, and serum ferritin is an acute-phase response protein. Dr. Filteau responded that preliminary data from Tanzania show that deworming with albendazole did decrease levels of some acute phase proteins.
6. MALARIA AND ANEMIA

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Fundació Clínic
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The impact of malaria control on iron status

Malaria-associated anemia

Anemia is the most common consequence of *Plasmodium falciparum* malaria infection in both immune and semi-immune individuals. Intervention trials in Africa, where malaria was being controlled through either efficacious chemoprophylaxis or impregnated bednets, showed an increase in mean, packed cell volume (PCV) and/or hemoglobin concentration (Alonso et al., 1991; Dolan et al., 1994).

The impact of *P. falciparum* malaria infection on anemia is most marked in young children and pregnant women, especially in primigravidae. This is probably related to a lower level of malaria-specific immunity in these groups. A study on malaria chemoprophylaxis given to pregnant women in The Gambia showed a significant increase in PCV only in primigravidae, although parasite rates were also significantly reduced in multigravidae (Greenwood et al., 1989). Similarly, a recent placebo-control trial on vaccinating Tanzanian children between 1 and 5 years old with the SPf66 antimalarial vaccine showed no difference between the placebo and control groups with respect to PCV levels, despite a significant reduction in both the incidence of clinical malaria and parasite density (Alonso et al., 1994); however, preliminary unpublished results of a descriptive study of malaria risk among infants from the same area suggest a negative correlation between clinical malaria episodes and PCV level (Menéndez et al., in prep.). This would imply that the impact of malaria on anemia correlates inversely with the level of immunity against the infection.

Mechanism of malaria-associated anemia

The pathophysiology of malaria-associated anemia is multifactorial. The most likely mechanisms include the following:

- Hemolysis or the direct destruction of parasitized red blood cells that occurs both intravascularly and by sequestration in the microcirculation, mainly in the spleen.

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1. No generally accepted definition for semi-immunity exists for malaria. It is defined here as having acquired immunity against malaria to the extent that these individuals are generally resistant to the severe effects of the disease, although they may still get the infection and mild clinical symptoms, that is, they are not totally immune.
Iron Interventions for Child Survival

- Specific/nonspecific immune responses, whereby red cell survival is shortened.

- Nonspecific, defective, red cell production, which depresses erythropoiesis, inhibits reticulocyte release, and prematurely destructs red cells during maturation in the bone marrow. Defective red cell production has been observed mainly in children with severe anemia, low reticulocyte count, and low parasitemia (Abdalla, 1990). Nonspecific features, commonly found in vitamin B12 and folic acid deficiencies, were observed in the bone marrow. It appears that vitamin B12 and folate deficiencies are associated with malaria because the situation reverses to normality once the malaria parasites have disappeared from the blood and after these two vitamin deficiencies have been ruled out. The explanation could be that under situations of high antigenemia, for example, in repeated reinfections in partially immune children, the lymphocyte-released cytokines overactivate macrophages, which will then cause erythrophagocytosis.

- Hypersplenism associated with a reduction in all three blood cell series, that is, causing not only anemia but also thrombocytopenia and leucopenia.

**Impact of malaria infection on iron status**

Malaria parasites may affect iron status through the following mechanisms:

- Reducing intestinal iron absorption
- Sequestrating iron within the malarial pigment hemeozoin
- Consuming iron for its own metabolism
- Promoting/stimulating the mobilization of iron to body stores
- Releasing iron into the circulation during intravascular hemolysis

The impact of malaria on iron metabolism is a combination of both the effects of hemolytic anemias and that of infections; the outcome can be either an increase or reduction in serum iron levels. Several studies have shown that the assessment of iron status in the presence of malaria is further complicated by modifications of most of the routinely used biochemical and hematological indices of iron status (Filteau and Tomkins, 1994). For example, serum ferritin levels are often higher in infected individuals, probably as a result of increased synthesis, but they may also be lower due to the deposition of iron in body stores or higher as a result of intravascular hemolysis. Transferrin saturation can be higher due to hemolysis or lower because of the infection. Moreover, red blood cell indices, such as mean corpuscular volume (MCV), may be increased due to reticulocytosis following hemolysis, whereas mean corpuscular hemoglobin concentration (MCHC) could be lower due to an increased ratio of red cell volume in relation to the hemoglobin content (Abdalla, 1990).

The conclusion, therefore, is that no clear evidence exists of the real impact of malaria infection and of malaria control on iron status. This important question needs to be answered in a properly designed
intervention study of malaria control that compares iron parameters between individuals that are malaria-protected and -unprotected.

**Impact of iron supplements on malaria: implications for malaria control**

Evidence exists from both in vitro and clinical studies, albeit inconclusive, of an increased susceptibility to malaria infection with the use of iron supplements. Early observations and uncontrolled studies in both children and adults as well as in pregnant women have shown an increased risk of malaria in iron-deficient individuals who received iron (Byles and D’Sa, 1970; Murray et al., 1978). A few well-designed intervention studies in children have confirmed those results (Oppenheimer et al., 1986; Smith et al., 1989); however, an intervention trial carried out in school children did not show a difference in the risk of malaria between children who received iron supplements and those who did not (Harvey et al., 1989). Differences in the levels of acquired immunity between the two study populations may explain this discrepant result.

Among pregnant women, a recent study on the administration of oral prophylactic iron supplements to multigravid women in The Gambia showed, overall, no increase in susceptibility to malaria between the supplemented and placebo-control groups. Moreover, the mean birth weight of babies increased and the hematological and iron parameters were higher in the iron-supplemented group than in the placebo group (Menéndez et al., 1994); however, a negative interaction existed between iron and hemoglobin genotype; women with the AS genotype (sickle-cell trait or heterozygous for sickle-cell disease) who took iron supplements had a lower PCV hemoglobin concentration and gave birth to babies with a lower birth weight than women with the same genotype who received a placebo. Furthermore, an increased prevalence of placental infection existed among women who received iron supplements (Menéndez et al., 1995). Again, different defense mechanisms against malaria for AS and AA individuals may account for the negative effect of iron supplements in women with the AS genotype.

The conclusion is that providing iron supplements to individuals with low levels of malaria-specific immunity such as young children, those with the hemoglobin AS genotype, and possibly primigravidae pregnant women in malaria-endemic areas may not be beneficial. The situation with infants is unknown and studies to determine if iron supplements during infancy are also ineffective or even harmful are needed before they are routinely recommended in malaria-endemic areas. In this context, a double-blind, placebo-controlled, randomized trial of iron supplements in prophylactic doses with concurrent antimalarial chemoprophylaxis to infants is under way in Ifakara, Tanzania, which is an area of high and perennial malaria transmission. The main objective of the study is to evaluate the most efficacious strategies to prevent malaria and anemia in infants with a high exposure to malaria. The results of the study will also help to estimate the relative contributions of iron deficiency and malaria to anemia in infants.
References


Discussion

Dr. Jalal asked if Dr. Menéndez’s results also applied to nontherapeutic interventions, for example, fortification. Dr. Menéndez replied that this is unknown but the negative effect of malaria on iron status is probably related to the dose of iron and the route of iron. Most of the studies that gave iron parenterally to malaria-infected patients showed an increased risk of anemia, which was associated with the total dose of iron and how much was bioavailable; thus, the results cannot be applied to nontherapeutic interventions.

Dr. D’Alessandro asked Dr. Menéndez to clarify if an inverse correlation exists between anemia and malaria immunity and if, the iron has a negative effect in women with the sickle-cell trait. Dr. Menéndez replied that no effect exists between the sickle-cell trait and iron treatment during pregnancy, but there may be an effect post partum due to placental infection.
7. IRON SUPPLEMENTS TO CONTROL ANEMIA

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An iron supplement program is defined as the distribution of hematinics that may be iron and/or folate or iron and other nutrients in a tablet or, for younger children, in a liquid form. Supplements are applicable to the therapeutic management of severely affected individuals or children. In addition, the improvement of iron status in high-risk groups can be implemented within a fairly short time using supplements. In primary prevention programs, prophylaxis supplements as opposed to therapeutic supplements are needed to prevent the incidence or onset of iron deficiency anemia. Several factors can influence the effectiveness of an iron supplement program, for example, dietary iron inhibitors and intestinal parasites; no reason exists for a supplement program not to proceed alongside a fortification program. In some situations, this would be ideal because supplements address the more acute issues, while fortification addresses the more long-term issues. The distribution of any supplement will vary with the target group, the distribution facilities in the community, and other factors.

Although it is important to focus on preschool children as a target group, a number of issues need to be considered. Clearly, any child with iron deficiency anemia should be treated with a therapeutic course of iron; however, in an iron prophylaxis supplement program, the main issue is which age groups to target. Priority groups include low birth weight babies and preterm babies, because very good evidence exists that both groups have low iron stores (Bowering and Sandez, 1976). Low birth weight babies, whose growth is retarded but who are born at term also have significantly reduced body stores of iron (Siimes, 1985). These children start life with a deficit and are bound to become iron deficient by 2 to 3 months of life, even if they are breastfeeding satisfactorily, unless they get adequate supplements or adequate iron in their diet. A third group are those infants who do not receive complementary foods between 4 and 6 months old, because breast milk does not provide sufficient iron for infants beyond this age range.

The dose of iron supplement is related to iron requirements, which are fairly well established for children of different ages. Young infants have the highest iron requirements, because the infant is growing more rapidly at that time and because the increase in blood volume relative to body weight is greatest in the first year of life; thus, the question is whether to use a standard dose of iron for a given age range or a dose that is related to iron requirements. In other words, should there be different dosing schedules during the preschool years?

Although there is variation in iron requirements with age, consensus exists on the absolute amounts required. The confounding factor is absorption. To marry these two variables to calculate the dose of a supplement needed, a pilot prophylaxis or possibly therapeutic supplement trial is needed. The fact that low birth weight babies and preterm babies are born iron deficient means that another variable dictates iron requirements related to iron deficit. The only way to determine this is to carry out experimental trials. The standard sequence of events is to look first at the situation, including the distribution channels,
under field conditions. If effectiveness is demonstrated, programs can be scaled up to a regional or national level.

Whatever the dose decided on, the next question is how to deliver it, particularly to preschoolers. In the United Kingdom, most iron supplements are given as a syrup to young children using a spoon. Mothers are told how to do this and, in general, this approach is fairly successful. The question exists whether spoons would be reliable for dosing with all iron supplements in tropical countries, because very little information exists on how successful this would be. An ongoing trial, involving the Liverpool School of Tropical Medicine, the Tropical Epidemiology Group in Barcelona, and the Swiss Tropical Institute, in collaboration with Tanzanian scientists, is looking at the efficacy of low-dose oral iron supplements in young babies between 2 and 6 months old. In this trial, an oral syringe for measuring the exact dose of iron to be given as a supplement to young babies was developed. The scale on the syringe was marked in body weight increments so that the exact dose required for a child could be given based on its body weight and the concentration of iron in the syrup.

A case can also be made for using a simple fixed-dose strategy, instead of an exact dose based on body weight, when prescribing for infants and young children. For example, using the recommended 2 mg/elemental iron/kg body weight in the first year of life and assuming the average weight of a child in this age range is 5 kg, all infants over 2 to 3 months old could be given 10 mg elemental iron each day for the period of the supplementation. This will involve errors because some infants will be underdosed, while others may be overdosed. The question of overdosing is always important with iron supplements. It takes only 1 g of iron to kill a child from toxic effects, which is usually related to liver damage and hemorrhagic manifestation. It is very important in iron supplement trials to consider not only the required doses, given the circumstances, but also the upper level of normal that should not be exceeded. Establishing these upper levels is important.

Compliance, too, can be an important factor although little information seems available on this subject for preschool children. Compliance is influenced by the mother’s motivation, which may relate to the severity of the condition. The latter is particularly important, because a lot of children with mild or even moderate iron deficiency seem perfectly well. The question is how to motivate mothers to give a supplement in this situation.

A study carried out in Israel about ten years ago (Palti et al., 1987) looked at some of the reasons why mothers stopped giving oral iron supplements to their young infants. The findings showed that side effects were not really a problem. Breastfeeding, however, was reported as the main reason for not starting and for stopping administering iron supplements to young infants. In the first 3 to 4 months of life, the iron content of breast milk is adequate for an iron-replete newborn baby. But, if the infant is iron deficient, breast milk will not provide enough iron; thus, iron supplements may be needed from as early as 2 months old. In this study, about one-third of the mothers who should have been giving their infants iron supplements were failing to comply. Another important issue is to identify “windows of opportunity” for reaching the high-risk groups, as well as distributing the iron supplements through the health care delivery system.

Many different pharmaceutical iron preparations exist, but the elemental iron content is the critical factor. The amount of soluble ferrous iron in the supplement is crucial, because absorption is affected by whether it is collated to another compound or is in a sequestered form. A popular supplement used in the
United Kingdom for small babies is an unsweetened sodium EDTA complex in its collated form known as “Sytron.” Another is a sweetened ferrous glycine compound, known as “Plesmet,” which is not favored as much by pediatricians because of its sugar content. Both supplements are stable in milk, and their chelation increases the stability of iron without risking oxidation to the ferric form on storage. Most of the oral iron products produce the same prevalence of side effects, which is related to the amount of available iron in them. The manufacturing process may also influence biological availability.

In adults, the amount of iron absorbed as well as intolerance and side effects is closely related to the dose of iron (Solvell, 1970). There is no reason to believe that the same associations do not exist in children. Apart from the gastrointestinal side effects, other less obvious side effects include those that might occur in chronic hemolytic states in children who already have adequate body iron stores. A recent study from Indonesia showed a marginal but statistically significant poorer weight gain in iron-replete preschool children receiving an iron supplement (Idjradinata, Watkins, and Pottit, 1994); thus, other types of side effects have to be considered in evaluating the use of iron supplements.

The use of iron supplements in neonates presents additional problems because of the evidence for increased susceptibility to bacteremia, particularly in neonates receiving parenteral iron. Important interactions with the gut microflora exist, for example, there is evidence that E. coli counts may be increased. There are also various micronutrient interactions, for example, the well-described syndrome of hemolytic anemia occurring in premature babies receiving oral iron. This has been shown to occur only in babies who are vitamin E deficient and relates to enhanced lipid peroxidation of red cell membranes.

In terms of cost, an all-ferrous sulfate liquid preparation is available but not licensed in the United Kingdom. Although ferrous sulfate is a cheap and well-absorbed iron compound, it has cost implications because it has to be prepared specially by pharmacists. According to the British National Formulary, the current price of Plesmet is UK£0.20 to UK£0.30/100 mg of iron (US$0.30 to US$0.45), while ferrous sulfate is UK£6.33/100 mg of iron (US$9.50). In many countries ferrous sulphate remains the cheapest preparation available, but it must be prepared fresh in a liquid form, which has a short shelf life of about 2 weeks, after which oxidation starts to occur.

In conclusion, defined iron requirements exist for preschool children; however, pilot trials are necessary to establish doses for iron supplements. Several good iron compounds are available that can be used in supplements, and some are reasonably inexpensive. The sequestered forms of iron seem to be the most stable. With regard to iron supplement programs, questions related to the modes of delivery and distribution remain a challenge. The need exists to look for “windows of opportunity” to ensure that both therapeutic and prophylactic iron supplements are made available for high-risk infants and young children. Recent information on the relative value of weekly or biweekly dosing with iron supplements as an alternative to daily dosing may prove important for future programs (Schultink et al., 1995).
**References**


**Discussion**

*Dr. Jalal* asked whether liquid iron supplements affect teeth. *Dr. Brabin* replied that ferrous sulfate stains teeth in young children, which is one reason why collated irons are more popular. The risk of teeth staining with iron EDTA is thought to be considerably less than with the other ferrous salts. Although teeth staining is a disadvantage and has cosmetic implications, it is generally thought to be reversible.

*Mr. Alnwick* commented that UNICEF does not presently stock iron supplements for young children. Indeed, they only stock the standard 60 mg ferrous sulfate tablets with and without folic acid. This is a major impediment to iron programs for young children going ahead, and it would be very useful for this meeting to identify whether UNICEF should go ahead and investigate whether it should stock these compounds and what compounds might be best for a particular problem in different field settings. *Mr. Alnwick* also made the point that a growing international enthusiasm as well as evidence points to periodic use of supplements. A number of ongoing studies seem to show it is possible to get the same effect using weekly supplements as with daily supplements. This would reduce the costs, as well as most of the side effects that have been raised.

*Dr. Gopaldas* noted that in India, it is possible to get 1,000 sugar-coated ferrous sulfate tablets for just 18 rupees (US$0.60) and it is one of the cheapest medicines that can be given. *Dr. Brabin* replied that the cost of the supplement will depend on where it is manufactured and liquid preparations are more appropriate for infants and young children. *Dr. James* noted that the problem with ferrous sulfate is that a chemist has to make up the liquid preparation, because it is not stable; thus, the labor involved drives up the cost. *Dr. Brabin* added that the shelf life of liquid ferrous sulfate is about 2 weeks, after which it oxidizes into the ferric state, which is not as well absorbed.

*Dr. Nestel* noted, on the subject of weekly versus daily dosing, that there is concern regarding compliance. The history of getting people to take malaria prophylaxis regularly is not encouraging; there
are questions on why people would behave differently with iron supplements. This is an area that needs to be looked at carefully before proposing a change in dosing schedules. Dr. Schultink reported that his group recently completed a study in which mothers of 300 children under 5 years old in one village were instructed but not supervised to give their children iron supplements over a 2-month period. Stool samples showed that compliance was between 70 and 80 percent, which is high. Dr. Brabin noted that there is some evidence that compliance falls very rapidly after the first few months; how long supplements are needed is still to be determined.

Dr. Stoltzfus commented that 10 to 15 years ago multicenter studies were conducted to determine the formulation for iron tablets for pregnant women, that is, whether folate and B₁₂ were also important, and to give some guidance on the best preparations for different regions of the world.

Although this workshop focuses on iron, similar trials may be required for preschool children because, if liquid preparations are to be put together, it is important to look at the most cost-effective combination of micronutrients. Dr. Brabin commented that although ferrous sulfate may be very cheap and easily available in a tropical situation, other issues exist in addition to its shelf life, for example, it is not palatable and has a number of other problems that may affect compliance in preschool children.

Dr. Tomkins commented on a recent study in southern Tehran in which children were screened for anemia, after which the anemic ones were divided into two groups. In one group, children were given enough syrup for treatment purposes, which was to be taken on Mosque day. In the other group, mothers were told that their child was anemic and were advised to buy the syrup in the market; there is only one form of ferrous sulfate in Tehran, which is made locally and is in a stable form. At recruitment, mean hemoglobin concentration was 9.6 g/dl in both groups. Three months later it was 10.6 g/dl, and 6 months later it was 11.0 g/dl in both groups. The important finding in this study was that there was great value in doing blood tests for anemia to actually heighten awareness among mothers, who were very concerned. Mothers did treat their children, even if they had to buy it themselves. Another important finding was that there were almost no side effects.
Numerous publications exist on the interactions between iron and other micronutrients or compounds. This presentation focuses on seven micronutrients or compounds, namely EDTA, ascorbic acid, meat, peptides, zinc, phytic acid, vitamin A, and copper. The first five (EDTA, ascorbic acid, peptides in meat, zinc, and phytate) have been shown to affect iron absorption, while the other two (vitamin A and copper) have been shown to affect iron metabolism, that is, after iron has been absorbed.

EDTA, a commonly used food additive in developed countries, chelates iron as well as other micronutrients including calcium and magnesium. EDTA binds to iron (Fe³⁺) in the stomach and, in this complex, much of the Fe³⁺ is reduced to Fe²⁺ as shown in figure 8.1. This reduction process is important because Fe²⁺ is much more soluble and, after being released from EDTA in the lumen of the small intestine, is more effectively absorbed than Fe³⁺. Despite the fact the EDTA is a chelating agent, long-term human studies have demonstrated that the inclusion of EDTA in the diet does not affect other minerals known to chelate to EDTA. For maximal iron absorption, the molar ratio of EDTA to iron in the diet should be 0.5 (MacPhail et al., 1994). A ratio both below or above 0.5 results in a dramatic reduction in iron absorption.

**Figure 8.1: Interaction between EDTA and metal ions in the lumen of the stomach and duodenum**

Source: INACG (1993)

1. Ethylenediamine tetra acetic acid.
Phytate also reduces iron absorption by binding to iron. Unlike EDTA, much of the iron bound to phytate is not released in the small intestine and, therefore, remains bound to phytate in a complex that is not well absorbed. In addition to iron, phytate binds zinc, selenium, and calcium. Soaking and fermenting foods abundant in phytate, such as grains and cereals, results in the release of these minerals from phytate complexes, thereby increasing intestinal absorption. Hallberg et al. (1989) have shown that as the level of phytate increases in the diet from 2 mg to 250 mg, the percent of iron absorbed decreases (see table 8.1). The addition of ascorbic acid to diets containing 25 or 250 mg phytate improves the absorption of iron significantly. Ascorbic acid reacts with iron in a manner similar to EDTA, in that the solubility of iron is increased, allowing for enhanced absorption. The Hallberg et al. study also showed that adding meat to the diet improved iron absorption but not to the extent observed for ascorbic acid.

**Table 8.1:** Iron absorption from study meals containing wheat

<table>
<thead>
<tr>
<th>Study meal</th>
<th>Absorption ratio with and without phytate, ascorbic acid, or meat</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg phytate</td>
<td>0.82 (0.04)</td>
</tr>
<tr>
<td>5 mg phytate</td>
<td>0.61 (0.04)</td>
</tr>
<tr>
<td>10 mg phytate</td>
<td>0.41 (0.04)</td>
</tr>
<tr>
<td>25 mg phytate</td>
<td>0.36 (0.04)</td>
</tr>
<tr>
<td>+50 mg AA</td>
<td>2.17 (0.02)</td>
</tr>
<tr>
<td>+100 mg AA</td>
<td>3.56 (0.53)</td>
</tr>
<tr>
<td>+50 g meat</td>
<td>1.12 (0.08)</td>
</tr>
<tr>
<td>50 mg phytate</td>
<td>0.31 (0.03)</td>
</tr>
<tr>
<td>100 mg phytate</td>
<td>0.29 (0.04)</td>
</tr>
<tr>
<td>250 mg phytate</td>
<td>0.18 (0.03)</td>
</tr>
<tr>
<td>+50 mg AA</td>
<td>2.84 (0.48)</td>
</tr>
<tr>
<td>+100 mg AA</td>
<td>3.43 (0.53)</td>
</tr>
<tr>
<td>+50 g meat</td>
<td>1.86 (0.22)</td>
</tr>
</tbody>
</table>

*Source: Hallberg, Brune, and Rossander (1989)*

Zinc is thought to reduce iron absorption by competing for the carrier involved in the uptake of nonheme iron; thus, as the level of dietary zinc increases, the percent of iron absorbed is reduced. Evidence for this comes from a study by Yadrick et al. (1989) of the effects of zinc and zinc plus iron supplementation on iron status in rats. They found that rats supplemented with only zinc had reduced iron status, based on serum ferritin and hematocrit measurements, while iron status was restored in those supplemented with both zinc and iron (see table 8.2).
Table 8.2: Status measurements for zinc and iron-zinc supplemented groups before treatment and after 6- and 10-week supplementation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Zinc-supplemented group</th>
<th>Iron-zinc-supplemented group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>6 week</td>
</tr>
<tr>
<td>Hemoglobin (g/l)</td>
<td>149±4</td>
<td>148±4</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.437±0.009a</td>
<td>0.431±0.009ab</td>
</tr>
<tr>
<td>Serum ferritin (µg/l)</td>
<td>36.6±7.4a</td>
<td>30.1±4.4ab</td>
</tr>
<tr>
<td>ESOD (nmol/g RBC)³</td>
<td>4.059±0.340a</td>
<td>3.433±0.184a</td>
</tr>
<tr>
<td>Ceruloplasmin (mg/l)</td>
<td>294±20</td>
<td>297±13</td>
</tr>
<tr>
<td>Serum Zn (µmol/l)</td>
<td>12.9±0.6a</td>
<td>15.5±0.7b</td>
</tr>
<tr>
<td>Salivary-sediment Zn (µmol/g dry wt)</td>
<td>1.20±0.11</td>
<td>1.27±0.15</td>
</tr>
</tbody>
</table>

Source: Yadrick et al. (1989)

2. ± Mean and standard error, where means have superscripts, values in a row not sharing a common superscript are significantly different (p<0.05).
3. Erythrocyte superoxide dismutase activity.
Mejia et al. (1979) showed that rats fed a vitamin A–deficient diet had significantly lower plasma iron values compared with rats fed a control, vitamin A–replete diet; however, the hepatic iron levels of rats fed the vitamin A–deficient diet were noticeably higher compared with the control animals (see figure 8.2). The authors concluded that the reduced plasma iron concentration in rats fed a low vitamin A diet was due to the impaired release of iron from the liver; thus, vitamin A status affects the release of iron bound to ferritin, which affects plasma iron concentration.

Figure 8.2: Values for plasma iron (upper panel) and hepatic iron (lower panel) for the three groups of rats fed diets either sufficient or deficient in vitamin A.

Values bearing a different superscript are significantly different at a level of $P < 0.05$. With growth, there appeared to be a gradual increase in the plasma level of iron in the two.

Source: Mejia et al. (1979)
Serum vitamin A levels are also positively correlated with hemoglobin levels. This was demonstrated in a large study conducted in Paraguay as well as a study that combined status data from eight developing countries (see figure 8.3). Suharno et al. (1993) showed that adding vitamin A to the Indonesian diet increased blood hemoglobin levels and reduced the prevalence of anemia in pregnant women, although the impact was lower than that from iron supplements. The most dramatic improvement was seen in the group that received both vitamin A and iron supplements (see figure 8.4).

**Figure 8.3:** Relationship of hemoglobin and plasma vitamin A as observed in several Interdepartmental Committee on Nutrition for National Defense (ICNND) nutrition surveys (nonpregnant, nonlactating females, 15 to 45 years old).

![Graph showing correlation between plasma vitamin A and hemoglobin](image)

Correlation between plasma vitamin A and hemoglobin where \( r = 0.777 \) (\( P < 0.05 \)) and \( y = 10.81 + 0.07X \).


Van Houwelingen *et al.* (1993) looked at the effect of vitamin A and copper on iron status. In rats fed a copper-deficient/vitamin A–adequate diet, plasma iron, transferrin saturation, hematocrit, and blood hemoglobin concentration were significantly lower than in those fed a copper- and vitamin A–adequate diet. Indeed, as iron status declined, liver iron levels increased. When rats were fed a copper- and vitamin A–deficient diet, iron status declined further, but both liver and spleen iron concentrations were markedly elevated compared with those in rats fed the copper-deficient/vitamin A–adequate diet (see table 8.3). The authors concluded that, like vitamin A, copper is important for the release of iron from the liver.
Figure 8.4a: Proportion of women who became nonanemic

![Bar graph showing the proportion of women who became nonanemic under different interventions.]

Source: Suharno, et al. (1993)

Figure 8.4b: Effect of vitamin A and iron on hemoglobin in anemic pregnant women

![Bar graph showing the effect of vitamin A and iron on hemoglobin in anemic pregnant women.]

Increase in treatment group minus increase in control group; mean and 95 percent CI.

Source: Suharno, et al. (1993)
Table 8.3: Iron status of male rats fed the experimental diet for 42 days

<table>
<thead>
<tr>
<th>Measure</th>
<th>5 mg/kg copper 4,000 IU/kg vitamin A</th>
<th>1 mg/kg copper 4000 IU/kg vitamin A</th>
<th>5 mg/kg copper 0 IU/kg vitamin A</th>
<th>1 mg/kg copper 0 IU/kg vitamin A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal Fe (μg/d)</td>
<td>392.4 ± 36.2</td>
<td>387.5 ± 56.6</td>
<td>395.6 ± 47.7</td>
<td>402.80</td>
</tr>
<tr>
<td>Blood hemoglobin</td>
<td>9.2 ± 0.4</td>
<td>8.7 ± 0.6†</td>
<td>9.0 ± 0.3</td>
<td>8.1 ± 0.9**</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>42.2 ± 1.7</td>
<td>40.1 ± 2.4†</td>
<td>41.0 ± 1.6</td>
<td>37.40</td>
</tr>
<tr>
<td>Red blood cell count x</td>
<td>7.00 ± 0.41</td>
<td>6.90 ± 0.55</td>
<td>6.89 ± 0.26</td>
<td>6.35</td>
</tr>
<tr>
<td>Plasma iron (μmol/l)</td>
<td>35.1 ± 3.3</td>
<td>25.7 ± 7.6†</td>
<td>33.2 ± 4.7</td>
<td>22.60</td>
</tr>
<tr>
<td>TIBC3 (μmol/l)</td>
<td>89.5 ± 4.4</td>
<td>91.1 ± 5.0</td>
<td>89.1 ± 5.1</td>
<td>90.50</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>39.3 ± 3.4</td>
<td>28.0 ± 7.9†</td>
<td>37.4 ± 5.8</td>
<td>24.90</td>
</tr>
<tr>
<td>Liver Fe (μg/g dw)</td>
<td>252 ± 27</td>
<td>506 ± 177†</td>
<td>256 ± 38</td>
<td>583.00</td>
</tr>
<tr>
<td>Spleen Fe (μg/g dw)</td>
<td>1,261 ± 219</td>
<td>1,432 ± 586</td>
<td>1,396 ± 272</td>
<td>1,981 ± 1,279</td>
</tr>
<tr>
<td>Kidney Fe (μg/g dw)</td>
<td>315 ± 41</td>
<td>302 ± 29</td>
<td>302 ± 36</td>
<td>292.00</td>
</tr>
<tr>
<td>Heart Fe (μg/g dw)</td>
<td>478 ± 114</td>
<td>447 ± 154</td>
<td>437 ± 82</td>
<td>395.00</td>
</tr>
<tr>
<td>Tibia Fe (μg/g dw)</td>
<td>78.8 ± 7.6</td>
<td>63.9 ± 7.4†</td>
<td>74.1 ± 13.0</td>
<td>62.00</td>
</tr>
<tr>
<td>Femur Fe (μg/g dw)</td>
<td>85.6 ± 8.2</td>
<td>71.6 ± 11.9†</td>
<td>83.2 ± 5.9</td>
<td>74.6 ± 8.4**</td>
</tr>
</tbody>
</table>

Source: Van Houwelingen (1993)

4. ± Mean and standard error, where means have superscripts, values in a row not sharing a common superscript are significantly different (p<0.05). Liver iron concentration was subjected to ANOVA after log transformation of the data.
5. Total iron binding capacity.
Based on the interactions discussed here as well as other interactions that can affect iron status and the difference in absorption between heme iron and nonheme iron, it is not surprising that dietary absorption of iron is so variable (see figure 8.5). Given that many factors affect iron absorption, the challenge is to develop an algorithm that predicts the bioavailability of iron from a particular food or meal.

**Figure 8.5:** Radioiron measurements of the absorption of iron from foods by adults, infants, and children.

The length of the bars indicates the variation among different subjects for each food; the heavy vertical line across each bar indicates the average value. The amount of iron in each feeding varies from 1 to 17 mg. Clear bars: normal subjects; cross-haired bars: iron-deficient patients.

*Source:* Moore (1973)
References


Discussion

*Dr. Tomkins* inquired about the mechanism for delaying the release of iron in vitamin A deficiency, to which Dr. Trumbo replied that it is not well understood. Vitamin A may affect the release of iron from ferritin or disassociation of the two may occur, but the problem may be getting the iron out so that it can link up with the transferrin protein. *Dr. Yeung* commented that on electrophoresis the retinol binding protein and the ferritin are very close. Indeed, they used to be considered one and the same.

*Dr. Menéndez* asked if there is any information on the role of riboflavin on increasing the utilization of iron. *Dr. Fairweather-Tait* reported that work in The Gambia showed that riboflavin deficiency impairs iron utilization and that there is a definite interaction between iron and riboflavin.

*Dr. Blum* noted that studies show an interaction between vitamin A and iodine. Indeed, a study even shows that all three are related: iodine, iron, and vitamin A. Because micronutrients are related, they need to be considered together rather than as discrete entities.
9. IRON DEFICIENCY ANEMIA IN THE UNITED KINGDOM

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Iron deficiency anemia in the United Kingdom

Iron deficiency anemia (IDA), defined as a hemoglobin less than 11 g/dl, occurs most commonly in children under 2 years old. Table 9.1 shows that the prevalence of IDA has been estimated to be between 11 and 38 percent (James and Laing, 1994). IDA is more common in children living in poverty and in some ethnic minority groups. Particular risk factors include premature births and low birth weight due to insufficient iron stores; prolonged breastfeeding in association with late weaning, because the iron content of breast milk is inadequate for infants older than 6 months old despite its high bioavailability; and the early introduction of cow’s milk, in which the bioavailability of iron is poor.

Table 9.1: Prevalence of IDA (Hb<110g/l) in the United Kingdom

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Age (months)</th>
<th>Characteristics</th>
<th>Prevalence (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erhart (1986)</td>
<td>Bradford</td>
<td>6-48</td>
<td>Asian, Hospital</td>
<td>25</td>
</tr>
<tr>
<td>Aukett et al. (1986)</td>
<td>Birmingham</td>
<td>17-19</td>
<td>Deprived Community</td>
<td>26</td>
</tr>
<tr>
<td>Grundulis (1986)</td>
<td>Birmingham</td>
<td>21-23</td>
<td>Asian</td>
<td>20</td>
</tr>
<tr>
<td>Marder (1990)</td>
<td>Notthingham</td>
<td>15-24</td>
<td>European</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asian</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Afro-Caribbean</td>
<td>20</td>
</tr>
<tr>
<td>Mills (1990)</td>
<td>London</td>
<td>8-24</td>
<td>European</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asian</td>
<td>26</td>
</tr>
</tbody>
</table>

Source: James and Laing (1994)

The majority of the studies in the United Kingdom have focused on children living in deprived areas, which may overestimate the prevalence in the United Kingdom as a whole. Nevertheless, more than one-quarter of all children in the United Kingdom are now living in relative poverty (U.K. Department of Health and Social Services, 1994b).
Approaches to IDA in the United Kingdom

Debate on the best intervention to use to reduce the prevalence of IDA in children has intensified in the United Kingdom, following the recognition that IDA is associated with psychomotor delay (Oski and Honig, 1978; Aukett et al., 1986; Idjradinata and Pollitt, 1993). The fact that the psychomotor delay is reversible with iron therapy, at least in the short term, has emphasized the importance of identifying children who need treatment. Dietary education, iron fortification of foods, iron supplements, and screening at specific ages have all been suggested as viable interventions.

Dietary education

A dietary education program targeted to mothers was implemented in an inner city family practice, characterized by severe socioeconomic deprivation, where 70 percent of mothers are single parents and 45 percent belong to an ethnic minority group, principally Afro-Caribbean (James et al., 1989). The program was started following the discovery in 1986 that 38 percent of the 102 one-year-old children who came for screening had IDA. Of the 48 Afro-Caribbean children screened, 46 percent were anemic. It was apparent that children had been given cow’s milk at an early age rather than the recommended iron-fortified formula milk. The doctors, health visitors, nurses, and midwives working in the practice met with the community dietitian to develop clear guidelines for the prevention of IDA as well as a dietary information package for mothers. The emphasis was on the importance of breastfeeding and the need to use iron-rich formulae, avoid using cow’s milk in the first year of life, and give iron-rich weaning foods. The program was introduced by midwives as part of antenatal care, and the same advice was given by health visitors and doctors after the baby was born. Within a year of introducing the program, the prevalence of IDA at 14 months was reduced from 38 percent to 24 percent among all children and to 28 percent in the Afro-Caribbean children. Although the program reduced the prevalence of IDA significantly and children continue to be screened, one in four or five children were still anemic at 14 months old. The highest prevalence of IDA was in 1990 and the lowest was in 1994 when 34 and 21 percent of children respectively were anemic.

Not all education programs, however, have been successful. A large, controlled intervention in Birmingham, in which families received specific health education, showed no reduction in the prevalence of IDA after 18 months (Child et al., 1994).

Fortification of foods with iron

Cow’s milk formula is fortified with iron in the United Kingdom as are most commercially prepared weaning foods. Formula milk is available to low-income families at no cost through a voucher system. Current U.K. guidelines recommend the use of fortified milks in the first year of life (U.K. Department of Health and Social Services, 1994a), yet the high prevalence of IDA in toddlers suggests that these milks are not being used. The practice of exchanging milk vouchers for other consumables, for example, cigarettes at local stores is common in deprived urban areas; thus, despite the availability of iron-fortified foods, children in the United Kingdom still develop iron deficiency.
Iron Deficiency Anemia in the United Kingdom

The above contrasts with the success of the Women, Infants, and Children (WIC) Program in the United States. Tunisian and Oski (1987) found that the prevalence of IDA among infants from deprived inner city families enrolled in the WIC program and receiving iron-rich formulae during their first year of life was 1 percent at 12 months old. This was considerably lower than the 20 percent prevalence observed for the same age group not enrolled in the WIC program. A more recent placebo-controlled study by Moffatt et al. (1994) on iron-fortified formula, demonstrated that the prevalence of IDA was significantly lower among infants from very low-income families receiving the iron-rich formula. The same study also showed that psychomotor scores declined among infants who did not receive the iron-rich formula but not among those fed the formula, suggesting benefits beyond improving iron status in using iron-rich formulae.

Iron supplements

Although iron supplements can be used for high risk groups, a number of unanswered questions remain. First, it is unclear how such groups should be defined. Second, the appropriate dose of iron to use is unknown. Third, how can the dangers of overdosing be avoided? Finally, little is known about compliance in administering daily medication to infants and children over a prolonged period of time. At the other end of the spectrum, Idjradinata et al. (1993) have suggested that administering iron supplements to iron-replete children may retard their growth.

Screening

There has been considerable discussion over the introduction of IDA screening into routine child health surveillance in the United Kingdom. Screening for iron deficiency, using capillary techniques to estimate hemoglobin (Hb) levels is acceptable to parents, and a number of studies have shown that a high consent rate is possible. Several questions, however, remain unanswered because the natural progression of IDA in this age group is not completely understood (Hall, 1989). The latter complicates the design and evaluation of both screening and intervention programs.

James et al. (1995) evaluated their screening program using a prospective cohort study. All children in their practice who had been screened for IDA at 14 months old were invited to reattend for screening at 2 years old. Between 1989 and 1992, 301 children were screened for IDA at 14 months old. Of these, 25 percent had IDA and were treated with iron supplements. At 2 years old, 79 percent of children were still registered with the practice and were sent an appointment for a repeat Hb estimation. Of these, 63 percent attended (50 percent of the original 14-month-old children). Ethnic group and weight were recorded for all children and parents were asked whether their child was difficult to feed. Among the children followed up at 2 years old, 24 percent had IDA (see table 9.2). Little correlation existed between Hb concentration at 14 months and at 2 years old ($r^2 = 0.2$, 95 percent confidence interval = 0.0–0.3), and there was no difference in the risk of anemia at 2 years old between those children who were and were not anemic at 14 months (risk ratio = 1.4, 95 percent confidence interval = 0.9–2.2).

Of the 48 children described as difficult to feed, 44 percent were anemic at 2 years old (risk ratio 3.5, 95 percent confidence interval = 1.9–6.7), and of the 24 children whose weight was below the 10th centile at 2 years old, 46 percent were anemic (risk ratio = 2.2, 95 percent confidence interval = 1.3–3.8).
Iron Interventions for Child Survival

Table 9.2: IDA at 14 months and 2 years old in an inner city practice

<table>
<thead>
<tr>
<th>Status</th>
<th>Percent</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemic at 14 months</td>
<td>100</td>
<td>43</td>
</tr>
<tr>
<td>Anemic at 2 years</td>
<td>30.2</td>
<td>13</td>
</tr>
<tr>
<td>Not anemic at 14 months</td>
<td>100</td>
<td>107</td>
</tr>
<tr>
<td>Not anemic at 2 years</td>
<td>21.5</td>
<td>23</td>
</tr>
<tr>
<td>Overall, anemic at 2 years</td>
<td>24.0</td>
<td>36</td>
</tr>
</tbody>
</table>

The evaluation reflects the difficulty of managing IDA in young children. Among those children identified as anemic and who received iron supplements and extensive dietary advice at 14 months old, nearly one-third were anemic at 2 years old (see table 9.2). Furthermore, over one-fifth of the nonanemic 14-month-old children in this population became anemic by 2 years old. This implies that different, although overlapping, groups of children will have IDA at different ages; therefore, screening children for IDA at one point in time and prescribing iron supplements to those who are anemic may be relatively ineffective and will not catch the substantial number of children who will become iron deficient after screening.

Conclusions

Controlling IDA depends on identifying individuals with IDA or individuals or groups at high risk of developing IDA. An alternative approach may be to try specifically to increase the intake of bioavailable iron within the vulnerable age groups. The association between IDA and poverty and evidence that inadequate diets among the poorer groups are largely the result of low income rather than ignorance suggests that measures that address poverty could potentially have a considerable impact on reducing and even eliminating IDA. In the short term, health promotion strategies to increase the use of iron-rich foods in the weaning diet should be considered. The choice of diet depends on the complex interaction of resources, knowledge, availability, and cost of different foods. Successful health promotion needs to be based on building alliances among local health authorities, health workers, and the business sector (Vaandrager et al., 1993).

Iron deficiency anemia is a common problem with potentially serious consequences; unfortunately, the appropriate preventive strategy remains unclear. Population-based interventions may prove to be the most fruitful approach.
References


Discussion

Dr. Kevany asked Dr. James, in his capacity as a primary health care provider working in the context of a local area health authority, to what extent he felt the local authority recognized the problem and adopted some policy in relation to it. Furthermore, has it identified a strategy for general practitioners that indicates that anemia control is a priority and that resources are available? Dr. James replied that his practice did impact on the health authority. Indeed, it has now approved supplying the microcuvettes for Hb measurements and is encouraging and supporting the program because it recognizes that screening is important. The screening program has been piloted in six similar practices, in which around 60 percent of mothers are participating, because doctors are enthusiastic and the health authority now pays for the program. The situation, however, differs. Dr. Laing, for example, has been trying to do screening in a very deprived area in south London where child surveillance is being done by clinical medical officers, who are government-employed doctors, rather than general practitioners. When mothers have been invited to come, very few turned up.

Dr. Yeung asked what were other dietary sources of iron for these children besides the iron supplements. Dr. James replied that for infants under 1 year old, the medical staff are insisting that fortified baby milks be given. Mothers who buy proprietary weaning foods are encouraged to buy those that are fortified. Nevertheless, there is a difficulty in promoting healthy nutrition, which means that children are given foods that the family eats, because of the very confusing health messages. In the Western world, people are advised to have lots of fiber, cut down on fats, and do all sorts of things, and a well-motivated mother will give their baby the same things. This means that a different message has to be given, which is a complicating factor.

Dr. Yeung commented that in the United States, the incidence of anemia in children from poor families participating in the WIC program dropped from 6.8 percent to 3.1 percent in 1984. Dr. James noted that this remarkable program gave mothers a lot of dietary education and provided all the food free. In Britain, the problem is that recipients swap the coupons for consumables, such as cigarettes.

Dr. Persson asked for the definition of iron deficiency and anemia in these studies. Dr. James replied that it was a hemoglobin level below 11 g/dl, but children were also screened for hemoglobinopathy. Dr. Persson commented that he is involved with a European growth and nutrition study from birth through 3 years old. In many countries, there is a lot of iron deficiency at 12 months old. Using the present cutoff point, the anemia prevalence was around 30 percent in countries such as Sweden, Austria, Ireland, and the Eastern European countries; however, the relations between iron deficiency and low hemoglobin varies widely: there is no association in countries such as Sweden, Austria, and Eastern Europe. In the European setting, there is a lot of confusion, because of the mix of low-serum ferritin values, which may be normal for that age group, and iron depletion. Dr. James replied that it is a very complicated matter that is not helped by the lack of consensus among pediatric hematologists on how to define iron deficiency. Nevertheless, it is important to remember that the studies on developmental delays have used hemoglobin measurements. Dr. James added that many children with iron deficiency may be missed in their program and others who are not iron deficient but who have a low hemoglobin level may be receiving treatment. A large number of high-risk children will be treated. Screening on its own is not enough, but it is useful in identifying that a problem exists to both health care providers and mothers. In other words, it increases the awareness that there is a huge problem.
Iron deficiency, which often results in anemia, is the most common nutritional deficiency in many countries. The well-known effects of iron deficiency anemia, including physical growth retardation, learning difficulties, and poor school and work performance later in life, whether they are reversible or not, are serious enough to warrant appropriate and prompt interventions. Various interventions are now available and have been used in different countries. Nevertheless, none has proved easy to implement and no “magic bullet” has been found to combat iron deficiency.

Background

Throughout the past decade, malnutrition has contributed to approximately 30 percent of infant deaths in Romania. To investigate the prevalence of malnutrition in noninstitutionalized children under 5 years old, a National Nutritional Survey was initiated in 1991 by the Ministry of Health and implemented by the Institute for Mother and Child Care (IMCC) in Bucharest.

Anemia is a major health problem in infants and young children in Romania. In the survey conducted in 1991 on 4,495 children, 49 percent of children under 2 years old and 24 percent of those between the ages of 2 and 5 years old were anemic (IMCC, 1991), using the WHO cutoff point of 11 g/dl for hemoglobin (Hb). Previous small-scale clinical studies (unpublished reports) had shown that iron deficiency was the main cause of anemia; the prevalence of other causes, including malaria, thalassemia, and hookworm infection, were very low. The high prevalence of anemia was again confirmed by data collected in 1993 through the Pediatric National Nutritional Surveillance System, in which 52 percent of children between 11 and 13 months old were anemic (IMCC, 1993). Both the 1991 survey and 1993 surveillance data identified several factors that could contribute to the high rates of anemia, including feeding patterns. Table 10.1 shows that the age at which bottle feeding begins, often with whole cow’s milk, has declined since 1989 and more so in urban areas than in rural ones. Indeed, between 1992 and 1994 the mean age at which bottles were introduced fell by 50 percent in urban areas (from 3.2 to 1.6 months old) and over 35 percent in rural areas (from 3.7 to 2.3 months old). Overall, solid foods, primarily nonfortified cereals, were introduced into infants’ diets at around 4 months old. Urban infants tended to be given solid foods about a month earlier than rural infants. Table 10.1 also shows that there has been a noticeable decline since 1992 in the mean age that infants are fully weaned. The fact that the mean age at which infants were fully weaned was earlier than the age at which solid foods were introduced indicated that not all infants were ever breast-fed.

1. Technical assistance was provided by the U.S. Centers for Disease Control, and financial and material support was provided by UNICEF/Romania.
Table 10.1: Mean and standard deviation age (months) of introducing bottle feeding, age of introducing solid foods, and age at full weaning

<table>
<thead>
<tr>
<th>Year of Birth</th>
<th>Age bottle feeding introduced (months)</th>
<th>Age solid foods introduced (months)</th>
<th>Age fully weaned (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urban Mean and SD</td>
<td>Rural Mean and SD</td>
<td>Total Mean and SD</td>
</tr>
<tr>
<td>1989</td>
<td>3.6 ± 3.1</td>
<td>4.2 ± 3.2</td>
<td>3.8 ± 3.1</td>
</tr>
<tr>
<td>1990</td>
<td>3.4 ± 2.8</td>
<td>4.1 ± 2.9</td>
<td>3.6 ± 2.9</td>
</tr>
<tr>
<td>1991</td>
<td>3.3 ± 2.9</td>
<td>3.8 ± 2.8</td>
<td>3.5 ± 2.9</td>
</tr>
<tr>
<td>1992</td>
<td>3.2 ± 2.7</td>
<td>3.7 ± 2.9</td>
<td>3.4 ± 2.8</td>
</tr>
<tr>
<td>1993</td>
<td>2.4 ± 2.2</td>
<td>3.2 ± 2.4</td>
<td>2.7 ± 2.3</td>
</tr>
<tr>
<td>1994</td>
<td>1.6 ± 1.5</td>
<td>2.3 ± 1.6</td>
<td>1.9 ± 1.5</td>
</tr>
<tr>
<td>ANOVA</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

2. Standard deviation.
As an immediate response to the situation, the IMCC conducted an iron supplement trial both to investigate the feasibility of an iron supplement program and to identify its immediate impact on the iron status of infants. Other longer-term interventions, such as the promotion of breastfeeding and local production of infant formulae and solid foods, including iron-fortified products, are being considered. Commercial production of infant and child foods are difficult to implement quickly, but preliminary steps have been taken. An information, education, and communication (IEC) campaign on child nutrition that includes the promotion of breastfeeding has been recently implemented. The goal is to modify infant-feeding patterns and ultimately promote good nutrition in infants and young children. This paper presents results of the iron supplement trial.

**Iron supplement trial**

**Research methods**

Approximately 2,000 infants from 110 primary health care (PHC) clinics in twenty districts as well as Bucharest were included in the trial. The trial was designed to provide infants with liquid ferrous sulphate for a minimum of 3 months. Infants in four districts, in which the mean hemoglobin levels were lower than the national average, were to receive a 6-month course of treatment. The liquid ferrous sulphate was manufactured by a Belgian company, purchased by UNICEF, and donated to participating families. Bottles of liquid ferrous sulphate were distributed by the IMCC to the local PHC clinics included in the Nutritional Surveillance System. Parents received the iron supplement from the local physician and administered the drops themselves to infants from the age of 6 months old.

A single daily dose of 12 mg ferrous sulphate was to be administered to all children. Physicians also recommended to parents that vitamin C, an iron absorption enhancer in the form of tablets or fruit juices, be given in between meals.

Local physicians filled out a form providing data on the PHC clinic, characteristics of the child, and his or her identity code, duration of treatment, reasons for noncompliance, use of vitamin C tablets and fruit juices and their duration, occurrence of side effects pertaining to iron treatment, and the hemoglobin level of the child at the age of 12 months old. Hemoglobin measurements were taken using a HemoCue (photometer) donated by UNICEF to each PHC clinic.

Anemia was defined using the WHO hemoglobin cutoff point of 11 g/dl for this age group. No hemoglobin measurements were performed before treatment began because the data from both the 1991 survey and the 1993/1994 surveillance system were considered sufficient.

**Results**

Data were obtained from 101 of the 110 (92 percent) of the participating clinics, by which time the majority of children included in the trial had reached their first birthday. About 15 percent of infants did not have their hemoglobin level measured 6 months after the study began, because they were temporarily
or permanently away at the time of the survey and were not included in the data analyses. The results presented are from 1,698 children.

The mean duration of treatment was 83 days. Three-quarters of the children received supplements for 61 to 90 days (see table 10.2), with 70 percent receiving them for the full 90 days. Mean hemoglobin values were positively and significantly correlated with duration of treatment. Overall, children who received supplements for fewer than 61 days had mean hemoglobin levels below the WHO cutoff point defining anemia, that is, 11 g/dl.

### Table 10.2: Percent distribution for duration of iron treatment and mean Hb concentration and percentage anemic children by duration of treatment

<table>
<thead>
<tr>
<th>Duration of treatment (days)</th>
<th>% of children (n = 1,698)</th>
<th>Mean Hb (g/dl)</th>
<th>% Anemic (Hb &lt;11 g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11</td>
<td>1.7</td>
<td>10.4</td>
<td>65.8</td>
</tr>
<tr>
<td>11-30</td>
<td>7.7</td>
<td>10.4</td>
<td>65.8</td>
</tr>
<tr>
<td>31-60</td>
<td>8.3</td>
<td>10.7</td>
<td>57.1</td>
</tr>
<tr>
<td>61-90</td>
<td>75.8</td>
<td>11.2</td>
<td>41.3</td>
</tr>
<tr>
<td>91-179</td>
<td>4.4</td>
<td>11.4</td>
<td>40.0</td>
</tr>
<tr>
<td>180+</td>
<td>2.1</td>
<td>11.7</td>
<td>22.9</td>
</tr>
</tbody>
</table>

ANOVA: p<0.001

The reasons for a shorter-than-expected duration of treatment included poor parental compliance. Among the 18 percent of the children who received iron supplements for fewer than 61 days, the reasons for noncompliance included: negligence (4 percent), temporary or permanent absence (2 percent), incomplete treatment (3 percent), side effects (diarrhea and vomiting), admittance to hospital for an illness (4 percent), and unknown (5 percent).

Vitamin C tablets and fruit juices were reported to have been given to 60 percent and 64 percent of children respectively but not necessarily on a regular basis. Nevertheless, as table 10.3 shows, there was a trend, albeit weak, for hemoglobin levels to improve among children who took vitamin C for more than 61 days.

Among the iron-supplemented children, the mean hemoglobin level was 11 g/dl; hemoglobin levels were significantly lower in rural (10.8 g/dl) than in urban areas (11.2 g/dl). Table 10.4 shows that compared with the 1993 data, those receiving iron supplements had higher Hb levels.
Table 10.3: Among children that consumed vitamin C, mean Hb by number of days vitamin C consumed

<table>
<thead>
<tr>
<th>Number of days</th>
<th>Mean Hb (g/dl)</th>
<th>Vitamin C tablets</th>
<th>Fruit juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 1,019)</td>
<td></td>
<td></td>
<td>(n = 1,087)</td>
</tr>
<tr>
<td>1–30</td>
<td>11.0</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>31–60</td>
<td>10.4</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>61+</td>
<td>11.2</td>
<td>11.1</td>
<td></td>
</tr>
</tbody>
</table>

Table 10.4: Mean Hb level at 12 months old

<table>
<thead>
<tr>
<th>Year</th>
<th>Mean Hb (g/dl)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993 unsupplemented</td>
<td>10.7</td>
<td>2,402</td>
</tr>
<tr>
<td>1994 supplemented</td>
<td>11.1</td>
<td>1,698</td>
</tr>
</tbody>
</table>

Table 10.5 shows the cumulative distribution of hemoglobin by severity of anemia. The proportion of children supplemented in 1994, who were not anemic, was noticeably higher (55 percent) than in 1993 when there was no iron supplement program (47 percent). This decline was across the board, suggesting that the hemoglobin distribution had shifted to the right.

Table 10.5: Distribution of anemia at 12 months old

<table>
<thead>
<tr>
<th>Year</th>
<th>Severe (&lt;7 g/dl)</th>
<th>Moderate (7–8.9 g/dl)</th>
<th>Mild (9–10.9 g/dl)</th>
<th>Normal (11+ g/dl)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993 unsupplemented</td>
<td>1.2</td>
<td>12.2</td>
<td>39.1</td>
<td>47.5</td>
<td>2,402</td>
</tr>
<tr>
<td>1994 supplemented</td>
<td>0.5</td>
<td>8.0</td>
<td>36.3</td>
<td>55.2</td>
<td>1,698</td>
</tr>
</tbody>
</table>

These results suggest that an iron supplement program may be feasible and the existing health services could be used to deliver iron drops. Further analyses of the data will determine whether this could become a sustainable intervention.

Despite these encouraging results, the administration of the supplement could not be strictly controlled and the actual amount of the intended dose ingested by a child was unknown. At the time of the trial, the social marketing strategy to promote the use of the liquid iron supplement had not been designed, mainly because of the lack of resources. This issue has since been addressed and the program has been initiated. On a long-term basis, the sustainability of using a liquid iron supplement could be affected by the fact that the iron supplements were given to families free of charge. For this to continue, the government will need to have financial resources to purchase the liquid iron supplement and make it available to children through the PHC services. Alternatively, parents could pay for the supplement. The major disadvantage
of the latter is that, although the actual price may be reasonable, it might be prohibitive for families in the lower income groups whose children are at a higher risk of being anemic.

Discussion

The iron supplement trial was the first step in a wider effort to control and prevent iron deficiency anemia in infancy and early childhood, which clinical studies had identified as the main cause of anemia in Romania. Regression analyses of all the children between 3 and 59 months old included in the 1994 national nutrition survey showed that those between 4 and 24 months old were at greatest risk of being anemic. This was after controlling for birth weight, age at introducing bottle feeding, age at introducing solid foods, and age at full weaning.

The results of the iron supplement trial showed a smaller improvement in the hemoglobin status of children than was expected. The reasons for this may include:

♦ *Low parental compliance.* This was because of the lack of information and awareness of the importance of anemia on child health or sheer negligence. Information available to parents was insufficient; it was up to the physicians to advise parents of the importance of anemia control on an individual basis, without the benefit of many educational materials. In addition to the above, a daily schedule might also account for the lower parental compliance.

♦ *Lack of control in the use of the iron supplement.* In a family with more than one child, the iron drops may have also been given to the other children.

♦ *Anemia may not be caused by iron deficiency.* No specific tests for iron deficiency were performed, due to the lack of resources, but data from previous small-scale, ad hoc studies, and the opinion of physicians suggest this is unlikely. Nevertheless, it may be necessary to investigate in a small clinical trial whether iron deficiency is indeed the most frequent cause of anemia in Romanian children.

♦ *Increasing prevalence of anemia.* The prevalence of anemia may be increasing; thus, the data may be better than they first appear, if the iron supplement program not only halted an increase in anemia but also decreased it. This assumption is obviously optimistic and further processing of data would be necessary to confirm it.

♦ *The dose used.* An average of 2 mg/kg body weight/day may have been too low to normalize hemoglobin levels and replenish iron stores.

The fact that hemoglobin values were directly related to the duration of treatment (see table 10.2) supports the argument that iron deficiency is the cause of anemia in Romanian children. A longer duration of supplementation or a higher dose could have brought about a more significant improvement in hemoglobin status.
The association between intake of vitamin C and iron drops on hemoglobin levels was weak. Hemoglobin values were slightly lower for the group who took vitamin C for 31 to 60 days but, because this was not a controlled clinical trial, this issue cannot be properly evaluated.

The liquid ferrous sulphate supplement was well tolerated by the majority of infants, and there was a low incidence of side effects: only 2 percent had vomiting and 2 percent had diarrhea.

In-depth analyses of the Pediatric National Nutrition Surveillance data have shown that hemoglobin status is correlated with birth weight (IMCC, 1994). Among infants born between 1990 and 1993, mean birth weight steadily decreased (see table 10.6), although this trend appeared to be reversing in urban areas in 1994.

<table>
<thead>
<tr>
<th>Year</th>
<th>Birth weight (g) Mean and SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>3,207 ± 506</td>
</tr>
<tr>
<td>1990</td>
<td>3,219 ± 507</td>
</tr>
<tr>
<td>1991</td>
<td>3,186 ± 505</td>
</tr>
<tr>
<td>1992</td>
<td>3,167 ± 508</td>
</tr>
<tr>
<td>1993</td>
<td>3,150 ± 510</td>
</tr>
<tr>
<td>1994</td>
<td>3,164 ± 497</td>
</tr>
</tbody>
</table>

Hemoglobin values were also correlated with the mean age at weaning. Children who received solid foods, mostly unfortified cereals, before the age of 3 months old were at much higher risk of anemia (see table 10.7). Traditionally, Romanian women breast-feed their infants for at least 9 months, especially in the rural areas; however, breastfeeding practices have changed in parallel to the changing economic situation. Forced industrialization has meant that many people moved from rural to urban areas and women, many of whom had been housewives, have had to get a job and, thus, have less time to spend with their children. Even now, women in rural areas tend to breast-feed their infants for a longer period of time than those in urban areas. Nevertheless, the urban-rural gap in the duration of breastfeeding is beginning to narrow and the decline in the mean duration of breastfeeding is more dramatic in rural than in urban areas, even though food availability may seem better. Furthermore, iron with a higher bioavailability is found mostly in foods of animal origin, which are comparatively more expensive than those of vegetable origin and less accessible to rural people.
Table 10.7: Percent distribution of anemia and mean hemoglobin by mean age

Age solid food introduced (months) | Severe (<7 g/dl) | Moderate (7-8.9 g/dl) | Mild (9-10.9 g/dl) | Normal (11+ g/dl) | Mean Hb (g/dl) | n
---|---|---|---|---|---|---
<3 | 4.2 | 22.9 | 39.6 | 33.3 | 9.8 | 548
<4 | 1.7 | 13.9 | 39.3 | 45.1 | 10.5 | 8,863
4 | 1.4 | 12.4 | 40.2 | 46.0 | 10.7 | 25,824
6 | 1.2 | 12.7 | 39.6 | 46.5 | 10.7 | 32,740

Outcome and prospects for the future
Iron deficiency anemia is a problem with clearly defined causes for which treatment is available. Its most challenging aspect remains finding the best and most cost-effective strategy to control and prevent it. Supplements are only one option because, even if fully successful, they only bring about a temporary, short-term solution. Medium- and long-term interventions, such as promoting breastfeeding and consumption of iron-rich foods, fortifying food, improving prenatal services, and improving the standard of living, will eventually make prevention possible.

Different countries have different experiences in controlling iron deficiency anemia. Sharing knowledge and learning about the experiences of others will eventually help to find the right answers and solutions to the problem. Without the coordinated effort of professionals in health care, education, and communication and without the full commitment of politicians and administrators, one cannot hope to achieve the 1990 World Summit for Children goal of reducing iron deficiency and ultimately improving nutritional status in children.

Acknowledgments
Thanks to all the local general practitioners in the 110 PHC clinics; maternal and child health officers in the twenty-one District Health Authorities; Ministry of Health officials; UNICEF/Romania Special Representative Mrs. Maie Ayoub von Kohl; Drs. Ray Yip and Abe Parvanta of the Centers for Disease Control/Atlanta, Georgia, USA; and Dr. Adrian Georgescu, all of whose expertise and support were essential to the completion of the trial.

References


Discussion

Dr. Schultink asked if data exist on compliance, given that this could be a reason why there is only a modest decrease in the prevalence of low hemoglobin levels. Dr. Ciomartan replied that they are now going back to the field to try to identify the causes of noncompliance, because the reporting system used was very simple and not at all sophisticated. Indeed, the general practitioner asked the mother the number of days she administered the supplement. A ten-day supply of supplements was given in a little bottle, so mothers were coming back every 10 days. In areas where mothers received a month’s supply, compliance was higher, but whether the mother was really telling the truth is not known. There were situations in which mothers were so poor they might have sold the drug and not actually given it to their children.

Dr. Ciomartan emphasized that this was not a clinical trial but a real-life situation. There were six reports of teeth staining, but these were infants, so that should not have been a constraint. Very few mothers reported that the child did not like the supplement. Even where adverse reactions occurred, it is not known whether these were directly related to the iron treatment or an illness. Dr. Ciomartan noted that hemoglobin levels were determined using the HemoCue and that discussions are now under way on whether to test hemoglobin at 2 years old to see whether the downward trend in anemia prevalence is going to be maintained.

Dr. Gopaldas asked whether the survey was nationally representative, to which Dr. Ciomartan replied that it was.

Dr. Nestel asked how much the iron preparation cost. Dr. Ciomartan replied that at the time it was bought, it was 3,000 Lei (US$2.00) for a month's supply. Most people would be able to afford the supplements if a social marketing strategy was in place; however, a segment of the population would still not buy the supplements. Mr. Alnwick commented that UNICEF specifically procured this iron preparation in Belgium. It is not something UNICEF routinely does on a large scale, and it recognizes that a high price was paid for the supplement. The point was made that to continue using this preparation, a dry preparation that can be rehydrated by mothers should be manufactured in Romania. Dr. Ciomartan agreed that this could be done, but the problem is that the pharmaceutical companies are not very willing to do this because it would not be profitable for them to market such drugs. Another concern relates to the quality control procedures that would be used in manufacturing these preparations.

Dr. Brabin asked whether iron-fortified weaning foods are available in the market. Dr. Ciomartan replied that they are available but unaffordable. Dr. Brabin also asked whether continued use of cow’s milk in infancy may explain the high prevalence of anemia and whether anything was being done to change this practice. Dr. Ciomartan responded by saying that this is one of the major factors. Indeed, the data on bottle feeding presented reflect the use of cow’s milk. A very small percent of the population uses formula, and where formula is used, it is usually unfortified. The general practitioners were to recommend to mothers not to use cow’s milk. Nevertheless, it is important to note that many mothers did not have the money to pay for formula. The government gives a limited supply of formula to every primary health care clinic for distribution. Because the amount is so limited, it is only used for the highest risk groups such as twins and low birth weight babies; thus, the majority of mothers are using cow’s milk.
Background

The 1993 Philippines national nutrition survey found a 49 percent prevalence of anemia among infants ages 6 to 11 months old and a 27 percent prevalence among children ages 1 to 6 years old. Although these rates are lower than the 70 and 30 percent for infants and preschoolers respectively in the 1987 national nutrition survey, anemia among infants and preschool children remains a serious public health problem (Food and Nutrition Research Institute, 1987 and 1994). The 1993 survey also found that the prevalence of anemia among pregnant and lactating women was 44 percent and 43 percent respectively suggesting that their infants may have been born with low iron stores and their breast milk may have provided inadequate iron in early infancy.

In most populations, the leading cause of iron deficiency is an imbalance between dietary iron supply and the increasing iron needs of preschoolers due to a rapid phase of growth. The national surveys did not have specific indices of iron deficiency anemia (IDA), such as serum ferritin; however, it is very likely that iron deficiency is the major cause of anemia among the country’s high risk groups, including infants and preschoolers.

The 1987 Philippine survey showed that iron intake of children 6 years old and less ranged from 73 percent to 98 percent of the Filipino recommended daily intake (RDA). Because the bioavailability of iron is far more important than the total dietary iron intake, iron deficiency in the country among preschool children appears to be related to the low and less frequent consumption of heme iron–containing foods, such as meat, poultry, and fish, as well as nonheme iron–containing fruits and vegetables. The traditional Filipino infant diet is inadequate in terms of both its quantity and quality and often comprises a rice porridge mixed with broth, salt, or sugar. This porridge is gradually replaced by ordinary rice with very few additions as a child gets older. There are practically no processed iron-fortified weaning foods that are affordable and available to the segment of the population who need it most.

The contribution of parasitic infections to anemia among the country’s preschoolers needs to be evaluated. The prevalence of Trichuris trichiura is reported to be high throughout the country and Schistosomiasis japonicum is endemic in five regions. Hookworm, which is known to be associated with iron deficiency, appears to be relatively rare; however, malaria infection certainly contributes to the anemia of preschoolers. One hospital-based study showed that, among children 3 to 6 years old with malaria parasites, 94 percent were anemic and 40 percent severely so with hemoglobins below 7 gm/dl (Sy, Strattan, and Ilagan, 1981). Malaria is endemic to varying degrees in seventy-one out of the seventy-one
six provinces in the Philippines. Indeed, malaria infection is one of the ten leading causes of morbidity in seven of the twelve regions in the country (Philippine Department of Health, 1991).

The high prevalence of anemia among infants and preschool children in 1987 compared with 1993 may have been the result of the economic crisis and political upheaval between 1984 and 1986. The Food and Nutrition Research Institute (FNRI) has found no evidence of programmatic changes to explain the decline in anemia among this age group between 1987 and 1993, but there has been an improvement in the overall economic situation in the country (National Nutrition Council, 1991). Indeed, other nutrition indicators also improved in this period, including the prevalence among children under 6 years old of underweight, which declined from 17 percent to 8.4 percent, and wasting, which fell from 12.7 percent to 6.2 percent. Malaria morbidity also declined markedly from an average of 1,024 per 100,000 population in 1986 to 73 per 100,000 in 1991 (Philippine Department of Health, 1991).

**Micronutrient initiatives**

In 1993 the National Nutrition Council (NNC) of the Government of the Philippines (GOP) in response to the global call for the reduction of micronutrient malnutrition formulated the Philippine Plan of Action for Nutrition (PPAN), which was launched by the president that year (National Nutrition Council, 1994). The main thrusts of the PPAN, which is part of the medium-term development plan of the country, are food security, micronutrient interventions, nutrition education, credit assistance, and food assistance. A National Micronutrient Team (NMAT) was created by the NNC to formulate and implement a national micronutrient program, which includes interventions (pharmacological supplements, food fortification, dietary education, and horticulture/agriculture) to control and prevent deficiencies (Philippine Department of Health, 1993).

In 1993 the NMAT conceived of and successfully launched the Araw ng Sangkap Pinoy (ASAP) or Micronutrient Day. Sangkap is the Filipino word for ingredient, a term used for micronutrients and Araw ng Sangkap Pinoy literally means “Day of Filipino Ingredients.” ASAP is a nationwide, one day-per-year effort to distribute 200,000 IU vitamin A supplements to children between 1 and 4 years old and iodine oil capsules to women of child-bearing age (Philippine Department of Health, 1993); however, the ASAP campaign did not use a pharmaceutical approach for iron because of the absence of a low-cost, acceptable iron preparation for young children and the difficulty in dispensing a 2- to 3-month supply of iron to families with infant and preschool children without replenishment. Instead, the program used education and a food-based approach to promote increased iron intake. Green leafy vegetables, particularly mahunggay (*Moringa olifera* or drumstick tree), were promoted in conjunction with nutrition education on the use of green leafy vegetables, fruits, fish, meat, and poultry whenever possible.

In the 1994 ASAP iron campaign, seeds for kangkong (*Ipomea batatas aquatica* or swamp cabbage) and camtoe leaves (*Ipomea batatas* or sweet potato) were distributed to the families receiving vitamin A and iodine supplements. The objective was to promote the production and consumption of iron- and vitamin C–containing vegetables.

The green, leafy vegetables promoted contain nonheme iron and inhibitors, such as tannin and phytates, and have a low bioavailability; however, the presence of ascorbate and other acids in these vegetables...
and fruits as well as the heme iron from the fish in the everyday Filipino diet may improve the bioavailability and enhance the absorption of nonheme iron (Madriga et al., 1991).

A nationwide cluster survey for vitamin A and iodine supplements was conducted in 1993 and included 1,568 respondents; 784 mothers of children aged 1 to 5 years old and 784 pregnant women from fourteen of the country’s fifteen administrative regions. Ninety percent of children had received a vitamin A capsule and 86 percent of pregnant women had received an iodine supplement. Of the respondents who answered the questions on whether they had received malunggay cuttings, only 17 percent said they did, of which 83 percent said they planted the cuttings (Philippine Department of Health, 1993). Of the 751 pregnant women who responded to the question of whether they received a packet of assorted vegetable seeds, such as kangkong (swamp cabbage), pepper, tomato, carrot, and others, 40 percent said they received seeds, of which 69 percent planted the seeds. The main reasons cited for not receiving the cuttings and seeds were that these were “not available at the Sangkap Center,” they were already “abundant in the area,” and the respondents “did not go to the Sangkap Center. “

Prospects for iron supplementation

In the current 10-year Philippine Plan of Action for Nutrition, priority for pharmaceutical iron supplements is given to pregnant women, followed by infants and preschoolers. The iron supplement program is a standard preventive health program in the Maternal and Child Health Services of the Department of Health. The public health administration is being devolved or decentralized to the local government units (LGUs). In this setup, the local executives through the health units plan and manage health and nutrition programs and projects in the municipality using local resources; however, certain activities such as the National Immunization Day (NID) and the ASAP are conducted nationwide in cooperation with the LGUs.

In the event that the government should implement a national policy for iron supplements for infants and preschool children, highest priority should be given to the 6-month- to 2-year-old age group, who are at greater risk of becoming iron deficient. The next important step for the Department of Health is to recommend a suitable iron supplement. This may be done in consultation with the Iron Expert Group that advises the NMAT.

In a recent consultation with a reputable drug company in the Philippines, it was suggested that two different iron syrup supplements could be prepared to provide 30 mg elemental iron per 5 ml and 15 mg elemental iron per 1 ml. The estimated cost of the preparation ranged from P6.75 (US$0.26) per 30 ml bottle to P13.90 (US$0.53) per 120 ml bottle, excluding the warehousing and distribution costs. A daily dose of the above preparations over a 2- to 3-week period may correct the mild to moderate anemia usually found in this age group. The addition of vitamin A to the iron syrup should be encouraged, because the added cost would be minimal and a fixed-dose combination could be both a cost-effective and convenient way to deliver both nutrients (Sapalo, 1995). Once the studies on the effectiveness of weekly iron supplementation on iron status are concluded, the delivery of a weekly fixed dose of iron/vitamin A combination could become doubly beneficial, because it has been established that weekly administration of a low dose of vitamin A is effective in reducing mortality in vitamin A-deficient children.
A potential delivery system for iron supplements for preschool children is through the NID (February and March) and ASAP (every October). The success of the NID and ASAP is primarily due to the massive support from the media, industry, private sector, government agencies, and external organization. Another reason for their success has been the establishment of thousands of “Patak Centers” (patak is a local term meaning “a drop”) for the NID and “Sangkap Centers” in schools, chapels, and residences throughout the country, where immunizations are conducted and micronutrients are distributed. The existence of these centers means that parents do not have to travel long distances for their child(ren) to receive the supplements (Solon, 1993).

Iron supplements can also be delivered through the regular health center system. By law, every village (barangay) can have a barangay health worker (BHW) with a specific role assigned by the health unit. The BHW may be assigned to a cluster of twenty-five to thirty households. The midwife, who is assigned to every five barangays, may utilize the BHW as the link to households thereby providing access to infants and preschoolers for supplementation with iron. This approach has been successfully used in delivering iron supplements to pregnant women (Solon, 1989).

Another approach to delivering iron supplements to children under 5 years old, which goes beyond the health system, is through the institutionalized Teacher-Child-Parent approach used by the Department of Education, Culture, and Sports (DECS), in which teachers are used to relay messages on health and nutrition to parents through the school child. Through this system, the students would be required to submit the names and ages of preschooler siblings living at home. The teacher would call a parent-teachers meeting for parents with preschool children and the iron supplement scheme would be discussed. The school child could become the carrier of the supplements, and educational messages on anemia could be relayed through the child to parents.

**Rice fortification**

Food fortification with iron is a practical approach where anemia is widespread. A study conducted by the FNRI identified rice as a vehicle for iron fortification (Florentino and Pedro, 1990). Rice is a suitable vehicle, because Filipinos are a rice-eating people and rice is consumed in constant amounts by different groups of the population, regardless of economic status.

Ferrous sulfate was chosen as the fortificant, because it has a high relative bioavailability, is widely used in iron fortification, and is the cheapest form of iron; however, ferrous sulfate produces off flavors and unacceptable color changes in cereals. Furthermore, even though Filipino housewives buy clean, white rice grains, they wash them two to three times prior to cooking. Because of these problems, a coating that would cover the surface of the rice grain was devised. The coating material is made from an ethyl cellulose-methyl cellulose-chloroform-isopropyl alcohol mix and gives the rice grains a creamy white color, which is hardly distinguishable from the unfortified rice grains. Moreover, the coating prevents discoloration and off flavors as well as the washing off of the iron fortificant prior to cooking.

The coated rice premix is processed by spray or roller mixing followed by air drying. Iron premix rice is evenly mixed with ordinary unfortified rice at a 1:200 dilution providing 2 mg elemental iron per 100 g rice, after compensating for losses during washing and cooking. The daily rice consumption of a child
below 6 years old is 143 g, and fortifying rice with 2 mg iron per 100 gm rice grains would be sufficient to meet the iron gap.

The iron premix rice was intended for nationwide coverage; however, rice cultivation and milling in the Philippines is not centralized: most of the rice is cultivated by tens of thousands of small farmers and milled in more than 20,000 mills throughout the country, thereby posing a huge problem in monitoring the quality of enrichment. In addition, about 10 to 15 percent of the rice produced is pounded in the home.

The National Food Authority (NFA), a government corporation that sells rice at controlled prices to the lowest income group, which comprises about 10 percent of the population, had planned to fortify the rice it procured, milled, and distributed; however, the government’s decision to discontinue the sale of NFA rice put a halt to the project before it could start.

An alternate plan was developed to involve local millers at the provincial level. Specifically, in the province of Nueva Ecija, the Grain Retailer’s Association (NEGRA) promotes and directly sells 5 gm sachets of premix rice to the community through the sari-sari store (village variety store) and public market. The enriched rice is green in color to distinguish it from ordinary rice grains. This would reduce the likelihood of mothers picking out and throwing away the premix grains and to prevent false promotion of uncolored, fortified rice. The color green was chosen after focus group discussions with consumers and retailers.

The rice fortification program is being implemented in five municipalities with the assistance of the local government, which disseminates information through print materials and radio messages. Information is given to the target population on the benefits and availability of the iron premix rice, as well as proper instructions on how to use the premix rice; however, few members of the NEGRA have participated in the project, thus limiting the distribution of the enriched rice to town centers and making it inaccessible to distant villages. Furthermore, slow sales have discouraged the NEGRA from pursuing the program. The final evaluation will determine the future course of action to be taken.

Iron-fortified complementary food

In developed countries, consumption of processed iron-fortified complementary foods has resulted in a decline of iron deficiency and anemia in infants and young children (Viteri, 1995). In the late 1970s, the Nutrition Center of the Philippines (NCP), a nongovernmental organization embarked on the formulation, production, and marketing of an energy- and protein-rich, vitamin A–fortified complementary food. The food known as “Nutri-pak” was designed to be used as a complementary food for infants and a supplementary food in the rehabilitation of underweight preschool children.

Between 1979 and 1981, there was an intensive social marketing campaign to sell “Nutri-pak” in 4,500 of the 42,000 villages in the country. This was supported by 32 Nutribuses, which were mobile units that carried TV monitors to show behaviorally designed videotapes about Nutri-pak and other nutrition and health topics, as well as a trained communicator who interacted with the viewers. This social marketing approach was used, because a 1978 study in Leyte showed that the videotape strategy was three times more effective than face-to-face communication and comics (Solon and Briones, 1983).
The Nutri-pak was well accepted by children and bought by parents. Likewise, the field trial on Nutri-pak showed that it reduced significantly the proportion of moderately and severely underweight children in the community (Solon and Briones, 1983). In the 1982 national nutrition survey, 11 percent of households mentioned that Nutri-pak was used in feeding children (Flores et al., 1985).

The NCP has improved this complementary food, and six varieties of Nutri-pak Plus are now available under the new name of "Nutri-pak Plus." Common to all these varieties is the iron premix rice. Each 100 gm pack of two servings contains approximately 8 mg of iron from premix rice and 270 g vitamin A.

The Nutri-pak Plus products are marketed by the Philippine Nutrified Corporation (PFC), a subsidiary of the NCP. The targeted clientele are health, social welfare, and private agencies, which use ready-to-cook food in their feeding programs in the health and daycare centers in Metro Manila and selected regions. The Department of Social Welfare and Development also uses Nutri-pak Plus as a relief food for children in disaster areas. The PFC plans to expand marketing Nutri-pak Plus gradually in the sari-sari stores and public markets at the village level. The price of the iron- and vitamin A--fortified, energy- and protein-rich Nutri-pak Plus ranges from US$0.23 to US$0.31 per 100 gm/pack.

**Iron-fortified wheat flour**

Although no data exist on the efficacy of iron-fortified wheat flour, data from developed countries suggest that iron-fortified flour has reduced and prevented anemia (Nestel, 1993). Wheat flour with a low extraction contains less phytic acid, fiber, and fat, making it a good vehicle for iron fortification; however, the shelf life of the flour will influence which iron compound can be used as the fortificant.

Wheat is not grown in the Philippines, and all wheat is imported. Wheat-based foods are consumed by all groups of the population, including the lower-income groups. A recent study on the consumption of wheat-based foods, particularly bread and biscuits among preschool children in randomly selected depressed areas in the country, showed that 80 percent of preschoolers consumed bread or biscuits daily (Florecio, unpublished).

Twelve wheat millers operate in the country, all in the Metro Manila area; they mill 1.3 million MT of wheat flour annually. According to the Philippine Flour Millers Association, all wheat flour is enriched with iron (8 to 12 mg of iron/kg flour) and the B vitamins (1.8 mg thiamine/kg flour, 1.1 mg riboflavin/kg flour, and 15 mg niacin/kg flour) (Ching, 1995).

One of the NMAT's micronutrient initiatives has been to advocate food fortification, which has resulted in two of the big wheat flour millers becoming involved in vitamin A fortification of wheat flour. The potential to fortify wheat flour with iron is great; however, the NCP and Department of Health would

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1. *(a)* Champorado (chocolate porridge): iron premix rice, *monggo*, skinned milk, cocoa, and vegetable oil containing retinyl palmitate; *(b)* *monggo* (green gram): iron premix rice, green gram, skinned milk, and vegetable oil containing retinyl palmitate; *(c)* ginataan (coconut milk): iron premix rice, malagkit (glutinous rice), cocoa powder, dried *gabi* (taro), dried banana, and sugar containing retinyl palmitate 250-CWS; *(d)* *raisins and nuts*: iron premix rice, malagkit, cocoa powder, peanuts, raisins, and sugar containing retinyl palmitate 250-CWS; *(e)* chicken: iron premix rice, TVP (texture vegetable soy protein), *kasubha* (saffron flower), chicken flavor containing retinyl palmitate 250-CWS, and iodized salt and oil; and *(f)* *beef*: iron premix rice, TVP, dried carrots, beef flavor containing retinyl palmitate 250-CWS, and iodized salt and oil.
like first to succeed in fortifying flour with vitamin A before taking the next step, which is to persuade millers to double-fortify wheat flour with vitamin A and iron.

Dietary modification and education

One of the strategies to prevent iron deficiency is to reduce the consumption of iron absorption inhibitors and to promote the consumption of iron absorption enhancers, such as vitamin C and heme iron (De Maeyer et al., 1989). To do this, families need to be persuaded to add more nonheme and heme iron food more frequently to diets of preschool children. Adding *malunggay* (drumstick) leaves and ripe mango to a standard meal of rice and shellfish has been shown to increase the bioavailability of nonheme iron threefold (Madriga et al., 1991). Fish and shellfish are readily available and cheap in many coastal towns of the thousands of islands that make up the country. It is also possible to modify an infant’s diet by preparing complementary foods rich in iron and vitamin C, such as purées of raw fruits and cooked vegetables that are easy to prepare in the home. Parents need to be motivated and taught how to prepare such meals.

In the mid-1970s, the government implemented a special radio campaign in Iloilo Province (Manoff International, Inc., 1977) to inform and educate mothers about the right age to introduce complementary foods and the values of earlier feeding. Mothers were advised to add specially prepared adult foods such as fish, green leafy vegetables, and fats and oils to the widely used *lugaw* complementary rice porridge. After 6 months, 22 percent of mothers with children 3 to 9 months old gave their infants *lugaw* with either chopped fish, mashed vegetables, or cooking oil compared with 20 percent at the outset. Although the investigators admitted that mixing green leafy vegetables was one of the most difficult objectives to achieve for the younger age group, their adoption was similar to that for other foods. The amount and frequency of giving the recommended foods also increased.

Based on lessons learned from this social marketing project, many radio and TV programs followed to “sell” nutrition information to the public, especially the promotion of food rich in micronutrients. A Filipino advertising agency in collaboration with the NCP has mounted two nutrition campaigns through mass media. Both campaigns were supported by the Kapisanan ng mga Brodkaster ng Pilipinas (Philippine Association of Broadcasters), which broadcasts the materials for all TV and radio stations, including noncommercial stations, nationwide. One campaign, known as the Food Values Campaign, aimed to promote the nutritive “worth” of inexpensive, widely available foods and to increase acceptance and consumption of these inexpensive foods. This campaign was targeted to housewives and meal planners, particularly those in the low-income groups who were striving to meet their food needs (Solon et al., 1991). The following foods were promoted: five, dark green, leafy vegetables (*kangkong, malunggay, ampalaya, gabi*, and *saluyot*), two fruits rich in vitamin C (*guava and papaya*), and sea foods (*anchovies and shellfish*).

Although there was no presurvey, the advertising agency persuaded the Philippine Survey Research Center to include tracking questions about the campaign in one of their projects. The findings showed that 70 percent of viewers were aware of the advertisements and, among those, 86 percent could recall or even memorize portions of the advertisement and its source (printed material, TV, or radio), while 78 percent used the food items mentioned in the campaign.
The single biggest constraint in these campaigns has been the lack of funds, but the advertising agency and the NCP were able to reduce the costs and keep the program running. The bottomline in any dietary modification and education intervention is to get sustainable behavior change in that parents feed their children balanced meals, specifically with an adequate amount and the right quality of micronutrient-rich foods.

References


Discussion

Dr. Nestel asked Dr. Solon to comment on how the impact of the Nutri-pak on iron status is being monitored. Dr. Solon replied that the Nutri-pak is owned by the NCP, which is, therefore, responsible for monitoring. The extent to which it is used was picked up in a national survey that showed that 11 percent of households used Nutri-pak; however, due to the lack of resources, it is not possible to evaluate the impact of use on iron status.

Dr. Tomkins asked what percent of the poorer sections of society eat subsistence as opposed to centrally processed foods. Dr. Solon responded by saying Nutri-pak was really developed as an educational tool rather than as a commercial venture. The packet contains sachets of oil, rice, beans, and milk that are clearly identifiable but that the mother makes up. The advertising emphasized the different sachets by stating this is milk, this is rice, this is beans, and so forth, which can be bought in the market, so the mother has the option to make her own Nutri-pak using local ingredients or to buy it prepackaged. The packages sold for about 26 cents, which is one-half the price of Nestlé and other baby food products. Furthermore, it appeals to the Filipino taste. The most important thing is that the Nutri-pak can be brought to the village to be sold in both the village variety store and the public market.

Mr. Alnwick stated that he understood that plans are at an advanced stage to provide a combined iron and vitamin A supplement on the national immunization day and that adding vitamin A to the iron syrup or drops does not increase its price; however, he wondered how the distribution would be done on the national immunization days, that is, would mothers be given a bottle and told to take it home and dose their children daily or weekly and would there be any screening for hemoglobin status? Dr. Solon replied that the children brought to the centers are the same children that would be targeted for iron. The problem is that universal distribution will not be possible because of cost constraints, and some form of targeting is necessary. The latter could be based on nutritional status, that is, underweight or wasting.
The government’s policy on iron is that preschoolers are secondary to pregnant mothers, and the focus should be on pregnant women. If iron supplements are made available for children, every mother bringing a child will want a 120 ml bottle. Dr. Solon added that the liquid iron-vitamin A preparation has a shelf life of 1 month. The preparation would contain 5,000 IU vitamin A, and mothers would be told how much to administer.

Dr. Blum asked whether the vitamin A–iron product has already been developed or whether it is still in the research and development phase, because it is difficult to develop such a product with the shelf life required. Furthermore, liquid products tend to be more expensive than dry products. Dr. Blum also cautioned about the dose, regardless of whether the supplement is to be given daily or weekly, because of the risk of iron and vitamin A overdosing. Dr. Solon replied that the vitamin A content is only 5,000 IU and the supplement would only be given daily for 1 month, which would provide less vitamin A than a megadose capsule. If the megadose, vitamin A supplements continue to be distributed, then the iron preparation would not contain vitamin A.
Dietary iron deficiency is one of the most prevalent nutritional problems worldwide. Infants, young children, and women of reproductive age are the most vulnerable to iron deficiency (Hallberg, 1984). Iron deficiency in infancy and young children is a particular concern, because it can have adverse long-term physical and mental consequences. This paper reviews the prevalence of iron deficiency in infancy and early childhood in China, strategies for the elimination of iron deficiency, and results of the positive effect of iron-fortified cereals on reducing iron deficiency among infants in China.

Prevalence of iron deficiency in infancy and early childhood in China

The National Nutrition Survey (Chinese Hygienic Research Institute, 1982) showed that the weaning diet of Chinese infants consisted mainly of plant foods and rarely animal products such as meat, organ meat, eggs, or milk. Thus, the iron in the diet is primarily nonheme iron, which is not well absorbed. Furthermore, a large proportion of infants and young children in China are not consuming adequate levels of iron from the diet.

The Beijing Union Medical College Hospital has estimated that 100 million children in China suffer from nutritional anemia (Zhang, 1985). This estimate is derived from various studies conducted in the early and mid-1980s, which are summarized in table 12.1. More specifically, a study conducted in Chengdu (Liao et al., 1983) showed that the incidence of anemia was higher among infants under 12 months old than among children between 1 and 3 years old and among older children. Another study by Ma et al. (1983) showed that in Shanghai 46 percent of the anemia detected in infants under 6 months old and all the anemia in infants between 6 months and 2 years old was due to iron deficiency. Wang et al. (1986) found 16 percent of all children under 3 years old and 36 percent of infants 7 to 12 months living in urban Beijing were anemic, while in rural areas the corresponding figures were much higher at 35 percent and 49 percent respectively. The mean iron intake of these children was 8.3 mg per day, which is lower than the Chinese Recommended Daily Allowance (RDA) of 10 mg for infants and preschool children under 7 years (Chinese Nutrition Society, 1990); however, the hemoglobin (Hb) levels of the children increased after iron supplementation in the form of an iron-fortified soft drink, suggesting that a lack of dietary iron was the most probable cause of iron deficiency. The weaning diets of most infants consisted of rice porridge, vegetables, and some egg yolk. Occasionally the diet included a small amount of iron-rich foods.
The low bioavailability of dietary iron could be another reason for the high prevalence of anemia. Many clinicians in China believe the iron content in diets is adequate but the iron is not bioavailable in weaning foods. These impressions are based on the high carbohydrate content of traditional weaning foods, in which there is a high probability that the diet contains high levels of substances, such as phytates and oxalates, that interfere with iron absorption. Furthermore, infant diets are low in meat, fish, and ascorbic acid, which promote the absorption of iron.

### Strategies for eradicating iron deficiency

The high prevalence of anemia among young children in China is a serious problem. To minimize and eventually eliminate the problem, the following strategies are recommended.

**Promotion of breastfeeding**

In general, iron deficiency anemia among full-term, breast-fed infants is rare (Duncan et al., 1985). Although the iron content in breast milk is low, it is highly bioavailable. Indeed, between 50 and 80 percent of the iron in breast milk is utilized (Searinen, Siimes, and Dallman, 1977). Where mothers are not successful at breastfeeding, an iron-fortified infant formula is the best alternative.

**Education on infant feeding**

Parents should be advised that by the time an infant is 4 to 6 months old, iron-rich foods should be part of the infant's daily diet. An important consideration is to choose foods such as meat, organ meats, and fish, in which the iron is highly bioavailable. Foods that promote iron absorption, such as citrus fruit juices, should also be included in the meal.

**Food hygiene**

Food hygiene should be emphasized in nutrition education programs. Good food and environmental hygiene will minimize parasitic infestation and gastrointestinal infections that cause blood loss or inhibit iron absorption, both of which can result in anemia.

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**Table 12.1: Summary of surveys on iron status in China**

<table>
<thead>
<tr>
<th>Date</th>
<th>No. provinces and cities</th>
<th>Sample size</th>
<th>Age group</th>
<th>Hb cutoff (g/dl)</th>
<th>Percent anemic</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980–82</td>
<td>12</td>
<td>39,940</td>
<td>&lt;7 years</td>
<td>&lt;12</td>
<td>55.5</td>
<td>Li (1983)</td>
</tr>
<tr>
<td>1980–82</td>
<td>8</td>
<td>7,500</td>
<td>&lt;7 years</td>
<td>&lt;11</td>
<td>39.0</td>
<td>Li (1983)</td>
</tr>
<tr>
<td>1981</td>
<td>16</td>
<td>19,853</td>
<td>&lt;7 years</td>
<td>&lt;11</td>
<td>37.9</td>
<td>Hu (1985)</td>
</tr>
</tbody>
</table>
Iron supplements

Ferrous sulphate is an effective oral therapy for treating iron deficiency. The effectiveness of this treatment has been demonstrated. An iron preparation made with heme iron is now available in China and has been shown to be efficacious.

Food fortification

In China, iron-fortified juices and drinks, developed in Beijing and Guangzhou and the iron-fortified instant baby foods manufactured by Heinz-UFE Ltd. in Guangzhou can be used to eliminate iron deficiency anemia in infants and young children. Ferrous sulphate and ferric ammonium citrate, both of which are known to be relatively bioavailable, are used in fortification. The effectiveness of these foods in the prevention and treatment of iron deficiency has been confirmed by nutrition research and will be described in this paper; however, iron fortification of foods must be controlled by the government with advice from scientific experts to prevent excessive intake of iron. Parents should be advised that iron overload is harmful to human health but within a realistic context that does not give conflicting messages.

Iron-fortified infant cereals and iron deficiency in infants in China

Iron deficiency among infants can be eliminated through the use of iron-fortified infant foods and is effective in doing so in industrialized countries (Brown and Picciano, 1987; Yeung, Scythes, and Zimmerman, 1986). In the mid-1980s, Heinz-UFE Ltd. introduced the concept of fortifying infant cereals with iron in Guangzhou. Ferric ammonium citrate was the only form of iron available in China at that time, which was suitable for human consumption. Cereals were fortified with 40 mg iron/100 gm, providing 100 percent of the RDA per serving when 25 g/day are consumed.

A test of the efficacy of iron-fortified infant cereal in the prevention of iron deficiency in infants was conducted by the Beijing Children’s Hospital in August 1986. A total of 408 healthy infants of normal weight, length, and head circumference were recruited for the study. The infants were selected from three urban and one suburban district in Beijing. Parents were informed of the experimental protocol, and consent to participate in the study was obtained.

Of the 408 infants recruited, 64 (15.7 percent) for various reasons dropped out of the study. The remaining 344 infants were randomly divided into two groups, one experimental and one control. The two groups were matched for age and sex, as shown in table 12.2, as well as place of residence.

The infants in the experimental group were fed 25 g Heinz-UFE Nutritious Infant Cereal daily in addition to their usual traditional diets for 3 months. Within the experimental group, infants younger than 5 months old were fed the Nutritious Rice Cereal, which was designed as the first supplementary food for young infants, while those 5 months and older were fed the High Protein Cereal. Both types of cereal were fortified with ferric ammonium citrate to provide 40 mg of iron per 100 g of cereal. Infants in the control group were fed their usual traditional diet. Iron preparations and other iron-fortified foods were not permitted in the diet of either group of infants during the 3-month study period.
Table 12.2: Population Profile of Study Population

<table>
<thead>
<tr>
<th>Sex and age group</th>
<th>Total population n = 344</th>
<th>Intervention n = 170</th>
<th>Control n = 174</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Boys</td>
<td>54</td>
<td>56</td>
<td>53</td>
</tr>
<tr>
<td>Girls</td>
<td>46</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>&lt;5 months</td>
<td>27</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>&gt;5 months</td>
<td>73</td>
<td>75</td>
<td>70</td>
</tr>
</tbody>
</table>

A general physical examination, including measurements of weight, length, and head circumference were taken for all infants at the start of the study. At this time and again at the end of the 3-month feeding trial, blood was drawn from the earlobe and analyzed for hemoglobin content, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC). Statistical analyses of differences between the two groups of infants was done using Student’s t-test.

The 408 recruited infants were healthy and within the normal ranges of length, weight, and head circumference for infants living in Beijing. Twenty-three percent had hemoglobin (Hb) levels below 12 g/dl (see table 12.3) and were classified as anemic. Among these, 10.1 percent had a Hb concentration below 11 g/dl, of which 2.2 percent were below 10 g/dl and 0.5 percent were below 9 g/dl. The lowest Hb measurement was 8.4 g/dl. Among the infants with a Hb concentration below 12 g/dl, 35.8 percent were microcytic (MCV < 80 μm³) and 15.8 percent were hypochromic (MCHC < 30 percent); thus, most of the anemia could be considered mild.

Table 12.3: Prevalence of anemia (Hb <12 g/dl) in infants 1 to 13 months old

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>n</th>
<th>Hb&lt;12 g/dl (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3</td>
<td>42</td>
<td>50.0</td>
</tr>
<tr>
<td>4–5</td>
<td>126</td>
<td>17.5</td>
</tr>
<tr>
<td>6–8</td>
<td>139</td>
<td>18.7</td>
</tr>
<tr>
<td>9–13</td>
<td>101</td>
<td>25.7</td>
</tr>
<tr>
<td>Overall</td>
<td>408</td>
<td>23.3</td>
</tr>
</tbody>
</table>

The prevalence of anemia (<12 g/dl) was higher in the suburban than urban districts (see table 12.4).

---

1. The mean hemoglobin concentrations in blood drawn from the earlobe have been found to be higher than those from finger tips (Li, Liao, and Yang, 1983). Because of this, a hemoglobin concentration below 12 g/dl is used to define anemia in this paper rather than the conventional 11 g/dl.
Table 12.4: Prevalence of anemia in infants by urban and suburban districts

<table>
<thead>
<tr>
<th>District</th>
<th>n</th>
<th>% with Hb levels below &lt;12 g/dl</th>
<th>&lt;11 g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban</td>
<td>355</td>
<td>9.9</td>
<td>22.3</td>
</tr>
<tr>
<td>Suburban</td>
<td>53</td>
<td>11.3</td>
<td>30.2</td>
</tr>
<tr>
<td>Overall</td>
<td>408</td>
<td>10.0</td>
<td>23.3</td>
</tr>
</tbody>
</table>

At the start of the study, the mean Hb concentration among infants in the experimental and control groups were similar at 13.3 g/dl and 13.8 g/dl respectively (see table 12.5). Twenty-five percent of infants in the control group and 18 percent in the experimental group had Hb levels below 12 g/dl.

Table 12.5: Mean standard deviation Hb concentration pre- and post-intervention prevalence of anemia

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean +SD Hb (g/dl) Before 3 months after</th>
<th>t-test</th>
<th>% Hb &lt;12g/dl Before 3 months after</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>170</td>
<td>13.3±1.0 13.6±1.0</td>
<td>p&lt;0.01</td>
<td>25.3 8.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>174</td>
<td>13.8±1.0 13.2±1.0</td>
<td>p&lt;0.05</td>
<td>18.4 19.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

At the end of the 3-month feeding trial, the mean hemoglobin concentration in the intervention group had increased significantly by 0.3 g/dl to 13.6 g/dl. Correspondingly, the proportion of infants having Hb levels below 12 g/dl had dropped significantly from 25 to 8 percent. The mean hemoglobin level in the control group fell significantly by 0.6 g/dl to 13.2 g/dl at the end of the study period, but the proportion of children having Hb below 12 g/dl did not change. These results show that the impact on iron status was only in the intervention group.

Among the children who had an Hb level below 12 g/dl at the start of the study, the mean hemoglobin levels in both groups of infants were similar (see table 12.6). At the end of the study, the infants in both groups attained mean Hb levels above the critical level of 12 g/dl. The gain in Hb concentration among infants fed the iron-fortified infant cereals was significantly greater than among those in the control group.

Table 12.6: Hemoglobin concentration in anemic infants (mean ± SD)

<table>
<thead>
<tr>
<th>Mean±SD</th>
<th>Intervention mean ± SD Hb (g/dl) n = 46</th>
<th>Control mean ± SD Hb (g/dl) n = 29</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of the study</td>
<td>10.96±0.86</td>
<td>11.06±0.72</td>
<td>ns</td>
</tr>
<tr>
<td>End of the study</td>
<td>12.99±1.50</td>
<td>12.40±1.72</td>
<td>ns</td>
</tr>
<tr>
<td>Gain in Hb level</td>
<td>2.00±1.48</td>
<td>1.27±1.55</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>
The Heinz-UFE Nutritious Infant Cereals are acceptable to Chinese infants, and the form of iron added to the cereals appears to be bioavailable, based on the impact on Hb levels. Indeed, these cereal formulae are efficacious in preventing and treating the iron deficiency that is prevalent among Chinese infants and young children (Chen, Zhang, and Zhang, 1990).

Summary

Iron deficiency is a prevalent nutrition problem in China. This is due to the low intake and low bioavailability of dietary iron. In the past decade, the economic development of the country has increased markedly. There has also been substantial growth in communication activities; thus, there is greater knowledge of nutritional needs as well as money to purchase more nutritious foods.

To eradicate iron deficiency in China, iron fortification of some commonly consumed foods is important. The data presented in this paper show that fortified complementary foods for infants are viable. To be effective in the population, however, nutrition education must be carried out concurrently.

China has a long history of traditional medicine. There is a willingness among the people to accept health information, be it scientifically proved or not. There is also a proliferation of copying what others are doing or providing; thus, there is a danger of misinformation and excessive consumption of what is purportedly "good." Misuse and excessive intake of iron supplement and iron-fortified foods are reported to be common.

For China, the methods for alleviating iron deficiency are generally available; however, there is a need to implement more effective ways of educating the populace about modern nutrition, control food fortification, and distribute nutritious foods more equitably.

References


The past: India’s National Nutritional Anemia Prophylaxis Program (1970–91)

In 1965 the Indian Council of Medical Research (ICMR) undertook a multicenter iron deficiency anemia (IDA) prevalence survey in six representative regions of India among children ages 1 to 5 years old in rural, tribal, and slum areas (ICMR, 1974). The prevalence of IDA was 54 percent, using the World Health Organization (WHO) hemoglobin (Hb) cutoff point of 11 g/dl. Among those anemic, 78 percent, 9 percent, and 2 percent were mildly, moderately, and severely so respectively.

Following the survey, the vertical National Nutritional Anemia Prophylaxis Program (NNAPP) was launched by the Union Ministry of Health in 1970. Pregnant women and children ages 1 to 11 years old were the target groups (Iyenger and Apte, 1970). Only children with Hb concentrations 8 g/dl or more were eligible to receive a tablet or 2 ml of syrup containing 20 mg elemental iron and 100 g folate for 100 days. Children with Hb levels below 8 g/dl were referred for treatment.

In 1977 the ICMR (1977) undertook a second multicenter survey on the prevalence of IDA, that is, 7 years after the NNAPP had been in place. The prevalence of IDA among children under 3 years old and children between 3 to 6 years old was 63 percent and 44 percent respectively, using an Hb concentration of 10.8 g/dl as the cutoff to define anemia. Dietary iron intake (6.3 g/day) was well below the ICMR’s Recommended Daily Allowance (RDA) of 15 to 20 mg iron/day. Average intakes were particularly low among children between 1 and 2 years old and those between 2 and 3 years old (9.6 g/dl), suggesting that the quantity of the cereal-pulse diets available to these children was grossly inadequate. This was the first indication that the NNAPP was not working well.

A study by the National Institute of Nutrition (Raman, Pawashe, and Rainalakshmi, 1992) showed that children between 1 and 3 years old were the most affected by IDA. The prevalence of IDA was 63 percent among children 12 to 23 months old, 67 percent among those 24 to 35 months old, and between 27 and 44 percent in the 3- to 5-year-old age group.
In 1984 the ICMR undertook another comprehensive survey in eleven states on about one-quarter of a million women and children (ICMR, 1989) to evaluate the NNAPP. The findings showed the following:

- The coverage of iron supplements among children 1 to 5 years old and 6 to 11 years old was only 0.8 percent, and 0.6 percent respectively. Coverage through the Anganwadis (village centers) of the All-India Integrated Child Development Services Program (ICDS) for children 1 to 6 years old was a mere 0.9 percent.

- The few children who received the iron supplements (Folifer tablet) received between one and thirty tablets, which was well below the stipulated 100 tablets.

- The major reason for poor coverage was the gross underestimation of the quantities of Folifer tablets/syrup required.

- The procurement and logistical delivery to the Primary and Sub-Health Centers was poor.

- Appreciation of IDA control among the providers and receivers was very poor.

- The micronutrient supplement program (iron and vitamin A), which are both vertical programs within the Union Health Ministry, were given low priority compared with the National Family Planning and other health programs.

The present: The National Nutritional Anemia Control Program (1991–)

The NNAPP was renamed the National Nutritional Anemia Control Program (NNACP) in 1991. Pregnant women and preschool children between the ages of 1 to 5 years old remain the priority groups. The policy improvements include the following:

- Integration of IDA control programs with relevant programs in the Ministry of Health and Family Welfare, the Department of Woman and Child in the Ministry of Human Resource Development, and the Department of Food in the Ministry of Food and Civil Supplies

- Multiple strategies or combinations thereof, including iron supplements, dietary modification/diversification, food fortification, and social marketing

- Implementing relevant information, education, and communication activities through the media, especially TV

- Declaring all children between the ages of 1 and 5 years old to be eligible to receive iron supplements irrespective of their Hb status, that is, blanket coverage to be implemented.
The future: An innovative pilot program in Rajasthan to improve the nutrition of children under 3 years old

Integrated child development services framework

The Integrated Child Development Services (ICDS) currently operates in all 32 states and union territories and covers 150 million preschoolers (6 months to 6 years old), of which 70 million are between 6 and 36 months old. This unique child development program delivers health, nutrition, nutrition health education, and preschool education services at the village level through the Anganwadi, which is served by a female worker (generally with primary school education) and a helper. Theoretically, a village with a total population of a thousand people would have 150 preschoolers. Generally, one-half of these children (i.e., 7.5 percent of the population) are eligible and enrolled in the ICDS program. One-half of these, or 3.7 percent of the total population, are under 36 months old and go to the Anganwadi for an on-site supplementary meal. These are the most undernourished and invisible children (National Institute of Public Cooperation and Child Development, 1992).

In 1994 the Government of India decided to give the ICDS a predominant position with respect to nutrition and child development and to make supplementary feeding the key intervention for improving the nutritional status of the young child. The program changed from on-site to take-home supplementary feeding (Gopaldas et al., 1975) so that management of child feeding remained the responsibility of the family and within the home. Given this framework, innovative programs have been developed to do the following:

- Improve the appropriateness and nutrient density of the take-home supplementary food.
- Fortify the supplementary food with iron or educate the family on the importance of crushing the 20 mg elemental iron tablet and either adding it to a food supplement or administering it to the child regularly after the supplementary meal has been eaten.
- Retrain the providers (functionaries of the ICDS) on the “dos” and “don’ts” of the take-home supplementary food program.
- Convince lactating mothers that, if they eat more food and take the iron tablets, they would have more breast milk for their infants. In this regard, a culturally acceptable take-home food supplement for the lactating mother may be more acceptable. “Methi-pak” is a well-accepted food throughout Western India (Rajasthan, Gujarat, Maharashtra, and Karnataka) and could be tried. It is an energy-dense confection made from wheat, fat, jaggery, and generous amounts of “methi” or fenugreek powder. Although the confection is bittersweet, it is considered to be a galactagogue that strengthens the mother-child dyad. Fenugreek is very rich in iron (6.5 mg iron/100g), but because it is bitter, the chances of it being shared in a take-home program are minimal (Mittal and Gopaldas, 1985; Mittal, 1986; Mittal and Gopaldas, 1986).
Figure 13.1: Population of preschool children in India and integrated child development services sanctioned projects in 1995

Total No of ICDS Projects in 1993: 3066

Figures in map denote size of the projects.

INDIA'S POPULATION, 1995
TOTAL - About 1 Billion
PRESCHOOL (0-6 years), 15%, 150 million
INFANTS (0-12 months), 3%, 30 million
WEANING AGE (6-24 months), 4%, 40 million.

India's Control Programs for IDA in Preschool Children

Rajasthan model of “Bal Poshan” within ICDS

Rajasthan was identified as a state with a dismally low participation of children under 3 years old in the ICDS program. Families live in scattered hamlets, and the very young children were not able to go to the Anganwadi for on-site meals. Furthermore, these children were fed little food once fully weaned. Other problems included the high prevalence of water- and soil-transmitted intestinal parasite infections, poor personal hygiene, and a high prevalence of upper respiratory infections and gastrointestinal tract morbidities. The children appeared pale, indicative of IDA. Added problems were that the Anganwadi workers were as illiterate as the parents and the State Health Department was not pulling its weight in delivering health services, which should have included the delivery of both iron and vitamin A supplements to the ICDS beneficiaries.

To address the above problems, a pilot program, known as Bal Poshan (nutriture of the young child), is being tested in five geographically dispersed community development blocks in Rajasthan, each with an average population of 100,000. Approximately 50,000 children between the ages of 6 and 36 months old are the target population.

A plan of action was developed (Gopaldas, 1992), which gave due consideration to the various problems. The main elements of the “nutrition package” include the following:

- A “single window” delivery in which the State’s Department of Woman and Child procures and delivers all the nutrition and nutrition-related inputs. The package consists of a fortnightly take-home, ready-to-eat (RTE) food supplement in powder form (about 1 kg), a small packet of about 100 g germinated wheat powder or amylase-rich food (ARF), a packet containing 14 Folifer tablets, and a small ration of edible oil. Other activities include biannual deworming and vitamin A campaigns, repeated demonstrations on how to use the ARF to make an energy-dense gruel, timely use of oral rehydration salts, and demonstrations on how to use the Folifer tablets (either crushed and administered or powdered and put into the cooked gruel). Parents collect refills every fortnight, and children should be brought once every 2 months for weighing.

- Training groups of women from the Development of Women and Children in Rural Areas (DWCRA) program to germinate and dry whole wheat grains. Women are given 2 kg of whole wheat, which they germinate and sun dry at home. The DWCRA supervisor weighs the germinated grains and pays the woman Rs8/kg (US$0.25/kg) for labor. The dry, germinated grains are ground in a grinder, and women pack and seal them in 100 g packets. The wheat ARF is sold back to the ICDS at Rs15/kg (US$0.50/kg). This mini-cottage industry generates income and is popular and easy to accomplish.

- Training the staff of three local Home Science Colleges in sampling and survey methods before conducting the baseline survey on 2,000 children under 3 years old in five experimental blocks. The follow-up impact survey will be conducted shortly. Despite some teething problems, the intervention appears to be doing well. The major problems have been the transfer of officials who started the project and almost universal illiteracy in the Anganwadi workers and parents.
Increasing the intake of the habitual diet and providing more take-home food would certainly increase the availability of dietary iron. Project Poshak delivers instant corn-soya-mix, which is fortified with a vitamin-mineral premix. The addition of a crushed tablet of Folifer to the weaning gruel would further fortify and enhance the iron content (Forman, 1987).

It is necessary periodically to deworm all children (preschoolers or schoolers) in rural, tribal, and slum areas. Periodic deworming has been shown to bring down the prevalence and severity of intestinal parasitic infection and helps to increase and sustain Hb levels for 3 to 3.5 months (Kanani, 1984; Gujral, Chattopadyay, and Mehan, 1989). Furthermore, iron and vitamin A have a beneficial synergistic effect (Gujral and Gopaldas, 1995).

**Delivering micronutrients and antihelminths to preschool siblings**

The midday meals program (MDMP) is an important supplementary feeding program for underprivileged elementary school children (6 to 15 years) in many states of India. Large budgetary enhancements have been made in the 1995 India Union budget for both primary education and the MDMP. Since 1994 the State of Gujarat included the School Health Inputs package (deworming, iron, and vitamin A supplements) to its ongoing MDMP. The impact evaluation, completed in one of the three study districts, has shown positive results particularly in terms of improved Hb levels, improved growth, a reduction in ocular signs of vitamin A deficiency, and a reduction in the prevalence of intestinal parasitic infections (Gopaldas and Gujral, unpublished). It has been suggested that school children between 10 and 15 years old be responsible for dosing one preschool sibling or another preschool child in their neighborhood. School children have been found to be much more convincing communicators to their family than health or nutrition educators. Even if one-half of the expected elementary school population (about 100 million) could do this, approximately 50 million preschool children could be reached.

**Commercialization and social marketing of foods fortified with iron**

As stated earlier, the ICDS only has the capacity to cover about 7 million children under 3 years old in the country. The government of India cannot forever be the provider of all goods and services free of cost. It is possible that affordable and accessible fortified food commodities would be bought even by low-income groups, if only they were available. Three products that could be easily fortified with a vitamin-mineral premix and would be suitable for the children under 3 years old would be the following:

- A ready-to-eat or prepared weaning mix fortified with a vitamin-mineral premix and ARF. It is anticipated that low-income families would buy it at about Rs30/kg (US$1.00/kg), because proprietary brands sell at five times as much.
- Double-fortified salt (iron and iodine) is ready to be marketed (Narasingha Rao, 1994). Iodized salt is being freely bought by the rich and the poor because it is readily available for only Rs3.0/kg (US$0.10/kg). Iodized salt has reduced the prevalence of iodine deficiency disorders (IDD) and doubly fortified salt could do the same for IDA.
The tremendous potential of nutrient dense and easily swallowed gruels for the weaning child has not been sufficiently recognized by the food industry. This can be easily done by marketing small 5 g sachets of barley, wheat, or millet ARF (germinated, sun dried, and powdered whole grains) fortified with a vitamin-mineral premix. A gruel can be made up using up to 30 g of any staple flour, the ARF (about 5 g), some sugar, and a little oil (if available) in 100 or 150 ml of water. This would provide a fortified gruel with an energy density of about 2 kcal/ml and concurrently address the twin problem of overt and covert hunger in the preschool child. Furthermore, unless a food is of the right consistency, that is, semiliquid, no weaning-age child can consume enough at one sitting to ingest about 100 to 200 kcal (Gopaldas and John, 1992; John and Gopaldas, 1993). Studies have shown that growth can be improved if a child between 6 to 24 months old is able to increase his food energy intake by about 150 kcal/day, over and above his meager home diet of about 450 kcal/day (Gopaldas and John, 1992).

The liquor industry in India is growing rapidly with the new liberalization policies. India has ten RTE plants making 100,000 MT of RTE per annum to be used in the ICDS for the weaning-age beneficiaries. The Government of India should make it mandatory that the liquor industry divert 10,000 MT of barley malt (an excellent source of ARF) to be incorporated in the 100,000 MT of RTE. It is a question of "spare some malt for the babies, not all for booze."

References


India's Control Programs for IDA in Preschool Children

Discussion

Dr. Premji commented that the idea of using school children to deliver hematinics to younger siblings at home is very good and, if it works, a major part of the problem could be solved; however, in situations such as Tanzania, anemia is also very prevalent in the school child. This is an issue on which it appears that nothing is being done for the anemic school children, yet they are to deliver hematinics to the younger children at home. Dr. Gopaldas replied that a study was done on whether school children could be effective in taking home food to his younger brothers and sisters in Project Poshak, which went very well. The deworming and vitamin A campaigns are done twice a year, but administering iron tablets would have to be done every day. This needs to be tried, and people need to keep an open mind about this. Illiterate parents trust and listen to their school-going child. Dr. Solon agreed that the school child is an important component in delivering both nutritional messages and goods to the home. Furthermore, school children can be used as a source of health statistics, for example, identifying pregnant women and morbidity patterns but not, perhaps, mental disease that may be the result of iodine deficiency.

Dr. Kevany asked whether the delivery of iron supplements is envisioned to be continued indefinitely and whether deworming twice a year is sufficient or varied according to ecological zones and health conditions. Dr. Gopaldas responded that she personally felt the ICDS program will continue for a long time, although many of her nutrition colleagues in India, do not share this view and feel more has to be done on diet diversification; however, iron supplements are very cheap and readily available and an aggressive approach is needed to eliminate iron deficiency, which affects physical work capacity, morbidity, and many other things. Dr. Gopaldas stated that deworming twice a year is feasible and gives a good cure rate.

Dr. Brabin commented that in a population, as in India, where there are a large number of vegetarians, there could be a significant number of children with B12 or even folate deficiency. He asked whether an improved iron status might show a more obvious problem of folate deficiency anemia, because iron deficiency can mask folate deficiency anemia and this may become more apparent as the program succeeds. Dr. Gopaldas replied that she did not think this would be a problem because folate is given with the iron supplements. In terms of vitamin B12 deficiency, she thought it better to first tackle the bigger problem of iron-folate deficiency, which is the cause of 90 percent of anemia. Dr. Gopaldas went on to say that, on paper, the ICDS gives iron-folate to preschoolers. Whether it is going into the child or not is unknown, because children below 3 years old are a very invisible age group: they are never brought to the center, so program inputs are sent home to the extent possible, but whether the parents follow the instructions is not known. Indians tend to regard the government as the nursemaid and believe the government should take care of children; however, after 19 years, the government has decided that the responsibility for children's welfare lies with the parents. Government is willing to provide the inputs every 14 days, but parents must dose and feed their own children, which is probably a good move on the part of the government.

Dr. Lorri asked about the source of the ARF and the level that should be added to food. Dr. Gopaldas replied that the government advises that ARF be added at a level of 5 percent. The problem is that there are no suppliers. The best source would be germinated barley, which is available from the liquor industry, because barley ARF is better than any other ARF. If this is not possible, the ten RTE plants must get funds and set up their own ARF units using appropriate locally available foods, so long as they are not sorghum, maize, yeast or rice. Rice does not germinate properly.
Dr. Lorri also asked about the double fortification of salt given the problems associated with hygroscopy. Dr. Gopaldas replied that she did not think discoloration should be a deterrent to using doubly fortified salt. Dr. Blum commented that it is important to clarify that there is a difference between a fortified food that is used at the household level and a specially formulated product (doubly fortified salt) that is applied to special products. If a cost-effective high-tech product can be added to a food, such as a weaning food, and is shown to be efficacious, this is clearly an excellent solution that should be implemented; however, if it is to be used at the household level, there may be problems because the purity of the salt is critical. In developed countries, salt is highly purified, which means there is no decomposition of iodine. In many developing countries salt is not pure, and the impurities interact with iron and iodine, which decomposes chlorine; thus, there are different applications for different purposes.

Dr. Solon asked whether micronutrients are included in the school curriculum. Dr. Gopaldas replied that this is very much part of the program involving school children. The Gujarat government has made it very simple, which is appropriate, by telling the child what each nutrient is and its impact on him/her without confusing the child by putting a lot of theory in it. The idea is that the child will tell his/her family. In terms of the more widespread education effort, which UNICEF is supporting in eight states, tier on tier of primary school teachers are being trained in public health and nutrition to deliver messages to the children. Dr. Tomkins mentioned that a recent, independent, evaluation in Andhra Pradesh found that there were complaints from the parents, because school children were coming home saying, “please, can we have some green vegetables” and “please, can you buy us some iron syrup because that is what we learned in school,” suggesting that this approach is having a positive impact.
14. TANZANIA: MALARIA CONTROL USING INSECTICIDE-IMPREGNATED BEDNETS

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Malaria is a major health problem in Tanzania, especially in the coastal areas and is often associated with anemia. This presentation describes an insecticide-impregnated bednet program to control malaria in Bagamoyo District. Details of the study have been published elsewhere (Premji, Hamisi, Shiff, et al., 1995; Makemba et al., 1995). The area is holoendemic; Plasmodium falciparum malaria has exceptionally high entomological inoculation rates (Shiff et al., 1995). Thirteen village communities were involved in the study. These villages were divided into four groups based on geographic areas for convenience of operation and to allow sequential implementation of the intervention in a systematic manner; thus, the program was implemented in 6-month phases, commencing with group I in April 1993 and the remaining groups following sequentially. The phased implementation enabled the collection of baseline data prior to the intervention and follow-up for a full year of the health status of children sleeping under treated bednets in group II villages and comparison of this data with children in the group VI villages who had not yet received their nets. The results presented here compare the prevalence of anemia pre- and post-intervention in seven villages in two of these areas.

Data were collected toward the end of the rainy season, which is the period of peak malaria transmission, and continued over approximately 5 months. Data were collected on randomly selected children between the ages of 6 and 40 months old over a 20-week period starting in May 1992. At enrollment, children were provided with a medical examination. In addition, age, weight, spleen size, temperature, immunization records, and history of recent illness were recorded. Blood was taken to measure packed cell volume (PCV) and blood slides were made for malaria counts. All children were treated with the antimalarial Fansidar to clear any current infection. Children were followed up after 1, 12, and 20 weeks when the examinations and measurements carried out at enrollment were repeated. (Premji, Hamisi, Shiff, et al., 1995).

Any enrolled child who developed a fever (>37.5°C) at any time during this follow-up period was treated with chloroquine by a trained village health worker, who also made a blood slide. These were later read by one of the research team. This also indicates that chemotherapy for clinically determined malaria was available on demand.

The results are presented in table 14.1, which records the sequence of events in the villages of groups II and IV from initial recruitment in May 1992 through the end of the project in November 1994. At baseline (May 1992), none of the children were sleeping under bednets. Out of a total of 335 children (between 6 and 40 months old), 77 percent were classified as anemic with PCV below 33 percent (DeMaeyer, 1985). The prevalence of anemia among children from the two groups of villages was similar (OR = 0.91). Following 20 weeks of baseline observation, there was no change in the prevalence
of anemia between the two groups; however, children who were anemic at baseline suffered clinical attacks of malaria 5.8 more times than those who had not been anemic.

### Table 14.1: Prevalence of anemia according to bednet treatment with malarial insecticide

<table>
<thead>
<tr>
<th>Date</th>
<th>Group II villages</th>
<th>Group IV villages</th>
<th>Intergroup difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Months&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n</td>
<td>% anemic</td>
</tr>
<tr>
<td>May 1992</td>
<td>0</td>
<td>142</td>
<td>76.1</td>
</tr>
<tr>
<td>May 1993</td>
<td>6</td>
<td>185</td>
<td>54.0</td>
</tr>
<tr>
<td>Oct. 1993</td>
<td>11</td>
<td>146</td>
<td>24.0</td>
</tr>
<tr>
<td>May 1994</td>
<td>17</td>
<td>119</td>
<td>45.3</td>
</tr>
<tr>
<td>Nov. 1994</td>
<td>24</td>
<td>96</td>
<td>28.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Months postintervention (0 means no intervention has commenced).

Insecticide-impregnated bednets were made available to group II in November 1992, 6 months after the study began. Most children (88 percent) in group II slept under the insecticide-impregnated bednets, however, because the nets were not provided free of charge, a small number of children were still unprotected. In other words, children in group II became the intervention group, while those in group IV remained the control group. The results show that anemia had dropped to 54 percent in the intervention area, while 73 percent of children in the control area were still anemic, (OR = 0.46) and this decline was statistically significant. By October 1993, after 11 months of implementation, the protected children had improved further when compared with the controls (OR = 0.29), representing a 46 percent decline in the prevalence of anemia.

In the design of the program, net sales in group IV villages commenced in October-November 1993, which ended the period of parallel observations. With implementation of the intervention in group IV, a decline occurred in the prevalence of anemia among children that was similar to that seen previously in group II and the difference between group II and group IV became less obvious (OR = 0.73 in May 1994 and 0.90 in November 1994).

These results suggest that the prevalence of anemia can be reduced by 40 to 50 percent after 12 months with the use of insecticide-impregnated bednets. They stress the importance of malaria in the etiology of childhood anemia. Other data (Premji, Lubega, Hamisi, et al., 1995) indicate that use of treated bednets reduced other malaria indicators. The challenge, therefore, is to have a sustainable program in which bednets are obtained, used, and do indeed get impregnated on a 6-month cycle.

Throughout the course of the study, it was clear that even in the absence of control measures, there was a strong negative, age-specific association between anemia and age of the child. In other words, the prevalence of anemia declined with age. The critical age appears to be 2 years old, after which the prevalence of anemia decreases in older children (see figure 14.1). The importance of anemia in the health of this age group is suggested by the fact that malaria-specific mortality is very high among children between 2 and 24 months old. One aspect of the project was to record any deaths in children under 5 years old and attempt to determine the cause of death through verbal autopsies carried out by a
Tanzania: Malaria Control Using Insecticide-Impregnated Bednets

trained medical assistant. The verbal autopsies were reviewed independently by two physicians. One-hundred and ninety deaths were recorded between June 1992 and June 1994. Of these, 136 (72 percent) were among children between 2 and 24 months old. A study of autopsies on children for whom malaria was specified as the cause of death showed that the majority had characteristics of congestive cardiac failure, suggesting that anemia is very likely a major cause of malaria-specific mortality among young children in this area.

**Figure 14.1: Age prevalence of anemia in children in Bagamoyo District, Coastal Tanzania**

![Figure 14.1: Age prevalence of anemia in children in Bagamoyo District, Coastal Tanzania](image)

**Analysis of 325 children at enrollment**

The progression to anemia that all too often applies to Tanzania is summarized in figure 14.2. As shown by Redd et al. (1994), an infected placenta is an important risk factor for anemia in children. It may be that some of these children are born with iron depletion, which is characterized by diminished iron stores (Chimsuku et al., 1994). Under normal feeding practices during the first year, the child depends on breast milk, which is a poor source of iron after 6 months. Following that, the child is gradually weaned on staple cereals, roots, or tubers, which are also low in iron. Between the ages of 1 and 2 years old, such a child is likely to be faced with repeated bouts of malaria, diarrhea, pneumonia, perhaps measles, and other problems. If the child survives, he or she is then exposed to nematode infestations, such as hookworm, *Trichuris*, and *Ascaris*. The net result is malnourishment and anemia. In addition to the above, genetic and cultural factors can also be associated with anemia. Among the former is sickle-cell trait, which is quite prevalent in Tanzania. Cultural factors found to occur in rural areas include uvulectomy, which is believed to prevent coughs and respiratory ailments. Infants or young children with coughs may be taken to a traditional healer who cuts off the uvula. A history of uvulectomy is definitely an important causal factor for anemia, because there is profuse hemorrhage following the procedure.
Figure 14.2: Staircase of anemia: diminished iron stores with no effect on hemoglobin production or tissue enzymes that is characterised by enhanced absorption of dietary iron.

Although malaria is known to cause anemia, and anemia appears to increase susceptibility to clinical episodes of malaria, a number of questions with programmatic implications still remain unanswered. These include the long-term effects of low parasitemia on the development of anemia, susceptibility to reinfection, and acquisition of antimalarial immunity. Additionally, there is the issue whether prophylactic treatment using iron and vitamins can change the occurrence of anemia and episodes of malaria both in the mother and in the child. Reports exist that if iron status is improved, people may be more susceptible to malaria (Oppenheimer et al., 1986). This needs further investigation. There is also the serious problem of chloroquine-resistant malaria parasites, which implies that giving chloroquine as a symptomatic cure does not necessarily clear the parasitaemia. This raises the question: to what extent is chronic parasitemia the cause of anemia both in the mother and child? There are also issues relating to the pathogenesis of anemia and how this relates to susceptibility to cerebral malaria. Anemia is more common among children under 3 years old, whereas cerebral malaria is more common among children over 3 years old. Finally, the prognostic factors for developing severe anemia in anemic individuals are not clear and should be investigated to assist in the goal of preventing malaria-related mortality.
References


Discussion

Dr. Menéndez asked for clarification of the correlation between anemia and protection against malaria. Dr. Premji responded by first stating that there is still no standard definition for malaria, which differs among researchers. In this study, a malaria episode was defined as having a temperature over 37.5°C and a positive blood slide. All children were cleared of parasites at the outset of the study and the number of malaria episodes encountered during 20 weeks was recorded. A comparison of the number of malaria episodes in the following 20 weeks between children who were anemic at the beginning of the study and those who were not showed that the anemic children experienced about six times more malaria than those who were not anemic.

Dr. Tomkins commented that this project was clearly an effective antimalarial project to reduce the prevalence of anemia and wondered whether anyone had looked at the impact of bednets plus iron, as opposed to bednets alone, on iron status. Dr. Premji replied that when the clinics were started and many children were identified as being anemic, about 100 blood slides were made and given to a hematologist. The results showed 42 percent of the anemic children had iron deficiency with a microcytic hypochromic picture, 25 percent showed a hemolytic normochromic picture, 10.5 percent a macrocytic picture, and 5.3 percent a combined deficiency; thus, the majority of these children had iron deficiency; however, the question of why iron deficiency should develop with malaria has not been resolved, given that iron is not lost in malaria. There are speculations that iron is immobilized in the bone marrow. A placebo-controlled intervention is currently being set up in which iron and other supplements, for example, vitamin C, will be given; however, the children will not receive insecticide-impregnated bednets because the budget does not allow for this. The question, thus, cannot be properly answered.

Mr. Alnwick commented that malaria control does not need to be justified as a mechanism for reducing anemia. Mortality from malaria is horrendous, and malaria control programs have their own justification; however, at the end of the day, is there sufficient evidence to say that if malaria control is promoted, for example, using bednets, there can also be legitimate claim that this is going to have a beneficial effect on reducing the prevalence of anemia in children and, therefore, the damaging effects of anemia? Mr. Alnwick also noted that children with malaria are very sick, lose their appetite, and do not eat very much, which surely means that food intake goes down during malaria. This is a possible mechanism for developing anemia. Dr. Premji agreed but noted that no data exist on energy and micronutrient intake during an acute malaria episode. In parts of Tanzania, a child can be expected to have at least five malarial episodes a year; this will affect food intake during these times. Even when not sick, food intake may be marginal. Dr. Fleming noted that the interactions observed could be multiple because the anemia could be increasing the absorption of iron. He asked whether water-clear plasma, which is seen with iron deficiency, was found. Colorless plasma is a very useful field test for iron deficiency. Dr. Premji replied that plasma coloring was not investigated in this study.

Dr. Stoltzfus commented that Dr. Menéndez said their vaccine trial in Tanzania appeared to be efficacious in preventing malaria but did not improve anemia or hemoglobin status, while the bednet program did. She asked if the nature of the interventions were different in their potential effect on hemoglobin or were the environments within Tanzania strikingly different? Dr. Premji replied that the epidemiology of malaria in the two areas is similar. The reason for the difference in the morbidity between the two interventions is because the bednet program is a vector control strategy, that is, it reduces overall transmission, while the vaccine is a disease control strategy that will reduce morbidity.
With vaccination, immunity will go up. The introduction of insecticide-impregnated bednets will change the environmental scenario and reduce immunity. Malaria vaccine could complement vector control by increasing immunity, which would be a good strategy to prevent malaria epidemics; however, this is an intervention for the future.

Dr. Menéndez commented that an intervention trial has been started in Tanzania to answer the critical question of whether iron supplements should be included in malaria control programs to control anemia. The trial includes four groups of children, one group receiving only iron supplements, another receiving chemical prophylaxis for malaria, another both iron supplements and the chemical prophylaxis, and another receiving neither, that is, a control group. A total of 800 normal healthy children born at the hospital will be recruited into the study. To date, 400 have been enrolled. All the iron parameters will be measured to be able to make a good assessment and comparisons of iron status between the groups.

Dr. Brabin noted that Dr. Premji had mentioned that the reduction in malaria incidence might lead to an increased susceptibility to malaria in older children. In older children, those with cerebral malaria are sometimes less anemic, and there seems to be some association between cerebral malaria and less risk of anemia. Dr. Brabin asked whether children are to be followed through to later life to see what happens to their anemia, their risk of malaria, and the risk of developing cerebral malaria. Dr. Premji replied that he would very much like to do a prospective field study that followed the same cohort of children over time, but the chances of getting such funding are almost nil.
15. MALARIA, ANEMIA, AND THEIR CONTROL IN THE GAMBIA

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In The Gambia, malaria is seasonal with moderate levels of transmission (i.e., fewer than ten infective bites per year) during a few months of the rainy season (July to December). The dominant parasite is *Plasmodium falciparum* and the dominant vectors belong to the *Anopheles gambiae giles* species complex. Among the latter, the saltwater species *Anopheles melas* breeds extensively in mangrove swamps, which border the River Gambia estuarine's lower reaches, while *Anopheles gambiae sensu strictu* is the dominant vector throughout the rest of the country and *Anopheles arabiensis* occurs in small numbers throughout the hinterland (Greenwood and Pickering, 1993).

After promising results from small-scale trials undertaken with untreated and treated bednets (Snow, Rowan, and Greenwood, 1987), a large controlled trial was undertaken in a population of 20,000 people in central Gambia. Sleeping under insecticide-treated bednets was associated with a reduction in overall mortality of about 60 percent in children ages 1 to 4 years old (Alonso et al., 1991). Episodes of fever associated with malaria parasitemia were reduced by 45 percent (Alonso et al., 1993). On the basis of these results, the Government of The Gambia with support from the World Health Organization (WHO) initiated a National Program of Insecticide-treated Bednets (NIBP), with the objective of introducing this form of malaria control into all large villages in The Gambia over a 2- to 3-year period.

At the beginning of 1991 five areas were chosen as sentinel sites to reflect the varied cultural and ecological settings within The Gambia. Within these areas, 104 Primary Health Care villages were identified. The villages were paired by size within each area. The intervention was implemented in one randomly chosen village in each pair in June and July 1992 and in the other of the pair the following year. A census of the villages under surveillance was done between March and May 1992.

The treatment of bednets was associated with a reduction in all-cause mortality in all age groups in all areas, with the exception of children between 1 and 2 years old in one of the sentinel sites (area 5) (D'Alessandro et al., 1995). Overall, a 25 percent reduction in mortality in children ages 1 to 9 years old was seen in treated villages. Excluding area 5, a 38 percent reduction in mortality was found.

Morbidity surveys were done at the end of the 1991 rainy season (preintervention) and at the end of the 1992 rainy season (postintervention). Each year, 1,500 children, one-half from treated and one-half from untreated villages, were sampled, 300 from each of the five areas. Clinical examinations were done, anthropometric measurements taken, body temperature recorded, and a blood sample collected by finger prick to determine the packed cell volume (PCV) and for preparing thick blood films.
Iron Interventions for Child Survival

Overall, 67 percent of children resident in treated villages regularly slept under insecticide-treated bednets, but this percentage varied from area to area. About 10 percent of all children and 23 percent of those having fever and a high density of parasitemia were anemic (PCV 25 percent).

Overall, the reductions in the percentage of parasitemia, high density parasitemia, splenomegaly, and anemia were not statistically significant. The increase in PCV was also not statistically significant; however, if area 5 was excluded from the analysis, there was a statistically significant reduction of about 50 percent in both parasitemia and high density parasitemia and an increase of 0.9 percent in mean PCV (D’Alessandro et al., in press).

After the intervention, the mean z-scores for weight-for-age and weight-for-height were higher among children in treated villages than those in untreated villages. The mean z-score of height-for-age was similar in both groups of children.

All malarialimic indices were lower and the mean PCV higher in children who slept regularly under an insecticide-treated bednet compared with those who did not use a net (D’Alessandro et al., in press). After controlling for area, age, sex, type of village, and ethnic group, the odds ratio for parasitemia, high density parasitemia, and an enlarged spleen was about two times higher in children who had no nets than in children who slept regularly under an insecticide-treated bednet. The difference in the mean PCV was 1.1 percent.

In a country in which bednets are widely used and that has a good Primary Health Care system, it is possible to achieve insecticide treatment of bednets at a national level with a satisfactory reduction in child mortality and malaria morbidity. In 1993 a cost-recovery program was introduced. Villages were given free insecticide during the first year of intervention and asked to pay 5.00 Dalasi (US$0.5) per bednet treated. Unfortunately, this led to a dramatic drop in coverage and a return of child mortality rates in these villages to their preintervention values. Finding new ways of financing such programs is now a priority.

References


**Discussion**

Dr. Jalal asked how much behavior change is needed to make the best use of nets, assuming that the inputs are available. Dr. D'Alessandro replied that from an operational point of view, this is not an easy intervention to implement because all the bednets have to be treated within a short period of time; however, it is not yet clear whether the mosquitoes are killed or are repelled by the insecticide. The question of how to use the insecticide-impregnated bednets is not as important as how to use untreated bednets, in which case the net has to be tucked under the mattress. With insecticide-treated bednets, the bednets can just hang and the most important factor is that people sleep under it. In areas where people are not used to sleeping under bednets, education and promotion are important. A trial in Ghana and another in Kenya, where people do not normally use bednets, is looking at compliance; the results should be available later this year.

Dr. Nestel asked Dr. Premji to comment on how the insecticide-impregnated bednet program was set up in Tanzania, particularly the issue of the community purchasing the insecticide themselves rather than it being a free handout from the government. Dr. Premji replied that they have seen a decrease in vector capacity over the last 2 years. Vector capacity is calculated from the entomological inoculation rate, which means that for a mosquito to transmit malaria, it has to bite, pick up the gametocyte, survive a minimum of 10 days, and then bite another person to transmit the sporocytes. If the mosquito can be killed within that 10-day period, transmission can be reduced. Initially, the mosquitoes are repelled; however, in the long term, because the entomological inoculation rate goes down, the mosquitoes are killed.

When the program was started, nets were not given out free of charge to a community, because it was felt that this would not be appropriate. A committee was set up in each of the 13 villages. Using the committees, it was possible to achieve a coverage of 70 to 80 percent. The impact of the net, however, depends on the mass effect because if one house has a net, the mosquito will be repelled and go to another house and so on; thus, the higher the coverage the better the impact. In 1992 nets were first sold at around 800 Tanzanian shillings each (about US$1.50), which included a 15 percent subsidy. The money collected from each village was deposited in the bank and the account is being run by the villagers themselves as a revolving fund. Each village in the study area now has an average of 1 million Tanzanian shillings; it is intended that this money be used by the villagers to continue and expand the program. To collect a million Tanzanian shillings in a rural setting is an immense task; some government officials, with whom this revolving fund has been discussed, are really surprised at how this was achieved. At the time the village bednet committees were set up, there were many committees, for example, health committees, water committees, latrine committees, but none of the committee members were being paid. Instead, they were doing voluntary or charitable work. Because of this, the committees were essentially redundant and never met. In setting up the bednet committee, it became apparent that a major deficiency with the other committees was that members were not paid, despite their input. The
money being collected in the bednet program is banked and generates interest, which is used to pass committee members a modest allowance. In other words, the interest on the capital investment in the bank is the "lubricant" for the committee's functioning.
16. ANEMIA IN NORTHERN NIGERIA AND TWO SOUTH AFRICAN CITIES

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This presentation is based on two studies: one in northern Nigeria (Fleming and Werbliska, 1982) and another that was recently conducted in Johannesburg and Soweto (Wagstaff et al., 1995). The northern Nigeria study was in an area where malaria was hyperendemic and the vector capacity great. The number of mosquito/person bites during the rainy season was on average 250 per night. The number of malaria infections was over 100 per annum. All cross-sectional surveys showed that, among children under 4 years old, 80 to 90 percent had parasitaemia with *P. falciparum* being the dominant species. The infant mortality rate was between 150 and 250 per 1,000; this was reduced by two-thirds by antimalarial interventions over two wet seasons and the intervening dry season. Two percent of all infants were born with sickle-cell disease; 30 percent of the adults were carriers. The study set out to identify the causes of anemia seen in preschool children presenting at the hospital. To do this, the first 24 preschool children between the ages of 3 and 36 months old who came to the outpatient wards on any weekday over a 5-month period were included in the study. The outpatient services were provided free of charge. A total of 664 children were examined, of whom 11 percent had a packed cell volume (PCV) below 30. Fifty-nine of these 71 anemic children were enrolled in the study and matched by age and gender to nonanemic controls. Table 16.1 shows the age at presentation with anemia; the peak of anemia is around 1 year of life. The PCV for the majority of anemic children was between 20 and 29 percent, but the PCV fell as low as 8 percent, indicating severe anemia.

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The majority of children, both anemic and nonanemic, showed clinical evidence of infection (71 and 81 percent respectively), but the infections were generally trivial or mild. Nevertheless, these pyogenic infections were having a significant effect on erythropoiesis in the anemic children as eight (14 percent) of the fifty-seven children, in whom aspiration of bone marrow was satisfactory, had hypoplastic erythropoiesis associated with bacterial infections. *P. falciparum* malaria contributed to 62 percent of the anemic cases, based on malaria parasitaemia or malarial pigment in bone marrow.

Iron deficiency, measured as the absence of iron in the bone marrow, was found in 60 percent of the children, but none of the other measures of iron deficiency anemia were present. In fact, there was an inverse correlation between the presence of iron in bone marrow and red cell count, suggesting that infection was immobilizing iron and causing anemia. The presence of iron in the bone marrow was directly related to the number of metamyelocytes in the peripheral blood. Folate deficiency was seen in 40 percent of the anemic children by megaloblastic erythropoiesis. Protein deficiency, diagnosed by hypoalbuminemia, was also present in 30 percent of the anemic children. Over one-quarter of these anemic children had sickle-cell disease. The above shows that any child who was anemic had up to four causes of identifiable anemia, which were not simply coincidental. Immunity is depressed by infection, in particular malaria and measles. (Today, HIV is a very potent cause of anemia in Africa, although not highly prevalent in this particular age group.) Decreased immunity leading to secondary infection—upper respiratory, lower respiratory, and gastrointestinal tract infections—commonly complicates the course of malaria.

Infections cause malnutrition through anorexia, malabsorption, protein, or other losing enteropathies, interference with iron metabolism, and blocking of dihydrofolate reductase by pyrexia. Even in areas where food is plentiful, kwashiorkor can be found. Dietary inadequacy is only one contributory factor to malnutrition as seen in the African rural population. Protein-energy malnutrition, iron deficiency, folate deficiency, all in their different ways affect immunity, leading many children to get caught in a vicious cycle. Even when there are identifiable causes of anemia such as sickle-cell disease, children enter this cycle because the sickle-cell disease has immune defects as well as liability for folate deficiency. Sickle-cell disease cannot simply be considered the sole cause of anemia, because that child is already caught in the vicious cycle.

There is a serious question of whether vertical interventions, such as iron supplements, would have an impact on the prevalence or severity of anemia in the African setting. In northern Nigeria, acute treatment of anemia on its own was followed by mortality in the subsequent few weeks. There was, thus, a need for further antimalarial protection and hematinsics. In this particular population, the highly effective treatment recommended included a curative dose of chloroquine followed by prophylaxis with Prognamtil for 3 weeks to protect against malaria, folate for 3 weeks, iron supplements, and antibiotics if indicated. Oral iron supplements were stopped if sickle-cell disease was diagnosed.

The Johannesburg and Soweto study was the outcome of the Johannesburg City Council asking whether they should continue to give iron supplements to preschool children. One study included two clinic populations in Johannesburg comprising 92 children under 2 years old. These were a fairly elite group of children, attending crèches at which they were given iron supplements. The other study, which is not directly comparable, included older children in Soweto. These were a most socially deprived group of children, but they were not exposed to malaria. The prevalence of anemia in Johannesburg and Soweto was 9 and 28 percent respectively. Hypochromia was seen in both groups as microcytosis by low mean
Anemia in Northern Nigeria and Two South African Cities

cellular hemoglobin (MCH). Serum ferritin, reflecting low iron stores, was present in 23 percent of the Johannesburg children and 55 percent of the Soweto children. Low serum iron was only seen in the Soweto group.

An interesting finding was that there was a strong correlation between serum ferritin and hemoglobin levels among the fairly elite Johannesburg children. In other words, the depletion of iron stores was associated with anemia. But this was not the case in Soweto, where there was no correlation between serum ferritin and hemoglobin concentration; thus, in this socially deprived group, there is both iron deficiency and anemia, but there is no correlation between the two and many of the anemias are not due to iron deficiency. The reason for this is most likely the high rate of intercurrent infections among the Soweto children, but no data are available to confirm this. In the African context, outside of the malarial areas, factors other than iron deficiency, particularly infections, are probably making important contributions to the anemias, which raises the question of how relevant and how effective a program that only prevented iron deficiency would be in Africa.

The prevention of anemia in the African setting requires a very broad approach, rather than a vertical intervention focusing only on one aspect. The question is what can be done at the three different levels, that is, in the community at the primary health care clinic, the health center, and the district hospital, bearing in mind that there are four functions: prevention, diagnosis, treatment, and referral.

Prevention goes far beyond what is generally considered to be prevention for anemia. It includes prevention of infections, improving nutrition, prevention of malaria and mosquito avoidance, immunization, and antenatal care. For the prevention of anemia in childhood, antenatal care is vital. If there is not good antenatal care, the infant is born with intrauterine growth retardation, low birth weight, prematurity, poor nutritional status, and poor immune status and starts life already in the vicious cycle described before. Many of these complications could be prevented if anemia and other complications in pregnancy are prevented.

Anemia can be diagnosed at the community level by measures other than the recognition of pallor. For example, severe anemia could be assessed by primary health care workers who are able to recognize breathlessness at rest.

At the community level, oral iron treatment of anemia and the presumptive treatment of malaria are important interventions. These could be improved by using the parasite dipstick for diagnosing malaria.

Referral, which should be considered a positive function of the primary health care worker, is important for cases of severe anemia, that is, breathlessness at rest, and anemia that is unresponsive to treatment. Referral can start at the village level and continue along the line to the district hospital. Complicated malaria, including cerebral malaria, should be referred.

Anemia control measures can be carried out at the village level by volunteer workers, traditional birth attendants, and visiting health professionals. At the health center level, maternal and child health programs, including preventing malaria and anemia in pregnancy, especially in primigravidae, are vital in preventing the anemias seen in childhood. Delaying the first pregnancy until adolescent growth is completed is a fundamental right for any girl.
Simple laboratory facilities are needed in health centers to diagnose the etiology and severity of malaria. In complicated cases, including HIV, serum can be referred to the district hospital for further assessment. The personnel required at the health center includes medical laboratory technicians.

At the district hospital, the apex of this small pyramid of care, the emphasis should be on training and supervision of people running the antenatal and postnatal clinics and taking great responsibility for family planning. Severe iron deficiencies, including the need for parenteral iron, would be treated here, and the referrals would be the rare diseases that interest hematologists. The framework described here is the basis within which any anemia intervention must be made. An intervention that simply focuses on one aspect of the etiology of anemia is unlikely to reduce, much less eliminate, the problem.

References


Discussion

*Dr. Tomkins* asked what response was given to the Johannesburg City Council, that is, should they continue to give iron syrups? He also asked *Dr. Fleming* whether he would advise that iron syrup be incorporated within a multidisciplinary program. *Dr. Fleming* replied that the Johannesburg City Council was told to continue distributing iron supplements. In response to the second question, *Dr. Fleming* noted that in the rural African setting, the focus should be on children at particular risk of iron deficiencies, such as the premature infants. *Dr. Fleming* emphasized the importance of having an overall package for prevention in the community, once the etiological patterns have been identified.

*Dr. Jalal* asked whether a correlation between low serum ferritin and iron deficiency anemia is a prerequisite to starting a fortification program. If there is no correlation between serum ferritin and iron deficiency, this means that there are other complicating factors and an intervention of iron alone is much less likely to have an effect. *Dr. Fleming* responded by saying that, if iron deficiency exists that can be prevented by fortification, this is an appropriate intervention to use. If that correlation is lacking, there are obviously other factors that are not going to be prevented by giving iron and may be interfering with the usefulness of the iron intervention.

*Dr. Brabin* asked *Dr. Fleming* to comment on the association between pregnancy anemia and early infancy anemia. For example, if a mother has a moderately severe anemia in delivery due to iron deficiency, would this be sufficient reason to target that baby for supplementation? *Dr. Fleming* replied that a mature infant born to a moderately iron-deficient woman is not one to be targeted. The situation would be different for a severely anemic woman who risks giving birth to a small, premature infant that rapidly falls into the vicious cycle.
17. PANEL DISCUSSION

Chair: John Kevany, M.D., M.Sc., Trinity College, University of Dublin
Panelists: David Alnwick, UNICEF, New York
Imelda Ayaso-Sapalo, Ph.D., United Laboratories, Philippines
Fasli Jalal, Ph.D., Ministry of Planning, Indonesia
Guillermo López de Romaña, M.D., Instituto de Investigación Nutricional, Peru
Rebecca Stoltzfus, Ph.D., Johns Hopkins University, USA
Penelope Nestel, Ph.D., OMNI Project, Arlington, VA., USA

Dr. Kevany opened the discussion by defining the purposes of the session as the following:

- To pursue issues raised in both the presentations and discussions that were not pinned down in terms of applications, program planning, or resource needs
- To identify outstanding constraints on moving childhood anemia programs forward through public health mechanisms and other sectors, if appropriate. Some of the issues will identify research needs, and consideration will be needed on how best to approach these.

Dr. Kevany emphasized that the panel discussion was to be limited to the question of iron deficiency anemia (IDA) in the context of child survival, where IDA is defined in terms of hemoglobin (Hb) and hematocrit levels below critical points. Dr. Kevany noted that Hb levels below 11 g/dl was the cutoff point cited in several workshop presentations and that the age range for child survival extended from birth through 5 years old. There are clearly variations in the prevalence of IDA within that age range that should be considered in discussion.

The list of topics for discussion presented in the program were reviewed. Dr. Kevany noted that it was important to start by defining anemia in early childhood as a public health problem, because the responsibility for action lies principally with the public health authorities, directors of health services, and providers of health care at the district level and below. Related to this is the question of the contributory causes of anemia, which leads on to targeting the subgroups in need of most attention. The latter can be measured in terms of biological vulnerability, although the causes may vary, that is, one age group may be affected by dietary factors, another by malaria exposure, and yet another by helminths. Some regional or local adjustment may be needed to come up with targeting that covers most of the identifiable major causes and contributing factors. An obvious sequel to targeting is the choice of interventions; it is important to discuss the package of interventions that have been identified in presentations. A critical issue is delivery systems, which vary greatly from country to country and between income levels as well as by type of intervention. Delivery systems for fortified foods, for example, will be quite different to those for daily supplements of iron and folic acid.
Dr. Kevany indicated that after discussing the above areas, two speakers on the panel would relate their experiences in Indonesia and in Peru and present how their countries have structured and implemented anemia control programs. A discussion would follow on monitoring and evaluation, in particular the choice of indicators to evaluate program activities. The next important issue to discuss would be the policy environment, which would probably emerge from the other topics and is particularly important because it covers the public and private sectors, as well as community organizations themselves. Many different interests, institutions, and resources have to be brought together to create a successful approach to anemia control. For this to happen, it is important that the right policy environment exists at the national level so that the different institutions can function in a way that is both effective and rewarding. Finally, the future for control programs and research necessary to ensure effectiveness would be discussed.

Before opening discussion to the floor, Dr. Kevany requested that participants bear in mind that every setting can be quite different, which has important implications for the way in which programs are set up. At one extreme is the model presented by Dr. James, a general practitioner in Bristol, United Kingdom. He works in a comprehensive health service providing full primary care through a national health insurance system with universal access. The middle ground would be a setting in which the basic health infrastructure operates down to the district level and perhaps subdistrict level, such as in India. The majority of people are covered by this health system, although it is immature, and constraints exist on the use of services. Such constraints can be defined in terms of physical access where topography may limit movement; social access where cultural and social factors may operate; and economic access, including the inability to pay for care or transport costs. In this setting, community-based services are usually developed to some degree through an array of community-based workers including the community health workers, trained birth attendants, and other auxiliary personnel. At the other extreme is the low-income setting characterized by an undeveloped infrastructure, such as in Tanzania, where district-level coverage is extremely limited. Primary health care coverage and access below the district level are limited by geographic, social, and economic factors and by the fact that no formal community-based services exist. Traditional healers and traditional care providers exist, as in every community, but nothing of the formal system stretches that far into the community.

Dr. Kevany reminded participants that the other issue to be considered is the range of sectors involved in anemia control programs. Traditionally, anemia control and prevention has been perceived to be in the domain of public health. For the preschool age group, maternal and child health care and safe motherhood services provided at the primary and district level provide an obvious delivery system. At the top of the age range, primary school services for childhood development, health, nutrition, and feeding must be considered. A substantial gap in coverage exists between services for the infant and for the school-age child, which needs to be examined. The private sector will also figure in discussions for fortification and for community-based distribution systems for supplements. The community itself is also an important resource: well-organized health committees, women’s groups, and similar bodies exist or can be readily established that can mobilize resources, purchase services, and operate distribution systems to a considerable extent independently. They usually operate in cooperation with the public sector, which acts as a resource for procurement and technical assistance. Finally, there is the individual perspective; the consumer with a specific health problem requiring treatment operates as an independent agent in purchasing private care. Dr. Kevany emphasized that the question of settings and sectors would
be important in the deliberations because they are critical to specifying program design and intervention packages.

**Definition of the problem**

Discussion was started by soliciting ideas from the floor for defining IDA in children under 5 years old as a public health problem in terms of magnitude and severity. Because ample documentation exists on the biosocial consequences of IDA, it was suggested that this aspect did not need to be discussed in detail. The World Health Organization (WHO) format for defining the magnitude (frequency) and severity (based on Hb and Hct levels) of IDA in pregnant women was suggested as a model for childhood anemia. *Dr. Fleming* proposed that Hb concentrations of 11 g/dl and 7 g/dl be used to define moderate and severe anemia respectively; similar cutoff points for hematocrit would be 32 and 24 percent respectively. *Drs. Ciomartan and Brabin* agreed with these values, although *Dr. Brabin* raised concern about applying a standard cutoff for all children under 5 years old because of anomalies in the blood profiles of infants under 6 months old. *Dr. Yeung* requested that the discussion not concentrate solely on anemia and that iron deficiency be included. By tackling the problem of iron deficiency, other health and social problems could be addressed as well. He noted that anemia alone is not an adequate basis for establishing an endpoint for iron deficiency. Iron deficiency indicators could be based on assessment of dietary intake of foods or meals rich in bioavailable iron. *Dr. Fleming* suggested that assessment of food availability is probably more important than diet history or food frequency measurement.

*Dr. Menéndez* pointed out that severe anemia can be a consequence of malaria and, in some hyperendemic situations such as occur in Brazil, the definition of severe anemia is an Hb concentration below 5 g/dl. *Dr. Fleming* added that this cutoff is generally used to highlight the child that is in danger of dying. *Dr. Premji* noted the difficulty of using 5 g/dl to define severe anemia in parts of East Africa because of the risks of actual or impending congestive cardiac failure. By definition a child with an Hb below 7 g/dl is severely anemic, but this child may be "running" around while another has impending cardiac failure. It is important, therefore, to consider the dynamics of developing a response to a low Hb level; the definition of 5 g/dl is a compromise in identifying the risk of cardiac congestion. *Dr. Luo* stated that in Zambia 5 g/dl is used to identify severely anemic children that require blood transfusion; this is a consequence of the high prevalence of HIV and demonstrates that the purpose of the definition is important in determining cutoff points. If screening for selective supplementation is the issue, 7 g/dl would probably be appropriate, while 5 g/dl may be a more suitable threshold for therapeutic purposes. *Dr. Kevany* summarized the discussion by suggesting that 5 g/dl would be a threshold below which referral for transfusion might be considered, while 7 g/dl and 11 g/dl would serve to identify severely and moderately anemic children respectively, for screening purposes.

*Mr. Alnwick* noted that it is important to get consensus on what is meant by "public health problem": is it something that needs different types of large-scale public health interventions as opposed to treatment? Cutoff points of 5 g/dl or 7 g/dl are essentially treatment guidelines for screening particular groups of children; it would be useful to agree on some parameters, perhaps using the three country settings Dr. Kevany referred to, that would define when governments should take public health or other measures (depending on whether fortification is defined as a public health or public nutrition measure). The
question is, When should governments take large-scale actions in an unscreened way? He noted that the WHO document on indicators for iron deficiency, which unfortunately remains unpublished, suggests anemia be defined as Hb below 11 g/dl for children under 5 years old. Mr. Alnwick also referred to a summary document, endorsed by the Joint Consultative Committee on Health Policy of UNICEF and WHO, which attempts to grapple with the issue of what is a public health problem and how prevalent anemia should be before governments are urged to apply public health measures. The document states that if 30 percent of pregnant women have hemoglobin concentrations below 11 g/dl, UNICEF and WHO urge governments to take immediate measures to introduce universal iron supplementation to children and women of child-bearing age without screening. Another statement in the recommended action states:

In populations where over 30 percent of pregnant and lactating women have iron deficiency anemia, iron supplementation programs should include infants and children from 6 months through 5 years old and all low birth weight infants should receive supplements at intervals from 3 through 12 months old.

Mr. Alnwick noted that it is not apparent from the text whether the prevalence of pregnant women had to be 30 percent or the prevalence in young children had to be 30 percent. Dr. López de Romañá mentioned that altitude cannot be ignored when discussing Hb levels. Dr. Fleming advised the group that the definition for pregnant women applies to sea level and that a formula exists for altitude effect. Dr. Kevany concluded the discussion on defining a threshold for anemia and the prevalence in relation to that threshold by noting that quantification is clearly important for advocacy in government, for department of health planning, and to enable district health services to seek additional resources to deal with the problem. Dr. Kevany suggested that, as a general standard, public health interventions should be considered in situations in which there is a 30 percent or greater prevalence of Hb below 11 g/dl in children under 5 years old; there should also be supporting evidence from dietary assessment that bioavailable iron intakes are low.

Targeting

Dr. Kevany opened the discussion on targeting by asking whether it is important to narrow the age group being considered under the rubric of child survival (birth to 5 years old), because this is a relatively wide age span and workshop presentations had indicated considerable variation in the frequency within this age range. Furthermore, the causes of anemia may not be the same for all ages; the contribution of malaria and helminths to iron deficiency anemia peak at different ages among children under 5 years old; thus, targeting may have to take into account different causal and contributing factors, as well as differences in age prevalence of anemia. Dr. Hall commented on targeting health services and on the notion that child survival is often taken to mean preschool children but which in fact may include children older than 5 years old. He referred to the Partnership for Child Development Program, which works in three districts in Tanzania covering 110,000 primary school children in 350 different schools. Children are supposed to enroll in school at 7 years old, which is the minimum entry age, but enrollment rates for this age group are very low and children actually enroll up to 9 years old; thus, if preschoolers
are defined as children 1 to 5 years old, a big gap in fact often exists before they actually go to school and take advantage of school health services. The Partnership for Child Development Program is looking at the possibility of using school health programs to deliver health services to children between 4 and 6 years old, because the programs provide mass treatment for parasitic infections and micronutrient deficiencies, notably vitamin A and iodine, and because of the concern that parasite infection is high in this age group. Data from a study in Ghana, which is just being completed, show that even at the bottom of the school age range quite a large proportion of children are classified as anemic, based on Hb levels below 11 g/dl, indicating that this age group is also vulnerable to iron deficiency.

*Dr. Hall* noted that in their programs, the two most important helminths responsible for blood loss in the gut are *Ascaris* and hookworm, although *Trichuris* also contributes; all three worms can be treated with a single dose of a thiaabendazole derivative. Two other causes of blood loss in the gut are *Schistosoma mansoni* and *Schistosoma hematobium*, which are largely found in Africa. *Dr. Hall* presented community-based data on the distribution of *Ascaris*, *Schistosoma*, hookworm, and *Trichuris* infections by age. Even among the 4-year-olds, the prevalence of infection is quite high; however, among this age group the intensity of infection is less than among older children. *Dr. Hall* suggested that for targeting purposes, late preschool children—maybe 2 to 4 years old—would be an appropriate group, but the group who are older than 4 years old and not yet at school, which in some countries may be children as old as 8 or 9 years old, should not be forgotten.

*Dr. Fleming* pointed out that there are also social factors that cannot be ignored. For example, hookworm is not a problem in many parts of West Africa, but in Bantu-speaking Africa, where women are engaged in farm work and their children are also in the fields and exposed to excreta, hookworm anemia is a problem. *Dr. Savioli* stated that the issue of hookworm and the prevalence of intestinal infections in various age groups should be considered according to the specific transmission modes in each country, which can vary. If excreta surround the houses, the intensity of infections can be high among the preschool age group, regardless of how this group is defined. The fact that there are no data on the impact of intestinal helminths on micronutrient status in preschool children is testimony to the fact that there has been no recognition of this as a problem; however, the situation seems to be changing, and there is more interest in looking at the older preschool children—from 2 to 6 or 7 years old—for whom the intensity of hookworm, *Trichuris*, and *Ascaris* infections results in an imbalance between iron intake and iron loss in blood. *Dr. Savioli* stated that work is needed in this area especially where transmission is very intense, for example, the east coast of Africa including the islands and parts of Southeast Asia. *Dr. Premji* reiterated Dr. Hall’s point about the difficulty of reaching children between the ages of 4 or 5 years old up to the time they start going to school, which is often around 8 or 9 years old in Tanzania. Within this age range, hookworm infection needs to be considered in relation to hookworm disease. In Tanzania, hookworm disease is endemic in this age group; by the time children are 5 or 6 years old, they are already iron depleted or have dysfunctional erythropoiesis and it is very easy for them to develop hookworm disease or hookworm anemia. If children under 5 years old are targeted and dewormed, so that they are caught before they go through this transitional period, they are likely to have adequate iron stores. Although they will definitely have hookworm infection, they may not necessarily get hookworm anemia; once at school, the school health deworming programs will definitely catch them.
Iron Interventions for Child Survival

Dr. Schultink noted that mental development is one of the most important reasons for making sure that the child is iron replete when targeting children under 5 years old. In targeting, it is important to make sure that children who have iron deficiency anemia are caught as early as possible because mental development is affected at a very early age. Dr. Schultink reminded participants that Dr. James showed that after supplementing children around 1 year old, the prevalence of anemia remained high 1 year later in the same cohort of children. This suggests that a blanket public health intervention done just once may not be sufficient, because in many countries the combination of insufficient dietary intake and helminth infection continues to predispose young children to anemia. Dr. Schultink described a study in Indonesia on anemic children between 2 and 5 years old who were given iron supplements. After 12 weeks of treatment, almost no children were anemic and after 18 months none were anemic. These data suggest that a decision is needed as to whether it is more important to intervene at an early age (up to 1 year old) with a follow-up intervention or to intervene once at a later age (say at 3 years old) when growth is no longer so rapid and the effect of a one-time iron supplement may last longer. Clearly, there is a trade off because the choice has cost and logistical implications.

Dr. Stoltzfus noted that all the data presented from the different countries show a similar pattern for the prevalence of anemia by age. She noted that the graph on prevalence of anemia by age presented by Dr. Filteau showing the coincidence of peak prevalence of anemia and peak parasitemia applies to England and Romania, where worms are not a problem, and to many countries where malaria is also not prevalent. This complicates the question of setting a prevalence cutoff for the under 5-year-old age group because it will depend highly on how the sample is selected and whether infants 6 to 12 months old are included. If children ages 3 to 4 years old are included with infants 6 to 18 months old, a very different impression of the prevalence of anemia in the under 5-year-old age group will emerge; this has implications when thinking about hookworm in this age group. The school-age population has been the focus of attention based on the peak prevalence of both worm infection and intensities. If the interest is in hookworms and their deleterious role in iron deficiency, that peak curve has to be combined with the probability of a negative iron balance. In healthy children, the balance between iron intake and iron needs for growth and development follow a different trend. The number of worms necessary to create hookworm disease in a 2-year-old child will be much fewer than in a 7-year-old child or in an adult man. This means that it is hard to look at the intensity of worm infections and conclude that preschoolers are at less risk of hookworm disease than school-age children because worm load intensity has to be overlaid with children’s iron needs. Furthermore, the species of worm and dominance of worms may complicate the picture even more.

Mr. Alnwick voiced a concern that no evidence has been presented on anemia being important to child survival, which is often defined in terms of perinatal and infant mortality, both of which have dropped dramatically over time in the absence of any major and effective iron interventions. If the objective of the workshop is to reduce the frequency of anemia for purposes other than the clinical condition per se, it is important to address this anomaly. Mr. Alnwick followed up on Dr. Schultink’s point that the evidence of cognitive development damage due to iron deficiency and anemia is greatest in infants and young children. Perhaps it is important to make a strong pitch for focusing on the youngest group of children and possibly children from 6 to 24 months or 6 to 36 months old because of the impact of anemia on this aspect of child development.
Dr. Kevany agreed that Mr. Alnwick’s comment was important from the targeting point of view. One of the reasons the age group usually included in child survival programs has been poorly serviced with iron interventions is precisely because mortality after the first year of life drops sharply and much health planning is based on mortality rather than morbidity statistics. The consequence of this is that anemia in children is a fairly low priority from a planner’s perspective; however, from the point of view of early childhood development, in particular, development of cognitive skills and abilities, it is important to intervene in a much earlier age group. Dietary and malaria interventions would be appropriate in younger age groups when developmental vulnerability is highest, while helminth control is required at a later age. The question then arises whether to provide a combined package, which may be logistically efficient because more than one intervention is being delivered, when not all children in the age range are vulnerable to the same underlying causes.

Dr. López de Romaña pointed out that geographic targeting is also important. In Peru, for example, the prevalence of anemia in the capital is 50 percent among children under 5 years old. In the mountains 70 percent of school children are anemic suggesting that urban-rural differences are important—at least in Peru. Dr. Menéndez commented that, when talking about targeting age groups, three things need to be considered: first, the prevalence of the problem by age; second, the area from which the data come because prevalence varies from place to place; and third, whether the intervention is for treatment or prevention. In Tanzania, for example, children younger than 1 year old have the highest prevalence of anemia, but it is not known whether this is due to malaria or iron deficiency. To have any impact on the consequences of anemia, it is important to intervene before the infant’s iron stores are exhausted, that is, to prevent anemia. Dr. Tomkins stated that it is important to recognize that a child’s intellectual and psychomotor functions are very sensitive in the second and third years of life. By focusing on this age group, there is an opportunity to change the prevalence of anemia in this age group and improve iron status in the fourth and fifth years of life, although the developmental benefit is much lower than in the second and third years. This emphasizes Dr. Menéndez’s point that it is important to split the issues by age very clearly.

Dr. Kevany noted that another aspect that inevitably influences targeting is the question of delivery systems in situations in which resources are scarce. At the lower end of the age range, there is the option of strengthening and extending maternal and child health services, which in practice rarely continue into the second year of life. On the other hand, an example of downward extension of school health services has been given by Dr. Hill for deworming to cover the later preschool years. Some countries are investing heavily, either through national programs or through community initiatives, in early childhood development centers. In the Philippines and Kenya, for example, early childhood development centers for children largely between 3 and 5 years old are developing very rapidly and are becoming a strong focus for the combined delivery of preschool learning, health, and nutrition services. The demand for these centers exists because parents want their children better prepared for primary school entry and because it also provides crèche facilities for the increasing number of women involved in the labor market.

Dr. Ayaso-Sapalo mentioned the importance of considering absolute numbers as well as prevalence. In the Philippines, for example, about 50 percent of infants are anemic but fewer than 2 million children are under 1 year old. Twenty-seven percent of children 1 to 5 years old are anemic, which represents 7 million children; in terms of targeting, far more preschoolers than infants have anemia.
Dr. Kevany summarized the discussion on targeting by noting that, within the under 5-year-old age range, three age groups can be identified for intervention. The first group is newborns through 6 months, for whom antenatal care and breastfeeding are key preventive measures and iron supplements are needed for premature and low birth weight infants. The second is the period from 6 to 24 months, during which dietary interventions and malaria control appear to be the most relevant interventions in terms of vulnerability and likely impact. The final group is children over 24 months, for whom infectious disease and helminth control are important interventions.

**Intervention and program approaches**

Dr. Stoltzfus presented table 17.1 on the next page, which lists the principle inventions talked about in the previous day and a half. For each intervention the time frame to get a response is indicated, followed by whether evidence exists of efficacy among children under 5 years old, as well as a list of the programmatic advantages and constraints.

**Dietary modification**

Under the heading of dietary modification, the evidence of efficacy is not well demonstrated. There have been a few trials with small samples, sometimes not in iron-deficient populations, and it has been hard to measure any response to, for example, the addition of ascorbic acid to the diet. More efficacy studies are definitely needed. Dr. Svanberg added that traditional food processing techniques have multiple nutritional benefits, such as germination and fermentation. Furthermore, lactic acid fermentation has important implications for both food safety as well as the improved bioavailability of other nutrients. Mr. Alnwick suggested that examples—such as the fermentation of cereals in southern Africa—exist for which dietary modification has resulted in improved iron status; however, none exist of government or agency programs that have been able to promote those changes within a short period of time. The difficulty, therefore, is how to promote the changes.

**Food fortification**

Dr. Stoltzfus went on to say that fortification has been proved efficacious and can be considered a medium-term strategy in terms of the time needed to see an effect. Overconsumption of fortified foods can be perceived as a problem, but guidelines for monitoring this risk have not yet been established. For example, Dr. Yeung mentioned that some countries have weak regulatory systems and iron intakes can become high if iron is added to many foods without any consideration being given to the total being added. Dr. Jalal mentioned that in Indonesia thalassemia and other genetic traits are important issues: whether these constraints are real or perceived, they can damage the acceptance of a fortification program.
Table 17.1: Summary Table: Iron Interventions For Children Under 5 Years Old

<table>
<thead>
<tr>
<th>Intervention: Time Frame to Get a Response</th>
<th>Evidence of Efficacy</th>
<th>Programmatic Advantages (+) and Constraints (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary modification (long term):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) through increased consumption of specific foods</td>
<td>Likely moderate to high; not yet clearly demonstrated</td>
<td>+ advantages beyond iron (i.e., other micronutrients can be added)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ low cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ sustainable?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- locally designed, that is, may be site specific</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- development time and expertise lacking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- time and motivation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- continued follow-up required</td>
</tr>
<tr>
<td>(b) changes in food processing procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fortification (medium term)</td>
<td>Proven moderate to high</td>
<td>+ low maintenance</td>
</tr>
<tr>
<td>(a) complementary foods for young children</td>
<td></td>
<td>+ low cost/beneficiary</td>
</tr>
<tr>
<td>(b) generally consumed foods</td>
<td></td>
<td>+ can add multiple micronutrients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- food industry must exist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- technical expertise often lacking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- food vehicle not consumed by poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- overconsumption due to lack of regulation</td>
</tr>
<tr>
<td>Deworming (medium term)</td>
<td>Likely moderate in high transmission areas; not yet demonstrated</td>
<td>+ low cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ simple</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ well-accepted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ advantages beyond iron</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- regular periodic contacts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- no guidelines regarding: age, endemicity, targeting, deworming schedule</td>
</tr>
<tr>
<td>Malaria (short-medium term)</td>
<td>High efficacy to decrease anemia (but not iron deficiency)</td>
<td>+ advantages beyond iron</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- sustainability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- wisdom in endemic areas</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>chemical prophylaxis</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- acceptability (may need to introduce)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- sustainability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(The most common malaria control strategy, which is prompt treatment and prophylaxis, will not affect population prevalence of anemia.)</td>
</tr>
<tr>
<td>Supplementation (short term)</td>
<td>Proven high; best formulation and dosing regimen need to be clarified</td>
<td>+ advantages beyond iron (i.e., other micronutrients can be added)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- availability of supplements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- no targeting guidelines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- no procurement, storage, and distribution system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- compliance and motivation</td>
</tr>
</tbody>
</table>
Dr. Henry reiterated that proper management and control of fortification is essential. Looking back in history to the 1930s, when Denmark started fortifying its milk products with vitamins A and D, the nation did not recognize they had a control problem and there was a massive outbreak of hypervitaminosis. Mr. Ahwick pointed out that consideration must be given to the different costs, risks, and benefits associated with fortifying a complementary food for infants and young children versus a staple food consumed by the majority of the population. Dr. Ayaso-Sapalo said it is also important to look at the vehicle in relation to collateral effects, for example, sugar causes dental caries, which is also a public health problem. Similarly, salt intake contributes to hypertension. Dr. Yeung pointed out that the efficacy of fortification is excellent, whereas effectiveness, that is, whether it is consumed by the population, is not always evident. In developed countries, effectiveness is extremely high. On the other hand, in developing countries the effectiveness of fortification in some sectors may be high, although this is not necessarily the case among the poorer strata of society. He noted that Dr. Solon has shown Nutripak to be efficacious, as well as moderately effective in the Philippines.

Dr. Tomkins made reference to food industry legislation, which can be influenced to a certain degree by industry itself, although at the end of the day it is set by the government. He noted there had been some remarkable opportunities for fortifying food in industrialized countries, such as Great Britain, which were delayed by legal problems. For example, increasing the folic acid intake of people in Great Britain as a strategy to reduce neural tube defects has been defeated because of legislation and not because of technical problems. Fortifying breakfast cereals with iron is perhaps the most important way to increase dietary intake in young children. Dr. Solon stated that for fortification to work, government must recognize that the food industry has a role to play and industry, in turn, must recognize the role of the food product in improving health status. This has been the experience with the fortification of margarine with vitamin A in the Philippines. In other words, the food industry can be a great ally in helping to develop a fortification program, as well as being a tremendous resource. If government policies alienate the food industry, there is no incentive for the industry to participate in fortification initiatives.

Mr. Ahwick made the point that governments can usually implement health interventions on their own; for example, health education, nutritional supplement delivery, malaria control, and so forth. There may be some advantages to collaborating with the private sector, such as getting people to pay for their malaria tablets. On the other hand, with perhaps one or two exceptions, no government produces any food that can be fortified. Furthermore, in democratic societies, governments are reluctant to regulate the food industry and will instead persuade and negotiate to achieve fortification. Another important issue that has to be dealt with is food standards, especially where liability is concerned. While industry may be prepared to introduce certain innovations on its own, there is always the issue of what their liability will be if consumers are adversely affected. If a government requires fortification by law, then it must accept some liability for any negative consequences; the issue of litigation can become very important. It would seem also that international guidelines are not conducive to changing legislated levels of fortification at the national level, which can present problems. At the moment, there is nothing to draw on to say “Look, you really should be fortifying that food with iron at this level,” which would be very helpful to governments. Dr. Yeung pointed out that it is important for the food industry to encourage governments to initiate fortification legislation and, at the same time, help legislators limit the foods that can be fortified, as is being done in China.
Helminth control

Dr. Stoltzfus went on to review the issues associated with deworming and noted that its efficacy has not yet been demonstrated clearly, but a strong age effect among children under 5 or 6 years old is likely. The main constraints are the lack of guidelines regarding the age issue and the level of hookworm prevalence or intensity that warrants widespread deworming as a targeted intervention. Furthermore, the deworming schedule for preschool children remains undefined for the purpose of program planning. Dr. Savioli mentioned that the World Health Organization (WHO) was obliged to address this question for the WHO Sick Child Initiative, and it restricted deworming in the preschool age group to children older than 24 months old and to areas where hookworm or Trichuris are endemic but did not define endemicity in terms of prevalence. Clearly, data are lacking for this age group and this issue. Dr. Hall mentioned that the Partnership for Child Development Program guidelines use a prevalence of 50 percent for implementing mass treatment.

Dr. Fleming mentioned that the prevention of hookworm transmission, such as by wearing plastic sandals and better sanitation, should also be considered as appropriate interventions.

Malaria control

Dr. Stoltzfus went on to discuss malaria control, which she noted is more complex than other interventions. It is highly efficacious in decreasing anemia, but not necessarily iron deficiency, in very young children with low malaria immunity or those not in a holoendemic area. Malaria control programs, however, have benefits far beyond any effects on iron nutrition and anemia. Dr. Fleming pointed out that mosquito control is particularly important under conditions of moderate transmission, such as periurban and urban shanty areas of African towns. Dr. Menéndez noted that Dr. D’Alessandro’s work in The Gambia found that in areas of moderate transmission, mosquito control was highly efficacious in decreasing mortality and increasing hematocrit and hemoglobin levels, but this has yet to be shown in areas of high transmission. Dr. Premji, however, stated that the situation in The Gambia is slightly different from other high transmission areas. Results from studies in Tanzania, which looked at the prevalence of malaria using impregnated bednets show a dramatic impact on both the vector as well as the disease. The question of whether insecticide-impregnated bednets work in holoendemic areas should be established soon, once the ongoing trials are completed. Dr. D’Alessandro noted that work around Lake Kisumu, Kenya, showed that impregnated bednets had a significant impact on reducing the prevalence of malaria.

Iron supplements

Dr. Stoltzfus moved on to discuss iron supplements, which are recognized to be efficacious even though the best formulation and dosing regimen still needs to be clarified. Supplements have advantages beyond iron nutrition because other micronutrients can readily be added.
Mr. Alnwick made a number of comments on the programmatic aspects of iron supplements. The lack of guidelines should not be a constraint because this could be overcome through an expert group meeting or by decisions at the local level. There are other major constraints to program implementation, particularly the cost of supplements. The primary cost issue is whether children are to be given a daily dose or a weekly dose. Iron syrups are not widely used in developing countries nor are they procured by UNICEF. The cost of tablets paid for by UNICEF—perhaps doubled if provided as a syrup—is on the order of US$0.30 per child per year for the supplement alone. If the supplement is given weekly instead of daily the cost may be as little as US$0.05. The foregoing estimate is hypothetical and assumes bulk purchasing and good supply tenders; nevertheless, the costs are relatively low. The US$0.30 per year, however, is considerably greater than the cost of a vitamin A supplement program, which is US$0.10 a year, assuming there is no additional delivery cost; thus, an iron supplement intervention, irrespective of the form of supplement, will cost two to three times more than a corresponding vitamin A intervention. Dr. Ayaso-Sapalo provided preliminary costing for a liquid vitamin A/iron supplement in the Philippines. The addition of vitamin A added very little to the cost, and it was assumed, perhaps prematurely, that weekly doses would be given for a period of 3 months. The cost of an iron course for infants would be on the order of US$0.26 and for preschoolers about US$0.52.

Dr. Tomkins said it was important that UNICEF put iron supplements for young children in their armamentarium. He suggested that the situation with iron supplements is very reminiscent of the situation with antibiotics. Antibiotics used to be bought at enormously different prices simply because some companies said it cost more than others to produce; however, when a country like Bangladesh put a ceiling on the price it would pay for antibiotics, they suddenly found that companies produced them at that cost. Another example is the recent situation in which Belgian companies have almost refused to drop their profits to export iron supplements to Romania, while Romanian companies are not prepared to make iron solutions because they are not profitable. There is a need to set minimum standards of intake, in terms of milligrams of iron and frequency of intake, after which an expert group of pharmacologists could come up with what they anticipate as the minimum cost. Mr. Alnwick responded that UNICEF would certainly take up Dr. Tomkins’ challenge and would like to do so with WHO. UNICEF’s procurement agency will want to know what precisely is required: is it iron supplements at 60 mg or 120 mg? Once procurement specifications are provided, for example, a syrup in bottles of a certain size, competitive quotes can be obtained. The next question will be what quantity is needed, as price depends on total volume required. A programmatic issue arises as to whether the use of supplements is to be encouraged and demand created and, if so, what the estimated demand might be. Mr. Alnwick emphasized the need for precision when talking about iron supplements. Dr. Kevany suggested that, if iron supplements were to be given priority by UNICEF in its support to governments, the demand issue could probably be estimated from existing data.

Dr. Kevany raised the issue of risk associated with the administration of iron supplements, which had been mentioned in relation to malaria. Dr. Schultink referred to the current recommendations for preschoolers, about 3 mg/kg body weight, which from a public health perspective seems to work. It may be possible to reduce this level to 2.5 or 2.0 mg/kg body weight, but the time and effort in fine tuning involved may outweigh the benefit of continuing current recommendations. Dr. Brabin pointed out that the risk levels have been worked out for preterm babies but not for older children for whom many factors affect absorption, especially in developing countries.
Mr. Alnwick noted that progress is made in international nutrition once a sufficient body of opinion has been built and consensus exists that it is better to act then not to act. It took 70 years to move on iodine deficiency, but there came a time when a clear consensus was reached that salt should be iodized; even so, there are still critics of salt iodization. Evidence of the efficacy of vitamin A supplements was greater than for any other public health intervention before action was taken on vitamin A deficiency. Large-scale interventions are promoted all over the world, but nobody criticizes them even when countries differ in opinions. Tuberculin vaccine (BCG), for example, is given in over 100 countries; yet, the United States does not believe it efficacious enough for its own national programs. Nobody is debating the issue—whether enough is known about iron to move forward with some reasonable consensus, recognizing that there will always be a few gaps—any more. Dr. Kevany suggested that this workshop was not the right forum to decide on risk as a constraint in planning and implementation. Obviously, it is an issue that needs to be addressed, but the necessary information for decision making is not available. Dr. Kevany summarized the above discussion stating that antenatal care, including maternal iron supplements, breastfeeding, and iron supplements for preterm infants, is indicated for infants under 6 months. For children 6 to 24 months old, dietary improvement, malaria control, and iron supplements appear to be the most appropriate activities. For children older than 24 months old, infectious disease control, deworming, and malaria control are additional priorities.

Program development: Indonesia

Dr. Kevany then called on Dr. Jalal to talk about his impressions in setting up programs from the perspective of a national (Indonesia) development implementation agency. Dr. Jalal started by saying that his agency is responsible for allocating budgets to the Ministry of Health, which submits proposals, of which nutrition is only one component. The key question when looking at any proposal is how much it addresses the government’s goals. An important problem in Indonesia is the very high maternal mortality rate and, for this reason, programs that deal with anemia during pregnancy are a priority. The government provides locally produced iron tablets to 65 percent of pregnant mothers at no cost; thus, there is, in principle, a sustainable program for pregnant women although there are problems in the delivery system. Dr. Jalal went on to say that the significance of taking action against anemia in preschool children must be clearly stated. In other words, is the purpose to reduce mortality, in particular, infant mortality, or is it investment in human resources or an approach to poverty alleviation? Program managers need to justify their programs because government deals with agencies such as the Asian Development Bank and World Bank, under whose umbrellas national programs must fit. Indonesia has 5-year National Development Plans, within which are two important components, namely poverty alleviation and human resource development. But where does control of anemia in preschool children fit—poverty alleviation or the formation of human capital and human resource development? Many studies have been done and publications produced in Indonesia on anemia; however, a well-written executive summary on the benefits of anemia interventions in preschool children that can be read by the president or by ministers is not available. Dr. Jalal noted two monographs that rationalize intervening with micronutrients for economic reasons. While the arguments presented were sound, they would not convince a minister of planning that intervening for preschool children is important, because the role of supplements in eliminating and controlling anemia in preschool children was not clearly stated. Dr. Jalal suggested that the impact of control of anemia in preschool children is perhaps best justified on the
grounds of educability. This was the argument used to get a deworming program started in schools, and it could also be used to get iron into supplementary feeding programs.

Dr. Jalal also raised the question of blanket or targeted supplementation. Indonesia, for example, has 25 million preschoolers; even if only infants are considered, this still implies 5 million beneficiaries. There is also the question of how to target; one-third of all villages in Indonesia have been classified as poor, and most interventions are directed to these locations. Should poor socioeconomic areas be targeted for delivering iron supplements? The feasibility of delivery also has to be considered. For example, the Expanded Program of Immunization’s coverage for infants up to 9 months old is high in Indonesia; this could provide service contacts for delivering iron supplements. But how much can anemia be reduced among this age group? Can a reduction in anemia be proved using ongoing monitoring and evaluation systems or through operational research on services to infants and young children?

Dr. Jalal then described the primary health care system in Indonesia, which has 195 million people, 27 provinces, 6,305 districts, 65,000 villages, and 240,000 integrated health posts run by communities and supervised by a health official. A recent study showed that more than 60 percent of children under 5 years old is covered by these integrated health posts. Does this mean that the integrated health post is the place to deliver iron supplements? If it is, does the whole distribution, that is, from the production unit through delivery to the district, need to be working properly, because Indonesia is the size of the United States and consists of 17,000 islands? Under these conditions, distribution is a major issue if iron supplements are to be delivered through 240,000 integrated health posts. If it is agreed that infants should be targeted, the integrated health post should be the delivery point and targeting should focus on the poor areas. Furthermore, should the budget for such a program be covered by the government alone or should there be some private/public mix? For example, the Government of Indonesia provides capital to village pharmacies, through which the community sells basic drugs, which do not presently include iron supplements for children. If a preventive program starts, supplements will have to be introduced as part of the village drug inventory. Dr. Jalal reported that a study is being planned in Indonesia that would include 10,000 preschoolers from two provinces for four different interventions and a control group. The purpose of the study is to show that it is feasible to target iron intervention for preschool children. One intervention would be to distribute an iron supplement through the integrated health post daily and free of charge. The second would be to distribute iron supplements through the integrated health posts on a weekly basis, again at no cost to the consumer. The third intervention would be to distribute iron supplements through the village pharmacy daily, financed by the community. In the fourth intervention, iron supplements would be distributed through the village pharmacy weekly, for which the consumer would pay. The study will take 8 months and will also include deworming and malaria control.

Dr. Jalal also noted that some people question the wisdom of intervening among preschool children before ensuring that all pregnant women are adequately covered. This has important resource implications because anemia in early childhood can be prevented through good antenatal care, breastfeeding interventions such as the baby-friendly hospital, and so forth. The question becomes: how much is government willing to reallocate money currently provided for antenatal care and iron supplements during pregnancy to start a small-scale iron supplement program for preschoolers? In addition to interventions through the health sector, Dr. Jalal talked about the role of agricultural extensionists. Weaning foods are an important part of dietary modification. Dr. Jalal asked whether a model exists for agricultural extension programs promoting effective home garden projects that are
primarily targeted to increasing micronutrient intake rather than to income generation or empowerment of people. What kind of agricultural activities can work? What kind of commodity mix can be supported by a national extension program? From the agricultural point of view, it is important to find alternative ways of improving anemia control in preschoolers, because this cannot be done solely through the Ministry of Health. Finally, Dr. Jalal asked whether there is any opportunity to intervene through preschool education programs. Dr. Kevany reiterated Dr. Jalal’s point that a very important challenge to government is prioritization and justifying the case for introducing a new priority of controlling anemia in preschool children when other programs are yet to be made effective. Dr. Kevany pointed out that one of the reasons for this workshop was to permit people to justify this as an independent priority.

Program implementation: Peru

Dr. López de Romaña then described the situation in Peru, which is quite different from Indonesia. In Peru, the problem of poverty and malnutrition, including anemia, is well-defined; it exists mainly in the tropical rain forest, mountainous jungle, and rural areas, followed by periurban areas. For the last 20 years the government’s solution, as perhaps in many other developing countries, has been to distribute food. A lot of money was spent distributing food, which was not well targeted to vulnerable areas because it is very difficult to cover rural communities and automatically reach the most vulnerable groups. Instead, food went to other areas, which is one of the reasons that there has been so much migration from the Andes to cities. Dr. López de Romaña mentioned that the government took heed of the situation in 1992 and requested the Nutrition Research Institute to develop a new model for distributing food to rural areas. A program was developed with three components: the community, private industry, and government. The first program activity was to go to communities in various parts of the country and, with the help of teachers, create executive units made up of several schools that include some 3,000 school children.

Meanwhile, the Nutrition Research Institute formulated the nutrient composition of the food supplement to be delivered to meet the dietary requirements of primary school children. A tender was issued to private industry to produce acceptable foods that would meet the specified nutritional requirements. The tender also stipulated that the price should include monthly delivery of the food to a point at which the executive units could collect it; the government’s role was to bank the money and nothing else. Food is delivered once a month, usually between the 26th and the last day of the month, at a central place. One person from each executive unit is responsible for signing the check made out to the food industry producer, which can be cashed after 5 days. The program is supervised by the Nutrition Research Institute, which monitors product quality at both the production site and in the communities.

Dr. López de Romaña went on to mention that various aspects of the program have been evaluated. When the program started, 66 percent of children then entering primary school were anemic, but, after 6 months of the intervention, the prevalence for this cohort had dropped to 14 percent. Program evaluation has also shown a positive impact on overall food consumption, child growth, and cognitive development. The current program has been in place 9 months and covers 500,000 children per day. Moreover, the same nutrient formulation is being used by other government agencies and the total number of school age children now benefitting from supplementary food is 1.5 million each day. Because of the success of the school-feeding program, it is to be expanded to include preschool children; this extension of the program
will probably start within the next 6 months. The formulation will most likely contain 100 percent of the requirements for iron, vitamin A, and vitamin C and 60 percent of the requirements for vitamins in the B-complex, calcium, phosphorus, and magnesium. The program for preschool children will start with 200,000 children a day, but this will increase to 1 million children a day. Dr. López de Romaña emphasized that the supplementary food covers many nutrients including protein, energy, iron, vitamins A and C, and so forth, all of which are important in a strategy for controlling iron deficiency anemia.

In response to a question asked on who pays for the supplementary food, Dr. López de Romaña said that the government pays, but there is also a cost to the community. Because the food reaches very remote areas, several communities rent a truck and travel for up to 12 hours to pick up the food. In addition, communities must prepare and cook the food, which requires fuel and running water. The food is delivered in two parts; one is an extruded cereal and milk preparation fortified with vitamins and minerals and the other is a cake that contains 50 percent of daily iron requirements. Because of flavor problems, the liquid portion containing the other 50 percent of iron requirements could not contain all the iron. The supplement provides 600 calories, which is one-third of the daily requirements. Studies had shown that the children were consuming only 1,200 calories a day and they should be getting about 1,800 calories a day. The Nutrition Research Institute has calculated that the community is probably paying around 30 percent of the total cost of moving the food from the storage areas to the different schools; thus, the cost is being divided between the government and communities.

Policy environment: Philippines

Dr. Kevany then invited Dr. Ayaso-Sapalo from United Laboratories, a national pharmaceutical company, to talk about the policy environment in the Philippines. The mix of public/private sector responsibilities and involvement, as well as community-based ownership, represents a useful model for collaboration between government and communities. She commented that in the Philippines, as in many other countries, politics, politicians, and personalities count a lot in the success of any project. In the past, the Philippines had a secretary of health who considered industry, particularly the pharmaceutical industry, an adversary whose prime motivation was to make large profits; this gave rise to tension. More recently, the Philippines had a very charismatic secretary of health who changed this perception because he realized that it is not possible to separate government from industry, given that industry drives economic development. Economic development, in turn, brings about an improvement in nutrition status, including iron status.

The current preventive health interventions in which industry is very much involved are nutrition and immunization programs. The Philippines, like Indonesia, is an archipelago with many islands, and the transport and distribution of goods, including drugs and food, is very difficult. Over the years, pharmaceutical companies, such as United Laboratories, and the food industry at large have developed a distribution network that works. The aforementioned secretary of health realized that these were routes to deliver both medicines and health care personnel. On national immunization days, which are also the days when vitamin A and iodine supplements are delivered, this distribution network is used. Pharmaceutical companies that have professional representatives, many of whom have cars, ferry health personnel to the immunization centers nationwide. Furthermore, the companies are encouraged to have their own immunization centers. Indeed, United Laboratories converts its big gymnasium into an
immunization center, and they promote service uptake in the surrounding community. This momentum, which is nationwide, could be expanded to include iron supplements as another preventive intervention. The former secretary of health was recently elected a senator, and the next secretary of health would be ill-advised not to continue these immunization centers, because they are very popular. Everybody knows about them, including people in the barrios, because they are well-advertised by TV, radio, and health personnel, as well as by movie stars, TV stars, politicians, talk-show hosts, and other personalities to whom Filipino people look up and listen. The open relationship between government and industry, specifically the Department of Health, the pharmaceutical industry, the media, and others, is helping the country and reducing costs because government gets the advertising free.

Dr. Kevany asked Dr. Ayaso-Sapalo to comment on what private sector perceives the requirements to be for it to act effectively in producing supplements, fortified foods, and so forth; are there certain principles that government should adopt that would enable the private sector to function more freely, such as regulation of imports and exports or the use of subsidies? Dr. Ayaso-Sapalo said that, in the case of the Philippines, the pharmaceutical industry is overregulated. Unlike some other countries, where vitamins and minerals are considered a food, the Philippines limits what can be called a food and what can be called a drug. For fat-soluble vitamins and minerals, anything over 105 percent of the Philippine RDA is considered a drug. For water-soluble vitamins, anything above 150 percent of the Philippine RDA is considered a drug. It has been suggested that industry should play a greater role in nutrition education, because they advertise their products and it would be logical to advertise iron supplements in relation to anemia control. Because of the regulations on drugs, however, any product containing iron beyond the RDA cannot be advertised; it has to be prescribed by a doctor. Dr. Ayaso-Sapalo went on to say that industry can and does help with nutrition education. In the Philippines, for example, industry is very involved in continuing medical education; United Laboratories, for instance, sponsors the regular Philippine Medical Association conventions, which are held nationwide several times a year. It would be only a matter of channeling this type of activity into more specific education campaigns, such as nutrition or micronutrient interventions and involving physicians working both in the private and public sectors.

Dr. Yeung pointed out that, as far as industry is concerned, it is important for government to recognize, encourage, respect, and form partnerships with them if things are to move forward. Industry does contribute to the community in terms of education; for example, Heinz Canada produces a newsletter that is totally generic and talks about infant nutrition. The purpose of the newsletter is to educate the educators to educate their patients. Heinz would very much like to establish some centers that give intensive nutrition training, for example, in India or in Russia, because very little nutrition education is given to pediatricians. These courses would not sell products, they would sell nutrition. The better pediatricians are educated, the better they can serve the community; thus, partnership is extremely important. Dr. Jalal made the point that information is a public “good” and that government can also help, but he wondered what the private sector would like government to do to help raise awareness. In other words, what is the distinction between the role of government and the private sector in creating awareness, in creating demand, and also in differentiating between public and private goods? Dr. Yeung replied by saying that the model of the Philippine market mentioned by Dr. Solon is extremely valuable. The Canadian newsletter mentioned previously has contributions from the Canadian Pediatric Society, which also monitors the content. This is a good partnership, but it is with a medical organization and not
with government, although the newsletter is implicitly sanctioned by government because it is openly
published and Heinz has never had a complaint from government. Government can complain, and it does
complain if industry does not do things right. It should not be a question of what government can do for
industry or what industry can do for government, but about partnerships—equal partnerships.

Dr. Kevany closed the discussion session by thanking everyone for their contributions.
18. SUMMARY AND FUTURE DIRECTIONS

Penelope Nestel, Ph.D.
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Summary

Dr. Nestel began by thanking all the speakers and participants for their contributions and input to the workshop. The workshop was of enormous benefit to the U.S. Agency for International Development (USAID), in particular, their Opportunities for Micronutrient Interventions (OMNI) project, and the Institute for Child Health (ICH) in identifying some of the program aspects that can be implemented to alleviate iron deficiency among children under 5 years old. It also highlighted some of the research issues that need to be pursued to develop more effective programs.

Anemia is a serious but commonly unrecognized problem in young children that has important implications for child survival, growth, and development. The data presented at the workshop indicate that anemia is widespread in both developed countries, where governments provide health care free of charge and access to health facilities is good, and in developing countries, where health resources are much more limited and restricted. Among children under 5 years old, those between 6 and 24 months old are most at risk of being anemic.

From a programming perspective, an obvious and critical issue is the translation of scientific knowledge into doable actions, which Dr. Jalal expressed so eloquently during the discussion. There is an urgent need to both develop and disseminate to policymakers and program managers information on the need for and importance of putting in place iron interventions for infants and young children. Clearly, this is something concrete that the OMNI project can do in collaboration with UNICEF and others.

The evidence to justify that anemia is a public health problem among young children already exists. As Mr. Alnwick pointed out, sufficient consensus also seems to exist that action is warranted; however, as Dr. Yeung noted, anemia alone is not an adequate basis for establishing an end point for iron deficiency; dietary intake of foods or meals rich in bioavailable iron need to be put in the equation, along with worm loads and the risk of malaria. Programs for young children, however, cannot be done in isolation. Dr. Fleming pointed out that the implications of anemia in pregnant women on the iron status of newborn children cannot be overlooked; thus, iron nutriture in the pregnant woman must continue to be addressed. Nevertheless, interventions for young children should be singled out and considered separately to help break the vicious cycle of anemic women giving birth to infants who have low iron stores, may never fully recover, and may become more anemic or iron deficient as they get older. Girls get doubly hit in adolescence before they become mothers; the cycle continues from generation to generation. Clearly, it is important to tackle iron deficiency at different points in the life cycle and, in the interest of child survival and development, specific interventions for infants and young children need to be put in place.
Within the context of children under 5 years old, the workshop identified three target age groups that, not coincidentally, relate closely to the feeding patterns of these children. The first are infants under 6 months old for whom antenatal care and breastfeeding are key preventive measures and, in the case of premature and low birth weight infants, iron supplements are needed. The second is the period from 6 to 24 months, in which dietary interventions and malaria control would be the most relevant interventions in terms of vulnerability and likely impact. These include both the promotion of breastfeeding and the introduction of micronutrient-rich complementary foods at the appropriate age. The final group is children older than 24 months old for whom infectious diseases and helminth control are important interventions.

Having identified appropriate interventions, the challenge will be to incorporate them into ongoing delivery systems, bearing in mind that multisectoral approaches are needed. Dr. Kevany opened the discussion by describing different types of scenarios and models that need to be considered and developed to fit existing situations. Dr. Fleming highlighted the importance of having a conceptual framework for programs that extend from the community through tertiary care. Such programs need to consider environmental issues, food systems, health systems, and so forth. Dr. Jalal emphasized the need for a food model that includes agricultural extension to promote home and school gardens. Consumption of foods grown in the gardens could be promoted through health posts. Such activities could result in dietary modification, which is essential to improving iron and other micronutrient nutriture.

The role of the private sector, both the food and pharmaceutical industries, needs to be better defined and further developed. Both Drs. Ayaso-Sapalo and Yeung have indicated that these sectors have an important but, perhaps, underutilized function. Industry, in partnership with government, may be able to take more responsibility to create the demand for iron-rich foods and pharmaceuticals, thereby increasing iron intake.

Once implemented, programs need to be monitored and evaluated. Assessment techniques to describe the iron status of populations exist. Iron deficiency can be distinguished from anemia, and both of these conditions are important in the context of public health programs. But, as Dr. Yeung noted, it is also important to carry out dietary assessments to see whether children are eating foods containing iron that is highly bioavailable. After all, nutrition is about food, not micronutrient supplements and often the underlying problem of anemia relates to poor feeding patterns. To this end, it is important to establish and develop relations with the food sector. This includes not just the giant multinationals, such as Heinz, but also local companies, in much the same way that the Nutrition Institute in the Philippines has developed an excellent relationship with United Laboratories. Indigenous food and pharmaceutical companies exist within countries; it is important that donors and programmers start working with them. The key component, however, is for industry and government to have mutual respect for one another and to develop an equal partnership.

Finally, there is a need to work out the appropriate iron formulations and supplement regimens for infants and young children. As Dr. Brabin pointed out, iron requirements by age are known but absorption factors complicate the issue; thus, more work is needed in this area.
The Future

A number of research questions were raised in the presentations and discussions. To recapitulate these, the floor was opened to discuss those areas important to moving programs forward, including:

- Determining an appropriate definition of iron status that can be used in community-based studies and program monitoring, in which the collection and transport of blood samples is difficult and assays for multiple indicators are not always possible
- Identifying the benefit on iron status of including iron supplements in effective malaria interventions, such as insecticide-impregnated bednets
- Determining the appropriate dose and regimen (daily, weekly, and for how long) of iron supplements for infants and young children
- Determining the frequency of prophylactic interventions, that is, how often should prophylactic iron courses be given (once a year or twice a year, for example)
- Developing a standard liquid supplement for young children that contains multiple micronutrients, for example, iron and vitamins A and C, that is not expensive and has an appropriate shelf life.
- Determining the relationship between pregnancy anemia and infant anemia and whether pregnancy anemia can be used as an indicator of high risk anemia in infants under 6 to 9 months old
- Identifying and defining the real risks of iron interventions in infants and young children
- Identifying the safety and risk of making iron supplements more widely available in the marketplace. (Chloroquine, for example, is a risky substance if it is misused, but the judgment was made that the benefits outweigh the risks and it should be available in local shops).
- Investigating the application of micronutrient fortification in emergency supplementary feeding programs
- Developing a standard protocol for testing the efficacy of iron in fortified foods

Drs. Davidson and Tomkins closed the meeting by stating that it had been a privilege to have such a diverse group of people with different areas of expertise and interests discussing such an important topic. A special thanks was given to Madeleine Green (ICH) and Lisa Sherburne (OMNI), who were instrumental in organizing the meeting.
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Appendix 2: AGENDA

May 17 1995

9:00 A.M. Welcome/meeting purpose, Frances Davidson
Agenda and expected outcomes, Andrew Tomkins
Rapporteur: Juana Willumsun

9:30 A.M. Review and discussion of iron requirements and field methods
of assessment in preschool children, Suzanne Filteau
Co-chairs: Frances Davidson and Andrew Tomkins
Rapporteur: Juana Willumsun

10:15 A.M. Bioavailability of iron, Susan Fairweather-Tait
Co-chairs: Frances Davidson and Andrew Tomkins
Rapporteur: Juana Willumsun

11:20 A.M. Potential interventions
Chair: David Yeung
Rapporteur: Suzanne Filteau

Dietary modification, Ulf Svanberg
Fortification, Max Blum
Antihelminths, Lorenzo Savioli
Malaria control, Clara Menéndez
Supplements, Bernard Brabin
Iron: other micronutrient interactions, Paula Trumbo

3:00 P.M. Country/program presentations
Chair: Charles Kihamia
Rapporteur: Paula Trumbo

Great Britain: supplements, John James
Romania: supplements, Tatiana Ciomartan
Philippines: supplements/fortification, Florentino Solon
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9:00 A.M.  Country/program presentations (continued)
           China: fortified foods, Li Tong
           India: preschool feeding, Tara Gopaldas
           Tanzania: malaria control, Zul Premji
           Gambia: malaria control, Umberto D'Alessandro
           Northern Nigeria and South Africa: intervention studies, Alan Fleming

11:20 A.M.  Panel discussion: programmatic issues
           Chair: John Kevany
           Panelists: David Alnwick, Imelda Ayaso-Sapalo, Fasli Jalal, Guillermo López de Romañá, Rebecca Stoltzfus
           Rapporteur: Penelope Nestel

           Priorities
           Targeting and access to age groups
           Options for interventions and packages of interventions
           Cost-benefit of interventions
           Evaluation
           Overcoming constraints (policy and programmatic levels)
           Pharmaceuticals
           Research needs

4:00 P.M.   Summary and recommendations, Penelope Nestel

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1. Dr. Yeung presented on behalf of Dr. Tong who was unable to attend.