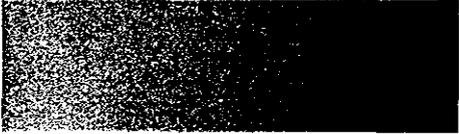


IRON/MULTI- MICRONUTRIENT SUPPLEMENTS FOR YOUNG CHILDREN

**Summary and conclusions of
a consultation held at UNICEF,
Copenhagen, Denmark, August 19-20, 1996**

Penelope Nestel and David Alnwick



In May 1995, the U.S. Agency for International Development (USAID) and the Institute of Child Health, London, held a meeting on "Iron Interventions for Child Survival." Among children under 5 years of age, three groups were identified for intervention: premature and low-birth-weight infants under 6 months of age, children 6 to 24 months of age, and children 24 months and older. Among children under 5 years old, those between 6 and 24 months were identified as most at risk of being iron deficient (Nestel 1996). Because there are no generic low-cost prophylactic iron supplements for this age group, one recommendation from this meeting was to identify an appropriate iron formulation and regimen for young children who are unable to swallow or who have difficulty swallowing tablets. To address this issue, USAID's Opportunities for Micronutrient Interventions (OMNI) Project and the United Nations Children's Fund (UNICEF) jointly organized this meeting with the participation of WHO, the pharmaceutical industry, and international experts.



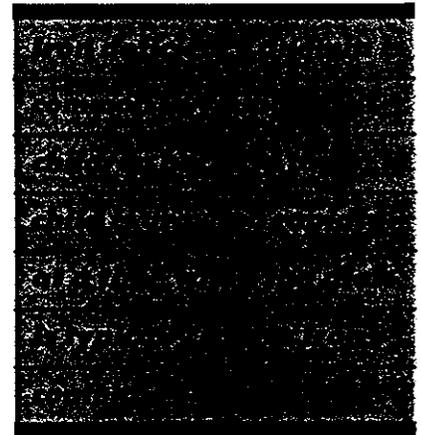
1.

Objectives

There is growing awareness that iron deficiency anemia (IDA) in young children is very common primarily because of the low content of bioavailable iron in a typical infant's diet and the high iron requirements for rapid growth. This has serious implications for child development and child survival beyond anemia because iron deficiency in infants and young children is associated with impaired cognitive and psychomotor development (Osiki 1983, Walter 1989, Lozoff 1987), reduced growth (Chwang et al. 1988, Latham et al. 1990), and decreased resistance to infection (Chandra and Vyas 1982, Cook and Lynch 1986).

In January 1995, the UNICEF/WHO Joint Committee on Health Policy (UNICEF/WHO 1994) endorsed a strategy for reducing IDA in children. The strategy called for implementing a preventive iron supplement program for all infants and young children in situations where the prevalence of IDA in pregnant women is 30 percent or more. In several countries, however, including Canada and Argentina, IDA was not a problem among women of child-bearing age but was still common among older infants and young children until the use of iron-fortified infant and child food became widespread. Epidemiologic data show that in virtually all developing countries, more than 40 percent of infants and young children have IDA.

Few developing countries have implemented an IDA control strategy for infants and young children because a dietary approach, such as fortification of commonly consumed complementary foods, is often not affordable. Routine iron supplementation has not been practiced partly because of the unavailability of low-cost, generic supplements. Furthermore, the lack of consensus on the formulation of such supplements has been a constraint hindering the development of iron supplementation programs. UNICEF, for example, stocks more than 200 essential drugs, including vitamin and mineral supplements, but does not presently stock an iron supplement suitable for young children.



The purpose of the meeting was to:

- review the available options for supplying iron supplements to children younger than 2 years old,
- make recommendations on the form of iron to be used, the dose to be given, and the duration of supplementation, and
- consider whether vitamins and other minerals could be combined with an iron supplement.

This information is needed by UNICEF, which may consider stocking such supplements for use in UNICEF-assisted programs, and by development agencies and developing country governments, which may wish to purchase these supplements and initiate iron supplementation programs to prevent IDA in infants and children.

The consultation focused on how to provide iron supplements to children 6 to 24 months old, who are at greatest risk of the irreversible, long-term consequences of iron deficiency, namely impaired physical and mental development. Iron stores present at birth and the highly bioavailable iron in breast milk protect an infant from iron deficiency anemia up to about 6 months of age (National Academy of

Sciences 1991). Breast milk cannot, however, provide the iron needs of the rapidly growing infant beyond the age of about 6 months.

The first foods fed to infants in developing countries are generally cereal- or root-based, which are poor sources of bioavailable iron; thus, infants are at greatest risk of developing severe IDA between the ages of 6 and 12 months. Beyond the age of about 12 months, children's diets become increasingly diverse as they partake in the family diet; thus, the intake of bioavailable iron increases. Providing infants 6 to 12 months old with iron supplements would therefore ensure that they are protected for the first 12 months of life and possibly beyond. If iron supplements are continued to 15 months of age, the child would be assured of protection against iron deficiency anemia for the first 2 years of life owing to the accumulation of iron stores.

Older children may continue to be at risk of iron and other mineral and vitamin deficiencies. Where the family diet is very limited in bioavailable iron, older children may need to be supplemented with iron and other micronutrients.

2.

Composition and method of packing/dispersing an iron supplement that could be made widely available in the near future

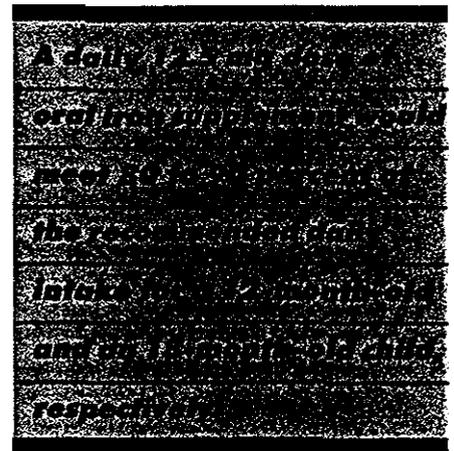
The most practical iron supplement for use in infants and young children is an aqueous solution of a soluble ferrous salt, such as ferrous sulfate, or a ferric complex, such as iron polymaltose. A single, safe dose that is effective for all children under 2 years old that can be easily dispensed by nonliterate mothers is required.

a) Dose For therapeutic purposes, an adequate and safe hematological response to oral iron intake can be achieved in 4 to 6 weeks with 3 mg elemental iron/kg body weight/day¹ (Reeves and Yip 1985). In a prophylactic program, between 1 and 2 mg iron/kg body weight/day is appropriate.

Assuming 5 percent iron absorption, which is a very conservative estimate of absorption (FAO/WHO 1988), a 12.5 mg oral dose of iron would provide 0.625 mg of absorbed iron. The 12.5 mg dose is equivalent to 2.5 mg/kg body weight for a 6-month-old child with an average weight of 5 kg, 1.6 mg/kg body weight for a 12-month-old infant weighing 8 kg, and 1.2 mg/kg body weight for an 18-month-old infant weighing 12 kg.

The total iron requirement remains at 0.7 mg per day for infants up to 18 months of age (Health and Welfare Canada 1990) and is not dependent on body weight; thus, the 12.5 mg dose would also meet almost 90 percent² of the estimated total iron requirement of children 6 to 18 months old. Where iron absorption is higher because of low iron stores, the upper safe limit of intake would not be exceeded with this dose. If compliance were poor, and children were dosed the equivalent of every other day, between 35 and 45 percent of the iron requirement would be available from the iron supplement alone.

b) Nature of the Preparation Infants can be given iron as drops of a concentrated solution or as a syrup. One drop is equivalent to 0.05 mL, whereas 1 teaspoon of liquid is equivalent to 5 mL. Assuming that 12.5 mg/day would be ingested, 10 drops of a solution containing 25 mg iron/mL or 1 teaspoon of a syrup containing 2.5 mg iron/mL would provide this amount of iron.



¹ 1 mg/kg will also have adequate response, but will take a little longer to correct hemoglobin concentration, i.e., 3 months instead of 4 to 6 weeks.

² Assume 5% absorption ($5\% \times 12.5 = 0.625$ mg; $0.625/0.7 \times 100 = 89\%$).

If the dropper bottle is completely child-proof and unbreakable, it is possible to make the iron drops more concentrated to reduce the number of drops per delivery. If a dropper is to be used, it is easy to draw up a fixed amount using the dropper, which can then be delivered into the child's mouth at one time. The dropper option, however, is less safe than a child-proof dropper bottle unless some adaptation to the bottle can be made, for example, if the bottle is made so that only the dropper can get the drops out but a child cannot drink the solution from the bottle.

Because of the high cost of packaging and transport, a more concentrated solution of iron, to be given in the form of drops, would be most cost effective, as long as it could be provided with a taste and color that is acceptable to both children and mothers. Cost and logistical considerations favor providing mothers with a sufficient supply of iron to last several months, minimizing repeat visits to clinics. A typical dropper bottle contains 30 mL, but it might be feasible to increase the volume of liquid to 45 mL or more. For safety reasons, the bottle could be designed so that 0.05 mL drops could be easily dispensed directly into the child's mouth, for example, by inverting the bottle. The plastic orifice that produces the drops must be firmly attached to the bottle so that it would be virtually impossible for a child to consume the entire contents of the bottle at one time. Such bottles and dropping devices are commercially available.

A 30 mL bottle would provide sufficient iron for 60 days; thus, a mother would need to collect a bottle of iron drops at a health center only three times during the second 6 months of her child's life. This was considered feasible in many situations.

Drops would preferably be given on an empty stomach, for example, early in the morning. Alternatively, the drops could be mixed with the child's food, which would probably be more appropriate and easier. This would reduce the absorption of iron when the supplement is given in the form of ferrous iron and may result in food color changes if the food is not consumed immediately. More complex and more expensive iron compounds might make delivery with food more feasible and are discussed in Section 6.

Darkening of the child's stool will occur with any dose of oral iron, and mothers need to be made aware of this. At the dose of iron supplement recommended above, the oral iron is unlikely to cause any intestinal discomfort.

3. Periodicity and duration of iron administration

The advantages of daily versus weekly administration of iron supplements were not discussed in detail because there have been no trials on infants. A meta-analysis of trials in adolescent girls and women of reproductive age is being conducted, but may not apply to infants. Until there are data to suggest otherwise, the use of daily supplements of iron for children between 6 and 24 months old is recommended as the most effective approach if logistically and economically feasible.

Because of the difficulties of maintaining long-term compliance and the fact that the period of greatest risk of IDA is between the ages of 6 and 12 months, iron supplements should be initiated as close to 6 months as possible, and the supplements should be given for 6 months. Programs of longer duration, that is, to 15 months of age, are likely to be more beneficial. With the liquid syrups presently available, the implementation of a long-duration iron supplement program based on this schedule may not be feasible or well complied with.

4.

Feasibility of including other minerals and vitamins in a combined supplement

Although commercial liquid preparations containing iron, vitamin A, and water-soluble vitamins are available in both developed and developing countries, there was consensus that insufficient data exist to show that the vitamins are stable for a sufficiently long period of time in the presence of reactive iron salts, such as ferrous sulfate, especially after the bottle containing the liquid is opened.³ The stability, taste, and acceptability of liquid supplements containing vitamin A, iron, and perhaps other micronutrients clearly need further investigation.

Given the evidence that zinc intake is relatively low among infants in many developing countries and that zinc deficiency may also affect child growth, health, and survival, zinc can be considered another mineral to include in iron supplements. Before this is done, however, a proper evaluation of the indications for routine zinc supplementation should be conducted before a full program similar to that for iron is implemented.

It would be feasible and straightforward to add 10 mg zinc to a 25 mg/mL iron supplement.⁴

Zinc sulfate is the compound of choice because zinc gluconate, although it might have some advantages such as fewer gastrointestinal disturbances, is considerably more expensive. At 5 mg/day however, zinc sulfate is unlikely to cause gastrointestinal side effects. At the above recommended doses of iron and zinc, there will be little interaction between the iron and zinc.

Furthermore, this level of zinc is unlikely to precipitate copper deficiency, but the desirability of adding copper to a combined zinc and iron supplement should be kept under review.

Other minerals, such as iodine or selenium, are not essential in an infant mineral supplement for widespread use at the present time. Iodized salt is becoming widely available in almost all countries where deficiency exists, so additional iodine from a supplement would not be useful. Currently there is not enough evidence of widespread selenium deficiency, so the routine addition of selenium to a daily iron supplement for infants and young children is not warranted at this time.

It is recommended that UNICEF actively encourage and support the use of iron supplements for infants and young children and that the UNICEF Supply Division request tenders from pharmaceutical companies that meet the following specifications:

- an oral solution containing the equivalent of 25 mg/mL elemental iron either in the form of ferrous sulfate or as a compound that is well documented to provide iron with a bioavailability equivalent to that of ferrous sulfate;
- no deterioration in the composition, appearance, or taste of the solution for 3 months after opening;
- a shelf life of at least 3 years in unopened bottles;
- acceptable palatability for children 6 to 24 months of age;
- contained in bottles with a composition/color suitable for the required shelf life;

Because the period of greatest risk for iron deficiency anemia is between the ages of 6 and 12 months, iron supplementation should be initiated at 6 months and continued for 6 to 9 more months.

³ An industry participant stated that an aqueous solution of an iron destroys vitamin A and some B vitamins within a period of a few months. A major US manufacturer of supplements subsequently informed UNICEF that it manufactures a product containing 1500 IU vitamin A (retinol palmitate) and 10 mg iron (ferrous sulfate) with a guaranteed shelf life of 2 years. Besides vitamin B₁₂, other vitamins in the B-complex are stable in the above preparation.

⁴ Until data are available to show the efficacy of 3 to 6 months of preventive zinc supplements on child growth and health, no recommendations can be made on whether zinc should be added to all iron supplements. Nevertheless, it is recommended that suppliers be invited to provide quotations for supply of a combined iron/zinc supplement.

5.

Recommendations on iron supplements

6. Future directions

- bottles to contain a dropping device that allows delivery of 0.05 mL; and
- bottles to be tamper resistant, making it exceedingly difficult for a young child to ingest the entire contents of a bottle at one time.

Additionally, potential suppliers should be asked to provide separate quotations for a supplement that also contains 10 mg zinc in the form of zinc sulfate, all other specifications above remaining the same.

Providing daily doses of liquid preparations of iron to entire populations of infants in developing countries will pose considerable difficulties, particularly in the poorest and most remote regions. The constraints include:

- Difficulty ensuring compliance. There is some evidence that mothers “tire” of giving daily doses of iron after about 3 months.
- Logistics of distribution and cost. The cost and weight of glass bottles is an important constraint. The volume and weight of liquid iron supplements would substantially increase the size of the present supply of essential drugs to maternal and child health clinics, which would pose significant transportation and storage problems.
- Difficulty adding vitamins to an iron supplement.

For these three reasons, it is important to encourage the development of improved technology for the delivery of mineral/vitamin supplements to young children. Two options were proposed that require further consideration, testing, and development.

a) Injectable Iron for Infants Historically, injectable iron has been used to treat and prevent iron deficiency anemia in infants. Single intramuscular injections of iron dextran were widely used in infants perceived to be at risk of IDA about 20 years ago. A large dose was given shortly after birth, which effectively protected a child against IDA for 2 years. A number of infant deaths were reported to be associated with the use of these injections in New Zealand, and this led to a dramatic reduction in the use of injectable iron in many countries. There also were reports of long-term sequelae at the injection site, including tissue necrosis. Despite these concerns, cause and effect were never clearly established in the case of New Zealand.

The injectable iron doses given in earlier years were found to be unnecessarily high. A lower dose of injectable iron that would protect a child for 6 months may be safe and effective and could be given at 6 months of age when the infant is more mature. Newer iron compounds, such as injectable iron complexes, might overcome some of the problems associated with the iron compounds used earlier.

The constraints to using injectable iron are well recognized, but the opportunities of the Expanded Program on Immunization (EPI) system for delivery are also recognized. It was recommended that a thorough review of the history of the use of injectable iron and of the potential for use in developing countries be conducted.

b) Solid Mineral/Vitamin Multi Mixes for Infants and Young Children⁵ The use of solid granules and powders offers many advantages, primarily the elimination of the cost of shipping aqueous solutions in glass bottles, the ease and greater stability of mixing minerals with vitamins in dry form, and the potential for adding these directly to food. Three options were discussed:

- i) Coated or microencapsulated “sprinkles” could be used. A reactive form of iron, such as ferrous sulfate, would be coated with an inert substance, such as a triglyceride, and formed into granules with other vitamins and minerals.

⁵ In developing the multi-mineral mixes, the efficacy of iron and zinc combination can be evaluated, as this will help to define the zinc question as well as the safety of providing iron alone.

These would be sprinkled directly onto a child's complementary food in a measured amount, probably from a small sachet. It was noted that work is currently under way to prepare iron/iodine-fortified salt, using potassium iodide crystals coated with triglyceride to prevent them from reacting before they are ingested. There also is some experience in the use of coated "sprinkles" for pharmaceutical delivery in industrialized countries.

- ii) A granulated product containing minerals and vitamins that can be sprinkled directly onto food has been developed. A less reactive form of iron, ferrous fumarate, is formed into granules with other minerals, but not coated. Granules of mixed vitamins are then mixed with the minerals. This product appears to be stable, but human trials have not been conducted.
- iii) Iron/vitamin granules could be packaged in a (possibly low-cost) bottle for reconstitution into liquid by the mother or local health worker.

Other options for delivering dry mixtures, including reusable plastic dispensers for mini-tablets similar to those used for artificial sweeteners for coffee and soluble or effervescent tablets, were discussed.

It was agreed that options i and ii are more feasible. It was recommended that work be undertaken in developing countries to test the acceptability to mothers of the delivery options: daily sachets to be sprinkled on food, weekly sachets, or perhaps larger packages of granules that would be dosed or reconstituted in some way.

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Participants

Dr. Lindsay Allen
Department of Nutrition
University of California-Davis
Davis, CA 95616-8669
Tel: 916-752-5920
Fax: 916-752-3406
E-mail: lhallen@ucdavis.edu

Mr. David Alnwick
Nutrition Cluster, H-10F
UNICEF
3 United Nations Plaza
New York, NY 10017
Tel: 212-824-6369
Fax: 212-824-6462
E-mail: dalnwick@unicef.org

Dr. Jutta Brandes
Lomapharm Rudolf Lohmann
GmbH KG
Langes Feld 5
D-31860 Emmerthal
Germany
Tel: 49-5155-63-200 and 203
Fax: 49-5155-63-210 and 240

Dr. Frances R. Davidson
G/PHN/HN
US Agency for International
Development
SA-18, Room 1200
Washington, DC 20523-1808
Tel: 703-875-4118
Fax: 703-875-4684
E-mail: fdavidson@usaid.gov

Dr. Samuel G. Kahn
G/PHN/HN
US Agency for International
Development
SA-18, Room 1200
Washington, DC 20523-1808
Tel: 703-875-4228
Fax: 703-875-4686
E-mail: skahn@usaid.gov

Dr. Georg Kokkinis
Vifor (International) Inc.
Pharmaceutical Products
Rechenstrasse 37
CH-9001 St. Gallen
Switzerland
Tel: 41-71-272-8484
Fax: 41-71-272-8485

Prof. E. Barbara Mawer
Department of Medicine
The Royal Infirmary
Oxford Road
Manchester M13 9WL
United Kingdom
Tel: 44-161-276-8631
Fax: 44-161-274-4833

Ms. Lucy Namkinga
Mona Limited
Kinondoni Road
P.O. Box 5385
Dar es Salaam
Tanzania
Tel: 255-51-67315
Fax: 255-51-68156

Dr. Penelope Nestel
OMNI/Johns Hopkins
University
11th Floor
1616 N. Fort Myer Drive
Arlington, VA 22209
Tel: 703-528-7474
Fax: 703-528-7480
E-mail: penny_nestel@jsi.com

Ms. Hanne Bak Pedersen
UNICEF
3 United Nations Plaza, TA-24A
New York, NY 10017
Tel: 212-824-6342 or 6333
Fax: 212-824-6462
E-mail: hpedersen@unicef.org

Dr. Timothy C. Quick
G/PHN/HN
US Agency for International
Development
SA-18, Room 1200
Washington, DC 20523-1808
Tel: 703-875-4542
Fax: 703-875-4686
E-mail: tquick@usaid.gov

Mr. Velimir Srdanovic
Health & Nutrition
UNICEF Plads
Freeport
Copenhagen 2100
Denmark
Tel: 45-3527-3020
Fax: 45-3526-9421

Mr. Donny Guntur Suparman
PT Kenrose-Indonesia
Jl. Raya Jakarta
Bogor Km. 28
Jakarta 13710
Indonesia
Tel: 62-21-871-0721/0722/
0723
Fax: 62-21-871-0234

Dr. Paula R. Trumbo
Associate Director
Human Nutrition Institute
International Life Sciences
Institute
1126 Sixteenth Street, NW
Washington, DC 20036-4810
Tel: 202-659-0524
Fax: 202-659-3617
E-mail: paula@dc.ilsa.org

Dr. Barbara Underwood
National Eye Institute
Room 6A-17
31 Center Drive, MSC 2510
Bethesda, MD 20892-2510
Tel: 301-496-1331
Fax: 301-480-3246

Mr. Wolfgang A. Vogl
Dr. Paul Lohmann GmbH KG
Hauptstrasse 2
D-31860 Emmerthal
Germany
Tel: 49-5155-63-140
Fax: 49-5155-63-118 and 119

Dr. Ray Yip
UNICEF
Wisma Metropolitan II, 10-11th
Floors
Jl. Jend. Sudirman Kav. 31
Jakarta 12920
Indonesia
Tel: 62-21-570-5816
Fax: 62-21-571-1326
E-mail: unicef@prad.net.id

Dr. Stanley H. Zlotkin
Hospital for Sick Children
555 University Avenue
Toronto, Ontario M5G 1X8
Canada
Tel: 416-598-6176
Fax: 416-813-4972
E-mail: zlotkin@sickkids.on.ca

Mr. Peter Zwyyer
Vifor (International) Inc.
Pharmaceutical Products
Rechenstrasse 37
CH-9001 St. Gallen
Switzerland
Tel: 41-71-272-8484
Fax: 41-71-272-8485



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The names and addresses of companies that supply the iron products mentioned in this document are available from INACG.

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