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Specific Strategies to Address Micronutrient Deficiencies in the Young Child: Targeted Fortification

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Introduction

Micronutrient deficiency during early childhood may be related to a series of factors including inadequate stores accumulated during the fetal period, low intake from maternal breast milk, early abandonment of breast-feeding, increased losses due to infections and inadequate micronutrient intake from complementary foods (foods taken in addition to breast milk from ~6 months until the child eats from the family diet, ~24 months). Current guidelines recognize that, while in most settings full breast-feeding is adequate to meet nutrient requirements for the first 6 months of life, the appropriateness of complementary feeding practices from 6 to 24 months is a major concern in many developing countries [1], especially micronutrient density (micronutrient content/100 kcal) and frequency of feeding due to small gastric capacity.

Assuming an average breast-milk intake, almost all iron and zinc, 5–30% of vitamin A, and 50–80% of thiamin, riboflavin and calcium must be supplied by complementary foods [2]. Very little or no vitamin B_6, B_{12} and folate are needed from complementary foods because of their higher concentration in breast milk. In settings where women do not breast-feed for extended periods, breast milk intake is low or breast-feeding women are deficient in these vitamins, the proportion provided by complementary foods should increase.

Micronutrients Most Likely to Be Inadequate in Complementary Foods

The density of many micronutrients, including zinc, iron, calcium, vitamin A, and vitamin B_{12} is low in foods of plant origin, typically used as the basis of complementary feeding in developing countries [2]. Dietary factors that inhibit absorption of some nutrients (phytates, polyphenols and dietary fiber) tend to be high [3] particularly in maize and legumes and although these foods also contain moderately high levels of trace elements such as iron and zinc, they are poorly absorbed.

Analysis of typical diets of breast-fed infants (6–24 months) indicate that several foods consumed by 6- to 11-month-old infants in Peru and Mexico have iron densities that could meet infant requirements, but only if 2–3 times more of the food was consumed than that reported for any child [2]. Zinc and calcium densities were adequate for children aged 18–24 months when animal source foods were included. Gibson et al. [3] found that very few complementary foods from Africa and Asia could meet the iron, zinc, calcium and riboflavin needs of infants 9–11 months of age. Vitamin A density may also be inadequate especially if breast milk retinol intake is low due to maternal deficiency or low breast milk intake. Recent studies have shown that the bioavailability of vitamin A from plant-based foods is much lower (~50%) than earlier estimates [4], and that in the absence of any preformed retinol, young children would have to consume about 4–5 times the current amount of plant-based foods such as spinach to meet their requirements [5].

Similar analyses of dietary intake data from Bangladesh, Ghana, Guatemala, Peru and the USA [6] using the updated nutrient requirements [7–11] indicate that iron, zinc and calcium densities remain low in almost all foods for children <12 months of age, despite the lower energy requirements. Calcium and iron densities were inadequate for children aged 12–23 months. Although the results were inconsistent for other micronutrients (riboflavin, vitamin B_6, niacin, thiamine, folate and zinc), they are most likely limiting in the diets of infants <2 years of age and it was concluded that more research is needed to establish appropriate nutrient densities for complementary foods.

Rationale for the Use of Targeted Fortification to Improve Micronutrient Status of Small Children

It is clear that the density of zinc, iron, calcium and possibly other micronutrients in unfortified foods from developed and developing countries is insufficient to meet the needs of infants and small children. Improved micronutrient density may be feasible through daily consumption of poultry, meat, fish or eggs and vitamin A-rich fruits and vegetables [1]. In many populations, however, economic and other constraints limit the inclusion of sufficient animal-source food to breech this gap [2]. Other mechanisms (fermentation, germination, ascorbic acid) can improve the availability of iron and zinc from plant-based foods, but are likely insufficient to meet the needs of infants [3]. Micronutrient supplement distribution can be very efficacious in improving micronutrient status especially when high-risk groups are targeted [12]. It has been challenging, however to implement supplementation programs due to technical and logistical problems, including interactions between nutrients in multinutrient syrups, safety, frequency of consumption (at least weekly for nutrients such as iron, zinc and water soluble vitamins), compliance, reliance on health systems for distribution, and sustainability [13].

The increased use of processed foods facilitates fortification as an effective strategy to improve micronutrient intakes of populations. Universal fortification of staples and condiments, however, is unlikely to improve micronutrient intakes of small children due to the small amount of these foods consumed. Commercial complementary foods have been available and used extensively in many developed countries since the 1950s. Consistent with nutrition knowledge at that time, emphasis was placed on adequate protein intake [6]. Fortified complementary foods (FCFs) now provide an important alternative to meet the micronutrient needs of young children [14]. As urbanization and women's participation in the work force increase, commercial complementary foods provide a convenient and timesaving alternative to home preparation and reduce the risk for microbial contamination [6].

Barriers to the Use of Fortified Foods in Developed and Developing Countries

There are a number of barriers to the widespread production and use of FCFs, particularly among the rural poor in developing countries. Because this is where the highest prevalence of micronutrient deficiencies exists, fortified foods have had little impact on the prevalence of child malnutrition to date [6].

Barriers on the Production Side

The amount of micronutrients needed from FCFs depends on total requirements and intake from breast milk and other sources. A large range in consumption of complementary foods can be expected, depending on child age and intake from other sources [6] and it may be difficult for manufacturers to estimate appropriate levels of fortification when target populations are heterogeneous. Lutter [15] recommends that the level of fortification be set to meet the needs of the largest possible proportion of non- or minimally breast-fed infants over the range of target ages. Typical breast milk intake, portion size, bioavailability, micronutrient interactions and inhibitors of absorption naturally occurring in the food vehicle should be taken into consideration in determining the level of fortificant. Nutrient bioavailability studies of fortified foods have been conducted in older children and adults [16–18] and in FCFs with different iron fortificants in the presence of enhancers (ascorbic acid) and inhibitors (phytates and milk) of iron absorption [19]. Unfortunately, there is a paucity of information on the bioavailability of other nutrients and the role of interactions when more than one nutrient is added to complementary food.

Quality control of food fortification, including fortification to the specified level and control of microbial contamination must be monitored; although this may be logistically difficult if foods are prepared by many disperse manufacturers. Where livelihood depends on small-scale agriculture, locally produced crops should be used in the production of FCFs to avoid undermining local markets [6].

The potential role of industry in the production of safe, affordable and high-quality FCFs is great, both as a partner in the production of FCFs for national programs and for sale in the market. A number of barriers must be overcome before industry is likely to make the investment needed for FCF production. Raw material costs can only be reduced to a certain degree, after which packaging and marketing expenses must decrease [20]. The demand for FCFs in developing countries is very low, especially among high-risk groups and a large investment would be necessary to create demand and brand loyalty in this setting [15]. Finally, many producers shy away from foods for small infants for fear of consumer boycott [20, 21] or even liability due to concerns of contamination from inadequate hygienic practices during food preparation that could be attributed to the product itself [20]. Public sector and advocacy groups must work with industry to reduce perceived risks related to FCF production and increase the market for high-quality, low-cost FCFs.

Reaching the Most Needy

In developing countries, FCFs have traditionally been expensive and available only to the wealthier, urban population. Recently FCFs have been included as part of national poverty alleviation programs in various Latin American countries, including Mexico, Peru, Guatemala, Columbia, Costa Rica and Chile (Neufeld and Hotz, unpublished document prepared for Global Forum, 2003). One such program, *Oportunidades* (previously *Progresa*) has been operating in Mexico since 1997 and has been evaluated by the National Institute of Public Health (INSP), Mexico, since its inauguration. A description of this program was published as part of a previous Nestlé Nutrition Workshop [22].

Creating a demand for FCFs among poor families with little disposable income may be a major barrier, particularly among rural dwellers, less accustomed to the use of commercial foods. Although some national programs distribute FCFs to poor families, they reach a small portion of those who could benefit [15], and unless steps are taken, may ultimately create dependency [6]. Furthermore, the nutritional quality of the products distributed through national programs has not always been adequate [15].

Education and social marketing may help create consumer demand for FCFs [15] and provide an opportunity to educate the population about appropriate feeding practices and promote breast-feeding [6]. Unlike breast-feeding, clear policy support and advocacy have been lacking for specific recommendations related to complementary feeding [21]. An abundance of research exists on issues related to complementary feeding including nutrient composition, consistency, hygiene, control of microbial contamination and feeding environment (e.g. responsive feeding practices) but the implementation of this information into action has been inadequate [21].

Fortification and Micronutrient Status of Infants and Young Children: Experiences from Universal and Targeted Food Fortification

Many examples of the effectiveness of untargeted fortification to improve the micronutrient status of older children and adults have been published. The iron status of children improved after universal fortification of rice (Philippines) and flour (Venezuela) [23]. Several studies have also evaluated the efficacy of fortified foods targeted to school-age children (drinks, cookies, candies) with positive effects on iron [24–28], vitamin A [24–26], and zinc status [24]. In Morocco, the iron and iodine status of children improved with the use of salt fortified with microencapsulated iron and iodine [29].

Recent studies suggest that fortified foods may contribute 10–20% of micronutrient intakes in older children and adults from developed countries. Fortified foods were shown to contribute ~80% vitamin B_6, 40–50% vitamins C, B_2, E and niacin, 10–20% iron, vitamin A and folate, and 5% calcium intakes in German children (2–15 years) [30]. Fortified ready to eat cereals and fruit juices are significant sources of iron and vitamin C, respectively, among US children (2–18 years) [31]. Berner et al. [32] concluded that fortification substantially increased micronutrient intakes in all age/sex groups in the US, especially young children, based on nationally representative dietary intake data. However, micronutrient intakes from fortified foods among children <2 years of age are not well documented.

Although essential to improve the micronutrient status of older children and adults, these strategies are unlikely to have substantial impact on the micronutrient status of children <2 years of age. Micronutrient density is insufficient to meet requirements during complementary feeding and the small quantities that can be consumed due to limited gastric capacity will not compensate for lower nutrient density.

Developed Country Experiences in Targeted Fortification

Breast milk substitutes and complementary foods have been fortified, especially with iron, since the 1970s in many developed countries and the observed decline in rates of anemia and iron deficiency has been attributed to this [33]. The best evidence comes from the United States where the prevalence of anemia declined among low income young children between 1974 and 1985 [34, 35], corresponding to the introduction of iron-fortified formula and complementary foods in the national Women, Infants and Children program.

An important lesson from developed countries is the active role of the private sector in the development and marketing of FCFs. A wealth of experience exists in the selection of appropriate fortificant, acceptability of the final product, etc. For example, many efficacy trials [36–38] have compared the impact of different iron fortificants on young child iron status and the advantages and disadvantages are well documented [39]. The challenge is to share this knowledge and make it relevant to developing country settings where it is most needed.

Developing Country Experiences in Targeted Fortification

While evidence exists that FCFs may improve outcomes such as child growth and morbidity [2, 22], less is known about their impact on micronutrient status in developing country settings. The results of published efficacy trials [40–44] are mixed and methodological details (table 1) show that there is considerable variability in study design, micronutrients and food vehicles used.

Most studies showed positive effects of complementary foods fortified with iron on iron status. In China [44], no drop in hemoglobin concentration was observed in the fortified food group (-0.8 ± 0.1 g/l) while it declined significantly in the control group (-7.9 ± 1.2 g/l). Similarly, a significant drop in ferritin and hemoglobin concentration was observed in infants receiving unfortified porridge or porridge with fish powder in Ghana, while no drop occurred among those receiving fortified porridge [43]. At 12 months of age, 11% of infants receiving the fortified porridge had low serum ferritin compared to 50% in all other groups. In South Africa [42], a smaller drop in serum iron but not hemoglobin concentration was observed in the fortified food group. In Chile [41], infants receiving iron fortified rice cereal had a higher hemoglobin concentration and a lower prevalence of anemia at 8, 12 and 15 months of age than infants receiving unfortified cereal.

FCFs provided protection against a drop in serum retinol in South Africa [42] and Ghana [43]. In Ghana, the prevalence of vitamin A deficiency (retinol <0.7 μmol/l) was 10.4% in the fortified group and 27.0–34.3% in the other groups. There was no change in serum zinc in South Africa, China or Ghana and no data were reported for Chile. In one older study [40], riboflavin status was adequate in the fortified food group at 9 months of age while riboflavin status worsened in the group not receiving the fortified food.

Therefore, there is some evidence that FCFs may help prevent micronutrient deficiencies under ideal circumstances. However, few program effectiveness trials have been conducted. Considering that national programs in different parts of the world provide FCFs, it is essential to determine whether FCFs provide benefits for infant micronutrient status over and above other program components (e.g. economic transfers).

Case Study of a Fortified Complementary Food in Mexico

The nation-wide poverty alleviation program, *Oportunidades* was implemented in 1997 in rural areas and expanded to urban areas in 2001. A fortified, milk-based complementary food, 'Nutrisano' is distributed to all participating low-income families with children 4–23 months of age and underweight children 2–4 years of age. Considering the enormous investment involved in the production and distribution of Nutrisano, a series of studies were conducted to determine the efficacy to improve micronutrient status, iron bioavailability and stability and acceptability of various iron fortificants.

Efficacy to Improve Infant Micronutrient Status

The efficacy of Nutrisano to improve iron, zinc and vitamin A status was assessed using supplementation with multiple micronutrient syrup as positive control [45]. This was used instead of placebo due to the high prevalence of micronutrient deficiency and provides the opportunity to compare two strategies currently implemented in Mexico. The micronutrient content and percent recommended intake are presented in table 2. Infants 4–12 months of age were randomly assigned to receive Nutrisano or syrup daily. After 4 months, the ferritin concentration dropped significantly in the Nutrisano group (−12.4 ng/dl) while no change was observed in the syrup group (+0.87 ng/dl). The prevalence of iron deficiency (ferritin <12.0 ng/dl) was significantly lower in the syrup group (12.5 vs. 37.5% Nutrisano). There was no difference between groups in hemoglobin concentration or anemia prevalence. Micronutrient syrup, but not Nutrisano provided protection against a drop in iron stores during the weaning period and further research was carried out to determine why. Laboratory results for serum zinc and retinol will be available shortly.

Bioavailability, Stability and Acceptability of Different Forms of Iron in Nutrisano

Following the efficacy trial, the bioavailability of ferrous sulfate (FS), ferrous fumarate (FF), or reduced iron + sodium EDTA (Fe-EDTA) in Nutrisano was assessed in children 2–4 years of age using stable isotope procedures [46]. Nutrisano labeled with ^{58}Fe was consumed after fasting and a reference dose of ^{57}Fe dissolved in grape juice with 50 mg ascorbic acid was administered the following day. Incorporation of iron into erythrocytes was

Table 1. Efficacy trials of the impact of fortified complementary foods on infant micronutrient status in developing countries

Country	Fortificant	Age at initial feeding in months	Food vehicle	Duration and details of supplementation	Micronutrient status outcomes measured
South Africa	MM[1]	6	Complementary food	12 months Randomized to fortified or unfortified food	Hemoglobin, serum iron, zinc, retinol
Chile (n = 515)	Elemental iron 55 mg/100 g dry cereal (no information-mentioned for other micronutrients)	4	Rice cereal (Gerber) 30 g/day	Randomized to fortified or unfortified cereal Stratified by breast or formula fed and by iron fortification within the formula group Daily feeding with encouragement to 15 months Ascorbic acid present in iron-fortified formula	Hemoglobin, prevalence of iron deficiency anemia (low Hb + 2 values low for mean corpuscular volume, serum ferritin, transferrin saturation)
Ghana (n = 190)	1 MM (electrolytic iron, zinc oxide) 2 Dried anchovy powder	6	Traditional maize porridge or improved porridge (Weanimix)	Randomized to traditional porridge plain or with fish powder, Weanimix plain, with fish powder or multiple micronutrients Daily feeding to 12 months	Hemoglobin, hematocrit, plasma retinol, zinc, TIBC, erythrocyte riboflavin

China (n = 226)	10 micronutrients (ferric ammonium citrate 10%, zinc gluconate 5%, retinol acetate 375% of RDA)	6–13	Rusk	Randomized to fortified or unfortified rusk by village Daily feeding for 3 months Direct monitoring of consumption	Hemoglobin, erythrocyte porphyrin, plasma vitamin A and erythrocyte glutathione reductase activity (riboflavin)
Gambia (n = 178)	Riboflavin in fortified wheat flour (1.4 μg/g fresh weight of supplement)	3–12	Locally prepared with wheat, soya, skim milk, ground nut oil, sugar	Supplemented 3–12 months of age with or without mother receiving supplement during pregnancy and lactation or nothing Assignment by community	Erythrocyte glutathione reductase activity (riboflavin)

[1]MM = Multiple micronutrients, stated as quantity similar to recommended dietary allowance (RDA).

Table 2. Nutrient content of a fortified food (Nutrisano) and a micronutrient syrup, distributed in different national poverty alleviation programs in Mexico

Nutrient	Nutrisano		Syrup	
	content[1]	% new DRI[2]	content	% new DRI
Energy, kcal	194	23	0	–
Protein, g	5.8	–	0	–
Total fat, g	6.6	–	0	–
Total carbohydrates, g	27.9	–	0	–
Sodium, mg	24.5	–	0	–
Vitamin A, μg	40.0	8	0	–
Vitamin E, mg	6.0	–	0	–
Vitamin C, mg	40.0	80	60.0	120
Vitamin B_{12}, μg	0.7	140	1.1	220
Folic acid, μg	50.0	63	95.0	119
Zinc (zinc sulfate), mg	10.0	333	20.0	666
Iron[3], mg	10.0	91	20.0	182
Riboflavin, mg	0	–	1.2	300
Thiamin, mg	0	–	1.1	367

[1]Content in one daily portion (44 g of dry mix Nutrisano; 20 drops, syrup).
[2]Selected micronutrients, US dietary recommended intakes (DRI) for 9–11 months of age [7–10] and energy based on WHO/UNICEF recommendations for total energy 9–11 months of age [2].
[3]Reduced iron in Nutrisano; ferrous sulfate in syrup.

assessed 15 days after administration. Iron absorption from Nutrisano with FS was 7.9%, 2.4% from FF, and 1.4% from Fe-EDTA. Considering 1 mg/day requirement, daily iron absorbed from Nutrisano fortified with FS would provide 144% of the requirement, and 50% if fortified with FF. Iron absorption from Nutrisano fortified with Fe-EDTA would be negligible.

Government authorities requested a recommendation for changing the iron fortificant in Nutrisano and further testing was conducted (Morales J, unpublished data). The taste, color, viscosity and microbial content of Nutrisano with each fortificant were assessed immediately after production and after 6-month storage. Expert judges were able to identify a slightly metallic taste in the food fortified with FS. Approximately 10–20 min after addition of water, color changes and jellification occurred in Nutrisano fortified with FS but not FF or Fe-EDTA. All samples were within acceptable limits for microbiological tests.

Acceptability and intake of Nutrisano with 3 fortificants was evaluated in blind testing among infants 4–23 months of age [47]. All forms received a rating of 4 on a 5-point Likart scale from the infants' mothers. Infants $>$12 months of age consumed more Nutrisano fortified with FF (28 g), than FS (23 g) or Fe-EDTA (24 g).

Based on this series of studies, researchers at the Instituto Nacional de Salud Publica recommended that the fortificant be changed from reduced iron to ferrous fumarate. This recommendation is now being implemented. Ongoing program evaluations should provide results for the effectiveness of Nutrisano to improve micronutrient and other outcomes.

Conclusions

Micronutrient intakes of children <2 years of age are inadequate in many parts of the world and specific interventions must be undertaken to improve micronutrient status and avoid deleterious consequences for child survival, growth and development. FCFs play an important role in maintaining adequate micronutrient status of small children in developed countries and are likely to play an increasing role in developing countries in the near future.

The inclusion of FCFs in national programs has great potential to improve micronutrient intakes in vulnerable groups. Nonetheless, additional marketing and promotion strategies to improve the use of FCFs is necessary as programs are unlikely to reach all those who could benefit from FCFs and may not be economically sustainable for some countries. Clear documentation of the cost-effectiveness of programs distributing FCFs through close monitoring and evaluation may provide the motivation necessary to expand the use of FCFs in programs, where feasible. Interchange between government policy-makers and researchers, such as the case in Mexico for the design and improvement of Nutrisano, are essential to ensure that state-of-the-art knowledge in the field is incorporated into program planning. Cooperation with industry should be increased by reducing real and perceived risk associated with investment in FCF production and by increasing consumer demand though education and social marketing. Communication of the effectiveness of FCFs for preventing micronutrient deficiencies and their negative consequences in a manner meaningful to rural populations with limited resources may increase demand for the products.

To make appropriate decisions about food vehicle and level of fortification in each population setting, manufacturers will require information regarding the range of nutrient intakes in the population (from breast milk and other complementary foods), the likely range of consumption of the fortified food, cultural traditions and taboos of foods appropriate for young children, prevalence and severity of micronutrient deficiency in the population and capacity of the population to purchase complementary foods. At least part of this information may exist for some developing countries. The impetus to motivate industry to get more involved in the production of FCFs lies with public and advocacy organizations. Ideally, these same bodies should then work with industry to ensure a product that responds to needs of the target population.

Recommended Research Areas

Experience in both developed and developing countries has resulted in a wealth of information on micronutrient needs, appropriate densities, bioavailability of different fortificants, interaction between nutrients, and enhancers and inhibitors of absorption. The food industry, especially manufacturers of infant foods also have considerable experience but this information is typically proprietary in nature and often not available in a manner that would benefit disadvantaged populations. Without doubt, better cooperation and trust between industry and public health/policy sectors with appropriate technology transfer (north–south) would help both increase demand and supply for low-cost FCFs. In this scenario, developing countries would evaluate FCFs in their own context, with appropriate assistance. This type of research is essential to reduce barriers related to the production of low-cost, acceptable and high-quality FCFs.

Many of the previously identified research needs [22] have not yet been adequately addressed and maintain relevancy. In addition:

(1) Appropriate nutrient densities based on type of diet including breastfeeding, amount and frequency of food consumed and foods typically consumed needs to be clarified.

(2) Bioavailability of micronutrients, particularly iron and zinc in various food vehicles needs to be established and guidelines should be produced for the use of specific fortificants, depending on food vehicle characteristics.

(3) Formative research at the population level must be conducted to understand how to appropriately present, promote and market FCFs, particularly in rural areas of developing countries.

(4) The effectiveness of programs distributing FCFs to improve child micronutrient status and incremental improvement over and above other program benefits needs to be assessed, as does cost-effectiveness. Clear solutions to ensure sustainability when programs are effective must be found.

(5) On-going process evaluation is essential to understand why programs distributing FCFs work or do not work, and provide feedback for their improvement.

(6) The relative contribution of FCFs to improving micronutrient status compared to other interventions in varying contexts should be evaluated.

References

1 Pan American Health Organization/World Health Organization: Guiding Principles for Complementary Feeding of the Breastfed Child. Washington, PAHO/Geneva, WHO, 2001.
2 World Health Organization/UNICEF: Complementary Feeding of Young Children in Developing Countries: A Review of Current Scientific Knowledge (who/nut/98.1). Geneva, WHO, 1998.
3 Gibson RS, Ferguson EL, Lehrfeld J: Complementary foods for infant feeding in developing countries: Their nutrient adequacy and improvement. Eur J Clin Nutr 1998;52:64–770.

4 West CE, Eilander A, van Lieshout M: Consequences of revised estimates of carotenoid bioefficacy for dietary control of vitamin A deficiency in developing countries. J Nutr 2002; 132(suppl):2920S–2926S.
5 Miller M, Humphrey J, Johnson E, et al: Why do children become vitamin A deficient? J Nutr 2002;132(suppl):2867S–2880S.
6 Dewey KG, Brown KH: Update on technical issues concerning complementary feeding of young children in developing countries and implications for intervention programs. Food Nutr Bull 2003;24:5–28.
7 Institute of Medicine: Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride. Washington, National Academy Press, 1997.
8 Institute of Medicine: Dietary Reference Intakes for Thiamine, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline. Washington, National Academy Press, 1998.
9 Institute of Medicine: Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, National Academy Press, 2000.
10 Institute of Medicine: Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, National Academy Press, 2001.
11 Joint Food and Agriculture Organization/World Health Organization Expert Consultation: Vitamin and Mineral Requirements in Human Nutrition. Geneva, WHO, 2002.
12 Allen LH: Iron supplements: Scientific issues concerning efficacy and implications for research and programs. J Nutr 2002;132(suppl):813S–819S.
13 Mora JO: Iron supplementation: Overcoming technical and practical barriers. J Nutr 2002;132(suppl):853S–855S.
14 World Health Organization/UNICEF: Global Strategy for Infant and Young Child Feeding 2002. Document A55/15. Geneva, WHO, 2002.
15 Lutter CK: Macrolevel approaches to improve the availability of complementary foods. Food Nutr Bull 2003;24:83–103.
16 Mendoza C, Viteri FE, Lönnerdal B, et al: Absorption of iron from unmodified maize and genetically altered, low-phytate maize fortified with ferrous sulfate or sodium iron EDTA. Am J Clin Nutr 2001;73:80–85.
17 López de Romaña D, Lönnerdal B, Brown KH: Absorption of zinc from wheat products fortified with iron and either zinc sulfate or zinc oxide. Am J Clin Nutr 2003;78:279–283.
18 Herman S, Griffin IJ, Suwarti S, et al: Cofortification of iron-fortified flour with zinc sulfate, but not zinc oxide, decreases iron absorption in Indonesian children. Am J Clin Nutr 2002;76: 813–817.
19 Walter T, Olivares M, Pizarro F, Hertrampf E: Fortification; in Ramakrishnan U (ed): Nutritional Anemias. Boca Raton, CRC Press, 2001, pp 153–184.
20 Setiadi A: Manufacturing Complementary Foods in Indonesia: Current Constraints and Future Opportunities. Conference on Food Fortification in Asia, Manila, 2000.
21 Piwoz EG, Huffman SL, Quinn VJ: Promotion and advocacy for improved complementary feeding: Can we apply the lessons learned from breastfeeding? Food Nutr Bull 2003;24:29–43.
22 Rivera-Dommarco JA, Lutter C: The potential role of processed complementary food in Latin America; in Martorell R, Haschke F (eds): Nutrition and Growth. Nestlé Nutrition Workshop Series Pediatric Program. Philadelphia, Lippincott Williams & Wilkins, 2001, vol 47, pp 281–304.
23 Mannar V, Boy GE: Iron fortification: Country level experiences and lessons learned. J Nutr 2002;132:856S–858S.
24 Abrams SA, Muchi A, Hilmers DC, et al: A multinutrient-fortified beverage enhances the nutritional status of children in Botswana. J Nutr 2003;133:1834–1840.
25 Ash DM, Tatala SR, Frongillo EA, et al: Randomized efficacy trial of a micronutrient-fortified beverage in primary school children in Tanzania. Am J Clin Nutr 2003;77:891–898.
26 van Stuijvenberg ME, Kvalsvig JD, Faber M, et al: Effect of iron-, iodine-, and β-carotene fortified biscuits on the micronutrient status of primary school children: A randomized controlled trial. Am J Clin Nutr 1999;69:497–503.
27 Giorgini E, Fisberg M, de Paula RA, et al: The use of sweet rolls fortified with iron bis-glycinate chelate in prevention of iron deficiency anemia in preschool children. Arch Latinoam Nutr 2001;51:48–53.
28 Sari M, Bloem MW, de Pee S: Effect of iron-fortified candies on the iron status of children aged 4–6 y in East Jakarta, Indonesia. Am J Clin Nutr 2001;73:1034–1039.

29 Zimmermann MB, Zeder C, Chaouki N, et al: Dual fortification of salt with iodine and microencapsulated iron: A randomized, double-blind, controlled trial in Moroccan schoolchildren. Am J Clin Nutr 2003;77:425–432.
30 Sichert-Hellert W, Kersting M, Manz F: Changes in time-trends of nutrient intake from fortified and non-fortified food in German children and adolescents – 15 year results of the DONALD study. Dortmund Nutritional and Anthropometric Longitudinally Designed Study. Eur J Nutr 2001;40:49–55.
31 Subar AF, Krebs-Smith SM, Cook A, Kahle LL: Dietary sources of nutrients among US children, 1989–1991. Pediatrics. 1998;102:913–923.
32 Berner LA, Clydesdale FM, Douglass JS: Fortification contributed greatly to vitamin and mineral intakes in the United States, 1989–1991. J Nutr 2001;131:2177–2183.
33 Ramakrishnan U, Yip R: Experiences and challenges in industrialized countries: Control of iron deficiency in industrialized countries. J Nutr 2002;132:820S–824S.
34 Leads from the MMWR: Declining anemia prevalence among children enrolled in public nutrition and health programs. Selected states, 1975–1985. JAMA 1986;256:2165.
35 Yip R, Walsh KM, Goldfarb MG, Binkin NJ: Declining prevalence of anemia in childhood in a middle-class setting: A pediatric success story? Pediatrics 1987;80:330–331.
36 Haschke F, Male C: Iron nutritional status during early childhood. The importance of weaning foods to combat iron deficiency; in Haltberg L, Asp NG (eds): Iron Nutrition in Health and Disease. London, Libbey, 1996, pp 325–329.
37 Haschke F, Pietschnig B, Vanura H, et al: Iron intake and iron nutritional status of infants fed iron-fortified beikost with meat. Am J Clin Nutr 1988;47:108–112.
38 Stekel A, Olivares M, Pizarro F, et al: Absorption of fortification iron from milk formulas in infants. Am J Clin Nutr 1986;43:917–922.
39 Hurrell RF: Fortification: Overcoming technical and practical barriers. J Nutr 2002;132: 806S–812S.
40 Bates CJ, Prentice AM, Paul AA, et al: Riboflavin status in infants born in rural Gambia, and the effect of a weaning food supplement. Trans R Soc Trop Med Hyg 1982;76:253–258.
41 Walter T, Dallman PR, Pizarro F, et al: Effectiveness of iron-fortified infant cereal in prevention of iron deficiency anemia. Pediatrics 1993;91:976–982.
42 Oelofse A, van Raaij JM, Benade AJ, et al: The effect of a micronutrient-fortified complementary food on micronutrient status, growth and development of 6- to 12-month old disadvantaged urban South African infants. Int J Food Sci Nutr 2003;54:399–407.
43 Lartey A, Manu A, Brown KH, et al: A randomized, community-based trial of the effects of improved, centrally processed complementary foods on growth and micronutrient status of Ghanaian infants from 6 to 12 mo of age. Am J Clin Nutr 1999;70:391–404.
44 Liu DS, Bates CJ, Yin TA, et al: Nutritional efficacy of a fortified weaning rusk in a rural area near Beijing. Am J Clin Nutr 1993;57:506–511.
45 Neufeld LM, Rivera JA, Villalpando S, Shamah Levy T: Changes in iron status after 4 mos supplementation with a micronutrient syrup or a fortified complementary food. FASEB J 2003; LB375.
46 Pérez-Expósito AB, Villalpando S, Abrams A, et al: Evaluación de la biodisponibilidad de hierro en el suplemento infantil distribuido por el programa Progresa utilizando isótopos estables (Evaluation of the bioavailability of iron in the infant food supplement distributed in the program, Progresa, using stable isotopes). X Congr Invest en Salud Pública, Libro de Resúmenes, 2003, TL087:155.
47 Flores ME, Safdie M, Sotres D, Rivera J: Evaluation of acceptability and intake by women and children of nutritional supplements fortified with three forms of iron. FASEB J 2003;LB371.

Discussion

Dr. Hurrell: I enjoyed your presentation very much. I have several comments on the iron fortification trials that you did. I was wondering what the composition of the complementary food was? You said it was just milk-based. Were the iron absorption studies in adults or were they in infants? The absorption of ferrous sulfate was about 3 times that of fumarate and in most of the adult studies they have been the same.

So if it was an infant study I was wondering why the absorption of fumarate was less than sulfate? Perhaps you could comment on that. Just one other point, and that is that it was not iron EDTA which was studied, but reduced iron plus EDTA which is not actually iron EDTA. So the results which you gave were not from iron EDTA but from elemental iron.

Dr. Neufeld: Yes, it is elemental iron with EDTA. The iron bioavailability studies were conducted in infants. I am not the person to answer the question about the difference between ferrous fumarate and ferrous sulfate. In our group it is Salvador Villalpando who does the isotope bioavailability studies, so I really wouldn't know.

Dr. Abrams: What about the data compared with what was found in Bangladesh?

Dr. Hurrell: I think that is part of the important finding that iron absorption from fumarate is less in infants than we would have expected. The present study agrees exactly with what we reported in Bangladesh where fumarate was found to have 25% the absorption of ferrous sulfate. Most of the guidelines for infant feeding recommend the use of fumarate based on adult studies which show that it is also absorbed as ferrous sulfate. I think that is quite an important finding.

Dr. Abrams: I would also point out that there are methodological problems in assessing the bioavailability of reduced iron because the isotope methods would probably overestimate the absorption. So I would consider 1.4% to be an upper limit of what was truly absorbed because the fumarate is certainly much more accurate than sulfate, and there are huge differences that you found previously. I am glad it has been found, but I think it needs to be discussed as the real impact on how we fortify foods.

Dr. Hurrell: The lower absorption of ferrous fumarate in infants may be due to gastric acid secretion. It may be that infants have less gastric acid than do adults, and perhaps this was one of the reasons why ferrous fumarate is less well dissolved in their gastric juices.

Dr. Tolboom: There is not much difference between the gastric acid secretion in infants compared to older children and adults, only in the very young, about the first weeks perhaps, so thereafter it is the same.

Dr. Barclay: Coming back to the absorption of ferrous fumarate versus ferrous sulfate versus iron EDTA: were these studies done as acute absorption studies or were the children consuming these products for a certain period of time beforehand for adaptation?

Dr. Neufeld: Yes, they were given an adaptation diet. So they were adapted and then given the different forms.

Dr. Zlotkin: The two strategies that have worked in terms of targeted fortification in the Western environment, one of which you emphasized and the other you didn't. It may be because you are unwilling to use the F word in a Nestlé meeting. But I do want to emphasize that two strategies for targeted fortification that have worked extremely well in the West are the targeted fortification of commercial infant foods and the targeted fortification of infant formulas, that is the F word I was referring to. It is worthwhile mentioning that, although everyone in this meeting would of course agree that the primary feeding methodology for infants everywhere in the world should be exclusive breast-feeding for 6 months followed by the appropriate introduction of fortified complementary foods, there are situations in which formula is going to be used in infants who cannot be breast-fed. One of the targeted fortification studies that we should emphasize is that if formula is to be used it should be a fortified formula because there is no doubt and good epidemiologic evidence that fortified formulas do work to prevent at least iron deficiency and probably most micronutrient deficiencies. So the two strategies where there is good proof of efficacy and effectiveness are the commercial formulas and the commercial cereals. A further point I would like to make, and maybe you could respond to this, is that I am not sure that it is necessary for us to reinvent the wheel in each and every country around the world. We do have multinationals who have the capacity to produce fortified cereal products at a relatively low cost, and although it may be possible that national companies can produce the cereal at lower cost, this may be at the expense of quality control. So I do think that one of the strategies that we should think about is ways to make the multinationals continue to distribute their highly fortified cereal products at a very reasonable cost even if that means strategies to subsidize the cost for those who can't pay for it.

Dr. Neufeld: I was hoping that somebody from Nestlé would discuss that because I agree with you. There are many fortified foods but they are not distributed at low cost. They are distributed at exorbitantly high cost for poor families in developing countries. So I don't know the answer to why that hasn't been done already, if we are already assuming that this is a need.

Dr. Guesry: We have been collaborating with the Minister of Health of Chile for more than 20 years in producing first infant formulas and milk fortified with iron and all the trace minerals. So this does exist. I don't know of any infant formula which is not fortified. There are norms and all the industry respects these norms. So discussing the existence or not of fortified infant formula is a bit esoteric to me.

Dr. Zlotkin: If I could just comment. In Canada and the US a percentage of formula is not fortified with iron.

Dr. Neufeld: That is true. In Mexico too there are many formulas not fortified with iron available on the market. You can get formula not fortified with iron if you want to.

Dr. Amancio: What do you think of these rules adopted for fortification?

Dr. Neufeld: I am not that familiar with the food industry development of these products. As we showed, the bioavailability of iron in this milk-based formula is dependent on the form of iron, and all of those estimates were made based on this milk-based formula.

Dr. Armancio: It is also the amount of calcium, as calcium decreases iron bioavailability.

Dr. Neufeld: Right, but I think that would be the major issue. If I understand the industry correctly, the level of iron that is put into the product needs to be set in order to have the amount of available iron. So in this product it has been set considering bioavailability, and what we are trying to deliver to the infants.

Dr. Lozoff: In the last several presentations people have been talking about the need to consider local beliefs and customs about food. I want to mention an analysis we did quite a number of years ago, using the Human Relations Area Files. There was a standard anthropologic sample of 186 pre-industrial societies representing all of the world cultures and communities. In that sample one third of the world societies introduced solid foods before 1 month, one third introduced between 1 and 6 months, and only one third introduced after 6 months. So in the context of our customs and beliefs, there may be room for discussion about the length of exclusive breast-feeding. These anthropologic data are there directly in front of us [1].

Dr. Neufeld: We find similar results in Mexico. Exclusive breast-feeding goes down dramatically at 1 month of age and is almost nonexistent by 3 or 4 months. They are called prevaritas, you give little bits, you give little tastes of food to children, but that happens from very early age. That is one, and second in terms of the importance of this more qualitative research, in terms of the development of a product. What we have found since the implementation of this program is that even though the program suggests that this product is consumed as a pabulum, as a sort of a thicker product, most women give it as a drink. It is the most common means of giving this food to the children. So what we are now working on is trying to decide whether that is all right in terms of the micronutrients that we want the child to consume and, if it isn't, we might have to change the concentration of the product as opposed to trying to convince these people to give the food in a form that they are not accustomed to use. This is one of the areas where local work needs to be done because cans of some kind of commercial product that sells all over the world wouldn't necessarily be consumed at the level that we would want in certain groups of the population.

Dr. Abrams: The low iron formula in the United States is less than 4.5–5 mg/l. So there are only two formulas that I am currently aware of in which the content of iron is 4 mg/l, which is truly low iron. Canada may have some lower ones. In the iron–calcium interaction, a long story we talked about before, there is no evidence whatsoever that complementary foods are a long-term problem.

Mr. Parvanta: Just one question. If I understood you correctly the pabulum is distributed by the government sector to a low income population. What products of similar nutrient quality or nutrient content are there for those populations that are just above that poverty level cutoff but may have just about the same high risk, and are there some products available for them?

Dr. Neufeld: I don't know if you are supposed to say this at Nestlé meetings but it is Gerber. On the Mexican market Gerber infant cereals and Gerber foods are available, but pretty much only the urban upper and middle classes would consider purchasing those because they are expensive; in terms of the general income, very expensive. This pabulum is actually produced by the government. The government has an organization called Liquanza. It is the milk, the government's milk production. So the product itself, the pabulum, and the milk that is the product for women, is produced by the government for this program. They are not for sale on the open market. They are exclusively distributed as part of this program. Now there has been debate about whether they should be, about whether they should put this product on the market, but it hasn't been done.

Dr. Mogrovego: I work at Nestlé in Ecuador and I would like to make some comments. First of all in my country nearly half of the population has iron deficiency. So the government implemented a policy directed to fortifying flour with iron, and also Nestlé mixed formulas and cereals with iron for children, and now we are introducing some complementary foods.

Dr. Neufeld: Distribution as part of a program or for sale?

Dr. Mogrovego: Only for sale, this was introduced 2 weeks ago. We also have communication and education programs for the consumers. We are beginning part of the education program that the government does not do. We are doing something that the government does not do, like working together to build a collaboration with local municipalities in the city. We have to work together: government, industry and policy makers.

Dr. Barclay: I would like to come back to the statement by Dr. Amancio about the relationship between calcium and iron absorption. It really would be doing a great disservice to children to deprive them of iron-fortified milk under the misconception that calcium has a significantly negative impact on iron nutrition. This has already been discussed in detail during this workshop; in the acute short-term studies, sharply increasing calcium intake has a negative effect on iron absorption, but in the long-term the effect is not there. In long-term studies looking at calcium intake versus iron status, there is only a very small negative correlation between calcium intake and iron status. I would even go further by saying that this is even more reason to have some iron in milk products if indeed calcium does have a slightly negative effect on iron absorption.

Dr. Neufeld: Actually in his presentation Dr. Castillo-Durán mentioned that Chile has been fortifying milk with iron and other micronutrients for many years with a positive impact on iron status in the country. Mexico has recently also started fortifying the milk that is redistributed as part of a program to older children; that milk is now fortified with iron and other micronutrients. We are currently evaluating that program too, so in a few years we will be able to say whether we find an impact on iron status.

Mr. Parvanta: Going back to the issue of consumer choice and the statistics. What was mentioned first about the issue of when and the age of the child at which certain micronutrients may be introduced. The reaction to that may be different, very young infants have a different risk versus the older infants. Given the reality of the world, people introduce different products at a much younger age, complementary foods at a very much younger age, what are your thoughts about that? I am not talking about formulas but the other products, about fortification of other products with nutrients, and which nutrients you might want to consider making sure that those foods have some kind of fortification.

Dr. Neufeld: First of all, although this is the reality I think we do need to do interventions to try to encourage exclusive breast-feeding according to the WHO recommendations. Because it is happening that doesn't mean we should not try to encourage people and improve those debates on breast-feeding. That being said, in Mexico a lot of what is given at very early ages isn't necessarily given for food reasons. For example teas are given, sweetened teas are given but they are considered medicinal, they are considered purgatives, and are given for many different reasons. So there are very traditional cultural beliefs and we might not want to influence those, we might not change them. But I don't know if we should be saying if you are going to give sugared tea why don't you give sugared fortified tea? I have to think about that a lot more before I could comment on that. It is the mothers who introduce the foods early by eating the tortillas and letting the child suck on a little bit. So the contribution at those very early ages is really minor, and I don't think we want to give the message that here is a good product, therefore give it early, because it is going to completely contradict our breast-feeding messages.

Dr. Gebre-Medhin: Thank you for an excellent presentation. You are doing remarkable and very important work and we wish you good luck. I would like to reinforce what Dr. Zlotkin and Dr. Guesry have said, and that is I don't think we can get away from the importance, imperative importance of the necessity of breast milk substitutes, commercially produced and enriched. Sweden is a remarkable example of a situation where the prevalence of breast-feeding was very low in the 1940s. It continued that way until the mid 1970s and during this time, in addition to socioeconomic development, it was possible to virtually eradicate all forms of deficiency and malnutrition, and that is no doubt due to the remarkable cooperation between health workers, pediatricians, nutritionists and the industry. I think it is very important to underline these things. As Dr. Guesry has said, it is very important to remember that these products are very carefully regulated, so the question of these products being additionally supplemented or fortified is not relevant at all. Now Sweden has decided to go over to exclusive breast-feeding and extended breast-feeding until the age of 6 months, and they do it extremely well. It is also important for us that wherever breast-feeding is low the solution is not the production of commercially produced formula, rather investing in breast-feeding, more breast-feeding. The problem that we have in Sweden is that we don't know whether we should give complementary feeding at 4 or 6 months as the WHO is recommending. We have no data for that. We need to do more research work on that. So I think the issue is cooperation around this, between different nations, and the production of complementary feedings that are enriched or fortified according to standard procedures, we have to work on that. In addition to that in areas where breast-feeding is not prevalent, our first emphasis, our first advocacy should be to elevate that part and complement it with production of industrially produced products and complementation.

Dr. Lozoff: Why would the government decide to go with ferrous fumarate based on those infant absorption data you had? There was a 4-gram difference in intake, but the absorption was much better.

Dr. Neufeld: It was much more a matter of cost and the characteristics of the supplement because there were physical changes in the product, in the pabulum, the formation of small red and green spots, and if I see green spots I do not give that food to my 1.5-year-old son. So there was that consideration and also ferrous sulfate is considerably more expensive than ferrous fumarate.

Dr. Vasquez-Garibay: The majority of formulas in Mexico, I would say almost all, have between 8 and 12 mg iron/l. The problem as I see it is how to decide to complement the infants between 6 and 12 months of age and to separate them from the 12- to 24-month-olds, because many, the majority, of the infants in rural areas are in fact receiving breast milk as opposite to the urban areas of Mexico. So the problem sometimes with this policy from Mexico is how to decide to give this kind of fortified food to the population which is most vulnerable to malnutrition and iron deficiency.

Dr. Neufeld: This program, Oportunidades, which probably has close to 2 million households in Mexico, including rural areas, was started in rural areas in 1997 but has now expanded to small and large urban areas. The only areas that are not included are the very large metropolitan areas such as Mexico City. As part of the health education and health services, the program itself strongly promotes breast-feeding in the first months of life, very strongly. The messages to improve breast-feeding are very strong. That is something we haven't monitored yet, but we are doing ongoing evaluations and we are always asking about exclusive breast-feeding and what else is given and for how many months. So eventually we will be able to monitor whether there are changes in the population, improvements in the prevalence of breast-feeding. The program was implemented when the WHO recommendations were still 4–6 months, so the program was reexamined a little bit according to that recommendation, providing the supplements as of 4 months of age. They are given universally to all children between 4 and 24 months of age, with the assumption that over 2 years of age the children gradually become more accustomed to the family diet and by 3 years they should be fully accustomed. But certainly there is strong encouragement to improve breast-feeding.

Dr. Bhutta: There are two issues that I would like to highlight. One is that in developing countries there is also the converse of continued exclusive breast-feeding well beyond 6 months of age, which is a real phenomenon at least in the part of the world where I come from. It is not insubstantial, we see it in something closed to 20–30% of the rural populations that we see. So I think the message in terms of appropriate complementary feeding at the right time is critical. I also think there is a need to emphasize that breast-feeding alone is not really the panacea in terms of micronutrient deficiency. In perhaps the most vulnerable part of infancy, micronutrient deficiency doesn't just magically develop at 6 months of age. In parts of the world we have low birth weight, it is a real phenomenon and these infants are significantly micronutrient deficient by 2–3 months of age, if not earlier, and there is the real challenge in terms of what strategies one needs. So I think one needs to throw micronutrient supplementation strategies into the equation for the mothers during pregnancy, and in lactation which may influence breast milk content, and also the real challenge of developing vehicles for giving micronutrients to young infants who are at risk of deficiency such as low birth weight infants well under 6 months of age. I don't think anybody in public health programs has got an answer to that yet.

Dr. Neufeld: I agree completely. I didn't stress it here at all because I was really speaking about complementary feeding but this program does provide the same type of products. It is a beverage to pregnant and lactating women, it is actually a fortified milk drink, with exactly that reason to improve infant stores at birth and to improve maternal micronutrient content of milk.

Dr. Barclay: In reply to your challenge to the food industry to produce lower-cost fortified infant cereals, if we wish to offer products that consumers will want to use, they have to be of a highest nutritional and organoleptic quality. I don't think this can be done cheaply. High-quality products require modern factories, quality ingredients, modern processing techniques, quality control, etc., and so they are going to come at a cost. The other solution that you describe, which has indeed been shown to be effective, is the WIC program whereby high-quality products are made available to those that need them.

Dr. Neufeld: Even if you lower packaging costs?

Dr. Guesry: We have done this. About 25 years ago we started a program called PPP, popularly positioned product. We looked at the raw material, the production cost, the packaging, and the distribution, In Nigeria for example, a soy maize product was launched which was very successful for this reason, and in the Philippines, Indonesia, and so forth. So this could be done, but only to a certain extent because we don't want to compromise on safety and quality.

Reference

1 Lozoff B: Birth and 'bonding' in non-industrial societies. Dev Med Child Neurol 1983;25:595–600.