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Specific Strategies to Address Micronutrient Deficiencies in the Young Child: Supplementation and Home Fortification

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Iron deficiency results from an imbalance between iron uptake, iron utilization and iron loss [1]. It can arise from several risk factors, alone or in combination, such as premature birth or intrauterine growth retardation, early cord clamping, inappropriate use of cow's milk, prolonged exclusive breast-feeding and malabsorption [2, 3]. However, the most important risk factors predisposing infants to iron deficiency and associated anemia include: low intake and low bioavailability of the dietary iron, and the presence of infection and blood loss [4].

During the first 2 years of life, infants require relatively large amounts of iron due to their high growth rate. On average, during the 1st year of life, the birth weight and blood volume of the full-term, normal birth weight infant will triple [5]. By 4–6 months of age, the abundant iron stores present at birth are usually exhausted and thus the full-term, normal birth weight infant can no longer depend on breast milk alone to meet iron requirements [6–8]. It is then recommended to introduce iron-rich complementary foods to meet the infant's iron needs [9]. The selection of weaning foods determines in large part whether an infant will be at risk of developing iron deficiency and associated anemia [6]. Complementary foods that have a low iron content of low bioavailability will increase the risk of iron deficiency.

Strategies to Treat and Prevent Iron Deficiency in Infants

There are three nutrition intervention strategies that can be used to prevent iron deficiency anemia in infants. These include: dietary diversification/modification; targeted iron fortification of infant foods, and iron supplementation [10, 11]. This article will primarily focus on the latter approach that can also be used to treat iron deficiency anemia [12].

Dietary Diversification/Modification

Dietary diversification/modification is an approach that aims at increasing the availability, access and utilization of foods with a high quantity and high bioavailability of micronutrients [10]. It is the most desirable and sustainable method of preventing micronutrient deficiencies [9]. It can improve and maintain not only iron status, but also nutritional status in general [9]. It involves changes in food production practices, food selection patterns and traditional methods for preparing and processing traditional foods with relatively low technological requirements [10, 13].

In most developing countries, complementary foods are usually prepared as thin gruels made from cereals or starchy roots and tubers high in phytic acid, a major inhibitor of non-heme iron absorption [8, 14, 15]. There are several methods that exist to increase iron intake or enhance the bioavailability of iron in these types of complementary foods. First, strategies such as soaking, fermentation and germination can be used to increase the bioavailability of non-heme iron and other minerals in cereal-based complementary foods by reducing the content of phytic acid [8, 16]. All three methods based at the household level induce some enzymatic and/or non-enzymatic hydrolysis of phytic acid [8]. Second, the bioavailability of non-heme iron in the complementary foods can also be improved by promoting the intake of enhancers of non-heme iron absorption such as ascorbic acid [8, 15, 16]. This can be achieved by consuming fruit juices with the meal or adding fruits and vegetables to the complementary foods. Finally, animal foods such as meat, poultry and fish, and small whole fish bones, all known to enhance non-heme iron absorption, can be added to complementary foods to increase iron intake and bioavailability [6, 8, 15]. However, consumption of such foods is rare in most developing countries due to economic, cultural and religious constraints [10, 16]. In addition, if such foods are available in a household, the adult males of the family will most likely benefit from it over the children because of cultural beliefs [17]. In contrast, in most developed countries, there is a high consumption of animal foods, especially meat, which partly explains why infants have better iron status in these countries [18].

Gibson et al. [8] studied the nutrient content of typical complementary foods used throughout the developing world and concluded that, even if the

strategies outlined above are used to improve iron intake and bioavailability, they may not be sufficient to overcome the deficits in iron. The authors proposed fortification of plant-based complementary foods as a solution [8].

Targeted Iron Fortification of Foods

Fortification is defined by the Codex Alimentarius as the addition of one or more essential nutrients to a food, whether or not it is normally contained in the food [19]. Fortification of foods with micronutrients is an effective strategy to increase micronutrient intake of a population [19]. It can be passively targeted to some or all population groups and thus does not necessitate any cooperation from the individuals who benefit from it [16]. An industrial infrastructure is required, and the fortified food needs to be well accepted by the targeted population group and affordable [16].

Iron fortification of complementary foods has been demonstrated to be efficacious and effective in preventing iron deficiency in infants [20, 21]. The reduction in the prevalence of iron deficiency anemia in infants in most industrialized countries during the latter half of the 20th century can be attributed in part to the introduction of iron-fortified complementary foods in the 1960s and 1970s [18, 22]. The success of iron fortification of complementary foods has been limited to developed countries primarily because of the reliance on processed foods by all income groups of the population [12, 23]. In most developing countries, access to industrially processed complementary foods is very limited if not impossible due to the high cost of these foods [9, 14, 15, 18, 24]. This partly explains why infants in the developing world are more affected by iron deficiency and its anemia as compared to infants in developed countries.

Davidsson [15] proposed that new approaches be explored such as fortifying complementary foods at the household level. Such an approach can be achieved through the use of Sprinkles, which will be outlined below.

Iron Supplementation

In clinical practice, once a patient is diagnosed with iron deficiency anemia, treatment with medicinal iron is prescribed accordingly. However, in large-scale public health programs, it is financially and logistically impossible to screen the entire population at risk of developing iron deficiency anemia, especially in developing countries [16]. Therefore, the most cost-effective approach is to give iron supplements to the entire population group at risk [16]. One of the advantages of iron supplementation is that it produces rapid improvements in iron status [16]. The INACG/WHO/UNICEF (1998) recommend providing iron supplementation to all children between 6 and 24 months

of age if the prevalence of anemia in this age group is at least 40% or more. Similarly, where the prevalence of anemia in the same age group is lower than 40% but the diet does not include or is limited in iron-fortified complementary foods, it is recommended to provide iron supplements to all infants between 6 and 12 months of age [9, 20]. This type of intervention is aimed at reversing the anemia in anemic individuals and preventing it from developing in the non-anemic individuals [16]. Infants are a challenging group to give iron supplements as they do not have the ability to swallow pills [16]. Two interventions targeting infants will be outlined below, and the advantages and drawbacks of each will be considered.

Iron Drops or Syrup

For the past 150 years or more, oral ferrous sulfate has been the main source of iron for the treatment of iron deficiency anemia [25]. When a proper dose of iron is ingested for a sufficient duration, this intervention has been shown to be efficacious in treating iron deficiency anemia [11]. Oral ferrous sulfate remains the standard against which the efficacy of other forms of iron treatment is compared [17]. For infants and young children, ferrous sulfate in the form of drops or syrup can be used for the treatment and prevention of iron deficiency anemia [16], and the recommended daily dosage for large-scale public health programs is 12.5 mg of iron for normal birth weight babies between 6 and 24 months of age [20]. However, to date, there has been no successful large-scale effectiveness trial with this form of iron therapy [14, 18, 26]. In 1994, an effectiveness trial in Romania involving about 2,000 infants showed a smaller improvement in hemoglobin concentrations than expected with the administration of ferrous sulfate drops once daily for a minimum of 3 months [27]. Low parental compliance in administrating the drops to their infants was suggested to be one of the reasons for the limited reduction in anemia prevalence. Indeed, compliance to long-term ingestion of oral iron drops is known to be poor [14, 16]. Low compliance has been attributed to several factors and these include: the gastrointestinal side effects when the dose of iron is high; the unpleasant and strong metallic taste of the drops which can also stain a child's teeth if not wiped off immediately, and the complicated dispensing instructions, especially for illiterate individuals as the caregiver is required to measure a decimal volume from a dropper [17, 28, 29]. There are also technical disadvantages associated with the use of a liquid iron preparation such as short shelf life and expensive transportation costs due to the weight of the bottles in which the liquid is stored [14, 16]. Another disadvantage of the iron drops is the potential for overdose if a child ingests the entire contents of a bottle [17, 26].

Due to the limitations associated with the use of liquid iron supplements for the treatment and prevention of iron deficiency anemia in infants and young children, a group of UNICEF consultants who met in 1996 encouraged the development of new methods for the delivery of micronutrients, including iron, to infants and young children [14].

Home Fortification

Responding to the UNICEF directive, Zlotkin [11] and his research team at the Hospital for Sick Children developed a new form of iron supplementation in powder form, Sprinkles, containing microencapsulated ferrous fumarate. More recently, instead of being referred to as an iron supplement, Sprinkles have been called a home fortificant [3, 28] or a complementary food supplement [24]. The iron in Sprinkles is encapsulated with a soya-based hydrogenated lipid to prevent any interaction with the food thereby avoiding any changes in color, taste or texture [30]. It is packaged in single-dose sachets which need to be sprinkled once daily onto infants' weaning food immediately before feeding [30]. Each sachet also contains a filler, maltodextrin, in order to add volume to the micronutrients so that they can be easily handled [24]. In vitro dissolution studies were initially performed to ensure the lipid encapsulation would dissolve in the low pH medium of the stomach, thereby leaving the iron available for absorption [11].

Sprinkles have several advantages: (i) other essential micronutrients such as vitamins A, C and D, folic acid, iodine or zinc can be added to the sachets; (ii) the sachets are lightweight and thus are simple to store, transport and distribute; (iii) the sachets are easy to produce, have a relatively low production cost (USD 0.02–0.03, depending on the volume produced) and are easy to use since one does not have to be literate to learn how to use them, and (iv) the potential for overdose is unlikely [26, 28, 30]. In addition, the use of Sprinkles does not require any change in food practices [24] and can help promote the transition from exclusive breast-feeding to complementary foods at 6 months of age. Moreover, Sprinkles can provide the daily dose of micronutrients to each child regardless of the quantity of complementary food that is fed [24]. A drawback is the waste disposal challenge that it poses due to the single-dose sachets [24]. However, packaging is necessary to protect the product from light, air and moisture for a long shelf life [24] and to avoid any potential overdose. The HJ Heinz Company has been assisting in the packaging and distribution of Sprinkles from various manufacturing facilities around the world, and has been producing Sprinkles on a 'cost-recovery' basis for research and humanitarian distribution purposes.

Between 1999 and 2000, two large clinical trials were conducted in rural Ghana to test the efficacy of Sprinkles in treating anemia in infants. The first study was a large randomized controlled trial involving approximately 560 anemic infants aged 6–18 months. The study demonstrated that Sprinkles were as efficacious as the ferrous sulfate drops in treating anemia after 2 months of therapy (table 1) [30]. In both groups, the mean recovery rate was about 60% and there were minimal side effects. In another trial involving about 300 infants 6–18 months of age, between 63 and 75% of the subjects were successfully treated after receiving Sprinkles for a 2-month period [31]. Treatment failure was attributed to several potential factors causing anemia

Table 1. Mean hemoglobin and percent anemic by treatment group at baseline and after 2 months of treatment (mean ± SD)

	Sprinkles (n = 246)	Drops (n = 247)
Baseline		
Hemoglobin, g/l	87 ± 8[a]	87 ± 9
Anemic, %	100[b]	100
Final		
Hemoglobin, g/l	102 ± 16[c]	100 ± 17
Anemic, %	42.3	43.7

[a]Values at baseline ($p = 0.63$) and final visit ($p = 0.23$) were similar in both groups.

[b]Values are percent anemic where anemia is defined as hemoglobin values of <100 g/l.

[c]Mean hemoglobin values significantly increased from baseline to the final visit in both groups ($p < 0.001$).

other than iron deficiency such as: malaria, parasitic infections, *Helicobacter pylori*, gastroenteritis, respiratory infections, or subclinical vitamin A deficiency [30]. To test the safety of Sprinkles, a study in China evaluated hemoglobin and serum ferritin levels in mainly non-anemic preschool children. Of the 285 children who received Sprinkles for 3 months (either 5-days/week or once/week) none had elevated ferritin levels (>400 μg/l) at the end of the trial, thus demonstrating the safety of the intervention [32]. Small trials in northern Canada and Bolivia also demonstrated that Sprinkles were efficacious in treating and preventing anemia when added to complementary foods at the household level (unpublished data).

The acceptability of Sprinkles by both the caregivers and their infants was evaluated in both Ghana and China [28]. It was shown that caregivers found the sachets easy to use and more acceptable than the iron drops. Children did not object to ingesting the foods to which Sprinkles were added because it did not change the taste of the food. In addition, Sprinkles were not associated with any major side effects other than changes in the color of the child's stool which is known to occur with any iron therapy.

The effectiveness of Sprinkles in non-study settings remains to be fully tested [26]. However, a large distribution program in Mongolia sponsored by World Vision Mongolia is currently under way. In this program, the sachets contain iron and vitamin D (with ascorbic acid, folate and zinc) since iron deficiency anemia and vitamin D deficiency rickets are the two most prevalent nutritional problems in young children in Mongolia. Although post-intervention biological outcome indicators (hemoglobin and clinical signs of rickets) have yet to be collected, Sprinkles have been successfully distributed

Table 2. Percent iron absorption from Sprinkles (%)[a,b]

Iron dose[c]	Hb group[d]	
	anemic (Hb <100 g/l)	non-anemic (Hb ≥100 g/l)
30 mg	8.7 (3.5–17.8; n = 19)	4.6 (1.1–12.3; n = 21)
45 mg	7.0 (2.9–13.0; n = 19)	4.5 (1.7–10.6; n = 19)

[a]Values are geometric means, with ranges and number of subjects in parentheses.

[b]Calculated with the use of oral (^{57}Fe) and intravenous (^{58}Fe) stable iron isotopes.

[c]There was no significant main effect for iron dose ($p = 0.35$).

[d]Significant main effect for Hb group, $p < 0.0001$.

to about 11,200 infants and young children over a 12-month period with 74% adherence to the intervention [33].

To determine iron absorption from Sprinkles in infants 6–18 months of age, we recently conducted bioavailability studies in Ghana (unpublished data). Results from these studies will help to determine the most appropriate dose of iron to add to a Sprinkles sachet that would be safe and effective in treating and preventing iron deficiency and associated anemia in infants. In our first bioavailability study, a dual stable isotope method was used to determine the amount of iron absorbed from two different doses of iron from Sprinkles provided to both anemic and non-anemic infants. Results indicated that the iron from Sprinkles, when added to a maize-based complementary food, was relatively well absorbed by both anemic and non-anemic infants (table 2). Data also demonstrated that anemic infants absorbed significantly more iron from Sprinkles as compared to non-anemic infants. From a 30-mg dose of iron, with an average iron absorption of about 9%, net absorbed iron was 2.6 mg/day in the anemic infants. In contrast, non-anemic infants had a mean percent absorption of about 5% and thus net absorbed iron was 1.4 mg/day. Therefore, it was concluded that administration of Sprinkles in a maize-based complementary food given to infants would result in significant iron absorption. To further determine the most appropriate dose of iron to add to a Sprinkles sachet, we recently conducted a dose-response randomized controlled trial using three iron doses from Sprinkles (12.5, 20 and 30 mg/day) compared to one dose of ferrous sulfate drops (15 mg/day) provided to infants 6–18 months of age (unpublished data). All infants were anemic at baseline. At the end of the 2-month intervention, the prevalence of anemia in all groups dropped to 45%, with no difference among the groups. Therefore, it was concluded that the three doses of iron from Sprinkles tested were as efficacious as ferrous sulfate drops in treating anemia in infants.

We are currently conducting a randomized controlled trial to determine the optimal intervention time for the treatment of iron deficiency anemia and maintenance of an anemia-free state in 'at risk' infants. One of our earlier studies demonstrated that, when infants are provided with a large dose of iron (80 mg/day) from Sprinkles, the positive effect on anemia status and iron stores may last for as long as 18 months after the intervention [34]. Our current study is designed to determine the long-term impact of Sprinkles on anemia status at a smaller iron dose (12.5 mg/day) when provided to infants for 2, 3 or 4 months.

Based on our clinical trials conducted to date in Ghana, China, northern Canada and Bolivia, and our bioavailability and dose-response studies conducted in Ghana, we have determined that doses of iron from Sprinkles ranging from 12.5 to 20 mg/day are efficacious for the treatment of iron deficiency anemia in infants. We can also conclude that Sprinkles are well accepted by caregivers, with few side effects. Based on our current distribution program in Mongolia, we have demonstrated so far that wide-scale distribution via non-governmental organizations is feasible.

The etiology of iron deficiency anemia is complex and multifactorial. It can result from a combination of limited iron reserves at birth, blood loss due to infections, and an inadequate source of iron-rich foods. Moreover, it occurs mostly in the poorest countries. The challenge of overcoming this complex social-biological amalgam is daunting. Although international activities, such as the GAIN initiative, are dealing with a part of the problem (i.e. fortification of staple foods), this strategy may not significantly benefit young children (who do not eat enough fortified staple foods). It is somewhat ironic that iron deficiency anemia is a serious public health problem with a potentially simple solution. As researchers, we must think (and act) 'out of the box' to redefine a framework for safe, sustainable, integrated and effective approaches to meet iron needs of 'at risk' infants and children including new systems to deliver iron and other essential problematic nutrients. We must continue to work towards convincing policy-makers and educating the public about the importance of the problem and must improve our abilities to do so. It is essential to form partnerships to address the problem and to use sustainable distribution systems once the right form and type of iron are determined. It is our belief that Sprinkles may be one of the ways of addressing this urgent and preventable problem.

References

1 Yip R: The challenge of improving iron nutrition: Limitations and potentials of major intervention approaches. Eur J Clin Nutr 1997;514:16S–24S.
2 Fleming AF: Iron deficiency in the tropics. Clin Haematol 1982;11:365–388.
3 Zlotkin S: Clinical nutrition: 8. The role of nutrition in the prevention of iron deficiency anemia in infants, children and adolescents. CMAJ 2003;168:59–63.

4 Florentino RF, Guirriec RM: Prevalence of nutritional anemia in infancy and childhood with emphasis on developing countries; in Stekel A (ed): Iron Nutrition in Infancy and Childhood. Nestlé Nutrition Workshop Series. Vevey, Nestec/New York, Raven Press, 1984, vol 4, pp 61–74.
5 Zlotkin S: Iron deficiency in Canadian children? Implications and prevention. Can J Pediatr 1992;4:18–23.
6 Dallman PR: Iron deficiency in the weanling: A nutritional problem on the way to resolution. Acta Paediatr Scand 1986;323:59S–67S.
7 Oski FA: Iron deficiency in infancy and childhood. N Engl J Med 1993;329:190–193.
8 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: 764–770.
9 World Health Organization: Iron Deficiency Anaemia Assessment, Prevention and Control: A Guide to Programme Managers. Geneva, WHO, 2001.
10 Gibson RS, Hotz C: Dietary diversification/modification strategies to enhance micronutrient content and bioavailability of diets in developing countries. Br J Nutr 2001;85: 159S–166S.
11 Zlotkin S: Current issues for the prevention and treatment of iron deficiency anemia. Indian Pediatr 2002;39:125–129.
12 Subbulakshmi G, Naik M: Food fortification in developing countries-current status and strategies. J Food Sci Technol 1999;365:371–395.
13 Hotz C, Gibson RS: Assessment of home-based processing methods to reduce the phytate content and phytate/zinc molar ratio of white maize (Zea mays). J Agric Food Chem 2001;49: 692–698.
14 Nestel P, Alnwick D: Iron/Multi-Micronutrient Supplements for Young Children. Summary and Conclusions of Consultation Held at UNICEF Copenhagen, August 19–20, 1996. Washington, International Life Sciences Institute, 1997.
15 Davidsson L: Approaches to improve iron bioavailability from complementary foods. J Nutr 2003;133:1560S–1562S.
16 DeMaeyer EM, Dallman P, Gurney JM, et al: Preventing and Controlling Iron Deficiency Anaemia through Primary Health Care: A Guide for Health Administrators and Programme Managers. Geneva, WHO, 1989.
17 Dallman PR, Siimes MA, Stekel A: Iron deficiency in infancy and childhood. Am J Clin Nutr 1980;33:86–118.
18 Yip R, Ramakrishnan U: Experiences and challenges in developing countries. J Nutr 2002;132: 827S–830S.
19 Darnton-Hill I, Nalubola R: Fortification strategies to meet micronutrient needs: Successes and failures. Proc Nutr Soc 2002;61:231–241.
20 Stoltzfus RJ, Dreyfuss ML: Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia. Washington, International Life Sciences Institute, 1998.
21 Yeung DL, Kwan D: Commentary: Experiences and challenges in industrialized countries. J Nutr 2002;132:825S–826S.
22 Ramakrishnan U, Yip R: Experiences and challenges in industrialized countries: Control of iron deficiency in industrialized countries. J Nutr 2002;132:820S–824S.
23 Mehansho H: Eradication of iron deficiency anemia through food fortification: The role of the private sector. J Nutr 2002;132:831S–833S.
24 Nestel P, Briend A, de Benoist B, et al: Complementary food supplements to achieve micronutrient adequacy for infants and young children. J Pediatr Gastroenterol Nutr 2003;36: 316–328.
25 Andrews NC: Disorders of iron metabolism. N Engl J Med 1999;341:1986–1995.
26 Mora JO: Iron supplementation: Overcoming technical and practical barriers. J Nutr 2002; 132:853S–855S.
27 Ciomartan T, Nanu R, Iorgulescu D, et al: Iron supplement trial in Romania; in Nestel P (ed): Proceedings, Iron Interventions for Child Survival. London, USAID and ICH, 1995, pp 89–98.
28 Schauer C, Zlotkin S: Home fortification with micronutrient sprinkles – A new approach for the prevention and treatment of nutritional anemias. Paediatr Child Health 2003; 82:87–90.

29 Viteri FE: Iron supplementation for the control of iron deficiency in populations at risk. Nutr Rev 1997;55:195–209.
30 Zlotkin S, Arthur P, Antwi KY, Yeung G: Treatment of anemia with microencapsulated ferrous fumarate plus ascorbic acid supplied as sprinkles to complementary (weaning) foods. Am J Clin Nutr 2001;74:791–795.
31 Zlotkin S, Arthur P, Schauer C, et al: Home-fortification with iron and zinc sprinkles or iron sprinkles alone successfully treats anemia in infants and young children. J Nutr 2003;133: 1075–1080.
32 Chan M, Zlotkin S, Yin SA, et al: Comparison of dosing frequency and safety of sprinkles on iron status in preschool children in northern China (abstract). International Nutritional Anemia Consultative Group Symposium, Marrakech, 2003. Washington, International Life Sciences Institute Research Foundation, 2003, p 42.
33 Schauer C, Zlotkin S, Nyamsuren M, et al: Process evaluation of the distribution of micronutrient sprinkles in over 10,000 Mongolian infants using a non-governmental organization (NGO) program model (abstract). International Nutritional Anemia Consultative Group Symposium, Marrakech, 2003. Washington, International Life Sciences Institute Research Foundation, 2003, p 39.
34 Zlotkin S, Antwi KY, Schauer C, Yeung G: Use of microencapsulated iron(II) fumarate sprinkles to prevent recurrence of anaemia in infants and young children at high risk. Bull World Health Organ 2003;81:108–115.

Discussion

Dr. Bloem: In Indonesia one of the problems we are facing with the Sprinkles is actually the approval by the government. Is it a drug; is it part of the fortificant? What kind of approvals are actually needed is very complicated and depends on how the product is named. It is an issue for the industries because they want to have the easiest way to get government approval. Could you comment on that?

Dr. Zlotkin: I think no matter what country one is working in, one will have to get regulatory approval from a government organization, and the regulations as to whether or not Sprinkles will be considered a pharmaceutical agent or a food, I think it is quite dependent on the individual country and may in fact differ from country to country. For example in Canada we have registered Sprinkles. In fact we had to register Sprinkles in order to do research with them and they had to be registered as a drug, despite the fact that there are no pharmaceutical agents in them, only minerals and vitamins and a bland excipient. In Canada all vitamin and mineral products have to be registered as drugs. So again to answer your question, no matter where you are working, whether in Indonesia or Canada, one has to go through the process of registration. It can readily be done but really depends on the individual requirements of the particular country.

Dr. Bloem: Do you think that international agencies can help to support this process? If we have global registration or something like that, is it easier to get these approved at the country level?

Dr. Zlotkin: I am not sure I can answer that question because I have limited experience with the regulatory approval process. My feelings are that countries are pretty strict about what one has to do with regard to registering a product in each individual country. Possibly the people from Nestlé who have more experience with the registration of products might be able to comment, but I feel that it has to be done on a country-by-country basis and there is probably no way of getting around it.

Dr. Bhutta: Once Sprinkles are introduced in developing countries one of the social science challenges would be getting mothers and families to accept this as not being a

drug. Have you given thought to the possibility of formulating these in a way that they could become part of the food preparation process, rather than something that just gets added at the end? If under circumstances where cereals or other complementary foods are made in household settings, this could be part of the cooking process or part of the addition during the course of preparation rather than something that is sprinkled on top at the end. Are there any technical limitations to that?

Dr. Zlotkin: In terms of the micro-encapsulation process, if one wants to ensure that the soluble form of iron does not come in contact with the food there are multiple methods of encapsulation, some of which will not be impacted by cooking. The problem is that the dissolution properties of the various micro-encapsulated minerals are quite different, depending on what you use to encapsulate your mineral. For example you can use polymers that will be quite inert. The problem will be for iron which is absorbed quite proximal in the small intestine. If in fact the encapsulate did not dissolve in the low pH of the stomach and did not dissolve in the duodenum, there would probably be close to zero iron absorption. So I do see some significant technical issues around developing a product that would be organoleptically acceptable that could be used in a cooking process. However bioavailability would be a problem.

Mr. Parvanta: I understand in Thailand that the premix that comes with instant noodles is being fortified, and it has been done with iron as well. Does this relate to the comment about using it in the preparation of foods? The other question I have is related to the point of not making a medical product. As was discussed in Ottawa recently, the regulatory agencies determine whether something is a pharmaceutical product versus a food product and that is important. But even if it turns out to have a pharmaceutical classification, I think the channel of delivery is going to be very important to eliminate, reduce or minimize this medical approach. But as far as prevention trials are concerned, I wonder if you have considered if the lack of response was related to the mothers sharing the dose among the other children in spite of the supplement dosage being only for one child, the index child, as we have found in Romania? Have you considered this because it may be an issue of parents distributing the product to others?

Dr. Zlotkin: It is interesting you mention the Romanian study because that is probably the only study that has identified a slightly efficacious response to a large scale distribution of iron drops, although it wasn't a very powerful response. Despite the fact that we target children under the age of 2 years because that is the most vulnerable population, there is no question that an older child or a pregnant woman would not be harmed in any way from ingesting Sprinkles. If the cost were right and if the message was that this had to be a family intervention, there is absolutely no reason why it could not be provided to other members of the family. Again I think it makes most sense that we primarily pay attention to the child under 2 years because that is of course the highest risk age group, but there is no reason at all why it could not be given to the entire family.

Mr. Parvanta: The point is that you have to take that into account if you do those trials. You may have to give them a larger supply than you would ordinarily think.

Dr. Pettifor: In many developing countries the problem of associated malnutrition is a key feature of young children and acid production tends to be relatively low in those children, as I understand it. Are there any data to suggest that your micro-encapsulated iron is equally well absorbed in that situation?

Dr. Zlotkin: I totally agree that children with malnutrition may not have normal gastric pH. The only point I can make is that the population that we chose for our labeled bioavailability study was a typical population of children living in central Ghana. They were chosen according to age and their initial hematologic status. We

really did feel that this population represented a typical group of infants. Their Z scores were around −1.5 and −2, which was typical in that population. If we had chosen a population whose Z scores were −0.5 or 0, it might have been a healthier population and we might have achieved a different rate of absorption. The important point is that our initial concern was that because we were using a microencapsulated form of iron we really didn't know what the bioavailability would be, and because we were using fumarate and because of the controversy around the absorption of fumarate versus sulfate, we didn't have any notion about what absorption would be other than we thought it would be very low. So we were quite reassured by finding that in the population with hemoglobins of <100 g/l the mean absorption was around 9%. Based on this absorption value we could then logically decide on the dose of iron to use for efficacy studies. Based on the percentage absorption we randomized children into 3 different doses of iron as Sprinkles (12.5, 20 and 30 mg doses), compared to an equivalent dose of ferrous sulfate drops. Our intervention was for 2 months and the subjects were all anemic infants. The response to anemia was identical in all 4 groups including the ferrous sulfate group. The 12.5-mg dose group actually did just as well as the 30-mg dose. These data suggest that infants have the ability to upregulate iron absorption when they need it.

Dr. Pettifor: I was thinking particularly from the multi-mineral supplement point of view that it may be considered useful in the management of malnourished children as a hospital treatment instead of providing powders or other forms of micronutrient supplement. In such a situation iron should not be provided in the initial stages.

Dr. Zlotkin: To be very clear, this product has no calories, no protein and no macronutrients. It could be used quite reasonably with a corn soya blend or corn wheat blend, if these types of cereal were used in the rehabilitation of malnourished children.

Dr. Guesry: I agree with everything you say but I would like to make two comments, one related to the fact that it would be either a drug or a food supplement. I think it is linked to the claim that you are going to make, and this is very universal. If you say this product is to treat the disease, which is iron deficiency anemia, then it is a drug. So that is something you have to think about. The other aspect is related to business and cost because I think the most expensive part of the product would be the packaging, the quality control, the shipping and the distribution. In the price you mentioned, I don't think everything was accounted for, so you have to increase it a little bit. One way to reduce all these variable costs would be to try a weekly version of 30 mg/week which would be a very good way to decrease the packaging, quality control, shipping and distribution cost. So I would encourage you to go that way rather than the everyday dose because my rough calculation is that for a family it would be about USD 10, perhaps a little bit more than USD 10/year/baby.

Dr. Zlotkin: Just let me comment. The price included quality control, it did not include shipping, nor did it include distribution which of course is a significant cost, for sure. We envision that Sprinkles will be used for prevention of micronutrient deficiencies. We believe that a 2-month intervention during the first 24 months of life will be adequate. Thus the estimated cost is closer to USD 1 per year, not USD 10 per year. In terms of the once weekly dose versus daily, Beaton [1] did a meta-analysis both for infants and children, women, pregnant women. It seems that a once weekly dose may be efficacious but only in situations where the dose is being given out in a school, in a daycare, or in a crèche where one can be absolutely certain that a responsible person is providing the iron once a week, because with the once-a-week

dose, if you have missed 1 dose you have actually missed 2 weeks, and if you have missed 2 doses you have missed 3 weeks. So Beaton's conclusion in the meta-analysis was that there was evidence of efficacy but only when the iron supplement was distributed or given out in a controlled manner.

Dr. Mannar: Given that the whole technology is very much dependent upon the specification of the individual nutrients, especially iron, and also the type of encapsulation and the type of packaging, I think it becomes very critical that all these are very precisely specified. I am just concerned that once you say that this works and countries start tendering for this process and they say we want a powder with so much iron and so much vitamin A, you could easily get someone just mixing these in a crude manner and putting them into small sachets, and you might have quite different bioavailability and other characteristics.

Dr. Zlotkin: I think that is an interesting question. There is nothing to prevent an inferior Sprinkles product from being produced and distributed. I am not sure that this is different from many other products in some developing countries where there is not much quality control. It does bring up another issue I should have mentioned: the technology for putting the micronutrients into the sachet is very simple. Most developing countries have the technology for putting either spices or foods into small sachets. It takes a machine that has the capacity to make and fill a sachet, and again this is not a high tech type of production facility. So part of our long-term plan is to transfer the technology to countries in the developing world so that there would be the facility, for example in Bangladesh, to produce it locally.

Dr. Tolboom: I am worried: Ghana, tropics, malaria of course. Did you look at the malaria outcome in your interventions?

Dr. Zlotkin: Yes, we examined malaria status and parasite load. We also looked at the number of fever episodes. There were no differences between groups. However, I have to emphasize that in these anemic populations we did not have a control group, for ethical reasons.

Dr. Tolboom: Because of the folic acid, I get a little bit of a 'black box feeling', about the effects of supplementation on severity of malarial illness.

Dr. Zlotkin: Since we did not include a control or placebo group, it really is not possible for us to say that the outcome in terms of malaria status or the number of fevers, would have been different in a similar population receiving no intervention. However, we feel quite strongly that since we are dealing with an anemic population we have an obligation not to use a placebo group.

Dr. Bloem: When we started the program about 2.5 years ago, we didn't want to import Sprinkles so we started to think about how we could produce it in Indonesia. We got the funding to do the trial and to look at sustainable approaches to distribute this product. We are almost ready to start, but it took us about 2.5 years to actually bring it to Indonesia which is a quite sophisticated country with a lot of big industries when it comes to this kind of thing. So I would be a little bit cautious when it comes to how you implemented it in a country like Bangladesh when it comes to quality control, when it comes to all these other issues, because it took us a long time.

Dr. Bhutta: Have you considered the possibility of alternative methods of dispensing? Why does it have to be a sachet, is it technically possible to put a multi-dose dispenser of the kind that is used for sugar dispensing? That would save substantial costs and make it somehow or other more acceptable to families as a non-medical food-based intervention.

Dr. Zlotkin: In Pakistan for example, sachets are used for foods and condiments more than medicine. So I don't think that the use of a sachet is necessarily associated with the delivery of pharmaceuticals. Our concern really with iron is to give enough

but not too much, so that any dispensing methodology that has the potential to be easily misused by an older child in a family or any one had us extremely worried. In Canada the most common death from poisoning is from iron overdose and toxicity, and it is because young children can get into the iron that their mothers are using and typically the prenatal supplements contain 60 mg iron, so iron toxicity is certainly a real issue that is associated with death. So our great concern was to ensure that (1) the intervention is easy to use, and (2) there is absolutely safety. We have considered other methods of delivery. For example it has been suggested that it might be more acceptable if Sprinkles were sweet. Children would like it more. But again the response to that is that if it is sweet it is more likely to be ingested inappropriately as a treat, and we would again have the problem of potential toxicity. So we feel that the delivery via the sachet is a way to ensure safety. One would have to ingest something like 30 or 40 sachets even to approach toxicity, and because they have a very neutral taste, they are neither sweet nor particularly pleasant tasting but also not unpleasant, we really think that there would not be the incentive for an older child to use them as a treat.

Dr. Gebre-Medhin: Some concerns have been raised and the first is the issue of the medication and the concepts and thoughts of mothers and families that this is no longer a nutrient but a medicine. The second is the risk of it being used in other age groups and, as Dr. Lönnerdal said, landing in the hands of those who don't need it. The third, the one that concerns me most, is the use of this for purposes other than intended. The minute there is a sachet out and some benefits are attributed to it, it may be used for purposes of enhancing one or the other or a third thing in the community. Finally there is the risk of allegations that such sachets cause other problems, in other words families and individuals and groups may very well associate other complications to the addition of this sachet. There is pedagogical problem here that may be very important.

Dr. Zlotkin: Concerning the last question, a component of the social marketing strategy would be to warn parents that, for example, the color of the stool may change when the fortificant is added to food. It is our experience that if you warn parents in advance of a potential change in the infant, and again I am not saying an adverse change because I think coloring the stool dark is not really an adverse change, but if we warn parents that this is likely to occur then the chances of the parents associating it with a negative connotation are less. It is quite possible, and as you well know if an infant in the developing world has 7 or 9 episodes of gastroenteritis per year there is no doubt that a baby is going to have diarrhea at some point while taking Sprinkles. Again I think part of the social marketing strategy would have to include a comment that Sprinkles are not going to prevent every disease in your child and your child is still going to get diarrhea, a cold or an upper respiratory tract infection. Again I think the social marketing strategy has to address those issues. In terms of the medication, families are quite used to adding things to the foods as condiments. We add salt to our food, we add sugar to our food, and in fact sugar is a good example because at least in the Western world we often find sugar in a sachet and most people would not say that by adding sugar to a food you are medicating the process by adding it to a food. So our hope is that it will not be medicalized but that it is being put forward as a food based strategy, not as a supplement but as a home fortificant. Because there is experience with using condiments, it is hoped that it will be recognized as a condiment or a fortificant but not as a medical supplement. It is quite different from the delivery of pills or capsules or even syrups or liquids for young children.

Dr. Gibson: One question I would like to ask you is what was the food vehicle that was used to test iron bioavailability? Was it refined maize porridge?

Dr. Zlotkin: We used the exact recipe that we got from the mothers in the village. It consisted of 80% maize, 10% groundnuts and 10% beans.

Dr. Gibson: I would like to make a comment in relation to a study that I am involved in with a group in Thailand. We have just completed an efficacy trail on a seasoning powder which is sold in sachets with noodles, and certainly in that setting in Thailand it hasn't been perceived as a medicine. An efficacy trial was done in schoolchildren and the results are being analyzed at the moment. The seasoning powder is fortified with iron, vitamin A, iodine and zinc and it was very well accepted.

Dr. Zlotkin: The reason I was slightly hesitant in talking about acceptability is that it is very difficult to assess acceptability in an efficacy study. We had field workers in the village who were reminding the mothers what to use. It wouldn't be fair to say that this was a typical free-living population. The families and children were randomized into a drops group and a Sprinkles group. The same questions were asked of both groups and inevitably the number of parents who complained about the drops was relatively high and inevitably the number of parents who accepted the Sprinkles without any complaints at all was also relatively high. I don't have the final results of our study in Mongolia, so I can't tell you what they are. I have been there twice and I visited the people who are using them, and although they probably said it because it was me asking the question, anecdotally they were extremely well received. The child is very passive in this case and really doesn't know that he is ingesting the micronutrients because the taste or the look of the food to which it has been added doesn't change, so I would expect that with a reasonably good social marketing program we could get families to accept the intervention.

Dr. Gibson: Certainly the seasoning powder in Thailand has been on the market for some time although its efficacy and effectiveness have not been formally tested. It has been used by families over a number of years already.

Mr. Parvanta: Here is a crazy idea for you following the discussion about the cost of transportation and distribution. Recently I heard some news, I don't know if it is true or not, that in Brazil the distributors of Mary Kay cosmetics reach the farthest villages in the deepest parts of the Amazon jungle, and then in the heart of Atlanta in the Coca Cola Museum one of their pieces of promotion is that they also reach the farthest villages of the Amazon. I am wondering if there is some way that we could combine distribution. I think you said that one of the strengths of the Sprinkles is that it is so light, you can carry large amounts and maybe Coca Cola wouldn't mind putting a few on their trucks with no cost, strange idea, but to get it into these deepest villages.

Dr. Tolboom: The lack of controls in your study still keeps bothering me. You said it was unethical to do that, but you could have control villages without any intervention. I mean is the problem so widespread that you could not get control villages, because still I would like to find out what you are doing exactly in terms of malaria morbidity and mortality because I still think it is a relevant point.

Dr. Zlotkin: I don't disagree with your point. I think it is an important question because we are adding iron. Of course bacteria proliferate in the presence of iron, and my understanding from the analysis of the various studies that have looked at the impact of iron supplementation on malaria is that the current recommendation is that if you are treating malaria in an area where iron deficiency is also present that it is quite acceptable to both treat the malaria as well as provide an iron supplement. Again Dr. Lönnerdal made the point that there is a difference between the response to a supplement that is often taken on an empty stomach versus what may be a food-based product where the response may not be identical. But I think the question is very important, it just can't be answered with the design we used.

Dr. Tolboom: But the control village, would you agree with control villages? To have a control village in which you don't intervene? That is what was done in Tanzania, villages where no intervention was used at all.

Dr. Zlotkin: It is not a perfect design but it certainly could be done.

Reference

1 Beaton GH: Iron needs during pregnancy: Do we need to rethink our targets? Am J Clin Nutr 2000;72(suppl):265S–271S.