Micronutrient Deficiencies and Effect of Supplements on Correcting Them

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Abstract

The etiology of micronutrient deficiencies in infancy is well described. The deficiencies are caused by one of the following four scenarios: (a) low initial stores of micronutrients from micronutrient deficiency during gestation, premature birth or low birthweight; (b) rapid postnatal growth; (c) ingestion of foods with low concentration of micronutrients, and (d) gastrointestinal pathology resulting in the malabsorption of nutrients, including micronutrients. Understanding the cause of the deficiencies is essential in planning interventions to either prevent or treat them. This chapter will focus on the dietary causes of micronutrient deficiencies and recent strategies to correct them.

Dietary Origins of Micronutrient Deficiencies

Human breast milk will provide all of the nutrients needed for the otherwise healthy infant during the first 6 months of life [1]. With the exception of vitamin D, this is true. However, it is paradoxical that if dietary variety is the key to the prevention of micronutrient deficiencies, a single food, breast milk, would be recommended as the only source of nutrition in the first 6 months life. However, as is well described in the nutrition literature, if variety is limited, then the quality of the foods eaten becomes even more important in preventing deficiencies. Thus, human milk is of extremely high quality, and this single food meets the needs of rapidly growing infants during the first 6 months of life. However, after 6 months of age, breast milk is not sufficient on its own. There is a need for additional sources of nutrients, especially iron and energy [2]. To meet the energy needs of the infant between 6 and 24 months, there is a need for a source of calories from complementary foods. Similarly,
as illustrated in table 1, there is a need for micronutrients in addition to those found in breast milk and unfortified complementary foods [3]. From this table, it is apparent that the combination of breast milk and unfortified complementary foods is significantly deficient in vitamin A, niacin, vitamin B6, vitamin D, iron and zinc. The information provided in the table provides a compelling illustration of the rationale for fortification.

Public Health Approaches to the Prevention of Micronutrient Deficiencies

Types of Fortification
There are three types of fortification: general staple food (commodity) fortification, targeted fortification and ‘home’ or point-of-use fortification. Staple food fortification is the process of adding micronutrients to commodity type foods such as flour, vegetable oil or salt. The major advantage of staple food fortification is that it is inexpensive, and the commodity used is a common food eaten by the majority of the population. Examples of staple food fortification include the fortification of wheat flour with iron and folic acid, cow’s milk with vitamins A and D and salt with iodine. The vehicle for the fortificant is generally a staple food eaten by the majority of the population, including rich and poor, urban and rural. With staple food fortification, the level of fortification must be safe for all consumers of the product, including those who eat the largest amount. Since adult males generally eat the largest amount of food (including staple foods), the level of fortification has to be safe for adult males. By contrast, adult males generally have the lowest requirement for micronutrients. As a result, the concentration of the fortificant in the staple food is often very low. Since children and women (the population at highest risk of micronutrient deficiencies) eat less total food than adult males, staple food fortification is of limit value for women and especially children. Many countries have national legislation for the fortification of the most typical staple foods used in their jurisdiction. In Canada, for example, there is legislation for the mandatory fortification of milk with vitamins A and D, and wheat flour with iron and folic acid [4].

Food fortification plays an important role in ensuring the health of individuals after early childhood. Adding vitamins and minerals to food helps:

- Protect against nutritional deficiencies, for example requiring all milk to be fortified with vitamin D virtually eliminated childhood rickets since the 1970s in Canada;
- Maintain and improve the nutritional quality of the national food supply, for example enriching flour with B vitamins and iron replaces those same nutrients lost in processing;
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**Table 1.** Mean daily nutrient intakes from complementary foods and breast milk compared with recommended intake for 9- to 12-month-old infants living in Bangladesh [3]

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Intake from complementary food</th>
<th>Intake from breast milk</th>
<th>Total intake</th>
<th>Recommended intake</th>
<th>Percent of recommended intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, g</td>
<td>3.6±2.7</td>
<td>7.16±2.0</td>
<td>10.6±2.6</td>
<td>9.6</td>
<td>110</td>
</tr>
<tr>
<td>Vitamin A, µg RE</td>
<td>20±49</td>
<td>170±48</td>
<td>191±60</td>
<td>400</td>
<td>48</td>
</tr>
<tr>
<td>Folate, µg</td>
<td>16±17</td>
<td>64±18</td>
<td>80±22</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Niacin, mg</td>
<td>1.22±0.91</td>
<td>1.13±0.32</td>
<td>2.36±0.88</td>
<td>4</td>
<td>59</td>
</tr>
<tr>
<td>Pantothenic acid, mg</td>
<td>0.36±0.25</td>
<td>1.36±0.38</td>
<td>1.71±0.35</td>
<td>1.8</td>
<td>95</td>
</tr>
<tr>
<td>Riboflavin, mg</td>
<td>0.08±0.07</td>
<td>0.26±0.08</td>
<td>0.34±0.08</td>
<td>0.4</td>
<td>85</td>
</tr>
<tr>
<td>Thiamin, mg</td>
<td>0.06±0.05</td>
<td>0.16±0.04</td>
<td>0.22±0.06</td>
<td>0.3</td>
<td>73</td>
</tr>
<tr>
<td>Vitamin B₆, mg</td>
<td>0.08±0.10</td>
<td>0.07±0.02</td>
<td>0.15±0.10</td>
<td>0.3</td>
<td>50</td>
</tr>
<tr>
<td>Vitamin B₁₂, µg</td>
<td>0.09±0.24</td>
<td>0.73±0.21</td>
<td>0.82±0.27</td>
<td>0.5</td>
<td>164</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>4±9</td>
<td>30±9</td>
<td>34±10</td>
<td>30</td>
<td>113</td>
</tr>
<tr>
<td>Vitamin D, µg</td>
<td>0.22±0.44</td>
<td>0.42±0.12</td>
<td>0.63±0.40</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>43±46</td>
<td>211±60</td>
<td>254±54</td>
<td>270</td>
<td>94</td>
</tr>
<tr>
<td>Iron, mg</td>
<td>0.65±0.49</td>
<td>0.23±0.06</td>
<td>0.87±0.48</td>
<td>9.3</td>
<td>9</td>
</tr>
<tr>
<td>Magnesium, mg</td>
<td>18±13</td>
<td>26±7</td>
<td>44±12</td>
<td>54</td>
<td>81</td>
</tr>
<tr>
<td>Phosphorus, mg</td>
<td>63±49</td>
<td>106±30</td>
<td>169±42</td>
<td>400</td>
<td>61</td>
</tr>
<tr>
<td>Potassium, mg</td>
<td>120±109</td>
<td>396±112</td>
<td>516±115</td>
<td>700</td>
<td>74</td>
</tr>
<tr>
<td>Selenium, µg</td>
<td>11±8</td>
<td>15±5</td>
<td>25±10</td>
<td>10</td>
<td>250</td>
</tr>
<tr>
<td>Zinc, mg</td>
<td>0.44±0.30</td>
<td>0.91±0.26</td>
<td>1.34±0.30</td>
<td>2.8</td>
<td>45</td>
</tr>
</tbody>
</table>

- Reduce the risk of diet-related chronic diseases, for example fortification contributes to adequate intakes of calcium and vitamin D which help build strong bones and may reduce the risk of osteoporosis.

In most countries, the addition of vitamins and minerals to food is controlled by Food and Drug Regulations, and only foods fortified with certain nutrients, and to levels specified in the Regulations, may be distributed. For example, in Canada, the current Food and Drug Regulations permit food fortification to:
- replace nutrients lost in the manufacturing process;
- act as a public health intervention;
- ensure the nutritional equivalence of substitute foods, or
- ensure the appropriate vitamin and mineral nutrient composition of foods for special dietary purposes.
Targeted fortification is a proven successful strategy for groups at the highest risk of micronutrient deficiencies. With targeted fortification, the vehicle is specifically a food eaten only by the ‘at risk’ population. For example, only infants eat infant cereals and infant formula; thus, for these two foods, the level of fortification is tailored to the specific micronutrient needs of young infants and pre-school children. Since adults generally do not eat infant cereals and formula, there is no concern for use by an inappropriate age group. Most of the iron ingested by infants and young children comes from fortified cereals despite the ready availability of foods containing heme iron, such as meats and poultry [4]. Although targeted fortification is, at least in theory, an efficient method to ensure the micronutrient adequacy of the diet, it assumes that infants are eating foods commercially fortified in the factory where they are cooked and packaged. In most households in developing countries, however, infants do not eat commercially prepared baby foods, but rather eat complementary foods prepared from local commodities and cooked in the home. Similarly, in some households in Western countries, home-prepared baby foods are used in preference to commercially prepared foods. Typical home-prepared porridges are made from rice, wheat, maize or a combination of grains. Although rice, wheat and maize are reasonably high-quality grains, they are low in micronutrients and high in phytate. The phytate binds the micronutrients and inhibits their gut absorption. Thus, on their own, these grains are not good sources of bioavailable micronutrients. The low rates of micronutrient deficiencies in developed countries are to a large degree due to the common practice of feeding infants with commercially fortified cereals. Alternatively, the high rates of micronutrient deficiencies in developing countries are to a large degree due to the common use of unfortified cereals as complementary foods.

From a public health perspective, the use of supplements to prevent micronutrient deficiencies has not been successful with the exception of high-dose vitamin A capsule supplementation to prevent vitamin A deficiency during early infancy.

Globally, it is estimated that 140–250 million children under 5 years of age are affected by vitamin A deficiency [5]. These children suffer a dramatically increased risk of death, blindness and illness, especially from measles and diarrhea [6]. As part of the global call to action, the UN Special Session on Children in 2002 set as one of its goals the elimination of vitamin A deficiency and its consequences by the year 2010. The strategy to achieve this goal is to ensure that young children living in areas where the intake of vitamin A is inadequate receive the vitamin through a combination of breastfeeding, dietary improvement, food fortification, and supplementation.

Combining the administration of vitamin A supplements with immunization is an important part of this effort. Since 1987, WHO has advocated for the routine administration of vitamin A with measles vaccine in countries where vitamin A deficiency is a problem [5]. Many millions of children have been
reached by including vitamin A with National Immunization Days to eradicate polio [7]. Providing immunization-linked high-dose supplementation to new mothers soon after delivery has provided a further benefit to young infants through enriched breast milk. Provision of vitamin A supplements every 4–6 months is an inexpensive, quick, and effective way to improve vitamin A status and save children’s lives. The Beaton Report concluded that all-cause mortality among children aged 6–59 months was reduced by 23% through vitamin A supplementation in areas where vitamin A deficiency was a public health problem [8]. However, comprehensive sustainable control of vitamin A deficiency must also include dietary improvement and food fortification.

**WHO Perspective**

Vitamin A is essential for the functioning of the immune system and the healthy growth and development of children. Immunization contacts offer unrivalled opportunities for delivering vitamin A to children who suffer from deficiency. Studies show that vitamin A does not have any negative effect on seroconversion of childhood vaccines. As well as routine immunization services, national immunization days for polio eradication, measles, and multi-antigen campaigns have been used safely and successfully to provide vitamin A to a wide age range of children at risk (table 2).

In the late 1990s, the global nutrition community was challenged by UNICEF to come up with an alternate solution to targeted fortification that would be applicable to infants and young children in the developing world [9]. Despite isolated successes in many developing countries with general staple food fortification such as with the iodization of salt and targeted supplementation with the use of vitamin A capsules, most countries with high rates of undernutrition were failing to reach malnourished children with effective evidence-based interventions supported by appropriate policies to improve the micronutrient status of children. It is estimated that exclusive breastfeeding and the appropriate use of fortified complementary foods has the potential to reduce mortality among children under 2 years of age by as much as 13 and 6%, respectively. However, commercially prepared fortified baby foods are generally not used in the developing world [10].

The concept of ‘home fortification’ was introduced and developed by researchers at the Hospital for Sick Children in Toronto, Canada [11]. ‘Home’ or point of use fortification is a strategy to improve the nutritional quality of home-prepared foods with micronutrient powders containing powdered mineral and vitamin fortificants. For circumstances where the macronutrient and energy density of food provided to children is adequate, but the foods are lacking in micronutrients, micronutrient powder can be added to the food just before it is eaten; thus, the concept of ‘home fortification’. The rationale for home fortification was based on the observation that rates of anemia were
very low in infants living in developed countries because most commercially prepared foods commonly eaten by infants are highly fortified with iron. Based on the notion that all infants, independent of their socioeconomic status, transition from breast milk to ‘table’ foods by eating semi-liquid complementary foods, it was postulated that ‘home fortification’ could achieve the same results. To accomplish the task of fortifying foods in the home, minerals and vitamins in a powder format are packaged in small single-serving packages (like a sugar sachet) that caregivers could sprinkle over whatever food was prepared for their infant. The advantage of this format is that the powdered minerals and vitamins can be added to any home-prepared complementary food. Thus, there was no need to change traditional feeding practices. To prevent powdered iron from changing the taste or color of the food to which it was added, the iron (ferrous fumarate) is microencapsulated with a thin coating of a vegetable lipid to protect the food from the iron (and the iron from the food) and to ‘taste-mask’ the iron. Thus, microencapsulation prevents any organoleptic changes to the food to which it is added.

Our group has published a summary of the research from six different countries, which demonstrates that the powdered iron in the micronutrient-containing sachets, mixed in maize-, wheat- or rice-based weaning food, is well absorbed, and that cure rates for anemia range from 40 to 90% depending on whether malaria is a predisposing cause of the anemia [10]. A systematic review and meta-analysis of home fortification of complementary foods

### Table 2. Potential target groups and immunization contacts in countries with vitamin A deficiency

<table>
<thead>
<tr>
<th>Target group</th>
<th>Immunization contact</th>
<th>Vitamin A dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>All mothers irrespective of their mode of infant feeding up to 6 weeks postpartum if they have not received vitamin A supplementation after delivery</td>
<td>BCG, OPV-0 or DTP-1 contact up to 6 weeks</td>
<td>200,000 IU</td>
</tr>
<tr>
<td>Infants aged 9–11 months</td>
<td>Measles vaccine contact</td>
<td>100,000 IU</td>
</tr>
<tr>
<td>Children aged 12 months and older</td>
<td>Booster doses¹</td>
<td>200,000 IU</td>
</tr>
<tr>
<td>Children aged 1–4 years</td>
<td>Special campaigns¹</td>
<td>200,000 IU</td>
</tr>
<tr>
<td></td>
<td>Delayed primary immunization doses¹</td>
<td></td>
</tr>
</tbody>
</table>

¹ The optimal interval between doses is 4–6 months. A dose should not be given too soon after a previous dose of vitamin A supplement: the minimum recommended interval between doses for the prevention of vitamin A deficiency is one month (the interval can be reduced in order to treat clinical vitamin A deficiency and measles cases).
was recently completed by Dewey et al. [12] who reviewed the efficacy and effectiveness of home fortification of complementary foods with micronutrient powders (e.g. Sprinkles®) as well as crushable tablets and lipid-based or soy-based products. Sixteen studies (5 anemia treatment trials, 11 prevention trials) met the inclusion criteria for the review. Treatment trials indicate that Sprinkles are as effective as iron drops, are better accepted and have fewer side effects. In prevention trials, the risk of anemia was cut in half. Acceptability of home fortification by caregivers and young children was high, and side effects rare. The authors suggest that the safety of home fortification using 'bolus' doses of iron, particularly in malaria endemic areas, needs further investigation. In one study of Sprinkles in a low-income country, estimates of cost per disability-adjusted life year regained compared favorably with other micronutrient delivery approaches, but the authors of the review indicate that more data on operational and cost considerations for the various home fortification products are still needed [12, 13].

Conclusions

Of the three modes of fortification, general staple food, targeted and home fortification, only the latter two are effective for use in infants and young children. There is evidence that supplements are both efficacious and effective for some vitamins (e.g. vitamin A), but not others (iron). With fortification of staple foods, like wheat flour and salt, the level of fortification is too low for the amount of food eaten by infants and young children. Thus, this mode of fortification is unlikely to be efficacious for this age group. Targeted fortification is efficacious, since the food vehicle and the level of fortification are targeted to infants and young children. However, this mode of fortification is not effective in developing countries because the fortification takes place in the factory where the products are centrally prepared and packaged. Although this type of fortification works well in developed countries, where typically infants are fed with store-bought centrally processed baby foods, in developing countries, where local crops are used to prepare food in the home, targeted fortified foods are simply not available. Most recently, a third type of fortification, home fortification, has been developed. Home fortification has been made possible with the development of micronutrient powders, which are minerals and vitamins in a powder form that are packaged in a small sachet and then added to foods at the point of use. Research studies in developing countries, including Ghana, India, and Bangladesh have proven the efficacy and effectiveness of home fortification as a means to fortify food in the home and to effectively both treat and prevent micronutrient deficiencies.

As a result of these advances, home fortification with micronutrient powders has recently been incorporated as a component of established World Health Organization/UNICEF-recommended feeding strategies [14].
Acknowledgements

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References


Discussion

Dr. Haschke: If we look at costs, you mentioned 0.015 dollars (costs of goods) per sachet. We know that the costs of goods are 5–10% of the total costs until the product reaches a person. Therefore, the cost of giving one sachet per day is in the range of 15–20 cents. Do you know the real cost of the project? It is very important whether such a project can be maintained over a long period. It looks quite impressive.

Dr. Zlotkin: The cost that I gave, the one and half cents, is simply the cost of the ingredients, the package and the production process. It did not include any of the downstream costs, and I think multiplying that number by 8 or 10 is probably a reasonable estimate of the total cost. One of the strategies that we have taken around the
cost issue is to not develop a silo or a vertical program for the distribution of micro-
nutrient powders but to include micronutrient powders in programs that are already
in progress. So, for example, UNICEF has programs for the support of breastfeeding
and ongoing programs for the appropriate introduction of complementary feeding. So
what we have tried to do with my partnership with UNICEF is to include the use of
micronutrient powders in the programs that are already paid for by the individual
countries. When UNICEF works, it’s always with governments, so we try and incorpo-
rate the micronutrient powders into ongoing programs. That doesn’t negate the total
cost of the program but at least spares the necessity to find new dollars for the distri-
bution part. So I totally agree that the cost that I gave you is an underestimate of the
total cost, but there are strategies to incorporate those costs into ongoing programs.

Dr. Michel: What can we do in Mexico to get the sprinkles?

Dr. Zlotkin: I am glad you asked that question because in fact my organization
has been working with Mexico for the Oportunidades program. Mexico has the dual
problem of an increasing rate of obesity in young children and at the same time an
increasing rate of micronutrient deficiencies, primarily iron deficiency. The Mexican
government has made the decision at least in a number of pilot regions to discontinue
or to compare their current strategy, which is giving a fortified milk product to all
children, to the use the micronutrient powders instead, so that they can theoretically
not contribute to the problem of obesity and theoretically contribute to the successful
prevention or treatment of iron and micronutrient deficiency.

Dr. Klassen: My question concerns consumer understanding. During the last
World Congress of Public Health, the World Food Program presented data that were
not as convincing as your data because after initial explanation of the program com-
pliance went down to 40–60% depending on the country. The major reasons for this
effect were mentioned as: First, a high level of migration led to loss of knowledge of
the program. Secondly, the consumers did not understand or misunderstood the pack-
age. And lastly, the benefit of taking the supplement was often not understood, since
the wording used was not comprehensible to the consumer. Did you do any consumer
research to test the understanding of claims related to the supplement?

Dr. Zlotkin: We did some consumer research, but again it was in a control
fashion. I think like all programs when they are being delivered to a free living
population, when they are true programs, it is really at that time that one has to
review the programs, measure things and continue to adapt to the needs of the
population. What you say doesn’t surprise me at all, and it’s not atypical of some of the
problems that we have with complementary feeding, even with breastfeeding.
There are new children born all the time, and the message that you gave for your
first child may have to be repeated it for your second child. The advantage of this
intervention is that it is really simple. One doesn’t have to be literate to use it, it
doesn’t change the taste or the color of the food, and it actually works, so I think
there are a number of advantages. The disadvantages and especially the disadvan-
tages around iron deficiency anemia is that oftentimes it’s very difficult to convince
people that their child either has anemia that there is a need to prevent it. I think
there must be ongoing education, communication and information in order for these
programs to be totally sustainable.

Dr. Kleinman: I noticed as you were talking about Pakistan that the prevalence of
anemia decreased from 70 to 30% in children aged under 2 years and then to 20% at
60 months. Does that imply that it’s necessary to continue the intervention beyond 5
years of age?

Dr. Zlotkin: Again, to give you a short answer to the question, the anemia rate
for under 5 was 56% and 78% for under 2. Of course, we know that the blood volume
doubles and triples in the first 2 years of life, and after that growth is pretty slow. So,
between 2 and 5 years of age, the problem of anemia probably is not quite as severe as it is under that. But an ongoing discussion that I have with many of my partners is, who should we target? Should it be children between the age of 6 months and 2 years of age when growth is so rapid, or should it be between 6 months and 59 months of age or 5 years of age? It really depends on the jurisdiction. Some organizations decide that they are going to target all children under the age of 5, others will target the children between 6 months and 2 years of age. It has to do with the amount of funding available, the amount of personnel available and the priorities of the organization.

Dr. Mohanty: What was the impact of parasitic infections, for example hookworm, that cause so many problems?

Dr. Zlotkin: The infants that we included in our studies were generally infants whose average age was 12, 13 or 14 months. Generally, in children under 2 years of age parasite problems do not seem to be a major factor contributing to their anemia. Certainly, above 2 years of age hookworm and other parasitic infections do play a role. So, as you know there are many programs which include the intermittent treatment of parasitic infections above 2 years of age. There are no recommendations for infants under 2 years of age as far as I know. So, although above 2 years it's an important problem, our focus was on infants between 6 and 24 months of age, in which case parasitic infection at least in the younger group does not seem to be a major problem.

Dr. Hussain: I just want to thank and congratulate you and your team for this intervention. After we have adopted it in Bangladesh, our general perception is that it will be as successful in reducing malnutrition as ORS was in reducing diarrhea, and this sachet will definitely contribute to reducing micronutrient deficiency.

Dr. Zlotkin: Thank you. Bangladesh is one of the countries that we did most of the research in. Bangladesh now has probably 5 or 6 distribution models. Distribution has been taken on by the private sector, so it's actually sold in Bangladesh, it's distributed through a number of NGOs, it's distributed through the government and it's distributed through UN agencies. Bangladesh is probably a model country for a multiple distribution methodology, and you need that in order to have good enough coverage.

Dr. Lack: You had your strategy slide and discounted a number of strategies. I note you didn't include GMO crops, and a while ago there was a lot of talk about vitamin A introduction into rice. I just wondered whether that was a strategy that you thought might have any value. Of course, it's very convenient if you can just eat your local food and it provides everything you need, or do you think that's sort of science fiction?

Dr. Zlotkin: I am not aware of universal success or national programs which include vitamin A golden rice, but I think the idea is a reasonable one. I think there are many fabulous ideas available. In fact, if you look at the Lancet series from 2 years ago on the prevention of child mortality, there are probably 20 or 22 evidence-based interventions that are known to work, that if they were implemented, it would decrease the rates of infant and child mortality in the world by probably 80%. So, if I were to give advice to young scientists in the nutrition field on the area that they should work in in order to have the biggest impact, I would say it would be in the new field of what people are calling implementation science. It is a science or should be a science, and I think that's where the money should be spent.

Dr. Siega-Riz: I was wondering, what you have actually dealt with is developing a product that helps us improve the micronutrient deficiencies. However, this doesn't actually address the issue of additional calories for the wasted or stunted child. I was wondering if you could talk a little bit about whether or not you actually see beneficial effects on growth perhaps.

Dr. Zlotkin: We don't see effects on growth, and you are absolutely right, the micronutrient powders contain no source of energy, no sources of protein, and in fact these are only micronutrient supplements. They do not solve the problem of global
undernutrition, where one assumes that it’s a combination of inadequate energy intake as well as inadequate micronutrient intake. Micronutrient powders are not going to solve all the problems of malnutrition. As you know, there are some other innovative interventions that are used for children with severe malnutrition and starvation, including the ready to use foods, that have been very successful.

Dr. Stettler: When you see such high rates of iron deficiency and it’s so hard to address, one wonders whether there is some type of evolutionary benefit to it and how human mankind evolved with such a high rate. I wonder what your thoughts are about that and if we are really successful in addressing iron deficiency. Are there going to be negative health consequences that we may not have thought about?

Dr. Zlotkin: The last question was, are there negative consequences of action preventing it?

Dr. Stettler: I mean if there is an evolutionary benefit to iron deficiency, if you are able to address it successfully like you seem to be addressing it, might there be any possible negative impact?

Dr. Zlotkin: Just very briefly, one of the concepts is that when we became an agrarian society, we actually changed our diet which was primarily based on meat or fish to a diet that was based on wheat and other crops that we could grow. There are a number of people who talk about the evolutionary consequences of changes in diet. I think iron is certainly needed by the human; it’s also needed by the organisms that live with us, including the organisms that make us sick, and the best example of that is malaria. Researchers are asking whether or not there is a negative impact of providing iron to children with iron deficiency in a malaria-endemic area. There are a number of research projects now which are studying that question. The theory is that the malaria parasite uses the iron somehow or it has an effect on the immune system such that a child who has a better iron status is actually less able to cope with the malaria parasite than a child whose iron status is poor. So, I think the issue is a true issue but actually too big for a brief discussion right now.

Dr. Lake: In one of your early slides where you looked at the prevalence of iron deficiency by country, I was struck by how low the prevalence appears to be in China. What is China doing right?

Dr. Zlotkin: We have done actually two studies on iron, and I worked with the Chinese CDC, which is the equivalent of the American CDC in Atlanta. We went to the first area which was in Inner Mongolia. We started the study, and we could not find any children with anemia. So the CDC said, ‘no problem, we’ll go to a different area’. We went to another rural area, and once again although I was told that the rates would be in the range of 30–40%, the ranges were actually less than 10%. I don’t know exactly what it is that they are doing in China to change the rates from what they were probably 50 years ago, but the slide that I showed on poverty is probably the right answer. I think China is a great example of a country in transition from a very underdeveloped country to a developed country, although it is still in transition. When we talk about China, there is western China which is poor, there is Shanghai that is rich, so there is no such thing as one China, but I think that the answer is a combination of improved economics in the family, improved hygiene, improved food, having bathtubs in the house, watching television, etc. I think it’s a combination of effects that is changing the life and the health of Chinese.

Dr. Stoll: I have a question concerning safe intake. When you provide the treatment for a month are you not afraid of overdosing, especially zinc and vitamin A?

Dr. Zlotkin: We addressed that in a number of ways. The first way was that the micronutrients are in a powder and part of that powder is what is called an excipient or a filler. Originally, we thought it would be a good idea to use sugar as the filler because then it would be easy to get the child to take the micronutrient powders. We
quickly decided that that would not be a good idea, so the filler we use is a malto-
dextrin, which really isn't sweet at all, it has a very neutral taste. If you were to taste
the powder, it tastes slightly sour from the ascorbic acid, but otherwise it has a very
neutral taste. So there is no real reason why an older child in the family would open
a package and want to eat more than one package because they simply don't have a
good taste. In addition, although it's easy for a parent to open the package, it's a 3
layer package with paper, polyethylene and foil or aluminum, a young child would
have a hard time opening it. And the final thing is, because the amount of iron in the
package is approximately 10 or 12.5 mg, in order to approach the amount of iron that
would be lethal, a child would have to eat something like 16 or 17 packages. So, the
combination of having a neutral taste, the package that is not too easy to open but not
too hard to open, and having to use 16 or 17 packages before toxicity would occur we
think addresses the issue of safety and in all of the many studies that we have done,
including many of the distribution programs, we have not heard anyone who has actu-
ally used more than one or two packages a day.

Dr. Stoll: I was not concerned about iron but mainly zinc. You mentioned that you
are adding 5 mg of zinc per sachet, and you can easily overdose if you have 2 or 3
sachets per day.

Dr. Zlotkin: Good point.

Dr. Lack: Just getting back to the evolutionary question and the comments made
about China, I wondered whether there are any epidemiological data on migrant eth-
nic communities say in the US comparing rates of anemia in Chinese, black African,
Hispanic communities and correcting for demographic factors to see whether there
might be sort of genetic tendencies.

Dr. Zlotkin: That's a great question, and maybe someone in the audience knows the
answer. I actually don't know whether that has been done. Does anyone else know?

Dr. Kleinman: In the US, WIC covers a very large proportion of young infants, and
those who are in need of support are given foods and supplements that would reduce
the risk of anemia. In fact, the WIC program has reduced the prevalence of anemia
significantly in the low-income population in the US. I think one evolutionary issue
that you didn't bring up is that for most of human history, infants crawled in the dirt,
and the soil is a fairly rich source of iron that isn't available anymore to most babies,
particularly in our hyper-hygienic society.

Dr. Stettler: I have a comment, not a question. I really like the concept that you
tested about flexibility, that it's OK if you miss one day. I think this is really something
that should be an inspiration for those of us who work in a wealthy country on chronic
disease, obesity, and cardiovascular prevention. Our messages so far have been pretty
rigid: 5 servings of fruit and vegetables every day, physical activity every day. I think if
we were able to give the people some flexibility and permit them to miss one day once
a while, this would be a really nice approach. I thought that was really inspiring for
domains other than the one you are working on.

Dr. Ganguly: Is there any form of nutrition counseling which is being given along
with the distribution of these sachets to make a positive impact on the dietary habits?

Dr. Zlotkin: As I mentioned earlier, we try not to place the micronutrient powders
into a silo program, which is a program that specifically and only addresses micro-
nutrient deficiencies. In working with government organizations, non-government
organizations and the UN organizations, we try to include the use of micronutrient
powders with on complementary feeding and general feeding advice. So, what we
might say is that 6 months of age is an appropriate time to introduce complementary
foods. In order to increase the nutritional value of the complementary foods we sug-
gest that you use one sachet or 30 sachets over the next 2 months, and in the sachets
are those ingredients which you might not be able to get from your local food. We
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would also give advice on most appropriate local foods to use, so the answer is yes, we try and include the concept of home fortification with other horizontal programs as opposed to including new vertical programs for the appropriate age groups. The only time when that might not be done is when the private sector is involved in distributing the sachets. There, we have little control over what information is provided.

**Dr. Agarwal:** For children, we should not fix any age when to give iron. The situation varies from country to country. For a country like India, pregnancy anemia and lactation anemia remains the number one priority because it is in the later part of pregnancy that the iron is transferred and needed for neurotransmitter formation. Transfer of iron through placenta is reduced as we have showed in our studies [1–9]. I think we should not make any recommendation as to what should be the age to supplement iron.

And point two; you said that the wheat flour should not be fortified because adults eat it. How will a pregnant woman get it, how will a lactating woman get it? In India, the sprinkles are supplied but the national level of iron is zero, 100% have iron anemia, and therefore in this nation iron in any form is essential.

**Dr. Zlotkin:** I totally agree, and I absolutely think that large commodity should be fortified, and they are of great value to adults who eat large amounts of those fortified foods. My point was that food fortification is important but will not impact very much on the young child. I hope I didn’t say that we should get rid of large commodity food fortification. I didn’t mean that, I just simply meant that it doesn’t work for very young children.

**Dr. Jones:** The salt problem with iodine has been an issue in Tasmania. We are mildly iodine deficient, but the recommendations are to limit salt because of blood pressure and other issues. So we put iodized salt in bread, and that actually works at the population level. Also, did you look at how much vitamin C should be taken, because obviously vitamin C has a major effect on iron absorption?

**Dr. Zlotkin:** We actually did some research looking at a dose-response for vitamin C in the sachets and how much iron would be absorbed using our stable isotope methodology. We found that between 30 and 50 mg was the right amount. The other important issue was the issue of practicality. If we used more than 50 mg, the sour taste of the vitamin C actually changed the taste of the food into which it was added.

**References**