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HEALTH IN ACTION

Micronutrient Sprinkles to Control Childhood Anemia

A simple powdered sachet may be the key to addressing a global problem

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Competing interests: Stanley Zlotkin is an occasional consultant to Bristol Myers, Squibb, Mead Johnson Ltd. and the Gerber Company, USA and General Foods in Canada. He owns the intellectual property rights to Sprinkles. The HJ Heinz Company Ltd. is supporting the technical development of the sprinkles on a cost- recovery basis. Any profit from royalty fees on the technology transfer of sprinkles is currently donated to the Hospital for Sick Children Foundation, Toronto.

Recent WHO/UNICEF estimates suggest that the number of children with iron deficiency anemia (IDA) is greater than 750 million [1]. Iron deficiency is the most common preventable nutritional problem despite continued global goals for its control. Historically, the problem of IDA in children largely disappeared in North America when foods fortified with iron and other micronutrients became available for children. In this group, the prevalence of IDA has fallen from 21% in 1974 to 13% in 1994 [2]. Although pockets of infants and children remain at risk, generally the eradication of iron deficiency in the West is recognized as a successful public health accomplishment. This solution has not worked in developing countries where commercially purchased fortified foods are not available or are not used.

In the developing world, there are three major approaches available to address iron deficiency: dietary diversification to include foods rich in absorbable iron; fortification of staple food items (like wheat); and the provision of iron supplements. When dietary or fortification strategies are not logistically or economically feasible, supplementation of individuals and groups at risk is an alternative strategy. For the past 150 years or more, oral ferrous sulphate syrups have been the primary strategy to control IDA in infants and young children [3]. However, adherence to them is often limited due to a combination of their unpleasant metallic after-taste, dark staining of the child's teeth and abdominal discomfort [4]. Thus, despite the ongoing work of the UN Standing Sub-Committee on Nutrition and others to solve the problem of poor adherence in infants and young children, all interventions to date have been universally unsuccessful [1,5]. In this article, we describe our efforts, stage by stage, towards achieving the goal of controlling iron deficiency anemia.

The Strategy

Our research group at the Hospital for Sick Children in Toronto conceived of the strategy of 'home-fortification' with 'Sprinkles'— single-dose sachets containing micronutrients in a powder form, which are easily sprinkled onto any foods prepared in the household. We hypothesized that this would be a successful method to deliver iron and other micronutrients to children at risk [6]. The idea of 'Sprinkles' was formulated in 1996, when a group of consultants determined that the prevention of childhood IDA was a UNICEF priority, yet available interventions (syrup and drops) were not effective [7].

In Sprinkles, the iron (ferrous fumarate) is encapsulated within a thin lipid layer to prevent the iron from interacting with food. This means that there are minimal changes to the taste, color or texture of the food upon adding Sprinkles. Other micronutrients including zinc, iodine, vitamins C, D and A, and folic acid may be added to Sprinkles sachets. Any homemade food can be fortified with the single-dose sachets, hence the term 'home-fortification'. Two formulations have been developed, a 'nutritional anemia formulation' (Table 1) and a complete micronutrient formulation (Table 2).

Clinical Trials

Efficacy

To investigate the bioavailability of the iron in Sprinkles, we used a dual stable isotope method and demonstrated that anemic infants absorbed iron from Sprinkles about twice as efficiently as non-anemic infants when delivered in a maize-based diet in West Africa. The study was conducted in collaboration with the Kintampo Health Research Centre of the Ministry of Health in Accra. Geometric mean iron absorption from two doses of iron from Sprinkles (30 vs. 45 mg of elemental iron) was 8.3% (range: 2.9-17.8%) in infants with anemia and 4.5% (range: 1.1-10.6%) in infants without anemia [8]. Comparing these absorption values to the new American/Canadian Dietary Reference Intake standards (DRIs) for infants, we concluded that during infancy: (i) iron absorption of Sprinkles from a maize-based porridge met and surpassed iron needs for absorbed iron; and (ii) iron absorption is up-regulated in infants with IDA [9-11]. Based on these results, we estimated through computer simulations that a 12.5 mg iron dose (as recommended by WHO) from Sprinkles should be adequate for use in large-scale distribution programs for the prevention and treatment of mild to moderate anemia.

It has been suggested that zinc may compete with iron for the same receptor sites on intestinal mucosal cells in the proximal duodenum thereby compromising the absorption of both minerals [12]. To address this important issue, we recently conducted a bioavailability study in rural Ghana using the same dual stable isotope method as previously used [8]. Sixty-three young children 12-24 months of age with varying hemoglobin levels were studied in order to determine the effect of two doses of zinc on the absorption of iron from Sprinkles (with 30 mg elemental iron) . We found that 10mg of zinc (in the form of zinc gluconate) added to Sprinkles significantly reduced the absorption of iron, whereas a 5 mg dose had no effect. Thus, we concluded that adding 5 mg of zinc to the formulation of Sprinkles was appropriate (unpublished data).

Over the past five years, we have completed seven community-based trials in four different countries [13-19]. The goal of these studies was to test the efficacy of Sprinkles in diverse settings. When we pooled data from two of our studies that compared Sprinkles to the 'reference standard', ferrous sulfate drops, we had a total of 518 anemic infants (hemoglobin < 100g/L) who were given one of two ferrous sulfate doses (15 or 40 mg of elemental iron as ferrous sulfate) and 318 similar infants who received one of four doses of iron from Sprinkles (12.5, 20, 30 or 80 mg of elemental iron as microencapsulated ferrous fumarate) [13, 18]. This gave us greater than 97% power (alpha = 0.05) to detect whether the mean difference in 'end of study' Hb concentrations between ferrous sulphate and Sprinkles regimens was within ± 5g/L (a range of equivalence). Using a random effects model (for study and dose) that adjusted for baseline hemoglobin, we found no significant difference between Sprinkles and drops.

We further examined this through quantile-quantile (QQ) plots of hemoglobin concentrations at the end of the studies for Sprinkles and ferrous sulphate drops (figure 1). The overlaid plots of hemoglobin concentrations of the Sprinkles and drops groups demonstrate that these two distributions overlapped at all quantiles. These plots clearly indicate that the hemoglobin response to the two different forms of iron were equivalent.

Thus, we have concluded that Sprinkles are as efficacious as the current reference standard for the treatment of anemia. Overall, 55 - 90% of the anemic infants who were provided with Sprinkles were cured.

Acceptability

During our studies we also asked the caregivers about their perception of their infants' response to Sprinkles compared to drops, Sprinkles' impact on the food to which they were added (change in taste, color or consistency), the use of sachets as a delivery vehicle and their perceived side-effects [13, 18, 19]. Invariably, the response to Sprinkles has been positive. No appreciable change in the food with Sprinkles has been reported; no one reported staining of the infants' teeth; and Sprinkles were reported to be easy to use. The only consistently reported 'side-effect' was darkening of the infant's stool, which is expected since most of the iron is excreted in stool. In a recently conducted study in Bangladesh, using a four point measurement scale, 60% of the mothers 'extremely liked', 30% 'liked' and the remaining 10% 'somewhat liked' the Sprinkles intervention; no one disliked Sprinkles. Major reasons cited for liking Sprinkles included ease in mixing Sprinkles with complementary food and that their use promoted the appropriate introduction of complementary foods since Sprinkles could only be used if complementary foods were used [19].

Ensuring a Sustainable Supply

As the results of the first studies **showing** the efficacy of Sprinkles were becoming available, the need for a reliable high quality supply became apparent. In 2000, the HJ

Heinz Company of Pittsburgh expressed an interest in the Sprinkles program as a component of their ‘corporate social responsibility’ program. Since 2001, the H.J. Heinz Company has provided support and expertise in evaluation of consumer needs and a supply of Sprinkles for research, while the HJ Heinz Foundation has provided financial support for research activities. Through a formal process of technology transfer, local overseas Sprinkles production is encouraged. Currently an independently licensed co-packer is supporting local production for a national program in Guyana and plans are in place for technology transfer to Bangladesh and Pakistan.

Scaling Up For Country-Wide Distribution

The final stage, the scale-up process, is by far the most challenging. This process involves the identification of sustainable methods of distribution that are able to reach and provide Sprinkles to the most vulnerable populations in the developing world. From our experience in Mongolia, we have determined that it is feasible to distribute Sprinkles in partnership with a non-governmental organization (NGO), World Vision. Sprinkles sachets distributed in Mongolia over a two-year period include both iron and vitamin D. Sprinkles have been successfully distributed by World Vision field staff to over 15,000 children in 7 districts. Coverage has been over 80%, at a cost of about USD $0.03 per sachet. In the project area, the prevalence of anemia ($Hb<115$ g/L) and rickets decreased from 42 to 24% and 48 to 33%, respectively [20].

Notwithstanding these positive results on anemia control, without committed, long-term financial input from the national governments, international agencies or NGOs, sustainability is not guaranteed. Clearly, sustainability over the long-term can most likely be achieved if a program can become self-financing. This may be achieved through public- and private-sector partnerships that use effective social marketing models or possibly through programs which include micro-credit in order to reach hard-to-reach population groups. To scale-up Sprinkles from small-scale research projects to larger scale programs, we quickly realized that our research group did not have the necessary funding, experience or personnel needed to influence health-policy, develop a social marketing strategy or maintain a distribution network at a country-wide level. We have thus partnered with organizations that specialize in each of these areas to help achieve our goal of sustainable distribution. For example, the government of Pakistan is planning to distribute Sprinkles through their ongoing 'Lady Health Worker Program' that is the largest public sector primary health care program implemented by the Federal Ministry of Health. In Bangladesh, BRAC (formerly known as Bangladesh Rural Advancement Committee), the largest national NGO in the country, is planning to distribute Sprinkles through their on-going Female Community Health Worker program (popularly known as *Shahthya Shebika*). In both of these countries, Sprinkles would be produced locally through public-private partnerships, via a technology transfer agreement. The cost per sachet of locally produced Sprinkles should range from USD $0.010 to $0.015, depending on the volume of production as compared to USD $0.020 to $0.025 if imported.

Conclusion

Each stage in the evolution of the Sprinkles intervention has been evaluated in a controlled manner. We determined that the use of encapsulated iron did not appreciably change the taste or color of the food to which it was added; we showed that the hemoglobin response in anemic infants was equivalent to the current standard of practice; and we documented the acceptability of Sprinkles among caregivers who used Sprinkles in their homes. Finally, through various partnerships, we have developed a successful model to scale up the intervention for country-wide use. Our challenge for the future is to demonstrate the cost-effectiveness of this new intervention and to advocate for the adoption of Sprinkles in the nutrition policy of developing countries.

Acknowledgements

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Table 1. Dose and derivation of 'Sprinkles Nutritional Anemia Formulation' for home-fortification of complementary foods for infants and young children, 6-24 months of age.

	6-11 months		*12-24 months*		*6 – 24 months*
	WHO[1]	IOM DRI[2]	WHO	IOM DRI	Sprinkles
Vitamin A, µg RE	400	500*	400	300	300
Vitamin C, mg	30	50*	30	15	30
Folic Acid, µg	80	80*	160	150	160
Iron, mg[3]	9.3	11	5.8	7	12.5
Zinc mg[4]	4.1	3	1.1	3	5

[1] Recommended Nutrient Intake. Source: Joint FAO/WHO Expert Consultation. Vitamin and mineral requirements in human nutrition. World Health Organization, Geneva, Switzerland. 2002.

[2] Recommended Dietary Allowances (RDA). Sources: Institute of Medicine, Dietary Reference Intakes. National Academy Press, Washington D.C. 2000.

[3] Assuming medium bioavailability (10%)

[4] Assuming moderate bioavailability (30%)

* Based on Adequate Intake (AI) estimates

Table 2. Dose and derivation of 'Sprinkles Complete Micronutrient Formulation' for home-fortification of complementary foods for infants and young children, 6-24 months of age.

	6-11 months		*12-24 months*		*6-24 months*		
	WHO[1]	IOM DRI[2]	WHO	IOM DRI	Lutter and Dewey [3]	Upper limit [2]	Sprinkles
Vitamin A, µg RE	400	500*	400	300	250	600	300
Vitamin C, mg	30	50*	30	15	70-140	1000	30
Vitamin D, µg	5	5*	5	5	1-2	25	5
Vit. E, µg a-TE	NA	5*	NA	6	NA	2000	6
Vitamin B1, mg	0.3	0.3*	0.5	0.5	0.18	NA	0.5
Vitamin B2, mg	0.4	0.4*	0.5	0.5	0.18	NA	0.5
Vitamin B6, mg	0.3	0.3*	0.5	0.5	0.22	30	0.5
Vitamin B12, µg	0.5	0.5*	0.9	0.9	0.26	NA	0.9
Folic Acid, µg	80	80*	160	150	41.5	300	160
Niacin, mg	1.5	4*	6	6	3.3	10	6
Iron, mg[4]	9.3	11	5.8	7	7-11	40	12.5
Zinc mg[5]	4.1	3	4.1	3	4-5	5-7	5
Copper, mg	NA	0.22*	NA	0.34	0.2-0.4	1	0.3
Iodine, µg	NA	130*	90	90	90	200	90

[1] Recommended Nutrient Intake (RNI). Source: Joint FAO/WHO Expert Consultation. Vitamin and mineral requirements in human nutrition. World Health Organization, Geneva, Switzerland. 2002.

[2] Recommended Dietary Allowances (RDA). Sources: Institute of Medicine, Dietary Reference Intakes. National Academy Press, Washington D.C. 2000.

[3] Recommended nutrient composition of complementary foods (per 50 g of food as daily ration) is based on a total intake of 1 RNI for all children 6-23 mo after accounting for the amounts already present in breast milk and complementary food.

[4] Assuming medium bioavailability (10%)

[5] Assuming moderate bioavailability (30%)

* Based on Adequate Intake (AI) estimates

Figure 1. Overlaid quantile-quantile (QQ) plots of Hemoglobin (Hb) concentrations at the end of studies for Sprinkles and ferrous sulphate drops. The graph shows that the two distributions overlap at all quantiles, thus proving that there was an equivalent response to the two treatments for Hb concentrations. Circles represent individual subjects who received iron drops; crosses represent individual subjects who received Sprinkles.