12

Acceptance and Effect of Ferrous Fumarate Containing Micronutrient Sprinkles on Anemia, Iron Deficiency and Anthropometrics in Honduran Children

Teresa M. Kemmer[1], Preston S. Omer[2],
Vinod K. Gidvani-Diaz[3] and Miguel Coello[4]
[1]Health and Nutritional Sciences, SDSU Extension and Agricultural Experiment Station South Dakota State University, Brookings,
[2]U.S. Army, U.S. Army Medical Command, Fort Riley,
[3]U.S. Air Force San Antonio Uniformed Services Health Education Consortium, Pediatric Residency San Antonio,
[4]U.S. Medical Element, Joint Task Force-Bravo, Soto Cano Air Base
[1,2,3]USA
[4]Honduras

1. Introduction

Anemia is reflective of global inequalities between developing and developed countries and is an endemic problem (Balarajan et al., 2011). Global Iron deficiency anemia (IDA) is one of the top ten risk factors contributing to the global burden of disease and economic costs are estimated at 4.05% of gross domestic product per capita from loss in productivity and $14.46 (U.S.) per capital in lost cognitive function (World Bank, 2004). One-quarter of the world's population is affected by anemia (McLean et al., 2009). Using data from the World Health Organization (WHO) Vitamin and Mineral Nutrition Information System for 1993-2005 (WHO, 2008), McLean et al. estimated an anemia prevalence of 47.4% (293 million) in preschool-aged children (2009). Iron deficiency (ID) is attributed annually to 20,854 global deaths in children under 5 years of age (Black et al., 2008), anemia affects 1.62 billion people (24.8% of the population) and anemia prevalence is highest in preschool-age children (47.4%) (WHO, 2008). The WHO categorizes the prevalence of anemia as a public health problem as follows: <5% – no problem, 5–19% – mild public health problem, 20–39% – moderate public health problem, and >40% – severe public health (Badham, 2007). According to the 2011 World Bank World Development Indicators, in children less five years of age, the prevalence of anemia is greatest in South Asia at 71% and is estimated at

66% in low income areas of the world (World Bank, 2011). The average prevalence of anemia in Europe and Central Asia is 30%, Latin America and the Caribbean is 38%, and Middle East and North Africa is 48% (World Bank, 2011).

Iron deficiency anemia contributes to poor growth and cognitive impairment which in turn has a negative effect on learning potential and productivity (Lozoff et al., 2006; Grantham-McGregor & Ani, 2001). At school entry, children that had chronic, severe ID during infancy are at a behavioral disadvantage as compared to their peers (Corapci et al., 2006). Hemoglobin has been shown to be associated with a decrease in verbal short-term memory and the severity of anemia has an impact on neurocognitive deficits, indicating reduced oxygen delivery to the brain as an etiological mechanism (Hijmans et al., 2011). Iron deficiency anemia in infancy results in children and young adults with poorer inhibitory control and executive functioning as well as other negative effects on neurotransmitters, myelination, dendritogenesis, neurometabolism in hippocampus and striatum, gene and protein profiles, and there associated behaviors (Lozoff, 2011). The long term affects of iron deficiency during infancy on poorer cognitive, motor, affective, and sensory system functioning highlight the requirement to focus on early intervention strategies that minimize the long-term effects (Lozoff, 2011). In a review by Madan, et al. (2011) ID resulted in negative developmental and neurophysiologic deficits and lower scholastic achievement. Results from an inner-city study revealed poorer object permanence and short-term memory problems in infants with IDA at 9 months and concluded that these cognitive effects were partially due to IDA related deficits in socioemotional function (Carter et al., 2010). Analysis of multiple trials found 1.73 lower IQ points per 1 g/dL decrease in hemoglobin (Stoltzfus et al., 2004). The predicted rate of mental retardation in a population with hemoglobin distribution shifted 1 g/dL downward due to iron deficiency is estimated at 2.94% (Stoltzfus et al., 2004).

Indirectly, ID negatively impacts the earning potential and entire economy of third world countries throughout the world. It was estimated that 0.2% of deaths and 0.5% of disability-adjusted life-years (DALYs) in children under 5 years of age are attributed to ID (Black et al., 2008). Iron deficiency results in 0.5%of maternal and child deaths in the world and 1.3% of DALYs and are higher in low income countries at 0.8% and 1.6% respectively. Estimated attributable DALYs to maternal and child iron deficiency are 19.7 million (WHO, 2009).

Approximately a quarter of children under five years of age in the developing world are undernourished based on the Millennium Development Goals (MGD) Report (United Nations, 2011), and progress in reducing the proportion of people suffering from hunger is insufficient to reach the target goal by 2015. If this MDG is to be achieved, nutrition must be given higher priority and should include simple, cost-effective measures delivered particularly from conception to two years after birth such as improved maternal nutrition and care, breastfeeding within one hour of birth, exclusive breastfeeding for the first 6 months of life, and timely, adequate, safe, and appropriate complementary feeding and micronutrient intake between 6 and 24 months of age (United Nations, 2011).

According to the Oxford Poverty and Human Development Initiative for Honduras (2010), 18% of the population are poor according to the $1.25 a day poverty line and 51% are poor according to the national poverty line. Inequities in under-5 mortality rate exist within Honduras where the mortality rate spans from 20 deaths per 1000 live births in the wealthiest to 50 per 1000 in the poorest (WHO, 2011). Anemia is very prevalent in

Honduras. A study by Nestel et al. (1999) showed that the prevalence of anemia in Honduran children ages 12 to 71 months was approximately 30%. Albalak and colleagues reported anemia prevalence in Honduran children at 40% in ages 12 to 36 months and 18% in children 36 to 60 months (Albalak et al., 2000). As a developing country, Honduras suffers from the negative impact anemia has on health, growth, and cognitive development, which indirectly decreases the productivity of the country. The estimate of economic loss from IDA as a percent of gross domestic product in Honduras is 2% (Horton & Ross, 2003). Programs within Honduras have tried to decrease the prevalence of anemia through different methods that include fortification of staples as well as supplementation (Dewey et al., 1998, 2004; Darnton-Hill et al., 1999; Darnton-Hill, 1998; Venkatesh Mannar, 2006). In addition, studies by Dewey et al. support the Honduran Ministry of Health's efforts to improve the iron status of breast-fed infants (Dewey et al., 1998, 2004).

The prevalence of ID can be reduced by increasing the consumption of iron-containing foods in the diet, supplementation with iron, or fortification of foods with iron (Finch & Cook, 1984; Provan, 1999; Trowbridge, 2002). The International Nutritional Anemia Consultative Group (INACG), WHO, and United Nations International Children's Emergency Fund (UNICEF) recommend introducing iron supplementation to healthy term infants with normal birth weight at 6 to 12 mo of age if the prevalence of anemia is less than 40% in the population, and supplementing the infants onward until 24 mo of age if the prevalence of anemia is 40% or higher in the population (Zlotkin & Tondeur, 2007). Ferrous sulfate is mainly used to supplement food stuffs (Dary, 2007). An alternative supplement method is adding iron into the diet with "Micronutrient Sprinkles" which were developed at the Hospital for Sick Children (Schauer & Zlotkin, 2003). Sprinkles refer to a blend of micronutrients in powder form that are added to foods to target susceptible populations at higher risk of anemia and micronutrient deficiencies (Sprinkles Global Health Initiative, 2008). Sprinkles may contain any combination of micronutrients and are packaged in a small sachet, the contents of which can be added to any semi-solid food. Sprinkles can be designed and produced based on the population needs and allow susceptible populations to fortify home cooked foods.

The objectives of this randomized case-control study in non-anemic rural Honduran children ages 6 to 60 months were to determine if micronutrient sprinkles 1) are an effective method of preventing anemia and reducing ID, 2) result in improved growth parameters, and 3) are acceptable to the population.

2. Methods

This randomized case-control nutritional assessment study in rural Honduras was conducted in collaboration with the Honduran Ministry of Health (MoH); medical liaison officers at Joint Task Force Bravo, Medical Element, Soto Cano, Honduras; the San Antonio Military Pediatric Center; and South Dakota State University in 2006-2007. Immunization records obtained from the local health centers of children within the age range of 6 to 60 months were used for randomization of the household. Immunization records were used for the randomization since 98% of 1-year-old children in Honduras are immunized against Hepatitus B; measles; diphtheria, pertussis and tetanus (DPT); and tuberculosis (TB) and 94% of newborns are protected against tetanus (UNICEF, 2010). A minimum of 10% of the children within each health center were randomly selected for participation. Each child's household was visited with the assistance of local volunteers from the MoH clinics and community. Data collection included anthropometrics, survey data, blood collection, and altitude. Written consent was obtained from one of the primary care providers prior to participation. Completion of the survey required approximately 15 to 20 minutes and was administrated by a fluent Spanish speaker. The household was excluded if consent was not obtained or the household did not have children within the specified age range. No eligible family refused study participation. Officials of the Honduran Ministry of Health approved and supported this project and the protocol was approved through Wilford Hall Medical Center, San Antonio, TX; and the Office of Research/Human Subjects Committee, South Dakota State University, Brookings, SD. Research was conducted in compliance with the Declaration of Helsinki guidelines.

2.1 Anthropometric measurements

Weight and height/length were recorded during home visits using standardized equipment and procedures (WHO, 2006). Child weight was measured without clothing to the nearest 10^{th} of a kilogram of body weight using a Seca® scale (Seca, Vogel & Halke, Germany). A child who was unable to stand on the scale was held and weight was obtained using the tare weight function. Child length was measured without shoes to the nearest 0.1 cm if the child was younger than 2 years using the infant/child Shorrboard® (Shorr Productions, Olney, MD). Height was obtained for children $\geq$ 2 years of age. World Health Organization Anthro program (WHO, 2005) was used to calculate anthropometrics. The cut-off values used to identify children as stunted was length/height-for-age < -2 z-scores (HAZ), underweight was weight-for-age < -2 z-scores (WAZ), and wasted was weight-for- length/height < -2 z-scores (WHZ) using the WHO standards (WHO, 2006). Following anthropometric data analysis, there were no outliers based on the following definitions: height-for-age < -6.0 and > +6.0, weight-for-age < -6.0 and > +5.0, and weight for height < -5.0 and > +5.0 (WHO, 2006).

2.2 Blood analysis

On-the-spot hemoglobin (Hb) was used to determine study eligibility. Hemoglobin was measured using the HemoCue Hemoglobin Photometer (HemoCue US, Mission Viejo, CA) and was adjusted for altitude (Ruız-Arguelles, 2006). Altitude adjusted age-specific cutoff Hb values of <11.0 g/dL were used to determine anemia (WHO, 2001). The households of non-anemic children were randomly assigned to the sprinkles or non-sprinkles arm. All non-anemic children of the household in the target range were enrolled. All eligible children in one household were randomized to the same arm of the study. Anemic children were not enrolled in the study, were treated with ferrous sulfate, and their names were provided to the local MoH clinic personnel for follow-up.

Finger prick blood samples were obtained from the children. A global positioning system (GPS) was used at the household to determine altitude.

Analysis of transferrin receptor (TfR) to determine iron status was obtained using dried blood spot (DBS) samples on filter paper. The use of DBS is a convenient way of collecting samples in the field compared to venous blood sampling that would require a phlebotomist, centrifugation of samples, and immediate cold storage (Flowers & Cook, 1999). Care was taken not to touch the pre-printed circles on the filter paper before, during, and after blood collection and to avoid having one blood spot flow into another spot. Following blood spot collection, filter papers were exposed to air for a short period of time to allow drying, were placed in an airtight/watertight container with a desiccant, were stored away from light and heat, and were dried overnight in the drying box. Following the drying process, the filter papers were stored in a zip-closure plastic freezer bag with desiccant and were kept at refrigerator or freezer temperature until analysis. The analysis of TfR from DBS was completed by The Craft Technologies, Inc., Wilson, NC, using the quantitative sandwich enzyme linked immunoassay (ELISA) (Erhardt et al., 2004). Iron deficiency was defined based on the manufacture's TfR assay reference. Iron deficiency anemia was defined as anemia in combination with ID.

Participants were enrolled during three separate trips to Honduras over the span of 12 months. A four month supply of sprinkles packets and pictorial and verbal instructions for use were provided for each child assigned to the sprinkles arm. The micronutrient sprinkle formula for this study contained iron (12.5 mg), zinc (5 mg), folic acid (150 µg), vitamin A (1600 I.U.), vitamin C (50 mg), and vitamin D (300 I.U.) and cost $0.025 (U.S.) per packet. Parents were asked to save the empty sachets and to return the empty and unused sachets during the four month follow-up visit as a measure of usage compliance. Measurements of Hb and TfR as well as anthropometric measurements were obtained at the initial visit and at the four and eight month intervals. Enrollees were provided Albendazol for helminthes infestation at each visit. Children found to be anemic at 4 months were started on supplemental iron therapy and were not included in the 8 month follow-up. A survey was administered at the four month follow-up visit to assess compliance, acceptability, side effects, and any logistical problems.

Statistical analysis was performed using SPSS computer software. Differences between the groups were assessed by independent samples t-test. Paired t-test was used to analyze change within groups. Chi-square test was used to compare the proportion of change in prevalence. The acceptable level of statistical significance was $P<0.05$.

3. Results

In the households visited, there were 220 children. Of these, 21 were diagnosed with anemia and were ineligible for the study. Those found to be anemic were treated and referred directly to the MoH clinic. The remaining 199 children were enrolled in the study and randomized into the sprinkles (n=114) and non-sprinkles (n=85) groups.

3.1 Baseline characteristics

The mean age was 34.66 months (± 15.31 SD), mean Hb was 12.47 g/dL (± 0.81 SD), mean TfR was 7.02 mg/L (± 2.52), mean altitude was 5,023.98 ft (± 558.57 SD) and 55% were male. The groups did not differ significantly at base-line in age, gender, Hb, TfR, weight or height; however, average altitude was significantly different ($P < 0.001$). Children within the sprinkles group were at a higher mean altitude (5134 ft vs 4876 ft). Within this study population, Hb and TfR were not significantly correlated with altitude. Of the 199 children enrolled in the study, four children (2%) did not return for the four month follow-up visit, an additional 3 children did not provide a blood sample to evaluate Hb. At the 4 month follow-up visit 20.3% of participants were anemic, treated with iron, referred to the MoH clinic and were removed from the study. At the 8 month follow-up, an additional 15.2% were anemic.

3.2 Primary outcome measures

There was no significant difference seen in mean Hb between the sprinkles and non-sprinkles groups between visits (Table 1). At the 4 and 8 month visits, 4.4% and 2.4%

respectively had IDA. The prevalence of anemia and IDA by visit for the sprinkles and non-sprinkles groups is presented in Table 2. There was no significant difference between groups for ID or IDA at 4 or 8 months.

At baseline, 23.8% of the sprinkles group and 22.8% of the non-sprinkles group were iron deficient (ID). Within children that were ID at baseline, 58.3% of the sprinkles group and 55.6% of the non-sprinkles group were no longer ID at 4 months and 60.9% of the sprinkles group and 77.8% of the non-sprinkles group were no longer ID at 8 months. There was no significant difference in TfR change from baseline to 4 or 8 months between groups (Table 1). At 8 months, 24.5% of the sprinkles group and 20.0% of the non-sprinkles group were ID. Paired T-test results for change in Hb from baseline to 4 months was 0.20 (p=0.13) for the sprinkles group and 0.31 (p<0.05) for the non-sprinkles group respectively. From baseline to 4 months there were significant paired T-test differences in TfR of -1.37 within the sprinkles group (p< 0.001) and -.076 within the non-sprinkles group (p< 0.05).

	Sprinkles (SD)	Non-Sprinkles (SD)	P-value*
Initial Hb (gm/dL)	12.45 (0.80)	12.55 (0.83)	
4 months	12.13 (1.19)	12.22 (1.26)	0.63
8 months	12.46 (1.35)	12.47 (1.17)	0.73
Overall change			0.56
Initial TfR	7.02 (2.07)	7.02 (2.39)	
4 months	8.39 (2.93)	7.78 (2.29)	0.98
8 months	7.19 (1.64)	7.02 (1.81)	0.12
Overall change			0.52

* Significance determined at P <0.05.

Table 1. Change in Mean Hemoglobin (Hb) and Serum Transferrin Receptor (TfR) between Visits for Sprinkles vs Non-Sprinkles.

	Anemia (%)*	IDA (%)*
Initial	n=199	n=182
Sprinkles	0	0
Non-Sprinkles	0	0
4 Months	n=192	n=180
Sprinkles	16.5	4.0
Non-Sprinkles	25.3	5.0
8 Months	n=132	n=123
Sprinkles	17.5	4.1
Non-Sprinkles	11.5	0

* No significant differences was seen in prevalence between Sprinkles and non-Sprinkles groups. Significance determined at P<0.05.

Note: No anemic children were enrolled in the study. If children were anemic at 4 months, they were treated and removed from the study.

Table 2. Prevalence of Anemia and Iron Deficiency Anemia (IDA) by visit for Sprinkles vs. non-Sprinkles groups.

3.3 Anthropometric measurements

There was no significant difference between baseline and 4 and 8 months in the sprinkles group compared to the non-sprinkles group when comparing change in mean height, weight, weight-for-age Z-score, height-for-age Z-score, or weight-for-height Z-score (Tables 3 & 4). There was also no significant change between groups in the prevalence of stunting, underweight or wasting (Table 5).

	Sprinkles	Non-Sprinkles	P-value*
Initial weight (kg)	11.74	12.25	
4 months	12.54	12.89	0.63
8 months	13.01	13.59	0.27
Overall change			0.25
Initial height (cm)	84.45	85.94	
4 months	87.05	88.65	0.62
8 months	89.82	91.07	0.35
Overall change			0.35

*Significance determined at P <0.05.

Table 3. Change in Mean Weight and Height between Visits for Sprinkles vs Non-Sprinkles.

	Sprinkles	Non-Sprinkles	P-value*
Initial weight-for-age Z-score	-0.99	-0.91	
4 months	-0.98	-1.0	0.89
8 months	-1.09	-0.98	0.73
Overall change			0.68
Initial height-for-age Z-score	-2.04	-1.99	
4 months	-2.09	-2.05	0.75
8 months	-2.07	-2.09	0.94
Overall change			0.96
Initial weight-for-height Z-score	0.20	0.31	
4 months	0.29	0.25	0.84
8 months	0.17	0.34	0.66
Overall change			0.48

*Significance in mean change between time intervals for Sprinkles vs non-Sprinkles. Significance determined at P<0.05.

Table 4. Change in Mean Weight-for-Age Z-score, Height-for-Age Z-score, and Weight-for-Height Z-score by Visit.

	Stunting (%)*	Underweight (%)*	Wasting (%)*
Initial (n=195)			
Sprinkles	48.6	16.2	0.9
Non-Sprinkles	54.8	14.3	0
All	51.3	15.4	0.5
4 Months (n=187)			
Sprinkles	51.9	13.5	0
Non-Sprinkles	54.2	10.8	0
8 Months (n=168)			
Sprinkles	46.3	14.7	0
Non-Sprinkles	58.9	9.6	1.4

* No significant difference was seen in prevalence between Sprinkles and non-Sprinkles groups. Significance determined at P<0.05.

Table 5. Prevalence of Stunting, Underweight and Wasting by Visit for Sprinkles vs. Non-Sprinkles groups
Stunting = height-for-age Z-score <-2; Underweight = weight-for-age <-2 Z-scores; wasting = weight-for-age <-2 Z-scores.

3.4 Sprinkles use and acceptability

Based on parental responses and counting of the returned empty sprinkles packets, children who received sprinkles used an average 108 of 120 (90%) packets. The number of packets consumed ranged from 24 to 120. Of children who received sprinkles, 55% used all 120 packets, and 86% used more than 100 packets. The majority of families, 92%, used seven packets per week with a range from 3 to 7 packets per week. Parents reported that only 3 children (2.75%) disliked food with sprinkles added, 1 child had diarrhea, and one had difficulty in administering sprinkles. Rice, beans and soup were the foods most commonly mixed with the sprinkles. Sprinkles in food were not noticed by 54.1% of the children, 32.1% liked the food better with the sprinkles and 13.8% did not like the food with sprinkles. They were found easy to use in food preparation by 98.2% of the families and one parent reported that it was difficult to use daily and another reported that it took added time. All of the participants reported that they would continue to use the sprinkles if they were delivered free through the MoH clinic.

4. Discussion

4.1 Anemia and iron status

Only three other studies were located that reported information on sprinkles trials in subjects that were not anemic at the beginning of the study (Lundeen et al., 2010; Giovannini et al., 2006; Zlotkin et al., 2003a). Daily use of sprinkles for 2 months in anemic (72%) and non-anemic children ages 6 to 36 months revealed that within the non-anemic children receiving sprinkles 28% became anemic compared to 50% in the non-sprinkles group (Lundeen et al., 2010).
A 12 month double-blind, placebo-controlled trial in children aged 6 months by Giovannini et al. (2006) included both anemic and non-anemic children within the analysis (mean

baseline Hb $\geq$ 10.1 g/dL) and did not report results for non-anemic children only. Prevalence of anemia was significantly reduced in infants receiving either of the sprinkles supplements (Giovannini et al., 2006). A 6 month study performed by Zlotkin et al. looked at the effectiveness of microencapsulated iron (II) fumarate sprinkles with and without vitamin A, iron (II) sulfate drops or placebo sprinkles in preventing the recurrence of anemia in non-anemic (Hb $\geq$ 10.0 g/dL) children between the ages of 8-20 months (2003a). From baseline to the end of the supplementation period, there were no significant changes seen in the mean Hb or ferritin within the four groups and the children that became anemic were equally distributed among groups (Zlotkin et al., 2003a). Within the study, 82.4% of the children from all four groups remained in their non-anemic status, while 77.1% of children maintained their non-anemic status during the post-supplementation period (Zlotkin et al., 2003a). Zlotkin et al. (2003a) concluded that their findings do not support the continued use of long-term prophylactic iron supplementation to maintain iron status in children treated previously for IDA. Within the current study, there were also no significant changes in Hb or iron status between the sprinkles or non-sprinkles groups. Though the change in Hb over the study and the anemia prevalence was not significantly different between groups, a decrease in Hb is a late finding in IDA (Provan, 1999). An additional study being conducted by Bilenko et al. (2010) is similar to the current study in that the objective is to evaluate the efficacy of sprinkles in primary prevention of iron and other micronutrient deficiencies; however, results of the study are pending.

Studies performed in several countries have shown that sprinkles are effective in treating IDA, and that sprinkles are more effective and more easily administered than iron drops due to less side effects (Hirve et al., 2007; Schauer & Zlotkin, 2003; Zlotkin et al., 2004). Efficacy has been shown with sprinkles including formulations containing relatively low amounts of iron, and better results were achieved with daily dosing versus weekly dosing (Christofides et al., 2006; Giovannini et al., 2006; Menon et al., 2007; Shareiff et al., 2006). An analysis of studies that used dispersion of micronutrients in sachets completed by Horton et al. (2010) resulted in an increase in Hb concentration of 0.057 g/dL and IDA was reduced as compared to controls. When allowing flexible administration of micronutrient sprinkles compared to daily administration Hb was significantly higher in the group allowed flexible administration and resulted in an anemia prevalence decrease by 65% vs. 51% (Ip et al., 2009).

In comparison with other studies (Adu-Afarwuah et al., 2008; Giovannini et al., 2006; Zlotkin et al., 2003a), this study attempted to determine the utility of sprinkles to prevent anemia in non-anemic children. The prevention of anemia within children can lower the risk of developing cognitive and physical impairments (Grantham-McGregor & Ani, 2001). Giovannini et al. compared the efficacy of iron plus folic acid and zinc, iron plus folic acid alone, or a placebo and within the two sprinkle supplement groups there was no significant change in the rate of ID; however, the occurrence of ID increased in the placebo group (Giovannini et al., 2006).

A study completed by Adu-Afarwuah et al. compared the effectiveness of sprinkles, crushable Nutritabs, fat-based Nutributter, or a placebo on Ghanaina infants from 6 to 12 months of age (2008). This study showed that the risk of ID or anemia was significantly lower in the three intervention groups compared to the control group (Adu-Afarwuah et al., 2008). A meta-analysis evaluating the effect of multiple micronutrients in micronutrient deficient children, resulted in small but significant improvements in Hb (effect size=0.39) (Allen et al., 2009). In a randomized comparison of the effects of sprinkles, foodlets and iron drops, iron status improved in all treatment groups though there was no difference in change in anemia prevalence; however, drops resulted in significantly greater changes in Hb and serum ferritin (Samadpour et al., 2011).

Other studies determined the effectiveness chewable tablets in the prevention of iron deficiency (Smuts et al., 2005; Lopez de Romaña et al., 2005). Children from South Africa, Peru, Vietnam, and Indonesia were randomly assigned to one of four intervention groups: a daily placebo, a weekly multiple micronutrient supplement, a daily multiple micronutrient supplement, or a daily iron supplement and results showed that the overall prevalence of anemia decreased over the course of the study in all four intervention groups (Smuts et al., 2005). Iron deficiency increased in the placebo and weekly micronutrient supplement groups while decreasing in the daily iron and daily micronutrient supplement groups (Smuts et al., 2005). Lopez de Romaña et al. determined the efficacy of different micronutrient supplements in preventing growth failure, anemia, and other micronutrient deficiencies in Peruvian infants (2005). Infants between the ages of 6 to 12 months were randomly assigned to receive a placebo, a weekly dose of multiple micronutrients, a daily dose of multiple micronutrients, or a daily dose of iron (Lopez de Romaña et al., 2005). The prevalence of anemia decreased in all intervention groups; however, the decrease was not significant in the placebo group and anemia was best controlled by daily micronutrient supplements containing iron (Lopez de Romaña et al., 2005).

Additional studies have included treatment for anemic children (Rosado et al., 2010; Christofides et al., 2006; Menon et al., 2007; Zlotkin et al., 2004; Zlotkin et al., 2001). The use of sprinkles in the treatment of anemia has been shown to be successful within children and infants (De-Regil et al., 2011; Zlotkin et al., 2001; Zlotkin et al., 2003b). In a compilation of six studies, home fortification with sprinkles resulted in anemia reduction by 31% (RR 0.69) and in four studies, iron deficiency was reduced by 51% (RR 0.49) (De-Regil et al., 2011). In an efficacy study of different strategies to treat anemia in children, all treatments significantly increased Hb and total iron concentration; however, ferritin did not change significantly (Rosado et al., 2010). A study by Zlotkin et al. looked at the treatment of anemic children ages between 6 months to 18 months in Ghana and demonstrated that over 50% of children treated with sprinkles were successfully cured (Zlotkin et al., 2001). Menon et al. showed a drop in anemia prevalence from 52.3% to 28.3% in children receiving sprinkles with the fortified wheat-soy blend (WSB) compared to the WSB only, which showed an increase in anemia prevalence from 37% to 45% (2007). Christofides et al. found that various doses of sprinkles and iron drops garnered significant changes in Hb concentration and the prevalence of IDA decreased significantly over the course of the study (2006).

4.2 Anthropometric measurements

Higher rates of stunting are seen in Honduras than in its neighboring countries and income peers (World Bank, 2010). Within Honduran children under five years of age, 29% suffer from stunting, 11% from underweight and 1% from wasting (UNICEF, 2010). Growth parameters measured in Honduran children ages 12 to 71 months during the 1996 National Micronutrient Survey revealed that 38% were stunted, 24% were underweight, and 1% were wasted (Nestel et al., 1999). The prevalence of stunting, underweight and wasting within rural Honduran children ages 6 to 60 months was 57%, 33%, and 3.5% respectively (Tolson et al., 2010). Analysis of the 2006 Honduran Demographic and Health Survey data revealed that children that were wanted and had adequate parental care resulted in significant effects on children's height-for-age growth status (Sparks, 2011).

In a pooled analysis of 55 studies completed by Horton et al. (2010) they noted no benefit of iron supplementation on growth. Multi-micronutrient fortified energy-dense, fat-based Nutributter resulted in significantly greater WAZ and HAZ, than the use of micronutrient home fortification in either sprinkles or crushed tablets (Adu-Afarwuah et al., 2007). Even though sprinkles was successful in treating anemia in infants and young children, it did not promote catch-up growth in a stunted and wasted population in Ghana (Zlotkin et al., 2003a). Prevention of growth faltering was not noted in a double-blind, masked, controlled trial in infants provided iron or multiple micronutrients as compared to placebo (Lopez de Romana et al., 2005). When pooling data from four countries, a daily micronutrient supplement proved the most effective in promoting significant weight gain; however, there was no difference in height gain (Smuts et al., 2005). A compilation of eight trials (3748 participants) on the use of micronutrient powders in home fortification of foods showed no effect on growth (De-Regil et al., 2011). A four month evaluation of iron supplements in varying forms provided to anemic children also resulted in no difference in growth parameters (Rosado et al, 2010). In a meta-analysis evaluating the effect of multiple micronutrients on child growth, the intervention resulted in small but significant improvements in height/length (effect size=0.13) and weight (effect size= 0.14) (Allen et al., 2009). In a 4 month trial comparing efficacy of sprinkles, foodlets and drops, there was no significant difference in anthropometric measurements, or change in prevalence of underweight, stunting and wasting between treatment groups (Samadpour et al, 2011).

4.3 Sprinkles use and acceptability

The overall use of sprinkles within this study was well accepted with 55% of participants using all of the packets provided for the 4 month intervention. Lundeen et al. (2010) found that on average 45 of 60 sprinkles packets were consumed with 38.8% of participants consuming all 60 packets and 83.1% of children eating the entire portion of food mixed with the sprinkles. In a study conducted by Loechl et al. (2009), 63% of mothers reported using the sprinkles every day based on survey results and 86% based on exit interview results.

Other studies have compared alternative treatments of anemia to sprinkles (Christofides et al., 2006). One study showed that 92.9% of children had a strong dislike for the iron drops while only 6.5% objected to the consumption of sprinkles (Zlotkin et al., 2003a). Hirve et al. (2007) found that the side effects such as diarrhea, vomiting, staining of teeth, and stool discoloration were all significantly higher in the iron drops group than compared to sprinkles. In a study conducted by Adu-Afarwuah et al. (2008), 96.9% of mothers thought it was easy to give the sprinkles supplement, 89.6% said that the child accepted the food well, 95.9% did not have any major problems feeding the sprinkles to the child and 100% had a good impression of the sprinkles supplement. Allowing flexible administration vs. daily administration of micronutrient sprinkles improved adherence and was more acceptable (Ip et al., 2009). In an evaluation of iron drops vs. sprinkles, both groups had generally pour adherence and overall, there was no significant difference between groups (Geltman et al., 2009). Eighty percent of respondents in the sprinkles group vs. 69% in the drops group would use them again; however, the difference was not significant. There was a significant difference between the sprinkles vs. the drops group of respondents being concerned about using a new products and about the product's safety (Geltman et al., 2009).

4.4 Use of anti-parasitic medication

At each home visited anti-parasitic medication for children > 2 years of age was provided per MoH protocol. Because helminth infection is common in Honduras (Smith et al., 2001) and is a significant contributing factor to anemia (Bethony et al., 2006; Brooker et al., 2006), this intervention itself likely impacted the prevalence and severity of anemia in both groups (Stoltzfus et al., 1998) thus confounding results focused on the effect of sprinkles. It is important to note that at end of the study, the percentage of children with anemia in each group was less than the general prevalence of anemia among Honduran children.

Study strengths included the large number of participants in this randomized design used to determine efficacy of sprinkle supplements for the prevention of anemia in children ages 6 to 60 months. The large number of participants helps to prove the reliability of the effectiveness of the sprinkles compared to no treatment (Brooker et al., 2006). Altitude was collected at the household for accurate determination of the participants altitude adjusted Hb. Household data collection was convenient for participants. As a measure of compliance, participants were required to turn in empty and leftover sprinkle packets at the 4 month follow-up visit. The field friendly DBS method allowed measurement of iron status and eliminated the requirements for venipucture, a highly trained phlebotomist, centrifugation, and immediate ultra cold storage. Limitations of the study include the DBS were obtained in a field environment and they were not available for all participants due to parental refusal or inadequate blood sample size for analysis. Regarding sprinkle acceptability, parent reports were relied upon and may not be entirely accurate. The areas where the study was conducted were assigned by the Honduran MoH and included rural homes with low socioeconomic status. While this may be a representative sample for much of the population in Honduras, our results may not be applicable to children in different settings.

5. Strategies to address anemia and iron deficiency

If the MDG of reducing the proportion of people suffering from hunger is to be achieved by 2015, nutrition must be given higher priority and should include simple, cost-effective measures delivered particularly from conception to two years after birth (United Nations, 2011). These measures should incorporate improved maternal nutrition and care, breastfeeding within one hour of birth, exclusive breastfeeding for the first 6 months of life, and timely, adequate, safe, and appropriate complementary feeding and micronutrient intake between 6 and 24 months of age (United Nations, 2011).

A lifecycle approach to the problem is required to control iron deficiency and should include effective public health programs that consider the whole reproductive cycle and create a combination of strategies that are complementary and comprehensive across vulnerable periods (Stoltzfus, 2011). Anemia prevention and control strategies include: 1) increased food diversity with increased iron bioavailability and improved dietary quality and quantity; 2) biofortification, fortification of staples with iron, open market fortification of processed food, targeted fortification; 3) iron and folic acid supplementation to high-risk groups; 4) disease control; and 5) improved knowledge and education on anemia prevention and control for policy makers and the general public (Balarajan et al., 2011).

When implementing large-scale programs it is essential to assess the coverage, compliance and effectiveness and the programs should promote a food-based approach, including fortification of staple foods and condiments for the general population as well as home fortificants for specific target groups, since they are more sustainable, less perceived as treatment of a condition and are applicable for use in malaria-endemic areas (Badham et al., 2007). Prevention of ID requires policy and program guidance and working closely with decision makers about the what, when and how to implement and manage the program (Lutter, 2008). The widespread endemic of iron deficiency can be approached through a number of options which include dietary measures, fortification, supplementation, and treatment of infections/infestations and it is essential to consider that an effective resolution may vary by population subgroups, region and country (Milman, 2011). Using existing maternal and child health and nutrition programs to distribute micronutrient sprinkles and educate parents on their use is feasible and acceptable (Loechl et al., 2009).

Several recommendations from the World Bank Scaling up Nutrition paper (Horton et al., 2010) that can be implemented in partnership with the health sector in support of reducing the prevalence of anemia and iron deficiency include: 1) the use of multiple micronutrient powders and deworming drugs in children under the age of five years of age; 2) complimentary and therapeutic feeding interventions that provide micronutrient fortified and/or enhanced complementary foods for the prevention and treatment of moderate malnutrition among children 6-23 months of age; 3) promotion of breastfeeding, appropriate complementary feeding practices, and proper hygiene; and 4) iron fortification of staple foods for the general population.

Public health interventions addressing iron deficiency are one of the most cost effective with a cost-benefits ratio for iron programs estimated at 200:1 (Badham et al., 2007). On a worldwide scale, it would take an additional $10.3 billion (U.S.) in public resource support to begin successfully alleviating undernutrition on a worldwide scale benefiting over 360 million (Horton et al., 2010). On a nationwide basis in Honduras, it is estimated that it would take $6 million (U.S.) per year to scale up core micronutrient nutrition interventions and the costs are as low as $0.05-8.46 per person annually with a return on investment as high as 6-30 times the cost (World Bank, 2010; Horton et al., 2010). To alleviate much of iron deficiency's burden, iron fortification of staple foods would cost $0.20 (U.S.) per person per year, deworming cost would be $0.25 (U.S.) per child 24–59 month per round per year, and iron-folic acid supplements for pregnant women would cost approximately $2.00 (U.S.) per pregnancy (Horton et al., 2010). For sprinkles supplementation targeted to children 6–12 mo, it is estimated that cost per DALY saved could be as low as $12 with a benefit: cost ratio of 37:1 (Horton, et al., 2006). When determining the cost effectiveness of home-fortification programs in a low income country with a high infant mortality rate and high prevalence of anemia, it is estimated that cost per DALY saved is $12.2 and the present value of the gain in earnings is $37 for each dollar spent on the micronutrient sprinkles program (Sharieff et al., 2006).

Iron fortification continues to be evaluated in a variety of food stuffs for efficacy and acceptance (Karn et al., 2011; Angeles-Agdeppa et al., 2011; Varma et al., 2007; Andersson et al., 2008; Adu-Afarwuah et al., 2008; Wegmuller et al., 2006; Hurrell et al., 2010; Faber et al., 2005; Torrejon et al., 2004); however, it is essential that the fortification efforts are supported politically, adequately marketed, cost effective and have long-term commercial commitment (Angeles-Agdeppa et al., 2011). Iron supplementation and fortification are effective in controlling iron deficiency in populations and bioavailability of the iron is an important factor, iron status should be used and monitored to assess fortification requirements and efficacy (Zimmermann & Hurrell, 2007).

When implementing anemia prevention strategies the focus should be on preschoolers and adolescent women and on integrated public health programs (Boy et al., 2009). Lutter (2008) recommends iron prevention programs targeted during pregnancy, at birth, the immediate postnatal period and during the first 24 months of life and to not underestimate the challenges of delivery through the public health systems. Recommended practices for children ages 6-24 months include iron rich complementary foods, micronutrient supplements (medicinal iron supplements, micronutrient sachets, fortified complementary foods, lipid-based spreads) and deworming (Lutter, 2008).

National decision makers in each country are responsible to select the type and quantity of micronutrients added to foodstuffs and their decision should be based on their country's situation. The WHO recommends designing flour fortification programs based on four average wheat flour consumption ranges, the type of iron fortification compound (NaFeEDTA, ferrous sulfate, ferrous fumarate, or electrolytic iron) and flour extraction rate (low or high) (Hurrell et al., 2010). Wheat flour fortification programs were evaluated in 78 countries and only nine of the national programs could potentially result in a significant positive impact on iron status and that updated legislation is required to maximize the potential of meeting iron needs through fortification of wheat flour (Hurrell et al., 2010).

Genetic engineering of grains to increase iron content and bioavailability and selective plant breeding are also avenues being explored to combat iron deficiency (Zimmermann & Hurrell, 2007; Lucca et al., 2001 & 2006). Biofortified crops complement fortification and supplementation programs and are an option that provides a rural-based intervention that reaches more remote populations and then transfers into urban populations as production surpluses are marketed (Bouis et al., 2011). New iron fortification technologies that eliminate detrimental effects on taste, appearance, and product stability and that do not interfere with iron bioavailability show promising results (Mehansho, 2006).

Sustainable strategies for the prevention and control of iron deficiency require food based and non food based approaches incorporating agriculture, health, commerce, industry, education, communication and local nongovernmental organizations (Lokeshwar et al., 2011). Barriers to effective implementation of anemia prevention and control strategies include insufficient political priority, lack of resource commitment, lack of institutional and operational capacity, restricted financial access, poor awareness of the magnitude of disease burden, and lack of knowledge and education (Balarajan et al., 2011).

Strategic research is required to address the effective prevention and control of iron deficiency and its consequences in young children living in low-income countries and should address: 1) scaling up known effective interventions, 2) evaluating cost-effective alternatives that are likely to work, 3) efficacy research to discover promising practices that lack proven interventions, and 4) determining physiological processes and mechanisms underlying the risks and benefits of supplemental iron for children exposed to infectious diseases (Stoltzfus, 2008).

6. Conclusions

Within this study of non-anemic rural Honduran children ages 6 to 60 months, there were no statistically significant differences between the sprinkles and non-sprinkles groups when comparing change in mean Hb, TfR, and anthropometric measurements or prevalence in anemia, iron deficiency, stunting, underweight and wasting. However, at the end of the study, prevalence of anemia in each study group was less than the general prevalence of anemia for Honduran children. Sprinkle compliance was good; they were well tolerated by children and were accepted among the participating families. Additional research is required to determine efficacy of sprinkles for anemia prevention in larger populations and over longer periods of time.

7. Acknowledgements

Funding was provided by Wilford Hall Medical Center, San Antonio, TX; South Dakota State University Agricultural Experiment Station, Brookings, SD; and the Center for Disaster and Humanitarian Assistance Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD. Micronutrient sprinkles were provided by Heinz Company, Canada.

8. References

Adu-Afarwuah S, Lartey A, Brown, KH, Zlotkin S, Briend A, Dewey K. (2008). Home fortification of complementary foods with micronutrient supplements is well accepted and has positive effects on infant iron status in Ghana, *Am J Clin Nutr*, 87:929-38

Adu-Afarwuah S, Lartey A, Brown, KH, Zlotkin S, Briend A, Dewey K. (2007). Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: Effects on growth and motor development, *Am J Clini Nutr*, 87:929-38

Albalak R, Ramakrishnan U, Stein AD, Van der Haar F, Haber MJ, Schroeder D, Martorell R. (2000). Co-Occurrence of Nutrition Problems in Honduran Children, *J Nutr*, 130:2271-2273

Allen LH, Peerson JM, Olney DK. (2009). Provision of multiple rather than two or fewer micronutrients more effectively improves growth and other outcomes in micronutrient-deficient children and adults, *J Nutr*, 139(5):1022-30

Andersson M, Thankachan P, Muthayya S, Goud RB, Kurpad AV, Hurrell RH, Zimmermann MB. (2008). Dual fortification of salt with iodine and iron: a randomized, double-blind, controlled trial of micronized ferric pyrophosphate and encapsulated ferrous fumarate in southern India, *Am J Clin Nutr*, 88(5):1378-1387

Angeles-Agdeppa I, Saises M, Capanzana M, Juneja LR, Sakaguchi N. (2011). Pilot-scale commercialization of iron-fortified rice: effects on anemia status, *Food Nutr Bull*, 32(1):3-12

Badham J, Zimmermann MB, Kraemer K (ed). (2007). *The Guidebook Nutritional Anemia*. Sight and Life Press, Basel, Switzerland. (51 pages)

Balarajan Y, Ramakrishnan U, Ozaltin E, Shankar AH, Subramanian S. (2011). Anaemia in low-income and middle-income countries, *Lancet.* 2011 Aug 1, [Epub ahead of print]

Bethony J, Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, Hotez PJ. (2006). Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm, *Lancet*, 367:1521-32

Bilenko N, Belmaker I, Vardi H, Fraser D. (2010). Efficacy of multiple micronutrient supplementations on child health: study design and baseline characteristics, *Isr Med Assoc J*, 12(6):342-7

Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, Mathers C, Rivera J. (2008) Maternal and child undernutrition: global and regional exposures and health consequences, *Lancet*, 371:243-60

Bouis HE, Hotz C, McClafferty B, Meenakshi JV, Pfeiffer WH. (2011). Biofortification: a new tool to reduce micronutrient malnutrition, *Food Nutr Bull*, 32(1 Suppl):S31-40

Boy E, Mannar V, Pandav C, de Benoist B, Viteri F, Fontaine O, Hotz C. (2009). Achievements, challenges, and promising new approaches in vitamin and mineral deficiency control, *Nutr Rev*, 67:S24-30

Brooker S, Clements ACA, Hotez PJ, Hay SI, Tatem AJ, Bundy DAP, Snow RW. (Nov 2006). The co-distribution of Plasmodium falciparum and hookworm among African schoolchildren, *Malaria Journal*, 5(99), Accessed July 7, 2009, Available at http:www.malaria journal.com/ content/5/1/99

Carter RC, Jacobson JL, Burden MJ, Armony-Sivan R, Dodge NC, Angelilli ML, Lozoff B, Jacobson SW. (2010). Iron deficiency anemia and cognitive function in infancy, *Pediatrics*, 126(2):e427-34. Epub 2010 Jul 26

Christofides A, Asante KP, Schauer C, Sharieff W, Owusu-Agyei S, Zlotkin S. (2006). Multi-micronutrient sprinkles including a low dose of iron provided as microencapsulated ferrous fumarate improves haematologic indices in anaemic children: a randomized clinical trial, *Matern Child Nutr*, 2(3):169-80

Corapci F, Radan A, Lozoff B. (2006). Iron deficiency in infancy and mother-child intereaction at 5 years, *J Dev Behav Pediatr*, 27(5):371-378

Darnton-Hill I, Mora JO, Weinstein H, Wilbur S, Ritu Nalubola P. (1999). Iron and folate fortification in the Americas to prevent and control micronutrient malnutrition: An analysis, *Nutrition Reviews*, 57(1): 25-31

Darnton-Hill I. (1998). Overview: Rationale and elements of a successful food-fortification programme, *Food Nutr Bull*, 19(2):92-100

Dary O. (2007). The importance and limitations of food fortification for the management of nutritional anemia. In: Badham J, Zimmermann MB, Kraemer K (eds). *The Guidebook Nutritional Anemia*. Sight and Life Press, (pages 42-43)

De-Regil LM, Suchdev PS, Vist GE, Walleser S, Peña-Rosas JP. (2011). Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age, *Cochrane Database Syst Rev*, Sep 7;9:CD008959 (83 pages)

Dewey KG, Cohen RJ, Rivera LL, Brown KH. (1998). Effects of age of introduction of complementary foods on iron status of breast-fed infants in Honduras, *Am J Clin Nutr*, 67: 878-84

Dewey KG, Cohen RJ, Brown KH. (2004). Exclusive breast-feeding for 6 months, with iron supplementation, maintains adequate micronutrient status among term, low-birthweight, breast-fed infants in Honduras, *J Nutr*, 134:1091-98

Erhardt, JG, Estes, JE, Pfeifer, CM, Biesalski, HK, Craft, NE. (2004). Combined measurement of ferritin, soluble transferrin receptor, retinol binding protein, and C-reactive protein by an inexpensive, sensitive, and simple sandwich enzyme-linked immunosorbent assay technique, *J Nutr*, 134: 3127-32

Faber M, Kvalsvig JD, Lombard CJ, AJ Spinnler Benadé. (2005). Effect of a fortified maize-meal porridge on anemia, micronutrient status, and motor development of infants, *Am J Clin Nutr*, 82(5):1032-1039

Finch CA, Cook JD. (1984). Iron Deficiency, *Am J Clini Nutr*, 39:471-77

Flowers CH, Cook JD. (1999). Dried plasma spot measurements of ferritin and transferrin receptor for assessing iron status, *Clini Chem*, 45(10):1826-32

Geltman PL, Hironaka LK, Mehta SD, Padilla P, Rodrigues P, Meyers AF, Bauchner H. (2009). Iron supplementation of low-income infants: a randomized clinical trial of adherence with ferrous fumarate sprinkles versus ferrous sulfate drops, *J Pediatr*, 154(5):738-43

Giovannini M, Sala D, Usuelli M, Livio L, Francescato G, Braga M, Radaelli G, Riva E. (2006). Double-blind, placebo-controlled trial comparing effects of supplementation with two different combinations of micronutrients delivered as sprinkles on growth, anemia, and iron deficiency in cambodian infants, *J Pediatr Gastroenterol Nutr*, 42(3):306-12

Grantham-McGregor S, Ani C. (Feb 2001). A review of studies on the effect of iron deficiency on cognitive development in children, *J Nutr*, 131(2S-2):649S-666S; discussion 666S-668S

Hijmans CT, Grootenhuis MA, Oosterlaan J, Heijboer H, Peters M, Fijnvandraat K. (2011). Neurocognitive deficits in children with sickle cell disease are associated with the severity of anemia, *Pediatr Blood Cancer*, 57(2):297-302

Hirve S, Bhave S, Bavdekar A, Naik S, Pandit A, Schauer C, Christofides A, Hyder Z, Zlotkin S. (2007). Low dose 'Sprinkles'-- an innovative approach to treat iron deficiency anemia in infants and young children, *Indian Pediatr*, 44(2):91-100

Horton S, Shekar M, McDonald C, Mahal A, Brooks JK. (2010). *Scaling Up Nutrition: What Will it Cost*? World Bank (136 pages)

Horton S. (2006). The economics of food fortification, *J Nutr*, 136:1068–1071

Horton S, Ross J. (2003). The economics of iron deficiency, *Food Policy*, 28:51-75

Hurrell R, Ranum P, De Pee S, Biebinger R, Hulthen L, Johnson Q, Lynch S. (2010). Revised recommendations for iron fortification of wheat flour and an evaluation of the expected impact of current national wheat flour fortification programs, *Food Nutr Bull*, 31(1) S7-S21

Ip H, Hyder SM, Haseen F, Rahman M, Zlotkin SH. (2009). Improved adherence and anaemia cure rates with flexible administration of micronutrient sprinkles: a new public health approach to anaemia control, *Eur J Clin Nutr*, 63(2):165-72

Karn SK, Chavasit V, Kongkachuichai R, Tangsuphoom N. (2011). Shelf stability, sensory qualities, and bioavailability of iron-fortified Nepalese curry powder, *Food Nutr Bull*, 32(1):13-22

Loechl CU, Menon P, Arimond M, Ruel MT, Pelto G, Habicht JP, Michaud L. (2009). Using programme theory to assess the feasibility of delivering micronutrient Sprinkles through a food-assisted maternal and child health and nutrition programme in rural Haiti, *Maternal Child Nutr*, 5:33-48

Lokeshwar MR, Mehta M, Mehta N, Shelke P, Babar N. (2011). Prevention of iron deficiency anemia (IDA): How far have we reached? *Indian J Pediatr*, 78(5):593-602

López de Romaña G, Cusirramos S, López de Romaña D, Gross R. (2005). Efficacy of multiple micronutrient supplementation for improving anemia, micronutrient status, growth, and morbidity of Peruvian infants, *J Nutr*, 135(3):646S-652S

Lozoff B. (2011). Early iron deficiency has brain and behavior effects consistent with dopaminergic dysfunction, *J Nutr*, 141: 740S–746S

Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. (2006). Long-lasting neural and behavioral effects of iron deficiency in infancy, *Nutr Rev*, 64(5 Pt 2):S34-43; discussion S72-91

Lucca P, Hurrell R, Potrykus I. (2001). Genetic engineering approaches to improve the bioavailability and the level of iron in rice grains, *Theor Appl Genet*, 102:392–397

Lucca P, Poletti S, Sautter C. (2006). Genetic engineering approaches to enrich rice with iron and vitamin A. *Physiologia Plantarum*, 126: 291-303

Lundeen E, Schueth T, Toktobaev N, Zlotkin S, Ziauddin Hyder SM, Houser R. (2010). Daily use of Sprinkles micronutrient powder for 2 months reduces anemia among children 6 to 36 months of age in the Kyrgyz Republic: a cluster-randomized trial, *Food Nutr Bull*, 31:446-460

Lutter CK. (2008). Iron deficiency in young children in low-income countries and new approaches for its prevention, *J Nutr*, 138:2523-2528

Madan N, Rusia U, Sikka M, Sharma S, Shankar N. (2011). Developmental and neurophysiologic deficits in iron deficiency in children, *Indian J Pediatr*, 78(1):58-64

McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. (2009). Worldwide prevalence of anaemia, WHO vitamin and mineral nutrition information system, 1993–2005, *Public Health Nutr*, 12: 444–54

Mehansho H. (2006). Iron fortification technology development: New approaches, J Nutr, 136:1059-1063

Menon P, Ruel MT, Loechl CU, Arimond M, Habicht JP, Pelto G, Michaud L. (2007). Micronutrient sprinkles reduce anemia among 9- to 24-mo-old children when delivered through an integrated health and nutrition program in rural Haiti, *J Nutr*, 137(4):1023-30

Milman N. (2011). Anemia- still a major health problem in many parts of the world! *Ann Hematol*, 90:369-377

Nestel P, Melara A, Rosado J, Mora JO. (1999). Vitamin A deficiency and anemia among children 12-71 months old in Honduras, *Pan Am J Public Health*, 6(1): 34-43

Oxford Department of International Development. (2010). Oxford Poverty and Human Development Initiative (OPHI). Country Briefing: Honduras

Provan D. (1999). Mechanisms and management of iron deficiency anemia, *Br J Haem*, 105:19-26

Rosado JL, González KE, Caamaño Mdel C, García OP, Preciado R, Odio M. (2010). Efficacy of different strategies to treat anemia in children: a randomized clinical trial, *Nutr J*, 9:40

Ruız-Arguelles G (2006). Altitude above sea level as a variable for definition of anemia. *Blood,* 108, 2131-2132

Samadpour K, Long KZ, Hayatbakhsh R, Marks GC. (2011). Randomised comparison of the effects of Sprinkles and Foodlets with the currently recommended supplement (Drops) on micronutrient status and growth in Iranian children, *Eur J Clin Nutr*, doi: 10.1038/ejcn.2011.124. [Epub ahead of print]

Schauer C, Zlotkin SH. (2003). "Home-fortification" with micronutrient sprinkles—A new approach for the prevention and treatment of nutritional anemias, *J Paediatr Child Health*, 8:87–90

Sharieff W, Yin SA, Wu M, Yang Q, Schauer C, Tomlinson G, Zlotkin S. (2006). Short-term daily or weekly administration of micronutrient sprinkles has high compliance and does not cause iron overload in Chinese schoolchildren: a cluster-randomized trial, *Public Health Nutr*, 9(3):336-44

Sharieff W, Horton SE, Zlotkin S. (2006). Economic gains of a home fortification program: evaluation of "Sprinkles" from the provider's perspective, *Canadian J Pub Health*, 97:20-23

Smith HM, DeKaminsky RG, Niwas S, Soto RJ, Jolly PE. (Apr 2001). Prevalence and intensity of infections of Ascaris lumbricoides and Trichuris trichiura and associated socio-demographic variables in four rural Honduran communities, Mem Inst Oswaldo Cruz, Rio de Janeiro, 96(3):303-14

Smuts CM, Lombard CJ, Spinnler Benade AJ, Dhansay MA, Berger J, Hop LT, Lopez de Romaña G, Untoro J, Karyadi E, Erhardt J, Gross R. (2005). Efficacy of a foodlet-based multiple micronutrient supplement for preventing growth faltering, anemia, and micronutrient deficiency of infants: the four country IRIS trial pooled data analysis, *J Nutr*, 135:631S-638S

Sparks CS. (2011). Parental investment and socioeconomic status influences on children's height in Honduras: an analysis of national data, *Am J Hum Biol*, 23:80-88

Sprinkles Global Health Initiative. (2008). Micronutrient sprinkles for use in infants and young children: guidelines on recommendations for use and program monitoring and evaluation. Accessed Sept 20, 2011, Available from: http://sghi.org/resource_centre/GuidelinesGen2008.pdf

Stoltzfus RJ, Albonico M, Chwaya HM, Tielsch JM, Schulze KJ, Savioli L. (1998). Effects of the Zanzibar school-based deworming on iron status of children, *Am J Clin Nutr*, 68:179-86

Stoltzfus RJ, Mullany L, Black RE. (2004). Iron deficiency anaemia. In: Ezzati M, Lopez AD, Rodgers A, Murray CLJ, eds. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Geneva: World Health Organization, 163–209

Stoltzfus RJ. (2008). Research needed to strengthen science and programs for the control of iron deficiency and its consequences in young children, *J Nutr*, 138:2542-2546

Stoltzfus RJ. (2011). Iron interventions for women and children in low-income countries, *J Nutr*, 141:756S-762S

Tolson DJ, Kemmer TM , Lynch J, Lougee D, Aviles R, Amador WE, Duron CA, Guifarro Fino RO. (2010). Identifying children at risk for nutritional crisis in rural Honduras, *J Hunger Env Nutr*, 5:1, 13-22

Torrejon CS, Duran-Castillo C, Hertrampf E, Ruz M. (2004). Zinc and iron nutrition in Chilean children fed fortified milk provided by the Complementary National Food Program, *Nutrition*, 20:177-80

Trowbridge, F. (2002). Prevention and control of iron deficiency: priorities and action steps, *J Nutr*, 132:880S-882S

United Nations. (2011). *Millennium Development Goals Report*. New York (72 pages). Accessed Sept 10, 2011, Available from: http://www.un.org/millenniumgoals/pdf/(2011_E)%20MDG%20Report%202011_Book%20LR.pdf

UNICEF. (2010). *UNICEF Honduras Statistics*. Accessed Sept 10, 2011, Available from: <http://www.unicef.org/infobycountry/honduras_statistics.html>

Varma JL, Das S, Sankar R, Venkatesh Mannar MG, Levinson FJ, Hamer DH. (2007). Community-level micronutrient fortification of a food supplement in India: a controlled trial in preschool children aged 36-66 mo, *Am J Clin Nutr*, 85:1127-1133

Venkatesh Mannar MG. (2006). Successful food-based programmes, supplementation and fortification, *J Ped Gastro and Nutr*, 43:S47–S53

Wegmüller R, Camara F, Zimmermann MB, Adou P, Hurrell RF. (2006). Salt dual-fortified with iodine and micronized ground ferric pyrophosphate affects iron status but not hemoglobin in children in Côte d'Ivoire, *J Nutr.* 136:1814-1820

World Bank. (2011). *2011 World Development Indicators*, Accessed Sept 1, 2011, Available from: <http://data.worldbank.org/data-catalog/world-development-indicators>

World Bank. (2010). *Nutrition at a Glance: Honduras*. Accessed September 20, 2011, Available from: <http://siteresources.worldbank.org/NUTRITION/Resources/281846-1271963823772/Honduras.pdf>

World Bank. (2004). *Public Health at a Glance: Anemia-World Bank Group*. Accessed September 17, 2011, Available from: <http://siteresources.worldbank.org/INTPHAAG/Resources/anemiaAAG.pdf>

World Health Organization. (2001). *Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers*. (114 pages)

World Health Organization. (2005). WHO Anthro, Accessed June 20, 2011, Available from: http://www.who.int/childgrowth/software/en/

World Health Organization Multicentre Growth Reference Study Group. (2006). WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization (312 pages)

World Health Organization. (2008). *Worldwide Prevalence of Anemia 1993-2005: WHO Global Data Base on Anemia*

World Heath Organization. (2009). *Global Health Risks: Mortality and burden of disease attributable to selected major risks*. (62 pages)

World Heath Organization. (2009). *Recommendations on Wheat and Maize Flour Fortification Meeting Report: Interim Consensus Statement* (3 pages)

World Heath Organization. (2011). *Honduras: health profile*. Accessed September 9, 2011, Available from http://www.who.int/gho/countries/hnd.pdf

Zimmermann MB, Hurrell RF. (2007). Nutritional iron deficiency, *Lancet*, 370:511-520

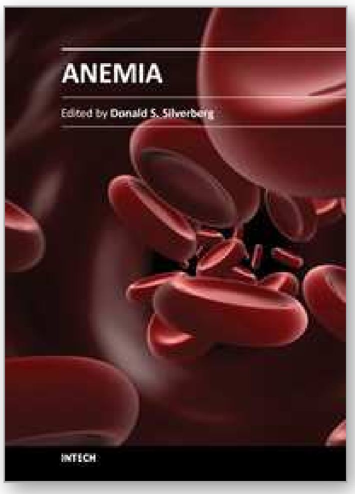
Zlotkin S, Arthur P, Antwi K, Yeung G. (2001). Treatment of anemia with microencapsulated ferrous fumerate plus ascorbic acid supplied as sprinkles to complementary (weaning) foods, *Am J Clin Nutr*, 74:791-5

Zlotkin S, Antwi KY, Schauer C, Yeung G. (2003a). Use of microencapsulated iron (II) fumarate sprinkles to prevent recurrence of anaemia in infants and young children at high risk, *Bull WHO*, 81:108-15

Zlotkin S, Arthur P, Schauer C, Antwi KY, Yeung G, Piekarz A. (2003b). Home-fortification with iron and zinc sprinkles or iron sprinkles alone successfully treats anemia in infants and young children, *J Nutr*, 133:1075-80

Zlotkin SH, Christofides AL, Hyder SM, Schauer CS, Tondeur MC, Sharieff W. (2004). Controlling iron deficiency anemia through the use of home-fortified complementary foods, *Indian J Pediatr*, 71(11):1015-9

Zlotkin S, Tondeur M. (2007). The importance and limitations of food fortification for the management of nutritional anemia: in Badham J, Zimmermann MB, Kraemer K, (eds). *The Guidebook Nutritional Anemia*. Sight and Life Press, 2007 (pages 36-37)



Anemia
Edited by Dr. Donald Silverberg

ISBN 978-953-51-0138-3
Hard cover, 440 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

This book provides an up- to- date summary of many advances in our understanding of anemia, including its causes and pathogenesis, methods of diagnosis, and the morbidity and mortality associated with it. Special attention is paid to the anemia of chronic disease. Nutritional causes of anemia, especially in developing countries, are discussed. Also presented are anemias related to pregnancy, the fetus and the newborn infant. Two common infections that cause anemia in developing countries, malaria and trypanosomiasis are discussed. The genetic diseases sickle cell disease and thalassemia are reviewed as are Paroxysmal Nocturnal Hemoglobinuria, Fanconi anemia and some anemias caused by toxins. Thus this book provides a wide coverage of anemia which should be useful to those involved in many fields of anemia from basic researchers to epidemiologists to clinical practitioners.