

Home-Fortification with Iron and Zinc Sprinkles or Iron Sprinkles Alone Successfully Treats Anemia in Infants and Young Children¹

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ABSTRACT Although iron deficiency is the most common single-nutrient deficiency in infants and children, other deficiencies may develop concurrently, including zinc deficiency. In previous studies, we used home-fortification with “Sprinkles,” single-serve sachets containing microencapsulated ferrous fumarate added to weaning foods, to successfully treat anemia. This mode of micronutrient delivery is amenable to the delivery of other micronutrients. However, the relative efficacy of multiple micronutrient supplements for the treatment of anemia requires evaluation due to possible nutrient interactions. Thus, we evaluated the relative efficacy of Sprinkles formulated with iron and zinc in anemic infants, compared with Sprinkles formulated with iron alone. We studied 304 anemic infants (mean age 10.3 ± 2.5 mo; hemoglobin 87.4 ± 8.4 g/L) in rural Ghana. A combined supplementation group (FeZn) received daily Sprinkles containing 80 mg iron and 10 mg zinc; a comparison group (Fe) received Sprinkles (80 mg iron) without zinc for 2 mo. The rate of recovery from anemia was higher in the Fe group compared with the FeZn group (74.8 vs. 62.9%; *P* = 0.048). The plasma zinc concentration decreased significantly in both groups (*P* < 0.05). A significant decline in the height for age Z-score was observed in the FeZn group (*P* = 0.0011), but there was no change in the Fe group. These results suggest that in a controlled setting, home-fortification using micronutrient Sprinkles with iron, or iron and zinc, was very successful in treating anemia; however, this intervention alone was insufficient to improve zinc status or promote catch-up growth in this stunted and wasted population. *J. Nutr.* 133: 1075–1080, 2003.

KEY WORDS: • iron deficiency • anemia • zinc • infants and young children • sprinkles

Micronutrient deficiencies, including iron-deficiency anemia and zinc deficiency, are common consequences of the plant- and cereal-based complementary diet typically fed to infants and children in developing countries (1,2). These complementary foods are often low in energy and poor sources of bioavailable iron and zinc because the absorption of both micronutrients is inhibited by the presence of dietary phytate. Micronutrient deficiencies in infancy are associated with impairments in cognitive and physical development that may not be reversible (3,4). To improve the nutritional status and development of these infants, it has been suggested that supplementation with multiple micronutrients may be the most appropriate strategy (5).

In an effort to improve the iron status of infants, we recently developed a novel home-fortification approach,

which provides microencapsulated ferrous fumarate and ascorbic acid in powder form. Packaged in single-serve sachets, the fortificant is designed to be sprinkled onto complementary foods after the food is cooked. In a randomized controlled trial, we demonstrated that microencapsulated ferrous fumarate “Sprinkles” were as efficacious as ferrous sulfate drops in the treatment of anemia in infants 6–18 mo of age (6).

This mode of micronutrient delivery is amenable to the concurrent delivery of other essential micronutrients. However, a paucity of data exists on the efficacy of multiple micronutrient supplements to improve hematologic status, which could be negatively affected by nutrient interactions. Relevant to supplementation strategies is the interaction between iron and zinc, which has been well described (7–10). This interaction may affect the absorption and bioavailability of both iron and zinc. Thus, the relative efficacy of multiple micronutrient supplementation for the treatment of anemia must be evaluated and compared with iron supplementation alone (11,12).

In the prospective, masked, randomized, controlled trial reported here, we tested the hypothesis that anemic infants receiving combined daily iron and zinc supplementation in the form of Sprinkles would show concurrent improvement

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in iron and zinc status compared with anemic infants receiving iron Sprinkles alone. Our objectives were to determine the relative efficacy of home-fortification with iron and zinc vs. iron-alone on improving hematologic and zinc status in anemic infants.

SUBJECTS AND METHODS

Study area, subjects and recruitment. The research took place between February and May 2000, at the end of the dry season, in the field study area of the Kintampo Health Research Centre (KHRC), located in the Brong Ahafo Region of Ghana. This is a malaria-endemic area in which the principal complementary food is a maize-based porridge, low in bioavailable iron and zinc. The prevalence of anemia in young children is estimated to be ~70%, a large proportion of which is due to iron deficiency (13).

Eligible infants were identified from an existing surveillance database of births in the district. Inclusion criteria included being 6 to 18 mo old at the time of recruitment, ingesting a weaning food in addition to breast milk and anemic with a hemoglobin concentration between 70 and 99 g/L, as measured during a baseline assessment. Children who were severely anemic (hemoglobin <70 g/L) were excluded from the trial and treated.

Study design. It would be unethical to provide a placebo to a child with anemia at the start of the trial; therefore, we did not include a placebo control. Randomization to one of the two treatment groups was done with sealed opaque envelopes containing group designations, which were generated randomly by computer with Microsoft Access 97 (Microsoft, Seattle, WA). All individuals involved in the study (including parents, field workers and staff) were unaware of group assignments until the code was broken at the completion of the data analysis.

The combined supplementation group (FeZn) received microencapsulated ferrous fumarate (80 mg of elemental iron) and zinc gluconate (10 mg of zinc) packaged in a sachet with ascorbic acid (50 mg). The contents of each sachet were added to the child's meal serving (after it was cooked) once daily for a 2-mo supplementation period. A comparison group (Fe) without zinc received iron sprinkles (80 mg of encapsulated ferrous fumarate plus 50 mg of ascorbic acid) administered similarly, once daily during the same period. The dose of iron was identical to the amount that had been shown to be efficacious in our earlier study (6). Because the ferrous fumarate was lipid-coated, there was minimal gastrointestinal irritation from this relatively high dose of iron.

During the baseline assessment, a questionnaire was administered to collect demographic, nutritional and health data for each infant. Field workers visited infants at 2-wk intervals after the baseline visit, for a total of 5 visits. At each visit, a questionnaire regarding side effects (diarrhea, constipation and general discomfort), ease of use and adherence over the preceding 7 d was completed. Questions related to ease of use included whether children objected to taking the supplement and whether Sprinkles changed the color, taste or texture of the infants' food. To evaluate adherence, the number of used and remaining sachets was counted. At each visit, fieldworkers provided parents with verbal educational support to maximize adherence to the intervention.

Anthropometric measurements, including weight and height, were completed during baseline and final visits as previously described (6). Capillary blood samples at baseline and final visits were obtained from a finger prick using aseptic techniques. Hemoglobin concentration was determined directly in the field using a portable HEMOCUE B-hemoglobin photometer (Hemocue, Angelholm, Sweden) by trained technicians using standardized techniques (14). Capillary blood samples were collected and preserved in ice-lined cold boxes. Blood samples were returned to the base station within 6 h of collection and the plasma was separated by centrifugation (10 min at 12,000 × g) before storage at -40°C. Serum ferritin was assayed in duplicate by a commercial ELISA (Ramco Laboratories, Houston, TX) (15). Plasma zinc concentration was determined by inductively coupled plasma mass spectrophotometry (16). Thick and thin blood smears from capillary blood were taken to identify the presence of malaria parasitemia, at the final visit only. Malaria slides were stained

with Giemsa and examined under oil immersion with a light microscope by a trained microscopist for the presence of malaria parasites. A slide was declared negative after examination of 200 thick film fields.

Sample size and power. In our previous study in Ghana (6), Sprinkles reversed anemia in 58% of subjects within 2 mo. We estimated that there would be at least a 15% difference in the relative efficacy of iron and zinc Sprinkles compared with iron Sprinkles alone in treating anemia. Using an $\alpha = 0.05$ and power = 0.80, the estimated sample size for a two-tailed analysis was 112 subjects per group (17). Assuming a 20% dropout rate, we planned to recruit 135 infants per group.

Data processing and analysis. Data were entered in Visual Fox Pro 6.0 (Microsoft), verified and checked for range and consistency with customized data entry and processing programs (Microsoft Access 97) as previously described (6). Data were analyzed with SAS, version 8.0 (SAS Institute, Cary, NC). Paired *t* tests were used to analyze the change in plasma zinc and anthropometric measurements, as well as hemoglobin and ferritin, over time within groups. Differences between groups in anthropometric measurements, plasma zinc, hemoglobin and ferritin, at the beginning and the end of the study were assessed by ANOVA (with proc GLM). Analysis of ferritin values was conducted on log-transformed data because of their skewed frequency distribution. Differences in the prevalence of anemia (hemoglobin <100 g/L), iron deficiency (ferritin <12 µg/L), and low plasma zinc concentrations (<10.7 µmol/L) were compared between the groups using χ^2 analysis. McNemar's test was used to compare changes in anemia and ferritin status from the beginning to the end of the study within groups. Differences were considered significant at $P < 0.05$. Values in the text are means ± SD.

Ethics approval and consent. Ethics approval was obtained from The Hospital for Sick Children (Toronto, Canada) and Ghana's Ministry of Health (Kintampo, Ghana). Verbal consent to conduct the study in the Kintampo district was obtained from the District Assembly of Elected Representatives and from elders in each village. Informed and signed consent was obtained individually from the mothers of infants in the study.

RESULTS

Initial screening in the region identified a total of 529 potentially eligible infants for the study. Of the infants screened, 304 (57.5%) had hemoglobin concentrations between 70.0 and 99.9 g/L and were therefore recruited. Infants were randomized into two groups; 65 (21.4%) of the 304 infants did not attend the final assessment visit. Consequently, a total of 239 infants completed the final assessment, including anthropometric measurements and blood sampling (Fig. 1).

The age of the infants at baseline was 10.3 ± 2.5 mo. The groups did not differ at baseline in plasma zinc ($P = 0.58$), age ($P = 0.78$), hemoglobin ($P = 0.95$) or serum ferritin ($P = 0.44$).

Compliance. Over the 2-mo intervention, 82.1% of the infants received Sprinkles at least 5 times a week. Only 3.4% of parents reported having any problems using Sprinkles. Of those who reported problems, 1.8% reported that they had an unpleasant odor, whereas 80.5% reported that the Sprinkles changed the color of their infant's food (much like the effect of adding a condiment such as pepper to food). Fewer than 3% of all caregivers gave the Sprinkles to a "nonstudy" child and 69.7% reported using the full contents of the sachet all of the time. All infants were breast-feeding at the start of the study and continued breast-feeding during the 2-mo period, although not exclusively. The primary complementary food to which Sprinkles were added was "koko," a thin, traditional porridge made from fermented maize dough. None of the children received commercial infant formulas.

Hemoglobin response. In both groups, hemoglobin concentration increased from baseline to the end of the study (P

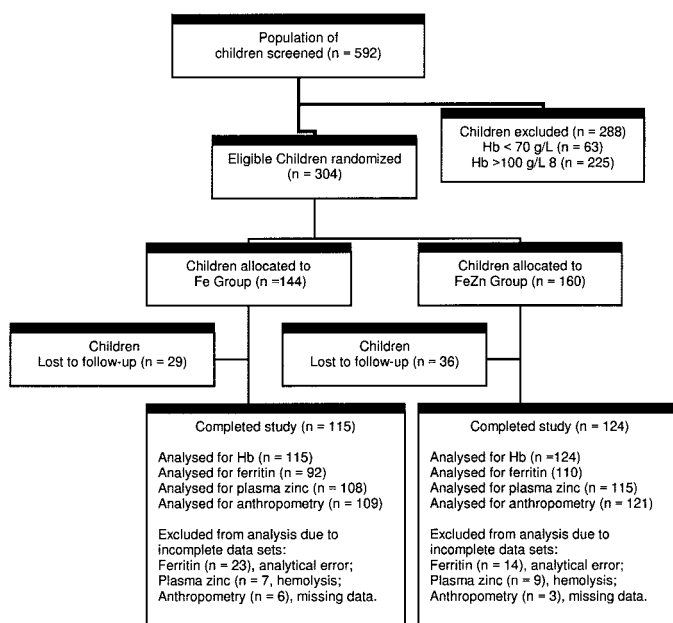


FIGURE 1 Trial profile.

< 0.0001; Table 1). At the end of the study, the hemoglobin concentration was significantly greater in the Fe group than in the FeZn group ($P = 0.024$). Furthermore, the rate of recovery from anemia ($\text{Hb} \geq 100$ g/L) was higher in the Fe group (86/115; 74.8%) than in the FeZn group (78/124; 62.9%) ($P = 0.048$). The relative risk of remaining anemic in the Fe group was 33% lower than the FeZn group ($rr = 0.67$, 95% confidence interval 0.46–1.0; $P = 0.048$). There was no effect of initial hemoglobin, gender or age on final hemoglobin concentration.

Ferritin response. Ferritin concentrations (geometric means) did not differ between the two groups at baseline or at the end of the study ($P = 0.44$; Table 1). However, concentrations increased in both groups during the 2-mo intervention ($P < 0.0001$). The variance for the ferritin values was elevated and had a wide range as is commonly found in malaria endemic regions (18). At baseline, the groups did not differ in the proportion of children who were iron deficient (ferritin $< 12 \mu\text{g/L}$) ($P = 0.49$); in total, 42.1% (85/202) of infants had ferritin concentrations below the cut-off value. There was a decrease in the proportion of infants with iron deficiency after 2 mo of treatment in both groups although the rate was lower in the zinc-supplemented group ($P < 0.0001$).

Plasma zinc response. At baseline, plasma zinc concentrations were similar in the groups (Table 1). From baseline to the end of the study, plasma zinc decreased significantly in both groups but the concentration tended ($P = 0.123$) to be higher in the FeZn group at the end. There was no difference between the groups at baseline in the proportion of infants with low plasma zinc; in total, 19.3% of infants (43/223) had plasma zinc concentrations $< 10.7 \mu\text{mol/L}$. The percentage of infants in both groups with zinc concentrations $< 10.7 \mu\text{mol/L}$ increased to 29.2% (65/223) at the end ($P = 0.015$). Of the 22 infants whose plasma zinc concentration fell below the cut-off value, a greater proportion were in the Fe group (16/22) than in the FeZn group (6/22) ($P = 0.003$).

Malaria status. There was no difference in malaria status between groups. Overall, 178/286 (62.2%) infants tested positive for malaria parasites. Infants who tested positive for

malaria were more likely to be anemic in both groups ($P < 0.0001$).

Anthropometric measurements. The weight-for-age, height-for-age and weight-for-height Z-scores at baseline and at the end of the study were all below zero and did not differ between groups (Table 1). Both groups had significant decreases in weight-for-age and weight-for-height Z-scores between baseline and the final assessment. Infants in the FeZn group had a significant decrease in their height-for-age Z-score ($P = 0.001$), whereas it did not change in the Fe group ($P = 0.099$). There was a significant negative association between initial age and final weight-for-age ($r = -0.205$; $P = 0.02$) and weight-for-height Z-scores ($r = -0.143$; $P = 0.02$) among the entire sample population. There was no effect of group, gender or their interaction on initial and final Z-scores.

DISCUSSION

In this study, we investigated the effect of “home-fortification” with iron and zinc-containing Sprinkles on iron and zinc status and growth compared with iron-Sprinkles alone. We were able to confirm our earlier observations that iron sprinkles (with and without zinc) are an efficacious way to treat anemia in infants (6). The overall mean rate of successful treatment for anemia in the current study (69%) was higher than in our original study in a similar population (59%) (6). The current study was conducted during the dry season, when malaria transmission is low. This likely accounted for the greater reduction in anemia prevalence compared with the original study, which was conducted during the rainy season when the burden of anemia associated with malaria is higher.

Combined home-fortification with iron and zinc was less efficacious than iron alone (62.9 vs. 74.8%, $P = 0.048$), but was still highly successful for the treatment of anemia in a malaria holoendemic region. The prevalence of malaria was similar in the two groups; thus, anemia associated with malaria could not account for the difference. The difference remained after adjusting for age, initial hemoglobin and initial plasma zinc concentrations. Similarly, Dijkhuizen et al. (19) showed that among Indonesian infants, reduction in the prevalence of anemia was greater in an iron-supplemented group (38% reduction) than in a combined iron and zinc-supplemented group (20% reduction). These results are indicative of an antagonistic interaction between the two micronutrients. Inhibition of iron absorption in the zinc-supplemented group may be a result of zinc competing with iron for the same receptor sites on intestinal mucosal cells in the lumen (20) or a possible postabsorptive interaction during metabolism (21).

Despite a weaning diet that was limited in zinc content and high in phytic acid, the proportion of subjects with low plasma zinc concentrations was quite low (19.3%) at baseline. Others have made similar observations (22). We believe that there are several possible explanations for this. First, zinc is likely underutilized when growth is limited. A rapidly growing infant requires more nutrients than one that is growing slowly. Thus, if growth is limited because of inadequate energy, zinc needs may be concomitantly decreased. Second, increased loss of zinc through the stool is often a predisposing cause of zinc deficiency, especially in populations whose zinc status is already marginal (23). The frequency of diarrhea in infants in the current study was not high, possibly because the study was conducted during the “dry season.” Third, zinc status as assessed by plasma zinc concentration is of limited value because of its poor sensitivity and specificity to changes in dietary zinc and the inability to adequately control for postprandial vari-

TABLE 1

Hemoglobin, ferritin and plasma zinc concentrations, the percentage of anemic and iron-deficient infants and infants with low plasma zinc concentration, and anthropometry in the iron only and combined supplementation (iron + zinc) groups, at baseline and at the end of the 2-mo intervention period¹

	Iron	Iron + Zinc
Baseline		
Hemoglobin, g/L	87.4 ± 8.2 [115]	87.4 ± 8.5 [124]
Anemic subjects, ² %	100	100
Ferritin, ^{3,4} μg/L	16.3 (0.2–316.8) [92]	13.7 (0.3–365.2) [110]
Iron deficient, ⁵ %	39.1	44.5
Plasma zinc, μmol/L	14.04 ± 4.42 [108]	14.36 ± 4.40 [115]
Low plasma zinc, ⁶ %	21.3	17.4
Anthropometry		
Weight-for-Age Z-score	−1.80 ± 1.14 [109]	−1.69 ± 1.01 [121]
Height-for-Age Z-score	−1.81 ± 1.12	−1.70 ± 1.14
Weight-for-Height Z-score	−0.65 ± 0.93	−0.60 ± 0.86
End of Intervention		
Hemoglobin, g/L	108.1 ± 15.5 [115]*	103.5 ± 15.8 [124]*, #
Anemic subjects, ² %	25.2	37.1#
Ferritin, ^{3,4} μg/L	37.4* (1.2–390.1) [92]	51.0* (1.4–386.1) [110]
Iron deficient, ⁵ %	23.9**	15.5*, #
Plasma zinc, μmol/L	12.44 ± 3.29 [108]**	13.36 ± 3.81 [115]**
Low plasma zinc, ⁶ %	36.1**	22.6#
Anthropometry		
Weight-for-Age Z-score	−1.95 ± 1.09** [109]	−1.89 ± 0.94* [121]
Height-for-Age Z-score	−1.86 ± 1.11	−1.81 ± 1.10**
Weight-for-Height Z-score	−0.92 ± 0.93*	−0.88 ± 0.71*

¹ Values are % or means ± SD, (ranges), [n]. * Different from baseline, $P < 0.0001$; ** different from baseline $P < 0.05$; # different from the iron group, $P < 0.05$.

² Anemia is defined as a hemoglobin concentration < 100 g/L.

³ Geometric means.

⁴ The analysis was done with log-transformed values because ferritin values were not normally distributed.

⁵ Iron deficiency is defined as a ferritin concentration < 12 μg/L.

⁶ Low plasma zinc is defined as a concentration < 10.7 μmol/L.

ation and infection (24). Finally, it has been suggested that as dietary intake becomes limited, endogenous zinc losses are homeostatically decreased (25).

One of the concerns associated with iron supplementation has been its potential to negatively affect zinc absorption. In the current study, the molar ratio of iron to zinc was relatively high at 9:1. However, studies have shown that fortifying infant foods with iron does not interfere with zinc absorption at Fe:Zn molar ratios as high as 57:1 (26,27). Although the literature is inconsistent regarding the effect of iron supplementation on zinc status, studies examining the effect of prenatal iron supplements in pregnant women have found a decrease in fractional zinc absorption and plasma zinc concentrations (28–30). Moreover, iron supplementation was also associated with impaired linear growth in Honduran infants (31), a principal clinical feature of zinc deficiency (32–34). In the current study home-fortification with zinc, combined with iron, failed to improve either zinc status or linear growth in infants over the study period.

A significant decrease in plasma zinc concentration occurred in both groups over the 2-mo study period; however, the decrease tended to be less ($P = 0.123$) in the FeZn group compared with the Fe group. Dirren et al. (35) recently documented an increase in plasma zinc concentrations in children supplemented with 10 mg of zinc/d compared with a placebo, but over a 15-mo period. Thus, duration of supplementation may be a contributing factor. This would suggest that either the amount of zinc provided in the sachet or the bioavailability of the zinc compound was insufficient to maintain zinc

status during the 2-mo study period or that the intervention period was too short. Lartey et al. in Ghana (22), observed a trend towards a higher proportion of infants with low plasma zinc concentrations from 6–12 mo of age despite an intervention that provided a weaning food fortified with vitamins and minerals, including zinc to all infants. An assessment to determine the factors associated with plasma zinc concentration in these infants found an inverse relationship between plasma zinc concentration and calcium and phytate from the diet. Thus, the bioavailability of zinc, when added to food as powdered sprinkles, is likely strongly influenced by the content of other nutrients in the food to which it is added.

The anthropometric assessment of the infants at baseline indicated a high rate of stunting and wasting, as is typical of a populations experiencing chronic undernutrition in West Africa (36). With the single exception of the height-for-age Z-score in the Fe group, weight-for-age, weight-for-height and height-for-age Z-scores decreased significantly in both groups during the study period. It is notable that infants in the Fe group were able to maintain their initial height-for-age Z-scores without any further significant growth faltering, whereas the linear growth in the FeZn group continued to decline. This suggests that zinc was not the limiting factor for linear growth and that growth faltering is likely due to multiple factors including infant and maternal nutrition status at birth, multiple macro- and micronutrient deficiencies and the burden of infectious diseases (37). Alternatively, iron may have had a protective effect on further faltering, possibly through the greater improvement of iron status. A limitation to this study

was that the effect of "home-fortification" with iron on growth could not be assessed directly; due to ethical concerns, the study design could not include a placebo group of anemic infants who would not receive iron (38). Despite this limitation, it appears that Sprinkles with iron alone did not contribute to an increased risk of linear growth faltering. This would be consistent with other studies that have shown an increased risk for growth decline in iron-replete children receiving iron supplementation (39,40), but improved growth or no effect in iron deficient and/or anemic children (19,39,40). In the past, the effect of iron supplementation on linear growth has been equivocal with some reports describing enhanced growth and others the opposite (37).

Our results showed a significant negative association between initial age and final underweight Z-scores (i.e., older children tended to have lower Z-scores). A decrease in mean weight-for-age and weight-for-height Z-scores in infants between 6 and 24 mo of age has been reported elsewhere (36,37,39). It is likely that with increasing age, infants are not meeting dietary energy and nutrient requirements (41). These observations are consistent with the conclusions of Brown et al. (42) that typical cereal-based complementary foods in the developing world are inadequate total sources of nutrition for breast-feeding infants in the first 2 y of life.

In conclusion, the results of our study suggest that in a controlled setting, micronutrient Sprinkles with iron, or iron and zinc, are very successful in treating anemia. This observation is important because early treatment of anemia will likely decrease mortality from malaria-associated anemia, which is especially important in a holoendemic malaria region. Multiple micronutrient supplementation alone, however, was insufficient to promote catch-up growth in this stunted and wasted population of infants. Although the addition of zinc had a marginally negative effect on linear growth, one must be careful not to overinterpret these results. The positive benefits of zinc supplementation have been well documented and include improvements in growth, cognitive development and immune functioning, in addition to a reduction in morbidity from diarrhea and pneumonia and possibly mortality due to infectious diseases (43–46). Decreased plasma zinc concentrations at the end of the study would suggest that infants might benefit from combined iron and zinc supplementation in the long term. Further research is in progress to examine directly the effect of multiple micronutrient Sprinkles over a longer period of time on the nutritional status of infants and young children.

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