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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

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ABSTRACT

Objectives: To assess and compare efficacy of two micronutrient sprinkle supplementation on growth, anemia, and iron deficiency in Cambodian infants.

Methods: A total of 204 infants aged 6 months and living in Kompong Chhnang Province, Cambodia were randomly assigned to receive daily supplements of either iron (12.5 mg) plus folic acid (150 μg) plus zinc (5 mg) (MMN, n = 68), or iron (12.5 mg) plus folic acid (150 μg) alone (FFA, n = 68), or placebo (n = 68) for a 12 month period in powder form as sprinkles. Anthropometrics was evaluated bimonthly. Biochemical assessment was performed at baseline and at the end of intervention period.

Results: At baseline, the overall mean (SD) of hemoglobin concentration was 101 g/L. No difference among groups was found for growth pattern. Significant decline was observed for weight-for-age and height-for-age *z*-scores in any group ($P < 0.0001$). The rate of recovery from anemia was significant ($P < 0.001$) and comparable between MMN (54%) and FFA (53%) groups and higher than in the placebo group (22%, $P < 0.0001$). Through the study period, no significant change in the rate of iron deficiency was found in MMN and FFA groups, whereas it increased in the placebo group (31%, baseline vs. 52%, end of study; $P < 0.0001$).

Conclusion: Both MMN and FFA supplements were effective for preventing or treating anemia in Cambodian infants and stabilizing plasma levels of ferritin. Use of micronutrients in a controlled home setting, as sprinkled daily supplements, may be promising in preventing and treating anemia in developing countries. ***JPGN 42:306–312, 2006.*** **Key Words:** Anemia-Iron deficiency—Growth—Sprinkles. © 2006 by Lippincott Williams & Wilkins

INTRODUCTION

In most infants living in developing countries, complementary foods are commonly cereal based and low in iron content and bioavailability (1). Daily iron requirements are seldom met, and infants are therefore at risk for iron deficiency and iron-deficiency anemia (IDA).

Despite global goals set by United Nations agencies for reduction in IDA (2), it still affects approximately one third of the world population. Cambodia faces prevalence in anemia in infants and young children of 63%, and the Ministry of Health (MoH) has a goal to reduce it to 42% by the year 2007 (3).

The long-term goal for the World Health Organization (WHO) is a balanced diet for pregnant women and preschool infants (4), which requires long-term changes in eating habits, involving social, cultural, and economic factors. At present, in countries where iron fortified complementary foods are not regularly consumed, infants should routinely receive iron supplements in the first 12 to 24 months of life. Indeed, iron supplements may provide an inexpensive approach to supply pregnant women and infants with adequate iron intake. Food fortification with iron and homestead food production might be an additional policy to be promoted.

Zlotkin et al. (5) found that sprinkles, as microencapsulated ferrous fumarate in powder form, are as efficacious as the gold standard ferrous sulphate drops in treating anemia among infants 6 to 18 months old and showed enhanced tolerability. In particular, sprinkles successfully treated 60% to 75% of infants studied despite 70% of them exhibiting malaria. Promising results were also found in recent studies using sprinkles with different combinations of iron and other micronutrients (6–8). Moreover, it has been suggested that

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supplying iron sprinkles daily may result in a better hematologic profile, as compared with intermittent iron supplements (9). Within this framework, daily home fortification with iron as sprinkles may be successful in treating anemia (6).

Although intervention programs would be strongly desirable in Cambodia, where anemia prevalence rate is high, no trial has been conducted on this population. The aim of the present study was to evaluate the effects of iron and iron plus micronutrient daily supplementation as sprinkles on growth, anemia, and IDA in Cambodian infants.

METHODS

Study Design, Location, and Subjects

The study was designed as a double-blind, placebo-controlled comparative longitudinal trial conducted on infants aged 6 months at recruitment and living in Tuk Phos district, Kompong Chhnang Province, Cambodia. This is a geographical area where people depend on farming, and the main crop and complementary food is rice, which is low in bioavailable iron.

A total of 204 infants were recruited according to the following eligibility criteria. Inclusion criteria included infants being born between January and July 2003 and aged 6 months ± 7 days at recruitment. Exclusion criterion was severe anemia (hemoglobin < 70 g/L).

Infants were recruited in 28 villages randomly selected to homogeneously represent the studied geographical area and randomly (same chance) assigned to receive either iron + folic acid + zinc + multivitamin (MMN) or iron + folic acid alone (FFA) or placebo, as sprinkled powder form. Active sprinkles and placebo, similar in powder form, were mixed and packaged by Heinz Company (Toronto, Canada) and shipped by air to Phnom Penh.

Randomization to treatment was performed with sealed opaque envelopes containing group designations based on allocation lists computer generated at blocks of 9 units and stratified on sex. All individuals involved in the trial (including parents, health workers, and research staff) were unaware of group assignment until code was broken after the completion of the data analysis.

The study protocol scheduled daily administration of MMN or FFA or placebo for a 12 month period. Treatments were distributed to mothers weekly by three trained health workers and given as sprinkles in one-dose sachets. Sprinkles were packaged in a paper/aluminium/polyethylene pouch. Lot number and an internal batch number were printed on the package. Administration of sprinkles started 7 ± 2 days after baseline blood assessment. Content of each sachet was mixed with the infant's meal after it was cooked. Nutrient composition of active sprinkles and placebo is reported in Table 1. The dose of iron was in accordance with international standardized recommendations (10). Immunization, vitamin A capsule, and mebendazole coverages were further provided in all infants according to the Cambodian MoH guidelines (11).

Measurements

At baseline, information about demographic, nutrition, and health data of the infant was gathered. Health workers visited infants at home at 1 week intervals through a 12 month period starting from baseline. At each weekly visit, mothers were interviewed about the health status of the infant and any adverse events, including diarrhea, constipation, and discomfort. Acceptance of sprinkles was evaluated by a questionnaire standardized previously, including questions that assessed whether the infant refused the treatment and whether sprinkles changed color, taste, or texture of the complementary food.

TABLE 1. *Nutrient composition of sprinkles*

Sprinkles	Composition	RDA
MMN		
Fe (iron II fumarate)	12.5 mg	10 mg
Zn (gluconate)	5 mg	5 mg
Vitamin C	50 mg	45 mg
Vitamin A	300 μg	400 μg
Vitamin D3	7.5 μg	10 μg
Folic acid	150 μg	50 μg
Potato maltodextrins	SQ to 1 g	–
FFA		
Fe (iron II fumarate)	12.5 mg	10 mg
Folic acid	150 μg	50 μg
Potato maltodextrins	SQ to 1 g	–
Placebo		
Potato maltodextrins	1 g	–

RDA, recommended daily allowance; MMN, iron + folic acid + zinc + multivitamin; FFA, iron + folic acid alone; SQ, standard quantity.

The same examiner using standard procedures performed anthropometric measurements, including body weight and length, bimonthly. Standardized weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length (WLZ) *z*-scores were calculated by the ANTHRO Pediatric Anthropometry Software Program, version 1.02 (Centers for Disease Control and Prevention [CDC], Atlanta, GA) (12).

Blood samples were taken at 9 hours ± 30 minutes as a 2 mL venous blood, at baseline, and at the end of the intervention period. Blood samples were immediately stored at 4 °C to prevent microhemolysis and transported within 6 hours from puncture to be analyzed at the Istitute Pasteur du Cambodge to be analyzed.

Whole blood on EDTA was analyzed by means of the CELL-DYN 3200 automated laboratory analyzer (Abbott, Abbott Park, IL) with a manufacturer's reported coefficient of variation 1% or less. For each series of samples, a three-level internal quality control material (CELL-DYN 26, Abbott) was analyzed in parallel. Hemoglobin concentration was determined using a CELL-DYN 3200 automated laboratory analyzer. Serum ferritin was assayed with an enzyme-linked immunoassay (AXSYM System, Abbott) with monoclonal antibodies using commercial test kits (AXSYM, Abbott). Three levels of quality control material (AXSYM, Abbott) were analyzed together with each series of samples. C-reaction protein (CRP) was measured by immunoturbidimetry (COBAS MIRA plus, Hoffmann-La Roche Ltd, Basel, Switzerland) using commercial test kits (bioMérieux, Marcy l'Etoile, France) with an internal quality control kit (bioMérieux), and this was analyzed together in each series of samples. Whole blood was also screened at baseline for hemoglobinopathies within 3 days of blood sampling by using electrophoresis on cellulose acetate membranes at alkaline pH with Sebia (Norcross, GA) material and electrophoretic position markers (PerkinElmer, Wellesley, MA). Thick and thin blood smears

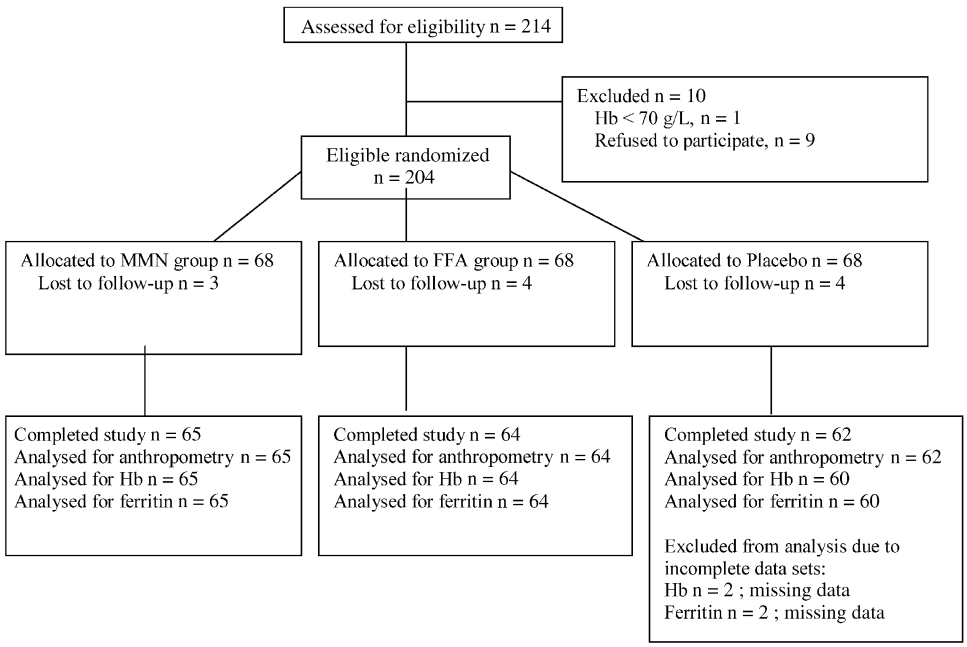

FIG. 1. Flow diagram of subjects' progress through the study.

were further taken and analyzed at the Istitute Pasteur du Cambodge to identify the presence of malaria parasitemia, at baseline and at the end of the study period. Malaria slides were stained with Giemsa and examined under oil immersion with a light microscope. A slide was considered negative after examination of 200 thick film fields. Stools were further collected at baseline and tested for parasites by culture at Istitute Pasteur du Cambodge.

Anemia was defined according to WHO classifications (7,8) and classified as severe (Hb < 70 g/L), moderate (70 g/L ≤ Hb < 100 g/L), or mild (100 g/L ≤ Hb < 110 g/L). Infants exhibiting Hb 110 g/L or greater were classified as nonanemic. Iron deficiency was defined as ferritin concentration below 12 μg/L (6).

Sample Size

The sample size was determined to detect a 5 g/L or more difference in mean hemoglobin at the end of the study period between any treatment groups. Allowing a type I error level of 5% with power of 80% and assuming a drop out rate of 25%, 68 infants needed to be recruited in each group.

Statistical Analysis

Descriptive data are reported as mean, standard deviation, or percentage. Log transformation was used for ferritin because it was not normally distributed. Analysis was performed on the intention-to-treat basis. The effect of treatments on growth was tested with analysis of variance (ANOVA) for repeated measures. The effect of treatments on hemoglobin or ferritin was assessed with ANOVA, including treatment as fixed factor and sex and CRP as covariates. Significance of post hoc multiple comparisons was adjusted by the Bonferroni correction. A significance level of 0.05 was used, and all the statistical tests are two-tailed. The SPSS software, version 12.0 (SPSS Inc., Chicago, IL), was used for the statistical analysis.

Ethics

The protocol was designed in accordance with the Cambodian MoH and received the approval of the National Ethical Committee of the Cambodian MoH. Parents were informed about the procedures and purpose of the study and signed a written informed consent.

RESULTS

A total of 214 infants were contacted. Figure 1 shows the flow diagram of the trial, according to CONSORT statement (13). One infant exhibited Hb less than 70 g/L and was excluded from the study, and nine families refused to participate. Accordingly, 204 eligible infants (109 males, 95 females) were recruited and randomly allocated to receive either MMN (n = 68) or FFA (n = 68) or placebo (n = 68). The participation rate at the end of the study was 93.6%.

Anthropometric Measurements

Overall prevalence of underweight (weight-for-age below the 5th percentile, according to the CDC growth curves) was 10% and 11.5% at, respectively, 6 and 18 months of age, with mean (SD) WAZ −0.87 (1.05) and −1.14 (0.76). Stunting prevalence (length-for-age below the 5th percentile) was 5.7% and 27%, respectively, with mean LAZ −0.80 (0.85) and −1.55 (0.74). Wasting prevalence (weight-for-length below the 5th percentile) was 7.8% and 4.7%, respectively, with mean

TABLE 2. *Weight-for-age z-score through the 12 month intervention period, according to treatment*

	Age (months)						
Sprinkles	6	8	10	12	14	16	18
MMN	−0.93	−0.89	−0.79	−1.05	−1.16	−1.17	−1.25
(n = 65)	(−1.21, −0.65)	(−1.13, −0.64)	(−0.98, −0.59)	(−1.24, −0.85)	(−1.35, −0.97)	(−1.34, −0.98)	(−1.41, −1.07)
FFA	−0.88	−0.89	−0.94	−0.98	−1.15	−1.18	−1.08
(n = 64)	(−1.16, −0.60)	(−1.15, −0.62)	(−1.16, −0.71)	(−1.19, −0.76)	(−1.35, −0.95)	(−1.35, −1.00)	(−1.30, −0.85)
Placebo	−0.80	−0.79	−0.79	−0.88	−1.10	−1.17	−1.08
(n = 62)	(−1.03, −0.57)	(−1.03, −0.56)	(−1.01, −0.57)	(−1.10, −1.30)	(−1.30, −0.91)	(−1.32, −1.01)	(−1.25, −0.91)

Values are means (95% confidence interval).

Significance of difference among groups, $P = 0.773$ (analysis of variance for repeated measures). Significance of within-group variation: $P < 0.0001$ in any group.

MMN, iron + folic acid + zinc + multivitamin; FFA, iron + folic acid alone.

WLZ −0.38 (1.21) and −0.37 (0.88). The growth pattern in the three groups through the 12 month study period is presented in Table 2–4. Trend of WAZ, LAZ, and WLZ were significantly under than the CDC curves in each group ($P < 0.0001$), but no difference was found between any groups. There was a significant decline in WAZ and LAZ in all groups ($P < 0.0001$), whereas WLZ was comparable at baseline and the end of the study.

Hemoglobin Response

Overall mean (SD) baseline hemoglobin concentration was 101 g/L. Table 5 reports the hematologic values at baseline and after the 12 months of treatment. Hemoglobin concentrations did not differ among groups at baseline. Hemoglobin mean levels increased from baseline to the end of the study in MMN (mean difference, 95% confidence interval [CI], 8.2 [5.1,11.2] g/L) and in FFA (8.3 [5.7,10.9] g/L) groups, whereas it decreased in the placebo group (−3.20 [5.81; 0.39] g/L). At the end of the study, hemoglobin concentration was higher in MMN and FFA than in the placebo group ($P < 0.0001$) but did not differ between the two intervention groups ($P = 0.522$). The rate of recovery from anemia was 28 of 52 (53.8%) and 27 of 51 (52.9%) in, respectively, the MMN and FFA groups ($P = 0.926$) and significantly higher than in the placebo group (10/46; 21.7%) ($P < 0.001$). Two infants in the MMN group and one infant in the FFA group worsened the anemic status at the end of the intervention period. In the placebo group, worsening of the anemic status was found in 14 of 60 (23.3%) infants. No significant association of sex or blood hemoglobin at baseline or polymerase chain reaction with hemoglobin level at the end of the study was found in any group.

Ferritin Response

Overall mean (median, range) baseline ferritin concentration was 44.7 (29, <0.1–289) μg/L. Ferritin concentrations did not differ among groups at baseline (Table 3). Ferritin concentration did not significantly change in the MMN group during the 12 month study period (mean difference of log ferritin [95% CI], 0.08 [−0.13; 0.29] μg/L), it significantly increased in the FFA group (0.15 [0.06; 0.25] μg/L), and decreased in the placebo group (−0.56 [−0.74; −0.38] μg/L). The coefficient variation (% ratio of SD over mean) for the ferritin values was high in all groups, ranging from 98% to 104% at baseline and from 74% to 96% at the end of the study. At baseline, overall prevalence of iron deficiency was 13.2 % (25/189), and prevalence did not differ among groups. The rate of iron deficiency did not differ from baseline to end of the study in the MMN or FFA groups, whereas it increased approximately four times in the placebo group ($P < 0.0001$). At baseline, concomitant anemia and iron deficiency occurred in 15 infants (MMN, n = 7; FFA, n = 2;

TABLE 3. *Length-for-age z-score through the 12 month intervention period, according to treatment*

	Age (months)						
Sprinkles	6	8	10	12	14	16	18
MMN	−0.79	−1.11	−1.33	−1.50	1.53	−1.64	−1.56
(n = 65)	(−1.03, −0.54)	(−1.33, −0.89)	(−1.53, −1.12)	(−1.70, −1.31)	(−1.71, −1.34)	(−1.81, −1.46)	(−1.75, −1.37)
FFA	−0.83	−1.17	−1.46	−1.54	−1.61	−1.73	−1.48
(n = 64)	(−1.01, −0.65)	(−1.34, −1.00)	(−1.63, −1.29)	(−1.70, −1.38)	(−1.76, −1.45)	(−1.87, −1.57)	(−1.67, −1.28)
Placebo	−0.78	−0.91	−1.26	−1.43	−1.64	−1.78	−1.63
(n = 62)	(−0.99, −0.57)	(−1.14, −0.67)	(−1.48, −1.04)	(1.63, −1.22)	(−1.82, −1.44)	(−1.95, −1.60)	(−1.80, −1.45)

Values are means (95% confidence interval).

Significance of difference among groups, $P = 0.865$ (analysis of variance for repeated measures). Significance of within-group variation: $P < 0.0001$ in any group.

MMN, iron + folic acid + zinc + multivitamin; FFA, iron + folic acid alone.

TABLE 4. *Weight-for-length z-score through the 12-month intervention period, according to treatment*

	Age (months)						
Sprinkles	6	8	10	12	14	16	18
MMN	−0.45	−0.01	0.32	0.04	−0.20	−0.26	−0.46
(n = 65)	(−0.75, −0.15)	(−0.27, 0.24)	(0.10, 0.53)	(−0.19, 0.27)	(−0.42, 0.01)	(−0.45, −0.06)	(−0.66, −0.29)
FFA	−0.37	0.00	0.23	0.15	−0.13	−0.23	−0.35
(n = 64)	(−0.68, −0.06)	(−0.29, 0.27)	(−0.05, 0.50)	(−0.11, 0.40)	(−0.35, 0.09)	(−0.43, −0.04)	(−0.60, −0.10)
Placebo	−0.30	−0.12	0.24	0.19	−0.03	−0.16	−0.26
(n = 62)	(−0.61, 0.01)	(−0.40, 0.17)	(−0.05, 0.53)	(−0.08, 0.46)	(−0.25, −0.19)	(−0.36, 0.04)	(−0.47, −0.06)

Values are means (95% confidence interval).

Significance of difference among groups, $P = 0.916$ (analysis of variance for repeated measures). Significance of within-group variation: MMN, $P = 0.140$; FFA, $P = 0.296$; placebo, $P = 0.514$.

MMN, iron + folic acid + zinc + multivitamin; FFA, iron + folic acid alone.

placebo, n = 6). The rate of recovery from IDA was four of seven (57.1%) and two of two (100%) in the MMN and FFA groups, respectively. In the placebo group 2 of 6 (33.3%) recovered from IDA, whereas 16 of 54 (29.6%) infants not exhibiting IDA at baseline showed IDA at the end of the study.

Compliance

During the 12 month intervention period, no death occurred. Two females (MMN, n = 1; FFA, n = 1) developed severe protein-energy malnutrition (marasmus). A total of 39 out of 191 (20.4%) infants showed chronic/recurrent infections. Fourteen (7.4%) infants had recurrent respiratory infections (MMN, n = 5, 3 males, 2 females; FFA, n = 5, all males; placebo, n = 4, 2 males, 2 females). Two infants had recurrent episodes of diarrhea (MMN, 1 female; FFA, 1 male). Seventeen (8.9%) infants had both recurrent respiratory infections and recurrent diarrheal diseases (MMN, n = 8, 5 males, 3 females; FFA, n = 5, 1 male and 4 females; placebo, n = 4, 2 males, 2 females). Two infants (FFA, males) reported

TABLE 5. *Hemoglobin and ferritin plasma concentration and percentage of anemia or iron deficiency in infants at baseline and the end of the 12 month intervention period, according to treatment*

	Sprinkles			
Variable	MMN	FFA	Placebo	*P* value*
Hemoglobin (g/L)				
Baseline	99.4 (9.9; 76–119)	101.0 (10.1; 81–128)	102.9 (10.2; 80–123)	0.143
End of intervention	107.6 (11.0; 80–130)[1]	109.3 (11.7; 90–150)[1]	99.7 (10.3; 80–120)[2]	<0.0001‡
P value†	<0.0001‡	<0.0001‡	0.026‡	
Anemia (%)				
HB (g/L) at baseline				
70–99.9	50.8	46.9	28.3	
100–109.9	29.2	32.8	48.3	0.096
≥110	20.0	20.3	23.3	
HB (g/L) at end of intervention				
70–99.9	13.8[1]	10.9[1]	32.3[2]	
100–109.9	24.6	26.6	38.7	<0.0001‡
≥110	61.5	62.5	29.0	
P value†	<0.0001‡	<0.0001‡	0.730	
Ferritin (μg/L)§				
Baseline	46.4 (48.3; <0.1–289)	40.5 (39.8; 5–188)	47.2 (49.1; 4–266)	0.859
End of intervention	41.6 (30.7; 4–145)[1]	53.2 (42.3; 8–236)[1]	14.1 (13.5; <0.1–89)[2]	<0.0001‡
P value†	0.804	0.015‡	<0.0001‡	
Iron deficiency ¶(%)				
Baseline	15.4	10.9	13.3	0.418
End of intervention	13.8[1]	7.8[1]	51.6[2]	<0.0001‡
P value†	0.796	0.705	<0.0001‡	

Values are mean (SD; range) or percentage.

*Significance of difference among groups. Different superscripts indicate significant difference between groups ($P < 0.001$) after Bonferroni correction.

†Significance of within group longitudinal variation.

‡Statistically significant.

§The analysis was performed on log-transformed values because ferritin was not normally distributed.

¶Ferritin plasma concentration less than 12 μg/L.

recurrent skin infections (scabies and furunculosis). Two infants had arthritis (MMN, n = 1; FFA, n = 1), and one had meningitis (FFA group). No infant received commercial infant formula milk. Reported adverse events possibly related to treatment, including frequent or loose stools or diarrhea, occurred within the first 14 days of administration (MMN, n = 7; FFA, n = 7; placebo, n = 4). Darkening of stool or mild constipation or mild vomiting were more frequently reported in the FFA group (MMN, n = 3; FFA, n = 57). No caregiver reported that sprinkles changed color or taste or texture of any complementary food, but four infants refused complementary foods mixed with active sprinkles (MMN, n = 2; FFA, n = 2) starting from the 2nd to 34th week of treatment.

DISCUSSION

Protein-energy dense foods are required in developing world through the first 2 years of life to improve the nutritional status and growth of the infant. The present study examined the effects of daily supplements of iron combined either with folic acid plus zinc and multivitamin nutrients (MMN) or with folic acid alone (FFA) administered for a 12 month period as sprinkles daily added to complementary foods on growth, anemia, and iron deficiency in Cambodian infants aged 6 months at baseline.

Growth profile did not differ among active sprinkles or placebo and showed a progressive impairment of WAZ and LAZ in each group. This result is not unexpected and is in agreement with findings by other authors (6). Indeed, cereal-based complementary foods commonly consumed in the developing countries are inadequate sources of nutrients for the infant (14).

Active sprinkles showed comparable effectiveness in raising plasma hemoglobin levels of the infant at the end of the study and revealed similar values in recovery from anemia. Indeed, in the active treatment group, more than 50% of anemic infants at baseline exhibited hemoglobin 110 g/L or greater after 12 months of supplementation. On the contrary, in the placebo group, hemoglobin level significantly decreased; approximately 23% of infants worsened in anemia status, and only 22% of anemic infants recovered hemoglobin to nonanemic levels. Ferritin levels did not change in the MMN group, slightly increased in the FFA group, and were markedly reduced in the placebo group. At the same time, the rate of iron deficiency (plasma ferritin < 12 μg/L) did not show any significant change with active sprinkles but increased approximately fourfold in the placebo group. Finally, whereas in the MMN and FFA groups no infant developed IDA through the study period, the incidence of IDA in the placebo group (30%) was high and worrying. The relative comparability in efficacy on anemia and iron deficiency between active sprinkles might suggest that the addition of micronutrients to iron and folic acid may not completely counteract the final use of iron for hemoglobin synthesis, as it could be hypothesized on the basis of the results from a large trial (15), except that ferritin showed slightly better improvement in the FFA group.

It the present study, addition of zinc did not show any satisfactory effect on infants' growth. However, it should be pointed out that the investigated population showed both a marked overall nutrition imbalance and a remarkable detriment in anthropometric variables at baseline. Further large trials need to elucidate the effectiveness of zinc supplements on growth in high-risk populations. At any rate, recent studies point out the positive role of zinc in reducing the risk of infectious diseases (16).

The MMN sprinkles also contained multivitamins. Vitamin C is a well-known enhancer of iron absorption, particularly in a molar ratio of 4:1 with iron (17). In addition, supplements of vitamin D and vitamin A might play a role in improving the general metabolic conditions. Indeed, favorable metabolic interactions among iron, zinc, and vitamin A have been observed both in preschoolers (18) and nonpregnant, anemic women living in developing countries (19). It might therefore be hypothesized that although supplementation of iron plus zinc alone might result in competitive mechanisms in micronutrient use, further addition of vitamins could improve the use of iron, at least.

Last, compliance was satisfactory. Less than 3% of infants discontinued consuming active sprinkles. In regard to tolerability, only minor adverse events were reported, possibly related to treatment, more in infants receiving FFA than MMN supplements.

On the whole, the results of the present study suggest that starting supplements at the age of 6 months, when human milk alone fails to meet the dietary requirements and complementary foods of poor nutritional value are introduced, may be favorable both in improving hemoglobin levels and preventing the onset of IDA during the complementary feeding period in infants at risk of anemia who live in developing countries where common complementary foods are poor in nutritive value. Unfortunately, the current literature cites few studies examining the efficacy of sprinkled iron supplements that included infants /or young children at different ages (5–7); related findings are not fully comparable, and therefore no definite conclusion can be drawn on the optimal timing of the introduction of sprinkles. Further research needs also to evaluate the effects of sprinkles after the supplementation period.

Within the limitations of the present trial, it may be concluded that single daily supplement of ferrous fumarate plus folic acid, zinc, and other micronutrients or plus folic acid alone, administered for a 12 month period, may be both effective in prevention/treatment of anemia and satisfactorily safe. Indeed, a slightly better

improvement in plasma ferritin level and a higher occurrence of minor adverse events was observed in infants receiving supplement of iron plus acid folic alone.

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