Use of microencapsulated iron(II) fumarate sprinkles to prevent recurrence of anaemia in infants and young children at high risk

Stanley Zlotkin,[1,2,3] Kojo Yeboah Antwi,[4] Claudia Schauer,[2,3] & George Yeung[1,2,3]

Objective To compare the effectiveness of microencapsulated iron(II) fumarate sprinkles (with and without vitamin A), iron(II) sulfate drops, and placebo sprinkles in preventing recurrence of anaemia and to determine the long-term haematological outcomes in children at high risk of recurrence of anaemia 12 months after the end of supplementation.

Methods A prospective, randomized, placebo-controlled design was used to study 437 Ghanaian children aged 8–20 months who were not anaemic (haemoglobin ⩾100 g/l). Four groups were given microencapsulated iron(II) fumarate sprinkles, microencapsulated iron(II) fumarate sprinkles with vitamin A, iron(II) sulfate drops or placebo sprinkles daily for six months. Primary outcome measures were change in haemoglobin and anaemic status at baseline and study end. Non-anaemic children at the end of the supplementation period were reassessed 12 months after supplementation ended.

Findings Overall, 324 children completed the supplementation period. Among the four groups, no significant changes were seen in mean haemoglobin, ferritin or serum retinol values from baseline to the end of the supplementation period. During the trial, 82.4% (267/324) of children maintained their non-anaemic status. Sprinkles were well accepted without complications. At 12 months post-supplementation, 77.1% (162/210) of children with no intervention remained non-anaemic. This proportion was similar for children among the four groups.

Conclusion In most children previously treated for anaemia, further supplementation was not needed to maintain their non-anaemic status. These results may have important implications for community intervention programmes in which initial high-dose treatment is needed because of a high prevalence of anaemia.

Keywords Anemia, Iron-deficiency/drug therapy/prevention and control; Vitamin A/administration and dosage; Hemoglobins/analysis; Food, Fortified/utilization; Iron, Dietary/administration and dosage/therapeutic use; Ferrous compounds/administration and dosage/therapeutic use; Drug compounding; Patient compliance; Treatment outcome; Child; Infant; Ghana (*source: MeSH, NLM*).

Mots clés Anémie ferriprive/chimiothérapie/prévention et contrôle; Vitamine A/administration et posologie; Hémoglobines/analyse; Aliments enrichis/utilisation; Fer alimentaire/administration et posologie/usage thérapeutique; Ferreux composés/administration et posologie/usage thérapeutique; Préparation médicament; Observance prescription; Evaluation résultats traitement; Enfant; Nourrisson; Ghana (*source: MeSH, INSERM*).

Palabras clave Anemia ferropriva/quimioterapia/prevención y control; Vitamina A/administración y dosificación; Hemoglobinas/análisis; Alimentos fortificados/utilización; Hierro en la dieta/administración y dosificación/uso terapéutico; Compuestos ferrosos/administración y dosificación/uso terapéutico; Composición de medicamentos; Cooperación del paciente; Resultado del tratamiento; Niño; Lactante; Ghana (*fuente: DeCS, BIREME*).

Bulletin of the World Health Organization 2003;81:108-115.

Voir page 114 le résumé en français. En la página 115 figura un resumen en español.

Introduction

Iron-deficiency anaemia is a leading cause of morbidity and mortality worldwide and affects up to two-thirds of children in most developing countries (*1*). Infants and young children aged 6–18 months are particularly vulnerable to iron-deficiency anaemia because their requirement for iron is high (*2*). The effects of anaemia on child development are especially serious: poor cognitive development, decreased future learning and school achievement, decreased resistance to illness and disease, and eventually reduced wages and quality of life (*3–6*). Numerous studies have shown that moderate anaemia (haemoglobin <100 g/l) is associated with depressed mental (social and cognitive) and motor development in children, which may not be reversible (*7–9*). Prevention of anaemia in early childhood must therefore be the goal of intervention programmes.

In 1996, a group of consultants from the United Nations Children's Fund (UNICEF) reviewed possible interventions to treat and prevent anaemia. Although the available interventions (syrup and drops for infants and children, and capsules for women) were efficacious, they were not always effective (*10*). For many reasons, adherence to such treatments is poor — despite multiple efforts to influence and improve it — and this renders them ineffective for use as long-term prophylac-

[1] Departments of Paediatrics, Nutritional Sciences and Centre for International Health, University of Toronto, Toronto, Canada.

[2] Division of Gastroenterology and Nutrition, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8 (email: stanley.zlotkin@sickkids.ca). Correspondence should be addressed to Dr Zlotkin at this address.

[3] Programs in Metabolism and Integrative Biology, Research Institute, The Hospital for Sick Children, Toronto, Canada.

[4] Kintampo Health Research Centre, Health Research Unit, Ministry of Health, Ghana.

Ref. No. **02-0258**

tics. The challenge therefore was to develop a new strategy to provide micronutrients (including iron) to at-risk populations. As a result, "sprinkles" — through which encapsulated micronutrients in powder form could be added directly to food at the household level — were developed. The micronutrients are encapsulated in a thin coating of a soy-based hydrogenated lipid, which prevents the micronutrients from oxidizing the food. Thus the colour or taste of food to which sprinkles are added does not change. The encapsulated micronutrients are packaged in single-dose sachets to ensure that the correct amount of iron is given. The contents of the sachets are then sprinkled onto whatever food is served in the household, including typical complementary and family foods. This type of intervention is called "home fortification", to distinguish it from "commercial fortification", in which the addition of fortificants to a complementary cereal occurs in a large central facility.

We recently showed that sprinkles are as efficacious as iron(II) sulfate drops in treating anaemia when added to complementary foods at the household level; treatment of anaemia was successful in 58% of Ghanaian infants who received sprinkles for two months (*11*). Moreover, the common side-effects associated with drops — such as teeth staining, unpleasant metallic taste, gastrointestinal upset and measurement difficulties — were avoided.

Concurrent multiple micronutrient deficiencies may limit the response of haemoglobin to iron. For example, strong evidence shows that concomitant iron and vitamin A deficiencies may exacerbate anaemia by limiting erythropoiesis. It has been suggested, therefore, that multiple micronutrient supplementation may be beneficial and might improve outcomes (*12*). Vitamin A and iron deficiency often coexist and result in nutritional anaemia (*13*). Nutrient interactions, however, mean that liquid iron–vitamin combination supplements suitable for use in infants and young children are not available widely (*14*). As the iron in "sprinkles" is micro-encapsulated, other micronutrients — such as vitamin A, folic acid, vitamin B_{12} and ascorbic acid — can be included without significant loss of nutrient stability (*11*).

Long-term follow-up of infants and young children successfully treated for moderate anaemia, who are at high risk of recurrence, has not been documented. Whether these children would benefit from continued prophylactic supplementation and which form of iron would be most suitable for long-term use are uncertain. In the current study, our primary objectives were to compare the efficacy of microencapsulated iron(II) fumarate sprinkles (with and without vitamin A) and iron(II) sulfate drops with placebo sprinkles in preventing recurrence of anaemia and to determine the long-term haematological outcome in a cohort of high-risk children 12 months after supplementation ended.

Methods

Study area, participants and recruitment

The current study took place in the field study area of the Kintampo Health Research Centre in the Brong-Ahafo Region of Ghana. Directly before the study, all children had received treatment for moderate anaemia (haemoglobin, 70–100 g/l) with iron for two months (August–September 1999) (*11*). Only children who had been treated successfully to achieve haemoglobin levels ⩾100 g/l were eligible for the current study. Further eligibility criteria included that children were aged 8–20 months at recruitment, were ingesting a weaning food in addition to breast milk, and were expected to remain in the study district for 18 months.

Prophylactic supplementation was provided to children for six months between October 1999 and March 2000. Children who maintained a haemoglobin level ⩾100 g/l at the end of the treatment period were reassessed at 12 months post-supplementation. Children who became anaemic by the end of the supplementation or post-supplementation periods were discharged and provided with appropriate treatment.

Study design

Children were randomized individually to one of four treatment groups (Fig. 1). Randomization used sealed opaque envelopes that contained group designations generated randomly by computer (Microsoft Access 97, Microsoft Corporation, Seattle, WA, USA). Blinding of the field staff or mothers to the group assignments was not feasible, because one group received drops, while the other three received sachets of sprinkles. All were blinded to the content of the sachets, however, and the people responsible for laboratory and data analyses were blinded to the group designations. The entire contents of a sachet were added to each infant's meal serving (after cooking) once daily. Iron drops were provided once daily on an empty stomach.

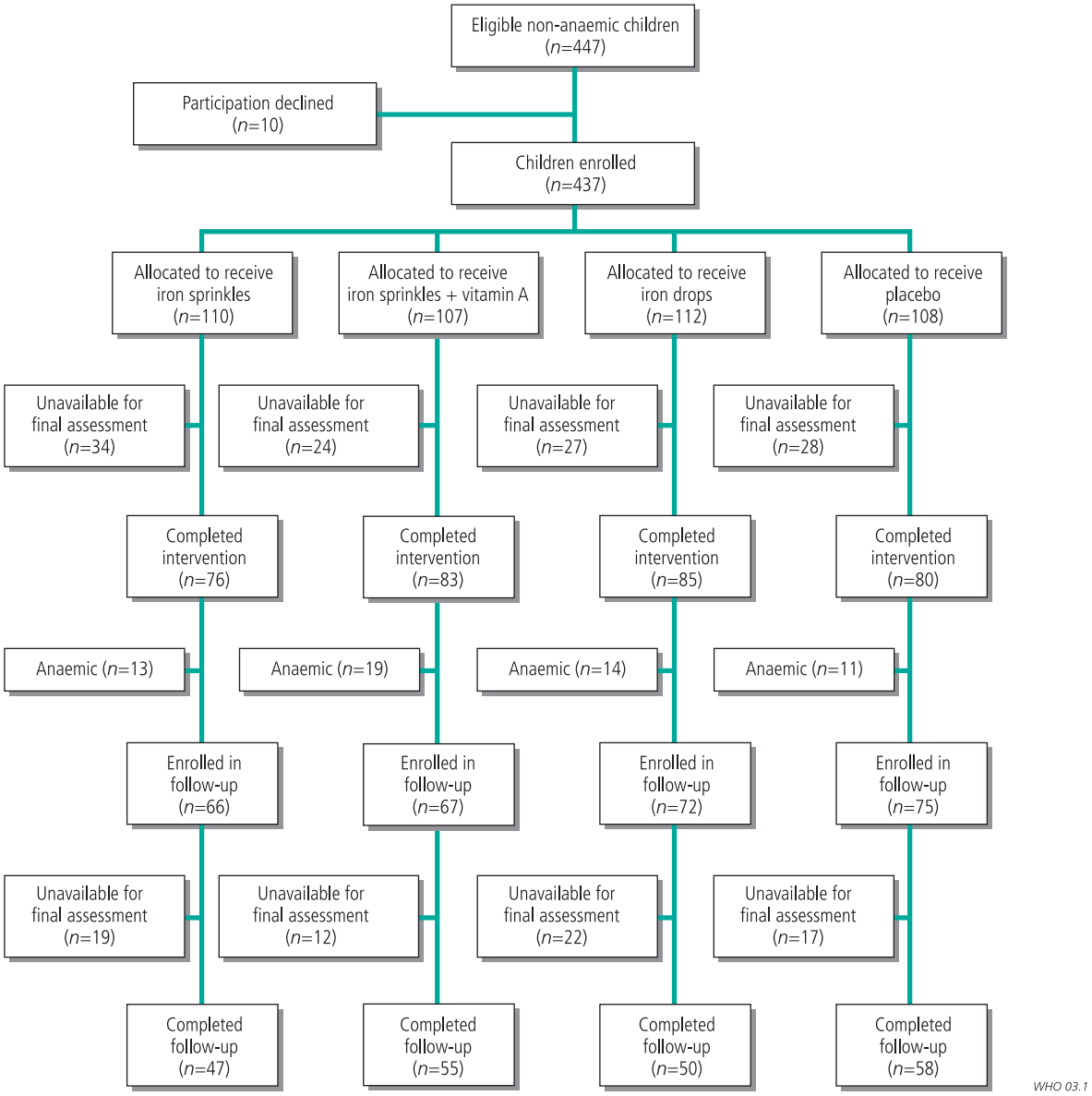
The dosage of elemental iron (12.5 mg/day) in the "gold standard" group (iron(II) sulfate drops) was based on recommendations from a UNICEF consultation group (*10*). The dosage of iron in the sachets (40 mg/day) was approximately three times that of the drops. This dosage was chosen on the basis of estimates that absorption of microencapsulated iron(II) fumarate sprinkled onto food would be about one-third of that of drops because of the presence of dietary phytate — a potent inhibitor of iron absorption (*15*). In addition to iron (40 mg), sachets in the iron + vitamin A group were formulated to contain a daily dose of vitamin A (600 μg retinol equivalents) as retinol acetate.

Field workers visited children every two weeks over a six-month period to distribute drops or sprinkles. Baseline assessments involved a questionnaire on sociodemographic, nutritional and health factors. At bi-monthly and final visits, side-effects, ease of use, and adherence to treatment were determined by questionnaire. Empty sachets were counted, and the height of liquid remaining in bottles of iron drops was measured.

During the post-supplementation period, parents were given no specific advice on feeding practices or prevention of anaemia, and they were not given any iron or vitamin supplements.

Weight and height were measured at baseline and at the end of the supplementation period using techniques previously described (*11*). Capillary blood samples (0.5 ml) were obtained at baseline, the end of the supplementation period, and the end of the post-supplementation period. Haemoglobin levels were determined using portable HemoCue photometers (HemoCue AB, Ångelholm, Sweden) (*16*). Blood samples were preserved in ice-lined cold boxes, which were returned to the base station within six hours of the blood being collected. The serum was separated by centrifugation (10 min at 12 000 g) before being stored at –40 °C. Serum ferritin was assayed in duplicate with a commercial enzyme-linked immunosorbent assay (ELISA); vitamin A was determined at the Naguchi Memorial Institute

Fig. 1. **Trial profile**



of Medical Research, Accra, Ghana, by means of high-performance liquid chromatography that used retinyl acetate as an internal standard (*17, 18*).

Sample size and power

The primary outcome was prevention of anaemia (proportion of children with haemoglobin ⩾100 g/l). We assumed that 30% of children in the placebo control group would be anaemic at the end of the intervention. We wanted to detect a two-thirds reduction in the prevalence of anaemia (to 10%) with a type I error set at 0.05 and a 0.9 probability of detecting a true difference. The final sample size estimate was 97 children per group. The actual power of this study based on a comparison of the sprinkles plus vitamin A group with the control group was 0.8.

Data processing and analysis

Data were entered in Visual Fox Pro 6.0 (Microsoft Corporation, Seattle, WA, USA), verified and checked for range and consistency with customized data-entry and processing programs (Microsoft Access 97, Microsoft Corporation, Seattle, WA, USA) as previously described (*11*). Data were analysed with Statistical Analysis Software 8.0 (SAS Institute, Inc, Carey, NC, USA). We used a χ^2 test to compare the proportion of children who became anaemic in each group and to test for differences in rates of anaemia after supplementation due to potential confounding from breast-feeding history, diarrhoea, and hospitalization status. Paired *t* tests were used to analyse the change in haemoglobin, ferritin, and anthropometric measurements within groups. Differences between the groups in terms of haemoglobin and ferritin levels as well as in anthropometric measurements at the beginning, the end of the intervention and factors affecting haemoglobin values were assessed by ANOVA (Proc Glm). Changes in the proportions of children with iron depletion (ferritin <12 μg/l) within groups were assessed by McNemar's test. All analyses of ferritin values were conducted on log-transformed data because of their skewed

frequency distribution. The acceptable level of statistical significance was $P<0.05$.

Ethics and consent

Ethical approval was obtained from the Hospital for Sick Children (Toronto, Canada), the London School of Hygiene and Tropical Medicine (London, England) and Ghana's Ministry of Health (Kintampo, Ghana). Informed consent to conduct the study in Kintampo District was obtained verbally from the District Assembly of Elected Representatives, village elders in each village and through signed consent from the mothers of children in the study.

Results

Randomization and progress through study

Of the 437 children enrolled in the study, 113 (25.9%) were lost to follow-up by the end of the supplementation period (Fig. 1). Losses to follow-up were similar among the four treatment groups, and no differences in baseline characteristics were found between children lost to follow-up and those who completed the study. Many of the children who did not complete the study were from farming communities, the members of which periodically leave their villages for seasonal jobs. Of the 324 children who completed the supplementation period, 280 were non-anaemic and therefore were eligible for follow-up. At 12 months post-supplementation, a further 70 (25%) children were unavailable for reassessment. This loss was similar among the treatment groups and no differences were found in baseline characteristics between these children and those who completed the trial.

Baseline characteristics

There were no significant differences among groups in terms of sex, distribution, mean age, and mean haemoglobin, serum ferritin, and serum retinol values at baseline (Table 1). Overall, 202/324 (62.3%) of all children tested positive for malaria; these children were distributed equally among the four groups.

Primary outcome measures

Mean haemoglobin levels did not change significantly over the supplementation period in any of the four groups (Table 2). Final haemoglobin levels were not associated with initial age ($P=0.15$), initial haemoglobin levels ($P=0.26$), sex ($P=0.86$), group designation ($P=0.76$), or their interactions ($P=0.19$). The children who became anaemic were distributed equally among the groups (Table 2). Overall, 267/324 (82.4%) children maintained their non-anaemic status (haemoglobin $\geqslant$100 g/l) (Fig. 2).

At 12 months post-supplementation, significant decreases in mean haemoglobin levels were seen within each of the groups, although there was no difference in mean decrease between the four groups. Overall, mean ± SD haemoglobin levels decreased from 112.6 ± 14.7 g/l at the end of the supplementation period to 107.6 ± 19.0 g/l 12 months later ($P<0.001$). The proportion of children who became anaemic was similar among the four groups. Overall, 77.1% (162/210) maintained their non-anaemic status during the post-supplementation period (Fig. 2).

Secondary outcome measures

Geometric mean ferritin values within groups did not significantly change over the supplementation period and were similar among groups at the end (Table 2). No change was seen in the proportion of children with iron depletion (ferritin <12 μg/l), including those who received placebo: overall 18/297 (6.1%) children were iron depleted at baseline and 17/297 (5.7%) at the end of the supplementation period ($P>0.05$). At 12 months post-supplementation, modest decreases were seen in the ferritin values; these only reached significance for the iron sprinkles group (81.0–51.8 μg/l, $P=0.03$).

To conserve resources, serum retinol concentrations were analysed only from the blood samples of children in the iron and iron + vitamin A sprinkles groups. At baseline, 70/159 (44.0%) had serum retinol levels <0.7 μmol/l, which indicated mild vitamin A deficiency, and 17/159 (10.7%) had levels <0.35 μmol/l, which suggested severe deficiency (*7*). No significant changes were seen in mean retinol values over the supplementation period within the two groups ($P=0.45$) (Table 3), and no difference was seen between the groups. No change from baseline was seen in the proportion of children with moderate or severe deficiency after supplementation.

Table 1. **General baseline characteristics of study children**

Characteristic	Sprinkles			Iron drops (*n* = 85)
	Iron (*n* = 76)	Iron + vitamin A (*n* = 83)	Placebo (*n* = 80)	
Boys (%)	47	57	54	52
Girls (%)	53	43	46	48
Malaria positive (%)	62	60	61	66
Mean ± SD				
Haemoglobin ± SD (g/l)	112.3 ± 9.1	112.7 ± 9.2	112.8 ± 8.5	113.3 ± 8.8
Age ± SD (months)	15.4 ± 4.4	15.9 ± 5.0	15.2 ± 4.1	16.5 ± 3.9
Serum ferritin (μg/l)[a]	69.1 (7.3–346.5)[b]	53.2 (3.7–341.2)	72.7 (6.6–363.6)	63.4 (4.4–333.7)
Serum retinol ± SD (μmol/l)	0.82 ± 0.25	0.79 ± 0.34	NR[c]	NR
Weight-for-age *Z* score ± SD	–1.27 ± 0.99	–1.50 ± 0.)	–1.48 ± 1.07	–1.48 ± 1.01
Height-for-age *Z* score ± SD	–1.33 ± 1.40	–1.35 ± 1.71	–1.43 ± 1.27	–1.74 ± 1.00
Weight-for-height *Z* score ± SD	–0.53 ± 0.87	–0.82 ± 1.15	–0.75 ± 0.88	–0.53 ± 0.87

[a] Geometric mean.
[b] Figures in parentheses are the range.
[c] NR = not recorded.

Table 2. **Mean haemoglobin, serum ferritin, and serum retinol levels and percentage of anaemic participants by treatment group at baseline and after six-month supplementation period**

Variable	Sprinkles			Iron drops (*n* = 85)	*P*-value across groups
	Iron (*n* = 76)	Iron + vitamin A (*n* = 83)	Placebo (*n* = 80)		
Mean ± SD haemoglobin (g/l)					
Baseline	112.3 ± 9.1	112.7 ± 9.2	112.8 ± 8.5	113.3 ± 8.8	0.904
End of supplementation	112.4 ± 17.1	110.7 ± 13.2	113.3 ± 13.9	112.5 ± 14.6	0.705
Difference	0.2 ± 16.8	–2.1 ± 13.6	0.5 ± 14.1	–0.8 ± 15.4	0.705
P-value for difference	0.924	0.172	0.770	0.643	
Participants with anaemia (%)					
Baseline	0	0	0	0	NA[a]
End of supplementation	13 ± 17.1	19 ± 22.9	11 ± 13.8	14 ± 16.5	NA
Geometric mean ferritin (μg/l)[b]					
Baseline	69.1 (7.3–346.5)[c]	53.2 (3.7–341.2)	72.7 (6.6–363.6)	63.4 (4.4–333.7)	0.711
End of supplementation	62.8 (2.5–318.4)	75.9 (5.5–384.7)	86.0 (0.5–369.2)	71.0 (5.1–365.9)	0.477
Difference	–6.2	22.7	13.3	7.61	0.519
P-value for difference	0.803	0.105	0.548	0.877	
Mean ± SD retinol (μmol/l)					
Baseline	0.82 ± 0.25	0.79 ± 0.34	NR[d]	NR	0.536
End of supplementation	0.78 ± 0.23	0.74 ± 0.30	NR	NR	0.448
Difference	–0.04 ± 0.28	–0.05 ± 0.43	NR	NR	0.952
P-value for difference	0.336	0.449			

[a] NA = non applicable.
[b] Analysis done with log transformed values because ferritin concentrations were not normally distributed.
[c] Figures in parentheses are the range.
[d] NR = not recorded.

The mean weight-for-age, height-for-age and weight-for-height *Z* scores at the start and end of the supplementation period were similar among all groups. A significant decline was seen in overall weight-for-age and height-for-age *Z* scores (Table 3).

Other sources of dietary iron and ascorbic acid

Breastfeeding history and dietary characteristics did not differ significantly among the groups. Breast milk was the primary food source for 402/437 (92%) of children at the start of the intervention and 227/324 (70%) six months later. Fewer than 8/437 (2%) of children received milk powder or formula (non-iron fortified). Porridge made from local corn (fermented maize) was the food consumed most frequently.

Use of supplements

More than 80% of children in all groups received drops or sprinkles on at least four days per week, and most received the intervention every day for the entire six-month supplementation period. Most children expressed a dislike for the drops: 301/324 (92.9%) closed their mouth tightly, made a "funny face" or objected in some way. In contrast, only 21/324 (6.5%) objected to taking sprinkles. Less than 1% (3/324) of parents reported having any problem giving the sprinkles. Only 7/324 (2%) reported that they had an unpleasant odour and 213/324 (65.7%) said that the sprinkles changed the colour of their infant's food from a creamy white to a speckled white (much like adding pepper to food). In total, 323/324 (99.7%) used the entire contents of the sachet and 323/324 (99.7%) of children ate all the food in the bowl to which the sprinkles were added. Only 1/324 (0.3%) gave the sprinkles to a "non-study" child or shared their food bowl with another child in the household.

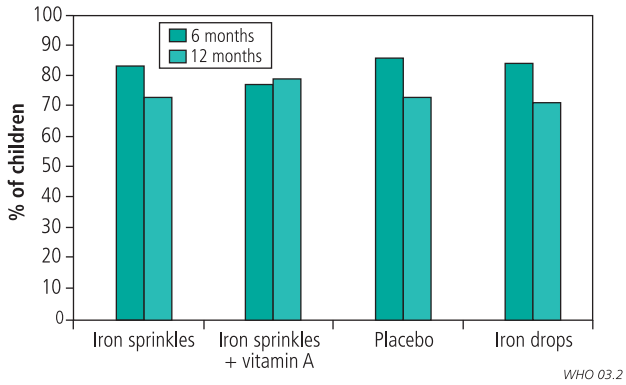
Discussion

In a setting rife with intestinal parasites, malaria and infectious diarrhoea, and where the typical diet is fermented maize porridge (a very poor source of bioavailable iron), we hypothesized that children previously treated for anaemia would quickly redevelop the condition unless provided with supplemental iron. Results from the current study did not support this hypothesis. Iron and haematological status were maintained equally well by iron supplements (with and without vitamin A) and placebo supplements. Of the children reassessed at 12 months post-supplementation who received no iron or dietary interventions during this period, mean haemoglobin concentrations decreased; however, 77% of children maintained their non-anaemic status.

Reasons for lack of effect

A number of possible explanations exist for why iron supplements were no more effective than placebo in maintaining iron status. Iron absorption increases and decreases in response to body stores of iron (*19*). In the presence of adequate iron stores, the intestinal iron transporter, divalent metal transporter 1 (DMT-1), is downregulated (*20*). As all children were non-anaemic with adequate stores at the time of enrolment, absorption from the iron supplements was likely to be minimal. In addition, iron requirements during the study period were decreasing as the children aged. During the study, children were in the second year of life (mean age at baseline, 16 months). The rate of haemoglobin formation, and hence the amount of iron needed for erythropoiesis, is a function of increase in blood volume, which is directly proportional to growth rate. During the first year of life, blood volume doubles between 6 and 12 months of age, but in the

Fig. 2. **Proportion of children remaining non-anaemic (haemoglobin >100g/l) in each group at end of six-months supplementation period and 12 months post-supplementation**



second and subsequent years until adolescence, growth, and hence blood volume expansion, slows considerably; thus iron needs are considerably lower for children aged 12–24 months than for those <12 months (*21*).

In addition to diminished iron needs and absorption, there are at least three other possible explanations for why iron supplements were no more effective than placebo in maintaining iron status. The most obvious is that iron stores were full enough after adequate treatment to maintain active haematopoiesis and iron status for the next six months. Secondly, during the second year of life, the variety of foods eaten was likely to be wider; this would increase the amount of dietary iron consumed from haeme and non-haeme sources. Unfortunately, we did not collect detailed records on food intake from participants in the current study, but recent data from the study area on food intake for children in the age range included in the current study show that approximately 16% of children would have ingested at least one source of haeme over a one-week period (Arthur P, personal communication, 2000). This small source of haeme, in addition to the mobilization of iron stores, may help explain why the placebo group responded like the other groups. Finally, the supplementation period began at the end of the rainy season and had finished by the end of the dry season. Malaria is likely to have been less severe during this six-month period than during the rainy season, when its burden is increased and thus, anaemia is more prevalent. Although the risk of micronutrient deficiencies at the end of the dry season is high because of food scarcity, higher haemoglobin values have been reported among young children in northern Ghana during this period than in the rainy season (*22*). Iron supplementation in our study may have shown no effect because children were at lower risk of developing malaria and iron deficiency than expected due to previous treatment and decreased iron needs.

Similarly, the above factors probably explain the surprisingly slow decline in haematological status during the 12-month post-supplementation period. Although mean haemoglobin levels decreased significantly across all groups, the values were still well above our cut-off for anaemia (haemoglobin 100 g/l). Moreover, the proportion of non-anaemic children one year post-supplementation was 70–80%.

At baseline, approximately 44% of children were found to have mild vitamin A deficiency (serum retinol <0.7 μmol/l). An array of epidemiological studies indicates that vitamin A

Table 3. **Mean weight-for-age, height-for-age and weight-for-height *Z* scores at start and end of the supplementation phase**

Time	*Z* score[a]		
	Weight-for-age	Height-for-age	Weight-for-height
Start of supplementation period	–1.49	–1.55	–0.67
End of supplementation period	–1.59	–1.75	–0.74
P-value for difference	0.0002	<0.0001	0.08

[a] *Z* scores were similar among groups, so they were collapsed across groups to give overall mean at start and end of supplementation period. Mean differences were compared with a paired *t*-test.

deficiency and anaemia often coexist and that significant associations exist between serum retinol and biochemical indicators of iron status (*13*). Nutritional interventions with vitamin A have resulted in a positive effect on iron status. For example, Hodges et al. reported that human adults depleted of vitamin A developed mild anaemia that responded to iron treatment only after their vitamin A status had been improved (*23*). In the current study, the provision of iron and vitamin A did not improve haematological outcomes compared with the other groups and, indeed, did not improve biochemical vitamin A status. A possible explanation for the failure of vitamin A supplementation to improve serum retinol concentrations may have been the presence of concurrent zinc deficiency, which has been shown to limit the mobilization of vitamin A from the liver and its transport into the circulation (*24*). A number of studies have reported a response to vitamin A supplementation in malnourished or zinc-deficient children only when zinc and vitamin A supplementation were combined (*25, 26*). A significant proportion of our participants was likely to have been zinc deficient because iron and zinc deficiencies often coexist in West Africa, where the primary food source, fermented maize porridge, is such a poor source of iron and zinc (*15*).

The observation that ferritin values were similar among groups and did not increase more with iron supplementation than with placebo during the supplementation period seemingly is inconsistent with what might have been expected. However, the insensitivity of ferritin as a marker of iron stores under tropical field conditions is well documented. Wide intra- and inter-individual variabilities of ferritin measurements have been documented even under controlled situations, and ferritin is an acute phase reactant, with inflammation resulting in spuriously high levels (*27*). In the current study, over 60% of subjects had evidence of malaria parasites in their blood. This undoubtedly resulted in high concentrations of ferritin across the groups, which may have masked the effect of supplementation (*28*).

Generalizability of results

An issue of relevance to this study is the generalizability of the results. A considerable limitation was the significant loss to follow-up, which is a common cause of missing data, especially for long-term studies. We had a 25% drop-out rate over the supplementation period; this was due mainly to the mobile nature of farmers in this agricultural community. The baseline characteristics of those who did not complete the study were, however, not different from those who were available for reassessment. Moreover, despite a high loss to follow-up, the

study still had sufficient power (80%) to detect a true difference between the iron interventions (sprinkles and drops) and placebo. On the basis of these results, we accepted the null hypothesis that no differences existed in the proportion of anaemic children or in the change in haemoglobin levels between the groups. At 12 months post-supplementation, we had a similar rate of loss to follow-up (25%); as before, the baseline characteristics of those who were not available for follow-up were not different from those who completed the study. A reasonable conclusion therefore is that the results for the children who did not complete the study would have been similar to those for children who did.

Alternatively, those who were not available for the reassessment surveys may have been at higher risk for anaemia because of iron deficiency or malaria. We believe this was unlikely, however, because the population studied was homogeneous in terms of socioeconomic status and because exposure to malaria is endemic among the entire population. Moreover, the study was community-based — among many villages in the region — and all eligible children from a village were recruited into the study, thus preventing selection bias. Nevertheless, taking the worst-case scenario — that all those unavailable would have been anaemic — 56% would have remained non-anaemic after a further 12 months without prophylactic iron. The generalizability of these results depends on which of these two scenarios most closely reflects "reality". If we take a "middle-of-the-road" position, 65–70% would have remained free of anaemia — still a significant number of children.

Conclusions

Much can be learned from this study about pragmatic approaches to reducing the prevalence of anaemia. In populations where the baseline prevalence of anaemia is high (as in Ghana), we believe that it is necessary to supply therapeutic iron at a dose high enough to treat the condition but within a safe limit for those who are non-anaemic. In the current study, prophylactic iron supplementation that continued after anaemia was resolved showed no advantage over placebo for most children. These findings do not support the continued use of long-term prophylactic iron supplementation to maintain iron status for children previously treated for iron-deficiency anaemia. This latter observation is of particular importance because long-term interventions have been neither available nor successful. This study was the first to use microencapsulated iron(II) fumarate sprinkles for a prolonged period of time. Our observation that sprinkles were well tolerated and better accepted by children and their mothers than iron drops over the six-month supplementation period suggests that this intervention may play a role in reducing the prevalence of anaemia. Our study population was representative of typical populations in Ghana in terms of socio-demographic composition; therefore, results from this study may be generalizable to other countries within west and sub-Saharan Africa, where the etiology and prevalence of anaemia are similar. ■

Acknowledgements

This research was supported by a grant from US Agency for International Development's Opportunities for Micronutrient Interventions Research Program through the Human Nutrition Institute of the International Life Sciences Institute Research Foundation and the Canadian Institutes of Health Research. Mead Johnson Canada generously provided material support. This research is dedicated to the memory of Dr Paul Arthur, who was co-principal investigator, but who suddenly and tragically died soon after the project was completed.

Conflicts of interest

Dr Zlotkin is an occasional consultant to Bristol Myers Squibb, General Mills Canada and Mead Johnson Ltd. Dr Zlotkin owns the intellectual property right to Supplefer Sprinkles. The H.J. Heinz Company Ltd supports the technical development of the sprinkles on a "cost-recovery" basis.

Résumé

Utilisation de microgranules de fumarate ferreux pour empêcher les récidives d'anémie chez les nourrissons et les jeunes enfants à haut risque

Objectif Comparer l'efficacité de microgranules de fumarate ferreux (avec ou sans vitamine A), de gouttes de sulfate ferreux et de microgranules de placebo pour empêcher les récidives d'anémie, et déterminer les résultats hématologiques à long terme (12 mois après la fin de la supplémentation) chez des enfants à haut risque de récidive de l'anémie.

Méthodes Une étude prospective randomisée contre placebo a été réalisée chez 437 enfants ghanéens âgés de 8 à 20 mois, non anémiques (hémoglobine $\geqslant$ 100 g/l). Quatre groupes ont reçu, respectivement, des microgranules de fumarate ferreux, des microgranules de fumarate ferreux avec vitamine A, des gouttes de sulfate ferreux ou des microgranules de placebo chaque jour pendant six mois. Les principaux résultats recherchés étaient les modifications du taux d'hémoglobine et la présence ou non d'une anémie avant l'étude (valeurs de référence) et à la fin de celle-ci. Les enfants non anémiques à la fin de la période de supplémentation ont été réexaminés 12 mois plus tard.

Résultats Au total, 324 enfants ont reçu la supplémentation jusqu'à la fin. Parmi les quatre groupes, aucune modification significative n'a été observée, que ce soit au niveau des taux moyens d'hémoglobine, de ferritine ou de rétinol sérique, entre les valeurs de référence et celles mesurées à la fin de la période de supplémentation. Au cours de l'essai, 82,4 % (267/324) des enfants sont restés indemnes d'anémie. Les microgranules ont été bien acceptés, sans complications. Douze mois après la fin de la supplémentation, 77,1 % (162/210) des enfants n'ayant fait l'objet d'aucune intervention étaient restés indemnes d'anémie. Cette proportion était du même ordre dans tous les groupes.

Conclusion Chez la plupart des enfants déjà traités pour une anémie, une nouvelle supplémentation n'était pas nécessaire pour empêcher les récidives d'anémie. Ces résultats peuvent avoir des répercussions importantes sur les programmes d'intervention en communauté dans lesquels un traitement initial par de fortes doses est nécessaire du fait de la forte prévalence de l'anémie.

Resumen

Uso de microgránulos de fumarato ferroso para prevenir la reaparición de anemia en los lactantes y los niños pequeños con alto riesgo

Objetivo Comparar la eficacia de los microgránulos de fumarato ferroso (con y sin vitamina A), las gotas de sulfato ferroso y microgránulos placebo como medios de prevención de la reaparición de la anemia y determinar los resultados hematológicos a largo plazo en los niños con alto riesgo de reaparición de la anemia 12 meses después del término de la administración de los suplementos.

Métodos Se emprendió un estudio prospectivo, aleatorizado y controlado mediante placebo para estudiar a 437 niños de Ghana de 8-20 meses que no presentaban anemia (hemoglobina $\geqslant$100 g/l). Cuatro grupos recibieron microgránulos de fumarato ferroso, microgránulos de fumarato ferroso con vitamina A, gotas de sulfato ferroso o microgránulos placebo durante seis meses. Los efectos principales determinados fueron la variación del nivel de hemoglobina y el cambio en el estado de anemia entre la situación de partida y el final del estudio. Los niños sin anemia al final del periodo de suplementación fueron reexaminados 12 meses después de la conclusión de la administración de los suplementos.

Resultados Globalmente, completaron la suplementación 324 niños. En los cuatro grupos, no se observaron cambios importantes entre la situación basal y el final de la suplementación en lo referente a los valores medios de hemoglobina, ferritina o retinol sérico. Durante el ensayo, el 82,4% (267/324) de los niños mantuvieron su estado no anémico. Los microgránulos fueron bien aceptados, sin complicaciones. A los 12 meses de acabada la suplementación, el 77,1% (162/210) de los niños privados de intervención seguían sin anemia. Esa proporción fue semejante en los cuatro grupos.

Conclusión En la mayoría de los niños previamente tratados contra la anemia, no hubo necesidad de administrar nuevos suplementos para mantenerles libres de esa enfermedad. Estos resultados pueden tener implicaciones importantes para los programas de intervención comunitaria en los que la alta prevalencia de anemia exige tratamientos iniciales con dosis altas.

References

1. World Health Organization. *Malnutrition. The global picture.* Geneva: World Health Organization; 2000.
2. Institute of Medicine. *Dietary reference intakes. Vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, zinc.* Washington (DC): National Academy of Sciences; 2001.
3. Walter T. Infancy: mental and motor development. *American Journal of Clinical Nutrition* 1989;50:655-66.
4. Oski FA, Honig AS, Helu B, Howanitz P. Effect of iron therapy on behavior performance in nonanemic, iron-deficient infants. *Pediatrics* 1983;71:877-80.
5. Watkins WE, Pollitt E. Iron deficiency and cognition among school-age children. In: *Nutrition, health, and child development: research advances and policy recommendations.* Washington (DC): Pan American Health Organization, The World Bank and Tropical Medicine Research Unit; 1997. p.179-97.
6. Thomas D, Frankenberg E. Health, nutrition and prosperity: a microeconomic perspective. *Bulletin of the World Health Organization* 2002;80:106-13.
7. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. *Journal of Nutrition* 2001;131:649S-68S.
8. Lozoff B, Brittenham GM, Wolf AW, McClish DK, Kuhnert PM, Jimenez E et al. Iron deficiency anemia and iron therapy effects on infant developmental test performance. *Pediatrics* 1987;79:981-95.
9. Lozoff B, Jimenez MD, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics* 2000;105: 852. Available from: URL: http://www.pediatrics.org/cgi/content/full/105/4/e51
10. Nestel P, Alnwick D, editors. *Iron/multi-micronutrient supplements for young children. Summary and conclusions of a consultation held at UNICEF Copenhagen, Denmark, 1996 August 19-20.* Washington DC: International Life Sciences Institute;1997.
11. Zlotkin S, Arthur P, Antwi KY, Yeung G. Treatment of anemia with microencapsulated ferrous fumarate plus ascorbic acid supplied as ''sprinkles'' added to complementary (weaning) foods. *American Journal of Clinical Nutrition* 2001:74;791-5.
12. Allen LH. Iron supplements: scientific issues concerning efficacy and implications for research and programs. *Nutrition* 2002;132(4 Suppl):813S-9S.
13. Bloem MW, Wedel M, Egger RJ, Speek AJ, Schrijver J, Saowakontha S et al. Iron metabolism and vitamin A deficiency in children in Northeast Thailand. *American Journal of Clinical Nutrition* 1989;50:332-8.
14. Mejía LA, Chew F. Hematological effect of supplementing anemic children with vitamin A alone and in combination with iron. *American Journal of Clinical Nutrition* 1988;48:595-600.
15. Gibson RS, Ferguson EL, Lehrfeld J. Complementary foods for infants feeding in developing countries: their nutrient adequacy and improvement. *European Journal of Clinical Nutrition* 1998;52:764–70.
16. Cohen AR, Seidl-Friedman J. HemoCue system for haemoglobin measurement. Evaluation in anemic and nonanemic children. *American Journal of Clinical Pathology* 1988;90:302-5.
17. Miles LEM, Lipschitz DA, Bieber CP, Cook JD. Measurement of serum ferritin by a 2-site immunoradiometric assay. *Analytical Biochemistry* 1974;61:209-24.
18. International Vitamin A Consultative Group. *Biochemical methodology for the assessment of vitamin A status.* Washington (DC): Nutrition Foundation; 1982.
19. Cook JD, Layrisse M, Finch CA. The measurement of iron absorption. *Blood* 1969;33:421-9.
20. Eisenstein RS. Iron regulatory proteins and the molecular control of mammalian iron metabolism. *Annual Review of Nutrition* 2000;20:627-62.
21. Dallman PR. Changing iron needs from birth through adolescence. In: Fomon SJ, Zlotkin SH, editors. *Nutritional anemias, Nestlé Nutrition Workshop Series, Volume 3.* New York (NY): Lippincott/Raven Press;1992. p.29-38.
22. Koram KA, Owusu-Agyei S, Utz G, Binka FN, Baird JK, Hoffman SL, et al. Severe anemia in young children after high and low malaria transmission seasons in the Kassena-Nankana district of northern Ghana. *American Journal of Tropical Medicine and Hygiene* 2000;62:670-4.
23. Hodges RE, Sauberlich HE, Canham JE, Wallace DL, Rucker RB, Mejia LA et al. Hematopoietic studies in vitamin A deficiency. *American Journal of Clinical Nutrition* 1978;31:876-85.
24. Smith JE, Brown ED, Smith JC Jr. The effect of zinc deficiency on the metabolism of retinol-binding protein in the rat. *Journal of Laboratory and Clinical Medicine* 1974;84:692-7.
25. Shingwekar B, Mohanram M, Reddy V. Effect of zinc supplementation on plasma levels of vitamin A and retinol-binding protein in malnourished children. *Clinica Chimica Acta* 1979;93:97-100.
26. Christian P, West KP Jr. Interactions between zinc and vitamin A. An update. *American Journal of Clinical Nutrition* 1998;68:435S-41S.
27. Cooper MJ, Zlotkin SH. Day-to-day variation of transferrin receptor and ferritin in healthy men and women. *American Journal of Clinical Nutrition* 1996;64:738-42.
28. Odunukwe NN, Salako LA, Okany C, Ibrahim MM. Serum ferritin and other haematological measurements in apparently healthy adults with malaria parasitaemia in Lagos, Nigeria. *Tropical Medicine and International Health* 2000;5:582-6.