Randomized efficacy trial of a micronutrient-fortified beverage in primary school children in Tanzania[1–3]

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ABSTRACT

Background: Dietary supplements providing physiologic amounts of several micronutrients simultaneously have not been thoroughly tested for combating micronutrient deficiencies.

Objective: We determined whether a beverage fortified with 10 micronutrients at physiologic doses influenced the iron and vitamin A status and growth of rural children (aged 6–11 y) attending primary schools.

Design: In this randomized, double-blind, placebo-controlled efficacy trial, children were assigned to receive the fortified beverage or an unfortified beverage at school for 6 mo.

Results: There were nonsignificant differences at baseline between children in the fortified and nonfortified groups in iron status, serum retinol, and anthropometry. At the 6-mo follow-up, among children with anemia (hemoglobin < 110 g/L), there was a significantly larger increase in hemoglobin concentration in the fortified group than in the nonfortified group (9.2 and 0.2 g/L, respectively). Of those who were anemic at baseline, 69.4% in the nonfortified group and 55.1% in the fortified group remained anemic at follow-up (RR: 0.79), a cure rate of 21%. The prevalence of children with low serum retinol concentrations ($< 200\ \mu g/L$) dropped significantly from 21.4% to 11.3% in the fortified group compared with a nonsignificant change (20.6% to 19.7%) in the nonfortified group. At follow-up, mean incremental changes in weight (1.79 compared with 1.24 kg), height (3.2 compared with 2.6 cm), and BMI (0.88 compared with 0.53) were significantly higher in the fortified group than in the nonfortified group.

Conclusion: The fortified beverage significantly improved hematologic and anthropometric measurements and significantly lowered the overall prevalence of anemia and vitamin A deficiency. *Am J Clin Nutr* 2003;77:891–8.

INTRODUCTION

More than 3 billion persons worldwide are afflicted by vitamin A deficiency, iron deficiency, or iodine-deficiency disorders. Vitamin A deficiency increases mortality risk for 250 million children (1), whereas iron deficiency leads to poor cognitive performance and other health problems (2). Iodine deficiency causes goiter and a range of deficiency-related disorders (3).

Deficiencies of vitamin A, iron, and iodine often occur simultaneously because of 4 underlying factors. First, poverty limits food choices and thereby affects the adequacy of the diet. Second, unfavorable ecology combined with seasonal cycles limits the availability of micronutrient-rich food sources. Third, nutrients interact synergistically, and absorption and metabolism are influenced by total diet quality; thus, a deficiency of one nutrient may lead to a deficiency of another. Finally, parasitic infections may cause blood loss, reduced appetite, or decreased absorption of nutrients, thereby adversely affecting micronutrient status. Together, these 3 micronutrient deficiencies constitute a devastating public health problem that greatly contributes to the cycle of underdevelopment and hinders the attainment of education, health, and productivity goals in countries throughout the world.

The 3 main strategies used to control these and other important micronutrient deficiencies are food diversification, fortification, and medicinal supplementation (4, 5). Food diversification usually involves actions that increase the production, availability, and consumption of foods rich in particular micronutrients. Fortification consists of adding a nutrient to a food that is widely consumed by those at risk of developing the micronutrient deficiency. Medicinal supplementation is generally achieved by 2 different methods. The first typically involves daily consumption of a pill or liquid containing a dose of a particular micronutrient; the most widely used is ferrous sulfate during pregnancy. The second method consists of megadoses given at intervals, for example, consumption of a high dose of vitamin A every 4–6 mo.

In an effort to make an additional strategy available for combating micronutrient deficiencies, we tested the efficacy of a fortified orange-flavored beverage that provides 10 micronutrients in physiologic doses; the beverage was tested among children in primary school. Although schoolchildren are not considered the group at highest risk of micronutrient deficiencies, we chose this study population to ensure good compliance and monitoring in this first trial of a new product manufactured for research purposes. Schools provide a unique social service system that is well

TABLE 1
Amounts of nutrients in the micronutrient-fortified beverage[1]

Nutrient	Amount of nutrient in 25-g sachet	Percentage daily value	Percentage of RDA for children aged 7–10 y
		%	%
Iron[2]	5.4 mg	30	54
Vitamin A (retinyl palmitate)	1750 IU	35	75
Iodine	45 μg	30	37.5
Zinc	5.25 mg	35	52.5
Ascorbic acid	72 mg	120	160
Riboflavin	0.6 mg	35	50
Folic acid	0.14 mg	35	140
Vitamin B-12	3 μg	50	200
Vitamin B-6	0.7 mg	35	50
Vitamin E	10.5 mg	35	150

[1] One individual-serving sachet was provided Monday through Friday at school during the 6-mo intervention period. RDA, recommended dietary allowance.
[2] Ferrochel: Albion Laboratories, Inc, Clearfield, UT.

suited for the delivery of cost-effective public health measures (6, 7). Our objective in this paper is to describe the main effects of the micronutrient-fortified beverage on iron status, anemia, vitamin A status, and growth of the schoolchildren who participated in the study.

SUBJECTS AND METHODS

Study population

This study was conducted in Mpwapwa District, which is located on the Maasai Steppe, or central plateau, of Tanzania. The Wagogo and Wakaguru people who inhabit this semi-arid area are mainly subsistence farmers. In Mpwapwa, there is usually one short rainy season in December and a longer rainy season extending from March through April. The average rainfall is 50 cm/y. The marginally arable land is used for subsistence farming and animal husbandry, but not for extensive cash-crop production. The main crops grown are sorghum, bulrush millet, cassava, maize, cowpeas, and groundnuts. There is very little irrigation, which accounts for the significant seasonal variation in the availability of fruits and vegetables. Consumption of animal products is minimal. Consumption of vitamin A–rich foods is likely to vary seasonally.

The children who participated in the study were recruited from 6 rural primary schools located between 10 and 50 km from the town of Mpwapwa, the District Headquarters. We selected the schools on the basis of geographic location and size. All children between the ages of 6 and 11 y at each of the schools were invited to participate. The age data for the subjects were copied from the school registers, which reflect information on the birth certificates or health cards. A total of 841 children were selected for the baseline examination. Exclusion criteria included ocular signs of xerophthalmia, hemoglobin concentration < 70 g/L, and evidence of serious chronic disease. After examination, eligible study participants were stratified at each school into 2 groups on the basis of the median hemoglobin concentration observed at baseline, 120 g/L. Each child in each stratum was then randomly allocated to receive either the fortified or unfortified beverage in a

double-blind manner. At the conclusion of the study, all children in both groups who had a hemoglobin concentration < 110 g/L were provided with a 2-wk supply of ferrous sulfate and clear instructions on how to take it. Their names were given to the school principal, who was told to refer them to the local health center or district hospital if needed.

The sample size calculation for this study was done on the basis of a review of the published data regarding the effect of iron supplementation on hemoglobin concentrations in this age group (8–16). We calculated that a total of 336 children in each of the 2 groups would be required to detect a minimum change of 3.0 g/L in hemoglobin concentration with an estimated SD of 12 g/L, a confidence interval of 95%, and a power of 0.90. The target enrollment sample size was increased to 405 in each group, including an additional 20% to allow for attrition.

The study protocol was approved by the Commission for Science and Technology, Tanzania; the Tanzania Food and Nutrition Centre's Research and Ethics Committee; and the University Committee on Human Subjects of Cornell University. Communal consent was obtained from District Officials and in meetings with Village Councils, schoolteachers, and parents in Mpwapwa. The purpose and details of the study were explained to the schoolchildren.

Fortified beverage

The dietary supplement used was developed and produced by food technologists at Procter & Gamble and was made available in the form of a multiple-micronutrient beverage powder. The beverage was developed to be nutritionally adequate and pleasant-tasting without problems of nutrient instability, off color, or off flavor. The fortified beverage and the unfortified (placebo) beverage were identical in terms of taste and appearance and provided 90 kcal in each 25-g individual-serving sachet. The supplement was formulated to provide 30–120% of the daily value, the US food industry standard. The amounts of each of the 10 micronutrients in a single 25-g sachet are shown in **Table 1**, which also shows the percentage of the recommended dietary intake and US recommended dietary allowance for children aged 7–10 y. The amounts of the nutrients selected for the supplement were best estimates, because no previous efficacy data existed for a beverage fortified with multiple micronutrients that provides physiologic doses of several nutrients.

Field and laboratory methods

The baseline examinations (November–December 1995) and the 6-mo post-intervention follow-up examinations (July–August 1996) were conducted at the schools by the same examiners and consisted of a clinical examination and anthropometric measurements. Anemia and iron status were assessed by measuring concentrations of hemoglobin, erythrocyte protoporphyrin, and serum ferritin in 5 mL of venous blood collected in evacuated tubes. It is known that infection can influence these biochemical indicators, but we were not able to do immunologic assays, measure C-reactive protein, or monitor morbidity. Immediately after the venous samples were collected, a drop of blood was pipetted to measure hemoglobin concentration with the HemoCue hemoglobinometer (HemoCue AB, Angelhom, Sweden). The precision of the Hemo-Cue was ± 0.3 g/L and was checked daily with control cuvettes. Erythrocyte protoporphyrin was measured with an AVIV hematoflurometer (AVIV Biomedical, Lakewood, NJ). The

hematoflurometer was calibrated to measure zinc protoporphyrin in µg/µg hemoglobin. This value was converted to µmol/mol heme of erythrocyte protoporphyrin by using a factor of 25.76, according to the AVIV conversion tables. The AVIV machine was standardized daily by using control solutions supplied by AVIV Biomedical.

The evacuated tubes were placed under black cloth, and the remaining blood was allowed to clot at a cool temperature for > 3 h. The blood was then centrifuged at 3000 × *g* for 5 min at room temperature. The serum was collected, and aliquots of sera were transferred to 2.0-mL cryogenic vials, frozen, and transported in a liquid nitrogen container to the laboratories of the Tanzania Food and Nutrition Centre in Dar es Salaam where they were stored at −40 °C. Within 4 mo of sample collection, serum ferritin was measured by using an enzyme-linked immunoassay. These iron-status measurements were chosen because they were appropriate and feasible in this research setting. Serum samples for retinol determinations were stored at −40 °C and then transported on dry ice to the United States for analysis via HPLC at Craft Technology Laboratory.

Stool samples were collected at the baseline examination only. Specimen containers were distributed and the children were instructed to bring in a stool sample the next day. The presence and type of parasitic ova were determined by using the Kato-Katz method (17). Quantitative egg counts were not performed. Children with intestinal helminthic infections received a single dose of 400 mg of albendazole and those with *Schistosoma mansoni* were given 40 mg praziquantel/kg body weight. Children were weighed without shoes in light clothing. Weight was measured to the nearest 0.1 kg and height was measured to the nearest 1 cm with a standard balance beam with radiometer.

Intervention procedures

One serving of the beverage was provided at school during the morning recess, 5 d/wk for the 6-mo intervention period. The fortified- and unfortified-beverage sachets had a blue or green label for identification purposes and contained powder that had an identical taste and appearance regardless of fortification. The research team, schoolteachers, and schoolchildren were blinded as to whether the sachets were fortified or unfortified, ie, the meaning of the label colors was not revealed. The content of one sachet was mixed with 250 mL previously boiled water to make a pleasant-tasting, orange-flavored beverage. The children lined up according to the 2 groups and were served in a manner that prevented an exchange of drinks. The teachers recorded attendance in the compliance notebooks and watched the children drink their full servings of the beverage. A serious effort was made to bring children to school during holidays and breaks to continue the intervention without interruption.

Data analysis

The one-sample Kolmogorov-Smirnov test was used to investigate whether the concentrations of hemoglobin, erythrocyte protoporphyrin, serum ferritin, and serum retinol and the anthropometric indicators followed normal distributions. We performed normal logarithmic transformation of the erythrocyte protoporphyrin and serum ferritin data because the distributions were skewed to high values. Geometric means are presented for these data.

We used analysis of variance to test for differences between groups in concentrations of biochemical indicators at baseline.

Between-group differences in the effect of treatment on concentrations of biochemical indicators and anthropometric indicators were measured by using the Student's *t* test. The within-subject change from baseline to follow-up was measured by using a paired *t* test for each group. Between-group differences in the effect of treatment on within-subject change from baseline to follow-up (ie, treatment-by-time interaction) were measured by using the Student's *t* test. These 3 tests, taken together, yield an analysis that is exactly equivalent to a two-factor repeated-measures analysis of variance. All analyses were performed with SPSS-PC (SPSS Inc, Chicago).

Anemia was defined a priori as a hemoglobin concentration < 110 g/L; severe anemia was defined as hemoglobin < 70 g/L, according to World Health Organization guidelines (18). Iron-deficient erythropoiesis was defined as erythrocyte protoporphyrin > 90 µmol/mol heme. Vitamin A deficiency was defined as serum retinol concentration < 200 µg/L. Height-for-age *z* scores were calculated by using EpiInfo, version 6.0 (Centers for Disease Control, Atlanta). Stunting was defined as a height-for-age *z* score < −2 on the basis of National Center for Health Statistics and World Health Organization reference data (19).

RESULTS

A total of 841 children were eligible and were examined for enrollment in the trial. After the baseline clinical and nutritional assessment, 11 were excluded from the study. Of these 11 children, 4 had xerophthalmia at stage XIB (Bitot's spots), suggestive of advanced vitamin A deficiency. The other 7 children were excluded because they had severe anemia (**Figure 1**). These children were treated immediately and reexamined periodically. Data are presented on the children who completed the study (n = 774). The dropout rate of 7% was very low and was mainly a result of relocation and low attendance (Figure 1). The dropouts did not differ in terms of any indicator from the subjects who remained in the study.

Characteristics of the children

The baseline characteristics of the subjects in the fortified and nonfortified groups were similar (**Table 2**). There were approximately equal numbers of boys and girls. Several characteristics of the study sample are noteworthy. The age of the study children was advanced relative to the school classes they were in (first through fourth grade), with 77% of the sample between 9 and 12 y of age. Entering school at an advanced age is common in this community. The beverage was very acceptable; the children liked the taste and the consumption rate was very high. The proportion of days of actual consumption of the beverage during the 120 d of supplementation did not differ between the 2 groups (81.1% and 79.9% in the nonfortified and fortified groups, respectively; *P* = 0.177). Testing showed that the nutrients remained stable after 12 mo under local storage conditions.

More than 95% of the children returned urine and stool samples. Our goals were to determine which parasitic infections were common in the study population and to administer anthelmintics to those children with parasitic infections. We did not attempt to assess the severity of the infections. The test results showed that a small percentage of children had parasitic infections in this semi-arid area (Table 2).

Changes in hematologic measurements

At the baseline examination, there was no significant difference between the 2 groups in the mean hemoglobin concentration
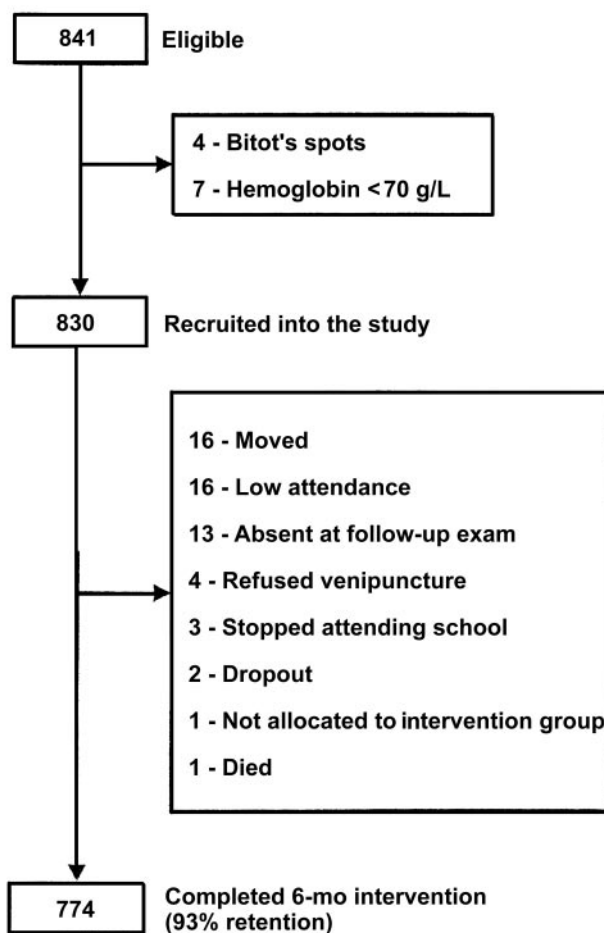
FIGURE 1. Recruitment and retention of study participants.

TABLE 2
Baseline characteristics of the 774 children who completed the study

	Nonfortified group (n = 382)	Fortified group (n = 392)
Female (%)	52	50
Age (y)	9.9 ± 1.2[1]	10.1 ± 1.1
Hemoglobin <110 g/L (%)	19.1	18.5
Serum retinol <200 μg/L (%)	20.6	21.4
Protoporphyrin >90 μmol/mol heme (%)	34.5	36.2
Ferritin <12 μg/L (%)	5.4	13.2[2]
Height-for-age z score < −2 (%)	49.5	50.5
Positive for *Schistosoma mansoni* and intestinal helminths (%)	11.3	13.8

[1] $\bar{x}$ ± SD.
[2] Significantly different from the nonfortified group, $P < 0.01$ (ANOVA).

both groups but had risen more in the nonfortified group than in the fortified group (35.6% and 26.3%, respectively; $P < 0.001$). The overall prevalence of anemia at follow-up was 27% lower in the fortified group than in the nonfortified group (relative risk: 0.73). Consumption of the fortified beverage did not have an effect on the prevalence of iron-deficient erythropoiesis at follow-up. In the fortified group, 29.5% of the children had iron-deficient erythropoiesis compared with 27.9% in the nonfortified group ($P = 0.618$). The overall prevalence of exhausted iron stores (<12 μg/L) at follow-up was 1.3% in the fortified group compared with 6.7% in the nonfortified group (relative risk: 0.18). This indicates that the children in the fortified group were 82% less likely to have exhausted iron stores than were the children in the nonfortified group (**Table 4**).

Effect of fortified beverage on cure rate and prevention of anemia

Of the children who were anemic at baseline, the percentage who remained anemic at follow-up was 69.4% in the nonfortified group and 55.1% in the fortified group (relative risk: 0.79). This indicates that the risk of continuing to be anemic was reduced by 21% in fortified group relative to the nonfortified group. Despite the significantly higher cure rate in the fortified group, anemia persisted in about one-half of the children who were anemic at baseline. For those who were not anemic at baseline, the cumulative incidence of anemia was 26.3% in the fortified group compared with 19.1% in the nonfortified group. The relative risk was 0.73, indicating that 27% of the potential new cases of anemia were avoided by providing the fortified beverage.

Vitamin A status

At baseline, approximately equal proportions of children in the 2 groups (20.6% and 21.4% in the nonfortified and fortified groups, respectively) had low serum retinol concentrations, defined as <200 μg/L (**Table 5**). In contrast, at the follow-up examination 6 mo later, there was no significant change in the nonfortified group, whereas there was a very significant drop (from 21.4% to 11.3%) in the percentage of children with low serum retinol concentrations in the fortified group.

Growth rates

Mean weight, height, and BMI at the baseline and follow-up examinations for children with complete data are shown in **Table 6**. There were no significant differences in weight, height, or BMI between the 2 groups at baseline. At follow-up 6 mo later, children in both groups showed increased weight and height as expected, but there were significant differences between groups

(119.7 and 119.2 g/L in the nonfortified and fortified groups, respectively; $P = 0.639$). At the follow-up examination, the mean hemoglobin concentration had dropped in both groups (112.9 and 116.0 g/L in the nonfortified and fortified groups, respectively; $P < 0.001$). However, the decrease was smaller ($P < 0.001$) in the fortified group ($-3.2 ± 13$ g/L) than in the nonfortified group ($-6.7 ± 13$ g/L) (**Table 3**). Protoporphyrin concentrations increased significantly in the nonfortified group but dropped significantly in the fortified group (4.90 ± 70 and $-18.35 ± 71$ μmol/mol heme, respectively; $P < 0.01$). Iron stores, as measured with serum ferritin, improved significantly from baseline to follow-up in the fortified group. The within-individual incremental change was 15.9 μg/L in the fortified group compared with 2.05 μg/L in the nonfortified group. Among the children with anemia at baseline, the incremental change in hemoglobin after the 6 mo intervention was very small and not significant in the nonfortified group ($n = 72$), whereas the change in the fortified group ($n = 70$) was larger and was highly significant (0.2 and 9.2 g/L, respectively; $P < 0.001$).

Change in prevalence of anemia and iron deficiency

The iron status of the children was poor overall. The prevalence of anemia at baseline was essentially equal in the 2 groups (19.1% and 18.5% in the nonfortified and fortified groups, respectively; $P = 0.820$). At follow-up, the prevalence of anemia had increased in

TABLE 3
Concentrations of hemoglobin, protoporphyrin, and serum ferritin at baseline and after the 6-mo intervention

Endpoint	Nonfortified		Fortified		
	Value	Paired t test P	Value	Paired t test P	Between-group P
Hemoglobin (g/L)					
Baseline	119.7 ± 13 [376][1]		119.2 ± 14 [373]		0.639
Follow-up	112.9 ± 15 [376]		116.0 ± 13 [373]		0.001
Difference[2]	−6.7 ± 13 [376]	0.001	−3.2 ± 13 [373]	0.001	0.001
Serum ferritin (µg/L)					
Baseline	33.88 (30.97, 37.83) [148][3]		29.51 (25.97, 33.02) [149]		0.054
Follow-up	36.31 (33.43, 40.13) [148]		45.71 (42.20, 50.15) [149]		0.001
Difference	2.05 (28) [148]	0.180	15.90 (33) [149]	0.001	0.001
Protoporphyrin (µmol/mol heme)					
Baseline	53.70 (46.67, 62.78) [174]		61.66 (53.30, 70.93) [163]		0.224
Follow-up	61.66 (55.00, 70.15) [174]		53.70 (48.36, 60.13) [163]		0.067
Difference	4.90 (70) [174]	0.035	−18.35 (71) [163]	0.037	0.003

[1] $\bar{x}$ ± SD; n in brackets.
[2] Mean within-individual incremental change between baseline and follow-up.
[3] Geometric $\bar{x}$ with 95% CI in parentheses; n in brackets.

for all anthropometric measurements in that the fortified group had better growth. After the 6-mo intervention, the fortified group had gained 0.55 kg more weight, 0.57 cm more height, and 0.32 more BMI units compared with the nonfortified group.

DISCUSSION

Anemia and iron deficiency were common in the population studied. The functional consequences of anemia in school-age children point to the urgency of addressing this public health problem in many developing countries. After the children in the treatment group had consumed the micronutrient-fortified beverage for 6 mo, we observed significant improvements in all the hematologic measurements of the children in the fortified group compared with the nonfortified group. Although the beverage greatly reduced the risk of exhausted iron stores, hemoglobin concentration did decrease in both groups over the 6-mo period. We believe the decline in hemoglobin and the increase in anemia in both groups resulted from a strong seasonal influence on dietary quality and morbidity patterns, particularly with regard to malaria. The distinctly seasonal rainfall and agricultural patterns in this area lead to great variation in food availability. We conducted the baseline examinations in December during the dry season, when food is more plentiful from the July harvest and malaria transmission is lower than it is during the wet season. In contrast, we conducted the follow-up examination in July, when food stores are low, dietary quality is poor, and malaria transmission is at its peak.

Malaria, which is endemic in Mpwapwa District, causes hemolytic anemia with reduced hemoglobin. Despite these influences, we observed that the fortified beverage had a protective effect on the declining hemoglobin concentrations and achieved a significant reduction in the overall prevalence of anemia relative to the non-fortified group. We also observed a significant effect of the supplemental beverage on both the treatment and prevention of anemia in the fortified group, with 27% of new cases of anemia avoided. Notwithstanding these significant improvements in iron status and reduction of anemia, we did not observe complete recovery of hemoglobin or prevention of anemia. This could be the result of multiple factors, including incomplete recovery from deficiencies of iron, vitamin A, folate, vitamin B-12, and other nutrients necessary for optimal hematopoiesis. Other investigators have observed a lack of hemoglobin response to iron supplements with and without micronutrients despite improved iron status and reduction of iron deficiency (20, 21).

Although we did not directly measure the iron content or iron availability in the diet, observed food consumption patterns are consistent with the poor iron status of the school children. A situational analysis conducted by UNICEF and the Tanzania Food and Nutrition Centre identified inadequate food intake as the most important cause of nutritional anemia throughout Tanzania (22, 23). Results from a nutritional survey conducted in Lindi District in Tanzania indicate that iron deficiency is a major cause of anemia across all ages of the population and that the iron content of the diet is high but the soluble iron content is very low (24).

TABLE 4
Prevalence of anemia and iron deficiency at baseline and after the 6-mo intervention

	Nonfortified	Fortified	Relative risk (95% CI)	Chi-square
Hemoglobin <110 g/L (%)				
Baseline	19.1	18.5	0.96 (0.72, 1.51)	0.820
Follow-up	35.6	26.3	0.73	0.005
Protoporphyrin >90 µmol/mol heme (%)				
Baseline	34.5	36.2	1.08 (0.69, 1.69)	0.742
Follow-up	29.5	27.9	0.92 (0.68, 1.26)	0.618
Ferritin <12 µg/L (%)				
Baseline	5.4	13.2	2.5 (1.14, 6.27)	0.013
Follow-up	6.7	1.3	0.18 (0.07, 0.48)	0.001

TABLE 5
Distribution of children according to serum retinol concentrations at baseline and after the 6-mo intervention

	Fortified group (n = 364)		Nonfortified group (n = 370)	
	Baseline	Follow-up	Baseline	Follow-up
	%			
Serum retinol (μg/L)				
<200	21.4	11.3	20.6	19.7
200–290	35.5	34.9	37.0	33.5
≥300	43.1	53.8	42.4	46.8

Ascorbic acid substantially increases the absorption of iron. The fortified beverage contained ascorbic acid as well as folate and vitamin B-12.

Serum ferritin and serum retinol can be falsely elevated because of infection or inflammatory conditions. Although we did not measure acute phase proteins, on the basis of our study design we can expect that the influence of infection would be randomly distributed across the 2 groups. We did observe a relatively small proportion of children with parasitic infections, particularly *S. mansoni* infection, which can result in mild or moderate blood loss and malabsorption of vitamin A (25, 26).

We observed relatively better nutritional status in our study population, located in a semi-arid area, compared with studies of other school children living elsewhere in Tanzania. Tatala et al (24) reported that the prevalence of anemia among schoolchildren in Lindi District on the southeast coast of Tanzania was 68%. Stoltzfus et al (27), who reported on the epidemiology of iron deficiency among school children on the island of Pemba, Tanzania, observed that 62.3% of the children were anemic and 82.7% of the anemia was associated with iron deficiency. It is important to note that the environment of coastal East Africa is characterized by intense transmission of *Plasmodium falciparum* malaria (28, 29) and high prevalence of infection with *Schistosoma haematobium* and intestinal helminths. The coastal areas at low altitudes are truly tropical, whereas Mpwapwa is at an altitude of ≈1000 m and thus is more temperate.

Providing physiologic amounts of 10 micronutrients to the children in the fortified group almost certainly raised their intakes of all these nutrients to above the recommended dietary allowances. In Tanzania in general, and in this population in particular, intakes of iron, ascorbic acid, folate, vitamin A, and zinc are very frequently well below the recommended dietary allowances. The unfortified and fortified beverages in our trial both provided 90 kcal/sachet, and 1 sachet was consumed on each school day attended. This small amount of extra energy, identical for both groups, was not expected to influence growth differentially. We postulate that the observed improvement in growth in the fortified group was related to the increased intakes of micronutrients, which may have improved appetite, thereby leading to increased food intake.

In 2 separate studies in Kenya (8, 30), the provision of ferrous sulfate in medicinal doses to primary school children improved their growth in a manner and in amounts similar to the current Tanzanian trial. One of the Kenyan studies was a placebo-based, randomized, double-blind investigation in which appetite was measured. Both appetite and growth improved to a greater extent in the children receiving iron than in the children receiving the placebo. In the present study, we did not attempt to measure appetite and we were unable to determine whether the improved growth resulted from the iron, zinc, or some other micronutrient in the supplement.

Reducing micronutrient deficiencies is now a high priority of United Nations agencies, organizations, and many governments, with special attention being paid to iron, vitamin A, and iodine deficiencies. The 3 strategies that are being promoted and used most widely are food diversification, food fortification, and medicinal supplementation (4). Food diversification is viewed as the most sustainable, but also the slowest and most difficult of the 3 to adopt. It entails wider availability and increased consumption of foods providing adequate micronutrients for at-risk populations. In many countries, it also involves poverty reduction to allow families access to a balanced diet. The second intervention strategy is fortification, which has had successes and failures. Its effectiveness is dependent on the at-risk population purchasing adequate amounts of foods that pass through a manufacturing process in which the nutrient can be added in well-controlled and safe amounts. Fortification is most successfully and widely used in the control of iodine-deficiency disorders, because much of the world's population purchases salt, which in many countries passes through relatively few manufacturing plants. Fortification could

TABLE 6
Anthropometric measurements at baseline and after the 6-mo intervention[1]

Endpoint	Nonfortified		Fortified		
	Value	Paired *t* test *P*	Value	Paired *t* test *P*	Between-group *P*
Weight (kg)					
Baseline	24.8 ± 4.1 [382][2]		24.9 ± 3.8 [376]		0.75
Follow-up	26.1 ± 4.4 [382]		26.7 ± 4.3 [376]		0.04
Difference[3]	1.24 ± 1.2 [382]	0.001	1.79 ± 1.2 [376]	0.001	0.001
Height (cm)					
Baseline	125.0 ± 8.1 [382]		125.0 ± 7.5 [368]		0.66
Follow-up	127.0 ± 8.1 [382]		128.0 ± 7.6 [368]		0.15
Difference	2.6 ± 1.6 [382]	0.001	3.2 ± 1.8 [368]	0.001	0.001
BMI (kg/m^2)					
Baseline	19.78 ± 2.2 [377]		19.79 ± 2.09 [365]		0.93
Follow-up	20.32 ± 2.3 [377]		20.65 ± 2.29 [365]		0.03
Difference	0.53 ± 0.89 [377]	0.001	0.88 ± 0.89 [365]	0.001	0.001

[1] For each of the anthropometric measurements, data were included in the analysis only if the baseline and follow-up paired data were available.
[2] $\bar{x}$ ±SD; *n* in brackets.
[3] Mean incremental change between baseline and follow-up.

be more widely used to control iron and vitamin A deficiencies, but few national programs have shown evidence of success. Medicinal supplementation is widely used to control iron deficiency anemia in pregnant women. In most countries, including Tanzania, women are offered iron (or iron plus folate) at prenatal clinics, but compliance is a major problem (31, 32). Several countries have attempted to reduce vitamin A deficiency by providing megadoses of vitamin A (usually 200 000 IU every 4 or 6 mo). These projects have generally proved not to be sustainable, and most have been mainly aimed at preschool children. Where iodized salt is not available, high doses of medicinal iodine have been given by injection or orally every 2–4 y to control iodine-deficiency disorders. In the case of both fortification and medicinal supplementation, programs have usually attempted to control only a single micronutrient deficiency, and frequently only in one group of the population.

We have shown in this trial that it is feasible and efficacious to provide a beverage fortified with multiple micronutrients to schoolchildren to improve their nutritional status. We do not intend that this micronutrient-fortified beverage would replace current programs in Tanzania or elsewhere. Currently, fortification of commonly eaten foods with iron and vitamin A is only in a small-scale, pilot stage in Tanzania. Neither vitamin A nor iron supplements are provided to schoolchildren through the national micronutrient deficiency control programs in Tanzania. We believe that further investigation of the effectiveness of the micronutrient-fortified beverage is warranted. One would need effectiveness data to determine whether providing the fortified beverage in the school setting could be a cost-effective public health strategy (6, 7) for improving nutritional status during the important learning years, building iron stores for the adolescent growth spurt and adulthood, and improving overall health.

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