Effects of the Zanzibar school-based deworming program on iron status of children[1–3]

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ABSTRACT We evaluated the effects of the Zanzibar school-based deworming program on the iron status of primary school children. Parasitologic and nutritional assessments were carried out at baseline, 6 mo, and 12 mo in 4 nonprogram schools (n = 1002), 4 schools in which students received twice-yearly deworming (n = 952), and 4 schools in which students received thrice-yearly deworming (n = 970) with 500 mg generic mebendazole. Schools were randomly selected for evaluation and allocated to program groups. Relative to no treatment, thrice-yearly deworming caused significant decreases in protoporphyrin concentrations and both deworming regimens caused marginally significant increases in serum ferritin concentrations. The average annual changes in protoporphyrin concentrations were −5.9 and −23.5 μmol/mol heme in the control and thrice-yearly deworming groups, respectively ($P < 0.001$). The average changes in ferritin concentration were 2.8 and 4.5 μg/L, respectively ($P = 0.07$). Deworming had no effect on annual hemoglobin change or prevalence of anemia. However, the relative risk of severe anemia (hemoglobin < 70 g/L) was 0.77 (95% confidence limits: 0.39, 1.51) in the twice-yearly deworming group and 0.45 (0.19, 1.08) in the thrice-yearly deworming group. The effects on prevalence of high protoporphyrin values and incidence of moderate-to-severe anemia (hemoglobin < 90 g/L) were significantly greater in children with > 2000 hookworm eggs/g feces at baseline. We estimate that this deworming program prevented 1260 cases of moderate-to-severe anemia and 276 cases of severe anemia in a population of 30 000 schoolchildren in 1 y. Where hookworm is heavily endemic, deworming programs can improve iron status and prevent moderate and severe anemia, but deworming may be needed at least twice yearly. *Am J Clin Nutr* 1998;68:179–86.

KEY WORDS Humans, hookworms, schoolchildren, anemia, iron deficiency, deworming, Africa, helminth, anthelmintic drug, Zanzibar

INTRODUCTION

Iron deficiency anemia afflicts approximately half of the children in Asia and sub-Saharan Africa (1). However, outside of Europe and the Americas, relatively few interventions have been implemented to prevent childhood iron deficiency. The major strategies used to combat iron deficiency are supplementation and food fortification. The logistical difficulties of providing iron supplements to young children and the lack of centrally processed fortifiable foods outside of urban areas have prevented these interventions from reaching children in parts of Africa and Asia where anemia is most prevalent and severe.

Hookworms (*Ancylostoma duodenale* and *Necator americanus*) infect ≈880 million people globally and are most prevalent in Asia and sub-Saharan Africa (2). Hookworms cause chronic intestinal blood loss by attaching to the mucosa of the upper small intestine and ingesting tissue and blood. Blood loss occurs both from ingestion by the worm and through bleeding from the damaged mucosa (3). The quantity of blood lost is directly related to the intensity of the infection (4, 5). Where hookworm infections are prevalent and iron status poor, hookworm infection is an important cause of iron deficiency anemia, especially more severe anemia (6).

Apart from treating individuals with clinical hookworm-related anemia, hookworm control has not often been included in public health strategies to control iron deficiency anemia (7). This is in part because evaluations of the effects of hookworm control programs on iron deficiency in populations have been rare. An exception is an evaluation of anthelmintic therapy in combination with an iron-fortification pilot project in India, in which anthelmintic therapy significantly enhanced the benefit of iron-fortified salt at the population level (8).

School-based deworming is advocated as a highly cost-effective public health intervention (9) and might improve children's iron status in some populations. This benefit is most likely to be attained in populations where hookworm infections are prevalent and iron intakes poor. Blood loss may also occur in *Trichuris*

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trichiura infection (10), but probably becomes significant only in heavy infections (11); additionally, the importance of trichuriasis as a cause of iron deficiency in populations is questionable (12, 13). Ascariasis is associated with a small deficit in hemoglobin in some populations (6, 14), for reasons that are not well understood.

This paper reports the effects of the Zanzibar school-based deworming program on the iron status of children in primary school. The program was implemented by the local Ministry of Health and school personnel and consisted of a single 500-mg dose of generic mebendazole as an anthelmintic treatment. The evaluation measured effects on helminth infections, growth, iron status, and school attendance of children receiving either twice-yearly or thrice-yearly deworming. Effects on growth are reported elsewhere (15).

METHODS

The school-based deworming program

School-based strategies for parasite control were begun in Zanzibar in 1988, with a test-and-treat program for control of urinary schistosomiasis (*Schistosoma haematobium* infection). From 1988 to 1992, all children in primary school were tested annually for microhematuria with Hemastix test strips (Ames Laboratories, Elkhart, IN). Those who tested positive were treated with praziquantel. This program effectively controlled urinary schistosomiasis (16), but from 1992 to 1994 the program was temporarily discontinued as a result of a lack of funds. The school-based deworming program that we evaluated began in 1994 on Pemba Island, the smaller of the two islands of Zanzibar, and included a test-and-treat component for urinary schistosomiasis and mass treatment for geohelminths. All program activities were implemented by the Pemba Island Helminth Control Team, a unit of the local Ministry of Health, in cooperation with the Ministry of Education.

A single dose of mebendazole was chosen as the anthelmintic treatment on the basis of both cost and efficacy. A previous randomized trial conducted in Pemba had compared the efficacy of a single dose of 500 mg generic mebendazole with a single dose of 400 mg albendazole. Compared with that of albendazole, the efficacy of mebendazole was somewhat less against hookworms, very similar against *Ascaris lumbricoides*, and somewhat better against *T. trichiura* (17). The cost of generic mebendazole, US$0.027 per dose, was one-tenth of that of albendazole at that time (L Savioli, personal communication, 1993). Because children became rapidly reinfected with all three helminths (18), annual treatment was inadequate.

Program evaluation

Although improved sanitation practices in Zanzibar are a goal of the Ministry of Health, anthelmintic therapy will be the mainstay of helminth control in the coming decade. Given the scarcity of resources for public health programs, evidence of program effectiveness was considered essential for the Ministry of Health to garner sustained program support. A program evaluation that included nonprogram schools was therefore justified and could be done because the program was designed to be implemented over a 2-y period. In addition, a twice-yearly deworming program was implemented in some evaluation schools and a thrice-yearly deworming regimen in others to evaluate the relative effectiveness of the two regimens.

Twelve evaluation schools were selected from the 72 public schools on Pemba Island. From each of the 4 districts on the island, 3 schools were randomly selected and then allocated to the nonprogram, twice-yearly deworming, and thrice-yearly deworming program groups. The same deworming treatment was administered to all children in the selected schools. Placebos were not given in the nonprogram schools, and children, teachers, and investigators were not blinded to the programs being administered. In the twice-yearly deworming group, mebendazole was given in March-April and October-November 1994. In the thrice-yearly deworming group, mebendazole was given in March-April, August, and December 1994. The evaluation was planned and the schools selected before the program was implemented in any school on Pemba Island. The nonprogram schools became program schools in 1995.

Only morning classes of children were assessed in the evaluation so that laboratory work could be completed in the afternoon. Children in grades 1–4 were eligible for the evaluation, but grades 1 and 2 were deliberately oversampled because we expected the program to have the greatest effect on nutritional status in younger children.

Parent meetings were held at each school to provide information about the deworming regimen to be implemented in the school in either 1994 or 1995, the purpose of the evaluation, risks and benefits of children's participation, and alternatives to participation. Anthelmintic drugs were available in local pharmacies to children in all three program groups. The study was approved by the ethical review committees of The Johns Hopkins School of Public Health, the World Health Organization, and the Ministry of Health of Zanzibar.

We estimated that 1000 children per group would be sufficient to detect a difference in mean within-individual changes in hemoglobin of 5 g/L. This estimate accounted for the design effect of randomizing at the school level and allowed for subgroup analyses. The evaluation was designed to compare the effects of twice-yearly and thrice-yearly deworming with no deworming. The sample size was not sufficient for testing differences between the two deworming regimens.

According to the teachers' rosters of classes selected for the survey, 3959 children were enrolled and therefore eligible to participate in the evaluation. The baseline survey conducted in March-May 1994 included 3605 children, 91.1% of those eligible. Children with hemoglobin < 70 g/L (n = 125, or 3.5% of the sample) were treated with mebendazole and oral iron and were excluded from these analyses. The deworming regimens were begun at the time of the baseline survey in the program schools. Six-month and 12-mo follow-up assessments were conducted in October-November 1994 and March-May 1995, respectively. Eighty-four percent of children (n = 3028) completed the 12-mo follow-up. The losses to follow-up in each program group are described elsewhere (15).

Nutritional and parasitologic assessments

Iron status was assessed by measuring hemoglobin, erythrocyte protoporphyrin, and serum ferritin in a venous blood sample at baseline and 12 mo. At the 6-mo follow-up, only hemoglobin and erythrocyte protoporphyrin were measured in a capillary sample. We chose these 3 measures because they provide complementary information across the range of iron statuses and because they were feasible in this research setting. Although falciparum malaria is highly endemic in Zanzibar,

these indicators performed reliably in this population (19). Hemoglobin and protoporphyrin were measured directly in a drop of whole blood at the school by using a HemoCue hemoglobinometer (HemoCue AB, Angelhome, Sweden) and a fluorometer (Aviv Biomedical, Lakewood, NJ), respectively. At baseline and 12 mo, the remaining blood was allowed to clot at a cool temperature for ≥30 min and then centrifuged at 1000 × *g* for 20 min at room temperature. Serum samples were stored at −20 °C for up to 10 wk, transported to Baltimore in liquid nitrogen, and stored at −70 °C until analyzed. Ferritin was measured by using a fluorescence-linked immunoassay (DELFIA system; Wallac Inc, Gaithersburg, MD). The children's weights and heights were measured by use of standard methods (20).

Dietary intakes of the children were not ascertained because dietary interviews could not be conducted reliably with young schoolchildren in the absence of their parents. However, the iron bioavailability of the Pembian diet is certainly low. Cassava is the primary staple food, being the least expensive choice and the easiest to raise in home gardens. Maize, rice, plantains, and breadfruit are added to the diet if affordable. These foods are typically eaten with curries or stews made of legumes, vegetables, and small fish. Larger fish and other seafoods are consumed in small amounts occasionally. Meat is a luxury item not regularly consumed. Bananas and papaya are available throughout the year, whereas mangoes, citrus fruit, and other fruit are available seasonally.

Fecal samples were collected from ≈95% and urine samples from 100% of children surveyed. Blood films were stained with Giemsa stain and malarial parasites were counted against leukocytes, helminth fecal egg counts were determined by the Kato-Katz method, and microhematuria, an indication of urinary schistosomiasis, was determined by using Hemastix (Ames Laboratories, Elkhart, IN). These standard parasitologic methods are described elsewhere (6, 19).

Data analysis

Stunting was defined as a height-for-age *z* score < −2 on the basis of the National Center for Health Statistics and World Health Organization (WHO) reference data (21). Anemia was defined as a hemoglobin concentration < 110 g/L. This is lower than the WHO recommended definition for this age group of 120 g/L (22); however, a 10-g/L lower cutoff screens more efficiently for anemia in blacks (23). Hemoglobin cutoffs < 90 and < 70 g/L were used to define moderate-to-severe anemia and severe anemia, respectively. Exhausted iron stores were defined as a serum ferritin concentration < 12 g/L and iron-deficient erythropoiesis was defined as a protoporphyrin concentration > 90 μmol/mol heme.

Children's baseline characteristics in each treatment group were compared by using Student's *t* test for continuous variables and the chi-square test for categorical variables (24). Estimates of program effects and their variances were adjusted for correlations among children within the same school by using generalized estimating equations (25). Because some child characteristics differed significantly between the program groups at baseline, these estimates were adjusted for baseline factors in multiple regression models. Program effects on hemoglobin, protoporphyrin, and ferritin were measured as the difference between the within-child change from baseline to 12 mo in each program group compared with the control group. Program effects on the prevalence of abnormal values for iron-status indicators was measured as the difference between the change in prevalence within each program group from baseline to 12 mo compared with the control group.

We also measured program effects on the incidence of moderate-to-severe anemia. Children who had moderate-to-severe anemia at baseline were excluded from this analysis. The incidence rate was calculated on a person-by-time basis by using the 6-mo intervals from baseline to 6 mo and from 6 to 12 mo as independent intervals. The program effect was measured by the relative risk of moderate-to-severe anemia in program groups compared with the control group. An analogous analysis was carried out on the incidence of severe anemia. Multivariate linear and Poisson regression models were used with the generalized estimating equation approach (25) to account for the clustered randomization.

Finally, we tested for predictors of benefit, that is, baseline characteristics of children that were associated with a greater program effect. To do this, we tested the interaction between program group and baseline child characteristics by using multiple regression. Interactions with *P* values < 0.15 were considered potentially significant, depending on their magnitude and biological significance.

RESULTS

Characteristics of study children

The study sample included about equal numbers of boys and girls (**Table 1**). The children's median age was 10 y. More than two-thirds of children were infected with *A. lumbricoides* and > 90% of children were infected with *T. trichiura* or hookworms. Malarial infection and microhematuria were also common. Children were short for their ages; the overall prevalence of stunting was 48.5%. The pattern of growth retardation in this group of children has been described in detail elsewhere (20). The iron status of the children at baseline was poor.

Several characteristics of children in the three program groups differed significantly at baseline (Table 1). The two deworming groups had slightly more trichuriasis and hookworm infection than did the control group. The twice-yearly deworming group had less ascariasis, less microhematuria, and better height-for-age *z* scores than did the other groups. The thrice-yearly deworming group tended to have the worst iron status. These baseline factors were included in multivariate regression models of the effects of the program on iron status and retained if found to confound or modify the estimate of program effects.

Program effects on helminth infections

The effects of twice-yearly and thrice-yearly deworming on helminth infections are reported in greater detail elsewhere (15), but are summarized here because they are essential to the interpretation of the nutrition findings. The program achieved high coverage in the first year, with 90% of children in the schools treated twice yearly and 89% in those treated thrice yearly receiving the full regimen. Both deworming regimens effectively controlled ascariasis. The geometric mean (+1 SD, −1 SD) fecal egg counts per g feces for *A. lumbricoides* at 12 mo were 653 (25, 17367), 54 (2, 1433), and 10 (0, 289) in the control, twice-yearly deworming, and thrice-yearly deworming groups, respectively. The deworming programs did not have a large effect on the prevalence of *T. trichiura* or hookworm infections, which

TABLE 1
Baseline characteristics of the study children by program group

Characteristic	Program group		
	Control (n = 1002)	Twice-yearly deworming (n = 952)	Thrice-yearly deworming (n = 970)
Male sex (%)	50.7	49.6	49.5
Age (y)	10.5 ± 1.6[1]	10.6 ± 2.6	10.5 ± 1.7
Hookworms			
Infected (%)[2]	91.0	94.4	95.7
Eggs/g feces[2]	321 (37, 2775)[3]	492 (75, 3234)	583 (101, 3362)
Trichuris trichiura			
Infected (%)[4]	94.8	96.5	97.1
Eggs/g feces	527 (82, 3370)	577 (108, 3109)	614 (126, 2998)
Ascaris lumbricoides			
Infected (%)[2]	72.7	66.7	75.8
Eggs/g feces[4]	229 (7, 8066)	152 (4, 6432)	314 (10, 10155)
Malaria parasitemia (%)[2]	57.1	56.8	65.4
Microhematuria (%)[2,5]	30.4	19.9	35.0
Height-for-age z score	−1.93 ± 1.23	−1.78 ± 1.44	−1.97 ± 1.39
Body mass index (kg/m^2)	14.6 ± 1.3	14.7 ± 1.5	14.7 ± 1.3
Hemoglobin (g/L)[2]	106 ± 12	107 ± 13	104 ± 13
Hemoglobin < 110 g/L (%)[2]	60.2	56.3	66.3
Protoporphyrin (μmol/mol heme)[4]	89 (55, 144)	92 (57, 150)	97 (58, 164)
Protoporphrin > 90 μmol/mol heme (%)[2]	44.3	45.0	51.7
Ferritin (μg/L)	14.4 (7.8, 26.6)	14.8 (7.6, 28.7)	14.2 (7.5, 27.1)
Ferritin < 12 μg/L (%)	40.2	38.9	40.9

[1] $\bar{x}$ ± SD.
[2] Group proportions are significantly different, $P < 0.01$.
[3] Geometric $\bar{x}$ (−1 SD, + 1 SD).
[4] Group means are significantly different, $P < 0.05$.
[5] An indicator of urinary schistosomiasis.

remained at 85–97% in all three groups. However, deworming did reduce the intensity of infections with these parasites in a frequency-dependent manner. At 12 mo, the geometric mean fecal egg counts for *T. trichiura* were 788 (96, 6449), 340 (41, 2633), and 147 (19, 1256), and for hookworms were 778 (94, 6728), 329 (41, 2826), and 262 (30, 2044) in the control, twice-yearly deworming, and thrice-yearly deworming groups, respectively. The prevalence of moderate-to-heavy hookworm infections (> 2000 hookworm eggs/g feces) at 12 mo were 28%, 14%, and 9%, respectively.

Overall program effect on iron status

Children's hemoglobin concentrations improved significantly from baseline to the 12-mo follow-up survey in all program groups. The average hemoglobin concentration increased by ≈11 g/L and the prevalence of anemia declined by almost one-half. This improvement happened in the second 6-mo period of follow-up. At the 6-mo follow-up survey, the mean (±SD) hemoglobin concentration was 105 ± 15 g/L and the prevalence of anemia was 58.8%, values similar to those found in the baseline survey.

The deworming programs did not significantly improve the mean hemoglobin concentration relative to the control group, nor did they reduce the prevalence of anemia relative to the control group (**Table 2**). However, the thrice-yearly deworming regimen did have a positive effect on iron status. The mean values of protoporphyrin were highly significantly improved and those of ferritin were marginally significantly improved in the thrice-yearly deworming group, and the prevalence of iron-deficient values of both indicators was significantly decreased. Twice-yearly deworming had a marginally significantly positive effect on the serum ferritin concentration, but otherwise had no significant effect on iron status of the entire study cohort.

Although the deworming programs had no overall effect on the prevalence of anemia, the incidence of more severe forms of anemia was lower in the thrice-yearly deworming group (**Table 3**). Severe anemia was reduced by 23% in the twice-yearly deworming group and by 55% in the thrice-yearly deworming group. Although the reduction was large in the thrice-yearly deworming group, the 95% CI included unity.

Predictors of benefit from deworming

No child characteristics that we measured were predictive of biologically significant improvements in hemoglobin concentrations from deworming. Lower baseline hemoglobin concentration, male sex, and age > 10 y were statistically associated with greater increases in hemoglobin concentration (ie, their interaction terms with the program group had P values < 0.15), but in no subgroup was the hemoglobin gain associated with either deworming program ≥ 3 g/L (data not shown).

However, the intensity of hookworm infection at baseline was predictive of the reduction in incidence of moderate-to-severe anemia (Table 3). In children with < 2000 hookworm eggs/g feces at baseline, nether program had a significant effect. In chil-

TABLE 2
Program effects on iron status[1]

Characteristic	Program group		
	Control	Twice-yearly deworming	Thrice-yearly deworming
12-mo Change[2]			
Hemoglobin (g/L)	11.3 ± 1.7	10.3 ± 1.7	12.7 ± 1.7
Protoporphyrin (μmol/mol heme)	−6 ± 3	−13 ± 3	−24 ± 3[3]
Ferritin (μg/L)	2.8 ± 0.7	4.6 ± 0.7[4]	4.5 ± 0.7[4]
12-mo Change in prevalence (%)[5]			
Hemoglobin < 110 g/L	−31.3 ± 5.3	−24.3 ± 5.3	−33.1 ± 5.3
Protoporphrin > 90 μmol/mol heme	−2.9 ± 2.5	−5.3 ± 2.5	−15.8 ± 2.5[3]
Ferritin < 12 μg/L	−10.3 ± 1.5	−11.1 ± 1.7	−14.2 ± 1.5[6]

[1] $\bar{x}$ ± SE.

[2] Values are within-individual differences for each indicator between baseline and 12 mo, adjusted for iron status, sex, age, hookworm infection, district, and height-for-age at baseline, and accounting for within-school correlations.

[3,4,6] Significantly different from control: [3] $P < 0.001$, [4] $P = 0.07$, [6] $P = 0.06$.

[5] Values are changes in prevalence of abnormal values for each indicator from baseline to 12 mo, adjusted for iron status, sex, age, hookworm infection, district, and height-for-age at baseline, and accounting for within-school correlations.

dren with moderate or heavy hookworm infections (≥2000 hookworm eggs/g feces), both deworming programs had a large protective effect. Twice-yearly deworming reduced the incidence of moderate-to-severe anemia by 47% and thrice-yearly deworming reduced the incidence by 57%. Put another way, in the control group, children with heavier hookworm infections at baseline had a more than twofold greater risk of developing moderate-to-severe anemia (incidence of 9.8% compared with 4.7%). Both deworming regimens greatly reduced this excess risk.

A similar pattern of effect modification was seen on the prevalence of iron-deficient erythropoiesis (ie, protoporphyrin > 90 μmol/mol heme) at 12 mo (**Figure 1**). In children without hookworm infection or with light infection, thrice-yearly deworming reduced the adjusted prevalence from 39.2% to 33.9%, but twice-yearly deworming had virtually no effect. In children with moderate-to-heavy hookworm infection, the adjusted prevalences were 53.2%, 46.4%, and 35.8% in the control, twice-yearly deworming, and thrice-yearly deworming groups, respectively. Again, thrice-yearly deworming essentially removed the excess risk of iron-deficient erythropoiesis found in children with heavier hookworm infections.

The children's age and baseline hemoglobin concentration strongly predicted the change in protoporphyrin associated with deworming. Children > 10 y of age had larger decreases in protoporphyrin concentrations associated with deworming than did younger children (12 μmol/mol heme greater in the twice-yearly deworming group and 9 μmol/mol heme greater in the thrice-yearly deworming group; interaction of age and both deworming regimens, $P < 0.025$). The decrease in protoporphyrin was significant for both age groups in the thrice-yearly deworming group but for only older children in the twice-yearly deworming group (data not shown). In the thrice-yearly deworming group, children with an initial hemoglobin concentration of 80 g/L had a sixfold greater reduction in protoporphyrin concentration after deworming than did those with a hemoglobin concentration of 120 g/L (−40.0 compared with −6.1 μmol/mol heme, values for children > 10 y; **Figure 2**). In the thrice-yearly deworming group this interaction was highly significant ($P < 0.005$), but in the twice-yearly deworming group it was not as strong.

The benefit to serum ferritin from deworming occurred only in children who had some iron storage at baseline. Children in whom iron stores were exhausted at baseline (serum ferritin < 12 μg/L) showed no improvements in ferritin concentration associated with deworming, whereas those with some iron stores at baseline had 12-mo increases of 3.1 and 3.4 μg/L over the control group (twice-yearly and thrice-yearly deworming groups, respectively; $P < 0.01$ for both groups). This interaction was highly significant in both deworming groups ($P < 0.001$). In children with baseline iron stores, the improvement in serum ferritin concentration was also modified by the child's height-for-age *z* score (data not shown). Children who were more stunted accumulated more storage iron in association with deworming.

DISCUSSION

The Zanzibar school-based deworming program significantly reduced the burden of iron deficiency and moderate-to-severe anemia in schoolchildren in its first year of implementation. Thrice-yearly deworming caused improvements in iron status measured both by protoporphyrin, a measure of iron-deficient erythropoiesis, and serum ferritin, a measure of iron stores. The most striking benefit was the prevention of moderate-to-severe anemia in children with heavier hookworm infections at baseline. Thus, deworming had the greatest benefit for children at greatest risk for the morbidity and mortality caused by anemia. This benefit was achieved even though the prevalence of hook-

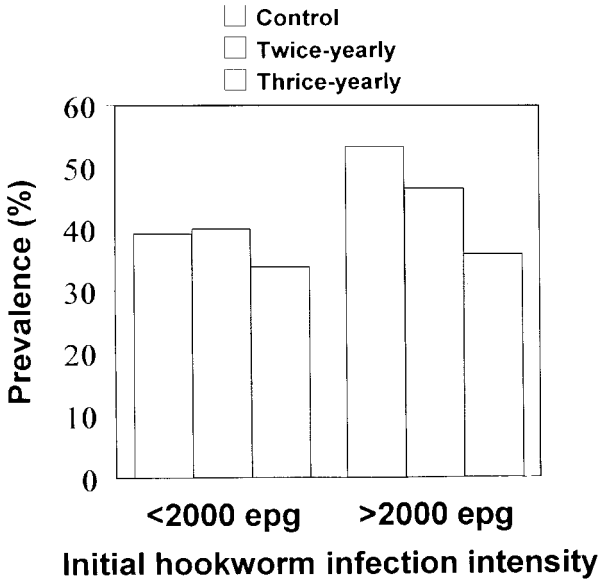

FIGURE 1. Prevalence of iron-deficient erythropoiesis (protoporphyrin > 90 μmol/mol heme) at the 12-mo follow-up in children in the control, twice-yearly deworming, and thrice-yearly deworming program schools stratified by baseline hookworm infection intensity. Epg, eggs/g feces. Values are adjusted for district and for hemoglobin concentration at baseline. Interaction between hookworm infection and twice-yearly deworming, $P = 0.20$; interaction between hookworm infection and thrice-yearly deworming, $P = 0.03$.

TABLE 3
Effect of twice-yearly and thrice-yearly deworming on incidence of moderate-to-severe and severe anemia

Severity of anemia and program group	Incidence per 100 intervals[1]	Relative risk[2]	95% CI
Moderate-to-severe anemia (hemoglobin < 90 g/L)			
Control	5.6	1.00	—
Twice-yearly deworming	5.8	1.19	0.72, 1.98
Thrice-yearly deworming	3.5	0.75	0.44, 1.29
Hookworm infection at baseline			
< 2000 eggs/g feces			
Control	4.7	1.00	—
Twice-yearly deworming	5.8	1.43	0.87, 2.34
Thrice-yearly deworming	3.2	0.75	0.43, 1.30
≥ 2000 eggs/g feces			
Control	9.8	1.00	—
Twice-yearly deworming	5.4	0.53	0.29, 0.97
Thrice-yearly deworming	4.7	0.43	0.28, 0.66
Severe anemia (hemoglobin < 70 g/L)			
Control	0.84	1.00	—
Twice-yearly deworming	0.60	0.77	0.39, 1.51
Thrice-yearly deworming	0.35	0.45	0.19, 1.08

[1] Based on estimates from linear regression models, adjusted for hemoglobin, ferritin, and protoporphyrin at baseline.
[2] Based on estimates from Poisson regression models.

worm infection was only modestly reduced, and the intensity of infection was reduced by two-thirds, as measured by fecal egg counts after 1 y.

Despite improvements in iron status, the deworming program had no detectable effects on average hemoglobin concentrations or the prevalence of mild anemia. The differential responsiveness of iron-specific indicators and hemoglobin suggests that factors apart from iron status are important regulators of erythropoiesis in this population and that those other factors were the main causes of the hemoglobin changes we observed. This is corroborated by the fact that hemoglobin concentrations increased dramatically from 1994 to 1995 regardless of treatment (11.3 g/L in the control group), whereas the iron-specific indicators, ferritin and protoporphyrin, changed relatively little in the control group (2.8 μg/L and −6 μmol/mol heme, respectively). Predicting from the empirical relations between hemoglobin and iron-status indicators in our data at baseline (data not shown), the improvements in protoporphyrin and ferritin in the control group would account for a hemoglobin increase of only 0.5–0.6 g/L—about 5% of the increase we observed in the control group.

If not iron status, what then might explain the change in hemoglobin concentration from 1994 to 1995 in these children? Although we did not measure dietary or household food availability, there was anecdotal evidence that 1994 was a lean year, whereas the harvest in 1995 was exceptionally good. Thus, it is possible that other nutritional influences caused by better diet contributed to the increase. The difference in hemoglobin cannot be explained by a systematic error in hemoglobin measurement because the same method was used in all surveys and controls were run daily. Nor did the difference relate to malaria trends because the prevalence and intensity of malaria parasitemia were nearly identical in 1994 and 1995. In sum, the secular change in hemoglobin is perplexing because it is not well explained by the variables we measured and because it appears to have obscured the potential effect on mild anemia that we would expect to be associated with improvements in iron status.

The greater effect of deworming in children with more severe forms of anemia was predicted by the cross-sectional relation between hookworm infection and anemia in these children at baseline. In these analyses, the attributable fraction of anemia associated with hookworm infection was 25%, but the attributable fraction of severe anemia was 73% (6). We expected the actual reduction in anemia and severe anemia achieved from deworming to be less than these attributable fractions because hookworm infection was reduced but not eradicated by periodic deworming.

The pattern of effects that we observed within and between program groups agrees with a continuous relation between the intensity of hookworm infection (ie, the worm burden) and the degree of blood loss. Thrice-yearly deworming reduced hookworm burdens substantially better than did twice-yearly deworming (based on fecal egg counts) and by almost every indicator the effect on iron status was greater in the thrice-yearly deworming group. Furthermore, the effect of deworming on iron-deficient erythropoiesis and moderate-to-severe anemia was significantly greater in children with heavier hookworm infections at baseline. Because even thrice-yearly mebendazole did not reduce the prevalence or intensity of hookworm infection to very low levels, our results suggest that more effective anthelmintic regimens (ie, more frequent administration or more efficacious drugs) would have larger effects on children's iron status.

Anthelmintic therapy might bring about an improvement in children's growth as well as in erythropoiesis and iron storage. These benefits are likely to be in competition, however, because growth is iron costly (26). Previous efficacy trials of deworming of east African schoolchildren (27–31), carried out over periods lasting from 5 wk to 8 mo, found impressive effects on growth but in general did not report impressive effects on iron status. In only one trial of albendazole treatment of hookworm-infected boys was there was a statistically significant effect on hemoglobin of 4 g/L over 4 mo (29).

As predicted by this competition between indicators of iron status and growth, we found that the subgroups of children who benefited most in terms of growth tended to benefit least in terms of iron status. Specifically, age < 10 y predicted greater growth benefit from deworming (15) but predicted less benefit in hemoglobin and protoporphyrin concentrations. Also, the twice-yearly deworming group had the greatest overall weight gain from deworming (15), which possibly explains why the decrease in prevalence of anemia was smallest in this group. Finally, children who were more stunted at baseline benefited least in terms of ponderal and linear growth (15) but accumulated the most storage iron. When evaluating the effect of deworming programs on iron status, it may be necessary to account for the iron costs of growth if a significant growth effect is observed. We did not take this approach in these analyses because the observed growth effect was small (15) and equations for estimating total body iron have not been validated in growing children. The small growth effect that we observed would tend to cause us to underestimate the effect of deworming on iron status.

Benefits to serum ferritin were small, which is not surprising because the population had a high burden of iron deficiency anemia at baseline. The iron saved from reduced intestinal

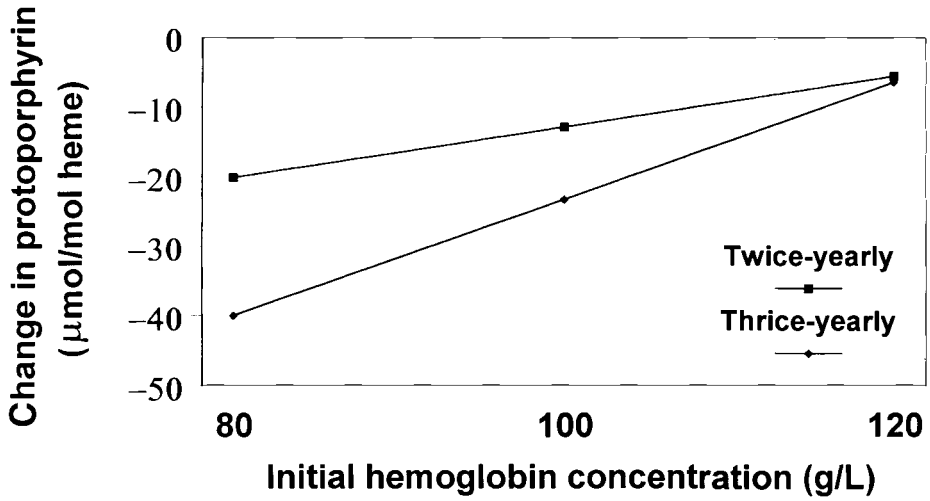

FIGURE 2. Effect of twice-yearly and thrice-yearly deworming on 12-mo change in protoporphyrin concentration according to baseline hemoglobin concentration. Value of zero represents no effect relative to the control group. Values are plotted for children > 10 y of age at baseline, adjusted for district, age, and protoporphyrin and hemoglobin concentrations at baseline. Interaction between hemoglobin and twice-yearly deworming, $P = 0.16$; interaction between hemoglobin and thrice-yearly deworming, $P = 0.001$.

blood loss was utilized for erythropoiesis and growth, not for stores. This explains why the serum ferritin concentration did not increase in children who had no iron stores at baseline.

Because deworming acts primarily by decreasing iron loss, in populations with limited absorbable dietary iron the expected effect from deworming would be to halt or slow the decline in iron status associated with hookworm infection. If the population continues to eat the same poor diet, growing children may not be able to gain body iron, even when hookworm burdens are reduced. Thus, the major effect of anthelmintic therapy in this malnourished population was to prevent children from sliding into moderate or severe iron deficiency anemia. The greatest effects of deworming have been seen in trials in which anthelmintic therapy was combined with increased dietary iron. Significant increases in hemoglobin concentration were reported when deworming was provided along with iron-fortified soup to iron-deficient South African schoolchildren (32), along with iron-fortified salt to an Indian community (8), or along with nutritionally adequate meals to prisoners in Papua New Guinea (33).

This program was administered and implemented by a local unit of the Ministry of Health in collaboration with schoolteachers. The staff of the Helminth Control Team are high-school-educated government employees. The program was well-received by teachers, parents, and students, as shown by the 90% coverage rate achieved. The generic mebendazole tablet is chewable and orange flavored. It was palatable to the children and produced few and mild side effects (17).

The cost of the program, prorated over 10 y, was estimated to be US$4500 per year to cover a population of 30 000 primary school children (Ministry of Health of Zanzibar, unpublished data, 1993). Based on the data in Table 3, we estimate that in 1 y the program prevented 1208 cases of moderate-to-severe anemia at a cost of US$3.57 per case and 276 cases of severe anemia at a cost of US$16.30 per case. These benefits were achieved in a calendar year when children's hemoglobin concentrations improved dramatically apart from the deworming program, and may underestimate the benefit in a more typical year.

We conclude that where hookworm infections are prevalent and iron intakes are poor, deworming programs can marginally improve the iron status of populations and may substantially reduce the incidence of moderate and severe anemia. Those individuals with moderate or heavy hookworm infections will benefit most. This has implications not only for children but also for women, in whom hookworm infections may also be an important cause of anemia (34, 35).

However, hookworm control is not sufficient as an anemia-control strategy. Where delivery systems exist or can be built, increased iron intake through supplementation, fortification, or improved diet should be combined with deworming programs. The addition of iron supplementation to the school-based deworming program in Zanzibar is being evaluated. Drug costs for the thrice-yearly deworming program are $0.08 per child per year and the costs of weekly or daily iron supplementation in schools are at least as low ($0.02 and $0.08 per child per year, respectively). Additional applied research is needed to develop guidelines for when and how deworming is most cost-effectively integrated with other iron interventions.

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