Treatment of *Trichuris trichiura* Infections Improves Growth, Spelling Scores and School Attendance in Some Children[1,2]

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ABSTRACT The effects of treating *Trichuris trichiura* infections were investigated in 407 Jamaican children age 6 to 12 y. The children were randomly assigned to receive treatment (albendazole) or a placebo. The outcome variables included growth, tests of reading, spelling and arithmetic, and school attendance. After 6 mo of treatment, there was no significant main effect on any of the outcomes. However, there were significant treatment-by-infection intensity interactions with spelling ($P < 0.05$) and body mass index ($P < 0.01$), and a significant treatment-by-stunting interaction with school attendance ($P < 0.01$). In spelling, the children with heavy infections showed improvements with treatment that approached significance ($P = 0.06$), whereas those with lower intensities did not. However, the children with lower infection intensities had increased body mass index with treatment ($P = 0.02$), although there was no difference in children with heavy infections. In school attendance, the stunted children improved with treatment ($P < 0.04$), whereas there was no difference in the nonstunted children. These findings suggest that in the sample of Jamaican children examined, the treatment of *T. trichiura* was more likely to benefit school performance in children of poor nutritional status and those with heavy infections, and to improve weight gain in children with lighter infection intensities. J. Nutr. 125: 1875–1883, 1995.

INDEXING KEY WORDS:

- *school achievement* • *school attendance*
- *Trichuris trichiura* • *growth* • *humans*

In developing countries, there is concern that poor health and nutrition may detrimentally affect children's ability to benefit from school (Pollitt 1990). Associations between poor nutrition and deficits in cognition and school achievement levels have frequently been demonstrated (Simeon and Grantham-McGregor 1990). Recently, there has been renewed interest in whether helminth infections also have detrimental effects (Braddeley 1992, Connolly and Kvalsvig 1993, Halloran et al. 1989, Nokes and Bundy 1994).

It is estimated that helminth infections affect as many as 800 million people and the prevalence and intensity of *Trichuris trichiura* and *Ascaris lumbricoides* are greatest in school-aged children (Bundy and Cooper 1989). There is considerable evidence that helminth infections affect children's growth (Hall 1993, Stephenson et al. 1993a and 1993b), but less evidence exists regarding an effect on cognition (Connolly and Kvalsvig 1993). Associations have been found between *T. trichiura* infections and school grades and attendance in one study (Nokes and Bundy 1994) but not in others (de Carneri 1968, de Carneri et al. 1967). Kvalsvig et al. (1991) found an association between mixed helminth infections and cognitive functions in two studies and an association between helminth infections and school grades in one of them. Many more studies have been conducted that included children with schistosomiasis, but the findings have been inconsistent (Connolly and Kvalsvig 1993).

Infected children usually come from poor homes and frequently have many other disadvantages that detrimentally affect their mental development. In most of the observational studies mentioned above, there was little attempt to control for these disadvantages, and it may not be possible to control for all of them (Richardson 1974). Treatment trials are therefore the only satisfactory way of isolating the effects of infection.

Boivin and Giordani (1993) demonstrated that children infected with hookworm had improved cognition with anthelmintic and iron treatment. Several

[1]Funded by a grant from the James S. McDonnell Foundation.

[2]The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 USC section 1734 solely to indicate this fact.

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Manuscript received 2 August 1994. Initial review completed 4 September 1994. Revision accepted 9 February 1995.

treatment trials with children with schistosomiasis have shown small benefits in mental ability (Bell et al. 1973, Castle et al. 1974, Jordan and Randall 1962) whereas one did not (Kimura et al. 1992). However these studies suffered from many design problems. Some of the trials had no control group, some did not have random assignment to treatment, and others had small samples.

In Jamaica, children suffering from Trichuris Dysentery Syndrome had very low developmental levels and after 1 y of anthelmintic treatment and a short course of iron, they improved in motor development compared with uninfected controls (Callender et al. 1994). In a clinical trial, children with moderate to heavy infections of *T. trichiura* improved with treatment in three of eight cognitive tests (Nokes et al. 1992), but the pattern of cognitive effects was not easily understood (Baddeley 1992). In addition, it is not always clear to policy makers how these functions relate to children's everyday performance.

The problem is probably more complex than is generally recognized because different helminths have distinct pathogeneses and are likely to have varying effects on the hosts' performance. In addition, the intensity of infection and the underlying nutritional status of the children may be critical, and more often than not, these factors have not been taken into account.

In the present study, we determined the effects of giving anthelmintic treatment to children with *T. trichiura* infections on school attendance, achievement and growth. Treatment interactions with intensity of infection and nutritional status were also examined.

SUBJECTS AND METHODS

Sample. The subjects were children in grades 2 to 5 attending six primary schools in Kingston and eight in the parish of Manchester, Jamaica. Kingston is the capital city of Jamaica and the areas chosen generally had a poor standard of housing. Manchester is a hilly rural parish in the center of the island where most householders are small farmers. To identify the children for the study, 44 government schools were screened. The schools were chosen on the advice of local health professionals and the results of previous surveys, which suggested that they were located in areas with a high prevalence of geohelminthiasis. Small schools were excluded, and the 14 schools selected had sufficient numbers of infected children to be studied. The enrollment in grades 2 to 5 in the selected schools ranged from 145 children in the smallest to 532 in the largest.

To identify the subjects, stool samples were collected and analyzed using the Kato thick smear technique (Martin and Beaver 1968). The latter was used to determine the presence and intensity of *T. trichiura* infections. The prevalence of *T. trichiura* infection among the children in the 14 study schools ranged from 43 to 74%. The presence and intensity of *A. lumbricoides* infections were determined for study children only.

All children with *T. trichiura* infection intensities of >1200 eggs per gram of stool (epg) were recruited for the study. The present investigation included 407 children who were assigned to either the treatment or the placebo group. It was not known what the effects of treating children with *T. trichiura* infections would have been on school achievement. Therefore to determine the sample size for the present study, the results from a previous clinical trial conducted in Jamaica were used. In that study, giving a school meal to children for 3 mo resulted in improved arithmetic scores (Powell et al. 1983). We hypothesized that deworming children for 6 mo would result in at least the same effect. It was therefore calculated that 200 children were needed in each group to identify significant treatment effects with 80% power at the 5% significance level.

Children with mental handicaps, identified by the opinion of their teachers, were excluded from the study. This was recognized to be a crude method but was considered to be the best available considering the limited time and resources.

Study design. The children were randomly assigned to receive treatment ($n = 206$) or a placebo ($n = 201$). In each class, the study children were first assigned consecutive numbers, then placed in the treatment or the placebo group using a table of random sampling numbers. The children in the treatment group received 800 mg of albendazole (400 mg on each of 2 d), and the children in the placebo group were given placebos that looked identical to the albendazole tablets. Treatment and placebos were given after the baseline measurements, 12 wk later, and 24 wk later. The post-test measurements were conducted ~26 wk after the first round of treatment.

A further stool sample was collected ~8 wk after the second round of treatment to determine the infection status of the children. These samples were also analyzed using the Kato thick smear method to determine the presence and intensity of *Trichuris* infections and the presence of *Ascaris* infections.

Permission to conduct the study was obtained from the ethics committees of the University of the West Indies and the Ministry of Health as well as from the Ministry of Education. Parental permission was also obtained for each child studied.

School achievement. School achievement was measured using the Wide Range Achievement Test (WRAT) (Jasak and Bijou 1946). This test was composed of reading, spelling and arithmetic subtests and was administered by trained testers. The words in the reading and spelling tests were rearranged in order of difficulty for the Jamaican children after extensive piloting. The reading test was given individually, whereas the spelling and arithmetic tests were given in small groups except for the children in grade 2, who were given all of the subtests individually. Before the study began, 47 nonstudy children were tested twice, 1 wk apart, and the test-retest reliabilities were high, ranging from 0.92 to 0.99. Test-retest reliabilities were also determined over the 6-mo duration of the study for the total sample and were also high, ranging from 0.89 to 0.96.

The scores used in the present study were the number of correct responses. The WRAT has previously been used successfully in Jamaica (Clarke et al. 1991).

School attendance. School attendance data from the previous academic year (baseline) and the academic year of the present study (post-test) were collected from the school registers. Data for the previous academic year were available for only 264 children because of the loss of class registers in some of the schools.

Attendance was measured as the percentage of school days that the children attended school.

Anthropometry. All children had their weight and height measured according to standard techniques (Lohman et al. 1989). Before data collection, the anthropometrists were trained and interobserver reliabilities conducted. The intraclass coefficients were 0.99 for both weight and height. The children's heights were expressed as Z-scores of the National Center for Health Statistics (NCHS) standards (Hamill et al. 1979) and their body mass indices calculated (kg/m^2).

Iron status. Blood samples were collected at baseline only. The samples were obtained from the children via antecubital venipuncture. Hemoglobin concentration was determined using a Coulter Counter (Model S+4, Coulter Electronics, Florida) and plasma ferritin was measured with an immunoradiometric assay kit (Diagnostic Products, CA).

Socioeconomic status index. A questionnaire was administered to the children to obtain a measure of their socioeconomic status. The interviewers were trained and data collection did not begin until there was >90% agreement for all questions in 10 consecutive interviews. The three types of data collected were family possessions, sanitation facilities at home and school materials. The children were questioned about the first two of these. To assess school materials, the reading and writing materials that the children brought to school were observed and the quality of the uniforms and shoes that they were wearing were rated. A socioeconomic status index, which ranged from 0 (poorest) to 12 (richest), was computed giving equal weight to the three categories. A similar questionnaire was previously used and validated with Jamaican children (Clarke et al. 1991).

Data analysis. Differences between the treatment and placebo groups in age, socioeconomic status, school achievement test scores, school attendance and nutritional status were analyzed using Student's *t* tests. Chi square tests were used to examine group differences in gender, presence and intensity of *Ascaris* infections, area of residence and iron status. The Mann-Whitney U test was used to examine differences in baseline *Trichuris* intensities between the treatment and placebo groups (Armitage 1971).

The children were divided into groups based on stunting and the severity of their initial *T. trichiura* infection. Stunted children were defined as those with height-for-age Z-scores <−1 of the NCHS standards (Hamill et al. 1979) and nonstunted children as those with height-for-age Z-scores >−1 of the NCHS standards. To examine intensity of infection, the sample was divided into those with heavy infection intensities, i.e., >7000 epg (Nokes and Bundy 1993), and those in whom the initial *Trichuris* infections were not heavy (<7000 epg). There were 109 stunted children and 55 had heavy initial *Trichuris* infections.

Fifteen children were not included in the post-test analyses because they changed schools during the academic year. Five were from the placebo group and 10 were from the treatment group.

Treatment effects were determined using multiple regression analyses. First, residualized gain scores were calculated for each outcome variable. To do this, linear regression analyses were conducted with the post-test measures as the dependent variable and the pretest measures as the independent variable. The residuals from these analyses were saved for use as the dependent variables in subsequent analyses. In these multiple regression analyses, treatment group was entered as a dummy variable and other potentially confounding variables were entered as covariates. The latter included gender, age, socioeconomic status, the intensity of *Ascaris* infections (log transformed) and school attended (as dummy variables). The analyses were repeated with treatment-by-stunting and treatment-by-intensity interactions as additional independent variables.

The SYSTAT statistical software (SYSTAT, Evanston, IL) was used to analyze the data. Differences were considered significant at $P < 0.05$. Results are expressed as means ± SD.

RESULTS

Baseline characteristics. The baseline characteristics of the sample are shown in **Table 1**. There was no difference between the treatment and placebo groups in any of the variables at baseline. The children were 6 to 12 y old, with the mean being 9.2 y. Fifty percent of the sample was male, and 34% lived in Kingston. Forty-six percent of the children

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TABLE 1

Baseline characteristics of the treatment and placebo groups of Jamaican school children

	Group		
	Treatment (n = 206)	Placebo (n = 201)	Significance P
Age,[1] *y*	9.2 ± 1.2	9.2 ± 1.3	0.63
Gender, *% boys*	52	47	0.35
Residence, *% Kingston*	35	33	0.77
Ascaris infection			
% Infected	42	50	0.13
Light	11	10	
Moderate	25	29	
Heavy	7	11	
Socioeconomic index[1]	5.9 ± 2.2	6.1 ± 2.2	0.28
Trichuris intensity,[2,3] *epg*	2421 (1200–25,458)	2667 (1200–41,733)	0.06
Anemia,[4] *% hemoglobin <110 g/L*	10	16	0.20
Low ferritin,[4] *% <12 μg/L*	6	9	0.39

[1]Means ± SD.
[2]epg = eggs per gram of stool.
[3]Values are medians, with the range in parentheses.
[4]Blood samples were obtained from only 264 children.

were infected with *Ascaris*, 10% had light infections (<5000 epg), 27% had moderate infections (5000–35,000 epg), and heavy *Ascaris* infections (>35,000 epg) were present in 9% of the sample (Table 1). Although the intensity of *Trichuris* infection in the placebo group tended to be higher than in the treatment group, the difference was not significant (P = 0.06) (Table 1).

Iron status. Blood samples were obtained from 264 children, 128 in the placebo group and 136 in the treatment group. The remaining children refused to have a venipuncture. There were no significant group differences in the prevalence of anemia (hemoglobin <110 g/L) or low ferritin concentration (<12 μg/L) (Table 1). Thirteen percent of the children were anemic and 7% had low plasma ferritin.

Parasitic infections. A second stool sample was collected from 97% of the children ~8 wk after the second round of treatment. The analyses of these samples indicated that 50 and 8% of the children in the treatment and placebo groups, respectively, were not infected with *Trichuris* and 5 and 57% of them, respectively, had infection intensities >1200 epg. In addition, 7% of the treatment group and 42% of the placebo group were infected with *Ascaris*.

School achievement. The mean school achievement test scores at baseline are given in **Table 2**. The results of the t tests indicated that there was no significant group difference in any of the WRAT subtests. However, the stunted children had lower scores than those who were not stunted, in reading (21.7 ± 11.9 vs 25.1 ± 13.4, P = 0.02), spelling (13.1 ± 7.6 vs 15.3 ± 9.0, P = 0.02) and arithmetic (18.0 ± 6.7 vs 19.9 ± 6.7, P = 0.01).

At the post-test, the lack of difference persisted between the treatment and placebo groups for all of the WRAT subtests (Table 2).

The multiple regression of the residualized gain scores of each of the WRAT subtests indicated that there were no significant main treatment effects. When the analyses were repeated including the treatment-by-stunting and treatment-by-intensity interaction terms, there was no significant treatment-by-stunting interaction for any of the WRAT subtests. However, there was a significant treatment-by-intensity interaction in spelling (P < 0.05), which remained significant after controlling for the covariates (**Table 3**). In the children with low initial intensities of infection, there was no difference between the treatment and placebo groups. However, among the children with heavy infections, those who were treated had an improvement in spelling that approached statistical significance compared with those who received the placebo (P = 0.06) (**Fig. 1**). There was no other treatment-by-intensity interaction in school achievement.

Age was an independent predictor of reading (b = –0.38, P = 0.02) and spelling (b = –0.27, P = 0.01), which implied that the younger children had greater improvements in these two WRAT subtests over the study period compared with the older children. Gender was a significant predictor only for spelling, with the girls doing better than the boys (P = 0.02). The only other significant predictor was school attended, for reading (P = 0.002) and arithmetic (P = 0.001).

School attendance. The mean school attendance rates at baseline and at post-test are shown in Table 2. There was no significant difference between the

TABLE 2

Mean school achievement test scores, school attendance and anthropometry of Jamaican school children at baseline and at post-test[1,2]

	Group		
	Treatment (n = 206)	Placebo (n = 201)	Significance[3] P
Arithmetic			
Baseline	19.2 ± 7.1	19.6 ± 6.5	0.54
Post-test	21.4 ± 6.2	21.5 ± 6.2	0.92
Spelling			
Baseline	14.3 ± 8.7	15.2 ± 8.6	0.29
Post-test	16.9 ± 10.2	17.6 ± 10.0	0.43
Reading			
Baseline	23.7 ± 13.4	24.7 ± 12.6	0.45
Post-test	27.7 ± 15.2	28.4 ± 14.0	0.65
School attendance (%)			
Baseline	62.6 ± 20.4	66.3 ± 20.8	0.15
Post-test	67.3 ± 18.4	69.3 ± 17.5	0.40
Height-for-age, *Z-score*			
Baseline	−0.48 ± 0.95	−0.39 ± 0.90	0.35
Post-test	−0.48 ± 0.97	−0.41 ± 0.89	0.46
Body mass index, kg/m^2			
Baseline	15.3 ± 1.3	15.5 ± 1.3	0.07
Post-test	15.6 ± 1.3	15.8 ± 1.4	0.25

[1]Values are means ± SD.
[2]Fifteen children (10 from the treatment group and five from the placebo group) did not complete the post tests because they changed school during the study period.
[3]t tests.

treatment and placebo groups at either point. There was also no difference in school attendance between the stunted and nonstunted children.

The results of the multiple regression analyses of the residualized gain scores of school attendance indicated that there was no main treatment effect. However, when the analyses were repeated including the interaction terms, there was a significant treatment-by-stunting interaction (P = 0.007) (Table 3). The stunted children who were treated improved in attendance compared with those receiving the placebo (P < 0.04) whereas there was no significant difference between the treatment and placebo groups among the nonstunted children (**Fig. 2**). The interaction remained significant after controlling for the covariates. The treatment-by-intensity interaction was not significant for school attendance. School attended was the only other significant predictor of attendance (P < 0.001).

Growth. The mean height-for-age and body mass index at baseline and at post-test are shown in Table 2. The differences between the treatment and placebo groups were not statistically significant at baseline or post-test.

Multiple regression analyses of the residualized gain scores indicated that there was no main

TABLE 3

Results of the multiple regression analyses showing the significant treatment-by-stunting and treatment-by-intensity interactions for Jamaican school children, after controlling for the covariates[1]

	b[2]	P
Spelling		
Treatment	−0.1	0.62
Intensity	−0.3	0.57
Treatment × intensity	1.6	<0.05
School attendance		
Treatment	−3.2	0.08
Stunting[3]	−6.8	0.01
Treatment × stunting	9.9	0.007
Body mass index		
Treatment	0.12	0.003
Intensity[4]	0.13	0.15
Treatment × intensity	−0.35	0.009

[1]Covariates included age, gender, socioeconomic status, intensity of *Ascaris* infection and school attended.
[2]b is the unstandardized regression coefficient.
[3]Defined as height-for-age Z-score <−1.
[4]Defined as *Trichuris* infection intensities above and below 7000 eggs per gram of stool.

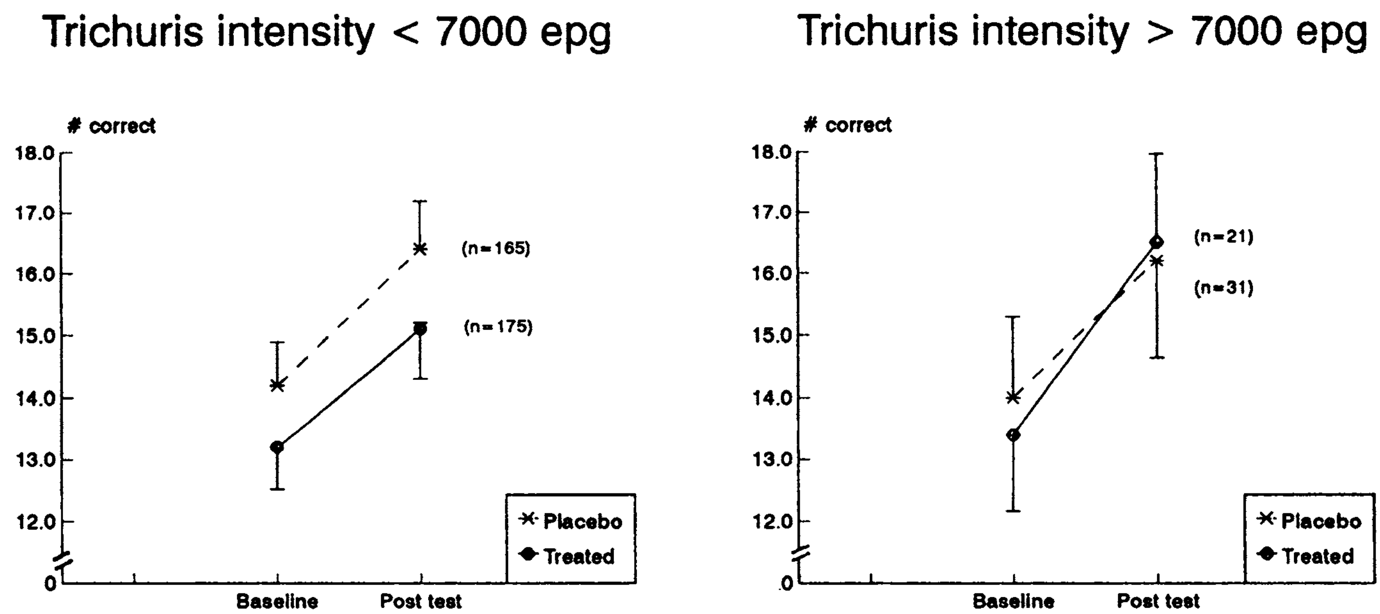

FIGURE 1 Treatment-by-infection intensity interaction in spelling. Values are means ± SEM. Among the children with a heavy *Trichuris* infection, i.e., >7000 eggs per gram of stool (epg), those who were treated tended to improve more than those who received the placebo ($P = 0.06$). There was no difference between the treatment and placebo groups among the children with a lower infection intensity (<7000 epg).

treatment effect on body mass index. However, when the analyses were repeated including the interaction terms, there was a significant treatment-by-intensity interaction ($P = 0.009$) that remained significant after controlling for the covariates (Table 3). The children with low intensities improved with treatment compared with those receiving the placebo ($P = 0.02$), whereas there was no significant difference between the treatment and placebo groups among children with heavy baseline intensities of *Trichuris* (**Fig. 3**).

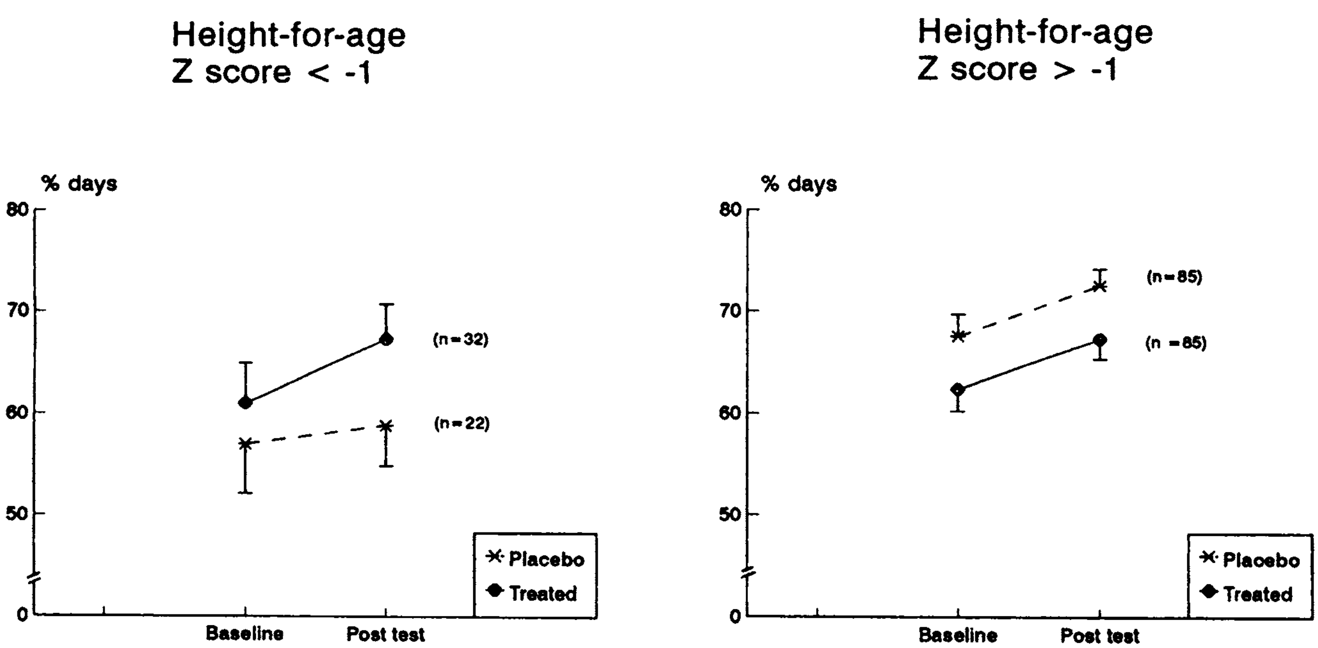

FIGURE 2 Treatment-by-stunting interaction in school attendance. Values are means ± SEM. Among the stunted children (height-for-age Z-score <–1), those who were treated improved more than those who received the placebo ($P = 0.05$). However, there was no difference between the nonstunted children (height-for-age Z-score >–1) who received treatment or a placebo.

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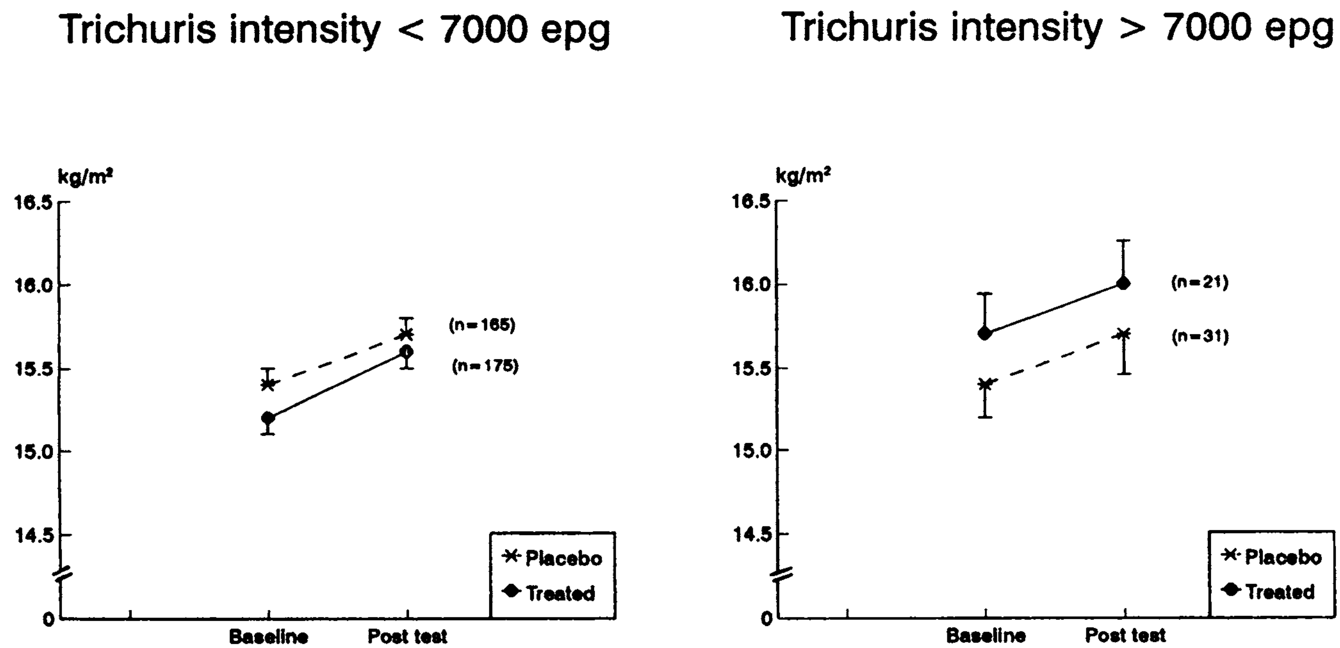

FIGURE 3 Treatment-by-infection intensity interaction in body mass index. Values are means ± SEM. Among the children with a low infection intensity, i.e., <7000 eggs per gram of stool (epg), those who were treated increased their body mass index compared with those who received the placebo ($P = 0.02$). There was no difference between the children with a heavy infection (>7000 epg) who received treatment or a placebo.

There was no significant treatment-by-stunting interaction in body mass index.

When the children's height-for-age was examined, there was no significant main treatment effect or treatment interactions with intensity or stunting.

Post-hoc analyses. Fifteen children in the placebo group were no longer infected with *T. trichiura* when their stools were reexamined, and 10 children in the treatment group had infection intensities >1200 epg. To be certain that this did not affect the results, the analyses to determine the effects of treatment on the various outcome variables were repeated excluding these 25 children. The findings were unchanged.

DISCUSSION

The present study was a double-blind, randomized treatment trial with 80% power to detect differences in school achievement in children treated for *T. trichiura* infections. The children were treated with two doses of albendazole every 3 mo, which is considerably more than that recommended by WHO (1992). In addition, malaria and schistosomiasis do not occur in Jamaica and the prevalence of hookworm infections is low. *Ascaris* is the only other helminth of importance (Rawlins et al. 1991) and this was controlled in the analysis. Protozoan infections such as *Giardia* are also uncommon in Jamaican school children (Rawlins et al. 1991). Therefore the present study was likely to have been a valid assessment of the effects of 6 mo of treatment for *T. trichiura* infections. There was no overall benefit in the measured outcomes, although certain subgroups of children did show benefits. The observed treatment interactions with intensity of infection and stunting were not taken into account in the initial design of the study, in that the groups were not stratified by infection intensity or by nutritional status before random assignment to treatment. Therefore, the findings need to be replicated in further studies. However, the observed interactions were particularly interesting.

The children with a heavier infection who were treated were more likely to improve in spelling compared with those who received a placebo, whereas there was no difference in children with a lighter infection. Conversely, children with a lighter infection had a higher body mass index after treatment, whereas those with heavier infections did not. This latter finding is difficult to explain, but suggests a different mechanism from that affecting spelling. The mechanism whereby these infections may have affected spelling is not clear, but heavy *Trichuris* infections cause iron deficiency anemia and growth retardation, both of which are associated with poor cognition (Simeon and Grantham-McGregor 1990). A study, concurrent with the present one, was conducted to determine whether *Trichuris* infection was associated with iron deficiency anemia. The results indicated that, compared with uninfected children, an increase in the prevalence of anemia was only present in children with a heavy *Trichuris* infection (Ramdath et al. 1995). However, because no blood samples were taken at the end of the study period, it is not known if the anemia status of the treated children improved. Another possible mechanism is that a chronic inflammatory response may be present (Cooper et al. 1992) that could also affect cognition, although there has been little research on this.

The nutritional status of the children also seemed to be important in determining benefits from treatment. The stunted children who were treated improved in school attendance more than those who received the placebo, whereas there was no difference in the nonstunted children. This interaction is of particular interest because an interaction between two biological conditions on children's performance has been previously demonstrated (Simeon and Grantham-McGregor 1989). In that study, the cognitive functions of stunted children and children who were severely malnourished in early childhood were detrimentally affected by short-term food deprivation, whereas those of adequately nourished children were not. In the present study, there were no baseline school attendance rates for 35% of the sample due to the loss of class registers in some of the schools. This was not expected to introduce a bias in the study because the loss was not related to the independent variables being examined. Also the post-test attendance rates in the children who had missing data at baseline were not different from those for whom data were available. However, the loss of data would have resulted in a reduction of power to identify treatment effects in school attendance. The mechanism for the improved attendance is not clear. It may be that the children generally felt better and less tired and so were more inclined to go to school.

Children's biological state is one of many factors affecting school achievement. Other factors include the quality of instruction, availability of school books, family attitudes toward school, level of parental education, the children's age at enrollment in school, attendance levels and innate ability. If other conditions are extremely poor, it is possible that improving the children's biological state may not be sufficient to improve their school performance, or improvement may take place very slowly. The poor homes from which the children came and the relatively poor conditions in the schools may have reduced the possibility of a rapid and marked improvement. Therefore, it is possible that if the study had continued for a longer period, greater benefits would have ensued.

The nutritional status of the Jamaican children was relatively good compared with those in many other developing countries, and there was a relatively low prevalence of heavy infections. It is possible that in populations where children are more heavily infected than the Jamaican children and have poorer nutritional status, the benefits of deworming would be greater. It is also possible that children with mixed parasitic infections may show greater benefits.

In the sample of Jamaican children studied, there were no overall improvements in growth or school performance after the treatment of *T. trichiura*. However, the attendance and spelling ($P = 0.06$) performance of children who were stunted or had heavy infections improved with anthelmintic treatment. Children who had lower levels of infection improved in body mass index, which is more difficult to explain. Because the observed treatment interactions were not hypothesized, these findings need to be replicated in further studies. However, the results suggest that benefits in school performance and growth from the treatment of *Trichuris* infections depend on children's nutritional status as well as their infection intensity.

ACKNOWLEDGMENTS

We thank the field staff of the Tropical Metabolism Research Unit for their excellent work. The cooperation of the principals, teachers and especially the children in the participating schools was greatly appreciated.

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