INSTRUCTION IN BEHAVIOR MODIFICATION CAN SIGNIFICANTLY ALTER SOIL-TRANSMITTED HELMINTH (STH) RE-INFECTION FOLLOWING THERAPEUTIC DE-WORMING

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Abstract. Five elementary ("prototypic") schools located in five districts in central Java were selected and the children examined for helminth infections (*Ascaris, Trichuris*, hookworm). They were de-wormed with a course of mebendazole and provided with 6-7 months of "behavioral remediation instruction" (BRI). In other ("control") schools, children were treated with mebendazole but were not provided BRI. The objective was to determine the effectiveness of BRI in minimizing infection/re-infection following deworming. After the 6-7 month course of BRI in the prototypic schools, all the children (in both the prototypic and control schools) were re-examined for geohelminth infection. The schools in two of the five districts were omitted from further analysis because the overall prevalence of infection was low (<10%) and the infections were dominated by hookworm which are only moderately susceptible to mebendazole. Comparisons of prototypic and control schools in the other three districts provided compelling evidence that BRI was quite effective in reducing both the frequency and intensity of infection with *Ascaris* and *Trichuris*. We suggest that instructing children and adults corrects personal habits which are conducive to infection and can be an effective and safe substitute for repeated deworming, reducing the opportunity for the emergence of drug-resistant helminthes, which should prolong the time benzimidazoles may be used for treatment of geohelminth infection.

INTRODUCTION

In many regions of the world infection with soil-transmitted helminths has been considered relatively harmless and a phase in the process of growing up. During the past two decades childhood infection with STH (*Ascaris, Trichuris*, hookworm) has received increasing attention consonant with accumulating evidence that STH infections may interfere with normal growth and maturation in children (Stephenson *et al*, 1993; Adams *et al*, 1994; Simeon *et al*, 1994; Hadju *et al*, 1996; Hutchinson *et al*, 1997; Oberhelman *et al*, 1998;Crompton and Nesheim, 2002; Hlaing *et al*, 2003) and impair cognitive abilities (Kvalsvig *et al*, 1991; Nokes *et al*, 1991; Nokes and Bundy, 1992; Simeon *et al*, 1994; Hutchinson *et al*, 1997; Kvalsvig, 2003). There is currently a program championed by the WHO designed to minimize, if not eliminate, STH infections worldwide (http://www.who.int/wormcontrol/about_us/en). The program calls for drug-induced deworming of children twice a year with a single dose of albendazole. Deworming begins at age two years or younger (Montresor *et al*, 2003) and continues through age 12 to 14, or longer. Over the course of 10 to 12 years, each child will receive 20 or more doses of the drug. Whether there may be a cumulative side-effect from so many exposures to the drug, or the parasites may become refractory to the drug, is not clear.

Several reports (Siharath *et al*, 2000; Hohmann *et al*, 2001; Ndenecho *et al*, 2002; Luong, 2003; Gunawardena *et al*, 2004) focus on the benefits of teaching children how STH infections are acquired and how to avoid them. The results of those efforts, although limited, have been positive. They provide evidence that

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training children and instilling in them a desire to be worm free [behavior remediation instruction (BRI)] should be an important adjunct to drug-induced deworming or even a substitute for repeat deworming. Our report deals with the second phase of a program concerned with STH infections among schoolchildren in central Java, Indonesia. The first phase (see Albright *et al*, 2005) was a survey of prevalences and intensities of infection among more than 500 children (grades 1 through 6), an evaluation of factors which favor the acquisition of infection, and an assessment of the environmental and nutritional conditions of the children.

MATERIALS AND METHODS

Schools and children

One school in each of five different districts located in central Java was selected for deworming and BRI. The children in these schools were the same as those involved in the previous study (Albright *et al*, 2005). Each school serves approximately 100 students in grades 1 through 6. The names of the districts, and the letters we used as codes, are as follows:

Code	Official name of district
A	Kebumen
B	Kulon Progo
C	Bantul
D	Gunungkidul
E	Wonogiri

In addition to the one, prototypic school in each district, subsequent deworming was carried out in 9-10 other schools in each of the 5 districts. Only the children in the prototypic school received BRI. The schools and the districts in which they are located were selected for the study because they differed considerably in terrain and environment and in the characteristics of the inhabitants. There was, however, one common characteristic in all the children included in the study: they all received a package of fried noodles fortified with iron and zinc and selected vitamins (an activity of the Student Health Improvement Program, or SHIP). Nearly all the students involved in the study were 6-12 years of age and approximately equal numbers of girls and boys were included. The study reported here is a continuation of a study already reported (Albright *et al*, 2005).

Nutritional status of the children

As reported previously (Albright *et al*, 2005), measurements of height and weight suggested that the students enrolled in the five schools displayed mild, but not severe, undernutrition. As an additional index of nutritional status, a group of schoolchildren involved in a separate but related project, from schools in the same districts, were evaluated for anemia. Those children were also recipients of the nutritional supplemental "snack noodles" on school days. Both hemoglobin content and hematocrit were assessed. Those parameters were evaluated at the Department of Pathology, Gadjah Mada University School of Medicine.

Parasitological examinations

Baseline data obtained during Phase 1 from the five prototypic schools has been reported previously (Albright *et al*, 2005). Six-to-seven months after Phase 1, a second parasitological survey was performed (Phase 2). Phases 1 and 2, which involved only the children from the five prototypic schools, were conducted during late 2003 and early 2004 (Phase 1) and early to mid 2004 (Phase2). Phase 3, involved the children of all the schools except the prototypic schools, extended over the same period, during 2004 and 2005. Children were carefully taught to collect stool specimens and deliver them as quickly as possible to IRD personnel at school. Each morning the specimens were assembled, carefully identified, placed in an ice chest and delivered to the Department of Medical Parasitology at Gadjah Mada University School of Medicine. Helminth eggs (*Ascaris lumbricoides, Trichuris trichiura* and hookworm) were assessed by a combination of standard wet mounts stained with iodine and Kato-Katz thick smears. Each specimen was coded so that the examining parasitologists were unaware of the identities of the specimen donors.

Study design and behavior remediation in the five prototypic schools

Approximately three months after the initial parasitological survey, drug-induced deworming commenced. During that three month interval, the results of the initial survey were reported to parents and students and the meaning of the results explained. At the same time, a campaign was initiated to explain to parents, students and teachers the findings of the behavioral and personal hygiene studies and to discourage characteristics of behavior and hygiene that were conducive to acquisition of STH infections ("risk elements"). Concomitant with the deworming process, efforts to teach the children how to avoid acquiring STH infections were intensified and the concept of living worm-free was strongly emphasized. This was achieved primarily by members of our project team who spent many hours with the students socializing, singing songs, making posters, all with a worm-free theme. In addition, members of the team organized community meetings with parents and teachers for the purpose of: (a) describing the objectives and desired results of the study, (b) explaining how children can be taught to avoid STH infections, and (c) instilling in them (especially the parents) the realization that the children can be protected from worms without strain on their financial resources or family lives.

Control groups

The control groups comprised most of the students in 9 or 10 schools in each district who were treated with mebendazole but did not receive BRI. An interval of about 7 months separated the two parasitological surveys, one of which preceded the deworming treatment. In all, several thousand stool specimens were examined in the two surveys.

Deworming procedure

Children in all the schools were provided with deworming medication. Their parents or guardians, with few exceptions, consented. Each worm-infected child was provided two, 100 mg tablets of mebendazole each day for three days. In the prototypic schools, members of the project team were present each day to insure that the children took the pills. In one case, children were provided pills to take home on Sunday and were questioned at school the next day to be sure they had complied. Only children found infected on the initial survey were given mebendazole. Those not infected were given a placebo. There was one exception. In one school, parents of the unifected children requested deworming treatment as well. This was done. The data from that school were considered separately.

Final parasitological survey

Six to seven months following deworming, the children again were asked to provide fecal specimens for parasitological examination. The interval of 6-7 months was based on two considerations: first, evidence that in areas of high STH intensity the prevalence of repeat infection 6 months after a single course of treatment is high (Cabrera and Valeza, 1980; Albonico *et al*, 1995; Albonico, 2003; Hadju *et al*, 2003; Gunawardena *et al*, 2004) and, second, a longer length of time would result in higher number lost to follow-up.

RESULTS

Effects of deworming on prevalence of infection

The proportions of children by gender enrolled in the five prototypic schools who were infected before and 6-7 months after deworming are shown in Table 1. Statistical analysis shows the effects of deworming did not differ significantly by gender or age (except for the low prevalence of parasites in the post-deworming evaluation of female students at school A). The students who were infected after deworming (last column, Table 1) comprised children whose infections were not cured, children who were cured but became reinfected, and children who were not previously infected but acquired initial infection subsequent to the deworming exercise.Very few children in schools C and D were infected (Tables 1 and 2). Many of those infected had hookworm rather than *Ascaris* or *Trichuris*. In the case of children in schools C and D, the proportion of students who were infected after deworming and BRI was greater than prior to deworming. This reflects the low cure rate using mebendazole for hookworm.

Intensity of infection (IoI) and frequency of mono- and poly-helminth infections following deworming and BRI.

Tabulation of the data pertaining to children in the five prototypic schools is provided in Table

2. The IoI data are presented in the form of geometric means because counts of eggs in fecal samples were not normally distributed. The data were obtained from (a) the initial parasitological survey prior to initiating deworming and BRI (Phase 1) and (b) the second survey performed approximately 6 months after deworming and the six-month course of BRI (Phase 2). The data displayed under Phase 1 (Table 2) are the same as those published previously (Albright *et al*, 2005) and are shown to enable comparison with the data under Phase 2. The comparison reveals two striking differences: (a) the proportion of infected children in all three schools who were infected with two or three helminths simultaneously was much less in Phase 2 than in Phase 1, and (b) the number of children who were infected with hookworm alone was twice more in Phase 2 than in Phase 1 (27 and 14, respectively). This result reflects, in part, a propensity of children in schools C and D to acquire hookworm infections following deworming.

Impact of BRI on acquisition/re-acquisition of infection following deworming

The data are presented in Table 3. In the three schools included in the Table, a proportion of the students was not infected at the time of the Phase 1 parasitological examination (23/107 in A, 34/118 in B, and 63/93 in E). The remainder were infected either with *Ascaris* or *Trichuris* or both (hookworm not included in this analysis). After deworming and a 6-month course of BRI, the second parasitological examination (Phase 2) revealed that a sizeable proportion of those who had been infected were now clear of infection (65/84 = 77% in A, 51/84 = 61% in B, and 17/20 = 85% in E). A few children in each school were judged to have experienced a partial cure (column 6, Table 3). Columns 8 (re-infected) and 9 (newly infected) require a brief explanation. In a number of children the type and intensity of infection found on Phase 2 examination differed markedly from the Phase 1 examination. Those children were judged to have been cured but re-infected during the 6-7 month interval following deworming. Column 9, Table 3, shows the number of children who were not infected at the time of the initial, Phase 1, examination who became infected with *Ascaris* or *Trichuris* prior to the second, Phase 2, examination. Adding together the numbers of re-infected and newly infected children in each school gives a sum which can be used to calculate a crude index of infection acquired during the 6-7 months following deworming. Thus, in the case of school A (Table 3) adding the data in Columns 8 and 9 gives the sum 11. The sum of columns 3, 5 and 8 (23 + 63 + 11) is an approximation of the number of children at risk during the 6-7 months following de-

Table 1
Effects of deworming and behavioral remediation instruction on intestinal helminth infections in school children six (6) months after treatment.

School	Gender of students	Number of students	Percent of gender infected	
			Before deworming[a]	After deworming[b]
A	F	51	65	6
	M	56	93	29
B	F	60	70	32
	M	58	69	26
C	F	52	9	12
	M	56	12	14
D	F	43	5	12
	M	49	9	15
E	F	43	19	7
	M	50	24	10

[a]Parasitological examinations performed at the beginning of the study.
[b]Parasitological examinations performed 6-7 months after deworming and a 6-7 month course of behavioral remediation instruction.

Table 2
Intensity and frequency of mono- and poly- helminth infection prior to (Phase 1) and 6-months after (Phase 2) deworming and behavioral remediation instruction.

School	Para-meter	Geometric means of egg counts/g feces					
		Mono-helminth infection			Poly-helminth infection		
		A[a]	T	H	A	T	H
PHASE 1							
A	x[b]	2.65	2.02	0.78	3.10	2.34	1.82
	s	0.76	0.41	-	0.57	0.53	0.39
	n	4	39	1	36	41	10
B	x	2.27	1.93	-	3.21	2.19	1.86
	s	0.42	0.43	-	0.71	0.49	0.38
	n	5	26	0	33	37	10
C	x	2.77	1.60	2.17	-	2.50	3.22
	s	-	0.20	0.18	-	1.17	-
	n	1	5	3	0	3	2
D	x	-	1.87	2.00	-	2.22	2.00
	s	-	-	-	-	-	-
	n	0	2	2	0	1	2
E	x	2.16	1.74	2.03	3.28	2.25	2.00
	s	0.58	0.37	0.31	0.66	0.58	0.52
	n	3	7	8	3	8	4
PHASE 2							
A	x	2.64	1.86	1.52	3.49	1.00	0.70
	s	1.12	0.76	-	0.58	0.47	0.17
	n	9	4	2	3	3	3
B	x	2.98	1.10	1.65	2.69	1.25	0.60
	s	0.63	0.48	0.68	0.70	0.67	-
	n	13	12	3	6	7	1
C	x	2.82	-	1.46	2.69	0.90	2.02
	s	-	-	0.77	-	-	1.23
	n[b]	1	0	7	1	2	3
D	x	-	1.16	1.50	1.52	1.45	1.82
	s	-	0.61	0.48	-	-	-
	n	0	3	6	1	2	1
E	x	3.55	1.81	1.04	-	2.12	2.47
	s	-	1.12	0.46	-	-	-
	n	1	3	9	0	1	1

[a]One letter code: A = *Ascaris*, T = *Trichuris*, H = hookworm
[b]Statistical parameters: x = geometic mean, s = standard deviation, n = sample

worming. Those sums can be used to calculate the "rate" of infection preceding the Phase 2 parasitological examination, as follows:

Rate of infection = 11/97 X 100 = 11.3%

Similarly, in the case of schools B and E, the rates of infection during Phase 2 were 19.6% and 7.2%, respectively. The low rates of infection during Phase 2 in schools A and B, where both the prevalence and IoI were so high initially (Phase 1), would appear to reflect the success of the course of BRI during Phase 2.

BRI retards reinfection following drug-induced deworming

Conventional evaluation of BRI involved comparison of the data from the prototypic schools, where students were treated with

Table 3
Re-acquisition of *Ascaris* and *Trichuris* infection among schoolchildren approximately 6 months following deworming and behavioral remediation instruction.

	PHASE 1 Number of students			PHASE 2 Number of students				
School	Total	Not infected	Infected (A/T)[a]	Cured	Partially cured[b]	Not cured	Re-infected[c]	Newly infected[d]
A	107	23	84	65	6	2	11	0
B	118	34	84	51	7	8	13	6
E	93	63	20	17	0	2	3	3

[a]Infected with *Ascaris* (A), *Trichuris* (T) or both.
[b]Children with both *Ascaris* and *Trichuris* (Phase 1) who retained one or the other but not both (Phase 2).
[c]Children whose spectrum of infection in Phase 2 was quite different from that in Phase 1.
[d]Children who were not infected in Phase 1 but became infected in Phase 2.

Table 4
Effectiveness of behavioral remediation instruction with respect to maintaining absence of *Ascaris* and *Trichuris* following deworming.

District	Number of students	Prevalence BD[c] (%)	Prevalence AD[d] (%)	Success ratio[e]
A (P)[a]	107	79	17	0.78
A (cont)[b]	1,539	82(9)	53(15)	0.36(0.2)
B (P)	118	71	28	0.61
B (cont)	683	32(15)	20(8)	0.38(0.15)
E (P)	93	22	5	0.77
E (cont)	923	9(4)	4(2)	0.53(0.11)

[a](P)= prototype school where both deworming and intensive BRI of students occurred
[b](cont) = control schools where deworming of students occurred but no BRI
[c]BD = before deworming (standard diviation in parentheses)
[d]AD = after deworming (standard diviation in parentheses)

[e]$1 - \frac{\text{Prevalence AD}}{\text{Prevalence BD}}$

mebendazole and received intensive BRI, with the data from the control schools where BRI was not provided. It should be noted that approximately one year separated the study in the prototypic schools from the control study. It should be stressed however that both the prototypic and control studies were performed in schools in the same districts and at the same time of the year. Thus, presumably, the influence of seasonal variation, such as rainfall and number of wet days (Gunawardena *et al*, 2004), was minimized. Table 4 displays the results of the combined effect of drug treatment and BRI in comparison to drug therapy alone. The last column in the Table is labeled the success ratio (SR). The figures in that column were obtained using the following equation:

$$SR = 1 - \frac{\text{Prevalence after deworming}}{\text{Prevalence before deworming}},$$

where a ratio of 1 would indicate complete success, *ie,* no infected children 6-7 months after deworming. The first row in the pair for each district [A (P), B (P), E (P)] represents the prototypic

Table 5
Prevalence of anemia among schoolchildren in the five school districts involved in this study of intestinal helminths.

School District	Number students tested	Number anemic students	Prevalence of anemia (%)
A	179	10	5.6
B	79	6	7.6
C	110	6	5.5
D	130	6	4.6
E	101	8	7.9
Total	599	36	6.0 ±1.4[a]

[a]Standard diviation

school where the children were both dewormed and provided BRI. The second row of each pair represent 8 or 9 schools in the district where the children were dewormed but not given BRI. It appears that BRI was effective in prolonging the worm-free condition. This is particularly clear in District A where the SR in the prototypic school exceeds that in the control schools by more than 2 standard deviation. The mean SR of prototypic schools B and C differs from the mean of the corresponding control schools by well over 1 standard deviation. In order to obtain sufficient data for rigorous statistical evaluation, it will be necessary to conduct both deworming and BRI in several protypic schools in the same districts. This may be difficult both for reasons of inadequate financial support and ethical questions.

Nutritional status of the children included in this study

As explained above, all of the children involved in the present study were included in the Student Health Improvement Program (SHIP). They received a package of enriched snack noodles each school day. Previous analysis of height and weight data indicated that the children in the five prototypic schools were, at worst, mildly undernourished. Additional evidence that the children were not significantly undernourished was provided by a survey of the prevalence of anemia among the children. The results, shown in Table 5 reveal a low prevalence of anemia. These results represent children both in the prototypic and the control schools.

DISCUSSION

Altogether the survey of intestinal helminth infections included 518 students in five prototypic schools and more than 4,000 students in more than 40 control schools located in the five districts. Prior to treatment, the prevalences of infection in the schools of the five districts were: District A, 82%; B, 38%; C, 9%; D, 12%; and E, 10%. The prevalence of hookworm infection in the five districts was less than 10%. Because the overall prevalence of the infection was quite low in Districts C and D, and the prominent infection was hookworm, which was only moderately susceptible to benzimidazole compounds, this study focused on the schools in Districts A, B and E.

The frequency of infection with *Ascaris* and *Trichuris* among students in all schools in District A was quite high, ranging from 41% to 93%. In seven of nine control schools, the frequency exceeded 85% of the students. After an interval of about six months following mebendazole treatment alone, the mean frequency was 53%. In the prototypic school, the frequency of infection in children was 17% following mebendazole treatment combined with BRI. This difference was judged to be highly significant upon evaluation in two ways (Tables 3 and 4).

Review of each child's parasitological examination before and after treatment provided the opportunity to judge the occurrence of new or renewed infections during the 6-7 months of BRI after deworming. Eleven children were judged to have been re-infected and there were no new infections (Table 3). Moreover, 65/107 (61%) of the children remained free of infection compared to 23% prior to treatment. The experience of other investigators working in areas of high prevalence has been that a return of infection to near pre-treatment levels occurs about 6 months after deworming (Cabrera and Valeza, 2003; Albonico *et al*, 1995, 2003; Hadju *et al*, 2003; Gunawardena *et al*, 2004). The other way of evaluating the effect of BRI is presented in Table 4, where the results from the prototypic school are compared with the results from the control schools. For District A, the comparison strongly supports the conclusion that BRI was an effective procedure. The success ratio (SR) in the prototypic school exceeded the SR of the control schools by more than 2 standard deviation suggesting confidence that the SRs are different.

When considering the two ways of evaluating the results (Tables 3 and 4), the comparison of prototypic and control schools in Districts B and E also supports the conclusion that BRI is effective. In both cases, the success ratio in the prototypic schools exceeds the mean ratio of the control schools by well over one standard deviation. The data do not allow an exact test of confidence but the argument in support of the benefits of BRI is eminently reasonable. Although the present study deals primarily with *Ascaris* and *Trichuris*, BRI should apply equally well to hookworm following therapy with an effective drug, such as tribendimine, which has been reported to have cure rates of 85-90% (Xiao *et al*, 2005).

The possibility that variations in the nutritional status of different children in different locations may explain, in part, the beneficial effects of BRI is unlikely because: (a) an earlier analysis of height and weight data (Albright *et al*, 2005) showed that the children included in this study were, at worst, only mildly undernourished; and (b) the low frequency of anemia (Table 5) suggests that the children were not seriously undernourished. As explained above, all of the children included in the present study received a package of fortified, fried noodles each school day.

There are sound reasons for suggesting that an effective single course of deworming medication followed by frequently-repeated instructions regarding preventive behavior and habits of good hygiene should be the most satisfactory approach to minimizing helminth infections around the world. First, the approach excludes the possibility that repeated courses (up to 20 or more) of benzimidazole compounds may have side effects, possibly neurological or mutational. A study which deserves more attention (Van Hummelen *et al*, 1995) demonstrated the mutagenic potency of benzimidazole compounds, including mebendazole, in the cytokinesis-block micronucleus assay on human lymphocytes. Second, it is possible that repeated exposure to benzimidazole compounds could induce immunological hypersensitivity (allergies). Third, repeated exposure to drugs may induce immunological or pharmacological resistance to the drug. Fourth, and perhaps most important, it is likely that extensive repeated treatment with benzimidazole compounds will produce drug-resistant strains of helminths. This has occurred, and is well-documented in the veterinary medical use of benzimidazoles (Roos *et al*, 1990; Jackson, 1993). Drug resistance in human helminths has been reported and discussed (Geerts *et al*, 1997; Albonico *et al*, 2004).

There are extremely important reasons why the spread of drug-resistant human helminths must not be allowed. First, there is compelling evidence that helminth infections interfere with normal growth and development in children, including mental acuity. The widespread appearance of drug-resistant parasites could greatly compound that problem. Second, there is a rapidly expanding body of evidence which suggests concurrent intestinal helminth infection (co-infection) exacerbates HIV infection and shortens the interval between infection and the onset of AIDS (Borkow and Bentwich, 2000). Intestinal helminth infection may also complicate tuberculosis and possibly malaria (Ferreira *et al*, 2002; Tristao-Sa *et al*, 2000; Nacher, 2002). Third, helminth infections and co-infections with other parasites complicate the course of pregnancy and subsequent lactation and contribute to low birth weight and stunting of infants (Egwunyenga *et al*, 2001; Steketee, 2003).

The findings presented in this report and other similar reports (Siharath *et al*, 2000; Hohmann *et al*, 2001; Ndenecho *et al*, 2002; Luong, 2003; Gunawardena *et al*, 2004; Albright *et al*, 2005) provide compelling arguments for the introduction of programs of instruction on good habits of behavior and hygiene for the reduction and control of geohelminth infections. Such programs of instruction are effective, inexpensive, have no unwanted side effects, do not facilitate the emergence of drug resistance or more virulent strains of helminths and provide an excellent opportunity for engendering trust and desire among the populace that leads to other advances in hygiene and sanitation. Furthermore, such programs of instruction will result in the transmission of good behavior and hygiene from one generation to the next, mitigating the need for drug therapy in each new generation. Finally, behavioral and hygienic remediation instruction can replace the need for frequently repeated deworming, thus reducing the opportunity for emergence of drug resistant helminths and preserving the effectiveness of anthelmintic drugs for use in eliminating co-infections, treating pregnant women and other emergencies.

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