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A double-blind placebo-controlled study of the concurrent administration of albendazole and praziquantel was conducted in >1500 children with high prevalences of geohelminths and schistosomiasis. The study sites were in China and the Philippines, including 2 strains of *Schistosoma japonicum,* and 2 different regions of Kenya, 1 each with endemic *Schistosoma mansoni* or *Schistosoma haematobium.* Neither medication affected the cure rate of the other. There was no difference between the side effect rate from albendazole or the double placebo. Praziquantel-treated children had more nausea, abdominal pain, and headache but these side effects were statistically more common in children with schistosomiasis, suggesting a strong influence of dying parasites. The subjects were followed for 6 months for changes in infection status, growth parameters, hemoglobin, and schistosomiasis morbidity. In all 4 sites, a significant 6-month increase in serum hemoglobin was observed in children who received praziquantel, strongly supporting population-based mass treatment.

Intestinal helminths chronically affect about a third of the world population. Prevalence is estimated at 1 billion for ascariasis, 900 million for trichuriasis, and 500 million for hookworm. One-sixth of the world's population is at risk for schistosomiasis, with ~200 million currently infected. The highest prevalence and intensity of all helminth infections occurs in school-aged children. Significant progress has been made over the past 2 decades in child survival initiatives, resulting in more children reaching primary school age. Deworming and micronutrient supplementation have been suggested as the next steps in improving the health of school-aged children [1]. As the first step toward this goal, Tropical Disease Research of the World Health Organization (WHO/TDR) sponsored a double-blind placebo-controlled trial using two antiparasitic agents: praziquantel for schistosomiasis and albendazole for geohelminths.

The study was conducted in 4 communities, 2 in Africa and 2 in Asia. Each site had endemic ascariasis, hookworm, *Trichuris* species, and only one species of schistosome. The sites were rural communities, characteristic of much of the developing world, with mild to moderate degrees of malnutrition and anemia. Areas of severe malnutrition and anemia were avoided in order that data from this study could be extrapolated to a broad population base.

The study was designed to compare cure rates for the simultaneous administration of praziquantel and albendazole. The two drugs have similar side effect profiles when taken alone. Current recommendations have been to treat separately with each medication. If the side effect profile for the combination is no more severe than separate administration, then major economic and logistic advantages could be gained by simultaneous administration. The inclusion of placebo groups allowed the determination of the impact of deworming on a variety of morbid parameters, including childhood growth and anemia, as well as determining the sustainability of mass treatment over time.

Subjects and Methods

Four groups of study subjects, all school-aged children, were chosen. In the initial group, 384 children were enrolled from Leyte,

Received 24 August 1998; revised 2 December 1998.

Informed consent was obtained from the children and the parents. Ethical clearance was obtained from WHO, the institutional review board of the sponsoring institution in the site country, national clearance in China, and the sponsoring institutions of the principal investigators.

Financial support: Product Development Unit of WHO/TDR. Praziquantel from Bayer (Biltricide) and an identical placebo tablet (both, Merck, Darmstadt, Germany) and albendazole (Zentel) and an identical placebo tablet (both, SmithKline Beecham, Brentfore, UK) were donated to WHO/TDR.

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The Journal of Infectious Diseases 1999; 179:996–1003

0022-1899/99/7904-0029$02.00

Philippines, which has endemic *Schistosoma japonicum* Philippine strain; 409 from Sichuan Province, People's Republic of China, which has endemic *S. japonicum* Chinese strain; 363 children from Usenge, the Kisumu district of Kenya, which has endemic *Schistosoma mansoni;* and 380 children from Kajiwe, the Kwale district of Kenya, which has endemic *Schistosoma haematobium.* The *S. mansoni* and *S. haematobium* sites were selected in areas where schistosome species did not overlap. Malaria was endemic in the African but not the Asian sites. Children from all 4 sites were also infected with hookworm, *Ascaris* species, and *Trichuris* species as determined by stool examination. The age ranges (in years), reflecting local primary school enrollment, were as follows: Philippines, 6–17; China, 5–16, *S. mansoni* site in Kenya, 6–19; *S. haematobium* site in Kenya, 4–18. Female subjects were questioned as to possible pregnancy risk and excluded if necessary from the study, since albendazole is teratogenic. Follow-up studies confirmed that pregnant subjects had not been treated. A sample size of 90/treatment group at each study site was estimated to have a 90% power at $\alpha = .05\%$ to detect a moderate difference in adolescent catch-up growth in height after treatment.

Eligibility was limited to school-aged children. Exclusion criteria were failure to submit 2 stool specimens prior to the initial treatment, known allergy to either drug, treatment with either drug within 6 months, lack of consent, and marriage or possible pregnancy. Fewer than 10 children from any site were eliminated by these criteria, primarily because of recent treatment.

Prior to treatment, two 50-mg stool slides each were prepared from 2 separate stool samples for Kato-Katz determination. Slides were cleared with glycerol and read for *S. mansoni, S. japonicum, Trichuris* and *Ascaris* species, hookworm, and strongyloides eggs. Two urine samples were also collected in the *S. haematobium* site. Eggs from 2×10 mL samples were filtered on membranes (Nuclepore, Pleasonton, CA). Urine was examined for hematuria and proteinuria using dipsticks [2].

A trained interviewer using a standard questionnaire took a history of symptoms during the last 2 weeks, as well as food consumption prior to medication. Prior symptoms were elicited both to establish a baseline and to determine whether questionnaires could be developed to eliminate children likely to have severe side effects from treatment in a school setting. An abdominal physical examination was performed. Ultrasound examination was made of the liver and spleen in *S. mansoni* and *S. japonicum* sites and of the kidney and bladder in the *S. haematobium* site, by physicians experienced in the diagnosis and ultrasound of schistosomiasis using WHO diagnostic criteria. Children were weighed. Height; skinfold thickness at the subscapular, triceps, and abdominal positions; and midarm circumferences were measured in duplicate [3]. By use of samples from venous blood or a pinprick, hemoglobin was measured by fluorimetry on a portable hemoglobinometer (Hemocue, Laguna Hills, CA), which was calibrated daily against its own standard [4].

Children in each site were randomized into 1 of 4 treatment groups: albendazole plus praziquantel, praziquantel plus an albendazole placebo, albendazole plus a praziquantel placebo, and both placebos. Randomization lists were prepared by WHO/TDR using a randomized block design with a block size of 80. All subjects were treated immediately after being randomized. The study was double-blinded, and the randomization code was not broken until after the 6-month results were tabulated and submitted to WHO. Physically identical placebos were manufactured and packaged on the same equipment, and all bottles were identified only with a letter code. Praziquantel was administered in one dose of 40 mg/kg of body weight in *S. mansoni* and *S. haematobium* areas and a split dose of 2 times 30 mg/kg of body weight with 3 h between doses at *S. japonicum* sites. Albendazole was given in a single dose of 400 mg.

After administration of drugs, children were observed and questioned for side effects for the next 4–6 h and passively followed for 48 h. Children were encouraged to report symptoms to local health care workers who stayed in the villages. At the 48 h follow-up interview, the children were actively questioned about symptoms in their native language. Side effects were judged moderate by the interviewer, rather than mild, if the child asked for medication for symptomatic relief or the side effect interfered with normal activity. Side effects were considered severe if there was medical intervention. One case of vomiting was judged as a severe side effect although it resolved in<1 h. The baseline rate of symptoms at each site was determined from the placebo group.

At 45 days and again at 3 months, 2 additional stool samples, and urine in the *S. haematobium* site, were collected and assayed for eggs; anthropometric measurements were repeated. At 6 and 12 months, the ultrasound, physical examination, history of recent symptoms, anthropometric measurements, and hemoglobin determinations, as well as the duplicate stool and urine measurements of egg counts, were repeated for all subjects. Infected children were treated with one or both drugs as needed on the basis of egg detection at the 6-month follow-up. All subjects were followed 48 h, 99% were followed 45 and 90 days, 90% were followed for 6 months, and 83% were in the 1 year study.

Side effects of medication were compared with parasite egg counts, symptoms over the previous 2 weeks, physical examination, and treatment group. Albendazole and praziquantel were given separately and in combination to determine whether combining the medications changed the side effect profile or efficacy of either drug. Subjects were followed for 48 h for nausea, vomiting, fatigue/malaise, abdominal pain, itching/urticaria, rash/dermatitis, wheezing, headaches, seizures, diarrhea, bloody diarrhea, vomiting a worm, drowsiness, or dizziness. Medication for side effects, locally available over-the-counter analgesic (acetaminophen) or antispasmodic (paregoric) was available on request. Children were also asked for an overall rating of side effects and whether side effects limited activity. Requests for medication for symptoms and hospitalization were recorded.

Frequency of side effects in each treatment group at each site was examined using Pearson's χ^2 with a Bonferroni correction for multiple comparisons of the 10 most common side effects for an overall significance level of $P \leqslant .05$. Symptoms were considered significant when the individual P value was <.005 for the 4 treatment groups. Subgroup differences were then compared. Individual symptoms after treatment were modeled in logistic regressions adjusting for site, treatment group, recent symptoms, physical findings, eating before treatment, infection status/egg number, sex, and age. Prevalence, and egg output in those still infected, was compared for both drugs singly and in combination. Both infection status and egg output were followed for 6 months to determine the incidence of reinfection and egg burden. Growth parameters (liver

and spleen size as determined by ultrasound and hemoglobin levels) in the 4 treatment groups initially and 6 months after treatment were compared in analysis of variance (ANOVA) for short-term benefits of treatment.

Results

The total subjects (1518) were randomized into 4 treatment groups. The 4 initial treatment groups were not statistically different in terms of age, weight, height, hemoglobin level, sex ratio, history of recent symptoms, or infection status (table 1). Ninety percent of the original subjects were followed at 6 months and 83% at 1 year. Subjects who were lost to follow-up were not statistically different in terms of treatment, infection status, or side effects.

Major symptoms reported for each treatment group at the separate sites are shown in figure 1. Other symptoms after treatment were rare or not seen at all, and the rates did not differ by treatment group. Both prior symptoms and side effects after treatment were reported at very different frequencies in the 4 sites. The most frequently observed side effects after treatment were headache (8% in China, 72% in *S. mansoni* site in Kenya) and abdominal pain (35%–75%) which were also the most frequent preexisting conditions.

The 2 *S. japonicum* sites were very similar in both the infection prevalence and the report of side effects with treatment. Both areas have local schistosomiasis control programs that lower worm burden. The rate of symptoms was low in the placebo and albendazole groups. Abdominal pain, headache, and the total frequency of side effects were significantly higher in children after treatment with praziquantel alone or in combination. Children who were given praziquantel were more likely to report that the treatment interfered with activity and to request over-the-counter medication for symptomatic relief. Headache after praziquantel was much more common at these 2 sites than in the African sites.

In the Kenyan site with endemic *S. mansoni,* children given praziquantel had significantly higher frequencies of abdominal pain, diarrhea, and bloody diarrhea and higher rates of interference with activity. Diarrhea, bloody diarrhea, and malaise were rarely reported in the other 3 sites. The number of schistosome eggs per gram of stool was a significant predictor for abdominal pain in this group ($P < .05$) in logistic regression, indicating that abdominal pain as a symptom after treatment was more common in heavily infected children. Of the children in the double-placebo group, 88% reported symptoms. Abdominal pain (75%), diarrhea (41%), and rectal bleeding (37%) were also commonly reported in the history by these children, who are not routinely treated for helminths. At the *S. haematobium*–endemic site in Kenya, no individual side effect was statistically significantly different for the treatment groups, although nausea, vomiting, and headache were more common in children given praziquantel.

In the African sites, most of the reported side effects (*S. mansoni,* 88%; *S. haematobium,* 65%) were present in the 4- to 6-h survey. In both *S. japonicum* sites, most of the symptoms were reported during the 3-h interval between the two doses of praziquantel. In the Philippines, the estimated duration of symptoms was also recorded. Symptoms usually resolved within 2 h, whether or not the child took medication for relief. Symptoms that appeared many hours after treatment were much more common in the placebo group in all of the sites.

Except for recent diarrhea, which had an impact only on reports of diarrhea after treatment, or a history of headache

Table 1. Randomization to treatment group in *Schistosoma* study.

	Praziquantel + albendazole (n = 392)	Praziquantel (n = 380)	Albendazole (n = 387)	Placebo (n = 381)
% male	52.8	51.9	50.5	47.5
Age, years (SD)	10.6 (2.9)	10.5 (2.8)	10.4 (2.8)	10.5 (2.9)
BMI, kg/m^2 (SD)	16.1 (2.9)	15.8 (1.9)	16.0 (1.9)	16.0 (2.0)
Hemoglobin, mg/dL (SD)	11.9 (1.8)	11.8 (1.7)	11.9 (1.8)	11.8 (1.8)
Recent history of				
Headache, %	25.5	24.7	25.1	24.7
Abdominal pain, %	60.3	59.6	59.4	60.1
Prevalence of helminths, %				
Hookworm	51.7	48.2	44.4	52.1
Ascaris species	60.5	57.2	56.6	60.2
Trichuris species	81.8	79.4	76.8	81.0
Prevalence of schistosome by site, % (n)				
S. japonicum				
Philippines	50.0 (93)	53.8 (97)	59.3 (99)	44.8 (95)
China	52.0 (103)	53.5 (106)	45.0 (100)	46.0 (100)
S. mansoni	83.7 (98)	84.0 (82)	71.6 (95)	78.9 (92)
S. haematobium	89.7 (98)	83.2 (95)	80.4 (93)	87.1 (94)

NOTE. Randomization was based on block design with block size of 80. No parameters shown were statistically significantly different for treatment groups. Age, body mass index (BMI), and hemoglobin are means (SD). History of headache or abdominal pain within preceding 2 weeks was considered in analysis of side effects of medication. Values for prevalence of hookworm, *Ascaris* species, and *Trichuris* species are combined for all 4 sites. Prevalence of schistosomiasis is shown for each treatment group at each site (no. of subjects) in group.

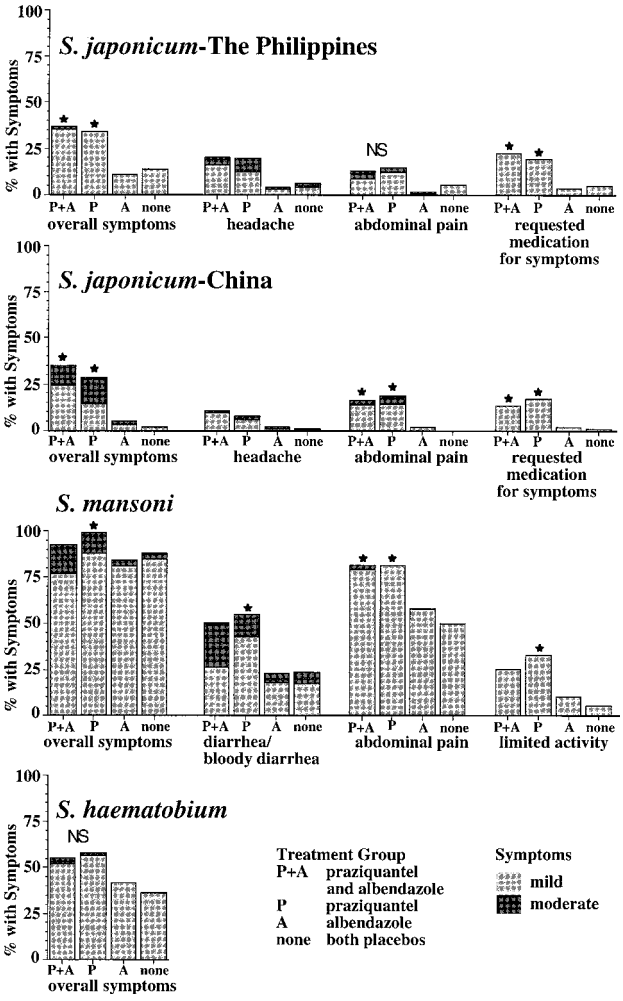

Figure 1. Symptoms after treatment by site. Comparison of praziquantel vs. no praziquantel was significant ($P < .005$, χ^2) for all symptoms shown except for overall judgement of side effects in *S. haematobium* and abdominal pain symptom in Philippines, which are shown for comparison. Individual groups averaged 96.25 subjects (range, 82–106). Praziquantel and praziquantel plus albendazole groups were not statistically different from each other in any comparison, nor were placebo and albendazole alone groups statistically different from each other. * Groups individually significantly different from placebo for that symptom ($P < .005$, χ^2).

or abdominal pain, none of the parameters in the recent history questionnaire, the physical examination, or a recent meal were related to the incidence of symptoms after treatment in a logistic regression, using data from all 4 sites. The two most important factors for predicting new symptoms were study site and treatment group. In comparing the 4 treatment groups across the 4 sites, the only treatment factor that was statistically significant was whether or not the subject received praziquantel (table 2). Vomiting, abdominal pain, headache, interference with normal activity, diarrhea, bloody diarrhea, requests for additional medication for symptoms, and total side effects were all higher in children with documented schistosomiasis (table 3). Almost all diarrhea and bloody diarrhea reports were in the *S. mansoni* site. After adjustment for age, sex, history, and schistosomiasis, the odds ratio of being in the praziquantel group in Usenge (*S. mansoni,* Kenya) was 3.8 (95% confidence interval, 2.4–6.1) for children who reported diarrhea or bloody diarrhea.

Neither drug affected the cure rate of the other. Forty-five-day prevalences are shown in table 4. After 45 days, prevalence rose slowly for hookworm and schistosomiasis but rapidly for ascariasis due to reinfection. Prevalence of schistosomiasis was significantly reduced for all 3 species ($P < .00001$, χ^2) at 45, 90, and 180 days after treatment with praziquantel. At 6 months, the original placebo-treated infected children and any reinfected children were all treated with active medication on the basis of the results of stool samples. At the end of a year, there was no significant difference in the prevalence of schistosomiasis among children treated once a year previously and those treated once 6 months previously, indicating a rather low rate of reinfection. There was a significant decrease in the number of eggs excreted by children who were treated but not cured in all 3 species of schistosome at 45, 90, and 180 days (Mann-Whitney *U,* all $P \leq .0001$ except in *S. japonicum* at 180 days, for which there were very few egg-positive cases left). The 2 Asian sites were very similar in initial prevalence of ~50% stools positive for schistosomiasis, pretreatment egg excretion, cure rate, and the incidence and type of side effects with treatment.

Initially 93% of the children had at least 1 species of geohelminth and ~25% had 3. The initial prevalence of hookworm ranged from 21% in China to 89% in Kajiwe (*S. haematobium,* Kenya). In children treated with albendazole, reductions in prevalence ($P < 0001$, χ^2) and in hookworm egg excretion in children in whom the infection was not eliminated ($P < .01$, ANOVA) were significant at 45, 90, and 180 days. The elimination of hookworm lasted for the 6-month period, when most children were again treated with albendazole for *Ascaris* species.

Ascaris prevalence ranged from ~34% in Kajiwe to 84% in China. The elimination of infection and the decrease in egg

Table 2. Logistic model for one or more side effects in *Schistosoma* study.

Variable	Odds ratio	95% confidence interval	*P*
Site (Leyte = base)			.000
China	0.70	0.48–1.02	.063
Kajiwe	2.93	2.08–4.13	.000
Usenge	29.19	18.40–46.32	.000
Age	1.06	1.02–1.11	.008
Sex (male is 1)	1.05	0.92–1.20	.444
History of abdominal pain (1)	1.55	1.17–2.04	.002
History of headache (1)	1.24	0.92–1.67	.165
Praziquantel (1)	3.52	2.68–4.62	.000
Schistosoma eggs detected (1)	1.31	0.97–1.76	.077

NOTE. No. of cases included in analysis was 1518. Presence of ⩾1 side effects was adjusted for treatment site, age, sex, presence of schistosome ova on ⩾1 Kato-Katz slide, and whether child was in praziquantel group. Albendazole, interaction between drugs, and interaction between praziquantel and schistosomiasis were not significant in any model.

Table 3. Adjusted odds ratio for praziquantel and symptoms in *Schistosoma* study.

Symptom (dependent variable in logistic regression)	Odds ratio	95% confidence interval
Nausea	2.11	1.49–2.98
Vomiting	3.84	2.16–6.83
Abdominal pain	3.25	2.39–4.42
Headache	2.33	1.73–3.12
Interfered with activity	4.96	2.86–8.62
Requested medication for symptoms	4.53	2.75–7.44
⩾1 side effects	3.52	2.68–4.62
Usenge only		
Diarrhea and/or bloody diarrhea	3.81	2.39–6.06

NOTE. All *P* values for praziquantel were .000. Same adjustment factors used for adjusting for presence of ⩾1 side effects (table 2) were used in logistic regressions of individually significant side effects. Only odds ratio of being in praziquantel group is shown. Diarrhea data includes only children from *S. mansoni* treatment group in Kenya, since diarrhea was prevalent only in that site.

excretion where the parasite was not eliminated with albendazole were both statistically significant ($P < .0001$, χ^2 and Mann-Whitney *U)* at 45 days. Both the prevalence and the egg burden rose rapidly and were essentially at pretreatment levels within 6 months.

The original prevalence of *Trichuris* species ranged from 59% in Usenge to 95% in the Philippines. The effect of albendazole treatment on prevalence was significant initially only in Kajiwe ($P = .012$, χ^2). The difference between the control and treatment groups was gone by 6 months in Kajiwe. There was essentially no benefit of treatment with 400 mg of albendazole in reducing *Trichuris* infection in the other 3 sites.

A variety of morbid parameters were measured in this study. The most important clinical improvement 6 months after treatment was an increase in hemoglobin in children treated with praziquantel. The initial hemoglobin level was 11.65 ± 1.77 (SD) g/dL in schistosomiasis-positive subjects and 12.23 ± 1.75 g/dL in egg-negative children ($P < .0001$, *t* test). At 6 months, hemoglobin level in the praziquantel-treated children had risen to 12.11 ± 1.70 g/dL, while those in the placebo group had hemoglobin levels averaging 11.83 ± 1.89 g/dL. This improvement following praziquantel treatment was highly significant (paired *t* test, $P < .001$).

The average increase in hemoglobin was 0.271 ± 1.802 (SD) g/dL in the praziquantel-treated children and 0.017 ± 1.938 g/dL in the placebo-treated group. Improvement was seen in both sexes and in both young children and adolescents; adolescent males showed the largest gain. Of perhaps greatest importance, improvement was seen both in children who tested positive and in those found to be stool-negative for schistosomiasis on two separate examinations. Iron supplementation was not given in the study, and the recovery of hemoglobin after praziquantel treatment was slow. At 1 year, for example, children who were initially schistosomiasis-positive had not quite caught up to the hemoglobin level of those who initially tested negative. Although the hemoglobin level was lower in children initially infected with hookworm (11.7 ± 3.3 g/dL in infected and 12.01 ± 1.7 g/dL in uninfected, $P = .001$ *t* test), no statistically significant improvement was seen after albendazole treatment.

In the study population as a whole, no significant differences between treatment groups were seen in any of the growth and anthropometric measurements. A positive effect was documented in China, however, where children were significantly thinner than any other study group on the initial sum of skinfolds ($P < .0001$, ANOVA). There was a very small but statistically significant ($P = .035$) increase in the sum of skinfold thickness in these children following treatment with albendazole at 3 and 6 months.

At 6 months, there were no significant differences overall in physical examination and ultrasound findings in 3 of 4 sites. A significant reduction in midsternal liver size in praziquantel-treated children in the *S. mansoni* site in Kenya was documented. In that site (Usenge), liver enlargement below the midsternum was observed in 21.52% of the children before treatment. This was reduced to 6.71% of subjects by the end of the study. By use of each child as his/her own control (paired *t* test), the overall reduction in liver size was highly significant, from a mean of 0.787 ± 1.677 cm to a mean of 0.295 ± 1.217 cm at the end of the year.

Discussion

Reductions in prevalence and intensity of helminth infections after treatment. Geohelminths and schistosomiasis exact a heavy toll in growing children in much of the world. This study was designed to look at the efficacy and side effects of mass deworming in the primary school setting. One treatment arm received albendazole and praziquantel simultaneously to determine whether the combination led to more side effects than separate treatment or changed the cure rate of either drug. Even though praziquantel affects the pharmacodynamics of albendazole [5], neither drug interfered with the cure rate of the other in this study. Cure rates in infected subjects are generally defined by individuals no longer having helminth eggs in their stool several weeks after treatment. The cure rate with praziquantel depended on the species of schistosome. An 89% cure rate has been reported for *S. japonicum* using a split dose of 60 mg/kg [6]. In *S. mansoni,* published cure rates usually are estimated to be ~85% (range, 63%–96%) [7–11]. Reported cure rates for *S. haematobium* range from 36% to 90% [12–16]. In most previous studies, the reduction in egg output in individuals treated but not cured is ~90%. In *S. mansoni* [7], and especially in *S. haematobium* [17], it has been observed that the effective cure rates are high in light infection and lower in heavy infections.

In this study, the observed cure rates with praziquantel, when adjusted for the placebo, were lower than expected for the 2 African species. The multiple stool determinations in this study detected more light infections after treatment, lowering the ob-

Table 4. Prevalence of parasite eggs 45 days after treatment in *Schistosoma* study.

Helminth	% infected (egg count)			
	Praziquantel + Albendazole	Praziquantel	Albendazole	Placebo
S. japonicum	6.7 (10.5)	6.0 (9.5)	38.8 (27.7)	39.3 (34.9)
S. haematobium	38.5 (2.7)	35.1 (1.4)	72.2 (35.1)	79.8 (29.8)
S. mansoni	43.6 (28.9)	43.8 (37.0)	79.6 (157.7)	78.3 (149.0)
Hookworm	13.1 (27.0)	40.1 (121.9)	10.0 (35.9)	40.3 (97.4)
Ascaris species	20.9 (625.8)	60.2 (6097.5)	18.4 (353.3)	59.9 (5903.3)
Trichuris species	72.3 (161.1)	78.0 (233.2)	66.8 (145.9)	75.9 (233.4)

NOTE. 2 stool samples were collected for each subject; 2 slides were examined for each stool sample. *S. haematobium* nos. are based on 10-mL urine samples. Prevalences in placebo-treated subjects were not statistically different from original prevalences. Reduction in prevalence of schistosomiasis after treatment with praziquantel was statistically significant for all 3 schistosomes ($P < .0001$, χ^2). Reduction in prevalence of hookworm and *Ascaris* species after albendazole treatment was statistically significant ($P < .0001$, χ^2). Egg counts are geometric means in subjects who remained infected. Reduction in egg no. after treatment in infected children was significant in all infections at 45 days ($P < .0001$, Mann-Whitney *U*).

served treatment rate [18]. This problem of case detection is exaggerated in *S. japonicum,* in which eggs are excreted in clusters. The sensitivity of the Kato-Katz test in *S. japonicum* between the duplicate samples was especially poor at low levels of infection. Mass treatment would circumvent the problem of case detection, especially in areas with *S. japonicum* or in areas with a history of previous population-based treatment where most infections are light.

A single dose of 400 mg of albendazole was used in this study. In previous studies of albendazole, the reported cure rate for *Ascaris* species was 100% [19–21] and for hookworm was 64%–84% [20–23], with a significant reduction in egg output in subjects who were not cured. Although there is some evidence for efficacy against trichuriasis at this dose [23], in general the cure rate has been poor unless larger doses or repeated treatments are given [19–24]. In our study, there was sustained reduction of hookworm, *Ascaris* species were effectively eliminated, but reinfection was rapid, while *Trichuris* was largely unaffected by treatment. Hookworm, like *S. japonicum,* was poorly detected due to low numbers of eggs. The current study suggests that an annual mass treatment program with both praziquantel and albendazole would substantially reduce the community's burden of hookworm and schistosomiasis but have less sustained effect on *Ascaris* species and little or no impact on *Trichuris* species. *Ascaris* species have been successfully reduced in other control programs with more frequent treatments [25].

Side effects after treatment. Praziquantel appears in the blood within 15 min. Peak serum levels are observed at 1.5–6 h, with complete elimination by 24 h [26]. The side effects from praziquantel in this study were mild to moderate and transient and usually occurred within 3 h of the initial dose, which is consistent with reports from previous studies [6, 27–30]. The rate and intensity of side effects have been correlated loosely with the intensity of infection [31, 32] and the dose of praziquantel [8]. This is also consistent with our finding that headache and abdominal pain after treatment were more common in children with documented schistosomiasis than in stool-negative subjects. Side effects may be due in part to the intravascular killing of worms by the immune system after treatment.

Though high rates of side effects with praziquantel have sometimes been observed [8, 32], in a previous double-blind study, many of the side effects were felt to be preexisting conditions, especially intestinal schistosomiasis [17]. We noted a very high rate of complaints in the *S. mansoni* site in Kenya, but both the history and the use of a placebo group indicated that many of the side effects reported following treatment were reflective of preexisting complaints. Relatively serious side effects have also been rare in other praziquantel mass treatment programs [28]. Albendazole treatment alone or in combination with praziquantel produced no appreciable side effects in this study. Since the side effects of both medications together were no worse than those observed with praziquantel alone, we conclude that coadministration is both safe and potentially more cost-effective.

The history of recent symptoms was not found to be useful for eliminating children at risk to have severe side effects from treatment in a school setting. For example, 44% of the children who developed headaches after treatment had no recent history of headache. This is not surprising, since the symptoms found after praziquantel treatment were similar to the symptoms of schistosomiasis. In addition, highly symptomatic children included most with heavy infections.

Six-month benefits of treatment. The most important short-term benefit of treatment observed in this study was an increase in hemoglobin levels in children treated with praziquantel. Hemoglobin levels have been reported to be lower in individuals infected with schistosomiasis, hookworm, and *Trichuris* species, so both praziquantel and albendazole treatment could have affected this health parameter [33]. Hemoglobin levels were also increased significantly over 6 months in a recent randomized study of praziquantel versus placebo in *S. japonicum*–endemic areas of Leyte, Philippines [34]. The small but highly significant improvement in hemoglobin in the children treated with pra-

ziquantel in this study, including those who were negative for schistosomiasis on 2 stool examinations, is a strong argument for mass treatment and for the relative importance of schistosomiasis as a cause of childhood anemia in settings with mixed helminth infections.

The change in hemoglobin values for the whole group took place even though most of the children were only lightly infected. Mass treatment has an advantage over control programs based on case finding, in that lightly infected children are often missed by a single stool or urine examination, yet this study demonstrates that these children clearly benefit from treatment. In areas of poor nutrition, iron supplementation has been reported to produce a much more rapid rise in hemoglobin levels following deworming [35]. Considering the logistic difficulties associated with community-based iron supplementation, the significant improvement in hemoglobin level following a single treatment strongly supports mass treatment with praziquantel.

Rapid benefit in growth and activity after treatment with albendazole has been largely seen in communities where baseline growth is poor and in heavily infected children [19, 36–38]. These populations are in general not characteristic of the overall population of school-aged children. In this study, children were not markedly undernourished, and infection intensities were similar to those observed throughout most areas with endemic schistosomes. Catch-up growth was not observed during the follow-up period. Scholastic benefits may make an in-school treatment program attractive. Treatment of *S. haematobium* has resulted in an improvement in mental tests in schoolchildren [39], while treatment of *S. japonicum* in China showed a similar result [40].

We also found improvement in liver enlargement only in the more heavily infected *S. mansoni* endemic site. In schistosomiasis, short-term community improvement in organomegaly is generally seen only in communities with very heavily infected individuals. Significant improvement by ultrasound of liver or bladder generally has taken 2–3 years [5, 13, 41, 42]. Most of the children in this study were not heavily infected and would not be expected to show dramatic differences in ultrasound findings within 6 months.

Conclusion. Combined mass treatment of schoolchildren with praziquantel and albendazole produced no more side effects than treatment with praziquantel alone. Many of these side effects were observed in children with schistosomiasis, who presumably benefitted from the praziquantel. Yearly mass treatment should have an important and sustained impact on schistosomiasis and hookworm prevalence and intensity. The side effect profile would support administration by primary school teachers provided with appropriate instructions. Mass treatment with praziquantel in schistosomiasis-endemic areas was associated with improved hemoglobin levels without iron supplementation in schoolchildren, whether or not schistosome eggs were detected in the stool. The risk/benefit ratio therefore strongly supports the use of mass treatment of school-aged children with praziquantel in areas of mixed helminth infections including schistosomiasis. This characterizes many rural areas of the world. Since albendazole was not associated overall with any measurable side effects above the level seen with praziquantel, the major issue for its inclusion in mass deworming is whether the financial expenditure for this drug is worth the potential benefit to the most heavily infected and malnourished children within a population and on the prevalence and intensity of hookworm within the population.

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