Comparison between Albendazole and Pyrantel Pamoate Once and Twice Yearly in Urban Slum School Children in Ujung Pandang

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Abstrak

Penelitian ini membandingkan efikasi dari pemberian obat cacing pyrantel dan albendazole satu atau dua kali per tahun pada anak sekolah dasar di daerah kumuh Kotamadya Ujung Pandang. Anak sekolah (n=507) dibagi secara random ke dalam 4 group yang menerima obat cacing (pyrantel satu atau dua kali, albendazole satu atau dua kali) dan satu group lainnya yang menerima plasebo, berdasarkan jenis kelamin dan intensitas Ascaris lumbricoides. Anak menerima dosis tunggal pyrantel atau albendazole atau plasebo pada awal penelitian dan 6 bulan sesudahnya sesuai dengan groupnya. Prevalensi dan intensitas infeksi Ascaris lumbricoides dan Trichuris trichiura diukur pada 0, 3, 6, dan 12 bulan setelah pemberian obat cacing pertama. Tidak ditemukan perbedaan yang bermakna diantara kelima group di awal penelitian. Setelah 12 bulan, intensitas dari kedua infeksi menurun secara drastis pada group yang diberi obat cacing (P < 0,001) dan sedikit menurun pada group yang mendapat plasebo (P < 0,05). Pemberian dua kali dalam setahun dari kedua obat yang digunakan dapat menurunkan prevalensi dan intensitas A. lumbricoides lebih besar dibanding group lainnya. Di samping itu, dua group yang memperoleh albendazole memperlihatkan penurunan prevalensi dan intensitas dari T. trichiura lebih besar dari group lainnya. Penelitian ini menunjukkan bahwa dua kali pemberian obat cacing per tahun dari kedua jenis yang digunakan lebih efektif dari pada pemberian satu kali dan pemberian albendazole baik satu maupun dua kali per tahun menurunkan intensitas dari T. trichiura.

Abstract

This study examined the comparison between pyrantel and albendazole, in terms of their effectiveness by once and twice yearly in school-age children. School children (n=507) were assigned randomly to four anthelminthic groups (pyrantel once or twice; albendazole once or twice) and a placebo group, according to gender and Ascaris lumbricoides eggs counts. Children received single doses of either pyrantel, albendazole, or placebo at baseline and again at 6 mo. The prevalence and intensity of Ascaris lumbricoides and Trichuris trichiura infections were determined at baseline, 3, 6, and 12 mo. No differences were found between the five groups at baseline in prevalence and intensity of both infections. At 12 mo, the intensity of both infections was greatly reduced in the dewormed groups (P < 0.001) and reduced slightly in the control group (P < 0.05). Both pyrantel and albendazole twice reduced the prevalence and intensity of A. lumbricoides greater than other groups. However, albendazole-treated children reduced the prevalence and intensity of T. trichiura greater than other groups. This study suggests that two doses yearly of both drugs are more effective than once dose yearly and albendazole treatment once or twice could decrease the intensity of T. trichiura infection.

Key words : *albendazole, pyrantel, helminthiasis, children*

INTRODUCTION

A high incidence of transmission of *Ascaris lumbricoides* and *Trichuris trichiura* infection together has been found in mostly urban areas in developing countries.[1] This is very much related to the very poor sanitation and high population density observed in many slum areas. Controlling for the helminth infections with mass chemotherapy, thus one of the priority in this such areas.

It is recommended that deworming should be carried out at a 4-6 mo interval in areas where *A. lumbricoides* and *T. trichiura* are most prevalent.[2] However, some studies have shown that *A. lumbricoides* infection returns to the initial levels of infection 6 mo to 1 year after community treatment[3,4] while *T. trichiura* infection, as observed in population dynamics studies, reaches preintervention levels less than 6 mo.[5] This is due to a higher potential transmission of *T. trichiura*, as measured by its basic reproductive rate.

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A randomized intervention trial was designed to examine the effectiveness of different intervals of pyrantel and albendazole in school-age children living in an urban slum. We hypothesized that groups receiving one or two doses of anthelmintic drug per year would have a significantly lower prevalence and intensity of *A. lumbricoides* and *T. trichiura* infections and that two doses per year would be more effective than one dose.

MATERIALS AND METHODS

Study population

This study was carried out in a slum area of Ujung Pandang municipality, South Sulawesi, Indonesia. Overcrowding and lack of sanitation are evident in this area. Two primary schools, close one to another, were chosen for the study. There were several reasons for choosing these schools: 1) Parasitologically, a high prevalence and intensity of *A. lumbricoides* and *T. trichiura* infections were found in both schools during a preliminary study; 2) no deworming program has been done in the community in the last two years; 3) a high prevalence of malnourished children was found during the preliminary study; 4) there was a willingness of school principals and teachers to participate in the study; and 5) the number of children available for the study was sufficient. Details of the study site and the population are described elsewhere.[6]

Permission from the local government was obtained prior to the study. A meeting with parents, teachers, the head of local health department, and investigators was held to clarify the objectives and benefits of the study. Informal parental consent for the children's participation was obtained. The study protocol was approved by the Human Subjects Committee of Cornell University and the Indonesian Government. Children were free to withdraw at any time.

Experimental design

The study design was a randomized, placebo-controlled intervention trial. All primary school children (6-11 years old) in Grades 1, 2, and 3 in both schools were screened to be eligible for the study. Children with signs of severe protein energy malnutrition (marasmus and kwashiorkor) or had any deformity or congenital abnormality were excluded. All eligible children were randomly allocated to five treatment groups. Randomization was performed based on sex and egg count of *A. lumbricoides*. *A. lumbricoides* was chosen since the anthelmintic drugs used in the study are highly effective in treating *A. lumbricoides* infection. These five groups consisted of placebo, pyrantel once (pyr.1x), pyrantel twice (pyr.2x), albendazole once (alb.1x), and albendazole twice (al 2x). Children in the alb.1x and pyr.1x groups were treated (albendazole 400 mg and pyrantel pamoate 10 mg/kg body weight, respectively;[7] after the baseline exam, whereas those in the alb.2x and pyr.2x groups were treated after the baseline and also after the 6-mo exam. For ethical reasons, at the end of 12 mo, all groups received pyrantel pamoate.

Children were followed for 12 mo. Fecal examination were performed at 0, 3, 6, and 12 mo following the same standardized protocol. During the study period, children had free access to a Primary Health Centre located just in front of the schools and run by one physician and several nurses.

Single doses of albendazole and pyrantel pamoate (400 mg and 10 mg/kg body weight, respectively) were used, as recommended for areas where *A. lumbricoides* infections are predominant.[7] In addition, a single dose of albendazole has been reported as useful for *T. trichiura*.[8,9,10] It was thought that both drugs could be compared in the study since pyrantel pamoate has a lower efficacy against *T. trichiura*.

The placebo tablet was similar to the albendazole tablet (provided by SmithKline Beecham, Indonesia), but pyrantel pamoate was different (Kimia Farma, Indonesia). Children and field workers were not informed of the actual name of both drugs. Each treatment, albendazole, pyrantel, and the placebo, was put in three different boxes labeled A, B, and C for albendazole, pyrantel, and placebo, respectively. No one, except the principle investigator, was made aware of the labels. Field workers administered the assigned drug (A, B, or C) to each child during school hours an investigator's supervision: When a child had difficulty swallowing the tablets, the drug was crushed and then given to the child via a spoon. Children were asked to open their mouths to check if the drug had actually been swallowed. Absent children were visited at their homes by field workers. For this activity, field workers were given the drug in an envelope for each child.

Fecal examination

Stool samples were taken from the children in the morning. A 25 ml plastic bottle, a bamboo spatula, and instruction were given to the children the day before. Collected samples were brought for examination to the Parasitology Lab at the Medical School of Hasanuddin University, Ujung Pandang. Two trained analysts performed all stool sample analyses throughout the study

under the supervision of one of the investigators (KA). Stool samples were examined for the presence of parasite eggs using a modified Kato-Katz technique recommended by WHO.[11] A cardboard template with a hole of known capacity (28 mg) and a cellophane coverslip soaked in glycerin-malachite green solution were used. Eggs of *A. lumbricoides* and *T. trichiura* were counted about one hour after smear preparation and expressed as eggs per gram (epg) of feces, as estimated of worm burden, or as intensity of infection.

Statistical Analysis

Data analyses were performed using the statistical package SYSTAT version 5.2[12] for Macintosh. The intensities of *A. lumbricoides* and *T. trichiura* infections, indicated as eggs per gram (epg) of feces, have a negative binomial distribution and were transformed by conversion to natural logarithms (log x +1) wherever possible. To assess the differences between treatment groups, one-way analyses of variances and chi-square test were performed. In addition, Scheffe's test was used for multiple mean comparisons. The changes in prevalence and intensity of both helminth infections between two exams were assessed by McNemar's test and Student's paired t test, respectively. The percentage of egg reduction rates of *A. lumbricoides* and *T. trichiura* infections between two exams was calculated from geometric mean egg counts with the formula: % egg reduction = [(initial epg - final epg) : initial epg] x 100.

RESULTS

Initially, a total of 507 children were measured at baseline. However, during the 12 mo follow-up, only 330 children (65%) completed all exams. Of the 177 children who did not complete all examinations, 28 children were not fully examined beyond the baseline exam, whereas 24 children were not measured beyond the 3-mo exam. In addition, 55 children were followed up only to 6 mo. It should be noted that, during the study period, 24 children quit school, 10 moved to other schools, and 22 refused to participate. Absenteeism, either sickness or for unrecognized reasons, and 22 refused to participate. Absenteeism, either sickness or for unrecognized reasons, and compliance of stool sample submission were the foremost reasons for the other incompletely measured children. No important differences were noted at baseline between these children and those who complete the study.

Comparison of baseline characteristics

The baseline characteristics of parasitic infection are presented in Table 1. As expected, no significant differences were found in prevalence and intensity for both *A. lumbricoides* and *T. trichiura* infections. Children in the alb.1x and alb.2x groups had higher mean egg counts and also a higher proportion of heavy *A. lumbricoides* infections compared to the other groups, but these differences were not significant.

Table 1. Baseline comparison of parasitic infections of children in five treatment groups

Parasitic infection	Treatment group				
	Placebo (n=74)	Pyr.1x (n=60)	Pyr.2x (n=61)	Alb.1x (n=66)	Alb.2x (n=69)
Ascaris lumbricoides					
Prevalence (%)	93	93	89	94	97
Intensity (epg)[a,b]	4518	3431	2863	5058	6026
Light (%)[c]	36	43	43	36	39
Moderate (%)	51	48	46	46	44
Heavy (%)	12	8	11	18	17
Trichuris trichiura					
Prevalence (%)	97	100	100	99	99
Intensity (epg)	2427	3522	2754	2924	2232
Light (%)	27	18	30	23	29
Moderate (%)	54	62	53	56	54
Heavy (%)	19	20	18	21	17

[a]Epg=egg per gram feces.
[b]Geometric mean was used for intensity.
[c]Category of intensity: light (0-5000 epg), moderate (5000-50 000 epg), and heavy (> 50 000 epg) for *Ascaris* and light (0-1000 epg), moderate (1000-10 000 epg), and heavy (> 10 000 epg) for *Trichuris*.

Changes in prevalence

The change in prevalence of *A. lumbricoides* and *T. trichiura* infections at 3, 6, and 12 mo after the initial anthelmintic drug administration in all five groups is shown in Table 2. Overall, the prevalence of *A. lumbricoides* infection in the four dewormed groups combined (pyr.1x, pyr.2x, alb.1x, and alb.2x) was 48% and 77% at 3 and 6 mo after the first deworming. These prevalences were significantly lower than those in the placebo group, 87% and 89% at 3 and 6 mo, respectively.

After 3 mo of deworming, the prevalence of *A. lumbricoides* in the albendazole groups (alb.1x and alb.2x) and in the pyrantel groups (pyr.1x and pyr.2x) was significantly lower than in the placebo group (partitioned chi-square, both at $P < 0.0004$). At the 6-mo exam, there was no significant difference between the albendazole and the placebo group, but there was a significant difference between the pyrantel and the placebo groups (partitioned X^2, $P < 0.003$). At the end of the study, as seen in Table 2, the alb.2x group did not differ from the alb.1x group but the pyr.2x group was significantly lower than the pyr.1x group (partitioned X^2, $P < 0.05$). However, both albendazole and pyrantel groups were significantly lower than the placebo group (partitioned X^2, $P < 0.005$ and $P < 0.01$, respectively).

The prevalence of *T. trichiura* infection in the albendazole group after 3 mo of deworming was not different from that in the pyrantel and placebo groups. Similar results were also observed after 6 mo of deworming. However, at the end of the study, the prevalence in the albendazole groups was significant lower than it was in the pyrantel groups (partitioned X^2, $P < 0.02$) and marginally lower than in the placebo group (partitioned X^2, $P < 0.09$). The difference between the alb.2x and alb.1x groups was not significant.

Changes in intensity

The changes in intensity of *A. lumbricoides* and *T. trichiura* infections are presented in Table 3. As seen, the intensity of both *A. lumbricoides* and *T. trichiura* was greatly decreased in the dewormed groups (paired *t* test, $P < 0.001$) and slightly decreased in the placebo group (paired *t* test, $P < 0.05$).

At the 3-mo exam, the intensity of *A. lumbricoides* infection in the four dewormed groups was significantly lower than in the placebo group (Scheffe, $P < 0.003$). At the 6-mo exam, no significant difference in intensity of *A. lumbricoides* was seen between the albendazole and the placebo groups, but there was a significant difference between the pyrantel and the placebo groups (Scheffe, $P < 0.005$). At the 12-mo exam, as seen in Table 3, the intensity of ascariasis in the alb.2x and pyr.2x groups differed significantly from the intensity in the placebo group (Scheffe, $P < 0.005$ and $P < 0.0005$, respectively). The pyr.2x group marginally differed from the pyr.1x group (Scheffe, $P < 0.06$), but no difference existed between the alb.2x and alb.1x groups in *A. lumbricoides* intensity.

Table 2. Changes in prevalence of infections after once and twice yearly of albendazole and pyrantel pamoate in all children

Parasitic infections		Percent Positive				Change, McNemar *P*		
	Group (n)	Exam 1[a]	Exam 2	Exam 3	Exam 4	Exam 2-1	Exam 3-1	Exam 4-1
Ascaris lumbricoides	Contr. (74)	93	87	89	82	NS	NS	0.059
	Pyr.1x (60)	93	38	62	73	0.0002	0.0004	0.003
	Pyr.2x (61)	89	48	80	56	0.0002	NS	0.0004
	Alb.1x (66)	94	56	80	74	0.0002	0.029	0.005
	Alb.2x (69)	97	48	83	64	0.0002	0.004	0.0004
Trichuris trichura	Contr. (74)	97	96	99	89	NS	NS	0.034
	Pyr.1x (60)	100	95	92	95	NS	NS	NS
	Pyr.2x (61)	100	95	93	87	NS	NS	0.05
	Alb.1x (66)	99	86	92	80	0.005	0.102	0.001
	Alb.2x (69)	99	93	96	80	NS	NS	0.0004

[a]Exam 1=baseline, exam 2, 3, and 4=3-, 6-, and 12-months after first dose.

Table 3. Changes in intensity of infections after once and twice yearly albendazole and pyrantel pamoate in all children

Parasitic infections		Geometric mean epg				Percent egg reduction		
	Group (n)	Exam 1[a]	Exam 2	Exam 3	Exam 4	Exam 2-1	Exam 3-1	Exam 4-1
A. lumbricoides	Placebo (74)	4518	1803	1853	1119	60[b]	59[b]	75[c]
	Pyr.1x (60)	3431	16	175	442	100[d]	95[d]	87[d]
	Pyr.2x (61)	2863	37	530	55	99[d]	82[d]	98[d]
	Alb.1x (66)	5058	52	604	348	99[d]	88[d]	93[d]
	Alb.2x (69)	6026	24	932	92	100[d]	85[d]	99[d]
T. trichiura	Placebo (74)	2427	1351	1402	663	44[d]	42[b]	73[b]
	Pyr.1x (60)	3522	2106	951	934	40[a]	73[d]	74[d]
	Pyr.2x (61)	2754	1223	770	385	56[c]	72[d]	86[d]
	Alb.1x (66)	2924	493	648	260	83[d]	78[d]	91[d]
	Alb.2x (69)	2232	603	897	206	73[d]	60[d]	91[d]

[a]Exam 1=baseline, exam 2, 3, 4= 3-, 6-, 12-months after first dose.
[b,c,d]Student paired *t* test was [b] $P < 0.05$, [c] $P < 0.01$, [d] $P < 0.0001$.

The intensity of *T. trichiura* infection in the albendazole groups was significantly lower than that in the pyrantel groups (Scheffe, $P < 0.002$) and the placebo group (Scheffe, $P < 0.03$) at the 3-mo exam. However, at the 6-mo exam, there was no significant difference between the albendazole and the pyrantel groups, or between the albendazole and the placebo groups in *T. trichiura* intensity. As expected, at the end of the study, the alb.2x group had the lowest intensity of *T. trichiura,* followed by the alb.1x group and then by the other groups, but the difference was not significant.

The changes in intensity by different categories of egg counts at baseline, 3, 6, and 12-mo exams are presented in Figures 1 and 2 for *A. lumbricoides* and *T. trichiura,* respectively. As seen, after 3 mo of deworming, the number of heavily *A. lumbricoides* infected children (> 20000 epg) was reduced significantly in all dewormed groups and, to some extent, in the placebo group. However, after 6 mo of deworming, the percentage of heavily infected children was similar in all groups. At the end of the study, groups of children who received a second treatment at 6 mo showed less heavy *A. lumbricoides* infection (Figure 1). The heavy *T. trichiura* infections were also reduced in all groups throughout the study, although the lowest number of infection in children at the end of the exam (12-mo) were in the groups who received a second dose of albendazole. Both figure show the reduction of intensity in all groups, including the placebo group, partly due to the decreased number of the heavily-infected children.

DISCUSSION

This study showed that, after 12 mo of deworming, the prevalence and intensity of *A. lumbricoides* infection was markedly reduce in all dewormed groups and decreased slightly in the placebo group. Similarly, the prevalence and intensity of *T. trichiura* infection definitely decreased in all groups, although it decreased more markedly in the albendazole groups. The two dose groups decreased significantly in prevalence and intensity more than the other group did for *A. lumbricoides,* but not for *T. trichiura.*

These result are in agreement with a community-based study conducted in Okpo village in rural Burma.[13] These authors compared one with two yearly doses (6- with 12-monthly) in areas where the prevalence and intensity of *A. lumbricoides* infection are very high, but *T. trichiura* and hookworm infections are very low. They reported that 6-monthly deworming markedly reduced the intensity of *A. lumbricoides* infection in children and adults, whereas a 12-monthly deworming lowered the intensity in adults only. Another study, in Kenya,[14] reported that the second dose per school year further decreased the prevalence and intensity of the three helminth infections (hookworm, *T. trichiura,* and *A. lumbricoides*) prevalent in that area, while one dose did not. Repeated treatments works well to prevent new infections and to decrease the transmission rate of infection in the community.

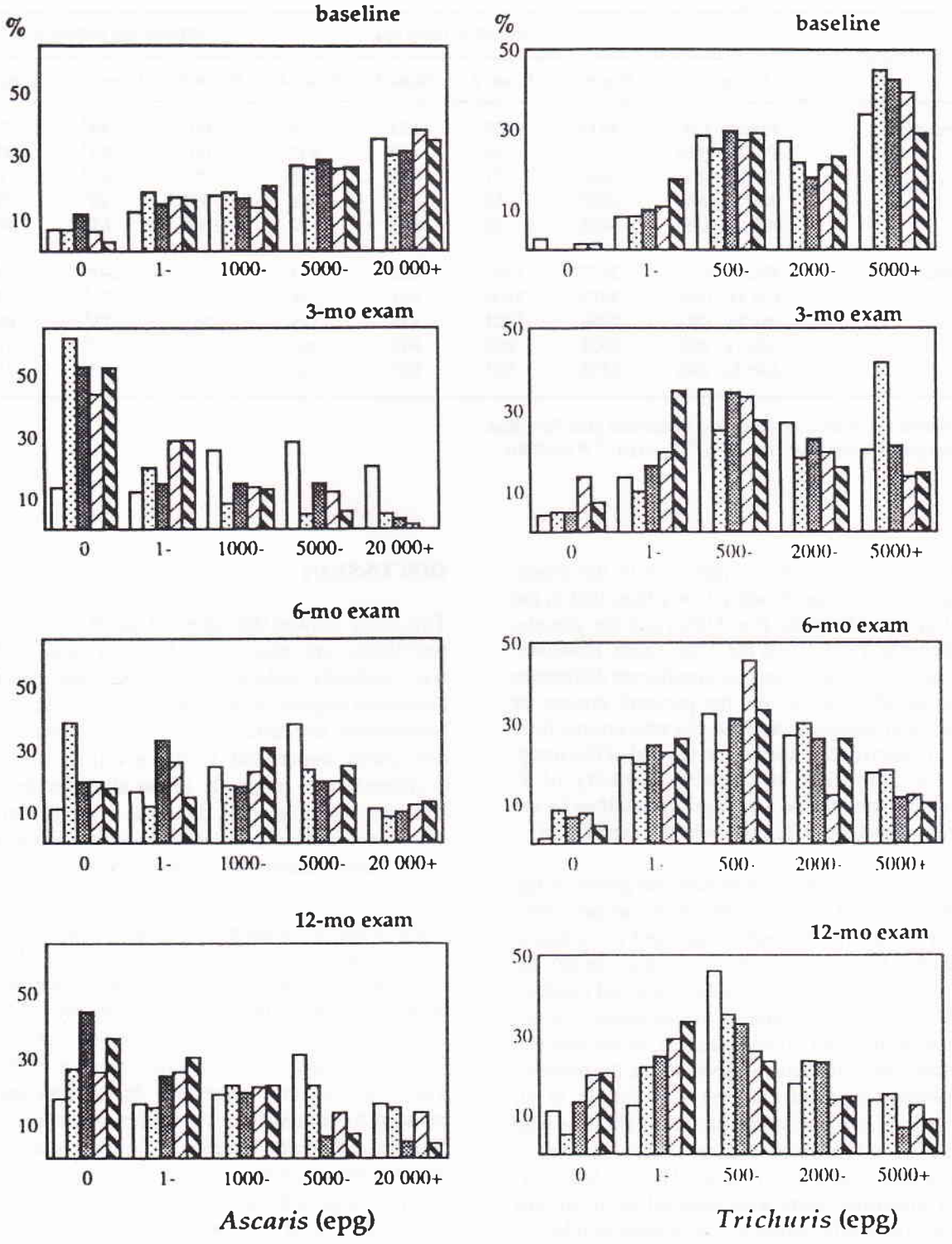

Figure 1. Frequency distribution of egg per gram of feces (epg) category for A. lumbricoides (left) and T. trichiura (right) infections at baseline, 3, 6, and 12 months after deworming in five groups; placebo (⊓), pyrantel once (▥), pyrantel twice (■), albendazole once (▨), and albendazole twice (▩); n = 330.

It is interesting to note that the intensity of both infections in the placebo group decreased throughout the study, although a significant reduction of intensity of *T. trichiura* infection was also seen in the pyrantel groups over the period of the study. This phenomenon contradicts what we expected. Studies in Kenya[14,15] found that the intensity of *T. trichiura* infection after deworming in the placebo group increased, whereas in other studies[16,17] it hardly changed. This reduction has been related to seasonal variation,[18] measurement variation,[19] and the effect of the treatment itself on untreated groups.[20,21,22] Seasonal variation can be excluded since this study was done for an entire year, so that the baseline and final exams were performed during the same season. Basically, measurement variation can also be excluded since the reductions happened at all exams, and all stool exams were conducted by the same analyst and identical protocols. However, the reduction likely can be related to the effect of the treatment itself on untreated groups, as deworming in targeted children has been reported to decrease helminth transmission within a study population. Studies in Bangladesh,[20] in Jamaica,[21] and in Burma,[4,22] have shown that anthelmintic drugs administered to targeted children also had an impact on the non-targeted population. The authors showed that deworming in targeted children, particularly from 1 to 15 years old, also decreased the prevalence and intensity of helminth in adult or in the entire population. They suggested that most of the helminth eggs in the environment were decreased since 1-15 years old children are the highest risk group and harbor the most worms in the population. Thus, the reduction of both prevalence and intensity shown in the placebo group in this present study could be due to a decrease of the transmission rate, as a result a decrease in infection of the treated groups. The impact may be even more marked in this study since children live close to each other, and the number of children in the placebo group was much lower than the number of those treated.

It should be pointed out that the advantage of using a single 400 mg dose of albendazole, compared with a single dose of pyrantel, for reducing *T. trichiura* infection was only statistically significant in this study at 3 mo. As efficacy studies have shown varying results, it has been accepted that regional or local conditions affect the amount and frequency of doses of albendazole needed in order to have a high cure rate for *T. trichiura.* A recent study in 2294 Tanzanian school children[10] found that the cure rate for *T. trichiura* was only 11%, but the egg reduction rate was 73%. Another study of Bangladeshi children[23] found only one out of 128 children was cured, and the egg reduction rate was 49%. In this study, we measured a subsample of 98 boys at 6 weeks after deworming and found that the cure rate and the egg reduction rate were 6% and 67%, respectively. Some investigators have observed a higher efficacy when they used 400 mg for more than one day[23,24] or a single dose of more than 400 mg.[25] Other authors have observed no difference in results by using two doses on consecutive days[26] and a single dose of 600 mg;[14] however, both studies had a limited sample size. As one study showed that worm expulsion of *T. trichiura* occurred more than two days after deworming,[24] it is possible that a single 400 mg dose for two consecutive days may get a higher cure rate and a lower reinfection rate. The optimum dose regimen still needs to be elucidated further for the community reported here.

In summary, this study showed that two doses of anthelminthic drugs reduced prevalence and intensity of *Ascaris* infection more than one dose, and the reduction of *Ascaris* intensity was associated with a height increment, while a decreased intensity of *Trichuris,* seen over a year period, was highly correlated with increases in midarm circumferences. This study supports the notion that deworming should be provided to children in areas with a high transmission of helminth infections and a high prevalence of malnutrition.

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