ASCARIS AND *TRICHURIS* DO NOT CONTRIBUTE TO GROWTH RETARDATION IN PRIMARY SCHOOL CHILDREN

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Abstract. To assess the effectiveness of the treatment of soil-transmitted helminthiasis (STH) on the growth of primary school children, 353 children were block stratified to receive either mebendazole plus pyrantel oxantel pamoate every three months or a placebo. The children were followed for two years with 89% completing the trial. Follow-up stools indicated that the treatment was efficacious for ascariasis and trichuriasis. There was virtually no hookworm infection. The children were malnourished as measured by the number below -2 SD of height and weight standards. There was no difference in height or weight between the treatment and control groups by sex initially or at the end of two years of follow-up. The treatment of *Ascaris* and *Trichuris* had no effect on growth parameters. The effect of STH on growth may be mediated through hookworm infections.

INTRODUCTION

Soil-transmitted helminthiasis (STH) is a common affliction of much of the world's population. It has been estimated that between one quarter (*Ascaris lumbricoides*) and one eighth (*Trichuris trichiura*) of the individuals in the world harbor one or more species of STH (Pawlowski *et al*, 1984). The highest incidence of infection is in the 5-15 year olds in poor communities (WHO, 1981). These same children are also at high risk for malnutrition (Latham, 1982). It has been postulated that there is a causal association between the high rates of infection with STH's and protein energy malnutrition (Stephenson *et al*, 1980; Willett *et al*, 1979). However both of these studies were in preschool children. Stephenson *et al* (1980) found an effect after 14 weeks, Willett *et al* (1979) failed to find a significant difference in growth rates at one year. A review in 1982 of the literature on growth and infection found that the effects of deworming on growth were inconclusive (Schultz, 1982; Reddy, 1982). Ismail and Perera (1986) carried out a two year followup of children ages 3-12 years and failed to established a clear cut effect of treatment. Recently Stephenson *et al* (1989) have studied the effect of a single treatment for STH on the growth of Kenyan school children (Stephenson *et al*, 1989). In this study an increase in growth rate was found following a single treatment with albendazole in a 6 month followup.

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In view of the lack of specific evidence linking STH and malnutrition and because there has been a suggestion that mass programs should be undertaken to control STH with a view to improving the nutritional status of children (Stephenson *et al*, 1989; Latham, 1984; Stephenson, 1984), we undertook a study in Malaysian school children to determine the effectiveness of treatment for STH in Malaysia on the height and weight of school children followed over a two year period.

METHODS

The study population was recruited from 16 primary schools in the Kuala Lumpur and Selangor area. These schools were attended by children from a Tamil origin population. This is a lower socio-economic strata group with a previously documented high prevalence of *Ascaris* and *Trichuris* (Kan, 1982; Sinniah, 1984). There were five schools in the urban area and 11 in peri-urban areas.

The subjects were grade 2 children, 8 years of age, enrolled in the study schools. Information on the study was sent home and informed consent was obtained for enrolment in a series of studies to be done with this population. The total pool was 526 or 97.8% of the grade 2 population. Six were ruled ineligible due to concurrent illnesses. None of the subjects were eliminated because of having received anti-helminthic drugs in the past three months. Initial heights and weights were done on all children and they were requested to supply a stool sample. Only those who complied with the initial stool specimen request were assigned to the treatment or control group using a block assignment design by school, then by sex, then by presence of worms as none, light or moderate/heavy, and then by rank order of body weight in the group. In the urban area, the odd numbered children were assigned to the treatment group, while in the peri-urban schools, the even numbered children were assigned to the treatment group.

The study cohort consisted of those individuals who had been assigned to either the treatment or control groups, who had at least one height and weight taken during the follow up period and who had at least one stool specimen submitted one month before the second or any subsequent treatment. This resulted in a cohort of 353 children, 68% of those eligible, being available for analysis. The other children failed to participate beyond the initial examination due to school leaving or transfer or non-compliance.

The study population did not know which medication they were on, treatment or placebo. However, the study staff knew which group the children were in. Medication was given to the children every three months under the direct supervision of the study team member who placed the pills into the mouth and checked that they had been swallowed. The treatment was mebendazole 100 mg, one tablet, plus pyrantel oxantel pamoate 100 mg, two tablets. The placebo was three sugar tablets of similar sizes to the antihelminthics.

Stool collections were done initially and then one month after the treatment was given. There were nine stool collections possible. The children were given a container at school and told to return it the following morning. Although three stools were initially requested, the subsequent collections were for single specimens. The stools were collected from the schools and transported daily to the laboratory where they were processed immediately and examined within 24 hours. A count was done for egg concentration using the Stoll (1923) dilution technique. The egg concentrations in eggs/ml (Formed stool basis) were categorized as follows: *Ascaris:* light < 50,000 eggs/ml, moderate/heavy > 50,000: *Trichuris* <5,000 eggs/ml, moderate/heavy > 5,000.

Anthropometric measurements were carried out six monthly on all children, following the initial determination. Weight was measured to the nearest 0.1 kg using a SECA beam-balance scale. Calibration was checked at each site using a 5 kg standard before use. Weights were measured in normal clothing but without shoes. Heights were measured to the nearest 0.1 cm using the vertical scale attached to the weigh scale. The children stood straight and then a horizontal plane was lowered to the head and the reading taken. Following the initial measurements, there were four susequent measurements in the two year followup period, giving a maximum of five measurement points.

Data analysis was carried out using SAS on the mainframe and graphics programs on the Macitosh computer. The initial heights and weights were used as each individual's reference point. Changes in heights and weights were calculated for each of the measurement periods, five in number including the initial measurements. The weight for age, height for age and weight for height were determined using the CDC Anthropomorphic Software Program (CASP) version 3.1, Division of Nutrition, CCDPHP, Centers for Disease Control, 1988. Heights and weights were standardized to the WHO recommended NCHS growth reference (Hamill *et al*, 1669). The comparisons of means were carried out with paired *t*-test statistics for changes in height and weights from the initial values and a Student's *t*-test for means for the standardized anthropomorphic measures.

RESULTS

The inception group consisted of 210 females, 109 in the treatment group, 101 in the control, and 143 males, 77 in the treatment group and 66 in the control. The rates of compliance with anthropometric measurements are noted in Table 1. The overall compliance fell to 89% at the last measurement. The compliance with taking medications was in this same range as anthropometric measures as students were treated within the classrooms under observation. The compliance with returning stool specimens was however much lower than the physical measurements (Table 1). The initial specimens were all obtained. The 10 missing values represent the loss of data between the laboratory and data entry. Compliance fell from 68% for the second sample to 32% for the eighth. The compliance improved to 44% at the last stool specimen examination. At least some of the

Table 1

Compliance rates for followup measures, the total in the inception groups is 353.

Measurement period	Anthropmetric measurements		Stool specimens	
	Missing	Compliance rate/100	Missing	Compliance rate/100
Initial	0	100	10	97
Second	9	95	113	68
Third	24	93	212	40
Fourth	34	90	167	53
Fifth	39	89	225	36
Sixth			116	67
Seventh			203	43
Eighth			243	31
Ninth			197	44

Measurement interval for anthropometric measures is 6 months.
Measurement interval for stool specimens is 3 months.

variation in the number of cases in the worm egg count categories at the different stool collections may have been due to these levels of compliance.

The mean ages, heights and weights (Table 2), are similar for treatment and control groups. The percentage below -2 Z-score for height for age, Ht/ Age weight for age, Wt/Age, and height for weight Wt/Ht, are all similar as well. The expected number of individuals below -2 Z-score is 2.5%. The rates below -2 Z scores in the cohort were 15.6 and 8.9% in the treatment and control groups and 15.6 and 22.7% for males for the Ht/Age. The weight for height Wt/Ht, were 11.9 and 20.8% for females and 13.0 and 13.6% for males in the treatment and control groups respectively. The cohort started the trial well below the standards for their ages.

The cohort at the final anthropometric measurement consisted of 95 females in the treatment group and 86 in the control, 87% and 85% completion rates respectively (Table 2). For the males, 66 were in the treatment group and 59 in the control for compliance rates of 86% and 89% respectively. The ages, heights and weights were not different within the sexes. In females the Ht/Age score improved to 10.5 and 5.8% in the treatment and control groups as did the Wt/Ht at 9.2 and 17.2%. For males the standardized indices improved slightly for Ht/Age to 10.6 and 20.3% but fell for Wt/Ht to 18.2 and 16.9% for the treatment and control groups. The anthropometric indicies were not statistically different comparing initial and final scores, although 13.5% of the females were excluded from the weight for height calculation because of the age requirements of the CASP program (maximum age for females < 120 months).

The initial worm burdens were similar for the treatment and placebo groups (Table 3). There was a marked treatment effect noted in the rates of those students who had no eggs detected in their stool sample (Fig 1). The rates of those on treatment with no *Ascaris* eggs detected rose from 33.7% initially to 95.6% at sample seven, ending at 73% at sample 9. The control group was similar initially at 34%, but only at sample 8 were more than 50% without eggs (60%) ending at 42%. The results for *Trichuris* infections were similar but somewhat better with 87% with no eggs at sample 9. However the controls also did somewhat better, with nearly 60% having no detected *Trichuris* eggs in samples 7.8 and 9. There were too few individuals infected with hookworms to evaluate the stool egg results. Initially the treatment group had 48/179 (26.8%) moderate to heavy *Ascaris* infection and 73/179 (40.8%) moderate to heavy *Trichuris* infections. The control group had 43/166 (25.9%) and 57/166 (34.3%) respectively. Following

Table 2

Anthropometric measurements:

a) Comparisons of initial and final values (2 years) for the treatment and control groups.

	Initial number	Age yrs	Height cm	Weight kg	Final number	Age yrs	Height cm	Weight kg
Females								
Treatment	109	7.50	116.7	18.8	95	9.75	128.9	24.4
Control	101	7.54	118.1	19.0	86	9.69	130.5	24.6
Males								
Treatment	77	7.56	118.7	19.9	66	9.73	130.5	25.6
Control	66	7.53	118.5	19.3	59	9.71	129.9	24.0

b) Comparison of standardized growth measures.
Rate/100 below -2 SD.

	Ht/Age		Wt/Age		Wt/Ht*	
Females	Initial	Final	Initial	Final	Initial	Final
Treatment	15.6	10.5	22.9	20.0	11.9	9.2
Control	8.9	5.8	21.8	24.4	20.8	17.2
Males						**
Treatment	15.6	10.3	31.2	27.3	13.0	18.2
Control	22.7	20.3	40.9	25.4	13.6	16.9

* Females up to 120 months and < 137 cm: excludes 13.5% of individuals
** Males up to 138 months and < 145 cm: excludes no individuals.
Interval between initial and final is 2 years

the initiation of treatment, the treated group averaged 2.8% *Ascaris* and 4.0% moderate to heavy *Trichuris* infections while the control group averaged 18.3% and 20.0% moderate to heavy *Ascaris* and *Trichuris* infections respectively.

The changes in height and weight from the initial measurement, for the treated and control group (Table 2) showed no significant differences in the changes in height and weight between the two groups, using paired Student's *t*-tests. As shown in Fig 2, the rates of growth, whether measured by changes in height or changes in weight are also not different between the treated and control groups. The relative increase in the rates of growth between periods four and five are seen in both groups.

DISCUSSION

The two groups of children were recruited from high risk populations in the Kuala Lumpur area. Because the ethnic group is uniform, the food and eating habits are similar. If ethnic status plays a role in reinfection rates, the same ethnic status of the cohort will limit the chance of a selection bias accounting for any variation within the groups. As non-equal use of antihelminthics in the cohort could be a confounder, the observation on no anthelminthic use prior to the study indicates little use of antihelminthics in this population. The initial assignment of patients resulted in minor differences in the treatment and control groups, inspite of an assign-

Table 3

Rates of stool samples positive for helminth eggs from primary school children treated with antihelminthics compared to controls.

Collection	1st		2nd		3rd		4th		5th		6th		7th		8th		9th	
	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C
No. of samples	179	166	127	115	81	62	92	96	58	72	119	120	68	84	60	52	77	81
Ascaris*																		
none	31	34	87	37	90	35	77	41	79	36	66	48	96	46	82	60	73	42
light	42	40	9	37	9	44	22	41	19	44	30	32	4	36	18	37	19	47
mod/heavy	27	26	4	26	1	21	1	19	2	19	4	20	0	18	0	4	8	11
Trichuris*																		
none	34	31	82	40	94	50	87	43	84	39	88	45	97	61	95	60	87	58
light	26	35	8	33	2	32	7	31	12	34	7	28	3	26	5	31	12	32
mod/heavy	41	34	10	27	4	18	7	26	3	27	5	27	0	13	0	10	1	10
Hookworm*																		
none	94	95	97	93	96	93	97	96	97	99	95	94	99	90	98	98	99	96
present	6	5	3	7	4	7	3	4	3	1	5	6	0	10	2	2	1	4

T = treatment group
C = control group
Interval between samples is 3 months
* rates - samples positive/100 stool samples

ment strategy to ensure that the groups were similar. However, there does not appear to be a bias in the assignment which might explain the results.

It is highly likely however, that the attempt to blind the study was quickly broken by the subjects. It would be expected that with pills which tasted different and the expulsion of worms from only those who took the tasteless pills, the students and their parents would know who was on treatment and who was a control. However, the magnitude of any bias introduced appears to be low, as there were no differences in response rates, either to the anthropometric measurements or in stool sample returns. It is unlikely that the parents in this socio-economic

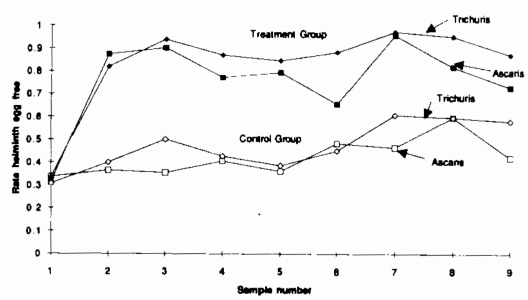

Fig 1–Treatment efficacy for *Ascaris* and *Trichuris*.

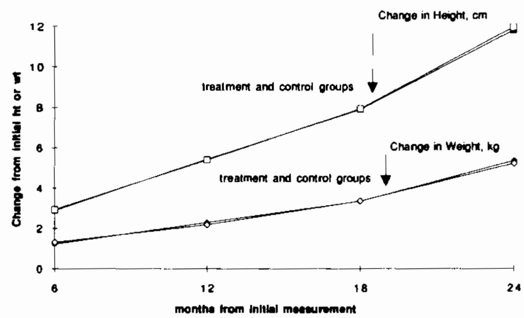

Fig 2–Changes in heights and weights.

group would seek treatment unless the child was ill, and unlikely that any illness would be attributed to STH. The difference in the worm burdens was consistent with less treatment in the control group, although it does not rule out all treatment of this group.

The blinding was also very likely quickly broken by the staff who knew that the child was in group one or two when the measurements were done and knew that the two sets of pills tasted differently. This bias would tend to lead to a difference in the two groups, as investigators tend to believe that an intervention would result in a beneficial effect, in this case, taller and heavier children in the treatment group. The results do not support this as being a bias causing concern.

A definite treatment result was noted, with fewer children in the treatment group having detected *Ascaris* or *Trichuris* eggs at all points of the trial following the first treatment. The quantity of eggs excreted was also less in the treated group. The observation that the control group varied in their worm eggs detected may reflect the variability in worm loads and in egg excretion or may be due to contamination of the control group by anthelminthic treatment.

Why there was the increase in growth rate in the last six months of the study is not clear. It may have been due to the dropouts, to some other program(s) being initiated which affected the growth curves, or it may have been some other secular trend. The increase in growth rates may also represent a physiologic growth curve acceleration, although the mean ages were only between 9.5-10 years. Whatever the cause of this acceleration, it was unlikely to be a direct treatment of worm burden affect as the acceleration was equal in the treatment and control groups. It was therefore an effect that acted on both groups equally.

Although there was the opportunity for bias to affect the study, it does not appear to have been sufficient to explain the results. Neither does confounding appear to be a likely explanation. With the two groups assigned to the treatment or control group based on school, sex, worm load, and weight, variables such as socioeconomic status, diet, food handling in the home, mother's education, *etc* should be approximately equal in the two groups. As anthropormetric measurements are associated with the socioeconomic conditions, having similar heights and weights should reduce the amount of confounding that may be in the data due to this source.

Stephenson and colleagues (1989) in Kenya have indicated that there is an effect on growth of the treatment of a group of children with high rates of hookworm infection. This study took place over a six month period and took anthropometric measurements at only two points. Our study, following children over two years, indicates that the growth parameters were not different in the two groups inspite of a treatment effect. However our study had few children infected by hookworm and so our results are generalizable only to children with *Ascaris* and *Trichuris* infections.

By applying the definition of effectiveness in assessing the impact of health interventions on health outcomes, namely: efficacy - can it work, effectiveness - does it work, and efficiency - is it worth doing (Last, 1988), we feel that our data shows a lack of effectiveness in spite of the efficacy of treatment. Helminths are not a critical component in the growth of children in Malaysia and mass programs for the control of helminths should be based on outcomes other than improving nutritional status, at least as measured by height and weight, as such an intervention was shown to be not effective. At this time, programs designed to improve the nutritional status of children should concentrate on supplying adequate nutrition, and not on treating STH infections.

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