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## Evaluation of the efficacy of pyrantel-oxantel for the treatment of soil-transmitted nematode infections

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### Abstract

A randomized controlled trial comparing the efficacy of pyrantel-oxantel (10 mg/kg) with mebendazole (500 mg) was performed on 1329 schoolchildren aged 6-9 years on Pemba Island in September-October 2000 to evaluate alternative single-dose drugs for regular treatment of intestinal nematode infections. Both mebendazole and pyrantel-oxantel were very effective in eliminating *Ascaris lumbricoides* infection, inducing cure rates of more than 96% and reducing the mean egg counts by more than 95%. Both drugs had a moderate efficacy against *Trichuris trichiura* infection, but pyrantel-oxantel had a higher cure rate (31.5% vs. 23.3%,  $P < 0.01$ ), though the reductions in egg counts did not differ significantly and were more than 80%. Pyrantel-oxantel and mebendazole had a similar, poor efficacy in curing hookworm infections and had a moderate effect in reducing the egg counts by 67% and 68%, respectively. Pyrantel-oxantel (10 mg/kg) offers a valuable alternative to mebendazole as a single-dose treatment for the control of intestinal nematode infections in children in endemic areas of sub-Saharan Africa, due to its comparable efficacy, its low cost and its suitability for use in young children.

### Keywords

helminths; *Ascaris lumbricoides*; *Trichuris trichiura*; hookworm; control; chemotherapy; pyrantel-oxantel; mebendazole; Pemba Island

### Introduction

Four single-dose anthelmintic drugs, albendazole, levamisole, mebendazole, and pyrantel are available for the treatment of soil-transmitted helminth (STH) infections in chemotherapy-based control programmes. These drugs are recommended by the WHO and are included in the List of Essential Drugs (WHO, 1995,1996).

A number of research studies have been carried out under the auspices of the WHO to reassess the efficacy of single-dose-anthelmintic drugs and to evaluate the effectiveness of drug combinations with a view to their use in large-scale chemotherapy-based helminth control programmes. A safety component to monitor serious adverse events or side effects

has been added in some trials. These studies included the co-administration of praziquantel and albendazole (OLDS et al., 1999), the comparative evaluation of mebendazole and albendazole (ALBONICO et al., 1994) and the assessment of levamisole and the co-administration of levamisole and mebendazole (ALBONICO et al., in press).

Ivermectin and albendazole have been assessed for the treatment of strongyloidiasis and intestinal nematode infections WARTI et al., 1996). and the administration of ivermectin alone or in combination with albendazole for the control of lymphatic filariasis is presently under evaluation (HORTON et al., 2000; ISMAIL et al., 2001).

Pyrantel has been extensively studied in the past and results demonstrated a good efficacy against *Ascaris lumbricoides* and the hookworms, but poor efficacy against *Trichuris trichiura* (DESOWITZ et al., 1976; HSIEH & CHEN, 1973; ISMAIL et al., 1991; LONG Qi et al., 1992). However oxantel, another pyrimidine derivative, has been reported to show high efficacy against *T. trichiura*, a species relatively resistant to other drugs (ZAMAN & SABAPATY, 1975; GARCIA, 1976; RIM et al., 1976; PELDAN & PITIUNEN, 1982) and the combination of pyrantel and oxantel to have good efficacy against the STHs (LIM, 1978; ZAHEDI et al., 1980; APONTE et al., 1982). However, no randomized placebo-controlled clinical trial has been recently carried out to evaluate the efficacy of the combination pyrantel-oxantel, a drug combination which is used more frequently in Latin America and South-East Asia, and to compare its efficacy with other anthelmintics given individually.

The availability of a single-dose pyrantel-oxantel treatment would increase the choice of anthelmintic drugs for public health planners and managers and facilitate implementation of strategies designed to cope with the possible emergence of anthelmintic drug resistance (SAVIOLI et al., 1997). The reassessment of the efficacy of the pyrantel-oxantel combination, in particular for the treatment of trichuriasis, was one of the recommendations from a recent meeting on controlling disease due to STHs which was organized by the WHO and the Ministry of Health of Indonesia in Bali in February 2000 (CROMPTON & NESHEIM, in press). The pyrantel-oxantel combination is currently used in large-scale helminth control programmes in Indonesia with good results (SASONGKO et al., in press).

The present trial evaluated the efficacy of a single-dose of pyrantel-oxantel (10 mg/kg) as a tool for the control of intestinal nematode infections in children in an endemic area of sub-Saharan Africa. In this study, pyrantel-oxantel was compared with mebendazole (500 mg), which is the drug used for mass treatment of children and women of childbearing age in numerous helminth control programmes, worldwide (WHO, 1996)

## Materials and Methods

### Study area and study population

The study was carried out on Pemba Island, the smaller of the 2 islands of Zanzibar, United Republic of Tanzania. Important features of the island have been described in detail elsewhere (ALBONICO et al., 1998). The study was conducted in September-October 2000 among children enrolled in the first grade (Standard 1; aged 6-7 years) and in the second grade (Standard 2; aged 8-9 years) of 7 public primary schools on Pemba Island. The

schools were randomly selected from the 72 schools on the island. All children were included in the national helminth control programme and Standard 1 children had received 1 round of treatment with mebendazole 500 mg in March 2000. Standard 2 children had received 2 doses of mebendazole in 1999 and a third dose in March 2000. not have parental or guardian permission to participate; (ii) did not provide a stool sample; (iii) had significant co-morbidities (e.g. severe diarrhoea, severe anaemia, high fever); and (iv) had received anthelmintic treatment in the previous month.

### Study design

The study was a randomized, placebo-controlled trial. Children enrolled in the study were randomly assigned to 1 of 3 treatment groups: (i) mebendazole 500 mg (Pharmamed, Zejtun, Malta); (ii) pyrantel-oxantel 10 mg/kg (Pfizer, Jakarta, Indonesia); and (iii) placebo. Pyrantel-oxantel was composed of pyrantel and oxantel in equal proportion, i.e. 150 mg of each drug in 1 tablet. Placebo pills resembled mebendazole in colour, size, taste, and shape. On the day prior to the scheduled treatment date, children eligible to participate in the trial were given a container in which to bring a fresh stool sample on the following day. On the day of treatment, their stools were collected, and their weight was measured and recorded. Randomization was blocked on weight and a computer-generated programme was used to create 3 randomized treatment lists, one for children weighing 15-20 kg receiving one tablet (150 mg) of pyrantel-oxantel, one for children weighing 21-30 kg receiving 2 tablets (300 mg) of pyrantel-oxantel, and one for children weighing 31-40 kg receiving 3 tablets (450 mg) of pyrantel-oxantel, according to the recommendations of the manufacturer. A single tablet of mebendazole and of placebo was given, irrespective of bodyweight. Treatments were placed in sealed, opaque envelopes and coded with a number. Children were identified solely by these numbers for the duration of the study.

Twenty-one days following treatment all children were revisited to collect a further stool sample. Any child who failed to bring a stool sample was followed up to 24 d. After both surveys stool samples were processed to assess egg counts within 6 h. All laboratory investigations were blinded, i.e. the technicians examining the slides were unaware of the treatment regimen of the patients.

Stools were analyzed using the Kate-Katz technique according to WHO guidelines (WHO, 1994) in order to assess prevalence & intensity of helminth infection, indirectly measured as egg count.

Before enrolment in the study, parents or guardians of the children in the selected schools were met and a comprehensive explanation of the risk and benefits of the trial was given and verbal consent was sought. Parents and children were instructed to report to the teacher and refer to the nearest health centre any severe adverse effects occurring in the week after treatment.

After the completion of the study, children in the placebo group and children positive after the follow-up survey were treated with mebendazole 500 mg. The study was approved by the Zanzibar Health Research Council, and by the ethical committees of the WHO and of the London School of Hygiene and Tropical Medicine, UK.

## Statistical analysis

Data were entered and analyzed using the Epi Info database package (CDC, Atlanta, GA, USA). Cure rates (CR) were calculated as the percentage of children with egg counts  $> 0$  before treatment who become negative after treatment. The percentage reduction in prevalence was calculated as  $[(N^+/n) - (N_{21}^+/n)] / (N^+/n)$ , where  $N^+$  is the number of positive children at baseline,  $N_{21}^+$  is the number of positive children 21 d after treatment, and  $n$  is the total number of children with samples from both day 0 and day 21. Daily variation of egg excretion in each individual meant that some children who were egg-positive before treatment became negative at the follow-up, irrespective of treatment, and that some children who were negative in the first survey were found positive at the second survey. Cure rates could be biased by the daily variation of egg excretion because they included only children who were positive at baseline and who became negative at the follow-up. Both CRs and the percentage reduction in prevalence were calculated and presented in the Tables. Proportions were compared using standard  $\chi^2$  tests. Geometric mean egg counts were estimated as  $\exp[(\log_e c + 1)/n] - 1$ , where  $c$  was the count (eggs per gram) for a particular individual and  $n$  the total number of samples. Geometric means were compared using analyses of variance (ANOVA) tests if Bartlett's test of heterogeneity indicated homogeneity of variances, and by the Kruskal-Wallis test if Bartlett's test was significant at the 5% level. The egg reduction rate (ERR) induced by treatment was estimated as  $100 [1 - \exp(-D)]\%$ , where  $D$  was the mean difference for a particular treatment.

## Results

In September 2000, 1435 children brought a stool sample for the first examination. Of these, a second stool sample was collected from 1329 (92.6%) children between 20 and 23 d after treatment, with 95% of the samples collected 21 d after treatment. A second stool sample was not collected from 38 (8.5%) children treated with mebendazole, from 38 (8.6%) children treated with pyrantel-oxantel, or from 30 (6.8%) children treated with placebo. The children enrolled at both surveys were between 8 and 13 years of age (mean = 9.4) and 44.6% were boys ( $P < 0.05$ ). Sex, age, prevalence of helminth infections, and geometric mean egg counts (before treatment) of the children who provided a post-treatment stool sample were compared with children who did not provide a second –stool sample (Table 1). The mean age did not differ between the 2 groups, whereas a higher percentage of the enrolled children lost at follow-up were boys (55.7% vs. 44.6%;  $P = 0.03$ ) and this difference was particularly evident in the mebendazole-treated group ( $P = 0.04$ ). Prevalences and egg counts were not different in the 2 groups for *T. trichiura* or hookworms, but for *A. lumbricoides* children treated with mebendazole who did not return a second stool sample had higher prevalence ( $P = 0.01$ ) and higher egg counts ( $P = 0.007$ ). Analysis of the efficacy trial was done on the 1329 children who returned a stool sample at baseline and also at the follow-up survey. The groups of children receiving mebendazole, pyrantel-oxantel and placebo were homogeneous for sex, age, and for prevalence and intensity of helminth infections (Table 1). The Figure shows the distribution of egg counts at baseline and at 21 d after treatment for *A. lumbricoides*, *T. trichiura* and hookworm infections, respectively. Prevalences and mean egg counts before treatment and CRs and ERRS 21 d after treatment in the 3 treatment groups are reported in Table 2.

The CRs, the reductions in prevalence, and the ERRS of the children treated with mebendazole and with pyrantel-oxantel were all significant ( $P < 0.001$ ), and were significantly different from placebo at follow-up ( $P < 0.001$ ).

Both mebendazole and pyrantel-oxantel were very effective in eliminating *A. lumbricoides* infection, producing CRs of more than 96% and reducing the mean egg counts by more than 95% (Table 2). As shown in the Figure all heavy and moderate infections and most of the light infections were cleared after treatment with either-drug. Both drugs had a moderate efficacy against *T. trichiura* infection, but pyrantel-oxantel had a higher CR ( $P < 0.01$ ), though the reduction in egg count did not differ significantly and was more than 80% for both drugs (Table 2). The Figure shows a comparable reduction of heavy and moderate infections, while light infections were cured more effectively by pyrantel-oxantel. Both mebendazole and pyrantel-oxantel had poor efficacy in curing hookworm infections, though pyrantel-oxantel was more effective in reducing heavy infections (Figure). Both drugs likewise had moderate effects in reducing egg counts, by 67% and 68%, respectively (Table 2). No adverse events were reported after any of the treatments.

## Discussion

This trial was the first randomized, placebo controlled study comparing the efficacy of single dose pyrantel-oxantel (10 mg/kg) with mebendazole (500 mg). In addition, the study was carried out in sub-Saharan Africa, where intestinal helminths are common and where pyrantel-oxantel has rarely, if ever, been used for control of intestinal nematode infections. This trial has confirmed the findings of previous studies that both mebendazole (ABADI, 1985; ISMAIL et al., 1991; ALBONICO et al., 1994) and pyrantel-oxantel (RIM et al., 1975; DISSANAIKE, 1978; LIM, 1978) are highly effective single-dose treatments for *A. lumbricoides* infection, with mean egg counts after treatment being reduced by more than 95%.

Pyrantel-oxantel achieved a CR of only 38% for *T. trichiura* infection, considerably lower than the majority of results obtained in previous trials using the same dosage of 10 mg/kg (RIM et al., 1975; CHO, 1976; LIM, 1978). Only a few previous studies have reported a similarly low CR (DISSANAIKE, 1978; SINNI AH & SINNI AH, 1981). This may be explained by the lower mean egg counts pretreatment which were reported in studies in which CRs of between 70% and 90% were achieved, and/or by different drug sensitivities of *T. trichiura* strains. It is noteworthy that all previous studies were carried out in Asia and that, for *T. trichiura*, sensitivity to ivermectin has been shown to be highly dependent on geographical location (MARTI et al., 1996). Cure rates with mebendazole were lower than those obtained with pyrantel-oxantel, though higher than CRs reported in a previous study from Pemba Island (ALBONICO et al., 1994). A lower mean egg count pretreatment may account for the higher CR reported in the present study, as it has been shown that light infections are more likely to be cured with benzimidazoles than heavy infections (PENE et al., 1981; ROSSIGNOL & MAISSONNEUVE, 1983). Both drugs were similarly effective in reducing mean egg counts by more than 80%; pyrantel-oxantel showed a better, though not significantly greater effect. The 87% reduction of *T. trichiura* mean egg count seen after pyrantel-oxantel treatment is consistent with previous studies (RIM et al., 1976;

DISSANAIKE, 1978; LIM, 1978). This comparable effect on intensity supports the suggestion that the higher CRs reported in the earlier studies is explained by lower pretreatment intensities. Previous direct comparisons with mebendazole suggested that pyrantel-oxantel was more effective against *T. trichiura* infection, although in those studies both the drugs were given in multiple doses. Thus, mebendazole given at 100 mg twice a day for 3 d was compared with pyrantel-oxantel given at 10 mg/kg daily for 3 d (SINNIAH & SINNIAH, 1981), or with pyrantel-oxantel given at 15-20 mg/kg daily for 2 (LEE & LIM, 1978) or for 3 consecutive days (DISSANAIKE, 1978).

Cure rates for hookworm infections were poor and ERRS were only moderate for both drugs. Pyrantel-oxantel has generally been reported to have a higher efficacy than this against hookworms (RIM et al., 1975; CHO, 1976; LIM, 1978), though low/moderate efficacy has been reported by some other authors (DISSANAIKE, 1978; SINNIAH & SINNIAH, 1981). The present data on mebendazole efficacy against hookworm infection are similar to those of another comparable study recently carried out on Pemba Island (ALBONICO et al., in press), though both CR and ERR were significantly lower than those reported in an efficacy trial carried out before the beginning of periodic chemotherapy in this population (ALBONICO et al., 1994). The possibility that this apparent reduction in mebendazole efficacy & due to emerging benzimidazole drug resistance means that the validation of pyrantel-oxantel as another broad spectrum, effective drug given as a single-dose may prove valuable in the development of strategies to delay the occurrence of anthelmintic drug-resistance (RAVIOLI et al., 1997). It would be advisable to repeat this efficacy trial in an area with high worm burden-and with less drug exposure, and to evaluate also the effect of both pyrantel-oxantel and mebendazole given in combination.

The results of this trial have significant implications for the use of targeted chemotherapy at the community and at school level for the control of STHs. Pyrantel-oxantel has been shown to have comparable efficacy to mebendazole (500 mg) in treating STHs, and to have a better efficacy in curing *T. trichiura* infections. Pyrantel-oxantel is available in Indonesia for targeted treatment of schoolchildren at a cost of only few US cents per tablet (A. Sasongko, personal communication) and competes with the very low cost of mebendazole as a generic product (ALBONICO et al., 1994). A possible disadvantage of pyrantel-oxantel \*is that patients need to be weighed, though the producing company does give alternative indications to treat based on weight and/or age. Furthermore, pyrantel-oxantel is not contraindicated in young children, and prescribing information indicates administration of 1 tablet of 150 mg to children between 6 months and 2 years. Pyrantel-oxantel is also available as a suspension containing 20 mg of each base drug (pyrantel pamoate and oxantel pamoate) per mL.

Further research is needed to better refine the spectrum of efficacy of pyrantel-oxantel against ST& in sub-Saharan Africa. For example, implementation of studies in areas of low endemic&, evaluation of the efficacy of pyrantel-oxantel at the -higher dosages (15-20 mg/kg) shown in Asia to be more effective (CABRER.& al., 1980), and assessment of combined treatment with pyrantel-oxantel and other single-dose anthelmintics, are some suggestions for work needed for scaling-up the use of pyrantel-oxantel in large-scale helminth control programmes.

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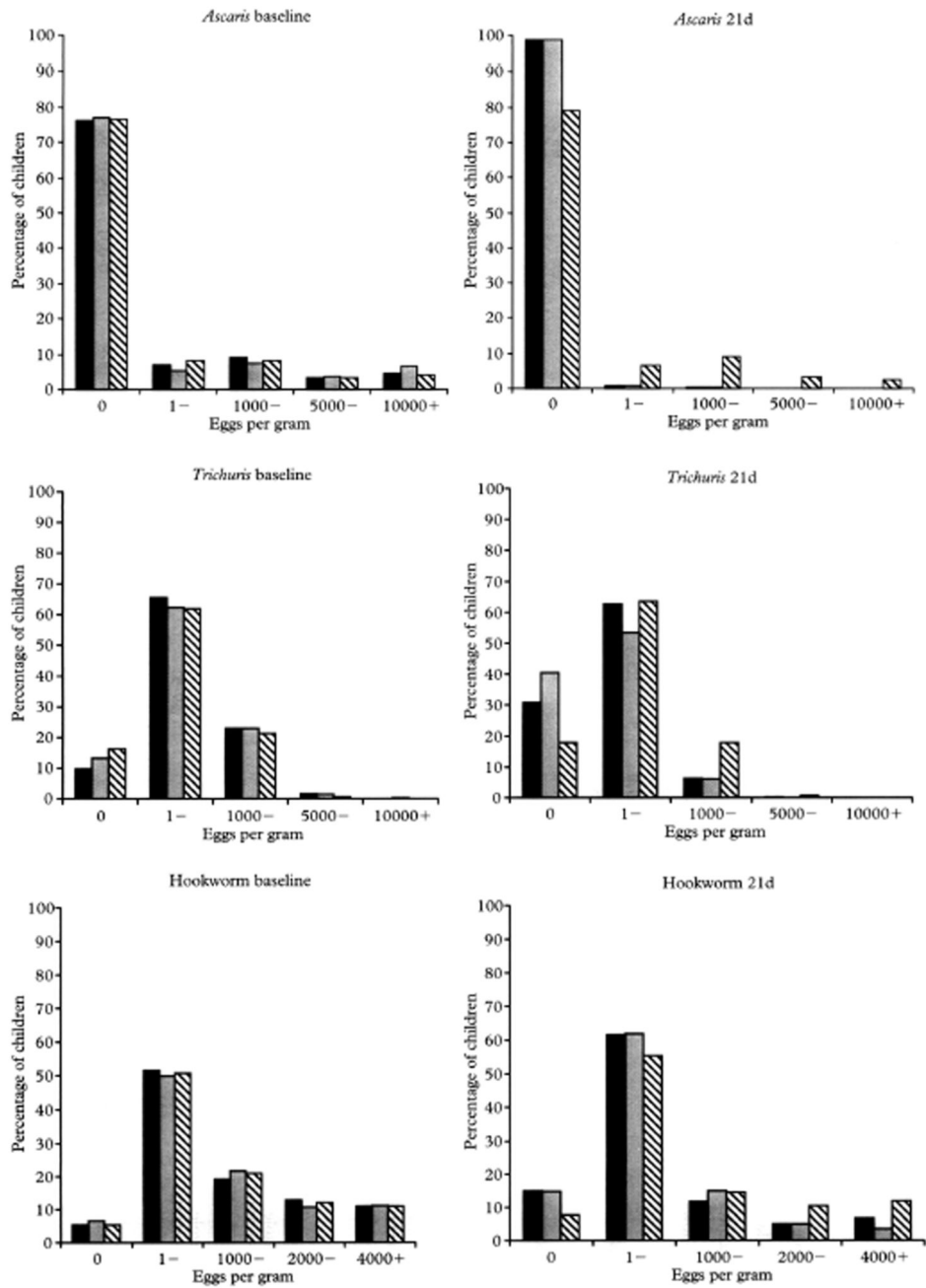
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**Figure.** Distribution of *A. lumbricoides*, *T. trichiura* and hookworms egg count before and 21 d after treatment with mebendazole, pyrantel oxantel and placebo.

**Table 1**  
**Baseline characteristics of children who provided a post-treatment stool sample at follow up compared to those children who were lost at follow up**

	Number of children	Age (year) (mean $\pm$ SD)	Sex (% boys)	Ascaris		Trichuris		Hookworm	
				Prevalence <sup>a</sup>	Egg count <sup>b</sup>	Prevalence <sup>a</sup>	Egg count <sup>b</sup>	Prevalence <sup>a</sup>	Egg count <sup>b</sup>
Mebendazole									
Sample	448	9.5 $\pm$ 1.9	46.4	23.9	5	90.2	257	94.6	588
Lost at follow-up	38	9.8 $\pm$ 2.1	63.2	42.1	29	94.7	329	92.1	745
<i>P</i>		NS	0.04	0.01	0.007	NS	NS	NS	NS
Pyrantel-oxantel									
Sample	440	9.5 $\pm$ 1.8	47.5	22.8	5	86.8	213	93.4	571
Lost at follow-up	38	9.4 $\pm$ 1.9	52.6	23.7	5	86.8	252	94.7	777
<i>P</i>		NS	NS	NS	NS	NS	NS	NS	NS
Placebo									
Sample	441	9.4 $\pm$ 1.5	39.9	23.4	5	83.7	163	94.6	573
Lost at follow-up	30	9.2 $\pm$ 1.4	50.0	23.3	4	90.0	200	93.3	571
<i>P</i>		NS	NS	NS	NS	NS	NS	NS	NS
Total									
Sample	1329	9.4 $\pm$ 1.3	44.6	23.4	5	86.9	208	94.2	577
Lost at follow-up	106	9.5 $\pm$ 1.4	55.7	30.2	9	90.6	260	93.4	701
<i>P</i>		NS	0.03	NS	NS	NS	NS	NS	NS

NS, Not Significant.

<sup>a</sup>Percentage positive.

<sup>b</sup>Eggs per gram expressed as geometric mean.

**Table 2**  
**Analysis of the efficacy of mebendazole, pyrantel-oxantel, and placebo against soil-transmitted helminths in 1329 schoolchildren on Pemba Island, September–October 2000**

	Number of children		Day 0		Day 21		Cure rate	Percentage reduction in prevalence	<i>P</i> (day 0/21)	ERR (95% CI) <sup>c</sup>	<i>P</i> (day 0/21)
	Prevalence <sup>a</sup>	Egg count <sup>b</sup>	Prevalence <sup>a</sup>	Egg count <sup>b</sup>	Prevalence <sup>a</sup>	Egg count <sup>b</sup>					
<i>Ascaris</i>											
Mebendazole	448	23.9	5	0.1	1.1	0.1	98.0	95.4	0.001	96.1 (94.3–97.9)	0.001
Pyrantel-oxantel	440	22.8	5	0.1	1.4	0.1	96.3	93.9	0.001	95.1 (92.3–97.9)	0.001
Placebo	441	23.4	5	4	21.1	4	27.9	9.8	NS	18.1 (–2.7–34.8)	NS
<i>Trichuris</i>											
Mebendazole	448	90.2	257	41	69.2	41	25.2	23.3	0.001	83.6 (79.1–87.2)	0.001
Pyrantel-oxantel	440	86.8	213	27	59.5	27	38.2 <sup>d</sup>	31.5 <sup>d</sup>	0.001	86.9 (82.2–90.3)	0.001
Placebo	441	83.7	163	129	82.1	129	11.7	1.9	NS	21.2 (–0.6–38.2)	NS
<i>Hookworm</i>											
Mebendazole	448	94.6	588	193	85.0	193	13.2	10.1	0.001	67.0 (58.5–73.8)	0.001
Pyrantel-oxantel	440	93.4	571	182	85.2	182	12.7	8.8	0.001	68.0 (59.2–74.8)	0.001
Placebo	441	94.6	573	466	92.3	466	6.2	2.4	NS	18.6 (–0.4–34.0)	NS

<sup>a</sup>Percentage positive.

<sup>b</sup>Eggs per gram expressed as geometric mean.

<sup>c</sup>Egg reduction rate 95% confidence interval.

<sup>d</sup>Different from mebendazole, *P* < 0.01.