

PARASITIC CO-INFECTIONS: DOES *ASCARIS LUMBRICOIDES* PROTECT AGAINST *PLASMODIUM FALCIPARUM* INFECTION?

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Abstract. A controlled randomized trial of antihelminthic treatment was undertaken in 1996–1997 in a rural area of Madagascar where populations were simultaneously infected with *Ascaris lumbricoides* and *Plasmodium falciparum*. Levamisole was administered bimonthly to 164 subjects, randomized on a family basis, whereas 186 were controls. While levamisole proved to be highly effective in reducing *Ascaris* egg loads in the treated group ($P < 10^{-3}$ at all bimonthly visits), subjects more than 5 years of age, treated with levamisole had a significant increase in their *P. falciparum* densities compared with controls ($P = 0.02$), whereas there was no effect of anti-helminthic treatment on children 6 months to 4 years of age. The demonstration of a clear negative interaction between *Ascaris* infection and malaria parasite density has important implications. Single community therapy programs to deliver treatments against several parasitic infections could avoid an increase of malaria attacks after mass treatment of ascariasis.

INTRODUCTION

In developing countries, people are simultaneously infected with several parasites as a general rule.^{1,2} These parasites interact with each other and probably have an important influence on the human immune system. Such interactions are difficult to study because they develop with time and probably induce different types of host responses, concerning different types of living organisms, such as protozoa or helminths.

Mixed infections have been mainly studied in animal models. Laboratory experiments have led to conflicting results (e.g., in protozoa-helminth co-infections in mice). Some studies suggested a facilitating effect of *Schistosoma* on *Plasmodium* infection,³ and others suggested a suppressive effect.⁴

The suppression or facilitation of one infection by another is even more difficult to evidence in humans where there is no possibility to control the burden of parasites. Observational studies in exposed populations^{5,6} or selected treatments of limited numbers of patients co-infected with *Ascaris lumbricoides* and *Plasmodium falciparum*⁷ have shown either a negative (i.e., protective effect) or a positive interaction. Recently, we showed in Senegalese children that light infections with *Schistosoma haematobium* were associated with lower *P. falciparum* densities than in children not infected with schistosomes.⁸

Randomized clinical trials represent a far better alternative to observational studies: significant decreases in the prevalence and the burden of a specific parasite can be obtained by means of a selective treatment, and their effects on the remaining parasites can be observed.

The island of Madagascar is a convenient setting for such trials, because a large variety of pathogens is likely to simultaneously infect human populations. Their spatial distributions differ according to environmental factors, mainly climate and altitude. For instance, malaria is hyperendemic in the hot and humid coasts, at low altitude, and scarce on the central plateaux, because of a cool and dry climate, and an-

nual indoor spraying of Dichloro-Diphenyl-Trichloroethane (DDT) carried out from 1993 to 1998. Conversely, geohelminths such as *Ascaris* are particularly abundant at high altitudes.⁹ Schistosomes (particularly, *Schistosoma mansoni*) are distributed within well-delimited clusters.

We report here a randomized trial of anti-helminthic treatment in a midwestern village mainly affected by malaria and ascariasis, two of the most widely distributed parasitic diseases in the world. The main objective was to evaluate the effect of *Ascaris*-reduced prevalence and egg load on patients exposed to *P. falciparum* infection and to find evidence for antagonistic or synergistic interactions between these two parasites.

MATERIALS AND METHODS

Study area. Our study was conducted in the highland village of Ambohimena (altitude 1,040 m), located 300 km southwest of Antananarivo, at the fringe of the malaria epidemic zone, outside the zone covered by routine DDT house-spraying (Opération de Pulvérisation Intra-Domestique de DDT [OPID]). It is a hilly area, where rice is cultivated in hollows. The climate is tropical, with a hot and humid season from November to April and a cool and dry season from May to October. *A. lumbricoides* and *Plasmodium* sp. are the main parasites affecting the human population. Malaria is mesoendemic, and transmission occurs mainly from January to June.¹⁰ Because of this limited duration of transmission, the acquisition of an immune protection is relatively slow among populations, and asymptomatic carriage of malaria parasites concerns mainly adults. Helminths are transmitted all year round in the study area.

Study population and protocol. Inhabitants and families were identified by the 1995 national census. Families were randomly allocated to a treatment or control group, and inclusion of new families was stopped after the third visit. All eligible subjects were orally informed of the study protocol and, when consent was given, they were included in their family group. There was no blinding in the treatment assignment. For practical and ethical reasons, infants less than 6 months of age were excluded from the study. Because of unproven innocuousness of levamisole during pregnancy, pregnant women ($N = 13$) were also excluded from the study. Eligible subjects seen after the onset of the study (newcomers

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to the village or babies having reached 6 months of age) were included in their family group.

On inclusion, questionnaires were filled for each subject. In particular, information was obtained on age, sex, notion of ongoing pregnancy or clinical symptoms such as diarrhea or fever in the preceding days, intake of drugs, or recent migration outside the study area.

From June 1996 to October 1997, all village residents were visited by investigators every 2 months (nine visits for the whole duration of the study). The main objective of this follow-up was to combine the observation of an entire malaria transmission season and the repeated treatment of intestinal helminths at intervals adapted to the life cycle of *Ascaris* (8 weeks from egg ingestion until sexual maturity of adult worms). At each visit, included subjects were clinically examined and stool and blood samples were taken for malaria parasites and helminth search. Updating of questionnaires was also done on the same occasion. In addition, subjects belonging to the treated group were administered an anti-helminthic single-dose oral treatment of levamisole (3 mg/kg in children, 150 mg in adults) under control of the investigators. At each visit, a multivitamin treatment (1/2 to 3 tablets every 2 months, each tablet containing 2500 IU vitamin A, 1.0 mg thiamine, 0.5 mg riboflavine, 7.5 mg nicotinamide, and 300 IU vitamin D3) was given to subjects from the control group. All villagers infected with malaria parasites and presenting clinical symptoms (temperature > 38°C) were treated with oral chloroquine (25 mg/kg in 3 days). At the end of the study, all the population (both treated and control groups) received a curative dose of mebendazole (500 mg, single oral intake), which is an efficacious treatment of most intestinal nematodes.

The protocol was given ethical approval by the Madagascar Ministry of Health (Direction de la Lutte contre les Maladies Transmissibles).

Biologic methods. Stool samples were processed by the merthiolate iodine formalin (MIF) concentration method on a calibrated amount of stool, which allows staining, concentration, and count of helminth eggs (*A. lumbricoides* as well as *S. mansoni* and *Necator americanus*).

At each visit, finger prick thick and thin blood smears were made on all subjects. Smears were stained with Giemsa and 100 oil-immersion microscopic fields were examined for malaria parasites. Parasites and white blood cells were enumerated, and parasite density was calculated according to an assumed average of 8,000 leukocytes/mm³.

Statistical analysis. We first performed a univariate analysis to compare the two groups on entering the study on the basis of general characteristics and prevalences and densities of the two main parasites (*P. falciparum* and *A. lumbricoides*). The χ^2 test was used to test differences in proportions, and Student *t* test or non-parametric Wilcoxon test was used to test differences in means.

We then examined malaria parasite density in relation to the treatment group. Only *P. falciparum* densities, which represented 93.2% of all diagnosed parasites, were analyzed. *P. malariae* accounted for 4.9% and *P. vivax/P. ovale* for 1.9% of single malarial infections. *P. falciparum* densities and helminth egg loads were log-transformed [$\log(DP + 1)$] to correct distribution asymmetry, which is usual in parasite infection data.

Because the study design was a randomized trial, we veri-

fied that subjects allocated to repeated anti-helminthic treatment and controls were similar for a number of variables (Table 1) that we did not take into account in further analyses.

Our aim was to show a difference between the two treatment groups. Because measures of malaria parasite densities were repeated (1–9 per individual; mean, 7.46) and subjects belonged to distinct families (60 families at the onset of the trial), data presented a typical nested structure involving three factors: treatment groups, families, and subjects. In this study, subject factor was nested within family factor, which in turn, was nested within treatment group factor. Finally, we performed an ANOVA on parasite density, where the nested factors family and subject were considered as random. Indeed, families and subjects could be considered as originating from a vaster population and allocated randomly to either treatment group. Thus, statistical inference was susceptible to be generalized to the whole population and not restricted to subjects included in the study.

Because there is generally a strong association between age and immunity to malaria, which in turn influences the parasite density in peripheral blood, we defined three age groups (6 months to 4 years, 5–14 years, ≥ 15 years), in which we tested the association between *P. falciparum* density and treatment group by a stratified analysis.

Finally, our analysis was performed using the following model:

$$Y_{ijk} = \underbrace{\beta_0 + \beta_1 X_i}_{\text{fixed effects}} + \underbrace{a_i + b_{ji} + e_{ijk}}_{\text{random effects}}$$

TABLE 1

Characteristics of treated and control subjects at inclusion (before anti-helminthic treatment, Ambohimena village, 1997)

	Treated (N = 164)	Controls (N = 186)	P
Age (years)			
0–4	31	36	
5–14	42	51	0.91*
15 and over	91	99	
Sex			
Male	85	86	0.30*
Female	79	100	
Family			
Number	28	32	—
Mean no. of subjects/family	5.9	5.8	0.35†
<i>Ascaris lumbricoides</i>			
No. infected subjects	43	51	0.80*
Prevalence rate	26.2%	27.4%	
Mean egg load	1.19	1.35	0.51‡
<i>Plasmodium falciparum</i>			
No. infected subjects	51	42	0.07*
Prevalence rate	31.1%	22.6%	
Mean parasite load	1.82	1.35	0.11‡
<i>Schistosoma mansoni</i>			
No. infected subjects	12	18	0.43*
Prevalence rate	7.3%	9.7%	
Mean egg load	0.21	0.30	0.35‡
<i>Necator americanus</i>			
No. infected subjects	12	21	0.20*
Prevalence rate	7.3%	11.3%	
Mean egg load	0.18	0.29	0.21‡

* χ^2 test.

† Wilcoxon test.

‡ Student *t* test.

with $a_i \sim N(0, \sigma_a^2)$ (between-family variation); $b_{ji} \sim N(0, \sigma_b^2)$ (between-subject within-family variation); $e_{ijk} \sim N(0, \sigma_e^2)$ (within-subject within-family variation); and Y_{ijk} is the k th log ($P. falciparum$ density + 1) for subject j from family i .

This model has two fixed parameters that were as follows: for β_0 , the overall mean of $P. falciparum$ density (log-transformed), and for β_1 , the effect of treatment of *A. lumbricoides* and three random effects variances that need to be estimated.

We estimated the mixed model parameters with PROC MIXED SAS procedure (SAS Institute, Cary, NC).

RESULTS

Study population. Three hundred fifty subjects belonging to 60 families were enrolled in the study. After a random sampling of families, 164 subjects were assigned to the treated group, and 186 were controls. The two groups were compared on the basis of age, sex, number and size of families, and parasite infections (*P. falciparum*, *A. lumbricoides*, *S. mansoni*, and *N. americanus*). Table 1 shows that, on entering the study, no significant difference between the two groups was recorded for any of these variables. However, although not significant, malaria prevalence and parasite density seemed to be slightly lower in the control group.

During the follow-up, we lost contact with 9 subjects after the first visit (5 in the treated group and 4 in the control group), and we excluded from the analysis three families totaling 14 subjects that had been enrolled 1 year after the beginning of the trial and thus followed-up for a short duration (< 6 months).

At each visit, depending on the month, 0–9 subjects (mean, 3.7) in the control group and 0–11 (mean, 4.2) in the levamisole-treated group presenting with fever and parasitemia received oral chloroquine treatment. An overall proportion of 2.5% (control group) and 3.3% (treated group) received chloroquine. The maximum number of treated subjects was between February and June 1997, during the malaria transmission season.

Effect of levamisole treatment on *Ascaris* and other helminths. At their inclusion in the study, all subjects from the treated group received a therapeutic dose of levamisole, which was repeated on each visit. By the end of the study, each of them had received an average of 7.4 intakes.

As shown on Figure 1A, *Ascaris* egg loads immediately collapsed after the first visit in the treated group, whereas they persisted at a high level throughout the follow-up in the control group (all $P < 0.001$ for each visit between the two groups). Prevalence rates followed a similar pattern (Figure 1B). However, it is noticeable that both prevalence and egg load progressively increased after 1 year of follow-up, which could be caused by a phenomenon of resistance to the administered treatment. Because a similar tendency was observed in the control group, a seasonal relapse in the transmission of intestinal helminths during the August to October period cannot be excluded in the whole population, even if no climatological data support this hypothesis.

With regard to *S. mansoni* and *N. americanus*, there was no difference between groups for egg loads or prevalence at any of the nine visits (all $P > 0.05$, data not shown).

Effect of anti-helminthic treatment on plasmodial infection. Mean *P. falciparum* densities in the treatment groups

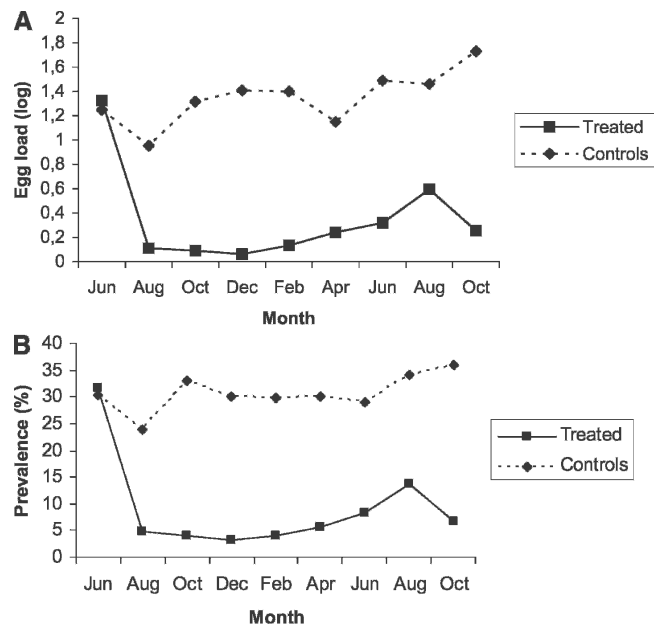


FIGURE 1. (A) Mean egg loads (*A. lumbricoides*, log-transformed) and prevalence rates in treated and control groups during the follow-up, Ambohimena, 1997. (B) Prevalence rates.

are shown in Figure 2 for each age group (Figure 2A: 6 months to 4 years; Figure 2B: 5–14 years; Figure 2C: ≥ 15 years). There were strong seasonal fluctuations on all three graphs, as parasite densities peaked in the humid season, between March and May, and decreased in the coldest and driest months, August to October (1996 and 1997). There also seemed to be an overall decrease in the mean parasite density in the oldest age group, confirming the strong influence of age (and immune status) on malaria infection. Treatment and control groups varied in similar ways, with a tendency to higher densities in the treated group, which was particularly pronounced in the two classes of 5–14 and ≥ 15 years of age.

Mixed model analysis (Table 2) confirmed that subjects more than 5 years of age, treated with levamisole, had a significant increase in their *P. falciparum* densities compared with controls ($P < 0.05$ for age classes 5–14 and ≥ 15 years). The potential effect of treatment on parasite density was roughly equivalent in these two age groups (ratio treatment/intercept effect of 0.5 for 5–14 years, and 0.6 for ≥ 15 years). Indeed, treatment estimates, but also baseline parasite densities were higher in younger children (0.96 and 1.88 for 5–14 years and 0.34 and 0.54 for ≥ 15 years respectively). We thus pooled the two last age groups to estimate an average increase for these subjects and included an age binary variable in the model, because *P. falciparum* density baseline values differed between groups. In this latter model, no interaction was found between age and effect of treatment ($P = 0.11$). The overall estimates in this broader age class showed a higher effect of treatment on *P. falciparum* density ($P = 0.018$; Table 2). There was no effect of levamisole treatment on children 6 months to 4 years of age.

Mixed model analysis also confirmed the overall decrease in the *P. falciparum* density baseline with age, with an intercept estimate of 2.66 in the youngest children, decreasing to 2.03 (0.49 + 1.54) in the intermediate age group and to 0.49 for the oldest subjects (≥ 15), which probably indicates the pro-

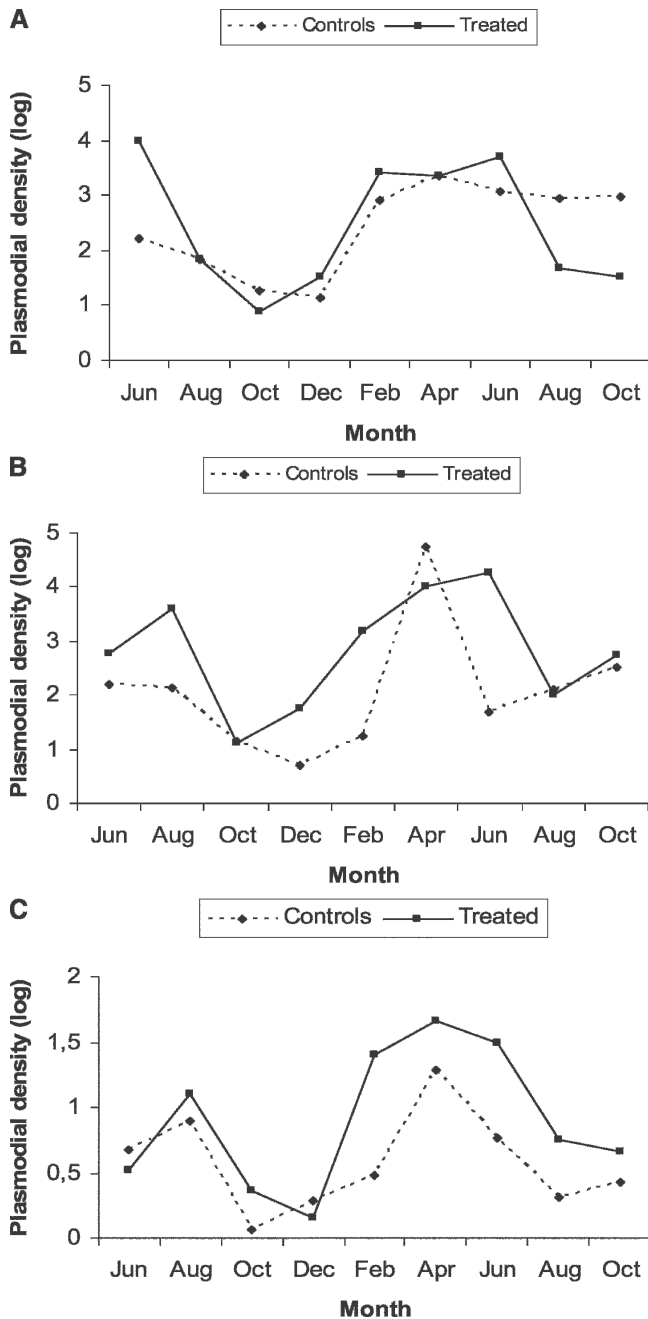


FIGURE 2. Mean parasite densities (*P. falciparum*, log-transformed) in treated and control groups by age group during the follow-up, Ambohimena, 1997. (A) Subjects 6 months to 4 years of age. (B) Subjects 5–14 years of age. (C) Subjects ≥ 15 years of age.

gressive build-up of an adequate immune control of parasitemia in older children.

DISCUSSION

The study of parasite co-infections has led to conflicting results. We previously showed a negative interaction between *P. falciparum* and *S. haematobium* light infections,⁸ and another team in Senegal found a synergistic effect between *P. falciparum* and *Schistosoma mansoni* for high *S. mansoni* egg loads only.¹¹ Concerning *Ascaris* infections, a protective ef-

TABLE 2

Relation between *P. falciparum* density (log-transformed) and treatment of *A. lumbricoides* in different age groups. Ambohimena, 1997

Age (years)	Effect of treatment (95% CI)	P*	Intercept† (95% CI)	P†
0–4 (N = 61)	-0.44 (-1.49–0.61)	0.415	2.66 (1.95–3.38)	< 0.0001
5–14 (N = 88)	0.96 (0.04–1.88)	0.047	1.88 (1.26–2.52)	< 0.001
15 and over (N = 178)	0.34 (0.01–0.67)	0.049	0.54 (0.31–0.77)	< 0.001
5 and over‡ (N = 266)	0.58 (0.10–0.95)	0.018	0.49 (0.18–0.80)	0.003

* One-way nested repeated-measures ANOVA.
 † Intercept = baseline parasite density within the age group. Test of intercept to 0.
 ‡ Pooling of 5–14 and > 15 classes. An age binary variable was added to the model (the estimate parameter is equal to 1.54).

fect on particular clinical forms of human malaria, such as cerebral malaria or acute renal failure, had been suggested by Nacher et al.^{5,6} Another recent study led to opposite results, showing a facilitating effect of *Ascaris* on severe malaria.¹²

We performed the first controlled clinical trial of anti-helminthic treatment, and we showed a clear negative interaction between *Ascaris* infection and malaria parasite density in children more than 5 years of age. Because these results seem to be quite convincing of a protective effect of *Ascaris* on malaria, we are in complete disagreement, for these two particular parasites at least, with a recent paper that dealt with the consequences on malaria control of a positive interaction (i.e., a facilitating effect), between *Plasmodium* and all kinds of worms considered as systematic in endemic areas.¹³

Because the study design was a randomized trial and not an observation study and the data were analyzed as “intention to treat,” we are quite confident that no major bias could interfere with our results and that it is indeed the effect of anti-helminthic treatment that led to an increase in malaria parasite density. It is noteworthy that the slight difference (although not significant) in malaria parasite densities observed between the groups at entry (before anti-helminthic treatment) vanished in the age classes (5–14 and ≥ 15 years), where a protective effect was shown.

It was rather logical that no effect was found in children 0–4 years of age, because in areas such as the Madagascar highlands where malaria is mesoendemic, it takes a few years of exposition to malaria to establish a stable immune response and an equilibrium between the two parasites.

In our study, *P. falciparum* and *A. lumbricoides* were the predominant, but not the only, parasites found in the followed up patients. We cannot categorically exclude that other helminths, such as *S. mansoni* or *N. americanus*, may have interfered with the two main parasites. However, because the two treatment groups were randomized, one can expect (and it can be verified in Table 1) that these two parasites were evenly distributed in each arm.

To our knowledge, levamisole has no efficacy on the treatment of trematodes. There is no particular reason for a selective interaction of *S. mansoni* with either of the groups. The situation is somewhat different with *N. americanus*, which is sensitive to the same drugs as *A. lumbricoides*, but at much higher doses. Nevertheless, there was no difference in either prevalence or egg loads between treatment groups for any of these parasites at each visit after inclusion. Therefore,

we do not think that these infrequent helminths interfered in our study population with *P. falciparum*–*A. lumbricoides* interaction.

We do not think that the intakes of drugs, other than anti-helminthics, had any effect on our results. Chloroquine was given in a similar way to both groups (2.5% of subjects in the control group versus 3.3% in the levamisole-treated group, $P = 0.21$) and concerned only a limited number of individuals. As for multivitamins, doses were very low and certainly unable to boost the immune system of control subjects.

From a pathogenic point of view, an explanation to such an interaction may be found in the immunomodulation generated by both parasites, particularly the effects of cytokines controlling the orientation toward the Th1 or the Th2 arm of the immune response. *Schistosoma* and *Plasmodium* are known to induce a Th2-like response, and a strong correlation has been recently shown between malaria- and schistosome-specific IgG3 responses in individuals from Kenya, Uganda, and the Sudan, indicating a cross-reactivity between helminths and plasmodia that could confer a protection to schistosome-infected subjects exposed to malaria.¹⁴ A similar phenomenon could be involved in *A. lumbricoides* and *P. falciparum* co-infections, as suggested by the demonstration of a reactivity of patients with *A. lumbricoides* to schistosome antigens.¹⁵ Other immunologic mechanisms, such as the inhibition of dendritic cell maturation by *P. falciparum*-infected erythrocytes,¹⁶ have also been put forward. Last, because such interactions between parasites are probably the outcome of several complex mechanisms, genetic susceptibility/resistance of the host may play a role, as suggested by the location in the same genetic region of loci controlling the levels of *S. mansoni* and *P. falciparum* infections.^{17,18}

There have been millions of years of host–parasite co-evolution, and it is not surprising that parasites have developed mechanisms to facilitate or to prevent host invasion by other infectious agents, even if such phenomena are difficult to show. From a public health point of view, positive or negative interactions may have crucial importance. Each pathogen, considered separately, contributes to the health weakening of exposed populations, especially in children. In the case of multiple infections in the same individuals, positive or negative interactions between parasites may have unexpected consequences on the efficacy of systematic treatments of parasites like helminths, such as an increase of malaria attacks after mass treatment of ascariasis.⁷ The advantage of using a single community therapy program to deliver treatments against several parasitic infections should be assessed after taking into account these considerations.

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