Effect of albendazole treatments on the prevalence of atopy in children living in communities endemic for geohelminth parasites: a cluster-randomised trial

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Summary

Background **Epidemiological studies have shown inverse associations between geohelminth (intestinal helminth) infection and atopy, leading to the suggestion that geohelminths might protect against allergy. Periodic deworming of school children with anthelmintics is a widely implemented intervention and has raised concerns that such programmes could increase allergy. We investigated the effect of repeated anthelmintic treatments with albendazole over 12 months on the prevalence of atopy and clinical indices of allergy.**

Methods **We did a cluster-randomised controlled trial in schoolchildren from 68 rural schools. Children were randomly assigned by school to either albendazole (34 schools, 1164 children) every 2 months for 12 months, or to no intervention (34 schools, 1209 children). The intervention schools received a total of seven albendazole treatments. The primary outcome was atopy at 12 months (allergen skin-test reactivity), and analysis was by intention-to-treat for whole-school analyses and per protocol for children. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN61195515.**

Findings **Data for analysis were available for all schools and from 67·4% (784 of 1164) and 70·1% (848 of 1209) of children in albendazole and no-treatment groups, respectively. Albendazole treatment caused large reductions in geohelminth prevalence over the study period (adjusted odds ratio 0·13, 95% CI 0·09–0·19, p<0·001), but there was no evidence that treatment was associated with an increase in atopy prevalence (0·97, 0·68–1·39, p=0·862), or clinical allergy (wheeze, 1·07, 0·54–2·11, p=0·848) in the albendazole compared with the no-treatment group.**

Interpretation **We saw no increase in the prevalence of atopy or clinical allergy associated with albendazole treatment. Deworming programmes for schoolchildren are unlikely to be accompanied by an increase in allergy.**

Introduction

Illness caused by the geohelminth parasites *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm is an important cause of disability in poor regions of the tropics, where such parasites are estimated to infect around 2 billion people.[1] In 2001, the World Health Assembly endorsed a strategy for the control of geohelminth infections and associated morbidity through the regular treatment of high-risk groups, particularly school-age children.[2] In line with these political developments, national governments and donor organisations such as the World Bank have prioritised anthelmintic treatment programmes for school-age children.[3]

A causal inverse association has been proposed between geohelminths and allergy because of the low prevalence of allergic disease seen in areas where geohelminth infections are highly prevalent.[4] Many epidemiological studies have investigated the relation between geohelminths and allergy and have provided conflicting evidence for an association,[4] with some studies showing a strong inverse relation between geohelminth infections and prevalence of allergy symptoms[5,6] or atopy.[7–9] Small intervention studies have suggested that anthelmintic treatment might increase the prevalence[10] and incidence[11] of atopy. Whether programmes of repeated anthelmintic treatments targeted at schools might have the adverse effect of increasing atopic reactivity and allergic disease remains to be established.

We have shown that geohelminth infections are inversely associated with risk of skin-test reactivity to allergens in children attending rural schools in Ecuador.[12,13] We postulated that geohelminth infections were suppressing skin-test reactivity to aeroallergens on the basis of a biological model in which helminth infections might inhibit actively allergic effector responses including immediate hypersensitivity.[14] We therefore did a cluster-randomised trial to establish the effect of anthelmintic treatments every 2 months for 12 months on the frequency of atopy and indices of clinical allergy in schools where the prevalence of geohelminth infections is high.

Methods

Study area and participants

The study was done between June 21, 2002, and Aug 24, 2004, in 68 rural schools in adjacent districts of Pichincha Province, Ecuador, where we have reported previously an inverse relation between risk of atopy and geohelminths.[12,13] The study area is a tropical and sub-tropical region at

altitudes between 126 and 1730 metres. All rural schools located within the study area, with fewer than 150 children, with road access during the wet season, and where initial meetings to explain the purpose of study were attended by most parents, were eligible. All children attending the second to seventh year of primary education in the schools were eligible. Informed written consent for participation of each child in the study was obtained from a parent. The study protocol was approved by the ethics committees of the Hospital Pedro Vicente Maldonado, Ecuador, and St George's Hospital, UK.

Study design

The design of the study was prospective cluster-randomised. Schools were randomly assigned to children receiving either albendazole every 2 months for a year or no treatment. A cluster design allowed mass treatment of schools and households of study children. We did not have a placebo comparison group because mothers cannot be masked to the deworming effects of albendazole. Because anthelmintic treatment might provide substantial health benefits to children,[1] mothers were told that participation in the study should not prevent them from giving children deworming medication if this was their usual practice. All eligible children attending albendazole-allocated schools received seven directly supervised doses of 400 mg albendazole, each dose spaced every 2 months in schools. Additionally, at all treatments a parent of every child was given sufficient albendazole to treat the whole family, except for children younger than 2 years or pregnant women. All children (including those in control schools) received one dose of 400 mg albendazole at the end of the study. To maintain parental and child compliance and continued participation in the control groups, all schools were visited every 2 months and health talks given separately to parents and children. The trial is reported in accordance with the CONSORT guidelines for cluster-randomised studies.[15]

Outcomes were at the individual and cluster levels. The primary outcome was the proportion of children with atopy at 12 months and secondary outcomes were the proportion of children with allergy symptoms, clinical evidence of flexural dermatitis, and exercise-induced bronchospasm at 12 months.

Numbered random-allocation sequences were generated in blocks of ten by computer (CLINSTAT software) by JMB. An experienced physician (MEC) enrolled all participants, measured all study endpoints, and was kept masked to treatment allocation of schools. The allocation was provided in serially numbered sealed envelopes to the treatment coordinator (MGV) who opened the correspondingly numbered envelope after baseline assessments were completed. The first albendazole treatment was provided by the treatment coordinator within a week of completion of initial assessments. To maintain masking, the treatment coordinator and assessment team worked independently. The assessment team visited the study communities on two occasions to assess outcomes at baseline and the end of the study.

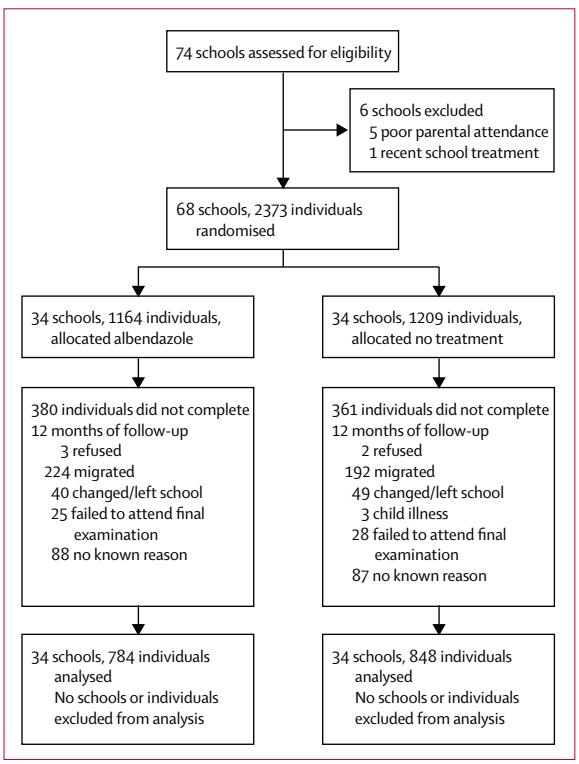

Figure 1: **Trial profile**

Assessments were done at 0 and 12 months. Skin-prick testing was done to mixed mite extract (*Dermatophagoides pteronyssinus* and *D farinae*; Greer Laboratories, Lenoir, NC, USA), *Alternaria tenuis* (Greer), American cockroach (Greer), cat (Greer), grass pollen mix (Greer), tree pollen (Greer), histamine (ALK-Abello, Horsholm, Denmark), and saline (ALK) controls. Allergens were pricked onto the volar surface of the forearm, and reactions recorded after 15 min. Reactions were positive if mean diameter was at least 3 mm greater than for saline. Atopy was defined as a positive reaction to any allergen. All skin testing was done by a skilled supervisor (MC), and the same allergen lots were used with expiration dates beyond the end of the study. Skin-prick testing and the reading of skin reaction sizes by MC were assessed periodically by PC through assessment of skin-testing technique to ensure that standardised methods were used. A pretested and validated questionnaire[16] that included the core questions on allergy symptoms of the ISAAC phase II studies[17] was distributed to the parents. Children were examined for flexural dermatitis with the ISAAC phase II protocol.[17] Exercise-induced bronchospasm and measurement of peak expiratory flow rate were done as previously reported.[18] Falls of 15% peak flow were regarded as indicating the presence of exercise-induced bronchospasm. Three stool samples were obtained (0, 6, and 12 months), with

the final sample taken immediately before the seventh treatment. Stools were examined with the modified Kato-Katz and formol ethyl acetate concentration methods.[19] Procedures for ensuring standardisation of stool examinations consisted of routine examination of a random sample of 10% of all slides by an independent supervisor. Geohelminth infection was defined by the presence of eggs of any of *A lumbricoides*, *T trichiura*, or *Ancylostoma duodenale*, or larvae of *Strongyloides stercoralis* in stool samples. The geometric mean intensity of infected individuals was measured as eggs per gram (epg) of faeces. The sensitivity of the Kato-Katz method for quantification of infection intensities was 70 epg.

Statistical analysis

Estimation of sample sizes took into account clustering within schools. From earlier data, the intraclass correlation coefficient was estimated as 0·03 (SD 0·01) with data from 55 schools,[12] and the design effect was three,[20] with an average cluster size of 52 children. The intraclass correlation coefficient was calculated by one-way analysis of variance with atopy as the unit of analysis and school as the factor. The unclustered sample size was based on the assumption that the prevalence of atopy in geohelminth-infected children would revert to that of uninfected children (18·7–28·4%),[12] and was thought conservative because a previous intervention study had shown a four-fold increase in prevalence of skin-test reactivity after anthelmintic treatment (eg, from 17% to 68% for house dustmite).[10] To detect a 52% increase in atopy prevalence, a study with 80% power and significance of $p<0·05$ would need a sample of 910 children in an area with 69% prevalence of geohelminths.[12] A total sample size of 2730 children was needed from 52 schools, taking into account the design effect. The cluster sample size was increased to 68 to allow for a school dropout rate of 25%. Intention-to-treat analyses were used for whole-school analyses. Risks for individual-level analyses were computed by logistic regression, allowing for clustering by school with robust standard errors. For adjusted analyses, appropriate baseline endpoint data, and the a priori confounder variables[16] age, sex, socioeconomic status, and overcrowding were included in the models. Socioeconomic status was calculated as a score based on paternal and maternal education and occupation, and material goods in the household. Cluster-level analyses for atopy were done with a weighted two-sample t test between the two groups of schools.[20] Analyses were done with Stata version 7.0 using the survey and cluster functions.

	Albendazole schools		No-treatment schools	
	All children (n=1164)	Analysed children (n=784)	All children (n=1209)	Analysed children (n=848)
Characteristic				
Age (years) (SD)	9·6 (2·0)	9·3 (1·8)	9·8 (2·1)	9·5 (1·9)
Sex				
Boy	603 (52%)	394 (50%)	638 (53%)	444 (52%)
Girl	561 (48%)	390 (50%)	571 (47%)	404 (48%)
Socioeconomic status (SD)	2·2 (1·0)	2·1 (1·0)	2·3 (1·0)	2·4 (1·0)
Crowding (people per room; SD)	2·6 (1·1)	2·6 (1·2)	2·6 (1·2)	2·6 (1·2)
Geohelminth infections*†				
Any geohelminth	793 (69%)	543 (70%)	886 (75%)	622 (74%)
A lumbricoides	590 (52%)	409 (53%)	702 (59%)	491 (59%)
Intensity	7030 (70–365 750)	6634 (70–270 130)	7176 (70–442 260)	7631 (70–442 260)
T trichiura	602 (53%)	416 (54%)	686 (58%)	480 (57%)
Intensity	604 (70–66 220)	608 (70–66220)	606 (70–81 270)	639 (70–81 270)
A duodenale	158 (14%)	87 (11%)	180 (15%)	113 (13%)
S stercoralis	19 (2%)	13 (2%)	18 (2%)	13 (2%)
Atopy				
Any allergen	287 (25%)	182 (23%)	293 (24%)	196 (23%)
House dustmite	106 (9%)	73 (9%)	102 (8%)	66 (8%)
Cockroach	215 (18%)	138 (18%)	183 (15%)	130 (15%)
Grass	44 (4%)	28 (4%)	51 (4%)	31 (4%)
Fungi	2	2	2	2
Alternaria	1	1	2	2
Cat	6 (1%)	6 (1%)	6	5 (1%)

Range shown in parentheses. *Denominators for stool examinations for all children were 1144 and 1187 for albendazole and no treatment schools, respectively. †Denominators for analysed children were 773 and 836 for albendazole and no-treatment schools, respectively. Percentages rounded to nearest whole number.

Table 1: **Baseline characteristics**

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. We recorded no adverse events relating to albendazole treatment. 74 schools were approached for inclusion, and six were excluded before baseline assessments because too few parents attended initial community meetings (five schools) and because of recent mass anthelmintic treatment (one). The average cluster size (range) was 35·5 (14–91) children in no-treatment and 34·3 (12–77) in albendazole schools. The design resulted in a similar distribution of baseline variables between the two treatment groups (table 1). All schools completed follow-up and 741 (31·2%) of 2373 children were lost to follow-up (29·9% of children in no-treatment and 32·6% in albendazole schools). 67 children moved between schools during the study. The baseline characteristics of children lost, and those completing follow-up were similar except for age (mean 10·4 [SD 2·3] years for children lost *vs* 9·4 [1·8] for those followed-up), hookworm prevalence (19·1% *vs* 12·4%) and atopy prevalence (27·3% *vs* 23·2%) in children lost indicating the greater likelihood of older children leaving schools. The intraclass correlation coefficient for atopy in this study for the 2373 children attending 68 schools was 0·01 (95% CI 0–0·03).

Adherence to the protocol was assessed from the number of treatments given to each child in the albendazole group and by questionnaire in the no-treatment group. The number of children receiving anthelmintic treatments in the albendazole group were: no treatment (none), one to four (22, 2·8%), five (12, 1·5%), six (33, 4·2%), and seven treatments (717, 91·5%); and for the no-treatment group were: no treatment (347, 40·4%), one (252, 29·7%), two (178, 21·0%), three (61, 7·2%), and four or more (ten, 1·2%). Treatments received by children in the no-treatment group were purchased directly by parents, distributed to schools through the Ministry of Education, or obtained through physician consultations. A high proportion of children in the albendazole (918 [78·9%] of 1164) and no-treatment (972 [80·4%] of 1209) schools had received anthelmintic treatment during the 6 months before the study, with a mean time from last anthelmintic treatment being much the same in albendazole and no-treatment groups (mean 4·4 [SD 3·4] *vs* 4·2 [3·2], respectively).

A pronounced fall in geohelminth prevalence was seen in the albendazole group (any geohelminth 69·3% at baseline *vs* 20·5% at 12 months; *A lumbricoides* 51·6% *vs* 4·1%; *T trichiura* 52·7% *vs* 18·3%; *A duodenale* 13·8% *vs* 0%; and *S stercoralis* 1·6% *vs* 0·3%) and declined slightly in the no-treatment group (any geohelminth 74·6% *vs* 65·7%; *A lumbricoides* 59·1% *vs* 42·6%; *T trichiura* 57·8% *vs* 52·2%; *A duodenale* 15.2% *vs* 9·6%; and *S stercoralis* 1·6% *vs* 2·2%). The treatment effect (albendazole *vs* no-treatment) on geohelminth prevalence was highly significant: any geohelminth (adjusted odds ratio 0·13, 95% CI 0·09–0·20, p<0·001); *A lumbricoides* (0·06, 0·04–0·11, p<0·001); *T trichiura* (0·17, 0·12–0·25, p<0·001); and *S stercoralis* (0·12, 0·03–0·54, p=0·005), indicating that repeated albendazole treatments were highly effective in reducing geohelminth prevalence. No infections with *A duodenale* were detected in the albendazole group at 12 months.

There was an inverse relation between geohelminth infection and skin-test reactivity to allergens at baseline (age-adjusted and sex-adjusted odds ratio 0·78, 95% CI 0·65–0·95, p=0·013) and in the no-treatment group at the end of the study (0·72, 0·47–1·11, p=0·129). These estimates are similar to age-adjusted and sex-adjusted odds ratios from previous cross-sectional studies in school-age children in the same area.[12,13] Further adjustment of the relation between allergen skin-test reactivity and geohelminth infection for overcrowding and socioeconomic status had little effect on the odds ratio (0·83, 0·68–1·02, p=0·078). The size and precision of the baseline odds ratio did not alter after adjustment for anthelmintic treatment.

We recorded no evidence of an increase in prevalence of atopy in children receiving albendazole (treatment effect for any allergen 0·97, 0·68–1·39, p=0·862), and no evidence for a treatment effect for skin-test reactivity to house dustmite, cockroach, and grass pollen (table 2). To control for non-random differences between children lost and those who completed follow-up that could have affected the study findings, we identified baseline factors predictive of losses to follow-up and adjusted the analysis for these factors. The only factors that significantly predicted losses to follow-up were age and prevalence of hookworm at baseline. Adjustment for such prevalence did not greatly affect these estimates of effect (for example, treatment effect for any allergen, 0·99, 0·69–1·43, p=0·970). School-level analyses gave identical values for outcome prevalences (atopy and secondary outcomes in table 2) as individual analyses, and none of the differences between intervention groups were significant apart from skin-test reactivity to *Alternaria* (p=0·043).

Subgroup analysis excluding children not infected with geohelminths at the beginning of the study showed no-treatment effect on the risk of atopy (1·03, 0·68–1·55, p=0·887). Analysis of the effect of treatment on the incidence of atopy showed that 42 (7%) of 602 of non-atopic children in the albendazole group became atopic over 12-months, and a similar proportion of non-atopic children (49 [7·5%] of 652) in the no-treatment group became atopic (treatment effect, 0·95, 0·61–1·48, p=0·826). Per protocol analysis of children in the albendazole group receiving five doses or more of albendazole (n=762) and children in the no-treatment group receiving no treatments (n=347) showed no treatment effect on atopy risk (1·03, 0·65–1·64, p=0·894).

	Albendazole (n=784)	No treatment (n=848)	Univariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Primary outcome						
Allergen						
Any	132 (17%)	144 (17%)	0·99 (0·70–1·39)	0·953	0·97 (0·68–1·39)	0·862
House dustmite	51 (7%)	46 (5%)	1·21 (0·70–1·95)	0·424	1·03 (0·58–1·85)	0·909
Cockroach	94 (12%)	101 (12%)	1·01 (0·70–1·46)	0·968	0·86 (0·60–1·25)	0·433
Grass	13 (2%)	21 (2%)	0·66 (0·30–1·49)	0·320	0·74 (0·31–1·74)	0·480
Fungi	3	2	..	..	..	..
Alternaria	4 (1%)	0	..	..	..	..
Cat	2	4	..	..	..	..
Secondary outcome						
Allergy symptoms						
Wheeze	22 (3%)	23 (3%)	1·04 (0·55–1·96)	0·915	1·07 (0·54–2·13)	0·848
Rhinitis/itchy eyes	17 (2%)	30 (4%)	0·60 (0·31–1·16)	0·130	0·59 (0·31–1·15)	0·107
Itchy flexural rash	30 (4%)	34 (4%)	0·95 (0·57–1·58)	0·851	0·88 (0·54–1·44)	0·606
Objective measures						
Flexural dermatitis	30 (4%)	35 (4%)	0·92 (0·56–1·53)	0·760	0·86 (0·53–1·39)	0·533
EIB	9 (1%)	14 (2%)	0·65 (0·24–1·80)	0·405	0·63 (0·23–1·69)	0·350

School-level analyses gave identical prevalences for primary and secondary outcomes. Shown are univariate and multivariate odds ratio. Multivariate analyses were adjusted for age, sex, socioeconomic status, crowding, and appropriate baseline outcome prevalence. EIB=exercise-induced bronchospasm.

Table 2: **Effect of albendazole treatment every two months on atopy and clinical allergy**

Anthelmintic treatment with albendazole did not affect the risk of allergy symptoms reported over the previous year (wheeze, rhinitis with itchy eyes, or itchy flexural rash), the prevalence of flexural dermatitis on clinical examination, or the risk of exercise-induced bronchospasm (table 2).

Discussion

Anthelmintic treatments with albendazole every 2 months for a year had no effect on the proportion of children with skin-test reactivity to aeroallergens or on the frequency of allergy symptoms or exercise-induced bronchospasm. This study is the largest published so far to examine the effect of anthelmintic treatment on atopy risk and provides evidence that an increase in allergy is unlikely to accompany deworming programmes.

Several potential limitations exist to the interpretation of the study findings. 31% of children were lost to follow-up, mostly because of migration from study area. Bias caused by such losses was probably minor because those lost were similar with respect to important prognostic factors to those who were followed up, apart from age and baseline hookworm prevalence, and adjustment for these factors did not greatly affect the estimates of effect. Losses to follow-up were much the same in both groups and were unlikely to be associated with the intervention since parents who wanted active treatment for their children could obtain it. Contamination of the no-treatment group with anthelmintic treatment probably contributed to the fall in geohelminth prevalence and could have attenuated the estimates of effect for study outcomes. This bias was probably minor because changes in prevalence were small in the no-treatment group compared with albendazole. Atopy was measured by the same masked assessor who was asked to guess the treatment allocation of every school at the time of final assessments. These estimates were correct for 29 (43%) of 68 schools, which indicated that masking was maintained during the study and systematic measurement errors were unlikely. Atopy prevalence fell during the study in both groups and the trend was unrelated to treatment. Potential explanations are a drop in potency of allergens during the study and temporal trends in atopy prevalence. Because the prevalence of hookworm in our study was low (14·5%), we cannot exclude a species-dependent effect of hookworm on atopy prevalence.

Our findings are contrary to those of two previous intervention studies, which have shown that repeated anthelmintic treatments given to geohelminth-infected children affect allergen skin-test reactivity. A non-randomised intervention study in Venezuela showed that monthly anthelmintic treatment (oxantel-pyrantel) over 18 months caused an increase in the prevalence of atopy (ie, an increase in skin-test reactivity to house dustmite from 17% to 68%) in 94 children with a high prevalence of infection before treatment.[10] The same investigators also assessed peak flow responses after inhaled bronchodilator and provided evidence that peak flow responses decreased in the treated group and increased in the untreated.[21] In an open-label placebo-controlled randomised intervention study in Gabon children were treated with anthelmintics (praziquantel and mebendazole) every 3 months and skin-test reactivity to house dustmite was examined every 6 months in skin-test negative individuals, and the results provided evidence that anthelmintic treatment resulted in a significant increase in the rate of developing skin sensitivity to house dustmite (hazard ratio 2·51, 95% CI 1·85–3·41) in 165 children followed up over 30 months.[11] The Venezuelan study[10] was probably subject to substantial bias (self-selected control group, restricted information on baseline variables, and different individuals compared at the beginning and end of study) and uncontrolled confounding (no confounders identified or controlled for in the analysis). The Gabonese study[11] was an open-label randomised-controlled trial that measured the incidence of atopy in non-atopic children. Although the study showed a treatment effect on the incidence of atopy, it did not show an effect on prevalence, and most children who converted to skin-test positivity reverted to negative during the study.[11]

There are several explanations for the lack of effect of albendazole on the prevalence of atopy seen in our study. First, other factors associated with geohelminths and not controlled for in the cross-sectional analysis at baseline might account for the inverse relation and could include lifestyle, behavioural, or dietary factors. The weak estimates of effect seen in the cross-sectional studies[7,8,9,12] and the conflicting results obtained by other studies[5,6,22] could be explained by uncontrolled bias or confounding. Second, no effect of anthelmintic treatment on atopy prevalence could represent reverse causality—atopy protects against geohelminths rather than geohelminths against atopy. Atopy represents a predisposition to allergic responsiveness, and allergic or type-2 immune mechanisms might mediate protective immunity against geohelminth parasites.[23,24] Third, the actual effect of geohelminths in suppressing atopy could be more important in the first years of life, and temporary elimination of infections later in childhood by anthelmintic treatment is probably unlikely to affect a phenotype programmed in infancy. Finally, anthelmintic treatment might need to be sustained for longer than 12 months to detect an increase in prevalence and to allow reversal of immunological mechanisms that mediate suppression of atopy. However, this explanation is unlikely because findings from previous studies show that the suppressive effects of helminths on host immune[25,26] and clinical[26] responses are reversed rapidly after chemotherapy.

The study population is representative of school-age children living in rural areas of the tropics that are highly endemic for geohelminth parasites. The trial was pragmatic, was done in an unselected sample of schools and schoolchildren, and did not attempt to prevent children

in the no-treatment group from receiving anthelmintic treatment. Anthelmintic drugs are widely available in such areas and can be purchased directly by parents without prescription. The important study question was whether an intensive programme of sustained anthelmintic treatment causes an increase in the prevalence of atopy and allergy under real-world conditions. The study findings are, therefore, probably relevant to school children living in areas of the rural tropics where ascariasis and trichuriasis are the dominant geohelminth parasites, and provide evidence that an intensive programme of periodic deworming in schools in such areas is unlikely to be associated with an increase in allergy.

Contributors

P J Cooper designed and supervised the conduct of the study, and drafted the manuscript. M E Chico did all study assessments. M G Vaca administered all albendazole treatments. A L Moncayo, F Sanchez, and E Mafla obtained and analysed study samples. L C Rodrigues, D P Strachan, and G E Griffin were involved in study design and obtaining funding. J M Bland did sample size estimates and the statistical analyses. All contributors reviewed the manuscript.

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Conflict of interest statement

We declare that we have no conflict of interest.

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