



Efficacy of albendazole against the whipworm *Trichuris trichiura* — a randomised, controlled trial

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Objectives and design. To test the efficacy of albendazole against the whipworm *Trichuris trichiura* for school-based deworming in the south-western Cape, South Africa. Children infected with *Trichuris* were randomised to 3 doses of albendazole (400, 800 or 1 200 mg), each repeated 4 times. The boy/girl ratio was 1. A group not infected with worms was treated with placebo, creating a negative control.

Subjects and setting. Pupils at a primary school serving a wine-producing area approximately 90 km east of Cape Town.

Outcome measures. *Trichuris* cure rates and reduction in the number of eggs/g in faeces, as well as the infection dynamics of *Trichuris* and *Ascaris* during treatment with placebo.

Results. Albendazole treatment was associated with *Trichuris*

cure rates of 23% (400 mg), 56% (800 mg) and 67% (1 200 mg) after the final treatment. The corresponding reductions in the number of eggs/g of faeces were 96.8%, 99.3% and 99.7%. Environmental pollution by human faeces was confirmed because worm egg-negative children in the placebo group became egg-positive while the study was in progress.

Conclusion. The 400 mg stat dose had a low *Trichuris* cure rate. To repeat the dose on 2 or 3 days would increase cost, reduce compliance and complicate management. Albendazole cannot be used in deworming programmes in South Africa because it is a Schedule 4 prescription medicine. De-scheduling is needed urgently, particularly because of high efficacy against hookworm in KwaZulu-Natal and neighbouring countries.

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Complications of helminthic infections in children and adults, such as intestinal and duct obstruction by *Ascaris* that requires surgery, are serious, costly, predictable and preventable.¹⁴ A much bigger problem is the enormous burden of subclinical morbidity impeding the physical and mental development of millions of children, and the health of women. That it can be solved countrywide, has been demonstrated in Japan and Korea.⁵ In May 2001, the World Health Assembly (WHA) urged member states, including South Africa, to implement control of soil-transmitted helminths and schistosomiasis by means of holistic public health measures.⁶

One of the targets is synchronised, school-based deworming that reaches 75 - 100% of school-aged children by the year 2010, to be implemented mainly by teachers. This is the quickest way to help those who need it most, in a cost-effective way because the price of generic anthelmintics has plummeted.^{2,6,7} Market research shows that in 2003, albendazole and mebendazole purchased in Europe or Asia could be delivered to schools in Cape Town for about 20% of the government's tender prices for equivalent South African generics.

In line with the WHA resolution, a school-based deworming, education and sanitation programme has started to develop in Cape Town. Communities living in poverty have priority because high rates of infestation with *Trichuris* and *Ascaris* have been detected, especially in children.^{8,9} In a pilot phase, teachers at 12 schools in Khayelitsha have dewormed the children twice a year since 1998, with minimal assistance. From January to August 2004 alone, deworming spread to 89 primary schools attended by close to 70 000 children. The overall cumulative total treatments at schools is approaching 200 000 doses of mebendazole, which can be used without a prescription (Schedule 1). No adverse effects of deworming have been reported.

Progress of this kind emphasises the importance of using effective anthelmintics under prevailing ecological and demographic conditions. Single-dose treatments are optimal in terms of management and cost, with albendazole 400 mg tablets being one option.⁶⁻¹⁴ However, *Trichuris* is relatively refractory to this kind of treatment, as has been shown locally,^{9,11} and albendazole should only be used under prescription (Schedule 4).¹⁴ A meta-analysis of 17 trials that reported on single-dose treatment with 400 mg of albendazole in tropical countries, found a median *Trichuris* cure rate of 44% and a range of 0 - 90.5%.¹⁵ In the context of school-based deworming in the winter-rainfall area of the south-western Cape, where few data on the efficacy of albendazole have been available, a study was undertaken to determine the suitability of this anthelmintic for treatment of trichuriasis.

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Methods

Ethics and informed consent

The research project was approved by the Ethics Committee of the Medical Research Council of South Africa, subject to a directive that placebo must not be given to children known to have worms. Researchers explained to parents, guardians and teachers how control of worm infestation could help to improve the health, nourishment, development and education of their children. Frank discussion took place and questions were answered. Parents or guardians gave consent for children to take part in the research and signed combined information and consent forms that are filed at the Medical Research Council. There was consensus that after the study had been carried out, all the children in the school should be dewormed. This was implemented.¹⁵

Setting, location and eligibility

In order to have 100% prevalence in treated groups, pupils at a primary school serving a village 90 km east of Cape Town were eligible to receive albendazole if they were infested by *Trichuris*. Children not infected by any species of helminth were suitable for the placebo group. Climatic features that could influence the epidemiology included winter rainfall that averages 488 mm/annum (range 37.2 - 814.5 mm/annum), mild to cold winter temperatures and hot, dry summers. Parents often worked in vineyards in the vicinity, and human population density in the area is low.

Interventions

To obtain treatment groups for the randomised controlled trial, a baseline survey was undertaken. Faecal samples from 462 children, ranging in age from 6 to 16 years (mean 10 years), were screened by microscopy, using standard methods. Helminth eggs were counted and expressed quantitatively as eggs/g of faeces. Seventy-seven per cent of the children had worm eggs in their stools: *Trichuris* 69%, *Ascaris* 34% and dual infections 26%. Gender did not influence the prevalence or intensity of worm infestation. Chronic prescription medication and/or clinically evident illness were exclusion criteria.

For the randomised controlled trial, treatment with albendazole (Zentel) was by means of 400 mg tablets. Each tablet was in a blister pack. Albendazole doses of 800 mg and 1 200 mg were obtained by repeating treatment on 2 or 3 successive days, which is the prescribed procedure for children.¹⁴ Placebo tablets matched the albendazole tablets in appearance, as did the blister packs, and were from the same source. To standardise the procedure, all treatments comprised 1 tablet a day for 3 days (Table I). Thus, children in the 400 mg albendazole group took 1 albendazole plus 2 placebo tablets; those in the 800 mg albendazole group took 2 albendazole

tablets and 1 placebo tablet; those in the 1 200 mg group took 3 albendazole tablets; and those in the placebo group took 3 placebo tablets. Children chewed the tablets before swallowing them with water, while being observed by a researcher and a teacher. Treatments were carried out during the course of a normal school day and were repeated 4 times at intervals of approximately 4 months.

Hypothesis and outcome measures

We hypothesised that control of trichuriasis as a public health measure might necessitate a dose of albendazole higher than 400 mg stat if treatment is to be at intervals of about 4 months. Outcome measures were cure rate and reduction in the number of *Trichuris* eggs in faeces, i.e. the egg-reduction rate.¹⁶ Cure rate reflects the percentage of egg-positive individuals who became negative after each treatment. Egg-reduction rate was evaluated in terms of geometric mean (GM) egg counts because this is a valid method to normalise skewed data such as the number of *Trichuris* eggs/g of stool. The GM after deworming was expressed as a percentage of the GM before deworming. Excretion of fewer eggs is a measure of the success of control in relation to the number of eggs available for perpetuation of infection.¹⁶ The 4 cycles of treatment and repeated outcome measurements strengthened the results. The incidence of infection with *Trichuris* and *Ascaris* in the group treated with placebo was an additional outcome measure.

Power calculations, randomisation and blinding

Calculations indicated that 50 children (25 girls and 25 boys) per treatment group should be sufficient to evaluate cure rates with 80% power. The calculations were based on projected cure rates of 25%, 35% and 50% for the 400, 800 and 1 200 mg doses of albendazole, respectively. On this basis, 150 children (75 boys and 75 girls) were sufficient to form 3 treatment groups. The gender means for the number of *Trichuris* eggs in faeces were 2 569 eggs/g of faeces (range 320 - 32 760) for the girls and 1 524 eggs/g of faeces (range 350 - 8 200) for the boys. Each girl or boy was identified by a unique numerical code. A statistician operating independently of the researchers in the field used random permutations to allocate the 150 *Trichuris*-infected children into 3 groups, which were again randomised to the different doses of albendazole. In accordance with the ethical directive, 50 children with no worms in their faeces were allocated to the placebo treatment group (25 boys and 25 girls). In effect, this created a negative control group which permitted an estimate of the rate (incidence) of infection under the prevailing epidemiological conditions.

The trial was blinded in several ways. The albendazole and placebo tablets were identical in appearance, including the single-tablet blister packaging. Sets of three blister packs for each coded recipient were prepared in the laboratory. Packs were marked for use on days 1, 2 and 3, respectively (Table I).



Table I. Treatments over 3 days, repeated 4 times at intervals of 4 months

Treatments	Day 1	Day 2	Day 3
Placebo	Placebo	Placebo	Placebo
Albendazole* 400 mg	400 mg	Placebo	Placebo
Albendazole* 800 mg	400 mg	400 mg	Placebo
Albendazole* 1 200 mg	400 mg	400 mg	400 mg

*Zentel, GlaxoSmithKline, 400 mg tablets.

At the school, neither the person administering the treatment, nor the child receiving the tablet, was aware of the dose. Faecal samples were coded and microscopists who processed and examined the specimens for helminth eggs were not aware which treatment group any sample corresponded to.

Statistical evaluation and faecal sampling

Samples of faeces were collected just before each treatment and within a month afterwards. This ensured that eggs from re-infection did not influence the cure rate because it takes more than 2 months for eggs from a new *Trichuris* infection to appear in faeces. Cure rates for each dose and treatment occasion were analysed by categorical linear modelling for repeated measures regression analysis. In addition, the Jonckheere-Terpstra test was used to test the hypothesis of a dose effect, versus the null-hypothesis of no effect, in terms of the geometric mean egg count on each occasion. Egg reduction in faeces after treatments did not require statistical evaluation because the results were not equivocal.

Results

No adverse drug-related effects were reported or detected in any treatment group. The only protocol deviation was failure to maintain group sizes (Table II). This happened because some children inevitably moved to other schools at the end of the school year, before the study had been completed. To avoid this problem, school-based studies should start and finish within a school year whenever possible.

Statistical power remained adequate because cure rates generally exceeded those used in the power calculations (Table III). Analysis showed that there was no imbalance between the initial geometric mean *Trichuris* egg counts of the groups for treatment with albendazole (Table II). Before treatments commenced, infestation by *Ascaris* was present in 47%, 50%, 54% and 0% of the groups treated with 400, 800, or 1 200 mg of albendazole, or placebo, respectively. *Ascaris* was eliminated by the first treatment with albendazole, regardless of the dose. No eggs of other helminth species were seen in the faecal samples.

Table II. Initial and final numbers of children and the geometric means and ranges of *Trichuris* eggs/g of faeces (epg) before treatments with albendazole (Zentel) or placebo

Treatment group	Initial number	Final number	Means and ranges (epg)
400 mg*	50	31	961 (323 - 11 232) [†]
800 mg*	50	43	1 015 (321 - 11 387) [‡]
1 200 mg*	50	39	973 (360 - 18 514) [‡]
Placebo group [†]	50	32	0

*Repeated 4 times at intervals of 4 months.

[†]Since these children were not infected by worms at the start, the group was a negative control.

[‡]The geometric means were not significantly different ($p < 0.05$).

Table III. Cure rates (%) at each treatment with albendazole (Zentel) after initial prevalence of 100%

Dose	Prevalence	N	After 1 Rx	After 2 Rx	After 3 Rx	After 4 Rx
400 mg	100	31 [†]	25.8	25.8	16.1	22.6
800 mg*	100	43 [†]	46.2 [‡]	46.5 [‡]	37.2 [‡]	55.8 [‡]
1 200 mg*	100	39 [†]	53.8 [‡]	53.8 [‡]	69.2 [‡]	66.7 [‡]

*Given as 400 mg on successive days.

[†]Number of children who completed 4 treatments.

[‡]Cure rates for the 800 and 1 200 mg doses were similar and were significantly different from that for the 400 mg dose by categorical linear modelling for repeated measures regression analysis ($p = 0.001$).

Rx = treatment



Table IV. Geometric means of *Trichuris* eggs/g of faeces during a series of 4 treatments with albendazole (Zentel) at 3 doses, or with placebo

Rx group	N	Before Rx	After 1 Rx	After 2 Rx	After 3 Rx	After 4 Rx
400 mg	31 [†]	961	35.9	16.5	36.1	30.7
800 mg*	43 [†]	1 015	12	4.5	11.8	6.5
1 200 mg*	29 [†]	973	6	4	3.6	2.8
Placebo [†]	32 [†]	0	1.4	1.1	2.1	1.7

*Given as 400 mg on successive days.

[†]Since these children were not infected with worms at the start, the group was a negative control.

[†]Number of children who completed 4 treatments.

Rx = treatment.

Table V. Egg-reduction rates (%) during a series of 4 treatments with 3 doses of albendazole (Zentel), relative to *Trichuris* egg counts before treatments commenced

Rx group	N	Before Rx	After 1 Rx	After 2 Rx	After 3 Rx	After 4 Rx
400 mg	31 [†]	961	96.3	98.2	96.3	96.8
800 mg*	43 [†]	1 015	98.8	99.5	98.8	99.3
1 200 mg*	39 [†]	973	99.4	99.6	99.4	99.7

*Given as 400 mg on successive days.

[†]Number of children who completed 4 treatments.

Rx = treatment.

Trichuris cure rate

The results supported the hypothesis in that the 400 mg dose of albendazole had an inferior cure rate (range 16.1 - 25.8%), even when repeated regularly at intervals of approximately 4 months. The data are summarised in Table III. On all the treatment occasions, the cure rates for the 800 and 1 200 mg doses were not significantly different but were better than those for the 400 mg dose ($p = 0.001$). The repeated treatments did not increase cure rates significantly after the initial differential effect of each dose. The Jonckheere-Terpstra test confirmed the dose-related cure rates (data not shown). The cure rate for the 400 mg dose was less than the 44% median value detected by meta-analysis of 17 trials in tropical environments.¹⁵

Trichuris egg-reduction rate

All the doses of albendazole had strong effects in terms of reducing the number of eggs returned to the environment (Tables IV and V). The geometric mean egg numbers/g of faeces before and after 4 treatments were 961 v. 30.7 (400 mg dose), 1 015 v. 6.5 (800 mg dose) and 973 v. 2.8 (1 200 mg dose). The final egg-reduction rates relative to the number of eggs/g of faeces before the treatments, were 96.8% (400 mg dose), 99.3% (800 mg dose) and 99.7% (1 200 mg dose). The egg-reduction rates for all the doses were excellent in relation to the minimal acceptable efficacy of 50%, as recommended by the World Health Organization (WHO).¹⁶

Rate of infection in the placebo group

The incidence of infection per annum was 15% for *Trichuris* and

29% for *Ascaris*, under the conditions of the study. This does not conflict with the higher prevalence of the former because *Trichuris* adults live for about 3 years in the host, whereas the lifespan of *Ascaris* is only about a year. These infection dynamics confirm that the rural environment in which the children lived was polluted by human faeces.

Discussion

A Cochrane review has reported on meta-analysis of deworming trials.¹⁷ Results indicated that a single deworming treatment with any anthelmintic had a positive effect on growth. Based on the models used, the mean gain was either 0.24 kg or 0.38 kg. Across millions of children, this degree of improved growth after 1 treatment would be an enormous benefit, even before adding the probable cumulative effect of regular treatment starting at 1 or 2 years of age.¹³ Anaemia in women and children *en masse* also responds positively to regular anthelmintic treatment,^{6,7} and serious complications of helminthiasis can be prevented in children and adults.¹⁴ All these potential benefits, as well as others related to education, would be additive and cost-effective.^{6,7} In terms of public and child health, the positive effects of helminth control should outweigh some possible immune-mediated adverse interactions with other conditions, which mainly affect individuals, such as atopy.^{18,19}

If long-term challenge from helminthic antigens can be minimised, there may be beneficial effects on HIV/AIDS and tuberculosis in terms of infection dynamics, disease progression and immunisation.^{9,18,22} Discordant immune responses owing to immunological challenge from worms have



been shown to impair the effectiveness of some existing vaccines.^{18,19,22} Potential anti-HIV vaccines that are intended to function via a cellular immune response may be particularly vulnerable.²² Sustained, synchronised deworming, especially of children, may be an economical, short-term way to minimise impairment of vaccine trials and effective immunisation.

Albendazole is a benzimidazole anthelmintic that is on the essential drug lists of South Africa and the WHO.¹⁴ In South Africa, the albendazole doses that have been authorised for children include 400 mg stat and 400 mg repeated daily for up to 3 days.¹⁴ The present randomised controlled trial tested the efficacy of the permitted doses in the winter rainfall area of the south-western Cape. The results have pharmacological, financial, managerial and epidemiological implications. Repeating treatment on successive days would increase costs, decrease compliance and complicate management. All the doses had powerful effects on egg output, making it likely that even at the 400 mg dose the cycle of re-infection could be broken by sustained, regular treatment for a few years. Furthermore, all the treatments were completely effective against *Ascaris*, which regularly causes acute medical emergencies that sometimes require surgery.^{1,2,4}

Current South African legislation categorises albendazole as a Schedule 4 medicine.¹⁴ This means that a prescription from a medical doctor (or a clinical nurse practitioner) is needed in order to dispense the drug and treat a specific patient. Without such authorisation, treatment by a nurse, paramedic, pharmacist, parent, teacher, health care worker or lay person contravenes the schedule. It follows that the schedule 4 status is not compatible with the use of albendazole in school-based, non-selective deworming programmes. However, albendazole has an excellent global safety record and is highly effective against hookworm, which is endemic in parts of KwaZulu-Natal, Mozambique and Zimbabwe.^{2,11-13} These helminths are one cause of anaemia because they feed on blood obtained by lacerating the intestinal wall and releasing anticoagulant. It is clear that albendazole should not be in a prescription niche that puts it out of reach of children and women living in poverty, but which might increase profit. Neither will the Schedule 4 rating serve to keep albendazole in reserve in case resistance develops to mebendazole (Schedule 1), because of cross-resistance between benzimidazoles. South Africa should conform to practice in other countries by de-scheduling albendazole as a matter of urgency in order to permit

unrestricted use in deworming programmes, especially where hookworm is endemic.^{11,12}

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