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Efficacy of co-administration of albendazole and diethylcarbamazine against geohelminthiases: a study from South India

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Summary The efficacy of single-dose combination drug therapy with diethylcarbamazine (DEC) plus albendazole (ALB), and single-drug therapy with DEC alone against geohelminths was compared as part of a mass drug administration (MDA) for elimination of filariasis. This study was conducted in two blocks of Villupuram District of Tamil Nadu State, India, covering a population of 321 000 including about 100 000 children 1–15 years of age. Prevalence and intensity of geohelminth infection were determined by the Kato–Katz technique immediately before and 3 weeks after the MDA. A pre-treatment cross-sectional survey was undertaken in 18 statistically selected villages out of 204 villages, including 646 school children. About 60% were infected with one or more geohelminths. The overall prevalence rates were 53.9%, 12.4% and 5.7% for *Ascaris lumbricoides*, hookworms and *Trichuris trichiura*, respectively. Combination therapy (DEC + ALB) produced a cure rate of 74.3% and an egg reduction rate of 97.3% for geohelminths, which were higher than the corresponding rates (30.4% and 79.0%) observed in the single drug therapy arm with DEC alone. The odds of cure with combination therapy were significantly higher for roundworm (5.3 times) and hookworms (3.5 times), then odds of cure with DEC alone. Both therapies were equally effective against trichuriasis, recording cure rates >77% and egg reduction rates >83%. In combination therapy, 53.5% of the children noticed expulsion of worms after MDA, while in single drug therapy only 20.9% did. Our study indicated that MDA of combination therapy was operationally feasible at the community level, and it may secure higher community compliance because of its perceived benefits and enhanced efficacy against geohelminths than single-drug therapy.

keywords geohelminths, albendazole, diethylcarbamazine, ascariasis, trichuriasis, hookworms

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Introduction

Large-scale chemotherapy plays a vital role in the control of many parasitic infections such as lymphatic filariasis (LF), onchocerciasis, schistosomiasis and intestinal nematode infections (Savioli *et al.* 1997). The greatest successes were through the development of single-dose therapy and mass treatment control programmes for a number of diseases (Stephenson & Wiselka 2000). Currently, the most practical and feasible method for the control of LF is the rapid reduction of microfilarial load in the community by mass annual single dose of diethylcarbamazine (DEC) and this is being attempted in India as a new initiative in a pilot programme (Ramaiah *et al.* 2000). Several antihelmintic drugs, especially when given in combination, have a significant antifilarial effect providing a number of good tools to control filariasis (Turner & Michael 1997). Two new drugs, ivermectin (IVR) and albendazole (ALB), when combined with DEC, have been shown to be highly effective in the management of microfilariasis because of lymphatic filarial worms (Ottesen *et al.* 1999). Hence, the revised elimination strategy for LF is designed to break the chain of transmission in populations exposed to the risk of infection by administering a single dose of two drugs, annually for 5–6 years (Karam & Ottesen 2000).

Consequent upon the formation of the Global Alliance to Eliminate Lymphatic Filariasis, free supply of albendazole tablets was announced by WHO and SmithKline Beecham for mass chemotherapy along with DEC towards filariasis elimination [World Health Organization (WHO) 1999]. About 40 million persons worldwide were expected to be covered by two-drug yearly mass drug administration (MDA) in the year 2001 by national programmes with two or three options for drug choices, including DEC + ALB (WHO 2001). The national programmes were expected to cover 80–90% population for five to six MDAs in this endeavour, which may ultimately lead to elimination of LF, and the current status was reviewed (Das *et al.* 2001; Sunish *et al.* 2002).

Intestinal helminth infections are widespread, causing nutritional deficiencies and impaired childhood cognitive development (Stephenson & Wiselka 2000). In India, most pre-school children are underweight and stunted, with intestinal helminth infestation being one of the contributing factors (Awasthi & Pande 1997). The availability of drugs such as DEC and ALB, which have antihelmintic and antifilarial properties, opens the possibility of integrating a geohelminth control programme with a filariasis control programme, where these nematodes occur concurrently (Beach *et al.* 1999; Ananthakrishnan & Das 2001). Single doses of albendazole (600 mg) in combination with DEC (6 mg/kg) proved to have both long-term effectiveness in decreasing microfilaraemia and adult filarial worm antigen levels in *Wuchereria bancrofti* infections (Ismail *et al.* 1998). Combination drug therapy with DEC + ALB has been suggested as a comprehensive measure to control both intestinal helminths and LF because of the 'ancillary benefits' of ALB and the resultant enhanced compliance of the population at risk (Ottesen *et al.* 1999). However, the current technical data does not clearly reveal the efficacy of the combination of DEC + ALB over DEC alone, although control of intestinal worms and filariasis together, particularly in children, could have a higher cost benefit (Das & Pani 2000). Therefore, a two-arm community-based research study was undertaken to examine the impact of co-administration of DEC + ALB on the prevalence and intensity of intestinal helminthic infections and filarial transmission and infection in one arm, and DEC alone in the other arm. The data pertaining to intestinal helminths are presented in this communication.

Materials and methods

The Villupuram District of Tamil Nadu state was covered by three MDAs by single-dose DEC alone from 1998 to 2000, as a part of a large-scale MDA programme for filariasis control/elimination in 12 districts, covering a population of about 27 million. During the fourth round (March 2001), the Tamil Nadu Government decided to co-administer ALB along with DEC in six districts, covering a population of about 14 million. However, the Villupuram District along with five other districts received DEC alone. Thus, the fourth round MDA by the Government of Tamil Nadu during the month of March 2001 was the first round for our new study. Two blocks, Tirukoilur and Mugaiyur from Villupuram District with 204 villages and a population of 321 000 (including about 100 thousand children between 1 and 15 years of age), were selected for this project. The health system distributed the drugs. All community members aged 1 year and above were targeted for drug consumption, after a well-orchestrated health education campaign in all the 12 districts. Tirukoilur Block was assigned for co-administration of two drugs and Mugaiyur block was assigned for the administration of a single drug (DEC) alone. In order to have baseline data for the two blocks, 24 villages from Tirukoilur and 27 villages from Mugaiyur (total of 51 villages) were screened and nine index villages were selected from each block, using statistical considerations based on population size of the villages. Representation was given to small, medium sized and big villages in this selection. The baseline survey on geohelminths was conducted in these 18 index villages by including all 18 primary schools in the area, whose students had never been treated against helminths by any community-based programme. Within a given school, children aged 9–10 years were selected by a simple random sampling technique, to draw the necessary numbers (20–50) from children of that age group.

A total of 321 school children (177 boys and 144 girls) were enlisted from Tirukoilur Block for baseline prevalence assessment prior to DEC + ALB intervention. Similarly, a total of 325 school children (180 boys and 145 girls) were examined to assess the prevalence rate for geohelminthiasis from Mugaiyur Block prior to intervention with DEC alone. After explaining the purpose of the study and obtaining informed consent from headmasters and parents, numbered sterile vials along with spatula were given to enrolled school children, who were asked to bring a stool sample on the following day. During the distribution of the vials, the amount of stool sample needed and the collection method by using the spatula were explained to them. Stool samples were collected in the morning of the next day and transported to the laboratory and examined by the Kato–Katz technique, following World Health Organization (WHO) recommendations (WHO 1993), to assess the prevalence of geohelminthiasis, species profile and intensity.

Microscopy of nematode eggs was used to diagnose a helminthic infection, while the concentration of those eggs was used to estimate the intestinal worm burden in the host. The prevalence rate was expressed as the percentage of subjects found positive for any of the three geohelminths, viz. roundworm (*Ascaris lumbricoides*), hookworms (*Ancylostoma duodenale* and *Necator americanus*) and whipworm (*Trichuris trichiura*). The intensity of geohelminth infections was defined as eggs per gram (epg) of faeces and the mean epg was calculated as the geometric mean (GM) intensity by using the following formula:

$$\text{Geometric mean of epg} = \text{antilog}\frac{\sum \log(\text{epg}+1)}{n} - 1$$

where $\sum$ log(epg + 1) is the sum of the logarithms of each individual epg, one egg was added to each count to permit calculation of the logarithm in case of epg = 0, and '*n*' the number of subjects investigated. The GM controls for the drift in epg among untreated subjects and takes into account the over-dispersed nature of the egg counts. In this procedure all children were included for calculations, including those without any eggs in their stool sample, similar to the procedure adapted by earlier workers (Kightlinger *et al.* 1995). The threshold proposed for use by a WHO Expert Committee in 1987 for the classes for intensity for each helminth in stools were followed to determine the classes of intensity of infections (Montresor *et al.* 1998). According to this, light intensity infection was defined as having < 5000 epg for roundworm, < 2000 epg for hookworms and < 1000 for whipworm.

Three weeks after MDA (post-treatment), 541 (83.7%) of the 646 children surveyed before the MDA were tested again to assess the impact of MDA on intestinal worm burden. In order to compensate for the loss of sample because of examination schedules, sickness and absenteeism, 131 children were selected as a replacement (age- and sex-matched bench-mates of missing children, from among those who had participated in the MDA but who were not covered for stool examination in the baseline studies earlier) bringing the total to 672 for post-MDA evaluation. All children in the class were requested to report sighting of expelled worms after MDA, at the first survey itself, in the school. While collecting the post-MDA stool samples, a questionnaire was used to enquire whether they noticed expulsion of worms in stools after the MDA. The proportion of children who had perceived the benefit of MDA by way of seeing expulsion of worms in stools after receiving MDA, were computed for each arm and were compared. The difference in the prevalence rates for each geohelminth between pre- and post-treatment values was expressed as percentage of pre-treatment value and was referred to as cure rate. Thus, the efficacy of combination therapy and single-drug therapy were evaluated for cure rate for the three nematodes studied. Egg counts (epg + 1) were transformed to common log for statistical application and are reported as the GM. The egg reduction rate was expressed as the percentage GM epg reduction, i.e. percentage fall in geometric mean epg counts. Pre- and post-treatment prevalences for each geohelminths within the two arms were compared using the chi-square test. Cure rates were tested by calculating log odds ratio between the two treatment arms, and Student's *t*-tests were conducted on transformed values of intensities of GM epg values to measure the significance of the egg output reduction within each treatment group.

Results

Prevalence and intensity of infection

Among the 646 stool samples examined from the two treatment groups of school children, the overall prevalence of geohelminths at enrolment was 53.9% for *Ascaris*, 12.4% for hookworms, and 5.7% for *Trichuris*; 59.6% of all school children examined had one or more geohelminthic infections. All infections were of light intensity according to the WHO classification. Of the 385 infected individuals, 79.2% had a single infection and 20.8% had mixed infections. Among 77 children who had mixed infection, dual infection constituted 95% and 5% triple infection. *Ascaris lumbricoides* with hookworms was the predominant dual infection (67.5%) followed by *Ascaris* plus *Trichuris* (28.4%). Hookworms plus *Trichuris* infection constituted a mere 4.1%.

In the combination therapy group (DEC + ALB), the prevalence of geohelminths was 60.4%, while it was 58.8% in single drug therapy group (Table 1). The two treatment groups did not differ significantly, except the prevalences of hookworms (16.5% *vs.* 8.3%; $P < 0.005$; Table 1). Whipworm infection was comparatively rare in both treatment groups with 5.0% and 6.8% prevalence, respectively.

Reported participation and side reactions

All the children covered in this study reported that they consumed drugs assigned to their families and the local health workers covered a small number who missed MDA, during mop-up operations in the schools. A separate questionnaire survey on about 850 households indicated that about 80% of the families participated in this 5-day MDA (17–21 March 2001) programme, by reporting consumption of tablets distributed by the health system, in both arms. There were no major

Table 1 Baseline prevalence and intensity of geohelminths

	Percent prevalence			Geometric mean epg†		
Geohelminths	DEC + ALB arm	DEC alone arm	χ^2 (*P*-value)	DEC + ALB arm	DEC alone arm	*t*-value (*P*-value)
Ascaris	54.83	52.92	0.17 (0.684)	23.51	20.60	0.54 (0.587)
Hookworms	16.51	8.31	9.27* (0.002)	1.48	0.53	3.47* (0.001)
Trichuris	4.96	6.77	0.95 (0.329)	0.27	0.40	−1.08 (0.280)
Any of three	60.44	58.77	0.12 (0.725)	36.45	29.85	0.83 (0.405)

*Significantly different.
†Eggs per gram of stool.

adverse side reactions, although mild side-effects such as fever, giddiness and vomiting were reported in about 9% of participants which could be managed by the local health authorities. These details are being reported separately.

Therapeutic efficacy

The prevalence and GM epg counts before and after treatment and the cure and egg reduction rates are given in Table 2. Within each arm the prevalences of individual parasites came down significantly after the MDA, except for DEC alone arm for hookworms. This is despite significantly greater prevalence for hookworms in the pre-treatment period in the combination therapy arm. The cure rates were significantly higher in the combined therapy arm for *Ascaris*, hookworms and any of three worms, but not so for *Trichuris*, for which both arms were equally effective. The GM epg values in both arms were significantly reduced after therapy, except for the DEC alone arm for hookworms. This pattern on intensity of worm burden was similar to the observations on the reduction of prevalences and both parameters behaved in a similar fashion. Though there were significant reductions in the GM epg in both arms, except for hookworms in the DEC alone arm, there were substantial differences in the magnitude of egg count reduction (egg reduction rate) for various parasites. The figures for any of three worms and for *Ascaris* were similar with 18–20% difference in favour of combined therapy (Table 2). Extreme patterns were seen for hookworms on the one hand and whipworm on the other, the latter did not show any difference between the arms, where as in the case of hookworms a 58% difference was observed between the two arms, registering very strong benefits for combined therapy. On the whole, combined therapy registered higher egg reduction rates except for *Trichuris*, and the same pattern was noted for cure rates derived from prevalences. Both treatments were very effective against *Trichuris*, each inducing cure rates >77% and egg reduction rates > 83%.

The odds of cure for *Ascaris* in DEC + ALB therapy was 5.3 times the odds of cure in DEC alone arm and the odds ratio was significant ($P < 0.001$; not shown in table). Similarly, the odds of cure in the combination therapy arm for any of three helminths (5.7 times; $P < 0.01$) and hookworms (3.5 times; $P < 0.001$) was higher than the odds of cure in the single-drug arm.

Perceived benefits

A greater proportion (53.5%) of school children perceived the benefits of expulsion of worms after the co-administration of DEC + ALB and noticed expulsion of worms after MDA, while only one-fifth (20.9%) gave such a history in DEC alone treatment group.

Discussion

Control of filariasis in India had taken a new turn with the introduction of single-dose, two-drug (DEC + ALB) mass administration by the Government of India on a pilot scale, with donation of ALB by SmithKline Beecham through WHO (WHO 1999). We had an opportunity to study and report the role of DEC + ALB on filariasis and intestinal geohelminths control, against the DEC alone arm, probably reporting for the first time from this region.

Our data reveal that the study population of this area was infested at a moderate level, the prevalence of soil-transmitted helminthiasis being about 60%. The intensity of helminth infections was comparatively low and all children had light infections according to WHO criteria. In general, there was higher prevalence of ascariasis and low prevalence of hookworms infection and trichuriasis. Intensity as measured by GM epg was very low and different from other developing countries. Hall & Holland (2000) have reported that school children from Mexico,

Table 2 Geohelminths prevalence and intensity during pre and post-treatments in the two arms of the study

Helminths	Treatment group	Pre-treatment % prevalence (*n*)	Post-treatment % prevalence (*n*)	Cure rate (%)	Pre-treatment intensity (geometric mean epg)	Post-treatment intensity (geometric mean epg)	Egg reduction rate (%)
Ascaris	DEC + ALB	54.83 (176/321)	14.12 (49/347)*	74.25†	23.51	0.81‡	96.55
	DEC alone	52.92 (172/325)	36.62 (119/325)*	30.80	20.60	4.81‡	76.64
Hookworms	DEC + ALB	16.51 (53/321)	1.73 (6/347)*	89.52†	1.48	0.09‡	94.18
	DEC alone	8.31 (27/325)	6.15 (20/325)§	25.99	0.53	0.34§	36.05
Trichuris	DEC + ALB	4.96 (15/321)	0.86 (3/347)¶	81.58	0.27	0.04**	83.96
	DEC alone	6.77 (22/325)	1.54 (5/325)¶	77.25	0.40	0.06‡	85.57
Any of three	DEC + ALB	60.44 (194/321)	15.56 (54/347)*	74.26†	36.45	0.97‡	97.34
	DEC alone	58.77 (191/325)	40.92 (133/325)*	30.37	29.85	6.26‡	79.02

* Significant reduction ($P < 0.00001$).
† Significantly different from DEC alone.
‡ Significant reduction ($P < 0.0001$).
§ No significant difference.
¶ Significant reduction ($P < 0.001$).
** Significant reduction ($P < 0.05$).

Madagascar, Myanmar, Nigeria, and Kenya bear a heavy burden of infection and considerable morbidity because of the soil-transmitted helminthiases. The heaviest worm burden of *Ascaris* in the world was reported from Madagascar (Kightlinger *et al.* 1995). The GM epg value was 675 for *Ascaris* in 1–10-year-old children, with an increase with age and 10-year-old children in Madagaskar had a GM epg value of 7161, against the very low value (< 25 GM epg) in our study. Srinivasan *et al.* (1987) observed very high prevalence (92%) but with moderate intensity of hookworms infection (> 2000 epg) in 4% of infected patients in South India, compared with high intensity in Nigeria (Udonsi 1984). In Nigeria, 58% of children studied had hookworm infection and 60% had epg counts of 10 000 or more. In the present communication, data on boys and girls and on the predisposition of some children with higher egg output after therapy were not taken up and these will be communicated separately.

There are limited studies comparing the efficacy of DEC + ALB with other drugs for geohelminths control. Ismail & Jayakody (1999) studied this combination in the treatment of trichuriasis in Sri Lanka and Njenga *et al.* (1999) in Kenya. Our current report contributes information along with the filariasis control programme in Tamil Nadu, India, which involves a large number of children. The co-administration of DEC and ALB was clearly more effective than DEC alone against *Ascaris* and hookworm infections, both in terms of cure rate (74.3% *vs.* 30.8%; 89.5% *vs.* 26.0%) and egg reduction rate (96.6% *vs.* 76.6%; 94.2% *vs.* 36.1%). The pattern of results in 541 children who were examined at both the points (541 *vs.* 541) were similar to the results mentioned above for the larger sample (646 *vs.* 672) given in Table 2. The cure rates for *Ascaris* (71.4 *vs.* 34.0 for 541 children as against 74.3 *vs.* 30.8 in the larger sample) and any of three worms (73.4 *vs.* 39.6 against 74.3 *vs.* 30.4) were similar for both samples. Likewise, the egg reduction rates for *Ascaris* (91.3 *vs.* 76.4 as against 96.6 *vs.* 76.6) and for any of three worms (94.1 *vs.* 78.5 as against 97.3 *vs.* 79.0) were similar, hence the results for the followed-up sample (541 *vs.* 541) and those for the replacement sample (646 *vs.* 672) were similar. Some drop-out children returned for the post-treatment survey, bringing the total to 672. High cure rates and egg reduction rates of *Ascaris* and hookworm infection with a single dose of ALB have been reported in many studies (Albonico *et al.* 1994; Norhayati *et al.* 1997).

As far as trichuriasis is concerned, both treatment regimens, viz. DEC + ALB and DEC alone produced very similar cure rates (81.6% *vs.* 77.3%) and almost the same egg reduction rates (84.0% *vs.* 85.6%). This shows that addition of ALB to DEC produced no appreciable impact on *T. trichuris* infection, unlike higher efficacies observed for the other two geohelminths. Similar findings on the effect of ALB on trichuriasis have also been recorded in Bangladesh (Hall & Nahar 1994), in Guatemala (Watkins & Pollitt 1996) and in Thailand (Sukontason *et al.* 2000). In a study in Sri Lanka, a significantly higher cure rate (79.3%) and egg reduction rate (93.8%) was recorded against trichuriasis, when ALB and IVR were co-administered, compared with ALB alone or ALB + DEC (Ismail & Jayakody 1999). In some studies, ALB alone produced a low cure rate but higher egg reduction rate for trichuriasis (Bartoloni *et al.* 1993; Albonico *et al.* 1994; Norhayati *et al.* 1997). High cure (67.4%) and egg reduction rates (87.0%) were also reported against trichuriasis with ALB in Thailand (Jongsuksuntigul *et al.* 1993) and a very high cure rate (90.5%) was reported by Jagota (1986) in India. In a small-scale field-based clinical trial in Kenya with 21–22 children in each group, 67.4%, 71.1%, 78.8% cure rates for intestinal helminths were obtained among persons treated with DEC, ALB and a combination of the two drugs, respectively, 6 months after treatment (Njenga *et al.* 1999). In this study, the identity of helminths was not specified and therefore we cannot directly compare data. However, our combined therapy arm recorded similar cure rate as was reported in Kenya.

Treatment with DEC alone has significant therapeutic effects on some enteric parasites including *Ascaris* (Turner & Michael 1997). Our current study has also brought out additional information on the efficacy of DEC against geohelminths in a public health scale intervention. In single-dose DEC treatment, although the cure rate was low in *Ascaris* infection (30.8%), the egg reduction was more evident (76.6%). Similar results were recently reported in 26 Tanzanian children using single-dose DEC, with 60.2% reduction of egg output, 7.7% cure rate for *Ascaris* infection and 10 children (38.5%) noticing expulsion of worms within 2 days after therapy (Meyrowitsch & Simonsen 2001). In our study, expulsion of worms was noticed by 20.9% of children in DEC alone arm.

Single-dose DEC therapy could produce equivalent cure (> 77%) and egg reduction rates (> 84%), as combination therapy for *T. trichuris*. However, DEC alone gave a poor cure (26%) and egg reduction rate (36%) for hookworm infection and was definitely inferior to combination drug therapy. Co-administration of ALB with DEC enhanced most of the properties of DEC alone (> 74%) and its benefits were perceived by more people (32.6%).

Integrated programmes for simultaneous treatment of multiple diseases appear to be an efficient and cost-effective approach for addressing geohelminthiasis (Beach *et al.* 1999). Periodic mass treatment is warranted when the prevalence of intestinal nematodes in school children exceeds 50%, although Guyatt (1999) considers mass treatment for intestinal nematodes 'good value' even if 25% of the children (community) are infected. The instant deworming effect of DEC + ALB may help secure higher community compliance in the forthcoming MDAs, from 56.5% in the second MDA in 1998 (Ramaiah *et al.* 2000) and 80% reported consumption of drugs in this study for the fourth MDA in 2001. Community co-operation has been found to be very encouraging when the LF elimination programme was integrated with control of intestinal helminth infections (WHO 2000a) and benefits regarding improvement of community acceptance and co-operation in filariasis control programmes were forecast by Meyrowitsch & Simonsen (2001) when studying DEC treatment and worm expulsion in children. The instant deworming of children after ALB treatment created immense confidence in the community (WHO 2000a). This was also reflected in our study among school children, who reported worm expulsions with enthusiasm. We have a built-in control group with DEC alone to nullify errors, if any, in this kind of self-reporting by school children.

Ottesen has stated in a meeting (WHO 2000b) that children stand to benefit most from the LF elimination efforts. This is also the case with geohelminth control, as the heaviest infections with worms typically occur among children aged between 5 and 14 years (Savioli *et al.* 1992; Ananthakrishnan & Das 2001) and this age group is therefore most likely to benefit from treatment (Hall *et al.* 1997).Childhood is the period when most filariasis infection is acquired, often as much as one-third children becoming infected before age 5 (Witt & Ottesen 2001). Sunish *et al.* (2002) also emphasized this aspect and proposed measurement of new infections in children reflected by childhood antigenaemia prevalence (CAP) as an important indicator of a successful filariasis control programme. These reviews indicate that the combined strategy (DEC + ALB) for multiple disease (filariasis and geohelminths) control can benefit children immensely and could be implemented in a cost-effective manner at the community level, as suggested by Beach *et al.* (1999), Cline *et al.* (2000) and Stephenson & Wiselka (2000). Our results indicate that future compliance for the overall filariasis control programme could be improved and/or sustained because of the higher perceived benefits felt by the beneficiary community, and will help in reducing the time period required for the control/elimination of filariasis, apart from substantial benefits for control of geohelminthiases.

In our study, the odds of cure with combination therapy were significantly higher than odds of cure with DEC alone for roundworm (5.3 times) and hookworms (3.5 times). This was also true for odds of cure (5.7 times) for any of three geohelminths, between arms, giving a distinct advantage to combination therapy. The combination resulted in enhanced efficacy of the broad-spectrum activity against geohelminths, especially against *Ascaris* and hookworms, and a greater proportion of school children (53.5% against 20.9%) under the combination drug therapy of DEC + ALB perceived the benefits of deworming. These positive factors could in turn lead to greater participation and sustained compliance at higher level by the community in forthcoming MDAs.

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