

Albendazole for the control and elimination of lymphatic filariasis: systematic review

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Summary

OBJECTIVES The Global Programme to Eliminate Lymphatic Filariasis recommends albendazole in combination with other antifilarial drugs. This systematic review examines albendazole in treatment and control of lymphatic filariasis.

DATA SOURCES The Cochrane Controlled Trials Register, MEDLINE and EMBASE to April 2005; contacting experts, international organisations and drug manufacturers.

METHODS Randomised or quasi-randomised controlled trials included; two reviewers independently assessed eligibility, quality, and extracted data. We calculated the relative risk of microfilaraemia (mf) prevalence using fixed effect, or random effects model in case of heterogeneity.

RESULTS Six trials met inclusion criteria. Three trials compared albendazole with placebo: no effect was demonstrated on mf prevalence, but density was lower in one of the three studies at 6 months. Three trials added albendazole to ivermectin, with no demonstrable effect; prevalence tended to be lower at 4–6 months but not at 12 months (4–6 months; RR 0.49, 95% CI 0.18 to 1.39, $n = 255$, 2 trials; 12 months: RR 1.00, 95% CI 0.88 to 1.13, $n = 348$, 2 trials). Mf density was significantly lower in two of the three trials; one of two trials measuring density at 12 months showed a difference. Three trials added albendazole to diethylcarbamazine; two were small trials with no difference demonstrated; the third study tended to favour combination at 6 months (RR = 0.62, 95% CI 0.32 to 1.21, $n = 491$), with a significant difference for density.

CONCLUSIONS The effect of albendazole against adult and larval filarial parasites, alone and in combination with other antifilarial drugs, deserves further rigorous research.

keywords lymphatic filariasis, albendazole, systematic review, mass drug administration

Introduction

Lymphatic filariasis affects about 120 million people in more than 80 countries. Adult worms live in the lymphatic system and produce larvae (microfilariae, mf), which migrate to the blood and are ingested by the mosquito vector. In the absence of a safe and effective drug to kill adult *Wuchereria bancrofti* or *Brugia malayi*, the current strategy is to interrupt transmission by reducing mf.

In the 1990s, research suggested enhanced suppression of mf with albendazole (Jayakody *et al.* 1993; Ismail 1998; Ottesen *et al.* 1999). In 1998, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) recommended annual mass treatment (treating all community members

where the disease is endemic) with two-drug regimens: albendazole plus either ivermectin or DEC (GPELF, 2005). Although albendazole has secondary benefits against intestinal helminths (Ottesen *et al.* 1999; Dickson *et al.* 2003), we were asked by the GPELF to assess the effects of albendazole alone or in combination with DEC or ivermectin on mf.

Methods

Searching for studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in

press, and in progress). We searched the Cochrane Infectious Diseases Group's trials register up to April 2005 (full details of the Cochrane Infectious Diseases Group's methods are published in *The Cochrane Library* in the section on Collaborative Review Groups) and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2005). We searched the following electronic databases using the search strategy defined by The Cochrane Collaboration: MEDLINE (1966 to April 2005); EMBASE (1980 to April 2005); and LILACS (<http://www.bireme.br>; 1982 to April 2005).

We used the following search terms for all trial registers and databases: filariasis; lymphatic filariasis; elephantiasis; lymphoedema; *W. bancrofti*; *B. malayi*; *Brugia timori*; filaricides; diethylcarbamazine (DEC); Banocide®; carbamazepine; Hetrazan®; luxuran; ivermectin; Mectizan®; benzimidazole; albendazole; metiazol; and valbazen. To identify unpublished and ongoing trials, we contacted the World Health Organization, GlaxoSmithKline (the company producing albendazole), and other experts. We checked the reference lists of existing reviews and of all identified trials for further reports.

Selection of studies

One reviewer (HE or JC) screened titles and abstracts identified from the search strategy. We retrieved hard copies of the published or unpublished trial reports potentially relevant to the review for further assessment. We used a pre-designed eligibility form to select studies. We included trials that met the inclusion criteria (HE or JC and PG). We resolved disagreements through discussion.

We included trials that (1) compared albendazole with placebo, DEC or ivermectin; (2) compared ivermectin alone with albendazole co-administered with ivermectin; or (3) compared DEC alone with albendazole co-administered with DEC. All drugs were given in single doses. We initially intended to include trials of mass treatment but none were identified [International Filariasis Review Group 2005 (David Addiss, Julia Critchley, Henry Ejere, Carrol Gamble, Paul Garner, Hellen Gelband)].

Assessment of methodological quality

Two reviewers (HE or JC and PG) assessed trials according to pre-defined quality criteria [Juni *et al.* 2001; International Filariasis Review Group (David Addiss, Julia Critchley, Henry Ejere, Carrol Gamble, Paul Garner, Hellen Gelband) 2005] in relation to: (1) generation of allocation sequence; (2) concealment of allocation; (3)

blinding of participants, investigators, and outcome assessors; (4) completeness of follow up (<10% loss to follow up defined as adequate). Each of these quality criteria was assessed as adequate, inadequate or unclear, except blinding, which was assessed as double blind, single blind or open.

Data collection and analysis

Data were extracted by one reviewer and checked by the second. We extracted data relating to trial and patient characteristics, and outcomes reported. For binary outcomes we recorded the number of participants experiencing the event in each group of the trial and calculated relative risks (RR). We grouped studies by the main comparator interventions (e.g. albendazole *vs.* placebo). We assessed heterogeneity among included studies by visually inspecting forest plots and carrying out a chi-squared test for heterogeneity (statistical significance at 10% level), and used the random effects model to pool data where heterogeneity was detected.

Most trials reported mf density for individuals mf positive at baseline only, which means the analysis excludes individuals who were newly infected over the course of the study (International Filariasis Review Group 2005). A re-analysis of data from the two Haiti trials (Addiss *et al.* 1997; Beach *et al.* 1999; Fox *et al.* 2005), using a different method of calculating geometric mean, led to a slight reduction in the percentage change in mf density across all groups, but did not influence statistical significance (International Filariasis Review Group 2005).

Results

Six trials were included; of the total 5668 participants, 966 had detectable mf (Addiss *et al.* 1997; Beach *et al.* 1999; Dunyo *et al.* 2000; Pani *et al.* 2002; Kshirisagar *et al.* 2004; Simonsen *et al.* 2004; Fox *et al.* 2005). All trials were individually randomised, double blind (except for Haiti 2004, Fox *et al.* (2005) where only outcome assessors were blind), with adequate allocation concealment. Losses to follow-up exceeded 20% in four trials (Table 1). A total of 103 participants were included from the efficacy component of one trial from India (Kshirisagar *et al.* 2004).

Reported trial inclusion criteria and outcomes varied. One small trial from India was conducted only in individuals who were mf positive at baseline (Pani *et al.* 2002); one trial from Ghana reported changes in mf prevalence only on those who were positive at baseline (Dunyo *et al.* 2000); one trial from Haiti 2005 reported mf prevalence in the whole study population, regardless of mf

Table 1 Description of studies

Studies & Refs.	Losses to follow-up	Participants	ⁿ (all)	(Mf +ve)	Alb [#]	DEC [*]	Iver [§]	A + D	A + I	Placebo	Time of reporting
Haiti 1999 (Addiss <i>et al.</i> 1997; Beach <i>et al.</i> 1999)	Inadequate: 585 analysed (61%)	Children (5–11 years) with or without <i>W. bancrofti</i> microfilaremia	965	113	Y	Y	Y	Y	Y	Y	Mf positive at 4 months
Ghana 2000 (Dunyo <i>et al.</i> 2000)	Inadequate: 273 (80%) of microfilarial-positive participants analysed	Adults and children with or without <i>W. bancrofti</i> filariasis	1425	340	Y	Y	Y	Y	Y	Y	Mf positive at 12 months
Tanzania 2004 (Simonsen <i>et al.</i> 2004)	Inadequate: 1221 (67%) analysed	School children (6–18 years) with or without <i>W. bancrofti</i> microfilaremia	1829	203	N	Y	Y	Y	Y	N	Mf positive at 6 and 12 months
India 2002 (Pani <i>et al.</i> 2002)	Adequate: implies no losses to follow up (54 analysed out of 54 randomised)	Asymptomatic volunteers (aged 10–57), all mf +ve	54	54	Y	Y	Y	Y	Y	N	Mf positive at 12 months
Haiti 2005 (Fox <i>et al.</i> 2005)	Inadequate: 990 (76%) analysed	Children (5–11 years) with or without <i>W. bancrofti</i> microfilaremia	1292	183	Y	Y	Y	Y	Y	Y	Mf positive at 3, 6 and 12 months
India 2004 (Kshirisagar <i>et al.</i> 2004)	No losses, but only 103 of 1403 patients initially enrolled in a safety study were assessed for efficacy	Adults and children over 5 years for safety study; males aged 18–50 for efficacy study	103	73	N	Y	Y	Y	Y	N	Mf positive at 3, 6 and 12 months

Alb, albendazole; DEC, diethylcarbamazine; Iver, ivermectin; A + D, albendazole and DEC; A + I, albendazole and ivermectin.

[#]Albendazole dose was 400 mg in all trials.

^{*}DEC dose was 6 mg/kg in all trials.

[§]Ivermectin dose was 200–400 µg/kg in Haiti 1999, but 150–200 µg/kg in all other trials.

Drugs were given as a single dose in all trials.

status at baseline (Fox *et al.* 2005), and one trial, again from Haiti 1999, reported results both for the whole population, and for those mf positive at baseline only (Addiss *et al.* 1997; Beach *et al.* 1999).

Figure 1 shows results for trials reporting only those mf positive at baseline; Figure 2 displays trials that reported mf prevalence for the whole community, including persons who were mf negative at baseline. One trial reported on mf at two time points; 3 and 6 months (Fox *et al.* 2005), and another trial reported results at three time points (3, 6, and 12 months) (Kshirisagar *et al.* 2004). Data for each time point are included on the figures.

Albendazole compared with placebo

Albendazole was compared with placebo in three trials (Addiss *et al.* 1997; Beach *et al.* 1999; Dunyo *et al.* 2000; Fox *et al.* 2005). In two trials reporting on participants mf positive at baseline (Addiss *et al.* 1997; Beach *et al.* 1999; Dunyo *et al.* 2000), the meta-analysis did not demonstrate a difference between albendazole and placebo in relation to prevalence of mf (RR 0.96, 95% CI 0.83 to 1.10, $n = 195$, Figure 1). In a third trial reporting mf prevalence in all children regardless of mf status at baseline (Fox *et al.* 2005) no difference between albendazole and placebo was

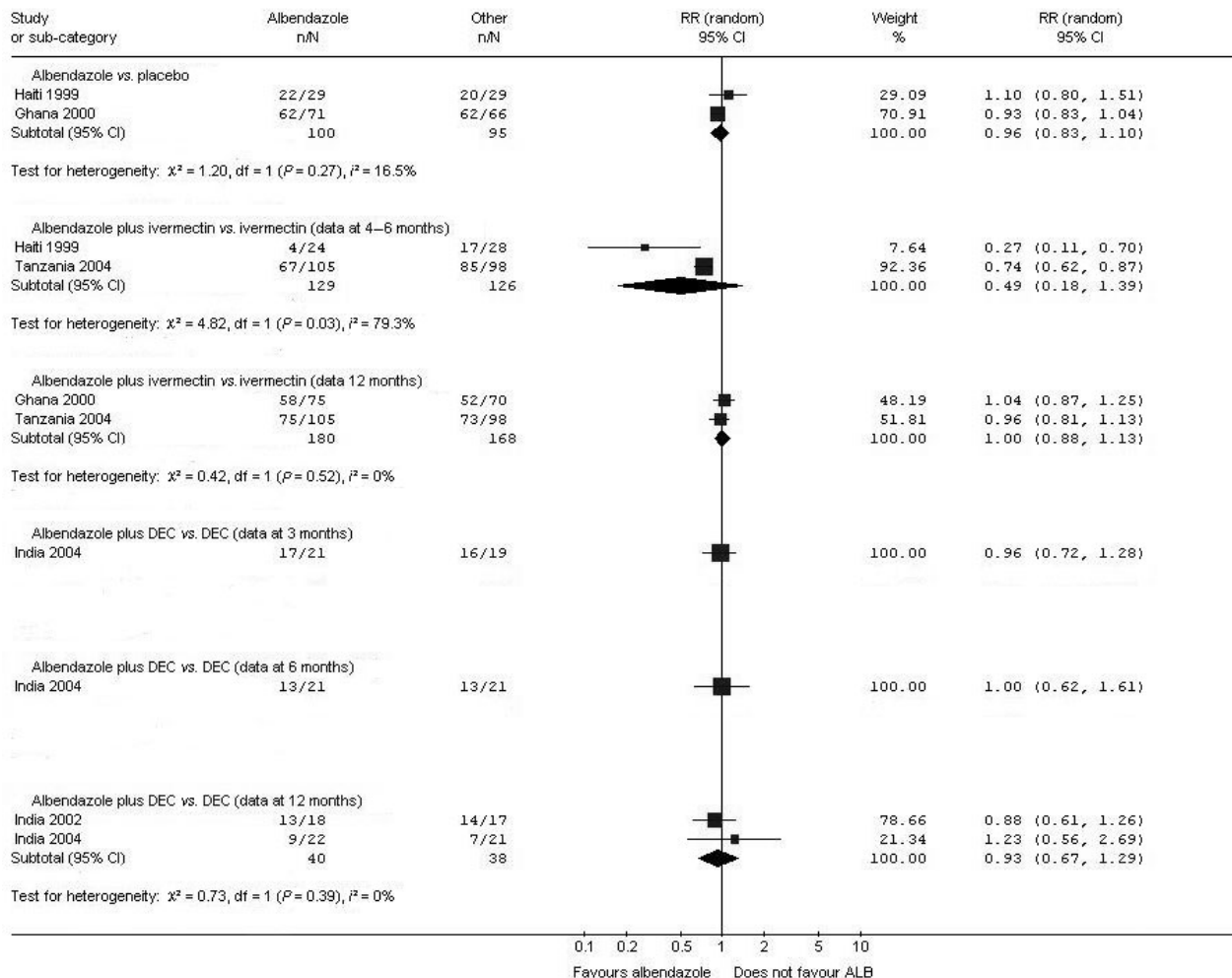


Figure 1 Albendazole and albendazole combinations compared with placebo or the single agents: relative risks of mf prevalence for participants mf positive at baseline.

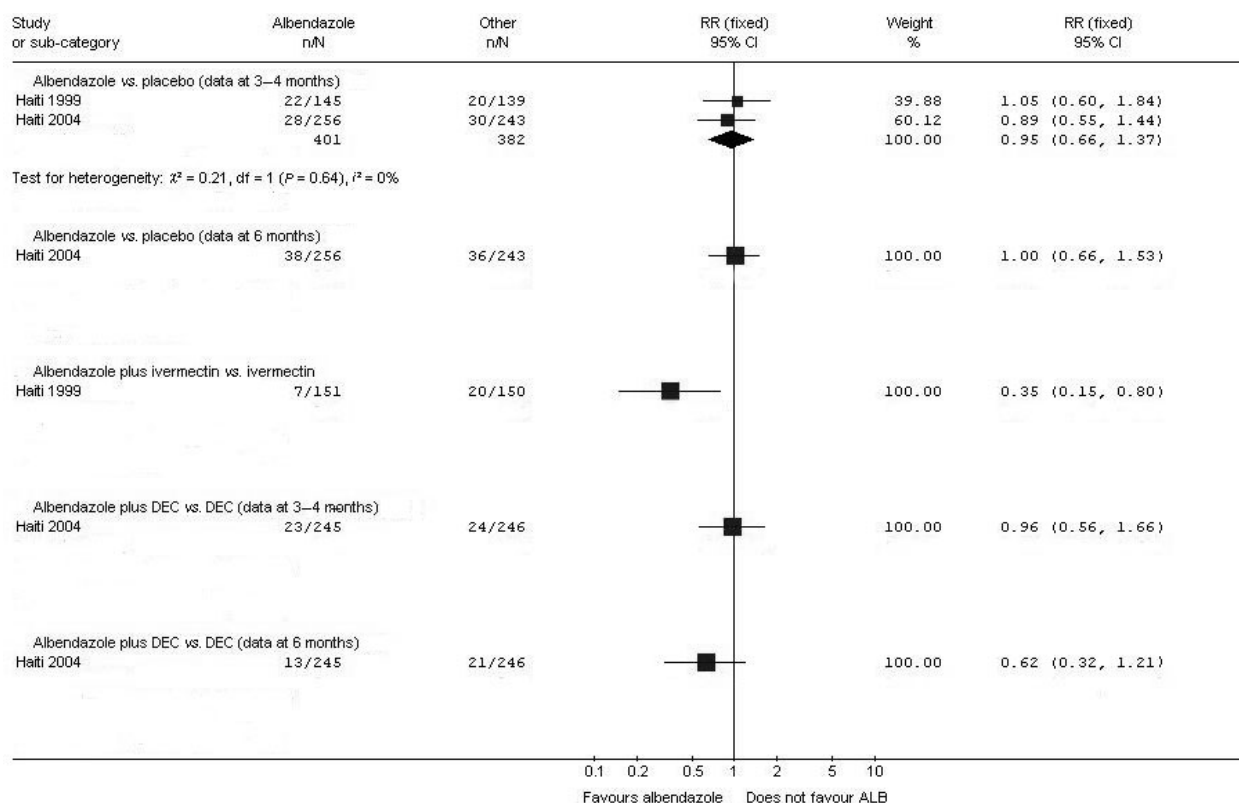
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Figure 2 Albendazole and albendazole combinations compared with placebo or the single agents: relative risks of mf prevalence for albendazole compared with other antifilarial drugs or placebo in participants mf positive or negative at baseline.

detected (RR = 1.0, 95% CI 0.66 to 1.53, $n = 499$ at 6 months; Figure 2).

All three trials reported on microfilarial density (Tables 2 and 3). In two trials, there were no statistically significant differences between albendazole and placebo (Addiss *et al.* 1997; Beach *et al.* 1999; Dunyo *et al.* 2000). In one trial (Haiti 2004), albendazole was significantly better than placebo at 6 months ($P < 0.05$, author's test), but not at 3 months (Fox *et al.* 2005).

Albendazole co-administered with ivermectin

In three trials reporting on participants who were mf positive at baseline, albendazole was co-administered with ivermectin and compared with ivermectin alone (Addiss *et al.* 1997; Beach *et al.* 1999; Dunyo *et al.* 2000). One study from Haiti reported a 73% reduction in mf prevalence for the combination compared with ivermectin alone at 4 months (RR 0.27, 95% CI 0.11 to 0.70, $n = 52$) (Addiss *et al.* 1997; Beach *et al.* 1999) (Figure 1). A second study from Ghana found no difference after 1 year (RR 1.04, 95% CI 0.87 to 1.25, $n = 145$) (Simonsen *et al.*

2004). The third study from Tanzania found a statistically significant reduction in mf prevalence after 6 months (RR = 0.74, 95% CI 0.62 to 0.87, $n = 203$), but after 1 year there was no difference (RR = 0.96, 95% CI 0.81 to 1.13, $n = 203$) (Simonsen *et al.* 2004). Meta-analysis of the two trials reporting outcomes at 4–6 months (Addiss *et al.* 1997; Beach *et al.* 1999; Simonsen *et al.* 2004), gave a reduction in mf prevalence of 51% with combination treatment, but this was not significant (RR = 0.49, 95% CI 0.18 to 1.39, $n = 255$). The two trials reporting at 1 year showed no difference between the treatment arms (RR = 1.0, 95% CI 0.88 to 1.13, $n = 348$) (Dunyo *et al.* 2000; Simonsen *et al.* 2004). The Haiti 1999 trial also reported on mf prevalence for individuals who were mf positive or negative at baseline; results are similar to those presented above (Figure 2).

All three trials reported on mf density (Table 2). One (Ghana) did not find a statistically significant difference between the two groups (Dunyo *et al.* 2000). The 1999 Haiti study found a significantly greater reduction in geometric mean microfilarial density in the combination group (from 13.7 to 0.3, 98.9%), compared with the

Table 2 Microfilarial density for albendazole *vs.* placebo, *vs.* ivermectin, and in combination with ivermectin (months of follow-up)

	Unit		Placebo	Albendazole	Ivermectin	Albendazole + ivermectin
Haiti 1999 (Addiss <i>et al.</i> 1997; Beach <i>et al.</i> 1999)	Mf/20 µl	<i>n</i>	29	29	28	24
		Baseline	9.3	14.1	15.5	13.7
		4 months	5.3	5.1	1.5	0.3
		% Change	17.2	28.7	76.1	98.9†
Ghana 2000 (Dunyo <i>et al.</i> 2000)	Mf/100 µl	<i>n</i>	66	71	70	75
		Baseline	971	798	640	614
		12 months	845	351	124	78
		% Change	13.0	68.5	80.6	87.3
Tanzania 2004 (Simonsen <i>et al.</i> 2004)	Mf/100 µl	<i>n</i>			98	105
		Baseline			763.5	812.6
		6 months			150.0	29.8
		12 months			124.9	59.4
		% Change 6 months			80.4	96.3‡
		% Change 12 months			83.6	92.7‡

† *vs.* ivermectin: $P < 0.05$.‡ *vs.* ivermectin P ANOVA (repeated measures) $P = 0.01$.**Table 3** Microfilarial density for albendazole *vs.* placebo, *vs.* DEC, and in combination with DEC (months of follow-up)

	Unit		Placebo	Albendazole	DEC	Albendazole + DEC
India 2002 (Pani <i>et al.</i> 2002)	Mf/100 µl	<i>n</i>		19	17	18
		Baseline		77.6 (range: from 22 to 606)	81.3 (range: from 22 to 542)	79.4 (range: from 22 to 223)
		% Change day 3		8.7	26.2	35.7
		% Change day 7		14.1	36.7	45.1
		% Change day 360		94.7	89.6	95.4
Haiti 2004 (Fox <i>et al.</i> 2005)	Mf/20 µl	<i>n</i>	243	256	246	245
		Baseline	17.3 (95% CI: from 14.5 to 20.6)	12.1 (95% CI: from 10.3 to 14.2)	12.9 (95% CI: from 11.0 to 15.2)	13.4 (95% CI: from 11.4 to 15.8)
		3 months	8.7 (95% CI: from 7.4 to 10.2)	4.7 (95% CI: from 3.9 to 5.7)	2.9 (range: from 2.5 to 3.4)	2.3 (95% CI: from 2.0 to 2.7)
		6 months	11.2 (95% CI: from 9.2 to 13.7)	4.4 (95% CI: from 3.7 to 5.3)	2.8 (95% CI: from 2.3 to 3.4)	0.76 (range: from 0.7 to 0.9)
		% Change 3 months	8.2	22.0	31.3	37.3
		% Change 6 months	10.3	34.7†	50.4	80.4‡

† *vs.* placebo $P < 0.05$.‡ *vs.* ivermectin $P < 0.05$.

ivermectin group (from 15.5 to 1.5, 76.1%) at 4 months ($P < 0.05$) (Addiss *et al.* 1997; Beach *et al.* 1999). As mf density was very low in both groups, the importance of this difference is uncertain. The Tanzania study also found a greater reduction at 6 months in the combination group (from 812.6 to 29.8, 96.3%, compared with 763.5 to 150.0, 80.4%, in the group receiving ivermectin alone, $P < 0.001$ for both groups compared with baseline) (Simonsen *et al.* 2004). Similar results were found at 12 months, although the difference between the two groups had narrowed (92.7% reduction in combination

group, compared with 83.6% in the ivermectin group) (Simonsen *et al.* 2004).

Albendazole co-administered with diethylcarbamazine

Three trials compared albendazole co-administered with DEC *vs.* DEC alone (Pani *et al.* 2002; Kshirisagar *et al.* 2004; Fox *et al.* 2005). The first small study from India randomised only hospital patients who were mf positive at baseline. This study found no significant difference in mf prevalence at 360 days (RR = 0.88, 95% CI 0.61 to 1.26,

$n = 35$) (Pani *et al.* 2002) (Figure 1). The second community trial from India found no significant differences in mf prevalence at any of the time points assessed (3, 6 and 12 months), but only a small proportion of the study population were included in this assessment (Kshirisagar *et al.* 2004) (Figure 1). The third, larger study from Haiti enrolled children who were mf positive or negative at baseline (Fox *et al.* 2005). It found no difference in mf prevalence at 3 months in the treatment arm receiving DEC alone compared with that receiving DEC and albendazole co-administered (at 3 months RR = 0.96, 95% CI = 0.56 to 1.66, $n = 491$). A non-significant 38% reduction was observed in the group receiving combination therapy at 6 months (RR = 0.62, 95% CI 0.32 to 1.21, $n = 491$), but the 95% confidence intervals are wide and the estimate is therefore imprecise (Figure 2).

The small hospital trial from India showed no difference in mf density between the treatment arms (Table 3) (Pani *et al.* 2002). In the 2004 Haiti study, there was no difference in mf density at 3 months, but a statistically significant difference was found at 6 months in favour of combination treatment (2.8 mf/20 μ l in the DEC arm compared with 0.76 in the combination arm, $P < 0.05$) (Fox *et al.* 2005). The community trial from India did not report on mf density (Kshirisagar *et al.* 2004).

Discussion

This review was designed to assess the effects of albendazole alone or in combination with antifilarial drugs currently recommended by GPELF. Albendazole alone did not appear to reduce mf prevalence when compared with placebo, and only one trial found any significant reduction in mf density.

Both ivermectin and DEC are known to kill microfilaria. It has been suggested that combination treatment of albendazole with ivermectin may be more effective than ivermectin alone in the short term, implying that the drug combination will have a greater impact on transmission. However, these findings are based on just three trials, which reported outcomes between 4 and 12 months only; further evidence is clearly required. Doses of ivermectin also differed between the trials; they were highest in the 1999 Haiti study, which showed the greatest relative reduction in mf for the combination treatment compared with ivermectin alone (see Table 1). Three trials compared albendazole co-administered with DEC to DEC alone (Pani *et al.* 2002; Kshirisagar *et al.* 2004; Fox *et al.* 2005). These also had mixed findings (Figures 1 and 2). Most trials had significant losses to follow-up which may influence their results.

A recently published review concluded that co-administration of albendazole was more effective in reducing mf

prevalence than one antifilarial drug alone (Gyapong *et al.* 2005). This review had different inclusion criteria (it included observational data, and did not assess the quality of the studies). Most importantly, it incorporated data from several studies twice (by counting results at 6 and 12 months and combining them in the same meta-analysis) which artificially narrows 95% CI, resulting in the authors erroneously concluding that overall the effect was 'statistically significant' (Gyapong *et al.* 2005).

This review does not consider the positive effects of administering albendazole to people with filariasis, many of whom are incidentally infected with intestinal helminths (Dickson *et al.* 2003). It is possible other health benefits from albendazole may improve the adherence to mass drug administration for filariasis, if communities perceive them to be valuable. The inclusion criteria do not include non-randomised data, comprehensively assessed by Ottesen *et al.* (1999), which may well be relevant to programme decisions.

With only six trials of albendazole plus either DEC or ivermectin, statistical power was limited for some of the combinations. Further, all include only a single treatment cycle, and not the annual treatment over at least 5 years recommended to eliminate the disease in a community. Several trials are under way which may provide further data (Kshirisagar *et al.* 2004). Other outcomes reported in the trials (including antigen prevalence and density, safety, and effects on clinical disease) were not qualitatively different from those described here (International Filariasis Review Group 2005). Ideally, studies should assess the effect of albendazole-containing regimens on adult worms but only two trials attempted this in a sub-group of patients (Pani *et al.* 2002; Kshirisagar *et al.* 2004). Further large well-designed studies and monitoring of on-going programmes are clearly required to assess the effectiveness of albendazole in combination with DEC or ivermectin on transmission of lymphatic filariasis.

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