Albendazole for lymphatic filariasis (Review)

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[Intervention Review]

Albendazole for lymphatic filariasis

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ABSTRACT

Background

Mass treatment with albendazole co-administered with another antifilarial drug is part of a global programme to eliminate lymphatic filariasis. We sought reliable evidence of the effects of albendazole on the disease and the parasite.

Objectives

To summarize the effects of albendazole alone or in combination with antifilarial drugs for clinical treatment and community control of lymphatic filariasis.

Search strategy

We searched the Cochrane Infectious Diseases Group Specialized Register (August 2005), CENTRAL (*The Cochrane Library* Issue 3, 2005), MEDLINE (1966 to August 2005), EMBASE (1974 to August 2005), LILACS (1982 to August 2005), and reference lists. We also contacted researchers, the World Health Organization, and GlaxoSmithKline.

Selection criteria

Randomized and quasi-randomized controlled trials of albendazole alone or combined with another antifilarial drug for treating individuals with lymphatic filariasis, or for reducing transmission in endemic communities.

Data collection and analysis

Two authors independently assessed eligibility and trial quality, and extracted data. Authors contacted investigators for missing information or clarification.

Main results

Seven trials including 6997 participants (995 with detectable microfilariae) met the criteria. A comparison of albendazole and placebo detected no effect on microfilariae prevalence (920 participants; 3 trials); one trial (499 participants) reported significantly lower microfilariae density at six months. Albendazole performed slightly worse than ivermectin in two trials (436 participants). Compared with diethylcarbamazine (DEC), two small trials (56 participants) found little difference in microfilariae prevalence over an extended follow up. One larger trial (502 participants) found a statistically significant effect for DEC at six months, but none at three months.

Microfilariae prevalence and density were statistically significantly lower with the combination of albendazole and ivermectin compared with ivermectin alone in two of three trials (649 participants). Two trials compared albendazole plus DEC with DEC alone and found no statistically significant difference in microfilariae prevalence, though one trial favoured the combination at six months (risk ratio 0.62, 95% confidence interval 0.32 to 1.21; 491 participants). This trial also found a statistically significant reduction in microfilariae density.

Authors' conclusions

There is insufficient evidence to confirm or refute that albendazole co-administered with DEC or ivermectin is more effective than DEC or ivermectin alone in clearing microfilariae or killing adult worms. Albendazole combined with ivermectin appears to have a small effect on microfilaraemia, but this was not consistently demonstrated. The effect of albendazole against adult and larval filarial parasites, alone and in combination with other antifilarial drugs, deserves further rigorous research.

PLAIN LANGUAGE SUMMARY

Not enough evidence on effectiveness of the drug albendazole, alone or in combination, for killing or interrupting transmission of threadlike worms that cause lymphatic filariasis

Filariasis affects about 120 million people in more than 80 countries and is spread by mosquitoes. Adult worms take up residence in lymph channels and when paired, produce larvae that circulate in the blood. The adult worms can live in the lymph system for five years or more. The infection can cause severe disability, due to massive enlargement of limbs, genitals, and breasts. On the other hand, many infected people have no symptoms, but do contribute to the perpetuation of the infection in the community. This review of trials found insufficient evidence to say whether a single dose of the drug albendazole kills the worms, or whether, if given in combination with diethylcarbamazine or ivermectin, it enhances the killing of these worms or the larvae they produce.

BACKGROUND

Epidemiology

Lymphatic filariasis is a parasitic infection of threadlike, filarial worms that affects about 120 million people in more than 80 countries (Michael 1996; WHO 2000). Bancroftian filariasis, caused by infection with *Wuchereria bancrofti*, occurs in tropical regions of Asia, Africa, China, and the Pacific islands, and in parts of the Caribbean and South America. Brugian filariasis is less common, with *Brugia malayi* occurring in parts of Asia, and *Brugia timori* in Indonesia (FGN 1996).

Filariasis is transmitted by mosquitoes from a number of genera (including *Culex, Anopheles, Mansonia, Ochlerotatus,* and *Aedes*) (Burkot 2002). Female mosquitoes transmit the disease. They are infected when they take blood meals from people with microfilariae (mf), early stage larvae. The larvae develop for about 12 to 15 days in the mosquito to a mature larval stage (Scott 2000). When the mosquito takes a subsequent blood meal, the larvae enter the skin, migrate to the lymph vessels, and develop into adult worms, where male and female worms pair. They later produce mf, which migrate to the blood causing microfilaraemia. The time between being infected and adult worms producing microfilaraemia is estimated to be about 12 months (Mahoney 1971).

Microfilariae move in and out of circulating peripheral blood according to a daily cycle. In most species, mf levels peak during the night, between 10 pm to 4 am (Simonsen 1997), a time when mosquito vectors are actively feeding. In Fiji, Polynesia, and the Philippines some strains of *Wuchereria bancrofti* mf peak during

the day (Scott 2000).

Clinical features

Many people with filariasis may be asymptomatic most of the time. However, even people without clinical symptoms often have lymphatic changes, including lymphangiectasia (widening of the lymphatic vessels) and thickening of the spermatic cord (Addiss 2000; Dreyer 2000), which can be detected through imaging studies. Clinical symptoms and signs include hydrocoele (excess fluid inside the scrotal sac), lymphoedema (swelling and enlargement of affected areas of the body), and elephantiasis (long standing enlargement and swelling of the limbs, scrota, or breasts associated with skin thickening).

Historically, filarial infection has been diagnosed by examining a blood smear for mf, but, even if blood is taken at night, not all infections are detected because mf levels are very low in many people. Antigen assays, which became available for field use during the 1990s, are more sensitive and can be used for blood collected during the day or night (Weil 1997) because they indicate the presence of the adult worm and do not depend on the temporal presence of mf. Ultrasound imaging can demonstrate the presence of live adult worms (Dreyer 1995).

How the filarial worm causes disease is not well understood. The following have been proposed: adult worms living in and damaging lymph vessels; immunologic reactions to the presence and death of filarial worms; secondary infections of affected areas, which contribute significantly to both acute and chronic disease manifestations (Dreyer 2000). Researchers have also suggested that toxins released by *Wolbachia* (endosymbiotic bacteria found within the cells of filarial worms) cause disease (Taylor 2001). Some or all of these processes may be important.

Control

Control strategies aim to reduce mf in the community to levels that prevent transmission (Ottesen 1997; Ottesen 1999). Treatment of individuals with clinical disease is generally only partially effective (at least in part because there is no drug that reliably kills the 'macrofilariae', the adult worms). Mass drug administration programmes therefore aim for a sustainable reduction in community mf loads below a critical threshold or a complete clearance of mf to have an appreciable impact on transmission. The Global Programme to Eliminate Lymphatic Filariasis recommends yearly, single-dose, two-drug regimens (albendazole plus diethylcarbamazine or albendazole plus ivermectin) for at least five years (corresponding to the reproductive lifespan of the adult worm) to prevent transmission. However, the critical threshold below which no further transmission will take place is unclear and may depend on the vector species in the locality. Some mosquitoes (eg *Aedes polynesiensis*, some culicine mosquitoes in India and the Americas) may be more efficient at lower mf densities (a process known as limitation). Higher treatment coverage for longer periods or other strategies such as vector control may be required in areas where these vectors are responsible for a high proportion of transmission (Burkot 2002; Pichon 2002).

Ivermectin and diethylcarbamazine (DEC) both kill mf. DEC may have some temporary sterilizing effects or actually kill adult worms, so one treatment with either drug can affect mf levels for many months. Reductions of 90% from pretreatment mf levels have been seen after a single dose of DEC or ivermectin even one year after treatment (Ottesen 1999). The impact of drug treatment on transmission can be enhanced, if currently available antifilarial drugs demonstrate a killing or sterilizing effect on adult worms, in addition to their effect on mf. There are concerns that an over reliance on a limited range of drugs may eventually cause resistance, although there is little direct evidence that this is currently a problem in filariasis (Barat 1997; Geerts 2001).

It has been observed that some infected people lose their mf in the absence of treatment (Vanamail 1990). However, overall mf prevalence rates are believed to be relatively stable over time in endemic communities in the absence of community treatment (Meyrowitsch 1995); new microfilaraemic infections replace those whose microfilaraemia subsides (Vanamail 1990; Weil 1999). Nevertheless, lymphatic filariasis has been eradicated using vector control methods from some areas such as the Solomon Islands, Australia (Burkot 2002; Pichon 2002), and parts of China using DEC-fortified salt and other DEC regimens (Gelband 1994).

DEC and ivermectin

DEC has been in use for filariasis for more than 50 years. In the early years of control the recommended regimen for DEC was 6 mg/kg daily for 12 days (WHO 1984). Later, clinical and community trials determined that single doses given at various intervals — weekly, monthly, annually, and biannually — were equally effective (Andrade 1995; Eberhard 1989; Simonsen 1995). There is reasonable evidence from ultrasound and clinical observations that DEC kills some adult worms (macrofilariae) after single doses (Addiss 2000; Figueredo-Silva 1996; Noroes 1997).

Ivermectin is used for the treatment and community control of onchocerciasis (caused by another filarial worm, *Onchocerca volvulus*). It has also been effective in community control programs for lymphatic filariasis (Cao 1997; Cartel 1990; Coutinho 1994). It can be used in many places, but it is particularly important in areas where both onchocerciasis and lymphatic filariasis coexist because DEC can cause eye damage if given to individuals with onchocerciasis. However, recent ultrasound studies suggest that adult worms are not killed by ivermectin, even at high doses over a period of six months (Addiss 2000; Dreyer 1996).

Adverse effects of antifilarial drugs can be serious (though almost never fatal) and prevent people from completing treatment. The most serious appear to be due to a host immunologic reaction to

the dying worms (Dreyer 1994; WHO 1984). These effects include fever, headache, malaise, muscle pain, and blood in urine. Local effects include localized pain, tender nodules, lymphadenitis (inflammation of the lymph nodes), and lymphangitis (inflammation of lymph vessels) (Addiss 2000).

Albendazole

Albendazole has been used widely to treat intestinal parasites since the late 1980s and may have a potential role in lymphatic filariasis control (Ottesen 1999). A report from an informal consultation organised by the World Health Organization suggests that repeated high doses of albendazole have a killing or sterilizing effect on *W. bancrofti* adult worms (CDS/FIL 1998). However, the data in the report are scanty and it remains unclear whether adding albendazole to either DEC or ivermectin improves cure, prevents further transmission, or influences the occurrence of adverse events. A narrative review by Horton 2000 from GlaxoSmithKline, which manufactures albendazole, did not demonstrate that adding albendazole to either drug increased the frequency or severity of adverse events. GlaxoSmithKline states that albendazole does not have a role in morbidity management — it will not treat the symptoms in people already affected by filariasis (GlaxoSmithKline 2003). But at least one trial has considered the effectiveness of albendazole in reducing both disease progression and incidence of new symptoms (such as hydrocoele) (Dunyo 2000). We therefore include this as a secondary outcome.

A recently published review concluded that co-administration of albendazole was more effective in reducing mf prevalence than one antifilarial drug alone (Gyapong 2005). This review had included observational data and did not assess the quality of the studies, whilst our analysis included only higher quality randomized controlled trials. Most importantly, Gyapong 2005 incorporated data from several studies twice (by counting results at six and twelve months and combining them in the same meta-analysis), which artificially narrows the 95% confidence intervals. This resulted in the authors erroneously concluding that overall the effect was 'statistically significant' (Gyapong 2005).

In this review, we aim to summarize the evidence for the effects of albendazole alone or in combination with DEC or ivermectin in both the individual treatment and transmission control of lymphatic filariasis.

OBJECTIVES

1. To assess the effects of albendazole on individuals or populations with filarial infection.

2. To assess the effects of albendazole on morbidity among individuals with filarial infection (incidence of new disease or progression of existing symptoms).

3. To assess the frequency of adverse events for albendazole both given singly or in combination with another antifilarial drug (DEC or ivermectin).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials; cluster-randomized controlled trials; and quasi-randomized controlled trials.

Types of participants

- Adults or children with filarial infection defined by the presence of mf parasites in the blood, filarial antigens in the blood, or ultrasound detection of adult worms in lymphatic vessels.
- Populations normally resident in endemic communities and who are eligible for treatment regardless of microfilaraemia status (community trials).

Types of interventions

- Albendazole alone versus placebo.
- Albendazole alone versus DEC.
- Albendazole alone versus ivermectin.
- Albendazole plus DEC versus DEC (DEC dose and regimen same in both arms).
- Albendazole plus ivermectin versus ivermectin (ivermectin dose and regimen same in both arms).

Types of outcome measures

Primary

- Mf prevalence.
- Mf density.
- Community mf density (in mass treatment trials).
- Antigenaemia prevalence or density.
- Adult worms (macrofilariae viability detected by ultrasound).

Secondary

- Acute filariasis (fever plus clinical evidence of inflammation of the lymphatic system, as defined by primary investigators).
- Appearance or disappearance of hydrocoele or lymphoedema.
- Reduction in size (or severity or grade) of hydrocoele or lymphoedema.

Adverse events

- Adverse events that prevent daily activities or require hospitalization.
- Systemic adverse events (eg fever, headache, malaise, myalgia, or haematuria).
- Local adverse events (eg localized pain and inflammation, tender nodules, lymphadenitis, or lymphangitis).

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (August 2005); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 3, 2005); MEDLINE (1966 to August 2005); EMBASE (1974 to August 2005); and LILACS (1982 to August 2005).

Researchers, organizations, and pharmaceutical companies

We contacted individual researchers working in the field, the World Health Organization, and GlaxoSmithKline (the company producing albendazole) for unpublished and ongoing trials.

Reference lists

We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

One author (Henry Ejere (HE) or Julia Critchley (JC)) screened titles and abstracts identified from the search strategy. Hard copies of the published or unpublished trial reports potentially relevant to the review were retrieved for further assessment. Two authors (HE or JC and Paul Garner (PG)) independently used a predesigned eligibility form to select trials that met the inclusion criteria. Disagreements were resolved through discussion.

Data extraction and management

One author (HE or JC) extracted data, which a second author (PG) checked. Where trials reported the same outcomes in different ways, we attempted to contact the primary investigators for further information, which might allow transformation of data. We extracted data relating to trial and participant characteristics, and reported outcome measures. We intended to extract data to allow an intention-to-treat analysis (all the participants analysed according to the intervention to which they were originally allocated, whether they received it or not). This was not possible, but may be attempted in future updates. Where the numbers randomized and the numbers analysed for each outcome were inconsistent, we calculated the percentage loss to follow up and recorded this information in Appendix 2. For dichotomous outcomes, we recorded the number of participants experiencing the event in each group of the trial. For continuous outcomes, we extracted arithmetic means and standard deviations. Where geometric means were reported, we extracted and recorded this information. We also tried to extract confidence intervals or standard deviations on the log scale. One author (HE or JC) entered data into Review Manager 5.

Assessment of risk of bias in included studies

Two authors (HE or JC and PG) independently assessed trials according to predefined quality criteria. We assessed the generation of allocation sequence and concealment of allocation to be adequate, inadequate, or unclear according to Jüni 2001. We assessed blinding as double blind (trial uses a placebo or a double dummy technique such that neither the participant or care provider/assessor knows which treatment is given), single blind (participant or care provider/assessor is aware of the treatment given), or open (all parties are aware of the treatment). We assessed the inclusion of all randomized participants in the analysis to be adequate if 90% or more were included.

Data synthesis

We grouped the trials by the main comparator interventions, such as albendazole versus placebo. Within comparator groups, we stratified trials into those of treatment in individuals and trials of mass treatment in communities. Where appropriate we combined trials in a meta-analysis using a fixed-effect model. We calculated risk ratios (RR) for dichotomous outcomes and used 95% confidence

intervals. We reported medians and ranges in tables only. We assessed heterogeneity by visually inspecting forest plots and carrying out a chi-squared test for heterogeneity (statistical significance at 10% level). We used the random-effects model to pool data where we detected heterogeneity. Too few trials were available to examine heterogeneity in any more detail, but this might be possible in future updates.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Trial selection

We identified 12 published trials of which seven met the inclusion criteria (*see* 'Characteristics of included studies'). We excluded five studies reported in eight publications (*see* 'Characteristics of excluded studies'). We are aware of one ongoing study (*see* 'Characteristics of ongoing studies').

Study design and location

All the trials randomized individual participants. The length of the follow up varied: four months (Beach 1999); six months (Fox 2005); 12 months (Dunyo 2000; Kshirsagar 2004; Simonsen 2004); 19 months (Jayakody 1993); and two years (Pani 2002). The trials were conducted in southern Ghana (Dunyo 2000), Haiti (Beach 1999; Fox 2005), India (Kshirsagar 2004; Pani 2002), Sri Lanka (Jayakody 1993), and Tanzania (Simonsen 2004).

Participants

Nine-hundred and ninety five of the 6997 randomized participants had detectable mf. Jayakody 1993 and Pani 2002 enrolled people who were mf positive. Dunyo 2000, Beach 1999, Simonsen 2004, and Fox 2005 enrolled people regardless of mf status at baseline. Kshirsagar 2004 enrolled 1403 participants for a safety study and included 103 of these in a separate analysis of efficacy. Forty-three of the 103 were mf positive, 30 had clinical disease, and 30 were mf negative and asymptomatic. However, at most time points, mf prevalence results were only available for the 43 mf-positive participants.

Intervention

The trials addressed all the pre-specified comparisons: albendazole alone versus placebo (Beach 1999; Dunyo 2000; Fox 2005); albendazole alone versus DEC (Fox 2005; Jayakody 1993; Pani 2002); albendazole alone versus ivermectin (Beach 1999; Dunyo 2000); albendazole plus DEC versus DEC (Fox 2005; Kshirsagar 2004; Pani 2002); and albendazole plus ivermectin versus ivermectin (Beach 1999; Dunyo 2000; Simonsen 2004).
All the trials used the same albendazole dose (400 mg). The three trials using ivermectin had different doses: 200 to 400 µg/kg (Beach 1999); and 150 to 200 µg/kg (Dunyo 2000; Simonsen 2004). The DEC dose was 6 mg/kg body weight. The drugs were given as a single treatment in all trials except for Jayakody 1993 in which DEC was given daily and albendazole twice daily for 21 days.

Outcomes

All trials reported on mf. The methods of measurement varied, including prevalence in 20 µL of blood (Beach 1999), prevalence and density in 20 µL of blood (Fox 2005), prevalence in 60 µL of blood (Kshirsagar 2004), prevalence in 1 mL of venous blood (Pani 2002), and prevalence in 1 mL blood using membrane filtration (Jayakody 1993), or prevalence in 100 µL using a counting chamber (Dunyo 2000; Simonsen 2004); *see* Appendix 3 and Appendix 5 for mf prevalence and mf density, respectively.
Several trials also reported antigen prevalence or density (Dunyo 2000; Fox 2005; Kshirsagar 2004; Pani 2002; Simonsen 2004); *see* Appendix 4 and Appendix 6. Two trials determined the effect of treatment on adult worms by ultrasound scan for a subgroup of participants (Kshirsagar 2004; Pani 2002); *see* Appendix 7.
All trials reported adverse events, but the methods of reporting varied (*see* 'Characteristics of included studies' and Appendix 8).

Reported statistical analysis

Standard deviations or confidence intervals were not reported for mf density outcomes; this information was obtained from the investigators for Fox 2005. As so few trials reported standard deviations, we could not pool results for changes in mf density; results quoted in this review are the original trial author's calculations.
Two trials, Jayakody 1993 and Pani 2002, did not clearly describe the method of calculating reductions in geometric mean mf density, but Pani 2002 provided further details on request. This trial calculated a William's mean (a modification of the geometric mean to take into account zero counts) (Basanez 1994) on the pretreatment and post-treatment mf densities. Dunyo 2000 calculated change in mf density by two methods the Williams mean and by using an 'area under the curve' analysis (an average density over the whole 12 month post-treatment period). Simonsen 2004 calculated a William's mean and estimated the combined effect over the one-year follow-up period using repeated measures techniques

(either ANOVA or generalized estimating equations). Beach 1999 and Fox 2005 calculated the geometric mean mf density reduction by dividing the difference between densities before and after treatment by the pretreatment mf density and log transforming the results. If pretreatment mf density was less than the density after treatment, the reduction was deemed to be zero. The trialists performed this adjustment to eliminate the problem of log transforming a negative value, but this method may bias estimates of treatment effectiveness, as increases in mf density after treatment are set to zero. For this reason, for Beach 1999, we present the trialists' results in the text and the percentage change using the group means in tables. The Fox 2005 trial authors recalculated geometric mean changes taking into account children where mf density increased post-treatment at our request (although estimates do not include children newly infected over the course of the trial), and we report these revised figures.

Risk of bias in included studies

See the 'Characteristics of included studies' for details and Appendix 2 for a summary.

Generation of allocation sequence

All trials were described as randomized, but Pani 2002 and Kshirsagar 2004 did not describe a method of randomization, and Jayakody 1993 only stated that the list was predetermined and restricted.

Allocation concealment

Beach 1999, Dunyo 2000, Pani 2002, and Simonsen 2004 used a third party in the allocation process to conceal allocation. Allocation concealment was unclear in the other trials.

Blinding

Five of the trials were double blind (Beach 1999; Dunyo 2000; Kshirsagar 2004; Pani 2002; Simonsen 2004). The outcome assessors were blinded in Fox 2005, and Jayakody 1993 did not mention blinding.

Inclusion of randomized participants in the analysis

Losses of participants during the follow-up period were significant in most of the trials. In Dunyo 2000, 1181 (82.9%) of the 1425 participants were re-examined at 12 months; 67 of the 340 mf-positive participants (20%) were also lost to follow up. Beach 1999 excluded 380 of 965 (39%) randomized participants who did not have both pretreatment and post-treatment blood examinations. However, there were few losses among the mf positive participants at baseline (3/113). In Jayakody 1993, six of 16 (37.5%) men allocated to albendazole and three of 13 (23%) allocated to DEC were lost to follow up by 15 to 19 months. Pani 2002 reported no losses to follow up. Fox 2005 reported on 990 of 1292 (24% lost) originally randomized. Simonsen 2004 analysed 1221 of 1829 (33% lost) randomized. Kshirsagar 2004 included only 103 of 1403 participants in the efficacy analysis (43 of whom were mf positive, 30 had clinical disease, and 30 were asymptomatic mf negative).

Effects of interventions

1. Albendazole versus placebo

Mf prevalence: all participants (mf positive or negative at baseline)

Two trials, Beach 1999 and Fox 2005, did not detect a statistically significant difference after three to four months (783 participants). There was also no statistically significant difference in prevalence in the one trial that reported at six months (Fox 2005). *See* Analysis 1.1.

Mf prevalence: only participants mf positive at baseline

Beach 1999 found no statistically significant difference in the prevalence between albendazole (22/29) and placebo (20/29) at four months. Similarly, Dunyo 2000 found no statistically significant difference between albendazole (62/71) and placebo (62/66) at 12 months. A combined estimate from these two trials also shows no statistically significant difference (RR 0.97, 95% CI 0.87 to 1.09; 195 participants). *See* Analysis 1.2.

Antigen prevalence: all participants (mf positive or negative at baseline)

There were no statistically significant differences in the prevalence of circulating filarial antigen positivity from two trials (Dunyo 2000; Fox 2005) after six to 12 months (1090 participants). *See* Analysis 1.3.

Mf density: all participants (mf positive or negative at baseline)

Fox 2005 reported a reduction in mf density at three and six months. The three-month reduction was by 8.2% (from 17.3 to 8.7 mf/20 µL) in the placebo group compared with 22% (from 12.1 to 4.7 mf/20 µL, not significant) in the albendazole group. At six months, it had reduced by 10.3% (17.3 to 11.2 mf/20 µL) in the placebo group compared with 34.7% (12.1 to 4.7 mf/20 µL) ($P < 0.05$) in the albendazole group. *See* Appendix 5.

Mf density: only participants mf positive at baseline

Beach 1999 estimated the reduction in geometric mean mf density at four months − 63.8% (from 14.1 to 5.1 mf/20 µL) in the albendazole group and 43.0% (from 9.3 to 5.3 mf/20 µL) in the placebo group; this reduction was not statistically significant. Dunyo 2000 reported a reduction in the geometric mean mf density between baseline and 12 months of 68.5% (from 798 to 251 mf/100 µL) in the albendazole group compared with 13% (from 971 to 845 mf/100 µL) in the placebo group, but this was not statistically significant (P = 0.10). An 'area under the curve' analysis from this trial found an 8.4% increase in geometric mean mf density in the placebo group (from 2536 to 2750 mf/100 µL) and a 19.7% decrease in the albendazole group (from 1535 to 1233 mf/100 µL); again this was not statistically significant (P = 0.12). This latter analysis was limited to those with a complete data collection and a mf density of over 100 mf/mL at baseline. *See* Appendix 5.

Antigen density: all participants (mf positive or negative at baseline)

There were no statistically significant differences in the geometric mean percent reduction in antigen density after six months in the albendazole group (3.2%) and the placebo group (1.7%) in Fox 2005. *See* Appendix 6.

Antigen density: only participants mf positive at baseline

Dunyo 2000 reported that the geometric mean mf density of the circulating filarial antigen unit had increased to 147.5% of the pretreatment level in the placebo group, but it decreased to 83.1% of the pretreatment level in the albendazole group; the difference was not statistically significant (P = 0.11). *See* Appendix 6.

Clinical disease: new and pre-existing

Twelve months after treatment Dunyo 2000 detected no statistically significant difference in the development of hydrocoele between participants in the albendazole group (1/129) and placebo group (1/126). No new cases of acute filariasis and leg lymphoedema were observed. Similarly, there were no statistically significant differences in the improvement of symptoms in lymphoedema between the albendazole group (3/13) and the placebo group (2/9), or in hydrocoele between the albendazole group (3/8) and placebo group (5/10). Although we did not detect statistically significant differences, the trials lacked power for clinical outcomes so clinically important differences cannot be ruled out. *See* Analysis 1.4 *and* Analysis 1.5.

Adverse events

Dunyo 2000 did not detect a statistically significant difference in systemic adverse events between the albendazole group (31/336) and the placebo group (33/314). No local or severe adverse events were reported. Fox 2005 reported statistically significant reductions in myalgias and cough for albendazole compared with placebo, but no statistically significant differences in headache, fever, or mean treatment impact score. *See* Analysis 1.6 *and* Appendix 8.

2. Albendazole versus ivermectin

Mf prevalence: all participants (mf positive or negative at baseline)

Beach 1999 did not demonstrate a statistically significant difference between the albendazole group (22/145) and ivermectin group (20/150). *See* Analysis 2.1.

Mf prevalence: only participants mf positive at baseline

Beach 1999 reported mf prevalence at four months of follow up: 22/29 in the albendazole group and 17/28 in the ivermectin group. Dunyo 2000 also reported this outcome: 62/71 in the albendazole group and 52/70 in the ivermectin group. Pooling the two trials, albendazole was slightly poorer in clearing mf, but this only just reached statistical significance (RR 0.84, 95% CI 0.72 to 0.98; 198 participants). *See* Analysis 2.2.

Antigen prevalence: all participants (mf positive or negative at baseline)

Dunyo 2000 reported no statistically significant difference in the number of participants positive for circulating filarial antigen at baseline or after 12 months for those treated with albendazole (105 and 110) or ivermectin (99 and 101). *See* Analysis 2.3.

Mf density: only participants mf positive at baseline

Beach 1999 reported on the percentage reduction in geometric mean mf density between baseline and four months follow up. There was a reduction of 28.7% (14.1 to 5.1 mf/20 µL) for the albendazole group and of 76.1% (15.5 to 1.5 mf/20 µL) for the ivermectin group, P = 0.02. Dunyo 2000 measured mean values at baseline and 12 months follow up, which changed from 798 to 251 mf/100 µL (68.5% reduction) for albendazole and from 640 to 124 mf/100 µL (80.6% reduction) for ivermectin; no statistical significance test was reported. An 'area under the curve' analysis from this trial found a 19.7% decrease in the albendazole group (from 1535 to 1233 mf/100 µL) and a 56.2% decrease in the ivermectin group (from 1731 to 759 mf/100 µL). This latter analysis was limited to those with complete data collection and a mf density of more than 100 mf/mL at baseline. *See* Appendix 5.

Antigen density: only participants mf positive at baseline

Dunyo 2000 reported that the geometric mean mf density of the circulating filarial antigen unit had decreased to 83.1% of the pretreatment level in the albendazole group and 70.3% in the ivermectin group (no statistical test applied). *See* Appendix 6.

Clinical disease

Dunyo 2000 found no statistically significant differences in the risk of developing hydrocoele (1/129 albendazole and 1/133 ivermectin), improvements in lymphoedema (3/13 albendazole and 2/13 ivermectin), and improvements in hydrocoele (3/8 albendazole and 2/9 ivermectin), but sample sizes were small and confidence intervals wide. *See* Analysis 2.4 *and* Analysis 2.5.

Adverse events

Dunyo 2000 did not detect a statistically significant difference in the number of systemic adverse events between the albendazole group (31/336) and ivermectin group (36/295). *See* Analysis 2.6.

3. Albendazole plus ivermectin versus ivermectin

Mf prevalence: all participants (mf positive or negative at baseline)

Beach 1999 estimated a statistically significant 65% reduction in mf prevalence for the combination (7/151) compared with ivermectin alone (20/150). *See* Analysis 3.1.

Mf prevalence: only participants mf positive at baseline

Beach 1999 reported a 73% reduction in mf at four months for the combination compared with ivermectin alone (4/24) mf positive at four months for the combination compared with (17/28) for ivermectin alone). Simonsen 2004 reported a smaller reduction at six months (203 participants). Overall, there was no statistically significant difference at four to six months (RR 0.49, 95% CI 0.18 to 1.39, random-effects model; 255 participants).
Two trials reported on this outcome at 12 months (Dunyo 2000; Simonsen 2004). Both trials found no statistically significant difference between the combination and ivermectin (RR 1.00, 95% CI 0.88 to 1.13; 348 participants). *See* Analysis 3.2.

Antigen prevalence: all participants (mf positive or negative at baseline)

Dunyo 2000 reported no statistically significant difference in the numbers positive for circulating filarial antigen at baseline or 12 months (121 to 122 for albendazole plus ivermectin; 99 to 101 for ivermectin alone). *See* Analysis 3.3.

Antigen prevalence: only participants antigen positive at baseline

Neither Dunyo 2000 nor Simonsen 2004 reported any statistically significant differences at six or 12 months. *See* Analysis 3.4.

Mf density: only participants mf positive at baseline

Beach 1999 reported a reduction in the geometric mean mf density at four months of 98.9% for the combination group compared with 76.1% for the ivermectin group ($P < 0.05$).
Dunyo 2000 reported that the reduction in geometric mean mf density in both groups after 12 months was 87.3% for the combination and 80.6% for ivermectin, but it was not statistically significant ($P = 0.80$). An 'area under the curve' analysis from this trial found that the 69.3% decrease in the combination group (from 1280 to 393 mf/100 µL) and the 56.2% decrease in the ivermectin group (from 1731 to 759 mf/100 µL) was also not statistically significant ($P = 0.26$). This latter analysis was limited to those with complete data collection and a mf density of over 100 mf/mL at baseline.
Simonsen 2004 reported reductions in the geometric mean mf density in the ivermectin group of 80.4% at six months and 83.6% at 12 months. The reductions were greater in the combination group, 96.3% at six months and 92.6% at 12 months. A repeated measures ANOVA demonstrated a statistically significantly higher rate of reduction in the combination group ($P < 0.0001$). *See* Appendix 5.

Antigen density: only participants antigen positive at baseline

There were no significant differences in the percentage reduction in antigen density for the combination group (59.3%) compared with ivermectin (70.3%) ($P = 0.8$). *See* Appendix 6.

Clinical disease

Dunyo 2000 found no statistically significant difference in the number of new cases of hydrocoele between the combination group (2/147) and the ivermectin group (1/133). This trial also observed no statistically significant differences in the improvement of lymphoedema (2/13 in combination group and 2/13 in ivermectin group) and hydrocoele (4/10 in combination group and 2/9 in ivermectin group). Again, the trials were not designed to detect changes in clinical outcomes; therefore confidence intervals are very wide. *See* Analysis 3.5 *and* Analysis 3.6.

Adverse events

Dunyo 2000 recorded more adverse events with the combination treatment (47/332) compared with ivermectin (36/295), but this was not statistically significant. *See* Analysis 3.7 *and* Appendix 8.

4. Albendazole versus DEC

Two of the three trials that made this comparison were very small and recruited only participants who were mf positive at baseline (Jayakody 1993; Pani 2002). Jayakody 1993 compared albendazole (16 participants) with DEC (13 participants) and attempted to follow the participants for 19 months. They reported that all participants in this extended follow up lived nearby and had received treatment in addition to the study intervention, but they did not report the specifics of the additional treatment. Pani 2002 compared albendazole (19 participants) DEC (17 participants), and albendazole plus DEC co-administered (18 participants). The third trial, Fox 2005, was larger and included children irrespective of mf status from an endemic community.

Mf prevalence: all participants (mf positive or negative at baseline)

Fox 2005 found no statistically significant difference at three months, but there was a statistically significant difference in favour of DEC at six months (RR 1.74, 95% CI 1.05 to 2.88; 502 participants). *See* Analysis 4.1.

Mf prevalence: only participants mf positive at baseline

Pani 2002 reported no statistically significant difference at 90 days or 360 days for albendazole (5/19) or DEC (3/17). Jayakody 1993 stated that 85% (numerator and denominator unclear) of the albendazole-treated participants and 67% (8/12) of the DEC-treated participants still had detectable mf at six months. After 15 to 19 months, 50% (5/10 for both groups) of participants in both groups were mf positive, but a substantial proportion of the participants had been lost during this follow-up period. Pani 2002 continued to follow the participants for up to two years, but they found no statistically significant difference in mf prevalence at this time. *See* Analysis 4.2.

Antigen prevalence: all participants (mf positive or negative at baseline)

Fox 2005 found no statistically significant difference in antigen prevalence at six months. *See* Analysis 4.3.

Antigen prevalence: only participants mf positive at baseline

Pani 2002 reported no statistically significant difference in the prevalence of filarial antigenaemia at any point during the trial (P > 0.05). The percentage reduction measured using immunochromatographic test (ICT) was 83% with albendazole and 87% with DEC; using Og4C3, it was 83% with albendazole and 80% with DEC. *See* Analysis 4.4.

Mf density: all participants (mf positive or negative at baseline)

Fox 2005 reported a fall in the geometric mean mf density in both groups from baseline to three months to six months. The percentage reduction at six months was 34.7% for the albendazole group and 50.4% for the DEC group, but this difference was not statistically significant. *See* Appendix 5.

Mf density: only participants mf positive at baseline

Pani 2002 reported no statistically significant difference in percentage reductions in geometric mean mf density at any of the time points this was measured (days 3, 7, and 360). The mf density appeared to fall faster during the first seven days with DEC compared with albendazole.

Jayakody 1993 also found large reductions in geometric mean mf density at six months for both treatment groups: 1.9% of its initial value for those treated with albendazole and 0.81% for those treated with DEC. After 15 to 19 months of follow up there was no statistically significant difference (geometric mean mf density 3 mf/mL for albendazole and 2 mf/mL for DEC). Similarly to Pani 2002, the mf density appeared to fall faster during the first 28 days with DEC compared with albendazole. *See* Appendix 5.

Antigen density: all participants (mf positive or negative at baseline)

Fox 2005 reported that after six months the geometric mean antigen density was reduced by 17% in the DEC group compared with 3.2% in the albendazole group (P < 0.05). *See* Appendix 6.

Antigen density: participants mf positive at baseline

Pani 2002 found statistically significant reductions in mean optical antigen density by Og4C3 assay in both groups at 360 days: 0.41 with albendazole (P < 0.0001) and 0.32 with DEC (P < 0.0001). *See* Appendix 6.

Adult worms

Pani 2002 reported no statistically significant differences in detection of adult worms by ultrasonography at one or two years, but only a small number of participants were included in this analysis. *See* Appendix 7.

Adverse events

Pani 2002 reported no life-threatening adverse events in any group. Those observed were transient (not lasting beyond six days) and included fever, myalgia, and headache. There was no statistically significant difference in the proportion reporting any systemic adverse events between albendazole (8/19) and DEC (9/17). The

mean score of adverse reaction intensity was lower for albendazole compared with DEC (P < 0.05), but the validity and clinical significance of this scoring system was uncertain.

Jayakody 1993 reported that 11 of 15 participants receiving the full treatment regimen for albendazole developed 'scrotal syndrome', which was classified as 'severe' for two men, moderate for two, and mild for the other seven. None of the participants on DEC developed similar symptoms. One participant on DEC had fever, right hypochondrial pain, and repeated vomiting, and was withdrawn from the trial. Drug doses were much higher in this trial than in the other three. Participants were given albendazole twice a day or DEC once a day for three weeks unlike the other trials that tested a single dose of albendazole plus DEC or ivermectin.

Fox 2005 reported more myalgias in the DEC group (8/44) than the albendazole group (1/46) (P < 0.05), and a higher treatment impact score at days one and two (P < 0.05), but there were no other statistically significant differences between the treatment groups. *See* Analysis 4.5 *and* Analysis 4.6*, and* Appendix 8.

5. Albendazole plus DEC versus DEC

Mf prevalence: all participants (mf positive or negative at baseline)

Fox 2005 showed no statistically significant difference in mf prevalence at three months or six months. *See* Analysis 5.1.

Mf prevalence: only participants mf positive at baseline

The two trials from India, Kshirsagar 2004 and Pani 2002, reported mf prevalence at various time points between three months and two years. There were no statistically significant differences at any time point. *See* Analysis 5.2.

Antigen prevalence: all participants (mf positive or negative at baseline)

Two trials, Fox 2005 and Kshirsagar 2004, showed no statistically significant difference in antigen prevalence at either six or 12 months. *See* Analysis 5.3 and Appendix 4.

Antigen prevalence: only participants antigen positive at baseline

Pani 2002 reported no statistically significant difference in prevalence of filarial antigenaemia by at any point during the trial (P > 0.05). The percentage reduction after one year was 75% on albendazole plus DEC compared with 87% on DEC, as measured by immunochromatographic test (ICT), and 81% on albendazole and DEC compared with 80% on DEC, as measured by Og4C3. *See* Analysis 5.4 and Appendix 4.

Mf density: all participants (mf positive or negative at baseline)

Fox 2005 reported similar geometric mean percent reductions in mf density at three months, but at six months they were statistically significantly greater in the combination arm (80.4% compared with 50.4%, P < 0.05). *See* Appendix 5.

Mf density: only participants mf positive at baseline

Pani 2002 reported no statistically significant difference in percentage reductions in the geometric mean mf density. *See* Appendix 5.

Antigen density: all participants (mf positive or negative) at baseline

After six months, the geometric mean reduction in antigen density was greater in the combination arm (26.7%) than the DEC arm (17.0%), but the difference was not statistically significant (Fox 2005). *See* Appendix 6.

Antigen density: only participants mf positive at baseline

Pani 2002 reported statistically significant reductions in mean optical antigen density by Og4C3 assay in both groups at 360 days compared with the pretreatment value: a reduction of 0.40 with albendazole plus DEC (P < 0.0001) and 0.32 with DEC (P < 0.0001). There were no differences in the reduction in antigen density between the combination and DEC group. *See* Appendix 6.

Adult worms

There were no statistically significant differences in detection of adult worms by ultrasonography in Pani 2002 or Kshirsagar 2004, but only a small number of participants were included in this analysis. *See* Appendix 7.

Adverse events

Pani 2002 reported no statistically significant difference in the proportion reporting any systemic adverse events (11/18 for albendazole plus DEC and 9/17 for DEC) or in the mean score of adverse reaction intensity (6.7 (sd 6.6) for albendazole plus DEC and 5.6 (sd 7.1) for DEC).

Fox 2005 found no statistically significant differences in specific symptoms or treatment impact scores for the combination compared with DEC alone.

Kshirsagar 2004 assessed adverse drug events in a large sample size (1403 participants). There were no statistically significant differences in the proportion of participants reporting an adverse drug

reaction by day seven in the DEC group compared with the combination group (128/693 versus 120/702)), or the proportions experiencing adverse events that interfered with daily activities (29/694, 4.2% and 31/702, 4.4% respectively). The adverse events generally appeared mild in both arms, with no life-threatening or disabling events (Common Toxicity Criteria grade 4) reported; most were mild or moderate adverse events. *See* Analysis 5.5 *and* Appendix 8.

DISCUSSION

This review was designed to assess the effects of albendazole alone or in combination with the currently recommended antifilarial drugs, ivermectin or DEC. Although the review has considered the effects of albendazole alone, the main interest and strategy of the Global Programme to Eliminate Lymphatic Filariasis is in the effectiveness of combinations of different antifilarial drugs (Ismail 1998; Shenoy 1999). Of particular interest is the effectiveness of adding albendazole (thought to be macrofilaricidal) (CDS/FIL 1998; Jayakody 1993) to single dose regimens of ivermectin (thought to be mainly microfilaricidal) or DEC (possibly both microfilaricidal and macrofilaricidal) (Ottesen 1999).

All the included studies were designed primarily to assess the effectiveness of albendazole for treatment of individuals, and none have explicitly considered its effects on transmission in whole communities. We identified seven trials, but most of these were small. All were described as randomized, but they had important limitations. In particular, the numbers of participants lost to follow up were very high (above 20%) in all trials except for Pani 2002, and this may lead to imbalances in the comparison groups.

Differences in design (mf positive only versus positive and negative participants at baseline, variable outcome measurement and reporting, and follow-up times) make it difficult to compare the trials. In particular, some trials reported outcomes mainly for those who were mf positive at baseline (Dunyo 2000; Kshirsagar 2004; Simonsen 2004). Outcomes for all participants in the trial, regardless of baseline mf status, are essential in assessing the community impact of mass treatment strategies. Most of the trials reported changes in antigenaemia prevalence or density in addition to mf prevalence and density (Dunyo 2000; Fox 2005; Kshirsagar 2004; Pani 2002; Simonsen 2004). There was broad agreement between changes in both these outcome measures in these trials. Only two trials objectively examined the effects of antifilarial medication on the viability of adult worms: Kshirsagar 2004 used a sample of the enrolled participants (101 men at baseline) and Pani 2002 used 25 men at baseline. Adult worms are responsible for the production of mf; therefore, the extent to which antifilarial drugs affect worm viability is an important outcome.

Albendazole alone was not effective in reducing mf prevalence (Beach 1999; Dunyo 2000; Fox 2005) or circulating filarial antigens (Dunyo 2000; Fox 2005) compared with placebo. Ivermectin was more effective than albendazole in both of these trials, and a meta-analysis indicates a marginal but statistically significant 16% reduction in the risk ratio of mf prevalence after treatment for those who were mf positive at baseline in favour of ivermectin.

In two trials the combination of albendazole and ivermectin was better than ivermectin alone in the short term (after four to six months follow up; Beach 1999; Simonsen 2004), but they were the same after twelve months of follow up (Dunyo 2000; Simonsen 2004). The lack of measurements at similar intervals in all three trials makes it impossible to know if the results were substantially alike. It is possible that by 12 months mf levels had risen sufficiently to dampen the actual effect of the drugs in Dunyo 2000, but this cannot explain the lack of effect in Simonsen 2004. The dose of ivermectin was also higher in the Haiti study (Beach 1999) than the other two trials. The trials used different techniques to assess mf: investigators in Haiti used the thick film method in 20 µL of blood and measurement at night; in both Dunyo 2000 and Simonsen 2004 the counting chamber method in 100 µL of blood was used, with measurement during the day (Dunyo 2000) or at night (Simonsen 2004).

Two very small trials in mf positive individuals and one larger population-based trial compared albendazole with DEC (Fox 2005; Jayakody 1993; Pani 2002). The two small trials found no statistically significant differences in mf prevalence or density at any of the time points measured. Fox 2005 found a statistically significant reduction in mf prevalence in favour of DEC at six months, but no difference at three months.

Three trials also compared albendazole and DEC with both drugs co-administered. The two small trials from India, Kshirsagar 2004 and Pani 2002, showed no statistically significant differences at any time point up to two years follow up between DEC alone and albendazole plus DEC. Fox 2005 found a reduction in mf prevalence favouring the combination at six months, but this was not statistically significant. There was no difference between the combination and DEC alone at three months. None of the three trials demonstrated any differences in antigen prevalence between the combination and DEC alone. However, one of the three trials, Fox 2005, did find a statistically significant reduction in geometric mean mf density at six months in favour of the combination (although there was no statistically significant difference in mf density at three months or antigen density at six months).

Although all trials provided data on geometric mean mf density, a lack of reporting of standard deviations or confidence intervals from most trials made it impossible to include these results in a meta-analysis. A reduction in mf geometric mean density was observed for all treatments including placebo, and the reduction appeared greater for active treatments (albendazole, DEC, and ivermectin), but tests of statistical significance were not always carried out or reported.

The effect of treatment on clinical disease was not remarkable in any of the comparison groups. This is not surprising as effect sizes for clinical outcomes were small and the trials were not powered to detect small clinical benefits.

No serious adverse events were observed in six of the trials (Beach 1999; Dunyo 2000; Fox 2005; Kshirsagar 2004; Pani 2002; Simonsen 2004). Jayakody 1993 found a very high incidence of "scrotal syndrome" among those treated with albendazole, but the doses of both albendazole and DEC were very much higher than in the other trials.

AUTHORS' CONCLUSIONS

Implications for practice

Based on limited data, the evidence suggests that albendazole when used alone is not better than placebo, ivermectin, or DEC in clearing blood microfilariae. Results from trials that compared albendazole plus ivermectin with ivermectin alone were inconsistent, although two of three showed a reduction in mf density. Two small trials found little difference in albendazole co-administered with DEC compared with DEC alone, but one larger trial tended to favour the combination at six months, with a significant reduction in mf density. Most trials were underpowered to assess the effects of albendazole, alone or in combination, on morbidity or adverse events. Only larger scale studies can determine if any effect is of practical importance.

The conclusions of this review are based on trials that have randomized and treated individuals, therefore they should be cautiously extrapolated to large-scale, population-based mass drug administration programmes.

Implications for research

Only limited data were found — further large well-designed trials are required in several areas including:

- the effectiveness of albendazole in combination with DEC or ivermectin on treatment and control of lymphatic filariasis;
- the impact of albendazole in mass drug administration campaigns; and
- studies of other interventions (against the parasite or the vector) to augment mass drug administration.

The complete clearance of blood mf (or reduction to levels below which transmission is unlikely) theoretically represents the most reliable strategy for interrupting transmission. But this may be difficult to achieve in practice, as ivermectin mainly acts on mf with no demonstrable macrofilaricidal activity. A drug that kills both mf and adults would clearly be ideal, and there is an argument for more research and development towards such a drug. Studies of potential macrofilaricides could be assessed objectively, as with ultrasound detection, to directly monitor adult worms. It is also not known how low microfilarial densities need to fall in order to successfully interrupt transmission from the various vector species. As microfilaraemia is an intermediate outcome reflecting infectivity of the human host, it is important to assess comparative effectiveness of drugs that aim to interrupt transmission. Techniques for assessing mf in blood and outcome measures for mf densities need to be standardized with complete reporting of geometric means and standard deviations.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Beach 1999

Methods	Individually randomized controlled trial Generation of allocation sequence: random-number table Allocation concealment: concealed by third party Blinding: "Double blind" stated, although drugs were not identical, patients had no way of identifying them; outcome assessors blinded Inclusion of all randomized participants in the analysis: 585 analysed of 965 randomized (61%) Length of follow up: 4 months Method of microfilariae (mf) assessment/volume of blood: thick smear; 20 µL of finger-prick blood
Participants	Number randomized: 965, of whom 113 were mf positive Children (male and female) aged 5 to 11 years with *Wuchereria bancrofti* filariasis
Interventions	1. Albendazole: 400 mg, 244 participants 2. Ivermectin: 200 to 400 µg/kg, 240 participants 3. Albendazole plus ivermectin: doses as above, 245 participants 4. Placebo: 229 participants
Outcomes	1. Post-treatment reduction in % mf prevalence 2. % reduction in geometric mean mf density (Note: standard deviation not reported; no values reported for the albendazole group) 3. Prevalence of W. bancrofti among all children in each treatment group 4. Frequency of the occurrence of specific systemic adverse events, such as fever, headache, weakness, muscle/joint pain, itching, rash, abdominal pain, and diarrhoea
Notes	Location: Leogane, Haiti Endemicity level: not stated

Dunyo 2000

Methods	Individually randomized controlled trial Generation of allocation sequence: computer generated Allocation concealment: concealed by third party Blinding: identical placebos used for each group Inclusion of all randomized participants in the analysis: 273 analysed of 340 microfilariae (mf) positive randomized (80%) Length of follow up: 12 months Method of mf assessment/volume of blood: mf in 100µL of finger-prick blood using the counting chamber technique, daytime collection Antigen testing: ELISA from finger-prick blood specimens
Participants	Number randomized: 1425, of whom 340 mf positive were followed up Individuals (male and female) aged 6 to 87 years with or without *Wuchereria bancrofti*

Dunyo 2000 (*Continued*)

Interventions	1. Albendazole: 400 mg, 88 participants 2. Ivermectin: 150 to 200 µg/kg, 79 participants 3. Albendazole plus ivermectin: doses as above, 90 participants 4. Placebo: 83 participants
Outcomes	1. Number of individuals mf positive at 12 months post-treatment 2. Geometric mean mf density (Note: standard deviation not reported) 3. % of pretreatment mf concentration 4. Geometric mean circulating filarial antigen (CFA) density 5. Geometric mean CFA density as % of pretreatment value 6. New infections (appearance of antigenaemia) 7. New disease events (lymphoedema or hydrocoele) 8. Mortality during follow up 9. Frequency of specific systemic adverse events as well as the number of individuals presenting with any adverse event post-treatment; reactions graded as 0 = none, 1 = mild (noticeable to patient but not interfering with daily activities), 2 = moderate (some interference with daily activities), 3 = severe (complete interruption of daily activities) (Note: Adjusted and unadjusted mf geometric mean mf intensities given)
Notes	Location: southern Ghana (Butre, Achowa, Adjan, and Miamia villages) Endemicity level: 18% to 25%

Fox 2005

Methods	Individually randomized controlled trial Generation of allocation sequence: random number table Allocation concealment: unclear Blinding: "Double blind" stated, although no dummy procedure; in reality, only outcome assessors likely to be 'blind' Inclusion of all randomized participants in the analysis: 990 of 1292 (76%) analysed Length of follow up: 6 months Method of microfilariae (mf) assessment/volume of blood: 20 µL thick smear between 7:30 and 9:30 pm Antigen testing: Og4C3 assay for circulating filarial antigen (CFA)
Participants	Number randomized: 990 Children aged 5 to 11 years attending any of 12 selected primary schools
Interventions	1. Albendazole alone: 400 mg, 256 participants 2. Diethylcarbamazine (DEC) alone: 6 mg/kg body weight, 246 participants 3. Placebo: 243 participants 4. DEC and albendazole: doses as above, 245 participants
Outcomes	1. % of children in each group who had no mf detected in blood 3 and 6 months post-treatment 2. Mean % reduction in mf density 3 and 6 months post-treatment 3. Geometric mean % reduction in mf density 3 and 6 months post-treatment 4. CFA: % of children with negative CFA 6 months post-treatment 5. Mean % reduction in CFA density, geometric mean 6. % reduction in CFA density 6 months after treatment 7. Adverse events: assessed every day for 7 d after treatment by blinded clinicians who questioned and examined children at school; adverse events recorded were self-reported or documented fever, headache, myalgias, and cough;

Fox 2005 (*Continued*)

	also reported a mean treatment impact score by day for the first seven days (1 = symptoms noticed, but did not interfere with daily activities, 2 = symptoms caused some interference with daily activities, 3 = symptoms prevented usual daily activities) (Note: standard deviations for geometric mean density changes reported on request)
Notes	Location: Leogane commune, Haiti Endemicity level: 14.7% of children had mf and 31.4% were positive CFA at baseline

Jayakody 1993

Methods	Individually randomized controlled trial Generation of allocation sequence: pre-determined randomization list Allocation concealment: states randomization list 'restricted' Blinding: unclear Inclusion of all randomized participants in the analysis: 20 analysed of 29 randomized (74%) Length of follow up: 19 months Method of microfilariae (mf) assessment/volume of blood: membrane filtration for using a Nucleopore filter (3 µm pore size)
Participants	Number randomized: 29 Asymptomatic men aged 18 to 65 with *Wuchereria bancrofti* mf Patients with mf density in night blood films > 100 mf/mL at least once during previous week included
Interventions	1. Albendazole: 400 mg given twice daily for 21 d, 16 participants 2. Diethylcarbamazine (DEC): 6 mg/kg daily for 21 d, 13 participants
Outcomes	1. Post-treatment % prevalence reduction 2. % reduction in geometric mean mf density 3. Adverse events: the prevalence and severity of "scrotal syndrome" (pain in the scrotum, enlargement of epididymis, and some systemic features, such as fever, thought to be caused by death of adult worms) during the treatment period
Notes	Location: Colombo, Sri Lanka Endemicity level: not stated

Kshirsagar 2004

Methods	Individually randomized controlled trial Generation of allocation sequence: states randomized, exact details unclear Allocation concealment: unclear Blinding: used identical placebos and double dummy procedure Inclusion of all randomized participants in the analysis: 1395/1403 (99%) analysed in safety study; 103 microfilariae (mf)-positive men were selected for the efficacy study, but follow up of these was adequate at some time points but inadequate at others Length of follow up: 12 months Method of mf assessment/volume of blood: thick smear, 60 µL of finger-prick blood or venepuncture between 9 and 11pm Antigen testing: immunochromatographic card Detection of adult filarial worm by USG machine; all regions of scrotum and spermatic cord systematically studied, and "filaria dance sign" identified
Participants	Number: 1403 randomized for safety study; 103 for efficacy assessment Safety study: males and females over 5 years old with and without *Wuchereria bancrofti* Efficacy assessment: males aged 18 to 50
Interventions	1. Diethylcarbamazine (DEC): 6 mg/kg body weight and albendazole 400 mg 2. DEC plus albendazole-placebo
Outcomes	1. Number mf positive at 3, 6, and 12 months (and % of pretreatment levels) 2. Number immunochromatographic card test (ICT) positive at 3, 6, and 12 months (and % pretreatment levels) 3. Number ultrasonography USG positive at 3, 6, and 12 months (and % pretreatment levels); results stratified for those mf positive at baseline (43 participants), with clinical disease (30 participants), and mf negative and asymptomatic (30 participants) 4. Adverse events: total incidence and number of participants with adverse drug reactions on days 2 or 5, number of early terminations, number of participants where adverse events interfered with daily activities, and global assessment of tolerability (very good or good, satisfactory, poor or insufficient, not assessable). Also categorized the severity of adverse reactions according to the National Cancer Institute Common Toxicity Criteria (NCI 1999)
Notes	Location: 2 endemic villages in Wardha, Maharashtra (Western India) Endemicity level: 7.27% in 1995 Efficacy data: at many time points there were no men with clinical disease or mf negative at baseline surveyed

Pani 2002

Methods	Individually randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: adequate - coding of drugs performed by independent monitor Blinding: comparable placebo and outcome assessors 'blind' Inclusion of all randomized participants in the analysis: implies no losses to follow up (54 analysed out of 54 randomized) Length of follow up: 24 months Method of microfilariae (mf) assessment/volume of blood: not clear, 1 mL venous blood collected between 7:30 to 8:30 pm Antigen testing: immunochromatographic card test and by Og4C3 ELISA test kit on 50 µL serum
Participants	Number randomized: 54 Asymptomatic volunteers (male and female) between 10 and 57 years old who were mf positive
Interventions	1. Albendazole: 400 mg, 19 participants 2. Diethylcarbamazine (DEC): 6 mg/kg, 17 participants 3. Albendazole plus DEC: doses as above, 18 participants
Outcomes	1. % of individuals mf positive post-treatment 2. % reduction in geometric mean mf 3. % reduction in filarial antigen prevalence 4. Adverse events: monitored all participants in hospital for adverse reactions at 8-h intervals for the first 24 h, then every 24 h for a further 3 d; proportion of individuals reporting any systemic adverse event and intensity (using a simple scoring system) of adverse events were noted (Note: no standard deviation reported for geometric mean mf density)
Notes	Location: Pondicherry, India Endemicity level: not given in report

Simonsen 2004

Methods	Individually randomized controlled trial Generation of allocation sequence: computer generated Allocation concealment: concealed by third party Blinding: used identical placebos and double dummy procedure Inclusion of all randomized participants in the analysis: 1221 of 1829 (67%) analysed Length of follow up: 12 months Method of microfilariae (mf) assessment/volume of blood: 100 µL finger-prick blood, counting chamber technique Antigen testing: circulating filarial antigen (CFA) on TropBio filter paper collection discs; blood sampling for mf and CFA started at 9 pm
Participants	Number randomized: 1829, of which 1221 (67%) followed up; 103 had mf School children aged 6 to 18 years with or without *Wuchereria bancrofti*
Interventions	1. Albendazole plus ivermectin: 400 mg albendazole, 150 to 200 µg/kg ivermectin, 586 participants 2. Ivermectin alone: dose as above, 635 participants

Simonsen 2004 (*Continued*)

Outcomes	Results reported only in 103 mf-positive participants at baseline 1. Number of individuals mf positive at 6 and 12 months post-treatment 2. Geometric mean mf concentration and % of pretreatment geometric means at 6 and 12 months 3. Number of children CFA positive at 6 and 12 months and % of pretreatment CFA 4. Geometric mean density CFA and % of pretreatment CFA geometric mean density 5. New cases of mf positivity amongst those mf negative at baseline 6. New cases of CFA positivity amongst those CFA negative at baseline 7. Adverse reactions: children followed for 5 d after treatment by passive observation; specific adverse reactions, such as headache, fever, joint pain, diarrhoea, dizziness, vomiting and itching noted, but number of events in each treatment group not clearly reported (Note: standard deviation not reported for geometric mean mf density)
Notes	Location: 6 primary schools in coastal Tanzania Endemicity level: known to be high; school mf prevalence was 17.3% overall for the 6 schools

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Dunyo 2002	Update of Dunyo 2000 following retreatment of each treatment group; retreatment carried out only with the combination (ALB plus IV), hence no comparison group given IV alone
Ismail 1998	The comparison groups - ALB versus ALB plus IV versus ALB plus DEC versus DEC plus IV - do not match those in the review; these comparisons do not provide answers to the question as to whether adding ALB to IV or DEC improves outcomes compared to IV or DEC alone; the comparisons would have to include IV alone or DEC alone as comparators to be relevant to the review
Makunde 2003	Comparison groups do not match those in review; for single infections with *Wuchereria bancrofti* these were ALB plus IV versus ALB alone; for co-infections of *W. bancrofti* and *Onchocerca volvulus* these were IV plus ALB versus placebo
Shenoy 1999	The comparison groups - ALB versus ALB plus IV versus ALB plus DEC versus DEC plus IV - do not match those in the review; excluded for reasons stated above for Ismail 1998
Shenoy 2002	Study of safety and tolerability of adding ALB to DEC; carried out only in patients without microfilariaemia (ie presumably uninfected)

ALB: albendazole; DEC: diethylcarbamazine; IV: ivermectin.

Characteristics of ongoing studies *[ordered by study ID]*

Dahoma (ongoing)

Trial name or title	Assessment of safety and efficacy of ivermectin and albendazole co-administration
Methods	-
Participants	1000 participants living in an area endemic for lymphatic filariasis and soil transmitted helminths in Zanzibar, Tanzania
Interventions	1. Ivermectin 2. Albendazole plus ivermectin
Outcomes	1. Reappearance of microfilariae at 12 months 2. Microfilariae at 3 and 6 months 3. Adverse drug reactions
Starting date	-
Contact information	Mark Bradley SmithKline Beecham GlaxoWellcome House West Berkeley Avenue Greenford Middlesex UB6 0NN UK Phone: +44 208 966 8543 Fax: +44 208 966 8827 Email: mhb38319@GlaxoWellcome.co.uk
Notes	-

The names of principal investigator is used as the study ID.

DATA AND ANALYSES

Comparison 1. Albendazole versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 At 3 to 4 months	2	783	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.66, 1.37]
1.2 At 6 months	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.66, 1.53]
2 Microfilariae (mf) prevalence: only participants mf positive at baseline	2	195	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.87, 1.09]
3 Antigen prevalence: all participants (both mf positive or negative at baseline)	2	1090	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.12]
4 New clinical disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Hydrocoele	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Pre-existing clinical disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Improvement in lymphoedema	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 Improvement in hydrocoele	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Systemic	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 2. Albendazole versus ivermectin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Microfilariae (mf) prevalence: only participants mf positive at baseline	2	198	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.72, 0.98]
3 Antigen prevalence: all participants (antigen positive or negative at baseline)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 New clinical disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Hydrocoele	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Pre-existing clinical disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Improvement in lymphoedema	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

5.2 Improvement in hydrocoele	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Systemic	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 3. Albendazole plus ivermectin versus ivermectin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Microfilariae (mf) prevalence: only participants mf positive at baseline	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 At 4 to 6 months	2	255	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.18, 1.39]
2.2 At 12 months	2	348	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.13]
3 Antigen prevalence: all participants (antigen positive or negative) at baseline	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Antigen prevalence: only participants antigen positive at baseline	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Data at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Data at 12 months	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 New clinical disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Hydrocoele	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Pre-existing clinical disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Improvement in lymphoedema	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 Improvement in hydrocoele	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Total	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 Systemic	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 4. Albendazole versus diethylcarbamazine (DEC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microfiliariae (mf) prevalence: all participants (both mf positive or negative at baseline)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 At 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 At 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

2 Microfilariae (mf) prevalence: only participants mf positive at baseline	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 After 3 months	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.10]
2.2 After 1 year	2	56	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.57, 2.49]
2.3 After 2 years	1	36	Risk Ratio (M-H, Fixed, 95% CI)	3.58 [0.44, 28.97]
3 Antigen prevalence: all participants (both antigen positive or negative at baseline)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Antigen prevalence: only participants antigen positive at baseline	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 ICT test	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Adverse events: scrotal syndrome	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 5. Albendazole plus diethylcarbamazine (DEC) versus DEC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 At 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 At 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Microfilariae (mf) prevalence: only participants mf positive at baseline	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 At 3 months	2	73	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.83, 1.36]
2.2 At 6 months	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.62, 1.61]
2.3 At 12 months	2	78	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.44]
2.4 At 2 years	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.06, 13.93]
3 Antigen prevalence: all participants (both antigen positive and negative at baseline)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Data at 6 months	2	592	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.82, 1.24]
3.2 Data at 12 months	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.69, 1.31]
4 Antigen prevalence: only participants antigen positive at baseline	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Any	2	1430	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.71, 1.08]
5.2 Interfered with daily activities	1	1395	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.64, 1.73]

Analysis 1.1. Comparison 1 Albendazole versus placebo, Outcome 1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline).

Review: Albendazole for lymphatic filariasis

Comparison: 1 Albendazole versus placebo

Outcome: 1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline)

Study or subgroup	Albendazole n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 At 3 to 4 months					
Beach 1999	22/145	20/139		39.9 %	1.05 [0.60, 1.84]
Fox 2005	28/256	30/243		60.1 %	0.89 [0.55, 1.44]
Subtotal (95% CI)	**401**	**382**		**100.0 %**	**0.95 [0.66, 1.37]**
Total events: 50 (Albendazole), 50 (Placebo)					
Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 0.26 (P = 0.80)					
2 At 6 months					
Fox 2005	38/256	36/243		100.0 %	1.00 [0.66, 1.53]
Subtotal (95% CI)	**256**	**243**		**100.0 %**	**1.00 [0.66, 1.53]**
Total events: 38 (Albendazole), 36 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					

Analysis 1.2. Comparison 1 Albendazole versus placebo, Outcome 2 Microfilariae (mf) prevalence: only participants mf positive at baseline.

Review: Albendazole for lymphatic filariasis

Comparison: 1 Albendazole versus placebo

Outcome: 2 Microfilariae (mf) prevalence: only participants mf positive at baseline

Study or subgroup	Albendazole n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Beach 1999	22/29	20/29		23.7 %	1.10 [0.80, 1.51]
Dunyo 2000	62/71	62/66		76.3 %	0.93 [0.83, 1.04]
Total (95% CI)	**100**	**95**		**100.0 %**	**0.97 [0.87, 1.09]**

Total events: 84 (Albendazole), 82 (Placebo)

Heterogeneity: Chi^2 = 1.20, df = 1 (P = 0.27); I^2 =16%

Test for overall effect: Z = 0.52 (P = 0.60)

Analysis 1.3. Comparison 1 Albendazole versus placebo, Outcome 3 Antigen prevalence: all participants (both mf positive or negative at baseline).

Review: Albendazole for lymphatic filariasis

Comparison: 1 Albendazole versus placebo

Outcome: 3 Antigen prevalence: all participants (both mf positive or negative at baseline)

Study or subgroup	Albendazole n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dunyo 2000	115/302	102/289		51.9 %	1.08 [0.87, 1.33]
Fox 2005	81/256	94/243		48.1 %	0.82 [0.64, 1.04]
Total (95% CI)	**558**	**532**		**100.0 %**	**0.95 [0.81, 1.12]**

Total events: 196 (Albendazole), 196 (Placebo)

Heterogeneity: Chi^2 = 2.87, df = 1 (P = 0.09); I^2 =65%

Test for overall effect: Z = 0.59 (P = 0.56)

Analysis 1.4. Comparison 1 Albendazole versus placebo, Outcome 4 New clinical disease.

Review: Albendazole for lymphatic filariasis

Comparison: 1 Albendazole versus placebo

Outcome: 4 New clinical disease

Study or subgroup	Albendazole n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Hydrocoele				
Dunyo 2000	1/129	1/126		0.98 [0.06, 15.45]

Analysis 1.5. Comparison 1 Albendazole versus placebo, Outcome 5 Pre-existing clinical disease.

Review: Albendazole for lymphatic filariasis

Comparison: 1 Albendazole versus placebo

Outcome: 5 Pre-existing clinical disease

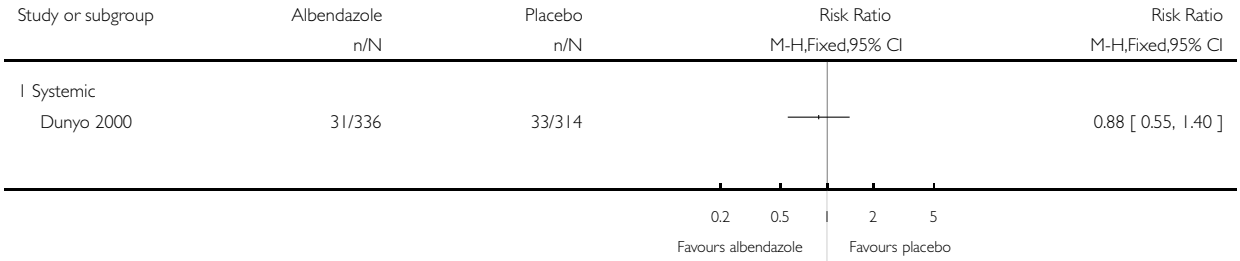
Study or subgroup	Albendazole n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Improvement in lymphoedema				
Dunyo 2000	3/13	2/9		1.04 [0.22, 5.01]
2 Improvement in hydrocoele				
Dunyo 2000	3/8	5/10		0.75 [0.25, 2.23]

Analysis 1.6. Comparison 1 Albendazole versus placebo, Outcome 6 Adverse events.

Review: Albendazole for lymphatic filariasis

Comparison: 1 Albendazole versus placebo

Outcome: 6 Adverse events

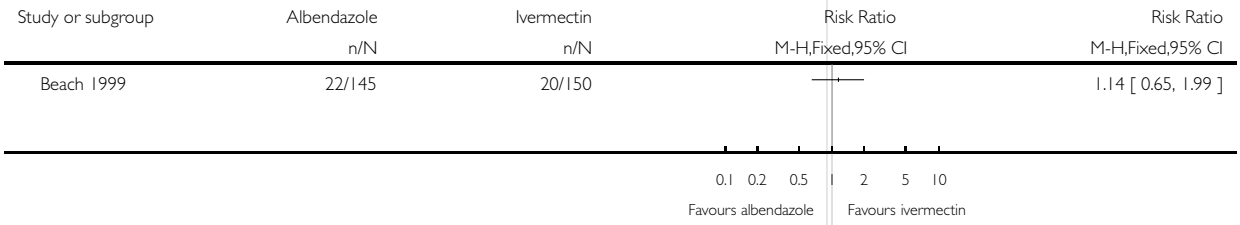


Analysis 2.1. Comparison 2 Albendazole versus ivermectin, Outcome 1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline).

Review: Albendazole for lymphatic filariasis

Comparison: 2 Albendazole versus ivermectin

Outcome: 1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline)



Analysis 2.2. Comparison 2 Albendazole versus ivermectin, Outcome 2 Microfilariae (mf) prevalence: only participants mf positive at baseline.

Review: Albendazole for lymphatic filariasis

Comparison: 2 Albendazole versus ivermectin

Outcome: 2 Microfilariae (mf) prevalence: only participants mf positive at baseline

Study or subgroup	Ivermectin n/N	Albendazole n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Beach 1999	17/28	22/29		26.0 %	0.80 [0.56, 1.15]
Dunyo 2000	52/70	62/71		74.0 %	0.85 [0.72, 1.00]
Total (95% CI)	**98**	**100**		**100.0 %**	**0.84 [0.72, 0.98]**

Total events: 69 (Ivermectin), 84 (Albendazole)

Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.76); I^2 =0.0%

Test for overall effect: Z = 2.27 (P = 0.023)

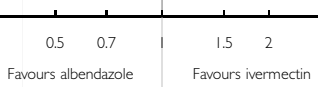
Analysis 2.3. Comparison 2 Albendazole versus ivermectin, Outcome 3 Antigen prevalence: all participants (antigen positive or negative at baseline).

Review: Albendazole for lymphatic filariasis

Comparison: 2 Albendazole versus ivermectin

Outcome: 3 Antigen prevalence: all participants (antigen positive or negative at baseline)

Study or subgroup	Albendazole n/N	Ivermectin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Dunyo 2000	115/302	101/283		1.07 [0.86, 1.32]



Analysis 2.4. Comparison 2 Albendazole versus ivermectin, Outcome 4 New clinical disease.

Review: Albendazole for lymphatic filariasis

Comparison: 2 Albendazole versus ivermectin

Outcome: 4 New clinical disease

Study or subgroup	Albendazole n/N	Ivermectin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Hydrocoele				
Dunyo 2000	1/129	1/133		1.03 [0.07, 16.31]

Analysis 2.5. Comparison 2 Albendazole versus ivermectin, Outcome 5 Pre-existing clinical disease.

Review: Albendazole for lymphatic filariasis

Comparison: 2 Albendazole versus ivermectin

Outcome: 5 Pre-existing clinical disease

Study or subgroup	Albendazole n/N	Ivermectin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Improvement in lymphoedema				
Dunyo 2000	3/13	2/13		1.50 [0.30, 7.55]
2 Improvement in hydrocoele				
Dunyo 2000	3/8	2/9		1.69 [0.37, 7.67]

Analysis 2.6. Comparison 2 Albendazole versus ivermectin, Outcome 6 Adverse events.

Review: Albendazole for lymphatic filariasis

Comparison: 2 Albendazole versus ivermectin

Outcome: 6 Adverse events

Study or subgroup	Albendazole n/N	Ivermectin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Systemic				
Dunyo 2000	31/336	36/295		0.76 [0.48, 1.19]

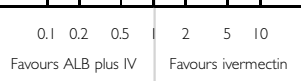
Analysis 3.1. Comparison 3 Albendazole plus ivermectin versus ivermectin, Outcome 1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline).

Review: Albendazole for lymphatic filariasis

Comparison: 3 Albendazole plus ivermectin versus ivermectin

Outcome: 1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline)

Study or subgroup	ALB plus IV n/N	Ivermectin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Beach 1999	7/151	20/150		0.35 [0.15, 0.80]



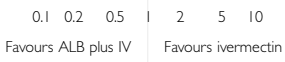
Analysis 3.2. Comparison 3 Albendazole plus ivermectin versus ivermectin, Outcome 2 Microfilariae (mf) prevalence: only participants mf positive at baseline.

Review: Albendazole for lymphatic filariasis

Comparison: 3 Albendazole plus ivermectin versus ivermectin

Outcome: 2 Microfilariae (mf) prevalence: only participants mf positive at baseline

Study or subgroup	ALB plus IV n/N	Ivermectin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 At 4 to 6 months					
Beach 1999	4/24	17/28		16.0 %	0.27 [0.11, 0.70]
Simonsen 2004	67/105	85/98		84.0 %	0.74 [0.62, 0.87]
Subtotal (95% CI)	**129**	**126**		**100.0 %**	**0.49 [0.18, 1.39]**
Total events: 71 (ALB plus IV), 102 (Ivermectin)					
Heterogeneity: Tau^2 = 0.46; Chi^2 = 4.82, df = 1 (P = 0.03); I^2 =79%					
Test for overall effect: Z = 1.34 (P = 0.18)					
2 At 12 months					
Dunyo 2000	58/75	52/70		49.3 %	1.04 [0.87, 1.25]
Simonsen 2004	75/105	73/98		50.7 %	0.96 [0.81, 1.13]
Subtotal (95% CI)	**180**	**168**		**100.0 %**	**1.00 [0.88, 1.13]**
Total events: 133 (ALB plus IV), 125 (Ivermectin)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.42, df = 1 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 0.08 (P = 0.94)					



Analysis 3.3. Comparison 3 Albendazole plus ivermectin versus ivermectin, Outcome 3 Antigen prevalence: all participants (antigen positive or negative) at baseline.

Review: Albendazole for lymphatic filariasis

Comparison: 3 Albendazole plus ivermectin versus ivermectin

Outcome: 3 Antigen prevalence: all participants (antigen positive or negative) at baseline

Study or subgroup	ALB plus IV n/N	Ivermectin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Dunyo 2000	122/307	101/283		1.11 [0.90, 1.37]

Analysis 3.4. Comparison 3 Albendazole plus ivermectin versus ivermectin, Outcome 4 Antigen prevalence: only participants antigen positive at baseline.

Review: Albendazole for lymphatic filariasis

Comparison: 3 Albendazole plus ivermectin versus ivermectin

Outcome: 4 Antigen prevalence: only participants antigen positive at baseline

Study or subgroup	ALB plus IV n/N	Ivermectin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Data at 6 months				
Simonsen 2004	227/247	242/266		1.01 [0.96, 1.07]
2 Data at 12 months				
Dunyo 2000	111/121	89/99		1.02 [0.94, 1.11]
Simonsen 2004	227/247	236/266		1.04 [0.98, 1.10]

Analysis 3.5. Comparison 3 Albendazole plus ivermectin versus ivermectin, Outcome 5 New clinical disease.

Review: Albendazole for lymphatic filariasis

Comparison: 3 Albendazole plus ivermectin versus ivermectin

Outcome: 5 New clinical disease

Study or subgroup	ALB plus IV n/N	Ivermectin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Hydrocoele				
Dunyo 2000	2/147	1/133		1.81 [0.17, 19.73]

Analysis 3.6. Comparison 3 Albendazole plus ivermectin versus ivermectin, Outcome 6 Pre-existing clinical disease.

Review: Albendazole for lymphatic filariasis

Comparison: 3 Albendazole plus ivermectin versus ivermectin

Outcome: 6 Pre-existing clinical disease

Study or subgroup	ALB plus IV n/N	Ivermectin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Improvement in lymphoedema				
Dunyo 2000	2/13	2/13		1.00 [0.16, 6.07]
2 Improvement in hydrocoele				
Dunyo 2000	4/10	2/9		1.80 [0.43, 7.59]

Analysis 3.7. Comparison 3 Albendazole plus ivermectin versus ivermectin, Outcome 7 Adverse events.

Review: Albendazole for lymphatic filariasis

Comparison: 3 Albendazole plus ivermectin versus ivermectin

Outcome: 7 Adverse events

Study or subgroup	ALB plus ivermectin n/N	IV n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Total				
Simonsen 2004	0/1	0/1		0.0 [0.0, 0.0]
2 Systemic				
Dunyo 2000	47/332	36/295		1.16 [0.77, 1.74]

Analysis 4.1. Comparison 4 Albendazole versus diethylcarbamazine (DEC), Outcome 1 Microfiliariae (mf) prevalence: all participants (both mf positive or negative at baseline).

Review: Albendazole for lymphatic filariasis

Comparison: 4 Albendazole versus diethylcarbamazine (DEC)

Outcome: 1 Microfiliariae (mf) prevalence: all participants (both mf positive or negative at baseline)

Study or subgroup	Albendazole n/N	DEC n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 At 3 months				
Fox 2005	28/256	24/246		1.12 [0.67, 1.88]
2 At 6 months				
Fox 2005	38/256	21/246		1.74 [1.05, 2.88]

Analysis 4.2. Comparison 4 Albendazole versus diethylcarbamazine (DEC), Outcome 2 Microfilariae (mf) prevalence: only participants mf positive at baseline.

Review: Albendazole for lymphatic filariasis

Comparison: 4 Albendazole versus diethylcarbamazine (DEC)

Outcome: 2 Microfilariae (mf) prevalence: only participants mf positive at baseline

Study or subgroup	Albendazole n/N	DEC n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 After 3 months					
Pani 2002	18/19	17/17		100.0 %	0.95 [0.82, 1.10]
Subtotal (95% CI)	**19**	**17**		**100.0 %**	**0.95 [0.82, 1.10]**
Total events: 18 (Albendazole), 17 (DEC)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
2 After 1 year					
Jayakody 1993	5/10	5/10		61.2 %	1.00 [0.42, 2.40]
Pani 2002	5/19	3/17		38.8 %	1.49 [0.42, 5.33]
Subtotal (95% CI)	**29**	**27**		**100.0 %**	**1.19 [0.57, 2.49]**

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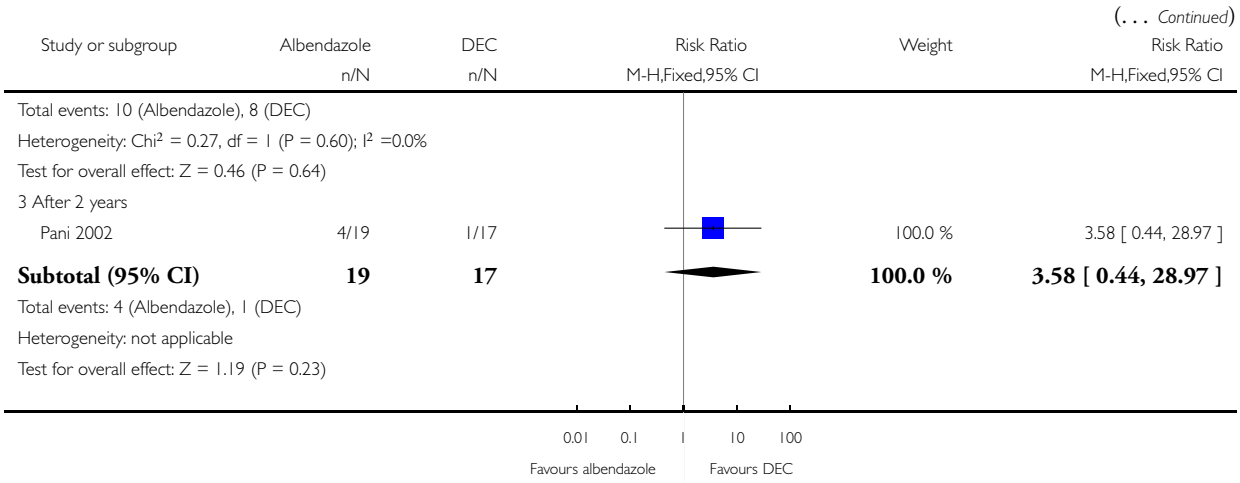
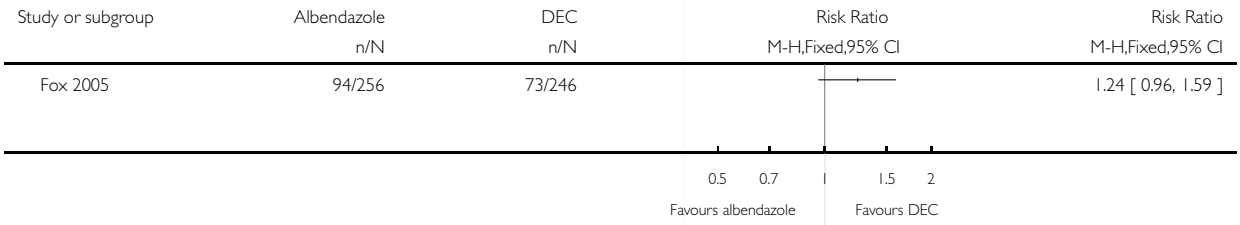


Analysis 4.3. Comparison 4 Albendazole versus diethylcarbamazine (DEC), Outcome 3 Antigen prevalence: all participants (both antigen positive or negative at baseline).

Review: Albendazole for lymphatic filariasis

Comparison: 4 Albendazole versus diethylcarbamazine (DEC)

Outcome: 3 Antigen prevalence: all participants (both antigen positive or negative at baseline)



Analysis 4.4. Comparison 4 Albendazole versus diethylcarbamazine (DEC), Outcome 4 Antigen prevalence: only participants antigen positive at baseline.

Review: Albendazole for lymphatic filariasis

Comparison: 4 Albendazole versus diethylcarbamazine (DEC)

Outcome: 4 Antigen prevalence: only participants antigen positive at baseline

Study or subgroup	Albendazole n/N	DEC n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 ICT test				
Pani 2002	6/19	2/17		2.68 [0.62, 11.56]

Analysis 4.5. Comparison 4 Albendazole versus diethylcarbamazine (DEC), Outcome 5 Adverse events.

Review: Albendazole for lymphatic filariasis

Comparison: 4 Albendazole versus diethylcarbamazine (DEC)

Outcome: 5 Adverse events

Study or subgroup	Albendazole n/N	DEC n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Pani 2002	8/19	9/17		0.80 [0.40, 1.59]

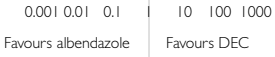
Analysis 4.6. Comparison 4 Albendazole versus diethylcarbamazine (DEC), Outcome 6 Adverse events: scrotal syndrome.

Review: Albendazole for lymphatic filariasis

Comparison: 4 Albendazole versus diethylcarbamazine (DEC)

Outcome: 6 Adverse events: scrotal syndrome

Study or subgroup	Albendazole n/N	DEC n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Jayakody 1993	7/15	0/12		12.19 [0.77, 194.03]



Analysis 5.1. Comparison 5 Albendazole plus diethylcarbamazine (DEC) versus DEC, Outcome 1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline).

Review: Albendazole for lymphatic filariasis

Comparison: 5 Albendazole plus diethylcarbamazine (DEC) versus DEC

Outcome: 1 Microfilariae (mf) prevalence: all participants (both mf positive or negative at baseline)

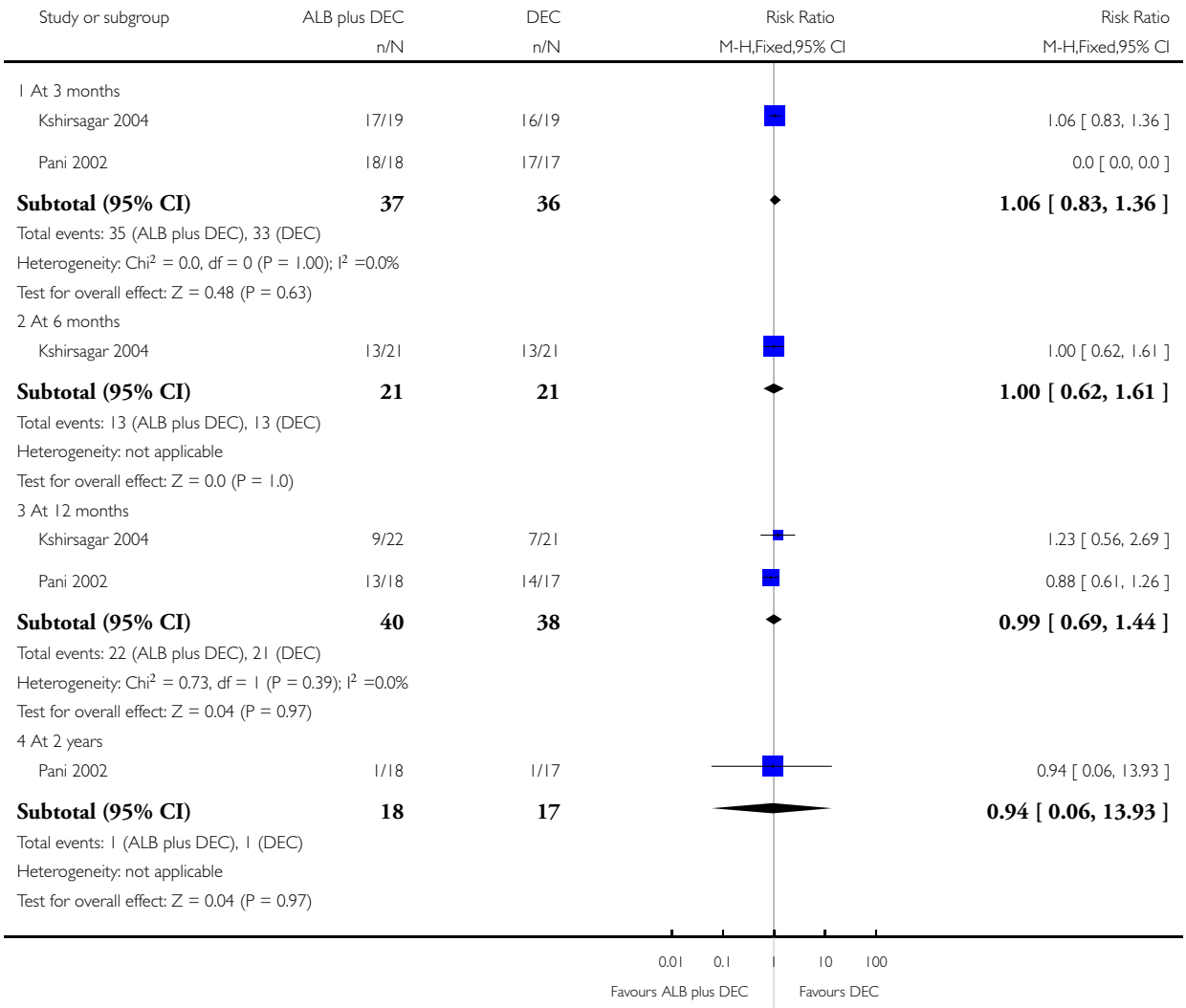
Study or subgroup	ALB plus DEC n/N	DEC n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 At 3 months				
Fox 2005	23/245	24/246		0.96 [0.56, 1.66]
2 At 6 months				
Fox 2005	13/245	21/246		0.62 [0.32, 1.21]

Analysis 5.2. Comparison 5 Albendazole plus diethylcarbamazine (DEC) versus DEC, Outcome 2 Microfilariae (mf) prevalence: only participants mf positive at baseline.

Review: Albendazole for lymphatic filariasis

Comparison: 5 Albendazole plus diethylcarbamazine (DEC) versus DEC

Outcome: 2 Microfilariae (mf) prevalence: only participants mf positive at baseline

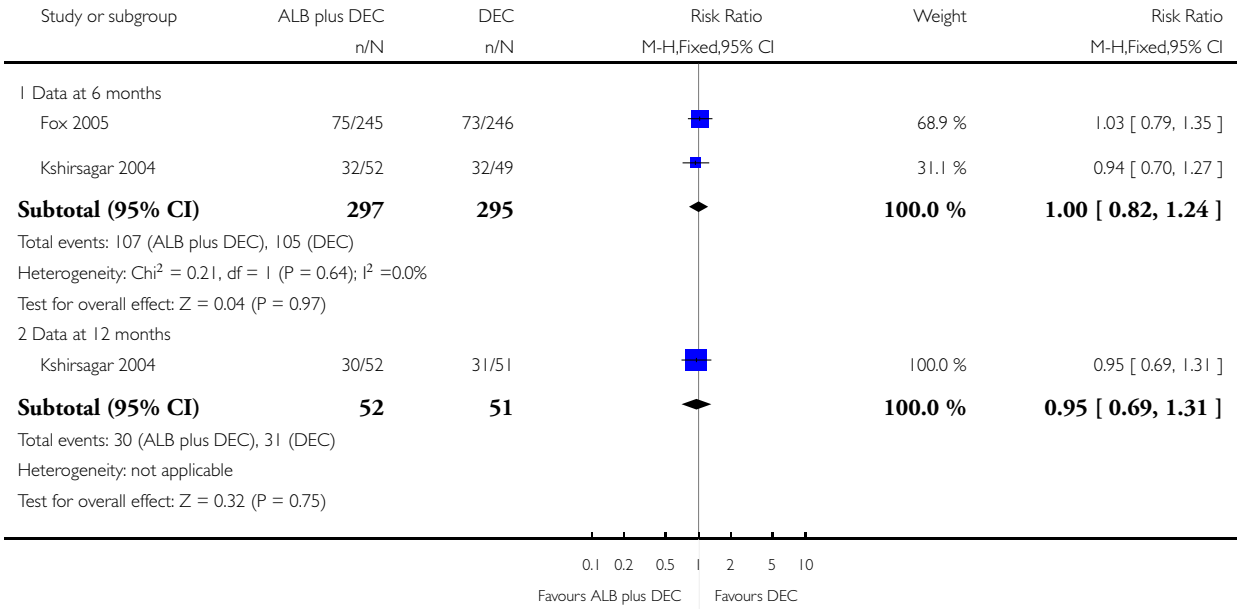


Analysis 5.3. Comparison 5 Albendazole plus diethylcarbamazine (DEC) versus DEC, Outcome 3 Antigen prevalence: all participants (both antigen positive and negative at baseline).

Review: Albendazole for lymphatic filariasis

Comparison: 5 Albendazole plus diethylcarbamazine (DEC) versus DEC

Outcome: 3 Antigen prevalence: all participants (both antigen positive and negative at baseline)

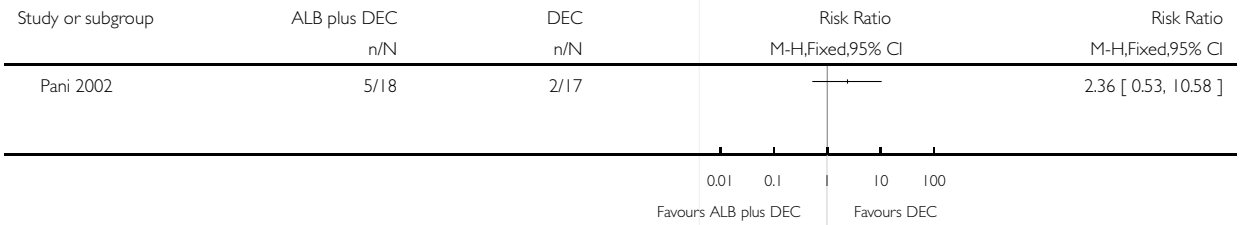


Analysis 5.4. Comparison 5 Albendazole plus diethylcarbamazine (DEC) versus DEC, Outcome 4 Antigen prevalence: only participants antigen positive at baseline.

Review: Albendazole for lymphatic filariasis

Comparison: 5 Albendazole plus diethylcarbamazine (DEC) versus DEC

Outcome: 4 Antigen prevalence: only participants antigen positive at baseline

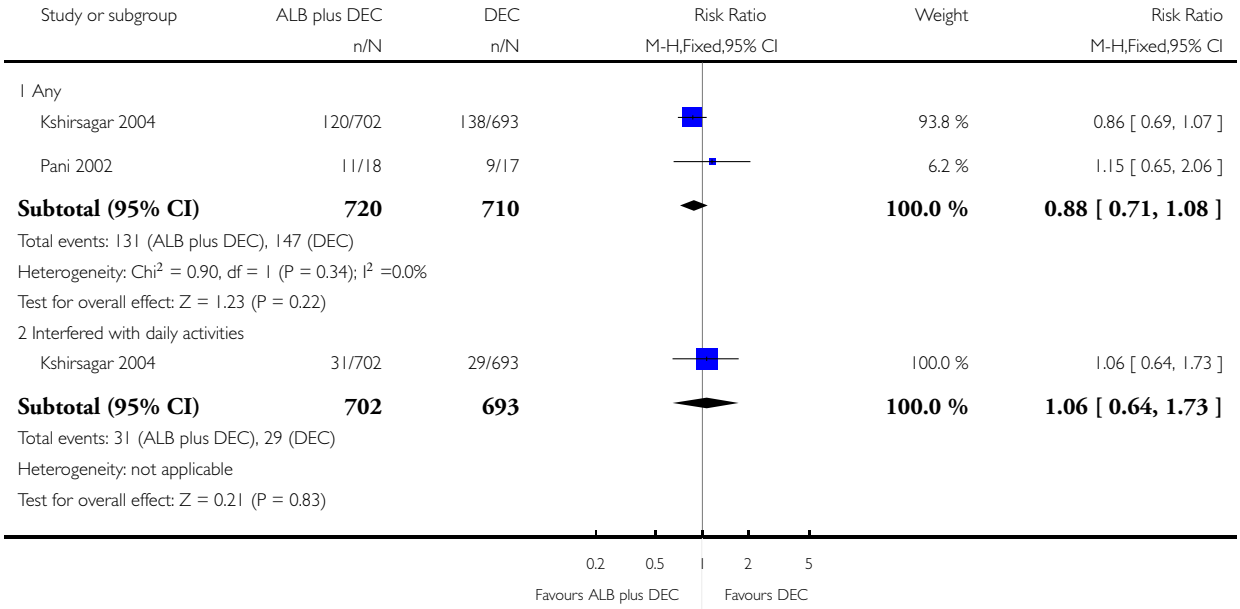


Analysis 5.5. Comparison 5 Albendazole plus diethylcarbamazine (DEC) versus DEC, Outcome 5 Adverse events.

Review: Albendazole for lymphatic filariasis

Comparison: 5 Albendazole plus diethylcarbamazine (DEC) versus DEC

Outcome: 5 Adverse events



APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	filaria*	filaria*	FILARIASIS	FILARIASIS	filaria*
2	albendazole	elephantiasis	lymphatic filariasis	lymphatic filariasis	elephantiasis
3	benzimidazole	lymphedema	ELEPHANTIASIS	ELEPHANTIASIS	lymphedema
4	-	wuchereria	LYMPHEDEMA	lymphedema	wuchereria
5	-	brugia	Wuchereria bancrofti	Wuchereria bancrofti	brugia

(*Continued*)

6	-	1 or 2 or 3 or 4 or 5	BRUGIA	BRUGIA	1 or 2 or 3 or 4 or 5
7	-	diethylcarbamazine	1 or 2 or 3 or 4 or 5 or 6	1 or 2 or 3 or 4 or 5 or 6	diethylcarbamazine
8	-	ivermectin	FILARICIDES	diethylcarbamazine	ivermectin
9	-	benzimidazole	diethylcarbamazine	ivermectin	benzimidazole
10	-	albendazole	ivermectin	benzimidazole	albendazole
11	-	carbamazine	benzimidazole	albendazole	carbamazine
12	-	hetrazan	albendazole	carbamazine	hetrazan
13	-	luxuran	carbamazine	hetrazan	luxuran
14	-	mectizan	hetrazan	luxuran	mectizan
15	-	metiazol	luxuran	mectizan	metiazol
16	-	valbazen	mectizan	metiazol	valbazen
17	-	7-16/OR	metiazol	valbazen	7-16/OR
18	-	6 and 17	valbazen	8-17/OR	6 and 17
19	-	Limit 18 to human	8-18/OR	7 and 18	-
20	-	-	7 and 19	Limit 19 to human	-
21	-	-	Limit 20 to human	-	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2005); Upper case: MeSH or EMTREE heading; Lower case: free text term.

Appendix 2. Risk of bias assessment[a]

Trial	Allocation sequence generation	Allocation concealment	Blinding	Inclusion[a]
Beach 1999	Adequate	Adequate	Reported as "double blind"	Inadequate
Dunyo 2000	Adequate	Adequate	Double blind	Inadequate
Fox 2005	Adequate	Unclear	Outcome assessors	Inadequate

(*Continued*)

Jayakody 1993	Unclear	Unclear	Unclear	Inadequate
Kshirsagar 2004	Unclear	Unclear	Double blind	Adequate (safety study) Adequate or inadequate depending on time point (efficacy study)
Pani 2002	Unclear	Adequate	Double blind	Adequate
Simonsen 2004	Adequate	Adequate	Double blind	Inadequate

[a] See the 'Assessment of risk of bias in included studies' for the assessment methods, and the 'Characteristics of included studies' for the methods used in each trial.
[b] Inclusion of all randomized participants in the final analysis.

Appendix 3. Microfilariae prevalence

Comparison	Trial	Intervention	No. participants	+ve post-treatment	% baseline [reductn]	Note
ALB vs placebo	Dunyo 2000	ALB	71	62	87.3	-
		Placebo	66	62	93.9	-
	Beach 1999	ALB	29	4 months: 22	75.9	Only participants mf positive at baseline
		Placebo	29	4 months: 20	69.0	-
	Beach 1999	ALB	145	4 months: 22	[15.4]	Values for participants regardless of mf status at baseline 26 (17.9%) mf-positive at baseline
		Placebo	139	4 months: 20	[20.0]	25 (18.0%) mf-positive at baseline
	Fox 2005	ALB	256	3 months: 28 6 months: 38	-	-
		Placebo	243	3 months: 30 6 months: 36	-	-

(*Continued*)

ALB vs IV	Dunyo 2000	ALB	71	6 months: 62	87.3	-
		IV	70	6 months: 52	74.3	-
	Beach 1999	ALB	145	4 months: 22	[15.4]	Values for participants regardless of mf status at baseline 26 (17.9%) mf-positive at baseline
		IV	140	4 months: 20	[23.1]	26 (17.3%) mf-positive at baseline
	Beach 1999	ALB	29	4 months: 22	75.9	Only participants mf positive at baseline
		IV	28	4 months: 17	60.7	-
ALB plus IV vs IV	Dunyo 2000	ALB plus IV	75	6 months: 58	77.3	-
		IV	70	6 months: 52	74.3	-
	Beach 1999	ALB plus IV	24	4 months: 4	16.7	Only participants mf positive at baseline
		IV	28	4 months: 17	60.7	-
	Simonsen 2004	ALB plus IV	105	6 months: 67 12 months: 75	6 months: 63.8 12 months: 71.4	-
		IV	98	6 months: 85 12 months: 73	6 months: 86.7 12 months: 74.5	-
ALB vs DEC	Pani 2002	ALB	19	30 d: 0 90 d: 18 360 d: 14 2 yr: 4	-	-
		DEC	17	30 d: 0 90 d: 17 360 d: 14 2 yr: 1	-	-

(*Continued*)

	Jayakody 1993	ALB	16	28 d: 12/15 3 months: denominator unclear 6 months: numbers unclear 5 to 19 months: 5/10	-	-
		DEC	13	28 d: 7/12 3 months: 9/12 6 months: 8/12 15 to 19 months: 5/10	-	-
	Fox 2005	ALB	256	3 months: 28 6 months: 38	-	-
		DEC	246	3 months: 24 6 months: 21	-	-
ALB plus DEC vs DEC	Pani 2002	ALB plus DEC	18	30 d: 0 90 d: 18 360 d: 14 2 yr: 1	-	-
		DEC	17	30 d: 0 90 d: 17 360 d: 14 2 yr: 1	-	-
	Fox 2005	ALB plus DEC	245	3 months: 23 6 months: 13	-	-
		DEC	246	3 months: 24 6 months: 21	-	-
	Kshirsagar 2004	ALB plus DEC	Varies	3 months: 17/19 6 months: 13/21 12 months: 13/18	-	-
		DEC	Varies	3 months: 16/19 6 months: 13/21 12 months: 14/17	-	-

ALB: albendazole; DEC: diethylcarbamazine; IV: ivermectin; mf: microfilariae.

Appendix 4. Antigen prevalence

Comparison	Trial	Outcome measure	Intervention	No. participants	% reduction	Pretreatment	Post-treatment
ALB vs placebo	Dunyo 2000	CFA positive	ALB	-	-	105	110
			Placebo	-	-	103	102
	Fox 2005	CFA positive[a]	ALB	256	-	89 (34.8)	94 (36.7%)
			Placebo	243	-	74 (30.5%)	81 (33.3%)
ALB vs IV	Dunyo 2000	CFA positive	ALB	-	-	105	110
			IV	-	-	99	101
ALB plus IV vs IV	Dunyo 2000	CFA positive	ALB plus IV	-	-	121	122
			IV	-	-	99	101
	Simonsen 2004	CFA positive*	ALB plus IV	247	6 months: 91.9% 12 months: 91.9%	247	6 months: 226 12 months: 227
			IV	266	6 months: 91.0% 12 months: 88.7%	266	6 months: 242 12 months: 236
ALB vs DEC	Pani 2002	Antigen positivity[b]	ALB	19	360 d: 83	-	-
			DEC	17	360 d: 87	-	-
	Pani 2002	Antigen positivity[c]	ALB	19	360 d: 83	-	-
			DEC	17	360 d: 80	-	-
	Fox 2005	CFA positive[a]	ALB	256	-	89 (34.8)	94 (36.7%)
			DEC	246	-	79 (32.1%)	73 (29.7%)
ALB plus DEC vs DEC	Pani 2002	Antigen positivity[b]	ALB plus DEC	18	360 d: 75	-	-
			DEC	17	360 d: 87	-	-
	Pani 2002	Antigen positivity[c]	ALB plus DEC	18	360 d: 81	-	-
			DEC	17	360 d: 80	-	-

(*Continued*)

	Fox 2005	CFA positive[a]	ALB plus DEC	245	-	85 (34.7%)	75 (30.6%)
			DEC	246	-	79 (32.1%)	73 (29.7%)

ALB: albendazole; CFA: circulating filarial antigen; DEC: diethylcarbamazine; IV: ivermectin.
[a]Among children CFA positive at baseline.
[b]Immunochromatographic card test on 50 µL serum.
[c]Og4C3 test kit on 50 µL serum.

Appendix 5. Microfilariae density (geometric mean)

Comparison	Trial	Measure	Intervention	No. participants	Pretreatment	Post-treatment	% reduction
ALB vs	Dunyo 2000	mf/100 µL	ALB	71	708	12 months:	68.5
			Placebo	66	971	12 months: 845	13.0
	Dunyo 2000	mf/ 100 µL measured by AUC[a]	ALB	42	1535	12 months: 1233	19.7
			Placebo	32	2536	12 months: 2740	108.4 (8.4% increase)
	Beach 1999[b]	mf/20 µL	ALB	28	14.1	4 months: 5.1	28.7 (63.8[c])
			Placebo	29	9.3	4 months: 5.3	17.2 (43.0[c])
	Fox 2005	mf/20 µL	ALB	256	12.1 (95% CI 10.3 to 14.2)	3 months: 4.7 (95% CI 3.9 to 5.7) 6 months: 4.4 (95% CI 3.7 to 5.3)	3 months: 22.0 6 months: 34.7
			Placebo	243	17.3 (95% CI 14.5 to 20.6)	3 months: 8.7 (95% CI 7.4 to 10.2) 6 months: 11.2 (95% CI 9.2 to 13.7)	3 months: 8.2 6 months: 10.3
			IV	70	640	12 months: 124	80.6

(*Continued*)

	Dunyo 2000	mf/ 100 µL mea-	ALB	42	1535	12 months: 1233	19.7
			IV	33	1731	12 months: 759	43.8
	Beach 1999	mf/20 µL	ALB	28	14.1	4 months: 5.1	28.7 (63.8[c])
			IV	28	15.5	4 months: 1.5	76.1 (90.2[c])
			IV	70	640	12 months: 124	80.6
	Dunyo 2000	mf/ 100 µL measured by AUC [a]	ALB plus IV	40	1280	12 months: 393	30.7
			IV	33	1731	12 months: 759	56.2
	Beach 1999[b]	mf/20 µL	ALB plus IV	24	13.7	4 months: 0.3	98.9 (97.8[c])
			IV	28	15.5	4 months: 1.5	76.1 (90.2[c])
	Simonsen 2004	mf/100 µL	ALB plus IV	105	812.6	6 months: 29.8 12 months: 59.4	6 months: 96.3 12 months: 83.6
			IV	98	763.5	6 months: 150.0 12 months: 124.9	6 months: 80.4 12 months: 83.6
ALB vs DEC	Pani 2002	mf/mL	ALB	19	77.6 (range 22 to 606)	-	3 d: 8.7 7 d: 14.1 360 d: 94.7
			DEC	17	81.3 (range 22 to 542)	-	3 d: 26.2 7 d: 36.7 360 d: 89.6
	Jayakody 1993	mf/mL	ALB	16	633 +/- 150	15 to 19 months: 3	6 months: 1.91
			DEC	13	566 +/- 120	15 to 19 months: 2	6 months: 0.81
	Fox 2005	mf/20 µL	ALB	256	12.1 (95% CI 10.3 to 14.2)	3 months: 4.7 (95% CI 3.9 to 5.7)	3 months: 22.0 6 months:

(*Continued*)

						6 months: 4.4 (95% CI 3.7 to 5.3)	34.7
			DEC	246	12.9 (95% CI 11.0 to 15.2)	3 months: 2.9 (95% CI 2.5 to 3.4) 6 months: 2.8 (95% CI 2.3 to 3.4)	3 months: 31.3 6 months: 50.4
ALB plus DEC vs DEC	Pani 2002	mf/mL	ALB plus DEC	18	79.4 (range 22 to 233)	-	3 d: 35.7 7 d: 45.1 360 d: 95.4
			DEC	17	81.3 (range 22 to 542)	-	3 d: 26.2 7 d: 36.7 360 d: 89.6
	Fox 2005	mf/20 µL	ALB plus DEC	245	13.4 (95% CI 11.4 to 15.8)	3 months: 2.3 (95% CI 2.0 to 2.7) 6 months: 0.76 (95% CI 0.7 to 0.9)	3 months: 37.3 6 months: 80.4
			DEC	246	12.9 (95% CI 11.0 to 15.2)	3 months: 2.9 (95% CI 2.5 to 3.4) 6 months: 2.8 (95% CI 2.3 to 3.4)	3 months: 31.3 6 months: 50.4

ALB: albendazole; AUC: area under the curve; CFA: circulating filarial antigen; CI: confidence interval; DEC: diethylcarbamazine; IV: ivermectin; mf: microfilariae.

[a] Only in those individuals with over 100 mf/µL blood before treatment, and those examined at baseline, and 3, 6, and 12 months.

[b] Only participants positive for mf at baseline.

[c] Change in group geometric means.

Appendix 6. Antigen density

Comparison	Trial	Outcome measure	Intervention	No. participants	Pretreatment	Post-treatment	% reduction
ALB vs placebo	Dunyo 2000	CFA unit (geometric mean density)	ALB	105	1370	1139	83.1
			Placebo	103	1869	2757	147.5 (47.5% increase)
	Fox 2005	CFA unit (geometric mean density)	ALB	256	2640 (95% CI 2279 to 3058)	2428 (95% CI 2071 to 2847)	3.2
			Placebo	243	2298 (95% CI 1951 to 2706)	2479 (95% CI 2105 to 2919)	1.7
ALB vs IV	Dunyo 2000	CFA unit (geometric mean density)	ALB	105	1370	1139	83.1
			IV	99	1689	1187	70.3
ALB plus IV vs IV	Dunyo 2000	CFA unit (geometric mean density)	ALB plus IV	121	1404	834	59.4
			IV	99	1689	1187	70.3
ALB vs DEC	Pani 2002[a]	Og4C3 test kit on 50 µL serum	ALB	19	0.49 (sd 0.16)	0.08 (sd 0.17)	0.40
			DEC	17	0.39 (sd 0.21)	0.07 (sd 0.15)	0.32
	Fox 2005	CFA unit (geometric mean density)	ALB	256	2640 (95% CI 2279 to 3058)	2428 (95% CI 2071 to 2847)	3.2
			DEC	246	2194 (95% CI 1842 to 2613)	1597 (95% CI 1375 to 1855)	17.0
ALB plus	Pani 2002[a]	Og4C3 test kit	ALB plus	18	0.47 (sd 0.18)	0.07 (sd 0.15)	0.40
			DEC	17	0.39 (sd 0.21)	0.07 (sd 0.15)	0.32
	Fox 2005	CFA unit (geometric mean density)	ALB plus DEC	245	2116 (95% CI 1798 to 2490)	1350 (95% CI 1176 to 1549)	26.7
			DEC	246	2194 (95% CI 1842 to 2613)	1597 (95% CI 1375 to 1855)	17.0

ALB: albendazole; CFA: circulating filarial antigen; CI: confidence interval; DEC: diethylcarbamazine; IV: ivermectin; mf: microfilariae; sd: standard deviation.

[a] Measured at 360 d.

Appendix 7. Adult worms

Comparison	Trial	Outcome measure	Intervention	No. participants	Pretreatment	Post-treatment
ALB vs DEC	Pani 2002	Ultrasonography (No. positive for FDS)	ALB	9	4/9	1 yr: 0/8 2 yr: 0/7
			DEC	7	5/7	1 yr: 0/7 2 yr: 0/6
ALB plus DEC vs DEC	Pani 2002	Ultrasonography (No. positive for FDS)	ALB plus DEC	9	5/9	1 yr: 1/9 2 yr: 1/9
			DEC	7	5/7	1 yr: 0/7 2 yr: 0/6
	Kshirsagar 2004	Ultrasonography	ALB plus DEC	51	35/51 (69%)	3 months: 15/45 (33%) 6 months: 9/46 (20%) 12 months: 15/50 (30%)
			DEC	50	30/50 (60%)	3 months: 14/44 (32%) 6 months: 8/45 (18%) 12 months: 15/49 (31%)

ALB: albendazole; DEC: diethylcarbamazine; FDS: filarial dance sign.

Appendix 8. Adverse events

Trial	Adverse event	Placebo	ALB	IV	ALB plus IV	DEC	ALB plus DEC
Dunyo 2000	Tactile fever	1/70 (1.4%)	3/80 (3.8%)	6/66 (9.1%)	16/80 (20.0%)	-	-
	Headache	0/70 (0%)	1/80 (1.3%)	7/66 (10.6%)	14/80 (17.5%)	-	-
	Muscle/joint pain	2/70 (2.9%)	3/80 (3.8%)	9/66 (13.6%)	10/80 (12.5%)	-	-
	Weakness	1/70 (1.4%)	1/80 (1.3%)	4/66 (6.1%)	7/80 (8.8%)	-	-

(*Continued*)

	Abdominal pain	1/70 (1.4%)	1/80 (1.3%)	0/66 (0%)	4/80 (5%)	-	-
	Diarrhoea	2/70 (2.9%)	0/80 (0%)	1/66 (1.5%)	2/80 (2.5%)	-	-
	Itching	0/70 (0%)	1/80 (1.3%)	2/66 (3.0%)	1/80 (1.3%)	-	-
	Rash	1/70 (1.4%)	0/80 (0%)	1/66 (1.5%)	1/80 (1.3%)	-	-
Beach 1999 (only participants mf positive at baseline)	Self-reported fever	7/29 (24%)	5/27 (19%)	-	-	-	-
	Headache	12/29 (41%)	6/27 (22%)	-	-	-	-
	Myalgias	3/29 (10%)	3/27 (11%)	-	-	-	-
	Cough	2/29 (7%)	3/27 (11%)	-	-	-	-
Pani 2002	Any adverse reaction (mainly fever, headache, myalgia)	-	42.1%	-	-	52.9%	61.1%
	Mean intensity score [a] (sd)	-	1.8 (3.0)	-	-	5.6 (7.1)	6.7 (6.6)
Jayakody 1993	Severe scrotal syndrome[b]	-	2/15 (13%)	-	-	0	-
	Scrotal syndrome: mild, moderate, or severe	-	11/15 (73%)	-	-	0	-
	Fever, right hypochondrial pain, and repeated vomiting	-	0/15	-	-	1/13 (8%)	-
Kshirsagar 2004	Total number of participants with adverse drug reactions by day 5	-	-	-	-	138/693 (20%)	120/702 (17%)

(*Continued*)

	Total number of adverse events	-	-	-	-	270	238
	Number of adverse events thought likely to be drug related	-	-	-	-	256 (95%)	221 (93%)
	OF LIKELY ADVERSE EVENTS:						
	CTC[c] Grade 1	-	-	-	-	144	116
	CTC[c] Grade 2	-	-	-	-	65	57
	CTC[c] Grade 3	-	-	-	-	47	48
	CTC[c] Grade 4	-	-	-	-	0	0
	No. of participants where adverse events interfered with daily activities	-	-	-	-	29/693 (4.2%)	31/702 (4.4%)
Fox 2005	SPECIFIC SYMPTOMS						
	Self-reported or documented fever	10/43 (23%)	9/46 (20%)	-	-	16/44 (36%)	25/47 (53%) (P < 0.05 compared with ALB)
	Headache	12/43 (28%)	11/46 (24%)	-	-	19/44 (43%)	23/49 (49%)
	Myalgias	7/43 (16%) (P < 0.05 compared with ALB)	1/46 (2%)	-	-	8/44 (18%) (P < 0.05 compared with ALB)	5/47 (11%)
	Cough	7/43 (16%) (P < 0.05 compared with ALB)	1/46 (2%)	-	-	6/44 (14%)	7/47 (15%)

(*Continued*)

	MEAN TREATMENT IMPACT SCORE (range)[d]					
	Day 1	0.79 (0 to 3)	0.76 (0 to 3)	-	-	1.46 (0 to 3) (P < 0.05 compared with ALB and placebo)	1.66 (0 to 3) (P < 0.05 compared with ALB and placebo)
	Day 2	0.49 (0 to 2)	0.26 (0 to 1)	-	-	0.84 (0 to 3) (P < 0.05 compared with ALB)	0.66 (0 to 3) (P < 0.05 compared with ALB)
	Day 3	0.16 (0 to 1)	0.2 (0 to 2)	-	-	0.36 (0 to 3)	0.32 (0 to 3)
	Day 4	0.16 (0 to 3)	0.07 (0 to 1)	-	-	0.20 (0 to 3)	0.13 (0 to 1)
	Day 5	0.05 (0 to 1)	0.02 (0 to 1)	-	-	0.11 (0 to 2)	0.06 (0 to 2)
	Day 6	0 (0)	0.02 (0 to 1)	-	-	0.07 (0 to 2)	0.02 (0 to 1)
	Day 7	0 (0)	0 (0)	-	-	0 (0)	0 (0)

[a] All systemic adverse reactions recorded by assigning score 0 (none), 1 (mild) 2 (moderate) or 3 (severe).
[b] Mild = epididymis felt enlarged and tender, and spermatic cord was tender and nodular, scrotal sac swollen; moderate = swelling of scrotal sac, tender epididymis, swelling, nodularity or cord and some systemic features, eg fever malaise; severe = whole scrotal sac swollen and palpation quite painful, features of acute inflammation eg redness, warmth, pain, swelling, systemic features such as fever, chills, anorexia, nausea.
[c] NCI Common Toxicity Criteria grades; Grade 1 = mild adverse event, 2 = moderate adverse event, 3 = severe adverse event, 4 = life-threatening or disabling adverse event, 5 = death.
[d] 1: symptoms were noticed, but did not interfere with daily activities; 2: symptoms caused some interference with daily activities; 3: symptoms prevented usual daily activities.

WHAT'S NEW

Last assessed as up-to-date: 13 August 2005.

Date	Event	Description
5 August 2008	Amended	Converted to new review format with minor editing.

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 1, 2004

Date	Event	Description
14 August 2005	New search has been performed	The first review update, published in Issue 4, 2005, includes three new trials, Fox 2005, Kshirsagar 2004, and Simonsen 2004, and a two-year update of results from the Pani 2002 trial.

CONTRIBUTIONS OF AUTHORS

Julia Critchley assessed studies for inclusion, extracted data, and is responsible for preparing and updating the review. Paul Garner edited the review, extracted data, and assessed the risk of bias in the trials. David Addiss and Hellen Gelband edited the review. Carrol Gamble edited the review and provided statistical input. Henry Ejere assessed studies for inclusion and extracted data.

DECLARATIONS OF INTEREST

For the first version of the review (IFRG 2004), Henry Ejere's salary was paid by The Lymphatic Filariasis Support Centre based in the Liverpool School of Tropical Medicine. The Department for International Development, UK and GlaxoSmithKline fund the Lymphatic Filariasis Support Centre. Dr Addiss is an author on one of the trials.

Julia Critchley, Paul Garner, Hellen Gelband, Carrol Gamble: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The first version of the review (IFRG 2004), published in Issue 1, 2004, deviated from the published protocol: Julia Critchley was invited to join the review team; the objectives were reworded; and the subgroups were removed from the review methods because they were no longer appropriate.

INDEX TERMS

Medical Subject Headings (MeSH)

Albendazole [*therapeutic use]; Diethylcarbamazine [therapeutic use]; Drug Therapy, Combination; Elephantiasis, Filarial [*drug therapy]; Filaricides [*therapeutic use]; Ivermectin [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans