Mass chemotherapy options to control lymphatic filariasis: a systematic review

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Understanding the efficacy of microfilaricidal drugs is important in guiding the global programme for the elimination of lymphatic filariasis as a public-health problem. We did a systematic review of the available literature to determine which currently available drug intervention most effectively decreases circulating *Wuchereria bancrofti* microfilaria in individuals and populations. 57 randomised studies of drug efficacy were identified. Data were combined and compared using weighted mean effect estimates taking into account the longitudinal nature of the data. Combined treatment with diethylcarbamazine plus ivermectin, diethylcarbamazine plus albendazole, and ivermectin plus albendazole resulted in average microfilarial intensity decreases that were 0·7%, 4·6%, and 12·7% of the pre-treatment values, respectively. Drug combinations containing diethylcarbamazine were the most effective against microfilarial prevalence and intensity relative to single drugs or other combinations. The relative efficacies of drug combinations have not been well documented from existing studies and therefore limit the application of evidenced-based recommendations for chemotherapy-based interventions to control lymphatic filariasis. These results provide valuable estimates of drug effect using existing data, but highlight the need for more comprehensive comparative drug studies.

Introduction

Lymphatic filariasis—a disease caused by the parasitic worm *Wuchereria bancrofti*—is widespread in Asia, Africa, the Pacific, and Latin America, with an estimated 43 million people having overt lymphatic pathology including hydrocele and lymphoedema (figure 1).[1] Extensive medical, social, and economic benefits are expected to result from decreasing or eliminating infection.[2–5] Population-based control strategies became practical with the discovery that a single administration of a drug could result in long-lasting microfilarial decreases similar to those seen with extended administrations.[6–9] Based on the rationale that reduction of the microfilarial reservoir would break transmission through the mosquito vectors of *W bancrofti*, the WHO resolved in 1997 to eliminate the infection as a public-health problem, organising an alliance of governments, health organisations, and pharmaceutical companies named the Global Program to Eliminate Lymphatic Filariasis (GPELF) to focus these efforts.[10–12]

Andy Crump, TDR, WHO/Science Photo Library

Figure 1: The right leg of a woman with lymphatic filariasis

There are currently three drugs effective against *W bancrofti* microfilaria that can be administered as single doses or in two-drug combinations—diethylcarbamazine, ivermectin, and albendazole.[13–20] The current global filariasis control effort advocates yearly mass administration of single dose albendazole plus ivermectin, albendazole plus diethylcarbamazine, or diethylcarbamazine alone for 4–6 years based on expected decreases in transmission and estimates of worm longevity.[21] Models have been created to predict the number of drug administrations needed to achieve this goal using existing estimates of drug efficacy.[22–26] However, uncertainty remains regarding the effectiveness of this programme because of difficulties in estimating and comparing the overall relative effects of these interventions.

Previous summaries and reviews have established the safety of the three drugs and efficacy of interventions containing ivermectin or diethylcarbamazine, or both. In 1997, Cao and colleagues[9] demonstrated the efficacy of ivermectin against *W bancrofti* by weighting the percentage decrease in microfilaraemia over time by sample size across 15 studies. Similarly, Brown and co-workers[27] demonstrated that 400 μg/kg bodyweight dose of ivermectin was the most effective ivermectin regimen using simple averages of observed percentage decrease in microfilaraemia estimated from 16 studies. In 2000, Horton and colleagues[28] published an analysis demonstrating the safety of co-administered drugs, again by using simple data averaging methods. Most

recently, Gyapong and colleagues[29] reviewed individual studies of efficacy and pooled effects to estimate selected relative efficacies. The different methodologies used and primary focus on one or the other of the drugs available means that we still lack a standardised and comprehensive comparative analysis of the effectiveness of the various proposed drugs or drug combinations.

We describe a systematic evaluation of all publicly available drug trials data to provide the best current estimates of drug effect against *W bancrofti* microfilaria in individuals and populations.

Methods

All available published randomised controlled trials, comparative efficacy trials, and cluster-randomised field trials examining the effect or safety of drug therapy, or both, on *W bancrofti* microfilaria-positive individuals were examined for inclusion in the analysis. Inclusion criteria were set a priori to include studies with (1) randomised allocation of any drug, dosage, and regimen as an intervention against *W bancrofti*; (2) concurrent study arms; and (3) primary data collection. Exclusion criteria were set a priori to exclude non-human studies, studies with non-randomised allocation of treatment, and studies with temporally non-concurrent study arms.

Panel: Data analysis

Given the follow-up nature of the data, a feature of our analyses is the derivation and use of outcome measures that explicitly account for the longitudinal dependence in the data. The pooled rate of reduction or change in microfilarial prevalence and intensity from baseline values in each study were quantified at a series of summary time points. For microfilarial prevalence:

$$\hat{P}_t = \Sigma_{j=1}^{k} (p_{tj} W_{tj}) / \Sigma_{j=1}^{k} W_{tj}$$

where $\hat{P}_t$ is the pooled proportion of patients positive at time t, p_{tj} is the proportion of patients positive at time t in the jth study, and W is the inverse of the variance of P_t, where the variance, Sp_t, for each of j trials is given by:

$$Sp_t = q_t p_t^2 (1 - p_t)$$

where $q_t = (1 - p_t)$.
For microfilarial density:

$$\hat{X}_t = \Sigma_{j=1}^{k} (X_{tj} n_{tj}) / \Sigma_{j=1}^{k} n_{tj}$$

where $\hat{X}_t$ is the pooled average percentage reduction in microfilarial density from baseline at time$t$, X_{tj} is the percentage reduction in mean microfilarial intensity in patients from baseline density at time t in the jth study, and n_{tj} is the sample size of each of j studies.

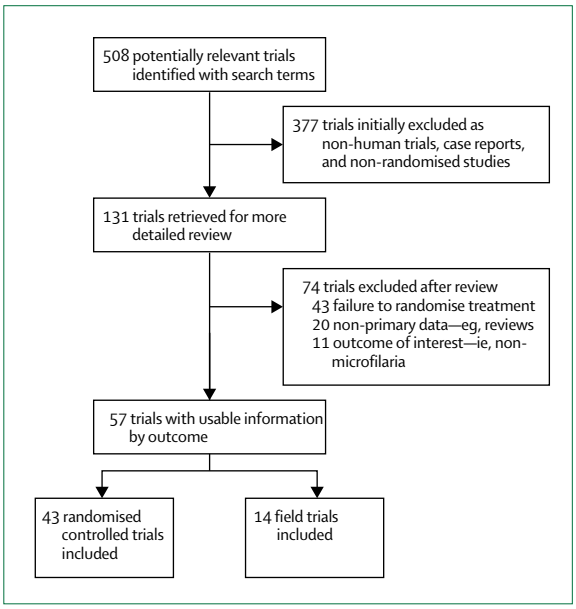

Figure 2: **Trial flow**
The methodological order of trial inclusion/exclusion is illustrated with the number of studies included at each step of the selection process.

Data abstraction

A reviewer recorded all basic parasitological and demographic information on a standardised data collection form for each study. Multiple articles detailing a single study were combined onto a single form and all compiled data were entered into a Microsoft Access database.

Extracted data included study characteristics (eg, study design and drug regimen), demographics (eg, location and study participant characteristics), and treatment effect. Data were extracted directly from text and tables within the publication, or measured from figures if tabulated results were not available. The primary outcome was the effect of different drug regimens or combinations on microfilarial prevalence (dichotomous variable) and microfilarial intensity (continuous variable) at a series of time points following treatment (0–7 days, 8–14 days, 15–31 days, 1–6 months, 7–12 months, 13–24 months, and 25–36 months).

Study characteristics

Studies were categorised by unit of randomisation into two groups: (1) randomised controlled trials that randomly allocated treatment to individuals, and (2) randomised field trials that randomly allocated treatment to groups of individuals. The separate analyses allowed the interpretation of efficacy (defined here as percentage reduction in microfilaria attributed to a single dose of a drug or drug combination as observed in a randomised controlled trials), as well as the overall population drug effectiveness (defined here as percentage reduction in microfilaria within

Reference	Geographic region	Number of study arms	Sample size
Addiss et al[31]	Caribbean	6	65
Addiss et al[14]	Caribbean	4	113
Andrade et al[32]	South America	3	87
Cartel et al[33]	South Pacific	4	40
Cartel et al[34]	South Pacific	4	40
Cartel et al[35–37]	South Pacific	5	58
Cartel et al[38]	South Pacific	3	58
Cartel et al[39]	South Pacific	2	37
Coutinho et al[40]	South America	4	43
Diallo et al[41]	Africa	2	16
Dreyer et al[42]	South America	2	107
Dreyer et al[43]	South America	7	249
Dreyer et al[44]	South America	6	67
Dreyer et al[45]	South America	3	31
Dunyo et al[46]	Africa	4	246
Eberhard et al[47]	Caribbean	4	44
El Setouhy et al[48]	Africa	2	58
Fan et al[49]	China	5	680
Glaziou et al[17]	South Pacific	3	57
Ismail et al[50]	India	3	37
Ismail et al[19]	India	4	50
Ismail et al[51]	India	3	47
Jayakody et al[52]	India	2	29
Kar et al[53,54]	India	4	60
Kazura et al[55]	South Pacific	5	50
Kumaraswami et al[56]	India	4	40
Makunde et al[57]	Africa	4	40
Malhotra et al[58]	India	2	46
McMahon et al[59]	Africa	4	18
Mouliat-Pelat et al[15]	South Pacific	5	49
Mouliat-Pelat et al[60]	South Pacific	3	57
Otteson et al[61]	India	4	40
Pani et al[62]	India	3	51
Prasad et al[63]	India	2	85
Richards et al;[64] Eberhard et al[65]	Caribbean	3	30
Sabry et al[66]	Africa	3	93
Sarma et al[67]	India	2	16
Sethumadhavan et al[68]	India	2	148
Sethumadhavan et al[69]	India	4	196
Simonsen et al[70]	Africa	2	80
Simonsen et al[71]	Africa	2	203
Subramanyam et al[72]	India	2	60
Zheng et al[73]	China	2	60

Table 1: **Included randomised controlled trials**

Study	Geographic region	Number of study arms	Population units	Total sample size
Beach et al[74]	Caribbean	4	Five schools	965
Bockarie et al[13,75]	South Pacific	2	14 villages	2534
Das et al[76]	India	3	15 villages	21 634
Dunyo et al[77]	Africa	4	Four villages	1425
Hawking et al[78]	South America	2	Two hospitals	21
Jain et al[79]	India	5	Five villages	4177
Kimura et al[80]	South Pacific	6	Nine villages	209
Meyrowitsch et al[81,82]	Africa	2	Two villages	1341
Meyrowitsch et al[83]	Africa	2	Four villages	824
Narasimham et al[84]	India	2	63 houses	769
Rao et al;[85] Krishnaro et al[86]	India	2	84 houses	511
Rajendran et al[87]	India	2	18 villages	461
Reuben et al[88]	India	2	Nine villages	8128
Sethumadhavan et al[89]	India	2	Two villages	46
Simonsen et al[90]	Africa	2	Two villages	534

Table 2: **Included randomised field trials**

populations as observed in randomised field trials). Based on the difficulty of objectively quantifying individual study quality, all included studies were assumed to represent valid information regarding drug effect.[30]

Data analysis

The effectiveness of each drug regimen or combination was quantified by estimating the mean rates of change of microfilarial prevalence and intensity over time (panel).

Results

Trial flow

508 articles were initially identified; of these, 377 clearly contradicted the inclusion/exclusion criteria. Two independent reviewers identified 57 of the 131 remaining papers that met the inclusion criteria. Reasons for exclusion were primarily failure to randomise treatment (43 of the 74 rejected papers), lack of primary data, and use of historic controls (figure 2). The two reviewers initially had 87% selection agreement. Following a single meeting to discuss the 16 discordantly reviewed papers, the reviewers achieved 100% agreement.

Study characteristics

Included studies represent two primary types of randomisation: randomised controlled trials in which drugs are randomised to individuals (table 1)[31–73] and cluster-randomised field trials in which drugs are randomised to groups of people (table 2).[74–90] The papers that met the inclusion criteria represent every major region of *W bancrofti* endemicity (table 3). In each study, drugs were provided after establishing baseline infection status. The randomised controlled trials observe individuals following a single drug administration. Subsequent study reports for randomised controlled trials where additional drugs were supplied in later years were not included because the subsequent drug administrations differed from the original study protocol and randomisation was no longer maintained. Randomised controlled field trials did not exhibit these limitations. The analysis of the field trials, therefore, included multiple administrations of diethylcarbamazine and ivermectin or cooking salt fortified with diethylcarbamazine, which provides daily exposure to low doses of the drug. Note that each study in the latter case estimated actual drug dosage for the population by measuring salt consumption per family.

Population characteristics for randomised controlled trials tended to over-represent men and older ages. The randomised controlled trials were on average 85% men with an average age of 27 years. Cluster-randomised field trials were more representative of study populations as a whole, with an average age of 16 years

and a nearly equal representation of both sexes (51% men). These disparities represent differences in individual selection criteria between these two types of study designs. Many of the randomised controlled trials used restrictive inclusion criteria and often included only men of military age, while the randomised field trials tended to include entire villages or large representative segments of the population. Comparative analyses of adverse events were not done because of incomplete and non-standard reporting.

The small number of studies with similar drug comparisons and follow-up times limited the use of standard meta-analytic tools. Calculation of average drug effect across studies, regardless of within-study comparisons, allowed the greatest number of studies to be combined and permitted the estimation of average absolute drug effect. In anticipation of different follow-up times, we maintained our a priori procedure for summarising results from studies in groups of representative post-treatment time periods. However, differences in analysis and reporting of time to follow-up, length of follow-up, and total number of studies done by intervention were still pronounced.

Region	Individual randomisation*	Population randomisation*
Africa	8	4
Caribbean	4	1
China	2	0
India	15	6
South America	6	1
South Pacific	9	2
Total studies	43	14

*The 56 studies that met the inclusion criteria were divided into two groups: studies that randomly allocated drug to the study participant (randomised controlled trials) and studies that randomised to groups of individuals—eg, villages (cluster-randomised field trials).

Table 3: **Regional characteristics**

Drug efficacy in randomised controlled trials

Combined drugs were more effective than single drugs, particularly the diethylcarbamazine combinations at 7–12 months and 13–24 months post-treatment (figure 3, table 4, and table 5). Diethylcarbamazine plus ivermectin exhibited the greatest effect through to 12 months, with a 95·2% average decrease in microfilarial prevalence and a 99·3% decrease in microfilarial density at 7–12 months post-treatment. The dramatic increase in prevalence observed at 13–24 months for diethylcarbamazine plus ivermectin treatment highlights the difficulty of plotting available data over time, since this data point represents only ten individuals in a single study, implying that some of the variability here may be attributed to using multiple time points with limited data.

Drug efficacy in field trials

On a population level after 12 months, medicated salt is similarly effective at decreasing microfilarial prevalence and density as a single administration of two drugs, and in one case considerably better. Repeated administration of diethylcarbamazine plus ivermectin decreased microfilarial prevalence to 43·6% of the baseline prevalence and decreased microfilarial density to 9·3% of the baseline (table 6 and table 7).[90–94] Medicated salt was more effective against microfilarial prevalence than single administration of drug combinations. For example, prevalence decreased to 12·4% of baseline in populations receiving diethylcarbamazine-medicated salt at 7–12 months post-treatment versus 87·8% in populations receiving ivermectin combined with albendazole (table 6). Diethylcarbamazine-medicated salt is also more effective against microfilarial density than ivermectin plus albendazole, and similarly effective to repeated doses of diethylcarbamazine plus ivermectin (table 7).

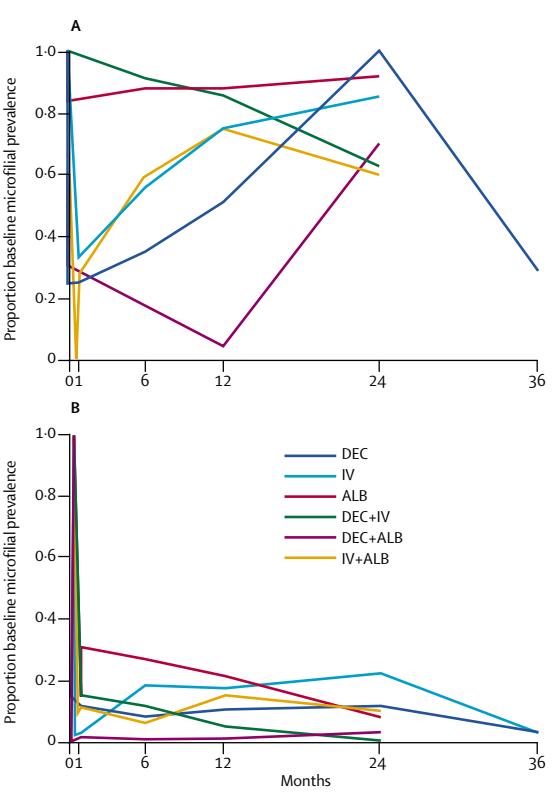

Figure 3: **Randomised controlled trial treatment effect on rates of change of *W bancrofti* microfilaria from baseline**

The mean percentage change in (A) microfilarial prevalence and (B) microfilarial density were combined across all randomised controlled trials. The inconsistent reporting of data across studies resulted in statistical artefacts, as observed with diethylcarbamazine at 24 months post-treatment based on a single study of eight people (see tables 4 and 5). Diethylcarbamazine plus ivermectin provided the greatest average decrease in microfilarial density and prevalence over time. ALB=albendazole, DEC=diethylcarbamazine, IV=ivermectin.

	Baseline			1 month		6 months		12 months		24 months		36 months	
Drug	Number of studies (n)	References	Mean baseline prevalence (%)	Number of studies (n)	Percentage baseline mf prevalence	Number of studies (n)	Percentage baseline mf prevalence	Number of studies (n)	Percentage baseline mf prevalence	Number of studies (n)	Percentage baseline mf prevalence	Number of studies (n)	Percentage baseline mf prevalence
DEC	15 (978)	17,31,32,47,49,59,61, 63,67–70,72,73	100	5 (225)	24·99	9 (292)	35·26	10 (352)	50·63	1 (8)	100·00	1 (14)	28·57
IV	13 (455)	14,17,31,34,40,41,47, 50,61,64,72,73,77	100	7 (209)	33·12	9 (313)	58·85	9 (316)	75·25	4 (32)	84·87	NA	NA
ALB	5 (134)	14,19,46,62,77	100	1 (13)	84·60	4 (107)	88·27	3 (94)	88·31	1 (12)	91·70	NA	NA
DEC+IV	3 (52)	17,19,45	100	NA	NA	NA	NA	1 (21)	4·80	1 (10)	70·00	NA	NA
DEC+ALB	3 (47)	19,62,51	100	NA	NA	2 (34)	91·35	2 (32)	86·70	2 (24)	63·56	NA	NA
IV+ALB	6 (247)	14,19,46,51,57,71,77	100	1 (12)	25·00	5 (192)	59·78	4 (207)	73·19	2 (45)	59·29	NA	NA

ALB=albendazole; DEC=diethylcarbamazine; IV=ivermectin; NA=not applicable for analysis.

Table 4: **Percentage change in baseline microfilarial (mf) prevalence in randomised controlled trials**

The similarity of results within these population randomised studies to those observed in individual randomised studies (figure 3 *vs* figure 4) suggest that similar interpretations may be made regarding the effectiveness of drugs in controlled and general populations. Note, however, that drug effectiveness at the population level also depends on host demography, transmission intensity, drug coverage, and compliance rates in addition to drug efficacy.[95]

Combined treatment was only assessed in the literature on a population level with diethylcarbamazine plus ivermectin and ivermectin plus albendazole. Ivermectin plus albendazole reduced microfilarial prevalence to 39·6% and 87·8% of the baseline at 1–6 months and 7–12 months post-treatment, respectively (table 6). Diethylcarbamazine plus ivermectin was applied repeatedly, and resulted in a consistent decrease in microfilarial prevalence and density at each time of follow-up. The repeated application of diethylcarbamazine plus ivermectin resulted in a decrease in population prevalence and density to below 10% of the original baseline levels by the 3rd year (table 6 and table 7). Notably, the efficacy of the diethylcarbamazine plus ivermectin repeated-application combination was similar to the activity of diethylcarbamazine-medicated salt (figure 4). All drugs except albendazole showed good efficacy over time.

Discussion

Despite over 50 years of filariasis drug research, precise data comparing relative drug efficacies against *W bancrofti* remain scarce. For example, only 57 studies met our inclusion criteria, many of which were dosing studies or comparative efficacy trials without replication in the literature. This lack of reliable and comparable studies hinders the application of meta-analytic techniques and evidenced-based medicine. Existing literature and policy are subsequently based on a small number of studies, or summaries that are compiled with methods most subject to bias. This study also suffers from the inadequacy of available data and biases resulting from the combination of potentially disparate data—eg, different doses. However, such techniques also permit the most comprehensive summary measures of observed effect. The application of standard meta-analytic techniques can protect against such bias, but only in cases where there are an adequate number of similar studies to combine results.

Overall, the results of this systematic review support the hypothesis that administration of multiple drug regimens (or diethylcarbamazine-medicated salt) is the most effective means of lowering *W bancrofti* microfilaria. A number of individual studies have reached similar conclusions,[13,14,74,96] as well as previous

	Baseline			1 month		6 months		12 months		24 months		36 months	
Drug	Number of studies (n)	References	Mean baseline mf density (range)	Number of studies (n)	Percentage baseline mf density	Number of Studies (n)	Percentage baseline mf density	Number of Studies (n)	Percentage baseline mf density	Number of Studies (n)	Percentage baseline mf density	Number of Studies (n)	Percentage baseline mf density
DEC	15 (535)	17,62,32,35,47,55,60, 61,66–69,72,73,91	652·7 (19·7–4689)	11 (402)	13·00	16 (535)	9·80	12 (356)	9·60	6 (102)	10·00	2 (45)	1·39
IV	21 629)	14,15,17,31,33–35,40,41,47, 50,53,55,60,61,64,66,72,73,92	886·6 (14·1–2000)	13 (441)	1·50	19 (623)	18·50	12 (413)	19·96	7 (137)	22·00	1 (48)	1·43
ALB	5 (121)	14,19,46,51,57,71,77	927·7 (77·6–1783)	2 (24)	32·59	5 (102)	25·78	4 (105)	21·85	1 (12)	9·80	NA	NA
DEC+IV	4 (71)	17,19,45,60	455·6 (203–1190)	2 (50)	1·10	3 (50)	0·50	4 (62)	0·70	1 (10)	2·80	NA	NA
DEC+ALB	4 (75)	19,62,48,51	639·7 (79·4–1013)	2 (41)	15·56	4 (75)	12·06	4 (73)	4·60	2 (24)	0·80	NA	NA
IV+ALB	6 (248)	14,19,51,57,71,77	615·2 (13·7–1585)	2 (26)	10·96	5 (206)	7·90	5 (221)	17·25	2 (42)	8·60	NA	NA

ALB=albendazole; DEC=diethylcarbamazine; IV=ivermectin; NA=not applicable for analysis.

Table 5: **Percentage change in baseline microfilarial (mf) density in randomised controlled trials**

	Baseline			6 months		12 months		24 months		36 months		48 months	
Drug	Number of studies (n)	References	Mean baseline mf prevalence (range)	Number of studies (n)	Percentage baseline mf prevalence	Number of studies (n)	Percentage baseline mf prevalence	Number of studies (n)	Percentage baseline mf prevalence	Number of studies (n)	Percentage baseline mf prevalence	Number of studies (n)	Percentage baseline mf prevalence
DEC	5 (6381)	[79,80,83,89,90]	0·10 (0·05–0·28)	6 (4003)	44·61	5 (4684)	49·22	1 (3195)	59·84	NA	NA	NA	NA
DEC (multiple)	4 (2766)	[13,80,81,90]	0·31 (0·07–0·49)	NA	NA	4 (2316)	82·72	1 (1055)	43·80	1 (949)	22·00	1 (804)	7·05
DEC (salt)	5 (1356)	[78,83,85,89,93]	0·32 (0·26–1·00)	4 (752)	7·82	5 (1126)	12·43	1 (316)	10·20	NA	NA	NA	NA
IV	3 (1126)	[74,76,94]	0·17 (0·14–0·24)	2 (781)	72·56	1 (334)	88·08	NA	NA	NA	NA	NA	NA
IV (repeated)	1 (614)	[76]	0·14 (0·14–0·14)	1 (611)	70·00	1 (601)	61·99	1 (603)	60·64	1 (603)	40·04	NA	NA
ALB	2 (540)	[74,94]	0·21 (0·15–0·24)	1 (167)	86·60	1 (316)	106·80	NA	NA	NA	NA	NA	NA
DEC+IV (multiple)	2 (12 223)	[13,88]	0·19 (0·15–0·55)	NA	NA	1 (1074)	43·60	1 (1101)	19·70	2 (12 267)	8·00	1 (1101)	3·76
DEC+ALB	1(553)	[87]	0·04 (0·04–0·04)	1(1117)	4·34	NA	NA	NA	NA	NA	NA	NA	NA
IV+ALB	2 (540)	[74,94]	0·20 (0·11–0·24)	1 (158)	39·60	1 (355)	87·80	NA	NA	NA	NA	NA	NA

ALB=albendazole; DEC=diethylcarbamazine; IV=ivermectin; NA=not applicable for analysis.

***Table 6*: Percentage change in baseline microfilarial (mf) prevalence in randomised controlled field trials**

reports that summarised existing data.[9,28] However, our study clearly demonstrates this effect through a comprehensive literature review of all available drug applications and by distinguishing individual and population-based studies. These results demonstrate that the greatest effectiveness against *W bancrofti* may be achieved with combined drug regimens, particularly those containing diethylcarbamazine. In addition, we show these results to be consistent across randomised controlled trials and cluster-randomised field trials.

Single-dose diethylcarbamazine plus albendazole, ivermectin plus albendazole, and diethylcarbamazine in table salt alone are the current regimens used by GPELF. We found ivermectin plus albendazole to decrease microfilaria more effectively than albendazole alone; however, this effect is not observed when comparing combined treatment with ivermectin alone, suggesting that the observed effect of combined treatment may be (nearly) completely attributed to ivermectin. With the exception of 2–6 months post-treatment prevalence, no significant difference was detected between the combination and either diethylcarbamazine or ivermectin alone.[62] The addition of albendazole to diethylcarbamazine or ivermectin does not appear to improve the effectiveness of either drug alone, and therefore may not directly benefit the transmission elimination aspect of the lymphatic filariasis control programme.[46,62] The single study that assessed diethylcarbamazine plus ivermectin against diethylcarbamazine plus albendazole demonstrated that the ivermectin combination is significantly superior at reducing microfilarial density up to 12 months post-treatment ($p<0·05$ based on data abstraction), but not at 15 months post-treatment.[19] Therefore, although diethylcarbamazine plus albendazole is an effective combination against *W bancrofti* microfilaria, current data do not support this combination as the best choice for the programme, based on estimates of relative efficacy against other drug combinations or single non-albendazole drugs. However, the fact that this evidence is based on single studies highlights the insufficiency of existing data to empirically determine the most efficacious regimen available. A recent Cochrane review reached a similar conclusion regarding the inadequacy of existing data to verify albendazole efficacy against

	Baseline			6 months		12 months		24 months		36 months		48 months	
Drug	Number of Studies (n)	References	Mean baseline mf density (range)	Number of studies (n)	Percentage baseline mf density	Number of studies (n)	Percentage baseline mf density	Number of studies (n)	Percentage baseline mf density	Number of studies (n)	Percentage baseline mf density	Number of studies (n)	Percentage baseline mf density
DEC	3 (5232)	[13,79,83]	82·1 (0·15–588)	3 (4238)	29·46	2 (3578)	28·60	NA	NA	NA	NA	NA	NA
DEC (multiple)	3 (3031)	[13,76,83]	198·7 (0·66–1122)	2 (1084)	56·00	2 (2250)	34·30	1 (1747)	20·00	1 (1641)	17·20	1 (804)	0·01
DEC (salt)	4 (875)	[78,83,85,93]	531·6 (13·5–933)	2 (362)	29·40	4 (761)	16·50	NA	NA	NA	NA	NA	NA
IV	3 (1100)	[73,76,94]	3·5 (0·62–15·4)	1 (611)	46·80	2 (428)	72·51	NA	NA	NA	NA	NA	NA
IV (repeated)	1 (614)	[76]	0·62 (0·62–0·62)	1 (611)	46·80	1 (601)	41·94	1 (603)	41·90	1 (603)	19·40	NA	NA
ALB	1 (369)	[94]	3·52 (3·52–3·52)	NA	NA	1 (251)	109·10	NA	NA	NA	NA	NA	NA
DEC+ALB	1(461)	[87]	0·10 (0·10–0·10)	1(1117)	13·00	NA	NA	NA	NA	NA	NA	NA	NA
DEC+IV (multiple)	2 (12 223)	[13,88]	1·8 (0·5–14·9)	NA	NA	1 (1074)	9·30	1 (1101)	3·70	2 (12 267)	9·90	1 (1016)	1·06
IV+ALB	2 (521)	[74,94]	6·4 (3·4–13·6)	NA	NA	2 (445)	54·60	NA	NA	NA	NA	NA	NA

ALB=albendazole; DEC=diethylcarbamazine; IV=ivermectin; NA=not applicable for analysis.

***Table 7*: Percentage change in baseline microfilarial (mf) density in randomised controlled field trials**

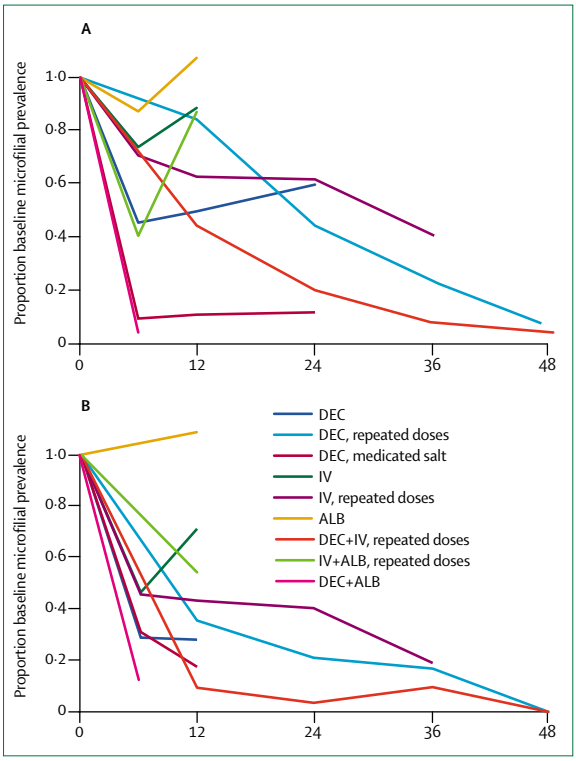

Figure 4: **Randomised field trial treatment effect on rates of change of *W bancrofti* infection from baseline**
The mean percentage changes in (A) microfilarial prevalence and (B) microfilarial density were combined across all cluster-randomised field trials. Diethylcarbamazine and ivermectin alone and in combination provided the greatest average reduction in microfilarial density and prevalence over time. ALB=albendazole; DEC=diethylcarbamazine; IV=ivermectin.

microfilaria.[97] Additional comparative randomised controlled studies are needed.

Regardless of limited evidence to support the use of albendazole in the lymphatic filariasis control programme, the addition of albendazole may provide peripheral benefits such as broad spectrum anthelmintic action against co-occurring intestinal helminth infections, potentially enhancing the health benefit of filariasis control.[21,98] Diethylcarbamazine is contraindicated for regions co-endemic for onchocerciasis due to potential adverse reactions. In these regions, a combined drug treatment would be limited to ivermectin plus albendazole. For regions without such contraindications, drugs with macrofilaricidal effect—eg, diethylcarbamazine—are generally favoured over microfilaricidal drugs like ivermectin.[99] If diethylcarbamazine is to be used when possible, and a second drug is added to improve efficacy, existing data suggest that ivermectin would provide greater reduction in microfilarial prevalence and density than the addition of albendazole. A poorly selected combination could potentially result in failure to stop transmission of the parasite within the specified time frame, especially in areas where transmission rates are very high.[95]

Search strategy and selection criteria

Between September 2001 and April 2004, articles were identified from the PubMed and Embase databases with three sets of search criteria: "*Wuchereria* and chemotherapy", "*Wuchereria* and therapy", and "*Wuchereria* and anthelmintic". Hardbound Index-Medicus were manually searched for years between 1947 and 1968—ie, the years between the discovery of the first major drug against *W bancrofti* (diethylcarbamazine) and the availability of online database records for medical publications. Reviewers also searched the references of retrieved articles for studies that were not identified in database searches. Attempts were made to include non-English language studies by using Chinese, Japanese, and French translators. However, none were included due to ineligibility or availability of identical information in English journals.

The present results have highlighted the continuing need for large, conclusive studies comparing the efficacy of drug regimens against bancroftian filariasis. In the interest of affected populations, the global community, and the GPELF partnership, it is clear that the most effective regimens must be scientifically determined and applied. We suggest that filling this existing gap in knowledge about drug effectiveness through additional standardised studies together with clearer reporting would improve the likelihood of successfully controlling infection and transmission of this parasite.

Conflicts of interest

We declare that we have no conflicts of interest.

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