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Ivermectin for the chemotherapy of bancroftian filariasis: a meta-analysis of the effect of single treatment

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Summary The efficacy and safety of ivermectin in the treatment of filariasis due to *Wuchereria bancrofti* was assessed by a meta-analysis of the results from 15 published clinical trials. Seven hundred and forty-eight microfilaraemic patients were enrolled in 7 dose-finding and 8 comparative studies. Administered as a single dose, ivermectin induced nearly complete clearance of microfilariae from the blood from the first day to 30 days post-treatment, followed by gradual recurrence of microfilaraemia and increase in its intensity. Higher doses of ivermectin showed greater clearance effects and maintained lower microfilaraemia levels for a longer time. The adverse reactions caused by the drug were flu-like, transient, generally mild and well tolerated by patients. The frequency and intensity of adverse reactions were strongly associated with pretreatment microfilaria counts in the blood, but independent of dose. The findings of the meta-analysis suggest that ivermectin given at a single annual dose of 200 μg/kg body weight or higher, whether or not in combination with DEC, has great potential for therapeutic strategies to control bancroftian filariasis.

keywords lymphatic filariasis, *Wuchereria bancrofti*, meta-analysis, ivermectin, chemotherapy, treatment safety, treatment efficacy, review

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Introduction

A recent estimate indicates that approximately 120 million persons are infected with lymphatic filariasis worldwide. *Wuchereria bancrofti*, the most common cause of human filariasis, is estimated to affect 106.2 million individuals, with about 40 million having overt physical disabilities associated with the infection (WHO/TDR 1994). The treatment of lymphatic filariasis has mainly relied on diethylcarbamazine (DEC; 12 days standard course) (Ottesen 1985). Although in a few Asian countries treatment strategies have eliminated lymphatic filariasis (WHO/TDR 1994), the use of multiple DEC dosage for community control programmes has been limited in most other endemic areas by inconvenience of drug delivery and uncertainty of compliance. Furthermore, DEC cannot be applied in regions where onchocerciasis or loiasis coexist (Ottesen & Ramachandran 1995) because of serious adverse reactions. A potential alternative, ivermectin, is now used extensively in the treatment and control of infection due to the filarial parasite *Onchocerca volvulus* (Taylor & Greene 1989). The success of ivermectin in the management of onchocerciasis promoted interest in its potential utility for the treatment of lymphatic filariasis. Since the first work on the treatment of bancroftian filariasis with ivermectin was published (Diallo *et al.* 1987) the drug has been evaluated in clinical trials around the world. These trials have

been designed to assess filaricidal activity and adverse reactions. Before the drug can be used in large-scale control programmes, a better understanding of important issues such as efficacy and safety is needed to determine its value for lymphatic filariasis.

We have done a structured review of the current literature on ivermectin in the treatment of bancroftian filariasis, using meta-analysis techniques for the aggregation and synthesis of evidence from prior research. The objectives of our study were to clarify efficacy and safety of single-dose ivermectin and to compare its performance with that of DEC.

Materials and methods

Methods and procedures for conducting this meta-analysis were developed with reference to the 'Methodologic Guidelines for Systematic Review of Randomized Control Trials in Health Care from the Potsdam Consultation on Meta-analysis' (Cook *et al.* 1995) and the recommendation for the use of meta-analysis in medicine (Jenicek 1989).

Literature search

Through a computer-assisted search of the bibliographic database MEDLINE, publications on ivermectin in combination with either of the following key words were selected: filariasis, *Wuchereria bancrofti*, clinical trial. Titles and abstracts of publications were scanned to eliminate articles which obviously did not address our questions. The full text of the remaining abstracts was then retrieved. Reference lists of these publications were reviewed to identify other articles on the same topic. 'Fugitive' literature, such as proceedings of conferences and published abstracts, were not included because they lacked the details necessary for meta-analysis.

Study selection

The inclusion criteria were as follows: (1) study subjects were identified as having *Wuchereria bancrofti* infection; (2) the efficacy or adverse reactions of ivermectin were evaluated in clinical trials; (3) only one course of treatment with ivermectin was administered in the study. Regarding multiple published reports about the same study, the information from each report was aggregated and included in the analysis only once.

Methodologic quality assessment

For each study, methodologic quality assessment was performed by 2 reviewers independently, based on criteria adapted from Chalmers *et al.* (1981). Only the Methods and Results sections of the reports were read. All identifying information, including authors and their institution, journal, title, and funding source, was removed. Discrepancies in the judgement of the 2 assessors were adjudicated by a consensus meeting. The maximal achievable quality score was 100 points.

Data extraction

Information from each eligible study was abstracted onto a standard form. The following data were collected: authors, title, year and source of publication, study site, number of patients, age range and average age, number of study groups, dosage, geometric mean of microfilaria (mf)-density and number of positive patients at baseline and after treatment for each group, times of post-treatment measurements, incidence and mean or peak intensity of various adverse reactions, and starting and peaking times and length of adverse reactions. In some cases, values had to be estimated from figures. The abstraction was performed independently by two investigators who met afterwards to cross-check their reports and reconcile differences.

Analysis

Subjects in the studies were divided into different groups according to treatment dosage. Effect size was defined as the percentage reduction of the pretreatment mf-density (per ml) and prevalence (% of mf-positive subjects). The following formula was used to calculate the percentage reduction in geometric mean of mf-density at a given follow-up time:

$$A = \{[\Pi(a_i + 1)^{n_i}]^{1/N}\} - 1$$

where a_i is the percentage of pretreatment geometric mean in each study; n_i is the sample size per study;

N is the total number of patients eligible for analysis. '(a_i+1)' was used to get a valid summary measure in case of zero value of 'a_i'. The effect size 'A' was computed for each regimen at each follow-up time point. By only weighting sample size, it is assumed that all trials included in the analysis had the same underlying variances for changes in the outcome measures (Peto 1987; Follmann *et al.* 1992). Safety was measured by both frequency and severity of adverse reactions. Severity was assessed using the score system of the original studies.

Treatment effects were graphed for each dosage to look for any indication of dose–response relationships. The χ^2-test for trend analysis was performed using the EPI-INFO program (Center for Disease Control and Prevention, Atlanta, Georgia, USA) to compare microfilaraemia prevalence and adverse reaction incidence of different ivermectin dose groups. χ^2 or Fisher's exact test was used to examine the difference in microfilaraemia prevalence between ivermectin and DEC regimens. In addition, an analysis was performed with weight based on both sample size and study methodologic quality.

Results

Through a literature search, 45 articles were retrieved that addressed the issue of treatment of bancroftian filariasis with ivermectin. Eighteen reports meeting all criteria were identified. Three trials were each reported in 2 articles, each report presenting different information on efficacy or safety. Therefore 15 eligible studies were included, which are summarized in Table 1. Of the 15 trials, 7 were dose-finding studies (studies 1–7 in Table 1); 8 were comparative studies of single-dose ivermectin with either standard course DEC (studies 8–11) or single-dose DEC (studies 12–15).

All 8 comparative studies were stated to be randomized; 4 described the procedures of randomization (studies 8, 9, 11 and 13). One dose-finding trial also randomly assigned patients to different dose groups (study 6). The 8 comparative studies and 3 dose-finding studies (studies 4, 6 and 7) were double-blind both to the physicians and patients, and 1 only blinded physicians caring for the patients (study 2). All studies except study 1 explicitly defined their inclusion and exclusion criteria. Only in 5 studies (2, 6, 7, 8 and 14) was a confidence interval or standard error for geometric mean reduction and for prevalence given. In most studies, 1 ml of blood was collected between 1930 h and midnight, and the membrane filtration technique used for counting microfilariae. Other blood volumes were used in studies 3, 5 and 12 (2 ml) and in study 13 (0.25 ml). Information on volume was lacking in study 1. In study 12, blood was collected between 0700 and 0900 h. Studies 1, 3 and 5 did not give information on sampling hours. Study 1 lacks information on the examination technique. Methodological quality scores were generally high (usually higher than 60, range 50–81), indicating the overall good methodology of the trials. The first published study (study 1) and one other trial (study 5) reported only briefly on methodology, resulting in a quality score lower than 60.

Seven hundred and forty-eight mf-positive patients in the 15 eligible studies were included for analysis, 544 of whom were treated with ivermectin. Of the 544 subjects, 313 were enrolled in 7 dose-finding trials, while the other 231 came from 8 studies on comparisons with DEC. The remaining 204 subjects were treated with DEC in comparative studies.

Efficacy

Because a multi-centre trial demonstrated that a priming dose of 20 μg/kg had no effect on efficacy (Chodakewitz 1995), patients receiving a normal therapeutic dose with or without priming dose were considered as one group. The combined results on the changes of mf-levels in each dose group are shown in Table 2. Each dose group showed an abrupt decline in the geometric mean of blood mf-count following a single treatment, with an average 98.6% (range 93.6–99.5) of circulating microfilariae being cleared up within 1 day. By 1 week, microfilariae almost completely disappeared from the blood. However, one month after treatment, microfilaraemia began to recur and the mf-load gradually increased, although even 2 years later relapsed mf-levels were much lower than pretreatment. Weighting effect size by both quality score and sample size gave essentially no difference in the overall results. Therefore only sample size weighting is used for the remaining results and discussion.

Table 1 Summary of eligible studies

Study number	Reference (e.a.=*et al.*)	Study area	Age range (years)	Range of mf (mf/ml) pretreatment	Ivermectin dosage (in μg/kg body weight) [No. of patients]	DEC dosage (in mg/kg body weight) [No. of patients]
1	Diallo e.a., 1987	Dakar, Senegal	Adult	15–4566	50 [7], 100 [9]	—
2	Kumaraswami e.a., 1988	Madras, India	18–47	62–3900	25 [10], 50 [10], 100 [10], 200 [10]	—
3	Cartel e.a., 1990; Roux e.a., 1989	French Polynesia	18–50	>20	50 [10], 100 [10], 150 [10], 200 [10]	—
4	Ismail e.a., 1991	Sri Lanka	17–55	70–6980	20 [11], 50 [9], 100 [11], 200 [9]	—
5	Cartel e.a., 1992; Moulia-Pelat e.a., 1993a	French Polynesia	21–84	1–10 121	100 [37], 400 [37]	—
6	Kar e.a., 1993	Orissa, India	18–40	123–10 000	20 [15], 50 [15], 100 [15], 200 [15]	—
7	Coutinho e.a., 1994	Brazil	18–46	105–6030	20 [12], 50 [10], 100 [11], 200 [10]	—
8	Ottesen e.a., 1990	South India	19–45	25–6000	21 [13], 126 [13]	6 (12 days) [14]
9	Zheng e.a., 1991	China	14–75	8–2764	100 [30]	6 (12 days) [30]
10	Sabry e.a., 1991	Egypt	15–55	87–4447	100 [41]	6 (12 days) [30]
11	Richards e.a., 1991; Eberhard e.a., 1992	Haiti	16–65	112–5174	200 [10], 400 [10]	6 (12 days) [10]
12	Cartel e.a., 1991	French Polynesia	18–50	⩾100	100 [23]	3 [24], 6 [11]
13	Addiss e.a., 1993	Haiti	16–65	530–983	20+400 [9], 20+200 [9], 220 [10]	6 [11], 1+6 [11], 6+IV 20 μg/kg [11]
14	Kazura e.a., 1993	Papua New Guinea	25–31	2985–5185	200 [10], 20+200 [10], 20+400 [10]	6 [10], 1+6 [10]
15	Dreyer e.a., 1995a	Brazil	18–44	103–14 135	200 [11], 20+200 [11], 20+400 [11]	6 [11], 1+6 [11], 6+IV 20 μg/kg [12]

mf, Microfilaria; IV, ivermectin.

Table 2 Density of mf following ivermectin treatment as a percentage of pretreatment level. The number of patients evaluated is given in brackets. Variability between studies is indicated by the range

Dose (μg/kg)	Time after treatment						
	1 day	1 week	1 month	3 months	6 months	1 year	2 years
20–25	6.4 (61)	0.16 (61)	0.7 (61)	8.7 (61)	22.3 (61)	—	—
Range	5.0–16.0	0–0.5	0–2.0	1.4–21.1	7.7–66.0		
50	2.0 (54)	0.07 (61)	0.9 (61)	11.8 (61)	28.8 (61)	56.2 (20)	—
Range	0.5–5.0	0–0.3	0–4.0	2.6–28.0	7.1–54.0	54.5–58.0	
100–150	1.0 (188)	0.06 (183)	1.2 (183)	8.9 (220)	22.2 (179)	35.5 (98)	—
Range	0.1–2.8	0–0.02	0–4.0	3.2–21.4	10.0–60.0	17.6–55.9	
200	0.5 (54)	0.49 (74)	1.0 (106)	6.8 (106)	9.3 (125)	13.8 (71)	23.1 (52)[1]
Range	0–1.3	0–2.4	0–3.5	1.8–19.0	1.0–21.2	4.9–26.3	6.4–30.8
400	0.6 (37)	0.05 (10)	1.0 (31)	3.0 (68)	2.9 (77)	8.1 (67)	9.2 (31)[2]
Range	—[3]	—[3]	0.5–2.0	1.0–8.0	0.4–6.0	0.9–11.0	4.4–13.7
All together	1.4 (394)	0.15 (389)	1.0 (442)	7.6 (516)	13.8 (503)	17.1 (267)	16.5 (83)

[1] Including 20 subjects evaluated 1.5 years after treatment. Exclusion results in a similar value of 19.2% (32 patients).
[2] Including 10 subjects evaluated 1.5 years after treatment. Exclusion results in a similar value of 9.1% (21 patients).
[3] One study only.

The dynamic patterns of change of mf-density following treatment with ivermectin were essentially similar for different dose groups. Even with a dosage of 20 μg/kg body weight, the drug caused nearly complete clearance of microfilariae from the blood. However, differences in mf-density return among dose groups were obvious (Table 2). Table 2 indicates that higher doses of ivermectin (200–400 μg/kg) are more effective in maintaining decreased mf-levels. Mf-density return rates have also been calculated for a subgroup of studies with complete data at each time point from 1 month to 1 year (real cohort). The results for this cohort appeared to be very similar to those obtained with all studies.

With respect to the microfilaraemia prevalence, 7 reports presented relevant information (studies 1–3, 7, 9, 11 and 13). The summary results are listed in Table 3. Combining all dose groups, approximately 90% of patients became mf-negative within one week after treatment. After one month, microfilariae were subsequently detected in the blood in one-third of the subjects. By 3 months, the prevalence rose to around three-quarters, which was sustained until one year follow-up. Apparently, prevalence reduction does not depend on dose. Only after one month was prevalence lower for those treated with higher doses ($\chi^2_{trend}=12.16$, $P<0.001$).

Safety

Adverse reactions following treatment with ivermectin were evaluated in all eligible studies, but presentation of results in each individual study varied. Two studies were excluded from the analysis for adverse reactions (studies 13 and 14 in Table 1), because no information was given on the number of patients experiencing these reactions. Of the remaining studies, 9 reported findings by dosage (studies 1, 3–7, 9, 11 and 12). Seven studies (2, 5–7, 9–11) listed all adverse events that were observed, while quantitative data were limited in the other 6 (studies 1, 3, 4, 8, 12 and 15).

Eighty per cent (316/395) of subjects experienced at least one adverse event. The most commonly seen, predominately flu-like, adverse reactions were fever (66%; 208/313), headache (72%; 203/280), weakness (49%; 122/250), myalgia (48%; 151/313), chill (51%; 121/239) and lethargy (74%; 73/99). The denominators of these fractions differ since only the studies reporting specific adverse reactions were taken into account. It is possible that in studies not reporting a specific reaction, this reaction did not occur; therefore, the percentages mentioned should be interpreted as upper limits. Other reported side-effects included diaphoresis, arthralgia, dizziness,

Table 3 Prevalence of microfilaraemia after ivermectin treatment as a percentage of pretreatment level[1]. The number of patients evaluated is given in brackets

Dose (μg/kg)	Time after treatment					
	1 week	1 month[2]	3 months	6 months	1 year	2 years
20–25	9.1 (22)	83.3 (12)	86.4 (22)	86.4 (22)	72.7 (11)	—
50	21.6 (37)	63.0 (27)	96.7 (30)	86.5 (37)	90.0 (20)	—
100–150	7.5 (80)	14.3 (70)	57.5 (80)	60.0 (70)	49.0 (51)	—
200	5.0 (40)	50.0 (20)	92.5 (40)	86.2 (58)	91.8 (49)	88.8 (9)
400	10.0 (20)	—	78.9 (19)	55.6 (9)	57.9 (19)	87.5 (8)
Total	10.1 (199)	36.4 (129)	76.4 (191)	75.5 (196)	71.3 (150)	88.2 (17)

[1] As only persons with microfilaraemia were treated, pretreatment prevalence equals 100%.
[2] $\chi^2_{trend}=12.16$, d.f.=1, $P=0.001$.

Table 4 Adverse reactions of ivermectin by dose group[1]

Dose (μg/kg)	20–25[2]	50	100–150	200	400	Total
No. of studies	4	5	8	4	2	9
% (No. with adverse reaction/ No. observed)	86.8 (59/68)	78.4 (40/51)	71.2 (104/146)	90.9 (40/44)	70.2 (33/47)	77.5 (276/356)

[1] Adverse reaction rates among groups were not significantly different. $\chi^2_{trend}=2.06$, $P=0.152$. Patients could experience more than one adverse event.
[2] Thirty patients treated with 1 mg of ivermectin in phase 1 of study 11 are included in this group.

anorexia, nausea, vomiting, abdominal pain, sore throat and dyspnoea. The time course of adverse reactions was essentially the same, usually beginning about 12–24 hours after administration, peaking in frequency and intensity at 24–48 hours, and subsiding by 48–72 hours. Even at their peak intensities, side-effects were generally mild and moderate, and usually did not require any medication. The most severe reaction, postural hypotension (a reduction in the arterial blood pressure in the standing position accompanied by tachycardia) was observed in 7.5% (21/279) of the subjects from 7 studies (2, 4, 6–8, 10, 11). This situation persisted for 8 hours to 3 days and required only symptomatic management. Local reactions, such as epididymitis, lymphangitis/adenitis and scrotal reaction were reported in only 11 patients of 3 studies (9, 10 and 15). Data collected on the basis of therapeutic dosage from 9 eligible studies (1, 3, 4–7, 9, 11, 12) were synthesized to look at the impact of dosage. Table 4 outlines the incidence of adverse reactions in different dose groups. A χ^2 for trend test showed no significant difference in adverse reaction frequency among the different dose groups ($\chi^2_{trend}=2.06$, $P=0.152$).

In all studies except the initial clinical trial (study 1), the severity of adverse reactions was quantitatively assessed using a score system usually on a scale of 0–3 (0 none, 1 mild, 2 moderate, and 3 severe). The main purpose of using the scores was to determine the relationship between side-effects of treatment and either drug dosages or pretreatment mf-loads of patients. All studies declared that the intensity of side-effects, particularly fever (the most objectively quantitative adverse reaction), was significantly associated with the pretreatment mf-density in the blood. Unfortunately, we could neither get a summary estimate of the association strength nor carry out an inference test because of insufficient information and the use of various assessment approaches in the original studies. Two dose-finding

Table 5 Density of mf following ivermectin or DEC treatment as a percentage of pretreatment level. The number of patients evaluated is given in brackets

Regimen	Time after treatment						
	1 day	1 week	1 month	3 months	6 months	1 year	2 years
Ivermectin (20–150 μg/kg)[1]	2.1 (97)	0.05 (120)	1.9 (120)	7.9 (120)	21.3 (79)	26.0 (30)	—
Ivermectin (200–400 μg/kg)[2]	—	1.43 (30)	1.5 (83)	5.6 (83)	5.2 (111)	7.7 (81)	15.6 (83)
Standard DEC	27.1 (74)	3.64 (74)	3.6 (74)	5.5 (74)	14.8 (44)	9.7 (40)	0.2 (10)
DEC 6 mg/kg	—	14.63 (73)	18.9 (31)	17.0 (73)	10.0 (73)	5.4 (42)	6.8 (42)

[1] Low dose group of ivermectin.
[2] High dose group of ivermectin.

Table 6 Microfilaraemia prevalence after treatment of ivermectin or DEC as a percentage of pretreatment level[1]. The number of patients evaluated is given in brackets

Regimen	Time after treatment					
	1 week	1 month	3 months	6 months	1 year	2 years
Ivermectin (20–400 μg/kg)[2]	10.1 (199)	36.4 (129)	76.4 (191)	75.5 (196)	71.3 (150)	88.2 (17)
Standard course DEC	10.0 (40)	17.9 (39)	22.5 (40)	30.8 (39)	20.0 (40)	33.3 (9)
Single dose DEC 6 mg/kg	54.8 (31)	—	77.4 (31)	74.2 (31)	73.3 (31)	—

[1] As only persons with microfilaraemia were treated, pretreatment prevalence equals 100%.
[2] Prevalence of all dose groups is combined, as there is no dose effect on microfilaraemia prevalence after treatment of ivermectin except at one month (Table 3).

studies indicated that patients treated with low-dose ivermectin (20 or 25 μg/kg) had lower adverse reaction scores than those in the higher dose groups, but the difference reached statistical significance only for 50 and 200 μg/kg groups (studies 2 and 7 in Table 1). Three other studies (3, 4 and 5) noted that intensity of side-effects was independent of dosage.

Comparison with DEC

In the comparative studies included in the meta-analysis, both efficacy and safety were assessed for single-dose ivermectin versus either standard (6 mg/kg for 12 days, studies 8–11 in Table 1) or single-dose DEC (studies 12–15). The doses of ivermectin used in these studies ranged from 20 to 400 μg/kg body weight. Taking all the studies together, ivermectin showed a more prominent reduction in mf-density during the first month after treatment than did either the standard course or single-dose DEC regimens (Table 5). Compared with low-dose ivermectin (20–150 μg/kg), both DEC-regimes suppressed mf-counts longer. The standard DEC treatment seemed to be most effective in suppression of microfilaraemia at the follow-up time of 2 years, but the numbers evaluated in this point are small (Table 5).

From 1 month follow-up and onwards, mf-prevalences after a standard course of DEC were significantly lower ($P \leqslant 0.03$) than for both the other regimes. Except for the first week, no significant differences are found between single-dose DEC and ivermectin (Table 6).

Systemic adverse reactions induced by the two drugs were similar both qualitatively and quantitatively, and they were tolerable to patients. However, some studies demonstrated that localized reactions (swelling and tenderness of lymph nodes, epididymitis, genital pain, etc) were more prominent with DEC (studies 9, 11, 13 and 15).

Discussion

Over the past few years, the value of ivermectin for treating bancroftian filariasis has been extensively investigated in clinical trials. Recently, a few papers have provided narrative reviews on this issue (Nanduri & Kazura 1989; Campbell 1991; Kazura 1993; Ottesen & Campbell 1994; Ottesen 1994). The traditional narrative reviews have two basic shortcomings. First, no systematic approach is used to obtain primary data and integrate findings; rather, the subjective judgement of reviewers is employed. Secondly, the narrative reviewer does not synthesize data quantitatively across literature and hence no summarized (pooling) estimates are given (Thacker 1988). We did a meta-analysis, in which the results of relevant studies were critically reviewed and statistically combined to summarize the efficacy and adverse reactions. Since the analysis integrates observations on large numbers of patients, it reduces random errors and enhances statistical power (Peto, 1987). As the included studies have an overall good methodological quality, the meta-analysis is likely to provide convincing arguments. A main problem is that information is combined from trials with different patient characteristics and study designs. To minimize this problem, only the studies recruiting patients with bancroftian filariasis receiving their first dose of ivermectin were included.

Although changes in microfilaraemia after treatment of ivermectin showed essentially the same pattern, different effect sizes are evident by looking across the results of the 15 eligible studies. To a large extent this variability of treatment effects is inevitable given the small numbers of patients enrolled per study. Other factors may be the diversity of pretreatment mf-densities, differences in ages of patients recruited in the studies (Table 1), and regional or population differences. We could not discover any systematic impact of these factors. Since there is much homogeneity in the hours of blood sampling, the amount of blood examined, and the examination techniques, it is unlikely that these factors are important determinants of between-study variability.

Regardless of dosage, the drug could almost completely eliminate the microfilariae from the blood, with about 90% patients becoming mf-negative within one week post-treatment. This status is maintained for about 1 month, followed by a return of microfilaraemia (Tables 2 and 3). With regard to the dose–response relationship, some studies indicated that the higher doses of ivermectin were relatively more effective in decreasing mf-levels (Diallo *et al.* 1987; Roux *et al.* 1989; Kar *et al.* 1993). In contrast, others argued that the effect size was independent of drug dose (Kumaraswami *et al.* 1988; Ottesen *et al.* 1990; Ismail *et al.* 1991; Coutinho *et al.* 1994). After weighting for population size, the meta-analysis showed that higher doses of ivermectin gave a greater clearance effect and maintained a lower mf-level for a long follow-up time (Table 2). The doses of 200–400 μg/kg of body weight appeared to be maximally effective in reducing mf-density and maintaining low levels (Table 2). For the mf-prevalence no dose–response relationship could be derived (Table 3).

Time points of re-examination varied across the individual studies. For example, not all persons observed at time 1 were re-examined at times 2 or 3. Some individuals were not examined until one year after treatment. Thus, the treatment cohorts reported in this study are quasi-cohorts with a variable number of patients per time point. We found that the results for these quasi-cohorts are similar to the results of a real cohort comprising patients with a complete follow-up between 1 month and 1 year (see Table 2).

After treatment with ivermectin, most patients experienced various flu-like adverse reactions which were transient and usually mild. The frequency and intensity of adverse reactions were associated with pretreatment mf-loads, but independent of the dosage of ivermectin (Table 4). Taken together with the fact that all side-effects occurred 12–72 hours after treatment and clearance of microfilariae from the blood, the conclusion seems justified that adverse reactions result from host inflammatory responses to antigens released by killed microfilariae rather than direct drug toxicity or metabolite reactions (Ottesen 1987). Postural hypotension, the more severe side-effect, occurred only occasionally. Few patients experienced local reactions. These results demonstrate that ivermectin is safe and well acceptable.

An important issue concerning ivermectin in the treatment of bancroftian filariasis is its potential

activity against adult worms. In the treatment of onchocerciasis, ivermectin does not kill adult *O. volvulus* parasites when given at a standard dose of 150 μg/kg body weight, unless the treatment interval is extremely short (Duke *et al.* 1992). Unlike onchocerciasis, in which microfilariae are the primary pathogen (Connor *et al.* 1985), the major pathologic manifestations of lymphatic filariasis are caused by adult parasites. Therefore a damaging effect on adult worms may slow or halt clinical progression of the disease. Furthermore, a macrofilaricidal activity has important implications for filariasis control programmes based on chemotherapy. The higher the efficacy against worms, the fewer treatments are required to bring the parasite burden down to insignificant levels. Meta-analysis provides no definitive evidence, but the significant long-term (1 and 2 years) suppression of microfilaraemia observed in high-dose (200–400 μg/kg) groups could indicate that ivermectin administered in a high single dose has some actions on adult filariae, as has been demonstrated for the impact of treatment on *O. volvulus* (Plaisier *et al.* 1995). It is not clear whether the activity is a killing effect or an interference with fertility or reproductive function of the adult female in onchocerciasis (Albiez *et al.* 1988). The paucity of local reactions following ivermectin treatment suggests a lack of macro-filaricidal effect of the drug. Ultrasound was recently used to observe movements of adult worms after treatment with a single 400 μg/kg dose of ivermectin, showing no observable effect on adult *W. bancrofti* (Dreyer *et al.* 1995b).

The relative merits of ivermectin in comparison with DEC have recently been debated but not clearly defined (Richards *et al.* 1991; Ottesen 1994). For community-based control programmes, the main considerations about the relative utility of any therapy are effectiveness and safety, ease of drug delivery, and costs. As has been stated, drug safety seems not to be an important criterion for the selection of regimens (Dreyer *et al.* 1995a), because the systemic adverse reactions induced by both ivermectin and DEC were comparable, generally mild and well tolerable. DEC has macro-filaricidal as well as micro-filaricidal effects (Ch'en 1964; Ottesen & Ramachandran 1995), while ivermectin shows a more rapid effect on clearance of microfilariae with little evidence of action against adult worms. It has been declared that the greatest advantage of ivermectin in the treatment of lymphatic filariasis is its ease of delivery in a single oral dose. The practical benefits of a single-dose regimen over a standard 12-day DEC regimen are obvious. Nevertheless, both the meta-analysis and a multi-centre trial (Chodakewitz 1995) have found that single-dose DEC is also rather effective in the suppression of microfilaraemia. These comparisons may be in favour of DEC administered in single dose. However, neither single-dose ivermectin nor single-dose DEC is as effective as standard-course DEC in reducing microfilaraemia prevalence in long-term follow-up (Table 6). When considering the possible utility of single-dose ivermectin or DEC for the prevention of bancroftian filariasis, frequency of drug administration is a critical point. Our meta-analysis suggests that single-dose 400 μg/kg ivermectin administered annually can be a safe and effective strategy for the control of bancroftian filariasis. Another alternative is a combination of ivermectin and DEC, which seems superior to either drug taken alone. The combined regimen clears microfilariae more rapidly and completely (Moulia-Pelat *et al.* 1994), and is more effective in sustaining decreased mf-levels (Glaziou *et al.* 1994) without inducing any more adverse reactions (Moulia-Pelat *et al.* 1993b). Although more research is required, the combination of single-dose ivermectin plus DEC could have potential value in the chemotherapeutic control of bancroftian filariasis.

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