

An analysis of the safety of the single dose, two drug regimens used in programmes to eliminate lymphatic filariasis

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SUMMARY

This review of the safety of the co-administration regimens to be used in programmes to eliminate lymphatic filariasis (albendazole + ivermectin or albendazole + diethylcarbamazine [DEC]) is based on 17 studies conducted in Sri Lanka, India, Haiti, Ghana, Tanzania, Kenya, Ecuador, the Philippines, Gabon, Papua New Guinea, and Bangladesh. The total data set comprises 90635 subject exposures and includes individuals of all ages and both genders. Results are presented for hospital-based studies, laboratory studies, active surveillance of microfilaria-positive and microfilaria-negative individuals, and passive monitoring in both community-based studies and mass treatment programmes of individuals treated with albendazole ($n = 1538$), ivermectin (9822), DEC (576), albendazole + ivermectin (7470), albendazole + DEC (69020), or placebo (1144). The most rigorous monitoring, which includes haematological and biochemical laboratory parameters pre- and post-treatment, provides no evidence that consistent changes are induced by any treatment; the majority of abnormalities appear to be sporadic, and the addition of albendazole to either ivermectin or DEC does not increase the frequency of abnormalities. Both DEC and ivermectin show, as expected, an adverse event profile compatible with the destruction of microfilariae. The addition of albendazole to either single-drug treatment regimen does not appear to increase the frequency or intensity of events seen with these microfilaricidal drugs when used alone. Direct observations indicated that the level of adverse events, both frequency and intensity, was correlated with the level of microfilaraemia. In non microfilaraemic individuals, who form 80–90% of the 'at risk' populations to be treated in most national public health programmes to eliminate lymphatic filariasis (LF), the event profile with the compounds alone or in combination does not differ significantly from that of placebo. Data on the use of ivermectin + albendazole in areas either of double infection (onchocerciasis and LF), or of loais (with or without concurrent LF) are still inadequate and further studies are needed. Additional data are also recommended for populations infected with *Brugia malayi*, since most data thus far derive from populations infected with *Wuchereria bancrofti*.

Key words: Lymphatic filariasis, albendazole, ivermectin, diethylcarbamazine, DEC, drug regimens for LF, drug safety, adverse events, *Wuchereria bancrofti*, *Brugia malayi*, Programme to Eliminate Lymphatic Filariasis (PELF), tropical disease control.

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INTRODUCTION

Lymphatic filariasis is one of the most important causes of chronic disablement in the developing world and, as such, produces a considerable economic burden. The actual extent has still to be defined but is likely to be considerable, given the estimated 120 million persons actually affected and up to 1 billion at risk of infection (Ottesen *et al.* 1997). Until recently, progress towards control of lymphatic filariasis was slow, even though it was recognized that high levels of control or even eradication was feasible (CDC, 1993). In the last few years, however, availability of new antigen detection kits has eliminated the need for night blood tests for bancroftian filariasis, there are better methods of treatment of established cases, and combinations of drugs have been shown to be more effective than single agents, thus opening new prospects for control or even elimination of this disease (Ottesen *et al.* 1997).

In 1997 at the World Health Assembly, the World Health Organisation (WHO) was instructed to proceed to undertake measures to eliminate lymphatic filariasis as a public health problem (WHO, 1997). The strategy to achieve this target is now based primarily on the use of either of the established microfilaricidal drugs, ivermectin or diethylcarbamazine, given together with albendazole. In using albendazole, an immediate benefit arises from its anthelmintic effectiveness (Ismail *et al.* 1998; Horton, this supplement), while at the same time there is increased antifilarial effectiveness from the use of 2-drug co-administration regimens (Ottesen, Ismail & Horton, 1999).

This review of the safety of co-administered albendazole plus either ivermectin or diethylcarbamazine (DEC) was undertaken following a similar review of the efficacy of the combinations (WHO, 1998). At that time it was recommended that a separate review be undertaken to confirm the impression held by all the investigators that such 2-drug regimen usage was indeed safe. To enable this evaluation, as much of the original and electronic data as possible were assembled from the individual clinical investigators, and a process of data entry, cross validation and analysis of data was undertaken. The data were derived from 17 sources (total data set 90635 individual exposures), each source having similar, but slightly different objectives and data collection methods. A standard procedure was adopted that enabled information from these different sources to be collapsed into data sets of similar material (see below). Some of the individual reports have also been prepared for publication, and these can stand examination as single entities and permit comparisons with similar data collected and published in the future.

METHODS

The WHO filariasis programme had funded a number of research projects of different sizes and designs since 1993 to investigate primarily the efficacy, but also the safety of 2-drug co-administration regimens for LF. In addition, independent studies had been conducted using similar approaches or protocols to look at co-administration drug efficacy in intestinal helminth infections. The data on the efficacy of these regimens in lymphatic filariasis was reviewed and a report, together with recommendations, was issued (WHO, 1998). The studies reviewed at that time, along with additional study material that had become available by September 1999, formed the database for this investigation and analysis (Table 1). Of particular importance was the addition of a substantial volume of data on the use of drug co-administration regimens in patients without microfilaraemia, since such individuals will eventually constitute the majority of those treated in the mass drug administration programmes in LF endemic countries.

The principal 'single dose' 2 drug regimens evaluated were the following: (1) albendazole (400 mg) + diethylcarbamazine (DEC, 6 mg/kg) and (2) albendazole (400 mg) + ivermectin (200 µg/kg). In certain of the early, in-hospital studies, higher doses of albendazole (600 mg) and ivermectin (400 µg/kg) were also studied (see Sri Lanka studies 0-2, Table 1). These drugs were administered concurrently for all patients who received them. As controls, other patients were treated with either placebo or matching doses of ivermectin, DEC or albendazole as single agents.

All available data were initially collected by WHO in Geneva and transferred to London for analysis, along with the protocols and sample case record forms. Data were available in a variety of formats, including electronic data bases, case record forms, investigator reports, laboratory records, and data base hard copy print outs. These were sorted, and further requests for data were made, as needed, by the WHO to the investigators. As a result, a number of inherent problems with the data were resolved prior to the overall analysis, thus extending the usefulness of many of the data sets. Following the collection of data, all investigator reports were reviewed and, where possible, the data were then validated to their sources (case record forms or electronic data bases). The validated data were then captured on an Excel spreadsheet for further analysis.

Since the methods for recording side effects often differed among sites, a standardised order was adopted for entry of information that could then be compared. Some forms had considerable blank areas, since only events recorded as being specifically solicited were entered, and in the analysis such blank

Table 1. Studies evaluating the safety of single dose, 2-drug regimens: albendazole + ivermectin or albendazole + DEC

Type of study	Country, study (publication reference ^c)	Regimen ^a					
		Albendazole + Ivermectin	Albendazole + DEC	Albendazole	Ivermectin	DEC	Placebo
Hospital-based	Sri Lanka 0 (Ismail)†	5*+		5*			
	Sri Lanka 1 (Ismail <i>et al.</i> 1998)	13*+	13*	12*			
	Sri Lanka 2 (Ismail <i>et al.</i> , in press)	31[15*+]	16*				
	Tanzania (Makunde)†	20 ^b		13			8 ^b
	Sub-total	69	29	30			8
Laboratory studies	Sri Lanka 0 (Ismail)†	5*+		5*			
	Sri Lanka 1 (Ismail <i>et al.</i> 1998)	13*+	13*	12*			
	Sri Lanka 2 (Ismail <i>et al.</i> , in press)	31[15*+]	16*				
	India (Shenoy <i>et al.</i> 1999)	16	16	3			
	India re-treat (Shenoy <i>et al.</i> 2000)	12	15	2			
	Tanzania (Makunde)†	20 ^b		13			8 ^b
	Sub-total	97	60	35			8
Active Surveillance Mf +ve	Haiti 1 cycle 1 (Addiss <i>et al.</i> 1997)	36		26	39		29
	Haiti 1 cycle 2 (Beach <i>et al.</i> 1999b)	26		33	15		
	Haiti 2 (Beach <i>et al.</i> 1999a)		92	46		45	44
	Ghana 1 (Dunyo <i>et al.</i> 2000)	150		80	66		70
	Ghana 3 (Awadzi)†	14		14	14		
	India (Shenoy <i>et al.</i> 1999)	16	16	3			
	India re-treat (Shenoy <i>et al.</i> 2000)	11	8				
	Sri Lanka-3 (Weerasooriya)†	32	41	34		35	
	Sub-total	285	157	236	134	80	143
Active Surveillance Mf –ve	Ecuador (Espinell)†	122	126	125	130		128
	Ghana 1 (Dunyo <i>et al.</i> 2000)	252		256	229		244
	Gabon (Richard-Lenoble)†	181		175	179		142
	Philippines (Belizario)†	155	159	156	159	155	
	India Re-treat (Shenoy <i>et al.</i> 2000)	1	7				
	Sub-total	711	292	712	697	155	514

Table 1 (contd.)

Type of study	Country, study (publication reference ^c)	Regimen ^a					
		Albendazole + Ivermectin	Albendazole + DEC	Albendazole	Ivermectin	DEC	Placebo
Passive Monitoring	Haiti 1 (Addiss <i>et al.</i> 1997; Beach <i>et al.</i> 1999 <i>b</i>)	209		218	201		200
	Haiti 2 (Beach <i>et al.</i> 1999 <i>a</i>)		561	285		283	279
	Haiti 2 re-treat (Beach <i>et al.</i> 1999 <i>a</i>)		331				
	Papua New Guinea Year 1 (Selve)†		28000				
	Year 2 (Selve)†		28000				
	Bangladesh (Hossain)†		11600				
	Kenya (Njenga <i>et al.</i> 1999; Wamae†)		50	57		58	
	Ghana 2 (Gyapong)†	6369			8790		
	Ghana 1 re-treat (Dunyo <i>et al.</i> 2000)	892					
	Sub-total	7470	68542	560	8991	341	479
Grand total		8535	69020	1538	9822	576	1144

^a Regimens: single doses of drugs used, alone or in combination, were: albendazole 400 mg, ivermectin 200 µg/kg body wt, and DEC 6 mg/kg body wt. except as indicated by * (albendazole 600 mg) or + (ivermectin 400 µg/kg). Numbers in columns represent sample sizes.

^b 7/20 patients treated with albendazole + ivermectin were infected with both *Onchocerca volvulus* and *W. bancrofti*, as were all of the placebo-treated group; all other patients had single infections with *W. bancrofti*.

^c Presents study design and efficacy results but not the same degree of detail concerning the safety data as reported here.

† Unpublished.

areas could not be considered to be zero values. The severity of clinical events was accepted as recorded in the data sets by the investigator. In general, the following were the terms described: 'mild' – no effect on daily activity and/or no treatment required; 'moderate' – limitation in daily activity and/or treatment needed; 'severe' – marked effect on daily activity and/or unable to work and/or hospitalised.

Once entry was complete, data were collapsed into summary tables to compare the event profile of the different compounds alone and in combination. This analysis allowed separate comparisons of data from: (1) hospital-based studies (where there were laboratory data in addition to event material recorded on a day by day basis); these laboratory data consisted of haematological indices, serum enzymes for liver function assessment, and measures of renal function; (2) active surveillance of microfilaria positive individuals (where outpatients were studied with regular collection of event data, normally by questionnaire); (3) active surveillance of microfilaria negative individuals (as for 2, but in microfilaria negative individuals); (4) passive surveillance of community-based studies (studies conducted in the community with collection of data on record forms as reported, generally without direct questioning by health workers); and (5) passive surveillance of mass treatment programmes (collection of data reported to health workers within large scale programmes – no direct questioning or formal reports generated).

The data from each study were reported as separate items, and the collapsed data were then reported for each individual study type (groups 1–5). In analysing the collapsed data, the frequencies of events were related to the population of individuals for whom a specific event had been recorded rather than to the population as a whole. This approach necessarily overestimates the frequency of events, since negative data on events are rarely recorded in clinical studies. Finally an overarching summary (which forms the basis for this paper) was produced in which all strands of the data were pulled together, conclusions drawn, and comments provided on the interpretation of the data and on areas where additional work might be appropriate.

RESULTS

Study populations

Table 1 indicates the source countries, number and types of studies in each country, and the treatments within each study that have contributed to this review. It is evident that there is a broad geographic distribution of data and that this roughly covers the global distribution of lymphatic filariasis. It is also clear that there is wide ethnic diversity among the study sites. Within the data sets there is also a balance of both males and females of all age groups, except for those specifically excluded. Three groups

of individuals were excluded: pregnant and lactating women, children below 2 years of age (or below 5 years of age where regimens containing ivermectin were used), and individuals who were clinically ill. These exclusions are not, however, a constraint on the implications of the findings, since these same groupings would be expected to be excluded in LF control programmes as well, at least for the immediate future. The types of monitoring in the various studies also reflect the levels of monitoring expected as the programmes advance; i.e. detailed daily recordings in the early stages of investigation and purely passive monitoring for the large scale operations at the later stages.

Hospital-based monitoring

Data were available from three studies in Sri Lanka in which 95 participants (85 of whom were microfilaraemic) were closely monitored daily for 3–7 days post-treatment in a hospital environment (Ismail, unpublished; Ismail *et al.* 1998; Ismail *et al.* [in press]). None of the amicrofilaraemic, uninfected volunteers complained of any adverse reaction on either the albendazole alone or albendazole + ivermectin regimen. Twelve were treated with albendazole alone, 74 with albendazole + ivermectin and 29 with albendazole + DEC. Few events occurred during the first 24 hours, although headache was reported particularly when ivermectin was included in the regimen. Beyond 24 hours post dose there remained few events reported with albendazole, while the patients on regimens containing the microfilaricidal drugs ivermectin or DEC began to experience a significant number of effects (Table 2). At this time the regimen containing ivermectin appeared particularly reactogenic, but the events reported were those that are normally associated with the destruction of microfilariae, including fever, headache, lethargy and weakness. The higher doses of ivermectin and albendazole used in Sri Lanka-1 appeared to produce more event reports. By the third post treatment day (day 2: 48–72 hours), events had reached a peak, with over half of all patients reporting fever, chills, headache, lethargy as well as increased frequencies of myalgia, arthralgia, and anorexia in all treatment groups. Up to 25% of the albendazole group also reported similar events at this time, suggestive of some microfilaricidal activity.

In general the albendazole + DEC regimen and the albendazole + ivermectin (standard doses) were less reactogenic than the higher dose regimens. By 72 hours and beyond, the frequency of events waned steadily and during the 4th to 7th day few events were recorded. Throughout the post treatment period, although there was a significant number of treatment associated events, few were recorded as moderate in severity (some impact on daily living); overall the events were assessed as mild and self

Table 2. Hospital monitoring of single dose, 2-drug regimens of albendazole + either ivermectin or DEC in microfilaraemic patients with bancroftian filariasis: clinical events recorded on days 2 and 3 from two studies in Sri Lanka (Ismail *et al.* 1998; in press)

Study/ Regimen ^a		Signs/symptoms																			
		Fever		Diaphoresis		Chills		Headache		Lethargy		Weakness		Myalgia		Arthralgia		Anorexia		Cough	
		2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3
Sri Lanka 1																					
Alb*	No. events	1	1	0	0	1	0	3	2	3	1	2	1	2	0	3	1	2	2	0	0
<i>n</i> = 12	% cases	8·3	8·3	0	0	8·3	0	25·0	16·7	25·0	8·3	16·7	8·3	16·7	0	25·0	8·3	16·7	16·7	0	0
Alb*	No. events	10	1	0	0	7	0	10	3	9	4	8	4	8	3	5	2	7	2	0	0
+ Iver ⁺	% cases	76·9	7·7	0	0	53·8	0	76·9	23·1	69·2	30·8	61·5	30·8	61·5	23·1	38·5	15·4	53·8	15·4	0	0
<i>n</i> = 13																					
Alb*	No. events	8	3	0	0	1	0	3	2	7	2	6	2	5	1	5	3	4	2	1	0
+ DEC	% cases	61·5	23·1	0	0	7·7	0	23·1	15·4	53·8	15·4	46·2	15·4	38·5	7·7	38·5	23·1	30·8	15·4	7·7	0
<i>n</i> = 13																					
Sri Lanka 2																					
Alb*	No. events	10	1	2	1	4	0	7	1	6	1	5	0	4	1	4	0	3	0	4	0
+ Iver ⁺	% cases	66·7	6·7	13·3	6·7	26·7	0	46·7	6·7	40·0	6·7	33·3	0	26·7	6·7	26·7	0	20·0	0	26·7	0
<i>n</i> = 15																					
Alb	No. events	9	2	0	0	2	0	7	3	4	1	2	0	3	1	4	1	2	1	3	2
+ Iver	% cases	56·3	12·5	0	0	12·5	0	43·8	18·8	25·0	6·3	12·5	0	18·8	6·3	25·0	6·3	12·5	6·3	18·8	12·5
<i>n</i> = 16																					
Alb	No. events	7	0	0	1	1	1	3	0	2	1	4	1	4	2	2	1	0	0	2	0
+ DEC	% cases	43·8	0	0	6·3	6·3	6·3	18·8	0	12·5	6·3	25·0	6·3	25·0	12·5	12·5	6·3	0	0	12·5	0
<i>n</i> = 16																					

^a Regimens: single doses of drugs used, alone or in combination, were: albendazole 400 mg, ivermectin 200 µg/kg body wt, and DEC 6 mg/kg body wt. except as indicated by * (albendazole 600 mg) or ⁺ (ivermectin 400 µg/kg).

Table 3. Active monitoring of single dose, 2- drug regimens of albendazole plus either ivermectin or DEC in lymphatic filariasis: clinical events in microfilaria positive patients occurring during the 5–7 days after treatment

	Of patients evaluable per event ^b	Regimen ^a					
		Placebo	Albend	Iver	Albend + Iver	DEC	Albend + DEC
No. patients evaluable per group ^b		143	202	134	183	45	72
Itch	<i>n</i> pos/total ^b	0/70	1/80	2/66	1/80		
	% pos	0	1.3	3.0	1.3		
Rash	<i>n</i> pos/total	1/70	0/80	1/66	1/80		
	% pos	1.4	0	1.5	1.3		
Joint pain	<i>n</i> pos/total	1/70	1/83	1/66	5/107		0/24
	% pos	1.4	1.2	1.5	4.7		0
Muscle pain	<i>n</i> pos/total	11/143	11/188	24/120	37/169	8/45	18/72
	% pos	7.7	5.9	20.0	21.9	17.8	25.4
Backache	<i>n</i> pos/total	0/70	1/80	1/66	1/80		
	% pos	0	1.3	1.5	1.3		
Headache	<i>n</i> pos/total	24/143	31/188	46/120	57/169	19/45	31/72
	% pos	16.8	16.5	38.3	33.7	42.2	43.7
Swelling limb	<i>n</i> pos/total	0/70	0/80	0/66	0/80		
	% pos	0	0	0	0		
Fever	<i>n</i> pos/total	18/143	28/202	43/134	56/183	16/45	38/72
	% pos	12.6	13.9	32.1	30.6	35.6	53.5
Breathing difficulties	<i>n</i> pos/total	2/143	0/185	0/120	2/142	3/45	1/48
	% pos	1.4	0	0	1.4	6.7	2.1
Loss appetite	<i>n</i> pos/total	0/70	1/97	3/80	4/107		1/24
	% pos	0	1.0	3.8	3.3		4.2
Nausea	<i>n</i> pos/total	4/143	4/202	2/134	3/183	4/45	10/72
	% pos	2.8	2.0	1.5	1.6	8.9	14.1
Vomiting	<i>n</i> pos/total	12/143	9/188	14/120	12/169	9/45	9/72
	% pos	8.4	4.8	11.7	7.1	20.0	12.7
Diarrhoea	<i>n</i> pos/total	15/143	20/185	11/120	11/142	8/45	9/48
	% pos	10.5	10.8	9.2	7.7	17.8	19.1
Dizziness	<i>n</i> pos/total	10/143	18/202	22/134	23/183	9/45	9/72
	% pos	7.0	8.9	16.4	12.6	20.0	12.7
Sleep disturbance	<i>n</i> pos/total	0/70	0/80	0/66	1/80		
	% pos	0	0	0	1.3		
Abdominal pain	<i>n</i> pos/total	35/143	53/202	33/134	43/183	30/45	29/72
	% pos	24.5	26.2	24.6	23.5	66.7	40.8
Constipation	<i>n</i> pos/total	1/70	2/94	1/80	0/94		
	% pos	1.4	2.1	0.7	0		
Nodules	<i>n</i> pos/total	0/70	0/80	0/66	0/80		
	% pos	0	0	0	0		
Weakness	<i>n</i> pos/total	13/143	10/199	16/134	25/156	9/45	6/48
	% pos	9.1	5.0	11.9	16.0	20.0	12.8
Worms passing	<i>n</i> pos/total	9/73	11/119	14/68	17/76	8/45	8/48
	% pos	12.3	9.2	20.6	22.4	17.8	17.0
Body pains	<i>n</i> pos/total		1/14	2/14	7/14		
	% pos		7.1	14.3	50.0		
Chest pain	<i>n</i> pos/total		0/17	5/14	2/41		0/24
	% pos		0	35.7	4.9		0
Cough	<i>n</i> pos/total	9/73	15/122	19/68	30/103	6/45	8/72
	% pos	12.3	12.3	27.9	29.1	13.3	11.3
Sore throat	<i>n</i> pos/total	0/73	1/180	4/54	5/89		2/24
	% pos	0	0.9	7.4	5.6		8.3

limiting, requiring no more than paracetamol for the worst cases. None of the events prolonged hospital stay.

Adverse event data were also investigated in hospitalized patients for a small Tanzanian population infected with both *Onchocerca volvulus* and

Wuchereria bancrofti (placebo, *n* = 8; albendazole + ivermectin, *n* = 7; Makunde, unpublished). Similar (and low) frequencies of adverse events were found in the two groups, the most significant being transient fever in 3 of the patients treated with albendazole + ivermectin. All symptoms were re-

Table 3. (contd.)

	Of patients evaluable per event ^b	Regimen ^a					
		Placebo	Albend	Iver	Albend + Iver	DEC	Albend + DEC
Chills	<i>n</i> pos/total		0/3		4/27		2/24
	% pos		0		14.8		8.3
Lethargy	<i>n</i> pos/total		0/3		0/27		2/24
	% pos		0		0		8.3
Palpitations	<i>n</i> pos/total		0/14	0/14	2/14		
	% pos		0	0	14.3		
Waist pain	<i>n</i> pos/total		5/14	3/14	5/14		
	% pos		35.7	21.4	35.7		
<i>n</i> other AEs ^c	<i>n</i> pos/total	0/73	0/105	1/54	0/62		
	% pos	0	0	1.9	0		
Total AEs ^c	<i>n</i> pos/total	165/143	223/202	268/134	354/183	129/45	183/72
	% pos	115.4	110.4	200.0	193.4	286.7	254.2
<i>n</i> with multiple AEs ^c	<i>n</i> pos/total	38/143	57/188	48/120	69/174	34/45	52/72
	% pos	26.6	30.3	40.0	39.7	75.6	72.2
<i>n</i> with single AE ^c	<i>n</i> pos/total	15/143	20/188	13/120	27/174	0/45	5/72
	% pos	10.5	10.6	10.8	15.5	0	6.9
<i>n</i> without AEs ^c	<i>n</i> pos/total	90/143	111/188	59/120	73/174	11/45	15/72
	% pos	62.9	59.0	49.2	42.0	24.4	20.8

^a Regimens: single doses of drugs used, alone or in combination, were: albendazole 400 mg, ivermectin 200 µg/kg body wt, and DEC 6 mg/kg body wt.

^b Total patients evaluable per regimen is often larger than total patients evaluable per event, since not all events were necessarily specifically recorded at each study site. *n* pos = number of patients reporting event in systematic examination; % pos = *n* pos ÷ total *n* known to have been systematically questioned for that event.

^c AEs = adverse events.

lieved by paracetamol. In two further groups of 13 patients infected with *W. bancrofti* alone and monitored in-hospital, there were similar frequencies of events in patients treated with either albendazole alone or albendazole + ivermectin. Adverse events more clearly associated with effective microfilarial clearance were seen in the ivermectin containing treatment.

Laboratory safety monitoring

Laboratory data were available from three studies in Sri Lanka, two cycles of treatment in India and the study of single LF or double infection (onchocerciasis and filariasis) from Tanzania (Ismail, unpublished; Ismail *et al.* 1998; Ismail *et al.* in press; Shenoy *et al.* 1999, 2000; Makunde, unpublished). A total of 200 patients and normal individuals had evaluable laboratory data (placebo, *n* = 8; albendazole, *n* = 35; albendazole + ivermectin, *n* = 97; and albendazole + DEC, *n* = 60). Comparison between studies was not feasible because of different sampling times and methods used. Analysis of mean data and treatment associated trends in the context of lymphatic filariasis was complicated by the reality that in the affected populations, minor laboratory abnormalities were often encountered. This point is emphasised in a study of 'normal' individuals, none of whom had microfilaraemia (Ismail, unpublished), in whom a number of laboratory abnormalities were

encountered at baseline. Meaningful analysis, therefore, depended on the examination of individuals over time, in addition to mean data from the treatment groups. In Sri Lanka-1 (Ismail *et al.* 1998), some abnormal values were seen in the individual data sets, and mildly abnormal liver function tests were a feature even pre-treatment. Whilst some of these values tended to increase temporarily, especially in the albendazole group, there were only slight trends (not statistically significant) apparent in the mean data. Similarly, although mean haemoglobin values were normal and remained within the normal ranges, a trend towards increased values at day 14 was apparent with all treatments. This increase was because a number of patients entered the study with significantly low values which normalised over the post treatment period, rather than because of a general, drug-induced trend.

In Sri Lanka-2 (Ismail *et al.* in press), there were similar findings of both isolated and sporadic abnormalities, and there was little evidence of trends in any of the data. In particular, the changes in haemoglobin were not apparent in this population, and all starting values were within the normal range. There were marginal increases in mean values of liver function tests in both the high and standard dose albendazole + ivermectin groups on day 4 which returned toward normal by day 14. The other notable trend in the data was a significant rise in the white

cell counts (particularly the blood eosinophils) on day 14 for all treatment groups. The change was greatest for the albendazole+DEC group, and a similar trend was seen in the Sri Lanka-1 study (Ismail *et al.* 1998) for this parameter.

In the Indian study (Shenoy *et al.* 1999, 2000), all values were within the normal range pre-treatment and remained within these limits during the period of follow up, both for the initial treatment and at the 1 year re-treatment. There was no evidence of any trend in the data at either time with either of the combinations (albendazole+DEC; albendazole+ivermectin). In the Tanzanian study (Makunde unpublished), the patients were followed over 7 days, though evaluation parameters were reported principally as raw means without measures of variance, there was no evidence for significant trends in the data. Specifically, haemoglobin values were generally at or below normal and showed little change; total and differential white cell counts showed little change over the 7 day period, and liver and renal function remained unchanged.

Active surveillance in microfilaria-positive cases

The data from communities in four countries (Ghana, Haiti, India and Sri Lanka) were assessed for the safety of single and combination treatments in microfilaraemia-positive individuals, monitored by active surveillance methods (Addiss *et al.* 1997; Beach *et al.* 1999a,b; Shenoy *et al.* 1999, 2000; Dunyo, Nkrumah & Simonsen, 2000; Awadzi, unpublished; Weerasooriya, unpublished). Data from the Ghana, Haiti and India study sites have been collapsed to form a single data set that includes all recorded events reported by the investigators. Since not all events were necessarily collected at each site, the denominator for each event varies, as seen in Table 3. A total of 779 patients were included in the analysis (placebo, $n = 143$; albendazole, $n = 202$; ivermectin, $n = 134$; DEC, $n = 45$; albendazole+ivermectin, $n = 183$; and albendazole+DEC, $n = 72$). The data were derived from a wide geographical area and include adults and children, males and females.

Comparison of the placebo data with those for albendazole treatment shows that there was little difference in the frequency of events following treatment of these microfilaraemic patients. Indeed, the results were very similar to the data for non microfilaraemic individuals (see below and Table 4), though the somewhat greater frequency of events among microfilaraemics suggests that microfilaraemia itself might produce some symptoms. The use of ivermectin in microfilaraemic patients led clearly to an increase in the frequency of events (approximately two-fold) compared to placebo or albendazole (Table 3), and this increase was most pronounced for symptoms likely resulting from microfilarial de-

struction. In addition there was a noticeable increase in the proportion of patients describing passage of worms after ivermectin treatment. In such patients, the addition of albendazole to ivermectin did not produce any increase in the frequency of adverse events overall, nor in the specific symptoms reported. The few instances where the incidence of events was higher with the co-administration treatments involved only small sample numbers.

For treatment with DEC alone, the frequency of adverse events was nearly three times that of placebo, and it was greater than that produced by ivermectin alone, particularly with regard to abdominal pain (Table 3). The addition of albendazole to the regimen did not, however, produce any general increase in the frequency of events reported, though fever appeared somewhat more common, and abdominal pain less common. The pattern of events was again that to be expected with drugs that destroy microfilariae, including the increase in fever reflecting a more generalized systemic effect.

Although the adverse event data in these studies were collected a few days after the 'peak' of responses seen on the 2nd/3rd post-treatment day, in the hospital-based studies, the increased incidence of events with either DEC or ivermectin was apparent, with a frequency approximately double that induced by the placebo. By contrast, the incidence of adverse events with albendazole alone was little different from placebo. Furthermore, the addition of albendazole to either ivermectin or DEC did not significantly increase the frequency or severity of events reported. Indeed, the evidence from all of these individual studies indicated that in general the events reported were relatively mild in nature, and they rarely caused any significant disturbance to activity. Most symptoms, when they occurred, were managed by analgesics and lasted only 1–3 days. Within a week of treatment, all symptoms had usually disappeared.

Furthermore, the important observation was made repeatedly (Addiss *et al.* 1997; Ismail *et al.* 1998; Dunyo *et al.* 2000) that the level of adverse events (both frequency and intensity) following treatment with these co-administration regimens correlated with the level of microfilaraemia in the study patients. Thus, in populations where there are expected to be some individuals with high microfilaraemias, it should also be anticipated that there will be more pronounced systemic adverse reactions.

Active surveillance in non-microfilaraemic individuals

Non microfilaraemic individuals form the majority of targets even in relatively severely affected LF-endemic areas of the world. The data from five countries (Ecuador, Gabon, Ghana, India and Philippines) in patients known to be from areas free

Table 4. Active monitoring of single dose, 2-drug regimens of albendazole plus either ivermectin or DEC used to eliminate lymphatic filariasis: clinical events in microfilaria negative patients occurring during the 5–7 days after treatment

	Regimen ^a						
	Of patients evaluatable per event ^b	Placebo	Albend	Iver	Albend + Iver	DEC	Albend + DEC
No. patients evaluatable per group ^b		514	712	697	711	155	292
Itching	<i>n</i> pos/total ^b	1/386	1/587	4/567	2/588	0/155	0/159
	% pos	0.3	0.2	0.7	0.3	0	0
Rash	<i>n</i> pos/total	3/386	0/431	1/408	1/433		
	% pos	0.8	0	0.2	0.2		
Joint pain	<i>n</i> pos/total	6/244	1/256	2/299	2/253		0/7
	% pos	2.5	0.4	0.9	0.8		0
Muscle pain	<i>n</i> pos/total	3/244	1/256	4/229	3/253		1/7
	% pos	1.2	0.4	1.7	1.2		14.3
Backache	<i>n</i> pos/total	1/244	0/256	1/229	1/252		
	% pos	0.4	0	0.4	0.4		
Headache	<i>n</i> pos/total	7/372	3/437	3/518	8/530	1/155	0/292
	% pos	1.9	0.7	0.6	1.5	0.6	0
Fever	<i>n</i> pos/total	4/244	3/412	5/388	5/408	0/155	0/166
	% pos	1.6	0.7	1.3	1.2	0	0
Breathing difficulties	<i>n</i> pos/total	0/244	0/256	0/229	1/252		
	% pos	0	0	0	0.4		
Loss of appetite	<i>n</i> pos/total	1/244	0/412	0/388	0/407	0/155	
	% pos	0.4	0	0	0	0	
Nausea	<i>n</i> pos/total	6/514	4/712	3/697	2/711	1/155	3/292
	% pos	1.2	0.6	0.4	0.3	0.6	1.0
Vomiting	<i>n</i> pos/total	5/514	3/712	5/697	5/711	0/155	0/292
	% pos	1.0	0.4	0.7	0.7	0	0
Diarrhoea	<i>n</i> pos/total	7/372	8/437	3/518	4/530	0/155	0/292
	% pos	1.9	1.8	0.6	0.8	0	0
Dizziness	<i>n</i> pos/total	3/244	1/412	1/388	3/408	1/155	2/166
	% pos	1.2	0.2	0.3	0.7	0.6	1.2
Sleep disturbance	<i>n</i> pos/total	1/244	0/256	0/229	0/252		
	% pos	0.4	0	0	0		
Abdominal pain	<i>n</i> pos/total	9/514	13/712	7/697	14/711	2/155	4/292
	% pos	1.8	1.8	1.0	2.0	1.3	1.4
Constipation	<i>n</i> pos/total	0/244	3/256	0/229	1/253		0/7
	% pos	0	1.2	0	0.4		0
Weakness	<i>n</i> pos/total	7/514	13/712	23/697	20/710	0/155	0/285
	% pos	1.4	1.8	3.3	2.8	0	0
Lethargy	<i>n</i> pos/total	0/128	0/281	0/289	0/278	0/155	1/292
	% pos	0	0	0	0	0	0.3

of lymphatic filariasis or shown to be free from microfilaraemia are included in this analysis of treatment effects (Dunyo *et al.* 2000; Shenoy *et al.* 2000; Belizario, unpublished; Espinel, unpublished; Richard-Lenoble, unpublished). Three of these studies (Ecuador, Gabon, Philippines) were conducted specifically to investigate the effects of single drugs and combinations on intestinal helminths (Belizario, unpublished; Espinel, unpublished; Richard-Lenoble, unpublished). A total of 3081 patients were included in the analysis (placebo, $n = 514$; albendazole, $n = 712$; ivermectin, $n = 697$; DEC, $n = 155$; albendazole + ivermectin, $n = 711$; and albendazole + DEC, $n = 292$). The data were derived from a wide geographical area and included

adults and children of both genders. The data from these study sites have been collapsed to form a single data set encompassing all recorded events reported by the investigators. The data are a consolidated reporting of events that occurred and that were actively collected over a 5–7 day period after treatment. Since not all events were necessarily collected at each site, the denominator for each event varies (Table 4).

From the total population of 3081 individuals, only 128 (4.15 %) reported clinical events during the follow-up period. Forty-two of these individuals (1.4 %) reported more than one event. Table 4 shows the breakdown and incidences of events in relation to treatment and permits comparison both among

Table 4. (Contd.)

	Regimen ^a						
	Of patients evaluable per event ^b	Placebo	Albend	Iver	Albend + Iver	DEC	Albend + DEC
Palpitations	<i>n</i> pos/total		0/156	0/159	0/155	0/155	0/159
	% pos		0	0	0	0	0
<i>n</i> other AEs ^c	<i>n</i> pos/total	0/128	0/281	0/289	0/277	1/155	1/285
	% pos	0	0	0	0	0.6	0.4
Total AEs ^c	<i>n</i> pos/total	64/514	61/712	62/697	72/711	6/155	13/292
	% pos	12.5	8.6	8.9	10.1	3.9	4.5
<i>n</i> with multiple AEs ^c	<i>n</i> pos/total	13/372	8/437	6/518	9/530	2/155	3/292
	% pos	3.5	1.8	1.2	1.7	1.3	1.0
<i>n</i> with single AE ^c	<i>n</i> pos/total	19/372	24/437	16/518	20/530	0/155	7/292
	% pos	5.1	5.5	3.1	3.8	0	2.4
<i>n</i> without AEs ^c	<i>n</i> pos/total	340/372	405/437	496/518	501/530	153/155	282/292
	% pos	91.4	92.7	95.8	94.5	98.7	96.6

^a Regimens: single doses of drugs used, alone or in combination, were: albendazole 400 mg, ivermectin 200 µg/kg body wt, and DEC 6 mg/kg body wt.

^b Total patients evaluable per regimen is often larger than total patients evaluable per event, since not all events were necessarily actively recorded at each study site. *n* pos = number of patients reporting event in systematic examination; % pos = *n* pos ÷ total *n* systematically questioned for that event.

^c AEs = adverse events.

active treatments and between active treatments and placebo. Importantly, all active treatments have fewer individuals reporting clinical events than found in the placebo group. In general, frequencies for individual events are also similar to, or less than, those seen in the placebo group.

Passive surveillance studies

Following acquisition of the evidence for safety of the various treatment regimens based on the hospital and community-based active monitoring, a number of large-scale programmes instituted treatment with passive monitoring techniques (i.e. not seeking adverse events but providing the necessary facilities for the reporting and managing of any unexpected and, particularly, any serious adverse events associated or possibly associated with treatment). These programmes involved a total of 86383 individuals from around the world (Haiti, Ghana, Kenya, Bangladesh, and Papua New Guinea) (Addiss *et al.* 1997; Beach *et al.* 1999*a, b*; Selve, unpublished; Hossain, unpublished; Njenga *et al.* 1999; Wamae, unpublished; Gyapong, unpublished; Dunyo *et al.* 2000). The vast majority of these passively collected data came from people treated with albendazole + DEC (68542 individuals), but there were also 479 placebo-treated individuals, 560 who received albendazole, 341 treated with DEC, 8991 given ivermectin, and 7470 who received ivermectin + albendazole.

In the Haitian studies, all 'passively monitored' individuals were amicrofilaraemic (Addiss *et al.* 1997; Beach *et al.* 1999*a, b*), and in the first

treatment round in PNG it was estimated that 21 000 out of 28 000 individuals (75 %) were similarly free of infection (Selve, unpublished). During the treatment periods at both of these sites no serious or unusual adverse effects were reported. In Ghana where treatment with ivermectin alone (*n* = 8790) was compared with albendazole + ivermectin (*n* = 6369) in a population whose microfilaraemia status was estimated at ~ 13 % (Gyapong unpublished), the frequency of side effects was low, none occurring more frequently than 0.11 % (vomiting and diarrhoea in individuals treated with albendazole + ivermectin). Similar numbers of events were reported for the two treatments, and none was severe or caused concern.

A small, field-based study conducted in Kenya compared albendazole, DEC and the combination in 57, 58 and 50 patients, respectively (Njenga *et al.* 1999; Wamae, unpublished). DEC could be safely used in this site since onchocerciasis was not present. There were only three events reported from this study; all three occurred in patients receiving DEC alone. A study conducted in Bangladesh provided very limited detail but was interesting because of a relatively high infection rate (32.8 %) in a population of 11 600 people (Hossain, unpublished). All were treated with albendazole + DEC, and there were only 175 (1.5 %) events reported (nausea, vomiting, giddiness, itching, urticaria and arthralgia). If one assumes that the majority of events occurred in the microfilaria positive individuals, this only represents a 4.6 % event rate in the microfilaraemics, which is appreciably lower than shown with active reporting methods.

DISCUSSION

This programme of safety analysis of the single-dose, 2-drug co-administration regimens for treating lymphatic filariasis has utilized data on over 90 000 subject exposures from a wide range of study designs and sites around the world. Although this analysis is *post hoc* (with the designs and captured data varying from site to site), the overall population was generally comparable to that expected to be treated in the major public health initiatives to eliminate lymphatic filariasis. Furthermore, the study population was generally balanced with respect to ethnicity, gender and age. During the process of analysis, there was validation of data among reports, electronic databases and, where possible, case record forms. Such auditing is consistent with the standards followed by the pharmaceutical industry in the preparation of regulatory files. The studies reviewed, however, were never intended for such use and therefore inevitably there were gaps in study design and data collection which, were they not there, would have made analysis considerably easier.

The data were processed so as to permit examination of blocks of similar information, and this processing has increased the power of the analysis, since it has been possible to look for consistent trends among data obtained in different ways. Examination of the individual reports and thereafter the collapsed data in the overarching reviews showed that there was a high degree of internal consistency with regard to the findings. Indeed, from the examination one can conclude that the use of any drug with microfilaricidal (and/or macrofilaricidal) activity will produce an array of clinical events that results primarily from destruction of the filarial parasites. The symptom complex has been well described, and includes, among others, a number of non-specific symptoms such as headache, fever, myalgia and arthralgia, anorexia etc. (Ottesen, 1987). It is also clear that this same symptom complex is not present with these same drugs in the absence of filarial infection. Thus, in an infected population such events as are reported or observed will more likely result from a drug/parasite interaction than from drug/patient toxicity.

The primary purpose of this analysis was to determine whether the addition of albendazole to a microfilaricidal drug (whether ivermectin or DEC) would have adverse safety implications. The data remain consistent across the various types of analysis, with the conclusion that there is no measurable impact either in the infected or in the non-infected populations studied. While there was some evidence that albendazole might also have, on its own, some early antimicrofilarial activity (as suggested by increased numbers of adverse events in daily monitoring [Table 2]), this increase was not seen with post-treatment active surveillance. Furthermore,

even if albendazole has a weak early microfilaricidal effect, it did not translate into an increase in the severity or duration of treatment-related events, compared to the use of DEC or ivermectin alone.

Furthermore, there was no evidence that consistent changes were induced in the laboratory parameters (either haematological or biochemical) assessed post-treatment for any regimen, the majority of abnormalities appearing to be sporadic. From the perspective of this investigation, the addition of albendazole to either ivermectin or DEC did not increase the frequency of abnormalities. There was also no evidence that albendazole, when given either alone or in combination, caused deterioration in liver function; in those few individuals having abnormal liver function tests pre-treatment, there was no deterioration following treatment.

From all reports and data supplied from the study sites came a clear message that clinical adverse events were normally mild and of short duration, rarely requiring any intervention. In the whole population of over 90 000, there were no instances of severe, unexpected treatment related effects. While much of this number comes from passively reported studies, negative data (the absence of reports) is equally powerful information, especially in looking for serious unexpected adverse reactions; the analysis of these study populations indicated that all adverse events fell into the 'expected' category.

In considering the implications of this analysis, it is important to note that in most areas endemic for filariasis, the prevalence of microfilaraemia will usually be less than 20 % in the overall population, and often much lower than this. Since clinical events seem to affect less than 50 % of even the microfilaraemic population, the proportion who will be affected is likely to be below 10 %, and based on current data these effects are mild; furthermore, the remaining 90 % of the population will be essentially unaffected. This conclusion has important implications for sustainability, since high adverse event frequencies would be highly demotivating. It is also important to note that the 'active' monitoring approach will tend to elevate frequencies, while a passive approach will underestimate them. This is well demonstrated in the Bangladesh data where, in the presence of > 30 % microfilaraemia in the treated population, the event frequency was < 2 %, and all events were reported as mild. Nonetheless, the pattern remained consistent, and the types of events reported were those that would be expected after active microfilaricidal medication.

The observations from the present studies focus on the 2-drug co-administration regimens in individuals either uninfected or microfilaraemic with one of the two principal species causing LF. There are, however, certain parts of Africa where double infections with onchocerciasis and LF occur and the present experience with such populations is limited

to a single small study. Though this study does not indicate any particular problem, further data should be collected to ensure the safety of the co-administration regimens in such situations; indeed, the current analysis should facilitate collection of such data by active monitoring, since a baseline of expected events has already been established. Similarly, the safety assessment of the albendazole + ivermectin 2-drug regimen needs to be extended to populations co-infected with LF and loiasis as well.

Overall, then, the evidence appears strong that the addition of albendazole to existing treatments will not result in any significant additional risk if used in public health programmes. Furthermore, it should be recognized that all three compounds under study have been established for many years, with many millions of treatments given. The known incidence of adverse events is very low with each of them when used as single agents; however, one must acknowledge that the sensitivity of the current analysis is probably insufficient to detect events that would be considered rare or very rare. Thus, while further specific studies to address safety issues with these 2-drugs co-administration regimens are not required (except as indicated above), continued vigilance is appropriate for detecting, and if necessary reacting to, any rare event that might develop.

CONCLUSIONS

In the safety assessment studies of the single-dose, 2-drug co-administration regimens recommended for treating populations at risk of lymphatic filariasis, over 90 000 individuals have been exposed to placebo (1144), DEC (576), ivermectin (9822), albendazole (1538), albendazole + ivermectin (7470), or albendazole + DEC (69020). The geographical distribution of studies mirrors that of lymphatic filariasis. The studies have included sufficient numbers of both genders and all age ranges, together with an adequate ethnic mix to provide data for the target populations. Studies have ranged from highly detailed studies in hospitalised patients, through active surveillance of safety in field studies to passive monitoring of large-scale programmes. Both microfilaricidal drugs (DEC and ivermectin) show an event profile compatible with reactions induced by the destruction of microfilariae, and the profile described in these studies differs little from that already known for these compounds. The addition of albendazole to treatment regimens in patients with microfilaraemia does not appear to increase the frequency or intensity of events seen with the microfilaricidal drugs when used alone. Laboratory studies do not suggest any significant problem associated with such co-administrations as single doses. In non-microfilaraemic individuals (who form the bulk of the 'at risk' populations to be treated in programmes to eliminate

lymphatic filariasis), the event profile with the compounds alone or in combination does not differ significantly from that of placebo.

It is considered that adequate data exist to confirm that co-administration of either ivermectin or DEC with albendazole is as safe as the use of the components alone for most 'at risk' populations being treated once yearly. Data on the use of ivermectin + albendazole in two specific situations (i.e. in double infections with onchocerciasis and lymphatic filariasis, and in loiasis with or without concurrent lymphatic filariasis) are currently inadequate, and further data need to be collected. The data available from populations infected with *Brugia malayi* are now much less extensive than those for *Wuchereria bancrofti*; whilst no differences in safety might be expected, further data are needed to confirm this expectation.

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REFERENCES

- ADISS, D. G., BEACH, M. J., STREIT, T. G., LUTWICK, S., LECONTE, F. H., LAFONTANT, J. G., HIGHTOWER, A. W. & LAMMIE, P. J. (1997). Randomised placebo-controlled comparison of ivermectin and albendazole alone and in combination for *Wuchereria bancrofti* microfilaraemia in Haitian children. *Lancet* **350**, 480–488.
- BEACH, M. J., FURNESS, B. W., TRAYNER, J. K., FREEMAN, A. R., ADISS, D. G., MILORD, M. D. & LAMMIE, P. J. (1999a). Nutritional assessment following treatment for intestinal helminth and *Wuchereria bancrofti* infections in Haitian schoolchildren. *American Journal of Tropical Medicine and Hygiene* **61**, S450.
- BEACH, M. J., STREIT, T. G., ADISS, D. G., PROSPERE, R., ROBERTS, J. M. & LAMMIE, P. J. (1999b). Assessment of combined ivermectin and albendazole for treatment of intestinal helminth and *Wuchereria bancrofti* infections in Haitian schoolchildren. *American Journal of Tropical Medicine and Hygiene* **60**, 479–486.
- CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) (1993). Recommendations of the International Task Force for Disease Eradication. *Morbidity and Mortality Weekly Report* **42**, 1–38.
- DUNYO, S. K., NKUMAH, F. K. & SIMONSEN, P. E. (2000). A randomised double-blind placebo-controlled field trial of ivermectin and albendazole alone and in combination for the treatment of lymphatic filariasis in Ghana. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **94**, 205–211.
- ISMAIL, M. M., JAYAKODY, R. L., WEIL, G. J., FERNANDO, D., DE SILVA, S. G., DE SILVA, G. A. C. & BALASOORIYA, W. K. Long term efficacy of single dose combinations of

- albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* (in press)
- ISMAIL, M. M., JAYAKODY, R. L., WEIL, G. J., NIRMALAN, N., JAYASINGHE, K. S. A., ABYEWEICKREMA, W., REZVI SHERRIF, M. H., RAJARATNAM, H. N., AMARASEKERA, N., DESILVA, D. C., MICHALSKI, M. L. & DISSANAIKE, A. S. (1998). Efficacy of single dose combinations of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **92**, 94–97.
- NJENGA, S. M., GATIKA, S. M., MBUI, J., LAMMIE, P. J. & WAMAE, C. N. (1999). Comparative efficacy of diethylcarbamazine, albendazole and a combination of diethylcarbamazine and albendazole in clearance of multiple helminth infections, Kwale District, Kenya. *American Journal of Tropical Medicine and Hygiene* **61**, S441–442.
- OTTESEN, E. A. (1987). Description, mechanisms and control of reactions to treatment in the human filariases. *Ciba Foundation Symposium* **127**, 265–283.
- OTTESEN, E. A., DUKE, B. O. L., KARAM, M. & BEHBEHANI, K. (1997). Strategies and tools for the control/elimination of lymphatic filariasis. *Bulletin of the World Health Organization* **75**, 491–503.
- OTTESEN, E. A., ISMAIL, M. M. & HORTON, J. (1999). The role of albendazole in programmes to eliminate lymphatic filariasis. *Parasitology Today* **15**, 382–386.
- SHENOY, R. K., DALIA, S., JOHN, A., SUMA, T. K. & KUMARASWAMI, V. (1999). Treatment of the microfilaraemia of asymptomatic brugian filariasis with single doses of ivermectin, diethylcarbamazine or albendazole, in various combinations. *Annals of Tropical Medicine and Parasitology* **93**, 643–651.
- SHENOY, R. K., JOHN, A., BABU, B. S., SUMA, T. K. & KUMARASWAMI, V. (2000). Two year follow up of the microfilaraemia of asymptomatic brugian filariasis after treatment with two annual single doses of ivermectin, diethylcarbamazine or albendazole, in various combinations. *Annals of Tropical Medicine and Parasitology* **94**, 607–614.
- WORLD HEALTH ORGANIZATION. (1997). *Resolution of the Executive Board of the WHO: Elimination of Lymphatic Filariasis as a Public Health Problem*. Fiftieth World Health Assembly, 13 May 1997, WHA50.29. Geneva.
- WORLD HEALTH ORGANIZATION. (1998). *Report from Informal Consultation on Albendazole Research Findings in Lymphatic Filariasis 13–14 October 1998*. Filariasis Elimination Programme (CDS/FIL), Division of Control of Tropical Diseases, Communicable Diseases, WHO/FIL/98.194, Geneva.