COMPARISON OF EFFECTS OF MASS ANNUAL AND BIANNUAL SINGLE DOSE THERAPY WITH DIETHYLCARBAMAZINE FOR THE CONTROL OF MALAYAN FILARIASIS

KN Panicker, K Krishnamoorthy, S Sabesan, J Prathiba and Abidha

Vector Control Research Centre, Indian Council of Medical Research, Indira Nagar, Pondicherry, South India - 605 006.

Abstract. Annual and biannual mass single dose diethylcarbamazine citrate (DEC) at 6 mg/kg body weight was administered to people in a *Brugia malayi* endemic area in Shertallai part of Kerala, India, in 1987 and 1988. The coverage of population ranged between 41.33% and 66.01% in different rounds. The highest percentage of treated population developing side reactions was 8.4%. Both annual and biannual regimens were effective in reducing the microfilaria prevalence significantly from 4.90% to 1.23% and from 6.27% to 0.62% respectively and the incidence of infection was minimal in the adult population and zero among children. There was significant reduction in mean microfilaria count in both annual (81.08%) and biannual (98.00%) areas. Marked reduction in the proportion of high density carriers and infectivity index of the population after DEC therapy was also observed. Beneficial effect of mass single dose DEC on clinical cases of filariasis was evident from the reduction in the prevalence of acute manifestations, recent edema cases and the proportion of chronic cases with acute episodes. Results obtained from mass treatment areas were compared with those of the control area.

INTRODUCTION

Diethylcarbamazine (DEC) still remains the drug of choice for treatment of lymphatic filariasis (Ottesen, 1985; Subrahmanyam, 1989) and has been used extensively (Duke, 1980; Ottesen, 1984) even though its therapeutic value is not fully satisfactory (Goodwin, 1984). Selective DEC therapy is being advocated under the National Filariasis Control Programme (NFCP) in India (Anonymous, 1984). The conventional method of finger prick blood sampling not only underestimates the microfilaria (mF) prevalence grossly (Edeson, 1959; Kimura *et al,* 1985; Das *et al,* 1990), but is also time consuming and difficult. Further, it fails to detect persons harboring worms of single sex and/or preadults. Hence, in highly endemic areas mass drug treatment is preferred to selective therapy (WHO, 1974). Extensive studies have been carried out on mass chemotherapeutic measures using various drug regimens (Hawking, 1962), some of the most strikingly successful results being from Tahiti and Samoa (Hawking, 1978). Mass drug treatment was an integral part of NFCP in India also, but was given up due to unsatisfactory coverage (Rao, 1985). The usefulness of annual single dose treatment on bancroftian filariasis has been demonstrated (Laigret, 1984; Kimura, 1985). Except for a few pilot studies on the effect of various control measures which included mass multi-dose DEC treatment on malayan filariasis (Joseph *et al,* 1960; Rao *et al,* 1980) mass single dose therapy has not been adequately evaluated. The present communication deals with the comparison of the efficacy of two schedules of mass single dose DEC therapy in *Brugia malayi* endemic area in Shertallai part of Kerala.

MATERIAL AND METHODS

The details of the study area and the epidemiological situation have already been described (Rajagopalan *et al,* 1988, 1989). Two areas with populations of 22,681 in 5,639 households and 6,192 in 1,749 households, respectively were selected for administering mass DEC at 6mg/kg body weight in a single dose annually and bian-

nually. Another area with a population of 5,572 in 1,467 households was maintained as a control without any intervention measures. All these three study areas are contiguous, and ecologically and epidemiologically comparable. This study was carried out for a period of two years from 1987 to 1988. Preschool children and school children were covered at "anganwadi centers" and schools respectively. House visits were also made to cover the adult population. These visits were made between 19.00 hours and 22.00 hours in order to cover all the family members who were expected to be at home during these hours. Infants and pregnant women were not included. Informed consent was obtained from all the individuals or the guardians in the case of children. Dosage was decided on body weight and was rounded off to the nearest 50 or 100mg. Palatable syrup base (Banocide 120mg/5ml, 50mg/5ml, Wellcome) was given to the children below 10 years and DEC tablets (Banocide, 50 mg, 100 mg, Wellcome) were given to the rest. Drugs were given after food. One day prior to the house visits for drug administration a social worker visited the houses, informed them of the details of the program and prepared them for drug administration. On the spot intake of drugs was ensured by the team. A team including a physician visited all the households/schools on the following day to monitor and treat side reactions, if any. Reactogenicity of DEC was assessed from symptoms and signs. Fever was considered when temperature recorded 99°F and above. The first rounds of annual and biannual treatments were initiated in the month of April 1987, the second biannual treatment in the month of October 1987, the third round of biannual and second round of annual treatments in the month of April 1988 and the fourth round of biannual treatment in the month of October 1988. All the rounds were completed within 2 to 3 months from the initiation of treatment.

Pre-control parasitological and clinical surveys were made concurrently in the study population during the months of February to March 1987. A stratified random sampling protocol with proportional allocation of 10% and 2% of the population in each study village was adopted for the microfilaria and clinical surveys respectively. The finger prick method with 20 mm^3 blood sample was followed for microfilaria survey (Rajagopalan *et al,* 1988). Clinical case detection was done following standard criteria (WHO, 1985). These surveys were repeated after six months of the completion of the trial as recommended by WHO (1974), following the same sampling procedure of pre-control surveys. In the control area the survey was repeated during January and February 1989. Age referred to the age on the date of survey. A cohort population of microfilaria carriers was also longitudinally followed to assess the impact of mass therapy on microfilaria carriers. Annual and biannual regimens assigned to the village was not known to the persons who were evaluating microfilaria prevalence.

Chi-square test, Mann Whitney U test and log odds ratio test were used wherever applicable (Kahn and Sempos, 1989). The average annual incidence of new mF positive persons in the age group 1-7 years and of filarial fever attacks in the age group 5-15 years were worked out following Kimura *et al* (1985). Annual incidence and recovery rates were also calculated for the whole population following the method of Bekessy *et al* (1976). Infectivity index of the population has been assessed in the pre and post control surveys following the method recommended by WHO (1974).

RESULTS

The age structure of the population and percentage treated in different rounds of annual and biannual treatment areas are shown in Tables 1 and 2. The eligible population for drug administration constituted 94.31% of the total population, while the rest included infants and pregnant women. The coverage was minimum in the age class 1-9 years, ranging from 27.94% to 49.10% and it was maximum in the age class 10-19 years, ranging from 57.54% to 98.18% in different rounds of mass therapy. Unwillingness of the parents was the cause for the poor coverage in the age class of 1-9 years. The nature and percentage of cases showing systemic reactions following DEC therapy in different rounds of biannual treatment are given in Table 3. The overall occurrence of side reactions ranged between 6.21% and 8.4% in different rounds of treatment. Fever was the predominant reaction (42.9% of cases with reactions), followed by headache (19.9%), pain in the gastric region (17.1%) and other reactions were minimal.

Table 1

Population covered under 1 and 2 rounds of annual single dose mass DEC.

Age class	Population	1st round		2nd round	
		No. given	coverage (%)	No. given	coverage (%)
1-9	6520	2602	39.91	2080	31.90
10-19	4808	4562	94.88	3995	83.08
20-29	3470	2487	71.67	2536	73.08
30-39	2858	1681	58.82	1782	62.36
≥ 40	4854	2650	54.60	2885	59.44
Total	22510	13982	62.11	13278	58.99

Table 2

Population covered under four rounds of biannual single dose mass DEC.

Age class	Population	Coverage (%)			
		1st round	2nd round	3rd round	4th round
1-9	1782	27.94	37.15	49.10	36.37
10-19	1314	71.63	57.54	72.46	98.18
20-29	948	46.51	33.75	43.35	72.56
30-39	781	45.59	39.06	49.69	69.68
≥40	1326	50.75	37.63	45.70	65.62
Total	6151	47.29	41.33	52.54	66.01

While there was no significant ($p > 0.05$) change in the proportion of cases with side reaction in the subsequent rounds, there was a significant ($p < 0.05$) reduction in the occurrence of fever in the third and fourth rounds when compared to that of first round. Localized symptomatic reactions such as lymphadenitis, lymphangitis and abscess were noticed only in 5, 2 and 1, cases respectively during the entire period of treatment.

A total of 465 and 41 randomly selected amicrofilaraemic and microfilaraemic individuals respectively was monitored after the single dose DEC therapy at 6 mg/kg body weight. The proportion of mF carriers developing side reactions (58.54%) was significantly ($p < 0.05$) higher than that of amicrofilaraemic individuals (3.23%).

The overall coverage in both the pre- and post-control parasitological and clinical surveys was well above the target minimum of 10% and 2% respectively in all the study areas. Age-specific analysis however showed that the coverage was not achieved in the 0-9 years age class and this was due to practical constraints.

Table 3

Development of side reactions following different rounds of biannual mass DEC therapy.

	Rounds of mass therapy			
	1	2	3	4
Number observed	1770	1017	1346	1634
Percentage of cases with side reactions				
1. Fever	2.60	1.67	0.67	0.98
2. Headache	1.24	1.97	3.12	2.45
3. Body ache	0.40	0.00	0.07	0.18
4. Stomach ache	1.07	1.97	1.49	1.04
5. Gidiness	0.28	0.29	0.45	0.43
6. General weakness	0.06	0.10	0.00	0.18
7. Vomiting	0.34	0.79	0.89	0.73
8. Others	0.23	1.08	1.71	0.37
Total	6.21	7.87	8.40	6.36

Microfilaremia prevalence and intensity

The age-specific pattern of pre- and post-control prevalence of microfilaria for annual, biannual treatment and control areas are given in Table 4. The overall mF rate during the pre-control surveys in all these three areas did not differ significantly (Chi-square = 3.12; $p = 0.21$). Age specific analysis of mF prevalence showed

Table 4

Age specific mF prevalence in pre and post control surveys in annual, biannual treatment and control areas.

Area	Age class	Pre-control		Post-control		change	Proportion significance p value
		Sample	%	Sample	%		
Annual mass treatment area							
	0-9	390	2.82	343	0.00	-100.00	-
	10-19	584	7.36	606	1.49	- 79.76	<0.05*
	20-29	445	5.39	475	2.11	- 60.88	0.014*
	30-39	317	5.36	351	1.14	- 78.74	0.002*
	≥ 40	673	3.42	663	1.06	- 68.98	0.006*
	Total	2409	4.90	2438	1.23	- 74.89	<0.05*
Biannual mass treatment area							
	0-9	130	3.08	105	0.00	-100.00	-
	10-19	229	8.73	170	0.00	-100.00	-
	20-29	184	6.52	161	1.86	- 71.43	<0.05*
	30-39	139	4.32	122	0.82	- 81.01	0.083
	≥ 40	275	6.55	253	0.40	- 93.96	>0.05*
	Total	957	6.27	811	0.62	- 90.17	>0.05*
Control area							
	0-9	52	3.85	124	6.45	+ 67.57	0.389
	10-19	149	8.72	144	8.33	- 4.43	0.939
	20-29	106	5.66	122	3.28	- 42.07	0.290
	30-39	92	8.70	121	7.44	- 14.51	0.936
	≥ 40	177	3.39	157	4.46	+ 31.52	0.825
	Total	576	6.08	668	5.99	- 1.51	0.957

* : Significantly different
\- : Decrease
\+ : Increase

that there was no significant difference between the age classes except ≥40 years in which the mF prevalence between annual and biannual areas was at its statistical limit (Chi-square = 3.89; p = 0.048). The mF prevalence during the pre-control surveys ranged from 2.82 to 7.36 in the annual treatment area, 3.08 to 8.73 in the biannual treatment area and 3.85 to 8.72 in the control area in different age classes. In all these areas the lowest mF prevalence was noticed in the 0-9 years age class and the highest in the 10-19 years age class (Fig 1). However, the linear trend in proportion (Chi-square method) analysis showed that there was no significant (p > 0.05) relationship between mF prevalence and age.

The overall reduction of 74.89% mF prevalence from pre-control level in the annual area (from 4.90% to 1.23%) and 90.11% in the biannual area (from 6.27% to 0.62%) was significant (p < 0.05). There were no microfilaria carriers in the age class 0-9 years in both the treatment areas during the post treatment surveys (Table 4). In addition, in the biannual treatment area the 10-19 years age class also recorded no carriers of microfilaria. While the proportion of mF carriers was significantly (p < 0.05) lower in the post-control surveys in the rest of the age classes in the annual treatment areas, in the biannual treatment area it was,

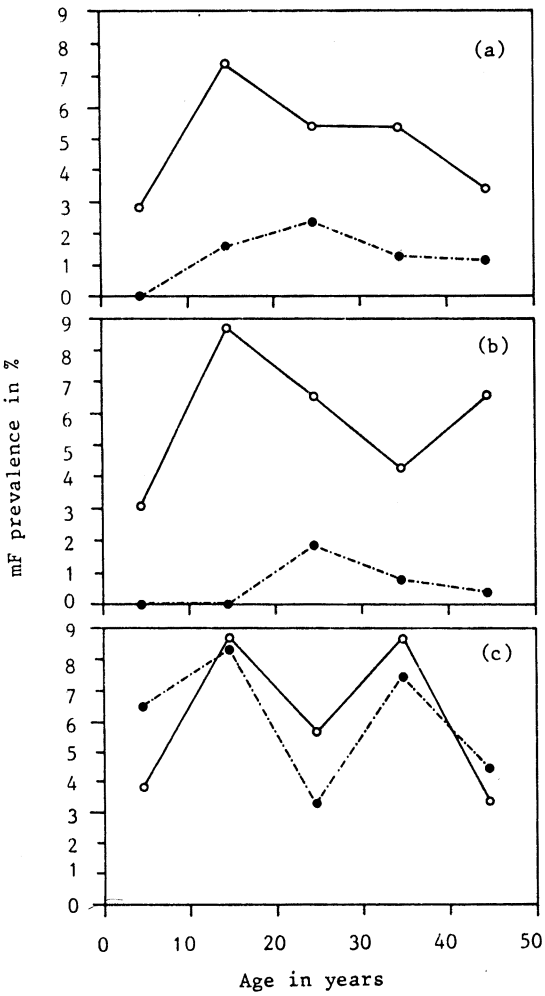

Fig 1—Microfilaria prevalence in pre (○) and post (●) control surveys in annual (a), biannual (b), treatment and control areas (c).

however, not significant in the age class 20-29 years. When broad age classes viz, children ($\leq$ 15 years) and adults (> 15 years) were considered, the reduction in mF prevalence was significant ($p < 0.05$) in both the areas. The reduction in mF prevalence was significantly ($Z = 5.435$ $p < 0.05$) higher in the biannual compared to the annual treatment area. In the control area, although, there was a reduction in the mF prevalence during the survey corresponding to the post-control surveys of treatment areas, it was minimal (Table 4). The change in mF prevalence was not significant in any of the age classes. There was an increase in the younger age class of 0-9 years and older age class of $\geq$40 years though it was not significant.

There was no significant ($p > 0.05$) difference in mean mF count (mfc) between children and adults in both the areas in pre control surveys. The overall mean mfc per individual was brought down from 0.69 to 0.13 and 0.86 to 0.02 in annual and biannual areas, respectively after DEC treatment and the reduction was significant (Mann Whitney U test, $p < 0.05$) in both the areas (Table 5). Comparison between the two areas showed that the reduction was relatively higher in the biannual treatment area than in the annual area in all the age classes as well as the total. Though the overall reduction in mfc was significant in both the areas, age-specific analysis showed that it was not significant in all the age classes. This may be because of small sample size resulting from the break down of the total into different age classess. In the control area the mfc has shown an increase in all the age classes except the age class 20-29 years and the change in mfc from the initial survey was not significant.

The percentage of mF carriers with more than five mF/20mm^3 in the pre- and post-control surveys was 54.17% and 33.40% in the annual, and, 54.73% and 20.00% in the biannual treatment area, respectively. Though the proportion of high mF carriers was not significantly ($p > 0.05$) different from the pre-control level in both the areas, there was a marked reduction in high density carriers. Thus, there was not only a reduction in mF prevalence and intensity in the population, but also a reduction in the proportion of high density carriers. In the control area the percentage of mF carries with more than 5 mF/20mm^3 in the initial and resurvey, respectively was 62.50% and 71.43%. Though it did not differ significantly ($p = 0.567$), there was an increase in high density carriers.

The proportion of mF carriers and mean mfc did not differ significantly ($p > 0.05$) between males and females in both pre-and post-control surveys in either areas. Similarly the reduction in mfc, following treatment also did not differ significantly ($p > 0.05$) between the sexes in both the areas, suggesting that there was no difference in the response to DEC by gender.

Incidence of new cases

The average annual incidence of new mF cases in the age class 1-7 years per 1000 children was

Table 5

Age specific change in microfilaria count in annual, biannual mass treatment and control areas.

Area	Age class	Mean mfc#			Mann Whitney U test p value
		Pre-control mean mfc#	Post-control mean mfc#	% change	
Annual mass treatment area					
	0-9	0.19	0.00	-100.00	-
	10-19	1.38	0.21	- 84.49	0.044*
	20-29	1.02	0.17	- 83.36	0.281
	30-39	0.45	0.06	- 87.71	0.006*
	≥ 40	0.29	0.14	- 51.96	0.239
	Total	0.69	0.13	- 81.08	0.018*
Biannual mass treatment area					
	0-9	0.49	0.00	-100.00	-
	10-19	1.34	0.00	-100.00	0.009*
	20-29	0.61	0.05	- 91.84	0.247
	30-39	0.37	0.03	- 91.24	0.376
	≥ 40	1.06	0.01	- 99.26	0.126
	Total	0.86	0.02	- 98.00	0.008*
Control area					
	0-9	0.12	0.77	+541.67	0.3908
	10-19	1.97	2.51	+ 27.41	0.4711
	20-29	1.59	0.72	- 54.72	0.3779
	30-39	1.09	6.22	+470.64	0.4363
	≥ 40	0.62	0.89	+ 43.55	0.4728
	Total	1.18	2.18	+ 84.75	0.4858

\# : Mean microfilaria count
* : Significantly different
\- : Decrease
\+ : Increase

calculated to be 4.86 and 9.18 in the pre-control surveys in annual and biannual treatment areas, respectively. Following DEC therapy there were no new cases in the age class of 0-9 years in either areas and thus the incidence of new cases was essentially nil.

A total of 783, 548 and 226 amicrofilaremic, and 31, 41 and 18 microfilaremic individuals detected in the pre-control survey in annual, biannual treatment and control areas, respectively, were reexamined after DEC trial. The percentage of amicrofilaraemic individuals who gained infection during the period between pre- and post-control surveys (900 days) in biannual treatment area was 0.18% which was less than that of annual treatment area (1.12%) but was not significantly different. In the control area it was as high as 2.21%. The percentage of microfilaria carriers who had lost the infection in annual, biannual treatment and control areas was 96.7%, 97.6% and 72.72% respectively. The instantaneous rate (per individual/day) of gain of infection was significantly lower ($p < 0.05$) in the biannual area (0.7×10^{-5}) than in the control (0.45×10^{-4}) as well as the annual treatment (0.51×10^{-4}) areas. The instantaneous rate of loss of infection was significantly higher ($p < 0.05$) in both annual (0.43×10^{-2}) and

Table 6

Change in the prevalence of clinical manifestations in the study population.

Area	Type of manifestation	Prevalence in %			Proportion significance p value
		Pre-control	Post-control	% change	
Annual mass treatment area		(n=751)	(n=807)		
	1. Filarial fever/ adenolymphangitis	5.86	0.62	89.42	<0.05*
	2. R O	1.86	0.12	93.55	0.0002*
	3. P O and Ele	9.64	7.56	21.58	0.239
	4. Chronic+acute	9.59	2.85	70.27	<0.05*
Biannual mass treatment area		(n=443)	(n=500)		
	1. Filalrial fever/ adenolymphangitis	3.39	1.80	46.90	0.740
	2. R O	2.26	0.20	91.15	0.0032*
	3. P O and Ele	11.29	9.40	16.74	0.398
	4. Chronic+acute	11.74	3.80	67.63	<0.05*
Control area		(n=155)	(n=825)		
	1. Filarial fever/ adenolymphangitis	8.39	4.97	40.76	0.091
	2. R O	1.29	0.61	52.71	0.289
	3. P O and Ele	16.13	11.88	26.35	0.182
	4. Chronic+acute	9.67	7.27	24.82	0.906

R O : Recent edema
P O and Ele : Persistent edema and elephantiasis
* : significantly different

biannual (0.42×10^{-2}) treatment areas when compared to control area (0.15×10^{-2}). However, it was not significantly ($p > 0.05$) different between annual and biannual treatment areas.

Infectivity index

The pre-and post-treatment infectivity index of the population was 2.1% and 0.5% in annual and 2.7% and 0.3% in biannual areas, repectively. The reduction in infectivity index from the pre-control level was higher in the biannual area (88.8%) compared to the annual (76.19%) area. In the control area the infectivity index of the population was 3.72 in the initial survey and it was 3.40 in the resurvey.

Clinical manifestations

The prevalence of acute manifestations, recent edema, persistent edema with or without elephantoid skin changes and chronic cases associated with acute manifestations in the study population in pre- and post-control surveys is given in Table 6. While the prevalence of acute manifestations was significantly reduced from the pre-control level in the annual area, it was not significant in both biannual and control areas. The prevalence of recent edema was significantly reduced in both the treatment areas and was not significant in the control area. There was no significant change in the prevalence of chronic cases, as expected, in all the three study populations. The overall reduction in acute manifestations from the pre-control level was 89.2% in the annual area and was significantly higher ($Z = 100.86$; $p < 0.05$) than that of the biannual area (65.4%). Further, there was a reduction in filarial fever

incidence (new cases for 1000 children) from 2.46 to 0.37 in the annual area.

The analysis on the proportion of chronic lymphedema cases associated with or without any one or a combination of various acute manifestations such as filarial fever, lymphangitis and lymphadenitis in different age classes in the annual and biannual areas showed that the proportion of chronic cases associated with acute manifestations was significantly ($p < 0.05$) reduced from 93.50% to 41.17% (70.3% reduction) and from 94.55% to 43.18% (67.0% reduction) in the annual and biannual areas, respectively. The reduction was not significantly ($Z = 0.118$; $p > 0.05$) different between these two areas. Age specific analysis showed that the reduction was significantly ($p < 0.05$) higher in the age class ≥ 40 years in both the areas. In the control area, though there was a reduction in the proportion of chronic cases associated with acute manifestations, this was not significant (Table 6).

The prevalence of recent edema cases (edema with less than six months of appearance) was significantly ($p < 0.05$) brought down from 1.86% to 0.13% in the annual area and from 2.48% to 0.09 in the biannual area after DEC treatment. In the control area the change in the prevalence of recent edema cases was not significant (Table 6). Log odds ratio analysis showed that the reduction was significantly ($Z = 11.54$; $p < 0.05$) higher in biannual area.

DISCUSSION

The present study revealed that both annual and biannual single dose mass DEC therapy when administered for two years resulted in significant reduction in mF prevalence as well as mean mfc in the population in periodic *B. malayi* infection. In addition, there was a marked reduction in infectivity index of the population, the proportion of mF carriers becoming amicrofilaremic and the proportion of high density carriers in both the treatment areas. Further, the incidence of infection was minimal in the population and was virtually zero among children (0-9 years) in both the areas. Attacks of filarial fever and recruitment of recent edema cases were also significantly reduced after DEC treatment. These results suggest that effective interruption in transmission is possible by both modes of mass therapy. The relatively higher efficacy of the biannual therapy was evident from the higher reduction in mF prevalence and mean mfc compared to the annual area, as expected. Though both modes of mass therapy are useful, the choice of the method will depend upon several factors such as operational feasibility, resources etc.

In Western Samoa, which is endemic for subperiodic *W. bancrofti,* the reduction in mF prevalence following annual single dose DEC administered for a period of two years was reported to be 47.2% in spite of very high coverage (85%) of the population (Kimura, 1985). The present study showed 75.0% reduction in prevalence in annual single dose area after two years. This may be due to the higher susceptibility of *B. malayi* to DEC as compared to *W. bancrofti* (Ottesen, 1984; Rao *et al,* 1985).

In an earlier study (Joseph *et al,* 1960) in this area, mass 5 day DEC therapy was reported to be unsuitable due to the problem of side reactions, although the details of side reactions were not given in that report. The low prevalence of side reactions (8.4%) and gradual increase in coverage in subsequent rounds in the present study on the other hand, suggest that mass single dose DEC therapy is not only ideal but also feasible. The increase in awareness achieved through intensive community motivation is the reason for their involvement in the program which is essential for community oriented program (WHO, 1984; Hii *et al,* 1988; Panicker *et al,* 1990).

Regarding the evaluation of chemotherapy programs, this study has considered detailed parasitological and clinical consequences of intervention. Appropriate statistical analyses could sensitively detect the changes on a short time scale, even when the initial prevalence was low. Such changes were difficult to observe in a vector control program alone for bancroftian filariasis (Subramannian *et al,* 1989). Though two successive annual treatments with single doses of Ivermectin on microfilaria carriers of *W. bancrofti* var. *pacifica* have been shown to be effective in reducing the mF (Cartel *et al,* 1990) it has not been evaluated at the community level as has been done with DEC in the present study. Further analysis of the situation is warranted if mass therapy is to be continued over many years.

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REFERENCES

Anonymous. National Filariasis Control Programme Operational Manual, Delhi: National Malaria Eradication Programme 1984; 152.

Bekessy A, Molineaux L, Storey J. Estimation of incidence and recovery rates of *Plasmodium falciparum* parasitaemia from longitudinal data. *Bull WHO* 1976; 54 : 685-93.

Cartel JL, Celerier P, Spiegel A, *et al.* Effect of two successive annual treatments with single doses of Ivermectin on microfilaraemia due to *W. bancrofti* var *pacifica. Trans R Soc Trop Med Hyg* 1990; 84 : 837-9.

Das PK, Manoharan A, Srividya A, *et al,* Frequency distribution of *Wuchereria bancrofti* microfilariae in human populations and its relationships with age and sex. *Parasitology* 1990; 101 : 429-34.

Duke BOL. Problems of chemotherapy with Diethylcarbamazine citrate in lymphatic filariasis. *WHO/FIL/80* 1980; 158 : 1-9.

Edeson JFB. Studies on filariasis in Malaya: The accuracy of blood surveys. *Ann Trop Med Parasitol* 1959; 53 : 388-93.

Goodwin LG. Recent advances in research on filariasis. Chemotherapy. *Trans R Soc Trop Med Hyg* 1984; 78 (suppl) : 1-8.

Hawking F. A Review of progress in the chemotherapy and control of filariasis since 1955. *Bull WHO* 1962; 27 : 555-68.

Hawking F. Diethylcarbamazine. A review on the literature with special reference to its pharmacodynamics, toxicity and its use in the therapy of onchocerciasis and filarial infections. *WHO/ONCHO/78* 1978; 142 : 1.

Hii J, Kan SKP, Parmar SS, *et al.* The effect of diethylcarbamazine citrate on incidence and recovery rates of *Brugia malayi* microfilaremia in Sabah, Malaysia. *Am J Trop Med Hyg* 1988; 38 : 582-6.

Joseph C, Menon MAV, Nair GK. Pilot studies on the control of filariasis due to *Brugia malayi* (Brug 1927) in India. *Indian J Malariol* 1960; 14 : 663-86.

Kahn HA, Sempos CT. Statistical methods in Epidemiology. New York : Oxford University Press 1989 : 292.

Kimura E, Penaia L, Spears GF. Epidemiology of subperiodic bancroftian filariasis in Samoa 8 years after control by mass treatment with diethylcarbamazine. *Bull WHO* 1985; 63 : 869-80.

Kimura E. Annual single-dose mass treatment with diethylcarbamazine citrate. In : Mak JW, Yong HS, eds, Proceedings of the WHO Regional Seminar on control of Brugian filariasis. WHO, JMR, Kuala Lampur 1985 : 55-61.

Laigret J. The effects of treatment with annual doses of Diethycarbamazine citrate in the control of human lymphatic filariasis : Experience in the Pacific islands. *WHO/FIL/84* 1984; 177 : 10.

Ottesen EA. The action of diethylcarbamazine on adult worms of the lymphatic dwelling filariae *Wuchereria bancrfti, Brugia malayi* and *Brugia timori* in man. *WHO/FIL/84* 1984; 174 : 1-27.

Ottesen EA. Efficacy of diethylcarbamazine in eradicating infection with lymphatic-dwelling filariae in humans. *Rev Infect Dis* 1985; 7 : 341-56.

Panicker KN, Pani SP, Sabesan S, *et al.* Choice and integration of different approaches to case detection with special reference to brugian filariasis in South India. *Indian J Med Res* 1990; 91 : 282-8.

Rajagopalan PK, Panicker KN, Sabesan S, *et al.* Control of brugian filariasis in Shertallai, South India : Pre-control epidemiological observations. *Misc Public Vector Cont Res Centre* 1988; 7 : 1-11.

Rajagopalan PK, Panicker KN, Pani SP. Impact of 50 years of vector control on the prevalence of *Brugia malayi* in Shertallai area of Kerala State. *Indian J Med Res* 1989; 89 : 418-25.

Rao CK. Experience in using diethylcarbamazine (DEC) in the control of lymphatic filariasis in India. *J Commun Dis* 1985; 17 : 36-45.

Rao CK, Chandarasekharan A, Kaul SM, Narasimham MV, Sharma SP. Relative effectiveness of different methods of control of brugian filariasis in India. *Indian J Med Res* 1980; 72 : 194-202.

Subrahmanyam D. Antifilarials and their mode of action. *CIBA Found Symp* 1989; 127 : 246.

Subramanian S, Pani SP, Das PK, *et al.* Bancroftian filariasis in Pondicherry, South India : 2. Epidemiological evaluation of the effect of vector control. *Epidemiol Infect* 1989; 103 : 693-702.

WHO. Third report of WHO expert committee on lymphatic filariasis. *WHO Tech Rep Ser* 1974; 542 : 1.

WHO. Fourth report of WHO expert committee on lymphatic filariasis. *WHO Tech Rep Ser* 1984; 702 : 1.

WHO. Report of the 12th meeting of the scientific working group on filariasis. Lymphatic pathology and immunopathology in filariasis. *TDR/FIL-SWG (12)/85* 1985; 3 : 1.