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Control of Lymphatic Filariasis by Annual Single-dose Diethylcarbamazine Treatments

E. Kimura and J.U. Mataika

It has long been stressed that diethylcarbamazine citrate must be given at a total dosage of 72 mg per kilogram of body weight in 12 divided doses of 6 mg kg^{-1} to obtain maximum effect against Wuchereria bancrofti. *However, recent studies revealed that only a single dose at 6 mgkg^{-1} could reduce microfilaria (Mf) counts by 90%, and that the effect would persist for 12–18 months. The annual repeat of the single-dose mass treatment was shown to be effective in reducing Mf prevalence and density in large-scale, long-term field trials. The scheme is simple and economic, and could be sustainable in many endemic areas, where health manpower and resources are often not sufficient. Annual single-dose mass treatments can be an effective weapon against human lymphatic filariasis, as discussed here by Eisaku Kimura and Jona Mataika.*

There are an estimated 78.6 million cases of lymphatic filariasis in the world[1], and only a small proportion of them is fortunate enough to be treated with the first drug of choice, diethylcarbamazine citrate (DEC). For more than 40 years, DEC has been used, worldwide, as the most effective and safest drug. The standard treatment scheme recommended by WHO[2] is to administer the drug at a dosage of 6 mg per kilogram of body weight daily, weekly or monthly for a total of 12 times in order to obtain the required overall dose of 72 mg kg^{-1} for the treatment of *Wuchereria bancrofti* infection, or a total dose of 36–72 mg kg^{-1} for *Brugia* spp infections. The standard treatment can effectively reduce filariasis and suppress its transmission, but ensuring that 12 doses are given poses considerable practical difficulties in a large-scale campaign. Recently, annual single-dose treatments with DEC at 6 mgkg^{-1} were reported to be effective in reducing the microfilaria (Mf) prevalence and density. The effect of each single dose is not very strong but is steadily progressive in a course of repeated treatments. In a filariasis control campaign in Samoa involving 160000 people over eight years, three single-dose treatments decreased the Mf prevalence from 5.6% to 2.5%, showing that single-dose chemotherapy is a practical strategy for filariasis control.

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What is the aim?

Annual single dose is given for mass treatment, eliminating the laborious and costly step of blood

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Table 1. Effects of a single-dose DEC treatment assessed[a] at six and at 12 months after treatment

	Six months			12 months		
	4 mg kg^{-1}	6 mg kg^{-1}	8 mg kg^{-1}	4 mg kg^{-1}	6 mg kg^{-1}	8 mg kg^{-1}
No. examined	47	112	50	51	41	45
No. Mf-negative after treatment	13	36	22	15	22	18
Cure rate (%)	27.7	32.1	44.0	29.4	53.7	40.0
Mf count, expressed as mean of log (Mf + 1)						
Before treatment (A)	2.278	2.096	2.250	2.117	2.003	2.198
After treatment (B)	1.271	1.126	0.900	1.384[b]	0.751[b]	1.010[b]
Change	1.006[c]	0.969[c]	1.350[c]	0.733[d]	1.251[d]	1.188[d]
Decrease (%)[e]	90.1	89.3	95.6	81.5	94.4	93.5

[a]Using 1 ml nucleopore filtration.
[b]ANOVA (analysis of variance) at 12 months: $p<0.05$.
[c]ANOVA at six months: $p<0.05$.
[d]ANOVA at 12 months: $p<0.01$.
[e]Calculated as 100 × [antilog(A) − antilog(B)] / antilog(A).

screening, and securing better treatment coverage in highly migratory communities. Two six-monthly treatments seem to be more effective than one annual treatment for *W. bancrofti*[3,4] and *B. malayi*[5] infections, but lose the operational simplicity.

The treatment aims to reduce Mf prevalence and density in a community and maintain them at low levels so as to reduce potential of transmission and prevent acute filarial fever and, possibly, early edematous change. But what are the desired Mf levels of prevalence and density? In Tahiti, no new cases of elephantiasis or hydrocele were found when the standard DEC treatment reduced the Mf rate from 38% to 6.5% (Ref. 6), and, on the basis of studies with 20–60 µl blood smears, Kessel[7] suggested an Mf rate of <4% and an MfD_{50} of approximately four per 20 µl to keep clinical filariasis down to an insignificant level. Brugian filariasis transmitted by *Anopheles sinensis* decreased spontaneously when chemotherapy reduced the Mf rate (as determined with two 60 µl smears) from 3–13% level to 1.55–2.23% of the population[8]. A critical Mf density in this case was considered to be less than 12 Mf per 60 µl. Based on the experience in Samoa using a 60 µl smear, we estimate that the 'low' desired level for the area would be an Mf rate of <3% and an Mf density (geometric mean) of the Mf positives of less than 10 per 60 µl. By maintaining this level, we can expect to stop the occurrence of new clinical cases and to improve or cure existing fever and edema in early stages. It is interesting to find that critical 'low' levels proposed for different areas are very similar. For some areas where a rate of clinical filariasis (lymphangitis, lymphedema, elephantiasis, hydrocele and chyluria combined) is very high and even exceeds the Mf rate* (Ref. 9), different criteria may have to be determined.

The six-monthly or annual single-dose treatments may be used for prophylaxis in a relatively large and confined population, such as schoolchildren[10].

How effective is the single-dose treatment?

Parasitological effects. With diurnally subperiodic *W. bancrofti*, DEC single-dose treatment was tested in French Polynesia, Samoa and Fiji. In Samoa, DEC treatments at 4, 6 and 8 mg kg^{-1} were compared at six and 12 months[3]. All three dosages were effective (Table 1); the 6 mg kg^{-1} was considered the best, with a higher rate of Mf reduction at 12 months than the 4 mg kg^{-1} treatment ($p<0.005$) and with fewer adverse reactions than the 8 mg kg^{-1} treatment ($p<0.025$). DEC at 6 mg kg^{-1} cleared Mf in 54% of the carriers and reduced the geometric mean Mf count by 94% after 12 months. The rate of Mf decrease was not lowered even when pre-treatment counts were more than 1000 per millilitre of blood. Three annual treatments with 300 mg for females and 400 mg for males (about 6 mg kg^{-1}) tested in French Polynesia reduced the Mf rate of a cohort of 120 Mf positives from 100% to 12% (Ref. 11). A detailed comparative study between single-dose and multidose treatments was carried out in Fiji (Fig. 1). In the study, five rounds of annual single-dose mass treatment with DEC at 6 mg kg^{-1} (a total of 30 mg kg^{-1} in five years) was compared with an intensive 28-dose mass treatment, given at 5 mg kg^{-1} weekly for six weeks and then monthly for 22 months (a total of 140 mg kg^{-1} in two years). In the annual treatment, the Mf rate with a 60 µl smear decreased steadily from 6.5% (the average of males and females) to 0.9% (an 87% reduction); in the multidose treatment, 11.6% dropped to 0.9% (a 93% reduction)[12]. A very interesting finding was that two years after the completion of the multidose treatment, there was a clear indication of increase in Mf rate, that is, in five of seven age groups, the Mf rates in 1990/1991 were higher than those in 1990 (Fig. 2a). This increase was statistically significant for people aged 11–59 years (Mantel-Haenszel's χ^2 test, $p<0.05$), whereas, with the annual treatments, the decrease from 1990 to 1990/1991 was apparent ($p<0.03$, Fig. 2b). It seemed possible that a few additional doses would surpass the efficacy of the multidose scheme. A similar increase in Mf rate was observed in Samoa three years after completion of the standard course of DEC treatment[13].

With nocturnally periodic *W. bancrofti*, a single dose at 6 mg kg^{-1} reduced the Mf count by 90.5% in Papua New Guinea[14] and by 91.8% in Haiti[15] when assessed 12–18 months after treatment. The effect against periodic *B. malayi* was studied in India. Panicker *et al.*[5] reported that two rounds of annual single-dose treatment at 6 mg kg^{-1} reduced the Mf count by 81% and the Mf rate of the population from 4.90% to 1.23% using the 20 µl thick-smear method. These results indicate remarkable impact of a single dose on the transmisssion of parasites.

*Control of brugian filariasis in Shertallai, South India: pre-control epidemiological observations. *Miscellaneous Publications of Vector Control Research Centre* (7) 1988, Pondicherry, India.

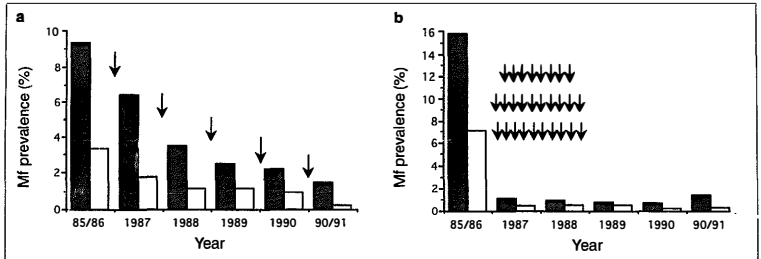

Fig. 1. Reductions of Mf prevalence in five rounds of annual single-dose DEC treatment with a total dosage of 30 mg kg^{-1} (a) and in an intensive 28-dose treatment over two years with a total dosage of 140 mg kg^{-1} (b). An arrow indicates one treatment. Male, closed bars; female, open bars. Data from Ref. 12.

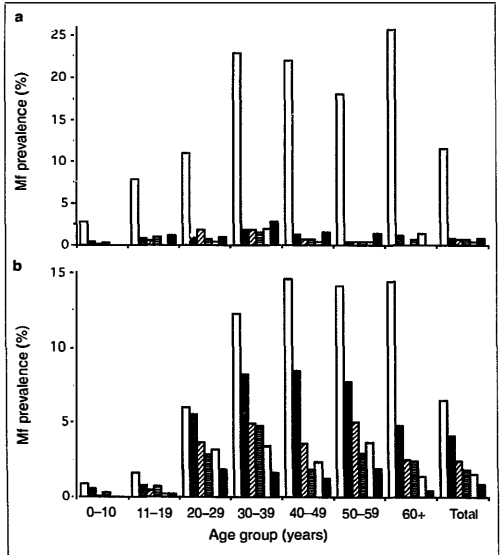

Fig. 2. Yearly change in Mf prevalence analysed by age group. With the 28 multidose treatment (given as in Fig. 1b), the Mf rate increased from 1990 to 1990/1991 in five of seven age groups (Mantel-Haenszel's χ^2 test, $p < 0.05$) (a). With five annual treatments given as in Fig. 1a, gradual decreases in Mf rate are seen in almost all age groups (b). 1985/1986, open bars; 1987, dark shaded bars; 1988, hatched bars; 1989, horizontal hatched bars; 1990, light shaded bars; 1990/1991, solid bars. Data from Ref. 12.

DEC in multidose treatments has been shown to be macrofilaricidal[16,17]. The effect could be quantified by measuring circulating parasite antigens, which probably reflect the existence of living adult worms[18]. Treatment with a 72 mg kg^{-1} dose of DEC reduced the antigen levels by 50–75% 12 months after treatment[19,20]. Can a single, low dose of 6 mg kg^{-1} kill or damage adult worms? A study by Kazura *et al.*[14] showed a surprising 40% decrease of circulating antigen relative to the pretreatment level 18 months after treatment. Although we cannot simply compare the percentages of different reports, and the relationship between antigen levels and adult worm burden has not been established clearly, it is possible that killing and damaging effects of the single dose are considerable, and much greater than generally imagined.

Clinical impact. There are a limited number of reports on the clinical effects of the single-dose treatment. The five annual doses in Fiji significantly reduced the occurrence of fever attack from 2.2% of all people examined to 0.8% (a 64% reduction, $p<0.01$) and prevented new cases[12]. With *B. malayi* in India, two annual doses at 6 mg kg^{-1} resulted in about 90% reduction in the prevalences of both acute filarial fever and recent edema[5]. In Papua New Guinea, Schuurkamp *et al.*[21] reported a significant reduction of *W. bancrofti*-associated splenomegaly following two annual single-dose treatments. These results clearly indicate that the annual treatments have clinical benefits.

Effects in a national campaign. The government of Samoa adopted the annual single-dose mass treatment as a national strategy to control filariasis and started the Filariasis Control Project in 1981 (Ref. 22). For several reasons the annual treatments could not be carried out, and only three mass treatments were possible in eight years. A single dose of DEC at 6 mg kg^{-1} was administered to more than 80% of the total Samoan population of

160000 in 1982, 1983 and 1986. The treatments reduced the prevalence of *W. bancrofti* infection from 5.6% to 2.5% (a 55% reduction), and the total number of microfilariae in the Samoan population was estimated to have been reduced by 80%. There was also an obvious decrease in clinical filariasis.

Single dose versus multidose

Problems often encountered in conducting a multidose mass campaign include: (1) those who are aware of the difficulty in implementing and maintaining the campaign are not willing to inaugurate or repeat the multidose scheme; (2) a government cannot allocate sufficient money and manpower when filariasis rates are decreasing and the priority of the disease has been reduced; (3) most people cannot complete a course of treatment, thus wasting a vast number of DEC tablets; and (4) the 12-dose treatment that aims to eradicate filariasis is not always relevant to the recent recognition that controlling the disease is more practical and cost-effective. The single-dose scheme does not encounter these problems, and leaves more money and time for health education and mosquito control.

The efficacy of the single dose is not as good as that of the multidose, and treatment must be repeated; but how many times? The weakness of the scheme is that we cannot answer this question. However, annual repetition will provide an opportunity to educate people and facilitate community participation for sanitation programs, which will eventually reduce the number of treatments required. In the past, after a successful multidose campaign, we often neglected or even forgot about the disease until it resurged and again became a public health problem[23].

In terms of adverse reactions of treatment, there are a few reports that compare single-dose with multidose treatments. In Papua New Guinea, where the intensity of *W. bancrofti* parasitemia was very high, no significant side effects were observed after a single dose of DEC at 6 mg kg^{-1}, whereas marked reactions (such as lasting fever, and swelling and pain of the extremities and scrotal contents) were noticed in 30% of subjects treated with a total of 72 mg kg^{-1} given during a 12-day course[14]. In India, with *B. malayi* infection, the single-dose treatment reported fewer adverse reactions compared with the five-day therapy[5]. Using a single dose, we may expect reactions that are less adverse in frequency and intensity.

Some people may be concerned with the possibility that the single-dose treatment produces low density Mf carriers who are undetectable by the conventional thick-smear method but are efficient in infecting vector mosquitoes. Our study in Samoa showed that the number of low-density carriers did not increase significantly and that they were not important as a source of infection[24], in spite of the fact that the vector, *Aedes polynesiensis*, concentrates Mf up to 4.7 times while feeding[25]. Similar studies with different combinations of vector mosquitoes and filarial parasites would be useful.

DEC single dose versus other chemotherapy

DEC-medicated common salt has been successfully tested in China, India, Brazil and Tanzania (TDR/FIL/PEN/92.3). The method was reported to be very effective parasitologically and clinically with no adverse reactions[26,27], and actually played a major role in large-scale control campaigns in China[28]. However, the preparation of medicated salt, its storage in a hot and humid climate, control of commercially available salt, and distribution and monitoring the consumption, will all pose considerable logistic difficulties in many endemic areas. The total DEC dosage taken as medicated salt was high in most cases. For example, in Fujian Province, 6–10.5 g of DEC per person was given over a period of 2–4 months[29]. This is equivalent to about 15–26 rounds of the single dose at 6 mg kg^{-1}.

A single-dose treatment with ivermectin has been tested on *W. bancrofti*[30,31] and *B. malayi*[32,33]. The antifilarial activity was shown to be strong and long-lasting[34]. However, at the moment, DEC has advantages of established safety, much lower cost and stronger macrofilaricidal effects over ivermectin[14,17,20]. Combined use of DEC and ivermectin is a recent development which is very promising[35,36].

Questions that remain

(1) *Is there any possibility of developing drug resistance?* Treatment failure with DEC (probably related to host variation in drug metabolism and immunological responses) is not uncommon, but there is no evidence of resistance in filarial parasites to the drug *per se*, and the chance of acquiring the resistance is said to be very low[37]. A trial to select DEC-resistant *B. pahangi* in Mongolian gerbils through repeated exposure to the drug over 15 generations in 11 years was not successful (Y. Aoki, pers. commun.). However, in conducting low-dose mass treatments, we must be vigilant in detecting any evidence of drug resistance.

(2) *What is the efficacy of biennial treatment with DEC?* In Samoa, only three mass treatments in a period of eight years reduced the Mf prevalence from 5.6% to 2.5% (Ref. 22) and, in French Polynesia, an average of 2.8 doses spread over four years was similarly effective[38]. A single dose was effective for at least 18 months[14]. These data indicate that biennial single-dose treatments may work in the control of filariasis. If so, the treatment scheme can be employed to cover a large area or in areas with limited health resources.

(3) *How susceptible are filarial parasites to DEC in different endemic areas?* Most of the large-scale studies on the single-dose scheme were with diurnally subperiodic *W. bancrofti* in the Pacific. Such studies with periodic type and with *Brugia* spp are necessary under local vector–parasite–human combinations. Also, a single-dose scheme has not been evaluated critically in a highly endemic area with Mf prevalence over 30–40%.

From research to control

Lymphatic filariasis, producing permanent, long-term disability in an estimated 43 million people, is ranked by WHO as the No. 2 cause of disability in the world behind mood (affective) disorders[39]. The disability could be prevented only if treatment is given at early stage of infection, and it has now been recognized that filariasis itself can be controlled or even eradicated by applying existing technology and health services system. Based on an extensive review of recent studies, three basic tactics have been proposed[40]:

They are: (1) annual (or semi-annual) single-dose mass treatment with DEC at 6 mg kg^{-1}; (2) DEC-fortified salt at 0.2–0.4%; and (3) the use of ivermectin at 400 μg kg^{-1} for or with DEC. Having a choice of effective treatment schemes which can be easily integrated into primary health care activities, it is now the time to start a worldwide fight to eliminate the misery of filarial disease.

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Corrigendum

In a recent Letter, 'Low malaria mortality among children and high rates of *Plasmodium falciparum* inoculation: a Congolese reality in the 1980s', by Bernard Carme (*Parasitology Today* 12, 206–208, 1996), the sentence, p. 207, col. 1, para. 2, should read: 'In a rural area of the Mayombe (Southern Congo) that also has a high annual inoculate, a longitudinal survey carried out in 1984–1985 found very weak incidence of severe malaria attack, although acute malaria was the third most common reason for seeking medical care for children under two years old'.