# Efficacy of five annual single doses of diethylcarbamazine for treatment of lymphatic filariasis in Fiji

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*Annual single-dose treatments with diethylcarbamazine citrate (DEC) at a dose of 6 mg/kg have been reported effective in reducing microfilariae (mf) rate and density and applicable to large-scale filariasis control campaigns. However, the efficacy of such treatments has not been studied quantitatively in relation to different pretreatment levels of endemicity. This study of 32 villages in Fiji revealed that five treatments repeated annually steadily reduced village mf rate, and that the degree of reduction was not influenced by pretreatment levels of mf density or rate. This indicates that an annual dosage scheme is applicable to high-endemicity areas. The results also suggest that such treatment affected juvenile forms of* Wuchereria bancrofti *and may prevent them from reproducing.*

## Introduction

Diethylcarbamazine citrate (DEC) has been widely used for the treatment of lymphatic filariasis since its filaricidal effect was first reported (*1*). A series of trials designed to find the most suitable treatment regimen in endemic areas showed that a 12-dose course of treatment (12 × 6 mg/kg body weight) was necessary to treat infection with *Wuchereria bancrofti* (*2*, *3*). This scheme has been employed worldwide with success, but repeating 12 doses can pose considerable operational difficulties. However, a satisfactorily strong effect from a single 6 mg/kg dose was reported in French Polynesia (*4*) and Samoa (*5*). In Samoa, when assessed 12 months after treatment, the single dose reduced the mf rate by 54% and mf density by 94%. A study in Fiji (*6*) revealed that five rounds of annual treatment with 6 mg/kg were as effective as a 28-dose course of treatment delivered over 2 years (total dose, 140 mg/kg) when assessed 5 years after commencement of treatment. A single-dose scheme was shown to be effective against *Brugia malayi* as well (*7*, *8*).

A single dose of DEC (6 mg/kg) has been reported to reduce mf counts by 85–95% in a cohort of mf-positive individuals (*5*, *9*, *10*). This implies that high-count carriers will remain mf positive after treatment, and therefore that a single treatment will not effectively reduce the mf rate in a community with many high-count carriers. It has been reported that the recurrence rate of microfilaraemia within a year of DEC treatment was higher where pretreatment mf density had been higher (*11*). A possible explanation is that juvenile parasites present during treatment were not affected and later began reproduction. It is possible that a high mf density facilitated filarial transmission by vector mosquitos and resulted in the accumulation of juvenile forms (3rd and 4th larval stages and young adults) in the human population. However, no study has compared the efficacy of annual single-dose treatment in areas with different endemicity. This article reports the influence of pretreatment levels of mf density and rate on reduction in mf rate after annual single-dose treatment.

## Materials and methods

### *Sample villages, blood examinations, and treatments*

The study was carried out on Kadavu Island, Fiji, and included 43 villages with a total population of 7600. Of these, 5799 (76.3%) persons were registered in the 1985 pretreatment survey. Eleven villages were excluded from the study because less than 30 persons were examined in each of them as a result of small size and/or poor compliance. All of those registered in 1985 (4686 people in 32 villages) were examined for mf using a 60-μl finger-prick (thick smear method). Single-dose mass treatment with DEC

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(6 mg/kg) was given in early 1986. Annual blood examinations and subsequent mass treatments were then performed in 1987, 1988, 1989, and 1990, with the final blood survey taking place in 1990–91. Villages were informed about a week before the arrival of the filariasis team. Residents gathered in the village community hall where names were called by household. Any new arrivals were included for treatment. Blood was collected and clinical examinations conducted where necessary. All slides were brought to the Filariasis Office in Suva for processing, microscopic examination, and recording. Only the results of those registered in 1985 were enumerated. Details of the villages, mass treatments, and blood examinations have been described (*6*). The village mf rates before and after treatment, and the pretreatment mf density (geometric mean of mf counts per 60 µl of blood) are shown in Table 1, together with data on the numbers of people examined and those found positive for mf.

### *Statistical analysis*

In order to study the influence of pretreatment endemicity, the villages were grouped into five categories based on pretreatment mf density: cat1 (mf density $< 10$, average mf density = 5.6, 10 villages); cat2 ($10 \leq$ mf density $< 15$, average mf density = 11.6, 8 villages); cat3 ($15 \leq$ mf density $< 20$, average mf density = 17.5, 6 villages); cat4 ($20 \leq$ mf density $< 30$, average mf density = 24.2, 3 villages); and cat5 (mf density $\geq 30$, average mf density = 48.4, 5 villages). A total of 192 observations of mf rate were obtained from the 32 villages during the six blood examinations. Under the assumption that treatment would reduce mf rate at a certain rate, all mf rates

Table 1: **Microfilariae (mf) rate before (1985) and after five annual treatments (1987–91) with diethylcarbamazine citrate**

| Village | mf density[a] 1985 | mf rate as % (No. mf positive/No. examined) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1985 | 1987 | 1988 | 1989 | 1990 | 1990–91 |
| Muani | 1.0 | 0.4 (1/238) | 0.0 (0/174) | 0.0 (0/168) | 0.0 (0/147) | 1.4 (1/72) | 0.0 (0/136) |
| Wailevu | 3.0 | 1.0 (1/101) | 1.4 (1/71) | 0.0 (0/67) | 0.0 (0/61) | 0.0 (0/60) | 0.0 (0/59) |
| Naqalotu | 5.6 | 7.3 (9/123) | 1.1 (1/88) | 1.1 (1/92) | 0.0 (0/84) | 0.0 (0/75) | 0.0 (0/74) |
| Namara | 6.8 | 2.6 (6/228) | 1.7 (3/172) | 0.0 (0/142) | 0.6 (1/161) | 0.0 (0/144) | 0.0 (0/143) |
| Tawava | 7.1 | 0.7 (1/145) | 0.0 (0/89) | 0.0 (0/101) | 0.0 (0/106) | 0.0 (0/86) | 0.0 (0/99) |
| Lomati | 7.9 | 1.3 (2/156) | 0.0 (0/112) | 0.0 (0/107) | 0.0 (0/98) | 0.0 (0/107) | 0.0 (0/110) |
| Dagai | 8.9 | 0.6 (1/159) | 0.0 (0/112) | 0.0 (0/98) | 1.1 (1/94) | 0.0 (0/100) | 0.0 (0/101) |
| Cevai | 9.3 | 9.0 (6/67) | 2.2 (1/46) | 0.0 (0/49) | 0.0 (0/46) | 0.0 (0/61) | 2.0 (1/51) |
| Ravitaki | 9.6 | 5.8 (18/309) | 3.3 (7/210) | 2.4 (4/170) | 1.0 (2/197) | 0.0 (0/166) | 0.0 (0/193) |
| Qalira | 9.8 | 4.5 (5/112) | 0.0 (0/65) | 0.0 (0/76) | 0.0 (0/79) | 0.0 (0/67) | 0.0 (0/74) |
| Drue | 10.2 | 1.6 (2/102) | 0.0 (0/71) | 0.0 (0/66) | 0.0 (0/70) | 0.0 (0/71) | 0.0 (0/57) |
| Namuana | 10.2 | 10.9 (15/137) | 7.9 (7/89) | 1.4 (1/71) | 2.4 (2/83) | 2.3 (2/88) | 1.6 (1/63) |
| Talaulia | 10.7 | 2.0 (2/102) | 0.0 (0/78) | 0.0 (0/55) | 0.0 (0/71) | 0.0 (0/60) | 0.0 (0/59) |
| Daviqele | 11.2 | 5.1 (11/217) | 2.0 (3/150) | 0.0 (0/133) | 0.0 (0/145) | 0.0 (0/131) | 0.0 (0/102) |
| Namalata | 11.2 | 10.1 (28/276) | 1.8 (3/163) | 5.0 (7/140) | 1.3 (2/157) | 0.0 (0/154) | 0.0 (0/92) |
| Galoa | 13.2 | 8.9 (15/168) | 1.7 (2/119) | 1.0 (1/103) | 1.0 (1/102) | 1.1 (1/93) | 0.0 (0/89) |
| Kabariki | 13.5 | 3.4 (5/146) | 0.0 (0/93) | 0.0 (0/103) | 0.0 (0/100) | 1.0 (1/100) | 0.0 (0/92) |
| Solovola | 13.8 | 11.0 (10/91) | 3.0 (2/67) | 4.3 (2/46) | 3.3 (2/60) | 1.6 (1/64) | 0.0 (0/64) |
| Nabukelevu-i-ra | 15.9 | 0.4 (1/274) | 0.0 (0/199) | 0.0 (0/164) | 0.0 (0/156) | 0.0 (0/158) | 0.0 (0/153) |
| Mokoisa | 17.0 | 0.7 (1/149) | 0.0 (0/110) | 0.0 (0/97) | 0.0 (0/99) | 0.0 (0/99) | 0.0 (0/71) |
| Solodamu | 17.4 | 12.1 (11/91) | 15.7 (8/51) | 2.4 (1/41) | 4.8 (3/63) | 2.9 (2/68) | 1.7 (1/60) |
| Levuka | 17.8 | 7.9 (12/151) | 2.4 (3/124) | 1.0 (1/98) | 0.0 (0/110) | 0.0 (0/89) | 0.0 (0/75) |
| Tavuki | 18.6 | 12.6 (18/143) | 8.0 (7/87) | 8.0 (4/50) | 1.4 (1/69) | 0.0 (0/77) | 0.0 (0/58) |
| Nasegai | 19.1 | 3.7 (8/216) | 3.0 (5/164) | 0.8 (1/131) | 0.7 (1/140) | 1.6 (2/129) | 0.0 (0/102) |
| Nalotu | 22.4 | 17.3 (28/162) | 8.5 (11/129) | 4.0 (4/100) | 2.9 (3/104) | 2.0 (2/101) | 3.4 (3/87) |
| Baidamudamu | 25.7 | 13.4 (11/82) | 19.4 (7/36) | 5.4 (2/37) | 11.4 (5/44) | 3.8 (2/53) | 0.0 (0/41) |
| Yakita | 26.9 | 15.8 (12/76) | 11.5 (7/61) | 3.9 (2/51) | 4.2 (2/48) | 0.0 (0/51) | 0.0 (0/45) |
| Korovou | 33.9 | 9.3 (4/43) | 12.1 (4/33) | 9.1 (3/33) | 16.1 (5/31) | 12.9 (4/31) | 6.5 (2/31) |
| Matanuku | 35.5 | 8.5 (7/82) | 5.9 (4/68) | 5.9 (3/51) | 4.5 (2/44) | 3.1 (2/65) | 3.5 (2/57) |
| Muaninuku | 38.9 | 28.0 (30/107) | 19.5 (16/82) | 15.7 (11/70) | 8.3 (6/72) | 6.8 (5/74) | 7.1 (4/56) |
| Nukunuku | 61.7 | 28.8 (19/66) | 23.7 (9/38) | 19.4 (6/31) | 13.2 (5/38) | 12.2 (6/49) | 4.7 (2/43) |
| Nasau | 67.6 | 16.8 (24/143) | 19.8 (21/106) | 12.8 (10/78) | 4.5 (4/88) | 8.0 (7/87) | 2.7 (2/74) |
| Total | | 6.9 (324/4686) | 4.1 (132/3257) | 2.3 (64/2819) | 1.6 (48/2967) | 1.3 (38/2830) | 0.7 (18/2611) |

[a] Geometric mean of mf counts per 60 µl of blood.

were reported as ln (100 × (No. positive + 0.5)/No. examined). Rates were grouped by category and year, and the averages are plotted in Fig. 1. The General Linear Models procedure (SAS/STAT, SAS Institute Cary, North Carolina, USA) was used to determine whether there was any difference in the change of mf rate across categories. Type II sum of squares was used as a control hypothesis test. "Year" was treated as a continuous variable.

There was a clear positive relationship between pretreatment mf densities and mf rates ($r = 0.747$, $P < 0.001$) in the 32 villages. The same analytical procedure was therefore applied to groups based on the pretreatment mf rate: cat1 (mf rate < 1%, average mf rate = 0.6%, 6 villages), cat2 (1% ≤ mf rate < 5%, average mf rate = 2.8%, 7 villages), cat3 (5% ≤ mf rate < 10%, average mf rate = 7.1%, 8 villages), cat4 (10% ≤ mf rate < 15%, average mf rate = 11.3%, 6 villages), and cat5 (mf rate ≥ 15%, average mf rate = 20.4%, 5 villages).

All statistical tests were considered significant at $P < 0.05$.

## Results and discussion

The analysis of covariance of log-transformed mf rates across the five groups defined by pretreatment mf density showed statistically significant differences between categories ($P < 0.001$). When the average mf rates of the five categories were compared using Scheffe's multiple comparison test, cat4 and cat5 each had a significantly higher rate than cat1, cat2, and cat3 ($P < 0.05$). Among the five regression lines obtained, there was no significant interaction between category and year ($P > 0.392$), which implies that the degree of reduction in mf rate was not different across all categories.

The analysis of covariance of transformed mf rates across the five groups defined by pretreatment mf rate (Fig. 2), showed a statistically significant difference between categories ($P < 0.001$). However, there was interaction between category and year among the five regression lines ($P < 0.002$). Further study showed that the regression line of cat1 was not significant ($P > 0.227$). After exclusion of cat1, the four remaining regression lines were without interaction ($P > 0.273$), indicating that the pretreatment mf rate did not influence the rate of reduction in cat2–cat5. The reason why treatment failed to reduce mf rate significantly in cat1 may reflect sampling problems rather than absence of drug effect.

Thus, annual treatments can reduce village mf rate steadily, and pretreatment mf density or rate do not influence the degree of reduction. This would imply that annual single-dose treatment (6mg/kg

Fig. 1. **Change in microfilariae (mf) rate before (year 0) and after (years 2–6) annual treatment in five endemicity categories defined by pretreatment mf density.** Cat1 (+): mf density < 10; cat2 (○): 10 ≤ mf density < 15; cat3 (■): 15 ≤ mf density < 20; cat4 (▽): 20 ≤ mf density < 30; cat5 (□): mf density ≥ 30.

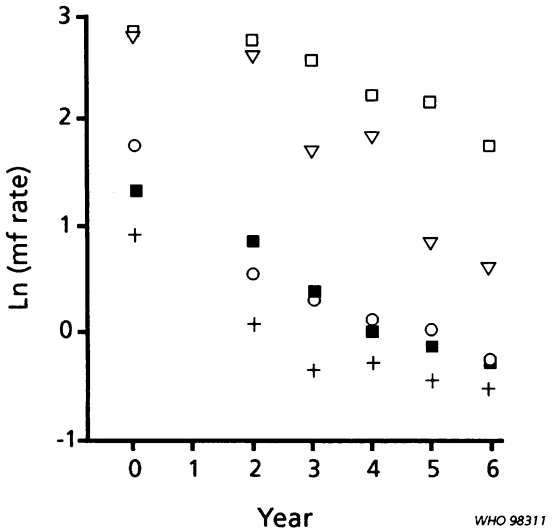
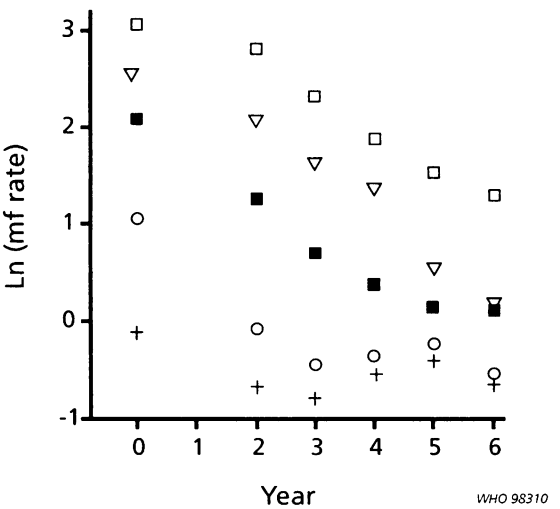



Fig. 2. **Change in microfilariae (mf) rate before (year 0) and after (years 2–6) annual treatment in five endemicity categories defined by pretreatment mf rate.** Cat1 (+): mf rate < 1; cat2 (○): 1 ≤ mf rate < 5; cat3 (■): 5 ≤ mf rate < 10; cat4 (▽): 10 ≤ mf rate < 15; cat5 (□): mf rate ≥ 15.



DEC) can be applied in highly endemic areas without loss of efficacy. These results imply that the drug may also prevent juvenile forms (3rd and 4th larval stages and young adults) from reproducing. The antilarval effect of DEC has been demonstrated in animal models (*12*, *13*). Although reinfection after treatment would counter the DEC effect, since very few mf positives were found among individuals under 1 year of age, reinfection apparently did not influence mf rate within a year.

Annual single-dose treatment with DEC is simple and economical. Since DEC has been proven safe, local people may be more ready to assist in a treatment campaign. In Samoa, a nationwide filariasis control programme covering 160000 people was successfully conducted with the participation of village women's committees (*14*). By employing the annual single-dose scheme, a filariasis control programme can economize on the resources required for multidose treatments and put more emphasis on vector control, sanitation programmes and health education. The present results were obtained in an area where diurnally subperiodic bancroftian filariasis is endemic. To judge from the single-dose effects of DEC reported in various other areas of the world (*7–10*, *15*), similar results would be expected with *B. malayi* and periodic *W. bancrofti*.

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## Résumé

### Efficacité de cinq doses uniques de diéthylcarbamazine par année pour le traitement de la filariose lymphatique à Fidji

Le traitement de la filariose lymphatique par l'administration d'une dose annuelle unique de 6 mg de diéthylcarbamazine (DEC) par kg de poids corporel est réputé réduire efficacement l'indice microfilarien (nombre de personnes infestées/nombre de personnes examinées) et la densité des microfilaires et être utilisable dans des campagnes de lutte de grande envergure. L'efficacité de cette thérapeutique n'a toutefois pas fait l'objet d'études quantitatives en fonction du niveau d'endémicité existant avant l'intervention. Il est particulièrement interessant de connaître l'efficacité du traitement monodose dans les zones de forte endémicité car il n'est pas exclu qu'il se révèle moins efficace dans ces conditions, étant donné que la DEC pourrait être inactive contre les formes juvéniles du parasite présentes au moment du traitement et leur laisser par conséquent la possibilité de se reproduire ultérieurement. Dans cet article, les auteurs étudient l'effet de la densité des microfilaires et de l'indice microfilarien avant intervention sur les résultats du traitement par cinq doses annuelles uniques de DEC.

En 1985, on a recherché la présence de microfilaires chez les habitants de 32 villages de l'île de Kudavu (Fidji) par prélèvement digital de 60 µl de sang (méthode de la goutte épaisse). Début 1986, on a procédé à un traitement de masse consistant dans l'administration d'une dose unique de 6 mg/kg de DEC. On a pratiqué ensuite des examens hématologiques annuels et procédé à d'autres traitements en 1987, 1988, 1989 et 1990, l'enquête hématologique finale ayant eu lieu en 1990–91. Pour étudier l'influence du degré d'endémicité avant traitement, on a réparti les 32 villages en cinq catégories de densité microfilarienne exprimée par la moyenne géométrique des numérations de microfilaires dans les échantillons de 60 µl de sang. Les résultats des mesures de l'idice microfilarien ont été exprimés sous forme logarithmique et répartis dans chaque catégorie selon les deux méthodes comme indiqué plus haut. On a étudié la modification de l'indice microfilarien dans chaque catégorie par une analyse de covariance.

L'étude fait ressortir une diminution constante de l'indice microfilarien dans les villages sous l'influence du traitement annuel, dans une proportion qui ne dépend pas de sa valeur antérieure ni de celle de la densité des microfilaires. Cela signifierait que le traitement annuel est applicable dans les zones de forte endémicité. On peut également en déduire que les formes juvéniles de *Wuchereria bancrofti* sont sensibles à la DEC et que le traitement les empêche de se reproduire.

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