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PNG Med J 37: 65–81, 1994

Diethylcarbamazine in the control of bancroftian filariasis in the Ok Tedi area of Papua New Guinea: Phase 2 — annual single-dose treatment

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SUMMARY

The Phase 1 semiannual single-dose 6mg/kg diethylcarbamazine (DEC) treatment program demonstrated a significant reduction for *Wuchereria bancrofti* in the Ok Tedi area of Western Province, Papua New Guinea. The rate of detectable microfilaraemia was effectively reduced from 39% to 11% and mean microfilarial (mf) densities from 79mf/20µl to 19mf/20µl. The Phase 2 annual single-dose treatment of 6mg/kg DEC not only maintained the gains made during Phase 1 but reduced the microfilaraemia rate to less than 5% by 1990, with mf densities remaining stable at less than 20mf/20µl, amongst all participating villagers screened within the 5 original villages. The annual treatment program was expanded into 7 remote villages not subject to any form of active vector control. The microfilaraemia rate in these villages declined from 41% before treatment to 17% after only two annual administrations of 6mg/kg DEC, and mf blood densities were reduced from 71mf/20µl to 20mf/20µl. As was observed in the 5 original villages participating in the program, a significant reduction in splenomegaly associated with the DEC treatment was reported for the 7 villages in the expanded program during Phase 2; enlarged spleen rates were reduced from 50% (1986) to 32% (1990) and from 76% (1988) to 48% (1990), respectively. Malaria rates on the other hand increased slightly or remained stable. Malaria infections associated with *W. bancrofti* (mixed parasite infections) stimulated a greater splenic response than either parasite detected on its own.

Introduction

Laigret (1) demonstrated the effectiveness of low-dose diethylcarbamazine (DEC) against *Wuchereria bancrofti* in well-spaced mass treatment programs on Tahiti, and Ottesen (2) produced clear evidence that DEC effectively kills lymphatic-dwelling adult worms. The macrofilaricidal effect of DEC was observed in 34% of 132 East Sepik villagers after treatment with 72mg/kg and was demonstrated by localized side-effects and long-term decreases in microfilarial (mf) counts 12 months after treatment (3). The successful annual single-dose 6mg/kg DEC treatment used by Laigret (1) was considered to be inadequate to reduce mf densities significantly in subjects with high pretreatment mf levels, i.e. mf counts over 100 per ml of blood (4).

The effects of a well-spaced DEC mass drug application in areas highly endemic for *W. bancrofti* in Papua New Guinea were not known. In 1986 a semiannual single-dose 6mg/kg body weight administration of DEC was initiated in the Ok Tedi area of Western Province, Papua New Guinea (5). The rate of bancroftian filariasis in the area was 39% before treatment. Within two years the rate of detectable microfilaraemia was reduced from 31% to 11% in the treated group. The mean blood density of the parasite was reduced from 79mf/20µl to 19mf/20µl. A survey of untreated villages in the outlying area showed a filariasis rate of 39%. A 14-fold difference in the total microfilaraemia count was noted between the two groups when the 1988 data were compared. Although the pretreatment mf densities of *W. bancrofti* were, according to Kimura et al. (4), considered to be high for adequate treatment with a single dose of 6mg/kg DEC, the results of the initial Ok Tedi study showed a marked improvement. The pretreatment mf densities in the two main

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ethnolinguistic groups treated (Wopkaimin and Ningerum) were 99mf/20µl and 78mf/20µl respectively (5).

It was suggested that a substantial number of the acute febrile episodes reported by aid post orderlies in the area were due to filariasis (6,7). Inguinal lymphadenopathy was found to be widespread throughout the population, presumably associated with leg sepsis, but in some cases it was almost certainly a consequence of filariasis. Despite the high rate of filariasis detected in the region, the clinical manifestation of chronic illness (elephantiasis) was low when compared to non-Ningerum-speaking villages along the Fly River south of Kiunga (6).

A significant observation made during the evaluation of Phase 1 (1986–1988) malario-filariometric data was that malaria parasite rates were similar in the DEC-treated and untreated groups (14–15%) but enlarged spleen rates were markedly different in those aged 2 years or more (47% and 76% respectively). It was postulated, and has since been demonstrated, that bancroftian filariasis is a significant contributing factor in splenomegaly amongst the highland fringe dwellers of the Ok Tedi area and that DEC was valuable in the control of spleen enlargement (8).

The above observation is of particular importance in areas of economic development where filariasis rates may be high. Kimura et al. (9) found 15% of Samoans with microfilaraemia presenting with some form of clinical manifestation, the most common being attacks of filarial fever lasting 3.5 days on average resulting in a loss of 27.1 working days per person per year.

The DEC treatment program was well accepted despite side-effects encountered in 20% of the treated population early on in the program (5). The success of the two-year Phase 1 program was expanded into an annual single-dose administration of DEC over a larger area in 1988. We now discuss the data for the Phase 2 – Modified Treatment Program implemented at Ok Tedi during 1988–1989 with a single-dose treatment of 6mg/kg DEC administered annually in areas hyperendemic for *W. bancrofti*.

Materials and Methods

Organization

The 5 villages originally participating in the Phase 1 semiannual treatment program (Finalbin, Bultem [Woktemunin], Wangbin, Migalsim and Ok Ma [Asikomban with its transit hamlets]) commenced annual treatment with 6mg/kg DEC in November 1988, after having received 4 semiannual treatments during 1986–1987 (5). These villages will be referred to as the 5 original villages in this paper. The 7 untreated villages surveyed as a comparison in 1988 became known as the 7 expanded program villages: they were Atemkit and Kavorabip [Wopkai speakers]; Korkit (Kwirok), Derongo (Kwari), Kumkit and Haidawogam [Ningerum speakers]; and Sissimakum [Awin speakers]. Kwiroknai village [Ningerum/Awin speakers] plus untreated individuals and hamlets within the 40km radius project area were used as controls for comparison in 1990. All villages are classed as highlands fringe (300–1400 metres above sea level) with the North Ningerum and North Awin occupying the 300–600m zone and the Wopkaimin/Kamfaiwolmin the 600–1400m zone.

The 5 original villages have been subject to a number of vector control measures since 1982 (10,11). Haidawogam and Sissimakum were sprayed once or twice before 1988 with residual DDT by provincial government malaria control workers based at Kiunga before government spraying operations were completely withdrawn in the region. The remaining 5 of the 7 expanded program villages are accessible only by foot or helicopter, and were not subject to active vector control measures. The reasons for expanding the DEC treatment program to villages without active vector control was to test the efficacy of a single dose of 6mg/kg DEC against a high rate of filariasis (41%) and blood microfilarial density (71mf/20µl), and to reconfirm the effect of DEC on high rates of splenomegaly (76%).

The improvements observed during Phase 1 were demonstrated through health education meetings in the 5 original villages and the next stage of the program, Phase 2, was discussed. Similar meetings were held in the 7 expanded program villages. A half-hour

Methods

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information video on public health projects within the immediate local area was prepared in late 1989 and presented with other health videos before and during the late-night blood collections in early 1990.

Annual treatments with a 6mg/kg single-dose DEC regimen for the Phase 2 – Modified Treatment Program commenced in November 1988. Treatment was administered at 2000 hours, after villagers had eaten sufficient to tolerate drug ingestion and assure maximum efficiency of the drug on active circulating parasites. Individuals under 10kg body weight, pregnant females and the ill were excluded. Villagers were monitored for 12–24 hours after treatment.

Filario-malariometric surveys

Night blood films, collected after 2200 hours, were made with a standard 40µl volume of finger-prick blood using a 20µl micropipette for the enumeration of detectable parasites. The thick smears were stained after 24 hours with 5% buffered Giemsa for 45 minutes. The entire blood film was examined under 100× magnification for microfilariae and enumerated. 100 high-power fields (×1000 magnification) were correspondingly examined for malaria parasites (12). Positive bloods films and counts were confirmed by a second technician and all negative smears reexamined. Night blood film collections were generally restricted to the age group 10 years and older, younger children being somewhat troublesome when wakened at a late hour.

Spleens were palpated by the same examiner using the Hackett grading system (13). Splenic enlargement was assessed with the patient supine.

Results

Effect of annual DEC treatment in villages previously treated semiannually before 1988

The marked improvement in the control of bancroftian filariasis with semiannual administration of 6mg/kg DEC was maintained with annual single-dose administrations during 1988 and 1989. The 1990 results in Table 1 clearly show that a 6mg/kg single dose was adequate to provide suppressive activity against *W. bancrofti* and to maintain the gains made during the 1986–1987 semiannual DEC campaign. The overall filariasis rate in the 5 original villages, for villagers indigenous to those villages, was reduced to 4.5% with an increase in the rate of malaria to 7.8% (Table 1A). The results for everyone tested in each village (including treated in-migrants or visitors from neighbouring kinship clans) were not significantly different, with rates of 4.4% and 5.9% respectively for microfilaria and malaria (Table 1B). The mean density of microfilaraemia amongst indigenous villagers remained consistent between the 1988 and 1990 surveys (16mf/20µl and 18mf/20µl respectively). The suppressive activity of diethylcarbamazine on bancroftian filariasis in the Ok Tedi area is presented graphically for each of the 5 original villages in Figure 1A,B.

The compliance rate for treatment continued to improve during Phase 2, which confirmed the continued acceptance of the program despite a few exaggerated rumours about the initial side-effects experienced by villagers with high microfilarial densities. The mean number of individuals treated per annual drug cycle was 835 with a mean body weight of 47.7kg and a mean dose of 279mg DEC dispensed.

4353 people were treated in the 5 original villages taking part in the DEC treatment program between 1986 and 1989, a mean of 726 people per treatment. To demonstrate the continuing response from local villagers 1196 presented for treatment in 1990, 1125 in 1991 and 1073 in 1992.

The question which now needs addressing is whether annual single-dose administration of DEC would be effective against hyperendemic *Wuchereria bancrofti* without prior semiannual treatment.

Single-dose DEC administered annually against previously unchallenged *Wuchereria bancrofti*

The 7 untreated villages referred to as the 7 expanded program villages (Atemkit, Kavorabip, Haidawogam, Sissimakum, Korkit, Derongo and Kumkit) demonstrated a marginally higher pretreatment microfilaraemia rate (41%) than the 5 original villages

TABLE 1

NIGHT BLOOD FILM SURVEY DATA ON FILARIASIS AND MALARIA IN DIETHYLCARBAMAZINE-TREATED VILLAGES IN THE OK TEDI AREA, 1986–1990

5 Original Villages

A. Indigenous villagers only

	1986 Pre-treatment	1988 Post-treatment[1]	1990 Post-treatment[2]
Total examined	242	211	268
Microfilaraemia positive	78 (32.2%)	27 (12.8%)	12 (4.5%)
Microfilariae/20µl	80	16	18
Total mf count for all 40µl smears	12464	888	427
Malaria positive	11 (4.5%)	5 (2.4%)	21 (7.8%)
With splenomegaly	122 (50.4%)	114 (54.0%)	92 (34.3%)

B. Indigenous villagers and others

	1986 Pre-treatment	1988 Post-treatment[1,3]	1990 Post-treatment[2,3]
Total examined	261	302	410
Microfilaraemia positive	80 (30.7%)	35 (11.6%)	18 (4.4%)
Microfilariae/20µl	78	16	20
Total mf count for all 40µl smears	12539	1154	727
Malaria positive	11 (4.2%)	12 (4.0%)	24 (5.9%)
With splenomegaly	131 (50.2%)	171 (56.6%)	131 (32.0%)

1 Blood smears collected 6–7 months after 4 semiannual village treatments

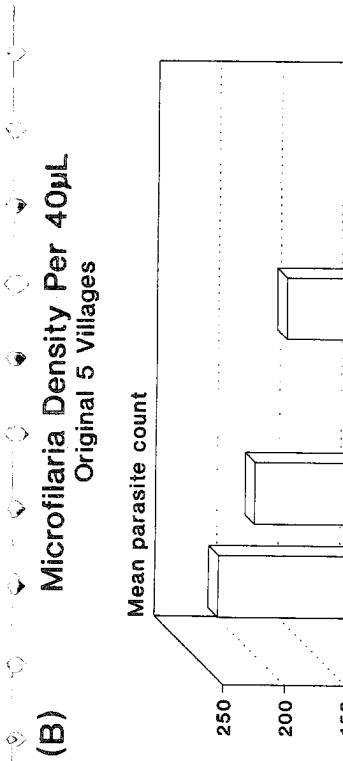
2 Blood smears collected 6–7 months after a further 2 annual village treatments

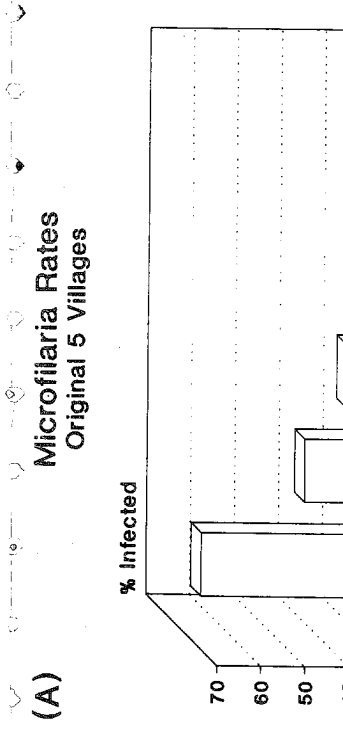
3 Anyone presenting from within the region

(31%), similar mean parasite densities per 20µl and higher malaria rates (Tables 1B and 2B). This provided an ideal situation to test the annual administration of DEC in a parasite population not previously challenged with DEC.

The result, after only two annual treatments with 6mg/kg DEC, was a reduction in the rate of detectable microfilaraemia (from 41% to 17%) and a reduction in blood densities of the parasite from 71mf/20µl to 20mf/20µl in treated individuals (Table 2). Figure 2A,B shows the rates of decline for each village. The rate of splenomegaly declined from 76% to 48% but no significant difference was observed in malaria rates between the two surveys.

Kavorabip is at 1350 metres above sea level and bancroftian filariasis could effectively be eliminated in this group because of the protracted incubation period in mosquitoes at





HYLCARBAMAZINE-

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(4.5%)
18

427
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92
(34.3%)

0 Post-treatment[2,3]

410
18
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Figure 1. Filario-malariometric data before and after treatment for villagers indigenous to the 5 original villages involved in the DEC treatment program.
Villagers from other villages are referred to as Others.

TABLE 2

NIGHT BLOOD FILM SURVEY DATA ON FILARIASIS AND MALARIA IN DIETHYLCARBAMAZINE-TREATED VILLAGES IN THE OK TEDI AREA, 1988–1990

7 Expanded Program Villages

A. Indigenous villagers only

	1988 Pre-treatment	1990 Post-treatment[1]
Total examined	323	317
Microfilaraemia positive	131 (40.6%)	57 (18.0%)
Microfilariae/20µl	70	20
Total mf count for all 40µl smears	18347	2329
Malaria positive	33 (10.2%)	32 (10.1%)
With splenomegaly	250 (77.4%)	157 (49.5%)

B. Indigenous villagers and others

	1988 Pre-treatment	1990 Post-treatment[2]
Total examined	331	337
Microfilaraemia positive	134 (40.5%)	58 (17.2%)
Microfilariae/20µl	71	20
Total mf count for all 40µl smears	18968	2333
Malaria positive	33 (10.0%)	32 (9.5%)
With splenomegaly	253 (76.4%)	163 (48.4%)

[1] Blood smears collected 6–7 months after 2 annual village treatments

[2] Blood smears collected 6–7 months after 2 annual village treatments, from anyone presenting

these altitudes, and the initially low blood parasite densities despite a high pretreatment microfilaraemia rate. It is most likely that infections within this population were contracted at lower altitudes. We were surprised at the higher than expected posttreatment rate for Korkit villagers, despite a reduction in blood densities. We have two possible explanations for this.

1. The people at Korkit reside in the 1000 metre zone but spend much of their time in sago gardens at lower altitudes and in smaller hamlets away from the main village which was used as the treatment centre. With such a rotating population and lifestyle (about half the people in the village being away at any given time) we may have treated each person only once over a 2-year period.

2. Another plausible answer is that Korkit villagers are host to a greater number of productive female filarial worms. Their sago-harvesting life-

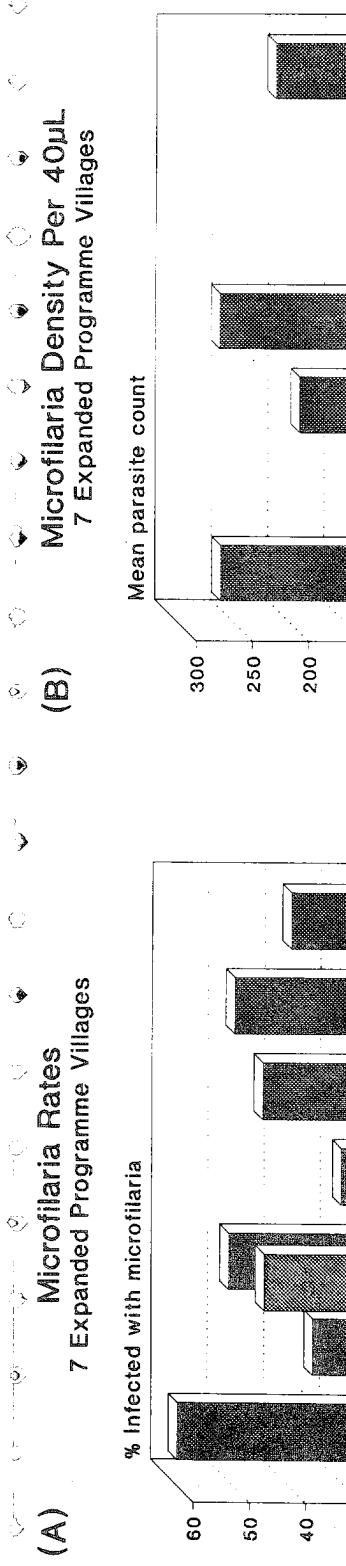

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Figure 2. Filario-malariometric data for each of the 7 expanded program villages before and after treatment with two annual single-dose administrations of DEC.

style makes them a target for the repeated bites of infected mosquitoes while in their gardens. This will lead to a slower decline in microfilaraemia as more DEC-tolerant female worms overcome the temporary sterilizing effect or toxicity of DEC.

Despite the higher than expected mf rate at Korkit, diethylcarbamazine demonstrated a dramatic impact on the parasite by reducing the mean blood parasite density, mf rate and splenomegaly in the treated population after only two annual single-dose administrations of 6mg/kg DEC.

837 individuals were treated in the 7 expanded program villages, a mean of 419 villagers per year. The mean weight of the people in the outlying villages was slightly lower, 43kg, with a mean DEC treatment dose of 252mg. The people in the outlying villages also responded well to an extension of the DEC program (Phase 3 – Maintenance Phase) with 614 presenting for treatment in 1990 and 639 in 1991. The lower number of 556 for 1992 might be explained by people being attracted to road settlements and villages closer to Tabubil.

In all, 5595 single-dose DEC treatments were administered within the 12 participating villages over the 4-year Phase 1 and 2 DEC treatment program.

The effect of bancroftian filariasis on splenomegaly

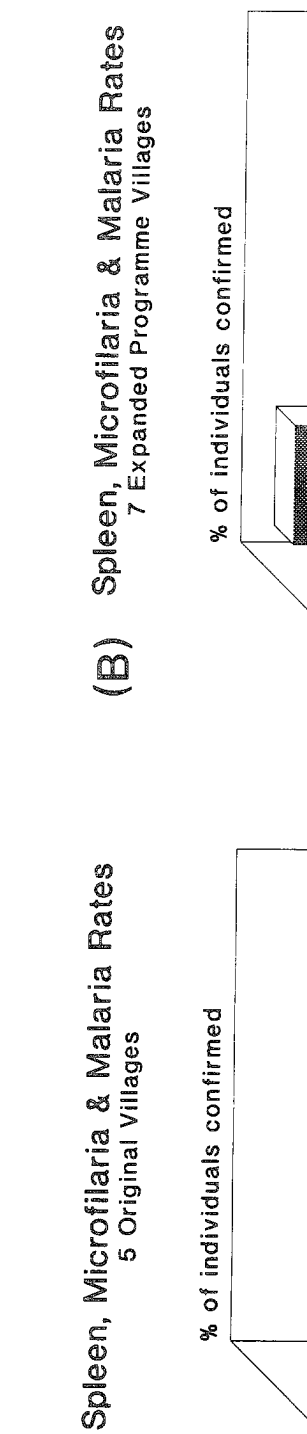
Taukuro et al. (14) noted a puzzling higher enlarged spleen rate (51%) amongst 104 villagers aged 10 years or older from the Atemkit area of the Star Mountains, Papua New Guinea despite a low rate of malaria parasitaemia (13%). Children under 10 years of age on the other hand demonstrated a higher malaria parasite rate (56%) and a somewhat lower enlarged spleen rate (44%). A decade later the situation was unchanged at Atemkit in the over 10 years age group with an enlarged spleen rate of 93% (39/42), a persistent average enlarged spleen (AES) size of 2.1, and a 12% malaria parasite rate (5). Microfilariae were detected in 29% of the above individuals, and they had the highest mean blood density recorded for the area, 138mf/20µl.

Of significant interest during the 1988 malario-filariometric surveys of the Ok Tedi coverage area (3000km^2) were identical low malaria parasite rates (14%) in DEC-treated and untreated populations but dissimilar spleen rates (47% and 76% respectively) (8,15). The puzzling high enlarged spleen rates associated with low malaria parasitaemia in older individuals was observed as recently as 1990 in 27 untreated Kawentinkin villagers at Atemkit. These villagers demonstrated rates similar to those reported in 1978 (14) for the same general area: 56% splenomegaly, 15% malaria and 82% microfilaraemia, as compared to rates of 47% (35/75) splenomegaly, 7% (5/75) malaria and 19% (14/75) microfilaraemia in villagers treated with diethylcarbamazine annually since 1988 in the same community.

Figures 1C and 3A do not indicate that enlarged spleen rates had decreased by 1988 in the 5 original DEC-treated villages though the data for Ok Ma show a slight decrease. The Ningerum speakers demonstrated a much higher rate of filariasis before treatment in 1986 (45%) than the Wopkaimin (19%) (5). The Wopkaimin villages nearest Tabubil (Bultem, Finalbin and Migalsim) suffered a series of malaria outbreaks in late 1986 to early 1987 as a result of nonimmune migrants and job-seekers flooding the villages during renewed construction activity of the Ok Tedi copper mine (16). Increased splenomegaly due to malaria persisted throughout 1987 and into 1988, which explains the elevated rate of splenomegaly in the four Wopkaimin and Kamfaiwolmin villages during the 1988 malario-filariometric surveys (Figure 1C).

In 1986 *Plasmodium falciparum* was responsible for 42% of all single parasite species infections detected. One would obviously assume a relationship between lower malaria rates and reduced splenic enlargement, but malaria rates were up in 1990 and enlarged spleen rates and microfilaraemia rates continued to decline (Figures 1D and 3A).

Figure 2C shows a consistent decline in enlarged spleen rates after two annual single-dose drug administrations of 6mg/kg DEC in each of the 7 expanded program villages. The effect of DEC on microfilaraemia rates and density for these villages is presented in



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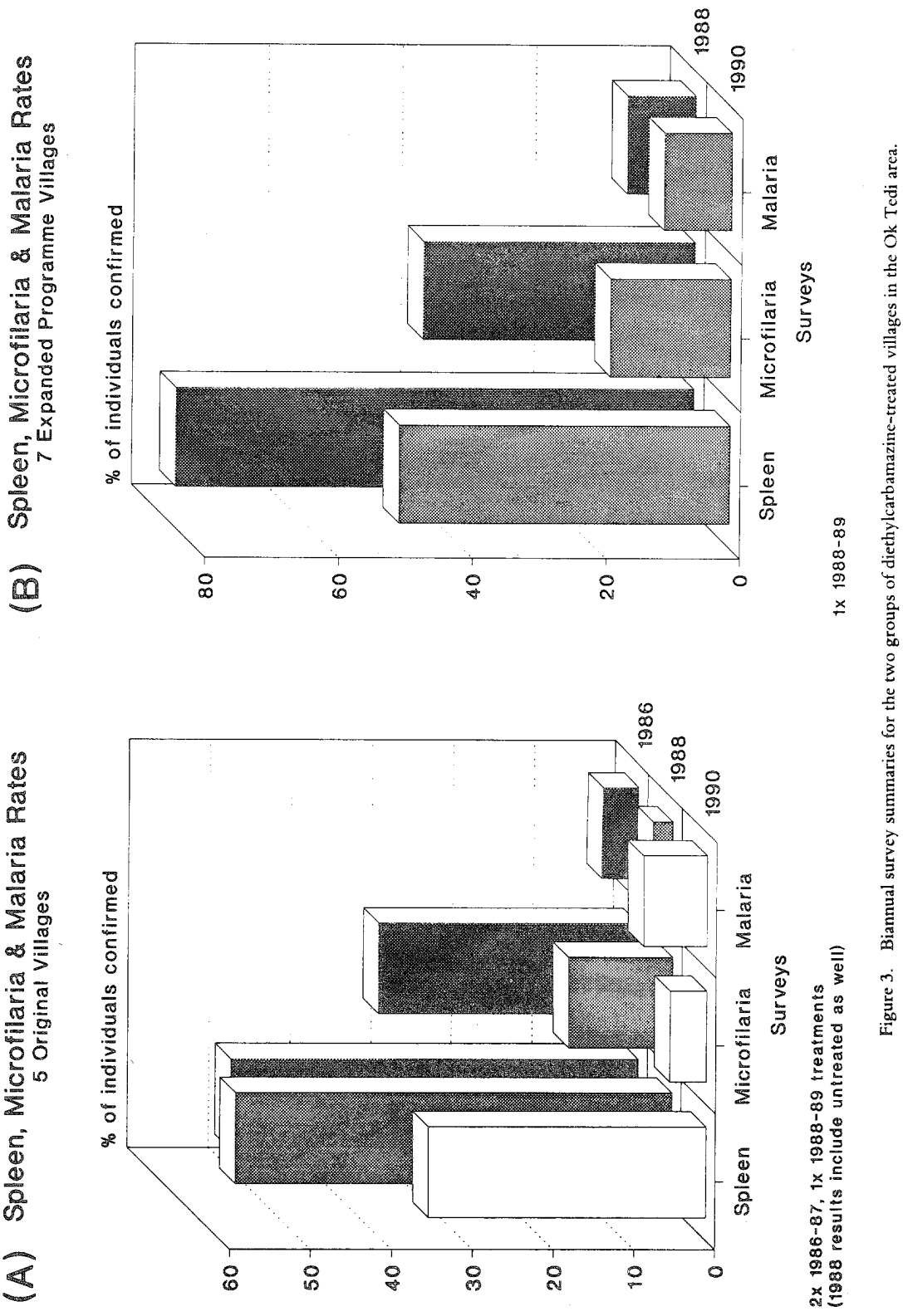

Figure 3. Biannual survey summaries for the two groups of diethylcarbamazinc-treated villages in the Ok Tedi area.

Figures 2A, B and Table 2.

Figure 3B demonstrates a marked reduction in splenomegaly and microfilaraemia rates yet malaria remained the same. The 7 expanded program villages were not actively involved in any form of malaria control other than the availability of treated mosquito nets since 1989. The nets are now available at a nominal, company-subsidized fee. Nets were initially distributed free of charge in the more remote border villages, one per family, but people did not use them as expected because they were considered to be a gift which was neatly tucked away (or passed along to someone else as gift). The nets, used occasionally in the village, were not considered to have had an impact on the Phase 2 results in this very mobile population.

The effect of malaria and filariasis on splenomegaly

The malario-filariometric results for the 1854 night blood films collected from juveniles and adults in the 13 villages within a 40km radius of the mining town of Tabubil participating in the filariasis control program were pooled to demonstrate the effect of parasitaemia on splenomegaly. The effect of the 3 species of malaria on splenomegaly was significant ($\chi^2 = 13.5$ for 2df, $p < 0.001$), with *P. falciparum* demonstrating the most prominent effect on enlarged spleen rate and size (AES). The overall malaria parasite rate was 7.4% with *P. falciparum* dominating the parasite formula (54% Pf: 31% Pv: 15% Pm). A significant difference was noted between enlarged spleen rates in malaria-infected and noninfected individuals ($\chi^2 = 9.2$ for 1df, $p = 0.002$) but no significant difference was observed between enlarged spleen sizes ($\chi^2 = 3.8$ for 3df, $p = 0.283$) (15).

The above information was further assessed for the presence or absence of patent microfilaraemia. Table 3 examines the relationship between malaria and splenomegaly in all individuals with microfilaraemia and Table 4 between malaria and splenomegaly in those with no microfilaraemia. No significant difference was observed in enlarged spleen rates between microfilaraemic villagers with or without detectable malaria parasitaemia ($\chi^2 = 0.6$ for 1df, $p = 0.423$) but a significant difference was reported between non-microfilaraemic villagers with or without detectable malaria ($\chi^2 = 8.8$ for 1df, $p = 0.003$) (8).

No significant differences in spleen size were observed between microfilaraemic individuals (with or without malaria) in Table 3, or non-microfilaraemic individuals (with or without malaria) in Table 4 ($\chi^2 = 4.1$ for 3df, $p = 0.249$). No significant differences were observed in the number of individuals infected by each malaria species between Tables 3 and 4 ($\chi^2 = 0.496$ for 2df, $p = 0.780$). The malaria parasite rate for villagers with microfilaraemia in Table 3 was 8.4%, with a parasite formula of 56% Pf: 26% Pv: 18% Pm. The malaria parasite rate in non-microfilaraemic individuals was 7.2%, with a parasite formula of 54% Pf: 32% Pv: 14% Pm (Table 4).

It is interesting to note that the enlarged spleen rate in individuals infected with *P. falciparum* and *W. bancrofti* (Table 3) was much higher than in individuals infected with *P. falciparum* only (Table 4). In general, the enlarged spleen rate was increased by 12% in microfilaraemic individuals (Table 3) when compared to individuals who were not microfilaraemic (Table 4).

The results suggest that filariasis has a significant impact on splenomegaly in the Ok Tedi area and most likely elsewhere in Papua New Guinea where *Wuchereria bancrofti* is endemic. *Plasmodium falciparum* has the greatest impact on enlarged spleen rate and spleen size of the three most commonly detected species in Papua New Guinea. A combination of both parasites (*Plasmodium* spp and *W. bancrofti*) increased splenomegaly (69% and AES 2.67) over single parasite infections (62% and AES 2.30 or 64% and AES 2.26) (Tables 3 and 4), but individuals with no detectable microfilaraemia or malarial parasitaemia still showed an enlarged spleen rate of 49% and AES 2.19 (Table 4).

Self-reported case detection of filariasis

Routine self-reported case detection of blood smears for malaria through Tabubil Hospital continued to monitor the impact of DEC on filariasis in the area between filariometric surveys. The annual frequency of

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TABLE 3

MALARIA AND SPLENOMEGALY IN *WUCHERERIA BANCROFTI*-INFECTED VILLAGERS IN THE IMMEDIATE OK TEDI DEC TREATMENT PROJECT AREA

Parasite(s) detected	Spleen size (Hackett grade) 0	1	2	3	4	5	Total spleens enlarged	Total people palpated	Enlarged spleen rate	Average enlarged spleen
Mf/*P. falciparum*	2	1	5	5	6	0	17	19	89%	2.94
Mf/*P. vivax*	6	0	2	1	0	0	3	9	33%	2.33
Mf/*P. malariae*	2	1	3	0	0	0	4	6	67%	1.75
Mf/Mixed infections	1	0	0	0	0	0	0	1	0%	0.00
Subtotal	11	2	10	6	6	0	24	35	69%	2.67
Mf/No malaria	147	54	91	60	30	2	237	384	62%	2.30
Total	158	56	101	66	36	2	261	419	62%	2.34

Mf = microfilaraemia
Mixed infections = more than one species of malaria detected

TABLE 4

MALARIA AND SPLENOMEGALY IN VILLAGERS WITH NO DETECTABLE *WUCHERERIA BANCROFTI* IN THE IMMEDIATE OK TEDI DEC TREATMENT PROJECT AREA

Parasite(s) detected	Spleen size (Hackett grade)					Total spleens enlarged	Total people palpated	Enlarged spleen rate	Average enlarged spleen
	0	1	2	3	4	5				
No Mf/*P. falciparum*	13	5	21	9	5	1	41	54	76%	2.41
No Mf/*P. vivax*	15	5	7	4	1	0	17	32	53%	2.06
No Mf/*P. malariae*	8	2	2	1	1	0	6	14	43%	2.17
No Mf/Mixed infections	1	2	0	0	0	0	2	3	67%	1.00
Subtotal	37	14	30	14	7	1	66	103	64%	2.26
No parasites detected	680	185	253	133	66	15	652	1332	49%	2.19
Total	717	199	283	147	73	16	718	1435	50%	2.20

Mf = microfilaraemia
Mixed infections = more than one species of malaria detected

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microfilaraemia, as reported since 1983 through monitoring at Tabubil Hospital, was as follows.

1983	1.4% (72/5149)
1984	1.7% (58/3414)
1985	2.2% (57/2607)
1986	2.5% (101/4059)
1987	1.4% (84/5819)
1988	0.5% (27/5571)
1989	0.4% (24/6091)
1990	0.3% (20/7359)
1991	0.2% (15/7056)
1992	0.2% (14/9266)
1993	0.1% (17/11826)

Periodic evaluation of hospital data within a consistent microfilarial screening program has proven to be a helpful guideline in the DEC mass drugging program. The DEC treatment program commenced in 1986 and one can see a decline in the annual rate of detectable microfilaraemia since then.

The period from mid-1984 to mid-1986 was one of minimal construction activity on the Ok Tedi mining lease area and led to a reduced number of self-reported examinations when compared to 1983. However, the ratio of locals to outsiders remained the same, which suggests that filariasis may have been on the increase as a result of construction and development within the area (15). As a growing township with excellent health services Tabubil became the hub of social activity for the region. Renewed construction activity in 1986 saw Tabubil inundated with job-seekers, followed by their families, resulting in a squatter/shanty settlement population of approximately 5000 around Tabubil. Tabubil township itself houses approximately 11 000 company employees, subcontractors and their dependants. The majority of those with microfilaraemia (if not all) detected during hospital screening in recent years have been from outside the DEC project area. This suggests that active transmission of filariasis may already have been interrupted within the DEC treatment area.

Discussion

Mass diethylcarbamazine (DEC) intervention programs may not always be accepted by a community if exaggerated dose-specific side-effects frighten off participants. A good health awareness program is essential. A DEC dose of 3mg/kg administered twice daily for 12 days (total 72mg/kg), usually considered as conventional treatment, can cause painful and debilitating systemic side-effects in a majority of patients for the first few days. A reduced number of localized side-effects over the following weeks can also be expected in areas where microfilaraemia rates and densities are high. Such side-effects may be extremely disturbing to suffering villagers, as was the case during the 1984 Dreikikir, East Sepik study (17). In the latter study mf densities were reduced from 113 to 7 per ml 12 months after treatment and the microfilaraemia rate from 66% to only 38% (18). Entomological data indicated that transmission of *Wuchereria bancrofti* was still occurring (a rate of 2% or less is required to curtail transmission effectively). Sera analyzed from subjects before and 6 and 12 months after treatment with 72mg/kg DEC showed that a heat-stable specific antigen had decreased in response to DEC but was still detectable in the sera of individuals who remained microfilaraemic after treatment (17).

Eberhard et al. (19) have confirmed that DEC kills or permanently sterilizes adult *W. bancrofti* after a 5-year study in Haiti with initial treatment with 12 daily or 12 weekly doses of 6mg/kg. Eberhard et al. (20) also reported an increased tolerance (or possible potential resistance) of *W. bancrofti* to DEC in Haiti. The long-term effect of single-dose annual treatments on the adult worm has yet to be confirmed but the results from the Ok Tedi study, supported by a consistent decline in self-reported case detections since 1986, look promising.

The intention of the Ok Tedi program was to use a 6mg/kg single-dose DEC treatment semiannually during Phase 1 because of the high pretreatment filariasis rate (39%) and mf density (84mf/20µl) (5). Invasive measures, such as drawing venous blood, were avoided to achieve optimum patient compliance. As with the Dreikikir study (18), different pretreatment rates and densities were reported for different linguistic groups and villages, as shown in Figures 1 and 2.

Filariasis is a more complex disease than

Mf = microfilaraemia
Mixed infections = more than one species of malaria detected

malaria. Temperature and humidity are determining factors in the transfer rate of infective larvae during a bloodmeal, which results in a greater geographic variability for bancroftian filariasis than malaria (21). Although *Culex annulirostris* and *Cx. (fatigans) quinquefasciatus* were considered of primary importance in the transmission of filariasis within the region (5), they are not the most efficient of vectors (22). Bryan (23), investigating vectors of *W. bancrofti* in two areas of East Sepik Province along the north coast of Papua New Guinea, found 47.3% of indoor-resting *An. punctulatus* infected and 3.4% with infective L3 larvae, but no infections were found in the *Cx. annulirostris* collected during night-landing catches. In one village Bryan (23) found only *An. koliensis* to contain L3 infective larvae while *An. punctulatus* and *Cx. quinquefasciatus* were infected with the junior stages of *W. bancrofti*. The protracted incubation period at higher altitudes would hinder development and transmission of this parasite, supporting the view that anophelines play a far greater role in the transmission of filariasis amongst the highland-fringe dwellers such as the Wopkaimin of the Star Mountains (300–1400m above sea level) (5). This was demonstrated by a decline in malaria and filariasis rates after the implementation of semiannual residual DDT spray applications between 1983 and 1986 (11). *Anopheles punctulatus* (79%), *An. farauti* (19%) and *An. koliensis* (2%) were found to be the main anopheline vectors throughout the construction period in the Ok Tedi area (11), with *An. koliensis* incriminated for more recent outbreaks of malaria in 1989–1990 (15). A survey of the North Fly (Ok Tedi) region and Western Province in May 1992 by the Australian Army Malaria Research Unit found *An. farauti* and *An. koliensis* to be predominant (R. Cooper, personal communication; and 15).

Charlwood and Bryan (24) reported that *W. bancrofti* infecting *An. punctulatus* in the Sepik did not affect mosquito survival rates and observed a shorter oviposition interval (2.90 days) than in similar species in other parts of Papua New Guinea. Burkot et al. (25) reported that malaria-positive *An. punctulatus* contained significantly higher numbers of L3 *W. bancrofti* larvae than malaria-negative mosquitoes but the former suffered greater mortality when larvae reached the L3 stage. The transmission potential of anophelines with a multiple parasite infection is thus offset by a greater mortality rate (25). The distance blood-engorged infected anophelines will travel was demonstrated by a release of marked *An. punctulatus*, a number being recaptured up to 1.8km from their point of release (24). These features support the view that anophelines are prime vectors of filariasis in the Ok Tedi area. Although interest has been revived in the capacity of anophelines of the punctulatus complex to transmit *W. bancrofti*, most of the work on transmission and vectorial capacity has been carried out in Africa (26–28). Further investigation is required into the capacity of the anophelines to transmit filariasis and which vectors predominate in the post-construction environment at Ok Tedi.

Treated nets have been made available to villagers in the Ok Tedi area since 1988 but they are not always used. Villagers in the border area to the west of Tabubil only began to accept the health benefits of treated nets in 1990–1991, despite being given treated nets gratis in 1988. The nets unfortunately have been used for other things such as a substitute for traditional ways of catching fish in small creeks and as sieves to strain sago in the bush gardens. Treated nets are not considered to have had a significant impact on filariasis transmission in Ok Tedi area villages because they were not used consistently or universally.

The annual single-dose treatment has been effective in maintaining the suppression of microfilaraemia (and possibly productive adult worms) in villagers previously treated semi-annually. It can also be beneficial as an annual treatment in previously untreated areas but the decline in the rate and density of mf will not be as rapid. Either method can be used; the choice will depend upon the time which can be allowed for reducing parasitaemia or the disease within a given area, and the availability of finance for staff, logistics and drugs. A target control microfilaraemia rate of 2% is attainable within a few years. Microfilaraemia rates have declined from 32.2% to 4.5% amongst indigenous villagers in the 5 original survey villages treated 6 times between 1986 and 1990 (Table 1), and from 40.6% to 18.0% in the 7 expanded program villages treated twice between 1988 and 1990 (Table 2); mf densities have also declined accordingly.

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In general the microfilaraemia rates have declined from 34.3% to 5.9% in the Wopkaimin villages monitored for response to vector control since 1983 and treated with DEC since 1986. Malaria parasite and enlarged spleen rates have remained stable in children 2–9 years of age and adults 15 years and older in indicator villages over the project area since 1986. The malaria parasite formula, which changed over the initial years of control, has been stable for all age groups since 1986 (10,11,15,29).

Kwan-Lim et al. (18) investigated IgG4 in the filarial-specific humoral immune response in two populations of adults in the East Sepik Province of Papua New Guinea, each being from an area with differences in transmission of *W. bancrofti*. Striking immunological differences were observed between the two groups, in particular a dramatic reduction in the filarial-specific IgG4 antibody response in villagers subjected to a 20-year DDT spraying program. In villages where filarial transmission was ongoing the microfilaraemia rate was 67% and adult worm activity, measured by a circulating phosphorylcholine antigen (PC-Ag), was present in 93%. The intensity of infection was demonstrated in children under 15 years of age with a 41% microfilaraemia rate and 81% PC-Ag rate. Chronic filariasis was observed in 25% of the population over 14 years of age in untreated Sepik villages. In the villages benefiting from a residual spray program the overall microfilaraemia rate was 4%, the PC-Ag rate was 24% and the rate of obstructive disease was 13% (18). It has now been proven that filarial worms stimulate abnormally high IgE and IgG4 responses, and the IgG4 antibody response was elevated by as much as 95% in patients with microfilaraemia (30). It is the living parasite that will continue to exert pressure on the immune response and it is most likely that enhanced production of IgG4 is related to worm load. Microfilariae appear to stimulate IgG4 more than adult worms. If the antigen dose is an important factor, the level of IgG4 may be influenced by the rapid killing of large numbers of the parasite by treatment with DEC. A massive antigen release from dying filariae may cause a general increase in all classes of IgG antibody (18).

Day et al. (31) reported IgM and IgG2 as the predominant class and subclass of antibodies made to the 3rd stage juvenile *W. bancrofti* larvae (L3). From the serology data presented by Schuurkamp et al. (8) there are indications that IgM and IgG are closely associated with *W. bancrofti,* and by treating infected individuals with a periodic dose of 6mg/kg DEC not only does the rate of microfilaraemia go down but it also appears that a large amount of antigen is released by the rapid killing of the parasites (18). This was demonstrated by a significant difference in total IgM and IgG levels for all villages receiving more than one treatment of DEC (8). As long as microfilaraemia rates remain high the IgM and IgG levels will also remain elevated, and although the emphasis for monitoring control has been on IgG and its subclasses, the IgM levels were also much lower in populations with a longer exposure to DEC (namely the Kamfaiwolmin, Wopkaimin and Faiwolmin).

Schuurkamp et al. (8) observed in the Ok Tedi project area significant IgM, IgG and spleen changes between DEC-treated and untreated villagers, which varied with the period of treatment.

Significant differences in IgM, IgG and splenomegaly (associated with a reduction in the prevalence of detectable microfilaraemia) were also observed by altitude of residence; in this study area malaria rates actually increased with altitude (15).

IgG4 as a diagnostic tool for field evaluation is still a long way off but looks very promising. Investigations in the Rumginae area, to the south of the present study, suggest that antigens detected in a diagnostic field ELISA test originate from the adult worm and may be beneficial in assessing filariasis control programs or targeting specific carriers (32).

Diethylcarbamazine is a very effective drug in the control of filariasis and other complications (splenomegaly) generally associated with malaria. The pretreatment rate of filariasis and its successful reduction with DEC in the Ok Tedi study were in sharp contrast to unfavourable observations made by Kimura et al. (4) in what appeared to be an ideal project situation. The Papua New Guinea Department of Health (33) is taking a serious look at filariasis as a result of recent findings even though its more important priorities lie elsewhere.

Lymphatic filariasis is not a benign disease. Besides being associated with lymphadenopathy, elephantiasis, pyomyositis and other abscess conditions (34), it may play a role in the development of amyloidosis (35), a disease common in Papua New Guinea (36).

The Ok Tedi DEC program progressed into the Phase 3 – Maintenance Program as of November 1990 involving some 17 villages and hamlets. The next major filariometric survey of the area is planned for early 1995 and a control target of 2% microfilaraemia or less, which should effectively curtail transmission, is anticipated (if not already achieved). As observed during self-reported case detection, the majority of individuals detected with microfilaraemia were from outside the project area. However, the maintenance of control is essential. The term eradication should not be used when promoting filariasis control because a resurgence or reintroduction of the disease with incremental annual increases can be expected if programs are not maintained, as observed by Laigret in Tahiti (1).

ACKNOWLEDGEMENTS

We thank the people of the Ok Tedi area for their patience and support, the Papua New Guinea Department of Health for assistance with DEC supplies, and Ok Tedi Mining Limited for its unwavering logistic and financial support. We also thank the Tabubil Hospital Laboratory staff Roberto Vergara and Philip Mayarom for their assistance with case monitoring, and William Popon, Health Extension Officer (Community Health).

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