

Efficacy of mass single-dose diethylcarbamazine and DEC-fortified salt against bancroftian filariasis in Papua New Guinea six months after treatment

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SUMMARY

The efficacy of two diethylcarbamazine (DEC) treatment strategies to control bancroftian filariasis, diethylcarbamazine-fortified salt (DEC-FS) and a single DEC dose on mass administration, was evaluated in two communities in Papua New Guinea with pretreatment antigen prevalence of 55% and 71%. In the first community 0.2% w/w diethylcarbamazine-fortified salt was distributed monthly to accepting households at no cost for 12 months. In the second community a single DEC dose based on body size but designed to give about 6 mg/kg was administered to eligible acceptors. Despite wide variation in antigen prevalence among study villages there were marked reductions in prevalences under both treatment strategies. Among individuals antigenaemic on day 0, DEC-FS and a single DEC dose gave filaria antigen clearance rates of 43% and 13%, respectively. In the salt-treated community the incidence of antigenaemia after 6 months in acceptors from households that received 5 kg or more of DEC-FS was 14% whereas in those receiving less than 5 kg salt was 4%. The incidence rates in the second community in those that received < 2.5 and ≥ 2.5 tablets were 16% and 8%, respectively. The two treatment strategies were simple to manage and appropriate for developing countries and were widely accepted. DEC-FS was more efficacious than single-dose DEC tablets but a single administration of DEC tablets is easier to administer.

Introduction

High prevalences of bancroftian filariasis, ranging from 50% to 70%, have been documented in Papua New Guinea (PNG) from as early as 1915 (1). The high prevalence of lymphatic filariasis in parts of PNG still exists, to date. There is no ongoing program to control bancroftian filariasis in the country.

Field trials of the efficacy of the two main antifilaria drugs, diethylcarbamazine (DEC) and ivermectin, have been conducted in PNG. Distribution of DEC on a semiannual basis to people in villages surrounding the Ok Tedi mine produced 64-72% reduction of microfilaria prevalence over 24 months (2,3).

A single dose of DEC was effective in reducing microfilaraemia of *Wuchereria bancrofti* in Samoa by 90% (4). In PNG a single dose of DEC was observed to reduce the prevalence of filarial antigenaemia significantly by 40% after 12 months (5).

The efficacy of DEC in combination with other antifilaria drugs has been investigated in PNG, but the relative efficacy of single-dose DEC tablets and DEC-fortified salt (DEC-FS) in the control of bancroftian filariasis in PNG has previously not been investigated. The effectiveness of DEC tablets and DEC-medicated salt to reduce the prevalence of bancroftian filariasis has been documented in endemic areas in China (6), Taiwan (7) and Tanzania (8).

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Previous studies aimed at examining the influence of antifilaria drugs on the prevalence of lymphatic filariasis infection. The purpose of this study was to compare the relative efficacy of mass administration of a single dose of DEC tablets and regular use of DEC-fortified salt on bancroftian filariasis in two endemic communities in PNG. Ethical approval was given by the PNG Medical Research Advisory Committee and the ethics committee of the University of Queensland.

Methods

Study population

The study was conducted in two areas in Milne Bay Province on the eastern tip of the main island of Papua New Guinea (Figure 1). The study included 6 villages in Buhutu Valley and 5 coastal villages in the Dogura District. Buhutu Valley is about 80 km from Alotau (capital town of Milne Bay Province) and is accessible by road using four-wheel drive vehicles. Due to the rugged Owen Stanley

Ranges there are no roads between Alotau and Dogura. The only access to Dogura is a 15-minute flight in small fixed-wing aircraft or a 12-hour trip in small coastal vessels.

The population eligible to be in the study included all persons aged 5 years or more and living in Buhutu Valley or in Dogura villages. Acceptors in the study were persons aged 5 years or more who agreed to give blood for filaria antigen detection, be treated and remain in the study for at least 6 months.

An initial visit was made to contact the village leaders to obtain permission to conduct the study in their villages. All study villages were visited and health education talks given on the purpose of the study, and the impact of the disease on health and social well-being. The drug effects and the procedures of blood collection for antigen analysis to confirm filarial infection were also explained. People were informed of exclusion and inclusion criteria and all persons were encouraged to participate in the study. Verbal consent was

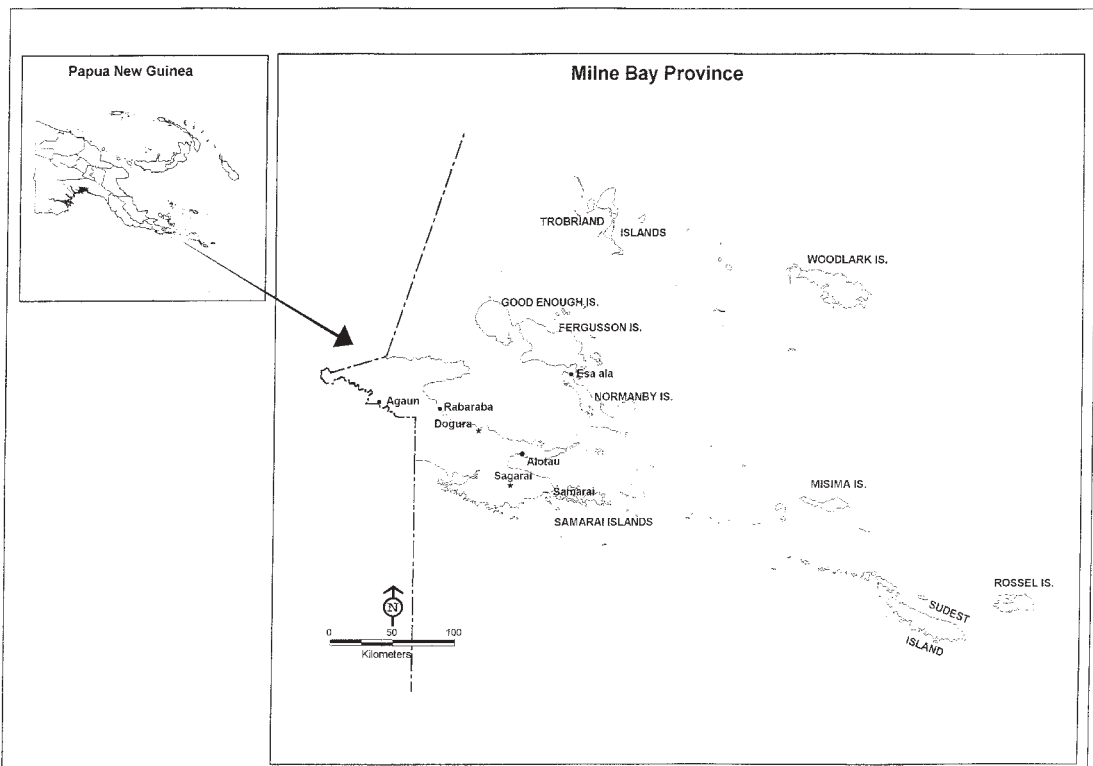


Figure 1. Map showing study location. Buhutu Valley and Dogura are marked with stars.

sought from heads of households for their family to participate in the study.

A house-to-house demographic survey was conducted in all villages and hamlets to enumerate the population and collect personal data. Heads of households were interviewed for information including names, sex, age or date of birth, number of children, and history of elephantiasis for all members of the household. Exposed extremities (mainly hands and legs) for each person were examined for clinical manifestations of filariasis (especially lymphangitis and lymphoedema). Men were questioned in private about hydrocele.

All information collected was recorded on survey forms and later entered in computer using EpiInfo version 6.04b.

Inclusion and exclusion criteria

Criteria for inclusion in the study were, age of 5 years or greater, agreeing to remain in the community until the first follow-up or until 12 months, agreeing to give blood for the detection of filaria antigen, and acceptance of DEC treatment. An acceptor was defined as an eligible person who agreed to remain in the study area, give blood and be treated with DEC at baseline and give blood during follow-ups. Exclusion criteria were arriving in the study area after the baseline assessment and migration to another province.

Chemotherapy schedule

Two treatment strategies were selected: 0.2% w/w DEC-fortified salt, Saarga brand (Biomedical Company Pty Ltd, India) for acceptors in Buhutu Valley and a single mass administration of DEC tablets in Dogura. Tablets containing 200 mg DEC citrate were obtained from MAVLAB Pty Ltd, Australia.

One or two packets of DEC-FS (each weighing 1 kg) were supplied at no cost to each household every month. A register was established to record salt distributed to each household. Every month stocks of DEC-FS were checked and new salt packets supplied as required. Families were encouraged to add salt every time they cooked or to eat salt with their meal.

In Dogura the DEC tablets were given to persons aged 5 years and over. The recommended dose of 6 mg/kg DEC per body weight (9) was used as a guide for the treatment schedule shown in Table 1. The dose of DEC was prescribed according to body size.

Blood collection and detection of filaria antigen

Processing of blood samples for filaria antigen (Ag) was by enzyme-linked immunosorbent assay (ELISA) following the method described by More and Copeman (10)

TABLE 1

DIETHYLCARBAMAZINE (DEC) DOSE SCHEDULE USED IN DOGURA

Body size	Age range (years)*	DEC (200 mg/tablet) dose	
		Tablet	Dose (mg)
Infants	<5	-	-
Children	5-14	0.5-1.0	100 - 200
Small adults	15-19	1.5-2.0	300 - 400
Medium adults	20-24	2.5-3.0	500 - 600
Large adults	25+	4.0	800

* Age was not a criterion for the estimation of the DEC dose but it is used here in assisting to illustrate the size of individuals according to the DEC dose given

using assay kits supplied by TROPBIO of James Cook University, Australia. Blood samples were collected during the day before treatment with DEC tablets or issue of DEC-fortified salt to households. Fingers were cleaned with alcohol swabs and pricked with sterile lancets. Blood was allowed to saturate fully each of the six protrusions on the pre-labeled specially made filter paper disc (10). Each fully saturated protrusion contains 10 μ l blood. The filter paper discs were left on a wooden rack to dry overnight and then packed in small plastic bags containing silica gel. The samples were stored at -20°C until analysis in Port Moresby.

In the laboratory 4 fully saturated protrusions were removed from the disc and placed in Eppendorf tubes containing 200 μ l of elution diluent. The tubes were placed in a hot water bath at 100°C for 5 minutes and then centrifuged at 2000 g for 15 minutes to separate the supernatant containing the heat-stable antigen from the cells. 50 μ l aliquots of supernatant were added to test wells in a 96-well round-bottom microtitre plate pre-coated with *Onchocerca gibsoni* monoclonal antibody (Og4C3). Conjugate control and standards were added to rows 11 and 12 to calibrate sample results. Plates were placed in a humid container and incubated at room temperature for 1.5 hours. The reaction was stopped by adding blocking agent to the wells. After washing, diluted rabbit antibody was added to the wells and incubated for 1 hour. Diluted anti-rabbit conjugate was added to the wells and incubated for 1 hour. The chromagen 2,2'-azino-di-[3-ethylbenzothiazoline sulphonate] (ABTS) was added to each well and incubated for 1 hour before optical densities (ODs) were measured at the wavelength of 414 nm by Multiscan spectrophotometer.

Assessment of filariasis intensity

The prevalence of filarial antigenaemia was estimated at baseline (day 0). Persons whose blood was negative for filaria antigen in the baseline study were used to estimate the incidence of filarial antigenaemia after 6 months.

Data analysis

Sample optical densities were entered using EpiInfo 6.04b software, and using the mean and range of OD the proportion of the population with positive Ag results were analyzed. McNemar's χ^2 test was used for comparisons of the effect of DEC and DEC-FS on filaria Ag prevalence. The efficacy of the two treatment strategies was assessed by outcome indicators such as prevalence reduction, clearance rate and incidence. Persons from whom blood was not obtained at the 6 months survey were excluded from the analysis. Comparisons between variables for significance were determined by confidence intervals at the 95% level.

Results

Study population

The acceptance rate in the baseline study for Buhutu Valley and Dogura was 100% in both areas. 434 participants from Buhutu Valley and 255 from Dogura were eligible for inclusion in analysis of the influence of treatment strategies on prevalence and other indicators of bancroftian filariasis after 6 months. The number of male and female acceptors was similar in Buhutu Valley. Dogura had more female than male acceptors. The highest proportion (24%) of acceptors in Buhutu Valley were in the 10-19 year age group and the lowest were above 70 years. The highest number of persons in Dogura were in the 5-9 year age group (23%) and the lowest were above 70 years.

Treatment strategies in the community

The treatment doses for diethylcarbamazine prescribed to study participants in Dogura are summarized in Table 1. After 6 months, 878 kg (mean of 2 packets per household, 1 packet = 1.0 kg) of DEC-FS and 574 DEC tablets (mean of 2 tablets, each tablet = 200 mg) had been distributed in Buhutu Valley and Dogura, respectively. Over 50% of the participants in Dogura were medium-sized adults who received a DEC dose of 500-600 mg (2.5-3 tablets). Children 5-9 years were the next most frequent group and they received a DEC dose of 0.5-1 tablet (100-200 mg).

TABLE 2

PREVALENCE OF FILARIAL ANTIGENAEMIA, ELEPHANTIASIS AND HYDROCELE IN BUHUTU VALLEY AND DOGURA IN MILNE BAY PROVINCE, PAPUA NEW GUINEA

	Study area	
	Buhutu Valley	Dogura
Filarial antigenaemia	55% (240/434)	71% (181/255)
Males	55%	72%
Females	55%	70%
Elephantiasis in persons ≥17 years	n=21	n=4
Leg elephantiasis only	14	2
Arm elephantiasis only	1	1
Combination of leg and arm elephantiasis	6	1
Hydrocele in males ≥17 years	2.5% (3/121)	1.3% (1/77)

Pretreatment prevalence of lymphatic filariasis

Chronic manifestations of lymphatic filariasis in the form of hydrocele or lymphoedema of extremities were more common in Buhutu Valley (6%) than Dogura (2%) (Table 2). Among the individuals with elephantiasis, leg involvement alone was the commonest manifestation (67% in Buhutu Valley and 50% in Dogura).

The initial prevalence of bancroftian filarial antigenaemia was higher in Dogura (71%) than in Buhutu Valley (55%) (Table 2). However, the difference in prevalence between the two areas was not significant. The prevalence of filarial antigenaemia at baseline (day 0) in 6 villages in Buhutu Valley ranged between 40% and 72% and in 5 villages in Dogura between 43% and 75%.

Effect of treatment on indicators after 6 months

Treatment doses were well tolerated and no person complained of any severe adverse reaction. A few people reported mild headache, nausea, malaise or transient dizziness. Amongst those who reported transient symptoms, dizziness (67%) was the commonest followed by malaise lasting for up to 3 hours.

Review after 6 months revealed a decline in the prevalence of filarial antigenaemia in both areas. 6 months after treatment the prevalence of filarial antigenaemia in Buhutu Valley declined by 34% of the pretreatment level. In Dogura, there was a 7% reduction of filarial antigenaemia prevalence. The highest

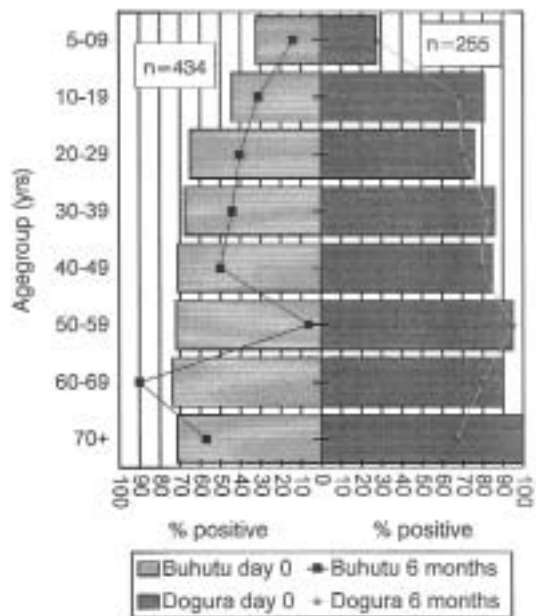


Figure 2. Persons positive for filaria antigen before and after treatment: DEC-FS for Buhutu Valley and DEC tablets for Dogura.

reduction was in the 50-59 year age group in Buhutu Valley (Figure 2). There was a significant reduction in prevalence of filarial antigenaemia among acceptors in households with mean salt of 5 kg or more in Buhutu Valley ($p<0.002$) and among those who took 2.5 tablets or more in Dogura ($p<0.001$).

Antigen clearance rate is estimated (in %) from the proportion of those positive at baseline and negative for filaria antigen at 6 months. The antigen clearance rate was 43% in Buhutu Valley where DEC-FS was used compared with 13% in Dogura where single doses of DEC tablets were given (Table 3). The antigen clearance rates among males and females in both Buhutu Valley and Dogura were very similar. The clearance rate in those from households that received less than 5 kg of salt in 6 months was 44% whereas it was 40% in those receiving 5 kg or more. The clearance rate in those who took less than 2.5 DEC tablets was 7% and in those who took 2.5 tablets or more was 30% (OR=5.55, 95% CI=2.20-15.42, $p<0.001$).

Incidence of bancroftian filariasis after 6 months of treatment

The incidence of filarial antigenaemia was estimated from the proportion of those who were negative for filaria antigen at baseline and positive at 6 months. Data from 194 acceptors in Buhutu Valley and 74 in Dogura were eligible for analysis of incidence. The overall incidence of filaria antigen was higher in Dogura (14%) than in Buhutu Valley (11%) (Table 3). The incidence rates observed in both areas are exceedingly high. The incidence of filaria antigen was higher in male than female acceptors in both areas but the difference was statistically significant only in Dogura. The high incidence of filarial antigenaemia in Buhutu Valley was attributed to those persons from households that took more than 5 kg salt, whereas in Dogura the high incidence was in those who took less than 2.5 tablets (Table 3).

Discussion

The two DEC treatment strategies employed in this study are appropriate in PNG and many

TABLE 3

EFFECT OF TREATMENT ON FILARIAL ANTIGENAEMIA AND INCIDENCE AFTER 6 MONTHS

Treatment effect	Buhutu Valley	Dogura
Clearance rate of antigenaemia	43%	13%
Males	42%	12%
Females	43%	13%
Incidence rate of antigenaemia	11%	14%
Males	11%	24%*
Females	10%	7%*
Recipients of <5 packets [†] of DEC-FS	4% (2/57)**	-
Recipients of ≥5 packets of DEC-FS	14% (19/137)**	-
Recipients of DEC tablets <500 mg [‡]	-	16% (8/49) [¶]
Recipients of DEC tablets ≥500 mg	-	8% (2/25) [¶]

* The difference in the incidence rates between males and females in Dogura was significant ($p=0.032$)

[†] Each packet weighed 1 kg

** The difference in the incidence rates between those persons from households that received less than 5 packets and those receiving ≥5 packets of DEC-FS was significant ($p=0.034$)

[‡] 2.5 tablets (200 mg each)

[¶] This difference was not statistically significant

developing countries where health care delivery has turned towards the involvement of personnel at the first level of health care delivery such as community health workers (CHWs) and village health aides (VHAs). DEC-fortified salt (DEC-FS) is probably the ideal mode of mass drug administration in countries like PNG where transport and labour costs are high and contribute to unsuccessful programs. Observations during the study indicated that acceptance of DEC-FS in the community was high and the monthly supply of the salt increased in some households. High consumption of the salt was indicated by the small amount in the packet recorded during monthly restocking. The study results also confirm high acceptance where the total number of salt packets taken by some households exceeded 6 packets or 1 packet per month (the expected consumption rate per household). The exceptionally high level of acceptance for DEC-FS observed in this study provides additional information on the poorly known aspect of community acceptance of medicated salt which past studies (8) were unable to establish. Salt delivery to the households was partly by the study team in vehicles as well as by people going to the nominated distribution centre. However, vehicles were used only on three occasions in a year during follow-up surveys.

Despite operational problems that could hinder DEC-FS as a potential intervention in a national control program, the results of this study indicate that DEC-FS is more efficacious than single-dose DEC in reducing the prevalence of antigenaemia with an overall high antigen clearance rate after 6 months. DEC consumption may explain these differences. The estimated mean DEC intake in the salt-treated community was about 20 g per person in 6 months compared with 400 mg per person in those taking tablets. A person would need to take at least 100 tablets to achieve equivalent DEC concentration in 6 months. However, multiple doses of DEC have been shown to be no more effective than single doses (11). Our results agree with those from Tanzania on the efficacy of medicated salt against bancroftian filariasis (8).

The advantage of single-dose DEC tablets is that less frequent visits to the community are

required than for DEC-FS. The treatment method of determining doses of DEC tablets is unique in this study because doses were given according to body size. Prescribing drug doses using body physique, such as height, has been used successfully with ivermectin in the treatment and control of onchocerciasis common in African countries (12). However, height was not used in this study as most Papua New Guineans are fairly short which therefore may lead to error in estimating DEC dose (mainly underdosing). From the PNG perspective the DEC tablet treatment schedule by body size, as a surrogate of weight, can easily be adopted by CHWs and VHAs after adequate training, eliminating the need for weighing scales to calculate doses which is problematic in many rural health centres and aid posts.

The incidence of filaria antigen after treatment was slightly higher in Dogura (14%) than Buhutu Valley (11%) suggesting that single-dose DEC tablets were slightly less effective than DEC-FS in preventing transmission. The high incidence is difficult to explain but new infection and some cases that may have been in an 'incubation' stage at baseline are potential contributing factors.

We believe our study is more sensitive than past studies because we determined the prevalence using antigens from adult filaria worms and not microfilariae which cannot be detected in amicrofilaraemic infections.

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