Randomised community-based trial of annual single-dose diethylcarbamazine with or without ivermectin against *Wuchereria bancrofti* infection in human beings and mosquitoes

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Summary

Background WHO has targeted lymphatic filariasis for elimination. Studies of vector-parasite relations of *Wuchereria bancrofti* suggest that a reduction in the microfilarial reservoir by mass chemotherapy may interrupt transmission and thereby eliminate infection. However, no field data exist on the impact of chemotherapy alone on vector efficiency and transmission intensity of *W bancrofti*. We compared the impact of an annual community-wide single-dose treatment with diethylcarbamazine alone or with ivermectin on rate and intensity of microfilaraemia, and transmission intensity in an area of Papua New Guinea endemic for intense *W bancrofti* transmission.

Methods We carried out clinical and parasitological surveys in 14 communities in matched pairs. People aged 5 years or older in seven communities received randomly assigned diethylcarbamazine 6 mg/kg and people in the other seven communities received diethylcarbamazine 6 mg/kg plus ivermectin 400 µg/kg. We made physical examinations for hydroceles and leg oedema and investigated microfilarial densities by membrane filtration before and after treatment. We selected five communities for monthly entomological surveys between September, 1993, and September, 1995. Mosquitoes were collected in these communities by the all-night landing catch method and were individually dissected to identify rates of infection and infectiveness.

Findings 2219 (87·6%) of 2534 eligible people received treatment. Microfilarial rate and density had decreased 1 year after treatment in all 14 communities; this decrease was significantly higher in communities given combined therapy than in those given diethylcarbamazine alone (mean decreases 57·5% and 30·6%, respectively; p=0·0013). Greater decreases were also seen in community-specific microfilarial intensity with combined therapy (mean reductions 91·1% and 69·8%, respectively; p=0·0047). The rate of leg oedema was not altered, but the frequency of advanced hydroceles decreased by 47% with combined therapy and 56% with diethylcarbamazine alone. 26 641 *Anopheles punctulatus* mosquitoes were caught during 499 person-nights of landing catches. Exposure to infective third-stage larvae decreased in all monitored five communities. Annual transmission potential decreased by between 75·7% and 98·8% in combined-therapy communities and between 75·6% and 79·4% in communities given diethylcarbamazine alone. Transmission was almost interrupted in two communities treated with combined therapy.

Interpretation Annual single-dose community-wide treatment with diethylcarbamazine alone or with ivermectin is effective for the control of lymphatic filariasis in highly endemic areas, but combination therapy brings about greater decreases in rates and intensity of microfilaraemia.

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Introduction

Lymphatic filariasis has been identified by WHO as a public-health problem and targeted for elimination.[1,2] The disease is a major cause of morbidity, primarily lymphoedema of the legs and hydroceles, and impedes socioeconomic development in 73 endemic countries, in which 1·1 billion people are at risk and 120 million are infected.[3] Filariasis-control programmes aimed at interrupting transmission of *Wuchereria bancrofti* have relied wholly or mainly on community-level drug administration. For nearly 50 years, diethylcarbamazine has been the drug of choice because it significantly decreases the intensity of microfilaraemia. However, many people remain microfilaraemic after taking full courses of the drug, and where culicine mosquitoes are vectors, these individuals may serve as reservoirs for continued transmission.[4] Studies have shown that treatment with ivermectin leads to more substantial and sustained reductions in microfilaraemia than diethylcarbamazine.[5,6] Limited clinical trials on selected individuals suggest that combined ivermectin and diethylcarbamazine is more effective than ivermectin alone, possibly because diethylcarbamazine is active against the adult stage of *W bancrofti*[7–9] or the combination has greater microfilaricidal activity than either drug alone. Community-wide treatment with combined ivermectin and diethylcarbamazine has,

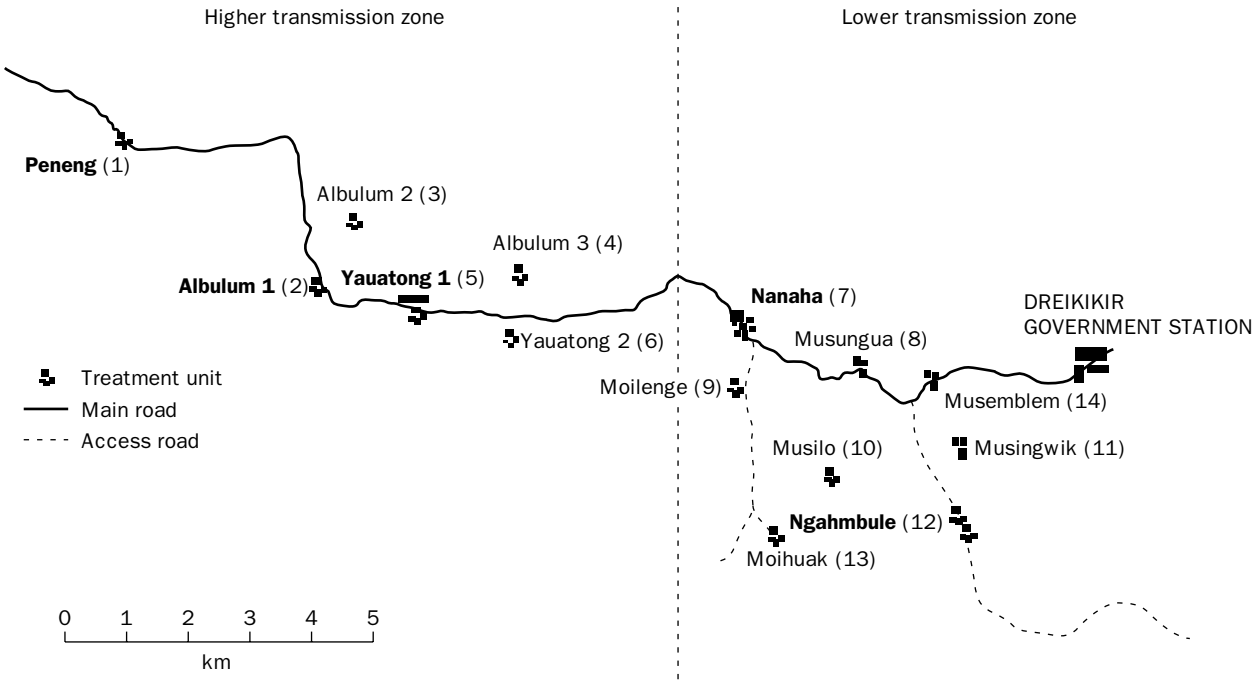

Figure 1: **Map of study area showing Dreikikir government station and entomology communities**
Entomology communities are in bold type. Numbers in brackets are treatment-unit numbers.

therefore, been identified as a possibly means for elimination of lymphatic filariasis.[10]

Analyses of the relation between *W bancrofti* and its mosquito vector suggest that reductions in vector density and intensity of microfilaraemia below certain thresholds could lead to breaks in transmission and, ultimately, eradicate anopheline-transmitted filariasis.[11,12] In areas where anopheline mosquitoes are the main vectors of *W bancrofti*, such as the Solomon Islands and Togo, transmission was completely interrupted through a reduction in vector density by the spraying of residual insecticides aimed at controlling malaria.[13,14] Since vector control alone is impractical or ineffective in many areas of the world endemic for filariasis, reduction of the microfilarial reservoir through community-wide chemotherapy has been proposed as a cost-effective alternative to limit or break transmission of *W bancrofti*.[10] Chemotherapy without vector control or a natural decline in vector density has not yet been shown to lead to breaks in transmission of *W bancrofti*.[11]

We compared, in a randomised study, the impact of community-wide treatment with annual single dose of diethylcarbamazine or combined diethylcarbamazine and ivermectin on bancroftian filariasis in a highly endemic area of East Sepik Province, Papua New Guinea. We studied the effects of treatment on infection, disease, and transmission and the prospects of achieving WHO's goal of elimination.

Methods

Study population

In 1994 we carried out parasitological and clinical surveys of people in 14 communities in the East Sepik Province, Papua New Guinea, located within 20 km of the Dreikikir government station (figure 1). The average annual rainfall in East Sepik Province is 1600 mm, and relative humidity varies between 80% and 100%. Rainfall is seasonal and most abundant between December and June (wet season). Lymphatic filariasis is highly endemic in these conditions, and anopheline mosquitoes are the main vectors of *W bancrofti*.[16]

Study design

Baseline entomological survey showed pronounced geographical variation in vector density. People living in villages located more than 10 km from Dreikikir experience more mosquito bites than those in nearer villages (figure 1). The distant villages are situated near fast-moving open rivers and streams, whereas communities closer to Dreikikir have cooler environments on ridges, above shaded rivers and streams. In the cooler villages the shade-preferring *Anopheles koliensis* mosquito is predominant. The more anthropophagic *A punctulatus* is predominant in villages further from Dreikikir. The boundary between transmission zones, which shows also the limit of distribution of *A koliensis*, is marked in figure 1.

To ensure comparability of treatment groups we separated the study area into seven pairs of geographically similar treatment units: three pairs in the higher transmission zone, and four pairs in the lower transmission zone. Within each transmission zone, pairs were matched by population size, and within each pair, one unit was randomly assigned diethylcarbamazine 6 mg/kg and the other diethylcarbamazine 6 mg/kg plus ivermectin 400 µg/kg. Randomisation was done in March, 1994, between the baseline survey and the first round of treatment.

We carried out entomological monitoring by monthly surveys between September, 1993, and September 1995 in five of the 14 treatment units: two in the lower transmission zone and three in the higher transmission zone. We selected units for mosquito collections by logistic criteria because we made catches simultaneously in the different communities, some of which were separated by more than 15 km. A minimum distance of 2 km was maintained between units because previous experiments showed this to be the maximum flight distance of infective mosquitoes in the area.[17]

Since we were assessing the impact of treatment on entomological indices of transmission, we carried out parasitological and clinical surveys before and after treatment of all community members 5 years or older in each treatment unit, including those who were not treated because mosquitoes might have fed on treated and untreated individuals.

Treatment and unit number		n		% of people with microfilaraemia				Intensity of microfilaraemia (mf/mL			
		1994	1995	1994	1995	% reduction	Difference*	1994	1995	% reduction	Difference*
Higher transmission zone											
DEC+IVR	1	65	88	61·5	20·5	66·8		26·6	1·3	95·3	
DEC alone	6	60	46	88·3	47·8	45·9	20·9	76·2	11·5	85·0	10·3
DEC+IVR	2	60	69	73·3	37·7	48·6		26·2	5·1	80·5	
DEC alone	4	39	35	71·8	51·4	28·4	20·2	54·1	19·6	63·8	16·7
DEC+IVR	3	156	161	84·6	35·4	58·2		82·3	3·5	95·7	
DEC alone	5	143	110	72·0	52·7	26·8	31·4	49·2	12·6	74·5	21·2
Lower transmission zone											
DEC+IVR	7	238	207	48·3	27·5	43·0		12·2	1·6	86·6	
DEC alone	13	242	188	59·9	37·2	37·9	5·2	29·7	5·9	79·8	6·8
DEC+OVR	8	122	137	68·0	24·1	64·6		20·9	1·1	94·7	
DEC alone	11	218	237	33·0	22·8	31·0	33·6	4·6	1·4	69·5	25·2
DEC+IVR	10	127	125	61·4	28·0	54·4		20·7	1·4	93·3	
DEC alone	9	97	93	47·4	37·6	20·6	33·8	11·6	6·2	47·1	46·3
DEC+IVR	14	309	290	32·4	10·7	67·0		4·2	0·4	91·5	
DEC alone	12	343	300	34·4	26·3	23·5	43·5	5·1	1·6	69·1	22·4

mf=microfilariae; DEC=diethylcarbarnazine; IVR=ivermectin.
*Difference DEC+IVR minus DEC alone.

% Rate and intensity of microfilaraemia before (1994) and after (1995) one single-dose mass treatment

Clinical examination, collection of blood samples, and treatment

We made physical examinations for advanced hydroceles and lymphoedema of the legs according to protocols described by WHO.[18] We found non-pitting lymphoedema, not reversible on raising of the leg (grade II), and gross increase in leg volume with dermatosclerosis and papillomatous changes (grade III). In our earlier surveys we found lymphoedema of the upper extremities in only 1·1% of the population.[15]

We assessed the rate of microfilaraemia from 1 mL blood samples obtained between 2200 h and 0200 h. We used membrane filtration and counted microfilarae according to the methods of Desowitz and Hitchcock;[19] results were expressed as number of microfilariae/mL blood. To measure average microfilarial density, we calculated the geometric mean from the microfilarial density plus a nominal value of one to allow for inclusion of zero counts. However, the values given have been adjusted back to the geometric means, which were also used in calculation of the pretreatment/post-treatment ratio so that the true effect would be represented.[20]

After we had collected blood, people eligible for treatment (all non-pregnant individuals aged ⩾5 years) received their assigned treatment. People aged younger than 5 years were not treated with either drug regimen since ivermectin was not approved for use in this age-group, about 15% of the entire study population, at the start of the study. The percentage of people aged younger than 5 years was similar in all villages. About 30% of such children are microfilaraemic (unpublished).

Side-effects of treatment were not systematically monitored because previous studies in this area had shown negligible adverse effects of single-dose diethylcarbamazine or ivermectin, even among people with very high rates of microfilaraemia.[6] However, health-care workers remained in or near the villages for 48 h after drug administration. People who received treatment were informed that fever and malaise are potential side-effects of the two drugs and antipyretics were given to those who complained of discomfort.

We obtained oral informed consent from all adults and from guardians of children younger than 16 years. Protocols for the study were approved by the appropriate medical authorities of Papua New Guinea and the Institutional Review Board of University Hospitals of Cleveland.

Sampling and processing of mosquitoes

Human-biting mosquitoes were caught by two adult residents of each treatment unit by the all-night landing catch method.[16] Mosquitoes were captured between 1800 h and 0600 h as they attempted to feed on volunteers whose feet and legs were exposed. Each of the five communities undergoing entomology monitoring was divided into four sections and mosquito collectors rotated through the sections on different nights for 4 nights per month for 24 months. Mosquitoes were identified in the field and stored in 70% ethanol for transport to the laboratory. They were stained for filarial parasites with Mayer's acid haemalum.[21] Mosquitoes were individually dissected to find out whether they were infected with filarial larvae.

Entomological measures of transmission intensity

Monthly biting rate, the estimated number of mosquitoes caught landing on volunteers every night for 1 calendar month, and monthly transmission potential, the number of *W bancrofti* larvae in the third stage (L3) with which that person would be inoculated, were calculated with formulae described by Walsh and colleagues.[22] We derived the monthly infective biting rate, the number of infective bites the collector would receive by multiplying the monthly biting rate by the monthly infective rate (ie, the proportion of mosquitoes containing at least one L3). Annual biting rate, annual infective biting rate, and annual transmission potential were calculated by adding the respective monthly values for 12 consecutive months.

Statistical analysis

To analyse the parasitological and clinical endpoints, we calculated one summary statistic for each study unit, and compared them by paired Student's t tests.[23] The assumption of normal distributions for these summary statistics was tested by the Shapiro-Francia W test.[24] Random-effects logistic regression may have given more information, but was not used because it required more model assumptions.

Changes in community-specific rate of infection were expressed as percentage differences from the rates before treatment. We tested the significance of differences in mosquito infection rates by the χ^2 test. The significance of correlation between different indices was tested with the Student's t test. The significance of differences in monthly transmission potential before and after treatment was tested with the non-parametric Mann-Whitney U test.

Results

The first round of parasitological and physical examinations and treatment occurred between June and October, 1994. Randomisation by transmission zone ensured that communities receiving different treatments were comparable for rate of microfilaria and mean intensity of microfilaraemia before treatment. Parasitological variables were generally greater in the higher than the lower transmission zones before treatment (table). 1 year after drug administration, microfilarial rate and intensity were reduced in all 14

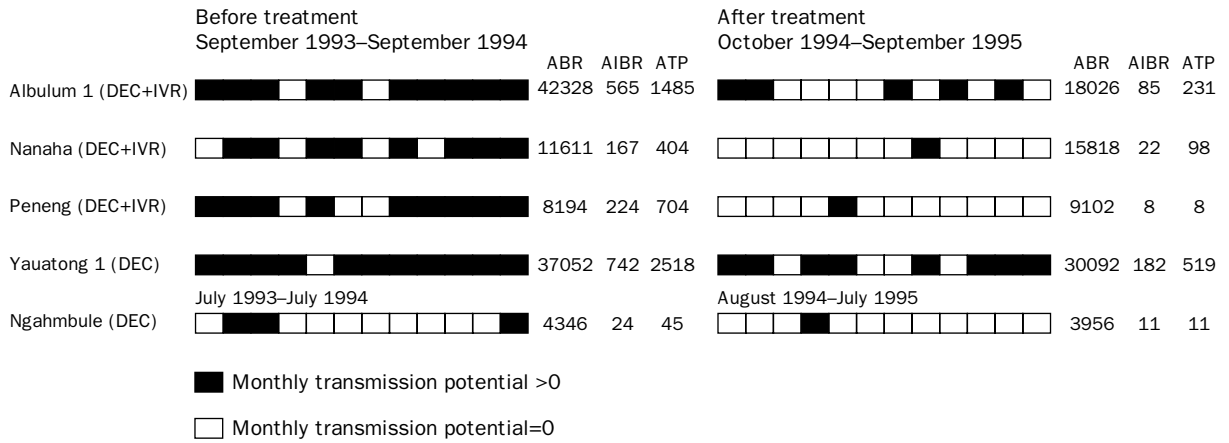

Figure 2: **Entomological indices of *W bancrofti* transmission 1 year before and after single-dose treatment**
DEC=diethylcarbamazine; IVR=ivermectin; ABR=annual bite rate; AIBR=annual infective bite rate; ATP=annual transmission potential. Monthly transmission potential >0=mosquitoes were captured containing one or more L3.

treatment units (table). The overall percentage of people with microfilaraemia decreased by between 43·0% and 66·8% (mean reduction 57·5%) in the treatment units given combined treatment and by between 20·6% and 45·9% (mean reduction 30·6%) in communities where diethylcarbamazine alone was given. The intensity of microfilaraemia was reduced by between 80·5% and 95·7% (mean reduction 91·1%) in the combined-treatment units, and by between 47·1% and 85·0% (mean reduction 69·8%) in the diethylcarbamazine units. Within each of the seven pairs of units, those that received combined treatment had a greater decrease in microfilarial prevalence and density than in units where diethylcarbamazine only was administered. Overall, the mean difference between the treatment groups in the reduction of microfilaraemia prevalence was 26·9% (95% CI 15·4–38·5; p=0·0013). The mean treatment-group difference in reduction of microfilarial density was 21·2% (9·4–33·1; p=0·0047).

The frequency of leg oedema did not change after either treatment. The rate for each of grade II and III lymphoedema before and after treatment with the combined regimen was 3·6%; values before and after treatment for units given diethylcarbamazine were 3·6% and 3·0%, respectively. By contrast, the rate of advanced hydroceles had decreased 1 year after drug administration. In treatment units that received combined treatment, the overall rate of hydroceles before and after treatment (in six of seven units) was 10·7% and 5·4%, respectively (49·5% reduction, p=0·004). In the diethylcarbamazine treatment units, the respective values (decrease in all seven units) were 12·3% and 4·9% (60·0% reduction, p=0·0003).

No side-effects occurred that required medical intervention other than antipyretics. No participants refused either drug in the second round of treatment because of adverse effects during the first round.

26 641 mosquitoes belonging to the *A punctulatus* complex were caught between September, 1993, and September, 1995 during 499 person-nights of landing catches. These included 24 448 *A punctulatus* and 2193 *A koliensis*, with 99% of the latter caught in the lower transmission zone (figure 1). 17 999 mosquitoes were dissected—10 237 before and 7762 after treatment. No mosquitoes were collected in October, 1993, for logistic reasons.

The total monthly transmission potential in the five monitored treatment units was similar during the wet and dry seasons (2255 L3/person December to June, and 2902 L3/person July to November), which shows little seasonal variation in transmission intensity. Annual transmission indices and the presence of infective larvae in wild mosquitoes collected in the five villages 1 year before and after treatment are shown in figure 2. The number of months in a year during which mosquitoes containing infective larvae were caught was less in all five units after treatment with either drug regimen. The degree of reduction in monthly transmission in the year after treatment was least in the two communities assigned diethylcarbamazine and was significant in only two villages assigned combined treatment (Nanaha p=0·007, and Peneng p=0·0009). We found significant reductions in annual transmission potential in the three villages assigned combined treatment (84·4% in Albulum 1, p=0·012; 75·7% in Nanaha, p=0·012; 98·8% in Peneng, p=0·001) and in one village assigned diethylcarbamazine only (Yauatong 1, 79·4% 0=0·002). The 75·6% decrease in annual transmission potential during the year after treatment in Ngahmbule, assigned diethylcarbamazine only was not significant (p=0·311).

Annual transmission potential before treatment correlated positively with prevalence of microfilaraemia (r=0·84, p=0·07) and microfilarial intensity (r=0·95, p=0·013). After treatment we also found a positive association between the annual transmission potential and the prevalence of microfilaraemia (r=0·98; p=0·003) and microfilarial intensity (r=0·99; p=0·001). Similarly, there were positive correlations between annual infective bite rate and microfilarial prevalence and intensity before and after treatment.

The mean number of L3 per infective mosquito correlated positively with microfilarial intensity before treatment (r=0·95; p=0·013). There was not, however, a significant correlation with the community-specific microfilarial rate (r=0·82; p=0·089). After treatment, the mean number of L3 per infective mosquito correlated significantly with microfilarial intensity (r=0·93; p=0·022) and rate (r=0·96; p0·010). The percentage reduction in mosquito infective rates correlated positively with the percentage decrease in microfilarial intensity (r=0·94; p=0·017), but the correlation of the former value with the percentage

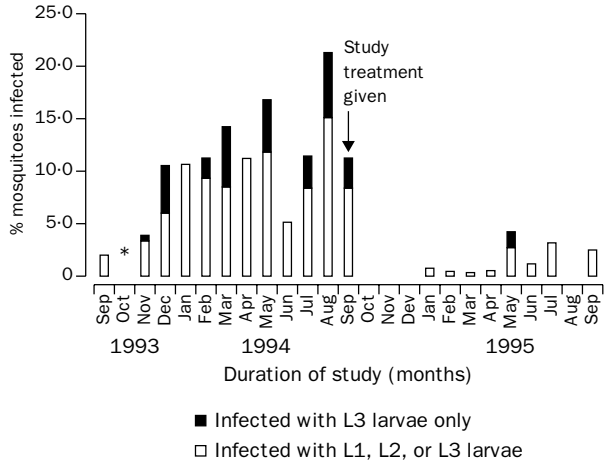

Figure 3: **Effect of treatment-induced reduction in intensity of *W bancrofti* microfilaraemia on uptake and development of microfilariae to infective larvae in wild-caught *A punctulatus* in Nanaha**

*No data collected.

reduction in microfilarial rate was not significant (r=0·80; p=0·107).

Among the entomologically-monitored communities where transmission was perennial before treatment, residents of Nanaha had the lowest microfilarial rate (48%) and intensity (12·2 microfilariae/mL) before treatment. Nevertheless, infected mosquitoes were seen in all collections at 1 year. By contrast, during the 3 months after treatment with combined therapy, none of the 313 mosquitoes collected contained L1, L2 (first and second stages) or L3. After 3 months, mosquitoes again contained L1 (ie, microfilariae ingested during a blood meal) but no L3. L3-containing infective mosquitoes were detected only in May, 1995—8 months after administration of combined therapy. The mosquito infection rates during this and subsequent months indicated a gradual increase in the uptake of microfilarae (figure 3).

Discussion

WHO has stated that elimination of lymphatic filariasis is achievable within 10 years.[1,2] In this trial, our main objective was to find out the efficacy of annual single-dose diethylcarbamazine alone compared with combined treatment with ivermectin in limiting the transmission of *W bancrofti* in a highly endemic area of Papua New Guinea. By monitoring entomological indices of transmission and the rate and intensity of microfilaraemia before and after treatment, we were also able to gain new insights into the quantitative relations of transmission intensity and the microfilarial reservoir under natural field conditions. Our results show that both diethylcarbamazine alone and combined treatment, without vector control, are highly effective in reducing anopheline-transmitted *W bancrofti*, even in this area of Papua New Guinea where the annual transmission potential is very high. Although longer periods of follow-up are required (based on the estimated median life span of adult *W bancrofti* worms being 5 years, we plan to administer both drug regimens annually for at least 5 years), examination of the mosquito populations during the first year after treatment suggests that the combined treatment is superior to diethylcarbamazine alone, and that this drug combination may have the potential to interrupt transmission of *W bancrofti*. About the relation between transmission and the microfilarial reservoir, the data indicate that transmission of *W bancrofti* by anopheline mosquitoes was greatly reduced, and, in some cases, interrupted for several months, despite incomplete elimination of the microfilarial reservoir. This observation provides field-based evidence in support of the notion that reduction of the microfilarial reservoir below a threshold value can lead to interruption of anopheline-transmitted *W bancrofti*.[11,12] The absolute value below which infection will no longer be sustained is not yet known.

Most filariasis-control programmes based on vector elimination alone are not practical or financially sustainable. Mass chemotherapy with diethylcarbamazine medicated salt or repeated annual doses of antifilarial medications represent effective and financially viable options.[10] A few clinical trials indicate that single doses of diethylcarbamazine or diethylcarbamazine combined with ivermectin lead to reductions in *W bancrofti* microfilaraemia that can be sustained for 12 months or longer.[5,6,25] Moreover, given the evidence that diethylcarbamazine has microfilaricidal and macrofilaricidal activity[9] and ivermectin has a rapid microfilaricidal effect,[26] the combination seems to be more effective than either drug alone. In Tahitian studies involving 350–500 people in each treatment group, Moulia-Pelat and colleagues[8] found that two treatments a year with this single-dose combined treatment led to a 32% reduction in microfilarial rate and a 96% reduction in mean intensity of microfilaraemia, and were superior to diethylcarbamazine or ivermectin alone. The greater efficacy of the combined regimen seen in our study (43–67% decrease in microfilarial rate, 80–95% decrease in intensity of microfilaraemia), despite the substantially higher rates before treatment in Papua New Guinea (combined-treatment communities 32–85% compared with 30% in the Tahitian study), may be due to differences in the rate of migration of previously untreated microfilarial carriers into the villages, the proportion of eligible individuals who actually took the medication, or varying susceptibility of parasites of different geographic origins to the study drugs. The reductions in microfilarial rate and intensity in all seven communities assigned combined therapy were similar to or higher than those reported 1 year after the start of twice-yearly single-dose diethylcarbamazine treatment in Tanzania[27] and the Western Province of Papua New Guinea.[28]

Our clinical observations suggest that single-dose mass chemotherapy will be well accepted in areas in which bancroftian filariasis is endemic. First, consistent with smaller studies of microfilaraemic individuals,[5–8,25] single doses of diethylcarbamazine or combined treatment have negligible side-effects. Although logistic and financial constraints precluded intense monitoring for adverse reactions in our study, we did find that even minor complaints such as malaise declined during the second round of treatment. A second benefit is the decrease in the rate of advanced hydroceles. The frequency of this manifestation decreased by about 50% after only one treatment with diethylcarbamazine or combined treatment. Meyerwitsch and colleagues[27] also noted a significant reduction in hydroceles in Tanzania

after a single or twice-yearly dose of diethylcarbamazine and, as in our study no change in the frequency of elaphantiasis. These findings suggest that the epidemiological risk factors for the two types of lymphatic disease differ. We previously reported that the frequency of advanced hydroceles did not correlate with annual transmission potential, whereas there was a positive relation between annual transmission potential and lymphoedema of the legs.[15]

Analyses of the correlation between the community-specific microfilarial reservoir (ie, microfilarial rate and intensity) and entomological measures of transmission intensity before and after treatment show several issues to be pertinent to the control of lymphatic filariasis, as well as the biological features of the interaction between anopheline vectors and *W bancrofti*. Substantial reductions in annual infective biting rate and annual transmission potential without vector control occurred in all five monitored treatment units and combined therapy was more effective than diethylcarbamazine alone. For example, the microfilarial rate before treatment in Peneng (61·5%) was higher than the 49·5% reported for Makundunchi in Zanzibar,[29] where an integrated approach of multiple-dose diethylcarbamazine mass treatment (72 mg/kg) and vector control with polystyrene beads in wet pit latrines decreased mosquito infective rates by 83·3% and annual infective biting rate by 99·7%. Despite a higher annual biting rate after treatment with combined treatment in Peneng, the reductions in infective rate and annual infective bite rate were similar to those in Makundunchi. The rapid and sustained reductions in monthly infective bite rates and monthly transmission potential after treatment shows that single-dose chemotherapy was the most important factor in changes in transmission intensity, although a transient and unusual upsurge in mosquito numbers and biting rates because of an unusual pattern of rainfall in the year before treatment may have influenced the results for annual infective bite rate in Albulum 1 (figure 2). Finally, the strong positive correlation between patent infection rates in human beings and entomological measures before and after treatment suggests that annual transmission potential can be used to monitor the success of control measures against lymphatic filariasis. (This conclusion should be tempered by the fact that entomological monitoring was done in only five of 14 treatment units.) Annual transmission potential of the *Simulium* vector has been used for this purpose in onchocerciasis-control programme.[30]

Despite the striking effect mass chemotherapy had on filariasis in our study, the frequency of microfilarial carriers ranged from 10·5% to 52·7% 1 year after treatment. This outcome raised concerns that single-dose treatment may result in a high rate of low-density microfilarial carriers, who could serve as reservoirs for efficient vectors such as *A punctulatus*.[4] Nevertheless, transmission was almost completely interrupted after treatment in Nanaha and Peneng, where transmission was perennial before treatment. The intensity of microfilaraemia may have been lowered to below a crucial threshold value, as predicted by the phenomenon of facilitation. This phenomenon, together with limitation and proportionality, describes the quantitative relation between microfilarial intake and L3 yield in the mosquito vector.[12] These concepts have arisen from experimental studies of mosquitoes fed on microfilaraemic volunteers,[13,31,32] and, as suggested by Wada and colleagues[33] should be considered in the context of chemotherapy rather than vector control. The positive relation in our study between the number of L3 in mosquitoes and microfilarial intensity, and the disappearance of L3 despite persistence of a lower microfilarial reservoir after treatment (figure 3) is in accordance with facilitation—the data show that the yield of L3 in mosquitoes increases disproportionately with the number of microfilarae taken up from the human host. Moreover, failure to detect infective mosquitoes containing L3 until 4 months after administration of combined therapy suggests that anopheline mosquitoes are not efficient vectors when microfilarial intensity is low. The practical implication of these findings is that breaks in anopheline-transmitted *W bancrofti* can be achieved by mass chemotherapy, even in areas of high vector density and with little seasonal variation in transmission. Our results, therefore, support the notion that annual single-dose combined therapy can lead to complete interruption and eventual elimination of bancroftian filariasis. The relevance of these promising findings to *Culex*-transmitted *W bancrofti* is not yet known, but studies of this vector-parasite complex in Pondicherry, India, suggest that community-wide treatment with drug regimens that include diethylcarbamazine also decrease microfilarial rate and density, and vector infectivity.[34]

Contributors

All of the authors were involved in data analysis and writing the manuscript. Moses Bockarie, Neal Alexander, Michael Alpers, and James Kazura were responsible for the design and implementation of the study. Philip Hyun and Zachary Dimber coordinated clinical field activities and helped with data management. Florence Bockarie and Ervin Ibam coordinated field and laboratory aspects of entomological monitoring and data management.

Acknowledgments

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