MASS TREATMENT TO ELIMINATE FILARIASIS IN PAPUA NEW GUINEA


ABSTRACT

Background The global initiative to eradicate bancroftian filariasis currently relies on mass treatment with four to six annual doses of antifilarial drugs. The goal is to reduce the reservoir of microfilariae in the blood to a level that is insufficient to maintain transmission by the mosquito vector.

Methods In nearly 2500 residents of Papua New Guinea, we prospectively assessed the effects of four annual treatments with a single dose of diethylcarbamazine plus ivermectin or diethylcarbamazine alone on the incidence of microfilariae-positive infections, the severity of lymphatic disease, and the rate of transmission of *Wuchereria bancrofti* by mosquitoes. Random assignment to treatment regimens was carried out according to the village of residence, and villages were categorized as having moderate or high rates of transmission.

Results The four annual treatments with either drug regimen were taken by 77 to 86 percent of the members of the population who were at least five years old; treatments were well tolerated. The proportion with microfilariae-positive infections decreased by 86 to 98 percent, with a greater reduction in areas with a moderate rate of transmission than in those with a high rate. The respective aggregate frequencies of hydrocele and leg lymphedema were 15 percent and 5 percent before the trial began, and 5 percent (P<0.001) and 4 percent (P=0.04) after five years. Hydrocele and leg lymphedema were eliminated in 87 percent and 69 percent, respectively, of those who had these conditions at the outset. The rate of transmission by mosquitoes decreased substantially, and new microfilariae-positive infections in children were almost completely prevented over the five-year study period.

Conclusions Annual mass treatment with drugs such as diethylcarbamazine can virtually eliminate the reservoir of microfilariae and greatly reduce the frequency of clinical lymphatic abnormalities due to bancroftian filariasis. Eradication may be possible in areas with moderate rates of transmission, but longer periods of treatment or additional control measures may be necessary in areas with high rates of transmission.


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weight and 400 µg per kilogram, respectively) with that of a single annual dose of diethylcarbamazine alone (6 mg per kilogram) in reducing the transmission of *W. bancrofti*. The method of randomization and the categorization of 8 treatment units as having a moderate rate of transmission and of 6 as having a high rate of transmission have been described previously.\(^3\)\(^-\)\(^12\)

The procedure for oral informed consent and the study design were approved by the Medical Research Advisory Committee of Papua New Guinea and the institutional review board for human investigations at Case Western Reserve University in Cleveland. Consent for the participation of subjects who were 16 years old or younger was obtained from a parent or guardian. Only persons who were at least five years old were eligible to receive drugs. Children who reached their fifth birthday within the 12-month period preceding an annual treatment were given their first treatment at that time. Pregnant women were excluded from receiving the drugs, because ivermectin cannot be used during pregnancy.

### Drug Distribution and Adverse Effects

Diethylcarbamazine (50-mg tablets) and ivermectin (1-mg tablets) were supplied by the World Health Organization. Because reactions to antifilarial drugs are most severe in persons with high levels of microfilariae,\(^13\)\(^-\)\(^16\) we closely monitored 966 subjects for side effects after the first treatment. Minor reactions (myalgia, headache, fatigue, and swelling of an arm, a leg, or genitalia) and severe reactions (high fever, shortness of breath, and collapse) that occurred within 48 hours after drug administration were recorded. Acetaminophen was given for minor reactions.

### Measures of Infection and Disease

Infection status was evaluated one day before the first treatment in 1994 and yearly after the first, second, third, and fourth annual treatments. The density of microfilariae in 1 ml of blood and the Og4C3 antigen level were quantified by membrane filtration and enzyme-linked immunosorbent assay (TropBioMed), respectively.\(^15\)\(^-\)\(^16\) The proportion of subjects who were positive for microfilariae and the geometric mean number of microfilariae per milliliter of blood before and one year after each treatment were calculated.

Physical examination was performed annually, and the severity of lymphatic abnormalities was graded according to standard criteria.\(^17\)

Only subjects who were at risk for advanced hydrocele (male subjects who were at least 16 years old) and moderate-to-severe lymphedema of the legs (subjects who were at least 21 years old) were scored as positive for disease. An adult with lymphedema of the legs and arms is shown in Figure 1.

### Entomologic Studies

Mosquitoes were captured for four nights per month as they landed on the legs of adult residents of the study area. The mosquito species was determined, and insects were examined for infective (third-stage) larvae.\(^18\)\(^-\)\(^19\) The biting rate (the number of mosquitoes attempting to take a blood meal per person), the infective biting rate (the number of *Aeopheles punctulatus* that had at least one infective larva), and the transmission potential were determined.\(^20\)\(^-\)\(^21\)

### Statistical Analysis

The frequency of adverse reactions according to the treatment regimen, differences in the proportion of subjects who were positive for microfilariae before and after each treatment, and changes in the antigen level and the severity of lymphatic abnormalities were evaluated for significance with the use of chi-square tests. Differences in the rates of transmission before and after each treatment were evaluated with use of the Mann–Whitney U test. A generalized estimating equation was used to assess the difference in the odds of having a microfilariae-positive infection according to the treatment regimen and rate of transmission (moderate or high) after adjustment for the correlation of observations within treatment units over time.\(^22\)

### Results

#### Community Participation in Mass Treatment

A total of 2586 persons were eligible to take antifilarial drugs in 1994, 2668 were eligible in 1995, 2695 were eligible in 1996, and 2690 were eligible in 1997. Ineligible persons (14 percent of the de facto population) were primarily children younger than five years old. Eighty-six percent of eligible subjects took antifilarial drugs during the first annual treatment, 78 percent during the second, 80 percent during the third, and 77 percent during the fourth. Of the 2586 subjects enrolled in 1994, 1 percent received no doses of
antifilarial drugs, 19 percent received one dose, 21 percent received two doses, 24 percent received three doses, and 35 percent received all four doses. Fifty percent of the episodes of noncompliance were not random (e.g., half the subjects who did not take the medication in 1997 also did not do so in 1995 and 1996). There were no significant differences between the number of doses of diethylcarbamazine plus ivermectin that were taken and the number of doses of diethylcarbamazine alone that were taken.

**Adverse Reactions**

No severe reactions were observed. Minor reactions were reported after the first treatment by 20 percent of subjects who took diethylcarbamazine plus ivermectin (93 of 472) and 11 percent of subjects who took diethylcarbamazine alone (53 of 494) ($\chi^2 = 14.3, P < 0.01$). Seven hundred fifty-four of these subjects took the medications the following year. Nine of 146 subjects who had minor side effects after the first treatment (6 percent) declined to take the second annual dose, as compared with 111 of 608 who did not have an adverse reaction after the first treatment (18 percent) ($\chi^2 = 11.9, P < 0.01$).

**Effect of Treatment on the Reservoir of Microfilariae**

Annual treatment reduced the reservoir of microfilariae (Table 1). The initial decrease was greatest in treatment units with a moderate rate of transmission whose inhabitants were randomly assigned to receive diethylcarbamazine plus ivermectin. Forty-seven percent of such subjects were positive for microfilariae before the initial treatment, as compared with 1 percent one year after the fourth treatment ($\chi^2 = 475.9, P < 0.001$). In units with a high rate of transmission, the rate of positivity for microfilariae decreased from 77 percent to 5 percent during the same period ($\chi^2 = 287.5, P < 0.001$). In units whose inhabitants were randomly assigned to receive diethylcarbamazine alone, the rates decreased from 42 percent before the initial treatment to 2 percent one year after the fourth treatment in areas with a moderate rate of transmission and from 76 percent to 11 percent in areas with a high rate of transmission.

A generalized estimating equation was used to account for the correlation of observations clustered within various treatment units. The model to estimate the odds of microfilarial infection included the drug regimen, the estimated transmission potential before treatment, the year of observation, and an interaction term for year and treatment regimen that was based on a logit link and an independent working correlation structure. The efficacy of diethylcarbamazine plus ivermectin was greater than that of diethylcarbamazine alone one year after the first, second, and third annual treatments (Fig. 2). For example, after the third treatment, residents of sites randomly assigned to receive diethylcarbamazine alone were 3.3 times as likely to be positive for microfilariae as those who lived in areas where diethylcarbamazine plus ivermectin was given (95 percent confidence interval, 1.04 to 10.57; $P = 0.04$), and the odds of being positive for microfilariae were 3.5 times as great for residents of areas with a high rate of transmission as for residents of areas with a moderate rate of transmission.

### Table 1. Effect of Four Annual Treatments with Diethylcarbamazine Plus Ivermectin or Diethylcarbamazine Alone on the Reservoir of Microfilariae in Treatment Units with a Moderate Rate of Transmission and Treatment Units with a High Rate of Transmission, According to Year.*

<table>
<thead>
<tr>
<th>Treatment and Variable</th>
<th>Moderate Transmission Rate</th>
<th>High Transmission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethylcarbamazine plus ivermectin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects examined</td>
<td>797</td>
<td>756</td>
</tr>
<tr>
<td>No. of microfilariae-positive subjects (%)</td>
<td>376 (47)†</td>
<td>156 (21)</td>
</tr>
<tr>
<td>Geometric mean no. of microfilariae/ml</td>
<td>9.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Diethylcarbamazine alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects examined</td>
<td>903</td>
<td>815</td>
</tr>
<tr>
<td>No. of microfilariae-positive subjects (%)</td>
<td>381 (42)†</td>
<td>238 (29)</td>
</tr>
<tr>
<td>Geometric mean no. of microfilariae/ml</td>
<td>8.8</td>
<td>2.6</td>
</tr>
</tbody>
</table>

*Four treatment units with a moderate transmission rate were randomly assigned to receive diethylcarbamazine plus ivermectin, and four were assigned to receive diethylcarbamazine alone; three treatment units with a high transmission rate were randomly assigned to receive diethylcarbamazine plus ivermectin, and three were assigned to receive diethylcarbamazine alone.

†$P<0.001$ for the comparison with all other years.
with a moderate rate of transmission (95 percent confidence interval, 1.30 to 9.09; P=0.02). After the fourth treatment, however, the odds of microfilariae-positive infection decreased to less than 0.1, regardless of whether subjects lived in an area with a moderate or a high rate of transmission and regardless of whether they were given diethylcarbamazine plus ivermectin or diethylcarbamazine alone.

**Effect of Treatment on Transmission**

Before treatment, there were 24 to 167 bites from mosquitoes containing infective larva per person per year in treatment units with a moderate rate of transmission and 224 to 742 infective bites per person per year in units with a high rate of transmission; the respective ranges for the transmission potential were 45 to 404 and 704 to 2518 infective larvae inoculated per person per year. Detailed entomologic indexes in two treatment units where diethylcarbamazine plus ivermectin was used are presented in Figure 3.

In the unit with a moderate rate of transmission, the overall transmission potential decreased by 97 percent (from 704 to 23 infective larvae inoculated per person per year). The effect of treatment was less marked in the unit with a higher rate of transmission. The pretreatment transmission potential of 1485 infective larvae inoculated per person per year decreased to 234 infective larvae inoculated per person per year the year after the third annual treatment (84 percent reduction). The pattern of exposure to infective mosquitoes also differed according to the pretreatment rate of transmission. In units with a moderate rate of transmission before treatment, after treatment there was an average of 0 bites from infective mosquitoes per person per month during 11 months of the year. In contrast, in units with a high rate of transmission before treatment, rates remained moderate to high (1 to more than 30 bites from infective mosquitoes per person per year) for five to seven months per year after treatment was initiated.

To estimate the effect of mass treatment on the establishment of new infections, we compared the prevalence of microfilariae-positive infections in previously untreated cohorts of five-to-six-year-old children from each year of the study for the treatment regimens combined. Before the initial treatment, 28 of 64 children (44 percent) were positive for microfilariae. A total of 9 percent were positive for microfilariae in 1995 (3 of 32), 11 percent in 1996 (8 of 71), 2 percent in 1997 (1 of 42), and 6 percent in 1998 (3 of 52) (χ²=12.9 for the comparison between the pretreatment value and the value in 1998, P<0.001).

**Effect on Filarial Antigen Level**

Estimates of the levels of circulating filarial antigen alone, independent of the blood level of microfilariae, are thought to reflect the burden of pre-adult and adult worms. Antigen levels were monitored between 1994 and 1997 in residents of two treatment units (Table 2). Fewer than 20 percent of subjects who were antigen-positive before the trial began were antigen-negative one year after the third annual treatment, though mean antigen levels decreased by 79 percent. There was no significant difference in these proportions between the two drug regimens. Changes in antigen status and level did not correlate with the number of treatments a subject received. No subjects who were identified as antigen-negative before the trial began were antigen-positive in subsequent years, and in no case did the antigen level increase relative to the pretreatment value.

**Effect of Treatment on Hydrocele and Leg Lymphedema**

The proportion of male subjects with advanced hydrocele who were at least 16 years old was 15 percent (110 of 726) before the trial began and 5 percent (27 of 563) one year after the fourth treatment (χ²=35.8, P<0.001). There was no significant difference in the frequency or odds of hydrocele between the two drug regimens, after adjustment for the clustering of treat-
ment units and time, although the odds did decrease with each year ($P=0.02$). In addition, the odds of hydrocele were 2.4 times as great among residents of areas with a high rate of transmission as among residents of areas with a moderate rate of transmission over the four-year period of the study (95 percent confidence interval, 2.05 to 4.76; $P=0.02$).

The frequency of lymphedema of the legs was 5 percent before treatment (68 of 1273 subjects) and 4 percent after the fourth treatment (99 of 998 subjects; $\chi^2=4.4$; $P=0.04$). There was no significant difference between the two drug regimens in the odds of lymphedema of the legs, although the odds decreased each year ($P=0.03$). Residents of units with a high rate of transmission were 3.3 times as likely to have lymphedema as residents of units with a moderate rate of transmission over the four-year study period (95 percent confidence interval, 1.33 to 8.33; $P=0.01$).

A separate analysis was performed that included subjects who had lymphatic disease at the beginning of the trial and who were monitored during the five-year study period. Ninety-one of 105 men who had advanced hydrocele (87 percent) and 62 of 90 adults who had lymphedema of the legs (69 percent) in 1993 to 1994 no longer had clinical signs of disease in 1998. The likelihood of the amelioration of lymphatic abnormalities did not correlate with the drug regimen, the number of treatments actually received, or the change in infection status as judged by the number of microfilariae or the antigen level.

**DISCUSSION**

In an effort to eradicate bancroftian filariasis, mass treatment with four to six annual doses of antifilarial drugs is being implemented in some parts of the world.\textsuperscript{26,27} Our findings support this strategy for areas with low-to-moderate rates of transmission in regions where anopheline mosquitoes transmit this infectious disease, such as in Melanesia and Africa. Additional measures or longer periods of treatment may be nec-

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**Figure 3.** Entomologic Indexes of Transmission in Two Units with Differing Rates of Transmission Randomly Assigned to Receive Diethylcarbamazine plus Ivermectin.

The biting rate (the estimated number of mosquitoes attempting to take a blood meal per person per year), infective biting rate (the estimated number of bites from mosquitoes containing infective larvae per person per year), and the transmission potential (the estimated number of infective larvae inoculated per person per year) are shown. In each horizontal bar, the sections represent the 12 months of the year.
ecules are released by dying microfilariae.28,29 
ed when filarial antigens and wolbachia-derived mol-
diated by inflammatory cytokines that are up-regulat-
treatment. Acute post-treatment reactions may be me-
effects were perceived as indicators of the efficacy of the
ipation the following year, possibly because adverse ef-
side effects such as myalgia and fatigue were noted by
one of the four annual treatments. Although minor
4 percent, and 69 percent of subjects with preexist-
phatic disease. The prevalence of hydrocele decreased
from 15 percent to 5 percent, and scrotal swelling
disappeared in 87 percent of male subjects with preex-
initially greater in areas with a moderate rate of trans-
mission than in areas with a high rate of transmission.
After the fourth treatment, however, the odds of being
positive for microfilariae were similar in all groups
and the reduction in the microfilariae-positive rates was
98 percent and the geometric mean density of mi-
crofilariae to less than 1 in all groups. Decreases in the
reservoir of microfilariae were more pronounced after
treatment with diethylcarbamazine plus ivermectin
than after treatment with diethylcarbamazine alone,
and the reduction in the microfilariae-positive rates was
initially greater in areas with a moderate rate of trans-
mision than in areas with a high rate of transmission.
After the fourth treatment, however, the odds of being
positive for microfilariae were similar in all groups
regardless of the rate of transmission or the drug reg-
iment. It is important to consider these results in the
context of the high rates of transmission and infection
in Papua New Guinea relative to other areas of en-
demic infection. Microfilariae-positive rates of 20 to
30 percent and transmission potentials of approximately
400 infective larvae per person per year (defined as
disease is reversed is not known, but the infection does
not need to be cured, since filarial antigenemia per-
stered in most subjects and there was no correlation
between this finding and the number of treatments
actually received. We speculate that mass treatment de-
creases exposure to the infective larvae and that this,
in turn, diminishes the intensity of inflammatory re-
sponses to newly inoculated W. bancrofti or their wol-
bachia endosymbionts. Studies have shown that the
rate of transmission correlates with both the prevalence
of lymphatic abnormalities and the cytokine profile
and strength of filarial-specific T-cell immunity.32,33
Four annual treatments reduced the proportion of
subjects who were positive for microfilariae by 86 to
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disease had a clinical cure. Reports from other ar-
from 15 percent to 5 percent, and scrotal swelling

eas in which bancroftian filariasis is endemic suggest
that the beneficial effects we observed may be gener-
alizable.30,31 The mechanism by which overt lymphatic
necessary in areas with a high rate of transmission. Since
the efficiency of transmission varies among mosquito
species, it is not yet clear whether similar conclusions
can be drawn in areas where non-anopheline mos-
quitos transmit W. bancrofti.

Our results suggest that mass treatment will be well
accepted. Serious adverse reactions were not observed
after 8335 doses of diethylcarbamazine plus ivermec-
tin or diethylcarbamazine alone had been given, and
77 to 86 percent of eligible subjects received at least
one of the four annual treatments. Although minor
side effects such as myalgia and fatigue were noted by
one sixth of subjects after the first treatment, such re-
actions were associated with increased rates of partic-
ipation the following year, possibly because adverse ef-
fects were perceived as indicators of the efficacy of the
treatment. Acute post-treatment reactions may be me-
adiated by inflammatory cytokines that are up-regulat-
ed when filarial antigens and wolbachia-derived mol-
cules are released by dying microfilariae.28,29

Mass treatment reduced the burden of clinical lymp-
phatic disease. The prevalence of hydrocele decreased
from 15 percent to 5 percent, and scrotal swelling
disappeared in 87 percent of male subjects with preex-
existing genital disease. Similarly, the prevalence of lymphe-
a moderate rate in our study) are considered high in most regions of Africa and the Pacific islands. In addition, recommendations to include albendazole in mass-treatment programs will most likely lead to even greater efficacy, since this drug, like diethylcarbamazine, is active against adult worms.

The remarkable decreases in the reservoir of microfilariae and the rates of transmission were accompanied by an 87 percent reduction from the pretreatment value in the number of microfilariae-positive infections in previously untreated five-to-six-year-old children after the fourth annual treatment. Since the children who were evaluated after the fourth treatment were 1 to 12 months old during the pretreatment period, the few infections in this group are most likely due to exposure to infective larvae before the transmission rate had been diminished by mass treatment. If this explanation is correct, the data indicate that new infections were completely prevented after four annual treatments.

Observations from other areas in which filariasis is endemic suggest that intense courses of diethylcarbamazine given over a period of 10 or more years interrupt transmission, whereas a recent report from India, where culicine mosquitoes transmit W. bancrofti, shows that the rates of microfilariae-positive infection decreased by 48 percent after four annual treatments with diethylcarbamazine alone. Comparison of these reports with our data is difficult, since none included a prospective analysis of the transmission potential, the levels of microfilariae or filarial antigen, the rate of new infections, or the influence of the baseline transmission rate.

Our results support the concept that infection and the burden of disease due to bancroftian filariasis can be reduced substantially with as few as four annual mass treatments that include single doses of diethylcarbamazine. It is not yet known whether and how long these benefits will be sustained after mass treatment ceases. Eradication may ultimately require more than four to six years of treatment, drugs with greater activity against adult worms, or adjunctive strategies that limit exposure to mosquitoes or enhance resistance to infection. Evaluation of changes in filarial ecology after the cessation of mass treatment in Papua New Guinea and other areas of endemic infection will provide this information and can be used to validate and refine mathematical models designed to predict the threshold necessary to achieve eradication.

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