SHORT REPORT: IMPACT OF IVERMECTIN COMMUNITY-LEVEL TREATMENTS ON ELIMINATION OF ADULT ONCHOCERCA VOLVULUS WHEN INDIVIDUALS RECEIVE MULTIPLE TREATMENTS PER YEAR

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Abstract. A reanalysis of several published reports indicates that when community-wide biannual treatment disrupts transmission of new infection, a profound macrofilaricidal effect of ivermectin (Mectizan) occurs that is accelerated for individuals treated 4 times a year (4×/yr). The effect is particularly obvious on adult male worms and suggests that this gender is susceptible to repetitive treatment after transmission has been blocked or greatly reduced as a result of community treatment.

The large-scale control of human onchocerciasis (“river blindness”) using ivermectin (Mectizan) is based largely on the drug’s ability to eliminate microfilariae rapidly from the skin without causing clinically-significant side effects.1 Depending on the specific goals of the campaign, annual treatment can be used to prevent skin and ocular morbidity,2 and biannual treatment (6-month intervals) can be used to reduce transmission of Onchocerca volvulus L₂s to the point that elimination of new infections occurs.3 Studies in Latin America (Guatemala) and Africa (Cameroon) also have shown that ivermectin becomes macrofilaricidal when given repetitively at 3- or 6-month intervals over a 2- to 3-year period.4,6 Here, we further analyze and compare the data from these three reports and show that when ivermectin is given on a quarterly basis (4×/yr) or biannual basis (2×/yr) to persons receiving treatment residing within a community where a high proportion of members also receives biannual treatments, new infections are prevented and elimination of adult worms accelerated.

Three key aspects of adult worm biology—live females, live males, fertile females—were first compared in individuals receiving 4×/yr treatment where (a) community level drug treatment at 6-month intervals was also ongoing7 or (b) there was no community-wide drug treatment or vector control.5 These three aspects were considered comparable between the two studies because the viability and reproductive status of the adult worms in the two locations were similar at the beginning of each trial, the ivermectin treatment regimen was the same (150 μg/kg every 3 months), the parasite material was prepared and evaluated in the same way (fixation of nodules, histologic sectioning, and H&E staining), and the same person evaluated the slides in both studies.

When persons receiving Mectizan at 3-month intervals resided in a community whose other occupants were being treated biannually, there was a strong and persistent macrofilaricidal effect over 3 years, resulting in a decline in live adult worms of 70% (females) to 78% (males) (Table 1). Production of microfilariae by female worms exposed to 4×/yr treatment in that environment ceased after 2 years (Table 1: fertile females following 8× tte = 0). In the situation where neither vector control nor Mectizan chemotherapy was available, adult worm numbers in subjects treated 4×/yr decreased by 28% (females) and 11% (males) after 3 years. These figures represent differences between the two situations of 42% and 67%, respectively. After 3 years of 4×/yr treatment where there was no community level control, 19% of female worms were still producing microfilariae (Table 1).

An earlier study demonstrated that ivermectin is not prophylactic against O. volvulus L₃s so we hypothesize that where there is no community-wide control, new infections of the treated subjects occur through seasonal transmission. Thus, new O. volvulus L₃s continue to be transmitted and the effect of 4×/yr treatment without elimination of infection results in the continued presence of adult worms. In Guatemala, biannual community treatments rapidly lowered O. volvulus L₃ transmission to 76–100% of pretreatment levels over a 3-month period so that new infections for replenishing the adult population were minimal.7 The analysis reported here further supports the conclusion that ivermectin is macrofilaricidal and highlights its potent effectiveness against male worms; that is, a 78% reduction in 3 years when new infections are eliminated or greatly reduced (Table 1). These data are quite similar to recently published field observations in Mexico, Guatemala, and Ecuador where 80–86% of nodules examined lacked an adult male worm, and female insemination rates were quite low (< 20%) after long-term semianual treatments.9 Interestingly, based on the linear mortality trend of female worms when individuals receive 4×/yr treatments in biannually treated communities (regression: r² = 0.96; Figure 1), extinction of the population is predicted to occur in less than 6 years. In the absence of biannual community-wide treatment, however, parasite persistence in the treated subjects was nonlinear (regression: r² = 0.46). The former approximation is important for future control strategies because it differs markedly from a recent estimate in which the life span of adult worms was expected to extend for 16 years when communities were treated twice a year.10 That estimate, however, was based on natural attrition with no drug effect and the unreplenished adult population dying from old age over a 12-year period.

We also reexamined the effects of 2×/yr versus 4×/yr treatments on adult O. volvulus survival where all persons receiving treatment lived within communities receiving mass chemotherapy with Mectizan4,6 (Table 2). Although the original data for these two groups were collected at different times and used different methods of analysis (collagenase extrac-
tion of adult worms for the 2×/yr treatment versus H&E slide examination for the 4×/yr group), we believe that they are validly comparable because an earlier study indicated that the ratio of female to male worms found with both techniques did not differ.11 Although the viability of adult female worms was similar for persons receiving 4×/yr or 2×/yr treatments within a community undergoing biannual treatments, after 24 months, the mean number of males per nodule dropped by 79% (4×/yr), compared with 44% (2×/yr); at 4×/yr, the number of female worms producing microfilariae per nodule reached zero (100% reduction) at 24 months, compared with an 82% reduction at 2×/yr. Nevertheless, if 2×/yr treatments were to continue, it is predicted that live female worms would be eliminated before Year 7 (13 treatments; regression: r² = 0.96; Figure 1) versus elimination just after Year 5 when treatments are given at quarterly intervals (21 treatments; regression: r² = 0.96; Figure 1). The successful control of onchocerciasis in Ecuador when biannual treatments were given over a

![Graph](image-url)

**Figure 1.** Reduction of female worms in nodules of patients exposed to 2×/yr and 4×/yr ivermectin treatments with (Guatemala) and without (Cameroon) 2×/yr community-level treatment.

6-year period at a high coverage rate reinforces the likelihood that this could be the case; that is, complete reduction of skin microfilariae with elimination of transmission followed by no discernable nodules in a sentinel population.12

We conclude that recurrent ivermectin treatment of onchocerciasis patients who reside within a community where *O. volvulus* transmission has largely been curtailed results in an enhanced rate of parasite elimination. In the case of adult male worms, there is a progressive reduction in numbers so that after 11 treatments at quarterly intervals, almost 80% of that population has been eliminated. Although it is assumed that a portion of the decrease in numbers of adult males in both the 2×/yr and 4×/yr treatment groups, where treatment is community-wide, is due to normal attrition associated with senescence in the presence of no new infections, the overall loss of males in the 4×/yr treatment group within the same community strongly suggests an enhanced killing of males associated with the increased rate of ivermectin treatments. Thus, these data suggest that when ivermectin is given 4×/yr, adult female infertility can be induced within 2 years, eliminating the possibility of new parasite transmission. Further, a trend predicting the annual death rate of female worms in this closed system, where eligible persons in an entire community are being treated at quarterly intervals, suggests that elimination of adult females may occur after 5 years (20 treatments; Figure 1). This appears not to be the case in an “open” system (ongoing transmission) where the infection may continue indefinitely5 (Figure 1). As such, this suggests that 4×/yr community-wide treatment may be the optimum regimen to attain parasite elimination within a short,logistically feasible period of time. Treatment at 2×/yr, however, may achieve essentially the same result with fewer treatments but require an additional 1–2 years.

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REFERENCES


TABLE 2
Comparison of 2×/yr versus 4×/yr ivermectin (Mectizan) treatments of individuals living in a community receiving biannual treatment*

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>After 6 months (1×)</th>
<th>After 24 months (4×)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C†</td>
<td>Mec (2×/yr)</td>
</tr>
<tr>
<td>Live females†</td>
<td>1.42</td>
<td>1.23 (13)§</td>
</tr>
<tr>
<td>Live males‡</td>
<td>1.02</td>
<td>1.03 (0)</td>
</tr>
<tr>
<td>Fertile females‡</td>
<td>0.89</td>
<td>0.47 (47)</td>
</tr>
</tbody>
</table>

* Data from Duke et al.4,6
† Placebo-matched control.
‡ Figures in row are expressed as mean number per nodule.
§ /H11505 % decrease from control.
¶ /H11505 data not available.

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