ASSESSMENT OF COMBINED IVERMECTIN AND ALBENDAZOLE FOR TREATMENT OF INTESTINAL HELMINTH AND WUCHERERIA BANCROFTI INFECTIONS IN HAITIAN SCHOOLCHILDREN

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Abstract. This randomized, placebo-controlled trial investigated the efficacy and nutritional benefit of combining chemotherapeutic treatment for intestinal helminths (albendazole) and lymphatic filariasis (ivermectin). Children were infected with Ascaris (29.2%), Trichuris (42.2%), and hookworm (6.9%), with 54.7% of children having one or more of these parasites. Wuchereria bancrofti microfilaria were found in 13.3% of the children. Children were randomly assigned to treatment with placebo, albendazole, ivermectin, or combined therapy. Combination treatment reduced the prevalence of Trichuris infections significantly more than either drug alone. Combination therapy also significantly reduced the prevalence and density of W. bancrofti microfilaria compared with placebo or ivermectin alone. Only combination therapy resulted in significantly greater gains in height (hookworm-infected children) or weight (Trichuris-infected children) compared with the placebo group. Combined albendazole and ivermectin was a more efficacious treatment for intestinal helminth and W. bancrofti infections in children and resulted in nutritional benefits not found with either drug alone.

The filarial parasite Wuchereria bancrofti, the major cause of lymphatic filariasis, infects 120 million persons worldwide, an estimated 40 million of whom have lymphedema, elephantiasis, or scrotal hydrocele.\(^1\,\^2\) Single-dose treatment with ivermectin has been shown to suppress microfilaria in humans;\(^3\) raising the hope that annual mass treatment programs could decrease transmission, leading to elimination of the infection. Towards this end, The World Health Assembly has recently called for the global elimination of lymphatic filariasis as a public health problem.\(^4\)

Infection with intestinal helminths is also an important public health problem in tropical countries. More than a billion persons are infected by Ascaris lumbricoides, Trichuris trichiura, or hookworm, with several million having serious clinical manifestations such as intestinal obstruction, anemia, chronic dysentery, or rectal prolapse.\(^4\,\^5\) Recognition that intestinal helminth infections also adversely affect child growth, nutrition, and even cognitive function\(^6\,\^12\) has led to development of school-based distribution programs for broad-spectrum anthelmintics (e.g., albendazole, mebendazole) in many tropical countries. However, little attention has been given to the possibility of combined treatment for simultaneous control of both intestinal helminth infections and lymphatic filariasis. Such programs would appear to be a cost-effective approach for control of these infections, but to date, the nutritional benefits and efficacy of combined drug administration are not well known.

We report here the results of a study to document the nutritional benefits, if any, and the efficacy of single-dose (combined albendazole/ivermectin) therapy against both filarial and intestinal helminth infections in Haiti, where these infections are endemic.

METHODS

Study design. The protocol for this double-blind, placebo-controlled study was approved by the Centers for Disease Control and Prevention (CDC) and the Hospital Ste. Croix Institutional Review Boards. The study began in January 1996 in Leogane, Haiti, a coastal town with a population of 10,000–15,000. After obtaining verbal informed consent from school masters and parents, all children attending five schools (grades 1–4) were enrolled. Headmasters verified the absence of any deworming programs in their schools during the previous year and no other treatment took place in the schools during the study period. Initial assessment included height (in triplicate to nearest 0.1 cm using a height measuring board) and weight measurements (in triplicate to nearest 0.1 pound wearing a school uniform without shoes and socks, Seca 770 scale); a stool examination for intestinal helminths; a finger prick blood specimen collected between 7:00 PM and 9:30 PM for measuring hematocrit (Hct) and microfilarial density in a 20-μl thick smear.\(^13\) Criteria for inclusion in the final study group included 1) age 5–11 years, 2) anthropometric measurements before and four months after treatment, 3) stool specimens before and 5 weeks after treatment, 4) random assignment to a treatment group and, 5) height, weight, and age within limits of the anthropometric database. Anemia was categorized as 1) mild (Hct ≥ 24% to < 33%), 2) moderate (Hct ≥ 15% to < 24%), or 3) severe (Hct < 15%). Four students with hematocrit levels < 22% were given a 30-day supply of iron sulfate/folic acid supplements, treated with albendazole, and excluded from the study. All laboratory specimens were collected and coded before treatment group assignment and the code, kept by CDC researchers, was only broken after completion of sample testing.

For each school, all eligible students were assigned, using a random number table, to four treatment groups and within seven days were given by CDC staff either a placebo (250 mg of vitamin C), 400 mg of albendazole (Zentel\(^\text{®}\)), SmithKline Beecham, Philadelphia, PA or generic drug, BeltaPharm Srl., Milan, Italy), 200–400 μg/kg (mean = 282.7 μg/kg) ivermectin (Mectizan\(^\text{®}\); Merck and Co., West Point, PA) or a combination of both albendazole and ivermectin. Children took the medication between 8:00 AM and
noon under direct investigator observation. All children with microfilarial densities greater than 50 per 20 μl of blood were hospitalized on the day of treatment to allow closer monitoring for adverse reactions to the therapy. All schools were revisited each school day for 3–5 days after treatment to systematically measure adverse reactions in the microfilaremic children and to provide medical consultation to other children. Five weeks post-treatment, another stool specimen was collected and four months after treatment, all measurements and tests performed before treatment were repeated.

Laboratory personnel, measurement teams, and personnel evaluating students for adverse reactions were blinded to the treatment status of the children. After completion of the project, all students received albendazole and all untreated, microfilaremic children received ivermectin. Students diagnosed with *Strongyloides stercoralis* infections were treated with a single 200 mg/kg dose of ivermectin if they had not received ivermectin during the study.

**Semen-quantitative stool examination.** Limited personnel and the need to collect and preserve hundreds of stool samples per day made the Kato-Katz protocol for helminth egg quantitation unsuitable. Therefore, a modification to the method of Stoll was used. Briefly, one gram of stool was measured by volume displacement into 10% formalin and mixed before storage. A formalin/ethyl acetate concentration was performed at a later date. The suspended stool was filtered through cheesecloth and centrifuged for 10 min at 500 × g at room temperature. The pellet was suspended in 10 ml of formalin, extracted with 3 ml of ethyl acetate, centrifuged as above, and resuspended in 10% formalin to a final volume of 2 ml. All organisms in 50 μl of the suspension were counted. The intensity of geohelminth infections was defined by egg count (eggs/gram of stool [epg]) as follows: *Ascaris*: light < 7,000 epg; medium 7,000 to ≤ 35,000 epg; heavy > 35,000 epg; *Trichuris*: light < 1,000 epg; medium 1,000 to ≤ 10,000 epg; heavy >10,000 epg; hookworm: light < 2,000 epg; medium 2,000 to ≤ 7,000 epg; heavy > 7,000 epg. Reductions after treatment (in epg) are reported as geometric means, using the (n + 1) transformation. Negative changes in egg count were set to 0 before the (n + 1) transformation.

**Statistical analysis.** Assuming a 50% prevalence, a sample of 1,000 children was selected to ensure an 80% probability (power) of detecting an actual 25% minimum change in any of three anthropometric measurements while maintaining a 5% probability (α) of falsely concluding there was a change. Data were analyzed using Epi-Info (version 6.04, CDC, Atlanta, GA) and SAS (version 6.11; SAS Institute, Cary, NC). Anthropometric indices are reported as Z-scores and were calculated using the Epi-Nut segment of Epi-Info. To control for the increased risk of declaring false significance when testing several hypotheses, multiple comparison or Fisher’s exact tests were performed between four treatment groups (intestinal helminth prevalence and intensity) or three treatment groups (filariasis prevalence and albendazole excluded). The Wilcoxon exact test was used to test for reduction in microfilarial intensity for combination therapy versus ivermectin or placebo. Data modeling used the general linear models procedure in SAS.

**RESULTS**

**Descriptive epidemiology.** Children (n = 996) were enrolled in January 1996 (Figure 1) for a final study group of 853. The 143 children who were excluded (see Methods for criteria) were similar to the final study group in all measured characteristics, although a trend towards a higher prevalence of some helminth infections and filariasis was noted in the excluded group. Children in the final study group had a mean age of 7.4 years and 407 (47.7%) were female. Mean anthropometric Z-scores for the study population were 1) height-for-age, −0.43 standard deviations (SD range = −4.1 to 3.5), 2) weight-for-age, −0.53 SD (range = −3.3 to 2.9) and, 3) weight-for-height, −0.37 SD (range = −2.6 to 2.8). The prevalence of intestinal helminths at enrollment was 29.2% (249 of 853) for *Ascaris*, 6.9% (59 of 853) for hook-
worm, and 42.2% (360 of 853) for Trichuris; 54.7% (467 of 853) of the children had one or more intestinal helminth infections. Most infections were categorized as light for Ascaris (96.8%), hookworm (100%), and Trichuris (97.2%). No heavy infections were observed. Of the 51 children with hookworm infections before treatment, 44 had other intestinal helminth infections (Ascaris, 49.0%; Trichuris, 84.3%). Hookworm-infected children were 7.6 times more likely to have Trichuris coinfections (relative risk = 7.6, \( P < 0.001 \)). Although differences in infection prevalence existed between schools, the four treatment groups did not differ significantly after randomization, except the prevalence of Ascaris was higher for the combination drug group than for placebo (14.3%) or ivermectin (73.6%) alone. These values for Ascaris, Trichuris, and hookworm were significantly lower than that during initial enrollment (Figure 3). Because all students received albendazole at the conclusion of the study, no comparisons between initial treatment and reinfected children who received the placebo (Figure 2).

We were unable to show any nutritional or anthropometric benefits significantly associated with clearance of W. bancrofti microfilariae when controlling for intestinal helminth infections. Reinfestation rates for intestinal helminths. One year after the study ended, a random sample (n = 141) of the study group submitted stool samples for diagnosis of intestinal helminths. For both Ascaris and Trichuris, but not hookworm, the prevalence of infection for the entire study group was significantly lower than that during initial enrollment (Figure 4). Because all students received albendazole at the conclusion of the study, no comparisons between initial treatment groups could be made.

**Discussion**

Diminishing resources and increasing numbers of high priority public health concerns are compelling public health practitioners to develop new approaches to maximize the use of health care resources. Integrated programs for simultaneous treatment of multiple diseases appear to be an efficient and cost-effective approach for addressing these problems. A 1996 World Health Organization (WHO) meeting and subsequent report discussed the advantages of integrating intestinal helmint control with other disease control programs, such as lymphatic filariasis, by taking advantage of the existing infrastructure of ongoing public health programs. We showed that combined treatment of a school-aged population was more efficacious and resulted in increased nutritional benefits when compared with either drug alone.
### Table 1
Helminth prevalence and intensity

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Pretreatment % prevalence (n)</th>
<th>Post-treatment % prevalence reduction 5 weeks</th>
<th>Post-treatment % prevalence reduction 4 months</th>
<th>Post-treatment % prevalence reduction* 4 months</th>
<th>Pretreatment intensity† [geometric mean, eggs/gm] (arithmetic range)</th>
<th>Geometric mean % intensity reduction (paired) 5 weeks</th>
<th>Geometric mean % intensity reduction (paired) 4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ascaris</strong>‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>31.0 (62/200)</td>
<td>19.5 (39/200)</td>
<td>37.1</td>
<td>18.5 (36/195)</td>
<td>40.4</td>
<td>352 (40–19.560)</td>
<td>32.9</td>
</tr>
<tr>
<td>Albendazole</td>
<td>28.3 (62/219)</td>
<td>0.5 (1/219)</td>
<td>98.4§</td>
<td>5.6 (12/216)</td>
<td>80.4§</td>
<td>284 (40–20.960)</td>
<td>100§</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>24.1 (52/216)*</td>
<td>1.4 (3/216)</td>
<td>94.2§</td>
<td>4.3 (9/208)</td>
<td>82.0</td>
<td>427 (40–8.960)</td>
<td>100§</td>
</tr>
<tr>
<td>Combination</td>
<td>33.5 (73/218)**</td>
<td>0.0 (0/218)</td>
<td>100§**</td>
<td>6.1 (13/213)</td>
<td>81.8§</td>
<td>334 (40–26.640)</td>
<td>100§</td>
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<td><strong>Hookworm</strong>‡</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>8.0 (16/200)</td>
<td>7.0 (14/200)</td>
<td>12.5</td>
<td>3.1 (6/195)</td>
<td>61.5</td>
<td>89 (40–720)</td>
<td>49.4</td>
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<tr>
<td>Albendazole</td>
<td>5.5 (12/219)</td>
<td>0.0 (0/219)</td>
<td>100§</td>
<td>0.0 (0/216)</td>
<td>100§</td>
<td>74 (40–320)</td>
<td>100§</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>6.5 (14/216)</td>
<td>2.3 (5/216)</td>
<td>64.3</td>
<td>1.4 (3/208)</td>
<td>77.7</td>
<td>80 (40–400)</td>
<td>91.8</td>
</tr>
<tr>
<td>Combination</td>
<td>7.8 (17/218)</td>
<td>0.0 (0/218)</td>
<td>100§</td>
<td>0.0 (0/213)</td>
<td>100§</td>
<td>67 (40–200)</td>
<td>100§</td>
</tr>
<tr>
<td><strong>Trichuris</strong>‡</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>43.0 (86/200)</td>
<td>31.0 (62/200)</td>
<td>27.9</td>
<td>31.3 (61/195)</td>
<td>27.3</td>
<td>144 (40–5,080)</td>
<td>30.3</td>
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<tr>
<td>Albendazole</td>
<td>42.5 (93/219)</td>
<td>20.1 (44/219)</td>
<td>52.7§</td>
<td>18.1 (39/216)</td>
<td>57.5§</td>
<td>120 (40–1,160)</td>
<td>42.2</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>40.7 (88/216)</td>
<td>22.7 (49/216)</td>
<td>44.3§</td>
<td>18.3 (38/208)</td>
<td>55.2§</td>
<td>121 (40–920)</td>
<td>42.7</td>
</tr>
<tr>
<td>Combination</td>
<td>42.7 (93/218)</td>
<td>8.7 (19/218)</td>
<td>79.6§**</td>
<td>8.9 (19/213)</td>
<td>79.1§</td>
<td>120 (40–6,760)</td>
<td>68.0§</td>
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<tr>
<td><strong>Wuchereria bancrofti</strong>‡‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>18.0 (25/139)</td>
<td></td>
<td></td>
<td>14.4 (20/139)</td>
<td>20.0</td>
<td>9.1 (1–82)</td>
<td>14.3</td>
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<tr>
<td>Albendazole‡‡</td>
<td>17.9 (26/145)</td>
<td></td>
<td></td>
<td>15.2 (22/145)</td>
<td>15.2</td>
<td>15.2 (1–386)</td>
<td>15.2</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>17.3 (26/150)</td>
<td></td>
<td></td>
<td>13.3 (20/150)</td>
<td>23.1#</td>
<td>15.4 (1–185)</td>
<td>73.6#‡‡</td>
</tr>
<tr>
<td>Combination‡‡</td>
<td>12.6 (19/151)</td>
<td></td>
<td></td>
<td>4.6 (7/151)</td>
<td>63.2§**</td>
<td>13.6 (1–105)</td>
<td>98.7§**</td>
</tr>
</tbody>
</table>

* Calculated for geohelminths using a cohort that required all three stools to be submitted.
† No significant differences between treatment groups.
‡ Non-exclusive infection, could have other intestinal helminth or filarial infections.
¶ Significantly different from placebo.
§ Significantly different from combination.
** Significantly different from ivermectin.
†† Significantly different from Albendazole.
‡‡ Analysis for this table necessitated excluding children without both pre- and post-treatment blood samples. These exclusions change the cohort size so that the prevalence is increased from 13.3% (see Results) to 16.4%.
§§ Not part of statistical testing.
¶¶ The ivermectin vs. placebo comparison was not tested statistically.
of deworming, previous studies have focused primarily on populations of children who were almost universally parasitized, had higher intensity infections, and were moderately to severely malnourished.\textsuperscript{5-10} Our study population was parasitized to a lesser degree; prevalence of each helminth infection was less than 50% and the intensity of helminth infections was comparatively low (\textasciitilde 95% were light infections). The children were relatively well nourished. Perhaps as a consequence, we were unable to detect a significant nutritional benefit of treatment when the entire study population was analyzed. Similarly, when limited to the 55% of children with any intestinal helminth infection, no significant benefits of treatment compared with placebo were observed, although a trend towards a benefit from combination therapy was noted. Subsequent stratification of the population by specific helminth infection allowed us to show the nutritional benefits of treatment for specific helminth infections.

Although other studies have shown a nutritional benefit after deworming of \textit{Ascaris}-infected children,\textsuperscript{5-10} we were unable to demonstrate such a benefit, perhaps as a result of our low initial infection intensities and the relatively short follow-up period. In contrast, children in the combination therapy group who were infected with hookworm or \textit{Trichuris}, respectively, had significant increases in height (hookworm, 0.62 cm, Table 2) or weight (\textit{Trichuris}, 0.56 kg, Table 3) when compared with placebo. When depicted graphically (Figures 2 and 3), the four-month changes in Z-scores in the combination therapy group for both hookworm and \textit{Trichuris} were seen as positive shifts of the entire population frequency curve compared with the placebo group, underscoring the beneficial effects of deworming as broad-based, rather than a result of an exclusive effect on a specific subpopulation.

The significant height and weight gains seen and the improvements in Z-score values are remarkable, considering the short, four-month follow-up period, the relatively well-nourished population, and the low intensity of infections. The improvements observed with combined therapy are of the same order of magnitude as seen in earlier studies that used a single anthelmintic drug in populations with higher intensity infections and follow-up periods of 6\textendash24 months.\textsuperscript{5-10} These data suggest that the benefits of combination therapy in populations with a high prevalence and intensity of intestinal helminths (where single drug therapy has demonstrable benefits) may be more dramatic. Furthermore, demonstrating nutritional benefits in such a moderately parasitized population underscores the insidious effects of even light intensity infections on growth and development of children. In a 1993 assessment of the benefits of helminth control in school age children, the World Bank concluded that intestinal helminth control be given the highest “health intervention priority” based on the cost-effectiveness of control programs, the efficacy of the treatment, and the prevalence of disease.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Four-month change in height-for-age by treatment group in hookworm-infected children.}
\end{figure}

\begin{table}[h]
\centering
\caption{Anthropometric measurements for hookworm*-infected children\textsuperscript{†}}
\begin{tabular}{lcccc}
\hline
Treatment & Mean of pretreatment & Mean of post-treatment & Mean of differences (paired) & \(P\) (2-tailed) & Difference between groups \\
\text{group}\textsuperscript{‡} & values\textsuperscript{§} & & & & \\
\hline
\text{Height (cm)} & & & & & \\
Placebo & 117.6 & 119.0 & 1.36 & & \\
Albendazole & 122.7 & 124.4 & 1.69 & & \\
Ivermectin & 120.2 & 122.1 & 1.86 & & \\
Combination & 121.4 & 123.4 & 1.98 & 0.01\textsuperscript{¶} & 0.62 cm \\
\text{Weight (kg)} & & & & & \\
Placebo & 20.8 & 21.5 & 0.67 & & \\
Albendazole & 22.6 & 23.5 & 0.89 & & \\
Ivermectin & 22.5 & 23.4 & 0.87 & & \\
Combination & 21.8 & 22.6 & 0.76 & & \\
\text{HAZ} & & & & & \\
Placebo & −0.770 & −0.850 & −0.080 & & \\
Albendazole & −0.445 & −0.467 & −0.020 & & \\
Ivermectin & −0.932 & −0.912 & 0.020 & & \\
Combination & −0.522 & −0.495 & 0.028 & 0.04\textsuperscript{¶} & 0.11 \\
\text{WAZ} & & & & & \\
Placebo & −0.859 & −0.867 & 0.008 & & \\
Albendazole & −0.715 & −0.681 & 0.035 & & \\
Ivermectin & −0.676 & −0.666 & 0.010 & & \\
Combination & −0.690 & −0.683 & 0.006 & & \\
\text{WHZ} & & & & & \\
Placebo & −0.471 & −0.400 & 0.071 & & \\
Albendazole & −0.589 & −0.527 & 0.063 & & \\
Ivermectin & −0.011 & 0.006 & 0.018 & & \\
Combination & −0.556 & −0.563 & −0.007 & & \\
\hline
\end{tabular}
\textsuperscript{*} Non-exclusive, could have other intestinal helminth coinfections but no \textit{filarial} infections.
\textsuperscript{†} HAZ = height for age Z score; WAZ = weight for age Z score; WHZ = weight for height Z score.
\textsuperscript{‡} Placebo (n = 16); albendazole (n = 12); ivermectin (n = 14); albendazole plus ivermectin (n = 17).
\textsuperscript{§} At pretreatment no significant differences were found between treatment groups.
\textsuperscript{¶} Significantly different from placebo.
\end{table}
Table 3
Anthropometric measurements for *Trichuris*-infected children²

<table>
<thead>
<tr>
<th>Treatment group³</th>
<th>Mean of pretreatment values§</th>
<th>Mean of post-treatment values</th>
<th>Mean of differences (paired)</th>
<th>P (2-tailed)</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Height (cm)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Placebo</td>
<td>120.3</td>
<td>122.2</td>
<td>1.90</td>
<td></td>
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<tr>
<td>Albendazole</td>
<td>120.2</td>
<td>122.0</td>
<td>1.83</td>
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<tr>
<td>Ivermectin</td>
<td>118.9</td>
<td>120.7</td>
<td>1.80</td>
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<tr>
<td>Combination</td>
<td>122.8</td>
<td>124.6</td>
<td>1.79</td>
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<tr>
<td><strong>Weight (kg)</strong></td>
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</tr>
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<td>22.8</td>
<td>0.71</td>
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<tr>
<td>Albendazole</td>
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<td>22.9</td>
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<td>Ivermectin</td>
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<tr>
<td>Combination</td>
<td>22.6</td>
<td>23.8</td>
<td>1.27</td>
<td>0.01‡</td>
<td>0.56 kg</td>
</tr>
<tr>
<td><strong>HAZ</strong></td>
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<tr>
<td>Placebo</td>
<td>−0.327</td>
<td>−0.312</td>
<td>0.015</td>
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<tr>
<td>Albendazole</td>
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<td>Ivermectin</td>
<td>−0.644</td>
<td>−0.647</td>
<td>−0.003</td>
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<td>Combination</td>
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<td>−0.007</td>
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<td><strong>WAZ</strong></td>
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<tr>
<td>Placebo</td>
<td>−0.420</td>
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<td>−0.502</td>
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<td>0.04‡</td>
<td>0.13</td>
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<tr>
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<td>−0.029</td>
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<td>−0.335</td>
<td>0.194</td>
<td>0.01‡</td>
<td>0.22</td>
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</table>

* Trichuris-only, no intestinal helminth or filarial coinfections.
‡ Significantly different from placebo.
# Significantly different from ivermectin.

in children 5–14 years of age.²² Further benefits to be derived from adding ivermectin to existing albendazole distribution programs include control of infections with *S. stercoralis*, a potentially autoinfective, chronic helminth infection,⁵,¹⁴ and scabies.⁵,²³ In addition, the effect of treatment in this setting was relatively long-lasting, as illustrated by the reduction in prevalence one year after treatment (Figure 4), suggesting that the reinfection rates were relatively low.

Data summarized earlier from this study showed that the combination therapy was also significantly more effective at reducing microfilarial prevalence and density than the other treatments.²⁰ Treatment with combination therapy resulted in the only significant decrease in the prevalence (63.2%) of *W. bancrofti* microfilaraemia when compared with placebo. As measured four months after treatment, the combination therapy was significantly more effective (98.7%) than ivermectin alone (73.6%) in reducing the geometric mean microfilarial density. Although systemic adverse reactions were significantly greater in children treated with ivermectin or the combination, the frequency and severity of these symptoms did not differ between children who received the combination and those who received ivermectin alone.²⁰ Others have also shown improved microfilarial suppression with combined albendazole and ivermectin compared with albendazole given either alone or in combination with diethylcarbamazine.²⁴ After controlling for intestinal helminth infections, we were unable to show any nutritional impact following treatment of filariasis. However, the potentially serious sequelae of filarial infections, the high efficacy of antifilarial

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*Figure 3.* Four-month change in weight-for-height by treatment group in *Trichuris*-infected children.

*Figure 4.* Prevalence of intestinal helminths after treatment. # = significantly less than starting prevalence (P = 0.001), * = significantly less than starting prevalence (P = 0.035).
treatment, and the fact that microfilarial prevalence is still increasing in this age group, argues for early intervention to decrease transmission and microfilaria-associated pathology.

Our data suggest that an ivermectin/albendazole combination can simplify the delivery infrastructure and enhance efficacy against both intestinal helminths and *W. bancrofti* compared with either drug alone. The opportunity to combine two separate control measures also opens the possibility for adding either drug to augment existing single-drug distribution programs (e.g., onchocerciasis, intestinal helminths). In light of these results, and the massive donation in 1998 of more than one billion doses of albendazole by SmithKline Beecham to WHO for lymphatic filariasis elimination, further studies of efficacy and adverse reactions of combined treatment are warranted in other age groups such as preschool age children and adults, in other regions with different prevalences and intensities of helminth infection, and in areas where coinfections with other filaria, including *Onchocerca volvulus* and *Loa loa*, occur. The apparent efficacy and safety of combined treatment in children suggests that other double- or triple-drug combinations should be studied for future helminth control programs.

**Note added in proof:** Our data do not support the suggestion of Forrester and others\(^25\) that albendazole treatment of low-intensity *Trichuris* infections (10–510 epg) or uninfected children may stunt growth. Reanalysis of our data to include only children within this range of infection intensities (94% of the Haitian children infected only with *Trichuris* had 10–510 epg) shows no stunting following albendazole treatment. In addition, since all children were mass-treated before stool test results were analyzed, we could examine the effect of treatment on uninfected children. No stunting of uninfected children was observed following albendazole treatment.\(^26\)

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REFERENCES


Course title: Review Course in Clinical Tropical Medicine and Travelers’ Health
Location: San Francisco, California; Hotel TBD
Dates: September 23–24, 1999
Sponsor: American Society of Tropical Medicine and Hygiene (ASTMH) in cooperation with the American Committee on Clinical Tropical Medicine and Travelers’ Health

Course description: This two-day course is designed for all health care providers working in tropical medicine or travelers’ health, and for physicians planning to take the ASTMH-sponsored certification examination in Clinical Tropical Medicine and Travelers’ Health. The course will provide sessions on tropical illness caused by viral, bacterial, mycobacterial, protozoal, helminthic and ectoparasitic agents. Information on pre- and post-travel consultations, immunizations and evaluations, and the proper care of moderate to high risk travelers and travelers with special needs, will also be presented. Speakers are internationally recognized authorities on tropical medicine and/or travelers’ health. Following this course, attendees should be better able to advise overseas travelers and diagnose and treat ill returned travelers and those living in developing countries.

The course precedes the annual ICAAC meeting of the American Society for Microbiology. The certification examination of the ASTMH will be administered on November 27, 1999 in Washington, DC, preceding the ASTMH annual meeting. For additional information, please contact ASTMH at (847) 480-9592, e-mail astmh@astmh.org, or visit our web site at www.astmh.org.