Efficacy of Current Drugs Against Soil-Transmitted Helminth Infections
Systematic Review and Meta-analysis

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Soil-transmitted helminthiasis (STH) is caused by an infection with intestinal nematodes, of which Ascaris lumbricoides, Trichuris trichiura, and the hookworms (Ancylostoma duodenale and Necator americanus) are the most widespread species.1,2 An estimated 4.5 billion individuals are at risk of STH and as many as 1.2 billion individuals might be infected with A lumbricoides, close to 800 million with T trichiura, and more than 700 million with hookworm.1,3 Infection intensity is a key factor in understanding the morbidity of STH; although light infections are often asymptomatic, heavy infections cause an array of morbidities, including dietary deficiencies and delayed physical and cognitive development. Additionally, hookworm and T trichiura infections contribute to iron-deficiency anemia.1,4 Estimates of the global burden due to STH range between 4.5 million and 39 million disability-adjusted life-years.3,6 Recent findings of increased susceptibility of individuals concurrently infected with hookworm and bacterial, protozoan, or viral infections, including human immunodeficiency virus (HIV)/AIDS and tuberculosis, are of considerable public-health concern because of large geographical overlaps of STH with HIV/AIDS and tuberculosis.1,3,6

Context More than a quarter of the human population is likely infected with soil-transmitted helminths (Ascaris lumbricoides, hookworm, and Trichuris trichiura) in highly endemic areas. Preventive chemotherapy is the mainstay of control, but only 4 drugs are available: albendazole, mebendazole, levamisole, and pyrantel pamoate.

Objective To assess the efficacy of single-dose oral albendazole, mebendazole, levamisole, and pyrantel pamoate against A lumbricoides, hookworm, and T trichiura infections.

Data Sources A systematic search of PubMed, ISI Web of Science, ScienceDirect, the World Health Organization library database, and the Cochrane Central Register of Controlled Trials (1960 to August 2007).

Study Selection From 168 studies, 20 randomized controlled trials were included.

Data Extraction and Data Synthesis Information on study year and country, sample size, age of study population, mean infection intensity before treatment, diagnostic method used, time between evaluations before and after treatment, cure rate (the percentage of individuals who became helminth egg negative following treatment with an anthelmintic drug), egg reduction rate, adverse events, and trial quality was extracted. Relative risk, including a 95% confidence interval (CI), was used to measure the effect of the drugs on the risk of infection prevalence with a random-effects model.

Results Single-dose oral albendazole, mebendazole, and pyrantel pamoate for infection with A lumbricoides resulted in cure rates of 88% (95% CI, 79%-93%; 557 patients), 95% (95% CI, 91%-97%; 309 patients), and 88% (95% CI, 79%-93%; 131 patients), respectively. Cure rates for infection with T trichiura following treatment with single-dose oral albendazole and mebendazole were 28% (95% CI, 13%-39%; 735 patients) and 36% (95% CI, 16%-51%; 685 patients), respectively. The efficacy of single-dose oral albendazole, mebendazole, and pyrantel pamoate against hookworm infections was 72% (95% CI, 59%-81%; 742 patients), 15% (95% CI, 1%-27%; 853 patients), and 31% (95% CI, 19%-42%; 152 patients), respectively. No pooled relative risks could be calculated for pyrantel pamoate against T trichiura and levamisole for any of the parasites investigated.

Conclusions Single-dose oral albendazole, mebendazole, and pyrantel pamoate show high cure rates against A lumbricoides. For hookworm infection, albendazole was more efficacious than mebendazole and pyrantel pamoate. Treatment of T trichiura with single oral doses of current anthelmintics is unsatisfactory. New anthelmintics are urgently needed.

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therapy was endorsed by World Health Assembly resolution WHA54.19, urging member states to control morbidity due to STH through regular administration of anthelmintic drugs. The declared aim is to regularly target at least 75% of school-aged children and other high-risk groups by the year 2010. Four anthelmintics are currently on the World Health Organization model list of essential medicines for the treatment and control of STH: albendazole, mebendazole, levamisole, and pyrantel pamoate. The former 2 are benzimidazoles, which are widely used against STH, often in combination with other drugs to form an integrated approach targeting the so-called neglected tropical diseases. However, there is considerable concern that large-scale administration of anthelmintics might result in the development and spread of drug-resistant nematodes, which is already a significant problem in veterinary medicine. Recent studies point to another growing problem in public health; administration of a single dose of mebendazole lacked efficacy against hookworm infections among schoolchildren in Zanzibar and Vietnam. Comparisons among these 4 anthelmintics in terms of efficacy are not available, but this kind of information is crucial for guiding national STH control programs.

We conducted a systematic review and meta-analyses to assess the efficacy of currently recommended single-dose, oral regimens of albendazole, mebendazole, levamisole, and pyrantel pamoate for treating infections with A lumbricoides, T trichiura, and hookworm. Our goal was to use both cure rate and egg reduction rate as primary outcome measures for anthelmintic drug efficacy. However, calculating the treatment and control groups’ mean weighted differences in egg count change before and after treatment was not possible due to an insufficient number of studies reporting egg counts in the same format (arithmetic or geometric mean, including standard deviation). Hence, cure rate, defined as the percentage of individuals who became helminth egg negative after treatment with an anthelmintic drug, served as the sole primary outcome measure in our meta-analyses. To gauge safety, we compiled adverse events in the few trials that reported such measures.

Efficacy of Current Anthelmintics

**Selection Criteria**

We selected studies and trials that reported single-dose drug administration with albendazole, mebendazole, levamisole, and pyrantel pamoate for treating infections with A lumbricoides, T trichiura, and hookworm. Studies and trials were stratified by parasite and drug, and the following information was retrieved: year and country where the study was implemented, sample size, age of study population, mean infection intensity before treatment, diagnostic method used, and time period between evaluations before and after treatment.

We were interested in both cure rate and egg reduction rate as primary outcomes. Whenever possible, we extracted data on reported adverse events as measure of safety. Within each of the 12 subanalyses (ie, 3 parasites and 4 drugs), we assessed the effect of dosage with an emphasis on the current recommended single-dose regimens, ie, albendazole (400 mg), mebendazole (500 mg), pyrantel pamoate (10 mg/kg), and levamisole (80 mg or 2.5 mg/kg).

We assessed all randomized controlled trials for the following quality criteria: randomization methods, description of withdrawals and dropouts, and blinding. A numerical score between 0 and 5 was assigned as a measure of study design and reporting quality with 0 being the weakest and 5 designated the strongest, based on the validated scale put forward by Jadad and colleagues.

Only those trials that were randomized and placebo-controlled were included in our meta-analyses. We allowed nonblinded trials to be included in our analysis by acknowledging that such studies are of poorer quality and hence might overestimate treatment efficacy.

**Statistical Analysis**

We used StatsDirect version 2.4.5 statistical software for meta-analyses (StatsDirect Ltd, Cheshire, England). If data from more than 2 randomized controlled trials were available, we combined data from trials within a class (eg, albendazole for treating hookworm infections) and calculated the relative risk (RR), including 95% confidence interval (CI) (significance level of $P < .05$). Because of large variations in study populations, sample sizes, designs, diagnostic methods, and duration be-
between appraisals before and after treatment, we applied random-effects models to compute the pooled relative effectiveness of the studies according to the method described by DerSimonian and Laird. Between-study heterogeneity was examined with Cochran Q statistics (significance level of $P \leq .10$) and $I^2$, whereas potential publication bias was measured using an Egger test and Begg test where a small-study bias is evident when $P \leq .10$.

**RESULTS**

**Studies Identified and Characteristics**

Figure 1 summarizes the search results of our systematic review. We identified 168 studies carried out in 54 countries using albendazole, mebendazole, pyrantel pamoate, and levamisole against *A lumbricoides*, *T trichiura*, and hookworm infections. Table 1 summarizes for each of the 4 drugs and the 3 parasites investigated the number of patients treated and overall cure rates achieved in non–randomized controlled trials.

There were 20 randomized trials published between 1974 and August 2007 that compared an anthelminthic drug with a placebo (TABLE 2). Four trials used Zentel (GlaxoSmithKline, London, England) whereas the source of albendazole was not given in the remaining 6 trials. Egg reduction rates of 86.5% to 100% were reported. Heterogeneity between the studies was pronounced ($Q=25.9; P=.003, I^2=65.3\%$). The pooled random RR for albendazole treatment against *T trichiura* infection relative to placebo was 0.12 (95% CI, 0.07–0.21; $P<.001$) and 12 studies (60%), respectively. According to the quality criteria set forth by Jadad and colleagues, the studies included in the current meta-analyses had scores ranging from 1 to 5.

**Albendazole**

For the treatment of *A lumbricoides* infection, there were 10 placebo-controlled trials including 557 individuals (TABLE 2). Four trials used Zentel (GlaxoSmithKline, London, England) whereas the source of albendazole was not given in the remaining 6 trials. Egg reduction rates of 86.5% to 100% were reported. Heterogeneity between the studies was pronounced ($Q=25.9; P=.003, I^2=65.3\%$). The pooled random RR for albendazole treatment against *A lumbricoides* infection relative to placebo was 0.12 (95% CI, 0.07–0.21; $P<.001$) (FIGURE 2). The results indicated the presence of a publication bias when an Egger test (intercept $-3.34$, $P=.03$) and Begg test, respectively.

**Table 1. Summary of Observational and Case Studies Reporting the Use of Single-Dose Oral Anthelminthic Drugs Against *A lumbricoides*, *T trichiura*, and Hookworm Infection**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Paraphrase</th>
<th>Studies Identified and Included, No.</th>
<th>Individuals, No.</th>
<th>Overall Cure Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albendazole (400 mg)</td>
<td><em>A lumbricoides</em></td>
<td>65</td>
<td>5126</td>
<td>93.9</td>
</tr>
<tr>
<td></td>
<td><em>T trichiura</em></td>
<td>64</td>
<td>5147</td>
<td>43.6</td>
</tr>
<tr>
<td></td>
<td>Hookworm</td>
<td>64</td>
<td>6334</td>
<td>78.4</td>
</tr>
<tr>
<td>Mebendazole (500 mg)</td>
<td><em>A lumbricoides</em></td>
<td>12</td>
<td>2036</td>
<td>96.5</td>
</tr>
<tr>
<td></td>
<td><em>T trichiura</em></td>
<td>12</td>
<td>3112</td>
<td>23.0</td>
</tr>
<tr>
<td></td>
<td>Hookworm</td>
<td>14</td>
<td>3192</td>
<td>22.9</td>
</tr>
<tr>
<td>P yrantel pamoate (10 mg/kg)</td>
<td><em>A lumbricoides</em></td>
<td>17</td>
<td>1208</td>
<td>87.9</td>
</tr>
<tr>
<td></td>
<td><em>T trichiura</em></td>
<td>11</td>
<td>458</td>
<td>28.1</td>
</tr>
<tr>
<td></td>
<td>Hookworm</td>
<td>21</td>
<td>1208</td>
<td>87.9</td>
</tr>
<tr>
<td>Levamisole (2.5 mg/kg)</td>
<td><em>A lumbricoides</em></td>
<td>3</td>
<td>202</td>
<td>91.5</td>
</tr>
<tr>
<td></td>
<td><em>T trichiura</em></td>
<td>2</td>
<td>186</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Hookworm</td>
<td>4</td>
<td>178</td>
<td>38.2</td>
</tr>
</tbody>
</table>

For the treatment of *T trichiura* infection, we used results from 9 randomized placebo-controlled trials, including 1 multicenter trial and 735 patients, for our meta-analysis (TABLE 2). Cochran Q statistics revealed heterogeneity ($Q=76.8; P<.001, I^2=89.5\%$). Relative to placebo, the pooled random RR for albendazole against *T trichiura* infection was 0.72 (95% CI, 0.61–0.87; $P=.001$) (Figure 2). There was an indication of a publication bias (Egger test, intercept $-1.48$, $P=.03$; Begg test, respectively).

**Figure 1. Decision Tree Showing Inclusion and Exclusion of Studies Identified**

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**Table 2. Summary of Observational and Case Studies Reporting the Use of Single-Dose Oral Anthelminthic Drugs Against *A lumbricoides*, *T trichiura*, and Hookworm Infection**

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Table 2. Randomized Placebo-Controlled Studies Reporting the Use of Single-Dose Oral Albendazole (400 mg) Against *Ascaris lumbricoides*, *Trichuris trichiura*, and Hookworm Infection

<table>
<thead>
<tr>
<th>Source (Location, Year Trial Was Implemented)</th>
<th>Age, y</th>
<th>Diagnostic Approach</th>
<th>Treatment Evaluation</th>
<th>Study Designb</th>
<th>Quality Assessmentb</th>
<th>Product Used</th>
<th>Parasite</th>
<th>Individuals, No.</th>
<th>Mean Pretreatment Infection Intensity (Eggs/g)</th>
<th>Cure Rate</th>
<th>Egg Reduction Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovedoff24 (Philippines, 1984)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Double-blind; follow-up and withdrawal not described</td>
<td>2</td>
<td>NA</td>
<td>A lumbricoides</td>
<td>16 NA 100 100</td>
<td>T trichiura 29 NA 68.9 NA</td>
<td>100 100</td>
<td></td>
</tr>
<tr>
<td>Sinniah et al28 (Malaysia, 1990)</td>
<td>6-13</td>
<td>Brine flotation technique and Beavers technique</td>
<td>3 wk after treatment</td>
<td>Blinding not known; follow-up and withdrawal not described</td>
<td>1</td>
<td>NA</td>
<td>A lumbricoides</td>
<td>56 80 953 91.1 99.2</td>
<td>T trichiura 52 21 635 42.3 71.2</td>
<td>100 100</td>
<td></td>
</tr>
<tr>
<td>Beach et al31 (Haiti, 1999)</td>
<td>7.4 (Mean)</td>
<td>Formalin ethyl acetate concentration technique</td>
<td>5 wk after treatment</td>
<td>Double-blind; follow-up and withdrawal described</td>
<td>4</td>
<td>Zentel29</td>
<td>A lumbricoides</td>
<td>62 284 98.4 100</td>
<td>T trichiura 93 120 52.7 42.2</td>
<td>100 100</td>
<td></td>
</tr>
<tr>
<td>Stephenson et al29 (Kenya, 1990)</td>
<td>6-12</td>
<td>Modified Kato-Katz technique</td>
<td>7 wk after treatment</td>
<td>Blinding not known; follow-up and withdrawal not described</td>
<td>2</td>
<td>Zentel</td>
<td>A lumbricoides</td>
<td>7 69 100 100</td>
<td>T trichiura 17 211 0 0</td>
<td>100 100</td>
<td></td>
</tr>
<tr>
<td>Olds et al22 (Africa, Asia, 1999)</td>
<td>10.4 (Mean)</td>
<td>Kato-Katz technique (2 samples)</td>
<td>45 d after treatment</td>
<td>Double-blind; follow-up and withdrawal described</td>
<td>5</td>
<td>NA</td>
<td>A lumbricoides</td>
<td>219 NA 81.7 NA</td>
<td>T trichiura 297 NA 33.3 NA</td>
<td>100 100</td>
<td></td>
</tr>
<tr>
<td>Bwibo and Pamba21 (Kenya, 1984)</td>
<td>13.2 (Mean)</td>
<td>Kato-Katz technique (2 samples)</td>
<td>21 d after treatment</td>
<td>Blinding not known; follow-up and withdrawal described</td>
<td>3</td>
<td>NA</td>
<td>A lumbricoides</td>
<td>40 NA 90.0 93.1</td>
<td>T trichiura 31 NA 83.9 89.7</td>
<td>100 100</td>
<td></td>
</tr>
<tr>
<td>El-Masry et al20 (Egypt, 1983)</td>
<td>25.7 (Mean)</td>
<td>Stool egg counts and merthiolate-iodine-formaldehyde concentration for 5 d</td>
<td>2 wk after treatment</td>
<td>Double-blind; follow-up and withdrawal not described</td>
<td>2</td>
<td>Zentel</td>
<td>A lumbricoides</td>
<td>11 515 100 100</td>
<td>T trichiura 19 404 89.0 NA</td>
<td>100 100</td>
<td></td>
</tr>
<tr>
<td>Oyediran and Oyejide19 (Nigeria, 1983)</td>
<td>8-17</td>
<td>Concentration and Kato-Katz technique</td>
<td>14 d after treatment</td>
<td>Double-blind; follow-up and withdrawal not described</td>
<td>4</td>
<td>NA</td>
<td>A lumbricoides</td>
<td>27 NA 85.2 99.8</td>
<td>T trichiura 29 NA 37.9 69.3</td>
<td>100 100</td>
<td></td>
</tr>
<tr>
<td>Upatham et al27 (Thailand, 1989)</td>
<td>Adults</td>
<td>Kato-Katz technique (up to 3 samples)</td>
<td>1 mo after treatment</td>
<td>Double-blind; follow-up and withdrawal not described</td>
<td>2</td>
<td>Zentel</td>
<td>A lumbricoides</td>
<td>78 931 94.9 99.3</td>
<td>T trichiura 146 655 33.6 59.4</td>
<td>100 100</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
P = .02). Egg reduction rates in these 9 trials ranged from 0% to 89.7%.

For the treatment of hookworm infection, we included 14 randomized placebo-controlled trials with 742 patients in our meta-analysis (Table 2).\textsuperscript{12-19,24-26,28-31} The effect of albendazole on \textit{N americanus} and \textit{A duodenale} was assessed in 6 and 2 trials, respectively. In the remaining 6 trials, hookworms were not identified at species level. Egg reduction rates varied from 64.2% to 100%. The random RR for albendazole treatment for hookworm infection (both species) was 0.28 (95% CI, 0.19-0.41; \textit{P} < .001) (Figure 2). There was considerable heterogeneity between trials (\textit{Q} = 83.6, \textit{P} < .001, \textit{I}^2 = 84.8%). According to the Egger test, there was a publication bias (\textit{P} = .003). However, the Begg test showed no statistical significance (\textit{P} = .12).

Albendazole was well tolerated. In 11 studies included in our meta-analysis, no significant adverse events were reported following albendazole administration.\textsuperscript{12,19-23,26-28,31,32} One trial carried out in the Philippines reported nausea and diarrhea in 2 and 1 individuals, respectively.\textsuperscript{34} There was no indication whether or not adverse events were assessed in the remaining 2 randomized placebo-controlled trials included in our meta-analysis.\textsuperscript{29,33}

**Mebendazole**

For the treatment of \textit{A lumbricoides} infection, only 3 studies including 309 individuals were placebo-controlled trials and hence were included in our meta-analysis (Table 3).\textsuperscript{11,25,34} Egg reduction rates ranged between 96.1% and 99.0%. A pooled random RR of 0.05 (95% CI, 0.03-0.09; \textit{P} < .001) was calculated (FIGURE 3). Heterogeneity was low (\textit{Q} = 1.7, \textit{P} = .42, \textit{I}^2 = 0%). Because there were only 3 studies included, it was not possible to investigate whether publication bias was an issue.

For the treatment of \textit{T trichiura} infection, only 3 studies (685 patients) fulfilled the selection criteria and were included in our meta-analysis (Table 3).\textsuperscript{11,25,34} Egg reduction rates were 81.0% to 92.8%. The pooled random RR was 0.64 (95% CI, 0.49-0.84; \textit{P} = .001). Heterogeneity was pronounced (\textit{Q} = 33.4; \textit{P} < .001, \textit{I}^2 = 94.5%) (Figure 3). Given the low number of studies entering our meta-analysis, we could not determine whether publication bias was an issue.

For the treatment of hookworm infection, 6 placebo-controlled trials (853 patients) met our inclusion criteria and were used for our meta-analysis (Table 3).\textsuperscript{11,12,25,30,33,34} The overall random RR was 0.85 (95% CI, 0.73-0.99; \textit{P} = .01). Heterogeneity was high (\textit{Q} = 49.3; \textit{P} < .001, \textit{I}^2 = 89.6%) (Figure 3).

Although 1 trial found no reduction in

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**Table 2.** Randomized Placebo-Controlled Studies Reporting the Use of Single-Dose Oral Albendazole (400 mg) Against \textit{Ascaris lumbricoides}, \textit{Trichuris trichiura}, and Hookworm Infection (cont)

<table>
<thead>
<tr>
<th>Source (Location, Year Trial Was Implemented)</th>
<th>Age, y</th>
<th>Diagnostic Approach</th>
<th>Treatment Evaluation</th>
<th>Study Designa</th>
<th>Quality Assessmentb</th>
<th>Product Used</th>
<th>Parasite</th>
<th>Efficacy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al\textsuperscript{26} (Malaysia, 1989)</td>
<td>8-9</td>
<td>Direct fecal smear</td>
<td>4 wk after treatment</td>
<td>Blinding not known; follow-up and withdrawal not described</td>
<td>1 NA</td>
<td>A lumbricoides</td>
<td>41 NA</td>
<td>90.2 86.5</td>
</tr>
<tr>
<td>Flohr et al\textsuperscript{12} (Vietnam, 2007)</td>
<td>≥16</td>
<td>Salt flotation technique (1 sample)</td>
<td>2 wk after treatment</td>
<td>Double-blind; follow-up and withdrawal described</td>
<td>5 Mekcazel\textsuperscript{1} Hookworm</td>
<td>47</td>
<td>1120\textsuperscript{c}</td>
<td>45.0 79.0</td>
</tr>
<tr>
<td>Sacko et al\textsuperscript{33} (Mali, 1999)</td>
<td>3-70</td>
<td>Kato-Katz technique (2 samples)</td>
<td>10 d after treatment</td>
<td>Single-blind; follow-up and withdrawal described</td>
<td>2 Zentel Hookworm (A americanus)</td>
<td>37</td>
<td>174.5\textsuperscript{c}</td>
<td>83.8 97.7</td>
</tr>
<tr>
<td>Farid et al\textsuperscript{32} (Egypt, 1984)</td>
<td>NA</td>
<td>Kato-Katz technique</td>
<td>NA</td>
<td>Blinding not known; follow-up and withdrawal not described</td>
<td>1 NA</td>
<td>Hookworm (A duodenale)</td>
<td>19 NA</td>
<td>89.4 NA</td>
</tr>
<tr>
<td>Morgan et al\textsuperscript{21} (Mâlaysia, 1963)</td>
<td>6-19</td>
<td>Kato-Katz technique</td>
<td>21 d after treatment</td>
<td>Double-blind; follow-up and withdrawal described</td>
<td>3 Zentel Hookworm (A americanus)</td>
<td>28</td>
<td>564\textsuperscript{c}</td>
<td>85.0 94.9</td>
</tr>
</tbody>
</table>

**Abbreviation:** NA, not available.

aAll studies were randomized, placebo-controlled trials.

bA numerical score between 0 and 5 was assigned as a measure of study design and reporting quality (0 being the weakest, 5 the strongest), based on the validated scale put forward by Jadad and colleagues.\textsuperscript{15}

\textsuperscript{1}Arithmetic mean.

\textsuperscript{2}Manufactured by GlaxoSmithKline, London, England.

\textsuperscript{3}Geometric mean.

\textsuperscript{4}Manufactured by Mekophar Chemical Pharmaceutical Joint Stock Co, Ho Chi Minh City, Vietnam.
hookworm egg burden following mebendazole treatment,\textsuperscript{10} 1 trial found a high egg reduction rate of 98.3%\textsuperscript{25} According to an Egger test, there was no indication of a publication bias ($P=.15$). Mebendazole was well tolerated. In 3 trials, no adverse events were observed.\textsuperscript{11,12,34} One study reported abdominal discomfort in 6 of 45 children who were treated with 500-mg mebendazole.\textsuperscript{25} No information on adverse events was given in the remaining 2 studies.\textsuperscript{30,33}

\textbf{Pyrantel Pamoate}

For the treatment of \textit{A lumbricoides} infection, there were 3 randomized placebo-controlled trials including 131 patients (Table 4),\textsuperscript{17,18,28} and the pooled random RR was 0.12 (95% CI, 0.07-0.21; $P<.001$). There was a low level of heterogeneity ($Q=2.3; P=3.2, I^2=11.5\%$) (FIGURE 4). One of the trials reported an egg reduction rate of 87.9%.\textsuperscript{28} Because of the small number of trials included in our meta-analysis, it was not possible to assess whether there was a publication bias.

For the treatment of \textit{T trichiura} infection, only 2 trials were randomized and placebo-controlled (Table 4), and calculating random RR was not feasible. The cure rates in these 2 trials were 11.5%\textsuperscript{28} and 38.1%.\textsuperscript{17} In one of the trials, an egg reduction rate was also reported; it was 52.0%.\textsuperscript{28}

For the treatment of hookworm infection, there were 4 randomized placebo-controlled trials (152 patients) (Table 4),\textsuperscript{17,18,28,30} resulting in a random RR of 0.69 (95% CI, 0.58-0.81; $P<.001$) (Figure 4). Heterogeneity was low ($Q=3.9; P=0.26, I^2=24.3\%$). Egg reduction rates ranged from 56.4% to 75.0%. Based on an Egger test, there was no indication of a publication bias ($P=.93$).

Almost half of the patients (47.8%) treated with pyrantel pamoate in a study in Nigeria experienced adverse events, mainly abdominal pain, nausea, and

\begin{table}[ht]
\centering
\begin{tabular}{|l|l|l|l|l|l|l|l|}
\hline
\textbf{Source (Location, Year Trial Was Implemented)} & \textbf{Age, y} & \textbf{Diagnostic Approach} & \textbf{Treatment Evaluation} & \textbf{Study Design\textsuperscript{a}} & \textbf{Quality Assessment\textsuperscript{b}} & \textbf{Product Used} & \textbf{Parasite} & \textbf{Active Treatment Group} \\
\hline
Albonico et al\textsuperscript{11} (Tanzania, 2003) & 7-18 & Kato-Katz technique (1 sample) & 21 d after treatment & Not blinded; follow-up and withdrawal described & 3 & Vermox\textsuperscript{c} & \textit{A lumbricoides} & 141 & 114 & 96.5 & 99.0 \\
\hline
Albonico et al\textsuperscript{33} (Tanzania (Pemba), 2002) & 9.5 (Mean) & Kato-Katz technique (1 sample) & 21 d after treatment & Not blinded; follow-up and withdrawal described & 3 & NA & \textit{A lumbricoides} & 107 & 5\textsuperscript{d} & 95.0 & 96.1 \\
\hline
Abadi\textsuperscript{25} (Indonesia, 1985) & 2-70 & Kato-Katz technique (1 sample) and Harada Mori & 2-4 wk after treatment & Double-blind; follow-up and withdrawal not described & 3 & NA & \textit{A lumbricoides} & 61 & 37.5\textsuperscript{e} & 99.4 & 99.0 \\
\hline
De Clercq et al\textsuperscript{17} (Mal, 1997) & 5-54 & Kato-Katz technique (2 samples) & 4 wk after treatment & Single blinded; follow-up and withdrawal described & 2 & Vermox & \textit{Hookworm (N americanus, Ancylostoma duodenale)} & 35 & 264.2\textsuperscript{f} & 22.0 & 0 \\
\hline
Flohr et al\textsuperscript{12} (Vietnam, 2007) & 6-11 & Salt flotation technique (1 sample) & 2 wk after treatment & Double-blind; follow-up and withdrawal described & 5 & Phardazone\textsuperscript{g} & \textit{Hookworm (N americanus)} & 90 & 263\textsuperscript{h} & 38 & 52 \\
\hline
Sacko et al\textsuperscript{33} (Mal, 1998) & 3-70 & Kato Katz technique (2 samples) & 10 d after treatment & Single-blind; follow-up and withdrawal described & 2 & Vermox & \textit{Hookworm (N americanus)} & 35 & 185.3\textsuperscript{i} & 51.4 & 68.5 \\
\hline
\end{tabular}
\caption{Randomized Placebo-Controlled Studies Reporting the Use of Single-Dose Oral Mebendazole (500 mg) Against \textit{Ascaris lumbricoides}, \textit{T trichiura}, and Hookworm Infection}
\end{table}
Efficacy of Current Anthelmintics

Dizziness. Two studies did not describe the occurrence of adverse events, and 1 trial found that pyrantel pamoate was well tolerated.

**Levamisole**

For the treatment of *A. lumbricoides* infection, 2 levamisole dosages are currently recommended: a single oral dose of 80 mg or 2.5 mg/kg (http://www.who.int/wormcontrol/statistics/useful_info/en/index3.html). For the latter dosage, which had been applied in 3 studies, an overall cure rate of 91.5% was obtained (Table 1). Two of these studies were placebo-controlled, but none was randomized, so calculating a random RR was not possible.

For the treatment of *T. trichiura* infection, we identified only 1 randomized placebo-controlled trial. It was carried out in Tanzania, and children infected with *T. trichiura* received either 40- or 80-mg levamisole, depending on weight (equivalent to 1.25-2.5 mg/kg). A low cure rate (9.6%) and a low egg reduction rate (41.5%) were found. The overall cure rate of 2 non-randomized placebo-controlled trials was 8.6% (Table 1).

For the treatment of hookworm infection, none of the studies identified fulfilled our inclusion criteria for meta-analysis, so calculating a random RR was not possible. One randomized placebo-controlled trial carried out in Tanzania and another one in Malawi administering levamisole at 40 or 80 mg and 80 or 120 mg, depending on the individual's weight or age, achieved cure rates of 11.9% and 10%, respectively. We calculated an overall cure rate of 38.2% in 4 non-randomized placebo-controlled trials (Table 1).

**COMMENT**

Hundreds of millions of people are affected by STH the world over, with a global burden that might be as high as 39 million disability-adjusted life-years, which is similar to the global burden owing to malaria. Nonetheless, STH and other helminth, protozoan, and bacterial infections have been called neglected tropical diseases (NTDs) because these diseases are particularly rampant in developing countries and inflict a disproportionate burden on the global poor. There is growing awareness of the public-health significance of NTDs, and concerted advocacy for their control has resulted in increased political will and financial means to combat NTDs. Preventive chemotherapy plays a seminal role. In 2006, for example, millions of school-aged children were given albendazole or mebendazole (http://www.who.int/wormcontrol/newsletter/PPC8_eng.pdf). However, to achieve the 2010 global target to regularly treat at least 75% of all school-aged chil-

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**Table 4. Randomized Placebo-Controlled Studies Reporting the Use of Single-Dose Oral Pyrantel Pamoate (10 mg/kg) Against Ascaris lumbricoides, Trichuris trichiura, and Hookworm Infection**

<table>
<thead>
<tr>
<th>Source (Location, Year Trial Was Implemented)</th>
<th>Age, y</th>
<th>Diagnostic Approach</th>
<th>Treatment Evaluation</th>
<th>Study Designa</th>
<th>Quality Assessmentb</th>
<th>Product Used</th>
<th>Parasite</th>
<th>Individuals, No.</th>
<th>Mean Pretreatment Intensity (Eggs/g)c</th>
<th>Cure Rate</th>
<th>Egg Reduction Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kane et al16 (Nigeria, 1973)</td>
<td>6-17</td>
<td>Quantitative egg count</td>
<td>42 d after treatment</td>
<td>Blinding not known; follow-up and withdrawal not described</td>
<td>1</td>
<td>Combantrind</td>
<td><em>A. lumbricoides</em></td>
<td>64</td>
<td>NA</td>
<td>93.8</td>
<td>NA</td>
</tr>
<tr>
<td>Chege et al17 (Kenya, 1974)</td>
<td>Children</td>
<td>Formol ether technique (1 sample)</td>
<td>2 mo after treatment</td>
<td>Blinding not known; follow-up and withdrawal described</td>
<td>3</td>
<td>NA</td>
<td><em>A. lumbricoides</em></td>
<td>20</td>
<td>NA</td>
<td>90.0</td>
<td>56.4</td>
</tr>
<tr>
<td>Sminiah et al18 (Malaysia, 1992)</td>
<td>6-13</td>
<td>Brine flotation technique and Beaver technique</td>
<td>3 wk after treatment</td>
<td>Blinding not known</td>
<td>1</td>
<td>NA</td>
<td><em>A. lumbricoides</em></td>
<td>47</td>
<td>107,958</td>
<td>85.1</td>
<td>87.9</td>
</tr>
<tr>
<td>De Oerçiq et al19 (Mali, 1997)</td>
<td>5-54</td>
<td>Kato-Katz technique (2 samples)</td>
<td>4 wk after treatment</td>
<td>Single-blind; follow-up and withdrawal described</td>
<td>2</td>
<td>Combantrin</td>
<td><em>Hookworm</em> (N americanus)</td>
<td>29</td>
<td>472.1</td>
<td>44.8</td>
<td>75.0</td>
</tr>
</tbody>
</table>

**Abbreviation:** NA, not available.

a All studies were randomized, placebo-controlled trials.

b A numerical score between 0 and 5 was assigned as a measure of study design and reporting quality (0 being the weakest, 5 the strongest), based on the validated scale put forward by Jadad and colleagues.

15 All means were arithmetic.

16 Manufactured by Pfizer, New York, New York.
dren and other populations at risk of STH, the frequency of benzimidazole administration will increase further. Knowledge on the safety and efficacy of anthelminthics is therefore crucial to guide clinicians and control program officers in selecting the appropriate drug against specific STH infections.12

Figure 2. Risk Ratio Estimates and Pooled Random Risk Ratios of Randomized, Placebo-Controlled Trials of Albendazole Against Ascaris lumbricoides, Trichuris trichiura, and Hookworm Infections

<table>
<thead>
<tr>
<th>Source</th>
<th>No. Not Cured/Total No.</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Albendazole</td>
<td>Placebo</td>
</tr>
<tr>
<td>Oyediran and Oyejide,19 1983</td>
<td>5/27</td>
<td>22/24</td>
</tr>
<tr>
<td>El-Masry et al,21 1983</td>
<td>0/11</td>
<td>4/40</td>
</tr>
<tr>
<td>Bebbo and Pamba,22 1984</td>
<td>4/43</td>
<td>31/36</td>
</tr>
<tr>
<td>Oyediran and Oyejide,21 1983</td>
<td>5/16</td>
<td>12/12</td>
</tr>
<tr>
<td>Chien et al,26 1989</td>
<td>4/41</td>
<td>29/41</td>
</tr>
<tr>
<td>Stephenson et al,27 1990</td>
<td>0/7</td>
<td>15/15</td>
</tr>
<tr>
<td>Upatham et al,27 1990</td>
<td>4/78</td>
<td>44/41</td>
</tr>
<tr>
<td>Sinniah et al,28 1990</td>
<td>5/56</td>
<td>10/10</td>
</tr>
<tr>
<td>Beach et al,29 1995</td>
<td>1/62</td>
<td>29/82</td>
</tr>
<tr>
<td>Oyediran and Oyejide,19 1983</td>
<td>0/16</td>
<td>12/12</td>
</tr>
<tr>
<td>El-Masry et al,20 1983</td>
<td>0/11</td>
<td>4/40</td>
</tr>
<tr>
<td>Bebbo and Pamba,22 1984</td>
<td>4/43</td>
<td>31/36</td>
</tr>
<tr>
<td>Oyediran and Oyejide,19 1983</td>
<td>0/16</td>
<td>12/12</td>
</tr>
<tr>
<td>Chien et al,26 1989</td>
<td>4/41</td>
<td>29/41</td>
</tr>
<tr>
<td>Stephenson et al,27 1990</td>
<td>0/7</td>
<td>15/15</td>
</tr>
<tr>
<td>Upatham et al,27 1990</td>
<td>4/78</td>
<td>44/41</td>
</tr>
<tr>
<td>Sinniah et al,28 1990</td>
<td>5/56</td>
<td>10/10</td>
</tr>
<tr>
<td>Beach et al,29 1995</td>
<td>1/62</td>
<td>29/82</td>
</tr>
</tbody>
</table>

Combined (random-effects model) | 0.12 (0.07-0.21) |

Rectangles indicate risk ratios (RRs), and sizes of the rectangles represent the weight given to each study in the meta-analysis. Diamond and vertical dashed line indicate combined RR; horizontal lines indicate 95% confidence intervals.

To our knowledge, we present the first systematic review and meta-analysis of the comparative efficacy of the 4 anthelmintic drugs that are currently on the
World Health Organization model list of essential medicines. The anthelminthic efficacy of albendazole has been reviewed before (although the review made no attempt to distinguish between randomized, nonrandomized, and placebo-controlled trials), and recently, a meta-analysis of randomized controlled trials was presented regarding the effect of simultaneous treatment targeting 2 or more NTDs.

An important observation of our systematic review is the paucity of high-quality studies, which are crucial to guide clinical decisions about which anthelminthic drug to use. This issue is underscored by the following considerations. First, only a few studies met our inclusion criteria; ie, they were randomized and placebo-controlled and used the currently recommended single oral dose regimen. Examining the effect of anthelminthics compared with placebo by means of meta-analysis would not have been possible at all if we would have included only double-blind studies. The lack of high-quality trials might be explained, at least partially, by the fact that the majority of trials were carried out more than 20 years ago. It is noteworthy that not a single randomized, placebo-controlled trial using levamisole at the recommended dose (ie, 80 mg or 2.5 mg/kg) could be identified in the peer-reviewed literature according to our selection criteria.

Second, results on both cure and egg reduction rates should be reported as primary outcome measures regarding the efficacy of anthelminthic drugs. The latter measure is of particular relevance because infection intensity correlates with worm burden and hence morbidity due to helminth infections. However, calculation of the combined mean difference of egg counts between treatment and placebo groups was not possible because some trials re-
ported no data on egg counts and others reported either arithmetic or geometric means, often in the absence of the standard deviation.

Third, a number of additional methodological issues need to be considered because they might have influenced our findings; therefore, caution must precede efforts to make policy recommendations. For example, the sample sizes in several of the trials included in our meta-analyses were small (eg, <50 individuals infected with a specific STH and treated with an anthelminthic drug), so these trials were likely underpowered. With regard to the diagnostic approach taken, most trials evaluated drug efficacy based on a single stool sample per individual examined before and after treatment, employing only 1 diagnostic test. It is widely acknowledged that there is significant day-to-day and intraspecimen variation in helminth egg output and that diagnostic tests lack sensitivity, particularly for low infection intensities.45,46

Fourth, our results point to a publication bias as evidenced by a considerable number of our subanalyses reporting significant P values according to either an Egger test or Begg test. It appears that anthelminthic drug trials resulting in significant cure rates were more likely to be reported in the peer-reviewed literature than those lacking efficacy. Finally, some trials failed to report whether adverse events were monitored at all, and safety measures overall lacked quality.

Although all 4 anthelmintics are considered to exhibit a broad spectrum of activity, we identified significant therapeutic differences when they were administered at single-dose oral regimens. Differences in helminth species-specific susceptibilities are multifactorial, including drug- and batch-related variations, differences between individual parasite strains, differences between infections with N americanus and A duodenale (in the case of hookworm), infection intensities before treatment, host-specific factors (eg, infections), and the emergence of drug resistance.12,30,47 All drugs were highly efficacious against A lumbricoides in a single dose. With regard to T trichiura, our results indicated that current anthelmintics were unsatisfactory as shown by low cure rates revealed by our meta-analyses. Indeed, the risk of still being infected with T trichiura after a single 400-mg oral dose of albendazole was only reduced by 28%. A similarly low risk reduction was found after a single 500-mg oral dose of mebendazole (36%). Low overall cure rates of 28.1% and 8.6% were calculated from non–randomized placebo-controlled trials for pyrantel pamoate and levamisole, respectively.

No conclusion on the effect on infection intensities can be made, although this outcome measure is of key importance from the point of view of morbidity control. It should be noted that clinical manifestations can be serious for T trichiura infection, such as chronic dysentery or rectal prolapse.1 Higher cure and egg reduction rates were reported when 3-day dose schedules of albendazole (400 mg for 3 days) and mebendazole (100 mg twice daily for 3 days) were administered.1 However, such treatment schemes are not

### Figure 4. Risk Ratio Estimates and Pooled Random Risk Ratios of Randomized, Placebo-Controlled Trials of Pyrantel Pamoate Against Ascaris lumbricoides and Hookworm Infections

#### Ascaris lumbricoides

<table>
<thead>
<tr>
<th>Source</th>
<th>No. Not Cured/Total No.</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chege et al,17 1974</td>
<td>2/20/18</td>
<td>0.12 (0.03-0.37)</td>
</tr>
<tr>
<td>Kale,18 1977</td>
<td>4/64/30</td>
<td>0.07 (0.03-0.18)</td>
</tr>
<tr>
<td>Sinniah et al,28 1990</td>
<td>7/47/10</td>
<td>0.15 (0.08-0.30)</td>
</tr>
<tr>
<td>Combined (random-effects model)</td>
<td></td>
<td>0.12 (0.07-0.21)</td>
</tr>
</tbody>
</table>

#### Hookworm

<table>
<thead>
<tr>
<th>Source</th>
<th>No. Not Cured/Total No.</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chege et al,17 1974</td>
<td>35/60/48</td>
<td>0.58 (0.46-0.71)</td>
</tr>
<tr>
<td>Kale,18 1977</td>
<td>39/55/24</td>
<td>0.80 (0.64-1.02)</td>
</tr>
<tr>
<td>Sinniah et al,28 1990</td>
<td>5/5/5</td>
<td>0.63 (0.39-1.41)</td>
</tr>
<tr>
<td>De Clercq et al,30 1997</td>
<td>16/29/24</td>
<td>0.71 (0.47-1.03)</td>
</tr>
<tr>
<td>Combined (random-effects model)</td>
<td></td>
<td>0.69 (0.58-0.81)</td>
</tr>
</tbody>
</table>

Rectangles indicate risk ratios (RRs), and sizes of the rectangles represent the weight given to each study in the meta-analysis. Diamond and vertical dashed line indicate combined RR; horizontal lines indicate 95% confidence intervals.
feasible for large-scale preventive chemotherapy because they are likely to result in reduced compliance rates.

With regard to hookworms, our data suggest that, when administered as single-dose therapy, albendazole was the most efficacious drug reducing the prevalence of hookworm infection. At the recommended single dose of 400 mg, albendazole cured hookworm infections by 72%. The efficacy of mebendazole and pyrantel against hookworm infections was 15% and 32%, respectively. Cure rates from nonrandomized, placebo-controlled trials following levamisole treatment were low (10%–38%). Pyrantel pamoate and levamisole are currently regarded as alternative drugs for the treatment of hookworms. Although the low efficacy of single-dose mebendazole against hookworm infection has been described and thus a 3-day mebendazole therapy (100 mg twice daily for 3 days) has been recommended, single-dose mebendazole treatment is widely used. For example, recently in Ghana, an estimated 4 to 5 million children aged 3 to 15 years were treated with single 500-mg mebendazole. Nonetheless, we do not disavow that single-dose mebendazole might have a significant impact on infection intensity and hence morbidity reduction.

CONCLUSION

Our systematic review and meta-analysis identified a number of gaps regarding the evidence base of current anthelminthic drugs. Well-designed, adequately powered, and rigorously implemented trials should address these gaps, not only providing new data regarding the efficacy (considering both cure and egg reduction rates) of anthelminthic drugs against the main species of STH, but also aiding in establishing benchmarks for subsequent monitoring of drug resistance. In turn, these findings will be crucial to enhance the effectiveness of national control programs targeting STH that might be implemented in an integrated fashion addressing multiple NTDs.

Our results showed that the efficacy of single-dose oral albendazole for curing hookworm infections was higher than that of mebendazole, levamisole, and pyrantel pamoate, although few studies compared the drugs head-to-head. Finally, our findings stress the pressing need for discovery and development of novel anthelminthic drugs, ideally with different mechanisms of action to complement the current therapeutic arsenal.

To our knowledge, tribendimidine is the only anthelminthic drug for STH in late-stage development and registration. Compared with albendazole, tribendimidine achieved superior cure rates against hookworm, particularly *N. americanus*, and is similarly effective against *A. lumbricoides*, but also resulted in disappoiting cure rates against *T. trichiura* infection when used in a single oral dose. Phase 4 trials in China involving more than 2000 individuals have been completed recently and confirmed the safety of tribendimidine also in school-aged children.

Author Contributions: Dr Keiser had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Keiser, Utzinger.

Acquisition of data: Keiser.

Analysis and interpretation of data: Keiser, Utzinger.

Drafting of the manuscript: Keiser, Utzinger.

Critical revision of the manuscript for important intellectual content: Keiser, Utzinger.

Statistical analysis: Keiser.

Obtained funding: Keiser, Utzinger.

Financial Disclosures: None reported.

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Role of the Sponsor: The Swiss National Science Foundation had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: We thank the library team of the Swiss Tropical Institute for its help in obtaining relevant articles.

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