Efficacy of Current Drugs Against Soil-Transmitted Helminth Infections

Systematic Review and Meta-analysis

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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 anthelminthic 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 anthelminthics is unsatisfactory. New anthelminthics are urgently needed.

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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.[1,2,4] Estimates of the global burden due to STH range between 4.5 million and 39 million disability-adjusted life-years.[5,6] 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]

Despite progress made in recent years, there is still no vaccine against STH.[7] In May 2001, preventive chemo-

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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 anthelminthic drugs. The declared aim is to regularly target at least 75% of school-aged children and other high-risk groups by the year 2010.[5,8] Four anthelminthics 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.[5,9] 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.[3,6,10] However, there is considerable concern that large-scale administration of anthelminthics 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[11] and Vietnam.[12] Comparisons among these 4 anthelminthics 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. We examined randomized, placebo-controlled trials and compared the efficacy of the different anthelminthics against placebo. Additionally, we extracted data on safety whenever possible.

METHODS

We adhered to the Quality of Reporting of Meta-analyses (QUOROM) guidelines.[13] We searched PubMed (http://www.ncbi.nlm.nih.gov) (1966 to August 2007), ISI Web of Science (http://www.isiknowledge.com) (1960 to August 2007), ScienceDirect (http://www.sciencedirect.com) (1960 to August 2007), the Cochrane Central Register of Controlled Trials (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html) (1960 to August 2007), and the World Health Organization library database (1960 to August 2007) to identify clinical trials, studies, and case reports pertaining to the use of albendazole, mebendazole, levamisole, and pyrantel pamoate for treating infections with *A lumbricoides*, hookworm, and *T trichiura*. No restrictions were set on year or language of publication. We used the terms *albendazole*, *mebendazole*, *levamisole*, and *pyrantel pamoate* in combination with *trial* or *study* or *case report* and *ascariasis*, *Ascaris lumbricoides*, *hookworm*, *Ancylostoma duodenale*, *Necator americanus*, *trichuriasis*, *Trichuris trichiura*, and *soil-transmitted helminths*. Bibliographies of identified articles were screened for additional relevant studies.

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*, hookworm, and *T trichiura*. 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).[1,5,8,9,14]

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.[15]

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.

Our goal was to use both cure rate and egg reduction rate as primary outcome measures for anthelminthic 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 anthelminthic 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.

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-

tween 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.[16] 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[11,12,17-34] (TABLES 2, 3, and 4). The efficacy of single oral doses of albendazole (400 mg), mebendazole (500 mg), and pyrantel pamoate (10 mg/kg) was assessed in 14, 6, and 4 randomized studies, respectively. We could not identify a single study that evaluated the efficacy of levamisole in a randomized placebo-controlled trial at current recommended doses. Anthelminthic drug efficacy was assessed by different diagnostic methods and at different time points after treatment (usually between 2 and 7 weeks following drug administration). Although some studies focused on school-aged children, others administered drugs to adults; hence, different age groups were involved. Infection intensities before treatment showed large variations from one trial to another.

Methodological Quality

Tables 2, 3, and 4 summarize methodological quality issues of the 20 trials included in our meta-analyses. According to our inclusion criteria, all studies included a placebo group. The design of the trials were double-blind (n=9), single-blind (n=2), or nonblinded (n=2), whereas no information was available regarding the blinding procedure in the remaining 7 studies. Concealment allocation and withdrawal from studies was clearly described in 5 (25%) and 12 studies (60%), respectively. According to the quality criteria set forth by Jadad and colleagues,[15] 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).[19,20,22,24,26-29,31,32] 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, $P=.001$) and a Begg test were used ($P=.03$).

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).[19,22,24,26-29,31,32] 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,

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

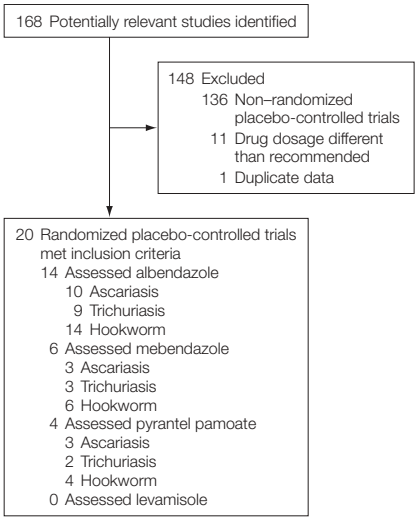


Table 1. Summary of Observational and Case Studies Reporting the Use of Single-Dose Oral Albendazole, Mebendazole, Pyrantel Pamoate, and Levamisole Against *Ascaris lumbricoides*, *Trichuris trichiura*, and Hookworm Infection

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

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

Source (Location, Year Trial Was Implemented)	Age, y	Diagnostic Approach	Treatment Evaluation	Study Design[a]	Quality Assessment[b]	Product Used	Parasite	Active Treatment Group			
								Individuals, No.	Mean Pretreatment Infection Intensity (Eggs/g)	Efficacy, %	
										Cure Rate	Egg Reduction Rate
Ovedoff[24] (Philippines, 1984)	NA	NA	NA	Double-blind; follow-up and withdrawal not described	2	NA	*A lumbricoides*	16	NA	100	100
							T trichiura	29	NA	68.9	NA
							Hookworm (*N americanus*)	15	NA	93.3	NA
Sinniah et al[28] (Malaysia, 1990)	6-13	Brine flotation technique and Beavers technique	3 wk after treatment	Blinding not known; follow-up and withdrawal not described	1	NA	*A lumbricoides*	56	80 553[c]	91.1	99.2
							T trichiura	52	21 635[c]	42.3	71.2
							Hookworm	16	2614[c]	100	100
Beach et al[31] (Haiti, 1999)	7.4 (Mean)	Formalin ethyl acetate concentration technique	5 wk after treatment	Double-blind; follow-up and withdrawal described	4	Zentel[d]	*A lumbricoides*	62	284[e]	98.4	100
							T trichiura	93	120[e]	52.7	42.2
							Hookworm	12	74[e]	100	100
Stephenson et al[29] (Kenya, 1990)	6-12	Modified Kato-Katz technique	7 wk after treatment	Blinding not known; follow-up and withdrawal not described	2	Zentel	*A lumbricoides*	7	69[e]	100	100
							T trichiura	17	2112[e]	0	0
							Hookworm	16	1027[e]	40.0	96.6
Olds et al[32] (Africa, Asia, 1999)	10.4 (Mean)	Kato-Katz technique (2 samples)	45 d after treatment	Double-blind; follow-up and withdrawal described	5	NA	*A lumbricoides*	219	NA	81.7	NA
							T trichiura	297	NA	33.3	NA
							Hookworm	172	NA	77.4	NA
Bwibo and Pamba[22] (Kenya, 1984)	13.2 (Mean)	Kato-Katz technique (2 samples)	21 d after treatment	Blinding not known; follow-up and withdrawal described	3	NA	*A lumbricoides*	40	NA	90.0	93.1
							T trichiura	31	NA	83.9	89.7
							Hookworm (*N americanus*)	34	NA	88.2	NA
El-Masry et al[20] (Egypt, 1983)	25.7 (Mean)	Stool egg counts and merthiolate-iodine-formaldehyde concentration for 5 d	2 wk after treatment	Double-blind; follow-up and withdrawal not described	2	Zentel	*A lumbricoides*	11	515[e]	100	100
							Hookworm (*Ancylostoma duodenale*)	19	404[e]	89.0	NA
Oyediran and Oyejide[19] (Nigeria, 1983)	8-17	Concentration and Kato-Katz technique	14 d after treatment	Double-blind; follow-up and withdrawal not described	4	NA	*A lumbricoides*	27	NA	85.2	99.6
							T trichiura	29	NA	37.9	69.3
							Hookworm (*N americanus*)	26	NA	53.8	82.8
Upatham et al[27] (Thailand, 1989)	Adults	Kato-Katz technique (up to 3 samples)	1 mo after treatment	Double-blind; follow-up and withdrawal not described	2	Zentel	*A lumbricoides*	78	9311[c]	94.9	99.3
							T trichiura	146	655[c]	33.6	59.4
							Hookworm	260	1516[c]	45.8	90.5

(continued)

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

Source (Location, Year Trial Was Implemented)	Age, y	Diagnostic Approach	Treatment Evaluation	Study Design[a]	Quality Assessment[b]	Product Used	Parasite	Active Treatment Group			
								Individuals, No.	Mean Pretreatment Infection Intensity (Eggs/g)	Efficacy, %	
										Cure Rate	Egg Reduction Rate
Chien et al[26] (Malaysia, 1989)	8-9	Direct fecal smear	4 wk after treatment	Blinding not known; follow-up and withdrawal not described	1	NA	*A lumbricoides*	41	NA	90.2	86.5
							T trichiura	41	NA	4.9	52.3
							Hookworm (*N americanus*)	41	NA	82.9	64.2
Flohr et al[12] (Vietnam, 2007)	≥16	Salt flotation technique (1 sample)	2 wk after treatment	Double-blind; follow-up and withdrawal described	5	Mekozetel[f]	Hookworm	47	1120[c]	45.0	79.0
Sacko et al[33] (Mali, 1999)	3-70	Kato-Katz technique (2 samples)	10 d after treatment	Single-blind; follow-up and withdrawal described	2	Zentel	Hookworm (*N americanus*)	37	174.5[c]	83.8	97.7
Farid et al[23] (Egypt, 1984)	NA	Kato-Katz technique	NA	Blinding not known; follow-up and withdrawal not described	1	NA	Hookworm (*A duodenale*)	19	NA	89.4	NA
Morgan et al[21] (Malawi, 1983)	6-19	Kato-Katz technique	21 d after treatment	Double-blind; follow-up and withdrawal described	3	Zentel	Hookworm (*N americanus*)	28	564[c]	85.0	94.9

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]
[c] Arithmetic mean.
[d] Manufactured by GlaxoSmithKline, London, England.
[e] Geometric mean.
[f] Manufactured by Mekophar Chemical Pharmaceutical Joint Stock Co, Ho Chi Minh City, Vietnam.

$P=.02$). 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).[12,19-24,26-29,31-33] The effect of albendazole on *N americanus* and *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; $P<.001$) (Figure 2). There was considerable heterogeneity between trials ($Q=85.6$; $P<.001$, $I^2=84.8\%$). According to the Egger test, there was a publication bias ($P=.003$). However, the Begg test showed no statistical significance ($P=.12$).

Albendazole was well tolerated. In 11 studies included in our meta-analysis, no significant adverse events were reported following albendazole administration.[12,19-23,26-28,31,32] One trial carried out in the Philippines reported nausea and diarrhea in 2 and 1 individuals, respectively.[24] There was no indication whether or not adverse events were assessed in the remaining 2 randomized placebo-controlled trials included in our meta-analysis.[29,33]

Mebendazole

For the treatment of *A lumbricoides* infection, only 3 studies including 309 individuals were placebo-controlled trials and hence were included in our meta-analysis (Table 3).[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; $P<.001$) was calculated (FIGURE 3). Heterogeneity was low ($Q=1.7$; $P=.42$, $I^2=0\%$). Because there were only 3 studies included, it was not possible to investigate whether publication bias was an issue.

For the treatment of *T trichiura* infection, only 3 studies (685 patients) fulfilled the selection criteria and were included in our meta-analysis (Table 3).[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; $P=.001$). Heterogeneity was pronounced ($Q=35.4$; $P<.001$, $I^2=94.5\%$) (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).[11,12,25,30,33,34] The overall random RR was 0.85 (95% CI, 0.73-0.99; $P=.01$). Heterogeneity was high ($Q=49.3$; $P<.001$, $I^2=89.6\%$) (Figure 3). Although 1 trial found no reduction in

hookworm egg burden following mebendazole treatment,[30] 1 trial found a high egg reduction rate of 98.3%.[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.[11,12,34] One study reported abdominal discomfort in 6 of 45 children who were treated with 500-mg mebendazole.[25] No information on adverse events was given in the remaining 2 studies.[30,33]

Pyrantel Pamoate

For the treatment of *A lumbricoides* infection, there were 3 randomized placebo-controlled trials including 131 patients (Table 4),[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 ($Q=2.3$; $P=.32$, $I^2=11.5\%$) (FIGURE 4). One of the trials reported an egg reduction rate of 87.9%.[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 *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%[28] and 38.1%.[17] In one of the trials, an egg reduction rate was also reported; it was 52.0%.[28]

For the treatment of hookworm infection, there were 4 randomized placebo-controlled trials (152 patients) (Table 4),[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 ($Q=3.9$; $P=.26$, $I^2=24.3\%$). 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

Table 3. Randomized Placebo-Controlled Studies Reporting the Use of Single-Dose Oral Mebendazole (500 mg) Against *Ascaris lumbricoides*, *Trichuris trichiura*, and Hookworm Infection

Source (Location, Year Trial Was Implemented)	Age, y	Diagnostic Approach	Treatment Evaluation	Study Design[a]	Quality Assessment[b]	Product Used	Parasite	Active Treatment Group			
								Individuals, No.	Mean Pretreatment Infection Intensity (Eggs/g)	Efficacy, %	
										Cure Rate	Egg Reduction Rate
Albonico et al[11] (Tanzania, 2003)	7-18	Kato-Katz technique (1 sample)	21 d after treatment	Not blinded; follow-up and withdrawal described	3	Vermox[c]	*A lumbricoides*	141	114[d]	96.5	99.0
							T trichiura	214	302[d]	22.9	81.0
							Hookworm	224	447[d]	7.6	52.1
Albonico et al[34] (Tanzania [Pemba], 2002)	9.5 (Mean)	Kato-Katz technique (1 sample)	21 d after treatment	Not blinded; follow-up and withdrawal described	3	NA	*A lumbricoides*	107	5[d]	98.0	96.1
							T trichiura	404	257[d]	25.2	83.6
							Hookworm	424	588[d]	13.2	67.0
Abadi[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	*A lumbricoides*	61	37 653[e]	93.4	99.0
							T trichiura	67	6434[e]	77.6	92.8
							Hookworm (*Necator americanus*, *Ancylostoma duodenale*)	45	1928[e]	91.1	98.3
De Clercq et al[30] (Mali, 1997)	5-54	Kato-Katz technique (2 samples)	4 wk after treatment	Single blinded; follow-up and withdrawal described	2	Vermox	Hookworm (*N americanus*)	35	264.2[e]	22.9	0
Flohr et al[12] (Vietnam, 2007)	6-11	Salt flotation technique (1 sample)	2 wk after treatment	Double-blind; follow-up and withdrawal described	5	Phardazone[f]	Hookworm	90	263[e]	38	52
Sacko et al[33] (Mali, 1999)	3-70	Kato Katz technique (2 samples)	10 d after treatment	Single-blind; follow-up and withdrawal described	2	Vermox	Hookworm (*N americanus*)	35	185.3[e]	51.4	68.5

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]
[c] Manufactured by Janssen, Beerse, Belgium.
[d] Geometric mean.
[e] Arithmetic mean.
[f] Manufactured by Central Pharmaceutical Company No. 1, Hanoi, Vietnam.

dizziness.[18] Two studies did not describe the occurrence of adverse events,[17,30] and 1 trial found that pyrantel pamoate was well tolerated.[28]

Levamisole

For the treatment of *A lumbricoides* infection, 2 levamisole dosages are currently recommended: a single oral dose of 80 mg[35] or 2.5 mg/kg (http://www.who.int/wormcontrol/statistics/useful_info/en/index3.html).[1,14] For the latter dosage, which had been applied in 3 studies,[36-38] an overall cure rate of 91.5% was obtained (Table 1). Two of these studies were placebo-controlled, but none was randomized,[36,37] 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.[11] The overall cure rate of 2 non–randomized placebo-controlled trials-[36,37] 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[11] and another one in Malawi,[39] 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).[36,37]

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,[1,5] which is similar to the global burden owing to malaria.[40] 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.[3,6,41] 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.[6,8] 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-

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

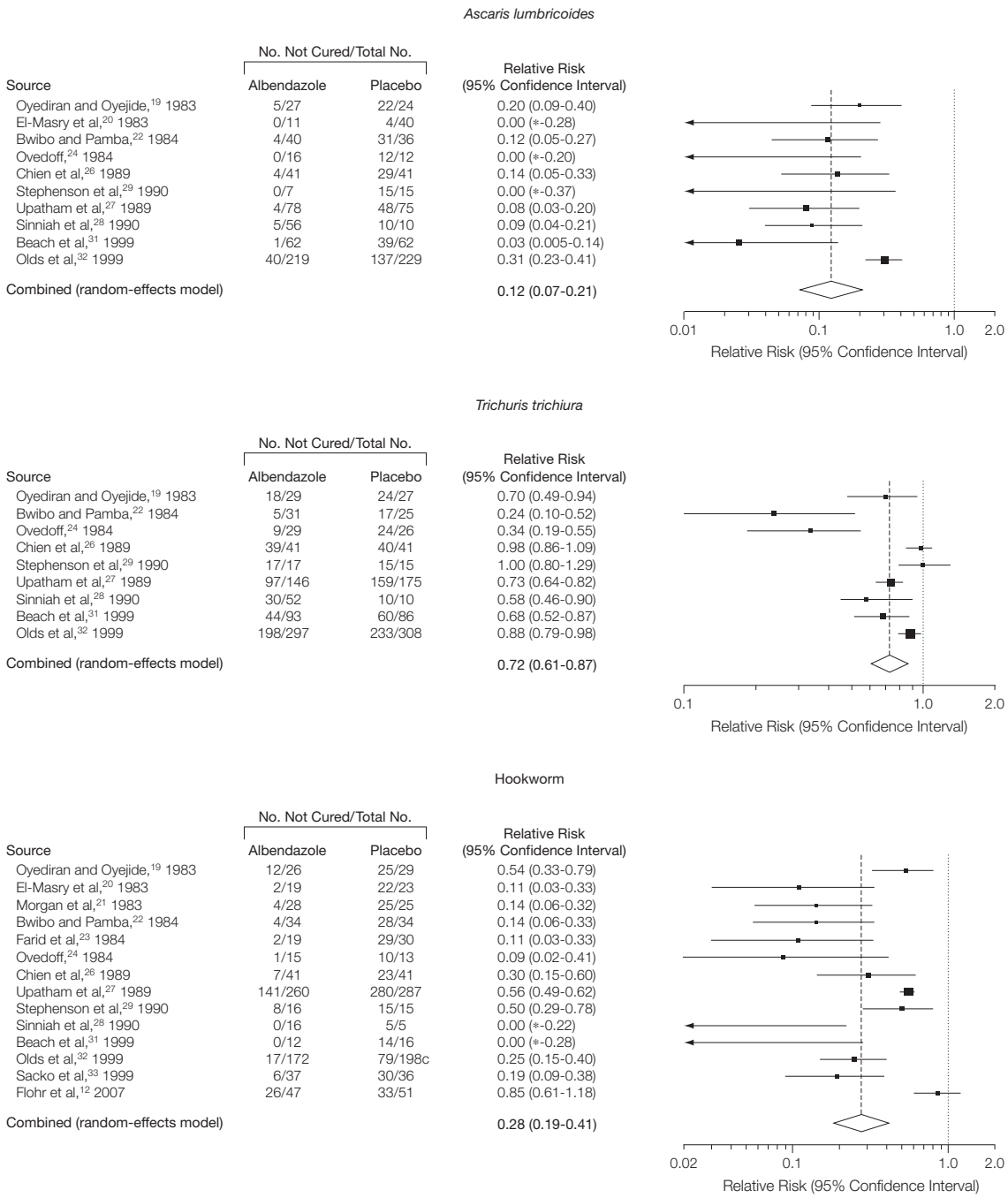
Source (Location, Year Trial Was Implemented)	Age, y	Diagnostic Approach	Treatment Evaluation	Study Design[a]	Quality Assessment[b]	Product Used	Parasite	Active Treatment Group			
								Individuals, No.	Mean Pretreatment Infection Intensity (Eggs/g)[c]	Efficacy, %	
										Cure Rate	Egg Reduction Rate
Kale[18] (Nigeria, 1977)	6-17	Quantitative egg count	42 d after treatment	Blinding not known; follow-up and withdrawal not described	1	Combantrin[d]	*A lumbricoides*	64	NA	93.8	NA
							T trichiura	63	NA	38.1	NA
							Hookworm	55	NA	29.1	56.4
Chege et al[17] (Kenya, 1974)	Children	Formol ether technique (1 sample)	2 mo after treatment	Blinding not known; follow-up and withdrawal described	3	NA	*A lumbricoides*	20	NA	90.0	NA
							Hookworm (*Necator americanus*)	60	NA	42.0	NA
Sinniah et al[28] (Malaysia, 1990)	6-13	Brine flotation technique and Beaver technique	3 wk after treatment	Blinding not known	1	NA	*A lumbricoides*	47	107 958	85.1	87.9
							T trichiura	52	3271	11.5	52.0
							Hookworm	8	3150	37.5	71.4
De Clercq et al[30] (Mali, 1997)	5-54	Kato-Katz technique (2 samples)	4 wk after treatment	Single-blind; follow-up and withdrawal described	2	Combantrin	Hookworm (*N americanus*)	29	472.1	44.8	75.0

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]
[c] All means were arithmetic.
[d] 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]

To our knowledge, we present the first systematic review and meta-analysis of the comparative efficacy of the 4 anthelminthic drugs that are currently on the

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



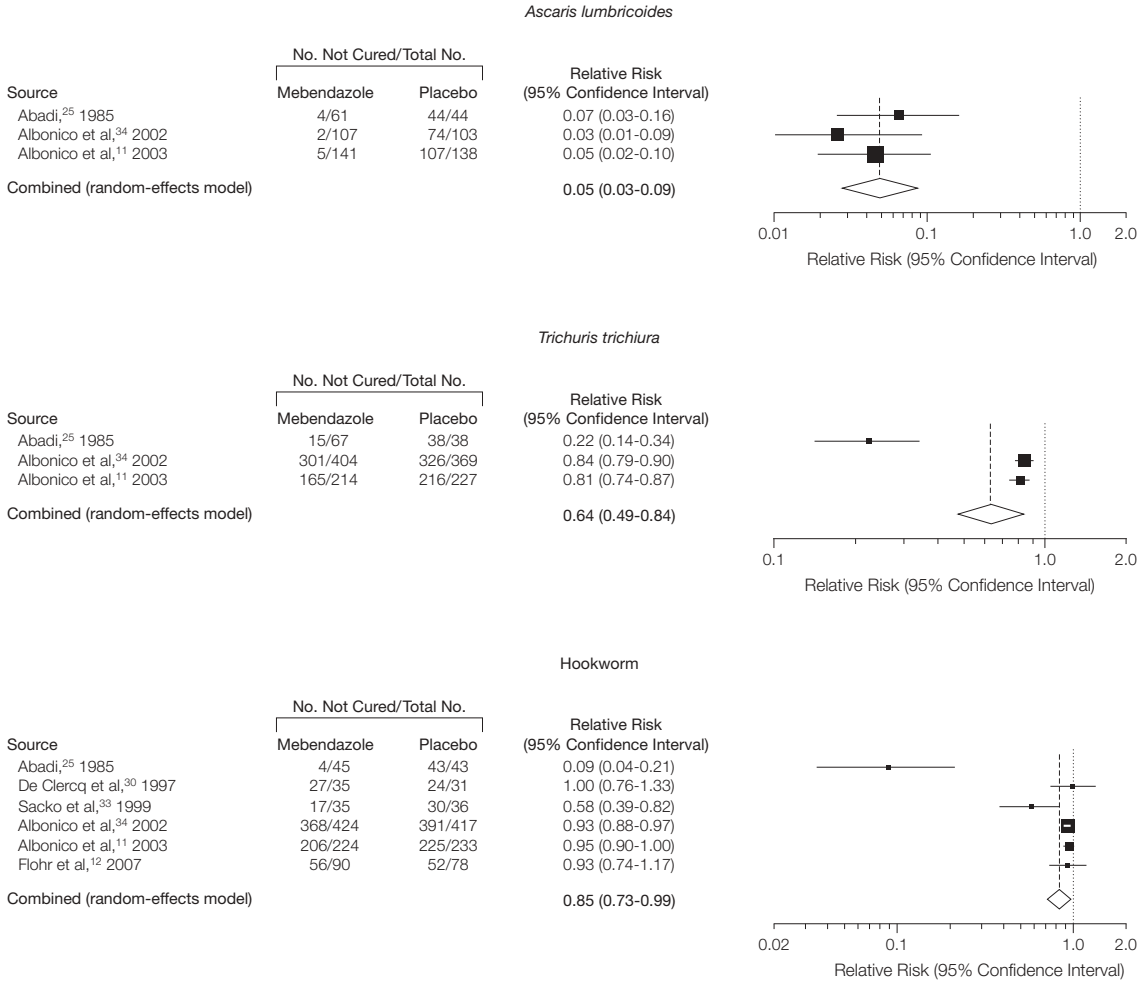
Rectangles indicate risk ratios (RRs), and sizes of the rectangles represent the weight given to each study in the meta-analysis. Diamond and vertical dashed line indicate combined RR; horizontal lines indicate 95% confidence intervals.

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),[42] and recently, a meta-analysis of randomized controlled trials was presented regarding the effect of simultaneous treatment targeting 2 or more NTDs.[43]

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.[1,2,5,44] However, calculation of the combined mean difference of egg counts between treatment and placebo groups was not possible because some trials re-

Figure 3. Risk Ratio Estimates and Pooled Random Risk Ratios of Randomized, Placebo-Controlled Trials of Mebendazole Against *Ascaris lumbricoides*, *Trichuris trichiura*, and Hookworm Infections



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.

ported no data on egg counts and others reported either arithmetic or geometric means, often in the absence of the standard deviation.

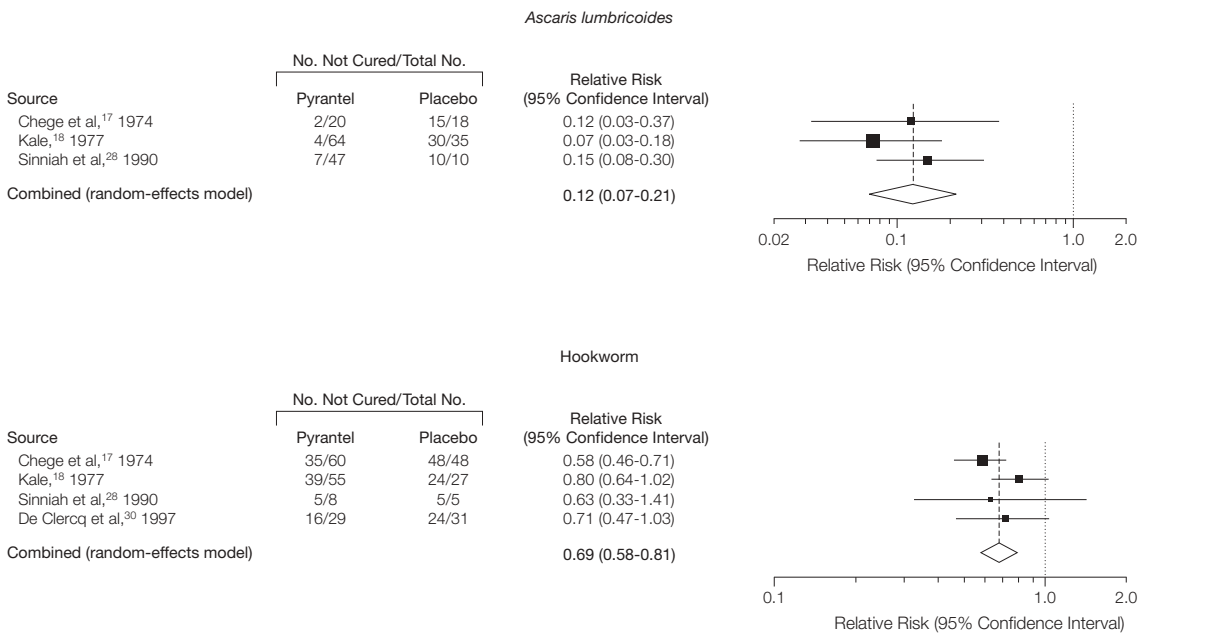
Third, a number of additional methodological issues need to be considered because they might have influenced our findings; therefore, caution must precede efforts to make policy recommendations. For example, the sample sizes in several of the trials included in our meta-analyses were small (eg, <50 individuals 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 anthelminthics 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, coinfections), 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 anthelminthics 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



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.[1] 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,[1,48] 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.[49] 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.[50,51] To our knowledge, tribendimidine is the only anthelminthic drug for STH in late-stage development and registration.[52] Compared with albendazole, tribendimidine achieved superior cure rates against hookworm, particularly *N americanus*, and is similarly effective against *A lumbricoides*, but also resulted in disappointing 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.[53]

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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.
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REFERENCES

1. Bethony J, Brooker S, Albonico M, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet*. 2006;367(9521):1521-1532.
2. Brooker S, Clements ACA, Bundy DAP. Global epidemiology, ecology and control of soil-transmitted helminth infections. *Adv Parasitol*. 2006;62:221-261.
3. Lammie PJ, Fenwick A, Utzinger J. A blueprint for success: integration of neglected tropical disease control programmes. *Trends Parasitol*. 2006;22(7):313-321.
4. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet*. 2007;370(9586):511-520.
5. Utzinger J, Keiser J. Schistosomiasis and soil-transmitted helminthiasis: common drugs for treatment and control. *Expert Opin Pharmacother*. 2004;5(2):263-285.
6. Hotez PJ, Molyneux DH, Fenwick A, et al. Control of neglected tropical diseases. *N Engl J Med*. 2007;357(10):1018-1027.
7. Loukas A, Bethony J, Brooker S, Hotez P. Hookworm vaccines: past, present, and future. *Lancet Infect Dis*. 2006;6(11):733-741.
8. World Health Organization. *Preventive Chemotherapy in Human Helminthiasis: Coordinated Use of Anthelminthic Drugs in Control Interventions: A Manual for Health Professionals and Programme Managers*. Geneva, Switzerland: World Health Organization; 2006.
9. World Health Organization. *The Use of Essential Drugs: Model List of Essential Drugs* (9th list). Geneva, Switzerland: World Health Organization; 1997.
10. Kabatereine NB, Fleming FM, Nyandindi U, Mwanza JC, Blair L. The control of schistosomiasis and soil-transmitted helminths in East Africa. *Trends Parasitol*. 2006;22(7):332-339.
11. Albonico M, Bickle Q, Ramsan M, Montresor A, Savioli L, Taylor M. Efficacy of mebendazole and levamisole alone or in combination against intestinal nematode infections after repeated targeted mebendazole treatment in Zanzibar. *Bull World Health Organ*. 2003;81(5):343-352.
12. Flohr C, Tuyen LN, Lewis S, et al. Low efficacy of mebendazole against hookworm in Vietnam: two randomized controlled trials. *Am J Trop Med Hyg*. 2007;76(4):732-736.
13. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement: Quality of Reporting of Meta-analyses. *Lancet*. 1999;354(9193):1896-1900.
14. Drugs for parasitic infections [published correction appears in *Med Lett Drugs Ther*. 1998;40(1021):28]. *Med Lett Drugs Ther*. 1998;40(1017):1-12.
15. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
17. Chege SW, Gitoho F, Wanene GS, Mwega VJ, Rees PH, Kinyanjui H. Single dose treatment of hookworm in Murang'a district. *East Afr Med J*. 1974;51(1):60-62.
18. Kale OO. Comparative trial of anthelmintic efficacy of pyrantel pamoate (Combantrin) and thiabendazole (Mintezol). *Afr J Med Med Sci*. 1977;6(2):89-93.
19. Oyediran ABOO, Oyejide CO. Double-blind comparative study of a new anthelminthic, albendazole, in the treatment of intestinal helminthes. In: Firth M, ed. *Albendazole in Helminthiasis: Royal Society of Medicine International Congress and Symposium Series No. 57*. London, England: Royal Society of Medicine; 1983:69-81.
20. El-Masry NA, Trabolsi B, Bassily S, Farid Z. Albendazole in the treatment of *Ancylostoma duodenale* and *Ascaris lumbricoides* infections. *Trans R Soc Trop Med Hyg*. 1983;77(2):160-161.
21. Morgan P, Yamamoto M, Teesdale CH, Pugh RN. Albendazole: a new treatment for hookworm. *Med Q J Med Assoc Malawi*. 1983;1(16):4-5.
22. Bwibo NO, Pamba HO. Double-blind comparative study of albendazole and placebo in the treatment of intestinal helminths. In: Firth M, ed. *Albendazole in Helminthiasis: Royal Society of Medicine International Congress and Symposium Series No. 61*. London, England: Royal Society of Medicine; 1984:47-53.
23. Farid Z, Bassily S, El-Masry NA, Trabolsi B. Treatment of ancylostomiasis and ascariasis with

albendazole. In: Firth M, ed. *Albendazole in Helminthiasis: Royal Society of Medicine International Congress and Symposium Series No. 61*. London, England: Royal Society of Medicine; 1984:31-35.
24. Ovedoff DL. Summary of albendazole trials in South-East Asia. In: Firth M, ed. *Albendazole in Helminthiasis: Royal Society of Medicine International Congress and Symposium Series No. 61*. London, England: Royal Society of Medicine; 1984:103-112.
25. Abadi K. Single dose mebendazole therapy for soil-transmitted nematodes. *Am J Trop Med Hyg*. 1985; 34(1):129-133.
26. Chien FL, Foon KLP, Hassan K. Efficacy of albendazole against the three common soil-transmitted helminthiases. *Tropical Biomed*. 1989; 6:133-136.
27. Upatham ES, Viyanant V, Brockelman WY, Kurathong S, Lee P, Chindaphol U. Prevalence, incidence, intensity and associated morbidity of intestinal helminths in south Thailand. *Int J Parasitol*. 1989; 19(2):217-228.
28. Sinniah B, Chew PI, Subramaniam K. A comparative trial of albendazole, mebendazole, pyrantel pamoate and oxantel pyrantel pamoate against soil-transmitted helminthiases in school children. *Tropical Biomed*. 1990;7:129-134.
29. Stephenson LS, Latham MC, Kinoti SN, Kurz KM, Brigham H. Improvements in physical fitness of Kenyan schoolboys infected with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* following a single dose of albendazole. *Trans R Soc Trop Med Hyg*. 1990; 84(2):277-282.
30. De Clercq D, Sacko M, Behnke J, Gilbert F, Dorny P, Vercruysse J. Failure of mebendazole in treatment of human hookworm infections in the southern region of Mali. *Am J Trop Med Hyg*. 1997;57(1): 25-30.
31. Beach MJ, Streit TG, Addiss DG, Prospere R, Roberts JM, Lammie PJ. Assessment of combined ivermectin and albendazole for treatment of intestinal helminth and *Wuchereria bancrofti* infections in Haitian schoolchildren. *Am J Trop Med Hyg*. 1999;60(3): 479-486.
32. Olds GR, King C, Hewlett J, et al. Double-blind placebo-controlled study of concurrent administration of albendazole and praziquantel in schoolchildren with schistosomiasis and geohelminths. *J Infect Dis*. 1999;179(4):996-1003.
33. Sacko M, De Clercq D, Behnke JM, Gilbert FS, Dorny P, Vercruysse J. Comparison of the efficacy of mebendazole, albendazole and pyrantel in treatment of human hookworm infections in the southern region of Mali, West Africa. *Trans R Soc Trop Med Hyg*. 1999;93(2):195-203.
34. Albonico M, Bickle Q, Haji HJ, et al. Evaluation of the efficacy of pyrantel-oxantel for the treatment of soil-transmitted nematode infections. *Trans R Soc Trop Med Hyg*. 2002;96(6):685-690.
35. Montresor A. *Helminth Control in School Age Children*. Geneva, Switzerland: World Health Organization; 2002.
36. Thienpont D, Brugmans J, Abadi K, Tanamal S. Tetramisole in the treatment of nematode infections in man. *Am J Trop Med Hyg*. 1969;18(4):520-525.
37. Gatti F, Krubwa F, Vandepitte J, Thienpont D. Control of intestinal nematodes in African schoolchildren by the trimestrial administration of levamisole. *Ann Soc Belg Med Trop*. 1972;52(1):19-31.
38. Ismail MM, Premaratne UN, Suraweera MG. Comparative efficacy of single dose anthelmintics in relation to intensity of geohelminth infections. *Ceylon Med J*. 1991;36(4):162-167.
39. Pugh RN, Teesdale CH, Burnham GM. Albendazole in children with hookworm infection. *Ann Trop Med Parasitol*. 1986;80(5):565-567.
40. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006;367(9524):1747-1757.
41. Kolaczinski JH, Kabatereine NB, Onapa AW, Ndyomugyenyi R, Kakembo AS, Brooker S. Neglected tropical diseases in Uganda: the prospect and challenge of integrated control. *Trends Parasitol*. 2007; 23(10):485-493.
42. Horton J. Albendazole: a review of anthelmintic efficacy and safety in humans. *Parasitology*. 2000; 121(suppl):S113-S132.
43. Reddy M, Gill SS, Kalkar SR, Wu W, Anderson PJ, Rochon PA. Oral drug therapy for multiple neglected tropical diseases: a systematic review. *JAMA*. 2007;298(16):1911-1924.
44. Montresor A. Arithmetic or geometric means of eggs per gram are not appropriate indicators to estimate the impact of control measures in helminth infections. *Trans R Soc Trop Med Hyg*. 2007;101 (8):773-776.
45. Booth M, Vounatsou P, N'Goran EK, Tanner M, Utzinger J. The influence of sampling effort and the performance of the Kato-Katz technique in diagnosing *Schistosoma mansoni* and hookworm co-infections in rural Côte d'Ivoire. *Parasitology*. 2003; 127(pt 6):525-531.
46. Goodman D, Haji HJ, Bickle QD, et al. A comparison of methods for detecting the eggs of *Ascaris, Trichuris*, and hookworm in infant stool, and the epidemiology of infection in Zanzibari infants. *Am J Trop Med Hyg*. 2007;76(4):725-731.
47. Albonico M, Mathema P, Montresor A, et al. Comparative study of the quality and efficacy of originator and generic albendazole for mass treatment of soil-transmitted nematode infections in Nepal. *Trans R Soc Trop Med Hyg*. 2007;101(5):454-460.
48. Georgiev VS. Necatoriasis: treatment and developmental therapeutics. *Expert Opin Investig Drugs*. 2000;9(5):1065-1078.
49. Dodoo A, Adjei S, Couper M, Hugman B, Edwards R. When rumours derail a mass deworming exercise. *Lancet*. 2007;370(9586):465-466.
50. Keiser J, Utzinger J. Artemisinins and synthetic trioxolanes in the treatment of helminth infections. *Curr Opin Infect Dis*. 2007;20(6):605-612.
51. Kaminsky R, Ducray P, Jung M, et al. A new class of anthelmintics effective against drug-resistant nematodes. *Nature*. 2008;452(7184):176-180.
52. Xiao SH, Wu HM, Tanner M, Utzinger J, Wang C. Tribendimidine: a promising, safe and broad-spectrum anthelmintic agent from China. *Acta Trop*. 2005;94(1):1-14.
53. Xiao SH, Wu ZX, Zhang JH, et al. Clinical observation on 899 children infected with intestinal nematodes and treated with tribendimidine enteric coated tablets [in Chinese]. *Chin J Parasitol Parasit Dis*. 2007; 25(5):372-375.

