



Efficacy of Albendazole Against Soil-transmitted Helminthiasis among Children in Asia: Systematic Review

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Abstract

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BACKGROUND: The World health organization reported that 875 million children worldwide require antihelminth preventive chemotherapy annually. Vast majority of STH infections (67%) and YLDs (68%) occurred in Asia.

METHODS: A systematic search was performed for relevant titles, abstract, and keywords from Cochrane Library, PubMed, and Scopus around October 2018 based on the PICO strategy. Out of 173 papers that were evaluated, final assessment for eligibility had yielded a total of five papers to be included for analysis covering period from 2013 to 2018.

RESULTS: Of the five selected studies, three were randomized controlled trial, one was cohort and another one was described more like a quasi-experimental trial. All infection intensity showed improvement post-intervention. Four of the five studies used Kato Katz as diagnostic method with one combined it with Baermann techniques. One used McMaster egg counting method. All except one study tested albendazole efficacy in their study either alone or in combination with other chemotherapy such as diethyl carbazide or combining with education pamphlet. Egg reduction rate was reported as low as 63% and as high as 99.9%.

CONCLUSION: In general, albendazole is efficacious enough to control STH.

Introduction

Soil-transmitted helminthiasis consists of parasitic infections transmitted through soil. There are four types of helminth classified as soil transmitted helminthiasis; *Ascaris lumbricoides*, *Trichuris trichiura*, *Ancylostoma duodenale*, and *Necator americanus* [1]. Ascariasis, which is known as roundworm, in 2013 infects 804 million people, mainly children and adolescents. *T. trichiura*, also known as whipworm estimated to affect 477 million individuals, mainly with high prevalence and intensity in children's. In contrast, hookworm which consists of *A. duodenale* and *N. americanus* has highest intensity in adults, although children's are also affected. Hookworms combined affect 472 million people [1]. The WHO reported that 875 million preschool and school aged children worldwide requires annual antihelminth preventive chemotherapy annually [2].

There is a shift of total DALY of STH, whereby majority of them constitute from the upper-middle income, low-middle income, and low income in 1990 to now concentrated in the lower-middle income and low-income countries [3]. Interestingly, vast majority of STH infections (67%) and YLDs (68%) occurred in Asia [4]. Mass drug administration (MDA) is a means of delivering safe and inexpensive essential medicines based on the principles of preventive chemotherapy, where populations or sub-populations are offered treatment without individual diagnosis [5]. WHO recommends the regular administration of preventive chemotherapy with albendazole or mebendazole as the main intervention for controlling soil-transmitted helminthiasis [2]. To the best of our knowledge, up till this date, no review was done to address the efficacy of the therapy in Asia. Thus, this review was conducted to know the efficacy of albendazole when used as MDA in Asia on different subgroups of STH.

Methods

The review was done based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [6]. Search was done in Cochrane Library, PubMed, and Scopus around October 2018. PICO strategy was performed to search for relevant titles, abstracts, and keywords. The studies were retrieved using keywords (children OR child OR preschool) AND (anthelmintics OR albendazole OR albendoral OR albenza OR andazol OR bundapar OR bilutac OR digezanol OR disthelm OR endoplus OR eskazole OR gascop OR lurdex OR metiazol OR valbazen OR zentel) AND Asia AND (efficacy OR cure rate OR egg reduction rate). The inclusion criteria were included (1) studies published since 2013; (2) English; and (3) has study design. Grey literatures were not searched.

The review was done by mainly 2 reviewers, one reviewer is medical doctor specialized in public health and other is a pharmacist and both have experience in conducting systematic review protocol. In the first stage, two reviewers independently screened the titles and abstracts for inclusion of all the potential studies. The studies were coded as either “retrieve” (eligible or potentially eligible/unclear) or “do not retrieve.” As for the second stage, the full-text was retrieved and another two reviewers independently screened the full-text, identified studies for inclusion, and stated reason for exclusion of the ineligible studies. The 3rd reviewer was just a back up in case of any discrepancy.

Data extraction of the accepted studies were done using an Excel table with the following particulars: Author, title, publication year, country, objective of study, sample size, age group of study population, study design, mean infection intensity (before and after treatment), diagnostic method, drug used and dosage, parasite involved, treatment evaluation period, and efficacy which was based on either cure rate or egg reduction rate, other reported outcomes and conclusion. All randomized controlled trials (RCT) were assessed 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 as the strongest, based on the validated scale put forward by Jadad *et al.* [7] As for non-RCT paper, Newcastle-Ottawa Quality Assessment Scale (NOS) was used.

Results

Literature search and study selection

The search strategy yielded 173 literatures. Following removal of duplicate literatures, there were

170 articles left for screening. Further screening of the remaining titles and abstracts excluded another 152 studies which were not relevant to the study objective. The remaining 20 articles were retrieved to be assessed for eligibility and detailed evaluation. This excluded another 13 studies. The reasons for exclusion were unretrievable article, different intervention looked at, for example, not specific to albendazole or similar anthelmintic groups but other intervention, different outcome looked at, for example, malaria and not interventional study, for example, article on overview of hookworm infection and its management. Five remaining articles [8], [9], [10], [11] were included for the review. The flow diagram of the selection process in line with the PRISMA flow diagram [12] as shown in Figure 1.

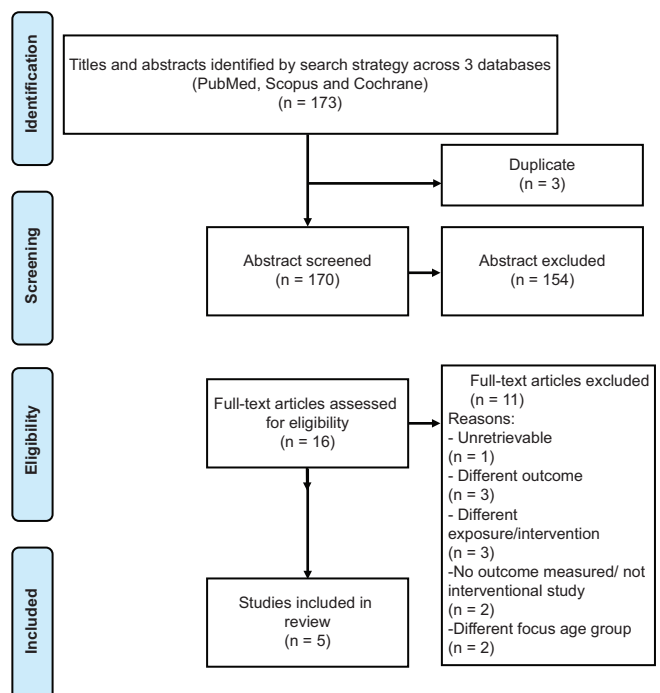


Figure 1: PRISMA flow diagram

Study characteristics

Table 1 listed the characteristics of the included studies. Of the five selected studies, three were RCT [8], [10], [11], one was cohort [13] and another one was described more like a quasi-experimental trial [9]. Two RCTs were done in China, one in Laos while the cohort study was done in India. The quasi trial was done in Cambodia and Vietnam. However, as mentioned earlier, these were two sites from six total sites in the trial – Brazil, Cameroon, Ethiopia, and United Republic of Tanzania. The three RCT studies involved participants ranging between 211 and 2179, the cohort study had 646 participants while the last trial involved between 69 and 211 participants in two sites in South East Asia from six sites globally. Participants age ranged were between 6 and 15 years old with means age majority was around 9 or 10. Mean infection

Table 1: Summary of studies characteristics

Author (Country)	Study design (Sample size)	Study population (age)	Mean infection intensity (before treatment)	Mean infection intensity (after treatment)	Diagnostic method	Drug used (dosage)	Parasite
Moser, et al. (2018) (Laos)	Randomized single blinded trial (n=414)	6–15	1) Albendazole, pyrantel pamoate and oxiartel pamoate (EPG arithmetic mean): 1373.7 2) Albendazole+oxantel pamoate (EPG arithmetic mean): 1269.2 3) Pyrantel pamoate+oxantel pamoate (EPG arithmetic mean): 1301.0 4) Mebendazole, pyrantel pamoate and oxiartel pamoate (EPG arithmetic mean): 1456.7 Mean fecal egg count EPG: infection intensity level: Low (%) , Moderate (%) , High (%) Arithmetic <i>A. lumbricoides</i> Vietnam - 20,657; 40.1, 48.8, 11.1 <i>T. trichiura</i> Cambodia - 9.4 Vietnam - 546, 82.6, 17.4, 0.0 <i>Hookworm</i> Cambodia - 406; 98.1, 1.3, 0.6 Vietnam - 679; 93.8, 5.0, 1.3	1) Albendazole, pyrantel pamoate and oxiartel pamoate (EPG arithmetic mean): 22.0 2) Albendazole plus oxiartel pamoate (EPG arithmetic mean): 114.1 3) Pyrantel pamoate plus oxiartel pamoate (EPG arithmetic mean): 48.1 4) Mebendazole, pyrantel pamoate and oxiartel pamoate (EPG arithmetic mean): 99.4	Kato Katz Method	Albendazole (Zentel, GlaxoSmithKline, London, UK) (400 mg) Mebendazole (Vermox, Janssen, Beerse, Belgium) (500 mg) Pyrantel pamoate (125 mg tablets) Combantrin, (Teofarma, Pavia, Italy) and Oxantel pamoate (University of Basel, Switzerland) (400 mg tablets) manufactured at 20 mg/kg bodyweight	Hookworm
Bruno et al. (2014) (Brazil, Cambodia ^a , Cameroon, Ethiopia, United Republic of Tanzania, Vietnam ^b)	Quasi trial (<i>A. lumbricoides</i> Vietnam (n=287), <i>T. trichiura</i> Vietnam (n=69) <i>Hookworm</i> Cambodia (n=160) Vietnam (n=80)	Mean age (years) <i>A. lumbricoides</i> Vietnam - 8.4 <i>T. trichiura</i> Vietnam - 8.3 <i>Hookworm</i> Cambodia - 9.4 Vietnam - 8.9	Mean FEC, geometric mean EPG (95% CI) Control 10.61 (10.56–10.66) Intervention 10.56 (10.50–10.61)	EPG (95% CI) Follow-up Control 533.32 (390.69 to 675.95); intervention 299.93 (193.98 to 405.89)	Stool samples individually processed by the McMaster egg counting method. A flotation technique used in veterinary parasitology to assess intensity of gastrointestinal parasite infections and to evaluate drug efficacy against these parasites	Mebendazole (Vermox) single 500mg oral dose, same manufacturer (Janssen-Cilag, Latina, Italy, batch no: BCL2F00)	<i>A. lumbricoides</i> hookworm <i>T. trichiura</i>
Liu, et al. (2017) (China)	Cluster-Randomized Controlled Trial (n=2179) Intervention group, 1084 Control group, 1095	Mean (95% CI) Control 10.61 (10.56–10.66) Intervention 10.56 (10.50–10.61)	Mean FEC, geometric mean EPG (95% CI) Baseline Control 493.68 (357.83 to 629.53); intervention 702.71 (491.07 to 914.34)	Kato-Katz thick-smear technique. Two smears from each of two fecal samples collected from each child: One smear from each of the two samples undergone same-day, on-site test. The second smear from each sample treated using a formaldehyde preservation technique and sent to the headquarters of the National Institute for Parasitic Diseases in Shanghai for quality control analysis and to perform egg counts for intensity of infection. Children were considered positive for STH infection if at least one of their fecal samples tested positive for one or more species of STH	Albendazole dose (400 mg; two 200 mg tablets) as per national Chinese treatment guidelines+TWO educational pamphlets (one for children and one for parents) about STH infection, treatment, and prevention. CDC health officials distributed ALZ in the classrooms twice over the course of the study – at baseline in May 2013, and 6 months later in November 2013 – and instructed the children to take the tablets at home. (China National policy forbids children from taking medication at school.)	<i>A. lumbricoides</i> (Ascaris) <i>T. trichiura</i> (Trichuris), <i>A. duodenale</i> or <i>N. americanus</i> (hookworm)	
Sunish et al. (2015) (India)	Cohort (n=646)	9–10 years old	DEC+ALB arm EPG (Geometric mean) Roundworm - 23.51, Hookworm - 1.48, whipworm - 0.27 ALB arm EPG (Geometric mean) Roundworm - 20.6, Hookworm - 0.53, whipworm - 0.40 Prevalence % (EPG): - <i>T. trichiura</i> 94.5%, (216.3) - <i>A. lumbricoides</i> 93.3%, (15,850) - Hookworm 61.3%, (130.4)	DEC+ALB arm EPG (Geometric mean) Roundworm - 0.60, Hookworm - 0.01, whipworm - 0.04 ALB arm EPG (Geometric mean) Roundworm - 7.71, Hookworm - 178, whipworm - 0.87 Prevalence % (EPG): - <i>T. trichiura</i> 74%, (24.3) - <i>A. lumbricoides</i> 8.1%, (1.3) - hookworm 2%, (1.2)	Kato Katz Method	Diethyl Carbazide (6 mg/kg) Albendazole: (400 mg)	<i>A. lumbricoides</i> (Ascaris) <i>T. trichiura</i> (Trichuris), <i>A. duodenale</i> or <i>N. americanus</i> (hookworm)
Yap et al. (2013) (China)	RCT (n=211) Intervention group, 99 Control group, 95	9–12 years of age Mean Age-albendazole: 10.4 yo- placebo: 10.3 yo	Prevalence % (EPG): - <i>T. trichiura</i> 94.5%, (216.3) - <i>A. lumbricoides</i> 93.3%, (15,850) - Hookworm 61.3%, (130.4)	Kato-Katz and Baermann techniques For Kato-Katz technique, a 41.7 mg template was used to prepare fecal thick smears. Thirty to 60 min after preparation, slides were read under a microscope at 100 magnification. For Baermann technique, about 20 g of stool was placed on medical gauze in a glass funnel fitted with a rubber tube sealed by a clip and filled with tap water. The whole setup was illuminated with artificial light directed at the bottom of the funnel for 2 h. The lowest 50 mL of the liquid was then collected and centrifuged. The sediment was subjected to microscopic examination for the larvae of <i>Strongyloides stercoralis</i> . Each stool sample was visually inspected for <i>Taenia</i> spp. proglottids	Albendazole (GlaxoSmithKline; London, UK) (3x400 mg) Started single dose on treatment Day 1 followed with another dose every day until treatment Day 3	<i>T. trichiura</i> <i>A. lumbricoides</i> hookworm	

(Contd...)

Table 1: (Continued)

Author (Country)	Treatment evaluation (follow-up duration post-treatment)	Efficacy a (cure rate, %)	Efficacy b (egg reduction rate, %)	Side effect (if reported)	Other analysis/outcome reported	Conclusion
Moser, et al. (2018) (Laos)	17–30 days	1) Albendazole, pyrantel pamoate and oxaatel pamoate arm (84.1%) 2) Albendazole+oxaatel pamoate (52.9%) 3) Pyrantel pamoate+oxaatel pamoate (52.2%) 4) Mebendazole, pyrantel pamoate and oxaatel pamoate: (69.6%)	1) Albendazole, pyrantel pamoate and oxaatel pamoate arm (98.4%) 2) Albendazole+oxaatel pamoate (91.0%) 3) Pyrantel pamoate+oxaatel pamoate (96.3%) 4) Mebendazole, pyrantel pamoate and oxaatel pamoate: (93.2%) FECR (95% CI) A. <i>lumbrioides</i> Vietnam - 93.9 (91.2, 96.5) T. <i>trichiura</i> Vietnam - 76.8 (67.7, 85.8) <i>Hookworm</i> Cambodia - 79.7 (73.7, 85.7) Vietnam - 95.0 (91.2, 98.9)	Before treatment, 44 (10%) children reported symptoms with headache (n=28), stomach pain (n=9), and itching (n=6) most often reported. 3 h after treatment, six (1%) children reported adverse events, including mild dizziness (n=3), mild (n=1) and moderate (n=1) stomach pain, and both moderate headache and mild dizziness (n=1). The highest number of adverse events (n=4) were reported by three children after treatment with albendazole plus oxaatel pamoate. 24 h after treatment, all adverse events had resolved	Cure rate and Egg reduction rate done for <i>T. trichiura</i> and <i>A. lumbrioides</i> as secondary analysis	TDT with albendazole, pyrantel pamoate, and oxaatel pamoate showed higher efficacy than the co-administrations albendazole plus oxaatel pamoate and pyrantel pamoate plus oxaatel pamoate and might become a key treatment for STH control and Elimination
Bruno et al. (2014) (Brazil, Cambodia, Cameroon, Ethiopia, United Republic of Tanzania, Vietnam)	Cambodia: 11–15 days Vietnam: 11–12 days			NR		FECR rates exceeding 95% for <i>A. lumbrioides</i> , 70% for hookworm, and 50% for <i>T. trichiura</i> should be expected in all future surveys, and that any FECR rate below these levels following a single oral dose of MEB (500 mg) should be viewed with concern in light of potential development of drug resistance in a population of schoolchildren with light-intensity Ascaris, Trichuris, and hookworm infection, a biannual deworming intervention reduced STH infection prevalence and intensity in the population, but had no impact on outcomes of nutrition, cognitive abilities, or school performance
Liu, et al. (2017) (China)	April 2014 (5 months post-treatment)	Any STH With ALB 35% Without ALB 23.6%			INTERVENTION EFFECT Unadjusted baseline 209.02 (-167.29–585.33); p-value 0.272 Unadj Followup -233.39 (-489.36–22.58); p-value 0.073 Adj baseline 115.29 (-101.48–332.06); p-value 0.293 Adj Followup -209.78 (-383.16–-36.39); p-value 0.018* Infection prevalence (adjusted) Baseline 1.15 (0.93–1.43); p-value 0.192 Followup 0.71 (0.52–0.96); p-value 0.026* Intention to treat analysis Nutritional indicators Hemoglobin (Hb) concentrations Baseline 0.24 (-0.67 to 1.14); p-value 0.604 F/up -0.33 (-1.64–0.98); p-value 0.623 Anemia prevalence (%) Baseline 0.83 (0.79 to 1.10); p-value 0.385 F/up 1.25 (0.91 to 1.72); p-value 0.174 % Stunted (HAZ < -2) Baseline 1.10 (0.92 to 1.31); p-value 0.291 F/up 1.15 (0.85 to 1.55); p-value 0.367 % Underweight (WAZ < -2) Baseline 1.29 (1.09 to 1.54); p-value 0.004* F/up 0.77 (0.56 to 1.06); p-value 0.113 Cognitive ability Processing Speed Index Score Baseline 0.16 (-1.28–1.59); p-value 0.827 F/up 0.63 (-0.22–1.49); p-value 0.143 Working Memory Index Score Baseline -0.05 (-0.98–0.89); p-value 0.922 F/up 0.51 (-0.09–1.11); p-value 0.093 School performance School attendance rate (%) Baseline 1.08 (0.75 to 1.56); p-value 0.692 F/up 0.86 (0.55 to 1.33); p-value 0.496 Normalized TIMSS (Trends in International Mathematics and Science Study) score Baseline 0.01 (-0.1–0.11); p-value 0.912 F/up -0.04 (-0.09–0.02); p-value 0.190	

(Contd...)

Table 1: (Continued)

Author (Country)	Treatment evaluation (follow-up duration post-treatment)	Efficacy a (cure rate, %)	Efficacy b (egg reduction rate, %)	Side effect (if reported)	Other analysis/outcome reported	Conclusion
Sunish <i>et al.</i> (2015) (India)	MDA were done annually 2001-2004 then on 2007, 2009 and 2010. The follow-up survey is done 3 weeks, 6 months and 1 year after MDA. Documentation point was not clearly mentioned.	NA	DEC+ALB arm (Percentage reduction) Roundworm (97.47%) Hookworm (99.32%) Whipworm (85.19%) ALB arm (Percentage reduction) Roundworm (62.57%) Hookworm (NA) Whipworm (NA) <i>T. trichiura</i> (88.8%) <i>A. lumbricoides</i> (91.5%) hookworm (96.7%)	DEC+ALBT. <i>trichiura</i> (80%) <i>A. lumbricoides</i> (72.2%) hookworm (98.9%) DEC <i>T. trichiura</i> (77.3%) <i>A. lumbricoides</i> (30.8%) hookworm (25.9%)	NA	
Yap <i>et al.</i> (2013) (China)	1 month	<i>T. trichiura</i> (19.6%) <i>A. lumbricoides</i> (91.5%) hookworm (96.7%)	(NA) Whipworm (NA) <i>T. trichiura</i> (88.8%) <i>A. lumbricoides</i> (>99.9%) hookworm (99.1%)		Reinfection pattern and dynamic <i>T. trichiura</i> 0-91.6% 1-74.8% 4-79.8% 6-82.8% 0-95% 1-8.1% 4-75.8% 6-83.8% hookworm 0-60.6% 1-2.0% 4-2.0% 6-5.1%	It was concluded that the observed re-infection patterns with soil-transmitted helminths after triple-dose albendazole re-emphasize the need for control programs that go beyond preventive chemotherapy, particularly for ascariasis and trichuriasis, and the need for a more effective drug or combination therapy against <i>T. trichiura</i> is further highlighted

*Only data from Asia sites were looked at. MDA: Mass drug administration, T. trichiura: Trichuris trichiura, A. lumbricoides: Ascariis lumbricoides.

intensity was measured using eggs per gram (EPG) of feces either calculated as geometric mean (GM) or arithmetic mean (AM).

Wenderlin *et al.* (2018) focusing their study in comparing efficacy of triple drug therapy with albendazole, pyrantel pamoate and oxantel pamoate, and the two coadministrations albendazole plus oxantel pamoate and pyrantel pamoate plus oxantel pamoate against hookworm infection with the highest mean infection intensity before treatment was for mebendazole, pyrantel pamoate and oxantel pamoate intervention arm at EPG (AM) 1456.7 [8]. The other studies looked at EPG for all soil-transmitted helminths in general. Chengfan *et al.* (2017) and Peiling *et al.* (2013), the other two RCTs in China had baseline EPG around 130 up to 16,000 in a range [10], [11]. The cohort study in India had pre-intervention EPG between -23.51 and -0.27 between the two intervention arm [13]. The quasi trial had EPG between 400 and 20,900 among the sites [9]. All infection intensity showed improvement post-intervention. Four of the five studies used Kato Katz as diagnostic method with one combined it with Baermann techniques. One used McMaster egg counting method. All except one study tested albendazole efficacy in their study either alone or in combination with other chemotherapy such as diethyl carbazide or combining with education pamphlet. Egg reduction rate was reported as low as 63% and as high as 99.9%.

Evaluation of quality of studies

Three studies were selected for the meta-analysis, two of the studies were randomized control trial. One of the RCT was single blinded while the other was double blinded. Both of the studies had proper treatment randomization using computer software and both accounted for loss of follow-up and drop outs. The double-blinded RCT employed placebo identical to the active comparator. The cohort study had somewhat representative samples from the study population. However, the exposed and non-exposed were recruited from different district. Both the outcome and expose were assessed by Kato Katz method.

There was demonstration that the samples were infected from the beginning of the study. Both the cohorts were comparable in respect to age, gender, and baseline intensity of eggs. Same methods were used on both exposed and case for the assessment of outcome; however, the non-responders were not described. The other two studies end up in the final search but were not included [9], [10]. Levecké [9] is particularly very poor in the quality (Jadad score=1). There was no mentioned of the word randomization and the randomization was not even described in the study. There is no indication whether the study is blinded in anyway. Although Liu [10] have fairly good quality, we did not include in the final analysis as it does not have separate cure rate for helminth species.

Main analysis

The meta-analysis data using random-effect model to explore the efficacy of albendazole against STH among children in Asia are shown in Figure 2.

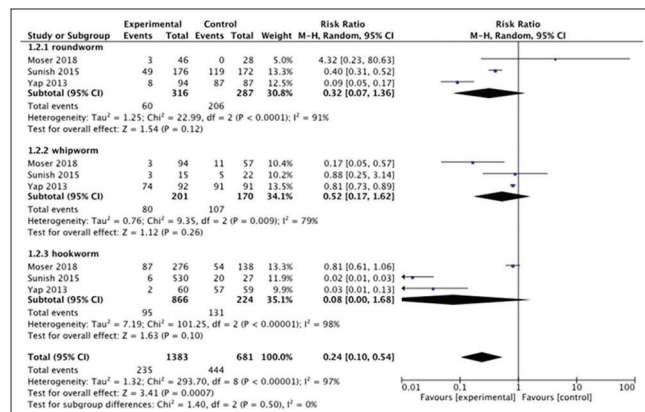


Figure 2: Forest plot analysis

The forest plot illustrates the spread of the three studies risk estimates and their confidence intervals (CI) in relation to the summary RR of meta-analysis. The Chi-square for the random-effect meta-analysis that test for equal variance between studies had a value of 293.7 ($p < 0.001$). While I^2 index which indicates level of heterogeneity was estimated to be 97%. Based on the four studies, the pooled RR estimates showed that albendazole has better protective effect against STH compared to comparators (RR = 0.24; 95% CI: 0.10–0.54).

Discussion

The review focused on the efficacy of albendazole against STH among children in Asia. Measure of the efficacy was done using the gold standard, either cure rate, or fecal egg reduction rate. In overall, the results showed that the intervention involving albendazole reduced infection prevalence relative to the control group. Out of five included studies in this review, only three were considered in meta-analysis [8], [11], [13]. All three studies subgrouped the STH according to parasites, namely, *A. lumbricoides* (roundworms), *T. trichiura* (whipworms), and hookworm. The forest plot analysis showed high heterogeneity of the studies with $I^2 = 97%$. Subgroup analysis showed non-significant findings ($p = 0.5$), yet the overall effect showed $p < 0.05$ ($p = 0.007$) which was significant. This can be explained by two reasons. First, the fundamental knowledge in interpreting the forest plot that due to smaller numbers (participants), CI in subgroups will always be wider than those for overall effect [14]. Second, effect of the varied methods or compared groups in the studies. Two studies included in this meta-analysis did a

comparison between drug and placebo [11], [13], while Moser *et al.* compared between two drugs [8]. This possibly had caused inconsistency of subgroups and overall effect. However, albendazole is less efficacious against whipworm. This finding supports similar result from the previous systematic review and study by Keiser and Utzinger (2008) [15] and Viswanath and Williams (2008) [16], respectively. Moreover, this result had proven that the emergence of drug resistance in controlling STH cannot be abandoned and requires more attention too.

In term of safety out of the five studies, only one reported side effects after initiation of treatment [8]. The side effects included dizziness, headache, and stomach pain, and all of them were only mild to moderate in severity. Symptoms had started as early as 3 h post-treatment and resolved within 24 h. These symptoms were encountered in the intervention group using combination of albendazole and oxtel pamoate, thus it is difficult to determine which drug caused a particular side effect. This review was done focusing on Asian population, which is the major contributor of STH. The review search strategy was ensured to be more comprehensive using MESH keyword. This was hoped to be able to capture all possible studies. Apart from that, independent review by two reviewers allowed for lesser bias in assessing the studies. One reviewer is a pharmacist which strengthened the understanding on the pharmacotherapy looked at grey literature was not searched due to time constrain rendering to the possibilities of missing local unpublished data. The limitation of the current study is that it does not cover all Asian countries because of our inclusion and exclusion criteria and data availability for the review. Future studies need to include more Asian countries.

Conclusion

Albendazole was proven to be efficacious against STH, but more studies are required in exploring on whipworm less efficacious related issues such as drug resistant. To strengthen the review, inclusion of more databases and studies published earlier than 2013 should be considered.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

- Jourdan PM, Lamberton PH, Fenwick A, Addiss DG. Soil-transmitted helminth infections. *Lancet*. 2018;391(10117):252-65. [https://doi.org/10.1016/s0140-6736\(17\)31930-x](https://doi.org/10.1016/s0140-6736(17)31930-x) PMID:28882382
- World Health Organization. Investing to Overcome the Global Impact of Neglected Tropical Diseases. Third WHO Report on Neglected Tropical Diseases. Geneva: World Health Organization; 2015. <https://doi.org/10.1128/9781555818753.ch10>
- Stolk WA, Kulik MC, Ie Rutte EA, Jacobson J, Richardus JH, de Vlas SJ, *et al*. Between-country inequalities in the neglected tropical disease burden in 1990 and 2010, with projections for 2020. *PLoS Negl Trop Dis*. 2016;10(5):e0004560. <https://doi.org/10.1371/journal.pntd.0004560> PMID:27171193
- Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. *Parasit Vectors*. 2014;7(1):37. <https://doi.org/10.1186/1756-3305-7-37> PMID:24447578
- Webster JP, Molyneux DH, Hotez PJ, Fenwick A. The contribution of mass drug administration to global health: Past, present and future. *Philos Trans R Soc Lond B Biol Sci*. 2014;369(1645):20130434. <https://doi.org/10.1098/rstb.2013.0434> PMID:24821920
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. *PLoS Med*. 2009;6(7):e1000097. <https://doi.org/10.1371/journal.pmed.1000097> PMID:19621072
- Jadad AR, Moore RA, Carroll D, Jenkinson C, ReynoldsDJ, GavaghanDJ, *et al*. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12. [https://doi.org/10.1016/0197-2456\(95\)00134-4](https://doi.org/10.1016/0197-2456(95)00134-4) PMID:8721797
- Moser W, Sayasone S, Xayavong S, Bounheuang B, Puchkov M, Huwyler J, *et al*. Efficacy and tolerability of triple drug therapy with albendazole, pyrantel pamoate, and oxantel pamoate compared with albendazole plus oxantel pamoate, pyrantel pamoate plus oxantel pamoate, and mebendazole plus pyrantel pamoate and oxantel pamoate against hookworm infections in school-aged children in Laos: A randomised, single-blind trial. *Lancet Infect Dis*. 2018;18(7):729-37. [https://doi.org/10.1016/s1473-3099\(18\)30220-2](https://doi.org/10.1016/s1473-3099(18)30220-2)
- Levecke B, Montresor A, Albonico M, Ame SM, Behnke JM, Bethony JM, *et al*. Assessment of anthelmintic efficacy of mebendazole in school children in six countries where soil-transmitted helminths are endemic. *PLoS Negl Trop Dis*. 2014;8(10):e3204. <https://doi.org/10.1371/journal.pntd.0003204> PMID:25299391
- Liu C, Lu L, Zhang L, Luo R, Sylvia S, Medina A, *et al*. Effect of deworming on indices of health, cognition, and education among schoolchildren in Rural China: A cluster-randomized controlled trial. *Am J Trop Med Hyg*. 2017;96(6):1478-89. <https://doi.org/10.4269/ajtmh.16-0354> PMID:28093533
- Yap P, Du ZW, Wu FW, Jiang JY, Chen R, Zhou XN, *et al*. Rapid re-infection with soil-transmitted helminths after triple-dose albendazole treatment of school-aged children in Yunnan, people's republic of China. *Am J Trop Med Hyg*. 2013;89(1):23-31. <https://doi.org/10.4269/ajtmh.13-0009> PMID:23690551
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. *Ann Intern Med*. 2009;151(4):264-9. <https://doi.org/10.7326/0003-4819-151-4-200908180-00135> PMID:19622511
- Sunish I, Rajendran R, Munirathinam A, Kalimuthu M, Kumar V, Nagaraj J, *et al*. Impact on prevalence of intestinal helminth infection in school children administered with seven annual rounds of diethyl carbamazine (DEC) with albendazole. *Indian J Med Res*. 2015;141(3):330-9. <https://doi.org/10.4103/0971-5916.156622> PMID:25963494
- Cuzick J. Forest plots and the interpretation of subgroups. *Lancet*. 2005;365(9467):1308. [https://doi.org/10.1016/s0140-6736\(05\)61026-4](https://doi.org/10.1016/s0140-6736(05)61026-4) PMID:15823379
- Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: Systematic review and meta-analysis. *JAMA*. 2008;299(16):1937-48. <https://doi.org/10.1001/jama.299.16.1937> PMID:18430913
- Viswanath A, Williams M. *Trichuris Trichiura* (Whipworm, Roundworm). Treasure Island, FL: StatPearls; 2018.

Supplemental Material

Source (Location, year trial was implemented)	Age (years old)	Diagnostic approach	Treatment evaluation	Study design	Quality assessment (Jadad)	Quality assessment (Newcastle-Ottawa Study)
Moser <i>et al.</i> , 2018, Laos 2018	6–15	Kato Katz	17–30 days after treatment	Single-blinded RCT	3	NA
Yap <i>et al.</i> , 2013 China	9–12	Kato Katz and Bauermann	1–6 months after treatment	Double-blinded RCT	5	NA
Sunish <i>et al.</i> , 2015 India	9–10	Kato Katz	10 years (2001–2010)	Cohort	NA	Good quality
Levecke <i>et al.</i> , 2014 Brazil, Cambodia, Cameroon, Ethiopia, United Republic of Tanzania, and Vietnam	4–18	McMaster	7–15 days on average	Multicenter clinical trial	1	NA
Liu, 2017	9–11	Kato-Katz	1 year later	Cluster-randomized trial	4	NA