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

Wendelin Moser, Somphou Sayasone, Syda Xayavong, Bangon Bounheuang, Maxim Puchkov, Jörg Huwyler, Jan Hattendorf, Jennifer Keiser

Summary

Background Albendazole and mebendazole are commonly used to control hookworm, but have shortcomings in their efficacy profiles. We assessed whether triple drug therapy (TDT) with albendazole, pyrantel pamoate, and oxantel pamoate was more effective than the co-administration of two drugs for the treatment of hookworm infections.

Methods A randomised, single-blind trial was done from Sept 27 until Nov 17, 2017, in Laos. Children (6–15 years) from six schools were invited to participate. Hookworm-positive children were randomly assigned (2:2:1:1) by a computer stratified list (block sizes of six and 12) to TDT with albendazole (400 mg), pyrantel pamoate (20 mg/kg), and oxantel pamoate (20 mg/kg); albendazole plus oxantel pamoate; pyrantel pamoate plus oxantel pamoate; or mebendazole (500 mg) combined with both pyrantel pamoate and oxantel pamoate (used as proof of concept to compare the two TDTs). Two stool samples were collected at baseline and follow-up (17–30 days after treatment) and analysed with the Kato-Katz method. The primary outcome was the proportion of hookworm egg-negative children at follow-up in all Kato-Katz slides (cure rate [CR]) in the TDT with albendazole, pyrantel pamoate, and oxantel pamoate group compared with the albendazole plus oxantel pamoate and pyrantel pamoate plus oxantel pamoate groups. Secondary outcomes were tolerability 3 h and 24 h after treatment, egg reduction rates (ERRs) against hookworm, and efficacy against concomitant soil-transmitted helminth infections. Participating children and field and laboratory technicians were masked to treatment allocation. All children with follow-up data were included in the primary analysis. This trial is registered with ClinicalTrials.gov, number NCT03278431.

Findings 1529 children were assessed for eligibility, of whom 533 provided complete baseline data and 414 provided complete outcome data. The CR was higher for the TDT albendazole, pyrantel pamoate, and oxantel pamoate (116 [84%] of 138) than with albendazole plus oxantel pamoate (73 [53%] of 138; odds ratio 4·7, 95% CI 2·7–8·3; p<0·0001) and pyrantel pamoate plus oxantel pamoate (36 [52%] of 69; 4·8, 2·5–9·3; p<0·0001). The geometric ERR of the TDT albendazole, pyrantel pamoate, and oxantel pamoate (99·9%) was higher than that for albendazole plus oxantel pamoate (99·0%; difference in ERR 0·9 percentage points, 95% CI 0·5–1·4), and pyrantel pamoate plus oxantel pamoate (99·2%; 0·7 percentage points, 0·3–1·3). Adverse events were reported by six (1%) children 3 h and none 24 h after treatment, without any difference across treatment groups.

Interpretation TDT with albendazole, pyrantel pamoate, and oxantel pamoate could make a difference, in particular in the context of soil-transmitted helminth elimination. Pyrantel pamoate might be a useful alternative to prevent benzimidazole resistance; however, larger trials are needed to confirm this finding.

Funding Swiss National Science Foundation.

Lancet Infect Dis 2018

Published Online
April 16, 2018
http://dx.doi.org/10.1016/S1473-3099(18)30220-2

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(18)30268-8

Department of Medical Parasitology and Infection Biology (W Moser PhD, Prof J Keiser PhD) **and Department of Epidemiology and Public Health** (J Hattendorf PhD), **Swiss Tropical and Public Health Institute, and Department of Pharmaceutical Sciences, Division of Pharmaceutical Technology** (M Puchkov PhD, Prof J Huwyler PhD), **University of Basel, Basel, Switzerland; and Lao Tropical and Public Health Institute, Vientiane, Laos** (S Sayasone PhD, S Xayavong MD, B Bounheuang MD)

Correspondence to:
Prof Jennifer Keiser, Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, CH-4002 Basel, Switzerland
jennifer.keiser@swisstph.ch

Introduction

About 1·5 billion people are infected with one of the three soil-transmitted helminths (STHs): *Ascaris lumbricoides*, hookworm (*Ancylostoma duodenale* and *Necator americanus*), and *Trichuris trichiura*.[1] STH infections are a major public health problem in poor and vulnerable populations, with the highest prevalence in Asia, followed by sub-Saharan Africa and the Americas.[1] The global burden

Research in context

Evidence before this study

Of the most widely used anthelmintic drugs albendazole and mebendazole, only albendazole has a moderate efficacy against hookworm and both show low performance against *Trichuris trichiura* when used as a single dose. Several co-administrations have been assessed, which revealed a broad spectrum of efficacy particularly against *T trichiura* infections. We searched PubMed for clinical trials on triple drug therapy for soil-transmitted helminthiasis before Nov 1, 2017, using different combinations of the following search terms: "hookworm", "albendazole", "pyrantel pamoate", "oxantel pamoate" , "mebendazole", "triple drug therapy", and "efficacy". Two preliminary studies using triple drug therapies were identified: one with albendazole, pyrantel pamoate, and oxantel pamoate (1989) and one with mebendazole, pyrantel pamoate, and oxantel pamoate (1990). However, neither study used the doses recommended by WHO.

Added value of this study

In this study, to our knowledge for the first time, the triple drug therapies albendazole, pyrantel pamoate, and oxantel pamoate, and mebendazole, pyrantel pamoate, and oxantel pamoate were thoroughly assessed. Triple drug therapy with albendazole, pyrantel pamoate, and oxantel pamoate had greater efficacy against hookworm than the co-administrations albendazole with oxantel pamoate and pyrantel pamoate with oxantel pamoate, with no differences among the co-administrations.

Implication of all available evidence

Almost 1 billion albendazole or mebendazole treatments are administered annually to at-risk populations in preventive chemotherapy programmes against soil-transmitted helminthiasis and lymphatic filariasis. The success of preventive chemotherapy is threatened by the development of drug resistance and by the moderate to low efficacy of the current drugs against hookworm and *T trichiura*. Apart from the discovery of new drugs, the combination of two or more drugs could improve efficacy and prevent resistance. The triple drug therapy albendazole, pyrantel pamoate, and oxantel pamoate might have a pivotal role in soil-transmitted helminth elimination. Pyrantel pamoate might be a useful treatment alternative against hookworm and in co-administration with oxantel pamoate against any soil-transmitted helminth in case of benzimidazole resistance.

of STH infections reached 3·3 million disability-adjusted life-years in 2016.[2]

To control the burden caused by moderate and heavy STH infections, preventive chemotherapy—that is, the administration of anthelmintic drugs in a single dose regimen, to at-risk populations—is the current strategy.[3] Although pyrantel pamoate and levamisole are on the WHO's Model Lists of Essential Medicines against intestinal helminth infections,[4] primarily albendazole and mebendazole are used for preventive chemotherapy programmes. Before and after pyrantel pamoate was added to WHO's Model Lists of Essential Medicines in 1983, its efficacy, as monotherapy and in combination with oxantel pamoate, was investigated in several clinical trials in human beings, including at different dose regimens.[5,6] Nonetheless, pyrantel pamoate was gradually replaced by albendazole and mebendazole, primarily because they are available as a weight-independent dose,[7] which is a major advantage for large-scale preventive chemotherapy programmes.[8]

Each year, almost 1 billion doses of albendazole or mebendazole are distributed in preventive chemotherapy programmes against soil-transmitted helminthiasis and lymphatic filariasis.[9] In 2016, about 166 million preschool-aged children and 467 million school-aged children were treated in STH preventive chemotherapy programmes, resulting in global coverage of 51% and 69%, respectively.[9] The goal of WHO is to expand the coverage of preventive chemotherapy to reach 75% of preschool and school-aged children in need of treatment, to reduce the burden caused by moderate and heavy infections by 2020.[3] Recent findings from a systematic literature review and network meta-analysis[5] showed that the efficacy of albendazole and mebendazole against hookworm and *T trichiura* has decreased over time, which might hint at anthelmintic drug resistance, although study confounders might have affected this result. Hence, novel therapeutic options should be assessed to fill the gap in the depleted anthelmintic drug pipeline.[10,11]

At present, no drug has high efficacy against all three STH species.[5] Hence, co-administration of drugs with different efficacy profiles is recommended to increase and broaden the spectrum of anthelmintic efficacy. Moreover, combining drugs with different modes of action could protect from the selection of drug resistance and, thus, extend the lifespan of effective and available anthelmintic drugs. Several studies in the past 5 years have assessed different co-administrations and found that albendazole plus oxantel pamoate is the treatment with highest and broadest efficacy against any STH.[12–14] After treatment with albendazole and oxantel pamoate, about half of hookworm-positive participants were cured (cure rate [CR] 45·5–51·4, egg reduction rate [ERR] 90·9–96·0), whereas the efficacy against *T trichiura* varied among the three clinical trials and was affected by baseline infection intensity (CR 31–83%, ERR 96·0–99·8).[12–14]

The combination of pyrantel pamoate and oxantel pamoate was approved for human use in Colombia, Peru,

 Published online April 16, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30220-2

and the Philippines; however, it is no longer produced.[15] Although both drugs are selective nicotinic acetylcholine receptor agonists, pyrantel pamoate acts on the L-subtype, whereas oxantel pamoate targets the N-subtype.[16] This combination has been widely tested, primarily using 10 mg/kg doses. In an analysis of 20–23 trials, the CR was high against *A lumbricoides* (96%) and moderate against hookworm (73%) and *T trichiura* (61%).[6]

In two preliminary studies,[17,18] efficacy against hookworm and *T trichiura* was improved by triple drug therapies (TDTs) with albendazole or mebendazole in combination with pyrantel pamoate and oxantel pamoate. TDTs are widely used in many therapeutic areas, including lymphatic filariasis,[19] but have not been explored systematically in randomised controlled trials for the treatment of STH infection.

The aim of this study was to comparatively assess the efficacy of TDT with albendazole, pyrantel pamoate, and oxantel pamoate, and the two co-administrations albendazole plus oxantel pamoate and pyrantel pamoate plus oxantel pamoate against hookworm infections. Moreover, we included a treatment arm of TDT with mebendazole, pyrantel pamoate, and oxantel pamoate as proof of concept to compare the activity of the two TDTs.

Methods

Study design and participants

We did this randomised, controlled, single-blind trial from Sept 27 until Nov 17, 2017, in Luang Prabang, Laos. Children (aged 6–15 years) from three primary (Nayang, Nakhone, and Phonmany) and three secondary schools (Xonphuao, Nayang, and Namthouama) were invited to participate. Children were deemed eligible if they provided two stool samples and were hookworm positive (eggs per gram of stool [EPG] >100), passed a physical and clinical examination, had no chronic illness, had no anthelmintic treatment in the past 4 weeks, and, if female, were not pregnant (≥12 years).

Before study start, the purpose, procedure, and potential risks and benefits of the study were explained to all eligible children and their parents or legal guardians. Parents or legal guardians were asked to sign a written consent and children an assent (≥12 years) according to Lao law. Before study start, permission for fieldwork was obtained from the Lao Ministry of Health, the Provincial Health Office, the District Health Office, and the District Office for Education and Sport. Ethical approval for the trial was granted by the National Ethics Committee for Health Research, Lao Ministry of Health (reference number 083/NECHR), and by the Ethics Committee of Northwestern and Central Switzerland (reference EKNZ ID:2017-00375).

Randomisation and masking

A computer-generated randomisation list with randomly selected block of sizes of six and 12 was provided by an independent statistician. The randomisation list was stratified according to the baseline infection intensity into light and moderate or heavy infections based on official WHO cutoffs.[20] Children were randomly assigned (2:2:1:1) to one of the four treatment arms: albendazole, pyrantel pamoate, and oxantel pamoate; albendazole plus oxantel pamoate; pyrantel pamoate plus oxantel pamoate; and mebendazole, pyrantel pamoate, and oxantel pamoate. Albendazole (Zentel, GlaxoSmithKline, London, UK) was used at a dose of 400 mg, mebendazole (Vermox, Janssen, Beerse, Belgium) at 500 mg, and pyrantel pamoate (125 mg tablets; Combantrin, Teofarma, Pavia, Italy) and oxantel pamoate (400 mg tablets manufactured at the University of Basel, Basel, Switzerland[21]) at 20 mg/kg bodyweight.

Participating children and field and laboratory technicians were masked to treatment allocation; only the investigator administering the drugs was aware of treatment allocation. Before study start, the drugs were prepared in plastic bags and labelled with a unique identification number by two independent pharmacists. Because of the large number of tablets administered, we did not include matching placebos. Hence, in theory children might have recognised the treatment because of the differing shape, colour, and number of tablets. However, the number of oxantel pamoate and pyrantel pamoate tablets varied depending on the weight of the children and they were probably unaware about the appearance of the specific drugs.

Procedures

All eligible children were asked to provide a stool sample and from all hookworm-positive children an additional sample was collected within 5 days. The stool samples were transported to the Nambak District Hospital (Nambak, Laos) for examination by the Kato-Katz method by experienced laboratory technicians. A 41·7 mg template was used for preparation of the Kato-Katz thick smear. Within 1 h after preparation, to avoid over-clearing of hookworm eggs, the slides were analysed quantitatively for helminth eggs under a light microscope.[22] To maintain high diagnostic standards, 10% of the slides were randomly re-read by the co-investigator (WM or SS) for *A lumbricoides* and *T trichiura* and discussed in case of discordance.[23] Because of the restricted time for analysing hookworm, one of the two slides was read by the co-investigator (WM or SS) and cross-checked with the second slide result to maintain high quality.

Before treatment, experienced physicians clinically and physically examined each eligible child for any acute or chronic illness. Medical history was assessed by active questioning using a standard questionnaire. Height was measured with a stadiometer (to the nearest 0·1 cm), weight with an electronic balance (to the nearest 0·1 kg), axillary temperature with an electric thermometer (to the nearest 0·1°C), and girls (age ≥12 years) were examined for pregnancy by taking a urine sample (ORANGE TEST, Artron Laboratories, Burnaby, BC, Canada). After

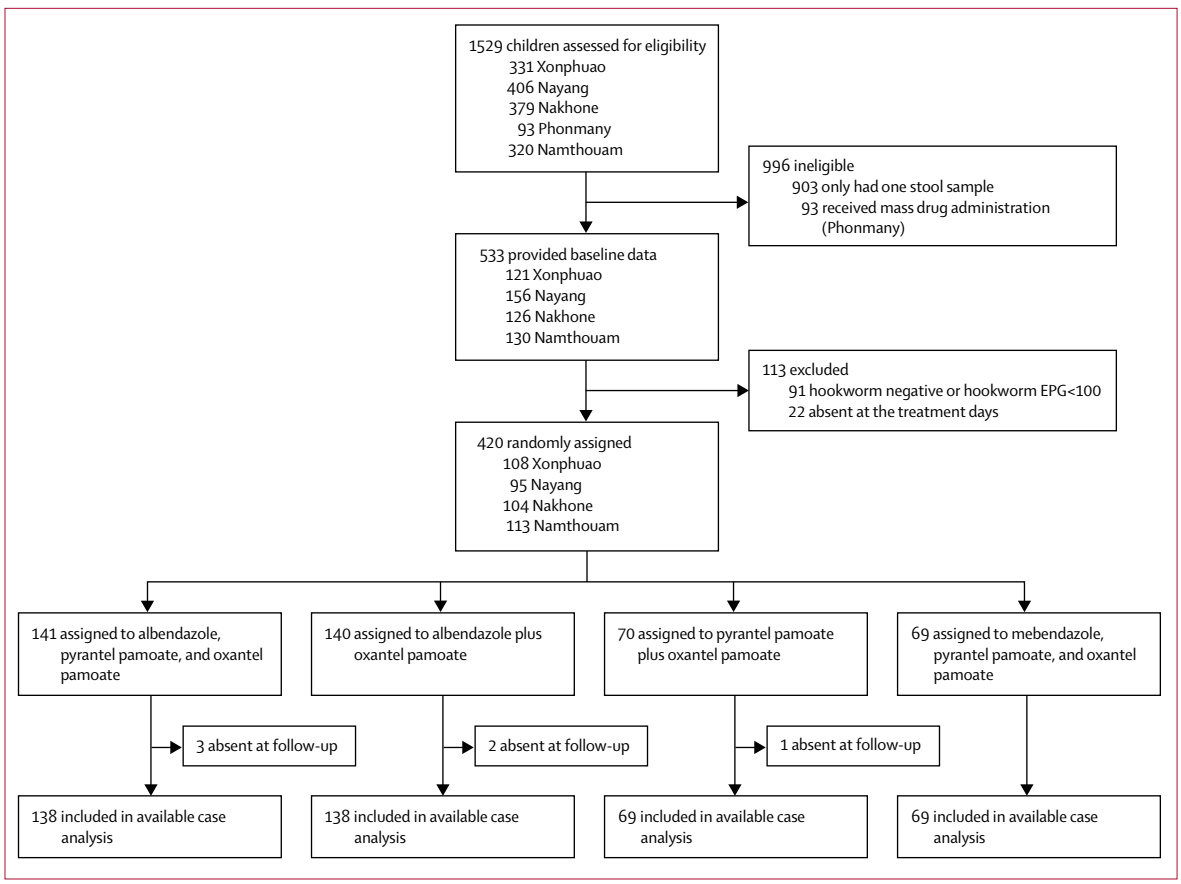

Figure 1: **Trial profile**
EPG=eggs per gram of stool.

treatment, children were monitored for 3 h. At 3 h and 24 h after treatment, children were actively questioned for adverse events by the study physicians. To assess treatment efficacy, another two stool samples were collected at follow-up, 17–30 days after treatment. Children remaining positive for any STH species were treated according to Laos national guidelines.[24]

Outcomes

The primary outcome was CR against hookworm after treatment measured by the Kato-Katz method. Secondary outcomes were tolerability at 3 h and 24 h after treatment, and efficacy against hookworm in terms of ERRs, and CRs and ERRs against *T trichiura* and *A lumbricoides*.

Statistical analysis

The primary hypothesis was that TDT with albendazole, pyrantel pamoate, and oxantel pamoate would have a higher efficacy than the co-administrations albendazole plus oxantel pamoate and pyrantel pamoate plus oxantel pamoate. We assumed CRs of 70% for TDT with albendazole, pyrantel pamoate, and oxantel pamoate, 50% for albendazole plus oxantel pamoate, and 35% for pyrantel pamoate plus oxantel pamoate against hookworm, on the basis of previous clinical trial data and expert opinions. To detect a difference with 90% power at a 5% two-sided significance, 121 children were required for the TDT with albendazole, pyrantel pamoate, and oxantel pamoate group and the albendazole plus oxantel pamoate group, and 38 children for the pyrantel pamoate plus oxantel pamoate group. However, we included 60 children in the pyrantel pamoate plus oxantel pamoate group to ensure balanced baseline characteristics after randomisation. As proof of concept, 60 children were allocated to TDT with mebendazole, pyrantel pamoate, and oxantel pamoate to assess efficacy. To account for potential loss to follow-up, the sample size was increased by 15% and resulted in a total of 420 children.

All children with follow-up data were included in the primary available case analysis. A sensitivity analysis was done to assess the potential effect of children lost to follow-up, with all missing data interpreted both as treatment failures and as treatment successes.

The mean egg count of the four Kato-Katz thick smears was multiplied by 24 to calculate the EPG. For the primary analysis, the CR was defined as the percentage of hookworm-positive children who were negative at follow-up (ie, no eggs in all Kato-Katz slides) in the

available case population, and odds ratios (ORs) were calculated using logistic regression unadjusted (primary analysis) and adjusted for age and sex. The ERR (ie, the percentage of mean reduction in egg count at follow-up compared with baseline) was calculated using the geometric mean and arithmetic mean. The geometric mean was calculated as follows:

$$ERR = \left(1 - \frac{e^{\frac{1}{n}\sum \log(EPG_{follow\text{-}up}+1)} - 1}{e^{\frac{1}{n}\sum \log(EPG_{baseline}+1)} - 1}\right) \times 100$$

To calculate the CIs for ERRs, a bootstrap resampling approach with 2000 replications was applied.[25] p values were calculated using a permutation test. No adjustment was made for multiple testing. All data were entered twice into a database (Microsoft Access 2003) and compared with EpiInfo version 3.3.2. Statistical analysis was done using Stata version 14.0 and R version 3.0.2.

This trial is registered with ClinicalTrials.gov, number NCT03278431.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1529 children were assessed for eligibility (figure 1), 533 of whom had complete baseline data (two stool samples). 113 children were excluded: 91 were hookworm negative or had a hookworm EPG less than 100 and 22 were absent at the treatment days. Thus, 420 hookworm-positive children were randomly assigned to one of the four treatment groups. Six children were lost to follow-up and 414 had complete outcome data. The first follow-up sample was taken between 17 days and 28 days after treatment and the second between 18 days and 30 days. All children completed the trial according to the protocol and therefore the available case population was identical to the per-protocol population (appendix). Treatment arms were well balanced according to age, sex, weight, height, and hookworm baseline infection intensity (table 1).

	Albendazole, pyrantel pamoate, and oxantel pamoate (n=141)	Albendazole plus oxantel pamoate (n=140)	Pyrantel pamoate plus oxantel pamoate (n=70)	Mebendazole, pyrantel pamoate, and oxantel pamoate (n=69)
Age (years)	12·3 (1·8)	12·4 (1·6)	12·4 (1·8)	12·2 (1·6)
Sex				
Boys	71 (50%)	74 (53%)	40 (57%)	43 (62%)
Girls	70 (50%)	66 (47%)	30 (43%)	26 (38%)
School				
Xonphuao	36 (26%)	36 (26%)	18 (26%)	18 (26%)
Nayang	32 (23%)	32 (23%)	17 (24%)	14 (20%)
Nakhone	36 (26%)	35 (25%)	16 (23%)	17 (25%)
Namthouam	37 (26%)	37 (26%)	19 (27%)	20 (29%)
Weight (kg)	36·4 (9·1)	36·5 (8·9)	34·8 (7·6)	35·2 (7·2)
Height (cm)	143·2 (10·1)	142·3 (14·1)	140·5 (14·7)	144·2 (9·8)
Hookworm				
Infected children	141 (100%)	140 (100%)	70 (100%)	69 (100%)
EPG geometric mean	690·8	696·9	656·5	703·1
Infection intensity				
Light (1–1999 EPG)	112 (79%)	112 (80%)	56 (80%)	56 (81%)
Moderate 2000–3999 EPG)	15 (11%)	20 (14%)	10 (14%)	9 (13%)
Heavy (≥4000 EPG)	14 (10%)	8 (6%)	4 (6%)	4 (6%)
Trichuris trichiura				
Infected children	43 (30%)	52 (37%)	31 (44%)	26 (38%)
EPG geometric mean	66·9	83·4	76·2	47·9
Infection intensity				
Light (1–999 EPG)	42/43 (98%)	48/52 (92%)	30/31 (97%)	25/26 (96%)
Moderate (1000–9999 EPG)	1/43 (2%)	4/52 (8%)	1/31 (3%)	1/26 (3%)
Heavy (≥10 000 EPG)	0	0	0	0
Ascaris lumbricoides				
Infected children	22 (16%)	24 (17%)	13 (19%)	15 (22%)
EPG geometric mean	3361·5	2708·3	3665·5	2718·8
Infection intensity				
Light (1–4999 EPG)	15/22 (68%)	16/24 (67%)	6/13 (46%)	11/15 (73%)
Moderate (5000–49 999 EPG)	5/22 (23%)	6/24 (25%)	7/13 (54%)	3/15 (20%)
Heavy (≥50 000 EPG)	2/22 (9%)	2/24 (8%)	0	1/15 (7%)

Data are mean (SD), number (%), or n/N (%), unless otherwise stated. Some percentages do not add up to 100 because of rounding. EPG=eggs per gram of stool.

Table 1: **Demographics and baseline characteristics**

Against hookworm, the CR of TDT with albendazole, pyrantel pamoate, and oxantel pamoate (84·1%) was significantly higher than that of albendazole plus oxantel pamoate (52·9%; OR 4·7, 95% CI 2·7–8·3; p<0·0001) and pyrantel pamoate plus oxantel pamoate (52·2%; 4·8, 2·5–9·3; p<0·0001; table 2). No significant differences were found between the OR of the unadjusted logistic regression and after adjusting for age and sex (data not shown). The highest geometric ERR against hookworm occurred with TDT with albendazole, pyrantel pamoate, and oxantel pamoate (99·9%), compared with albendazole plus oxantel pamoate (99·0%; difference 0·9 percentage points, 95% CI 0·5–1·4) and pyrantel pamoate plus oxantel pamoate (99·2%; 0·7 percentage points, 0·3–1·3). The arithmetic ERR was higher for TDT with albendazole, oxantel pamoate, and pyrantel pamoate (98·4%) than for albendazole plus oxantel pamoate (91·0%; difference 7·4 percentage points, 95% CI 3·4 to 12·0), but was not significantly different from pyrantel pamoate plus oxantel pamoate (96·3%; 2·1 percentage points, –0·4 to 5·1).

All children with a *T trichiura* infection were cured after treatment with albendazole plus oxantel pamoate

See Online for appendix

	Albendazole, pyrantel pamoate, and oxantel pamoate (n=138)	Albendazole plus oxantel pamoate (n=138)	Pyrantel pamoate plus oxantel pamoate (n=69)	Mebendazole, pyrantel pamoate, and oxantel pamoate (n=69)
Hookworm				
Children positive for infection				
Before treatment	138	138	69	69
After treatment	22	65	33	21
Cure rate (95% CI)	84·1% (76·9–89·7)	52·9% (44·2–61·4)	52·2% (39·8–64·4)	69·6% (57·3–80·1)
Children cured/total number with infection (%)				
From light infection	98/111 (88%)	59/110 (54%)	30/55 (55%)	41/56 (73%)
From moderate infection	8/15 (53%)	11/20 (55%)	4/10 (40%)	6/9 (67%)
From heavy infection	10/12 (83%)	3/8 (38%)	2/4 (50%)	6/9 (67%)
EPG geometric mean				
Before treatment	671·4	706·9	671·4	703·8
After treatment	0·9	7·2	5·6	2·5
Egg reduction rate (95% CI)	99·9% (99·8–99·9)	99·0% (98·5–99·4)	99·2% (98·5–99·6)	99·6% (99·3–99·8)
EPG arithmetic mean				
Before treatment	1373·7	1269·2	1301·0	1456·7
After treatment	22·0	114·1	48·1	99·4
Egg reduction rate (95% CI)	98·4% (96·7–99·4)	91·0% (85·9–94·5)	96·3% (93·4–98·0)	93·2% (86·3–98·7)
Trichuris trichiura				
Children positive for infection				
Before treatment	43	51	31	26
After treatment	3	0	8	3
Cure rate (95% CI)	93·0% (80·9–98·5)	100·0% (93·0–100·0)	74·2% (55·4–88·1)	88·5% (69·8–97·6)
EPG geometric mean				
Before treatment	68·1	88·8	77·4	49·1
After treatment	0·3	0	1·6	0·6
Egg reduction rate (95% CI)	99·6% (98·4–100·0)	100·0%	97·9% (95·1–99·2)	98·8% (96·8–100·0)
EPG arithmetic mean				
Before treatment	181·1	376·4	209·8	159·9
After treatment	9·9	0	51·7	11·3
Egg reduction rate (95% CI)	94·5% (87·5–100·0)	100·0%	75·4% (58·1–98·1)	92·9% (86·0–100·0)
Ascaris lumbricoides				
Children positive for infection				
Before treatment	22	24	13	15
After treatment	2	1	0	0
Cure rate (95% CI)	90·9% (70·8–98·9)	95·8% (78·9–99·9)	100·0% (75·3–100·0)	100·0% (78·2–100·0)
EPG geometric mean				
Before treatment	3363·8	2710·3	3670·3	2720·3
After treatment	0·5	0·2	0	0
Egg reduction rate (95% CI)	>99·9% (99·9–100·0)	>99·9% (99·9–100·0)	100·0%	100·0%
EPG arithmetic mean				
Before treatment	13531·4	18221·0	13062·0	21041·2
After treatment	8·2	5·0	0	0
Egg reduction rate (95% CI)	>99·9% (>99·9–100·0)	>99·9% (>99·9–100·0)	100·0%	100·0%

Data are number (%), unless otherwise stated. EPG=eggs per gram of stool.

Table 2: **Efficacy outcomes in the available case analysis**

(CR 100·0%; table 2). Three children treated with TDT with albendazole, pyrantel pamoate, and oxantel pamoate remained *T trichiura* positive after treatment, which resulted in a CR of 93·0% (95% CI 80·9–98·5), a geometric ERR of 99·6% (98·4–100·0), and an arithmetic ERR of 94·5% (87·5–100·0). Efficacy was lower for pyrantel pamoate plus oxantel pamoate, with a CR of 74·2% (95% CI 55·4–88·1), geometric ERR of 97·9% (95·1–99·2), and arithmetic ERR of 75·4% (58·1–98·1).

Pyrantel pamoate plus oxantel pamoate cured all children with an *A lumbricoides* infection (CR 100·0%; table 2). One child remained positive for *A lumbricoides* after treatment with albendazole plus oxantel pamoate (CR 95·8%, 95% CI 78·9–99·9) and two children after TDT with albendazole, pyrantel pamoate, and oxantel pamoate (90·9%, 70·8–98·9); for both treatments the geometric and arithmetic ERRs were higher than 99·9%.

In the comparison of the two TDTs, the CR was higher for TDT with albendazole, pyrantel pamoate, and oxantel pamoate against hookworm than for TDT with mebendazole, pyrantel pamoate, and oxantel pamoate (84·1% *vs* 69·6%; OR 2·3, 95% CI 1·2–4·6; p=0·017; table 2). Similarly, the geometric ERR of albendazole, pyrantel pamoate, and oxantel pamoate was higher than that for TDT with mebendazole, pyrantel pamoate, and oxantel pamoate (geometric ERR 99·9% *vs* 99·6%; difference in ERRs 0·2 percentage points, 95% CI <0·1 to 0·5), but the difference between arithmetic ERRs was not significant (98·4% *vs* 93·2%, 5·2 percentage points, –1·1 to 12·2). Against *T trichiura*, similar efficacy was observed for both TDTs, with a CR of 88·5% (95% CI 69·8–97·6), a geometric ERR of 98·8% (96·8–100·0), and an arithmetic ERR of 92·9% (86·0–100·0) for TDT with mebendazole, pyrantel pamoate, and oxantel pamoate. All *A lumbricoides*-infected children were cured after TDT with mebendazole, pyrantel pamoate, and oxantel pamoate.

Before treatment, 44 (10%) children reported symptoms (figure 2; table 3; appendix), 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 oxantel pamoate. 24 h after treatment, all adverse events had resolved.

Discussion

In our study, TDT with albendazole, pyrantel pamoate, and oxantel pamoate reached higher efficacy in terms of CR and geometric ERR than the two co-administrations. Although the CR of TDT with albendazole, pyrantel pamoate, and oxantel pamoate was higher by about 30 percentage points, the ERR was only slightly, yet clinically relevantly, increased compared with albendazole plus oxantel pamoate and pyrantel pamoate plus oxantel pamoate. Moreover, in children harbouring light infection intensities, a substantially higher CR of 88% was observed with TDT with albendazole, pyrantel pamoate, and oxantel pamoate compared with the other treatments. Once the strategy against STH moves from control towards elimination, TDT with albendazole, pyrantel pamoate, and oxantel pamoate might make a difference, similar to in the elimination of lymphatic filariasis. WHO guidelines for lymphatic filariasis were recently adapted

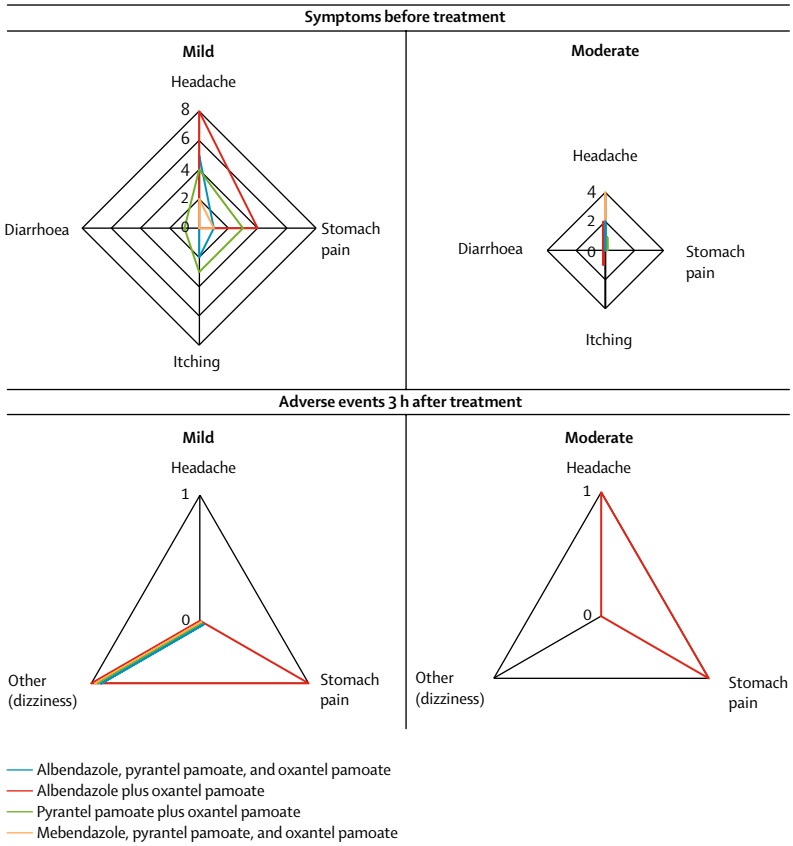

Figure 2: **Symptoms before and adverse events 3 h after treatment**
None of the children had adverse events 24 h after treatment.

	Number of children with mild/moderate symptoms				Number (%) of children with any symptoms
	Albendazole, pyrantel pamoate, and oxantel pamoate	Albendazole plus oxantel pamoate	Pyrantel pamoate plus oxantel pamoate	Mebendazole, pyrantel pamoate, and oxantel pamoate	
Symptoms before treatment					
Number of children	141	140	70	69	420
Headache	5/2	8/2	4/1	2/4	28 (7%)
Stomach pain	1/0	4/0	3/0	1/0	9 (2%)
Itching	2/0	0/1	3/0	0/0	6 (1%)
Diarrhoea	0/0	0/0	1/0	0/0	1 (<1%)
Total	8/2	12/3	11/1	3/4	44 (10%)
Adverse events 3 h after treatment					
Number of children	138	138	69	69	414
Headache	0/0	0/1*	0/0	0/0	1 (<1%)
Stomach pain	0/0	1/1	0/0	0/0	2 (<1%)
Other (dizziness)	1/0	1*/0	1/0	1/0	4 (1%)
Total	1/0	2/2	1/0	1/0	6 (1%)

All adverse events disappeared after 24 h. *One child reported moderate headache and mild dizziness.

Table 3: **Symptoms before treatment and adverse events 3 h after treatment**

and the TDT ivermectin, diethylcarbamazine, and albendazole is now the treatment of choice.[19]

The efficacy of TDT with albendazole, pyrantel pamoate, and oxantel pamoate was assessed in a previous study more than 30 years ago, in which slightly higher CRs (90·3% and 92·6%) and similar ERRs (99·8% and 99·3%) against hookworm were reported, regardless of lower albendazole doses (150 mg and 300 mg) compared with the 400 mg dose in our study.[17]

Powered as a proof-of-concept analysis, albendazole and mebendazole combined with pyrantel pamoate plus oxantel pamoate were compared in the present study. The efficacy of the albendazole TDT was higher against hookworm in terms of CR and geometric ERR. Our results might reflect the higher efficacy of the single-drug albendazole compared with mebendazole[5] and are in line with findings from two studies from the 1980s,[17,18] which suggested a lower efficacy (CR 67% and ERR 86%) for mebendazole, pyrantel pamoate, and oxantel pamoate compared with the albendazole TDT.

Albendazole plus oxantel pamoate and pyrantel pamoate plus oxantel pamoate had comparable efficacy against hookworm; however, our study was not designed to show equivalence between the two co-administrations. Nonetheless, this finding highlights the potential of pyrantel pamoate since it is a safe drug,[6] is produced by several pharmaceutical companies, and provides an alternative treatment option in case of benzimidazole-resistant hookworm infections. Currently, WHO recommends a single dose of 10 mg/kg pyrantel pamoate for light hookworm infections.[26] Pyrantel pamoate alone or in co-administration with oxantel pamoate was investigated in the 1970–80s with different dose regimens against infections with hookworm (pyrantel pamoate alone) and in co-administration with oxantel pamoate against infections with hookworm and *T trichiura*. For pyrantel pamoate monotherapy, inconclusive results were obtained using different doses.[6] However, findings from an almost half a decade old dose-finding study for pyrantel pamoate against hookworm infections suggested an increased ERR for higher doses,[27] and based on a more recent dose-finding study for oxantel pamoate against *T trichiura* infections,[28] a dose regimen of 20 mg/kg for both drugs was chosen for this study. Yet, the inconsistent results for pyrantel pamoate alone and in co-administration with oxantel pamoate in previous studies call for a thorough dose-finding study for pyrantel pamoate, as was done for oxantel pamoate,[28] which furthermore allow the development of a weight-independent dose of pyrantel pamoate for preventive chemotherapy.

The results against hookworm were limited by the inability of the Kato-Katz method to distinguish between the two hookworm species *N americanus* and *A duodenale*. However, ongoing work from PCR analysis suggests that *N americanus* was the predominant species in our study (data not shown). Both species are susceptible for pyrantel pamoate; however, *A duodenale* is more sensitive according to a study by Kale and colleagues from 1982.[29] Another limitation of our trial was that only a few *T trichiura* co-infections were observed. We confirmed the high trichuricidal activity of albendazole plus oxantel pamoate, to our knowledge for the first time, in an Asian setting, compared with three recent trials in Africa.[12–14] All children positive for *T trichiura* were cured with albendazole plus oxantel pamoate, which is probably associated with the low infection intensity of the children. Similarly, among the trials in the African settings, efficacy was greater for lower[13] compared with higher baseline infection intensity.[12] A lower efficacy was shown for pyrantel pamoate plus oxantel pamoate, which is not unexpected, since single-dose pyrantel pamoate has a lower efficacy against *T trichiura* than albendazole.[5]

Overall, in this study only six children had mild or moderate (headache and stomach pain) adverse events and all adverse events disappeared 1 day after treatment. Three (2%) children reported adverse events 3 h after treatment with albendazole plus oxantel pamoate, compared with 8–12% in the African trials.[12–14] Our findings are in line with low or absence of adverse events reported in clinical trials including pyrantel pamoate plus oxantel pamoate[30] and the two TDTs.[17,18]

In conclusion, TDT with albendazole, pyrantel pamoate, and oxantel pamoate showed higher efficacy than the co-administrations albendazole plus oxantel pamoate and pyrantel pamoate plus oxantel pamoate and might become a key treatment for STH control and elimination. Although pyrantel pamoate is readily available on the market, oxantel pamoate needs to be developed and registered by a stringent regulatory authority. Our study confirmed that pyrantel pamoate plus oxantel pamoate is a valuable candidate in preventive chemotherapy programmes to avoid the development of drug resistance.

Contributors

WM, SS, JHa, and JK planned and designed the study. The oxantel pamoate tablets were manufactured and produced by MP and JHu. WM, SS, SX, BB, and JK did the study. WM, JHa, and JK analysed and interpreted the data. WM and JK wrote the first draft and JHa revised the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was supported by the Swiss National Science Foundation (number 320030_14930/1). We thank the school children for participating; the headmasters for their support; the team at the Lao Tropical and Public Health Institute, Vientiane, Laos, for the field and laboratory work; the Nambak District Hospital for providing the facilities; Darryl Bordland for support in oxantel pamoate tablet production; and WHO for providing the albendazole, mebendazole, and pyrantel pamoate tablets.

References

1 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:** 37.

2 GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390:** 1260–344.

3 WHO. Soil-transmitted helminthiasis: eliminating soil-transmitted helminthiasis as a public health problem in children. Progress report 2001–2010 and strategic plan 2011–2020. Geneva: World Health Organization, 2012.

4 WHO. WHO Model Lists of Essential Medicines, 20th list. Geneva: World Health Organization, 2017.

5 Moser W, Schindler C, Keiser J. Efficacy of recommended drugs against soil transmitted helminths: systematic review and network meta-analysis. *BMJ* 2017; **358:** j4307.

6 Levecke B, Vercruysse J. Chapter 5—pyrantel parasiticide therapy in humans. In: Marchiondo AA, ed. Pyrantel parasiticide therapy in humans and domestic animals. London, UK: Academic Press, 2016: 109–28.

7 Hong S-T, Chai J-Y, Choi M-H, Huh S, Rim H-J, Lee S-H. A successful experience of soil-transmitted helminth control in the Republic of Korea. *Korean J Parasitol* 2006; **44:** 177–85.

8 Keiser J, Utzinger J. The drugs we have and the drugs we need against major helminth infections. *Adv Parasitol* 2010; **73:** 197–230.

9 WHO. Summary of global update on preventive chemotherapy implementation in 2016: crossing the billion. *Wkly Epidemiol Rec* 2017; **40:** 589–608.

10 Keiser J, Tritten L, Silbereisen A, Speich B, Adelfio R, Vargas M. Activity of oxantel pamoate monotherapy and combination chemotherapy against *Trichuris muris* and hookworms: revival of an old drug. *PLoS Negl Trop Dis* 2013; **7:** e2119.

11 Olliaro P, Seiler J, Kuesel A, et al. Potential drug development candidates for human soil-transmitted helminthiases. *PLoS Negl Trop Dis* 2011; **5:** e1138.

12 Speich B, Ame SM, Ali SM, et al. Oxantel pamoate–albendazole for *Trichuris trichiura* infection. *N Engl J Med* 2014; **370:** 610–20.

13 Speich B, Ali SM, Ame SM, et al. Efficacy and safety of albendazole plus ivermectin, albendazole plus mebendazole, albendazole plus oxantel pamoate, and mebendazole alone against *Trichuris trichiura* and concomitant soil-transmitted helminth infections: a four-arm, randomised controlled trial. *Lancet Infect Dis* 2015; **15:** 277–84.

14 Moser W, Coulibaly JT, Ali SM, et al. Efficacy and safety of tribendimidine, tribendimidine plus ivermectin, tribendimidine plus oxantel pamoate, and albendazole plus oxantel pamoate against hookworm and concomitant soil-transmitted helminth infections in Tanzania and Côte d'Ivoire: a randomised, controlled, single-blinded, non-inferiority trial. *Lancet Infect Dis* 2017; **17:** 1162–71.

15 Grayson ML, Cosgrove SE, Crowe S, et al. Kucers' the use of antibiotics: a clinical review of antibacterial, antifungal, antiparasitic, and antiviral drugs, seventh edition, three volume set. Boca Raton, USA: CRC Press, 2017.

16 Abongwa M, Martin J, Robertson A. A brief review on the mode of action of antinematodal drugs. *Acta Vet (Beogr)* 2017; **67:** 137–52.

17 Shichuan C. The efficacy of chemotherapy with albendazole, pyrantel and oxantel in combination for intestinal nematodiasis. *Acta Univ Med Nanjing* 1989; **4:** 270–72 (in Chinese).

18 Sinniah B, Sinniah D, Dissanaike AS. Single dose treatment of intestinal nematodes with oxantel-pyrantel pamoate plus mebendazole. *Ann Trop Med Parasitol* 1980; **74:** 619–23.

19 WHO. Guideline. Alternative mass drug administration regimens to eliminate lymphatic filariasis. Geneva: World Health Organization, 2017.

20 WHO. Assessing the efficacy of anthelminthic drugs against schistosomiasis and soil-transmitted helminthiases. Geneva: World Health Organization, 2013.

21 Alles R, Puchkov M, Jablonski C, Speich B, Keiser J, Huwyler J. Development of oxantel tablets for pediatric clinical studies: a technical note. *J Drug Deliv Sci Technol* 2013; **23:** 623–25.

22 Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick-smear technique in *Schistosomiasis mansoni*. *Rev Inst Med Trop São Paulo* 1972; **14:** 397–400.

23 Speich B, Ali SM, Ame SM, Albonico M, Utzinger J, Keiser J. Quality control in the diagnosis of *Trichuris trichiura* and *Ascaris lumbricoides* using the Kato-Katz technique: experience from three randomised controlled trials. *Parasit Vectors* 2015; **8:** 82.

24 Lao Ministry of Health. Diagnosis and treatment at the district hospital. A diagnosis and treatment guideline for the district hospitals in Lao PDR. Vientiane: Lao Ministry of Health, 2004.

25 Efron B. The bootstrap and Markov-chain Monte Carlo. *J Biopharm Stat* 2011; **21:** 1052–62.

26 WHO. Model prescribing information: drugs used in parasitic diseases, second edition. Geneva: World Health Organization, 1995.

27 Bell WJ, Gould GC. Preliminary report on pyrantel pamoate in the treatment of human hookworm infection. *East Afr Med J* 1971; **48:** 143–51.

28 Moser W, Ali SM, Ame SM, et al. Efficacy and safety of oxantel pamoate in school-aged children infected with *Trichuris trichiura* on Pemba Island, Tanzania: a parallel, randomised, controlled, dose-ranging study. *Lancet Infect Dis* 2016; **16:** 53–60.

29 Kale OO, Bammeke AO, Nwankwo EO. Field trials of pyrantel pamoate (Combantrin) in Ascaris, hookworm and Trichuris infections. *Afr J Med Med Sci* 1982; **11:** 23–31.

30 Albonico M, Ramsan M, Wright V, et al. Soil-transmitted nematode infections and mebendazole treatment in Mafia Island schoolchildren. *Ann Trop Med Parasitol* 2002; **96:** 717–26.