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

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Summary

Background Preventive chemotherapy is the current strategy to control soil-transmitted helminth infections (caused by *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*). But, to improve efficacy and avoid emerging resistance, new drugs are warranted. Tribendimidine has shown good anthelmintic efficacy and is therefore a frontrunner for monotherapy and combination chemotherapy.

Methods We did a randomised, controlled, single-blinded, non-inferiority trial on Pemba Island, Tanzania, and in Côte d'Ivoire. We recruited adolescents aged 15–18 years from four primary schools on Pemba, and school attendees and non-schoolers from two districts in Côte d'Ivoire. Only hookworm-positive participants were randomly assigned (1:1:1:1) to single, oral doses of tribendimidine 400 mg plus placebo (tribendimidine monotherapy), tribendimidine 400 mg plus ivermectin 200 µg/kg, tribendimidine 400 mg plus oxantel pamoate 25 mg/kg, or albendazole 400 mg plus oxantel pamoate 25 mg/kg. Randomisation was done via a computer-generated list in block sizes of four or eight. Participants were asked to provide two stool samples on 2 consecutive days at baseline and again 14–21 days at follow-up. The primary outcome was the difference in egg-reduction rates (ERRs; ie, the geometric mean reduction) in hookworm egg counts between treatment groups, measured by the Kato-Katz technique. Differences in coadministrated treatment groups were assessed for non-inferiority with a margin of –3% to albendazole plus oxantel pamoate based on the available-case population, analysed by intention to treat. Safety was assessed 3 h and 24 h after treatment. This study is registered with ISRCTN (number 14373201).

Findings Between July 26, and Dec 23, 2016, we treated 636 hookworm-positive participants, and outcome data were available for 601 participants (151 assigned to tribendimidine monotherapy, 154 to tribendimidine plus ivermectin, 148 to tribendimidine plus oxantel pamoate, and 148 to albendazole plus oxantel pamoate). Tribendimidine plus ivermectin was non-inferior to albendazole plus oxantel pamoate (ERRs 99·5% [95% CI 99·2–99·7] *vs* 96·0% [93·9–97·4]; difference 3·52 percentage points [2·05–5·65]). Likewise, tribendimidine plus oxantel pamoate was non-inferior to albendazole plus oxantel pamoate (ERRs 96·5% [95% CI 94·9 to 97·6] *vs* 96·0% [93·9 to 97·4]; difference 0·48 percentage points [–1·61 to 2·88]). 3 h after treatment, headache (n=50 [8%]) and vertigo (n=37 [6%]) were the most widely reported symptoms; 24 h after treatment, 50 (8%) patients reported vertigo and 41 (7%) reported headache. Mainly mild adverse events were reported with peak numbers (n=111 [18%]) at 24 h after treatment. Three participants had moderate adverse events 3 h after treatment: two (<1%) had vertigo and one (<1%) had headache, and two had moderate adverse events 24 h after treatment: one (<1%) had vomiting and one (<1%) had vomiting plus diarrhoea.

Interpretation Tribendimidine in combination with either ivermectin or oxantel pamoate had a similar, non-inferior efficacy profile as albendazole plus oxantel pamoate, hence tribendimidine will be a useful addition to the depleted anthelmintic drug armamentarium.

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Introduction

Soil-transmitted helminth infections are among the most common intestinal infections around the world and are caused by the nematodes *Ascaris lumbricoides*, hookworm (*Ancylostoma duodenale* and *Necator americanus*), and *Trichuris trichiura*. An estimated 1·5 billion people are infected with at least one soil-transmitted helminth species.[1] The estimated

Research in context

Evidence before this study

We searched PubMed for all articles published before June 1, 2017, with a combination of the search terms "hookworm", "tribendimidine", and "efficacy", without language restrictions. Clinical data about the efficacy of tribendimidine against soil-transmitted helminth infections exist only from China, and no published clinical data from other countries and continents exist.

Added value of this study

This study provides the first clinical data outside China for the efficacy of tribendimidine alone and in coadministration with ivermectin and oxantel pamoate against soil-transmitted helminth infections in two African countries (Tanzania and Côte d'Ivoire). The results from this randomised, controlled, single blinded, non-inferiority trial confirmed the good safety profile of tribendimidine, with only a few and mainly mild adverse events reported. The efficacy profile of tribendimidine resembles albendazole, the current standard drug against hookworm infections. Tribendimidine coadministered with ivermectin provided high efficacy against hookworm infection, indicating synergism. To tackle infections from all three soil-transmitted helminths, coadministration of tribendimidine plus oxantel pamoate showed promising results.

Implications of all the available evidence

The current strategy to control soil-transmitted helminth infections is preventive chemotherapy—ie, annual or biannual treatment of at-risk populations. For more than three decades, the two benzimidazoles (albendazole and mebendazole) have been the only drugs used in this area, leading to a high drug pressure and the risk of emerging benzimidazole resistance. Tribendimidine, which is currently under assessment towards approval by the US Food and Drug Administration, is the most advanced drug in the anthelmintic pipeline, and our data suggest that it will be a useful addition in preventive chemotherapy programmes.

global burden of such infections was 3·4 million disability-adjusted life-years in 2015.[2]

To reduce the morbidity caused by soil-transmitted helminths, the current control strategy is preventive chemotherapy—ie, regular (annual or biannual) administration of drugs to at-risk populations. One of WHO's goals for this disease area is to provide effective drugs to 75% of all at-risk populations by 2020.[3] In 2015, an estimated 59·5% of people in need of preventive chemotherapy were treated.[4] For the past three decades, mainly two benzimidazoles—albendazole and mebendazole—have been used. However, these drugs have shortcomings in their efficacy profiles of single-dose regimens against hookworm (mebendazole) and *T trichiura* (both albendazole and mebendazole).[5] And because of their long-standing use, the threat of benzimidazole resistance increases, as shown in veterinary medicine.[6] Alarmingly, there are only a few drugs that could serve as backups.

The Chinese drug tribendimidine is the most advanced therapy in the anthelmintic drug pipeline and is currently under assessment towards approval by the US Food and Drug Administration (FDA).[7] Tribendimidine, a B-subtype selective nicotinic acetylcholine receptor agonist, has a different mode of action compared with commonly used anthelmintic drugs.[8] Up to now, published data for the clinical use of tribendimidine have been restricted to Asia. The drug was discovered in the early 1980s, and approved for human use by the Chinese FDA in 2004,[9] hence its safety and efficacy is supported by several decades of clinical research and approved use. The efficacy profile of tribendimidine against soil-transmitted helminths is similar to albendazole—it has high efficacy against *A lumbricoides* and hookworm and low efficacy against *T trichiura*.[9] Additionally, tribendimidine has shown activity against several other parasitic diseases, such as those caused by *Enterobius vermicularis*, *Taenia* spp, *Opistorchis viverrini*, and *Clonorchis sinensis*.[9]

Tribendimidine could complement albendazole in the parasitic drug armamentarium to reduce drug pressure or serve as a backup in case of benzimidazole resistance. Neither tribendimidine nor current standard drugs are capable of successfully curing all three soil-transmitted helminths at a single dose. Hence, to broaden the range of efficacies and successfully treat hookworm and *T trichiura* infections, drug coadministrations will have an important role. The aim of our study was to investigate tribendimidine as an alternative to albendazole, and to assess tribendimidine coadministration with ivermectin or oxantel pamoate as therapy against all three soil-transmitted helminth infections.

Methods

Study design and participants

We did a randomised, controlled, single blinded, non-inferiority trial in Pemba Island in Tanzania and Agboville district in Côte d'Ivoire. Ethical approval was granted by the Zanzibar Medical Research and Ethical Committee in Tanzania (ZAMREC/0001/APRIL/016), the Comité National d'Ethique et de la Recherche in Côte d'Ivoire (083/MSHP/CNER-kp) and the Ethics Committee of Northwestern and Central Switzerland (EKNZ UBE-15/35).

We invited adolescents aged 15–18 years to participate in the study. In Tanzania, adolescents were recruited via secondary schools (Wingwi, Mizingani, Wesha, and Tumbe); in Côte d'Ivoire, they were recruited from

schools and non-schoolers from the districts Azaguié and Rubino. Participants were asked to provide two stool samples and only participants who tested positive for hookworm were eligible. Participants with any systematic illness (eg, clinical malaria, cancer, diabetes, or asthma) were excluded. Detailed inclusion and exclusion criteria are in the appendix (p 3). All parents or legal guardians, signed a written informed consent form and participants provided verbal (Tanzania) or written (Côte d'Ivoire) assent. Before the baseline screening, permission to do the trial was obtained from the school headmasters (Tanzania) or village chiefs (Côte d'Ivoire).

Randomisation and masking

Participants were randomly assigned (1:1:1:1) to tribendimidine 400 mg plus placebo (tribendimidine monotherapy), tribendimidine 400 mg plus ivermectin 200 µg/kg, tribendimidine 400 mg plus oxantel pamoate 25 mg/kg, or albendazole 400 mg plus oxantel pamoate 25 mg/kg. An independent statistician did the randomisation via a computer-generated list, block-randomised in sizes of four or eight and stratified according to baseline-infection intensity (light or moderate plus heavy infections). Participants, laboratory technicians, and field technicians were masked to treatment. The different

See Online for appendix

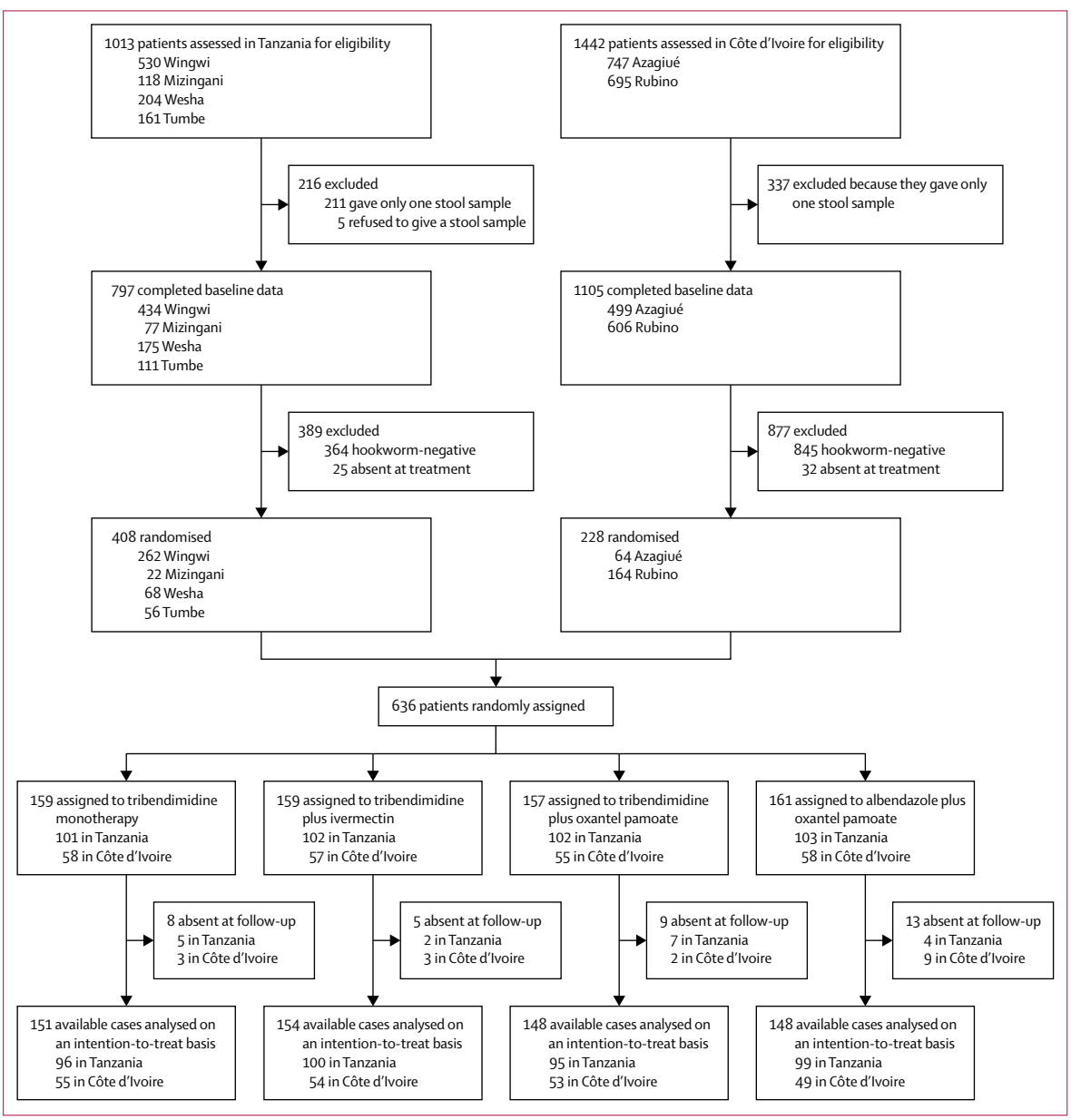

***Figure 1*: Trial profile**

	Tribendimidine monotherapy (n=159)	Tribendimidine plus ivermectin (n=159)	Tribendimidine plus oxantel pamoate (n=157)	Albendazole plus oxantel pamoate (n=161)
Age (years)	15·8 (0·9)	15·9 (1·0)	15·9 (1·0)	15·8 (1·0)
Sex				
Boys (%)	74 (47%)	65 (41%)	84 (54%)	75 (47%)
Girls (%)	85 (53%)	94 (59%)	73 (46%)	86 (53%)
Tanzanian schools or health districts				
Wingwi	64 (40%)	67 (42%)	66 (42%)	65 (40%)
Mizingani	7 (4%)	4 (2%)	5 (3%)	6 (4%)
Wesha	16 (10%)	17 (11%)	18 (12%)	17 (11%)
Tumbe	14 (9%)	14 (9%)	13 (8%)	15 (9%)
Côte d'Ivoire schools or health districts				
Azaguié	19 (12%)	18 (11%)	17 (11%)	10 (6%)
Rubino	39 (25%)	39 (25%)	38 (24%)	48 (30%)
Weight (kg)	47·9 (7·8)	48·9 (8·7)	48·2 (8·3)	48·5 (8·4)
Height (cm)	157·7 (8·7)	157·6 (9·8)	158·3 (13·6)	158·5 (9·8)
Hookworm infections				
Number of participants infected	159 (100%)	159 (100%)	157 (100%)	161 (100%)
Geometric mean number of eggs per g of stool	179·6	163·4	189·5	190·9
Light-intensity infection*	153 (96%)	153 (96%)	153 (97%)	154 (96%)
Moderate-intensity infection†	6 (4%)	4 (3%)	4 (3%)	3 (2%)
Heavy-intensity infection‡	0	2 (1%)	0	4 (2%)
Trichuris trichiura infections				
Number of participants infected	102 (64%)	106 (67%)	101 (64%)	103 (64%)
Geometric mean number of eggs per g of stool	735·6	646·1	693·9	751·0
Light-intensity infection§	56 (55%)	64 (60%)	61 (60%)	53 (51%)
Moderate-intensity infection¶	44 (43%)	41 (39%)	38 (38%)	50 (49%)
Heavy-intensity infection‖	2 (2%)	1 (<1%)	2 (2%)	0
Ascaris lumbricoides infections				
Number of participants infected	74 (47%)	77 (48%)	75 (48%)	79 (49%)
Geometric mean number of eggs per g of stool	2829·8	4255·8	2456·8	494·0
Light-intensity infection**	37 (50%)	32 (41%)	36 (48%)	35 (44%)
Moderate-intensity infection††	34 (46%)	39 (51%)	37 (49%)	40 (51%)
Heavy-intensity infection‡‡	3 (4%)	6 (8%)	2 (3%)	4 (5%)

Data are mean (SD) and n (%), unless otherwise stated. *1–1999 eggs per g of stool. †2000–3999 eggs per g of stool. ‡≥4000 eggs per g of stool. §1–999 eggs per g of stool. ¶1000–9999 eggs per g of stool. ‖≥10 000 eggs per g of stool. **1–4999 eggs per g of stool. ††5000–49 999 eggs per g of stool. ‡‡≥50 000 eggs per g of stool.

***Table 1*: Baseline characteristics of the intention-to-treat population**

treatments were prepacked by two independent pharmacists in plastic bags and labelled with a unique identification code according to the randomisation list. Each treatment consisted of at least two tablets. However, participants and the nurses administering the treatment could have recognised the different treatments because of the different shape and size of the tablets.

Procedures

All drugs and placebo were given as oral tablets at one timepoint. Oxantel pamoate 400 mg tablets and matching placebo tablets were manufactured at the University of Basel.[10] Tribendimidine 400 mg was donated by Shandong Xinhua (Zibo, Shandong, China). Albendazole (Zentel 400 mg) was purchased from GlaxoSmithKline and ivermectin (Mectizan 3 mg) from Merck.

Participants were asked to provide two stool samples on 2 consecutive days for baseline data. All stool samples were analysed in the Public Health Laboratory-Ivo de Carneri (Tanzania) or in the hospitals of Azaguié and Rubino (Côte d'Ivoire) by experienced laboratory technicians. Stool samples were prepared with a duplicate Kato-Katz thick smear using a 41·7 mg template, and quantitatively examined under a light microscope for helminth eggs.[11] The reading was done within 1 h after preparing the slides to avoid overclearing of hookworm eggs.[12] To maintain a high diagnostic quality, 10% of all slides were randomly selected and re-read for *A lumbricoides and T trichiura*, and if discrepancies occurred with the previous reading the results were discussed until a consensus was reached.[13] Stool samples were additionally analysed with FECPAK^{G2}, a new diagnostic tool (Techion Group Limited, Dunedin, New Zealand), and compared with the readings obtained with the Kato-Katz technique (data will be presented elsewhere).

Before enrolment, participants were physically examined and actively questioned about their medical history by the study physician. Participants were followed up 14–21 days after the treatment and asked to provide another two stool samples. Participants remaining positive for any soil-transmitted helminths were treated with a standard dose of albendazole 400 mg according to national guidelines. In Côte d'Ivoire, blood was collected for pharmacokinetic studies (these data will be presented elsewhere).

Outcomes

The primary outcome was the differences in egg-reduction rates (ERRs; ie, reduction of the geometric mean) in hookworm egg counts between treatment groups, measured by the Kato-Katz technique. Secondary outcomes were safety, cure rates, and ERRs against *T trichiura* and *A lumbricoides*. Data for faecal egg counts determined by FECPAK^{G2} and pharmacokinetic variables were also obtained and will be presented elsewhere. Adverse events were assessed by active questioning and grading of the severity at 3 h and 24 h after treatment.

Statistical analysis

We ran a series of computer simulations with artificial data and data from previous trials[14–17] to determine the required sample size. We calculated that with a sample size of 140 participants per treatment arm, the study would have 80% power to test the primary non-inferiority hypothesis that the ERRs for the comparator combination treatments (tribendimidine with ivermectin or oxantel pamoate) were non-inferior to the currently most

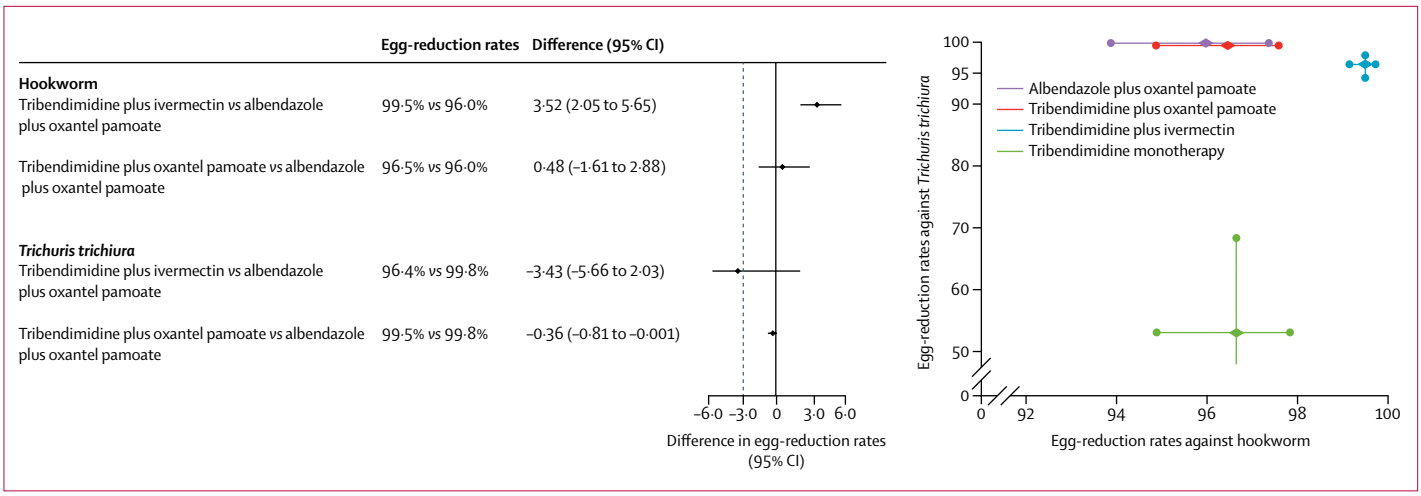

***Figure 2*: Egg-reduction rates**
Data shown are differences in egg-reduction rates (95% CIs; left panel) and direct comparison of ERRs (95% CIs; right panels) against hookworm and *Trichuris trichiura* with tribendimidine plus ivermectin and tribendimidine plus oxantel pamoate versus albendazole plus oxantel pamoate.

efficacious treatment (albendazole plus oxantel pamoate)[15,17] and close to 97%. On the basis of expert opinion, we postulated that a difference in ERRs of 3 percentage points could be assumed as clinically equivalent and set the non-inferior margin at this level. To account for loss to follow-up, we increased the sample size by 15% to 160 participants per treatment and enrolled them (2:1) in Tanzania (n=400) versus Côte d'Ivoire (n=240). Considering previous studies, a prevalence of 40% was estimated for both settings.[15–18]

For baseline characteristics, the average egg count of the four Kato-Katz slides was multiplied by 24 to determine the egg count per g (EPG) of stool. WHO guidelines[19] were used for infection-intensity cutoffs and the calculations of ERR—the percentage reduction of geometric mean EPG at follow-up compared with baseline:

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

Following intention-to-treat principles, the primary analysis tested non-inferiority on the available case population including participants with primary outcome data as randomised. The 95% CIs of the ERRs and of the differences between ERRs were constructed using a bootstrap-resampling approach with 5000 replications.[20] Non-inferiority between the comparator and the standard treatment was established if the lower bound of the CI of the difference in ERRs rates was above –3 percentage points. Post-hoc analyses not specified in the protocol included superiority of tribendimidine monotherapy versus coadministration, whereby p values were obtained by permutation tests. Cure rates were analysed using unadjusted and adjusted logistic regression models. A database (Access 2003, Microsoft) was created and all data were entered twice, compared with EpiInfo version 3.3.2, and analysed with Stata version 14.0. This trial is registered at ISRCTN (number 14373201).

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

Between July 26, and Dec 23, 2016, we assessed 2455 adolescents for eligibility (figure 1). Of 693 hookworm-positive participants, 57 did not present for treatment. 636 hookworm-positive participants received treatment (408 in Tanzania and 228 in Côte d'Ivoire). Most of the 412 participants co-infected with *T trichiura* and 305 co-infected with *A lumbricoides* were from Tanzania. Since all patients completed the study according to the protocol the available case population was identical to the per-protocol population. Baseline characteristics and ERRs based on arithmetic means are in the appendix (pp 4–9). Additionally, efficacy is presented, using all missing data once as treatment failure and once as treatment successes in the appendix (p 10).

Treatment arms were well balanced in terms of age, sex, weight, height, and baseline infection intensity for any helminths and no noteworthy between-group differences occurred (table 1). Demographic and baseline laboratory characteristics for the 636 treated participants are stratified by country in the appendix (pp 4–6). The number of days until the first follow-up sample was taken was balanced among the treatment arms.

Outcome data were available for 601 participants (151 assigned to tribendimidine monotherapy, 154 to

	Tribendimidine monotherapy (n=151)	Tribendimidine plus ivermectin (n=154)	Tribendimidine plus oxantel pamoate (n=148)	Albendazole plus oxantel pamoate (n=148)
Hookworm				
Number of participants positive for infection				
Before treatment	151 (100%)	154 (100%)	148 (100%)	148 (100%)
After treatment	70 (46%)	24 (16%)	71 (48%)	77 (52%)
Cure rate	53·6% (45·4–61·8)	84·4% (77·7–89·8)	52·0% (43·7–60·3)	48·0% (39·7–56·3)
Geometric mean number of eggs per g of stool				
Before treatment	183·1	165·7	192·1	194·6
After treatment	6·1	0·8	6·8	7·8
Egg-reduction rate	96·7% (94·9–97·8)	99·5% (99·2–99·7)	96·5% (94·9–97·6)	96·0% (93·9–97·4)
Trichuris trichiura				
Number of participants positive for infection				
Before treatment	97 (64%)	104 (68%)	95 (64%)	99 (67%)
After treatment	89 (59%)	69 (45%)	32 (22%)	17 (11%)
Cure rate	8·2% (3·6–15·6)	33·7% (24·7–43·6)	66·3% (55·9–75·7)	82·8% (73·9–89·7)
Geometric mean number of eggs per g of stool				
Before treatment	771·3	642·8	715·0	753·9
After treatment	362·0	23·1	3·8	1·3
Egg-reduction rate	53·1% (32·0–68·3)	96·4% (94·3–97·8)	99·5% (99·1–99·7)	99·8% (99·7–99·9)
Ascaris lumbricoides				
Number of participants positive for infection				
Before treatment	72 (48%)	76 (49%)	70 (47%)	78 (53%)
After treatment	1 (1%)	1 (1%)	4 (3%)	5 (3%)
Cure rate	98·6% (92·5–100·0)	98·7% (92·9–100·0)	94·3% (86·0–98·4)	93·6% (85·7–97·9)
Geometric mean number of eggs per g of stool				
Before treatment	2817·2	4153·7	2663·4	4826·2
After treatment	0·03	0·03	0·5	0·6
Egg-reduction rate	>99·99% (>99·99–100·0)	>99·99% (>99·99–100·0)	99·98% (99·93–100·0)	99·99% (99·96–100·0)

Data are n (%) or % (95% CI), unless otherwise stated.

***Table 2*: Efficacy outcomes in available cases**

tribendimidine plus ivermectin, 148 to tribendimidine plus oxantel pamoate, and 148 to albendazole plus oxantel pamoate). Tribendimidine plus ivermectin was non-inferior to albendazole plus oxantel pamoate for ERRs (99·5% [95% CI 99·2–99·7] *vs* 96·0% [93·9–97·4]; difference 3·52 percentage points [2·05–5·65]; figure 2, table 2), while cure rates were higher with tribendimidine plus ivermectin (figure 3, table 2). Non-inferiority was reached for tribendimidine plus oxantel pamoate and albendazole plus oxantel pamoate comparing ERRs (96·5% [95% CI 94·9 to 97·6] *vs* 96·0% [93·9 to 97·4]; difference 0·48 percentage points [–1·61 to 2·88] for tribendimidine plus oxantel pamoate), and cure rates did not differ. For *T trichiuria*, tribendimidine plus ivermectin did not reach non-inferiority compared with albendazole plus oxantel pamoate and cure rates were lower (figures 2, 3). Tribendimidine plus oxantel pamoate achieved non-inferiority compared with albendazole plus oxantel pamoate for T trichuria (table 2, figure 2), but cure rates were lower. Overall, 291 participants infected with *A lumbricoides*, mainly from Tanzania (n=282), with primary outcome data were analysed. ERRs reached almost 100% in all treatment arms and cure rates ranged from 93·6% to 98·7% with no differences among the treatment arms (table 2).

All participants were questioned for adverse events 3 h after treatment, while 31 were missing for the 24 h post-treatment interview (figure 4). Adverse events were mainly mild (table 3) and no serious adverse events were reported. Fewer participants reported adverse events 3 h (16%) and 24 h (18%) after treatment compared with symptoms before treatment (21%). Slightly more participants treated with one of the tribendimidine coadministrations reported adverse events—ie, 20% treated with tribendimidine plus oxantel pamoate after 3 h and 22% with tribendimidine plus ivermectin 24 h after treatment. The lowest numbers of adverse events at 3 h (12%) and 24 h (9%) after treatment were documented for albendazole plus oxantel pamoate.

Before treatment, the most common symptoms were headache (n=60) and abdominal cramps (n=55). 3 h after treatment, headache was still the most widely reported symptom (n=50), followed by vertigo (n=37). 1 day after treatment, 50 participants indicated vertigo and 41 headache. Results varied only slightly between both countries (appendix pp 11–13). Mainly mild adverse events were reported with peak numbers (n=111 [18%]) at 24 h after treatment. Three participants had moderate adverse events 3 h after treatment: two (<1%) had vertigo and one (<1%) had headache, and two had moderate adverse events 24 h after treatment: one (<1%) had vomiting and one (<1%) had vomiting plus diarrhoea. 2 days after treatment, none of the participants had any adverse events.

In a post-hoc analysis superiority of the two coadministrations over tribendimidine monotherapy was assessed. Against hookworm, the coadministration of tribendimidine plus ivermectin was superior over tribendimidine monotherapy in terms of ERR (difference 2·84 percentage points, 95% CI 1·63–4·50, p<0·0001) and cure rates (odds ratio [OR] 0·22, 95% CI 0·12–0·38, p<0·0001). Tribendimidine plus oxantel pamoate was not superior to tribendimidine for ERRs (difference –0·19 percentage points, 95% CI –2·22 to –1·83, p=0·85) and cure rates (OR 1·04, 95% CI 0·82 to 1·32, p=0·99).

The efficacy of tribendimidine plus ivermectin against *T trichiura* was superior to tribendimidine monotherapy in terms of ERRs (difference 43·30 percentage points, 95% CI 28·70–63·70, p<0·0001) and cure rates (OR 0·14, 95% CI 0·05–0·32, p<0·0001). Tribendimidine plus oxantel pamoate was superior compared with tribendimidine in terms of ERRs (difference 46·40 percentage points, 95% CI 31·56–66·76, p<0·001) and cure rates (OR 0·18, 95% CI 0·10–0·28, p<0·0001).

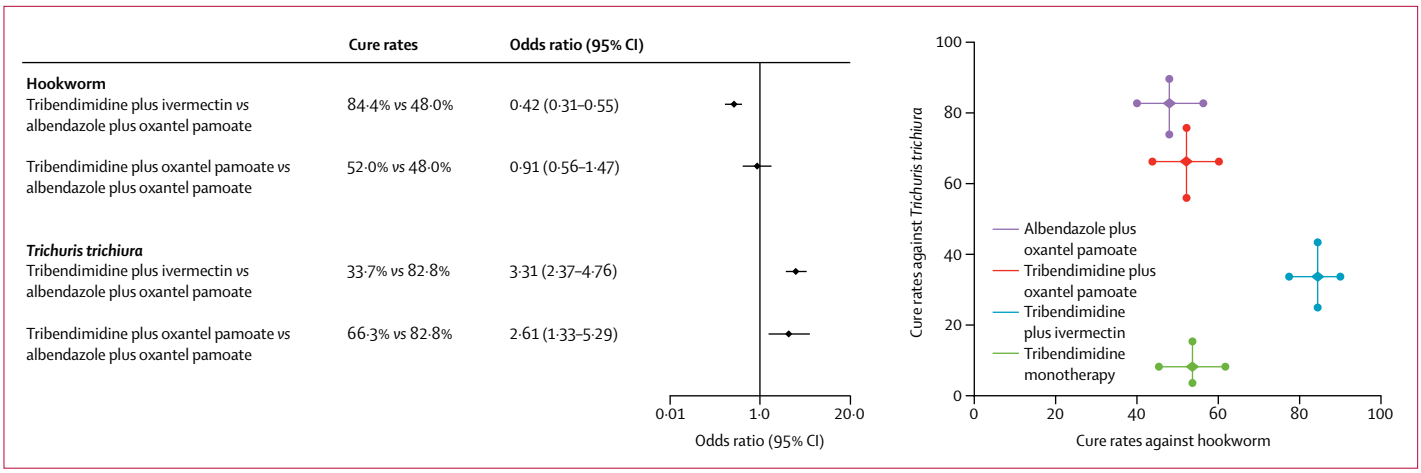

Figure 3: **Cure rates**
Data shown are odds ratios of cure rates (95% CIs; left panel) and direct comparison of cure rates (right panel) against hookworm and *Trichuris trichiura* of tribendimidine plus ivermectin and tribendimidine plus oxantel pamoate versus albendazole plus oxantel pamoate.

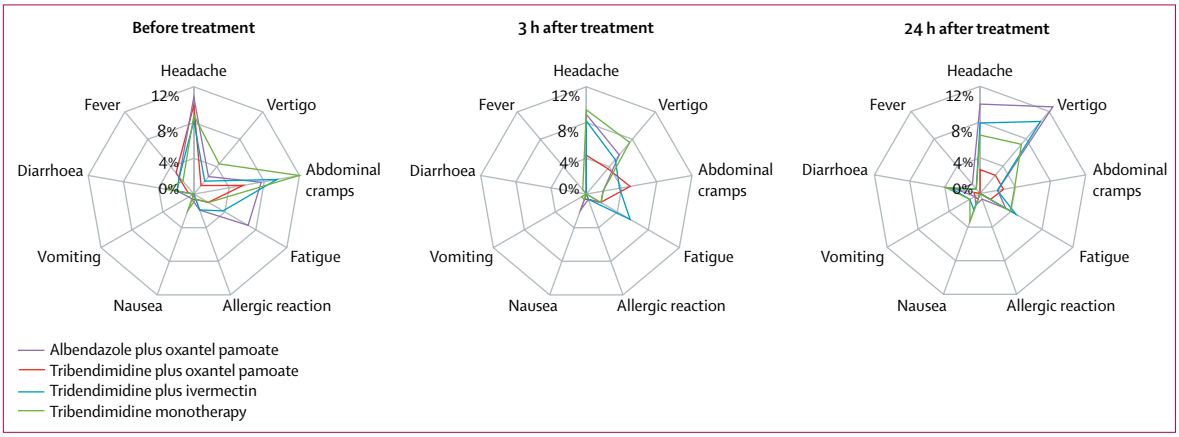

Figure 4: **Symptoms before treatment and adverse events 3 h and 24 h after treatment**
Spider plots showing percentage of reported mild clinical symptoms (before treatment) and adverse events 3 h and 24 h after treatment for the four treatment groups.

	Pre-treatment			3 h after treatment			24 h after treatment		
	Tanzania	Côte d'Ivoire	Total	Tanzania	Côte d'Ivoire	Total	Tanzania	Côte d'Ivoire	Total
Tribendimidine monotherapy	8/101 (8%)	29/58 (50%)	37/159 (23%)	8/101 (8%)	15/58 (26%)	23/159 (15%)	23/96 (24%)*	7/57 (12%)	30/153 (20%)
Tribendimidine plus ivermectin	10/102 (10%)	21/57 (37%)	31/159 (20%)	13/102 (13%)	14/57 (25%)	27/159 (17%)	26/100 (26%)	8/52 (15%)	34/152 (22%)
Tribendimidine plus oxantel pamoate	7/102 (7%)	30/55 (55%)	37/157 (24%)	14/102 (14%)	17/55 (31%)†	31/157 (20%)	27/99 (27%)	6/51 (12%)	33/150 (22%)
Albendazole plus oxantel pamoate	7/103 (7%)	19/58 (33%)	26/161 (16%)	12/103 (12%)	8/58 (14%)	20/161 (12%)	14/97 (14%)‡	0/53	14/150 (9%)
Total	32/408 (8%)	99/228 (43%)	131/636 (21%)	47/408 (12%)	54/228 (24%)	101/636 (16%)	90/392 (23%)	21/213 (10%)	111/605 (18%)

Data are n/N (%). Participants were treated with tribendimidine, tribendimidine plus ivermectin, tribendimidine plus oxantel pamoate, and albendazole plus oxantel pamoate and assessed at three timepoints (pre-treatment, and 3h and 24 h after treatment) in Tanzania and Côte d'Ivoire. *One participant with a moderate adverse event (vomiting). †Three participants with moderate adverse events (one headache and two vertigo). ‡One participant with moderate adverse events (diarrhoea and vomiting).

Table 3: **Number of participants with mild clinical symptoms or adverse events**

Discussion

Coadministration of tribendimidine plus ivermectin had the highest efficacy against hookworm. Tribendimidine in combination with other drugs had a similar, non-inferior efficacy profile as albendazole plus oxantel pamoate and would therefore be a useful addition to the anthelmintic drug armamentarium. Nearly a billion albendazole tablets are distributed every year in the framework of preventive chemotherapy against soil-transmitted helminth infections and lymphatic filariasis.[4] Albendazole has been in clinical use for almost half a century and as coverage of preventive chemotherapy further expands, emergence of anthelmintic resistance is likely to occur as evidenced in veterinary medicine.[6] To avoid or delay the emergence of drug resistance, new drugs should be discovered and developed to increase the armamentarium of drugs. In the absence of alternative treatments the use of drug combinations or coadministrations is a possible strategy to delay the occurrence of drug resistance. Moreover, drug combinations offer the benefit of an increased and broader spectrum of efficacy.

The Chinese drug tribendimidine is the frontrunner to complement or replace albendazole. Since a wealth of clinical data are already available,[9] tribendimidine is being assessed towards approval by the US FDA.[7] We present the first published data on the efficacy of tribendimidine against soil-transmitted helminth infections outside Asia, acquired in the framework of a randomised trial in two countries—Tanzania and Côte d'Ivoire. Against hookworm, our results confirmed the high ERRs of tribendimidine monotherapy reported by studies from China, while cure rates were lower as in previous studies,[9,21] but in line with findings from Steinmann and colleagues[22] in the Yunnan Province, China. No difference in ERRs between tribendimidine plus oxantel pamoate and albendazole plus oxantel pamoate against hookworm and *A lumbricoides* was observed. Hence, our data confirmed that tribendimidine had a similar efficacy profile as albendazole.

Tribendimidine plus ivermectin reached the highest ERRs against hookworm among all treatment arms and was non-inferior to the currently most efficacious treatment albendazole plus oxantel pamoate. ERRs based on arithmetic mean were generally lower in comparison with the geometric mean; however, tribendimidine plus ivermectin still had the highest ERRs among the four treatment arms (appendix pp 7–9). Tribendimidine plus ivermectin resulted in a several-fold higher cure rate in comparison with only low to moderate cure rates with tribendimidine (53·6%) and ivermectin (33·3%)[23] when given as monotherapy. Therewith, our data confirm the synergism of the co-administration of tribendimidine and ivermectin against hookworm reported by Wu and Qian.[24]

The treatment arms of tribendimidine plus ivermectin or oxantel pamoate were assessed for superiority of ERR and cure rates compared with tribendimidine in a post-hoc analysis. This analysis showed the superiority of tribendimidine plus ivermectin versus tribendimidine monotherapy. However, coadministration of tribendimidine plus oxantel pamoate was not superior for ERR and cure rates compared with tribendimidine monotherapy. This result confirms that oxantel pamoate has little effect on hookworm, which is in line with the efficacy findings of two previous studies (cure rates 11% and 33%, ERRs 37% and 77%).[15,16]

Preventive chemotherapy is limited by the absence of drugs with high efficacy against all three soil-transmitted helminths.[5] As mentioned, the drugs used exclusively in these programmes (albendazole and mebendazole) and the potential alternative tribendimidine have poor efficacy against *T trichiura*. Oxantel pamoate, a drug licensed for the treatment of soil-transmitted helminth infections several decades ago has proven high trichuricidal activity in previous trials.[15–17] Here we have shown that oxantel pamoate is not only an excellent partner drug for albendazole, in line with earlier findings,[15,17] but also in coadministration with tribendimidine high efficacy can be reached against any soil-transmitted helminth species.

Against *T trichiura*, there was no difference in ERRs between both coadministrated treatments, while albendazole plus oxantel pamoate had a higher cure rate than tribendimidine plus oxantel pamoate. On the basis of results from a dose-finding study,[16] we increased the oxantel pamoate dose from 20 mg/kg to 25 mg/kg. The slight dose increase might explain the higher ERRs and cure rates for albendazole plus oxantel pamoate in this study compared with two studies[15,17] using a lower dose (ERRs 96·0% and 99·2%, cure rates 31·2% and 68·5%).

Our study had several limitations. Efficacy results against *T trichiura* and *A lumbricoides* were mainly based on data from Tanzania, because only a few participants from Côte d'Ivoire had a co-infection. To confirm the results, further studies should focus on co-endemic settings. Furthermore, in this study most hookworm baseline infections were light. Considering that low infection intensities affect the efficacy,[25] our results might not be generalisable to high-transmission settings. Moreover, the sensitivity of Kato-Katz is reduced in low infection intensity settings.[26] To partly account for the lowered sensitivity, we collected additional stool samples compared with current WHO recommendations.[19]

Clearly a double-blind design—which is commonly used in clinical trials—would have improved the study. However, this trial included four different drugs, which were administered weight dependently (ivermectin and oxantel pamoate) and independently (tribendimidine and albendazole). By including matching placebos in each treatment arm, participants would have to swallow multiple tablets for each treatment and placebo. Apart from ethical considerations, this would have led to unnecessary complications and high dropouts.

Before this study, in-vitro studies with the human recombinant cytochromes P450 and in-vivo studies

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were done for the tribendimidine coadministrations, as described for albendazole plus oxantel pamoate.[27] No interactions were observed, indicating the safe use of these coadministrations (results will be published elsewhere). Indeed, adverse events were predominantly mild, with only three moderate adverse events observed at each time-point after treatment and no serious adverse events. All adverse events were resolved within 48 h after treatment. Adverse events 3 h and 24 h after treatment were similar to studies with tribendimidine from China,[9] Laos,[28] and recent studies with oxantel pamoate from Tanzania.[15–17] No difference in adverse events occurred between tribendimidine monotherapy and in coadministration with ivermectin, as shown in a previous study.[21] In Côte d'Ivoire, more participants reported symptoms before treatment than 24 h after treatment, in line with an earlier study in this country.[29] The large decrease in numbers of symptoms before versus after treatment might be explained by a perception bias; the participant's perceived improvement was driven by the expectations after treatment.

In conclusion, we showed that tribendimidine had a good safety profile and similar efficacy against hookworm—as shown in China[9]—in participants from two African countries. Tribendimidine showed a similar efficacy profile as albendazole. The co-administration of tribendimidine with ivermectin had high efficacy against hookworm, hinting at synergism. To tackle all three soil-transmitted helminths at once, tribendimidine could be combined with oxantel pamoate. Hence, we recommend tribendimidine to complement albendazole in preventive chemotherapy interventions, to decrease drug pressure on soil-transmitted helminths and avoid the emergence of drug resistance against benzimidazoles. Moreover, the coadministration of tribendimidine with ivermectin or oxantel pamoate could broaden the spectrum of activity.

Contributors

WM, JHa, and JK designed the study. MP and JHu formulated and manufactured the oxantel pamoate tablets. WM, JC, RBY, SMAl, SMAm, AKA, MA and JK did the study. WM, JHa, and JK analysed and interpreted the clinical 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.

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