Efficacy and safety of co-administered ivermectin and albendazole in school-aged children and adults infected with *Trichuris trichiura* in Côte d'Ivoire, Laos, and Pemba Island, Tanzania: a double-blind, parallel-group, phase 3, randomised controlled trial

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Summary

Background Preventive chemotherapy with albendazole or mebendazole remains one of the cornerstones of soil-transmitted helminth control. However, these drugs are less effective against *Trichuris trichiura*. Combined ivermectin–albendazole is a promising treatment alternative, yet robust evidence is lacking. We aimed to demonstrate superiority of co-administered ivermectin–albendazole over albendazole monotherapy in three distinct epidemiological settings.

Methods We conducted a double-blind, parallel-group, phase 3, randomised controlled trial in community members aged 6–60 years infected with *T trichiura* in Côte d'Ivoire, Laos, and Pemba Island, Tanzania, between Sept 26, 2018, and June 29, 2020. Participants with at least 100 *T trichiura* eggs per g of stool at baseline were randomly assigned (1:1) using computer-generated randomisation sequences in varying blocks of four, six, and eight, stratified by baseline *T trichiura* infection intensity, to orally receive either a single dose of ivermectin (200 µg/kg) plus albendazole (400 mg) or albendazole (400 mg) plus placebo. Patients, field staff, and outcome assessors were masked to treatment assignment. The primary outcome was cure rate against *T trichiura*, defined as the proportion of participants with no eggs in their faeces 14–21 days after treatment, assessed by Kato-Katz thick smears, and analysed in the available-case population according to intention-to-treat principles. Safety was a secondary outcome and was assessed 3 h and 24 h after drug administration. The trial is registered at ClinicalTrials.gov, NCT03527732.

Findings Between Sept 13 and Dec 18, 2019, Jan 12 and April 5, 2019, and Sept 26 and Nov 5, 2018, 3737, 3694, and 1435 community members were screened for trial eligibility in Côte d'Ivoire, Laos, and Pemba Island, respectively. In Côte d'Ivoire, Laos, and Pemba Island, 256, 274, and 305 participants, respectively, were randomly assigned to the albendazole group, and 255, 275, and 308, respectively, to the ivermectin–albendazole group. Primary outcome data were available for 722 participants treated with albendazole and 733 treated with ivermectin–albendazole. Ivermectin–albendazole showed significantly higher cure rates against *T trichiura* than albendazole in Laos (66% [140 of 213] *vs* 8% [16 of 194]; difference 58 percentage points, 95% CI 50 to 65, p<0·0001) and Pemba Island (49% [140 of 288] *vs* 6% [18 of 293], 43 percentage points, 36 to 49, p<0·0001) but had similar efficacy in Côte d'Ivoire (14% [32 of 232] *vs* 10% [24 of 235], 4 percentage points, –2 to 10, p=0·24). No serious adverse events were reported; observed events were mostly classified as mild (95% [266 of 279] in the albendazole group and 91% [288 of 317] in the ivermectin–albendazole group), and all were transient in nature.

Interpretation Treatment with ivermectin–albendazole resulted in higher efficacy against trichuriasis than albendazole alone in Laos and Pemba Island but not in Côte d'Ivoire. We recommend implementation of this combination therapy for soil-transmitted helminth control in countries with high *T trichiura* prevalence and proven enhanced efficacy of this treatment, particularly where ivermectin is beneficial against other endemic helminthiases.

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Introduction

Soil-transmitted helminthiasis affects approximately one in five people in the world and disproportionally affects the most neglected populations.[1] It is caused by infections with the nematodes *Trichuris trichiura*, *Ascaris lumbricoides*, and hookworm.[2] The mainstay of soil-transmitted helminth (STH) control is preventive chemotherapy as periodic mass drug administration with a single dose of either albendazole or mebendazole to at-risk populations without prior diagnosis, besides

Research in context

Evidence before this study

We searched PubMed, ISI Web of Science, ScienceDirect, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov from Jan 1, 1960, to April 15, 2021. We used "ivermect* [AND] albendaz* [AND] (hookworm [OR] trichuri* [OR] ascari* [OR] soil-transmitted helminth*) [AND] (cure* [OR] trial)" as search terms for PubMed, ISI Web of Science, and ScienceDirect, and the keywords "ivermectin" and "albendazole" for CENTRAL and ClinicalTrials.gov. The latest evidence on the efficacy and safety of co-administered ivermectin plus albendazole against soil-transmitted helminths is presented in our systematic review, meta-analysis, and individual-patient data analysis, which was published in 2018. In that study, we identified four randomised controlled trials that investigated the standard dose of combined ivermectin (200 µg/kg) and albendazole (400 mg). All four trials exclusively assessed efficacy and safety in school-aged children and adolescents (aged 6–20 years), yet adult populations are also targeted in preventive chemotherapy interventions against soil-transmitted helminths. Generalisability of the four trials to other endemic settings is limited. Two studies were done on the Zanzibar archipelago (Pemba and Unguja Islands), Tanzania; one in the Philippines; and one in Sri Lanka. The trials in the Philippines and Sri Lanka were done before 2000 and used a weak diagnostic approach, with only one stool sample analysed before and after treatment.

Added value of this study

We conducted a randomised controlled trial in three settings with distinct epidemiological profiles and treatment history with anthelmintic drugs. We targeted whole communities and recruited approximately 600 participants aged 6–60 years in each of the three settings to provide robust data and to allow for subgroup analysis. Our study showed higher efficacy against *Trichuris trichiura* if ivermectin–albendazole was used for treatment than if albendazole monotherapy was used in two settings. Both treatment regimens showed excellent safety profiles with mostly mild and transient adverse events. The trial results from Côte d'Ivoire highlight the existence of settings in which combination treatment does not show enhanced efficacy over albendazole alone, warranting the need for further investigation of emerging drug resistance, parasite genetics, and host–parasite interactions affecting drug efficacy.

Implications of all the available evidence

The availability of efficacious drugs to treat all types of soil-transmitted helminth infections is a requirement for progress in morbidity control. Our findings support the integration of combination therapy as recommended treatment in preventive chemotherapy schemes against soil-transmitted helminthiasis, although the efficacy needs to be confirmed in a pilot study.

other strategies tackling exposure (eg, by improving sanitation and providing access to safe water).[3] The main goal of preventive chemotherapy is to reduce morbidity by decreasing infection intensities and to ultimately eliminate soil-transmitted helminthiasis as a public health problem. Elimination as a public health problem is defined as the prevalence reduction of moderate and heavy intensities to below 2%, as assessed in preschool-aged and school-aged children, by 2030.[4]

Single-dose albendazole treatment shows high and moderate efficacy against *A lumbricoides* and hookworm infections, respectively.[5] Yet, performance against *T trichiura* is unsatisfactory, with egg reduction rates (ERRs) and cure rates below 50%.[5] Furthermore, albendazole has been used for many decades, and several hundred million doses are donated yearly to endemic areas for STH control.[5] Its consistent use makes it prone to drug resistance, a phenomenon common in veterinary medicine but not yet proven for human soil-transmitted helminthiases.[5,6]

In view of the empty pipeline of new potent anthelmintic drugs, the evaluation of drug combinations of already registered products has been identified as a research priority.[7] The use of drug combinations with different mechanisms of action might not only enhance efficacy but also delay the onset of resistance.[8] Ivermectin–albendazole is one of the most promising drug combination candidates and was recently added to the WHO List of Essential Medicines, which paves the road for its use in deworming programmes.[9] Since 2000, ivermectin–albendazole has been successfully used for the control of lymphatic filariasis, showing an excellent safety profile.[10] However, robust evidence on the potentially enhanced efficacy from co-administered ivermectin–albendazole against STHs in varying age groups and endemicity settings is lacking.[11–15] The primary objective of this trial was to assess the efficacy and safety of co-administered ivermectin–albendazole 14–21 days after treatment in community members aged 6–60 years infected with *T trichiura* in different transmission settings. This trial has the ultimate goal to inform STH preventive chemotherapy schemes put forth by WHO, and hence includes long-term follow-up outcomes that are presented elsewhere.[16]

Methods

Study design and participants

We did a phase 3, randomised, controlled, double-blind, parallel group, superiority trial in Côte d'Ivoire, Laos, and Pemba Island, Tanzania, between Sept 26, 2018, and June 29, 2020. Details on trial design and methodology were published elsewhere.[17] All community members aged 6–60 years who were positive for *T trichiura* in at least two slides of quadruplicate Kato-Katz smears, with an infection intensity of at least 100 eggs per g of stool (EPG), were eligible for trial inclusion. Excluded from

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the trial were individuals presenting with severe chronic or acute systemic illness (eg, severe anaemia with haemoglobin levels below 80 g/L, clinical malaria [positive rapid diagnostic test plus body temperature ≥38°C], reported or suspected diabetes, HIV, AIDS, or tuberculosis), pregnant women, lactating women in the first week after birth, and children who weighed less than 15 kg, as assessed upon baseline clinical examination.

This trial was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by independent ethics committees in Côte d'Ivoire (reference numbers 088–18/MSHP/CNESVS-km and ECCI00918), Laos (reference number 093/NECHR), Pemba (Zanzibar, reference number ZAMREC/0003/Feb/2018), and Switzerland (reference number BASEC Nr Req-2018-00494). Participating adults, or parents or guardians of participating children, provided written informed consent. Children provided written (Côte d'Ivoire) or oral (Laos and Pemba) assent. All authors take responsibility for the accuracy and completeness of the data and the fidelity of the trial to the protocol, which is available together with the statistical analysis plan in appendix 1.

Randomisation and masking

Computer-generated randomisation sequences in varying blocks of four, six, and eight participants, stratified by two levels of baseline *T trichiura* infection intensity (light=<1000 EPG; moderate to heavy=≥1000 EPG), were provided by the trial statistician. Enrolled participants were randomly assigned in a 1:1 ratio to receive either a single dose of albendazole (400 mg; Zentel; GlaxoSmithKline, London, UK) plus appearance-matched placebo (produced by the University of Basel) or albendazole (400 mg) plus ivermectin (200 µg/kg; Stromectol; Merck Sharp & Dohme, Readington, NJ, USA) using sealed, opaque, sequentially numbered envelopes containing the treatment assignment (A or B) and six ivermectin or corresponding placebo tablets (sufficient to dose participants weighing up to 97 kg). The envelopes were prepared in Basel, Switzerland, by people who were independent of the trial. Participants were randomly assigned in the order they presented to the administrating investigators on the day of treatment. Investigators verified whether participants had baseline light or moderate-to-heavy infection intensity, chose the treatment envelope from the respective pile based on treatment allocation, and opened the sealed envelopes. Albendazole tablets were kept in bottles of 100 pieces as provided by WHO, and a single tablet was administered to every patient together with the necessary number of ivermectin or placebo tablets according to the patient's weight. Through the use of pre-packed treatment group labels, together with ivermectin appearance-matched placebos, field staff, including investigators, participants, and outcome assessors, were masked to treatment assignment.

Procedures

At baseline, participants were asked to provide two stool samples from different days (ideally within a 5 day interval), from which duplicate Kato-Katz thick smears using 41·7 mg of stool were prepared and assessed under a light microscope for the identification of *T trichiura*, *A lumbricoides*, and hookworm ova by laboratory technicians.[18] In Laos, both stool samples of *T trichiura*-infected participants were also assessed for *Strongyloides stercoralis* larvae using the Baermann technique.[19] For participants who were identified as *T trichiura* positive after the second sample only, one *S stercoralis* examination of that sample was done. 10% of all Kato-Katz slides were randomly chosen for subsequent quality control by picking every tenth slide of all slides read by each laboratory technician on the respective day.

Before treatment, participants underwent a physical examination to ensure recruitment criteria were met. These examinations included rapid diagnostic testing for haemoglobin levels and malaria (in Côte d'Ivoire and Laos) and lymphatic filariasis (in Côte d'Ivoire and Pemba Island) parasites, as well as pregnancy tests in girls and women aged 10 years and older in Côte d'Ivoire and Pemba Island and aged 12 years and older in Laos. Participants were further examined physically, and a medical anamnesis was done by trial physicians to assess baseline conditions. On Pemba Island, treatment was administered on the same day as the clinical examination, whereas in Côte d'Ivoire and Laos, treatment took place approximately 1 week after baseline due to the preceding analysis of blood parameters to evaluate liver and kidney functions as a required safety measure put forth by the responsible ethical or drug safety boards.

See Online for appendix 1

Adverse events were assessed actively at 3 h and 24 h after treatment and graded into light, moderate, and severe using adapted Common Toxicity Criteria version 2.0 put forth by the Cancer Therapy Evaluation Program. Study physicians were asked to evaluate relatedness of the most common adverse events to drug administration. If causality could not be ruled out by other conditions or reasons, the adverse events were considered as possibly related. Newly emerging, as well as persistent, adverse events after 24 h and within 14–21 days of treatment were followed up using a passive monitoring scheme, as specified in the protocol. Treatment efficacy was determined 14–21 days after treatment by collecting another two stool samples per participant. At study termination, all participants positive for STH were offered the combination therapy, if found to be more efficacious, or standard therapy.

Outcomes

The primary outcome was the cure rate of *T trichiura*, defined as the proportion of participants with no eggs in their faeces 14–21 days after treatment. Secondary outcomes were the ERR against *T trichiura*; cure rates and ERRs against *A lumbricoides*, hookworm, and

S stercoralis; and infection status assessed by qPCR. Safety outcomes included adverse events assessed 3 h and 24 h after treatment, serious adverse events, and adverse events potentially related to treatment. In this manuscript we do not present the cure rates determined by qPCR analysis or related methods and results. At the time of writing, this analysis had been done only for samples from Pemba Island, and thus qPCR-based cure rates cannot be compared between countries. Furthermore, detailed results of this analysis have been published elsewhere.[20]

Statistical analysis

For the sample size calculation, we used the formula $n = (Z_{\alpha/2} + Z_{\beta})^2 \times [\pi_1 \times (1-\pi_1) + \pi_2 \times (1-\pi_2)] / (\pi_2 - \pi_1)^2$, where $Z_{\alpha/2}$ and Z_{β} denote the critical values of the normal distribution for significance level and type 2 error, respectively, and π_1 and π_2 denote the proportion of cured individuals in the two treatment groups. For each location, the trial was powered to detect a significant difference in cure rates between the two treatment groups with 90% power at a two-sided 5% significance level, assuming that the cure rate of albendazole for *T trichiura* was 30% and of ivermectin–albendazole was 50%.[5,15] We calculated that 121 participants per group would be sufficient to test the primary hypothesis that ivermectin–albendazole has a higher efficacy against *T trichiura* infection than albendazole alone. Taking a potential loss to follow-up of 15% into account, we anticipated that we needed to enrol 143 participants per treatment group. In view of the prolonged follow-up period to assess the long-term secondary outcomes (up to 12 months), we aimed to include 600 community members in each trial setting. For subgroup analysis, the data from all locations were pooled to ensure sufficient power to assess a potential difference in efficacy by baseline infection intensity (ie, light *vs* moderate to heavy) and age group (ie, 6–12 years *vs* 13–60 years).

The primary analysis estimated the cure rate of *T trichiura* using the available-case population according to intention-to-treat principles. The available-case population was defined as all randomly assigned participants, excluding those who entered the study despite not satisfying the entry criterion of positive at baseline, with at least one follow-up stool sample at 14–21 days post-treatment. To check the robustness of the primary analysis, the results were confirmed using the per-protocol population. Exact definitions of the different analysis populations are provided in the statistical analysis plan in appendix 1. As outlined in the statistical analysis plan, the available-case analysis was further complemented by an intention-to-treat analysis using multiple imputation if the proportion of missing data exceeded 10%. Major protocol deviations, leading to exclusion from the per-protocol analysis, included negative infection status for *T trichiura* at baseline, not satisfying the enrolment criteria, meeting withdrawal criteria, or receiving no treatment, the wrong treatment, or concomitant treatment with anthelmintics in the past 4 weeks or drugs with known interaction with the study drugs.

The mean egg counts from the quadruplicate Kato-Katz thick smears were multiplied by 24 to be expressed as EPG. Helminth infection intensity was classified as light or moderate to heavy depending on the species following cutoffs put forth by WHO.[21] We calculated the proportion of individuals with moderate-to-heavy infection intensities at baseline who had light infection intensities or no infection at follow-up. This indicator is used to assess progress within control programmes to eliminate morbidity due to STHs.[21]

A melded binomial test with mid-p correction was used to calculate differences in cure rates between the two treatment groups and to estimate the corresponding confidence intervals. The prespecified analytical code is provided in appendix 1 (p 171).

Geometric mean and arithmetic mean egg counts were calculated for the two treatment groups before and after treatment to assess the corresponding ERRs. Geometric mean-based and arithmetic mean-based ERRs were calculated as:

$$ERR_{GM} = 1 - \frac{\frac{1}{n} e^{\sum \log(\text{EPGfollow-up} + 1)} - 1}{\frac{1}{n} e^{\sum \log(\text{EPGbaseline} + 1)} - 1}$$

$$ERR_{AM} = 1 - \frac{\frac{1}{n} \sum (\text{EPG}_{\text{follow-up}})}{\frac{1}{n} \sum (\text{EPG}_{\text{baseline}})}$$

A bootstrap resampling method with 5000 replicates was used to calculate 95% CIs for geometric mean-based ERRs and the difference between them. The code for implementing the bootstrap routine is provided in the statistical analysis plan (appendix 1 p 171). All estimates presented are unadjusted estimates. Multiple imputations were done using the mi package in R. The missing outcomes were predicted using the variables sex, age, height, weight, treatment group, and baseline infection intensity. The imputation used six chains with 30 iterations each. Imputation performance was assessed via the R-hat statistics, and convergence was visually inspected.

No statistical testing was done on safety outcomes; adverse events are presented in frequency tables. Data were analysed using R software version 4.0.3 and Stata 16.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, interpretation of the findings, writing of the report, or the decision to submit for publication.

Results

Between Sept 13 and Dec 18, 2019, Jan 12 and April 5, 2019, and Sept 26 and Nov 5, 2018, 3737, 3694, and 1435 community members were screened for trial eligibility in Côte d'Ivoire, Laos, and Pemba Island, respectively (figure 1). The recruitment phase to assess the eligibility of community members finished after 133 days in Côte d'Ivoire, 83 days in Laos, and 40 days in Pemba Island. In Côte d'Ivoire, Laos, and Pemba Island, 256, 274, and 305 participants, respectively, were randomly assigned to and received albendazole co-administered with placebo, whereas 255, 275, and 308 participants, respectively, were randomly assigned to and received ivermectin–albendazole.

Demographic, baseline anthropometric, and helminth infection characteristics of the 1673 randomised participants are summarised in table 1. Co-infections with other STH species were common and found in 951 (57%) of 1673 participants, but endemicity profiles differed between countries. In Laos, hookworm was the predominant co-infection, whereas *A lumbricoides* co-infection was most common in Côte d'Ivoire and

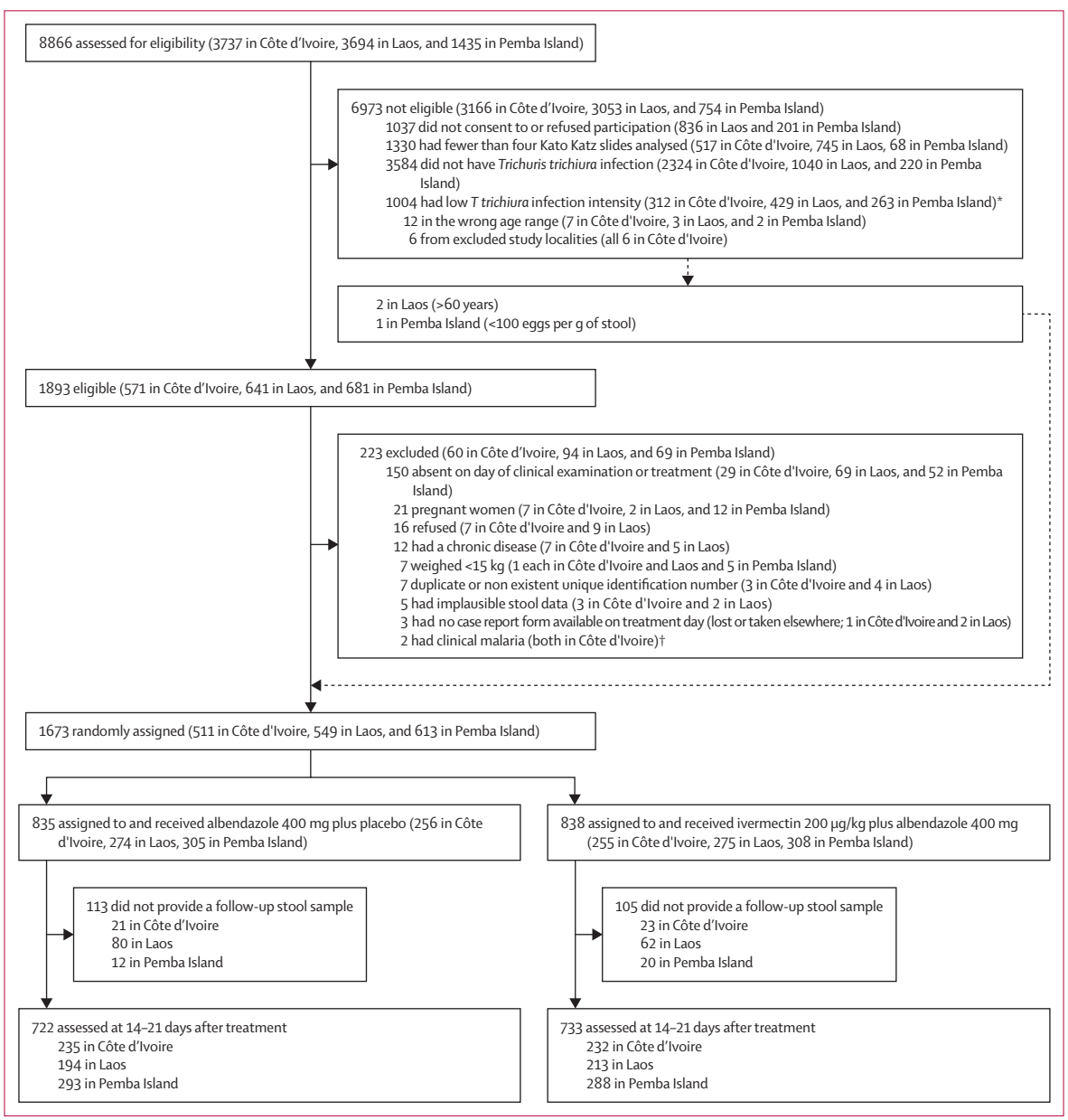

Figure 1: **Trial profile**

*Low *T trichiura* infection intensities not qualifying for trial inclusion were egg counts below 100 eggs per g of stool, fewer than two of four Kato-Katz slides found to be positive, or both. †Clinical malaria was defined as a rapid diagnostic test positive for *Plasmodium* spp, together with a body temperature ≥38°C.

Pemba Island. *S stercoralis* infection was only tested for in Laos and was found in 59 (11%) of 549 participants. *T trichiura* infection intensities were well balanced between treatment groups. Between study countries, differences were seen with respect to not only helminth co-infections but also demographic variables. The Laos study cohort was older (mean age 26·8 years [SD 17·4]) than the two African cohorts (mean age 16·3 years [13·7] in Côte d'Ivoire and 14·0 years [10·0] in Pemba Island).

	Côte d'Ivoire		Laos*		Pemba Island†	
	Albendazole (n=256)	Ivermectin–albendazole (n=255)	Albendazole (n=274)	Ivermectin–albendazole (n=275)	Albendazole (n=305)	Ivermectin–albendazole (n=308)
Age, years	16·5 (14·1)	16·0 (13·4)	27·7 (17·3)	25·9 (17·4)	14·0 (10·5)	13·9 (9·6)
Age group‡						
School-aged (6–12 years)	171 (67%)	168 (66%)	92 (34%)	113 (41%)	191 (63%)	184 (60%)
Youth or young people (13–24 years)	30 (12%)	36 (14%)	37 (14%)	30 (11%)	81 (27%)	90 (29%)
Adults (25–60 years)	55 (21%)	51 (20%)	145 (53%)	132 (48%)	33 (11%)	34 (11%)
Sex						
Female	120 (47%)	129 (51%)	144 (53%)	147 (53%)	171 (56%)	169 (55%)
Male	136 (53%)	126 (49%)	130 (47%)	128 (47%)	134 (44%)	139 (45%)
Weight, kg	37·5 (20·1)	37·2 (19·7)	41·1 (14·5)	39·7 (15·7)	34·2 (15·5)	34·0 (14·8)
Height, cm	136·7 (20·3)	135·8 (19·4)	144·3 (16·6)§	142·3 (16·7)	137·3 (18·6)	137·7 (18·9)
Trichuris trichiura infection						
Geometric mean EPG	480·5	469·9	365·9	349·3	466·9	460·9
Arithmetic mean EPG	1036·0	1079·9	607·2	636·7	846·7	923·9
Infection intensity¶						
Light	190 (74%)	192 (75%)	232 (85%)	232 (84%)	231 (76%)	234 (76%)
Moderate	64 (25%)	60 (24%)	42 (15%)	42 (15%)	74 (24%)	71 (23%)
Heavy	2 (1%)	3 (1%)	0	1 (<1%)	0	3 (1%)
Ascaris lumbricoides infection						
Infected	91 (36%)	91 (36%)	112 (41%)	96 (35%)	74 (24%)	90 (29%)
Geometric mean EPG	5499·1	4129·9	3991·2	3635·0	4515·3	2979·5
Arithmetic mean EPG	22 597·0	19 266·7	13 444·7	11 931·3	10 050·3	7593·1
Infection intensity‖						
Light	38 (42%)	42 (46%)	58 (52%)	48 (50%)	35 (47%)	52 (58%)
Moderate	40 (44%)	39 (43%)	47 (42%)	44 (46%)	38 (51%)	37 (41%)
Heavy	13 (14%)	10 (11%)	7 (6%)	4 (4%)	1 (1%)	1 (1%)
Hookworm infection						
Infected	31 (12%)	18 (7%)	250 (91%)	253 (92%)	53 (17%)	42 (14%)
Geometric mean EPG	82·1	91·3	804·8	840·3	100·5	79·9
Arithmetic mean EPG	214·5	830·0	1820·3	1743·4	236·8	205·1
Infection intensity**						
Light	31 (100%)	16 (89%)	182 (73%)	184 (73%)	53 (100%)	42 (100%)
Moderate	0	0	37 (15%)	43 (17%)	0	0
Heavy	0	2 (11%)	31 (12%)	26 (10%)	0	0
Strongyloides stercoralis infection††	ND	ND	29 (11%)	30 (11%)	ND	ND

Data are mean (SD) or n (%), unless otherwise stated. EPG=eggs per g of stool. ND=not determined. *549 randomised; two did not fulfill eligibility criteria (age >60 years) but were included in the available-case analysis. †613 randomised; one did not fulfill eligibility criteria (<100 EPG) but was included in the available-case analysis. ‡Age groups were classified and adapted into school-aged children according to WHO definitions (originally 5–12 years, but 6–12 years in this study) and youth or young people and adults according to UN definitions (originally 15–24 years for youth or younger people and >25 years for adults, but redefined as 13–24 years for youth or young people and >25 years for adults in this study). §One individual value omitted due to irrational value (479 cm). ¶*T trichiura* infection intensity was classified according to mean EPG into light (1–999 EPG), moderate (1000–9999 EPG), and heavy (≥10 000 EPG). ‖*A lumbricoides* infection intensity was classified according to mean EPG into light (1–4999 EPG), moderate (5000–49 999 EPG), and heavy (≥50 000 EPG). **Hookworm infection intensity was classified according to mean EPG into light (1–1999 EPG), moderate (2000–3999 EPG), and heavy (≥4000 EPG). ††The Baermann technique to detect *S stercoralis* infection was applied only to stool samples collected in Laos; two participants (one in each group) had no *S stercoralis* result.

Table 1: **Baseline characteristics of trial participants by country**

44 (9%), 142 (26%), and 32 (5%) participants were lost to follow-up in Côte d'Ivoire, Laos, and Pemba Island, respectively, with similar numbers in each group (figure 1). Data from 467, 407, and 581 trial participants in Côte d'Ivoire, Laos, and Pemba Island, respectively, were used for the final analysis. Of note, two participants in

	Côte d'Ivoire		Laos		Pemba Island	
	Albendazole (n=235)	Ivermectin–albendazole (n=232)	Albendazole (n=194)	Ivermectin–albendazole (n=213)	Albendazole (n=293)	Ivermectin–albendazole (n=288)
Trichuris trichiura						
Participants positive for infection after treatment	211	200	178	73	275	148
Cure rate, % (95% CI)	10% (7 to 15)	14% (10 to 19)	8% (5 to 13)	66% (59 to 72)	6% (4 to 10)	49% (43 to 55)
Difference in cure rate, percentage points (95% CI)*	..	4 (–2 to 10)	..	58 (50 to 65)	..	43 (36 to 49)
Cure rate by infection intensity, % (n/N)						
Light	13% (22/175)	15% (25/172)	9% (15/164)	74% (131/176)	8% (17/222)	53% (116/219)
Moderate	3% (2/58)	12% (7/57)	3% (1/30)	25% (9/36)	1% (1/71)	36% (24/66)
Heavy	0% (0/2)	0% (0/3)	..	0% (0/1)	..	0% (0/3)
Geometric mean EPG						
Baseline	488·8	475·4	369·8	361·0	462·8	463·2
After treatment	175·7	141·6	115·5	3·0	198·5	8·0
Geometric mean ERR, % (95% CI)	64% (54 to 72)	70% (61 to 77)	69% (61 to 75)	99% (99 to 99)	57% (48 to 65)	98% (98 to 99)
Difference in geometric mean ERR, percentage points (95% CI)*	..	6 (–6 to 18)	..	30 (24 to 38)	..	41 (34 to 50)
Arithmetic mean EPG						
Baseline	1048·8	1110·9	626·1	688·7	848·5	938·0
After treatment	874·6	866·8	403·2	70·8	698·9	105·1
Arithmetic mean ERR, % (95% CI)	17% (–14 to 39)	22% (–14 to 46)	36% (19 to 50)	90% (81 to 96)	18% (4 to 30)	89% (83 to 93)
Moderately or heavily infected participants with no or light infection after treatment, % (95% CI; n/N)	40% (27 to 53; 31/60)	52% (39 to 65; 24/60)	63% (45 to 82; 19/30)	97% (92 to 103; 34/71)	48% (36 to 60; 36/37)	94% (89 to 100; 65/69)
Ascaris lumbricoides						
Participants positive for infection						
Baseline	82	81	77	70	70	86
After treatment	4	5	0	0	2	1
Cure rate, % (95% CI)	95% (90 to 100)	94% (89 to 99)	100% (100 to 100)	100% (100 to 100)	97% (93 to 101)	99% (97 to 101)
Cure rate by infection intensity, % (n/N)						
Light	100% (34/34)	100% (36/36)	100% (44/44)	100% (38/38)	97% (33/34)	100% (50/50)
Moderate	92% (33/36)	86% (30/35)	100% (28/28)	100% (31/31)	97% (34/35)	97% (34/35)
Heavy	92% (11/12)	100% (10/10)	100% (5/5)	100% (1/1)	100% (1/1)	100% (1/1)
Geometric mean EPG						
Baseline	5315·6	4748·2	3458·5	3374·7	4378·8	3173·9
After treatment	0·1	0·2	0	0	0·3	0·1
Geometric mean ERR, % (95% CI)	100% (100 to 100)	100% (100 to 100)	100% (100 to 100)	100% (100 to 100)	100% (100 to 100)	100% (100 to 100)

(Table 2 continues on next page)

	Côte d'Ivoire		Laos		Pemba Island	
	Albendazole (n=235)	Ivermectin–albendazole (n=232)	Albendazole (n=194)	Ivermectin–albendazole (n=213)	Albendazole (n=293)	Ivermectin–albendazole (n=288)
(Continued from previous page)						
Arithmetic mean EPG						
Baseline	22 874·2	19 907·6	12 977·7	9801·6	9525·3	7782·0
After treatment	0·9	5·1	0·0	0·0	101·1	24·4
Arithmetic mean ERR, % (95% CI)	100% (100 to 100)	100% (99·9 to 100)	100% (100 to 100)	100% (100 to 100)	99% (97 to 99)	100% (99 to 100)
Moderately or heavily infected participants with no or light infection after treatment, % (95% CI; n/N)	100% (100 to 100; 48/48)	100% (100 to 100; 45/45)	100% (100 to 100; 32/32)	100% (100 to 100; 33/33)	100% (100 to 100; 36/36)	100% (100 to 100; 36/36)
Hookworm						
Participants positive for infection						
Baseline	28	17	180	194	49	39
After treatment	1	2	80	79	9	11
Cure rate, % (95% CI)	96% (89 to 104)	88% (71 to 105)	56% (48 to 63)	59% (52 to 66)	82% (70 to 93)	72% (57 to 87)
Cure rate by infection intensity, % (n/N)						
Light	96% (27/28)	93% (14/15)	63% (85/136)	67% (95/142)	82% (40/49)	72% (28/39)
Moderate	..	..	36% (10/28)	41% (14/34)	..	..
Heavy	..	50% (1/2)	31% (5/16)	33% (6/18)	..	..
Geometric mean EPG						
Baseline	94·4	108·6	731·4	861·8	100·6	80·5
After treatment	0·1	0·9	7·9	6·5	1·3	2·5
Geometric mean ERR, % (95% CI)	100% (100 to 100)	99% (97 to 100)	99% (98 to 99)	99% (99 to 100)	99% (97 to 100)	97% (93 to 99)
Arithmetic mean EPG						
Baseline	232·9	878·5	1620·6	1678·7	223·0	214·0
After treatment	0·4	89·3	146·6	129·5	30·6	48·0
Arithmetic mean ERR, % (95% CI)	100% (99 to 100)	90% (75 to 100)	91% (87 to 94)	92% (88 to 95)	86% (77 to 95)	78% (64 to 90)
Moderately or heavily infected participants with no or light infection after treatment, % (95% CI; n/N)	ND	100% (100 to 100; 2/2)	95% (89 to 102; 42/44)	98% (94 to 102; 51/52)	ND	ND
***Strongyloides stercoralis*†**						
Participants positive for infection						
Baseline	ND	ND	22	22	ND	ND
After treatment	ND	ND	4	1	ND	ND
Cure rate, % (95% CI)	ND	ND	82% (64 to 99)	96% (86 to 105)	ND	ND

EPG=eggs per g of stool. ERR=egg reduction rate. ND=not determined. *Significant differences are highlighted in bold; for cure rates, significance was defined when the p-value was <0·05 according to the melded binomial test for difference (mid-p version), whereas for ERRs, significance was defined when the 95% CI did not include 0. †*S stercoralis* infection was assessed qualitatively only (positive *vs* negative) in stool samples collected in Laos; 406 participants (193 in the albendazole group and 213 in the ivermectin–albendazole group) in Laos had at least one stool sample examined for *S stercoralis* at baseline and follow-up.

Table 2: **Efficacy against *T trichiura* and co-infecting soil-transmitted helminths by trial country (available-case analysis)**

Laos (aged >60 years) and one in Pemba Island (*T trichiura* intensity <100 EPG) were randomised erroneously. These participants were included in the available-case analysis.

Cure rates and ERRs of the available-case population are summarised in table 2. Treatment with ivermectin–albendazole resulted in significantly higher cure rates than albendazole alone in Laos (66% [140 of 213] *vs* 8%

[16 of 194], difference 58 percentage points, 95% CI 50 to 65, p<0·0001) and Pemba Island (49% [140 of 288] *vs* 6% [18 of 293], 43 percentage points, 36 to 49, p<0·0001). Similarly, ERRs were significantly higher in the combination therapy group than in the monotherapy group in Laos (geometric mean ERR 99% *vs* 69%, difference 30 percentage points, 95% CI 24 to 38) and Pemba Island (98% *vs* 57%, 41 percentage points, 34 to 50). In Côte d'Ivoire, ivermectin–albendazole showed similarly low efficacy to albendazole in terms of cure rates (14% [32 of 232] *vs* 10% [24 of 235], difference 4 percentage points, 95% CI –2 to 10, p=0·24) and ERRs (geometric mean ERR 70% *vs* 64%, difference 6 percentage points, 95% CI –6 to 18). Adjusting for age category, sex, and weight did not notably change point or interval estimates (data not shown). *T trichiura* egg distributions before and after treatment by treatment group, for each country, are shown in a violin plot (figure 2A–C). Of participants who received ivermectin–albendazole with moderate-intensity or heavy-intensity infections, 52% (95% CI 39 to 65; 31 of 60), 97% (92 to 103; 36 of 37), and 94% (89 to 100; 65 of 69) showed no or only light intensity infections after treatment in Côte d'Ivoire, Laos, and Pemba Island, respectively (table 2).

In Côte d'Ivoire, no major protocol deviations were observed and therefore the per-protocol population is identical to the available-case population. On Pemba Island, one participant in the ivermectin–albendazole group with a baseline infection intensity of 18 EPG was inappropriately randomised. Excluding this participant from the per-protocol analysis did not notably change the estimates (cure rate 48% in the ivermectin–albendazole group *vs* 6% in the albendazole group, difference 42 percentage points, 95% CI 36–49, p<0·0001). In Laos, one of the two participants older than 60 years who was erroneously randomised to the albendazole group provided a follow-up stool sample and was included in the available-case population. The per-protocol analysis excluding this participant showed similar estimates to the available-case analysis (66% *vs* 8%, 57 percentage points, 50–64, p<0·0001). The proportion of missing data in Laos was higher than expected. Missing data for the intention-to-treat analysis were imputed by multiple imputation but neither point nor interval estimates changed substantially from the available-case analysis (appendix 2 p 2).

Subgroup analysis showed higher cure rates against *T trichiura* in participants with light infection intensities (45% [156 of 348] in the ivermectin–albendazole group and 11% [37 of 339] in the albendazole group) than in participants with moderate or heavy infection intensities (16% [16 of 97] and 3% [three of 90]) at baseline, but the conclusions with respect to superiority of the ivermectin–albendazole combination did not change (appendix 2 p 3). The cure rate for ivermectin–albendazole in the 6–12 years age group (26%; 64 of 243) was lower than the cure rate in the 13–60 years age group (53%; 108 of 202),

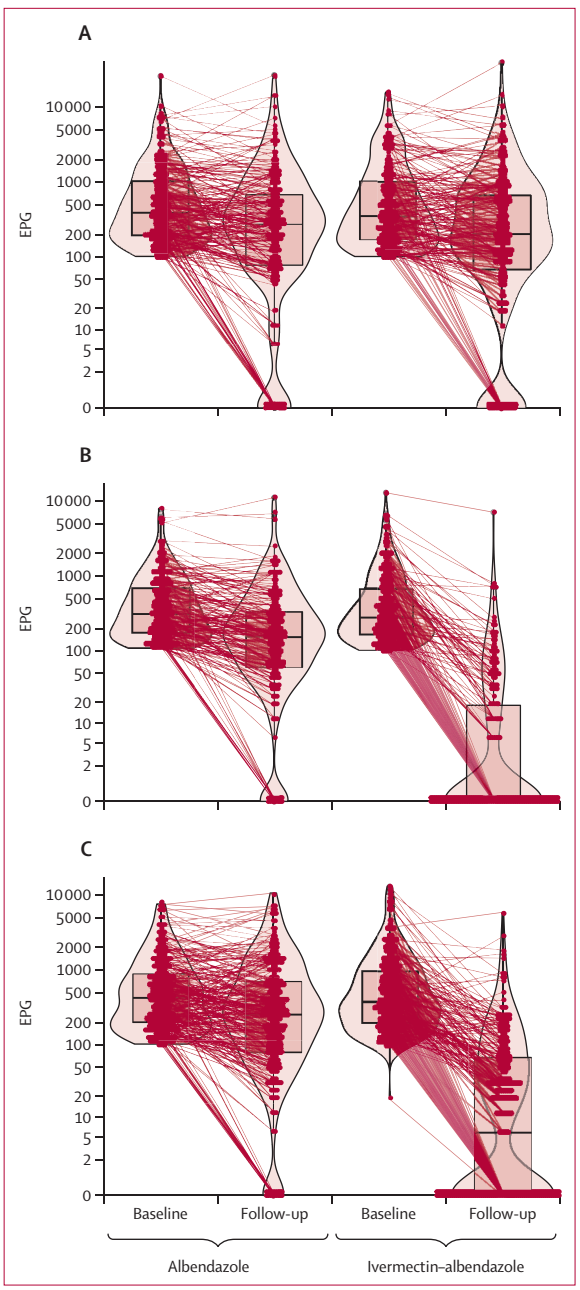

Figure 2: **Violin plots illustrating *Trichuris trichiura* egg reduction in Côte d'Ivoire (A), Laos (B), and Pemba Island (C), by treatment group**
Violins represent egg densities at baseline and follow-up; boxes represent IQRs and the dots connected by lines the individual participants. EPG=eggs per g of stool.

See Online for appendix 2

but we also observed higher baseline infection intensities irrespective of treatment group in the younger than in the older age group (median EPG at baseline was 444 [IQR 204–1236] *vs* 264 [159–525]; appendix 2 p 3).

Both treatment regimens showed high efficacy against *A lumbricoides*, with cure rates above 93% and ERRs of 99–100% in all trial settings. Cure rates in hookworm-infected participants differed between settings but not

	Albendazole				Ivermectin–albendazole			
	Number of participants assessed	Participants with adverse event (%)	Number of adverse events	Number of possibly related adverse events/number assessed for relatedness (%)*	Number of participants assessed	Participants with adverse event (%)	Number of adverse events	Number of possibly related adverse events/number assessed for relatedness (%)*
Baseline	830	324 (39%)	644	..	831	351 (42%)	699	..
Côte d'Ivoire	254	194 (76%)	467	..	254	198 (78%)	498	..
Laos	273	83 (30%)	110	..	273	94 (34%)	117	..
Pemba Island	303	47 (16%)	67	..	304	59 (19%)	84	..
3 h after treatment	829	111 (13%)	139	43/90 (48%)	834	121 (15%)	152	43/109 (40%)
Côte d'Ivoire	253	47 (19%)	61	29/54 (54%)	253	54 (21%)	77	22/61 (36%)
Laos	273	41 (15%)	50	14/36 (39%)	273	51 (19%)	59	21/48 (44%)
Pemba Island	303	23 (8%)	28	ND	308	16 (5%)	16	ND
24 h after treatment	779	104 (13%)	140	82/121 (68%)	786	109 (14%)	165	103/130 (79%)
Côte d'Ivoire	227	50 (22%)	77	59/65 (91%)	231	62 (27%)	110	78/86 (91%)
Laos	247	48 (19%)	57	23/56 (41%)	247	42 (17%)	49	25/44 (57%)
Pemba Island	305	6 (2%)	6	ND	308	5 (2%)	6	ND
2–21 days after treatment	356	15 (4%)	15	ND	361	14 (4%)	17	ND
Côte d'Ivoire†	15	0	0	ND	23	0	0	ND
Laos‡	42	8 (19%)	8	ND	39	4 (10%)	5	ND
Pemba Island§	299	7 (2%)	7	ND	299	10 (3%)	12	ND

ND=not determined. *On Pemba Island, only four out of 50 events were assessed for causality; relatedness was thus considered as ND. †Safety monitoring after the 24 h post-treatment period was done actively for participants showing moderate or severe adverse events or needing medical intervention at 24 h and passively for all remaining participants. ‡Mainly includes participants who were missed out at, or had persisting symptoms from, the 24-h assessment and symptoms occurring after 24 h but within 14–21 days after treatment that were mentioned by participants during monitoring visits. §We aimed to visit all trial participants to ask about symptoms occurring after 24 h; symptoms mentioned after 24 h could include persisting symptoms from the 24-h assessment or symptoms occurring after 24 h but within 14–21 days after treatment that were possibly related to drug administration.

Table 3: **Baseline symptoms and adverse events after treatment**

between treatment groups. We found the highest cure rate against hookworm in Côte d'Ivoire (96% [27 of 28] for albendazole and 88% [15 of 17] for ivermectin–albendazole), followed by Pemba Island (82% [40 of 49] and 72% [28 of 39]), where infections were primarily of light intensity. In Laos, we found moderate efficacy in terms of cure rates for both treatment groups (56% [100 of 180] and 59% [115 of 194]). Hookworm infections were well reduced in terms of ERRs (geometric mean ERR ≥97%) in all settings. Of 22 participants in Laos infected with *S stercoralis* in each treatment group, four were still infected after treatment in the albendazole group (cure rate 82%) and one in the ivermectin-albendazole group (96%).

Safety was assessed in 508, 546, and 613 trial participants in Côte d'Ivoire, Laos, and Pemba Island, respectively. Not all participants were available at each timepoint (table 3). We did not observe any serious adverse events in any of the three countries. Adverse event reporting was similar between treatment groups. Before treatment, any symptom or condition was reported by 392 (77%) of 508, 177 (32%) of 546, and 106 (18%) of 607 examined participants from Côte d'Ivoire, Laos, and Pemba Island, respectively. All reported baseline symptoms and adverse events assessed 3 h and 24 h after treatment are illustrated in figure 3. Details on country-specific adverse events are provided in appendix 2 (pp 4–6). 232 (14%) of 1663 participants reported any adverse event 3 h after treatment, and 213 (14%) of 1565 reported any adverse event 24 h after treatment. The most frequently reported adverse events in both groups were headache, abdominal pain, and itching. Adverse events were mostly transient and resolved within 24 h. Few participants experienced moderate (23 of 1663, 1%) and severe (six of 1663, <1%) adverse events. 61% (146 of 239) and 59% (125 of 211) of all assessed adverse events were classified as possibly treatment-related in the ivermectin–albendazole and albendazole groups, respectively. More moderate-to-severe adverse events were observed 24 h than 3 h after treatment (27 *vs* 15 events), with higher numbers in Côte d'Ivoire (21 events) than in Laos (18 events) and Pemba Island (three events). At 24 h after treatment, more moderate-to-severe adverse events were reported in the ivermectin–albendazole group (21 events) than in the albendazole group (six events). These mostly included allergy-like symptoms involving itching, rash, and disorders of the digestive tract, but also diarrhoea as a separate clinical symptom, that were resolved without intervention or with antihistamines and glucocorticoid treatment. Adverse events as a result of ivermectin acting on lymphatic filariasis parasites were negligible. None of 607 participants in Pemba Island and four (1%) of 510 participants in Côte d'Ivoire tested positive for IgG or

IgM antibodies against *Wuchereria bancrofti* before treatment, only one of whom reported mild abdominal pain 3 h after treatment.

Discussion

We did a randomised controlled trial in three distinct epidemiological settings in people aged 6–60 years with the overarching goal to inform STH control guidelines and programmes on the potential benefit of using ivermectin in combination with albendazole against trichuriasis. Our findings revealed superiority in terms of cure rate and ERR of the combination therapy over albendazole monotherapy against *T trichiura* infections in Laos and Pemba Island. Yet, in Côte d'Ivoire, ivermectin–albendazole showed unsatisfactory efficacy. The trial results further highlight the need for a change in treatment for mass drug administration campaigns, since we found low efficacy of albendazole according to the WHO reference efficacy (arithmetic mean-based ERR <50%) in all three settings.[22] The observed cure rates were even lower than the initially assumed cure rate for albendazole of 30%, which might be explained by a more rigid eligibility criterion (minimal egg count of 100 EPG) and diagnostic approach (four Kato-Katz slides analysed per timepoint) than used in earlier studies. Ivermectin–albendazole showed a good safety profile, with mostly mild and transient adverse events. More moderate and severe adverse events were observed 24 h after treatment than 3 h after treatment and in the ivermectin–albendazole group than in the albendazole monotherapy group. This finding might in part be explained by the half-life of ivermectin (ie, approximately 18–28 h in humans).[23] Nevertheless, trials like this one are not powered to assess statistical differences in safety outcomes.

The efficacy of ivermectin–albendazole on Pemba Island was slightly higher in our study (cure rate 49%) than in earlier studies in Zanzibari school-aged children (cure rates 38% and 28%);[13,14] however, in a subgroup analysis in which we considered only school-aged children (6–12 years), the cure rate was similar to the earlier studies (26%). Previous trials done in Asian settings showed similar or higher cure rates for combination therapy in *T trichiura*-infected children from the Philippines (65%) and Sri Lanka (79%) compared with children from Laos (52%),[11,12] yet these data were collected around 20 years ago and the diagnostic approaches used in those studies were less rigid than the diagnostic approach we applied. While the two African trial cohorts were relatively comparable with regard to age composition and baseline infection intensity of *T trichiura*, the mean age in Laos was much older and in turn baseline EPGs were lower. Subgroup analysis has shown that baseline infection intensities have an important role in treatment efficacy and thus might in part explain why the highest cure rates for ivermectin–albendazole were found in Laos.

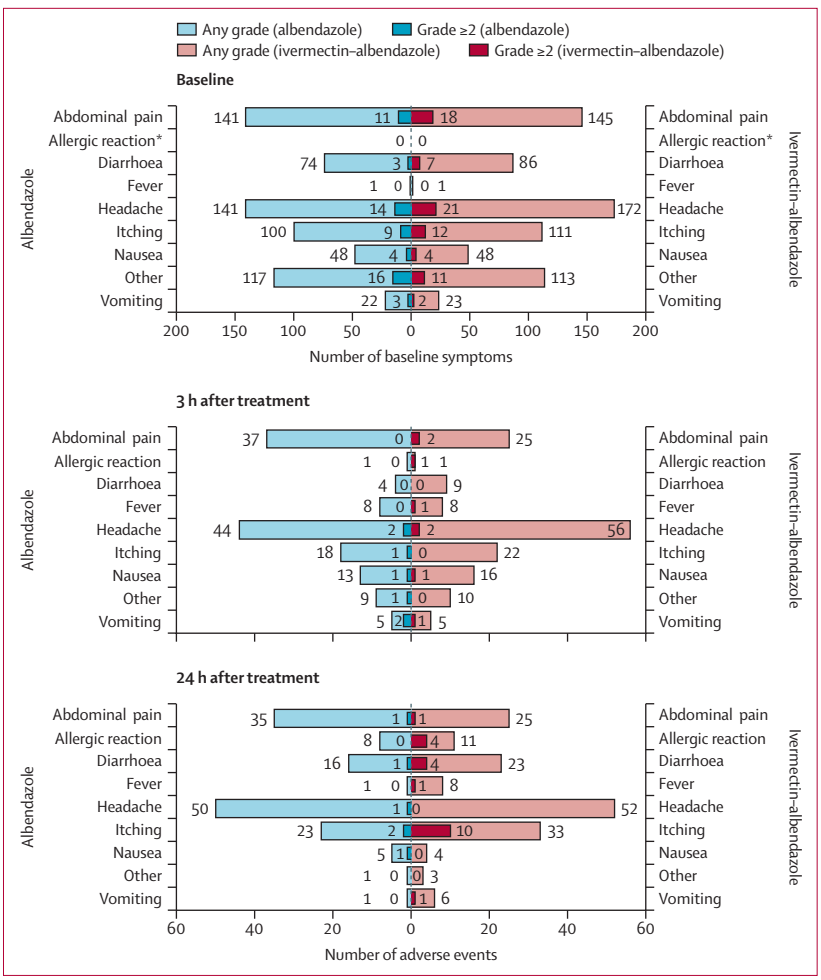

Figure 3: **Baseline symptoms and adverse events at each timepoint by group and grade**
*Not applicable at this timepoint.

The low efficacy of ivermectin–albendazole against *T trichiura* in Côte d'Ivoire warrants further investigation. Several patient factors might influence treatment outcome. Metabolisation and drug absorption are universally accepted to play a role in drug efficacy, but in the case of intestinal parasites, direct drug exposure in the lumen might be as important to kill them. To date, the influence of changes in drug disposition of albendazole and ivermectin on efficacy have not been described. Moreover, the nutritional and immunological status, as well as the intestinal microbiome, of patients are believed to have a potential impact on pharmacokinetics or how effectively parasitic infections are cleared.[24,25]

Acquired drug resistance might be another explanation for treatment failure. However, there is no evidence for resistance in human STH infections, and potential mechanisms of ivermectin resistance in *T trichiura* are yet to be fully understood.[23] Nonetheless, drug pressure might trigger anthelmintic resistance and should not be

underestimated. Côte d'Ivoire has the longest history of community-wide use of ivermectin to fight filarial diseases, compared with Laos, where to date ivermectin has not been used in any programme.[26,27] In Laos, mainly mebendazole is provided for STH control. On Pemba Island, mass drug administration against lymphatic filariasis was stopped in 2015 after six rounds.[28] We observed no typical patterns of acquired resistance in the data, such as geographical heterogeneity in efficacy, as efficacy was similarly low in villages situated within a perimeter of up to 40 km distance. Moreover, a surprisingly low efficacy of ivermectin was observed in dose-finding studies in another study area in Côte d'Ivoire.[29]

Differences in parasite genetics, causing variance in parasite defense systems (eg, drug efflux pumps and detoxification enzymes), among *T trichiura* strains might have a role in reduced treatment efficacy.[7,30] Whole-genome and amplicon sequencing of local *T trichiura* parasites or eggs might provide further insight into potential adaptations of the Côte d'Ivoire strain.[31]

The biggest limitation of our study was the reduced sensitivity of the Kato-Katz diagnosis technique compared with PCR-based diagnosis. However, to minimise potential overestimation of efficacy measures, we applied rigorous inclusion criteria for positive individuals (ie, 100 EPG and two out of four Kato-Katz slides positive). Furthermore, we performed qPCR diagnosis on samples from Pemba Island and compared efficacy measures. These findings revealed lower cure rates in PCR-based diagnosis than in diagnosis with the Kato-Katz technique, but ivermectin–albendazole still showed significantly higher cure rates against *T trichiura* than albendazole.[8] Our safety outcomes were descriptive and did not explore for multiple events nor account for differential follow-up between settings. Comparison of safety outcomes between settings should thus be interpreted with caution.

Countries affected by trichuriasis, strongyloidiasis, and scabies would clearly benefit from introduction or broader application of ivermectin–albendazole, which is currently exclusively used for onchocerciasis and lymphatic filariasis.[28] These efforts would go hand in hand with the recommendations put forth by WHO in the 2021–30 roadmap for neglected tropical diseases.[4] A current obstacle for use of ivermectin–albendazole in STH programmes is the prohibitive costs of good-quality ivermectin and the absence of donations for this purpose; the Mectizan Donation Program covers only lymphatic filariasis and onchocerciasis.[4] Challenges for community-wide ivermectin–albendazole implementation include administration to identified at-risk groups (preschool-aged children and pregnant and lactating women).[3] Ivermectin is not recommended for children shorter than 90 cm or weighing less than 15 kg, pregnant women, or lactating women in the first week after birth.[9] New evidence on ivermectin safety and field-applicable solutions for dosing are needed. Simultaneously, efforts should be made to identify and test alternative treatment options to effectively treat infections in areas with low ivermectin–albendazole efficacy against *T trichiura*. Alternative drug combination candidates could be oxantel pamoate or moxidectin with albendazole against *T trichiura* infections.[8]

For more on the **Mectizan Donation Program** see https://mectizan.org/

In conclusion, ivermectin–albendazole, the only approved and available combination anthelmintic therapy, is a valuable and safe alternative treatment to albendazole monotherapy, which showed low efficacy against *T trichiura* in all settings. Future trials might look at effectiveness rather than efficacy using cluster-randomised designs, allowing for inclusion of bigger sample sizes and more conclusive safety comparisons. Current diagnosis to assess STH efficacy in trials should be complemented by molecular techniques (eg, qPCR) in at least a subsample from each trial site to better depict the real-life performance.

Contributors

EH, JH, and JK designed the study. EH, LK, CP, SW, SMAl, SMAm, SS, JTC, and JK planned the study. EH, LK, CP, SW, SMAl, SMAm, SS, JTC, and JK implemented the study. EH, JH, and JK analysed and interpreted the trial data and wrote the first draft of the manuscript. LK, CP, SW, SMAl, SMAm, SS, and JTC revised the manuscript. All authors read and approved the final version of the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. EH, LK, CP, SW, and JH accessed and verified the data.

Declaration of interests

We declare no competing interests.

Data sharing

The study protocol is available on ClinicalTrials.gov, NCT03527732, and in appendix 1, together with the statistical analysis plan, which also includes key elements of the analysis code. Individual deidentified participant data that underlie the results reported in this Article will be available upon request directly after publication, with no end date. Supporting clinical documents, including approval of the proposals and the informed consent form plan, will be made available upon request immediately following publication for at least 1 year. Access will be granted to researchers who provide a methodologically sound proposal. The sponsor, investigators, and collaborators will approve the proposals on the basis of scientific merit. Requests should be directed to the corresponding author (jennifer.keiser@swisstph.ch). Researchers who request data will need to sign a data access agreement before they are granted access.

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