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Efficacy and Safety of Ivermectin Against *Trichuris trichiura* in Preschool-aged and School-aged Children: A Randomized Controlled Dose-finding Trial

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Background. Although trichuriasis affects millions of children worldwide, recommended drugs lack efficacy and new treatment options are urgently needed. Ivermectin has promising potential to complement the anthelminthic armamentarium.

Methods. A randomized placebo-controlled trial was conducted in rural Côte d'Ivoire to provide evidence on the efficacy and safety of ascending oral ivermectin dosages in preschool-aged children (PSAC) and school-aged children (SAC) infected with *Trichuris trichiura*. The primary outcome was the cure rate (CR) for *T. trichiura* infection, and the secondary outcomes were safety, egg-reduction rates (ERRs) against *T. trichiura* infection, and CRs and ERRs against other soil-transmitted helminth species.

Results. A total of 126 PSAC and 166 SAC were included in an available case analysis. In PSAC, efficacy against *T. trichiura* did not differ between 200 μg/kg ivermectin and placebo treatment arm, as expressed in CRs (20.9% [95% confidence interval {CI}, 11.9%–52.8%] vs 19.5% [10.4%–49.9%]) and geometric mean ERRs (78.6% [60.1%–89.5%] vs 68.2% [40.5%–84.8%]). In SAC, the highest administered ivermectin dose of 600 μg/kg had a low CRs (12.2% [95% CI, 4.8%–32.3%]) and moderate ERRs (66.3% [43.8%–80.2%]). Only mild adverse events and no organ toxicity, based on serum biomarkers, was observed.

Conclusion. Ivermectin can be administered safely to PSAC with trichuriasis. Given the low efficacy of ivermectin monotherapy against *T. trichiura* infection, further research should investigate the optimal drug combinations and dosages with ivermectin against soil-transmitted helminthiasis.

Clinical Trials Registration. ISRCTN15871729 (www.isrctn.com).

Keywords. ivermectin; *Trichuris trichiura*; trichuriasis; soil-transmitted helminth.

Soil-transmitted helminthiases are caused by the endoparasitic nematodes *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*. Almost half a billion persons are infected with *T. trichiura* alone, with children harboring the most intense infections [1, 2]. In children, *T. trichiura* infections can cause malnutrition, iron-deficiency anemia, and reduced physical and cognitive development, causing the major burden of disease among this most vulnerable age group [2–4]. Preventive chemotherapy in the form of population-based deworming programs is an effective public health measure to reduce morbidity [3, 4].

The efficacy of current first-line drugs against trichuriasis, the benzimidazoles albendazole and mebendazole as monotherapies and single dose-regimens, used in preventive chemotherapy programs, is unsatisfactory, displaying only low cure rates (CRs) and egg-reduction rates (ERRs) [5–7]. Furthermore, drug resistance, a major issue in veterinary medicine, is also of concern in humans, because these compounds have been in use for decades [5, 7, 8]. Hence, alternative treatments need to be studied for efficacy and safety, notably in the demographic groups most heavily affected.

Ivermectin, an antiparasitic drug used against a wide range of diseases, including onchocerciasis, lymphatic filariasis, strongyloidiasis, and scabies, is a promising candidate for treatment of soil-transmitted helminthiases [9–12]. Mass drug administration programs with ivermectin alone against onchocerciasis, or in combination with albendazole against lymphatic filariasis, have been shown to lower the prevalence of trichuriasis in endemic areas [13–15]. Ivermectin revealed efficacy comparable to the benzimidazoles against *T. trichiura* infection when administered alone, and in combination with either albendazole or mebendazole performed even better [16–20]. Owing to its broad antiparasitic spectrum, ivermectin would be an attractive agent within integrated treatment approaches in settings where multiparasitism is the norm [21]. Its coadministration with albendazole has recently been added to the World Health

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Organization (WHO) essential medicines list for the treatment of soil-transmitted helminth (STH) infection [22].

Despite its use for decades, important characteristics of ivermectin still remain unknown, for example, the optimal dosage of this drug against *T. trichiura* infection. Moreover, with the exception of a single retrospective study in 15 infants with scabies [23], the safety of this drug has never been thoroughly studied in children <5 years of age. Presently ivermectin is approved for use in children weighing ≥15 kg or ≥5 years of age. However, preventive chemotherapy is recommended as a public health intervention for all children, including preschool-aged children (PSAC) and school-aged children (SAC), living in STH-endemic areas [24]. Our trial intended to close these knowledge gaps by characterizing the dose-response relationship for efficacy of ivermectin and its safety in PSAC and SAC.

METHODS

Study Design and Participants

This randomized, placebo-controlled, single-blind trial was conducted in seven villages near Azaguié, Agboville department, southern Côte d'Ivoire, from 19 September to 3 November 2017. Children 2–12 years of age who were *T. trichiura* positive were considered eligible for the trial. To avoid high CRs in the placebo arms [25], only children with *T. trichiura* infection intensities of >60 eggs per gram of stool (EPG) in PSAC and 100 EPG in SAC were included. Excluded from the trial were children with any systemic illness (eg, symptomatic malaria or severe anemia, defined as hemoglobin <70 and <80 g/L in PSAC and SAC, respectively [26]), those who had received any anthelminthic treatment within the past 4 weeks, and those who were allergic to ivermectin.

Ethical Considerations

Ethical clearance was obtained from the National Ethics Committee of the Ministry of Health in Côte d'Ivoire (reference No. 052//MSHP/CNER-kp), and the Ethics Committee of Northwestern and Central Switzerland (reference No. 2017-00250). Written informed consent was obtained from all parents and guardians of the children after they had attended an information meeting and they had been encouraged to ask questions in an open discussion forum. SAC gave verbal assent.

Randomization and Treatment

Three-milligram ivermectin tablets were obtained from Elea, Argentina. For PSAC, minitablets were produced at the University of Basel. Minitablets were manufactured by milling the 3 mg tablets, with subsequent recompaction to white, round, uncoated minitablets containing 0.5 mg of ivermectin.

PSAC (aged 2–5 years) were randomly assigned placebo or ivermectin at 100 or 200 μg/kg. SAC (aged 6–12 years) were randomly assigned to placebo or ivermectin at 200, 400, of 600 μg/kg. Study-site investigators were aware of the study-group assignment, and participants and laboratory technicians were blinded. Randomization was performed using a computer-generated code with varying random blocks sizes of four or eight children for SAC and three or six for PSAC, stratified by their baseline infection intensities (light or moderate plus heavy infection, according to WHO guidelines) [27].

Study Procedures

At baseline, children provided two stool samples, obtained if possible on two consecutive days or otherwise within a maximum of five days. From each sample, duplicate Kato-Katz thick smears were prepared and examined for STH (*T. trichiura*, *A. lumbricoides,* and hookworm) and *Schistosoma mansoni* eggs [28]. Egg counts were recorded, and infections were classified as light, moderate, or heavy [27]. For quality control, 10% of the slides were randomly chosen and reexamined. If discordant egg counts were observed slides were reread for a third time and the results discussed until consensus was reached [29, 30].

Before treatment, children were physically examined and questioned for clinical symptoms. Adverse events were assessed through active asking and graded at 3, 24, and 72 hours after treatment. To assess organ toxicity, complete blood cell count and hepatic and renal function tests were conducted by means of venous blood samples at baseline and 72 hours after treatment. Treatment efficacy was assessed 14–21 days after treatment by examining additional quadruplicate Kato-Katz thick smears. At the end of the study, all children who remained positive for any STH infection were treated with albendazole (400 mg) [4]. All excluded children who were positive for any STH infection also received albendazole.

Outcomes

The primary outcome was CR against *T. trichiura* infection. Secondary end points were drug safety, geometric mean ERR against *T. trichiura*, and CR and ERR against other STH species and *S. mansoni*.

Statistical Analysis

The main aim of this study was to elucidate the dose-response relationship of ivermectin against *T. trichiura*. Computer simulations showed that with 40 children enrolled in each of the study arms (0, 200, 400, and 600 μg/kg or 0, 100, and 200 μg/kg ivermectin) the dose-response prediction model had a median precision (half of the 95% confidence interval [CI]) of 10%, assuming associated CRs of 2.5%, 30%, 50%, and 70% for 0, 200, 400, and 600 μg/kg ivermectin, respectively [31].

All data were entered twice into a database (Access 2016; Microsoft), compared using EpiInfo software, version 3.3.2 (Centers for Disease Control and Prevention), and analyzed using R software, version 3.4.1 (www.r-project.org). An available-case analysis was performed, including all children who were randomized and provided stool samples at follow-up.

The CR was calculated as the percentage of egg-positive children at baseline who become egg-negative after treatment at follow-up. The EPG was assessed by calculating the mean egg counts from the Kato-Katz thick smears, multiplied by 24.

The geometric mean egg counts were calculated for the seven treatment groups before and after treatment as follows: $e^{1/n \ \Sigma \ \log(x \ + \ 1)} \ - \ 1$ (where x is egg counts) to determine the corresponding ERR ([1 – geometric mean egg output after treatment/geometric mean egg output at baseline] × 100). Ordinary nonparametric bootstrap resampling (5000 replicates) was used to calculate 95% CIs for the ERR against *T. trichiura* infections.

We performed an available-case analysis including all randomized children with primary end-point data. We evaluated dose-response curves by fitting nonlinear E_{max} models for CRs and ERRs separately for each age group, using the DoseFinding package in R.

RESULTS

Baseline Characteristics

A total of 810 PSAC and 974 SAC were screened for eligibility; 703 children with complete parasitological data at baseline were *T. trichiura* negative, and 491 did not provide two stool samples. Of those who were *T. trichiura* positive, 242 were excluded owing to very light infection intensity, below the thresholds for eligibility mentioned above, and 46 children were oversampled.

We randomly assigned 130 PSAC to the three and 172 SAC to the four treatment arms of their respective age groups (Figure 1). At follow-up, 10 children (3.3%; range among treatment groups 0.0%–4.7%) were absent or did not provide stool samples. Fourteen children who provided only a single sample were included in the available case analysis.

Demographic and parasitological data at baseline for all children who received treatment are presented in Table 1. The treatment arms were balanced by *T. trichiura* infection intensities according to geometric means of EPG and WHO cutoffs [27], as well as with respect to age, height, and weight. One arm of the SAC subgroup consisted of considerably more boys than girls (28 vs 15); the other arms were balanced with respect to sex.

Among PSAC, 113 (86.9%) had a light *T. trichiura* infection (<1000 EPG), and 17 (13.1%) had a moderate infection (1000–9999 EPG); no heavy *T. trichiura* infection was recorded in PSAC. Among SAC, 137 (79.7%) had a light *T. trichiura* infection, 34 (19.8%) had a moderate infection, and one (0.6%) was heavily infected (≥10 000 EPG).

Efficacy Against *T. trichiura*

The CRs and ERRs against *T. trichiura* among the 292 children with follow-up data are shown in Table 2. The estimated dose-response curves of the E_{max} model are shown in Figure 2. The E_{max} models estimated low CRs for all treatment arms, with the 50% effective dose lying outside the dose range tested. For ERRs, the models predicted increasing efficacy with ascending doses, but the observed effect was small.

Among PSAC, CRs against *T. trichiura* were similar between the placebo arm and the highest ivermectin dose administered;

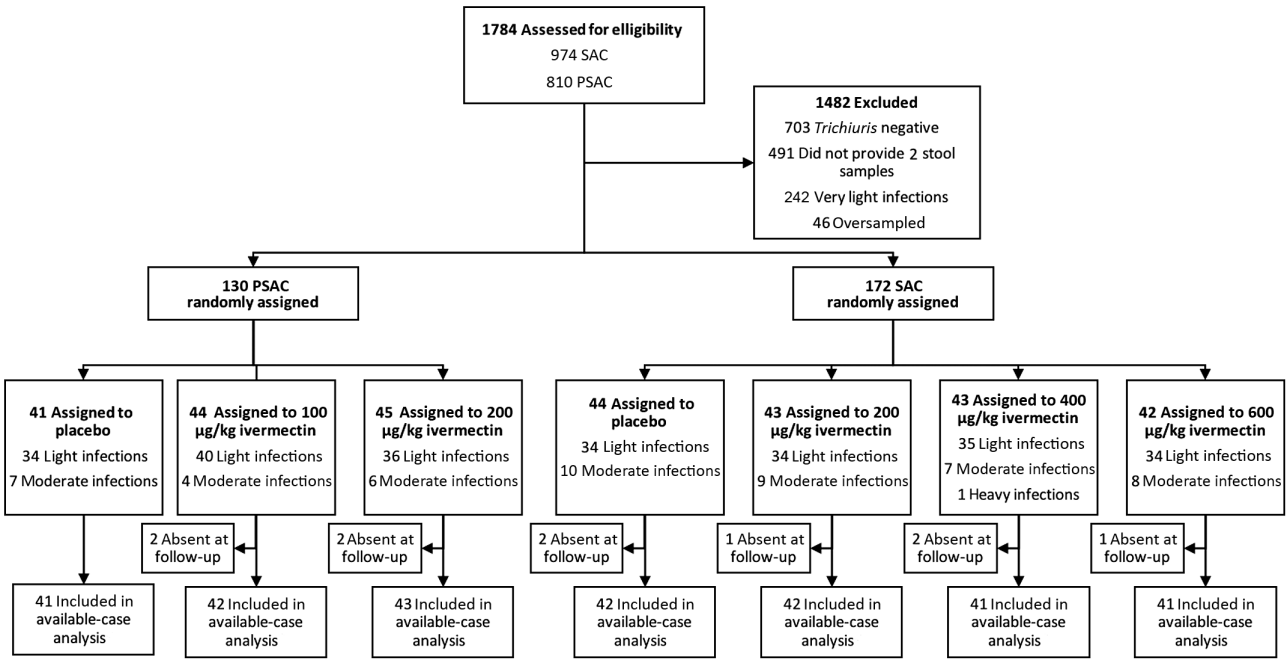

Figure 1. Trial profile. Fourteen children provided only 1 stool sample at follow-up. Abbreviations: PSAC, preschool-aged children; SAC, school-aged children.

Table 1. Baseline Data for Preschool-aged and School-aged Children

	Preschool-aged Children				School-aged Children				
Data	Placebo (n = 41)	Ivermectin 100 µg/kg (n = 44)	Ivermectin 200 µg/kg (n = 45)	Total (n = 130)	Placebo (n = 44)	Ivermectin 200 µg/kg (n = 43)	Ivermectin 400 µg/kg (n = 43)	Ivermectin 600 µg/kg (n = 42)	Total (n = 172)
Age, mean (SD), y	3.5 (1.1)	4.0 (0.9)	3.7 (1.0)	3.7 (1.0)	8.0 (2.0)	8.5 (1.6)	8.5 (2.1)	8.4 (2.0)	8.4 (1.9)
Sex, No.									
Female	20	23	21	64	20	15	20	18	73
Male	21	21	24	66	24	28	23	24	99
Weight, mean (SD), kg	13.8 (2.5)	14.7 (2.5)	14.4 (2.9)	14.3 (2.7)	22.7 (5.3)	23.7 (4.7)	22.9 (6.4)	22.9 (6.3)	23.1 (5.6)
Height, mean (SD), cm	90.6 (9.1)	94.5 (9.0)	92.9 (8.5)	92.7 (8.9)	119.6 (12.6)	123.1 (9.7)	121.4 (12.1)	120.8 (12.1)	121.2 (11.6)
Trichuris trichiura infection									
EPG, geometric mean	235.9	201.2	248.9	227.7	522.5	469.5	471.5	442.0	476.0
Infection intensity, No. (%)									
Light	34 (82.9)	40 (90.9)	39 (86.7)	113 (86.9)	34 (77.3)	34 (79.1)	35 (81.4)	34 (81.0)	137 (79.7)
Moderate	7 (17.1)	4 (9.1)	6 (13.3)	17 (13.1)	10 (22.7)	9 (20.9)	7 (16.3)	8 (19.0)	34 (19.8)
Heavy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (0.6)
Ascaris lumbricoides infection									
Children infected, No. (%)	10 (24.4)	14 (31.8)	9 (20.0)	33 (25.4)	11 (25.0)	14 (32.6)	13 (30.2)	8 (19.0)	46 (26.7)
EPG, geometric mean	3694.0	2809.0	1565.8	2602.5	2037.3	2826.8	2518.4	853.3	2054.3
Hookworm infection									
Children infected, No. (%)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.8)	3 (6.8)	4 (9.3)	4 (9.3)	2 (4.8)	13 (7.5)
EPG, geometric mean	0.0	0.0	378.0	378.0	40.6	207.7	18.3	24.2	48.9
Schistosoma mansoni infection									
Children infected, No. (%)	3 (7.3)	9 (20.5)	6 (13.3)	18 (13.8)	12 (27.3)	10 (23.3)	11 (25.6)	13 (31.0)	46 (26.7)
EPG, geometric mean	21.4	48.6	75.1	49.1	190.4	166.2	136.7	85.2	136.1

Abbreviations: EPG, eggs per gram of stool; SD, standard deviation.

Table 2. Cure Rates and Egg-reduction Rates

	Preschool-aged Children			School-aged Children			
Infection and Outcome	Placebo	Ivermectin 100 μg/kg	Ivermectin 200 μg/kg	Placebo	Ivermectin 200 μg/kg	Ivermectin 400 μg/kg	Ivermectin 600 μg/kg
Trichuris trichiura infection							
Children cured, No. (%; 95% CI)	8/41 (19.5; 10.4–49.9)	5/42 (11.9; 4.7–31.3)	9/43 (20.9; 11.9–52.8)	1/42 (2.4; .1–11.2)	1/42 (2.4; .1–11.2)	1/41 (2.4; .1–11.5)	5/41 (12.2; 4.8–32.3)
EPG, geometric mean							
Before treatment	235.9	190.9	249.4	548.2	476.5	488.8	448.7
After treatment	75.0	69.9	53.5	373.2	218.3	256.2	151.0
ERR, geometric mean (95% CI)	68.2 (39.6–84.3)	63.4 (36.9–79.9)	78.6 (59.2–89.3)	31.9 (–0.3 to 56.3)	54.2 (35.5–68.4)	47.6 (21.2–67.6)	66.3 (44.7–80.3)
EPG, arithmetic mean							
Before treatment	570.3	383.3	527.3	1159.1	892.1	1119.8	896.5
After treatment	384.0	382.4	293.7	1261.7	586.6	560.2	558.7
ERR, arithmetic mean (95% CI)	32.7 (–10.6 to 60.4)	0.2 (–54.5 to 44.1)	44.3 (30.3–62.0)	–8.8 (–54.9 to 17.0)	34.3 (12.5–51.2)	50.0 (19.5–65.5)	37.7 (13.4–53.6)
Moderately or heavily infected children with no or light infection after treatment (%)	57.1	66.7	66.7	20.0	11.1	25.0	25.0
Ascaris lumbricoides infection							
Children cured, No. (%)	1/10 (10.0)	14/14 (100.0)	9/9 (100.0)	3/11 (27.3)	14/14 (100.0)	12/13 (92.3)	7/8 (87.5)
EPG, geometric mean							
Before treatment	3694.0	2809.0	1565.8	2037.3	2826.8	2518.4	853.3
After treatment	575.2	0.0	0.0	646.2	0.0	0.7	0.3
ERR	84.4	100.0	100.0	68.3	100.0	100.0	100.0
Schistosoma mansoni infection							
Children cured, No. (%)	3/3 (100.0)	4/9 (44.4)	1/6 (16.7)	3/11 (27.3)	2/10 (20.0)	1/10 (10.0)	4/13 (30.8)
EPG, geometric mean							
Before treatment	21.4	48.6	75.1	163.5	166.2	120.5	85.2
After treatment	0.0	11.5	52.1	56.0	56.8	28.3	35.5
ERR	100.0	76.3	30.6	65.7	65.8	76.5	58.3

Abbreviations: CI, confidence interval; EPG, eggs per gram of stool; ERR, egg-reduction rate.

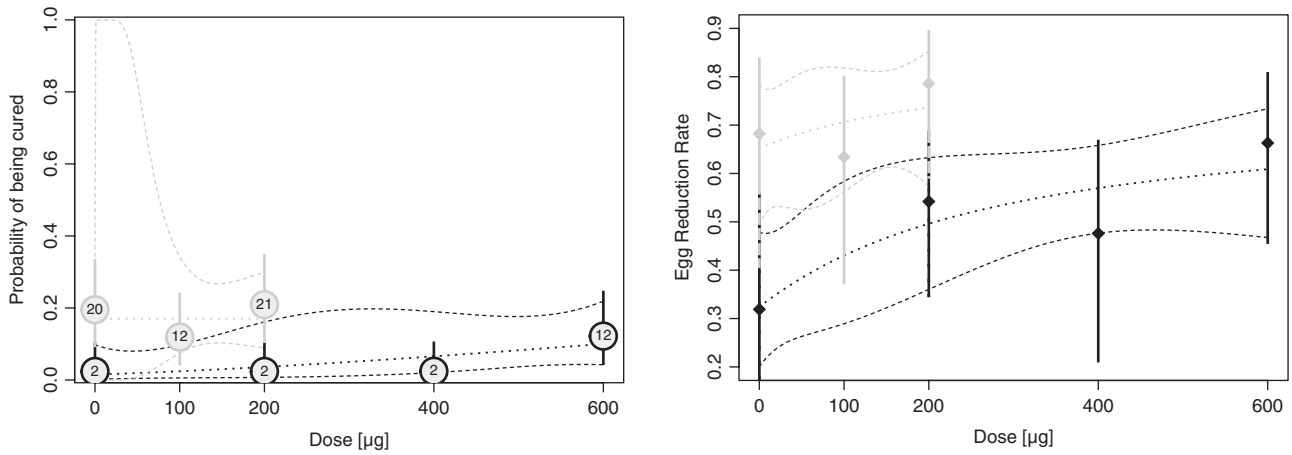

Figure 2. Dose-response curve based on cure rates (left panel) and egg reduction rates (right panel) in preschool-aged (grey) and school-aged (black) children.

they were 19.5% (95% CI, 10.4%–49.9%), 11.9% (4.7%–31.3%), and 20.9% (11.9%–52.8%) for PSAC treated with placebo and ivermectin at 100 or 200 µg/kg, respectively.

The corresponding geometric mean ERRs were 68.2% (95% CI, 39.6%–84.3%), 63.4% (36.9%–79.9%), and 78.6% (59.2%–89.3%) for placebo and ivermectin at 100 or 200 µg/kg. The arithmetic mean ERRs for these treatment groups were 32.7% (95% CI, −10.6% to 60.4%), 0.2% (−54.5% to 44.1%), and 44.3% (30.3%–62.0%), respectively.

In SAC, CRs against *T. trichiura* were 2.4% in the treatment arms receiving placebo (95% CI, 0.1%–11.2%) and ivermectin at 200 (0.1%–11.2%) or 400 µg/kg (0.1%–11.5%). The 600 µg/kg dose resulted in a slightly higher CR (12.2%; 95% CI, 4.8%–32.3%).

The geometric mean ERRs in SAC were 31.9% (95% CI, −0.3% to 56.3%) in the placebo arm and 54.2% (35.5%–68.4%), 47.6% (21.2%–67.6%), and 66.3% (44.7%–80.3%) in the treatment arms receiving ivermectin at 200, 400, or 600 µg/kg, respectively. The arithmetic mean ERRs were −8.8% (95% CI, −54.9% to 17.0%), 34.3% (12.5%–51.2%), 50.0% (19.5%–65.5%), and 37.7% (13.4%–53.6%), respectively, in these respective treatment arms.

Efficacy Against Other Helminth Infections

Data on efficacy against other helminth infections are presented in Table 2. Owing to the small sample sizes, no 95% CIs were calculated for CR and ERR (ERRs based on arithmetic means are presented in Supplementary Table 1). All 23 PSAC receiving either 100 or 200 µg/kg of ivermectin had their *A. lumbricoides* infection cured. Similar results were observed in SAC; only two of the 35 children receiving ivermectin at any dose were still positive for *A. lumbricoides* at follow-up (range of CRs among treatment arms, 87.5%–100%). The ERRs were 100% in ivermectin-treated children, compared with 84.4% and 68.3% in the PSAC and SAC placebo arms, respectively.

Few *S. mansoni* infections were observed in PSAC. Among the 44 SAC infected with *S. mansoni,* there was no difference between the efficacy of ivermectin at any dose studied and placebo. The CRs were 27.3% for placebo treated children and 10.0%–30.8% for ivermectin-treated children, and ERRs were also similar among the different trial arms.

Safety

Safety assessment included 302 children, although not every child was present at every time point (Table 3). Only mild clinical symptoms were reported by the children and their parents/guardians, with most symptoms occurring before treatment (70 symptomatic children; 23.2%). Decreasing numbers of adverse events were recorded at subsequent examination time points, with symptoms in 27 (8.9%), 14 (4.7%) and 11 (3.9%) of the children at 3, 24, and 72 hours after treatment, respectively.

Among PSAC, clinical symptoms after treatment were more common in the placebo arm than in children receiving either dose of ivermectin (13.2% vs 11.5%), whereas the opposite trend was seen with SAC (20.7% vs 13.2%). However, this difference was more pronounced before treatment (26.3% vs 15.3%). The most common symptoms after treatment in SAC were diarrhea (7.9% in placebo vs 6.9% in any ivermectin arm) and in PSAC headache (7.9% vs 6.6%, respectively) and abdominal pain (2.6% vs 13.2%). No allergic reaction to the drug was observed.

Safety data from blood samples were available for 274 children (119 PSAC and 155 SAC). No new-onset severe anemia [26], thrombocytopenia (cell count, <50 000/µL) or neutropenia (cell count, <500/µL) were observed 72 hours after treatment. No acute kidney injury, defined as a >1.5-fold increase over the baseline creatinine level [32], was observed. No child showed an

Table 3. Adverse Events

Adverse Event	PSAC, No. (%)			SAC, No. (%)			
	Placebo	Ivermectin 100 μg/kg	Ivermectin 200 μg/kg	Placebo	Ivermectin 200 μg/kg	Ivermectin 400 μg/kg	Ivermectin 600 μg/kg
Before treatment							
Headache	5/41 (12.2)	2/44 (4.5)	3/45 (6.7)	5/44 (11.4)	6/43 (14.0)	4/43 (9.3)	6/42 (14.3)
Stomach ache	5/41 (12.2)	2/44 (4.5)	4/45 (8.9)	5/44 (11.4)	6/43 (14.0)	11/43 (25.6)	6/42 (14.3)
Nausea	0/41 (0.0)	2/44 (4.5)	0/45 (0.0)	0/44 (0.0)	2/43 (4.7)	3/43 (7.0)	1/42 (2.4)
Vomiting	0/41 (0.0)	2/44 (4.5)	0/45 (0.0)	0/44 (0.0)	1/43 (2.3)	0/43 (0.0)	0/42 (0.0)
Diarrhea	1/41 (2.4)	3/44 (6.8)	6/45 (13.3)	1/44 (2.3)	3/43 (7.0)	4/43 (9.3)	4/42 (9.5)
Itching	3/41 (7.3)	3/44 (6.8)	3/45 (6.7)	1/44 (2.3)	3/43 (7.0)	3/43 (7.0)	3/42 (7.1)
3 h After treatment							
Headache	0/41 (0.0)	0/44 (0.0)	0/45 (0.0)	3/44 (6.8)	2/43 (4.7)	3/43 (7.0)	2/42 (4.8)
Stomach ache	0/41 (0.0)	0/44 (0.0)	0/45 (0.0)	0/44 (0.0)	5/43 (11.6)	7/43 (16.3)	5/42 (11.9)
Nausea	0/41 (0.0)	0/44 (0.0)	0/45 (0.0)	0/44 (0.0)	1/43 (2.3)	0/43 (0.0)	1/42 (2.4)
Vomiting	0/41 (0.0)	0/44 (0.0)	0/45 (0.0)	0/44 (0.0)	0/43 (0.0)	0/43 (0.0)	0/42 (0.0)
Diarrhea	0/41 (0.0)	0/44 (0.0)	0/45 (0.0)	0/44 (0.0)	0/43 (0.0)	0/43 (0.0)	0/42 (0.0)
Itching	2/41 (4.9)	0/44 (0.0)	0/45 (0.0)	0/44 (0.0)	2/43 (4.7)	1/43 (2.3)	1/42 (2.4)
24 h After treatment							
Headache	0/41 (0.0)	1/44 (2.3)	2/45 (4.4)	0/44 (0.0)	0/43 (0.0)	1/43 (2.3)	0/42 (0.0)
Stomach ache	0/41 (0.0)	1/44 (2.3)	0/45 (0.0)	1/44 (2.3)	0/43 (0.0)	3/43 (7.0)	0/42 (0.0)
Nausea	0/41 (0.0)	0/44 (0.0)	0/45 (0.0)	1/44 (2.3)	0/43 (0.0)	0/43 (0.0)	0/42 (0.0)
Vomiting	0/41 (0.0)	0/44 (0.0)	1/45 (2.2)	0/44 (0.0)	0/43 (0.0)	1/43 (2.3)	0/42 (0.0)
Diarrhea	0/41 (0.0)	2/44 (4.5)	1/45 (2.2)	0/44 (0.0)	0/43 (0.0)	0/43 (0.0)	0/42 (0.0)
Itching	0/41 (0.0)	1/44 (2.3)	0/45 (0.0)	0/44 (0.0)	1/43 (2.3)	0/43 (0.0)	0/42 (0.0)
72 h After treatment							
Headache	1/38 (2.6)	0/43 (0.0)	1/44 (2.3)	0/44 (0.0)	1/41 (2.4)	1/40 (2.5)	0/40 (0.0)
Stomach ache	0/38 (0.0)	1/43 (2.3)	0/44 (0.0)	0/44 (0.0)	0/41 (0.0)	0/40 (0.0)	0/40 (0.0)
Nausea	0/38 (0.0)	0/43 (0.0)	0/44 (0.0)	0/44 (0.0)	0/41 (0.0)	0/40 (0.0)	0/40 (0.0)
Vomiting	0/38 (0.0)	1/43 (2.3)	0/44 (0.0)	0/44 (0.0)	0/41 (0.0)	0/40 (0.0)	0/40 (0.0)
Diarrhea	3/38 (7.9)	0/43 (0.0)	3/44 (6.8)	0/44 (0.0)	0/41 (0.0)	0/40 (0.0)	0/40 (0.0)
Itching	0/38 (0.0)	0/43 (0.0)	1/44 (2.3)	1/44 (2.3)	0/41 (0.0)	1/40 (2.5)	0/40 (0.0)
New-onset severe anemia (hemoglobin, <70 g/L in PSAC or <80 g/L in SAC)	0/38 (0.0)	0/40 (0.0)	0/41 (0.0)	0/38 (0.0)	0/38 (0.0)	0/40 (0.0)	0/41 (0.0)
New-onset severe neutropenia (cell count, <500/μL)	0/38 (0.0)	0/41 (0.0)	0/41 (0.0)	0/38 (0.0)	0/38 (0.0)	0/40 (0.0)	0/41 (0.0)
New-onset severe thrombocytopenia (cell count, <50 000/μL)	0/38 (0.0)	0/41 (0.0)	0/41 (0.0)	0/38 (0.0)	0/38 (0.0)	0/40 (0.0)	0/41 (0.0)
Blood creatinine increased to >1.5 times baseline value	0/38 (0.0)	0/41 (0.0)	0/41 (0.0)	0/38 (0.0)	0/38 (0.0)	0/40 (0.0)	0/41 (0.0)
Elevation in alanine aminotransferase level to >2 ULN	0/38 (0.0)	0/41 (0.0)	0/41 (0.0)	0/38 (0.0)	0/38 (0.0)	0/40 (0.0)	0/41 (0.0)
Elevation in aspartate aminotransferase level to >2 ULN	0/38 (0.0)	0/41 (0.0)	0/41 (0.0)	0/38 (0.0)	0/38 (0.0)	0/40 (0.0)	0/41 (0.0)
Elevation in bilirubin level above ULN	0/38 (0.0)	0/41 (0.0)	0/41 (0.0)	0/38 (0.0)	0/38 (0.0)	0/40 (0.0)	0/41 (0.0)

Abbreviations: PSAC, preschool-aged children; SAC, school-aged children; ULN, upper limit of normal.

increase in transaminase levels to twice the upper limit of normal or an increase of bilirubin surpassing the upper limit of normal.

DISCUSSION

Trichuriasis is a neglected tropical disease of considerable public health significance [1]. Despite the high burden of disease, current first-line treatments have unacceptably low efficacy against this parasite in treatment regimen used in preventive chemotherapy [5]. Furthermore, a recent network meta-analysis indicated that the efficacy of albendazole and mebendazole against *T. trichiura* has decreased over the almost 50 years of their extensive use [7].

Albendazole-ivermectin has recently been added to the WHO essential medicine list to fill this gap and to be able to provide a broad-spectrum treatment covering all STH species, including *T. trichiura*. However, the optimal dose of ivermectin remains to be identified, with all studies evaluating its monotherapy or combination chemotherapy conducted to date using a standard dose of 200 μg/kg [16–18, 20].

Moreover, SAC have traditionally been the main target population for preventive chemotherapy programs [2], but WHO

guidelines highlight the importance of including other high-risk populations, such as PSAC, within the framework of these public health efforts [4]. Because neither optimal dosage of ivermectin nor its safety in PSAC were known, ascending doses of ivermectin known to be safe in the adult population were studied for the first time in children 2–5 years of age.

Surprisingly, ivermectin showed low CRs at all doses tested in PSAC and SAC, even at 600 μg/kg, a dose tested for the first time against *T. trichiura* infections. In both age groups, however, moderate ERRs were observed at increasing dosages. Yet, only ivermectin at 400 μg/kg in SAC performed above the WHO reference efficacy (≥50%) for *T. trichiura,* based on the arithmetic mean [30, 33].

The weak performance of ivermectin against trichuriasis in the present trial contrasts with the findings of the three studies by Wen et al [19], Beach et al [34], and Belizario et al [16], who reported CRs of 66.7%, 44.3%, and 35.1%, respectively using the standard dose of 200 μg/kg. These conflicting results might be explained by spatiotemporal differences, because these studies were performed 10–20 years ago in the Americas and Asia; moreover, two studies included patients with significantly less intense infections [19, 34], and one study also included adults [19].

The significantly higher CRs and ERRs for albendazole-ivermectin than for albendazole alone highlight the important contribution of ivermectin to the therapeutic effect of the combination [35]. Synergism of the two drug classes most likely occurs on the parasite level, since previous studies did not observe alteration in plasma concentrations of the individual drugs when administered in combination, compared with the administration of each drug alone [36]. The inhibition by ivermectin of membrane transporter proteins acting as efflux pumps on helminth cells, such as p-glycoprotein, causing accumulation of albendazole and its metabolites within the parasite cells, might be the underlying mechanism of this phenomenon [37].

High efficacy of ivermectin against *A. lumbricoides* is in agreement with previous findings [16, 19]. Our data do not suggest any schistosomicidal property of ivermectin.

Ivermectin is well known for its excellent safety profile [9, 11]. In the present study, it was well tolerated in both age groups at all doses studied. Data from blood samples taken at baseline and 72 hours after treatment did not reveal any significant hematotoxic, nephrotoxic, or hepatotoxic effect. The incidence of adverse events was especially low among PSAC, a finding in accordance with the results of Bécourt et al [23], who reported only two benign and transient adverse events in 15 infants treated with ivermectin for scabies. However, the small sample size is a limitation of our study, and conclusions on safety should be drawn with caution. Another limitation is that we explored dosages only up to 600 μg/kg, but an increase of >three-fold the recommended dose did not seem ethically and scientifically justified. Finally, owing to the low number of moderate and heavy infections, our results are not generalizable to all infection intensities, but only to mild infections.

In summary, extending ivermectin treatment to children <5 years of age is a clear asset of the current study. The good tolerability of ivermectin at 200 μg/kg in PSAC and 600 μg/kg in SAC suggests that these doses can be used safely in the respective age groups. Ivermectin doses of 100–200 μg/kg in PSAC and 200–600 μg/kg in SAC have low CRs similar to that that for placebo in the treatment of *T. trichiura* infections. At the highest doses administered, only moderate ERRs were observed. Because ivermectin doses as high as 2000 μg/kg seem to be safe in the adult population [38–41], the evaluation of higher doses of ivermectin against trichuriasis might be considered. However, the promising results of its coadministration with albendazole or mebendazole [16–18, 20], hinting at synergism, highlight the important role of ivermectin in combination chemotherapy rather than as monotherapy. Ivermectin combination chemotherapy should therefore be explored in the treatment of STH infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. D. W., J. T. C., J. Ha. and J. K. designed the study. M. P. and J. Huwyler formulated and manufactured the ivermectin minitablets. D. W., J. T. C., and J. D. S. performed the study. D. W., J. Hattendorf, and J. K. analyzed and interpreted the data. D. W. and J. K. wrote the first draft of the report. J. T. C., J. D. S., and J. Hattendorf revised the report. All authors read and approved the final version of the report.

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