Efficacy and safety of single-dose artesunate plus sulfalene/pyrimethamine combined with praziquantel for the treatment of children with Schistosoma mansoni or Schistosoma haematobium in western Kenya: a randomised, open-label controlled trial

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Abstract

Background

Reliance on praziquantel for treatment and control of schistosomiasis is likely to facilitate the emergence of drug resistance. Combination therapy targeting adult and juvenile schistosome worms is urgently needed to improve praziquantel efficacy and delay the development of drug resistance. We assessed the efficacy and safety of single-dose praziquantel combined with single-dose artesunate plus sulfalene-pyrimethamine in the treatment of Kenyan children with schistosomiasis.

Methods

This was an open-label, randomized clinical trial with 426 school-age children (7–15 years old) diagnosed with *S. mansoni* (by Kato-Katz) or *S. haematobium* (by urine filtration). They were randomly assigned (1:1:1) to receive a single dose of praziquantel (40 mg/kg) or a single dose of artesunate plus sulfalene-pyrimethamine (12 mg/kg artesunate) or combination therapy using a single dose of praziquantel (40 mg/kg) combined with a single dose of artesunate plus sulfalene-pyrimethamine (12 mg/kg artesunate). The primary outcome was cure and egg reduction rates at six weeks post-treatment in the available case population. Adverse events were assessed within 3 hours after treatment.

Results

Of the 426 children enrolled, 135 received praziquantel, 150 received artesunate plus sulfalene-pyrimethamine, and 141 received combination therapy. Outcome data was available for 398 children. For *S. mansoni*-infected children (n = 335), the cure rates were 75.6%, 60.7%, and 77.8%, and egg reduction rates were 80.1%, 85.0%, and 88.4% for praziquantel, artesunate plus sulfalene-pyrimethamine, and combination therapy, respectively. For *S. haematobium*-infected children (n = 145), the corresponding cure rates were 81.4%, 71.1%, and 82.2%; egg reduction rates were 95.6%, 97.1%, and 97.7%. 71 (16.7%) children reported mild-intensity adverse events. No serious adverse events were reported. Combination therapy was associated with a significantly higher proportion of adverse events.

Conclusion

A single oral dose of praziquantel combined with artesunate plus sulfalene-pyrimethamine cured a high proportion of children with *S. haematobium* but did not improve the treatment efficacy for either urinary or intestinal schistosomiasis. Sequential administration of praziquantel and the artesunate plus sulfalene-pyrimethamine may enhance the efficacy and safety outcomes.

Clinical Trial Registration:

Pan-African Clinical Trials Registry, PACTR202211501227743

INTRODUCTION

Human schistosomiasis is an infectious disease caused by the trematode worms of the *Schistosoma* genus [1]. The three most common schistosome species infecting human populations include *Schistosoma mansoni, S. haematobium*, and *S. japonicum.* The global burden of schistosomiasis is estimated at 1.4 to 3.3 million disability-adjusted life years annually [2]. Over 90% of the 250 million people infected with schistosomiasis reside in sub-Saharan Africa, where *S. mansoni* and *S. haematobium* are the most prevalent species [3]. The high-risk groups for schistosomiasis include preschool-aged and school-aged children, with consequences that include anaemia, school absenteeism, impaired child growth, physical fitness, and cognitive and intellectual development [4].

The main global schistosomiasis control strategy is preventive chemotherapy using praziquantel because it is effective against all the species of human schistosomiasis, can be administered as a single oral dose, and is affordable, safe, and partially effective [5, 6]. Praziquantel is effective against adult schistosome worms but less effective against the parasite's juvenile stages (schistosomula) [7]. Reliance on praziquantel for wide-scale preventive treatment exerts high drug pressure and could favour the emergence of praziquantel-resistant parasites. Although clinical resistance to praziquantel has not yet been established, laboratory and community studies have shown reduced schistosome susceptibility [8–10]. New drugs are urgently needed to replace or complement the use of praziquantel. Unfortunately, the schistosomiasis drug development pipeline is empty. A promising strategy to improve praziquantel efficacy and delay the development of drug resistance is combination therapy, where two or more drugs with different mechanisms of action are administered together. Drug repurposing may be a low-risk, cost-effective, and time-saving approach to developing new treatments by finding new indications for established drugs [11]. Possible candidates for anti-schistosomal combination therapy include praziquantel plus antimalarials such as mefloquine or artemisinin derivatives [12]. Artemisinin derivatives, such as artesunate, artemether, or dihydroartemisinin, are promising candidates for treating and preventing schistosomiasis [13, 14].

Artemisinin-based combination therapies (ACTs) are the most effective treatments for malaria [15]. Coincidentally, there is a large geographical overlap in sub-Saharan Africa's schistosomiasis and malaria co-endemic areas [16]. The artemisinin derivatives have anti-schistosomal activity in *vitro*, in *vivo*, and in clinical trials [17, 18]. Artesunate or artemether alone is less effective than praziquantel, but significantly higher cure and egg reduction rates were observed when artesunate or artemether was combined with praziquantel, compared to any of the medicines alone [19]. Unlike praziquantel, artemisinin derivatives are effective against juvenile schistosome worms [13]. The differences in the mechanism of drug action support a theoretical basis for combining praziquantel with an ACT in treating schistosomiasis. In high-transmission settings, the combination therapy is synergistic, acting at two stages of the schistosome life cycle to cure the primary infection and block further transmission. In clinical trials, ACTs are less effective than praziquantel in treating human schistosomiasis [20–23]. Laboratory studies with animal models

suggest that combined therapy using praziquantel and ACTs may be an attractive novel treatment for human schistosomiasis [24, 25]. However, two studies that assessed the efficacy of praziquantel plus an ACT for treating schistosomiasis showed mixed results [26, 27].

It is unclear whether the dosing regimen influences the efficacy of ACTs against schistosomiasis. For instance, a significantly lower cure rate of 14% was observed with a 3-day regimen (once daily for 3 days) of artesunate plus sulfalene-pyrimethamine against *S. mansoni* compared to 44% with a 24-hour treatment regimen against *S. haematobium* [21, 22]. Similarly, whether ACT doses used to treat malaria effectively cure schistosomiasis is unknown. If combination therapy using ACT plus praziquantel is found to be safe and effective, there could be concerns about the feasibility of a 3-day ACT course for mass drug administration. This study aimed to assess the role of single-dose combination therapy (praziquantel combined with artesunate plus sulfalene-pyrimethamine) in the treatment of schistosomiasis in an area of *S. mansoni* and *S. haematobium* co-endemicity, in western Kenya. For this study, we selected artesunate plus sulfalene-pyrimethamine because it is widely available as ACT for malaria treatment, is co-formulated, available for single daily dose therapy, has a well-established safety profile, and has been evaluated for the treatment of schistosomiasis with inconclusive results.

METHODS

Study design and participants

We conducted a phase III, open-label, parallel-group, randomized controlled clinical trial in western Kenya. The participants were recruited from 16 primary schools in Homabay and Migori Counties, western Kenya. These included four schools in the Rachuonyo sub-county, Homabay, and 12 schools in Nyatike and Suna West sub-counties, Migori. The schools were selected because of their proximity to previously identified schistosomiasis transmission sites. The study area has year-round malaria transmission and is endemic to *S. mansoni* with foci of *S. haematobium* [28–30]. The study was approved by the ethical review committee of the Kenya Medical Research Institute (KEMRI Scientific Ethics Review Unit # 2504).

Before starting the study, we met with parents, teachers, and community leaders to explain the study's objectives, procedures, and potential benefits and risks. Written informed consent was obtained from the parents or legal guardians of eligible children. All explanations and informed consent procedures were performed in the primary language of the parents or guardians. Children were invited to give informed consent for screening and enrollment by writing their name and ticking a box with the following statement: "I agree to participate in this study.".

The children were assessed for infection with *S. mansoni* or *S. haematobium.* Children positive for *S. mansoni* or *S. haematobium* infection were eligible to participate in the study if they were aged 7 to 15 years, in grades four to six, and could take oral medication. We excluded children who weighed more than 50 kg, were pregnant, had evidence of infection with *Plasmodium falciparum* or other *Plasmodium spp.*, had severe illness (such as epilepsy), signs of severe malnutrition, had used an anti-malaria or anti-

schistosomal drug within 28 days of the study, or a known history of hypersensitivity to artesunates, sulfonamides, or praziquantel.

Randomization and masking

Children with parasitologically confirmed *S. mansoni* or *S. haematobium* infection *w*ere randomly assigned (1:1:1) to receive praziquantel alone, artesunate plus sulfalene-pyrimethamine, or a combination of the two. This was done using a computer-generated stratified block randomization list provided by an independent statistician. The randomization sequence was stratified by schistosome species (*S. mansoni* or *S. haematobium)* in blocks of nine. The study nurse administered the treatment, and the participants were aware of the treatment group assignment. However, laboratory technicians and clinicians assessing the study outcomes were blinded to treatment assignments throughout the study.

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Procedures

Laboratory procedures

Each child was given plastic containers labelled with unique screening identification numbers and instructed to provide fresh stool and urine samples. The samples were transferred in cooler boxers to a nearby study laboratory in Migori or Homabay for processing. For *S. mansoni*, duplicate slides were prepared from the stool samples and examined under the microscope independently by two experienced laboratory technicians. *S. mansoni* and soil-transmitted helminth eggs were quantified using the Kato-Katz technique, with a template containing about 41.7 mg of faeces when filled [31]. Eggs of soil-transmitted infections, such as *Trichuris trichiura*, *Ascaris lumbricoides*, and hookworm, were also assessed and recorded for each species separately. The number of *S. mansoni* eggs was counted per slide, and the arithmetic mean from the two slides was multiplied by 24 to express them as eggs per gram (epg) of faeces. The intensity of the infection was categorized based on the WHO classification as light (1–99 epg), moderate (100–399 epg), or heavy (≥ 400 epg) [32].

For *S. haematobium*, a fresh urine sample was collected between 1000 and 1400 hours after rigorous exercise (to enable maximum egg excretion). Haematuria and proteinuria were tested using dipsticks. Quantitative analysis of urine was performed using the urine filtration technique. The urine sample was vigorously shaken, and 10 ml was filtered through a 13mm filter with an aperture of 12 μ pores (Sterlitech Corp., Auburn, USA). The filters were placed on microscope slides, a drop of iodine was added, and the slides were read under a microscope by two laboratory technicians independently. The number of *S. haematobium* eggs was counted and expressed as eggs per 10 mL of urine. The intensity of the infection was categorized as light (1–49 ep/10mL) or heavy (≥ 50 ep/10mL) based on WHO classification [32].

As a quality control measure for interobserver variability, a third technician re-read a random selection of 10% of slides and all slides for which the readings varied by more than 20% between the two technicians.

A capillary blood sample was taken by fingerprick to test for malaria and measure haemoglobin. Hemoglobin was estimated using a portable hemoglobinometer (HemoCue 301, Angelholm, Sweden). We used rapid diagnostic test strips (Paracheck, Orchid Biomedical Systems, India) to assess the presence of malaria antigens.

Participant screening and recruitment

The study clinician assessed the children for eligibility through a brief medical history and clinical examination. Children who tested positive for *S. mansoni* or *S. haematobium* and met all eligibility criteria were invited to participate in the study. The enrolling clinician took a standard baseline medical history and clinically examined the children, including weight (using a digital weighing scale) and height (using a Seca 213 portable stadiometer) measurements. The clinician also assessed the size of the liver and spleen. The study clinicians sequentially assigned study numbers to eligible children at enrollment.

Treatment and follow-up

The study nurse administered the study drugs according to the randomization sequence. All children received food items (orange juice and slices of bread) to reduce the nauseating effect of the study drugs and improve the drug bioavailability before drug ingestion [33]. The study had three treatment groups. Children assigned to the Praziquantel (Biltricide, Bayer Healthcare, Leverkusen, Germany) group received one 40 mg/kg dose of praziquantel to the nearest half tablet (600mg). Children assigned to the artesunate plus sulfalene-pyrimethamine (Coarinate Adult, Dafra Pharma, Turnhout, Belgium) received a single oral dose of 12 mg/kg of the artesunate component administered as one tablet for 15 ≤ 29.9 kg, two tablets for 30 ≤ 44.9 kg, and three tablets for 45–50 kg. Artesunate plus sulfalene-pyrimethamine is a co-formulated fixed-dose combination tablet consisting of artesunate (200mg), sulfamethoxypyrazine (500mg), and pyrimethamine (25mg). Children assigned to combination therapy received one dose of 40 mg/kg praziquantel and a single dose of 12 mg/kg artesunate plus sulfalene-pyrimethamine (one tablet for 15 ≤ 29.9 kg, two tablets for 30 ≤ 44.9 kg, and three tablets for 45–50 kg).

All study drugs were given orally by the study nurse, and children were observed for three hours after taking the drug to ensure retention and to check for any immediate adverse events. If vomiting occurred within an hour of drug ingestion, a second total dose was given. Children with repeated vomiting were withdrawn from the study. According to national treatment guidelines, all children with helminthic infections were treated with a single dose of 400 mg of albendazole.

All children were followed up for a total of 6 weeks. During the week six follow-up visit, children provided a stool and urine sample to be assessed for schistosome eggs, as described above. Participants who did not return for the scheduled follow-up visit were visited at home. At the end of the study, all children were treated with a single oral dose of 40 mg/kg of praziquantel.

Outcomes

The primary efficacy endpoints were cure and egg reduction rates at week six post-treatment. The cure rate was defined as the proportion of study participants not excreting schistosome eggs in stool or urine at week six after study treatment. The cure rate was computed separately for children diagnosed with *S. mansoni* or *S. haematobium* at enrollment. The egg reduction rate (ERR) was calculated from the arithmetic mean count and defined as the proportional reduction in the number of schistosome eggs in the stool or urine samples from baseline to post-treatment. The ERR was computed according to the following formula:

$$\left(1 - \lfloor \frac{arithmeticmeaneggcountaftertreatment}{arithmeticmeaneggcountatenrollment} \rfloor\right) * 100$$

Secondary efficacy endpoints included the proportion of participants cured by week six, according to the infection intensity at enrollment. The safety endpoint was the incidence of adverse events in each treatment arm. An adverse event was defined as a sign, symptom, intercurrent illness, or abnormal laboratory result that was not present at enrollment but occurred during follow-up. A serious adverse event was defined as an adverse event that was lethal, life-threatening, disabling, or required hospital admission. Within three hours of ingesting the study treatment, the clinician evaluated adverse events and classified them as mild, moderate, or severe, depending on their severity and impact on daily activities.

Statistical analysis

With 80% power and two-sided error of 5%, we calculated that 136 children would be needed in each treatment arm to detect a statistically significant difference in cure rates, assuming a cure rate of 72% with praziquantel [34] and 84% with combination therapy [35]. After an additional 14 (10%) children per treatment arm were included to allow for loss to follow-up, we computed a total sample size of 450 children (150 per treatment arm). For each treatment group, we stratified 2:1 by schistosome species (*S. mansoni* to *S. haematobium*).

Data collected from the participants were recorded on paper-based case report forms, entered into computers using MS Access, cross-checked, and analyzed with IBM SPSS for Windows version 20 (SPSS Inc, Chicago, IL) and STATA version 12.0 (StataCorp.; College Station, TX, USA) packages. Baseline characteristics and outcomes data were analyzed for all participants who received at least one dose of the study drug, whether they completed the study or not. The final analysis included participants who had received study medication, had at least one stool or urine sample examined at follow-up and were not withdrawn or excluded for any reason (available case analysis).

For each treatment group, cure rates were computed (separately for children with *S. mansoni* and *S. haematobium* at enrollment) as the proportion of randomized participants who were cured by week six post-treatment. We used Pearson's chi-square test for contingency tables to compare cure rates between treatment groups (in an available case population) and summed them up as risk ratios (RR) with 95% confidence intervals. The praziquantel-alone group was considered the control arm in all treatment

comparisons. Changes in continuous variables were examined using a one-way analysis of variance (ANOVA). The arithmetic mean egg count was calculated for all participants excreting schistosome eggs at enrolment and follow-up, and the reduction in egg count was expressed as a percentage. Two-sided p-values less than 0.05 were considered statistically significant.

RESULTS

Participant flow and baseline characteristics

Between September 11 and October 25, 2015, 1,500 children were invited to participate in the study. Overall, 822 (54.8%) children tested positive for schistosomiasis, of whom 166 (11.1%) had *S. haematobium*, 513 (34.2%) had *S. mansoni*, and 143 (9.5%) had mixed infections (i.e., both *S. haematobium* and *S. mansoni*). A total of 1074 children were excluded from the trial, including 340 (22.6%) children who had tested positive for malaria. 426 children were enrolled, of whom 135 were randomly assigned to receive praziquantel, 150 to artesunate plus sulfalene-pyrimethamine, and 141 to combination therapy (praziquantel combined with artesunate plus sulfalene-pyrimethamine). Figure 1 shows the trial profile.

The baseline characteristics assessed were balanced between treatment groups at enrolment. 319 (74.9%) children were recruited from Migori County; 222 (52.1%) were boys; 335 (78.6%) had *S. mansoni;* and 145 (34.0%) had *S. haematobium* infection. 54 (12.7%) of those enrolled had mixed schistosome infections: 17 were assigned to praziquantel alone, 20 to artesunate plus sulfalene-pyrimethamine, and 17 to combination therapy. In week six, 78 (18.3%) children were lost to follow-up and unavailable for analysis: 16 from the praziquantel alone group, 32 from the artesunate plus sulfalene-pyrimethamine group, and 30 from the combination therapy group. 348 (81.7%) children were available for analysis, of whom 119 (88.1%) were in the praziquantel alone group, 118 (78.7%), and 111 (78.7%) in the combination therapy group. Overall, 260 (77.6%) of those analyzed had *S. mansoni*, while 133 (91.7%) had *S. haematobium* at enrollment. Table 1 is a summary of the participant characteristics at baseline.

Table 1
Baseline characteristics of treatment groups

Variable	PZQ alone	As + SMP	PZQ plus As + SMP
S. mansoni infected children			
Number	106	119	110
Sex			
Male/female	56/50	64/55	51/59
Age (years)			
Mean (SD), median	12.08 (1.57), 12.0	12.03 (1.48), 12.0	11.86 (1.46), 12.0
County, N (%)			
Homabay	25 (23.6)	17 (14.3)	23 (20.9)
Migori	81 (76.4)	102 (85.7)	87 (79.1)
Body weight (kg)			
Mean (SD), median	37.1 (5.91), 37.0	37.5 (6.93), 37.4	36.3 (6.48), 36.0
Haemoglobin (g/dL)			
Mean (SD), median	12.7 (1.61), 12.9	12.8 (1.41), 12.9	12.4 (2.14), 12.7
Infection intensity, N (%)			
Light (1–99 epg)	69 (65.1)	80 (67.2)	67 (60.9)
Moderate (100–399 epg)	32(30.2)	31 (26.1)	32 (29.1)
Heavy (≥ 400epg)	5 (4.7)	8 (6.7)	11 (10.0)
S. haematobium-infected children			
Number	46	51	48
Sex			
Male/female	25/21	33/18	20/28
Age (years)			
Mean (SD), median	12.04 (1.30), 12.0	12.04 (1.50), 12.0	11.98 (1.35), 12.0
County, N (%)			
Homabay	11 (23.9)	20 (39.2)	16 (33.3)
Migori	35 (76.1)	31 (60.8)	32 (66.7)
Body weight (kg)			

Variable	PZQ alone	As + SMP	PZQ plus As + SMP
Mean (SD), median	36.7 (6.06), 35.0	36.6 (7.45), 35.0	38.2 (6.73), 37.8
Haemoglobin (g/dL)			
Mean (SD), median	12.8 (1.77), 12.8	12.5 (1.61), 12.7	12.3 (2.07), 12.9
Infection intensity, N (%)			
Light (1–49 ep/10mL)	35 (76.1)	41 (80.4)	43 (89.6)
Heavy (≥ 50 ep/10mL)	11 (23.9)	10 (19.6)	5 (10.4)

Table 1. Baseline characteristics of treatment groups

PZQ=praziquantel; As+SMP=artesunate plus sulfalene-pyrimethamine; SD=standard deviation; CI=confidence interval

Effect of treatment on S. mansoni infection

185 (71.2%) of the available 260 children were cured, while 75 (28.8%) were still parasitemic. The cure rates were 75.6%, 60.7%, and 77.8% in children who received praziquantel alone, artesunate plus sulfalene-pyrimethamine, and combination therapy, respectively. A significantly lower proportion of children in the artesunate plus sulfalene-pyrimethamine group were cured than in the praziquantel alone ($p = 0.032$). A similar number of children on combination therapy were cured as on praziquantel alone ($p = 0.732$). In all three treatment groups, cure rates decreased as infection intensity increased. However, the proportion of cured children was significantly higher in those with light-intensity *S. mansoni* infections at enrollment than those with moderate- or heavy-intensity infections. Of those not cured, 30/75 were light, 37/75 were moderate, and 8/75 were heavy-intensity infections. The egg reduction rates in week six were 80.1%, 85.0%, and 88.4% in children who had received praziquantel alone, artesunate plus sulfalene-pyrimethamine, and combination therapy, respectively. See Table 2.

Table 2
Efficacy endpoints for *S. mansoni*-infected participants

Variable	PZQ Alone	As + SP alone	PZQ plus As + SP
Cure rate at 6 weeks (%)	68/90 (75.6)	54/89 (60.7)	63/81(77.8)
[95%CI]	[66.7 to 84.5]	[50.6 to 70.8]	[68.7 to 86.9]
Risk ratio (95%CI)	1	0.80 (0.65 to 0.99)	1.02 (0.87 to 1.21)
P value	Ref	0.032	0.732
Cure rate by initial infection intensity			
Light infection (n/N (%))	50/55 (90.9)	43/61 (70.5)	44/51 (86.3)
Moderate infection (n/N (%))	15/30 (50.0)	6/21 (28.6)	15/22 (68.2)
Heavy infection (n/N (%))	3/5 (60)	5/7 (71.4)	4/8 (50.0)
Arithmetic mean EPG (95%CI)			
Before treatment	128.15 (87.63 to 168.68)	158.22 (90.09 to 226.34)	144.98 (106.97 to 182.99)
After treatment	25.47 (-6.44 to 57.38)	23.73 (13.39 to 34.08)	16.89 (7.12 to 26.65)
Egg reduction rate * (95%CI)	80.1(71.8 to 88.3)	85.0 (77.3 to 92.2)	88.4 (81.4 to 95.4)

Table 2. Efficacy endpoints for *S. mansoni*-infected participants

PZQ=praziquantel; As+SMP=artesunate plus sulfalene-pyrimethamine; Ref=reference; CI=confidence interval; *data presented as percent

Effect of treatment on S. haematobium infection

104 (78.2%) of the available 133 children were cured, while 29 (21.8%) were still parasitemic. The cure rates were 81.4%, 71.1%, and 82.2% in those who received praziquantel alone, artesunate plus sulfalene-pyrimethamine, and combination therapy, respectively. There was no significant difference in cure rates between artesunate plus sulfalene-pyrimethamine or combination therapy and the praziquantel-only group. Cure rates did not decrease with increasing infection intensity, except in the artesunate plus sulfalene-pyrimethamine group. Of those not cured, 16/29 were light, and 13/29 were heavy-intensity infections. The egg reduction rates in week six were 95.6%, 97.1%, and 97.7% in children who had received praziquantel alone, artesunate plus sulfalene-pyrimethamine, and combination therapy, respectively. See Table 3.

Table 3
Efficacy endpoints for *S. haematobium*-infected participants

Variable	PZQ Alone	As + SP alone	PZQ plus As + SP
Cure rate at 6 weeks (%) [95%CI]	35/43 (81.4) [69.8 to 93.0]	32/45 (71.1) [57.9 to 84.3]	37/45 (82.2) [71.0 to 93.4]
Risk ratio (95%CI)	1	0.87 (0.69 to 1.10)	1.01 (0.83 to 1.23)
P value	Ref	0.258	0.920
Cure rate by infection intensity			
Light infection (n/N (%))	27/33 (81.8)	31/36 (86.1)	34/41 (82.9)
Heavy infection (n/N (%))	8/10 (80.0)	1/9 (11.1)	3/4 (75)
Arithmetic mean EP/10mL (95%CI)			
Before treatment	50.22 (17.41 to 83.02)	47.25 (19.66 to 74.84)	35.10 (9.30 to 60.91)
After treatment	2.21 (-0.705 to 5.12)	1.38 (0.497 to 2.26)	0.822 (-0.099 to 1.74)
Egg reduction rate* (95%CI)	95.6 (89.7 to 100)	97.1 (92.5 to 100)	97.7 (93.5 to 100)

Table 3. Efficacy endpoints for *S. haematobium*-infected participants

PZQ=praziquantel; As+SMP=artesunate plus sulfalene-pyrimethamine; Ref=reference; CI=confidence interval; *data presented as percent

Effect of treatment on safety outcomes

Out of the 426 children enrolled, 71 (16.7%) children reported an adverse event; 25 (5.9%), 19 (4.5%), and 27 (6.3%) were among those who had received praziquantel alone, artesunate plus sulfalene-pyrimethamine, and combination therapy, respectively. Overall, 221 adverse events were reported: 61 (27.6%) in the praziquantel alone group, 58 (26.2%) in the artesunate plus sulfalene-pyrimethamine, and 112 (46.2%) in the combination therapy, respectively. All reported adverse events were mild and resolved within 24 hours after treatment. None of the reported adverse events required treatment. No serious adverse events were reported. The most common adverse events were abdominal pain, nausea, vomiting, and dizziness. See Table 4.

Table 4
Adverse events reported by the study participants.

Adverse event	PZQ alone	As + SP alone	PZQ plus As + SP	Total
Weakness of body	8	7	11	26
Nausea	9	6	14	29
Vomiting	9	8	17	34
Headache	9	8	8	25
Diarrhea	3	4	5	12
Dizziness	12	14	12	38
Body rash	4	2	4	10
Skin itchiness	3	1	4	8
Abdominal pain	4	8	27	39
Number of adverse events reported N, (%)	61 (27.6%)	58 (26.2%)	102 (46.2%)	**221**
Number of children reporting adverse events N, (%)	25 (5.9%)	19 (4.5)	27 (6.3%)	71 (16.7%)

Table 4. Adverse events reported 3h after treatment

PZQ=praziquantel; As+SMP=artesunate plus sulfalene-pyrimethamine; SD=standard deviation; CI=confidence interval

DISCUSSION

We assessed the role of single-dose combination therapy compared to praziquantel alone in treating African children with intestinal (*S. mansoni*) or urinary (*S. haematobium*) schistosomiasis. In general, cure and egg reduction rates, assessed at six weeks, were higher after treatment of *S. haematobium*-infected compared to *S. mansoni*-infected children. However, cure rates after combination therapy were not improved compared to praziquantel after treatment of children with either intestinal or urinary schistosomiasis. A single oral dose of artesunate plus sulfalene-pyrimethamine had a similar cure rate to praziquantel against urinary schistosomiasis but was inferior against intestinal schistosomiasis. Treatment of children with *S. haematobium* resulted in egg reduction rates above 90% in all three treatment groups, but these were below 90% in treating intestinal schistosomiasis. There was no difference in cure and egg reduction rates after treatment of children with mixed infections (data not shown). A similar number of children developed adverse events in the three treatment groups. However, the proportion of adverse events was significantly higher in the combination therapy group compared to the other two treatment groups. No serious adverse events were reported.

In our study site, the prevalence of schistosomiasis in school-aged children was 55%, with most children presenting with light-intensity infections, including 10% with mixed schistosome infections. A single oral dose of praziquantel cured 75.6% and 81.4% of children with *S. mansoni* and *S. haematobium*, respectively. Egg reduction rates for children with *S. mansoni* and *S. haematobium* were 80.1% and 95.6%, respectively. These cure and egg reduction rates are consistent with a meta-analysis of previous studies [36]. The WHO recommends a 90% egg reduction rate for satisfactory efficacy in treating schistosomiasis [37]. The egg reduction rates after treatment of *S. mansoni* were below 90%, indicating a reduced treatment efficacy by the WHO criteria. However, these were above 90% for *S. haematobium, suggesting* satisfactory treatment efficacy. We noted a higher cure rate in children with light-intensity *S. mansoni* infections than those with *S. haematobium*. This is consistent with the observation that cure rates after a single dose of praziquantel are usually inversely proportional to the infection intensities at baseline [8, 38, 39].

Artesunate plus sulfalene-pyrimethamine is an excellent antimalarial drug effective as a 24-hour or 3-day regime in treating uncomplicated falciparum malaria [40, 41]. In previous studies, artesunate plus sulfalene-pyrimethamine was less effective than praziquantel in curing children with *S. mansoni* (14% vs 65%, 3-day regime) or *S. haematobium* (44% vs 53%, 24-hour regime)[21, 22]. This study confirms that single-dose praziquantel is more effective than single-dose artesunate plus sulfalene-pyrimethamine for *S. mansoni.* These findings are consistent with a recent exploratory study that observed cure rates of 69% vs 80% when single doses of artesunate plus sulfalene-pyrimethamine and praziquantel were compared in the treatment of children with *S. mansoni* infection in Kenya [42]. These findings suggest a dose-response function indicating that a 3-day treatment regime using the same dose of artesunate plus sulfalene-pyrimethamine to treat malaria may be ineffective for curing *S. mansoni*. We found comparable cure rates between artesunate plus sulfalene-pyrimethamine and praziquantel against *S. haematobium* infection (71.1% vs. 81.4%). This may be attributed to the high percentage of light-intensity *S. haematobium* infection in our participants but may also suggest that the parasite is more responsive to ACT treatment tha*n S.mansoni* infection. For unclear reasons, our results contrast the study in Mali, where a similar treatment regime cured only 43.9% of children with *S. haematobium* [21].

In this study, combination therapy was as effective as praziquantel against urinary or intestinal schistosomiasis. However, for *S. haematobium*, combination therapy was associated with higher cure and egg reduction rates than *S. mansoni* infection. These differences in response rates can be explained by the high proportion of light *S. haematobium* infection intensity at enrollment and the differential sensitivity of the schistosome species to treatment. Overall, single-dose combination therapy did not improve treatment efficacy than praziquantel for either *S. mansoni* or *S. haematobium* infection. This contrasts the finding with praziquantel plus dihydroartemisinin-piperaquine vs praziquantel for *S.mansoni* [26], but is consistent with praziquantel plus artesunate-mefloquine for *S.haematobium* [27] and praziquantel plus artemether for *S. japonicum* infection [43]. It is unclear whether we would have found different cure rates if we had administered the study drugs sequentially rather than simultaneously.

The study drugs were well tolerated, and most adverse events were mild and transient. This study is consistent with previous studies that reported only mild adverse events with either praziquantel or artesunate plus sulfalene-pyrimethamine. The most frequent adverse events across the treatment groups were abdominal pain, nausea, vomiting, and dizziness, which is consistent with previous studies [39, 44–47]. However, participants in the combination therapy reported a significantly higher number of adverse events than the other two treatment arms. Drug-drug interactions from the simultaneous drug administration and the higher pill burden could explain the high risk of adverse events in the combined therapy group. The use of self-reports, limited sample size, and short duration of the study limited our ability to compare drug safety confidently. The relative safety of the drugs administered alone suggests that sequential, rather than simultaneous, administration may improve the efficacy and safety outcomes.

Our study had some limitations. Most of our participants had light-intensity infections at baseline, meaning these findings should be applied cautiously to high transmission areas since light-intensity infections are associated with high cure rates [8, 39, 40]. A double-blind design would have improved our study. However, incorporating matching placebo tablets for the drugs assessed in this study would have been impractical. We used single stool and urine samples during enrollment and follow-up for logistical reasons. Kato-Katz and urine filtration tests for schistosomiasis have low sensitivity to low-intensity infections and may have misclassified some participants. Six weeks following therapy may not have been the best time to determine Efficacy [48]. However, due to a lack of standardized treatment efficacy testing protocols, schistosomiasis treatment studies assessed efficacy three to 12 weeks post-treatment, making comparisons difficult. For this study, compliance was improved by the use of single-dose treatment. However, assessment of kidney and liver functions would have improved our drug safety evaluation.

If efficacious, safe, acceptable, and feasible, the introduction of combination therapy may shift schistosomiasis control from morbidity to transmission control and hasten the global elimination agenda. Combined therapy may be effective in malaria-free settings, in individuals with both malaria and schistosomiasis, as chemoprophylaxis for travellers to endemic areas, as a second-line treatment after praziquantel failure, and as seasonal chemoprophylaxis in malaria-endemic areas. Combination therapy is expensive and challenging to implement for mass drug administration. Additional studies are needed to validate these findings in different epidemiological settings, to assess other ACT-praziquantel combinations and drug-drug interactions, to evaluate appropriate dosing intervals, and the impact of sequential or simultaneous delivery. Other studies are needed to monitor the markers of antimalarial drug resistance and the beneficial impact of ACT implementation for malaria control on schistosomiasis control.

In conclusion, the role of combination therapy in treating and controlling schistosomiasis remains unclear. In this study, combination therapy was associated with a high risk of adverse events. It cured a high proportion of children with *S. haematobium*, but overall, it did not improve treatment efficacy for urinary or intestinal schistosomiasis. Sequential administration of praziquantel and artesunate plus sulfalene-pyrimethamine may improve the efficacy and safety outcomes.

Declarations

Ethics Approval

Ethics approval was obtained from the Scientific and Ethics Review Unit of the Kenya Medical Research Institute (SERU #3507). The trial was conducted per the Declaration of Helsinki and ICH Good Clinical Practice. The trial is registered with the Pan-African Clinical Trials Registry, PACTR202211501227743. Written informed consent was obtained from the parents/guardians, and assent from all eligible children.

Consent for publication

Not applicable

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Author Contributions

COO initiated the idea, wrote the study protocol, and sourced for funding. COO, FOR, NKM, and EMMO supervised the data collection. COO and EMMO analyzed and interpreted the data. COO drafted the manuscript. All authors contributed to the writing of the paper and approved the final version.

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Figures

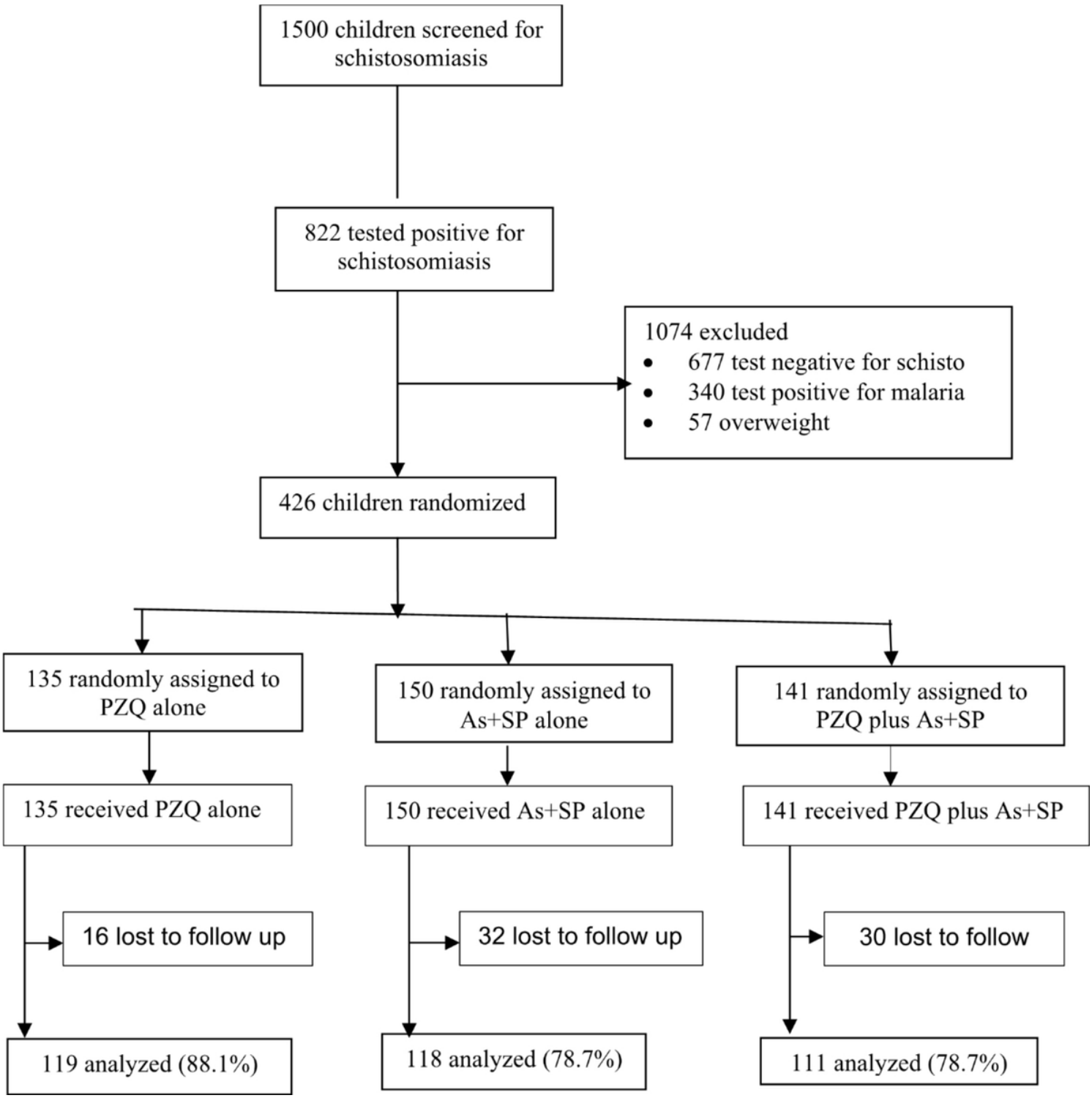

Figure 1

Trial profile