Safety and efficacy of praziquantel 40 mg/kg versus 80 mg/kg in preschool-aged children with intestinal schistosomiasis in Uganda: a 2 × 2 factorial, double-blind, placebo-controlled, phase 2 randomised trial

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Summary

Background Optimal dosing of praziquantel for schistosomiasis for children younger than 5 years is not established and some studies suggest this age group might need a higher dosing per kilogram. Our aim was to assess the safety and efficacy of a split dose of 80 mg/kg of praziquantel tablets given in a single day to preschool children versus the recommended single dose of 40 mg/kg for treatment of *Schistosoma mansoni*.

Methods We did a 2×2 factorial design, placebo-controlled, phase 2 randomised trial in Uganda. Children aged 12–47 months infected with *Schistosoma mansoni* were randomly assigned in a 1:1:1:1 ratio to receive crushed praziquantel tablets at single standard (40 mg/kg) versus double standard dosing (80 mg/kg delivered as two 40 mg/kg doses 3 hours apart) and same dose or placebo at 6 months. Coprimary outcomes were parasitological cure and egg reduction rate at 4 weeks. Secondary outcomes included antigenic cure at 4 weeks, adverse events and clinical toxicity 12 h after treatment, and key morbidity markers at 6 months and 12 months. This trial is registered with ClinicalTrials.gov (NCT03640377).

Findings Between Feb 18 and Dec 14, 2021, 354 children were randomly assigned to either praziquantel 40 mg/kg at baseline and placebo at 6 months (n=88); 40 mg/kg at baseline and 40 mg/kg at 6 months (n=86); 80 mg/kg at baseline and placebo at 6 months (m=89); or 80 mg/kg at baseline and 80 mg/kg at 6 months (n=91). 181 (51%) of 354 participants were boys. The median age was 36 months (28–42). Cure rate at 4 weeks was 67% in the 40 mg/kg group and 90% in the 80 mg/kg group (absolute difference 23% [95% CI 14–31]; p<0·001); for egg reduction rate the difference was 2% (95% CI 1–3; p<0·001) based on geometric mean and 22% (5–59; p<0·001) based on arithmetic mean. There were no differences in adverse event rates between the trial groups. At 12 months, biannual versus annual treatment reduced prevalence of faecal occult blood and 80 mg/kg dose reduced prevalence of faecal calprotectin. No severe adverse events related to the study drug were reported.

Interpretation Two 40 mg/kg doses given 3 hours apart are safe, well tolerated, and more effective in achieving parasitic cure than the current proposed single 40 mg/kg dose. Until a paediatric formulation of praziquantel is available in endemic areas, the use of crushed tablets with this dosing strategy can be recommended for young children living in *S mansoni* endemic areas. In addition, twice-a-year treatment compared with once-a-year treatment affected some intestinal morbidity markers.

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For the Alur translation of the abstract see Online for appendix 1

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Introduction

Schistosomiasis is a waterborne parasitic disease affecting over 250 million people worldwide.[1] The disease accounts for 1·64 million disability-adjusted life-years (DALYs),[2] which is probably an underestimation due to the scarcity of inclusion of key morbidities related to schistosomiasis; some of these include the effect of infection on cognitive impairment, reduced linear growth, and decreased quality of life.[3] Human transmission occurs through skin exposure to cercariae (larvae) in contaminated freshwater. Parasite eggs shed from mammalian hosts in faeces (*Schistosoma mansoni* and *Schistosoma japonicum*) and urine (*Schistosoma haematobium*) hatch into miracidia, which in turn infect intermediate snail hosts and shed cercariae. Cercariae penetrate the skin when humans come into contact with freshwater and continue the lifecycle, with adult worms developing in the mesenteric venules for intestinal species and in the venous plexus of the bladder for *S haematobium*. Among populations with limited access to sanitation and clean water sources, this

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Research in context

Evidence before this study

We searched PubMed for human studies with study designs including clinical trials, longitudinal cohort studies, and cross-sectional studies using the terms "schistosomiasis" OR "schistosoma mansoni" OR "schistosoma japonicum" OR "schistosomiasis" OR "praziquantel" in the title or abstract and restricted to paediatric studies with a time limit from Jan 1, 1979, to Nov 23, 2024. Control of schistosomiasis is promoted through the delivery of the drug praziquantel through mass drug administration programmes to school-aged children or communities that provide 40 mg/kg in most parts of the world. Children younger than 5 years were not included in the original safety and dose-finding studies for praziquantel that culminated in its approval in 1979. Two separate studies have suggested that 40 mg/kg and 60 mg/kg are inadequate doses in this age group. Currently, praziquantel tablets provided by donation programmes are the only available formulation in most endemic nations. A paediatric formulation of praziquantel has been recently developed and approved by the European Medicines Agency (2023) but is not yet widely available and will not be a donated drug. Furthermore, there has been little study of morbidity due to schistosomiasis in this age group despite studies that find high prevalence and intensity of infection across many settings.

Added value of this study

This study was the first to examine a higher dose of praziquantel (80 mg/kg) among preschool-aged children versus the 40 mg/kg recommended for older children and adults in sub-Saharan Africa for the treatment of schistosomiasis. The higher dose culminated in improved cure and egg reduction rates. In addition, this was the first study to examine the effect of different doses and frequency of dosing (twice *vs* once annually) on key morbidity outcomes in preschool-aged children. Both higher and more frequent dosing led to improvements in intestinal morbidities seen in schistosomiasis. Providing praziquantel using crushed standard tablets with juice was very well tolerated among young children and can be used in endemic areas where the paediatric formulation is not yet available. Adverse event rates between the two doses were similar. Both higher and more frequent dosing of praziquantel led to improvements in intestinal morbidities seen in schistosomiasis.

Implications of all the available evidence

This study found that a higher dose of praziquantel was needed to reach acceptable cure rates in preschool-aged children. A higher dose should be used in young children who might have lower absorptive capacity or differences in drug metabolism that might require higher dosing. Praziquantel can be given to young children using tablets delivered by mass drug administration programmes globally by crushing these until more paediatric-friendly formulations are widely available and affordable.

becomes a pervasive cycle for many individuals who depend on sources of contaminated water for daily activities.[1]

S mansoni is endemic in sub-Saharan Africa and South America, and is one of the most relevant species affecting human health. The most severe morbidities caused by *S mansoni* are due to egg entrapment in tissues, including in the liver and intestinal wall. In the liver, the human host creates granulomas around eggs, culminating in hepatic fibrosis. When these occur around the portal vessels, portal hypertension can develop and is the primary cause of death due to intestinal schistosomiasis.[1] Eggs traversing the intestinal wall for ultimate excretion in stool cause occult blood loss and contribute to anaemia.[4] This process, as well as eggs lodged in the wall, causes intestinal pathology due to their inflammatory action. Infection with *S mansoni* is also responsible for systemic inflammation, which has been linked to anaemia of inflammation as a second cause of anaemia.[1] Systemic inflammation also contributes to other schistosomiasis-related clinical morbidities, namely undernutrition,[5] decreased aerobic capacity,[6] linear growth stunting, and cognitive impairment.[7,8]

Control of schistosomiasis is promoted through the delivery of the drug praziquantel through mass drug administration programmes to school-aged children or communities at a dose of 40mg/kg. This dose is also recommended for individual treatment of schistosomiasis. However, preschool-aged children have been historically neglected in control efforts until recently.[9] Part of this neglect was due to the fact that children younger than 5 years were not included in the original safety and dose finding studies that culminated in its approval in 1979. In addition, school-based programmes, the approach used in most nations in sub-Saharan Africa, do not reach this age group and, as recently as 2022, there were no recommendations to include children aged 4 years and younger in community-based mass drug administration campaigns. This is despite the fact that young children are known to be infected.[10] Another barrier to treating this age group has been the scarcity of an age-appropriate acceptable formulation. Recently, a paediatric formulation of praziquantel has been developed and approved by the European Medicines Agency (2023) and the Access & Delivery strategy has been launched; however, this formulation is not yet widely available.[11] Furthermore, there are currently no plans to make this a donated drug once it is distributed to endemic settings, hindering its incorporation into control programmes. Therefore, mass drug administration programmes only have large tablets with a bitter taste, which can be challenging for

preschool-aged children to tolerate. However, treatment of preschool-aged children with crushed tablets under supervision is acceptable and encouraged for praziquantel delivery in the 2022 WHO guidelines.[9] The WHO-recommended single dose delivery of 40 mg/kg is based on studies of older children and adults, and has been insufficient for parasitic cure in a pharmacokinetic and pharmacodynamic study in children aged 3–8 years in Uganda.[12] Furthermore, no trials have been done in any age group to explore the potential benefit of biannual praziquantel delivery for the purpose of treating re-infections rather than repeating doses within a month of initial treatment to address potential treatment failure.[13]

Our aim was to examine the safety, tolerability, and effect of an 80 mg/kg dose of praziquantel (provided as two 40 mg/kg doses 3 h apart) versus 40 mg/kg on cure and egg reduction rates 4 weeks after treatment in preschool-aged children. We also aimed to assess the effect of the once versus twice annual dosing with the same dose as baseline, on anaemia, key nutritional and growth measures, intestinal and hepatic morbidities 12 months after baseline treatment as previously described, and the pharmacokinetics and pharmacodynamics of both baseline treatment strategies.[14]

Methods

Study design

We did a 2×2 factorial design, double-blind, placebo-controlled, phase 2 randomised trial in Uganda. The original protocol included an *S japonicum* endemic site in the Philippines but due to the COVID-19 pandemic and other delays, the site was ultimately not included. Details of the protocol have been published elsewhere[14] and the full protocol is in appendix 2. Also of note, the complex pharmacokinetic and pharmacodynamic results will be published separately. Briefly, children aged 12–47 months who were infected with *S mansoni* were randomly assigned (1:1:1:1) at baseline to receive standard dosing of praziquantel of 40 mg/kg or 80 mg/kg (split into two doses of 40 mg/kg, given 3 h apart) given as crushed tablets. Both these groups then received either the same dose as baseline or placebo at 6 months. The split dose approach was chosen to minimise side-effects and improve tolerability in young children who would otherwise need to take a large number of crushed tablets at once. Coprimary outcomes were parasitological cure and egg reduction rate at 4 weeks. The results from the groups at 6 months were also collected to examine the effect of more frequent treatment (twice *vs* once annual) on key morbidity outcomes captured at 12 months (figure 1). The study received ethical approval from the Uganda Virus Research Institute, the National Drug Authority, the Uganda National Council for Science and Technology, Rhode Island Hospital, and the London School of Hygiene & Tropical Medicine. This trial is registered with ClinicalTrials.gov (NCT03640377).

Participants

Eligibility criteria for enrolment were children aged 12–47 months, residents from five villages in the Buliisa and Hoima districts in Uganda, and were infected with the parasite *S mansoni* detected by parasitological methods (initially screened by a single urine circulating cathodic antigen [with point-of-care urine circulating cathodic antigen testing; POC-CCA, Rapid Medical Diagnostics, Pretoria, South Africa][15] and verified by positive stool with the Kato–Katz technique, averaged from two stool samples taken on consecutive days), for whom parental consent for participation was obtained, and who did not have severe anaemia (haemoglobin <7·0 g/dL), severe wasting (weight-for-age Z score of less than −3·0), or severe acute or chronic illness.

Randomisation and masking

At trial enrolment, each participant was assigned a unique study identification number. Study identification numbers were randomised into one of four groups by the trial statistician using a random number generator with randomly permuted block sizes. Participants were randomly assigned in a 1:1:1:1 ratio to receive praziquantel at single standard (40 mg/kg) versus two standard doses of 40 mg/kg 3 h apart (80 mg/kg) at baseline followed by the same dose or placebo at 6 months for each group (figure 1). A 40 mg/kg dose at either baseline or 6 months was given as a first dose of 40 mg/kg followed by placebo 3 h later as crushed tablets. A placebo dose at 6 months was given as a first dose of placebo followed by a second dose of placebo 3 h later. Bottles (four per participant) were pre-filled by a pharmacist with 600 mg tablets and contained either active study drug (praziquantel, Macleods Pharmaceuticals, Mumbai, India) or placebo matched for colour, size, and shape (Tedor Pharmaceuticals, Cumberland, RI, USA). Bottles were prepared by the research pharmacy (Uganda Virus Research Institute–International AIDS Vaccine Initiative HIV Vaccine Programme), who were not otherwise involved with the study, and labelled with the corresponding participant identification number. Based on the tablets, the child's dose was rounded to the closest dose available in 150 mg increments (150 mg per quarter tablet). Study staff administering were not aware of tablet allocation. Of note, the trial was quasi double-masked as the placebo was not matched for taste, which is often noticed by children and their caregivers upon dosing. All data were entered in electronic tablets in RedCap.

See Online for appendix 2

Outcomes

Coprimary outcomes were parasitological cure (no eggs observed at 4 weeks) and egg reduction rate at 4 weeks comparing the effect of 40 mg/kg versus 80 mg/kg delivered at baseline. Secondary outcomes included: (1)

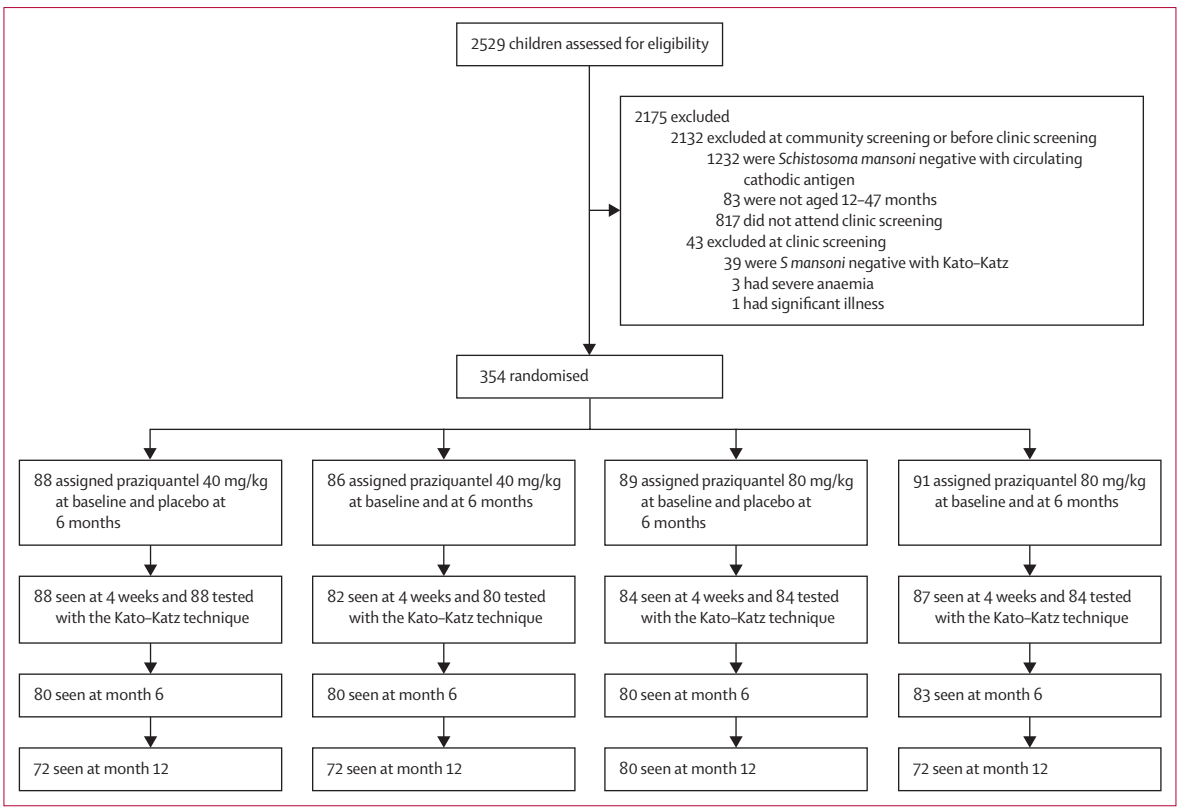

Figure 1: **Trial profile**

antigenic cure and absence of circulating anodic antigen (CAA) detected by upconverting particle-lateral flow with a cutoff of 2 pg/mL[16] at 4 weeks; (2) solicited adverse events for 12 h after dosing; (3) clinical toxicity as captured by complete blood count before dosing and 6–8 h after dosing (Poch 1000 Haematology Analyzer, Sysmex, Irvine, CA, USA), and renal and liver toxicity as captured by chemistry and liver function tests (Piccolo Express, Abbott Laboratories, Orlando, FL, USA); (4) anaemia (haemoglobin <11·0 g/dL) and haemoglobin levels at 6 months and 12 months; (5) anthropometric measures (height-for-age, weight-for-age, and weight-for-height Z scores as determined by WHO Anthro) at 6 months and 12 months; (6) intestinal morbidity captured by point-of-care tests for stool occult blood (eg, faecal occult blood test) and calprotectin (Quantum Blue, Alpha Laboratories, Hampshire, UK) at 6 months and 12 months (calprotectin >50 µg/g was considered positive); and (7) schistosomiasis-related liver fibrosis captured by ultrasound at baseline and at 12 months.[17]

Statistical analysis

The sample size of 600 was intended to allow examination of potentially different doses needed for the two different species (*S mansoni* and *S japonicum*) prevalent in Uganda and the Philippines, respectively. The target sample size of N=300 per site was informed by data from Uganda, which estimated cure rates for children aged 3–8 years infected with *S mansoni* of 70% for praziquantel 40 mg/kg and 82% for praziquantel 60 mg/kg, as described in the published protocol paper.[15] However, due to the onset of the COVID-19 pandemic and subsequent delays and restrictions, it was not possible to include a contemporaneous set of participants from the Philippines. Using a two-sided 5% significance level, approximately 173 children per trial group were required for 80% power to detect the specified difference in cure rate (70% *vs* 82%) at 4 weeks between the trial groups.

Analysis was done by intention to treat. Participant characteristics were summarised by trial group, as frequency and median (IQR). For outcomes assessed at 4 weeks and 6 months, the effect of baseline dosage (40 mg/kg *vs* 80 mg/kg) irrespective of dosing frequency was determined, as participants only differed in their dosing frequency from 6 months onwards. For outcomes assessed at 12 months, the effect of dosage and dosing frequency were both assessed. For binary outcomes, the number and proportion were calculated by trial group, and binary regression was used to estimate the absolute difference and corresponding 95% CI. Egg reduction rate was calculated in two ways, based on geometric mean and arithmetic mean.[16] A bootstrap resampling approach with 10 000 iterations was used to estimate 95% CIs. Adverse events (total, and by type) were summarised by trial group;

no formal statistical comparisons were done. Bone marrow, renal, and liver toxicity were defined based on levels increasing above toxicity thresholds from before treatment to 6–8 h after treatment for alanine transaminase (>36 units per L), aspartate aminotransferase (>50 units per L for participants aged <36 months, >60 units per L for participants aged ≥36 months), creatinine (>0·7 mg/dL), and bilirubin (>1·0 mg/dL). Haemoglobin and anthropometry outcomes were compared between trial groups using linear regression, adjusting for baseline measures of the corresponding outcome. For 12-month outcomes, the effects of both dosage (40 mg/kg *vs* 80 mg/kg) and frequency (biannual *vs* annual) were assessed, and interaction terms were included in regression models to determine whether effects of dosage differed by dosing frequency. Analyses were done in Stata version 17 and GraphPad version 10.0.0.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Total (n=354)	Group 1: praziquantel 40 mg/kg at baseline and placebo at 6 months (n=88)	Group 2: praziquantel 40 mg/kg at baseline and at 6 months (n=86)	Group 3: praziquantel 80 mg/kg at baseline and placebo at 6 months (n=89)	Group 4: praziquantel 80 mg/kg at baseline and at 6 months (n=91)
Age, months	36 (28 to 42)	37 (30 to 43)	36 (24 to 42)	36 (29 to 41)	35 (27 to 42)
Sex					
Male	181 (51%)	48 (55%)	51 (59%)	42 (47%)	40 (44%)
Female	173 (49%)	40 (45%)	35 (41%)	47 (53%)	51 (56%)
Weight-for-age Z score*	−0·0 (1·0)	−0·0 (1·1)	−0·1 (1·0)	−0·0 (1·1)	0·1 (1·0)
Height-for-age Z score*	−0·7 (1·5)	−0·7 (1·6)	−0·8 (1·5)	−0·7 (1·5)	−0·6 (1·5)
Weight-for-height Z score*	0·5 (0·9)	0·5 (1·0)	0·5 (0·9)	0·5 (0·9)	0·6 (0·8)
Haemoglobin, g/dL	10·7 (1·1)	10·8 (1·2)	10·8 (0·9)	10·6 (1·1)	10·7 (1·1)
S mansoni eggs per g	72 (24 to 258)	75 (24 to 333)	57 (24 to 180)	72 (24 to 282)	84 (18 to 252)
S mansoni eggs per g, WHO intensity category					
Light	201 (57%)	47 (53%)	55 (64%)	47 (53%)	52 (57%)
Moderate	85 (24%)	23 (26%)	16 (19%)	24 (27%)	22 (24%)
Heavy	68 (19%)	18 (20%)	15 (17%)	18 (20%)	17 (19%)
Urine circulating anodic antigen, pg/mL	165 (49 to 719)	159 (64 to 760)	193 (63 to 843)	184 (28 to 691)	144 (34 to 554)
Presence of faecal occult blood	88 (27%)	20 (25%)	21 (27%)	26 (32%)	21 (26%)
Positive malaria result on rapid diagnostic test	56 (16%)	12 (14%)	12 (14%)	18 (20%)	14 (15%)
Highest educational attainment of father†					
None	213 (60%)	54 (61%)	57 (67%)	50 (56%)	52 (57%)
Primary	130 (37%)	31 (35%)	26 (31%)	36 (40%)	37 (41%)
Secondary	10 (3%)	3 (3%)	2 (2%)	3 (3%)	2 (2%)
Highest educational attainment of mother‡					
None	210 (61%)	58 (67%)	53 (62%)	49 (56%)	50 (57%)
Primary	126 (36%)	26 (30%)	31 (36%)	35 (40%)	34 (39%)
Secondary or tertiary	10 (3%)	3 (3%)	1 (1%)	3 (3%)	3 (3%)
Participants with household electricity§	4 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Household toilet§					
None	65 (18%)	20 (23%)	14 (16%)	18 (20%)	13 (14%)
Shared	242 (69%)	57 (65%)	57 (67%)	61 (68%)	67 (74%)
Private	46 (13%)	11 (13%)	14 (16%)	10 (11%)	11 (12%)
Participants with access to lake for drinking water§	328 (93%)	83 (94%)	79 (92%)	82 (92%)	84 (92%)
Participants with faecal calprotectin >50 µg/g	246 (69%)	59 (67%)	63 (73%)	59 (66%)	65 (71%)

Data are median (IQR), n (%), or mean (SD). *Anthropometry measures missing for five children (one in group 1 and four in group 2). †Father's education missing for one child in group 2. ‡Mother's education missing for eight children (one in group 1, one in group 2, two in group 3, and four in group 4). §Data for household electricity, household toilet, and drinking water source missing for one child in group 2.

Table 1: **Baseline characteristics**

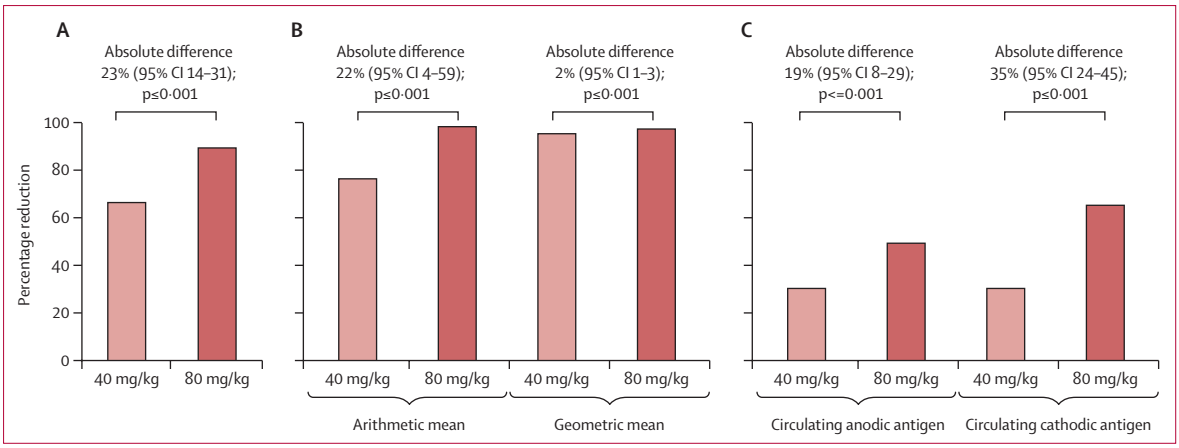

Figure 2: **Primary and secondary parasitic clearance outcomes comparing baseline dosage of 80 mg/kg *vs* 40 mg/kg 4 weeks after treatment**
(A) Parasitic cure rates. (B) Egg reduction rates. (C) Antigenic cure (with circulating cathodic antigen and circulating anodic antigen testing).

	Praziquantel 40 mg/kg at baseline	Praziquantel 80 mg/kg at baseline	Absolute difference (95% CI)	p value
Primary outcomes				
Cure rate based on Kato–Katz technique	113/168 (67%)	151/168 (90%)	23% (14 to 31)	<0·001
Egg reduction rate based on geometric mean (95% CI)	96% (95 to 97)	98% (98 to 99%)	2% (1 to 3)	<0·001
Egg reduction rate based on arithmetic mean (95% CI)	77% (40 to 94)	99% (97 to >99%)	22% (5 to 59)	<0·001
Secondary outcomes				
Cure rate based on CAA	51/163 (31%)	78/156 (50%)	19% (8 to 29)	0·001
CAA result, geometric mean (95% CI)	17 (12 to 24)	7 (5 to 10)	0·4 (0·3 to 0·7)*	0·001
Cure rate based on CCA	50/162 (31%)	103/157 (66%)	35% (24 to 45)	<0·001

Data are n/N (%), unless otherwise specified. CCA=circulating anodic antigen. CAA=circulating anodic antigen.
*Geometric mean ratio (95% CI).

Table 2: **Effect of praziquantel 80 mg/kg *vs* 40 mg/kg on primary outcomes and antigenic endpoints at 4 weeks**

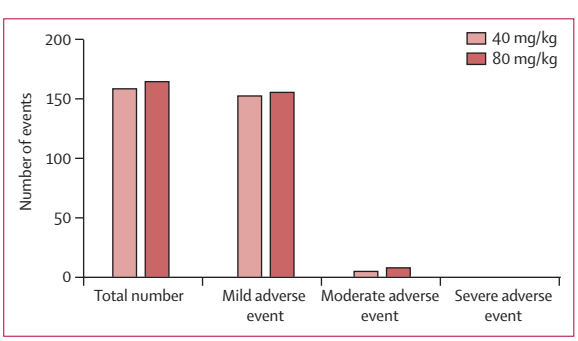

Figure 3: **Global summary of solicited adverse events captured during continuous clinical monitoring for 12 h after praziquantel administration at baseline**

Results

From Feb 18 to Dec 14, 2021, 2529 children were initially screened for eligibility by CCA test (figure 1). Recruitment started on April 21, 2021 with the final close-out visit on March 11, 2023. 354 participants were assigned to either praziquantel 40 mg/kg at baseline and placebo at 6 months (n=88); 40 mg/kg at baseline and 40 mg/kg at 6 months (n=86); 80 mg/kg at baseline and placebo at 6 months (m=89); or 80 mg/kg at baseline and 80 mg/kg at 6 months (n=91). Positive CCA results were then confirmed by stool Kato–Katz for enrolment. The median age was 36 months, and 181 (51%) of 354 participants were boys. Key baseline characteristics were balanced (table 1).

Primary outcome results comparing 40 mg/kg versus 80 mg/kg (as two 40 mg/kg doses) were recorded at 4 weeks (plus or minus 7 days) for 336 (95%) of 354 children. Cure rates were 67% in the 40 mg/kg at baseline group and 90% in the 80 mg/kg at baseline group, with an absolute cure rate difference of 23% (95% CI 14–31). Egg reduction rates based on geometric means were 96% for the 40 mg/kg at baseline group and 98% for the 80 mg/kg at baseline group, whereas egg reduction rates based on arithmetic means were 77% for the 40 mg/kg at baseline group and 99% for the 80 mg/kg at baseline group. Absolute differences in egg reduction rate were 22% (95% CI 5–59) for arithmetic and 2% (95% CI 1–3) for geometric mean (figure 2; table 2).

There were two serious adverse events reported, both unrelated to trial interventions: a child death due to burning and one hospitalisation due to severe malaria. Individual adverse events during the 12-h monitoring following praziquantel at baseline are summarised in figure 3. The most common adverse event for both groups was diarrhoea (33%), followed by abdominal pain (15%) and drowsiness (14%), which are commonly reported in older children and adults after praziquantel intake at similar rates, with no differences between baseline treatment doses (table 3). Increases in laboratory measures of bone marrow, renal, and liver toxicity from before treatment to 12 h after treatment were rare and similar between trial groups (appendix 2).

Results from antigenic cure outcomes at week 4 aligned with parasitological outcomes (primary endpoints) are

provided (figure 2; table 2). Absolute differences in circulating anodic antigen and CCA cure at the 4-week follow-up were 19% (95% CI 8–29) in the 80 mg/kg group and 35% (24–45) in the 40 mg/kg group. The geometric mean of circulating anodic antigen at 4 weeks was 2·4-fold lower (95% CI 1·5–3·9) in the 80 mg/kg group compared with the 40 mg/kg group.

Morbidity outcomes at 6 months were evaluated by baseline dosage (80 mg/kg *vs* 40 mg/kg). Morbidity measures at 12 months considered both baseline dosage and frequency (same dosage *vs* placebo delivered at the 6-month visit); there was no evidence of an interaction between the two interventions (dosage and frequency). With respect to dose provided at baseline, there were no significant differences in haemoglobin or nutritional status (anthropometry) at 6 months or 12 months between trial dosage groups irrespective of dosing frequency (tables 4, 5). There were no differences in frequency of calprotectin or faecal occult blood detection at 6 months based on baseline dose provided (table 4). However, at 12 months, calprotectin was less frequently detected among those who received 80 mg/kg compared with 40 mg/kg at baseline regardless of dosing frequency (adjusted mean difference –18% [95% CI –31 to –5%]). Faecal occult blood was less frequently detected among participants receiving twice yearly praziquantel compared with those who received praziquantel at baseline only, regardless of the 40 mg/kg or 80 mg/kg doses (adjusted mean difference –9% [95% CI –19 to 0]; table 5).

At baseline, seven (2%) of 347 children had ultrasound findings consistent with periportal fibrosis (Pattern C as per WHO staging of liver fibrosis)[1] and 58 (17%) had periportal thickening, suggestive of incipient fibrosis as reported elsewhere.[17] At the 12-month follow-up, only one child had persistent fibrosis.

	Praziquantel 40 mg/kg at baseline				Praziquantel 80 mg/kg at baseline			
	Any event	Total reported events*	Total mild events	Total moderate events†	Any event	Total reported events*	Total mild events	Total moderate events†
Headache	2 (1%)	2	2	0	0	0	0	0
Malaise	6 (3%)	7	6	1	5 (3%)	6	5	1
Drowsiness	25 (14%)	26	22	4	26 (14%)	27	18	9
Abdominal pain	26 (15%)	28	28	0	29 (16%)	31	30	1
Diarrhoea	57 (33%)	57	57	0	51 (28%)	51	51	0
Nausea	11 (6%)	12	12	0	15 (8%)	16	15	1
Vomiting	13 (7%)	14	13	1	17 (9%)	19	17	2
Shortness of breath	0	0	0	0	0	0	0	0
Dizziness	0	0	0	0	0	0	0	0
Rash	0	0	0	0	3 (2%)	3	3	0
Fever	13 (7%)	13	13	0	12 (7%)	12	10	2

Data are n (%) or n. Data collected during clinical monitoring for 12 h after praziquantel administration at baseline. *Some participants reported two separate instances of a particular event during monitoring. †There were no severe adverse events.

Table 3: **Summary of solicited individual adverse events**

	Praziquantel 40 mg/kg at baseline	Praziquantel 80 mg/kg at baseline	Adjusted difference* (95% CI)	p value
Haemoglobin, g/dL	11·2 (2·4)	11·2 (1·9)	0·08 (–0·39 to 0·55)	0·75
Weight-for-age Z score	–0·18 (0·98)	–0·07 (0·96)	0·03 (–0·05 to 0·10)	0·49
Height-for-age Z score	–0·73 (1·41)	–0·67 (1·40)	0·00 (–0·10 to 0·11)	0·96
Weight-for-height Z score	0·35 (0·89)	0·46 (0·89)	0·05 (–0·08 to 0·18)	0·48
Faecal calprotectin >50 µg/g	64/154 (42%)	63/156 (40%)	–1% (–12 to 10%)	0·83
Faecal occult blood	34/154 (22%)	23/155 (15%)	–7% (–16 to 1%)	0·10

Data are mean (SD) or n/N (%), unless otherwise specified. *Adjusted for corresponding baseline measure.

Table 4: **Effect of praziquantel 80 mg/kg versus 40 mg/kg on haemoglobin, anthropometry, and biomarkers of inflammation and enteropathy at 6 months**

Discussion

In this trial, treatment of preschool-aged children with intestinal schistosomiasis with praziquantel 80 mg/kg (given two doses of 40 mg/kg 3 h part) compared with the standard 40 mg/kg dose of praziquantel led to a significantly higher parasitic clearance at the 4-week follow-up with an excellent safety profile. Furthermore, the higher dose had significantly higher antigenic cure. Since this is a more sensitive method that better reflects worm burden, it is a more accurate assessment of worm clearance. Improvement in some key schistosomiasis-morbidity outcomes, such as intestinal morbidity, was shown in children receiving twice yearly compared with once yearly praziquantel (faecal occult blood) and receiving 80 mg/kg versus 40 mg/kg (calprotectin). Together, results from this trial support the approach of safe and effective dosing of 80 mg/kg and improved measures of morbidity when children receive twice-yearly versus once yearly praziquantel treatment for *S mansoni*.

Identifying the optimal dose of praziquantel has been a long-standing key gap for the treatment of preschool-aged children with intestinal schistosomiasis. Few randomised controlled trials have explored the optimal praziquantel dosing for parasitic cure in preschool-aged children, with heterogeneous study designs and doses tested.[13,18,19] However, the safety of praziquantel in this age group has been well established for all types of schistosomiasis, including the safe delivery of crushed tablets at a dose of 40 mg/kg.[20–23] Results from our trial, administering praziquantel crushed tablets, support these findings and provide important data on the safety of the 80 mg/kg dose when delivered as repeated 40 mg/kg doses in a single day. Crushed tablets, provided with juice, were well tolerated in this setting.

Historically, a second major gap has been the availability of a paediatric-friendly formulation. Different formulations have been tested for the treatment of schistosomiasis in young children, including a syrup formulation of praziquantel, which was impractical for mass drug administration programmes and also raised

	Annual praziquantel	Twice yearly praziquantel	Adjusted difference (95% CI)*	p value	40 mg/kg praziquantel	80 mg/kg praziquantel	Adjusted difference (95% CI)*	p value
Haemoglobin, (g/dL)	10·3 (1·4)	10·4 (1·3)	0·02 (–0·27 to 0·31)	0·87	10·3 (1·5)	10·4 (1·2)	0·14 (–0·15 to 0·43)	0·33
Weight-for-age Z score	–0·2 (0·9)	–0·2 (0·9)	0·00 (–0·07 to 0·07)	0·99	–0·3 (1·0)	–0·2 (0·9)	–0·01 (–0·08 to 0·07)	0·88
Height-for-age Z score	–0·7 (1·3)	–0·9 (1·3)	0·05 (–0·18 to 0·07)	0·40	–0·8 (1·4)	–0·7 (1·3)	0·04 (–0·08 to 0·17)	0·52
Weight-for-height Z score	0·3 (0·9)	0·4 (0·9)	0·06 (–0·09 to 0·20)	0·42	0·3 (0·9)	0·4 (0·9)	0·02 (–0·17 to 0·12)	0·74
Faecal calprotectin >50 µg/g	36/100 (36%)	38/99 (38%)	1% (–12 to 15)	0·83	45/98 (46%)	29/101 (29%)	–18% (–31 to –5)	0·01
Faecal occult blood	27/107 (25%)	14/107 (13%)	–9% (–19 to 0)	0·05	18 (17%)	23 (21%)	1% (–9 to 10)	0·88

Data are mean (SD) or n/N (%), unless otherwise stated. There was no evidence of effect modification between treatment frequency and treatment dosing (p values for effect modification 0·77 for haemoglobin, 0·34 for weight-for-age Z score, 0·44 for height-for-age Z score, 0·89 for weight-for-height Z score, 0·57 for calprotectin, and 0·37 for faecal occult blood). *Adjusted mean differences obtained from linear regression model controlling for corresponding baseline measure and including main effect terms for praziquantel frequency and dosing.

Table 5: **Effect of praziquantel frequency (twice yearly *vs* annual) and dosing (80 mg/kg *vs* 40 mg/kg) on haemoglobin, anthropometry, and biomarkers of inflammation and enteropathy at 12 months**

safe storage concerns.[24] A recent randomised controlled trial has been done in Côte d'Ivoire and Kenya with the new paediatric dispersible formulation, which was approved by the European Medicines Agency in 2023.[25] However, currently praziquantel tablets provided by the Merck donation programme remain the only available formulation in endemic nations.[25] The new paediatric dispersible compound is a mono-enantiomeric formulation, different from the commercially available praziquantel racemate used in our trial. There will remain a reliance on crushed tablets for treatment until the paediatric formulation is fully rolled out and adopted by programmes in endemic countries. In addition, the paediatric formulation will not be a donated drug.[11] The overall tolerability of crushed tablets in young children in our trial is reassuring and represents an excellent approach until the paediatric formulation is more widely available and affordable to countries.[11,21,26] Even when available, both formulations will likely coexist across endemic settings, supporting the need for clear guidance on the optimal dosing for crushed tablets.

Both our trial and other studies in preschool-aged children have consistently found low cure rates when praziquantel was given at the recommended dose of 40 mg/kg. In a dose-escalating trial of single doses of 20, 40, and 60 mg/kg of praziquantel in preschool-aged children with intestinal schistosomiasis in Côte d'Ivoire, cure rates of 62–71% were found at 4 weeks after treatment.[18] Low cure rates (42%) of praziquantel given at 40 mg/kg as a single dose were also found in a cross-sectional study in Uganda, particularly in previously treated children.[27] The only pharmacokinetic or pharmacodynamic study done in young children infected with *S mansoni* revealed a concerning underdosing at both 40 mg/kg and 60 mg/kg of praziquantel, given as a single dose, with further modelling providing evidence on superior clearance when the dose increased to 80 mg/kg.[12] Some of the reasons for this could be a markedly decreased drug absorption in this age group due to intestinal morbidity skewed towards inflammation and subsequent under-absorption. Furthermore, there could be differences in drug activity such as an enhanced first pass drug metabolism, or other reasons, which forthcoming pharmacokinetic or pharmacodynamic studies from this trial might help to elucidate. Our trial provides clear evidence of improved cure with the 80 mg/kg dose treatment strategy while assessing the safety and feasibility of giving two doses of 40 mg/kg of praziquantel 3 h apart. This approach can be applied for both mass drug administration and individual clinical treatment.

The secondary outcomes from this trial included more refined diagnostic modalities to define parasitic cure. The circulating anodic antigen is the most sensitive diagnostic assay available for any type of *Schistosoma* infection, capable of detecting infections with a single worm pair.[28,29] Antigenic clearance at 4 weeks was significantly higher in the 80 mg/kg dose group, despite being low in both groups. Similar results of poor antigenic clearance were also found in a recent trial in school-aged children done in Côte d'Ivoire comparing standard single dose to repeated dosing at 2-week intervals.[30] Some possible explanations for a limited antigenic clearance include impaired efficacy of praziquantel for larval stages that might continue to mature during the 4-week interval, needing follow-up retreatment. This effect has been previously observed in other studies in Uganda.[12]

In this trial, we also looked at the effect of twice yearly versus once yearly treatment of praziquantel, regardless of the baseline dose provided. Twice annual dosing regardless of dose provided was associated with a significant decrease in faecal occult blood while the higher dose (80 mg/kg) was associated with a significant decrease in calprotectin after 1 year regardless of frequency, although there were no effects on haemoglobin or anthropometry. The sustained effect of the higher baseline treatment in morbidity reduction after 1 year has health implications for children living in this setting, where scarce access to adequate safe water sources leads to regular parasite re-infection.[1] Furthermore, in low-resource settings, a major barrier

remains delivery of therapeutics in hard-to-reach populations such that use of a higher dose during these infrequent interactions with the health-care system is an efficient approach. With respect to dosing frequency, the use of repeated praziquantel dosing has been reported in a meta-analysis, but has not yet been adopted in endemic countries.[31] Findings from this trial support a higher per kilogram dose for this age group and suggest that biannual dosing might reduce key intestinal morbidities. A previous trial in Uganda comparing single dose and a repeated dose 2 weeks later found no significant differences in egg reduction or cure rates at 8 months.[13] In this trial, we followed up children for 12 months. Our results strongly support adoption of a higher per kilogram dose in preschool-aged children globally to improve parasite clearance and mitigate morbidity, rather than an over-emphasis on control of high intensity infections, as recommended by WHO.[9] Treating preschool-aged children will necessitate community-based treatment for mass drug administration rather than an over-reliance on school-based treatment employed in many endemic regions in sub-Saharan Africa. School-based treatment is efficient given the difficulties involved in accessing multiple remote communities; however, this approach misses vulnerable preschool-aged children as well as older adolescents and adults who have clinically significant morbidity without treatment and continue to contaminate the environment, perpetuating the lifecycle.

Optimal dosing for preschool-aged children was never evaluated during initial studies, but was carried out among participants aged 5 years or older. An examination of the longitudinal effect of different doses and frequency of dosing with four groups on key morbidity outcomes is an additional strength. Studies have not examined a second dose given at a time when re-infections have occurred in many children as is commonly the case in endemic areas. The major limitation is a relatively short period of follow-up of 1 year only, during which potential effect on linear growth and nutritional parameters and anaemia might not be realised. Viral and bacterial intestinal co-infections were not measured, and this might have affected our analysis. The generalisability of our findings to *S japonicum* infections is also limited by the inability to include data from the second site in the Philippines as initially planned.

For preschool-aged children with intestinal schistosomiasis, 80 mg/kg of crushed praziquantel given as two separate doses 3 h apart is safe, well tolerated, and significantly more effective than the current proposed single 40 mg/kg dose for parasite clearance. This superior dosing strategy is programmatically feasible as it delivers the drug within the same day and can be recommended for young children living in *S mansoni* endemic areas.

Contributors

ALB and JFF are responsible for conceptualisation, funding acquisition, investigation, methodology, and project administration. ELW contributed to the methodology, data curation, formal analysis, and supervision. ALB did the original draft with input from AEd, JFF, and ELW. AEl, NBK, and EM reviewed and edited the draft. All authors contributed to the writing. HW, GKA, PAM, and MA were responsible for resources, validation, and visualisation with input from RN, JN, GvD, and PC. VA, SM, and SP contributed to the validation and writing of the review. RN, AEd, and ELW were responsible for data curation. ALB, JFF, AEl, RN, SC, and ELW have directly accessed and verified the underlying data reported in this Article. All authors had access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The trial can share data with existing neglected tropical disease databases or portals, such as the Expanded Special Project for Elimination of Neglected Tropical Diseases and the Eukaryotes Pathogen Database, to make the data publicly accessible. In addition, the investigators will ensure that the proposed projects' data be findable, accessible, interoperable, and reusable, sharing data to enhance the rigour and reproducibility of research results and secondary use as per the data sharing guidelines of the US National Institutes of Health. Data from the trial will be made available to interested investigators following institutional review board approval to provide these de-identified data. Specifically, after the research dataset has been cleaned, finalised, and all identifiers removed, the principal investigators will provide timely release and sharing of the final research data for use by other researchers. In addition, this study will generate samples collected from young children. Upon discussion with the principal investigators and based on the availability of samples, residual stored samples might be shared following institutional review board approval to provide these de-identified samples to interested researchers. Ethical approval for this will be obtained from participants.

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