RESEARCH ARTICLE

Effect of intensive versus standard anthelminthic treatment on growth and cognition among children living in a high *Schistosoma mansoni* transmission setting: a study nested within a cluster-randomised trial

[version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Schistosomiasis and other worm infections have been associated with growth and cognitive impairments; however, whether treatment reverses these effects is uncertain. Moreover, mechanisms linking these infections to cognition are not clear. We aimed to compare growth and cognitive benefits of intensive versus standard anthelminthic treatment in school-aged-children and explore processes that might be involved. We hypothesised that intensive treatment would have greater benefits than standard treatment.
Methods: The study was nested within a cluster-randomised trial of either quarterly single-dose praziquantel of 40mg/kg to treat *Schistosoma mansoni* plus triple dose albendazole of 400mg (intensive treatment) to treat soil-transmitted worms including *Ascaris lumbricoides*, hookworm and *Trichuris trichiura*, or annual single-dose praziquantel 40mg/kg plus six-monthly single-dose albendazole 400mg (standard treatment) conducted in the Koome islands in Lake Victoria, Uganda (ISRCTN47196031). Children aged 5-9 years (N=384) were assessed on primary outcomes (height, weight and eight measures of cognitive ability), worm infection, and proposed mediators of worm effects (cytokines, iron status, physical activity) at

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one year (intensive n=85; standard n=64) and at two years (intensive n=158; standard n=128) of the intervention. Linear regression was used to examine intervention effects on height, weight and cognitive performance. Linear mixed effects models were used to study changes in growth and cognitive performance between the two arms across the two time-points.
Results: Intensive treatment resulted in lower *Schistosoma mansoni* prevalence than standard treatment (at one year, 41% versus 70%; adjusted odds ratio (aOR)=0.24, 95% CI: 0.12, 0.49; at two years, 39% versus 69%; aOR=0.27; 95% CI: 0.16, 0.43) but there were no significant differences in growth and cognitive outcomes at either time-point. Worms and treatment showed no consistent association with the proposed mediators of worm effects.
Conclusion: Reduction in worm burden may not improve growth and cognitive outcomes in high *S. mansoni* transmission settings. Possible implications are discussed.

Keywords
growth, cognitive performance, anthelminthic treatment, praziquantel, albendazole, Schistosoma mansoni

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Introduction

Many of the world's children still battle with disease, poverty and malnutrition which impact negatively on their developmental potential[1]. Parasitic worm infections affect about 90 million children (the majority from sub-Saharan Africa)[2] in whom they have been associated with impaired growth and cognition[3–10]. Of all children living in Lake Victoria islands, 80% are infected with *Schistosoma mansoni* or soil transmitted worms[11] and may therefore be at risk for growth and cognitive impairment.

However, findings of studies on worms and cognition lack consistency and are inconclusive with regard to which cognitive functions are affected. While some studies have reported impairment of different cognitive functions to be associated with worm infections, other studies have not found significant associations[12]. These discrepancies could be due to differences or flaws in study designs including unmeasured confounding by, for example, education, socio-economic status, nutrition and health related factors (in observational studies), as well as short follow-up periods, and modest sample size[12]. Furthermore, it may be that worms affect a wide range of structurally, functionally, or developmentally related cognitive skills, and the divergence between study findings may partly be because different studies have examined different outcomes. Studies suggest that attention (identified as ability on Picture Search[7]); working memory (as measured by Verbal Fluency and Digit Span Forward[4,7]); inhibition (as measured by the Stroop task[8]); and general cognitive ability (processing speed)[3,5] may be selectively impaired. These cognitive functions represent high order skills or executive functions that govern lower level cognitive processes[13,14] and are critical for children's behaviour and learning[15–17]. If worm infections cause impairment of these functions, this would have implications for children's educational and employment potential and success in life.

There has been much advocacy for mass de-worming, often based on the assumption that this will improve growth, cognitive ability and school performance. However, this assumption is largely extrapolated from data from observational studies. There is potential confounding driven by associations between worm infections and many other exposures; interventional studies are therefore key to determining specific effects of worm infections and the benefits of anthelminthic treatment. However, treatment trials to date have been inconclusive regarding benefits for growth and cognitive outcomes[12,18,19]. Indeed, the debate on whether worms actually impair cognitive function has become intense. This prompted a reanalysis of data from one of the previous trials which suggested that there had been over-reporting of treatment effects on academic performance in the original trial report[19]. Three Cochrane systematic reviews highlight the divergence in findings and that many studies have reported weak or no effects of deworming interventions on growth and cognitive function[20–22]. However, it is important to note that the Cochrane reviews focus on soil transmitted helminths and the majority of studies were rated as of poor or moderate quality.

The Entebbe Mother and Baby Study, one of the few randomised trials of anthelminthic treatment conducted to date, did not find significant effects of childhood anthelminthic treatment on cognitive functions[23] but there was an unexpectedly low background prevalence of worms among the children in the trial. Similarly, treatment of maternal helminths during pregnancy had no effect on cognitive functions in their infants[24] although there were some observational associations between maternal worms and measures of cognitive ability at 15 months[24]. Thus, while it is plausible that worms and their treatment may influence growth and cognitive outcomes, this is yet to be established.

Mechanisms by which worms may affect cognitive function have been hypothesized. These include anaemia and malnutrition, as well as more specific pathways such as changes in host immune responses leading to increased levels of circulating cytokines such as tumour necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-10[25–27]. Both nutritional and immunological pathways might impact negatively on availability of dopamine (a vital neurotransmitter), thereby interfering with cognitive processes. Additionally, these mediators are believed to cause malaise, which negatively affects the child's ability to play and learn from their environment, and to perform on cognitive assessments. These pathways have, however, not yet been examined.

We therefore took the opportunity of a community-based, cluster-randomised trial of intensive versus standard anthelminthic treatment, conducted in a high *Schistosoma mansoni* transmission setting[11], to investigate the impact of intensive versus standard anthelminthic treatment, particularly for schistosomiasis, on growth and cognitive outcomes. We also explored some of the pathways by which worms may impair cognition (Figure 1). We investigated associations of worm infection and their treatment with iron and inflammatory cytokines, and whether these parameters are in turn associated with the cognitive outcomes measured in this study. We aimed to test the hypothesis that intensive anthelminthic treatment reduces the prevalence of worms and improves child growth and cognitive functioning more than standard treatment; and that these benefits are mediated by improvements in iron status and physical activity, as well as modulation of circulating inflammatory markers.

Methods

Ethical statement

The study was approved by the Uganda Virus Research Institute Research and Ethics Committee (Ref: GC/127/13/12/12), Uganda National Council for Science and Technology (Ref: HS1534) and London School of Hygiene and Tropical Medicine. Written informed voluntary consent was obtained from parents or guardians for all children. Written informed assent was also obtained from children aged 8 years and above. Witnessed consent was conducted for parents or participants who were illiterate. Participating children received a small gift (a word-picture book) in appreciation for their participation.

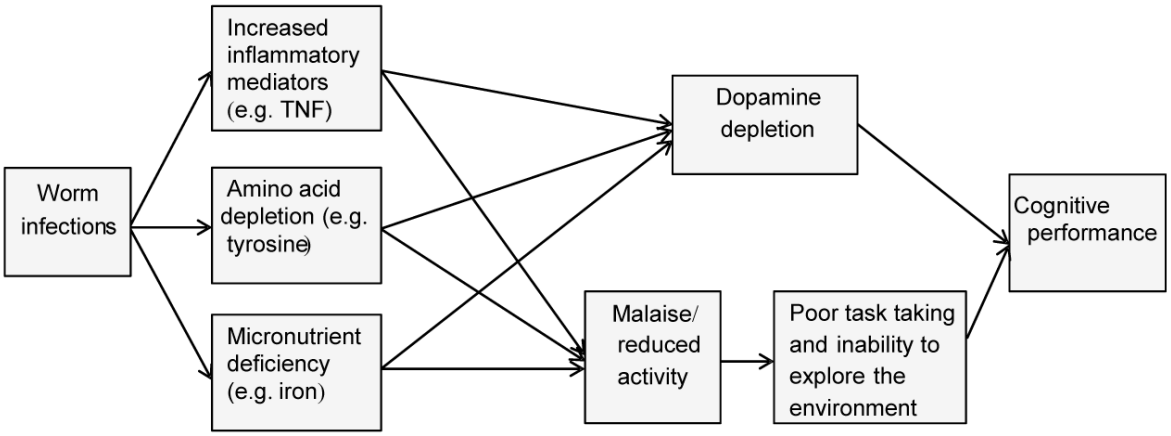

Figure 1. Mechanisms by which parasitic worm infections are hypothesised to affect cognitive function.

Trial registration

The main study (LaVIISWA) within which this sub-study was nested was registered with Current Controlled Trials (ISRCTN47196031) on 7th September 2012.

Design, setting and participants

This study was nested within the Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA) utilising its cluster randomised design of intensive mass anthelminthic treatment versus standard mass treatment in the Koome islands[11]. Within LaVIISWA, 26 fishing villages (clusters) of the Koome islands were randomised to receive intensive treatment for schistosomiasis and other worms (detailed below), or standard treatment (current government policy) with 13 villages (clusters) in each arm. Intensive treatment comprised of quarterly single-dose praziquantel 40mg/kg to treat *Schistosoma mansoni* plus triple-dose albendazole 400mg to treat soil transmitted worms including *Ascaris lumbricoides*, hookworm and *Trichuris trichiura*. Standard treatment comprised of single-dose praziquantel 40mg/kg plus six-monthly single-dose albendazole 400mg. The intervention was administered over a period of three years[11].

Funding for this nested study was limited to measurements at one and two years of intervention, and was not available for measurements at baseline or at three years (the formal end of the trial). Children within the window of rapid development and school entry (5–9 years) were enrolled into this nested study to investigate growth and cognitive effects of the intervention. In each village (cluster), children in the eligible age-group were identified from the treatment registers - this was a census that was updated at each treatment round within LaVIISWA, listing all households (with unique numbers) and all their occupants including children. We aimed to recruit 24 children per village. In the villages where the number identified were more than 24, names were entered into an excel file from which a list of 24 children was randomly selected using the random number generator function. Using household numbers, and with the help of the Village Health Teams, the selected participants were traced to their residences and those found eligible and whose parents were willing to consent were recruited into the study. By the time this nested study received funding, 12 of the 26 villages had already completed one year of follow-up and had started receiving the treatment for year two of the intervention, therefore were ineligible for inclusion in the first round of assessments. This left 14 villages that were available for recruitment into the sub-study at this time point, including two villages where there were no children. Hence initial recruitment was effectively done in 12 villages (seven in intensive and five in standard). After the second year of treatment, all 26 villages (13 villages in each arm) including those villages that could not be assessed at the first year were included in the assessments. In the villages that participated in the first year, the same participants were reassessed at the end of the second year.

General procedures

The intervention: Participants in the standard arm received annual praziquantel 40mg/kg (estimated with a height pole for individuals measuring 94cm and above) plus six-monthly single-dose albendazole, whereas those in the intensive arm received quarterly praziquantel 40mg/kg (estimated with a height pole extended downward to 60cm for inclusion of younger children)[11,28,29] plus albendazole 400mg for three days.

Measurements: At each time point (one year and two years), child's anthropometry (height and weight), temperature and general physical condition were assessed and recorded. Height and weight were measured using a Seca stadiometer and Seca digital weight scale, respectively (Seca Medical Measuring systems and scales). For height, three readings were recorded and the closest two (with a difference not exceeding 0.4cm) were used to calculate the average which was used for analysis. Weight was recorded twice to the nearest 0.1 kg

and the average of the two recordings used for analysis. The stadiometer and weighing scale were calibrated daily using a standard ruler and weights, respectively. Temperature was taken from the axilla using digital thermometers. For participants with a temperature greater than 37.5°C, subsequent procedures were postponed until they were well.

A single stool sample was obtained from each participant and examined for worms using the Kato Katz method[30] with two thick smears read by two different technicians. The stool samples were collected by three trained field workers. Participants were given containers the evening before and requested to put in a stool sample early in the morning. The samples were picked from them (participants) that morning and analysed by two laboratory technicians who were based on that particular village, hence there was no transportation involved between collection and analysis. Blood (venous) samples (4mls) were collected in EDTA tubes and examined for malaria and *Mansonella* parasitology, haemoglobin estimation, cytokine levels, and iron profiles.

Laboratory tests were done according to standard operating procedures and ISO standards. Quality control was done for the various tests: 10% of stool slides were randomly selected and read again by a different technician in the Vector Control Department of the Ministry of Health; 10% of blood slides were also read again by a different technician in CDLs Laboratories at UVRI and all results were consistent with the initial results.

Medical history was taken to capture a record of illnesses including previous (past 12 months) malaria episodes and the antimalarial medications received (artesunate containing regimens have anthelminthic effects on *S.mansoni*), pneumonia episodes, convulsions, term at birth, number of times they received albendazole, and praziquantel, using a questionnaire that was developed for this sub-study (a copy is attached as *Extended data*)[31]. The questionnaire was administered to the parents (or guardians) of the children by three trained interviewers at the study site (in each village). In addition, we collected information on the sanitation and hygiene within the household including details on whether the household owned their own latrine or used a public latrine, footwear, washing hands with soap, drinking unboiled water, use of bed nets and contact with lake water. We also collected family socio-demographic indicators including the materials with which the house is made (walls, roof, floor); the number and size of rooms, the number of people living in the house, whether they have electricity, and the source of water used in the household. We also collected information on schooling status of the child using an interview administered to the parents or guardians of the children. Quality of parent-child interactions is believed to influence cognitive development[32]; on a separate visit scheduled within two weeks of the cognitive assessments, observations for the quality of cognitive stimulation in the home environment were conducted. This was done using the Home Observation for Measurement of the Environment (HOME) tools[33]. The HOME assesses the physical and social aspects of the environment in eight domains which are Learning materials, Language stimulation, Physical environment, Responsivity, Academic stimulation, Modelling, Variety, and Acceptance. The domains consist of items that are observed or the caregiver interviewed about. Subscale scores are summed together to obtain a total score. We used the Early Childhood HOME (EC-HOME) and Middle Childhood HOME (MC-HOME) versions of the HOME tool. The EC-HOME used for children aged 5 years had previously been adapted and translated for Ugandan children in one of our previous projects. It was tested on a few participants and found to be appropriate for participants in this study[34]. The MC-HOME, used for children aged 6–9 years, was also translated and its appropriateness for this population assessed using a sample of 15 children aged between 6–9 years selected from the villages that did not participate in the first round of assessments. All the items in the MC-HOME were found to be appropriate, and were used in the main assessments. HOME was only administered at one year.

Primary outcomes: Based on findings of previous studies, the primary objectives were growth (height for age z-scores and weight for age z-scores), and cognitive scores (executive functions) i.e. attention control, cognitive flexibility, working memory, inhibitory control, and planning. These were assessed using Counting Span, Picture Search, Card Sort Test, Digit Span Backwards, Tower of London, and Delay Inhibition Task as shown in Table 1. The tests were directly administered to participating children by three trained assessors(nurses) who were supervised by a senior developmental psychologist. The assessments were conducted in individual sessions in a quiet room that was set up at each site (village). These tests were previously adapted for Ugandan children aged 4–5 years[35], but for this study they were extended (by including more difficult cues or adjusting the scoring) to cater for a wider age-group (5–9 years).

Table 1. Measures of motor and cognitive abilities.

Ability	Measure
Attention	Picture Search[36]
Mental flexibility	Card Sorting Task[37]
Working memory	Counting Span[38]
Working memory	Digit Span Backwards[39]
Inhibitory control	Delay Inhibition Task[40]
Planning	Tower of London[41]
General intellectual ability	Information Scale[42]
General intellectual ability	Pattern Construction (modification of Block Design)[43]
Motor function	Grooved Pegboard

Secondary outcomes were performance on general cognitive ability, and fine motor function. These abilities may affect performance on measures of specific cognitive abilities and may be on the pathway between worm infection and cognitive impairment. The two functions were therefore included as secondary outcomes and assessed using Information Scale and Pattern Construction, and Pegboard, respectively. These tests were administered together with the rest of the measures listed above in the same setting and under the conditions, as described above. All outcomes were measured first after one year and then after two years from the start of the intervention. Recruited participants continued to receive their quarterly or annual treatment doses as per their trial arm.

In line with the second objective, potential mediators of cognitive effects of worms were investigated as follows:

Immunological parameters: Tumour necrosis factor alpha (TNF-α) and interleukins (IL-6, IL-10) were measured in blood samples using ELISA technique as follows. Plates were coated with 50ul per well of capture antibody diluted in coating buffer (sodium bicarbonate/sodium carbonate pH 9.6) at a 1:250 dilution and incubated overnight at +4°C. The plates were washed three times with phosphate-buffered saline (PBS) - Tween (1X PBS + 0.05% Tween 20) (wash buffer) using an ELx405 micro plate washer and blocked using 150µl per well of 10% FBS in PBS + 0.05% Tween 20 for 2hrs at room temperature. Two-fold serial dilutions of standards up to seven standard points, starting at top standard concentration of 500pg/ml were prepared. These were later used to generate the standard curve. Plates were washed three times. 50µl of samples, standards and controls added to their respective wells and plates were incubated overnight at 4°C. The plates were washed five times, and then 50µl of detection mix (detection antibody and enzyme reagent at 1:250 dilutions each) was added to each well and the plates incubated for 1 hour at room temperature. Next, plates were washed seven times and developed for 30 minutes in the dark with 50µl per well of substrate mix (equal volumes of substrate A and B). The reaction was stopped using 25µl of peroxidase stop solution per well diluted 1:5 using distilled water. Absorbance was read at 450nm and correction at 570nm on a micro-plate reader and cytokine concentrations in pg/ml generated using the Gen 5 software. We used the ELx808™ Absorbance Microplate Reader from BioTek to read the ELISAs.

Iron concentration: Haemoglobin was measured as a crude estimate of iron status in the blood using an Hb Heamocue 201, but a more accurate estimation i.e. ferritin and transferrin receptor in plasma levels were also determined. Plasma and serum levels of soluble transferrin receptor and ferritin were measured using the Cobas Intergra 400 plus (Roche Diagnostics Ltd, Switzerland), an immunological technique utilising soluble transferrin receptor cassette and following the Cobas 400/700/800, method manual 4th edition (Feb, 2008). Relationships between these parameters and worm infections, treatment and cognitive performance were examined.

Statistical methods

Sample size calculation. Sample size and power were calculated based on the hypothesis that, after two years of intervention, intensive treatment would increase the mean height and weight and cognitive scores compared to standard treatment, by the amounts shown in Table 2 for the respective measures. With 26 clusters, a random sample of 20 children was required from each cluster to obtain sufficient power to detect meaningful differences at the 5% significance level and allowing for a design effect of 2. An extra four children were added to each village (bringing the total to 24 children from each village) to cater for an anticipated loss to follow up of 15–20%, hence 624 children were targeted from the 26 villages in the LaVIISWA trial. In the event, as described above, it was not possible to sample from all villages at one year (12 villages had already started receiving the second year of treatment, two villages did not have children of eligible age), hence power to detect differences in the one year outcomes was lower than anticipated.

Data analysis. Data were entered in Microsoft Access and analysed in STATA version 15.0 (StataCorp, College Station, TX). Means and standard deviations were used to describe continuous data whereas percentages and proportions were used to describe categorical data. Correlations between outcomes were explored to examine collinearity. Raw height and weight data were converted into height for age z-scores (HAZ) and weight for age z-score (WAZ), respectively, and these were used for analysis of effects of treatment and other exposures. At both time points (year one and year two), cross-sectional comparisons of worm status, growth and cognitive performance were conducted between the two treatment arms. Analyses were done at the individual level, but allowed for the clustering

Table 2. Sample size and power justification.

Outcome measure	Power	Anticipated difference between arms	Design effect	Between group standard deviation
Picture Search	84%	0.7	2	1.4
Counting Span	80%	1	2	2.1
Height (adjusted for age)	99%	5 cm	2	6.7
Weight (adjusted for age)	87%	1.1 kg	2	2.1

of participants within villages (clusters). Mean differences in HAZ, WAZ and cognitive scores on individual measures were compared, and using adjusted linear regression to allow for clustering (and adjusting for age and sex), the effect of treatment regimen was examined. To avoid the effect of collinearity, each outcome was examined separately. Within each arm, the same outcomes were examined for changes between the first and second time point of assessment using linear mixed effects models to account for the correlation of outcomes from the same individuals (at both time points) while adjusting for age, sex and clustering of children within villages. The effect of the intervention on changes between the first and second year was examined by fitting contrasts in the mixed effects models. Cytokine concentrations were not normally distributed, and hence were log transformed. Because of the multiple comparisons, a stringent p-value cut off of 0.01 was used to determine statistical significance for all analyses.

Results

Participants' characteristics

After the first year, a total of 419 children within the age range of 5–9 years were identified from the village treatment registers of 12 villages (excluding two villages that did not have children in the right age bracket) and traced to their homes. Numbers varied with village size and also whether it was school time or holiday; enrolment was higher in larger villages than smaller ones and during holidays than school-term time. In eight of the 12 villages, the lists generated more than 24 children in the age group, and for these random sampling was applied. However, in all the villages the number of children that were actually present was less than the target sample size. Hence the random selection was repeated until everyone in the lists was visited for availability. Altogether 149 participants (intensive=85; standard=64) from 12 villages (intensive=7, standard=5) were eligible and available to participate and were hence enrolled for the first round of cognitive assessments. 270 children were not recruited because they were away either on the mainland for school (n=95), the family had left the village and moved to the mainland (n=67), parents (and child) were away farming (n=25), parents declined to participate (n=5), children were over age (n=16), under age (n=1), not native Luganda speakers (n=1), had severe learning disability (n=3) or had died (n=2). Two children were excluded because they had moved to the islands for only two months and had not received any dose of mass treatment. The remaining 55 participants could not be found and there was no information about them.

After the second year, all 26 clusters (13 in each arm) were included and altogether 286 participants were assessed (intensive=158; standard=128). These included 87 of the 149 participants who were assessed at one year and 199 who were recruited from 11 additional villages (the 12th additional village had no children aged 5–9 years). A total of 62 participants tested at the first assessment were not available for the second assessment mainly because they were away on the mainland for school. 340 children were identified from the 11 additional villages. Of these, 141 were not recruited for reasons similar to those found after one year in the first block of villages i.e. migrated (n=73), on mainland for schooling (n=28), over age (n=29), parents not at home (n=5), parents refused to participate (n=4), language barrier (n=1), and one child had died. The breakdown of participants recruited and excluded is shown in the flow diagram (Figure 2), and the CONSORT flow diagram for the main study within which this project was nested has been previously published[29]. Participant characteristics in the two treatment arms were compared and found to be similar in all features except sex and age. Participants in the standard arm were slightly older, and there were more males than in the intensive arm in the first year and less in the second year (Table 3); therefore, age and sex together with clustering were adjusted for in subsequent analyses.

Effects of the intervention on worm prevalence, growth and cognitive performance

Data from the first year showed a lower prevalence of *Schistosoma mansoni* in the intensive arm (41%) than in the standard arm (70%); aOR= 0.24; p<0.001; 95% CI: 0.12, 0.49; Table 4). Similarly, the prevalence of *Trichuris*, hookworm and *Ascaris* was lower in the intensive than standard arm: the difference was statistically significant for *Trichuris* (17% in intensive versus 35% in standard; aOR=0.31; p=0.002; 95% CI: 0.14, 0.66).

There were no significant differences in growth outcomes (HAZ and WAZ) between the two arms after the first year of the intervention (Table 4). Participants in the intensive arm had a somewhat higher mean score on the Delay Inhibition Task than those in the standard arm (mean difference=1.34; p=0.04; 95% CI: 0.06, 2.21) after the first year of the intervention. For the remaining cognitive measures, the differences between the intensive and standard group were not statistically significant (Table 4).

Similar analyses were conducted for data collected after two years of the intervention. Results showed lower worm prevalence in the intensive arm than in the standard arm for both *S. mansoni* and *Trichuris* (Table 4) but no significant differences in growth and cognitive outcomes between the two treatment arms (p>0.01) (Table 4).

Longitudinal effects of the intervention

We further examined the data for changes in worm infection, growth and cognitive performance between the first and second time points for each arm (longitudinal analysis) in an analysis restricted to the 87 participants (intensive n=57; standard n=30) who had data at both time points (year one and year two). Prevalence of *Trichuris* increased in both arms, from 19% in the first year to 32% in the second year (intensive arm); and from 51% to 57% (standard arm). The prevalence of schistosomiasis remained similar between the two time points in both treatment arms i.e. 43% and 47% in intensive arm, and 72% and 67% in the standard arm. There were slight increases in the HAZ and WAZ in the standard arm which were not statistically significant (Table 5). There were improvements in performance in three measures of cognitive function

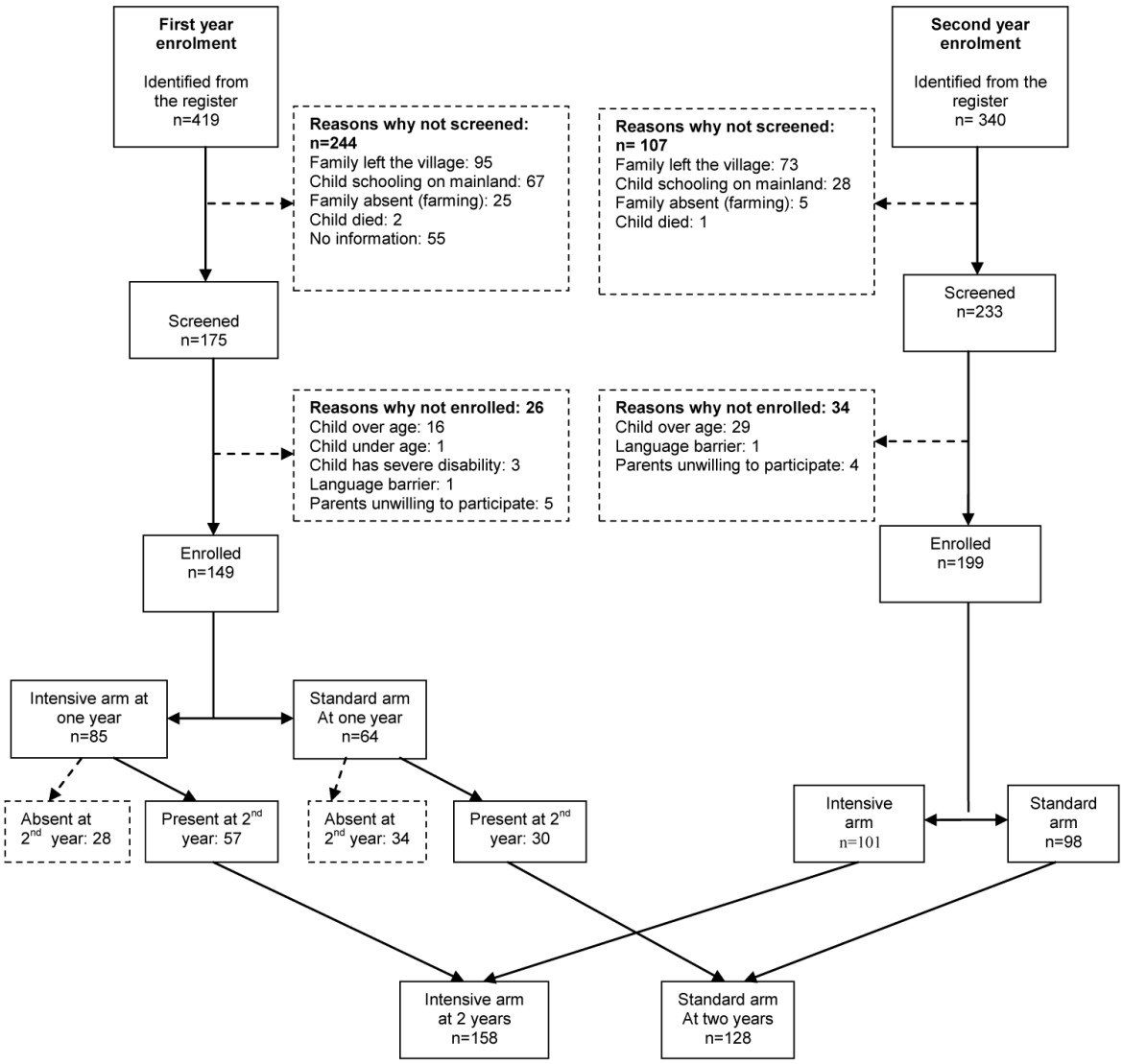

Figure 2. Participant recruitment.

Table 3. Participants' characteristics in each arm at the first year and second year.

	1st year		2nd year	
	Int N= 85	Std N=64	Int N= 158	Std N= 128
Mean child-age (months, s.d)	90.13 (16.82)	92.16 (12.15)	84.39 (17.64)	86.5 (17.04)
Sex (males)	43%	57%	50%	44%
Mothers' education (primary)	77%	82%	62%	61%
Fathers' education (primary)	68%	71%	39%	45%
Children attending school	92%	92%	92%	90%
Mothers' occupation (farming)	25%	30%	33%	37%
Fathers' occupation (fishing)	51%	50%	58%	49%
Mean HOME score (s.d)[a]	28 (6.40)	31 (4.60)		

Int = intensive treatment arm; Std = standard treatment arm; s.d = standard deviation; HOME = Home Observation for Measurement of the Environment.

[a]HOME assessments conducted only at year one.

Table 4. Worm infection, growth and cognitive outcomes after one year, and after two years of the intervention.

Test	Mean test score		#Coef/ #aOR	95% CI	P
Outcomes at one year of the intervention	**Int N=85**	**Std N=64**			
S. mansoni	41%	70%	0.24	0.12, 0.49	<0.001
*Trichuris	17%	35%	0.31	0.14, 0.66	0.002
*Hookworm	3%	5%	0.33	0.06, 1.76	0.20
*Ascaris	0%	8%	-	-	-
Weight (WAZ)	-.84	-.78	-.08	-0.36, 0.21	0.50
Height (HAZ)	-.92	-.62	-.32	-0.63, -0.008	0.05
Picture Search	4.71	5.65	-0.54	-2.23, 1.15	0.50
Card Sort Test	5.14	5.28	0.17	-1.08, 1.37	0.88
Counting Span	5.31	5.70	-0.30	-0.94, 0.34	0.53
Digit Span Backwards	2.17	2.47	-0.22	-0.94, 0.48	0.42
Delay Inhibition Task	9.85	8.78	1.34	0.06, 2.21	0.04
Tower of London	6.95	6.42	0.65	-0.61, 1.91	0.59
Information Scale	22.61	19.26	3.87	1.33, 6.40	0.17
Pattern Construction	4.76	5.07	-0.16	-1.17, 0.84	0.78
Grooved Peg Board	3.66	3.78	-0.11	-0.72, 0.50	0.28
Outcomes at two years of the intervention	**Int N= 158**	**Std N= 128**			
S. mansoni	39%	69%	0.27	0.16, 0.43	<0.001
*Trichuris	17%	39%	0.31	0.18, 0.54	<0.001
*Hookworm	0%	0.78%	-	-	-
*Ascaris	0%	3.1%	-	-	-
Weight (WAZ)	-.90	-.75	-.15	-0.40, 0.09	0.21
Height (HAZ)	-.86	-.73	-.13	-0.38, 0.11	0.28
Picture Search	4.4	4.1	0.35	-0.05, 0.77	0.09
Card Sort Test	5.3	5.1	0.29	-0.45, 1.03	0.42
Counting Span	5.1	5.1	0.08	-0.58, 0.74	0.81
Digit Span Backwards	2.1	2.0	0.05	-0.60, 0.69	0.89
Delay Inhibition Task	9.1	9.2	0.12	-0.59, 0.82	0.73
Tower of London	7.3	7.2	0.18	-1.08, 1.44	0.77
Information Scale	25.5	26.1	0.33	2.30, 2.96	0.80
Pattern Construction	4.3	4.4	0.13	-0.88, 1.14	0.79
Grooved Pegboard	4.7	5.0	-0.27	-1.20, 0.67	0.56

Int = intensive arm; Std = standard arm; aOR=adjusted odds ratio; HAZ = height for age z-scores; WAZ = weight for age z-scores.

*Odds ratios were used for worm comparisons.

Adjusted for age, sex and clustering.

(Delay Inhibition, Information Scale, and Tower of London) and in a measure of motor function (Pegboard) in both arms. These are shown in Table 5.

We assessed whether these changes over time differed by intervention arm (Table 6). Among the growth outcomes, there were no significant differences in the growth parameters

Table 5. Worm infection, growth and cognitive performance at one year and at two years of the intervention among children with data from both time points.

Outcome measure	Intensive (N= 57)			Standard (N= 30)		
	R1	R2	P*	R1	R2	P*
S. mansoni	43%	47%	0.13	72%	67%	0.17
Trichuris	19%	32%	0.50	51%	57%	0.68
Weight (WAZ)	-0.86	-0.92	0.71	-0.82	-0.58	0.13
Height (HAZ)	-1.08	-1.07	0.92	-.72	-0.61	0.57
Picture Search	4.7	4.6	0.92	4.9	4.2	0.16
Card Sort Test	5.1	5.4	0.58	5.3	5.6	0.57
Counting Span	5.1	5.2	0.75	5.1	5.3	0.45
Digit Span Backwards	2.4	2.3	0.37	2.5	2.2	0.30
Delay Inhibition Task	9.6	9.3	0.53	7.4	9.5	0.01
Tower of London	6.3	7.9	0.004	6.0	8.7	0.001
Information Scale	21.0	26.6	<0.001	20.2	26.2	<0.001
Pattern Construction	4.6	5.0	0.39	5.3	6.4	0.11
Grooved Pegboard	3.5	5.5	<0.001	4.3	5.9	<0.001

R1 = after one year of the intervention; R2 = after two years of the intervention; HAZ = height for age z-scores; WAZ = weight for age z-scores.

* P-value for the difference among children within each treatment arm.

Table 6. Differences in outcomes between treatment arms after one and two years of treatment among the 87 participants seen at both time points.

		Mean Difference	95% CI	P
Comparison	time			
Weight (WAZ)				
(Intensive vs Standard)	1	-0.04	-0.52,0.61	0.874
(Intensive vs Standard)	2	-0.33	-0.15, 0.82	0.174
Information scale				
(Intensive vs Standard)	1	3.22	-0.24, 6.69	0.069
(Intensive vs Standard)	2	-0.66	-4.13, 2.82	0.711
Delay Inhibition task				
(Intensive vs Standard)	1	2.70	1.19, 4.21	<0.001
(Intensive vs Standard)	2	0.02	-1.45, 1.49	0.979

WAZ = weight for age z-scores; CI, confidence intervals

between the treatment arms. Only two measures of cognitive function (i.e. Information Scale and Delay Inhibition task) showed significant differences in change from year one to year two between the two trial arms, with both showing greater improvement in the standard arm compared to the intervention arm (interaction term p-values = 0.015 and 0.004 for Information Scale and Delay Inhibition task, respectively) (Figure 3).

In line with our second objective, we assessed the association of iron, and immunological cytokines (IL 6, IL 10 and TNF-α) with worm infection, treatment and cognitive performance using regression analysis adjusting for age, sex and clustering. None of the associations were significant (p>0.01). These results are shown in Tables S1–S9 (see *Extended data*)[44].

Discussion

This study examined growth and cognitive benefits of treating children for worms intensively (compared with standard treatment) and explored pathways hypothesized to be involved in cognitive effects of worms. There was greater reduction in worm burden in the intensive treatment arm than in the standard arm, but there was no significant difference between the treatment arms in growth, cognitive outcomes, or in measured potential mediators of effects of worms on cognition, at the end of one year or two years of the interventions.

The cluster randomised controlled mass treatment trial used in this study was a robust design for the rigorous measurement of treatment effects in this highly endemic population. By the design, the intensive arm had a higher frequency of treatment and number of dosages of albendazole given at each treatment period than the standard arm. The intensive treatment was therefore expected to have a higher efficacy with regards to clearing worm infection. Lack of baseline data meant that we could not confirm that the trial arms were similar at baseline with regard to the primary outcome measures. The LaVIISWA trial, within which this work was nested, showed good baseline comparability between trial arms for relevant characteristics including markers of socio-economic status and occupation, as well as overall helminth infection prevalence[11]. However, in the age-group of interest (5–9 year olds) baseline prevalence of *S. mansoni* was 70% and 50% among villages allocated to standard and intensive treatment, respectively, implying that the different treatment regimens may not have been fully responsible for the differences in observed prevalence at one and two years in this sub-study.

While quarterly treatment may have reduced the worm burden compared to annual treatment in the first year of the intervention, further treatment did not further reduce worm infection prevalence in the second year in either trial arm and

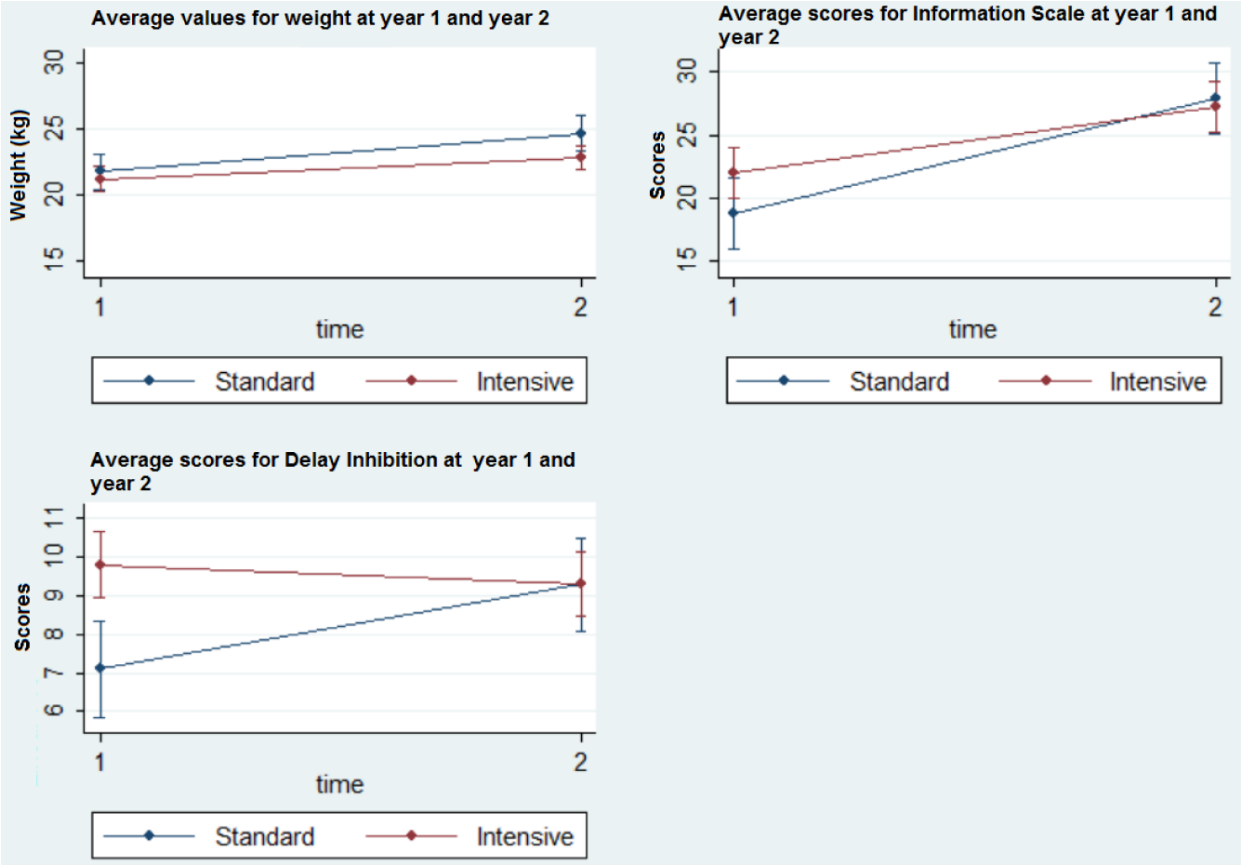

Figure 3. Average values for weight, Information Scale and Delay Inhibition Task between the two arms across the two time points.

there was no increase in divergence between the trial arms. At baseline of the main trial, the distribution of infection prevalence for both *S. mansoni* and *Trichuris* peaked in the 10–15 age group in this community[11]. Among the subgroup of children followed from year one to year two of the intervention, age increased by one year towards the peak prevalence age group, but helminth prevalence (particularly for schistosomiasis) did not increase, implying some element of infection control. Kato Katz stool analyses (used to assess helminth infection status in this study) under-estimate infection prevalence: in the LaVIISWA trial as a whole, intensive treatment was shown to reduce intensity of *S. mansoni* infection as assessed by Kato Katz analysis, but almost all community members were found to remain positive on the more sensitive urine circulating cathodic antigen test[29]. Communities (including children) in these islands are constantly exposed to schistosomiasis and soil transmitted worms. They bathe, wash, fetch water, play and swim in the lake water, which is heavily infested with schistosomiasis[11,29]. Poor hygiene including lack of footwear and lack of toilets, and open disposal of human waste, which is washed back into the lake, is a widespread characteristic of the community. Given these circumstances, it is almost impossible to clear or control worm infection with treatment alone. Additional strategies including health education, improved sanitation and hygiene (handwashing, footwear, using toilets) would be needed to achieve greater worm clearance in these communities.

In this context, intensive treatment of worms did not have significant impact on growth or cognitive outcomes. This could mean that a partial reduction in worm burden is not sufficient to improve growth or cognitive function. Based on the mean height and weight z-scores at the initial follow up, children in both treatment arms had sub-optimal growth for age. Within the sub-group followed from year one to year two, there were no significant increases in growth measures, and only borderline improvements in cognitive scores, between the first and second year within each arm. There were no differences in the changes between the trial arms. Similar findings were reported in a previous study where treatment for *Schistosoma japonicum* had short term improvements in cognitive function but did not have long term effects[7]. The WHO recommended dose for praziquantel is currently 40mg/kg including for children. Recent studies have shown that in school-aged children, a higher dose of praziquantel (60mg/kg) has higher efficacy (83%) than the 40mg/kg dose (69%)[45]; however, in the context of high transmission and reinfection rates, treatment alone may not fully clear the infection. It was not possible to use a different treatment regimen since our study was nested within the design of the bigger trial (LaVIISWA). Future studies could investigate whether effective treatment, combined with interventions to prevent re-infection over longer durations of follow up, can result in significant improvements in growth and cognition.

This sub-study had some limitations; we used a cluster-randomised design in which the villages (clusters) were randomised; however, not all the children that participated in the study were randomly selected; random sampling was only applied when there was a potential candidate pool of more than 24 children in a particular cluster (village). Seventy-one children from three villages were randomly selected. This method introduces potential bias to the study design.

Based on our power calculation, we aimed to recruit 24 participants from each cluster, and hoped to have a study population of 624. However, in the first round, 12 villages could not be included and two villages did not have children of the required age group. In some of the villages there were fewer numbers of eligible children. We achieved an enrolment of 149 for the one year follow up and 286 at the two-year follow-up. The target sample size was not achieved and study therefore was underpowered. This could have contributed to the lack of significant differences between the two arms.

Worms have lived with us for a long time. Studies of immunological and allergic outcomes of worms have indicated a protective effect of worms against allergy-related disease in humans[46], highlighting the evolutionary adaptations that have occurred. Although parasitic worm infections undoubtedly cause pathology, it is possible that worms and humans have mutually adapted to a greater extent than is generally recognised, such that, in the majority of infected individuals, and in the context of adequate nutrition, key biological functions such as neurocognitive development are spared. It is possible that parasitic worms do not inherently impair developmental outcomes of children in worm endemic settings.

Data availability

Underlying data

LSHTM Data Compass: LaVIISWA Round 1 and 2 Dataset. https://doi.org/10.17037/DATA.00001802[31]

This project contains the following underlying data:

- round1and2_merged_OA_dataset.xlsx (Anonymised dataset containing measurements collected during first and second data collection rounds in XLSX format)
- round1and2_merged_OA_dataset.csv (Anonymised dataset containing measurements collected during first and second data collection rounds in XLSX format)
- LaVIISWA_Round1-and-2_codebook-v2.html (Codebook for de-identified and full dataset)

Extended data

LSHTM Data Compass: Effect of intensive versus standard anthelminthic treatment on growth and cognition among children living in a high Schistosoma mansoni transmission setting - Supporting Information. https://doi.org/10.17037/DATA.00001895[44]

This project contains the following extended data:

- Cognitive_Function_Cohort_Table_s1.docx (Table S1. Descriptive summary for the cytokines at one year)

- Cognitive_Function_Cohort_Table_s2.docx (Table S2. Association between worm infection and cytokine concentration at one year)
- Cognitive_Function_Cohort_Table_s3.docx (Table S3. The effect of treatment on cytokine concentration)
- Cognitive_Function_Cohort_Table_s4.docx (Table S4. Associations between TNF- alpha concentrations (log 10) and motor and cognitive scores)
- Cognitive_Function_Cohort_Table_s5.docx (Table S5. Associations between IL-6 concentrations (log10) and motor and cognitive scores)
- Cognitive_Function_Cohort_Table_s6.docx (Table S6. Associations between IL-10 concentrations(log10) and motor and cognitive scores)
- Cognitive_Function_Cohort_Table_s7.docx (Table S7. Association between worm infection and treatment with iron measured using Ferritin and transferrin)
- Cognitive_Function_Cohort_Table_s8.docx (Table S8. Association between serum ferritin and cognitive outcomes)
- Cognitive_Function_Cohort_Table_s9.docx (Table S9. Association between soluble transferrin receptor and cognitive outcomes)

LSHTM Data Compass: LaVIISWA Round 1 and 2 Dataset. https://doi.org/10.17037/DATA.00001802[31]

This project contains the following extended data:

- LaVIISWA_questionnaire.pdf (Socioeconomic and medical information questionnaire)
- CFC_Scoring_Sheet_Cognitive_Tests.pdf (Scoring sheet for cognitive tests)

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We thank our participants, the parents and children of Koome islands for having taken part in this study and the study team for their hard work.

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Open Peer Review

Current Peer Review Status: ? ✓

Version 1

Reviewer Report 25 October 2021

https://doi.org/10.21956/wellcomeopenres.17658.r46223

✓ **Michael French**
RTI International, Washington, DC, USA

This is a really interesting paper worthy of publication. The impact of anthelminthic treatment – whether for SCH or STH – on growth or cognition has long been postulated and has been used as advocacy for deworming programs. The relationship is plausible but there is very little in the way of an evidence base to back it up. This paper doesn't provide strong evidence for that relationship. It is of course important that studies are judged on how well designed they are rather than whether they give you the answer you hope for.

The issue with the sampling strategy is of course a shame. I think it's still worth publishing even given this. Below I highlight some other areas where more information may help with clarity.

Comments

- Did the authors collect the intensity of infection as well as prevalence? Intensity often shows a greater immediate impact with treatment and could be a better proxy of morbidity (although, noting even that relationship doesn't have a strong evidence base).

- What is the history of treatment in the area? Were these areas at endemic equilibrium at baseline?

- There was no change in prevalence of infection between years 1 and 2 (and prevalence remained very high) – why do you think that is?

- Given the possibly complex mechanisms for infection to affect morbidity, the relatively short-time of follow-up could be important. Are there any plans to follow-up again over a longer time-frame? This could be even more important given that there is not a huge difference in treatment approach between the study arms (I recognize it would not be possible to leave one arm completely untreated).

- Sampling – that's a real disadvantage for the issue with villages already being treated. Giving the sample size of 85 children (7 villages) in the intensive arm and 64 (5 villages) in

the standard arm; and with follow-up being in only 87 children total, is it possible to do post hoc sample size calculations to determine how large the effect size would need to be to see significant differences?

- Are there any data on how the cognitive scores of these children compared to other areas in Uganda?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, Neglected Tropical Diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 30 March 2021

https://doi.org/10.21956/wellcomeopenres.17658.r43125

?

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The authors compared the effect of intensive and standard praziquantel treatment on the growth and cognition among children for 2 years. It was concluded that reduction in worm burden may

not improve growth and cognitive outcomes in high *S. mansoni* transmission settings. The manuscript is well-written, however, the results seem to be inconclusive because of the possible confounders. The following are the issues on the manuscript that needed to be addressed:

1. What is the basis of giving single dose praziquantel for every 3 months to the group getting the intensive anthelminthic treatment?

2. What is the baseline prevalence of schistosomiasis in the children for the 2 groups? What is the characteristic intensity of infection at the start of the study? The baseline prevalence and intensity of infection should be compared with the results at 2 time points.

3. Comparison should also be done on the baseline height and weight with those in the 2 timepoints.

4. What is the basis of assessing the effects to growth and cognition in 2 years? Is 2 years already enough to have a conclusion in this study?

5. Aside from testing the children for malaria and *Mansonella* infection at the 2 timepoints, did you check whether they got infected within the months before the timepoints?

6. No data on anemia, nutritional and dietary conditions, socioeconomic status of the children were shown in this study. How did you deal with the potential effects of these confounders in this study? This should be discussed in the paper.

7. Were the stool of the children examined every after treatment or just in the 2 timepoints? Can the authors know whether the children positive for *S. mansoni* are treatment failures or reinfection?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: medical parasitology, diagnostics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.