Baseline liver ultrasound findings in preschool children from the Praziquantel in Preschoolers (PIP) trial in Lake Albert, Uganda

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Word count: excluding abstract- 2973

Abstract: 249

Tables: 3

Figures: 2

Abstract

Background:
Periportal fibrosis is a late-stage manifestation of chronic infection with *S. mansoni.* Praziquantel (PZQ), the only drug available for the treatment of schistosomiasis, has limited effect in treating established morbidity. Preschool aged children (PSAC) are not considered to be an at-risk population for severe morbidity. However, the prevalence of periportal fibrosis in PSAC in *S. mansoni* endemic settings is unknown.

Methods:
As part of a phase II clinical trial comparing different dosing regimens of PZQ in children age 12-47 months infected with *S. mansoni* in Uganda ("praziquantel in preschoolers" (PIP) trial), we present baseline results assessing liver ultrasound (US) findings. Standard measures following the WHO Niamey protocol were obtained from study participants at baseline.

Results:
A total of 7/347 (2%) PSAC had Image Pattern C with pipe stems and echogenic rings suggestive of periportal fibrosis, 29/347 (8%) had Image Pattern B, and 58 (17%) had evidence of periportal thickening. There were higher adjusted odds of periportal thickening with older age (OR 1.04, 95% CI: 1.00, 1.07), primary maternal education (OR 1.04, 95% CI: 1.00, 1.07), and being taken to the lake weekly (OR 3.02, 95% CI: 1.19, 7.63). A further 44/347 children (13%) had a rounded caudal liver edge which was associated with high *S. mansoni* infection intensity (adjusted OR 3.31, 95% CI: 1.46, 7.51), compared to low intensity infection.

Conclusions:
Incipient schistosomiasis-related liver morbidity was detected in young children enrolled in the PIP trial. Adequate age-adjusted reference measurements for liver ultrasound findings in very small children are lacking but urgently needed. Schistosomiasis related-fibrosis may be delayed or averted with early and repeated PZQ treatment.

Introduction

Schistosomiasis is a waterborne parasitic disease causing significant morbidity and affecting over 123 million children worldwide[1]. *Schistosoma mansoni*, primarily causes intestinal disease which may progress to hepatosplenomegaly, presinusoidal portal hypertension, ascites, and hematemesis. Liver disease is caused by granuloma formation around schistosome eggs, resulting in obliteration of small vessels and perivascular fibrosis [2]. Hepatic function is initially preserved as there is no liver cell injury; morbidity relates to the characteristic Symmer's clay pipe fibrosis and its complications, most importantly portal hypertension[3].

Currently, preschool age children (PSAC) less than 4 years of age, are not considered to be at risk of severe liver morbidity despite the high burden of disease in this group, estimated at 50 million worldwide[4]. Significant morbidity has been reported in children including growth retardation[5], anemia[6], and neurocognitive deficits[7]. PSAC are much less studied than older children but likely experience similar or more severe growth restriction given more rapid growth in this population. PSAC are also a significant contributor to transmission in schistosomiasis endemic communities[8]. PZQ, the only drug available to treat schistosomiasis was only recently approved for children ages 1-4. However, WHO only recommends including children ages two and over in preventive chemotherapy campaigns for the control of schistosomiasis[9]. PZQ recommended dose in this population has recently been challenged in the first PK/PD study in PSAC with intestinal schistosomiasis, demonstrating that higher doses are needed to achieve cure[10]. Given this and the lack of a pediatric formulation, in practice this has led to the exclusion of PSAC during preventive chemotherapy campaigns globally[11129]

Ultrasound examination is an economical, noninvasive technique used in the evaluation of *S. mansoni*- associated abdominal pathology[13]. The Niamey Protocol is the standard ultrasound scoring protocol used for schistosomiasis related hepatic fibrosis. The protocol gives a qualitative assessment of liver parenchyma and an

adjustment of organ measurements for height[14]. *S. mansoni.*-related abdominal disease detected by ultrasound includes evidence of periportal fibrosis and periportal thickening, signs of portal hypertension and hepatomegaly[14]. Splenomegaly is generally not used as a marker in malaria endemic regions[14], however it has been shown that chronic exposure to *S. mansoni* and *Plasmodium falciparum* can have an additive effect on childhood hepatosplenomegaly[15]. Inter-observer variation as well as confounding with other pathologies such as hepatitis infection remain problems in US assessment of morbidity in schistosomiasis[1617]. Nonetheless, Niamey scoring remains useful for detection and comparison of morbidity related to schistosomiasis [13181916].

Liver morbidity due to *S. mansoni* detected by US, including periportal fibrosis, portal hypertension and hepatosplenomegaly, is significant in school-age children[2021]. However, US findings in PSAC are not well described. In one study of this population, liver fibrosis and size of the left liver lobe were associated with intensity of *S. mansoni* infection[22]. Another study found left lobe hepatomegaly and splenomegaly to be associated with *S. mansoni* infection, but not liver fibrosis[23].

As part of a phase II trial of PZQ exploring different dosing regimens in children age 12-47 months in Uganda (the Praziquantel in Preschoolers ("PIP" trial),[24] we assessed baseline liver US findings consistent with schistosomiasis related liver morbidity.

Methodology

The PIP trial enrolled PSAC from the shores of Lake Albert, in western Uganda, who screened positive for *S. mansoni* infection by stool parasitology. PSAC aged 12-47 months were enrolled and baseline data were collected from April 2021 until March 2022. Urine samples from potential participants were tested with circulating cathodic antigen testing (CCA)[25] by field staff in villages following informed consent for initial screening[24]. Children with positive eggs in stool by Kato-Katz test and otherwise healthy, were eligible for the study.

At the enrolment visit, children meeting eligibility criteria were admitted for up to 24 hours for administration of PZQ and assessment of pharmacokinetic parameters[24].

Information was collected on demographics, anthropometry, water exposure, biochemistry, full blood count, and co-infection (HIV and malaria). Ultrasound was performed by trained ultrasound technicians, following the WHO Niamey Protocol[14] to assess baseline presence or absence of any schistosomiasis-related pathology.

Ultrasound technicians assessed Image Pattern for liver parenchyma, giving a score of 0-8, corresponding to Image Patterns A- F in the Niamey Protocol[14]. Technicians also gave a score of 0 (no periportal thickening) or 1 (evidence of periportal thickening) as a subjective measure of periportal thickening, and assessed for abnormal liver shape, including a rounded caudal liver edge and surface irregularity. A measured height-adjusted liver size was obtained, including right liver lobe size as measured from the anterior axillary line (AAL) and left liver lobe as measured in the left parasternal line (PSL), presence of collateral veins, ascites, and a thickened gallbladder. Portal vein diameter and periportal vessel wall thickness was measured, with scores given in line with Niamey Protocol height adjustments.

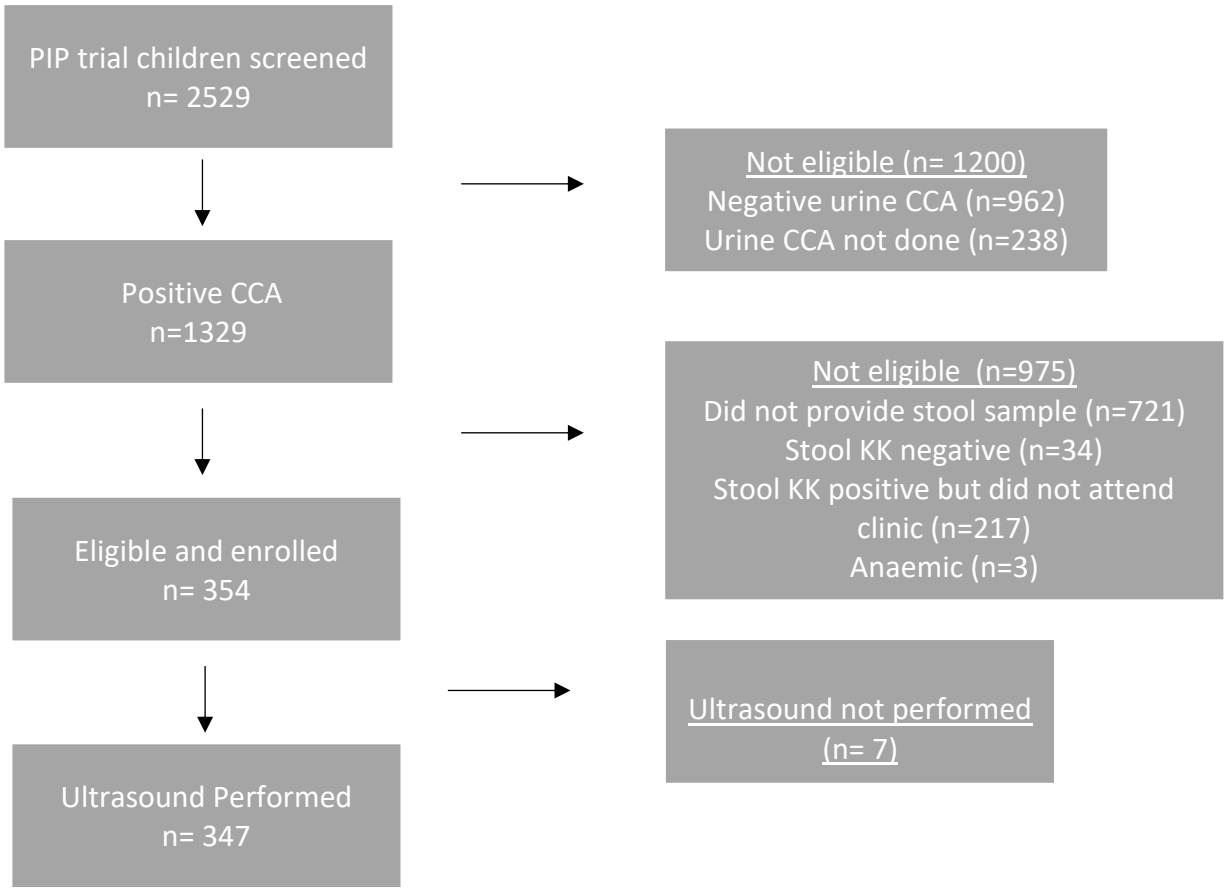
We performed statistical analysis using STATA 14.0 software for the baseline ultrasound parameters of all participants with recorded ultrasound data. Four parameters were investigated as outcomes as a significant number of children had abnormal values in these parameters. These four dependent variables, as measured per the Niamey Protocol, were a) subjective measure of *periportal thickening*, b) evidence of *periportal fibrosis* as measured by 'Image Pattern', c) the non-specific *rounded caudal liver edge* variable, and d) the thickness of *second order portal branches*. Variables and the socio-demographic and clinical characteristics of study participants were summarized, and logistic regression models were used to assess associations of each outcome with the following exposures: *S. mansoni* infection intensity, toilet access (none, private or shared), sex, age, maternal education, paternal education, nutritional and inflammatory biomarkers, as well as the frequency of children being taken to the lake. Characteristics showing evidence of an association with the outcome of interest at $P<0.10$ were then adjusted for age, sex and maternal education to assess if associations remained significant when adjusting for these confounders.

An expert ultrasound reviewer, who was part of the development of the initial Niamey Protocol (J.R.) performed a blinded review of 120 of the 360 sets of images, including 60 sets with abnormalities and 60 reported as normal by the ultrasonographers. The reviewer assessed for image pattern, caudal liver edge, and measured spleen length when possible. Cohen Kappa statistics were obtained to evaluate interobserver agreement between the ultrasound technologist and expert reviewer's assessment.

Results

Of 2,284 children screened, 1329 (57%) had a positive CCA and were invited for secondary screening with stool Kato Katz. A total of 367/1329 attended the clinic, and 354 met enrollment eligibility criteria. Baseline ultrasound results were obtained from 347 children.

Figure 1: Flowchart of Study Participants



Of the 347 children with ultrasound results recorded, 58 (16.7%) had evidence of *periportal thickening* as per subjective assessment by the ultrasonographer (Figure 2). When scored with Niamey Protocol Image Pattern for liver parenchyma (score 0-8, corresponding to A-F), 311 (89.6%) had no signs of *periportal fibrosis* (Image Pattern A), 29 children (8.4%) had Image Pattern B with a starry sky appearance, and 7 (2.0%) had Image Pattern C with pipe stems and echogenic rings suggestive of *periportal fibrosis*. Overall, 120 (34.6%) of children had *second order portal branch* thickness in the moderately abnormal range (>2SD from the mean as per reference ranges in the Niamey Protocol), with 27 (7.8%) in the abnormal range (>4SD). (Figure 2).

Of the 347 children screened, 44 (12.7%) had a *rounded caudal liver edge*, a non-specific liver abnormality and marker of morbidity (Figure 2). Five children (1.6%) had an abnormal *right liver lobe (AAL) score*, suggesting a shrunken right liver lobe, which can be a marker of hepatic schistosomiasis, but is relatively non-specific[14]. Two children had an enlarged left liver lobe (*PSL > 4SD* from the mean). None of the children assessed had late signs of fibrosis or portal hypertension such as an abnormal *portal vein diameter*, *ascites*, a *thickened gallbladder*, or the presence of *collateral veins*.

We performed unadjusted logistic regression to assess which variables were associated with *periportal thickening, periportal fibrosis*, a *rounded caudal liver edge* and *thickened second order portal branches*. Older age (per month increase) in the mothers was crudely associated with higher degree of subjective *periportal thickening* (OR 1.03, CI: 1.00, 1.07) and primary maternal educational attainment (compared to no education) showed some evidence of an association (OR 1.66, CI: 0.93, 2.97). When adjusting for sex and maternal educational attainment, age remained significant (OR 1.04, CI: 1.00-1.07). and primary education in mothers was significantly associated with periportal thickening (OR 1.86, CI: 1.03, 3.66) when adjusted for age and sex (Table 2). Children who were taken to the lake by their primary caregiver weekly had higher odds of *periportal thickening* compared to children who were never taken to the lake (OR 2.61, 95% CI: 1.07- 6.34**)**. This finding remained significant when adjusted for confounders (OR 3.02 95% CI: 1.19,7.63) (Table 2). No other variable

was found to be associated with the prevalence of *periportal thickening* or *established fibrosis* at baseline. No variables were associated with *thickened second order portal branches*.

As shown in Table 3, *rounded caudal liver edge* was associated with moderate (OR 2.25, 95 % CI: 1.02,4.98) or high *S. mansoni* infection intensity (OR 3.81, 95% CI: 1.76, 8.22) .The association was no longer significant in analysis adjusted for age, sex and maternal education in the case of moderate *S. mansoni* infection (OR 2.04, 95% CI: 0.90, 4.63), but remained significant in the case of high intensity infection (OR 3.31 95% CI: 1.46, 7.51). A *rounded caudal liver edge* was more common in children who were taken to the lake daily compared to never (OR 2.71, 95% CI: 1.02-7.20), however the association was no longer significant when adjusting for confounders(OR 2.68, 95% CI: 0.99, 7.29) (Table 3). This is explained by a confounding relationship between maternal education and going to the lake: higher maternal education was found to be associated with fewer visits to the lake (OR 0.64 95% CI: 0.42, 0.98). There were too few children with an abnormal *right liver lobe* (AAL) score for further analysis.

Reactive malaria RDT (56/354, 15.82%) was not found to be associated with US measures of liver morbidity. Spleen size was not measured on US, however of the 3/343 (0.87%) children with a palpable spleen on examination, none had a reactive malaria RDT. Of the 5/360 (1.38%) PSAC with clinical abdominal distension, 3 (60%) were positive for malaria on RDT. A number of children had biochemical abnormalities associated with liver morbidity: 54/347 (16%) had an elevated AST, 11/347 (3.2%) had an elevated ALT, and 2/346 (0.6%) had an elevated total bilirubin on blood tests. The majority of the children were anaemic (200/354, 56%) (Table 1).

Expert review, which consisted of reviews of static images (J.R.) compared with image patterns as determined by ultrasonographers in the field, found agreement of an image pattern of B or C in 23/36 (63.8%) of cases, yielding a Cohen Kappa of 0.65, indicating substantial agreement. The expert reviewer only agreed with 3/32 (9.3%) sets of images in the sample identified as having a *rounded caudal liver edge*. Spleen measurements were not routinely done as part of the ultrasonography performed in the field, however, the expert reviewer measured spleens where possible (58 cases). Of these 25 (46.5%) had a moderately abnormal height adjusted spleen measurement

(>2SD from the mean as per reference ranges in the Niamey Protocol), and a further 5/58 (8.6%) had an abnormal measurement (>4SD). Height adjusted spleen measurements were not found to be associated with malaria, and moderately abnormal measurements were not significantly associated with *S. mansoni* infection intensity (OR 4.1, 95% CI: 0.93- 18.1).

Discussion:

In our cohort of children aged 12-47 months from the shores of Lake Albert, Uganda, they had both detectable and incipient schistosomiasis-related hepatosplenic morbidity on ultrasound scans. A small (2%) but clinically relevant number of children in our trial had evidence of *periportal fibrosis*, consistent with other few studies on PSAC liver morbidity [22]. Importantly, 17 % of children had *periportal thickening*, considered to be a precursor of downstream liver fibrosis. A significant proportion of children had more non-specific findings such as *rounded caudal liver edge*, which was associated with *S.mansoni* heavy infection, and other findings like abnormally thick second order portal branches are of unclear clinical significance but likely deleterious to children's normal liver development.

Image Pattern C is characterized by echogenic rings which indicate pathognomic *S. mansoni* related 'pipe stem' fibrosis[14]. Image Pattern B indicates less prominent diffuse echogenic foci. Other PSAC studies in Uganda and Kenya [22] found a 10% and 15 % prevalence [23] of Pattern B respectively. In school-age children in Kenya, Samuels et al [26] found a higher prevalence of 25%. Image Pattern B is thought to be a possible intermediate stage in the development of hepatic fibrosis in adults[13], but its significance in children is unclear. Nalugwa et al.(REF) found Image Pattern B to be significantly more prominent in infected children compared to non-infected children, and found a strong association with *S. mansoni* infection intensity[22]. However, in Kenya , Image Pattern B was associated with high infection intensity pre Praziquantel treatment, but not associated post treatment, and was more closely related to malaria infection[23]. Samuels found no association between Image Pattern B and schistosomiasis. A greater understanding of the pathogical and biological significance of Image Pattern B in PSAC is needed.

Our finding of a significant number of children (42%) having moderately or significantly abnormally thick second order portal branches is in line with findings in older children [2026]. However, a large study of Kenyan and Egyptian adults, portal branch enlargement was found in 18-40% of participants with otherwise normal liver ultrasounds, suggesting that this measure may overestimate risk of hepatic morbidity[13]. Pathology studies have confirmed that hepatic morbidity in children begins with granulomatous change and inflammation in the small portal branches prior to increased portal pressure, splenomegaly and dilatation of the portal vein[2].

Other studies examining ultrasound markers of *S. mansoni* related morbidity in children have found a significant number of children with an enlarged left liver lobe, which has been linked to acute schistosomiasis[20272328]. In contrast, only 2 of the children in our cohort had this abnormality. However, some studies have found no association between left lobe enlargement and infection intensity in small children[2915], suggesting the possibility of another etiological agent at play. *S. mansoni* has been suggested to exacerbate underlying chronic *Plasmodium* infections[15]. A possible explanation for our low rates of hepatomegaly may be the relatively low malaria infection rates found in our study.

This study found important confounding relationships. Higher maternal education and fewer lake visits were associated with lower infection intensity, highlighting the importance of health education in the effort to combat schistosomiasis. However, the finding in adjusted analysis of a relationship between maternal education and the subjective measure of periportal thickening is unexpected and contrary to the literature in which higher maternal education is generally associated with decreased prevalence of schistosomiasis[303132]. The finding may be due to chance due to the number of tests conducted. Importantly, ultrasound markers of liver morbidity were not affected by malaria seropositivity in this cohort, which makes confounding of liver morbidity by malaria status unlikely. However, past/chronic malaria infection may still play a role in morbidity[15]. Spleen measurements were not available for all the children in the study limiting the association analysis.

To the best of our knowledge, this is the first study to measure interobserver variability to evaluate ultrasound-detectable schistosomiasis morbidity by expert review in

PSAC. Our expert review showed substantial agreement (Cohen's Kappa 0.67) with ultrasonographers in identifying Image Patterns of B or C, which is in keeping with interobserver agreement found in other studies in adults [3334]. However, there was poor agreement in identifying patients with a rounded caudal liver edge, a non-specific finding associated with hepatomegaly [3536]. Given the associations found between this outcome and both infection intensity and frequency of lake visits, more research should explore its clinical relevance in children living in endemic areas.

Our study had several limitations. Hepatitis B or C co-infection were not evaluated, which are important confounders in schistosomiasis-related hepatosplenic morbidity[3]. Based on other studies, prevalence of HbsAg positivity amongst pregnant women in Northern Uganda is close to 10%[37], with active Hepatitis C infection present in 2-8% of the population [3839]. Of note, the Niamey protocol helps to distinguish patterns of liver morbidity due to schistosomiasis from other etiologies, ameliorating this concern somewhat. Further, relatively few children had abnormal ultrasound findings, limiting the power of the study to detect associations, as evidenced by the wide confidence intervals.

Currently there is a lack of clear internationally accepted reference measurements for very small children (<80 cm) for key ultrasound parameters such as portal vein diameter, second order portal branch thickness, and even spleen and liver sizes. The Niamey Protocol provides reference values for children >80 cm based on Yazdapanah et al[40]. Spleen measurements are reported for a group of children 0-3 years old by Pelizzo et al, but those <80 cm are not differentiated[41]. Portal vein diameter measurements are available for 306 children from India, including PSAC, by height[42]. However, the majority of studies reporting organometry report the results of children >80 or 100 cm[4344], making it difficult to generalize to the smaller PSAC population.

Our study suggests that worryingly, incipient schistosomiasis related morbidity is already evident in this very young population in Uganda. Therefore, ensuring that PSAC are appropriately represented in research as well as for reference standards is of paramount importance. Findings of incipient schistosomiasis related hepatic morbidity is a call for action for the immediate inclusion of PSAC in MDA programmes, as the recent WHO guidelines recommend[9]. More work needs to be done on the

ground to implement this guideline given the partial reversibility of ultrasound changes with treatment and that later stages of hepatic fibrosis are difficult to reverse with treatment [4511]. Finally, pediatric formulations will help PZQ administration to young children, but access may be limited and crushed tablets, as shown in our trial, are a safe and effective alternative.

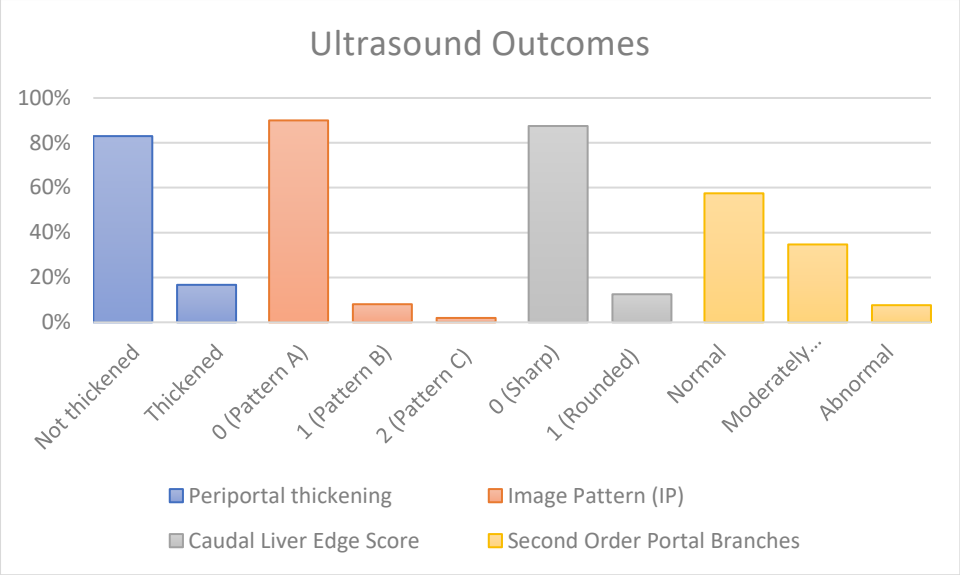
Tables

Table 1: Summary Statistics

Variable	Category	n/N (%)	Mean	Standard Deviation
Sex	Male	179/347 (51.6)		
	Female	168/347 (48.4)		
Age (months)		347	34.21	9.09
Father's Education	None	207/346 (59.8)		
	Primary School	129/346 (37.3)		
	Secondary School	10/346 (2.9)		
Mother's Education	None	204/339 (60.2)		
	Primary School	125/339 (36.9)		
	Secondary School/University	10/339 (3.0)		
Toilet Access	None	63/346 (18.2)		
	Public	1/346 (0.3)		
	Shared	237/346 (68.5)		
	Household	45/346 (13.0)		
How often is child taken to the lake	Never	72/345 (20.9)		
	Daily	214/345 (62.0)		
	Weekly	54/345 (15.7)		
	Monthly	5/345 (1.4)		
Clinical Splenomegaly	No	340/343 (99.1)		
	Yes	3/343 (0.9)		
Clinical Hepatomegaly	No	344/344 (100)		
	Yes	0/344 (0)		
Abdominal Distension	No	339/344 (98.6)		
	Yes	5/344 (1.4)		
Jaundice	No	362/344 (99.7)		
	Yes	1/344 (0.3)		
Malaria RDT	Reactive	56/344 (16.1)		
	Non-Reactive	291/344 (83.9)		
HIV Rapid Test	Reactive	4/347 (1.1)		
	Non- Reactive	343/347 (98.9)		

S. mansoni Infection intensity	Low	197/347 (56.8)		
	Moderate	83/347 (23.9)		
	High	67/347 (19.3)		
CAA baseline result	Geometric mean	336	140.89	8.90
CCA g-score		341	8.34	2.65
AST			35.02	8.17
	Normal (≤40 IU/L)	293/347 (84.4)		
	Abnormal (>40 IU/L)	54/347 (15.6)		
ALT		347	20.92	9.40
	Normal (≤40 IU/L)	336/344 (96.8)		
	Abnormal (>40 IU/L)	11/344 (3.2)		
Bilirubin		346	0.43	0.16
	Normal	351/346 (99.4)		
	Abnormal	2/346 (0.6)		
Fecal Calprotectin		346	215.0	246.8
	Normal	119/346 (34.4)		
	Abnormal	227/346 (65.6)		
Occult Blood in Stool	Present	86/315 (27.3)		
	Absent	229/315 (72.7)		
Anemia	No	154/354 (43.5)		
	Yes	200/354 (56.5)		

Figure 2: Frequency of Ultrasound Outcomes



Outcome	Categories	Frequency (N)	Percent
Evidence of periportal thickening	0 (No)	289 (347)	83.3
	1 (Yes)	58 (347)	16.7
Image Pattern for Liver parenchyma (Score 0-8)- IP score Niamey protocol	0 (Pattern A)	311 (347)	89.6
	1 (Pattern B)	29 (347)	8.36
	2 (Pattern C)	7 (347)	2.02
Caudal Liver Edge Score	0 (Sharp)	303 (347)	87.3
	1 (Rounded)	44 (347)	12.7
Right liver lobe (AAL score)	Mean + < 2SD	304 (309)	98.38
	Mean + >2 – 4 SD	5 (309)	1.62
Left liver lobe (PSL score)	Mean + < 2SD	308 (310)	99.35
	Mean + >2 – 4 SD	0 (310)	0
	Mean > 4SD	2 (310)	0.65
Portal vein diameter score	Mean + < 2SD	309 (309)	100
Surface irregularity score	0 (Sharp)	346 (347)	99.7
	1 (Rounded)	1 (347)	0.29
Presence of Collateral veins	Absent	347 (347)	100
Presence of Ascites	Absent	347 (347)	100
Thickened Gallbladder	Absent	347 (347)	100
Second Order Portal Branches	Mean + <2SD	200 (347)	57.6
	Mean + 2- 4 SD	120 (347)	34.6
	Mean > 4SD	27 (347)	7.78

Table 2: Associations between explanatory variables and periportal thickening, from logistic regression

Variable	Category	n/N (%) with periportal thickening	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Sex	Male	28/179 (15.6%)	1 (ref)	1 (ref)**
	Female	30/168 (17.9%)	1.17 (0.67, 2.06)	1.10 (0.62, 1.95)
Age	**Per month increase**		**1.03 (1.00, 1.07)**	**1.04 (1.00, 1.07)**
Father's education	None	32/207 (15.5%)	1 (ref)	1 (ref)
	Primary	26/129 (20.2%)	1.38 (0.78, 2.45)	0.99 (0.44,2.27)
	Secondary	0/10 (0%)	--	-
Mother's education	None	29/204 (14.2%)	1 (ref)	1 (ref)
	Primary	**27/125 (21.6%)**	**1.66 (0.93, 2.97)**	**1.86 (1.03, 3.37)**
	Secondary	1/10 (10.0%)	0.67 (0.08, 5.49)	0.76 (0.09,6.32)
Toilet access	None	9/63 (14.3%)	1 (ref)	1 (ref)
	Shared	5/45 (11.1%)	0.75 (0.23, 2.41)	0.77 (0.23,2.57)
	Household	44/238 (18.5%)	1.36 (0.63, 2.96)	1.42 (0.64,3.12)
Malaria result	Negative	47/291 (16.2%)	1 (ref)	1 (ref)
	Positive	11/56 (19.6%)	1.27 (0.61, 2.63)	1.13 (0.53,2.42)
S. mansoni infection intensity	Low (<100 epg)	37/197 (18.8%)	1 (ref)	1
	Moderate (100-399 epg)	11/83 (13.3%)	0.66 (0.32, 1.37)	0.62(0.29, 1.32)
	High (>=400 epg)	10/67 (14.9%)	0.76 (0.35, 1.62)	0.69(0.31,1.56)
How often is child taken to the lake	Never	10/72 (13.9%)	1 (ref)	1 (ref)
	Daily	31/214 (14.5%)	1.05 (0.49- 2.27)	0.94(0.42,2.09)
	Weekly	**16/54 (29.6%)**	**2.61 (1.07- 6.34)**	**3.02 (1.19,7.63)**
	Monthly	1/5 (20%)	1.55 (0.16- 15.32)	1.14 (0.11,12.0)

*Adjusted for Age, Sex and Maternal Education.

Table 3: Associations between explanatory variables and rounded caudal liver edge, from logistic regression

Variable	Category	n/N(%) with caudal liver edge score 1	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Sex	Male	24/179 (13.4%)	1 (ref)	1 (ref)
	Female	20/168 (11.9%)	0.87 (0.46 -1.65)	0.87(0.46,1.65)
Age	Per month increase		1.03 (0.99- 1.07)	1.02(0.98,1.06)
Father's education (highest)	None	29/207 (14.0%)	1 (ref)	1 (ref)
	Primary	14/129 (10.9%)	0.75 (0.38- 1.47)	1.42 (0.57, 3.55)
	Secondary	1/10 (10.0%)	0.68 (0.08- 5.59)	1.05 (0.10, 11.59)
Mother's education (highest)	None	32/204 (15.7%)	1(ref)	
	Primary	10/125 (8.0%)	0.47 (0.22- 0.99)	0.50 (0.23, 1.06)
	Secondary	2/10 (20.0%)	1.34 (0.27- 6.62)	1.43 (0.29, 7.16)
Toilet access	None	10/63 (15.9%)	1 (ref)	
	Shared	4/45 (8.9%)	0.52 (0.15 -1.77)	0.47(0.13, 1.68)
	Household	30/238 (12.6%)	0.76 (0.35- 1.66)	0.79 (0.36, 1.74)
Malaria result	Negative	36/291 (12.4%)	1 (ref)	1 (ref)
	Positive	8/56 (14.3%)	1.18 (0.52- 2.70)	1.08 (0.46, 2.52)
S mansoni infection intensity	Low (<100 epg)	15/197 (7.6%)	1 (ref)	
	Moderate (100-399 epg)	13/83 (15.7%)	**2.25 (1.02- 4.98)**	2.04 (0.90, 4.63)
	High (>400 epg)	16/67 (23.9%)	**3.81 (1.76- 8.22)**	**3.31 (1.46- 7.51)**
How often is child taken to the lake	Never	5/72 (6.9%)	1 (ref)	
	Daily	**36/214 (16.8%)**	**2.71 (1.02- 7.20)**	2.68 (0.99, 7.29)
	Weekly	3/54 (5.6%)	0.79 (0.18- 3.45)	0.84 (0.19, 3.78)
	Monthly	0/5 (0%)	1 (empty)	1 (empty)

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APPENDIX:

Table 1: Unadjusted Associations between explanatory variables and periportal thickening, from logistic regression

Variable	**Category**	**n/N (%) with periportal thickening**	**Unadjusted OR (95% CI)**	**p-value**
Sex	Male	28/179 (15.6%)	1 (ref)	
	Female	30/168 (17.8%)	1.17 (0.66, 2.06)	0.58
Age	**Per month increase**		**1.03 (1.00, 1.06)**	**0.08**
Father's education	None	32/207(15.5%)	1 (ref)	
	Primary	26/129(20.2%)	1.38 (0.78, 2.44)	0.27
	Secondary	0/10 (0%)	--	
Mother's education	None	29/204 (14.2%)	1 (ref)	
	Primary	**27/125 (21.6%)**	**1.66 (0.93, 2.97)**	**0.09**
	Secondary	1/9 (11.1%)	0.75 (0.09, 6.26)	0.79
Toilet access	None	9/63 (14.3%)	1 (ref)	
	Shared	5/45 (11.1%)	0.75 (0.23, 2.41)	0.63
	Household	44/238 (18.5%)	1.36 (0.62, 2.96)	0.44
Malaria result	Negative	47/291(16.2%)	1 (ref)	
	Positive	11/56 (19.6%)	1.27 (0.61, 2.63)	0.52
S. mansoni infection intensity	Low (<100 epg)	37/197 (18.8%)	1 (ref)	
	Moderate (100-399 epg)	11 /83 (13.2%)	0.67 (0.32, 1.37)	0.26
	High (>=400 epg)	10/67 (14.9%)	0.76 (0.35, 1.62)	0.48
Initial CAA result	Per unit increase		0.99 (.99, 1.00)	0.22
Initial CCA gscore	Per unit increase		.97 (0.87, 1.08)	0.56
How often is child taken to the lake	Never	10/ 72 (13.9%)	1 (ref)	

	Daily	31/214 (14.5%)	1.05 (0.49- 2.26)	0.90
	Weekly	**16/54 (29.6%)**	**2.61 (1.07- 6.34)**	**0.03**
	Monthly	1/5 (20%)	1.55(0.16-15.3)	0.71
WAZ[1]	Per unit increase		0.99 (0.76, 1.27)	0.92
HAZ[2]	Per unit increase		1.00 (0.84, 1.20)	0.96
WHZ[3]	Per unit increase		0.94 (0.71, 1.26)	0.71
BMI-for-age z-score	Per unit increase		0.96 (0.73, 1.26)	0.79
Underweight	No	57/335 (17.0%)	1 (ref)	
	Yes	1/11 (9.1%)	0.49 (0.06, 3.90)	
Stunted	No	46/279 (16.5%)	1 (ref)	
	Yes	12/64 (18.7%)	1.17 (0.58, 2.36)	0.66
Wasted	No	58/343 (16.9%)	1 (ref)	-
	Yes	0/3 (0%)	--	-
Haemoglobin	Per unit increase		0.87 (0.68, 1.12)	0.29
Anaemia	No	24/149 (16.1%)	1 (ref)	
	Yes	34/198 (17.2%)	1.08 (0.61, 1.91)	0.79
Occult blood in stool	No	42/229 (18.3%)	1.38 (0.69, 2.77)	0.27
	Yes	12/86 (13.9%)	1 (ref)	
Calprotectin	Per unit increase		1.00 (0.99, 1.00)	0.40

[1]Weight-for-age z-score, [2]Height-for-age z-score, [3]Weight-for-height z-score

Table 2. Unadjusted associations between explanatory variable and image pattern for liver parenchyma, from ordinal logistic regression

	Category	**Image pattern 0**	**Image pattern 1**	**Image pattern 2**	**Crude OR (95% CI)**	**p-value**
Sex	Male	166 (92.7%)	8 (4.5%)	5 (2.8%)	1 (ref)	
	Female	145 (86.3%)	21 (12.5%)	2 (1.2%)	1.95 (0.95, 4.00)	0.06
Age	Per month increase				0.03 (-0.01,0.07)	0.15
Father's education	None	184 (88.9%)	18 (8.7%)	5 (2.4%)	1 (ref)	
	Primary	116(89,9%)	11 (8.5%)	2 (1.55%)	0.89(0.43, 1.82)	0.75
	Secondary	10(100%)	0 (0%)	0 (0%)	--	
Mother's education	None	183(89.7%)	18 (8.8%)	3 (1.5%)	1 (ref)	
	Primary	110(88.2%)	11 (8.8%)	4 (3.2%)	1.21 (0.6,2.47)	0.60
	Secondary	9(100%)	0 (0%)	0 (0%)	--	
	University	1 (100%)	0 (0%)	0 (0%)		
Toilet access	None	57 (90.5%)	3 (4.8%)	3 (4.8%)	1 (ref)	
	Shared	41 (91.1%)	4 (8.9%)	0 (0%)	0.88 (0.22,3.16)	0.85
	Household	212 (89.1%)	22 (9.2%)	4 (1.7%)	1.12 (0.44, 2.85)	0.24
Malaria result	Negative	263 (90.4%)	23 97.9%)	5 1.7%)	1 (ref)	
	Positive	46 (85.7%)	6 (10.7%)	2 (3.6%)	1.58 (0.68,3.67)	0.29
S. mansoni infection intensity	Low (<100epg)	172 (87.3%)	20 (10.1%)	5 (2.5%)	1 (ref)	
	Moderate (100-399 epg)	78 (94%)	4 (4.8%)	1 (1.2%)	0.44 (0.16,1.19)	0.11

	High (>=400epg)	61 (91.0%)	5 (7.5%)	1 (1.5%)	0.67 (0.26,1.72)	
Initial CAA result	Per unit increase				0.99 (.99, 1.00)	0.78
Initial CCA gscore	Per unit increase				0.99 (0.87- 1.12)	0.88
How often is child taken to the lake	Never	65 (90.3%)	5 (6.9%)	2 (2.8%)	1 (ref)	
	Daily	197 (92.1%)	15 (7.0%)	2 (0.93%)	0.79 (0.31, 1.98)	0.61
	Weekly	43 (79.63%)	8 (14.8%)	3 (5.6%)	2.38 (0.86, 6.63)	0.09
	Monthly	4 (80%)	1 (20%)	0 (0%)	2.19 (0.22, 21.9)	0.51
Weight-for-age z-score	Per unit increase				1.07 (0.78, 1.47)	0.65
Height-for-age z-score	Per unit increase				1.00 (0.81, 1.25)	0.96
Weight-for-height z-score	Per unit increase				1.09 (0.76, 1.55)	0.64
BMI-for-age z-score	Per unit increase				1.10 (0.79, 1.54)	0.55
Underweight	No	299 (89.2%)	29 (8.7%)	7 (2.1%)	1 (ref)	
	Yes	11 (100%)	0 (0%)	0 (0%)	--	0.98
Stunted	No	251 (90.0%)	24 (8.6%)	4 (1.4%)	1 (ref)	
	Yes	56 (87.5%)	5 (7.8%)	3 (4.7%)	1.32 (0.57,3.05)	0.51
Wasted	No	307 (89.5%)	29 (8.4%)	7 (2.0%)	1 (ref)	
	Yes	3 (100%)	0 (0%)	0 (0%)	--	0.99
Haemoglobin	Per unit increase				1.09 (0.79, 1.50)	0.61
Anaemia	No	130 (87.2%)	18(12.1%)	1 (0.67%)	1 (ref)	0.25
	Yes	181 (91.4%)	11 (5.6%)	6 (3.0%)	0.66 (0.33,1.33)	
Occult blood in stool	Yes	78 (90.7%)	8 (9.3%)	0(0%)	1 (ref)	0.49
	No	202 (88.9%)	29 (9.2%)	6 (1.9%)	1.33 (0.58,3.06)	
Calprotectin	Per unit increase				0.99 (0.99, 1.00)	0.08

Table 3: Unadjusted associations between explanatory variables and rounded caudal liver edge , from logistic regression

Variable	**Category**	**n/N(%) with caudal liver edge score 1**	**Unadjusted OR (95% CI)**	**p-value**
Sex	Male	24/179 (13.4%)	1 (ref)	
	Female	20/168 (11.9%)	.87 (.46-1.64)	0.674
Age	Per month increase		1.02 (.99- 1.07)	0.17
Father's education (highest)	None	29/207 (14.0%)	1 (ref)	
	Primary	14/129 (10.8%)	.75(0.38- 1.47)	0.40

	Secondary	1/10 (10.0%)	.72 (.08- 5.58)	
Mother's education (highest)	None	32/204 (15.7%)	1(ref)	
	Primary	10/125 (8.0%)	.47(.22- 0.99)	0.05
	Secondary	2/9 (22.2%)	1.53(.30- 7.73)	0.60
Toilet access	None	10/63 (15.9%)	1 (ref)	
	Shared	4/45 (8.9%)	.51 (.144 -1.77)	0.29
	Household	30/238 (12.6%)	.77 (.35- 1.66)	
Malaria result	Negative	36/291 (12.4%)	1 (ref)	
	Positive	8/56 (14.3%)	1.18 (.51- 2.7)	0.69
S mansoni infection intensity	Low (<100 epg)	15/ 197 (7.6%)	1 (ref)	
	Moderate (100-399 epg)	13/ 83 (15.6%)	2.25 (1.02- 4.98)	.044
	High (>400 epg)	16/67 (23.9%)	3.80 (1.76- 8.22)	.001
Initial CAA result	Per unit increase		1.00 (1.00, 1.00)	0.255
Initial CCA gscore	Per unit increase		1.11 (0.97-1.28)	0.12
How often is child taken to the lake	Never	5/72 (6.94%)	1 (ref)	
	Daily	**36/214 (16.8%)**	**2.71 (1.03- 7.19)**	**0.045**
	Weekly	3/54 (5.6%)	0.79 (0.18- 3.45)	0.752
	Monthly	0/5 (0%)	1 (empty)	
Weight-for-age z-score	Per unit increase		1.13 (0.85- 1.51)	.385
Height-for-age z-score	Per unit increase		1.12 (0.93 -1.36)	.218
Weight-for-height z-score	Per unit increase		0.98 (0.71- 1.36)	.910
BMI-for-age z-score	Per unit increase		0.93 (.69 -1.26)	.648
Underweight	No	43/335 (12.8%)	1 (ref)	.715
	Yes	1/11 (9.1%)	0.68 (.08- 5.43)	
Stunted	No	39/279 (13.9%)	1 (ref)	
	Yes	5/64 (7.81%)	.52 (.19- 1.38)	.190
Wasted	No	43/343 (12.5%)	1 (ref)	
	Yes	0/3 (0%)		
Haemoglobin (per unit increase)	Per unit increase		.90 (0.68- 1.18)	.442
Anaemia	No	17/1549 (11.4%)	1 (ref)	
	Yes	27/198 (13.6%)	1.08 (.61-1.91)	.793
Occult blood in stool	No	27/229 (11.8%)	1 (ref)	
	Yes	16/86 (18.6%)	1.7 (0.87-3.36)	.120
Calprotectin	Per unit increase		.998 (.997-1.00)	0.06

Table 4 Unadjusted associations between explanatory variable and second order portal branches, from ordinal logistic regression

Variable	Category	Normal Range	Moderately Abnormal	Abnormal	Crude OR (95% CI)	p-value
Sex	Male	103(57.5%)	60 (33.5%)	16 (8.9%)	1 (ref)	0.83
	Female	97 (57.7%)	60 (35.7%)	11 (6.5%)	0.95 (0.68, 1.4)	
Age	Per month increase				0.99	0.52
Father's education	None	122 (58.9%)	64 (30.9%)	21 (10.1%)	1 (ref)	
	Primary	72 (55.8%)	52 (40.3%)	5 (3.9%)	1.01 (0.65, 1.5)	0.97
	Secondary	5 (50.0%)	4 (40.0%)	1 (10.0%)	1.36 (0.40, 4.6)	0.62
Mother's education	None	120 (58.8%)	63 (30.9%)	21 (10.3%)	1 (ref)	
	Primary	68 (54.4%)	52 (41.6%)	5 (4.0%)	1.05(0.68,1.63)	0.81
	Secondary	5 (55.5%)	3(33.3%)	1 (11.1%)	1.14(0.30,4.28)	0.84
	University	1 (100)	0 (0%)	0 (0%)	-	
Toilet access	None	34 (54.0%)	26 (41.3%)	3 (4.8%)	1 (ref)	
	Shared	27 (60.0%)	14 (31.1%)	4 (8.9%)	0.86(0.40,1.83)	0.70
	Household	138 (57.9%)	80 (33.6%)	20 (8.4%)	0.92(0.53, 1.58)	0.77
Malaria result	Negative	168 (57.7%)	105 (36.1%)	18 (6.2%)	1 (ref)	
	Positive	32 (57.1%)	15 (26.8%)	9 (16.1%)	1.2 (0.51, 2.16)	0.51
S. mansoni infection intensity	Low (<100epg)	113 (57.3%)	74 (37.6%)	11 (5.1%)	1 (ref)	0.28
	Moderate (100-399 epg)	47 (56.6%)	31 (37.3%)	5 (6.0%)	1.04(0.63,1.72)	0.87
	High (>=400epg)	40 (59.7%)	15 (22.4%)	12 (18.0%)	1.15(0.65, 2.02)	0.63
Initial CCA result	Per unit increase				1.15 (.34, 3.84)	0.82
Initial CCA gscore	Per unit increase				0.98 (0.90- 1.06)	0.64
How often is child taken to the lake	Never	40 (55.5%)	30 (41.7%)	2 (2.8%)	1 (ref)	
	Daily	123 (57.5%)	70 (32.7%)	21 (9.8%)	1.05(0.62,1.76)	0.95
	Weekly	34 (62.9%)	16 (29.6%)	4 (7.4)	0.82(0.40, 1.66)	0.58
	Monthly	1 (20%)	4 (80%)	0 (0%)	2.62(0.55, 12.5)	0.23
Weight-for-age z-score	Per unit increase				1.03(0.85, 1.25)	0.75
Height-for-age z-score	Per unit increase				1.03(0.90, 1.18)	0.67
Weight-for-height z-score	Per unit increase				1.01(0.82, 1.24)	0.94

BMI-for-age z-score	Per unit increase				1.01(0.83, 1.23)	0.92
Underweight	No	194 (57.9%)	115 (34.3%)	26 (7.76%)	1 (ref)	
	Yes	6 (54.5%)	5 (45.4%)	0 (0%)	0.99(0.31,3.12)	0.99
Stunted	No	164 (58.8%)	91 (32.6%)	24 (8.6%)	1 (ref)	
	Yes	34 (53.1%)	28(43.7%)	2 (3.1%)	1.11 (0.66,1.88)	0.68
Wasted	No	199 (58.0%)	118 (34.4%)	27 (7.6%)	1 (ref)	
	Yes	1 (33.3%)	2 (66.6%)	0 (0%)	1.9 (0.25, 14.1)	0.53
Haemoglobin	Per unit increase				0.90 (0.74, 1.1)	0.29
Anaemia	No	85 (57.0%)	54 (36.2%)	10 (6.7%)	1 (ref)	
	Yes	115 (58.1%)	66 (33.3%)	17 (8.6%)	0.99 (0.65,1.51)	0.97
Occult blood in stool	Yes	48 (55.8%)	28 (32.6%)	10 (11.6%)	1 (ref)	
	No	126 (55.0%)	88 (38.4%)	15 (6.5%)	0.94 (0.57,1.53)	0.81
Calprotectin	Per unit increase				1.00 (0.99, 1.00)	0.49