Am. J. Trop. Med. Hyg., 92(5), 2015, pp. 952–958
doi:10.4269/ajtmh.14-0346
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Morbidity Associated with Schistosomiasis Before and After Treatment in Young Children in Rusinga Island, Western Kenya

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Abstract. *Schistosoma mansoni* infection is a major cause of organomegaly and ultimately liver fibrosis in adults. Morbidity in pre-school-aged children is less defined, and they are currently not included in mass drug administration (MDA) programs for schistosomiasis control. We report results of a study of the association of schistosomiasis with organomegaly in a convenience sample of 201 children under 7 years old in Rusinga, Kenya on two cross-sectional visits, before and after praziquantel treatment. Data included stool examination and serology for schistosomiasis, the Niamey ultrasound protocol to stage hepatosplenic morbidity including organomegaly, and potential confounders including malaria. Unadjusted and adjusted Poisson regressions were performed. The baseline prevalence of schistosomiasis by antibody and/or stool was 80.3%. Schistomiasis was associated with hepatomegaly (adjusted prevalence ratio [aPR] = 1.4; 95% confidence interval [CI]: 1.0–2.1) and splenomegaly (aPR = 2.1; 95% CI: 1.2–3.7). The association with hepatomegaly persisted posttreatment (aPR = 1.4; 95% CI: 1.1–1.6). Schistosomiasis was associated with morbidity in this cohort. Efforts to include young children in mass treatment campaigns should intensify.

INTRODUCTION

Schistosomiasis, a chronic tropical parasitic disease caused by infection with *Schistosoma* spp., is a major cause of global disability[1] concentrated in sub-Saharan Africa.[2] Pathology results from egg deposition in host tissues, particularly liver tissue in the case of *S. mansoni*, causing inflammation, organomegaly, and fibrosis. Infection prevalence peaks in 8- to 15-year-olds,[3] but morbidity is best documented in older age groups in association with chronic infection. In addition to prevention through sanitation, the cornerstone of global schistosomiasis control is regular mass drug administration (MDA) using praziquantel,[4] with school-aged children as the priority target group for treatment due to the focus on reducing morbidity from chronic infection.

Currently, mass distribution of praziquantel for children under 4 years or 94 cm in height is not recommended, and in practice, children not in school for any reason are rarely treated. However, children too young or small for MDA have considerable infection prevalences[5,6] in multiple African countries, where they can be exposed through bathing and other activities,[7,8] and they can be treated with no serious adverse events.[9–13] The morbidity pre-school-aged children (PSAC) experience from infection is not well defined, though: effects are known to include fecal occult bleeding,[14,15] hematuria, proteinuria,[16] ultrasound abnormalities,[17,18] and possibly anemia,[19,20] but clinical implications remain unclear. Thus, although these findings have prompted calls for including PSAC in MDA,[21] a 2010 WHO meeting concluded that more evidence was necessary.

The major tool for assessing *S. mansoni* infection–associated morbidity in older patients is ultrasound[22–28] using the WHO-recommended Niamey scoring system.[29,30] It includes assessment of expected morbidities such as splenomegaly and left lobe hepatomegaly, as well as successively more pronounced liver ultrasound changes scored as image patterns (IP) A (normal), B ("starry sky," abnormal linear opacities of unclear significance), and C through F (progressive hepatic fibrosis). These characteristic, partially reversible[31,32] schistosomiasis-associated abnormalities in adults have also been found in school-aged children,[33,34] but morbidity in PSAC using this system or ultrasound more generally is again not well characterized.

Thus ultrasound investigations in PSAC have potential to provide clarity on morbidities associated with schistosomiasis, information that is needed to support decisions about inclusion in MDA. We investigated the association of *S. mansoni* infection in PSAC with Niamey liver texture pattern and organomegaly, as well as other indicators of morbidity including growth, anemia, and liver function tests (LFTs).

METHODS

Ethics statement. This study was approved by the Scientific Steering and Ethics Review Committees of the Kenya Medical Research Institute (KEMRI, SSC No. 2185) and of the Institutional Review Board of the U.S. Centers for Disease Control through a reliance agreement with KEMRI. Parents gave written informed consent for all participants. All children diagnosed with *S. mansoni* infection were treated with praziquantel (crushed, 40 mg/kg), those with soil-transmitted helminth (STH) infections with 400 mg albendazole, and those with malaria with Coartem® Dispersible. Any diagnosed with other abnormalities were referred for pediatric follow-up.

Study site and population. Rusinga is a Lake Victoria island in Mbita district in western Kenya, located in a region with known high prevalence of schistosomiasis among school-aged children.[35] Intestinal schistosomiasis attributable to *S. mansoni* is the main form of infection locally, with a few isolated foci of *S. haematobium* identified in adjacent districts.[36] Prior to

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this study, no MDA for schistosomiasis had been conducted in the area.

Study design, sample size, and recruitment. We conducted a nested study within a larger ongoing community-randomized trial of the impact of integrated programs for control of neglected tropical diseases. Inclusion criteria for the parent study were residence in the district, an initial reported age of 1 year or more, and willingness to participate; the exclusion criterion was acute illness requiring immediate treatment. The eight villages with the highest community prevalences of *S. mansoni* infection as determined in the parent study were selected for our nested study: Utajo, Kamayoge, Kaktemo, Wariga "A," Kamgere, Wakwala, Dier Aora, and Kakrigu (prevalence 34.0–92.5%) (Maurice Odiere, unpublished data). In each village, the community health worker and the study field team mobilized all willing mother-PSAC dyads enrolled in the parent study to participate in the nested study. The sample size of 201 in this exploratory study was limited by resources and willingness of enrolled dyads to participate.

We collected pre–post data on prevalence of schistosome infection and association with morbidities in PSAC, in the form of two serial cross-sectional studies in the same cohort before and after the administration of praziquantel. After the baseline visit, the praziquantel (40 mg/kg) was delivered to all children who could be located in one of two treatment campaigns conducted 3 or 5 months later. The interruption between treatment periods was due to local religious activities. The follow-up visit was then conducted, falling 1.5–2.0 months and 3.5–4.0 posttreatment of children treated in the first and second campaigns, respectively.

Data collection. Baseline data, obtained at either the nested study baseline visit (May 2012) or parent study enrollment up to 2 weeks prior, included a parental questionnaire assessing symptoms consistent with acute schistosome infection (fever, rash or swelling, headache, muscle aches, dry cough or wheeze or trouble breathing, decreased activity level, malaise, diarrhea, loss of appetite, weight loss, and diaphoresis) in the past 2 months; 2 mL venous blood collected for serology and LFTs; one stool for ova of *S. mansoni*; fingerstick blood for hemoglobin and thick blood smears for malaria; height and weight to assess nutritional status; and ultrasound examination according to the Niamey protocol by a single experienced research ultrasonographer, with additional image capture (see below). Community interviewers visited enrolled families at home to obtain documentation of birthdates using birth certificates, baptism cards, or antenatal clinic visit cards.

Data obtained at the posttreatment visit (December 2012) included 2 mL venous blood collected for rapid diagnostic test (RDT) for malaria due to *Plasmodium falciparum* or other species (SD Bioline Malaria Ag P.f/Pan, Borhagal-ro, Giheung-gu, South Korea), hemoglobin, and repeat ultrasound examination according to the Niamey protocol. A second height and weight measure was obtained in February 2013.

All ultrasounds were performed by the same research ultrasonographer, using a generator-powered Aloka SSD-900V portable ultrasound machine with a UST-979-3.5 MHz convex transducer, with image capture using a Medicap USB-200. The standard Niamey protocol was observed, with measurements including spleen length, liver span, and liver IP, and with scoring done per the protocol by the ultrasonographer. Images of standard liver views were also captured, for expert review by an ultrasound radiologist for any novel findings.

Laboratory methods. Duplicate slides were prepared by the Kato-Katz method to quantify ova of *S. mansoni*. The stool template held approximately 41.7 mg of feces. Slides were read within 12 hours of defecation. Thick blood smears for malaria were made on-site at the time of blood collection and stained with Giemsa stain in the laboratory.[37] Quality control for microscopy was performed by an independent, senior microscopist. This expert result was used in cases of conflict. Tests for antibodies to schistosomes were performed by enzyme-linked immunosorbent assay (ELISA) using soluble worm antigen preparation using previously described methods.[38] This test does not distinguish between *Schistosoma* spp.

LFTs were performed using the Cobas Integra 400 plus biochemistry analyzer (Roche, Berlin, Germany) with upper limit normal values of 37 U/L for aspartine aminotransferase (AST), 42 U/L for alanine aminotransferase (ALT), and 17.0 μmol/L for bilirubin. Detection of hepatitis B surface antigen (HBsAg) was performed using the KEMRI Hepcell kit, a reverse passive hemagglutination-based kit, with confirmation of positives via the Murex HBsAG Confirmatory Version 3 kit (DiaSorin,Vercelli, Italy).

Statistical analysis. Analysis was performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC). Each model was fit on the subsample of participants possessing complete data on all variables included in the model.

Cross-sectional analysis of baseline visit data. Children were classified based on infection testing results as either uninfected (egg-negative and antibody-negative) or infected (egg-positive and/or antibody-positive). Egg-positive (egg+) children were further classified according to WHO standards[39] as having infection of light (1–99 eggs per gram [epg]), moderate (100–399 epg), or heavy (equal to or greater than 400 epg) intensity.

Organomegaly was diagnosed based on height at the baseline visit using the height-based cutoffs originally determined by Yazdanpanah and others,[40] with organ spans > 2 standard deviations above height-adjusted means considered organomegalic.

Initially, we examined prevalences of infection categories and outcome findings, and associations of key findings with infection category. Based on the high prevalence of IPB, we then analyzed associations of key potential predictive factors and morbidities with IPB. Poisson regression was used except for serum transaminase and bilirubin outcomes, for which linear regression was used (after log transformation in the case of bilirubin). Both unadjusted and adjusted analyses (corrected for sex and age) were performed, with clustering by village accounted for via generalized estimating equations[41] and an exchangeable correlation structure. An exact model was fit for the analyses of malaria diagnosis by microscopy. A subanalysis limited to only children ineligible for MDA by virtue of height < 94 cm was also performed.

Cross-sectional analysis of posttreatment visit data. Because serology was not repeated at follow-up, individuals were classified only as egg-positive or egg-negative. Height at the time of follow-up was interpolated from height at the repeat measurement roughly 2 months later, assuming linear growth between the first and second anthropometry measures. Organometry outcomes were determined as before using this interpolated height.

Regressions were run using morbidity outcomes for schistosomiasis and those predictive factors for IPB that had shown significant associations at baseline, and with malaria

TABLE 1
Baseline and posttreatment prevalences of demographic traits and findings

Type	Trait	Baseline (N = 201)			Posttreatment (N = 180)		
		n	N	%	n	N	%
Age	< 2.5 years	32	198	16.2	7	180	3.9
	2.5 years ≤ age < 4 years	89	198	44.9	79	180	43.9
	Age ≥ 4 years	69	198	34.8	88	180	48.9
	Unable to confirm	8	198	4.0	6	180	3.3
	Schistosomiasis-infected	159	198	80.3	–	–	–
Infection status	Egg–/Ab+	70	198	35.4	–	–	–
	Egg+	89	198	44.9	62	180	34.4
	Egg+, Ab+	80	198	40.4	–	–	–
	Egg+, Ab–	9	198	4.5	–	–	–
	Light intensity (< 100 EPG*)	41	198	20.7	34	180	18.9
	Medium intensity (100–400 EPG)	28	198	14.1	19	180	10.6
	Heavy intensity (> 400 EPG)	20	198	10.1	9	180	5.0
	Malaria	(Smear) 7	198	3.5	(Smear) 30	180	16.7
					(RDT) 70	180	38.9
	Hepatitis B (surface antigen)	2	190	1.1	–	–	–
Liver pattern	Liver IPB	30	200	15.0	36	180	20.0
Morbidities	Anemia	161	196	82.1	106	173	61.3
	Undernutrition*	44	182	24.2	39	166	23.5
	Left lobe hepatomegaly†	91	182	50.0	99	152	65.1
	Right-lobe atrophy†	3	177	1.7	1	149	0.7
	Splenomegaly†	54	185	29.2	66	158	41.8
Serum findings	Elevated AST (> 37 units/L)	155	180	86.1	–	–	–
	Mild (< 148 units/L)	154	180	85.6	–	–	–
	Moderate/severe (≥ 148 units/L)	1	180	0.1	–	–	–
	Elevated ALT (> 42 units/L)	3	180	1.7	–	–	–
	Elevated bilirubin (> 17 μmol/L)	4	180	2.2	–	–	–

ALT = alanine aminotransferase; AST = aspartine aminotransferase; EPG = eggs per gram; IPB = image pattern B.
*Undernutrition = weight for age, height for age, or weight for height < –2 standard deviations below mean (WHO).
†Organomegaly = span > 2 standard deviations above mean for height as determined by Yazadanpanah and others.

determination by blood smear replaced with RDT data. An interaction term was included to test for interaction between schistosomiasis and malaria as predictors of organomegaly. The sub-analysis was performed as before.

Longitudinal analysis. For the set of children who had all organometric and *S. mansoni* diagnostic data available for both visits and had received praziquantel treatment between visits, analysis of change over time in morbidity findings which had been associated with *S. mansoni* infection at baseline was performed. Analyses accounted for clustering by individual; correlation by village was negligible and was not included in the model. Multivariable analyses controlled for age, sex, and malarial infection based on slide result, since malaria RDT was obtained only at follow-up. A subset analysis of "responders" was performed by restricting the regression to the subset of children who were egg+ at baseline and were then either egg-negative or in a less intense infection category post treatment.

Multiple imputation. Multiple imputation by chained equations[42] using IVEware version 0.2[43] was performed to assess whether the missing data influenced the model inferences. Baseline, follow-up, and longitudinal models were included in this assessment and revealed that the missing data would not substantially change associations reported in this study.

RESULTS

Cross-sectional analysis of baseline visit data. Two hundred and one children were enrolled at baseline, representing a minimum of 74% of eligible children in each village. Missing data were primarily due to baseline anthropometry not being performed or missing LFT data. Four additional children were missing sex or age data and were omitted from multivariable analyses. Fifteen "PSAC" were found on review of age documentation to be 5 years of age or older.

The mean age of enrolled children was 3.5 years (1.2–7.0 years); mean height was 94.6 cm. At baseline, 95/201 (47.3%) of those enrolled were male. Infection and morbidity findings are shown in Table 1. Notable findings included high proportions infected with *Schistosoma* spp., with 80.3% of children *S. mansoni* egg+ and/or antibody positive, and high intensity of infection, with over half of egg+ children having moderate or heavy infection. Proportion with schistosomiasis increased with age, from 62.5% (20/32) among children < 2.5 years to 80.9% (72/89) among children 2.5–< 4 years and 88.4% (61/69) among children ≥ 4 years. Corresponding proportions with egg+ infection were 25.0% (8/32), 40.4% (36/89), and 60.9% (42/69). Hepatitis B, malaria by smear, and hepatic right lobe atrophy were rare at baseline; other morbidities and findings, including anemia and organomegaly, were common (hepatomegaly 50.0%, splenomegaly 29.2%). Modest AST elevations were nearly universal. Morbidity complaints ranged in prevalence from 24.4% for decreased activity to 84.1% for fever (not shown).

Baseline associations between schistosome infection and IPB as predictive factors for the morbidity/finding outcomes are shown in Table 2 (see Supplemental Table 2 for *P*-values). No associations between infection status and morbidity complaints by parent report were significant (not shown). *S. mansoni* infection was associated with left lobe hepatomegaly (aPR = 1.4, 95% CI: 1.0–2.1) and splenomegaly (aPR = 2.1, 95% CI: 1.2–3.7). In the < 94 cm subset, the association between schistosomiasis and splenomegaly remained significant (Supplemental Table 4: aPR = 5.2; 95% CI: 1.001–27.3)

TABLE 2
Associations at baseline visit of morbidities and findings with *S. mansoni* infection status by stool and serum testing, and IPB

	Schistosomiasis (Egg+ or Ab+)				IPB			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
Finding	PR or coefficient (95% CI)	*N*	PR or coefficient (95% CI)	*N*	PR or coefficient (95% CI)	*N*	PR or coefficient (95% CI)	*N*
Anemia	1.1 (0.9, 1.3)	193	1.1 (0.9, 1.4)	186	0.9 (0.7, 1.2)	195	0.9 (0.6, 1.2)	188
Undernutrition	0.8 (0.4, 1.5)	171	0.8 (0.4, 1.4)	167	1.6 (1.0, 2.7)	181	**1.8 (1.1, 2.9)**	**176**
Left lobe hepatomegaly	**1.5 (1.0, 2.2)**	179	**1.4 (1.0, 2.1)**	172	0.6 (0.3, 1.4)	181	0.7 (0.3, 1.5)	174
Splenomegaly	**2.4 (1.4, 4.2)**	182	**2.1 (1.2, 3.7)**	174	1.5 (0.9, 2.6)	184	1.7 (0.9, 3.0)	176
AST (units/L)†	–5.1 (–10.8, 0.5)	177	**–5.4 (–10.3, –0.6)**	171	1.5 (–6.6, 9.7)	179	2.2 (–5.7, 10.2)	173
ALT (units/L)†	0.2 (–3.7, 4.1)	177	–1.0 (–4.3, 2.3)	171	0.1 (–4.5, 4.7)	179	0.9 (–2.9, 4.8)	173
Log bilirubin (μmol/L)‡	**–0.2 (–0.3, –0.1)**	177	**–0.2 (–0.3, –0.1)**	171	–0.8 (–1.8, 0.9)	179	–1.3 (–1.8, 1.0)	173

ALT = alanine aminotransferase; AST = aspartine aminotransferase; CI = confidence interval; PR = prevalence ratio. Bolded values are statistically significant at $P < 0.05$.
*Adjusted for sex and age.
†Increase (units/L) with presence of predictor.
‡Ratio to value in uninfected.

and a univariable association between schistosomiasis and anemia was seen (PR = 1.2; 95% CI: 1.0, 1.4).

Small, significant negative associations were seen between schistosomiasis and AST and bilirubin levels. The negative association with bilirubin persisted in the < 94 cm subset.

Associations between potential etiologies of IPB as predictive factors and IPB itself as an outcome were as follows (see Supplemental Table 1). At baseline, heavy intensity as compared with light intensity infection among egg+ children was associated with increased risk for IPB (aPR = 11.4, 95% CI: 2.7–48.3). The association with heavy intensity infection remained strongly significant in the < 94 cm subset of children (aPR = 7.9, 95% CI: 2.3–27.8). Hepatitis B could not be modeled as a predictive factor due to rarity, but neither of the two children positive for hepatitis B surface antigen had IPB. In the < 94 cm subset, IPB was associated with undernutrition (aPR = 1.3; 95% CI: 1.03–1.7) and splenomegaly (aPR = 3.8; 95% CI: 2.3–6.4).

No previously undescribed ultrasound findings associated with schistosomiasis in young children were found. Radiologist characterizations of liver texture and echogenicity were also not associated with liver pattern as designated by the sonographer.

Cross-sectional analysis of posttreatment visit data. Of 159 children with schistosomiasis at baseline, 152 were locatable and received praziquantel. 187 of the children examined in the baseline visit (93.0%) participated in follow-up at the posttreatment visit. Two children with AST and ALT > 300 U/L were excluded as having probable acute liver disease. Among included children, mean age was 4.2 years, 46.7% (84/180) were male, and mean height was 98.8 cm. The only outcome with missing data was organometry at 17%. The only covariable with missing data was age at 3%.

Prevalences of outcomes and covariables are shown in Table 1. Notably, at the posttreatment visit, prevalence of egg+ *S. mansoni* infection decreased from 44.9% to 34.4% (28.6% in children < 2.5 years, 36.7% in children 2.5–< 4 years, 33.0% in children > 4 years) whereas heavy-intensity infection decreased from 10.1% to 5.0%. Malaria prevalence increased from 3.5% by smear at baseline to 16.7% by smear and 38.9% by RDT at follow-up. Prevalence of IPB increased from 15.0% to 20.0%; left lobe hepatomegaly, 50.0% to 65.1%; and splenomegaly, 29.2% to 41.8%.

Associations between follow-up *S. mansoni* infection, malaria or IPB, and follow-up morbidity and other outcomes are shown in Table 3 (see Supplemental Table 3 for *P*-values). Right liver lobe atrophy was again too rare ($N = 2$) to analyze as an outcome. *S. mansoni* infection remained associated with left lobe hepatomegaly on univariable and adjusted analyses (aPR = 1.4, 95% CI: 1.1–1.6), but it was not associated with splenomegaly. With RDT as the mode of malaria testing, malaria was associated with both hepatomegaly (aPR = 1.3, 95% CI: 1.0–1.7) and splenomegaly (aPR = 2.8, 95% CI: 1.9–4.0). In the under-94 cm subset, egg-positive schistosomiasis remained associated with left lobe hepatomegaly (aPR = 1.8, 95% CI: 1.3–2.6), and malaria by RDT remained associated with both left lobe hepatomegaly (aPR = 1.8, 95% CI: 1.3–2.6) and splenomegaly (aPR = 3.0, 95% CI: 1.6–5.8). (Supplemental Table 5).The interaction term between malaria by RDT and schistosomiasis was not significant.

Associations between potential IPB etiologies as predictive factors and IPB as an outcome were as follows. Malaria, by smear (aPR = 1.6, 95% CI: 1.2–2.1) and RDT (aPR = 2.1, 95% CI: 1.3–3.2), was strongly associated with IPB. *S. mansoni* infection again was not associated with IPB. In contrast to the baseline visit, moderate infection intensity was negatively associated with IPB (aPR = 0.15; 95% CI: 0.03–0.75) and heavy intensity was not associated.

Longitudinal analysis of data from both visits. Of the 201 children examined in the baseline visit, 135 (67.2%) met

TABLE 3
Unadjusted and adjusted associations at posttreatment visit of morbidities and findings with *S. mansoni* infection status by stool testing alone, IPB, and malaria

	Schistosomiasis (egg+)				IPB				Malaria (RDT positive)			
	Unadjusted		Adjusted*		Unadjusted		Adjusted†		Unadjusted		Adjusted*	
Finding	PR (95% CI)	*N*	PR (95% CI)	*N*	PR (95% CI)	*N*	PR (95% CI)	*N*	PR (95% CI)	*N*	PR (95% CI)	*N*
Left lobe hepatomegaly	**1.3 (1.1, 1.6)**	152	**1.4 (1.1, 1.6)**	147	**0.7 (0.4, 1.0)**	152	**0.6 (0.4, 1.0)**	147	**1.3 (1.0, 1.7)**	152	**1.3 (1.0, 1.7)**	147
Splenomegaly	1.0 (0.6, 1.6)	158	0.9 (0.6, 1.6)	153	1.2 (0.8, 1.7)	158	1.2 (0.8, 1.7)	153	**2.8 (2.0, 4.0)**	158	**2.7 (1.9, 4.0)**	153

CI = confidence interval; PR = prevalence ratio. Bolded values are statistically significant at $P < 0.05$.
*Values drawn from the same model (including sex, age, malaria on RDT, and current *S. mansoni* infection by stool egg status).
†Sex and age.

analytic inclusion criteria for the longitudinal analysis. Covariables with missing data were age at 3.7% and malaria slide at 1.5%. Of 58 included children who were egg+ at baseline, 46 (79.3%) demonstrated a decrease in infection intensity (responders).

On univariable analyses, there were statistically significant increases between visits in the prevalence of hepatomegaly (PR = 1.3, 95% CI: 1.1–1.5) and splenomegaly (PR = 1.4, 95% CI: 1.1–1.8). On multivariable analyses, including malaria status by RDT, this increase remained significant for hepatomegaly (aPR = 1.2, 95% CI: 1.0–1.5) but not for splenomegaly. When children were stratified by initial infection status, increases in hepatomegaly prevalence remained significant on univariable analysis only for the group that was uninfected at baseline (PR = 1.2; 95% CI: 1.0–1.5); and in splenomegaly only in the group that was schistosomiasis infected at baseline (PR = 2.8; 95% CI: 1.1–6.7); increases were not significant on multivariable analysis in these strata. On analyses restricted to responders, increases in hepatomegaly and splenomegaly prevalence between visits were no longer statistically significant.

DISCUSSION

A high proportion of sampled young children were infected with *S. mansoni* in Rusinga Island, a previously treatment-naïve area. Our results showed an association between schistosomiasis and both hepatomegaly and splenomegaly in young children, which persisted for hepatomegaly after treatment with praziquantel. This association was still seen when analysis was restricted to children currently ineligible for MDA by virtue of height. Despite treatment of infected children, the overall prevalence of organomegaly increased between visits; we attribute this primarily to the increase in malaria prevalence, which was consistent with malaria seasonality in western Kenya.

The association of schistosomiasis with organomegaly is consistent with others' findings in older children.[29,33] Health implications of chronic hepatosplenomegaly in African children have been discussed recently by Wilson and others[44] and can include possible increased risk for stunting and wasting and, in extreme cases, esophageal varices. More broadly, an inflammatory mechanism is postulated in the genesis of hepatomegaly,[44] and long-term effects of this potential chronic inflammation are unknown.

In contrast to others,[45] we found no evidence for rapid improvement in organomegaly after praziquantel treatment, including among children whose stool egg densities decreased. The rising prevalence of malaria between visits is a likely cause; misclassification of children as responders due to low sensitivity of Kato-Katz on a single stool sample is another.

IPB, considered in adults to represent a possible intermediate stage in development of schistosomiasis-associated hepatic fibrosis, was not primarily attributable to schistosomiasis in our sample—consistent with recent findings in slightly older children[46]—and in fact appears more closely related to malaria infection. The biological significance of IPB is not known; it may represent a common pathway for multiple abnormal hepatic processes. Regardless, our findings suggest that this element of the Niamey protocol is not a measure of schistosomiasis-associated pathology at least in young children.

The high prevalence of modest AST elevations may reflect the need for a region-specific reference range, such as that recently proposed based on population biochemical data from western Kenya, giving 50.4 units/L as the upper limit of normal.[47] The reason for the negative association between *S. mansoni* infection and AST and bilirubin at baseline is unclear.

The low apparent curative efficacy of 40 mg/kg praziquantel against *S. mansoni* in our sample is striking, agreeing with some previous findings in PSAC[11] and contrasting with others.[10,48] Given the high transmission pressure in this setting, treatment failure is difficult to distinguish from reinfection, and others have noted substantial reinfection after treatment, though over somewhat longer intervals.[49] Concern has been raised about whether the extension of current height-based dosing calculations to young children would result in their undertreatment, and our results may further substantiate those concerns.

Several limitations of this study are worth noting. A convenience sample was used, selected from the highest-prevalence villages to ensure data were balanced by infection status. A few children initially identified as PSAC were found in home documentation to be school-aged. Further, unmeasured confounders may have affected the observed associations, given the large number of possible causes for organomegaly and the unknown causes and clinical importance of IPB. The sample size for this study was small, which may have resulted in missed associations, and larger studies are needed to confirm statistically significant associations. Water contact data, which might have been helpful in distinguishing nonresponders from reinfected children, was not collected. It is also possible that the multiple tests performed in this study at baseline might have led to appearance of spurious associations; however, at the posttreatment visit only associations found to be significant at the baseline visit were tested, and the persistence of the observed relationships suggests the key findings are robust. Finally, the lack of correlation between on-site liver pattern determination by sonographer and off-site echotexture and echogenicity determination by radiologist review may reflect loss of resolution in image transfer, but most importantly reflects the incompleteness of characterizing IPB in terms of echotexture and echogenicity. It became apparent in exploring this lack of correlation that echotexture and echogenicity did not reliably predict IPB even using selected teaching images.

The associations found here, particularly if confirmed in larger population-based studies, add to the growing body of evidence for measurable sequelae associated with schistosomiasis in children currently excluded from the global schistosomiasis control program by virtue of their young age. In addition to scaling up sanitation measures that benefit all age groups, this supports the continued pursuit of appropriate formulations and dosing standards for MDA in this population.

Received June 5, 2014. Accepted for publication January 19, 2015.

Published online March 9, 2015.

Note: Supplemental tables appear at www.ajtmh.org.

Acknowledgments: We gratefully acknowledge the Bill and Melinda Gates Foundation for providing the funding for this study, and the contributions of the KEMRI-CDC clinical field staff, and the participants, without whom this work would not have been possible. Special thanks to Patrick Lammie and W. Evan Secor for valuable input in

study design and manuscript development. This paper is published with the permission of the Director of the Kenya Medical Research Institute.

Disclaimer: The findings and conclusions in this report are the findings and conclusions of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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REFERENCES

1. King CH, 2010. Parasites and poverty: the case of schistosomiasis. *Acta Trop 113:* 95–104.
2. Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J, 2006. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infect Dis 6:* 411–425.
3. Gryseels B, Polman K, Clerinx J, Kestens L, 2006. Human schistosomiasis. *Lancet 368:* 1106–1118.
4. World Health Organization, 2006. *Preventive Chemotherapy in Human Helminthiasis: Coordinated Use of Anthelminthic Drugs in Control Interventions: A Manual for Health Professionals and Programme Managers*. Available at: http://Whqlibdoc.Who.Int/Publications/2006/9241547103_Eng.Pdf. Accessed June 6, 2014.
5. Ekpo UF, Oluwole AS, Abe EM, Etta HE, Olamiju F, Mafiana CF, 2012. Schistosomiasis in infants and pre-school-aged children in sub-saharan Africa: implication for control. *Parasitology 139:* 835–841.
6. Amuta E, Houmsou R, 2014. Prevalence, intensity of infection and risk factors of urinary schistosomiasis in pre-school and school aged children in Guma Local Government Area, Nigeria. *Asia Pac J Trop Med 7:* 34–39.
7. Poole H, Terlouw DJ, Naunje A, Mzembe K, Stanton M, Betson M, Lalloo DG, Stothard JR, 2014. Schistosomiasis in pre-school-age children and their mothers in Chikhwawa district, Malawi with notes on characterization of schistosomes and snails. *Parasit Vectors 7:* 153.
8. Seto E, Sousa-Figueiredo JC, Betson M, Byalero C, Kabatereine NB, Stothard JR, 2012. Patterns of intestinal schistosomiasis among mothers and young children from Lake Albert, Uganda: water contact and social networks inferred from wearable global positioning system dataloggers. *Geospat Health 7:* 1–13.
9. Namwanje H, Kabatereine NB, Olsen A, 2011. The acceptability and safety of praziquantel alone and in combination with mebendazole in the treatment of *Schistosoma mansoni* and soil-transmitted helminthiasis in children aged 1–4 years in Uganda. *Parasitology 138:* 1586–1592.
10. Coulibaly JT, N'gbesso YK, Knopp S, Keiser J, N'goran EK, Utzinger J, 2012. Efficacy and safety of praziquantel in pre-school-aged children in an area co-endemic for *Schistosoma mansoni* and *S. haematobium*. *PLoS Negl Trop Dis 6:* e1917.
11. Garba A, Lamine MS, Djibo A, Tahirou A, Aouami MA, Alfari A, Phillips AE, Fenwick A, Utzinger J, 2013. Safety and efficacy of praziquantel syrup (Epiquantel®) against *Schistosoma haematobium* and *Schistosoma mansoni* in preschool-aged children in Niger. *Acta Trop 128:* 318–325.
12. Sousa-Figueiredo JC, Betson M, Atuhaire A, Arinaitwe M, Navaratnam AM, Kabatereine NB, Bickle Q, Stothard JR, 2012. Performance and safety of praziquantel for treatment of intestinal schistosomiasis in infants and preschool children. *PLoS Negl Trop Dis 6:* e1864.
13. Mutapi F, Rujeni N, Bourke C, Mitchell K, Appleby L, Nausch N, Midzi N, Mduluza T, 2011. *Schistosoma haematobium* treatment in 1–5 year old children: safety and efficacy of the antihelminthic drug praziquantel. *PLoS Negl Trop Dis 5:* e1143.
14. Betson M, Sousa-Figueiredo JC, Rowell C, Kabatereine NB, Stothard JR, 2010. Intestinal schistosomiasis in mothers and young children in Uganda: investigation of field-applicable markers of bowel morbidity. *Am J Trop Med Hyg 83:* 1048–1055.
15. Betson M, Sousa-Figueiredo JC, Kabatereine NB, Stothard JR, 2012. Use of fecal occult blood tests as epidemiologic indicators of morbidity associated with intestinal schistosomiasis during preventive chemotherapy in young children. *Am J Trop Med Hyg 87:* 694–700.
16. Opara KN, Udoidung NI, Ukpong IG, 2007. Genitourinary schistosomiasis among pre-primary schoolchildren in a rural community within the cross river basin, Nigeria. *J Helminthol 81:* 393–397.
17. Stothard JR, Sousa-Figueiredo JC, Betson M, Bustinduy A, Reinhard-Rupp J, 2013. Schistosomiasis in African infants and preschool children: let them now be treated! *Trends Parasitol 29:* 197–205.
18. Meurs WL, Moustapha M, Vereecken K, Menten J, Souleymane M, Polman K, 2012. Bladder morbidity and hepatic fibrosis in mixed *Schistosoma haematobium* and *S. mansoni* infections: a population-wide study in Northern Senegal. *PLoS Negl Trop Dis 6:* e1829.
19. Green HK, Sousa-Figueiredo JC, Basáñez MG, Betson M, Kabatereine NB, Fenwick A, Stothard JR, 2011. Anaemia in Ugandan preschool-aged children: the relative contribution of intestinal parasites and malaria. *Parasitology 138:* 1534–1545.
20. Magalhaes RJ, Clements AC, 2011. Mapping the risk of anaemia in preschool-age children: the contribution of malnutrition, malaria, and helminth infections in West Africa. *PLoS Med 8:* e1000438.
21. Stothard JR, Sousa-Figueiredo JC, Betson M, Green HK, Seto EY, Garba A, Sacko M, Mutapi F, Vaz Nery S, Amin MA, Mutumba-Nakalembe M, Navaratnam A, Fenwick A, Kabatereine NB, Gabrielli AF, Montresor A, 2011. Closing the praziquantel treatment gap: new steps in epidemiological monitoring and control of schistosomiasis in African infants and preschool-aged children. *Parasitology 138:* 1593–1606.
22. Olveda DU, Olveda RM, Lam AK, Chau TN, Li Y, Gisparil A, Ross AG, 2014. Utility of diagnostic imaging in the diagnosis and management of schistosomiasis. *Clin Microbiol 3:* 142.
23. Lambertucci JR, 2014. Revisiting the concept of hepatosplenic schistosomiasis and its challenges using traditional and new tools. *Rev Soc Bras Med Trop 47:* 130–136.
24. Medeiros TB, Domingues AL, Luna CF, Lopes EP, 2014. Correlation between platelet count and both liver fibrosis and spleen diameter in patients with schistosomiasis mansoni. *Arq Gastroenterol 51:* 34–38.
25. Negrão-Corrêa D, Fittipaldi JF, Lambertucci JR, Teixeira MM, Antunes CM, Carneiro M, 2014. Association of *Schistosoma mansoni*-specific IgG and IgE antibody production and clinical schistosomiasis status in a rural area of Minas Gerais, Brazil. *PLoS ONE 4:* e88042.
26. Leite LA, Domingues AL, Lopes EP, Ferreira RD, Pimenta AD, da Fonseca CS, Dos Santos BS, Lima VL, 2013. Relationship between splenomegaly and hematologic findings in patients with hepatosplenic schistosomiasis. *Rev Bras Hematol Hemoter 35:* 332–336.
27. Dias HS, Domingues AL, Cordeiro FT, Jucá N, Lopes EP, 2013. Associating portal congestive gastropathy and hepatic fibrosis in hepatosplenic mansoni schistosomiasis. *Acta Trop 126:* 240–243.
28. Gouvras AN, Kariuki C, Koukounari A, Norton AJ, Lange CN, Ireri E, Fenwick A, Mkoji GM, Webster JP, 2013. The impact of single versus mixed *Schistosoma haematobium* and *S. mansoni* infections on morbidity profiles amongst school-children in Taveta, Kenya. *Acta Trop 128:* 309–317.
29. Richter J, Hatz C, Campagne G, Bergquist NR, Jenkins JM, eds, 2000. *Ultrasound in Schistosomiasis: A Practical Guide to the Standardized Use of Ultrasonography for the Assessment of Schistosomiasis-Related Morbidity*. Second International

Workshop, October 22–26, 1996, Niamey, Niger. UNDP/World Bank/Who Special Programme for Research and Training in Tropical Diseases.
30. El Scheich T, Holtfreter MC, Ekamp H, Singh DD, Mota R, Hatz C, Richter J, 2014. The WHO ultrasonography protocol for assessing hepatic morbidity due to *Schistosoma mansoni*. Acceptance and evolution over 12 years. *Parasitol Res 113:* 3915–3925.
31. Boisier P, Ramarokoto CE, Ravaoalimalala VE, Rabarijaona L, Serieye J, Roux J, Esterre P, 1998. Reversibility of *Schistosoma mansoni*-associated morbidity after yearly mass praziquanteltherapy: ultrasonographic assessment. *Trans R Soc Trop Med Hyg 92:* 451–453.
32. Hsiang MS, Carlton EJ, Zhang Y, Zhong B, Dongchuan Q, Cohen PA, Stewart CC, Spear RC, 2010. Use of ultrasonography to evaluate *Schistosoma japonicum*-related morbidity in children, Sichuan Province, China, 2000–2007. *Am J Trop Med Hyg 82:* 103–111.
33. Nafeh MA, Medhat A, Swifae Y, Moftah FM, Mohamed A, Soliman AG, Strickland GT, 1992. Ultrasonographic changes of the liver in *Schistosoma haematobium* infection. *Am J Trop Med Hyg 47:* 225–230.
34. Strahan R, Chiyesu K, Schneider-Kolsky M, 2012. Ultrasound study of liver disease caused by *Schistosoma mansoni* in rural Zambian schoolchildren. *J Med Imaging Rad Onc 56:* 390–397.
35. Odiere MR, Rawago FO, Ombok M, Secor WE, Karanja DM, Mwinzi PN, Lammie PJ, Won K, 2012. High prevalence of schistosomiasis in Mbita and its adjacent islands of Lake Victoria, western Kenya. *Parasit Vectors 5:* 278.
36. Sang HC, Muchiri G, Ombok M, Odiere MR, Mwinzi PN, 2014. *Schistosoma haematobium* hotspots in south Nyanza, western Kenya: prevalence, distribution and co-endemicity with *Schistosoma mansoni* and soil-transmitted helminths. *Parasit Vectors 7:* 125.
37. U.S. Centers for Disease Control and Prevention Dpdx. *Laboratory Diagnosis of Malaria: Staining for Malaria Parasites: Bench Aid*. Available at: http://www.cdc.gov/dpdx/resources/pdf/benchAids/malaria/Pfalciparum_benchaidV2.pdf. Accessed June 4, 2014.
38. Shane HL, Verani JR, Abudho B, Montgomery SP, Blackstock AJ, Mwinzi PN, Butler SE, Karanja DM, Secor WE, 2011. Evaluation of urine CCA assays for detection of *Schistosoma mansoni* infection in western Kenya. *PLoS Negl Trop Dis 5:* e951.
39. Montresor A, Crompton DWT, Hall A, Dap Bundy, Savioli L, 1998. *Guidelines for the Evaluation of Soil-Transmitted Helminthiasis and Schistosomiasis at Community Level*. Geneva, Switzerland: World Health Organization, Who/Ctd/Sip/98.1.
40. Yazdanpanah Y, Thomas AK, Kardorff R, Talla I, Sow S, Niang M, Stelma FF, Decam C, Rogerie F, Gryseels B, Capron A, Doehring E, 1997. Organometric investigations of the spleen and liver by ultrasound in *S. mansoni* endemic and non-endemic villages in Senegal. *Am J Trop Med Hyg 57:* 245–249.
41. Liang KY, Scott L, 1986. Longitudinal data analysis using generalized linear models. *Zeger Biometrika 73:* 13–22.
42. Raghunathan TE, Lepkowski JM, Van Hoewyk J, Solenberger P, 2001. A multivariate technique for multiply imputing missing values using a sequence of regression models. *Surv Methodol 27:* 85–95.
43. Raghunathan TE, Solenberger PW, Van Hoewyk J, 2013. *IVEware: Imputation and Variance Estimation Software*. Ann Arbor, MI: Survey Methodology Program, Survey Research Center, Institute for Social Research, University of Michigan. Available at: http://www.isr.umich.edu/src/smp/ive/. Accessed January 31, 2014.
44. Wilson S, Vennervald BJ, Kadzo H, Ireri E, Amaganga C, Booth M, Kariuki HC, Mwatha JK, Kimani G, Ouma JH, Muchiri E, Dunne DW, 2010. Health implications of chronic hepatosplenomegaly in Kenyan school-aged children chronically exposed to malarial infections and *Schistosoma mansoni*. *Trans R Soc Trop Med Hyg 104:* 110–116.
45. Strahan R, McAdam D, Schneider ME, 2013. Sonographic response in the liver and urinary bladder of children 14 months after treatment for schistosomiasis. *Trop Doct 43:* 71–74.
46. Samuels AM, Matey E, Mwinzi PN, Wiegand RE, Muchiri G, Ireri E, Hyde M, Montgomery SP, Karanja DM, Secor WE, 2012. *Schistosoma mansoni* morbidity among school-aged children: a SCORE project in Kenya. *Am J Trop Med Hyg 87:* 874–882.
47. Zeh C, Amornkul PN, Inzaule S, Ondoa P, Oyaro B, Mwaengo D, Vandenhoudt H, Gichangi A, Williamson J, Thomas T, Decock K, Hart C, Nkengasong J, Laserson K, 2011. Population-based biochemistry, immunologic and hematological reference values for adolescents and young adults in a rural population in western Kenya. *PLoS One 6:* e21040.
48. Sousa-Figueiredo JC, Pleasant J, Day M, Betson M, Rollinson D, Montresor A, Kazibwe F, Kabatereine FB, Stothard JR, 2009. Treatment of intestinal schistosomiasis in Ugandan preschool children: best diagnosis, treatment efficacy and side-effects, and an extended praziquantel dosing pole. *In Health 2:* 103–113.
49. Tukahebwa EM, Vennervald BJ, Nuwaha F, Kabatereine NB, Magnussen P, 2013. Comparative efficacy of one versus two doses of praziquantel on cure rate of *Schistosoma mansoni* infection and re-infection in Mayuge District, Uganda. *Trans R Soc Trop Med Hyg 107:* 397–404.