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%. Schistosomiasis 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 disability1 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 morbidities associated with schistosomiasis.

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 prevalences5,6 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 ultrasound22–28 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 reversible31,32 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, Kakteko, Wariga “A,” Kamgere, Wakwala, Dier Aora, and Kakrigu (prevalence 34.0–92.5%) (Maurice Odere, 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. 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. 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, 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 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, 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 and an exchangeable correlation structure. An exact model was fit for the analyses of malaria diagnosis by microscopy. A sub-analysis 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

<table>
<thead>
<tr>
<th>Type</th>
<th>Trait</th>
<th>Baseline (N = 201)</th>
<th>Baseline (N = 201)</th>
<th>Posttreatment (N = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>N</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 2.5 years</td>
<td>32</td>
<td>198</td>
<td>16.2</td>
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<tr>
<td></td>
<td>2.5 years &lt; age &lt; 4 years</td>
<td>89</td>
<td>198</td>
<td>44.9</td>
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<tr>
<td></td>
<td>Age ≥ 4 years</td>
<td>69</td>
<td>198</td>
<td>34.8</td>
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<td></td>
<td>Unable to confirm</td>
<td>8</td>
<td>198</td>
<td>4.0</td>
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<td></td>
<td>Schistosomiasis-infected</td>
<td>159</td>
<td>198</td>
<td>80.3</td>
</tr>
<tr>
<td>Infection status</td>
<td>Egg-/Ab+</td>
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<tr>
<td></td>
<td>Egg+</td>
<td>89</td>
<td>198</td>
<td>44.9</td>
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<tr>
<td></td>
<td>Egg+, Ab+</td>
<td>80</td>
<td>198</td>
<td>40.4</td>
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<tr>
<td></td>
<td>Egg+, Ab−</td>
<td>9</td>
<td>198</td>
<td>4.5</td>
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<td></td>
<td>Light intensity (&lt; 100 EPG*)</td>
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<td>198</td>
<td>20.7</td>
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<td></td>
<td>Medium intensity (100–400 EPG)</td>
<td>28</td>
<td>198</td>
<td>14.1</td>
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<tr>
<td></td>
<td>Heavy intensity (&gt; 400 EPG)</td>
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<td>Malaria (Smear)</td>
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<td></td>
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<td>Liver pattern</td>
<td>Liver IPB</td>
<td>30</td>
<td>200</td>
<td>15.0</td>
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<tr>
<td>Morbidities</td>
<td>Anemia</td>
<td>161</td>
<td>196</td>
<td>82.1</td>
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<tr>
<td></td>
<td>Undernutrition*</td>
<td>44</td>
<td>182</td>
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<tr>
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<td>Left lobe hepatomegaly†</td>
<td>91</td>
<td>182</td>
<td>50.0</td>
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<td>Right-lobe atrophy†</td>
<td>3</td>
<td>177</td>
<td>1.7</td>
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<td></td>
<td>Splenomegaly†</td>
<td>54</td>
<td>185</td>
<td>29.2</td>
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<tr>
<td>Serum findings</td>
<td>Elevated AST (≥ 37 units/L)</td>
<td>155</td>
<td>180</td>
<td>86.1</td>
</tr>
<tr>
<td></td>
<td>Mild (≤ 148 units/L)</td>
<td>154</td>
<td>180</td>
<td>85.6</td>
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<tr>
<td></td>
<td>Moderate/severe (≥ 148 units/L)</td>
<td>1</td>
<td>180</td>
<td>0.1</td>
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<tr>
<td></td>
<td>Elevated ALT (≥ 42 units/L)</td>
<td>3</td>
<td>180</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Elevated bilirubin (≥ 17 μmol/L)</td>
<td>4</td>
<td>180</td>
<td>2.2</td>
</tr>
</tbody>
</table>

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.

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)

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 using 1VEware version 0.2 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.
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 = 1.14, 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 characterization 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, 135 (67.2%) met malaria or IPB criteria. Schistosomiasis (Egg+ or Ab+) and malaria were associated with IPB (aPR = 1.2; 95% CI: 1.0, 1.4).

<table>
<thead>
<tr>
<th>Finding</th>
<th>Unadjusted</th>
<th>Adjusteda</th>
<th>PR or coefficient (95% CI)</th>
<th>N</th>
<th>PR or coefficient (95% CI)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>1.1 (0.9, 1.3)</td>
<td>1.7 (1.3, 2.2)</td>
<td>193</td>
<td>1.1 (0.9, 1.4)</td>
<td>186</td>
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<tr>
<td>Undernutrition</td>
<td>0.8 (0.4, 1.5)</td>
<td>0.7 (0.3, 1.3)</td>
<td>171</td>
<td>0.8 (0.4, 1.4)</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>Left lobe hepatomegaly</td>
<td>1.5 (1.0, 2.2)</td>
<td>1.3 (0.9, 1.7)</td>
<td>179</td>
<td>1.4 (1.0, 2.1)</td>
<td>172</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>2.4 (1.4, 4.2)</td>
<td>2.1 (1.3, 3.7)</td>
<td>182</td>
<td>2.1 (1.3, 3.7)</td>
<td>174</td>
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</tr>
<tr>
<td>AST (units/L)†</td>
<td>–5.1 (–10.8, 0.5)</td>
<td>–5.4 (–10.3, –0.6)</td>
<td>177</td>
<td>–5.4 (–10.3, –0.6)</td>
<td>171</td>
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<tr>
<td>ALT (units/L)†</td>
<td>0.2 (–3.7, 4.1)</td>
<td>–0.1 (–4.3, 2.3)</td>
<td>177</td>
<td>–0.1 (–4.3, 2.3)</td>
<td>171</td>
<td></td>
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<tr>
<td>Log bilirubin (μmol/L)†</td>
<td>–0.2 (–0.3, –0.1)</td>
<td>–0.2 (–0.3, –0.1)</td>
<td>177</td>
<td>–0.2 (–0.3, –0.1)</td>
<td>171</td>
<td></td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Finding</th>
<th>Unadjusted</th>
<th>Adjusteda</th>
<th>PR or coefficient (95% CI)</th>
<th>N</th>
<th>PR or coefficient (95% CI)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left lobe hepatomegaly</td>
<td>1.3 (1.1, 1.6)</td>
<td>1.5 (1.1, 1.7)</td>
<td>152</td>
<td>1.4 (1.1, 1.7)</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>1.0 (0.6, 1.6)</td>
<td>0.8 (0.6, 1.6)</td>
<td>158</td>
<td>0.9 (0.6, 1.6)</td>
<td>153</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Finding</th>
<th>Schistosomiasis (Egg+)</th>
<th>IPB</th>
<th>Malaria (RDT positive)</th>
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</thead>
<tbody>
<tr>
<td>Left lobe hepatomegaly</td>
<td>1.3 (1.1, 1.6)</td>
<td>1.4 (1.1, 1.6)</td>
<td>0.7 (0.4, 1.0)</td>
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<tr>
<td>Splenomegaly</td>
<td>1.0 (0.6, 1.6)</td>
<td>0.8 (0.6, 1.6)</td>
<td>1.2 (0.8, 1.7)</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Finding</th>
<th>Unadjusted</th>
<th>Adjusteda</th>
<th>PR or coefficient (95% CI)</th>
<th>N</th>
<th>PR or coefficient (95% CI)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left lobe hepatomegaly</td>
<td>1.3 (1.1, 1.7)</td>
<td>1.3 (1.0, 1.7)</td>
<td>152</td>
<td>1.3 (1.0, 1.7)</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>1.0 (0.6, 1.6)</td>
<td>1.2 (0.8, 1.7)</td>
<td>158</td>
<td>2.8 (2.0, 4.0)</td>
<td>153</td>
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</tbody>
</table>
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-naive 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. Health implications of chronic hepatosplenomegaly in African children have been discussed recently by Wilson and others 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, and long-term effects of this potential chronic inflammation are unknown.

In contrast to others, 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—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 Niamye 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. 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 and contrasting with others. 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. Concern has been raised about whether the extension of current treatment with praziquantel. This association was still seen when children were stratified by initial infec-

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 reinfeeted 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.

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REFERENCES


