RESEARCH ARTICLE

Associations between infection intensity categories and morbidity prevalence in school-age children are much stronger for *Schistosoma haematobium* than for *S. mansoni*

Ryan E. Wiegand1,2,3*, W. Evan Secor1, Fiona M. Fleming4, Michael D. French5, Charles H. King6, Arminder K. Deol7, Susan P. Montgomery1, Darin Evans8, Jürg Utzinger2,3, Penelope Vounatsou2,3, Sake J. de Vlas9

1 Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, 2 Swiss Tropical and Public Health Institute, Basel, Switzerland, 3 University of Basel, Basel, Switzerland, 4 SCI Foundation, London, United Kingdom, 5 RTI International, Washington DC, United States of America, 6 Center for Global Health and Diseases, Case Western Reserve University, Cleveland, Ohio, United States of America, 7 Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom, 8 United States Agency for International Development, Washington DC, United States of America, 9 Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

* rwiegand@cdc.gov

Abstract

**Background**

World Health Organization (WHO) guidelines for measuring global progress in schistosomiasis control classify individuals with *Schistosoma* spp. infections based on the concentration of excreted eggs. We assessed the associations between WHO infection intensity categories and morbidity prevalence for selected *S. haematobium* and *S. mansoni* morbidities in school-age children.

**Methodology**

A total of 22,488 children aged 6–15 years from monitoring and evaluation cohorts in Burkina Faso, Mali, Niger, Uganda, Tanzania, and Zambia from 2003–2008 were analyzed using Bayesian logistic regression. Models were utilized to evaluate associations between infection intensity categories and the prevalence of any urinary bladder lesion, any upper urinary tract lesion, microhematuria, and pain while urinating (for *S. haematobium*) and irregular hepatic ultrasound image pattern (C-F), enlarged portal vein, laboratory-confirmed diarrhea, and self-reported diarrhea (for *S. mansoni*) across participants with infection and morbidity data.

**Principal findings**

*S. haematobium* infection intensity categories possessed consistent morbidity prevalence across surveys for multiple morbidities and participants with light infections had elevated morbidity levels, compared to negative participants. Conversely, *S. mansoni* infection intensity categories lacked association with prevalence of the morbidity measures assessed.
Conclusions/significance

Current status infection intensity categories for *S. haematobium* were associated with morbidity levels in school-age children, suggesting urogenital schistosomiasis morbidity can be predicted by an individual’s intensity category. Conversely, *S. mansoni* infection intensity categories were not consistently indicative of childhood morbidity at baseline or during the first two years of a preventive chemotherapy control program.

Author summary

Infections with *Schistosoma* parasites are commonly classified by the presence and concentration of excreted *Schistosoma* eggs. Guidelines put forward by the World Health Organization (WHO) include classifications of *S. haematobium* infections assessed by urine filtration into light and heavy infections and *S. mansoni* infections assessed by Kato-Katz thick smears into light, moderate, and heavy infections. Past evidence has demonstrated an association between intensity of infection with morbidity for severe morbidities, but this was before recognition of the effect of light-intensity infections on morbidity and was done in treatment naïve populations. In these analyses, we assessed the associations between the WHO classifications for infection intensity and a wide array of *S. haematobium* and *S. mansoni* morbidity indicators in school-age children ascertained in monitoring and evaluation cohorts before and after initiation of deworming. Our analyses found a high correlation with *S. haematobium* intensity categories and morbidity indicators, especially microhematuria, but weaker correlation between *S. mansoni* intensity categories and morbidity indicators. The results indicate that, on the aggregate, the intensity categories represent a person’s *S. haematobium*-related morbidity but are poor at representing a person’s *S. mansoni*-related morbidity.

Introduction

Schistosomiasis is the disease caused by infection with the blood fluke *Schistosoma* spp. Morbidity is caused by the host’s response to parasite eggs. As part of the life cycle, eggs are excreted via urine (for *Schistosoma haematobium*) or stool (for *S. mansoni* and other species), but some eggs become lodged in host tissue and stimulate inflammation and granulomatous reactions, which are responsible for the pathology associated with the infection [1]. Chronic disease can manifest due to the accumulation of tissue damage by repeated infections or because schistosomes can survive in the human body and produce eggs for many years. Morbidity varies by species [1,2]. *S. haematobium* infections affect the urogenital system and most often clinically present as hematuria [3]. Chronic infections can result in urinary tract fibrosis [4], female [5] and male [6] genital schistosomiasis, and, in rare cases, bladder cancer [7]. *S. mansoni* infections affect the gastrointestinal tract and frequently are associated with abdominal pain and bleeding into the stool [3]. Longer term infections put patients at greater risk for periportal fibrosis [1], which can lead to portal vein hypertension, hepatosplenic disease, and esophageal varices that can result in exsanguination into the digestive tract.

Prior to the introduction of mass distribution of praziquantel as preventive chemotherapy, multiple studies in the 1970s and early 1980s found an association between the intensity of a schistosome infection and morbidity [8,9]. These studies became the basis for two important...
components of schistosomiasis morbidity control. First, they established the concept of infection intensity categorizations, now commonly used by the World Health Organization (WHO). *S. haematobium* infection intensity has consistently been characterized by the number of schistosome eggs per 10 ml of urine with 1–49 eggs per 10 ml of urine defining a light infection and ≥50 eggs per 10 ml of urine indicating a heavy infection [10,11]. For *S. mansoni*, infection intensity is measured as the number of schistosome eggs per gram (EPG) of stool. Different categorizations have appeared in WHO documents [10,12], but infection intensity is now commonly split into three categories: 1–99 EPG for a light infection; 100–399 EPG signifying a moderate infection; and ≥400 EPG for a heavy infection [11,13]. Second, they led to current WHO guidelines that use community-level prevalence of heavy-intensity infections as the basis for morbidity control [14], even though it is recognized that light and moderate infections can cause considerable morbidity [2,15].

The primary objective of this study was to determine whether the intensity categories, i.e., a measure of someone’s current infection status, can differentiate between participant’s morbidity prevalence for multiple, schistosomiasis-related morbidity indicators. For *S. haematobium*, we analyzed two aggregated ultrasound indicators, as well as microhematuria, and pain while urinating. For *S. mansoni*, we analyzed irregular liver image pattern, enlarged portal vein, laboratory-confirmed diarrhea, and self-reported diarrhea. We used data from preventive chemotherapy control programs in Burkina Faso [16–18], Mali [18,19], Niger [18], Uganda [20], Tanzania [21], and Zambia [21] between 2003 and 2008 supported by the Schistosomiasis Control Initiative (SCI) [22]. To our knowledge, no thorough evaluation of the association between infection intensity categories and morbidity before and after the mass distribution of praziquantel has been performed.

**Methods**

**Ethics statement**

The Imperial College Research Ethics Committee (ICREC_8_2_2, EC No. 03.36, R&D No. 03/ SB/003E) and the ethical review boards of the Ministries of Health of the six countries included here provided ethical approval for use of these data. The Centers for Disease Control and Prevention (CDC) was determined to be a non-engaged research partner.

**Study design and data collection**

Data collection was performed as part of national control programs for schistosomiasis and soil-transmitted helminthiasis. Details on country programs and development of SCI are presented elsewhere [16–22]. Briefly, all countries created a multifaceted, national program scale-up and initiated distribution of praziquantel and albendazole to target populations based on WHO guidance [23]. Schools were randomly selected from areas with various endemicity levels that were purposively selected. Countries created two monitoring and evaluation cohorts: a randomly selected group of children, aged 6–12 years in primary education, were followed for two or more years; and a second cohort of communities in the same geographic areas were tracked with a random sample of participants ascertained each year. The first survey (baseline) was the first known year of preventive chemotherapy in the area. The subsequent years of follow-up are referred to as follow up 1 and follow up 2. Data were collected from communities which had been treated annually and measured approximately one year after treatment. Treatment was usually immediately following survey times, but occasionally lagged by a few months. Details on surveys included in the analyses and reasons for exclusions are included in the supplementary materials (Table A in S1 Text). Participants were required to be above 94 cm in height and not currently ill. Consent was obtained from parents or guardians and assent
was obtained from children. Participants were surveyed and evaluated before receiving praziquantel (for schistosomiasis) and albendazole (for soil-transmitted helminthiasis). We pooled the monitoring and evaluation cohorts and limited the participants to 6-15-year-old children to include the largest number of participants possible and to align with the current monitoring and evaluation guidelines of sampling school-age children [24]. Datasets were created for each morbidity where participants were required to possess both infection and morbidity data.

**Schistosoma infection data**

Each control program chose independently how to evaluate *S. haematobium* and *S. mansoni* infections (Table 1). Urine filtration was used to determine *S. haematobium* infection intensity. A single urine sample was used in Burkina Faso, Niger, Tanzania, and Zambia. All countries performed a single filtration except Niger that prepared two filtrations from one urine sample. In Mali, program officials took two urine samples from consecutive days and filtered each. A stained filter was microscopically examined for *S. haematobium* eggs after passing approximately 10 ml of urine through it. An individual’s infection intensity was calculated as the arithmetic mean of the number of eggs per 10 ml of urine across all available samples. Participants were then grouped into three intensity infection categories: negative (0 eggs per 10 ml urine), light (1–49 eggs per 10 ml of urine), and heavy (≥50 eggs per 10 ml of urine) [11].

*S. mansoni* infection intensity was determined by the Kato-Katz technique. Mali, Niger, and the baseline Ugandan survey used a single stool with counting of two separately prepared Kato-Katz thick smears. Two stools from consecutive days with two slides each were used in Tanzania and all follow-up surveys in Uganda. Slides were microscopically examined for *S. mansoni* eggs. Individual intensity of infection was determined by calculating the arithmetic mean of the number of eggs on all available slides multiplied by a factor of 24 to scale the measurement to eggs per 1 g of stool. Participants were classified into four intensity infection categories: negative (0 EPG), light (1–99 EPG), moderate (100–399 EPG), and heavy (≥400 EPG) [11].

**Morbidity data**

Morbidity data were collected from the same participants as the infection data. *S. haematobium* ultrasound variables utilized in these analyses included all elements of an *S. haematobium* ultrasound evaluation [25] performed in accordance to the standardized Niamey protocol [26]. These included a distorted bladder shape, the presence of irregularities in the bladder wall, detection of any bladder wall masses >10 mm in size, presence of pseudopolyps, a focal or diffuse thickening of the bladder wall, any dilation of the left or right pelvis, and any visualization of the left or right ureter. The first five indicators were aggregated into an outcome denoting whether a participant was positive for any urinary bladder lesion while the

### Table 1. Summary of Schistosoma infection data collection procedures by country, Schistosomiasis Control Initiative (SCI) supported monitoring and evaluation data, 2003–2008.

| Country       | *S. haematobium* 10 ml urine filtrations | *S. mansoni* 41.7mg Kato-Katz (KK) slides |
|---------------|----------------------------------------|------------------------------------------|
| Burkina Faso  | One                                    | One stool sample with two slides         |
| Mali          | Two from different samples taken on consecutive days | One stool sample with two slides         |
| Niger         | Two from the same urine sample          | One stool sample with two slides         |
| Tanzania      | One                                    | Two stool samples with two slides        |
| Uganda        | No evaluation                          | Baseline: one stool sample with two slides |
|               |                                        | Follow-up: two stool samples with two slides |
| Zambia        | One                                    | Two stool samples with two slides        |

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pelvic dilation and ureter visualization indicators were aggregated into an outcome denoting whether a participant was positive for any upper urinary tract lesion. Participants missing any of the *S. haematobium* ultrasound indicators were excluded from these analyses. Additionally, as a sensitivity analysis, a second approach utilized the number of positive indicators and the total number of indicators measured and are referred to as the urinary bladder rate and upper urinary tract rate. All participants with at least one indicator measured were included in the second analysis. Two additional morbidity indicators were also analyzed: microhematuria assessed with Hemastix dipsticks [27] and self-reported pain while urinating [28]. The analyses of individual morbidity indicators are included in the supplementary material (S1 Text).

Four main morbidity variables were analyzed for *S. mansoni*. Two ultrasound indicators of *S. mansoni* infection, collected according to the Niamey protocol [26], were included in analyses: the presence of a hepatic image pattern of C or worse to measure where a participant has any echogenic fibrosis; and an enlarged portal vein, defined as a portal vein diameter with a score of >2 standard deviations from the Senegalese population data used in the Niamey protocol. Unfortunately, other indicators were not consistently measured in all countries. The final two morbidity variables for *S. mansoni* were laboratory-confirmed and self-reported diarrhea [29,30]. Laboratory-confirmed diarrhea was indicated by the technician, while self-reported diarrhea was based on participants’ responses when asked if they had experienced diarrhea in the last 2 weeks. Analyses of hepatic irregular image pattern B or worse, blood in stool, and abdominal pain for *S. mansoni* are included in the supplementary materials (S1 Text).

**Data analysis methods**

R version 4.0.3 [31] and the tidyverse package [32] were used to prepare data for analyses. All analyses that required a level of significance used the 5% level. Analyses included in this report’s figures treated the data as a stratified (country level) and clustered (school level) sample via the survey package [33]. Logistic regression was used to compare the relative odds of possessing a morbidity between categories within a survey. These models have the goal of comparing participants’ current infection status within the same survey and do not make comparisons between surveys or identify the best infection categories.

The regression model contained fixed effects for countries to control for differences between control programs, age and sex of participants, survey year, intensity infection category, and the interaction between survey year and intensity category. A random intercept for each school was included to account for any correlation between children sampled from the same school. Participants who contributed data at multiple surveys had individual random intercepts, while those participants who contributed for a single year did not. All comparisons were estimated via contrast statements and reported as odds ratios (ORs) with 95% Bayesian credible intervals (BCIs) from the posterior distributions. Regression models were fit via Markov chain Monte Carlo (MCMC) methods in JAGS [34] using the rjags package [35]. Three chains were chosen with an adaptive phase of 10,000 iterations and a total of 80,000 iterations per chain. The first 10,000 iterations were discarded. All fixed effect coefficients used have Cauchy prior distributions with a center of zero and a scale of 2.5 [36]. For *S. haematobium*-related morbidities, additional models were run without controlling for participants’ age and sex for comparison.

In addition, we explored whether using three categories of *S. mansoni* infection intensity (rather than four levels) might show a stronger association with morbidity indicator prevalence. Multiple categorizations were used to define the new *S. mansoni* infection intensity categories, each with zero EPG of stool treated as negative and the remaining two categories were
split at a new threshold. We chose thresholds of 100 EPG, 200 EPG, 300 EPG, and 400 EPG to split infected participants. Thus, for example, the threshold of 200 EPG, produced a categorization of 0 EPG, 1–199 EPG, and ≥200 EPG.

**Results**

*S. haematobium*

A range of 8,615 to 11,948 school-age children were included at baseline depending on each morbidity’s missing data (Table B in S1 Text). This dropped to a range of 5,107 to 6,941 for follow-up 1 and 3,599 to 3,672 for follow-up 2. The prevalence of any infection and heavy-intensity infection prevalence were demonstrably higher for participants sampled at baseline compared to those sampled at follow-up 1 as the confidence intervals did not overlap; however, infection levels did not differ between follow-up 1 and follow-up 2 (Fig 1, row A). Similarly, most morbidities were more prevalent among participants sampled at baseline compared to participants sampled at follow-up 1 or at follow-up 2 (Fig 1, row B and A in S1 Text).

With a few exceptions, infection intensity category prevalence estimates for *S. haematobium*-related morbidity indicators were consistent across surveys (Fig 2). Microhematuria prevalence was almost identical in each intensity category across surveys. Participants in the heavy intensity category at follow up 2 had a much higher prevalence of any urinary bladder lesion and the prevalence of pain while urinating, those morbidity indicators were consistent across surveys for the other intensity categories. The prevalence of any upper urinary tract lesion trended downward, for participants in the heavy intensity infection category, in each successive survey. Individual ultrasound indicators followed similar patterns but tended to have more variability (Table C in S1 Text).

ORs comparing participants in different intensity categories at each survey were roughly consistent for any urinary bladder lesions, any upper urinary tract lesions, microhematuria, and pain while urinating (Table 2). Compared to negative participants, participants with light infections were at increased odds for all morbidity indicators. The same was also true for participants with heavy infections, with the exception of the follow-up 2 survey for any upper urinary tract lesions. There was a lack of consistency between participants with heavy versus light infections for any upper urinary tract lesion, but differences were consistent at all timepoints for other morbidities. Similar results were found for binomial outcomes (Table C in S1 Text).

The differences in the odds of possessing a morbidity between intensity categories was dramatically different when age and sex were not controlled for in regression models (Table 3). When age and sex are not included, the OR estimates are more closely aligned with those found in the raw data (Fig 2), than those in models with age and sex included (Table 2).

*S. mansoni*

The sample sizes for *S. mansoni* analyses ranged from 5,158 to 13,483 school-age children at baseline, 4,881 to 11,484 for follow-up 1, and 3,901 to 6,216 for follow-up 2 (Table D in S1 Text). Although the prevalence of any infection and heavy-intensity infection prevalence was higher for participants sampled at baseline, as compared to those sampled at follow-up 1, the declines were modest and confidence intervals overlap (Fig 1, row A and C in S1 Text). *S. mansoni*-related morbidities, collected via ultrasound or in the laboratory and validated by a technician, also experienced decreases when participants at each follow-up survey are compared to baseline participants (Fig 1, row C and D in S1 Text), though the confidence intervals often overlap. The prevalence of enlarged portal vein slightly increased for participants in follow up 1, compared to baseline. Self-reported morbidities remained similar across the surveys.
In contrast to *S. haematobium*, *S. mansoni*-related morbidities demonstrated no clear pattern and fewer associations with intensity categories (Fig 3; Table 4 and D in S1 Text). For instance, while baseline participants with heavy and moderate intensity infections were more likely to have an enlarged portal vein than their negative counterparts (moderate versus
negative: OR = 1.53, 95% BCI = 1.09–2.13; heavy versus negative: OR = 2.48, 95% BCI = 1.86–3.30), these associations were much weaker at follow-up 1 (moderate versus negative: OR = 1.31, 95% BCI = 0.86–1.97; heavy versus negative: OR = 1.25, 95% BCI = 0.70–2.12), but then were much stronger at follow up 2 (moderate versus negative: OR = 3.29, 95% BCI = 1.91–5.47; heavy versus negative: OR = 4.68, 95% BCI = 2.24–9.18). Percentages of enlarged portal vein broken down by country (Fig E in S1 Text), show very high estimates of enlarged portal vein for Nigerien and Zambian participants with no infection. This resulted in negative participants having a higher estimate of enlarged portal vein than other intensities at both follow-up surveys (Fig 3). Though, since the modeled results take into account differences between countries and the age and sex of the participant, the ORs represent a more accurate comparison between the intensity categories (Table 4). Results for all *S. mansoni* morbidity indicators are included in the supplementary material (Table E in S1 Text).
Under the consideration that the different patterns observed between *S. haematobium* and *S. mansoni* could be a statistical artifact of the number of intensity categories between species, we explored using three *S. mansoni* intensity categories instead of four. Using 200 EPG as the breakpoint between the light- and heavy-intensity categories, patterns similar to the four-category definition were seen (Fig 4). This was also true when 100 EPG, 300 EPG, and 400 EPG were utilized as the breakpoint between a light and heavy infection (Fig E-H in S1 Text).

**Discussion**

These analyses indicated that there were consistent associations between infection intensity categories and the prevalence of some morbidity indicators for children aged 6–15 years for *S. haematobium*, as measured prior to the initiation of preventive chemotherapy (the baseline survey) and before each subsequent round of annual mass drug administration (follow-up 1 and follow-up 2 surveys). However, the same associations were not found for *S. mansoni* for the measures of morbidity that were collected. For the infection categories to effectively

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**Table 2.** Odds ratios (ORs) and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between intensity categories within surveys for *S. haematobium*-related morbidities. Bold font indicates the 95% Bayesian credible interval (BCI) does not contain one. Participants are school-age children (6–15 years), enrolled between 2003 and 2008 in Mali, Niger, and Tanzania.

| Morbidity                  | Survey      | Light versus negative | Heavy versus negative | Heavy versus light |
|----------------------------|-------------|------------------------|-----------------------|-------------------|
| Any urinary bladder        | Baseline    | 1.42 (1.22, 1.64)      | 1.76 (1.46, 2.11)     | 1.24 (1.04, 1.48)  |
|                            | Follow-up1  | 1.58 (1.33, 1.87)      | 1.39 (0.99, 1.94)     | 0.88 (0.62, 1.23)  |
|                            | Follow-up2  | 2.32 (1.85, 2.90)      | 2.73 (1.93, 3.85)     | 1.18 (0.84, 1.65)  |
| Any upper urinary tract     | Baseline    | 1.39 (1.02, 1.89)      | 1.74 (1.22, 2.48)     | 1.26 (0.92, 1.72)  |
| lesions                    | Follow-up1  | 1.19 (0.81, 1.74)      | 1.67 (0.86, 3.02)     | 1.41 (0.72, 2.58)  |
|                            | Follow-up2  | 1.96 (0.96, 4.02)      | 1.88 (0.54, 5.29)     | 0.96 (0.28, 2.67)  |
| Microhematuria              | Baseline    | 2.11 (1.92, 2.33)      | 3.25 (2.88, 3.68)     | 1.54 (1.36, 1.73)  |
|                            | Follow-up1  | 2.19 (1.91, 2.53)      | 2.84 (2.17, 3.74)     | 1.29 (0.97, 1.73)  |
|                            | Follow-up2  | 2.00 (1.69, 2.38)      | 4.40 (3.27, 5.93)     | 2.19 (1.62, 2.98)  |
| Pain while urinating       | Baseline    | 1.19 (1.07, 1.34)      | 1.58 (1.38, 1.81)     | 1.32 (1.15, 1.52)  |
|                            | Follow-up1  | 1.02 (0.87, 1.20)      | 0.93 (0.67, 1.27)     | 0.91 (0.65, 1.27)  |
|                            | Follow-up2  | 1.27 (1.06, 1.54)      | 1.26 (0.90, 1.77)     | 0.99 (0.70, 1.40)  |

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**Table 3.** Odds ratios (ORs) and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between intensity categories within surveys for *S. haematobium*-related morbidities without controlling for age and sex. Bold font indicates the 95% Bayesian credible interval (BCI) does not contain one. Participants are school-age children (6–15 years), enrolled between 2003 and 2008 in Mali, Niger, and Tanzania.

| Morbidity                  | Survey      | Light versus negative | Heavy versus negative | Heavy versus light |
|----------------------------|-------------|------------------------|-----------------------|-------------------|
| Any urinary bladder        | Baseline    | 3.49 (2.98, 4.10)      | 10.15 (8.37, 12.34)   | 2.91 (2.46, 3.44)  |
| lesions                    | Follow-up1  | 3.89 (3.15, 4.80)      | 13.10 (9.36, 18.36)   | 3.37 (2.42, 4.70)  |
|                            | Follow-up2  | 3.08 (2.47, 3.86)      | 10.07 (7.17, 14.23)   | 3.26 (2.34, 4.58)  |
| Any upper urinary tract     | Baseline    | 1.75 (1.30, 2.35)      | 3.35 (2.43, 4.63)     | 1.92 (1.46, 2.51)  |
| lesions                    | Follow-up1  | 1.15 (0.66, 1.94)      | 2.77 (1.29, 5.46)     | 2.41 (1.08, 5.03)  |
|                            | Follow-up2  | 1.93 (0.99, 3.80)      | 1.63 (0.47, 4.43)     | 0.84 (0.25, 2.27)  |
| Microhematuria              | Baseline    | 23.75 (20.67, 27.35)   | 296.27 (229.36, 388.21)| 12.47 (9.90, 15.95)|
|                            | Follow-up1  | 14.45 (12.10, 17.29)   | 249.79 (143.44, 470.70)| 17.28 (10.02, 32.37)|
|                            | Follow-up2  | 29.17 (22.56, 38.24)   | 1165.70 (506.17, 3363.16)| 39.82 (17.86, 112.05)|
| Pain while urinating       | Baseline    | 1.41 (1.26, 1.58)      | 2.40 (2.10, 2.75)     | 1.70 (1.48, 1.94)  |
|                            | Follow-up1  | 1.59 (1.35, 1.86)      | 2.37 (1.77, 3.16)     | 1.49 (1.09, 2.03)  |
|                            | Follow-up2  | 1.58 (1.31, 1.91)      | 4.58 (3.31, 6.38)     | 2.89 (2.07, 4.06)  |
discriminate between morbidity directly associated with schistosomiasis, the odds of morbidity should be greater for a higher intensity category. ORs between *S. haematobium* infection intensity categories were largely consistent for most morbidity indicators before and after praziquantel administration. For example, across the three surveys, participants with light intensity infections had approximately two (or 15 to 30 without controlling for age and sex) times higher odds of microhematuria compared to participants without *S. haematobium* eggs in their urine. Consistent ORs were also found for heavy versus negative intensity. For *S. mansoni*, there was no morbidity measure where ORs between infection intensity categories were consistent. When raw prevalence and confidence intervals were plotted (Fig 3 and D in S1 Text), the categories are indistinguishable as confidence intervals overlap for almost all categories. This transpired in the context of effective preventive chemotherapy programs [37].
Our analyses had some limitations. Only morbidity indicators that were measured in multiple countries were analyzed, meaning many indicators from the S. mansoni ultrasound protocol were omitted. Some of those indicators suffer from high intra-observer variability [38–40], which suggest that those measures may not have been as useful as anticipated. Of note, enlarged portal vein measurements were taken against the Senegalese population utilized in the Niamey protocol, which may not be an appropriate comparison given these data come from other countries. The collection of stools (for Kato-Katz thick smears) and urine (for urine filtrations) varied across countries. Furthermore, additional stool and urine samples would have provided a more accurate assessment of infection and infection intensity. Although similar data systems were used by most countries, there was variability in the data collected, meaning that only subsets of the SCI-supported countries appear in most analyses. While recommendations were made for an appropriate number of schools and participants per school to enroll, data collection was a part of monitoring and evaluation cohorts without specific hypotheses. In addition, control programs had the final say on sample sizes and utilized different approaches, which were likely driven by available financial and human resources in some countries. While we realize these sample size considerations influenced the analyses, we were limited in our ability to power these analyses appropriately given the context in which the data were collected. Finally, there is the potential for systematic selection bias in these analyses as the school-age children sampled from these communities may be consistently different from those who were not sampled. In addition, while some people were measured multiple times, others were not, meaning the loss to follow up is high in these data.

Table 4. Odds ratios (ORs) and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between heavy-intensity prevalence categories within surveys for S. mansoni-related morbidities. Bold font indicates the 95% Bayesian credible interval does not contain one. Participants are school-age children (6–15 years), enrolled between 2003 and 2008 in Mali, Niger, Tanzania, and Uganda.

| Morbidity                  | Survey     | Light versus negative | Moderate versus negative | Heavy versus negative | Moderate versus light | Heavy versus light | Heavy versus moderate |
|---------------------------|------------|-----------------------|--------------------------|-----------------------|----------------------|---------------------|----------------------|
| Image pattern C-F         | Baseline   | 1.95 (0.79, 5.05)     | 2.06 (0.86, 5.39)        | 3.97 (1.67, 10.19)    | 1.06 (0.50, 2.29)    | 2.03 (0.97, 4.37)  | 1.91 (0.96, 3.85)    |
|                           | Follow-up 1| 1.13 (0.45, 2.90)     | 0.70 (0.22, 2.12)        | 0.43 (0.07, 1.81)     | 0.62 (0.21, 1.68)    | 0.38 (0.06, 1.47)  | 0.62 (0.09, 2.69)    |
|                           | Follow-up 2| *                     | *                        | *                     | *                    | *                   | *                   |
| Enlarged portal vein      | Baseline   | 0.98 (0.74, 1.27)     | 1.53 (1.09, 2.13)        | 2.48 (1.86, 3.30)     | 1.57 (1.06, 2.31)    | 2.55 (1.79, 3.63)  | 1.62 (1.11, 2.39)    |
|                           | Follow-up 1| 1.18 (0.83, 1.65)     | 1.31 (0.86, 1.97)        | 1.25 (0.70, 2.12)     | 1.11 (0.68, 1.79)    | 1.06 (0.57, 1.91)  | 0.95 (0.49, 1.79)    |
|                           | Follow-up 2| 1.34 (0.81, 2.12)     | 3.29 (1.91, 5.47)        | 4.68 (2.24, 9.18)     | 2.46 (1.26, 4.82)    | 3.50 (1.52, 7.82)  | 1.42 (0.61, 3.23)    |
| Laboratory-confirmed      | Baseline   | 1.32 (1.05, 1.66)     | 1.58 (1.23, 2.02)        | 1.69 (1.32, 2.15)     | 1.20 (0.89, 1.60)    | 1.28 (0.96, 1.71)  | 1.07 (0.80, 1.44)    |
| diarrhea                  | Follow-up 1| 1.77 (1.38, 2.27)     | 1.76 (1.28, 2.40)        | 1.68 (1.14, 2.43)     | 0.99 (0.70, 1.40)    | 0.95 (0.63, 1.42)  | 0.96 (0.61, 1.48)    |
|                           | Follow-up 2| 1.47 (1.08, 1.97)     | 1.32 (0.80, 2.11)        | 0.86 (0.42, 1.60)     | 0.90 (0.52, 1.51)    | 0.59 (0.28, 1.13)  | 0.65 (0.28, 1.41)    |
| Self-reported diarrhea     | Baseline   | 1.17 (1.03, 1.33)     | 1.56 (1.34, 1.83)        | 1.43 (1.23, 1.66)     | 1.34 (1.11, 1.61)    | 1.22 (1.02, 1.46)  | 0.91 (0.75, 1.11)    |
|                           | Follow-up 1| 1.14 (0.98, 1.33)     | 1.18 (0.96, 1.45)        | 1.29 (1.00, 1.66)     | 1.04 (0.82, 1.32)    | 1.13 (0.86, 1.49)  | 1.09 (0.80, 1.48)    |
|                           | Follow-up 2| 1.16 (0.97, 1.40)     | 1.29 (0.96, 1.73)        | 1.09 (0.76, 1.57)     | 1.11 (0.80, 1.54)    | 0.94 (0.64, 1.39)  | 0.85 (0.54, 1.33)    |

* Due to the low prevalence of image pattern C-F, all comparisons between categories were unstable and possessed a large amount of uncertainty; therefore they were omitted from this table.

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Nevertheless, if the intensity categories, which are purported to measure a person’s current infection status, have a robust relationship with morbidity, then we should see a similar relationship regardless of whether selection bias, heterogeneous age distributions, and other potential biases are present.

Nevertheless, an important finding is that participants with light and moderate *Schistosoma mansoni* infections had elevated morbidity levels compared to their non-infected counterparts for ultrasound indicators and microhematuria. This appears to be at odds with the notion that morbidity is only caused by heavy-infections [41], which has driven monitoring and evaluation goals for schistosomiasis [11,14,42]. Our results add to the literature that morbidity is present in people with even light and moderate infections [2,43] and strengthens the evidence-base that morbidity control should be based on any infection instead of heavy infections [15].
We explored some potential reasons for the stronger association between *S. haematobium* infection categories and morbidity, as compared to the *S. mansoni* infection categories and morbidity. One consideration was whether the poorer performance could be due to *S. mansoni* possessing a fourth intensity category compared to three for *S. haematobium*. Additional analyses were performed to evaluate whether separating *S. mansoni* intensity into three categories would improve discrimination. None of the multiple thresholds chosen hinted at an improvement to the association between infection intensity categories and morbidity.

Differences between species could be due to the diagnostic tests. Both the urine filtration and Kato-Katz techniques have considerable day-to-day variability [44,45]. Separate studies of the day-to-day fluctuation in these tests using the intra-person correlation coefficient found reasonably similar estimates for *S. haematobium* in Gabon (0.81, 95% confidence interval (CI): 0.71–0.89) [46] and *S. mansoni* in Burundi (0.77, 95% CI: 0.66–0.85) [47]. Though, the latter result differed from a study in Côte d’Ivoire where the intra-specimen variation of egg counts was 4.3 times higher than the day-to-day variability [45]. A comparable analysis could not be found for *S. mansoni* egg counts, but this variation could explain the worse performance of the Kato-Katz technique. Finally, small changes in *S. mansoni* egg counts have a much larger effect on the final intensity measure than for *S. haematobium*. For a 10 ml sample of urine, 50 *S. haematobium* eggs are needed for a heavy-intensity infection. For a single Kato-Katz thick smear only 41.7 mg of stool are utilized, and hence, 17 *S. mansoni* eggs on a slide are defined as a heavy-intensity infection. Thus, measuring an additional egg in a positive sample has a considerably larger effect in a Kato-Katz thick smear examination compared to a urine filtration test.

The age at which these morbidity indicators commonly develop was shown to hugely influence the association between infection category and microhematuria and may have an impact with other morbidity indicators. Microhematuria and ultrasound-related morbidity associated with *S. haematobium* has been found to be more prevalent in children, as compared to adults [48,49]. Conversely, multiple studies have shown the risk for *S. mansoni* morbidity indicators of periportal fibrosis to be higher in adults, as compared to children [50–52]. This could be due to *S. haematobium* ultrasound indicators being observable sooner than *S. mansoni* ultrasound indicators and with the availability of more practical ultrasound examination equipment [53], potential challenges such as this will need to be addressed if such a tool will be programmatically useful. Regardless, the likelihood of *S. mansoni* morbidity indicators in these school-age participants was much lower than the likelihood of *S. haematobium* indicators and likely contributed to the poorer associations between *S. mansoni*-related morbidity indicators and *S. mansoni* infection prevalence. In addition, the lower prevalence of *S. mansoni* morbidity indicators potentially created a floor effect where *S. mansoni* indicators had less chance to decline, as compared to *S. haematobium* indicators. We conjecture that with the large sample size and analyses of ratios, we have guarded against this. Exploring how age and sex moderate relationships between morbidity and intensity categories will require a thorough evaluation.

Differences could also be due to variation in the effect of preventive chemotherapy. The follow-up time may not have been long enough for reductions in ultrasound to present at an aggregate level, especially for *S. mansoni*. For instance, past research suggested urinary tract pathology appears to reverse more rapidly than hepatic pathology [25]. More recent studies have suggested that *S. haematobium*-related morbidity improves in less than a year in school-age children [54] and in 1–2 years in adults [55], whereas liver pathologies have been shown to reduce in severity a year after initiation of treatment [56], but full resolution requires longer, approximately 2 years [57,58].

Bias or error in measurement was also possible for morbidity evaluations, though it is unclear how this affected the differences in results by species. Both *S. haematobium* and *S.
mansoni ultrasounds have had reliable inter-observer agreement [59,60], though there have been some differences in portal branch measurements [59] and portable ultrasonographic devices may have reduced sensitivity to detect bladder wall abnormalities [60]. The reliability of reagent strips is good for detecting infection [61], and a meta-analysis found that sensitivity and specificity were 81% and 89%, respectively, compared to measurement of eggs in urine [62].

In addition, some morbidities presented here are not specific to schistosome infection. For ultrasonic measures, there is the possibility for other causes of morbidity. Indeed, hepatosplenic disease in the absence of periportal fibrosis in children has been observed [63,64] and associated with current or recent malaria infection [64,65]. This could be due to some organ enlargement being caused by malaria infection [63]. There is potential that hepatitis C virus infection could lead to portal vein dilation [59], though this hypothesis is based on correlations at an aggregate level and may be due to different populations possessing different susceptibilities to liver disease [66]. Hematuria, painful urination, blood in stool, diarrhea, and abdominal pain are not solely caused by schistosomiasis and may introduce bias into the results. Self-reported morbidity also has moderate diagnostic performance [67] and many sources of bias are possible from questionnaires [68]. For these morbidities, reductions, or lack thereof, may not be wholly attributable to the decreases in infection and heavy-intensity infection observed after initiation of preventive chemotherapy.

Conclusion

Schistosoma infection intensity categories are utilized to evaluate disease burden and associate with other outcomes. The current analyses found that the infection intensity categories correlated reasonably well for S. haematobium but not for S. mansoni. Control programs and researchers that utilize Schistosoma infection intensity categories based on egg count thresholds should be aware that the S. mansoni categories do not appear to align with the morbidity indicators used in this study and that, for both schistosome species, low-intensity infections are not morbidity-free. These analyses show that heavy-intensity infections do not capture all morbidity in these school-age children. Control program infection thresholds for S. mansoni that utilize these intensity categories based on Kato-Katz thick smear examinations should be reconfigured in order to align with morbidity levels.

Supporting information

S1 Text. Supporting information including all additional tables and figures.

(DOCX)

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Author Contributions

Conceptualization: Ryan E. Wiegand, W. Evan Secor, Fiona M. Fleming, Michael D. French, Charles H. King, Arminder K. Deol, Susan P. Montgomery, Darin Evans, Jürg Utzinger, Sake J. de Vlas.

Data curation: Ryan E. Wiegand, W. Evan Secor, Fiona M. Fleming, Susan P. Montgomery.

Formal analysis: Ryan E. Wiegand, Penelope Vounatsou.

Funding acquisition: Fiona M. Fleming, Michael D. French, Susan P. Montgomery.

Investigation: Ryan E. Wiegand, W. Evan Secor, Penelope Vounatsou, Sake J. de Vlas.

Methodology: Ryan E. Wiegand, Penelope Vounatsou, Sake J. de Vlas.

Project administration: Ryan E. Wiegand, W. Evan Secor, Jürg Utzinger, Penelope Vounatsou.

Resources: Fiona M. Fleming.

Software: Ryan E. Wiegand.

Supervision: W. Evan Secor, Jürg Utzinger, Penelope Vounatsou, Sake J. de Vlas.

Validation: Ryan E. Wiegand.

Visualization: Ryan E. Wiegand, Sake J. de Vlas.

Writing – original draft: Ryan E. Wiegand, W. Evan Secor, Sake J. de Vlas.

Writing – review & editing: Ryan E. Wiegand, W. Evan Secor, Fiona M. Fleming, Michael D. French, Charles H. King, Arminder K. Deol, Susan P. Montgomery, Darin Evans, Jürg Utzinger, Penelope Vounatsou, Sake J. de Vlas.

References

1. Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. Lancet. 2014; 383(9936):2253–64. Epub 2014/04/05. https://doi.org/10.1016/S0140-6736(13)61949-2 PMID: 24698483.

2. King CH, Dickman K, Tisch DJ. Reassessment of the cost of chronic helminthic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. Lancet. 2005; 365(9470):1561–9. Epub 2005/05/04. https://doi.org/10.1016/S0140-6736(05)66457-4 PMID: 15866310.

3. van der Werf MJ, de Vlas SJ, Brooker S, Looman CW, Nagelkerke NJ, Habbema JD, et al. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. Acta Trop. 2003; 86(2–3):125–39. Epub 2003/05/15. https://doi.org/10.1016/s0001-706x(03)00029-9 PMID: 12745133.

4. Khalaf I, Shokeir A, Shalaby M. Urologic complications of genitourinary schistosomiasis. World J Urol. 2012; 30(1):31–8. https://doi.org/10.1007/s00345-011-0751-7 PMID: 21909645.

5. Christinet V, Lazdins-Helds JK, Stothard JR, Reinhard-Rupp J. Female genital schistosomiasis (FGS): from case reports to a call for concerted action against this neglected gynaecological disease. Int J Parasitol. 2016; 46(7):385–404. https://doi.org/10.1016/j.ijpara.2016.02.006 PMID: 27063079.

6. Kayuni S, Lampiao F, Makaula P, Juwiwelo L, Lacourse EJ, Reinhard-Rupp J, et al. A systematic review with epidemiologic update of male genital schistosomiasis (MGS): A call for integrated case management across the health system in sub-Saharan Africa. Parasite Epidemiol Control. 2019; 4:e00077. https://doi.org/10.1016/j.parepi.2018.e00077 PMID: 30662962.

7. Ishida K, Hsieh MH. Understanding urogenital schistosomiasis-related bladder cancer: an update. Front Med. 2018; 5:223. https://doi.org/10.3389/fmed.2018.00223 PMID: 30159314.

8. World Health Organization. Schistosomiasis control: Report of a WHO expert committee. Geneva: World Health Organization; 1973.

9. World Health Organization. Progress in assessment of morbidity due to Schistosoma mansoni/infection: a review of recent literature. In: Schistosomiasis Unit PDP, World Health Organization, editor. Geneva: World Health Organization; 1988. p. 66.
10. WHO Expert Committee on the Control of Schistosomiasis & World Health Organization. The control of schistosomiasis: Report of a WHO expert committee [meeting held in Geneva from 8 to 13 November 1984]. Geneva: World Health Organization; 1985. p. 113.

11. World Health Organization. Prevention and control of schistosomiasis and soil-transmitted helminthiasis. 2003/02/21 ed. Geneva: World Health Organization; 2002. i–vi, 1–57. back cover p.

12. Dixon H. Statistical Methods Applicable to Schistosomiasis Control Programmes. In: Schistosomiasis Unit PDP, World Health Organization, editor. Geneva: World Health Organization; 1987. p. 30.

13. Montresor A, Crompton DWT, Hall A, Bundy DAP, Savioli L. Guidelines for the evaluation of soil-transmitted helminthiasis and schistosomiasis at community level: A guide for managers of control programmes. Geneva: World Health Organization; 1998. p. 45.

14. World Health Organization. Schistosomiasis: progress report 2001–2011, strategic plan 2012–2020. Geneva: World Health Organization; 2013. 74 p.

15. King CH. It’s time to dispel the myth of “asymptomatic” schistosomiasis. PLOS Negl Trop Dis. 2015; 9 (2):e0003504. https://doi.org/10.1371/journal.pntd.0003504 PMID: 25695740

16. Koukounari A, Gabrielli AF, Touré S, Bosqué-Oliva E, Zhang Y, Sellin B, et al. Schistosoma haemato-bium infection and morbidity before and after large-scale administration of praziquantel in Burkina Faso. J Infect Dis. 2007; 196(5):659–69. https://doi.org/10.1086/520515 PMID: 17674306

17. Touré S, Zhang Y, Bosqué-Oliva E, Ky C, Ouédraogo A, Koukounari A, et al. Two-year impact of single praziquantel treatment on infection in the national control programme on schistosomiasis in Burkina Faso. Bull World Health Organ. 2008; 86(10):780–7. https://doi.org/10.2471/blt.07.048694 PMID: 18949215

18. Garba A, Touré S, Dembele R, Bossio P, Tohon Z, Bosqué-Oliva E, et al. Present and future schistosomiasis control activities with support from the Schistosomiasis Control Initiative in West Africa. Parasitol. 2009; 136(13):1731–7. Epub 2009/07/28. https://doi.org/10.1016/j.parasitology.2009.05.001 PMID: 19631007

19. Koukounari A, Sacko M, Keita AD, Gabrielli AF, Landoure A, Dembélé R, et al. Assessment of ultrasound morbidity indicators of schistosomiasis in the context of large-scale programmes illustrated with experiences from Malian children. Am J Trop Med Hyg. 2006; 75(6):1042–52. PMID: 17172363

20. Kabatereine NB, Brooker S, Koukounari A, Kazibwe F, Tukahebwa EM, Fleming FM, et al. Impact of a national helminth control programme on infection and morbidity in Ugandan schoolchildren. Bull World Health Organ. 2007; 85(2):91–9. https://doi.org/10.2471/blt.06.030353 PMID: 17308729

21. Kabatereine NB, Fleming FM, Nyandindi U, Mwanza JCL, Blair L. The control of schistosomiasis and soil-transmitted helminths in East Africa. Trends Parasitol. 2006; 22(7):332–9. https://doi.org/10.1016/j.pt.2006.05.001 PMID: 16713357

22. Fenwick A, Webster JP, Bosqué-Oliva E, Blair L, Fleming FM, Zhang Y, et al. The Schistosomiasis Control Initiative (SCI): rationale, development and implementation from 2002–2008. Parasitology. 2009; 136(13):1719–30. Epub 2009/07/28. https://doi.org/10.1016/j.parasitology.2009.05.001 PMID: 19631008.

23. Montresor A, Crompton DWT, Gyorkos TW, Savioli L. Helminth control in school-age children: A guide for managers of control programmes. Geneva: World Health Organization; 2002.

24. World Health Organization. Helminth control in school-age children: A guide for managers of control programmes. 2 ed. Geneva: World Health Organization; 2011.

25. Richter J. The impact of chemotherapy on morbidity due to schistosomiasis. Acta Trop. 2003; 86 (2):161–83. https://doi.org/10.1016/s0001-706x(03)00032-9 PMID: 12745135

26. Richter J, Hatz C, Campagne G, Bergquist NR, Jenkins JM. Ultrasound in schistosomiasis: a practical guide to the standard use of ultrasonography for assessment of schistosomiasis-related morbidity: Second International Workshop, October 22–26 1996, Niamey, Niger. Geneva: World Health Organization, 2000 Contract No.: TDR/STR/SCH/00.1.

27. French MD, Rollinson D, Basáñez MG, Mgeni AF, Khamis IS, Stothard JR. School-based control of urinary schistosomiasis on Zanzibar. Tanzania: monitoring micro-haematuria with reagent strips as a rapid urological assessment. J Pediatr Urol. 2007; 3(5):364–8. https://doi.org/10.1016/j.jpurol.2007.01.196 PMID: 18947774

28. Danso-Appiah A, Stol W, Bosompem KM, Otchere J, Looman CWN, Habbema JDF, et al. Health seeking behaviour and utilization of health facilities for schistosomiasis-related symptoms in Ghana. PLOS Negl Trop Dis. 2010; 4(11):e867. https://doi.org/10.1371/journal.pntd.0000867 PMID: 21072229

29. Stelma FF, Tall S, Verle P, Niang M, Gryseels B. Morbidity due to heavy Schistosoma mansoni infections in a recently established focus in northern Senegal. Am J Trop Med Hyg. 1994; 50(5):575–9. https://doi.org/10.4269/ajtmh.1994.50.575 PMID: 8203706

30. Polderman AM, Gryseels B, Gerold J, Npamila K, Manshande JP. Side effects of praziquantel in the treatment of Schistosoma mansoni in Maniema, Zaire. T Roy Soc Trop Med Hyg. 1984; 78(6):752–4. https://doi.org/10.1016/0035-9203(84)90007-5 PMID: 6335929
31. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.

32. Wickham H. tidyverse: Easily Install and Load the 'Tidyverse'. R package version 1.2.1 ed2017.

33. Lumley T. survey: analysis of complex survey samples. R package version 3.35–1 ed2019.

34. Plummer M, editor JAGS: A program for analysis of Bayesian graphical models using Gibbs sampling. Proceedings of the 3rd international workshop on distributed statistical computing; 2003: Vienna, Austria.

35. Plummer M. rjags: Bayesian Graphical Models using MCMC. R package version 4–10 ed2019.

36. Gelman A, Jakulin A, Pittau MG, Su Y-S. A weakly informative default prior distribution for logistic and other regression models. Ann Appl Stat. 2008; 2(4):1360–83. https://doi.org/10.1214/08-AOAS191

37. Deol AK, Fleming FM, Calvo-Urbano B, Walker M, Bucumvi VM, Gnaoudd I, et al. Schistosomiasis—assessing progress toward the 2020 and 2025 global goals. N Engl J Med. 2019; 381(26):2519–28. https://doi.org/10.1056/NEJMoai1812165 PMID: 31881138

38. Doehring-Schwerdtfeger E, Kaiser C, Franke D, Kardorff R, Ali QM, Abdel-Rahim IM. Inter-observer variation in ultrasonographic assessment of Schistosoma mansoni-related morbidity in young school-children. Acta Trop. 1992; 51(1):85–8. https://doi.org/10.1016/0001-706x(92)90022-p PMID: 1351357

39. Thomas AK, Dittrich M, Kardorff R, Taila I, Mbaye A, Sow S, et al. Evaluation of ultrasonographic staging systems for the assessment of Schistosoma mansoni induced hepatic involvement. Acta Trop. 1997; 68(3):347–56. https://doi.org/10.1016/s0001-706x(97)00112-5 PMID: 9492919

40. Sebastianes PM, Sales DM, Santos JEM, Leão ARDs, Costa JDD, Takemoto K, et al. Interobserver variability of ultrasonic parameters in portal hypertension. Mem I Oswaldo Cruz. 2010; 105:409–13. https://doi.org/10.1590/s0074-02762010000400010 PMID: 20721483

41. Mott KE. Schistosomiasis. In: Murray CJL, Lopez AD, Mathers CD, editors. The Global Epidemiology of Infectious Diseases. Global Burden of Disease and Injury. IV. Geneva: World Health Organization; 2004. p. 349–91.

42. World Health Organization. Monitoring and epidemiological assessment of mass drug administration for eliminating lymphatic filariasis. The Global Health Action Against Lymphatic Filariasis. Geneva: World Health Organization; 2011.

43. King CH, Dangerfield-Cha M. The unacknowledged impact of chronic schistosomiasis. Chron Ill. 2008; 4(1):65–79. https://doi.org/10.1177/1742395307084407 PMID: 18322031

44. Vinkeles Melchers NVS, van Dam GJ, Sharposki D, Kahama AI, Bienvan EAT, Vennervald BJ, et al. Diagnostic performance of Schistosoma Real-Time PCR in urine samples from Kenyan children infected with Schistosoma haematobium: Day-to-day variation and follow-up after praziquantel treatment. PLOS Negl Trop Dis. 2014; 8(4):e2807. https://doi.org/10.1371/journal.pntd.0002807 PMID: 24743389

45. Utzinger J, Booth M, N’Goran EK, Müller I, Tanner M, Lengeler C. Relative contribution of day-to-day and intra-specimen variation in faecal egg counts of Schistosoma mansoni before and after treatment with praziquantel. Parasitol. 2001; 122(5):537–44. Epub 2001/08/07. https://doi.org/10.1017/S0031182001007752 PMID: 11393827

46. Van Etten L, Kremsner PG, Krijger FW, Deelder AM. Day-to-day variation of egg output and schistosome related morbidity. Acta Trop. 1988; 40(4):361–8. https://doi.org/10.1016/0001-706x(88)90031-6 PMID: 3142286

47. Polman K, Engels D, Fathers L, Deelder AM, Gryseels B. Day-to-day fluctuation of schistosome circulating antigen levels in serum and urine of humans infected with Schistosoma mansoni in Burundi. Am J Trop Med Hyg. 1998; 59(1):150–4. https://doi.org/10.4269/ajtmh.1998.59.150 PMID: 9684644

48. King CH, Keating CE, Muruka JF, Ouma JH, Houser H, Siongok TK, et al. Urinary tract morbidity in Schistosoma mansoni-induced hepatic involvement. Acta Trop. 1997; 68(3):337–41. https://doi.org/10.4269/ajtmh.1997.68.337 PMID: 9311646

49. King CH, Magak P, Salam EA, Ouma JH, Kariuki HC, Blanton RE. Measuring morbidity in schistosomiasis mansoni: relationship between image pattern, portal vein diameter and portal branch thickness in large-scale surveys using new WHO coding guidelines for ultrasound in schistosomiasis. Trop Med Int Health. 2003; 8(2):109–17. https://doi.org/10.1046/j.1365-3156.2003.00994.x PMID: 12581434
52. Booth M, Vennervald BJ, Kabateriene NB, Kazibwe F, Ouma JH, Kariuki CH, et al. Hepatosplenic morbidity in two neighbouring communities in Uganda with high levels of *Schistosoma mansoni* infection but very different durations of residence. *T Roy Soc Trop Med Hyg.* 2004; 98(2):125–36. https://doi.org/10.1016/S0035-9203(03)00018-X %J Transactions of The Royal Society of Tropical Medicine and Hygiene.

53. Straily A, Mall AO, Wanja D, Kavere EA, Kiplimo R, Aera R, et al. Use of a tablet-based system to perform abdominal ultrasounds in a field investigation of schistosomiasis-related morbidity in western Kenya. *Am J Trop Med Hyg.* [Internet]. 2021; [https://doi.org/10.4269/ajtmh.20-1175 pp.]. PMID: 33432910

54. Bocanegra C, Pintar Z, Mendioroz J, Serres X, Gallego S, Nindia A, et al. Ultrasound evolution of pediatric urinary schistosomiasis after treatment with praziquantel in a highly endemic area. *Am J Trop Med Hyg.* 2018; 99(4):1011–7. https://doi.org/10.4269/ajtmh.18-0343 PMID: 30141396

55. Magak P, Chang-Cojulan A, Kadzo H, Iriei E, Muchiri E, Kitron U, et al. Case–control study of posttreatment regression of urinary tract morbidity among adults in *Schistosoma haematobium*–endemic communities in Kwale County, Kenya. *Am J Trop Med Hyg.* 2015; 93(2):371–6. https://doi.org/10.4269/ajtmh.15-0153 PMID: 26013375

56. Mohamed-Ali Q, Doehring-Schwerdtfeger E, Abdel-Rahim IM, Schlake J, Kardorff R, Franke D, et al. Ultrasoundochiography investigation of periportal fibrosis in children with *Schistosoma mansoni* infection: Reversibility of morbidity seven months after treatment with praziquantel. *Am J Trop Med Hyg.* 1991; 44 (4):444–51. https://doi.org/10.4269/ajtmh.1991.44.444 PMID: 19014196

57. Doehring-Schwerdtfeger E, Abdel-Rahim IM, Kardorff R, Kaiser C, Franke D, Schlake J, et al. Ultrasoundochiography investigation of periportal fibrosis in children with *Schistosoma mansoni* infection: Reversibility of morbidity twenty-three months after treatment with praziquantel. *Am J Trop Med Hyg.* 1992; 46 (4):409–15. https://doi.org/10.4269/ajtmh.1992.46.409 PMID: 1575287

58. Boisier P, Ramarokotra C-E, Ravoaallimalala VE, Rabarjona L, Seneje Y, Roux J, et al. Reversibility of *Schistosoma mansoni*–associated morbidity after yearly mass praziquantel therapy: ultrasonographic assessment. *T Roy Soc Trop Med Hyg.* 1998; 92(4):451–3. https://doi.org/10.1016/s0035-9203(98)91090-2 %J Transactions of The Royal Society of Tropical Medicine and Hygiene. PMID: 9850407

59. el Scheich T, Holtfreter MC, Ekamp H, Singh DD, Mota R, Hatz C, et al. The WHO ultrasonography protocol for assessing hepatic morbidity due to *Schistosoma mansoni*. Acceptance and evolution over 12 years. *Parasitol Res.* 2014; 113(11):3915–25. https://doi.org/10.1007/s00436-014-1117-0 PMID: 25260691

60. Akpata R, Neumayr A, Holtfreter MC, Krantz I, Singh DD, Mota R, et al. The WHO ultrasonography protocol for assessing morbidity due to *Schistosoma haematobium*. Acceptance and evolution over 14 years. *Systematic review. Parasitol Res.* 2015; 114(4):1279–89. https://doi.org/10.1007/s00436-015-4389-z PMID: 25711148

61. Stothard JR, Stanton MC, Bastinckay AL, Sousa-Figueiredo JC, Van Dam GJ, Betson M, et al. Diagnostics for schistosomiasis in Africa and Arabia: a review of present options in control and future needs for elimination. *Parasitol.* 2014; 141(4):1947–61. *Epub* 2014/08/27. https://doi.org/10.1017/S0035-9203(03)00018-X %J Transactions of The Royal Society of Tropical Medicine and Hygiene.

62. King CH, Bertsch D. Meta-analysis of urine hemoglobin dipstick diagnosis of *Schistosoma haematobium* infection, including low-prevalence and previously-treated populations. *PLOS Negl Trop Dis.* 2013; 7(9):e2431. https://doi.org/10.1371/journal.pntd.0002431 PMID: 24069486

63. Vennervald BJ, Kinyi L, Butterworth AE, Kariuki CH, Kadzo H, Iriei E, et al. Detailed clinical and ultrasound examination of children and adolescents in a *Schistosoma mansoni* endemic area in Kenya: hepatosplenic disease in the absence of portal fibrosis. *Trop Med Int Health.* 2004; 9(4):409–15. https://doi.org/10.1111/j.1365-3156.2004.01215.x PMID: 15078264

64. Davis SM, Wiegand RE, Mulama F, Kareko EI, Harris R, Ochola E, et al. Morbidity associated with schistosomiasis before and after treatment in young children in Rusinga Island, western Kenya. *Am J Trop Med Hyg.* 2015; 92(5):952–8. https://doi.org/10.4269/ajtmh.14-0346 PMID: 25758651

65. Samuels AM, Matey E, Mwinzi PN, Wiegand RE, Muchiri G, Iriei E, et al. *Schistosoma mansoni* morbidity among school-aged children: A SCORE project in Kenya. *Am J Trop Med Hyg.* 2012; 87(5):874–82. https://doi.org/10.4269/ajtmh.2012.12-0397 PMID: 22987651

66. Blanton RE, Abdel Salam E, Kariuki HC, Magak P, Silva LK, Muchiri EM, et al. Population-based differences in *Schistosoma mansoni*– and Hepatitis C-induced disease. *J Infect Dis.* 2002; 185(11):1644–9. https://doi.org/10.1086/340574 PMID: 120432910

67. Utzinger J, N’Goran EK, Ossey YA, Booth M, Traoré M, Lohourignon KL, et al. Rapid screening for *Schistosoma mansoni* in western Côte d’Ivoire using a simple school questionnaire. *Bull World Health Organ.* 2000; 78(3):399–86. PMID: 10912739.

68. Delgado-Rodríguez M, Llorca J, Blas J. *J Epidemiol Commun Health.* 2004; 58(8):635–41. https://doi.org/10.1136/jech.2003.008466 PMID: 15252064