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Increases in schistosome-specific IgE and CD23+ B cells in a cohort of Kenyan children undergoing repeated treatment and reinfection with *Schistosoma mansoni*

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Abstract

Background—Age prevalence curves from areas endemic for schistosomiasis suggest that humans develop partial immunity to reinfection beginning in early adolescence. We conducted a 2-year longitudinal study to determine if children infected with *S. mansoni* develop protection-related immune responses upon treatment with PZQ and if the development of these immune responses is accelerated by frequent treatment upon reinfection.

Methods—8-10 year old children were tested for *S. mansoni* every four months and treated with praziquantel (PZQ) when positive (Arm A, N=68) or tested and treated at the end of the 2-year follow-up (Arm B, N=49).

Results—Children in Arm A who remained free of infection during follow-up had significantly higher baseline levels of schistosome-specific IgE than children with ≥ 2 repeat *S. mansoni* diagnoses. Children with ≥ 2 repeat *S. mansoni* diagnoses significantly increased their levels of anti-schistosome IgE and CD23+ B cells after receiving ≥ 3 PZQ treatments over the course of follow-up. No increase in either parameter was seen in children who received only the baseline PZQ treatment.

Conclusions—B cell activation and anti-schistosomal IgE are associated with resistance to *S. mansoni* in children, and these immunological parameters can be increased by multiple rounds of infections and PZQ-induced cures.

Keywords

schistosomiasis; children; praziquantel; IgE; B lymphocytes

Introduction

Schistosoma mansoni age prevalence curves from endemic areas suggest that intensity and prevalence of infection peak in the early teen years. Prevalence then plateaus while infection

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intensity sharply declines as individuals enter the third decade of life. Immunologic studies suggest that the decline in intensity is in part attributable to development of immunity to new infections [1-3]. As the lifespan of *S. mansoni* worms is approximately 5-10 years [4,5], this resistance to reinfection coincides with the time at which worms from the initial infection begin to die. These findings have led to the hypothesis that worm death, rather than worm maintenance, is responsible for inducing resistance to reinfection [6]. We have previously shown that adult males occupationally exposed to *S. mansoni* developed increased resistance to reinfection upon repeated cycles of treatment, reinfection, and retreatment [7].

The most consistent immune parameter associated with resistance to reinfection is increased levels of schistosome-specific IgE [8-11]. B lymphocytes are the producers of all immunoglobulins, including IgE, and recently we have reported an association between the CD23+ B cell subset and increased resistance to reinfection in our cohort of adult males [12]. CD23 is the low affinity IgE receptor (FcεRII) and its expression on B cells is in part considered an indication of their maturity [13]. CD23 binds to a variety of membrane and soluble molecules, such as CD21, CD11b, CD11c and IgE and in its soluble form can act as a B cell proliferation factor [14]. The functional roles of the “a” and “b” isoforms of membrane-bound and soluble CD23 include B cell development, IgE binding, cell adhesion, antigen presentation to T cells and the regulation of IgE synthesis [15-19].

It has been postulated that resistance to reinfection can develop sooner than in the early adolescence in areas of high endemicity or where there are programs leading to early treatment of infections in children [20-22]. World Health Assembly Resolution 54.19 recommends periodic mass treatment of children with the drug praziquantel (PZQ) in areas endemic for schistosomiasis. Although intended to control morbidity, the periodic killing of adult worms might have the additional benefit of hastening the development of resistance to reinfection by inducing premature worm death. However, the appropriate interval at which treatment should be given to control morbidity or enhance resistance to reinfection has not been extensively evaluated in different epidemiologic settings. The purpose of the current study was to determine if 8-10 year old children infected with *S. mansoni* develop protective immune responses upon treatment with PZQ and if the development of these anti-schistosome immune responses is accelerated by more frequent treatment over a two-year time period.

Materials and Methods

Study population

All subjects began the study as 8-10 year old children recruited from eight primary schools located within three kilometers of Lake Victoria in the Asembo Bay area of the Nyanza Province in western Kenya. The area is highly endemic for *S. mansoni*. A 2001 survey of schools in this area found *S. mansoni* prevalence ranging from 35-80% [23].

After an initial screening of 485 children, 155 of the 179 children diagnosed positive for *S. mansoni* were enrolled in a 2-year longitudinal study. Children were assigned into treatment Arm A (N=88) or Arm B (N=67). Assignments were made by school except in the case of one school with the largest number of students and the highest *S. mansoni* prevalence. Students in this school were randomized to Arm A or Arm B. The final study population consisted of 68 children from Arm A (77.3%) and 49 children from Arm B (73.1%) who completed the 2-year follow-up.

Study procedures

In the baseline survey, all consenting children aged 8-10 years attending the study schools were tested for the presence of *S. mansoni* eggs by the Kato-Katz method using 2 slides from a single stool sample. Children positive for *S. mansoni* were then asked to enroll in a 2-year longitudinal study and assigned to arms A or B as described above. At baseline and each follow-up encounter, children provided a stool sample for testing for *S. mansoni* eggs as well as *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura* by the Kato-Katz method, again by 2 slides from a single stool sample. Children were also bled by venipuncture for immunological testing as well as testing for malaria parasitemia via Giemsa-stained blood smears. Children infected with *S. mansoni*, soil-transmitted helminths (STHs), or malaria were treated with PZQ (40 mg/kg), albendazole (400 mg), or Co-artem (6 doses administered over 3 days), respectively.

Children in Arm A were tested and treated every 4 months, for a total of 6 follow-up encounters following baseline testing. Children in Arm B were tested and treated only at baseline and again at the end of the 2-year follow-up.

At study entry, a short questionnaire was administered to students in both study arms in which they were asked to characterize how often they went to the lake to do such activities as bathing, swimming, or fishing as: almost every day; sometimes (once a week); rarely (once a month); or never. A similar questionnaire was administered to the parents regarding the water contact behavior of their child. All questionnaires were verbally administered in the local language.

Written informed consent was obtained from the parent/guardian of each child prior to enrollment, and the children gave verbal assent for participation in the study. Study procedures were approved by the institutional review boards of the University of Georgia and the Centers for Disease Control and Prevention, the Scientific Steering Committee of the Kenya Medical Research Institute (KEMRI), and the KEMRI/National Ethics Review Committee of Kenya.

Immunological testing

Antibody evaluation—Assays for soluble worm antigen preparation (SWAP)-specific IgE were performed on plasma from the venous blood using a standardized ELISA as previously described [24]. An external positive control (PC) comprised of a pooled sample of high-responding adults and a negative control of normal human serum (NHS) from non-endemic volunteers was run on each plate. The optical density of the anti-SWAP IgE value for each sample was standardized according to the following formula:

$$(\text{Sample} - \text{NHS}) / (\text{PC} - \text{NHS})$$

Whole blood phenotyping—EDTA-anticoagulated whole blood was analyzed by flow cytometry. Data acquisition and analysis were done on a dual laser FACS Calibur flow cytometer using FlowJo software. B cells were defined as cells that were CD19 positive. Gating to separate CD23-negative B cells from CD23-positive B cells was based on fluorescence minus one (FMO) stained samples as previously reported [12].

Statistical analyses

The Wilcoxon rank sum test or the Kruskal-Wallis test was used for two-sample or multiple-sample group comparisons, respectively. The Wilcoxon signed rank test was used for paired comparisons of the same children at different time points. All analyses were performed with GraphPad Prism 5 or SAS version 9.1.

Results

Baseline demographics

Baseline demographic characteristics of the study population are shown in Table 1. There were no significant differences between the two study arms in intensity of *S. mansoni* infection, gender, or coinfection with malaria or soil-transmitted helminths. Both groups had a similarly high frequency of self-reported water contact, with approximately 95% of children reporting contact with the lake at least once per month, and >85% reporting weekly contact with the lake.

In addition, there were no significant differences in any of these demographic factors between those children that did and did not complete the entire two years of follow-up.

S. mansoni infection over time

The prevalence of *S. mansoni* infection at each follow-up timepoint in Arm A is shown in Figure 1. Prevalence was reduced to 34% four months after the initial PZQ treatment. However, children became rapidly reinfected in this endemic area. Even with infected children being diagnosed and treated at four-month intervals, prevalence of *S. mansoni* never fell below 23% during the two years of follow-up.

Thirty-eight children (56%) in Arm A had two or more positive *S. mansoni* diagnoses following treatment for the *S. mansoni* infection present at baseline and prior to the two-year follow-up. Nineteen children (28%) had one repeat *S. mansoni* diagnosis during the course of follow-up, and 11 children (16%) went at least two years without becoming reinfected with *S. mansoni*, although 2 of these children were infected at the 24 month follow-up.

Geometric mean baseline egg counts (95% confidence interval) in children with 0, 1, and ≥ 2 repeat *S. mansoni* diagnoses were 54 (18, 159) 64 (32, 127), and 135 (87, 209) eggs per gram feces, respectively. Although there was a trend towards higher initial intensity of infection in children with a greater number of repeat *S. mansoni* diagnoses, the difference between the groups only approached statistical significance ($p=0.0591$). There were no differences in self-reported or parent-reported water contact between these groups.

Forty-three percent of children in Arm B were infected with *S. mansoni* at the 2-year follow-up, which approximates the overall baseline prevalence of 37% found in the initial survey of these schools. Mean intensity of infection among stool-positive children at the 2-year follow-up was 99 (± 172) epg in Arm A and 172 (± 219) epg in Arm B (difference between arms not significant, $p=0.2975$).

Changes in anti-SWAP IgE

Standardized anti-SWAP IgE levels at baseline and 2-year follow-up in Arms A and B are shown in Figure 2. Although anti-SWAP IgE slightly increased over the 2-year period, there were no statistically significant differences between baseline and 2-year follow-up anti-SWAP IgE in either arm. There were also no statistically significant differences in baseline anti-SWAP IgE between Arms A and B nor final anti-SWAP IgE between arms A and B.

Figure 3 depicts standardized anti-SWAP IgE levels at baseline and final follow-up for children in Arm A stratified by the number of repeat *S. mansoni* diagnoses during the two years of follow-up. The baseline anti-SWAP IgE level in children with ≥ 2 repeat diagnoses was significantly lower than the baseline anti-SWAP IgE in the children who went at least 2 years without becoming reinfected. There was also a significant trend for decreasing baseline anti-SWAP IgE among children with 0, 1, and ≥ 2 repeat *S. mansoni* diagnoses ($p=0.0019$). Children who had ≥ 2 repeat diagnoses, and thus received a total of 3 or more

treatments with PZQ over the two year follow-up, demonstrated significant increases in their anti-SWAP IgE between baseline and the final 2-year follow-up. There were no significant changes in anti-SWAP IgE over time in those children without a repeat diagnosis and thus who received only the initial PZQ treatment at baseline, nor in those children with one repeat diagnosis (total of 2 PZQ treatments, Figure 3).

Changes in CD23+ B cells

The mean percentage of CD23+ B cells in children in both study arms at baseline and final follow-up is shown in Figure 4. The percentage of CD23+ B cells significantly increased between baseline and the two-year follow-up in both arm A and arm B, but the difference in % CD23+ B cells between the two arms at the two-year time point was not statistically significant ($p=0.0761$).

When Arm A was stratified by the number of repeat *S. mansoni* diagnoses during follow-up (Figure 5), changes in CD23+ B cells showed a pattern similar to that seen with anti-SWAP IgE levels. Although the difference did not reach statistical significance ($p=0.0979$), children that were not reinfected before the 2-year follow-up had a higher percentage of CD23+ B cells at baseline than those children who had 2 or more repeat *S. mansoni* diagnoses over the course of follow-up. The percentage of CD23+ B cells increased between baseline and follow-up in children who had two or more repeat *S. mansoni* diagnoses over the course of follow-up, and therefore received ≥ 3 PZQ treatments, as well as in those children who had one repeat diagnosis and received 2 PZQ treatments. However, the percent of CD23+ B cells did not change significantly in those children who did not get reinfected before the final follow-up and therefore had received only the initial PZQ treatment.

Co-infection with malaria and soil-transmitted helminths

There was no difference in baseline anti-SWAP IgE level between children co-infected with *S. mansoni* and *P. falciparum* and children without *P. falciparum* (standardized ODs: 0.058 versus 0.055, $p=0.2819$) or between children co-infected with *S. mansoni* and STHs and children without STHs (0.062 versus 0.046, $p=0.9426$). There was also no difference in CD23+ B cells between children co-infected with *S. mansoni* and *P. falciparum* and children without *P. falciparum* (49.3% versus 46.9%, $p=0.5327$). There was a higher percentage of CD23+ B cells in children co-infected with *S. mansoni* and STHs than in children without STHs (57.8% versus 41.5%, $p=0.0184$). However, the difference in CD23+ B cells in children infected with STHs and those uninfected with STHs did not persist at the first follow-up 4 months after treatment with ALB and/or PZQ (50.8% in STH infected children and 51.6% in uninfected children). This was true regardless of *S. mansoni* infection status at 4 months (data not shown). At no other time throughout the course of follow-up did children infected with STHs have a higher percentage of CD23+ B cells than children not infected with STHs.

Discussion

Our data suggest a high force of *S. mansoni* transmission in this area along Lake Victoria in western Kenya. After two years of diagnosing and treating infected children every four months, the prevalence of *S. mansoni* in Arm A of our cohort was still approximately 30%. This is close to the overall prevalence of 37% found in our initial survey of 8-10 year old children in the study area. More than half (56%) of the children in Arm A had 2 or more positive *S. mansoni* diagnoses during the course of two years after treatment of the initial infection. Since we did not assess cure after each treatment, we cannot be certain that each positive diagnosis was a reinfection rather than a cure failure. Since the cure rate of PZQ is

>70% after one dose [25,26], the majority of these positive diagnoses likely represented true cures and reinfections.

The original design of the study was to examine differences in immune parameters between children kept as free from *S. mansoni* infection as possible for 2 years (Arm A) and children treated only once 2 years prior (Arm B). However, when Arm A was analyzed as a group, we did not find a difference in levels of schistosome-specific IgE between arms A and B at the end of the study. What we did not anticipate was that some children in this area had developed an apparent level of resistance to reinfection prior to age 8-10 when they were enrolled in this study, as they did not become reinfected for two years following one PZQ treatment. When Arm A was stratified according to the number of *S. mansoni* diagnoses each child had during follow-up, which is a close approximation to how many times the child was reinfected, those children that did not get reinfected for at least 2 years after treatment of their baseline infection had significantly higher levels of anti-SWAP IgE and borderline significantly higher levels of CD23+ B cells than the more susceptible children with at least 2 repeat *S. mansoni* diagnoses (and likely ≥ 2 reinfections) within 2 years. After 3 or more PZQ treatments, both anti-SWAP IgE and the percentage of CD23+ B cells had significantly increased in the more susceptible children, indicating that frequent treatment of infected children can drive immune responses to more closely resemble those of the children who remained uninfected over the course of follow-up.

Numerous studies have reported an association between higher levels of schistosome-specific IgE and resistance to reinfection with *S. mansoni* [8-11]. We recently reported increases in anti-SWAP IgE that paralleled the change from a state of susceptibility to *S. mansoni* infection to a state of increased resistance to reinfection in our cohort of adult males undergoing repeated cycles of treatment and reinfection [20]. We also recently reported a correlation between the percentage of CD23+ B cells and the level of resistance to *S. mansoni* reinfection in our cohort of adult males, suggesting that B cells expressing CD23 may play a role in the development of protective immunity [12]. CD23 is the low affinity receptor for IgE and has shown to be essential for IgE-mediated enhancement of specific immune responses in murine models [28].

We did not see an increase in anti-SWAP IgE in children who received 2 PZQ treatments during the course of follow-up. However, this group was likely a combination of children who failed to cure after the initial PZQ treatment, children who had already developed an intermediate level of resistance, and children who had more than one reinfection but were not diagnosed as repeat positives due to the insensitivity of the Kato-Katz test on a single stool. While there was an overall increase in CD23+ B cells over the two-year period in both study arms, this was not unexpected as studies have shown that the proportion of B lymphocytes expressing CD23 slowly increase until age 12 in normal pediatric populations [29,30]. However, within Arm A, the increase was more dramatic in the more susceptible children who received 3 or more PZQ treatments than in the more resistant children who only required 1 initial PZQ treatment.

A high level of co-infection between *S. mansoni* and malaria and STHs was present in this population. We found no association between levels of schistosome-specific IgE and co-infection with either malaria or STHs. Children co-infected with STHs and *S. mansoni* at baseline had a statistically significantly higher percentage of CD23+ B cells than children without STH infection. A higher percentage of CD23+ B cells in co-infected children was only seen at baseline when they likely had long term *S. mansoni* and STH infections. The difference did not persist after baseline treatment of their infections.

In conclusion, we found that some children in this highly endemic area exhibited a phenotype indicative of resistance to *S. mansoni* reinfection by 8-10 years of age. Infections in lakeside communities have been shown to begin very early in life [31], and some of our 8-10 year old subjects could have been infected for 7-9 years at the time of their enrollment, providing an opportunity for them to have already experienced dying worms. The resistant phenotype was characterized by high schistosome-specific IgE and elevated levels of CD23+ B cells. Frequent PZQ treatment of more susceptible children increased these immune responses towards protective levels. The effect of PZQ treatment on the production of anti-SWAP IgE and CD23+ B cells was obscured when data were analyzed without accounting for differences in prior development of apparent resistance to *S. mansoni*.

Acknowledgments

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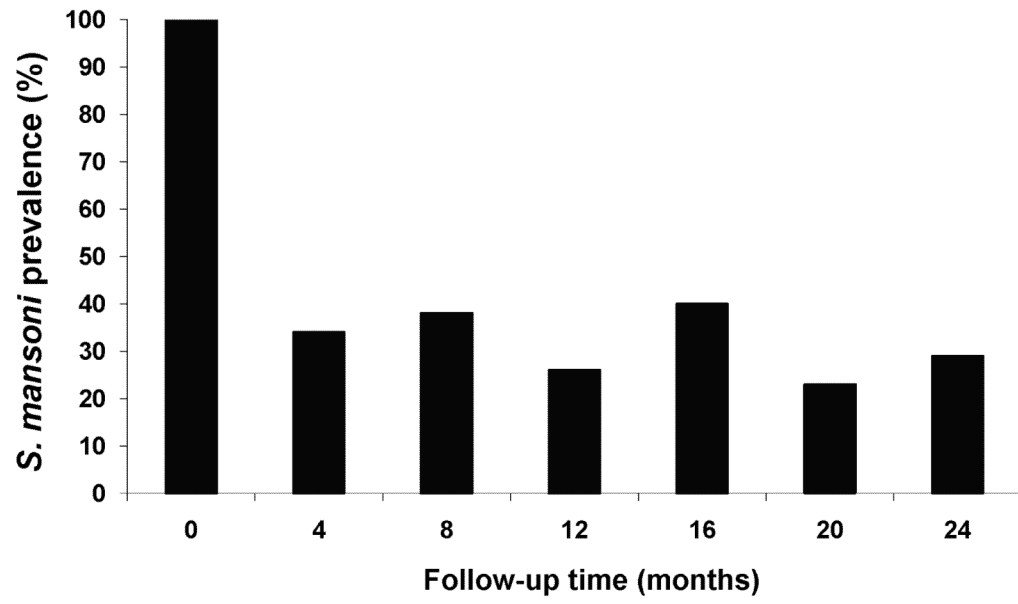


Figure 1.
Prevalence of *S. mansoni* infection at each follow-up timepoint in Arm A

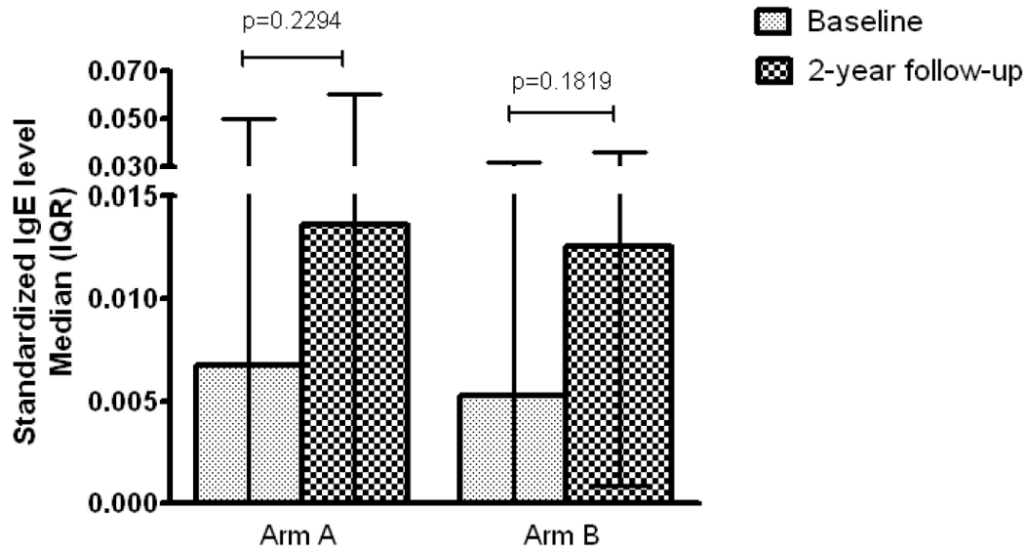


Figure 2. Anti-SWAP IgE at baseline and 2-year follow-up in Arms A and B

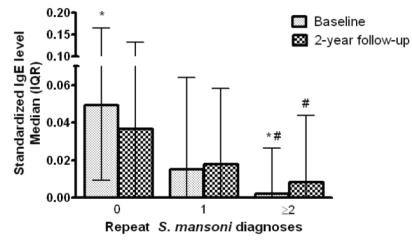


Figure 3. Anti-SWAP IgE at baseline and final follow-up in Arm A, stratified by the number of PZQ treatments received during the 2-year follow-up. *Difference in baseline anti-SWAP between 0 and ≥ 2 diagnoses groups $p < 0.05$; # Difference between baseline and final bleed $p < 0.05$ by Wilcoxon paired test.

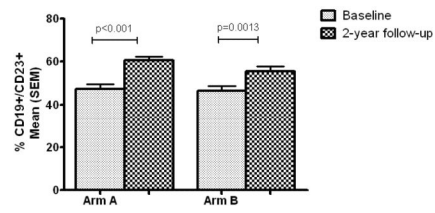


Figure 4. Percent CD19+/CD23+ cells at baseline and 2-year follow-up in Arms A and B

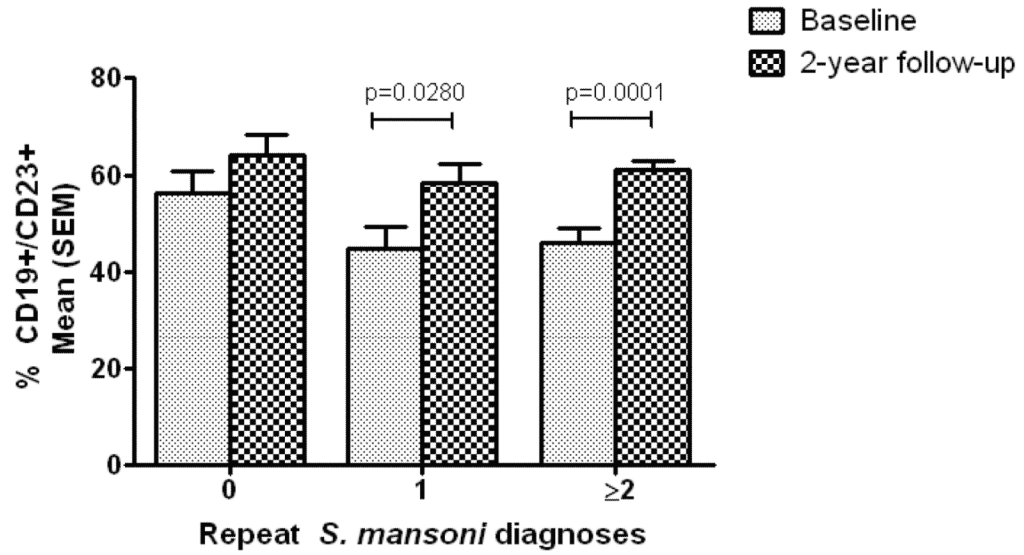


Figure 5. Percent CD19+/CD23+ cells at baseline and final follow-up, stratified by the number of PZQ treatments received during the 2-year follow-up

Table 1

Baseline demographic characteristics of study arms A and B

	Arm A N=68	Arm B N=49	p-value
Geometric mean <i>S. mansoni</i> eggs per gram feces (95% CI)	94 (66, 133)	79 (56, 110)	0.5599
Gender (% male)	55.9	57.1	0.8926
<i>Plasmodium falciparum</i> prevalence (%)	28.1	21.4	0.4545
Soil-transmitted helminth prevalence (%)	57.4	40.4	0.0756
Any water contact ^a (%)	94.9	95.7	0.8421
Frequent water contact ^b (%)	84.8	89.4	0.4877

^aContact with lake at least once a month

^bContact with lake at least once a week