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Anti-*Schistosoma* IgG responses in *Schistosoma haematobium* single and concomitant infection with malaria parasites

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Areas prone to schistosomiasis are also at risk of malaria transmission. The interaction between the causal agents of the two diseases could modulate immune responses tailored toward protecting or aggravating morbidity dynamics and impair *Schistosoma* diagnostic precision. This study aimed at assessing the effect of *Plasmodium* spp. in concomitant infection with *Schistosoma haematobium* in modulation of anti-*Schistosoma* IgG antibodies. The school-based cross-sectional study recruited a total of 322 children screened for *S. haematobium* and *Plasmodium* spp. Levels of IgG against *S. haematobium*-soluble egg antigen (SEA) in single *S. haematobium*/malaria parasites infection and co-infection of the two parasites in schoolchildren were determined. Data were analyzed using χ^2 , Fisher's exact test, and Tukey's multiple comparison test analyses. The prevalence of single infection by *S. haematobium*, *Plasmodium* spp., and concurrent infection due to the two pathogens was 27.7, 41.0, and 9.3%, respectively ($p < 0.0001$). Anti-*Schistosoma* IgG production during co-infection of the two pathogens (1.950 ± 0.742 AU) was significantly higher than the value recorded for single malaria parasites' infection (1.402 ± 0.670 AU) ($p < 0.01$) but not in *S. haematobium* infection (1.591 ± 0.604 AU) ($p > 0.05$). The anti-*Schistosoma* IgG production in co-infection status was however dependent on the intensity of *Plasmodium* spp. with individuals having high intensity of malaria parasites recording lower anti-*Schistosoma* IgG. This study has implication for diagnosis of schistosomiasis where anti-*Schistosoma* IgG is used as an indicator of infection. Efforts should be made to control the two infections simultaneously in order not to undermine the efforts targeted toward the control of one.

Keywords: Schistosomiasis, Malaria, Co-infection, Anti-*Schistosoma* antibodies, Children

Introduction

Schistosomiasis and malaria are two most important parasitic diseases in developing countries in terms of their socioeconomic impact and public health implications.¹ Despite efforts put in place to curtail the spread of these diseases in sub-Saharan Africa, their spread to new foci has made these efforts not to be well appreciated. Considering the overlap in the distributions of the two diseases, co-infection with the causal parasites is common. The coexistence of *Schistosoma haematobium* and *Plasmodium falciparum* may have a bearing on their epidemiology, on the development of acquired resistance to infection with one or other parasite, and may have implications for their control.²

Schistosoma infection, like many helminth infections, favors Th2-like immune response in human host, with skewing of host immune response to non-schistosomal

'bystander' antigens from Th1-like to Th2-like in murine model.³ It is likely that immunological interactions between *Schistosoma* spp. and malaria parasites have implications in the modulation of human immunological responses. These immunological interactions are closely related in schistosomiasis and malaria morbidities.^{4,5} More importantly, the balance of IgG4 and IgE is responsible for building up protective immunity to schistosomiasis.^{5,6}

The co-infection of the two parasites in the local government area in our previous studies^{7,8} and given that host immunological response is specific to a particular parasite, the idea that concomitant occurrence of *S. haematobium* and *Plasmodium* spp. could modulate host response specific to schistosomiasis is worth investigating. The quantification of specific anti-*Schistosoma* antibodies (IgG) and other antibodies' isotypes in infected individuals forms the basis for indirect immunodiagnosis of schistosomiasis with these antibodies' titers either correlating or not with the intensity of *Schistosoma* spp.⁹⁻¹¹ The anti-*Schistosoma*

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IgG response also serves as biomarker for schistosomiasis severity of which the presence of *Plasmodium* spp. infection in co-infection status¹² can modulate its course. We therefore assessed the specific anti-schistosomiasis antibody responses (IgG) in single *S. haematobium* and concomitant infection with malaria parasites.

Methods

Study Area

The study was carried out in Ijoun community located in Yewa North Local Government Area (LGA) of Ogun State, Nigeria. The community is rural, lacking some basic amenities. The sociocultural practices of the people are such that they favor exposure to *Schistosoma* and malaria parasite infections. Water from wells is not potable due to complaints about its hardness, thus leaving the dwellers with no option than making use of river bodies for their domestic purposes. The water hardness is a result of the presence of limestone in the area, which necessitated the establishment of a cement factory in the area. Two rivers, Idi and Iju, are present in the area and had been reported to harbor *Schistosoma* spp.-infected snails.^{13–15}

Sample Size Determination

The study which was conducted between March and August 2014 was cross-sectional and non-randomized. Informed consent was obtained from parents and guardians of primary school pupils of age range 5–19 years recruited for the study. Using the co-infection prevalence of *S. haematobium* and *P. falciparum* (28.0%) in our previous study,⁸ the minimum sample size computed with 0.05 precision was 310. The statistical power used was 90.0%. Overall, 399 individuals were recruited with 322 subjects included in the final analysis of the study.

Parasitological Screenings

Pre-labeled, clean, dry, screw-capped universal bottles were given to volunteered participants to collect freshly passed mid-day urine samples between 10 and 2 pm. Urine (10 mL) was measured and subjected to centrifugation at 4000 rpm for 4 min. The sediment, after discarding the supernatant, was placed on a clean microscope slide and viewed under the $\times 10$ magnification. *Schistosoma haematobium*-positive urine samples with characteristic egg shape (elliptical and terminal spine) were recorded.¹⁶ The intensity of *S. haematobium* infection was categorized into three according to the World Health Organization recommendations. These included light infection (1–9 eggs/10 mL of urine), moderate infection (10–49 eggs/10 mL), and heavy infection (≥ 50 eggs/10 mL).¹⁷ *Schistosoma haematobium*-infected children were treated with 40 mg/kg single dose of praziquantel.

Thick and thin blood smears prepared on a clean slide, fixed and stained with 10% Giemsa stain, were observed under $\times 100$ microscope objective lens in a drop of immersion oil for presence of either ring forms or gametocytes of

malaria parasites.¹⁶ Intensity of *Plasmodium* spp. infection was also classified into light, moderate, or heavy in the range 1–499 parasites/ μ L, 500–1999 parasites/ μ L, and 2000–9999 parasites/ μ L blood, respectively.¹⁸ Individuals with malaria parasite infection were referred to the health clinic center for medical attention.

Serological Assays

Intravenous blood (2 mL) from participants was collected in 5-mL plain bottles and processed as described by Mutapi et al.¹⁹ These individuals included those positive for single *S. haematobium* ($n = 92$) and malaria parasite infections ($n = 136$) and concurrent infections ($n = 31$). The clotted blood was stored at 4 °C overnight and serum was obtained after centrifugation at 30,000 rpm for 10 min. The serum was then stored in Nunc cryotubes at –20 °C until needed.

Schistosoma-specific antibody response was assayed using enzyme-linked immunosorbent assay (ELISA). The ELISA was carried out using *Schistosoma haematobium*-soluble egg antigens (SEA) and the serum was tested for IgG antibody. This assay employed the qualitative enzyme immunoassay technique.²⁰ The crude egg-soluble antigen (50 μ L) of 3 μ g/mL diluted 1:200 in carbonate buffer (pH 9.6) was used to coat the microtiter well plates and then incubated overnight at 4 °C. This was followed by washing of plates with 0.05% Tween 20 in PBS-Tween 20, thrice. Blocking buffer (150 μ L) containing 1% Bovine Serum Albumin in Phosphate Buffered Saline (1% BSA/PBS) was introduced on washed plates, dried on blotting paper, and incubated for 1 h at 37 °C. The plates were washed again thrice with PBS-Tween 20. Serum sample (50 μ L) at a dilution of 1:100 in 1% BSA in PBS was added to the plates in duplicate and incubated for 1 h at 37 °C. Washing with PBS-Tween 20 was repeated thrice and 100 μ L of Horseradish Peroxidase anti-human immunoglobulin G conjugate (Sigma, St. Louis, MO, USA) was added per well at a dilution of 1:2000 and then incubated for 30 min at 37 °C. Washing was repeated and 50 μ L of substrate A and B3 solution each was added, mixed, and reaction was allowed to proceed in the dark for 10 min at 37 °C. A stop solution was added and absorbance was determined with a microplate reader set at 450 nm.

Ethical Consideration and Informed Consents

The study's protocol was approved by the University of Ibadan/University College Hospital joint ethical review committee. Informed consents were obtained from parents of participants that volunteered to participate in the study.

Statistical Analyses

Data were carefully entered in Excel spread sheet (version 2007) and transferred to GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, CA 92037 USA) for analyses. χ^2 analysis was used to determine significant differences in categorical variables such as proportion of level of intensity of *S. haematobium* and infection status types. Fisher's

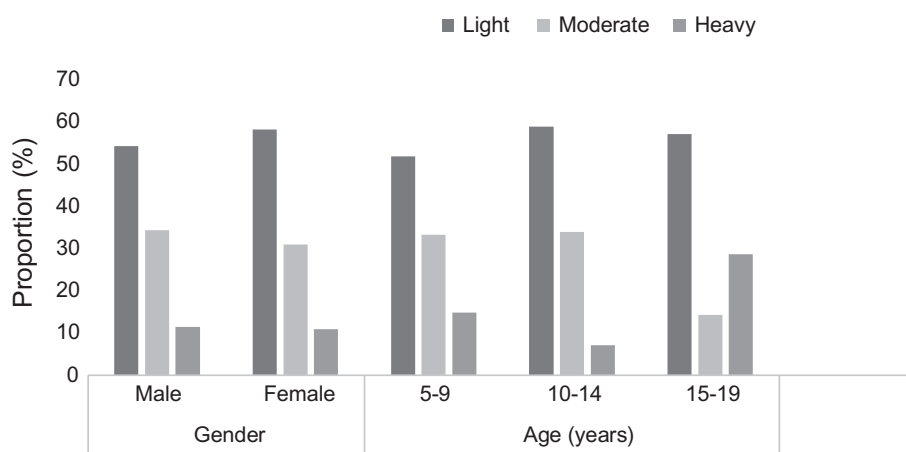


Figure 1 Gender- and Age-stratified *Schistosoma haematobium* intensity patterns.

exact test was used to determine differences in co-infection dynamic patterns. Tukey's multiple comparison test was used to test for differences in mean absorbance of anti-*Schistosoma* IgG between the different infection statuses. Pearson correlation was used to determine the relationships between anti-*Schistosoma* IgG absorbance and malaria parasite/*Schistosoma haematobium* densities.

Results

Gender- and Age-stratified *Schistosoma haematobium* intensity patterns

The gender and age distribution patterns of children with light, moderate, and heavy *S. haematobium* intensities showed no significant variations ($p > 0.05$, Fig. 1).

Prevalence of Single and Concomitant Infections

The *Plasmodium* spp. observed were *P. falciparum*, *P. malariae*, and *P. ovale*. The prevalence of single infection by *Schistosoma haematobium* and malaria parasites was 27.7 and 41.0%, respectively ($p < 0.0001$). The prevalence of concomitant infection of the two parasites was 9.3% (Table 1).

Anti-Schistosoma-Specific Antibodies in Single and Concomitant Infections

Anti-*Schistosoma* IgG production during co-infection of the two pathogens (1.950 ± 0.742 AU) was significantly higher than the value recorded for single malaria parasites infection (1.402 ± 0.670 AU) ($p < 0.01$), but not in *S. haematobium* infection (1.591 ± 0.604 AU) ($p > 0.05$) (Fig. 2). Anti-*Schistosoma* IgG although was higher in single *S. haematobium* infection, it was not significantly higher compared with the value recorded in single malaria parasite infection status ($p > 0.05$). While there was no significant relationship between antibody response and malaria parasite parasitemia ($r = 0.024$; $p = 0.420$), a significant positive relationship existed between intensity of *S. haematobium* and production of anti-*Schistosoma* antibodies ($r = 0.232$; $p = 0.029$).

Table 1 Single and co-infection statuses among children in Ijoun community (n = 332)

Disease	No. positive	Prevalence (%)	p value
<i>Schistosoma haematobium</i>	92	27.7	<0.0001
Malaria parasites	136	41.0	
Co-infection	31	9.3	

Note: Malaria parasites included *Plasmodium falciparum*, *P. malariae*, and *P. ovale*.

Effects of Parasite Intensities on Anti-Schistosoma IgG Production in Concomitant Infections

Six co-infection dynamics in terms of parasite burden measured by intensity of *S. haematobium* and malaria parasites were observed. These included LL, LH, HH, ML, MH, and MM representing light (L), moderate (M), and heavy infection (H) in *S. haematobium* and *Plasmodium* spp. infections, respectively. Children co-infected with light *S. haematobium* and heavy malaria parasites (LH) were the most prevalent (32.3%), while those with moderate (MM) and heavy (HH) infections for both parasites were the least (9.7% each) (Table 2). Anti-*Schistosoma* IgG production was highest in moderate infection of the two pathogens (2.473 ± 0.391 AU) but was least in individuals with heavy infections for the two parasites (1.690 ± 0.720 AU) (Table 2).

Discussion

This study showed the endemicity of the two parasites in the study area, an observation which is similar to a previous study in Kenya, reporting high risk of such concomitant infection among children.²¹ Although there had been no published data on malaria endemicity in the area, the prevalence of schistosomiasis (27.7%) was lower than the previously recorded value (57.1%) among children in Ijoun community.²² This high level of *S. haematobium* infection following an organized mass chemotherapy in the study population about five years ago stresses re-infection

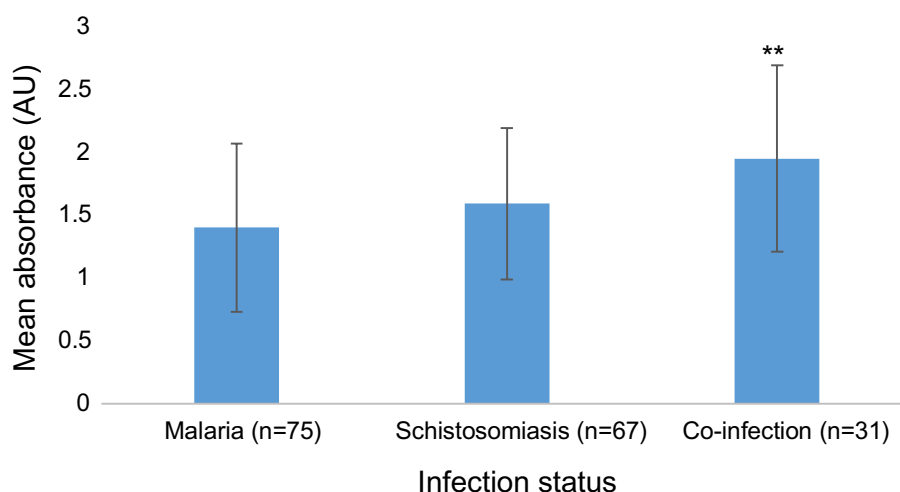


Figure 2 Mean anti-*Schistosoma* IgG antibody reactivity in single and concomitant *Schistosoma haematobium* and malaria parasite infections.

Note: Tukey's multiple comparison test used to test for significance between infection statuses; error bars, standard deviation. ** Anti-*Schistosoma* IgG antibodies in co-infection group significantly higher than malaria group ($p < 0.01$) but not in *Schistosoma* group. No significant difference in anti-*Schistosoma* IgG in *Schistosoma* and malaria groups ($p > 0.05$).

Table 2 Dynamics of co-infection patterns of *Schistosoma haematobium* and malaria parasites among participants

Co-infection patterns	No. examined	Proportion (%)	Anti- <i>Schistosoma</i> IgG (AU)	p value
LL	7	22.6	1.906±0.757	0.007
LH	10	32.3	1.861±0.855	
HH	3	9.7	1.690±0.720	
ML	7	22.6	2.044±0.810	
MH	1	3.2	1.703±0.000	
MM	3	9.7	2.473±0.391	

Note: L – light, M – moderate, and H – heavy infection for *Schistosoma haematobium* and malaria parasites; Fisher's exact test was significant.

as cardinal to persistence of *S. haematobium* transmission in the area. In the absence of an all-encompassing control measure, it is certain the occurrence of schistosomiasis may be brought to the pre-control level (57.1%) in the earliest future. The prevalence of co-infection of *S. haematobium* and malaria parasites in the present study is significantly lower than previous reports in neighboring villages in the same local government area.^{8,9}

Several studies have shown conflicting results regarding *Schistosoma* spp./malaria parasite pathological episodes in concomitant infections. While studies have particularly focused on effects of *Schistosoma* infection on protection against malaria,^{23,24} with one stressing the age-dependent manner of schistosomiasis protection against clinical malaria,²⁵ few however have examined anti-*Schistosoma* antibody production in co-infection with malaria parasites.² One other study has attempted to do this but did not find any *P. falciparum* infections.²⁶ More so, *Schistosoma* infection was reported to influence the production of pro- and anti-inflammatory cytokines in children.⁴ Similar to previous report,² anti-*Schistosoma*-specific antibodies produced during co-infection with *Plasmodium* spp. were

higher than in single *S. haematobium* infection. Therefore, a probable explanation for this finding could be the possibility of malaria parasites influencing the cytokine environment to favor the production of anti-*Schistosoma* IgG.² Polyclonal stimulation of B-cells could also be the cause of the increase in *S. haematobium*-specific antibodies in co-infected individuals.

The anti-*Schistosoma* antibodies recorded among individuals diagnosed for only *Plasmodium* spp. infection could mean the presence of false negative tests for *S. haematobium* in some individuals, especially in very light infection. Another possible reason for this is the persistence of humoral anti-*Schistosoma* antibody circulation in individuals treated for *Schistosoma* infection that were previously co-infected with malaria parasites. The inability of IgG enzyme-linked immunosorbent assay (ELISA) to distinguish active *Schistosoma* infection from chronic type is one of the major set-back in its application. Cross-reactivity between *Schistosoma* and malaria parasite antigens could also be the cause of presence of anti-*Schistosoma* antibodies in individuals only infected with *Plasmodium* spp.^{1,23}

Anti-*Schistosoma* antibody response was *Plasmodium* spp. density dependent. Although co-infection with malaria parasites seemed to increase anti-*Schistosoma* IgG, decrease in malaria parasite parasitemia seemed to increase the antibody production. Conversely, increase in intensities of *S. haematobium* infection had been reported to cause decrease in levels of the cytophilic subclass IgG1, IgG2, IgG3, and IgG4 directed against *Plasmodium falciparum*.²³ The effects of *Schistosoma* spp. and malaria parasites' concomitant infection could also be influenced by factors such as frequency, duration, and order of establishment of infection, besides intensity of the two co-existing parasites and background immunity to either pathogen earlier reported.²³

The limitations of this study include the use of non-molecular-based methods in infection detection which could undermine the true infection status. Also, there is a need to relate the influence of age, sex, and specific malaria parasite species to antibody response in single and co-infection statuses.

The co-infection of *Schistosoma haematobium* and *Plasmodium* spp. is common in the study area. This study has implication for diagnosis of schistosomiasis where anti-*Schistosoma* IgG is used as an indicator of infection. Since control efforts targeted at only one of the co-existing parasites may not solve the problem but may sometimes even aggravate the morbidity spectra, drug regimens capable of dual efficacy are highly recommended. Besides, policy-makers should augment efforts to reduce schistosomiasis burden as its neglect could undermine the various efforts targeted against the spread of malaria.

Disclaimer Statements

Authors' contribution

OAM designed and supervised the work, OA collected data and carried out laboratory analyses, ECO participated in laboratory analyses, and OTO analyzed data and drafted the first manuscript version. All authors read and approved the final manuscript version.

Competing interests

None declared.

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