Epidemiological Study of the Association Between Malaria and Helminth Infections in Nigeria

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Abstract. The relationship between intestinal helminth infection and susceptibility to malaria remains unclear. We studied the relationship between these infections. Seven schools in Ilero, Nigeria referred all pupils with febrile illness to our study center for free malaria treatment during a 3-month study period. At the end, all pupils submitted a stool sample for microscopic investigation for helminth eggs. We used an unmatched case-control design to calculate the odds ratios for helminth infection in children with at least one attack of malaria (cases) and children with no malaria episodes during the study (controls). We recorded 115 malaria cases in 82 of 354 (23.2%), 16 of 736 (2.2%), and 17 of 348 (4.7%) children ages ≤ 5, 6–10, and 11–15 years old, respectively ($P = 0.001$). Helminth infection rate in cases was 21 of 115 (18.3%) compared with 456 of 1,327 (34.4%) in controls. Weighted odds ratio stratified by age group for helminth infection in cases versus controls was 0.50 (95% confidence interval = 0.2–0.84, $P < 0.01$). *Ascaris* and hookworm were the most common helminths detected, with prevalence rates of 14 (12.2%) and 6 (5.2%) among cases compared with 333 (25.1%) and 132 (10.0%) in controls, respectively ($P = 0.001$). The negative association between helminth infection and malaria may be of importance in the design of deworming programs.

INTRODUCTION

About one-half of the world's population is at risk of contracting malaria, with an annual mortality rate up to 0.5 million.[1] Malaria remains one of the most common killers of young children in sub-Saharan Africa, where 90% of malaria-related deaths occur.[1] Although the World Health Organization (WHO) reports that malaria deaths have been reduced by 33% in the African region, a child still dies every 1 minute as a result of the disease.[2] However, up to one-third of the world population (more than 2 billion people) are infected with intestinal parasites, and about 300 million people are severely ill; at least 50% are school-aged children.[3] Although intestinal helminths are only rarely a direct cause of death, their public health impact is substantial because of the number of people affected.[4] About 4.98 million disability-adjusted life years (DALYs) are attributed to intestinal helminths, and these infections, thus, represent a substantial economic burden.[5] The most common intestinal helminths infecting humans include *Ascaris*, hookworm, and *Trichuris*; all three are widely distributed in tropical countries, infecting 1.4, 1.3, and 1.0 billion people, respectively.[6]

Malaria and intestinal helminths overlap extensively in their epidemiological distributions, and coinfections are frequently seen.[7,8] The possible interactions between coinfecting intestinal helminths and plasmodia have been investigated over the decades with conflicting results. According to a review that summarizes the outcomes of malaria–helminth coinfection, 13 studies suggested that intestinal helminths were associated with protection from malaria, whereas 8 studies showed increased malaria severity and incidence in coinfected individuals. Finally, five studies found no association between malaria and helminths infestation.[9]

This study was designed to identify the association of intestinal helminths with malaria incidence in a semirural area of Nigeria with a goal of contributing to the body of evidence on the role played by intestinal helminths in malaria epidemiology.

MATERIALS AND METHODS

Study site. The study was carried out in the town of Ilero (latitude: 8°4′0 N; longitude: 3°21′0 E) in Oyo State, southwestern Nigeria.[10] The vegetation of Ilero is Guinea Savanna, with a distinct rainy season from April to September and a dry season from October to March. Farming is the predominant occupation of the inhabitants of this community. The town has a population of about 35,000 inhabitants.[11]

Study population. All school- and pre–school-aged children from seven public primary schools in Ilero were recruited for the study. The schools and parents in the community were asked to refer children with febrile illness to our study center for free malaria treatment during a 3-month study period in the malaria transmission season (May to July of 2013). At the end of the study, the schools were visited to screen the children for intestinal parasites. Because all of the schools also have nursery facilities, it provided us with an opportunity to enroll children below the age of 5 years. Although as indicated below, participation in the study was strictly voluntary, all parents consented to their children's participation, likely because the access to free and timely treatment was considered a common good. Thus, no selection of study participants was done.

Study design. The study was designed as a case-control study involving children with and without malaria (cases and controls, respectively) over a 3-month period. Inclusion criteria were all of the children at all seven schools who submitted a stool sample at the end of the study period. Cases were febrile children referred to our study center with laboratory-confirmed malaria, whereas controls were the children who had no malaria. Controls were further questioned at the end of the third month to ensure that they had not experienced episodes of febrile illness during this period. Children with an undiagnosed febrile illness during the study period that did

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not test positive for malaria but received empiric antimalarial therapy were excluded.

Diagnosis of intestinal helminth infestations. At the end of the project, children in the case and control arms of the study were asked to submit stool samples, which were immediately preserved with 5% formalin, later processed, and examined by microscopy of direct smears of iodine-stained preparations for ova and parasites. As quality control, all samples were examined by two independent microscopists (a laboratory physician and a laboratory technologist); any discrepancies were resolved by microscopy of formol-ether–concentrated specimens by a third laboratory technologist.

Malaria diagnosis. Clinically suspected cases of malaria were subjected to laboratory tests. A rapid malaria diagnostic kit (SD Bioline Malaria *Plasmodium falciparum*; Standard Diagnostics, Gyeonggi-do, Korea) was used to screen clinically positive cases, which were later confirmed by light microscopy of blood smears.

Ethical issues. Ethical approval for the study was issued by the research and ethical committee of the Federal Teaching Hospital, Abakaliki, Nigeria. Written informed consent was also obtained from all of the parents or guardians of the participating pupils.

Statistical analysis. Data were entered into EPI-info (3.5.3) statistical software. Descriptive statistics were used to cross-tabulate the variables, and we used an unmatched case-control design to calculate the odds ratio (OR) for helminth infection in malaria patients (cases) and children with no malaria episodes during the study (controls). Because malaria prevalence was highest in younger age groups and helminth infestations were most common in older age groups, the data analysis was stratified by age group to avoid confounding caused by age difference. A P value < 0.05 in the χ^2 test with Yate's correction was considered significant. The study had approximately 90% power at 95% confidence to show a difference in helminth prevalence from 33% in controls to 20% in cases assuming a 10:1 ratio between controls and cases.

RESULTS

Cases and controls were enrolled from the total unselected population of the seven schools tested for intestinal helminths;

25 pupils who were not present for stool collection because of travel and 5–10 children per school who could not produce a stool sample were excluded. None of these children were among the malaria cases. Finally, five children with a febrile illness that could not be diagnosed were excluded. After exclusion, the total number of children who participated in the study was 1,442; 126 suspected malaria cases were tested by rapid diagnostic test (RDT) and microscopy during the 3-month study period, of whom 115 (91.3%) children had the malaria diagnosis confirmed. Two children presented with a second malaria episode toward the end of the third month, but they were not counted, because cases were defined as having at least one episode of malaria. All of the suspected malaria cases were tested by RDT as well as microscopy, and there was 100% agreement between the two laboratory methods. Malaria incidence was significantly different between age groups, with a relative risk of malaria in children under 5 years old compared with older children of 7.6 (95% confidence interval [95% CI] = 5.2–11.2, P < 0.001).

The prevalence of intestinal helminths was 476 of 1,442 (33.0%) children. *Ascaris* was the most common helminth identified in this study (22.3%) followed by hookworm (7.8%). Other species were rare, and 23 (1.6%) of the children were coinfected with two helminth species (Table 1).

The distribution of helminth species was similar in cases and controls (Table 2), but the prevalence of helminth infection was lower in cases (21 of 115; 18.3%) than among controls (455 of 1,327; 34.3%).

We noted that the prevalence of intestinal helminth infection differed significantly between age groups. For instance, the prevalence of helminths in control children 5 years old or younger was 29.8%, the prevalence of helminths in control children 6–10 years old was 37.6%, and the prevalence of helminths in control children 11–15 years old was 30.5% (Table 3) (P = 0.01). To compensate for confounding caused by different age distributions of malaria and helminth infection, we stratified our analysis by age. In children < 5 and 6–10 years old, the prevalence of helminth infection was significantly higher in controls than cases (P = 0.03 and P = 0.005, respectively), whereas no difference could be found in older children (P = 0.5) (Table 3). The weighted OR for helminth infection in cases

TABLE 1
Distribution of malaria cases and intestinal helminth species across age groups

	Age group (years), N (%)				
	≤ 5	6–10	11–15	> 15	Total
Malaria positive	82 (23.2)	16 (2.2)	17 (4.9)	0 (0)	115 (8.0)
Malaria negative	272 (76.8)	718 (97.8)	333 (95.1)	4 (100)	1,327 (92.0)
Total	354 (100)	734 (100)	350 (100)	4 (100)	1,442 (100)
Helminths					
Ascaris sp.	74 (20.1)	184 (25.1)	61 (17.4)	2 (50.0)	321 (22.3)
Hookworm	15 (4.2)	58 (7.9)	39 (11.1)	0 (0)	112 (7.8)
T. trichuria	0 (0)	5 (0.7)	2 (0.6)	0 (0)	7 (0.5)
Enterobius vermicularis	0 (0)	5 (0.7)	0 (0)	0 (0)	5 (0.4)
Ascaris sp. and hookworm	2 (0.6)	15 (2.0)	6 (1.7)	0 (0)	23 (1.6)
Ascaris sp. and *T. trichiura*	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (0.1)
Ascaris sp. and *E. vermicularis*	0 (0)	2 (0.3)	0 (0)	0 (0)	2 (0.1
Taenia sp.	3 (0.9)	0 (0)	0 (0)	0 (0)	3 (0.21)
Hookworm and *E. vermicularis*	0 (0)	1 (0.1)	0 (0)	0 (0)	1 (0.1)
Hookworm and *T. trichiura*	0 (0)	0 (0)	1 (0.3)	0 (0)	1 (0.1)
Helminth positive	95 (26.8)	270 (36.8)	109 (31.1)	0 (0)	476 (33.0)
Helminth negative	259 (73.2)	464 (63.2)	241 (68.9)	2 (100)	966 (67.0)
Total	354 (100)	734 (100)	350 (100)	4 (100)	1,442 (100)

TABLE 2
Distribution of intestinal helminth species among cases and controls

Malaria status	Intestinal helminths, N (%)												
	Asc	Hw	Tt	Ev	A+H	A+T	A+E	Tae	H+E	H+T	H.pos	H.neg	Total
Case	12 (10.4)	4 (3.5)	1 (0.9)	0 (0)	2 (1.7)	0 (0)	0 (0)	2 (1.7)	0 (0)	0 (0)	21 (18.3)	94 (81.7)	115 (100)
Control	309 (23.3)	108 (8.1)	6 (0.5)	5 (0.4)	21 (1.6)	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.1)	1 (0.1)	455 (34.3)	872 (65.7)	132 (100)
Total	321 (22.3)	122 (8.5)	7 (0.5)	5 (0.4)	23 (1.6)	2 (0.1)	2 (0.1)	3 (0.2)	1 (0.1)	1 (0.1)	476 (33.0)	966 (67.0)	1,442 (100)

A+E = *Ascaris* sp. and *E. vermicularis*; A+H = *Ascaris* sp. and hookworm; Asc = *Ascaris* sp.; A+T = *Ascaris* sp. and *T. trichiura*; Ev = *Enterobius vermicularis*; H+E = hookworm and *E. vermicularis*; H.neg = helminth negative; H.pos = helminth positive; H+T = hookworm and *T. trichiura*; Hw = hookworm; Tae = *Taenia* sp.; Tt = *T. trichuria*.

versus controls across all age groups was 0.50 (95% CI = 0.2–0.84; stratified χ^2 test $P < 0.01$).

Females tended to have higher incidence of malaria (68 of 724; 9.4%) than males (47 of 718; 6.5%), with a relative risk of malaria in females compared with males of 1.43 (1.00–2.05; $P = 0.06$).

DISCUSSION

Our study supports the possible protective effect of helminth infections against malaria. Most (71.3%) of the children who experienced a clinical malaria attack during the observation period were in the age group ≤ 5 years old, which is in agreement with the usual trend in malaria epidemiology.[2,12] This age group is most susceptible to malaria because of the time that it takes to acquire immunity to variant surface antigens of *P. falciparum*.[13] Notably, the protective effect of helminth infections was present in both the youngest age group, where the risk of malaria was high, and the 5- to 10-year-old age group, where the risk was low. Only the children older than 10 years old did not seem to benefit from a protective effect of helminth infection against malaria. Our findings contrast an intervention study from Madagascar, where bimonthly deworming resulted in a significant increase in *P. falciparum* density in cases compared with controls.[14] This change was seen only in 5- to 14-year-old children, and there was no effect of treatment in children ages 6 months to 4 years old or subjects > 15 years of age.[14]

In our study, males had a lower incidence of malaria than females (40.9% and 59.1%, respectively). This difference was borderline significant. This is not in agreement with a study in Uganda,[15] which showed that confirmed malaria was lower among girls (52.3%) than boys (57.3%), and it

had no bearing on the effect of helminth coinfection (data not shown).

There are wide variations in the prevalence of and helminth species involved in coinfections with malaria across study sites. Thus, the helminth coinfection rate among the malaria cases in our study was lower than what was observed in a recent study in Tanzania, where a 60% coinfection rate was seen among schoolchildren. In this study, a similar protective effect of malaria coinfection with *Schistosoma* spp. in particular was noted, whereas there was an opposite trend for hookworms.[16] Despite methodological differences between studies, geographic differences indicate a need to test helminth–malaria interactions in a range of settings. This study was, thus, undertaken as part of an evaluation of the policy to routinely deworm schoolchildren in Nigeria.

Our findings strengthen the worry that regular deworming of children in endemic areas could potentially be putting the children at increased risk of malaria.[17] It is particularly worrying that the protective effect of helminth coinfection was seen in the youngest children, who are at the highest risk of malaria. Because deworming is now a routine public health intervention in Nigeria,[18] it is unlikely that permission would be granted to conduct a randomized trial of the effect of deworming on malaria risk. Furthermore, historical controls cannot be used to compare malaria risk before and after deworming in a treatment series, because malaria transmission changes with season and annual variation. However, the study raises the question of whether deworming should routinely be combined with intermittent preventive treatment of malaria in children (IPTc)[19] or other interventions aimed at reducing malaria risk. As for many other aspects of public health interventions in Africa, this calls for an integrated approach to health problems instead of the common vertical campaigns.[20] In addition, additional studies should scrutinize the effect on malaria risk and other health consequences of deworming in groups with or without simultaneous administration of IPTc.

The results of our study also reinforce the fact that the helminth status of a potential malaria vaccine target population must be critically evaluated with deeper insight into the outcomes of helminth–malaria interactions before successful design and deployment of effective vaccines against malaria are undertaken. Helminths have been shown to reduce the efficacy of a number of vaccines, such as for bacille calmette-guérin (BCG),[21] tetanus,[22] and cholera.[23] The immunogenicity of human immunodeficiency virus (HIV)-1 and malaria candidate vaccines[24–26] was also shown to be reduced by helminth coinfection. Inhibition of vaccine-elicited immune responses is generally attributed to T-helper lymphocyte (Th)2 polarization and interleukin-4 (IL-4) production associated with most helminth infections.[26] Several studies have shown that

TABLE 3
Prevalence of helminth infestations in cases and controls by age group

Age group (years)/malaria status	N (%)	Helminth status, N (%)	
		Positive	Negative
< 5			
Positive	82 (23.2)	14 (17.1)	68 (82.9)
Negative	272 (76.3)	81 (29.8)	191 (70.2)
6–10			
Positive	16 (2.2)	0 (0)	16 (100)
Negative	718 (97.8)	270 (37.6)	448 (62.4)
11–15			
Positive	17 (4.9)	7 (41.2)	10 (58.8)
Negative	333 (95.1)	102 (30.5)	232 (69.5)
> 15			
Positive	0 (0)	0 (0)	0 (0)
Negative	4 (100.0)	2 (50.0)	2 (50.0)

elimination of helminth parasites before immunization seems to restore normal vaccine responsiveness.[26–29]

In conclusion, our study adds additional support to earlier observations of an association between the presence of intestinal helminth infection and the development of clinical malaria.

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