

COINFECTION WITH *PLASMODIUM FALCIPARUM* AND *SCHISTOSOMA HAEMATOBIIUM*: PROTECTIVE EFFECT OF SCHISTOSOMIASIS ON MALARIA IN SENEGALESE CHILDREN?

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Abstract. Studies with animal models have suggested the possibility of interactions between parasites during concurrent infections and have raised the question of a similar phenomenon in humans. The present survey was undertaken to assess the impact of urinary schistosomiasis on the susceptibility of children to malaria. It was carried out in Senegal between September 2001 and March 2002 among 523 children 3–15 years of age. We tested the association between *Plasmodium falciparum* densities and the load of *Schistosoma haematobium* egg excretion using a linear mixed model because data were not independent. After controlling for age, sex, and season, we showed that children lightly infected with *S. haematobium* (1–9 eggs/10 mL of urine) had lower *P. falciparum* densities than those not infected ($\beta = -0.34$, 95% confidence interval = $-0.85, -0.10$), suggesting a negative interaction between both parasites.

INTRODUCTION

In inter-tropical areas, multiple parasitic infections are common.^{1–3} Epidemiologic, clinical, or biologic outcomes are more often studied considering each parasite separately. Nevertheless, studies on animal models have shown that concurrent infections by two or more parasite species could affect the pathogenesis of each other.^{4,5} They have suggested the possibility of antagonistic or synergistic interactions between parasites, and have raised the question of a similar phenomenon in humans.

Malaria and helminth infections are the major parasitic diseases in developing countries and their epidemiologic coexistence is frequently observed, particularly in Africa. The implications of concomitant malaria and helminth infections have been mainly explored in animals under laboratory conditions.^{6–8} In human populations, only few studies have been conducted, with contradictory results. Some of them showed a protective role of helminths.^{9–11} For example, Nacher and others¹⁰ found that a helminth infection was associated with a protection from cerebral malaria, and Murray and others⁹ showed that treatment of severe ascariasis was accompanied by recrudescence of malarial attacks in children. Conversely, other studies suggested a deleterious effect of coinfection.^{12,13}

The purpose of this study was to investigate coinfection with malaria and urinary schistosomiasis in a population of children in Senegal exposed to both diseases. We compared malaria parasite densities in children coinfecting with *Schistosoma haematobium* with those not coinfecting for increasing levels of infestation. We also studied intestinal helminth infections to observe their possible effect on malarial infection.

MATERIALS AND METHODS

Study area. The study was conducted in Niakhar, Senegal, a rural area 135 km east of Dakar. This area is composed of 30 villages, with a population of approximately 30,000 persons, most of whom belong to the Sereer ethnic group. Each village is composed of several hamlets. Malaria and urinary schistosomiasis are endemic in the area. Their peak transmission occurs from July to October and low-level transmission continues through January. The predominant species of malaria-causing parasite is *Plasmodium falciparum*.¹⁴

Population study. The study population was selected from a cohort of 1,129 subjects living in two villages of Niakhar (Diohine and Toucar) that have been followed since June 2001 for general epidemiologic purposes. A total of 523 children between 3 and 15 years of age (corresponding to the age group at risk for urinary schistosomiasis) were recruited in March 2002. To be selected into the study, children had to be present in the villages the day of enrollment, agreed to provide stool and urine samples, and their parents had to provide consent for their participation.

Study design. Malaria investigations, consisting of obtaining a capillary blood sample for determination of parasite density, were done in September, October, and December 2001 and January 2002. In addition, at recruitment in March 2002, children were asked to provide single urine and stool samples for determination of helminth status. For all children, age, sex, village, and district of residence were recorded. The district was considered an indicator of the intensity of children exposed to malaria.

Laboratory studies. Malarial infection was determined by a Giemsa-stained thick smear made from capillary blood. Parasite count was estimated on 200 microscope fields, and the average number of leukocytes per field was estimated in 30 fields. Asexual-stage parasite densities were reported as parasite count per 100 leukocytes.

Urine and stool samples were processed within 24 hours of collection. Schistosomiasis status (infected or not infected) was determined by the detection of *S. haematobium* eggs using a urine filtration technique (Nytrel® filter; Vestergaard Frandsen Group, Kolding, Denmark). The load of *S. haematobium* egg excretion was determined per 10 mL of urine. In addition, hematuria was detected with a reagent strip, and was expressed as negative or in levels of positivity (trace, +, ++, or +++). Stools were screened for helminths by microscopic examination, and helminth number and species were recorded.

Statistical analysis. We examined malaria parasite density in relation to the load of *S. haematobium* egg excretion. Only *P. falciparum* density was studied. To determine the influence of coexisting infections of *P. malariae* and/or *P. ovale* on *P. falciparum* density, we compared mixed infections with nonmixed infections, with regard to *P. falciparum* den-

sities. Since these densities were similar in both groups, we analyzed all children infected with *P. falciparum*, whether or not infected with another plasmodial species.

Plasmodium falciparum density was transformed by computing the log +1 value and was considered a continuous variable (0 for noninfected children). Normality was checked using the Shapiro test and graphic methods.

The intensity of schistosomiasis was divided into four categories with slight modifications of World Health Organization recommendations¹⁵: no infection, light infection (1–9 eggs per 10 mL of urine), moderate infection (10–49 eggs/10 mL), and heavy infection (≥ 50 eggs/10 mL). Egg load was not considered when children had microscopic hematuria ($\geq 1+$) in the absence of eggs.

Intestinal helminth status was expressed qualitatively (as infected or not infected). Age was treated as a continuous variable. We considered the season during which *P. falciparum* density was measured as a binary variable: a high transmission season in September or November, and a moderate transmission season in December or January.

Since measurements of malaria parasite density were repeated (four per child) and children originated from various districts (17 districts in which malaria exposure intensity was considered homogeneous), our data were not independent. Data presented a hierarchical structure where malaria parasite densities were level 1 units, and children were level 2 units clustered within districts that were level 3 units (Figure 1).

To test the association between malaria parasite density and the load of *S. haematobium* egg excretion, statistical analysis was performed with a linear mixed model that took into account the hierarchical structure.¹⁶ We used a random intercept model as specified in the equation

$$Y_{ijk} = \underbrace{\beta_0 + \sum_{l=1}^p \beta_l X_{ijk,l}}_{\text{fixed effects}} + \underbrace{a_j + b_i + e_{ijk}}_{\text{random effects}}$$

where Y_{ijk} is the k th log (*P. falciparum* density +1) for child j living in district i for $k = 1, 2, \dots, 4$, $i = 1, 2, \dots, 17$ and $j = 1, 2, \dots, 14$; $b_i \sim N(0, \sigma_b^2)$ where σ_b^2 = district-to-district variation, $a_j | b_i \sim N(0, \sigma_a^2)$ where σ_a^2 = child-to-child variation, and $e_{ijk} \sim N(0, \sigma_e^2)$ where σ_e^2 = residual variation.

We assumed that random coefficients (b_i , a_j , e_{ijk}) were independent of each other. The child and district variance components were estimated by restricted maximum likelihood

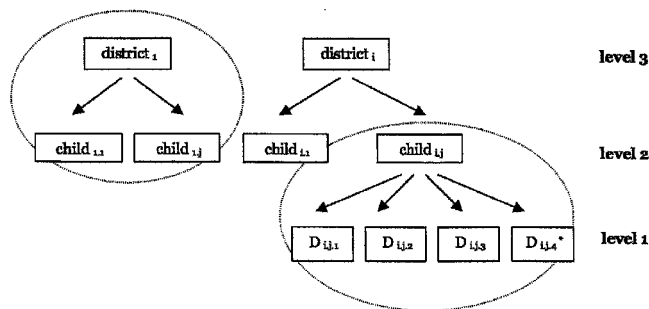


FIGURE 1. Hierarchical structure of data for Senegal 2001–2002. Level 1 = *Plasmodium falciparum* densities; level 2 = children; level 3 = districts. $D_{i,j,k}$ is the k th measurement of *P. falciparum* density taken on the j th child living in the i th district.

method and the fixed effects parameters were estimated by the maximum likelihood method. For analysis, we used the PROC MIXED SAS® procedure (SAS Institute, Cary, NC).

We carried out a univariate analysis using the abovementioned linear mixed model to study the same dataset as in the multivariate analysis to search for potential confounders. Variables studied included age, sex, intestinal helminth infection status, and season. A multivariate analysis was then performed that included variables with $P \leq 0.20$ in univariate analysis. We first took into account all children, and then considered only those who had at least one positive *P. falciparum* density during their follow-up to have a more homogeneous population regarding malaria exposure and possibly genetic susceptibility or immunity. Finally, we performed a stratified analysis on age of the child to search for a possible interaction between load of *S. haematobium* eggs and age. For this analysis only, we considered three age groups (3–7, 8–10, and 11–15 years old) in which we tested the association between *P. falciparum* density and the load of *S. haematobium* eggs after adjusting for variables included in the multivariate model. The Kruskal-Wallis test was used to compare non-Gaussian variables. Statistical analysis was performed by using the SAS system software (SAS Institute).

The study was reviewed and approved by the ethics committee of the Senegalese Ministry of Public Health. In March 2002, children who had *S. haematobium* infection or intestinal helminth infection were identified and treated with praziquantel and levamisole, respectively. All children who had fever and visited the clinic during the study period received a presumptive antimalarial treatment (chloroquine).

RESULTS

Description of the study population. Some of the 3–15-year-old children in the Niakhar cohort were not selected for the study because they were absent on the day of recruitment, urine or stool samples were not obtained, or consent of the parents was not obtained. These children were similar with regard to sex and malaria parasite density compared with the 523 children selected, but they were slightly older. Thus, there was no bias in the selection of the study group. Of the 523 children recruited, 55% (285 of 523) lived in Dioline and 54% (284 of 523) were boys. The mean age of this population was nine years (Table 1).

Malarial infection. Most (95%) children had at least three measurements of malaria parasite density during the follow-

TABLE 1
General characteristics of the 523 children included in data analysis in Senegal, 2001–2002

	No. of subjects	%
Sex		
Male	284	54
Female	239	46
Village		
Dioline	285	55
Toucar	238	45
Age (years)		
3–4	15	3
5–7	170	33
8–10	160	30
11–13	127	24
14–15	51	10

up. The prevalence of malarial infection ranged from 50% to 56% (Table 2). It was highest in September and November during the high malaria transmission period (56% and 55%, respectively), and then decreased in December and January, when malaria transmission was moderate (52% and 50%, respectively). More boys were infected than girls. Approximately 90% of the infections were *P. falciparum*. Between 5% and 10% of the children had mixed plasmodial infections each month. The mean *P. falciparum* density was estimated only in malaria infected children. It was highest in September and November, and then decreased in December and January (arithmetic mean = 86, 69, 25, and 19/100 leukocytes, respectively). Over the study period, 287 children received antimalarial treatment. A total of 199 were treated once, 63 twice, 20 three times, and 5 four times. There was no difference in antimalarial treatment distribution between *S. haematobium*-infected children and noninfected children.

Helminth infection. Five hundred five (97%) children were tested for *S. haematobium* infection (Table 3). The results of urinary filtration and hematuria (microscopic hematuria and absence of eggs) were discordant for 18 children, and the load of *S. haematobium* egg excretion was not taken into account. Three hundred thirty-six children (67%) were infected, and more than half (54%) had an egg load $\geq 50/10$ mL of urine. The prevalence and intensity of *S. haematobium* infection increased with age and was higher in boys than in girls. There was no difference in the prevalence between intestinal helminth-infected and noninfected children.

Information on intestinal helminth status was available for 474 children. One hundred forty-seven (31%) were infected with intestinal helminths. There were 119 infections with *Ascaris lumbricoides*, 25 with *Hymenolepis nana*, 9 with *Strongyloides stercoralis*, and 1 with *Trichuris trichiura*. Only seven children were infected with two different parasite species (six with *A. lumbricoides* and *H. nana* and one with *A. lumbricoides* and *S. stercoralis*).

Malaria parasite density and its relationship with *S. haematobium* infection. *Univariate analysis.* As shown in Table 4, age, sex, and season were significantly associated with *P. falciparum* parasite density. Parasite density decreased with age ($P < 0.001$), and was lower in girls than in boys and when malaria transmission was moderate (both $P < 0.001$). We found that children lightly infected with *S. haematobium* (1–9 eggs/10 mL of urine) had significantly lower *P. falciparum* densities than those who were not infected. No significant association was found for higher loads of eggs. We did not

observe any association between intestinal helminth infection and *P. falciparum* density.

Multivariate analysis. Age, sex, and season were included in the final model (Table 5). Adjustment for these factors did not change the association between *P. falciparum* density and age, sex, or season. Similar to the findings with univariate analysis, children lightly infected with *S. haematobium* had lower *P. falciparum* densities than noninfected children ($\beta = -0.34$, 95% confidence interval = $-0.58, -0.10$, $P = 0.07$, by global test for all *S. haematobium* egg loads). A mixed model approach allowed us to estimate that child-to-child variation in *P. falciparum* density was 70-fold more important than district-to-district variation. When we considered only children who had at least one *P. falciparum* parasitemia during the follow-up, the association between low intensity of *S. haematobium* eggs and low malaria parasite density persisted. In addition, stratified analysis suggested that this relationship varied according to the age of the child; it was stronger in children 11–15 years of age. However, we did not find any significant interaction between age and load of *S. haematobium* eggs ($P = 0.76$).

DISCUSSION

Since polyparasitism is common among populations in developing countries and there may be interactions between parasites, as suggested by previous studies,^{4,5} we studied the effect of urinary schistosomiasis on the susceptibility of children to malaria. We observed that children lightly infected with *S. haematobium* had significantly lower *P. falciparum* densities than those not infected, suggesting a negative interaction between the two parasites.

To our knowledge, only two studies have explored coinfection with malaria and schistosomiasis in human populations, and these were interested mainly in immunologic implications.^{17,18} However, a recent study of the incidence of malarial attacks in children in relation to the intensity of their *S. mansoni* egg load showed that those lightly infected with *S. mansoni* had fewer malaria attacks than those not infected (Le Hesran JY and others, unpublished data).

We are confident that the association observed was not ecologically determined. Indeed, even if malaria and schistosomiasis are water-associated diseases, their modes of transmission (place and time) are different, suggesting an independent risk of contamination. In addition, for schistosomiasis,

TABLE 2

Rate of malarial infection, species of malaria-causing parasite, and mean *Plasmodium falciparum* density, according to month of follow-up in Senegal, 2001–2002

	September % (n)	November % (n)	December % (n)	January % (n)
Malarial infection*	56 (262)	55 (275)	52 (249)	50 (232)
Males	62 (163)	57 (157)	55 (138)	59 (138)
Females	38 (99)	43 (118)	45 (111)	41 (94)
Plasmodium sp.				
<i>P. falciparum</i>	90 (236)	85 (234)	79 (197)	85 (198)
<i>P. falciparum</i> plus (<i>P. ovale</i> and/or <i>P. malariae</i>)	5 (13)	8 (22)	10 (24)	6 (13)
<i>P. ovale</i> and/or <i>P. malariae</i>	5 (13)	7 (19)	11 (28)	9 (21)
Mean <i>P. falciparum</i> density (CI)†	86 (65, 107)	69 (44, 93)	25 (19, 32)	19 (14, 25)

* Infection by *P. falciparum* and/or *P. ovale* and/or *P. malariae*.

† Arithmetic mean *P. falciparum*/100 leukocytes among infected children. CI = 95% confidence interval.

TABLE 3

Prevalence of urinary schistosomiasis and distribution of the load of *Schistosoma haematobium* egg excretion, according to sex, age and village of residence in Senegal, 2001–2002

	<i>S. haematobium</i> egg load			<i>P</i>	Urinary schistosomiasis prevalence		<i>P</i>
	1-9 % (n)	10-49 % (n)	≥ 50 % (n)		% (n)		
Sex							
Male	52 (49)	56 (34)	64 (115)	0.16	59 (198)	0.001	
Female	48 (45)	44 (27)	36 (66)		41 (138)		
Age (years)							
3-4	4 (4)	2 (1)	0 (0)	< 10 ⁻³	2 (5)	< 10 ⁻³	
5-7	42 (39)	21 (13)	18 (32)		25 (84)		
8-10	23 (22)	34 (21)	36 (66)		32 (109)		
11-13	23 (22)	31 (19)	32 (57)		29 (98)		
14-15	8 (7)	12 (7)	14 (26)		12 (40)		
Village							
Diohine	64 (60)	43 (26)	60 (109)	0.02	58 (195)	0.001	
Toucar	36 (34)	57 (35)	40 (72)		42 (141)		
Total	28 (94)	18 (61)	54 (181)		67 (336)		

studies have shown that in small areas children are infected independently of their place of residence and distance from bathing areas.¹⁹ We identified the area in which cases of schistosomiasis were found and observed that their distribution did not follow any systematic pattern and were not situated near bodies of water. If simultaneous transmission of malaria and schistosomiasis occurred, we would have observed a positive correlation between *P. falciparum* density and *S. haematobium* egg load. Thus, our results are compatible with a negative interaction between the two parasites.

No association was found between intestinal helminth infection (mainly ascariasis) and *P. falciparum* parasite density. Explanations for this may be that there is no effect of intestinal helminth infection on parasitemia, as suggested by Nacher and others,¹⁰ or that the number of infected children was not sufficient to observe a significant association. In a previous study, Ashford and others² showed a positive corre-

lation between egg load of *Ascaris lumbricoides* and *Plasmodium* density, but no adjustment was made for age or malarial exposure.

As expected, we observed that malaria parasite density decreased with age. It may be related to specific anti-malarial immunity that develops in disease-endemic areas with repeated infections. Moreover, we found that *P. falciparum* density was significantly lower in girls. When we considered only children with positive blood smears, since boys were infected more often than girls, the association remained ($\beta = -0.26$, 95% confidence interval = $-0.48, -0.04$).

We found that schistosomiasis was more prevalent and intense in boys than in girls and in older children. These age and sex effects are well known and are associated with the number and type of water contacts. It has been shown that boys are

TABLE 4

Plasmodium falciparum density in relation to age, sex, *Schistosoma haematobium* egg load, and season by univariate analysis* in Senegal 2001–2002

	No.	β †	95% CI‡	<i>P</i> value§
Age (years)	1,916	−0.06	−0.09, −0.03	< 10 ^{−3}
Sex				
Male	1,045	—	—	< 10 ^{−3}
Female	871	−0.35	−0.53, −0.17	
<i>S. haematobium</i> egg load¶				
0	623	—	—	0.10
1–9	349	−0.33	−0.58, −0.08	
10–49	225	−0.14	−0.43, 0.15	
≥ 50	656	−0.18	−0.40, 0.04	
Intestinal helminth infection				
No	1,218	—	—	0.76
Yes	533	−0.03	−0.23, 0.17	
Season				
December or January	947	—	—	< 10 ^{−3}
September or November	969	0.52	0.38, 0.65	

* Study of the log (*P. falciparum* density +1). Analysis was carried out with a random intercept model with levels being child and district.

† Coefficient of regression.

‡ CI = confidence interval.

§ *P* value (for variables with more than two categories, the *P* value of the global test is given).

¶ Number of *Schistosoma haematobium* eggs per 10 mL of urine.

TABLE 5

Relationship between *Plasmodium falciparum* density and *Schistosoma haematobium* egg load, multivariate analysis* in Senegal 2001–2002

Fixed effects	β †	95% CI‡	<i>P</i> §
Intercept	1.79		
Age (years)	−0.06	−0.09, −0.03	< 10 ^{−3}
Sex			
Male	—	—	< 10 ^{−3}
Female	−0.36	−0.54, −0.18	
<i>S. haematobium</i> egg load¶			
0	—	—	0.07
1–9	−0.34	−0.58, −0.10	
10–49	−0.09	−0.38, 0.20	
≥ 50	−0.12	−0.34, 0.10	
Season			
December or January	—	—	< 10 ^{−3}
September or November	0.52	0.38, 0.66	
Random effects			
Child-to-child variation (level 2)		0.34	
District-to-district variation (level 3)		0.01	
Residual variation		2.41	

* *N* = 1853 measures (log (*P. falciparum* density +1)), on 505 children. Analysis was carried out with a random intercept model with levels being child and district. Adjustment was done for age, sex, and season.

† Coefficient of regression.

‡ CI = confidence interval.

§ *P* value (for variables with more than two categories, the *P* value of the global test is given).

¶ Number of *Schistosoma haematobium* eggs per 10 mL of urine.

more exposed than girls because they take more baths,^{19,20} and that the level of infestation increases with age because schistosomiasis is a chronic affection and children have repeated episodes.²¹

Schistosomiasis status was determined from a single urine sample in March 2002. We believed that the probability of a change in this status between September 2001 and March 2002, and throughout the entire follow up, was very low. Because our study was conducted in a disease-endemic area among relatively older children (most > 5 years old), most of those infected had probably contracted the infection several years ago. With regard to uninfected children, we verified that none had received antihelminthic treatment before urine samples were collected.

Single urine and blood samples were used to classify children as infected and to determine their parasitic loads (malaria parasite density and *S. haematobium* egg load). Examinations were made using thick blood smear and urine filtration techniques, which have high specificities but lower sensitivities.^{22,23} This lack of sensitivity is due not only to the limitations of the techniques, but also to fluctuations in parasite counts in peripheral blood (for malaria) or urine (for schistosomiasis) in an individual during the course of a day. In our study, even if there were misclassifications (false-negative or underestimated parasitic loads) we believe that they did not modify the results. Indeed, schistosomiasis and malaria status were established independent of each other. We also compared malaria and schistosomiasis prevalences in our study with those of previous studies conducted in the Niakhar area. The prevalence of *S. haematobium* infection was consistent with the results of one study (Hamour S and others, unpublished data). We estimated that 56% of the children were infected with *P. falciparum* in November 2001, while Robert and others found an infection rate of 82% in November 1995.¹⁴ An explanation for this difference may be the particularly heavy rainfalls during 1995, thus causing higher transmission.

We adjusted for the main confounders (age and level of exposure to malaria). The latter confounder depends on environmental and behavioral factors. We considered only environmental exposure (adjusting for the district of residence) because it was shown in a study performed in 2002 in the same area that only 8% of the families used prophylaxis or bed nets (Rouget F, unpublished data).

We did not obtain any information on nutritional status or existence of hemoglobinopathies (sickle cell trait, thalassemias, glucose-6-phosphate dehydrogenase deficiency), which are known to influence malarial infection. We believe that even if they had been taken into account, they would not have affected the results. The impact of nutritional status has been reported for severe malaria, but not for parasitemia.²⁴ Moreover, the sickle cell trait would have been a confounder in our study only if it influenced not only malaria parasite density (as was shown in recent studies²⁵), but also the load of *S. haematobium* eggs, which has never been observed previously.

Our understanding of the mechanisms by which interactions between parasites occur is still limited. Recent studies have proposed an immunologic hypothesis based upon the T cell dichotomy.⁶ If one considers that for each parasite or pathogen, there is a corresponding protective T cell/cytokine response, concomitant infection could lead to synergistic or

antagonistic T cell responses, dependent upon what kind of response (Th1 or Th2) was induced by each parasite. Synergistic responses could decrease the pathologic impact of the infections, whereas antagonistic responses could exacerbate the diseases. In humans, the immune responses induced during malaria and schistosomiasis are complex and not well known. As a result, what occurs during coinfection is more difficult to understand. The nature of immune responses may vary according to the stage and intensity of infections.^{26,27} This could explain the non-linear relationship we observed between malaria parasite densities and *S. haematobium* egg loads.

Parasitic coinfection and interaction phenomena are complex. Until now, they have been investigated mainly in animal models. However, the underlying problem is whether observations made under controlled laboratory conditions are relevant in human populations. In humans, these phenomena require further study to understand their mechanisms and public health implications. Community therapy programs usually focus on a single parasitic disease, such as control of schistosomiasis in school age children. Since several diseases may co-exist in the same individuals and affect the severity of each other, it could be worthwhile to implement integrated control programs that deliver multiple treatments against several parasitic infections simultaneously. In coinfecting individuals, such programs could avoid possible deleterious effects of a single-targeted treatment on other diseases.

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