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Coinfection with *Plasmodium falciparum and Schistosoma haematobium*: Additional Evidence of the Protective Effect of Schistosomiasis on Malaria in Senegalese Children

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Abstract. Parasitic infections are associated with high morbidity and mortality in developing countries. Several studies focused on the influence of helminth infections on malaria but the nature of the biological interaction is under debate. Our objective was to undertake a study to explore the influence of the measure of excreted egg load caused by *Schistosoma haematobium* on *Plasmodium falciparum* parasite densities. Ten measures of malaria parasite density and two measures of schistosomiasis egg urinary excretion over a 2-year follow-up period on 178 Senegalese children were considered. A linear mixed-effect model was developed to take data dependence into account. This work showed that children with a light *S. haematobium* infection (1–9 eggs/mL of urine) presented lower *P. falciparum* parasite densities than children not infected by *S. haematobium* ($P < 0.04$). Possible changes caused by parasite coinfections should be considered in the anti-helminth treatment of children and in malaria vaccination development.

INTRODUCTION

In developing countries, parasitic infections are a major cause of morbidity and mortality. Concomitant parasite infections in humans are common, as for example the infections by schistosomiasis and malaria, which are two of the parasitic diseases with the heaviest economical and social burdens.

Several studies in animals have shown that biological, histological, and immunological responses induced by a parasite were modified in the presence of another parasite.[1–4] These studies suggest the existence of interactions between immune responses induced by the simultaneous presence of both parasites, however, the nature of those is under debate.[5,6]

A study of coinfection between malaria and schistosomiasis in humans, conducted in 2002 among children in Senegal, has concluded on the existence of a negative association between *Plasmodium falciparum* parasite densities and *Schistosoma haematobium* infection.[7] Another study among children in Mali in 2002–2003 with both an epidemiological and a biological approach, showed an age-dependent protection in children infected with urinary schistosomiasis against acute *P. falciparum* malaria.[8,9] However, other studies suggested an additive or synergic effect of coinfection,[10,11] as for example, Wilson and others[11] who showed that concurrent chronic exposure to *Schistosoma mansoni* and *P. falciparum* could have a synergistic effect on childhood morbidity.

In this context, a first cross-sectional study on a selected sample of Senegalese children belonging to a large cohort, initially devoted to the study of genetic susceptibility of malaria, was undertaken to investigate coinfection between *S. haematobium* and *P. falciparum*.[7] The present long follow-up study aims to confirm the protective effect of *S. haematobium* on *P. falciparum* infection found in the previous work thus establishing in a more stable way the infectious status of the individuals with both parasites.

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METHODS

Study area. The study was conducted in Niakhar, Senegal, a rural area 135 km east of Dakar. The climate is characterized by a long dry season from November to June and a short rainy season from July to October. Malaria and urinary schistosomiasis are both endemic diseases frequently associated in this region. Schistosomiasis is transmitted all year round because there are permanent ponds in the study area. Peak transmission of malaria occurs during the rainy season. The predominant species of malaria causing parasite is *P. falciparum*.[12]

Study population. The study population was selected from a cohort of 1,135 children living in Diohine and Toucar, two villages in the Niakhar area[13]; this cohort was originally developed to study genetic susceptibility to malaria in human populations and it was followed between June 2001 and December 2003.

In 2002, 523 children 5–13 years of age were selected in a cross-sectional study that explored the malaria–urinary schistosomiasis coinfection from data collected during one rainy season.[7] One measure of urinary schistosomiasis intensity per child had been considered in this analysis.

Among these 523 children, 178 were further followed up for malaria for the next rainy season and underwent one supplementary measure of urinary schistosomiasis. These children, who were regularly followed up for 2 consecutive years, were selected for this analysis.

All the children agreed to provide urine and stool samples, and their parents gave consent for their participation.

Biological methods. Malaria status was determined by a Giemsa-stained thick smear from capillary blood. Parasite quantity 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. Because malaria is an acute and labile disease, repeated measures were necessary to evaluate the infection intensity in children: 10 measures were made for each child (June, September, October, November 2002, January, April, June, September, October, and December 2003).

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 measured per 10 mL of urine.

The level of S. *haematobium* infection was evaluated from two measures, one in March 2002 and the other in September 2003.

In addition, hematuria was detected with a reagent strip, and was expressed as negative or as intensity levels when positive (trace, +, ++, or +++). Stools were screened for helminths by direct microscopic examination and after concentration by the merthiolate iodine formalin method on a calibrated amount of stool. This method allowed determination of the number of helminth eggs, helminths species were also recorded.

Data coding. *Plasmodium falciparum* density (DP) was transformed by computing the log (DP +1) value to decrease the asymmetry of the distribution and was considered as a continuous variable, this variable was called LDP in the study. Normality of the transformed distribution was checked using the Shapiro test and graphic methods.

The intensity of schistosomiasis was broken down into four categories according to the World Health Organization (WHO) recommendations[14]: no infection, light infection (1–9 eggs/10 mL of urine), moderate infection (10–49 eggs/10 mL), and heavy infection (≥ 50 eggs/10 mL). Age was considered as a continuous variable. Intestinal helminth status was expressed qualitatively (as infected or not infected). We considered the season as a binary variable: dry season and rainy season.

Statistical methods. A descriptive analysis to explore sociodemographic and parasitologic characteristics was conducted.

The changes between the two measures of urinary schistosomiasis were analyzed. We used the Cochran Mantel-Haenszel test for categorical variables and the Wilcoxon rank sum test for continuous variables.

We explored malaria parasite density according to the urinary schistosomiasis intensity infection. Statistical analysis considered 1,707 measures (~10 measures * 178 children, 73 measures were missing). The egg load for schistosomiasis measured in March 2002 was related to the malaria parasite density in June, September, October, November 2002, January, April, and June 2003 and the one measured in September 2003 to the malaria parasite densities in September, October, and December 2003.

In this study, several *P. falciparum* parasite densities per child and several children per family were considered. We used a linear mixed-effect model[15] taking into account observation dependence, to analyze parasite densities caused by *P. falciparum* according to the infection intensity as a result of *S. haematobium*. The model included three random effects, and accounted for correlation between measures in the same children, and between children within the same family (nested effect). The child variance, the family variance, and residual variance components were estimated by the restricted maximum likelihood method.

We carried out a univariate analysis using the linear mixed model to identify potential confounders. Variables studied included age, sex, intestinal helminth infection status, and season. Variables with a P value < 0.20 in the univariate analysis were selected for multivariate analysis. The interaction between *S. haematobium* egg load and age was tested. Statistical analyses were performed with SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

The study was reviewed and approved by the ethics committee of the Senegalese Ministry of Public Health (No. 000526/MS/DERF/DER). Children were given free access to the dispensary and a therapeutic treatment during the study period. Children infected with schistosomiasis were treated with praziquantel at the end of the study in March 2004.

RESULTS

General characteristics of the children. We compared the general characteristics of these children with those selected from the same cohort in the previous work[7]; they were similar in the previous study and in the 2003 cohort of 523 children. Here, we did not identify differences between age groups (P = 0.17), villages (P = 0.10), and prevalence of *P. falciparum* (P = 0.10). However, we found a difference for sex (P = 0.03) with a higher proportion of males in our study (61%) compared with that of the previous work (39%).

In this study, 61% (N = 108) of the children were male and 60% (N = 106) lived in Diohine (Table 1). The sample was composed of 137 families: 71% (N = 97) with one child, 28% (N = 39) with two children and 1% (N = 1) with 3 children. The mean age of the children was 8.4 years (SD 1.97) in 2002.

Prevalence of *P. falciparum* was highest in October: 44% (N = 77) and 53% (N = 91) of infected children respectively in 2002 and 2003 and lowest in April: 18% (N = 31) in 2003 (Figure 1). Parasite densities caused by *P. falciparum* were lowest in June 2002 (LDP = 1.8 SD 1.2) and June 2003 (1.4 SD 1.1), and were highest in November 2002 (3.1 SD 1.7) and October 2003 (3.3 SD 1.9). Males were more infected than females (P = 0.009) with lower parasite densities caused by *P. falciparum* for females than males (log [DP +1] = 0.80 SD 1.54 versus 0.96 SD 1.61, P = 0.004). Ninety-nine percent of infected children were infected with *P. falciparum*, among which 2% were also infected with *Plasmodium malariae*. In the following analyses, all *P. falciparum* infections were considered, either single or mixed with another plasmodial species.

Sixty-four percent (N = 114) of children were infected with urinary schistosomiasis in 2002 and 54% (N = 97) in 2003.

TABLE 1
Characteristics of the 178 children selected in the study

	Subjects	
Sex		
Male n (%)	108 (61)	
Female n (%)	70 (39)	
Village		
Diohine n (%)	106 (60)	
Toucar n (%)	72 (40)	
Year	2002	2003
Age (years)		
5–7 n (%)	63 (36)	38 (21)
8–10 n (%)	79 (44)	85 (48)
11–13 n (%)	36 (20)	55 (31)

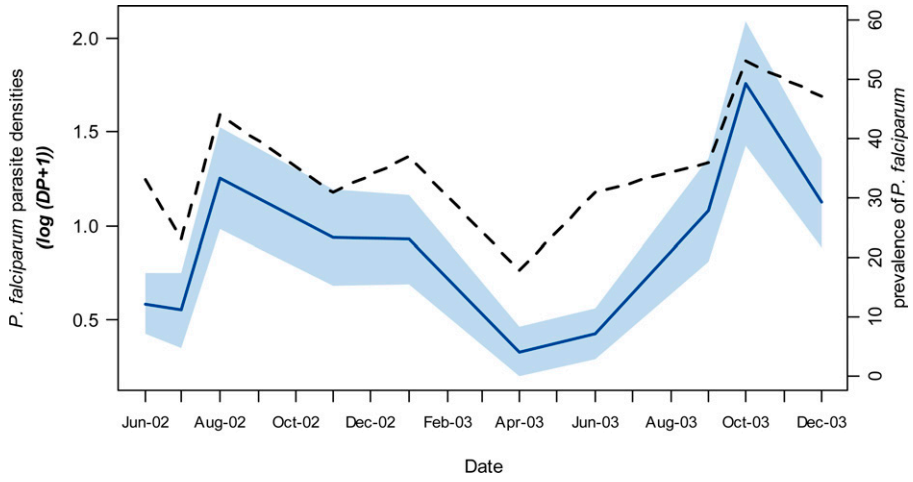

FIGURE 1. Mean and confidence interval of parasite densities caused by *Plasmodium falciparum* according to time in Senegalese children (blue line) and prevalence of *P. falciparum* (dotted black line).

More precisely, among children infected with *S. haematobium* in 2002 and 2003, 39% (N = 44) and 8% (N = 8) had a light infection, 17% (N = 20) and 24% (N = 23) were moderately infected, and 44% (N = 50), 68% (N = 66) presented a heavy infection, respectively.

The prevalence and intensity of infection caused by *S. haematobium* varied with age ($P \leq 0.0001$, Table 2) but did not differ according to sex and village.

Discordance was defined as a moderate or heavy infection in 2002 and no infection or a light infection in 2003. Discordance was observed for 16 children (Table 3). More precisely, 12 children who had a *S. haematobium* egg load ≥ 50 in 2002 were not infected nor had a light infection in 2003. Four children had a moderate infection (10–49 eggs/10 mL) in 2002 and were not infected in 2003.

Twenty-four percent (N = 42) of children in 2002 and 12% (N = 22) in 2003 were infected with intestinal helminths among whom 62% (N = 26) and 45% (N = 10) were also infected with *S. haematobium*, respectively. More precisely, we distinguished 3 species with 7 infections with *Hymenolepis nana*, 4 with *Strongyloides stercoralis*. Only 2 children were infected with two different parasite species (1 with *A. lumbricoides* and *H. nana* and 1 with *A. lumbricoides* and *S. stercoralis*). *Ascaris lumbricoides* was the most frequent intestinal infection with 31 children affected in 2002 and 18 in 2003.

Univariate analysis. Parasite densities caused by *P. falciparum* were higher during the rainy season ($P < 0.0001$). Children with a *S. haematobium* egg load between 1 and 9 presented lower parasite densities caused by *P. falciparum* (–0.37, 95% IC: –0.65; –0.091, $P = 0.009$), Table 4 shows that children who were not infected by *S. haematobium*. We did not observe any association between age, sex, village, or intestinal helminth infection and *P. falciparum* density (Table 4). Sex, *S. haematobium* egg load and season presented a P value under 0.20 in the univariate analysis and were considered in the multivariable analysis. Age was also included in the multivariable model.

Multivariable analysis. The negative relationship between *S. haematobium* egg load and parasite densities caused by *P. falciparum* was confirmed in the multivariate analysis (Table 4). As shown on Figure 2, children with a *S. haematobium* egg load between 1 and 9 had lower parasite densities caused by *P. falciparum* than children not infected by *S. haematobium* (–0.28, 95% CI: –0.52; –0.039, P = 0.04, Table 4 and Figure 2), and this relation was observed for each measure of *S. haematobium* (March 2002 and September 2003, Figure 2). As shown in Figure 2, children with a *S. haematobium* egg load between 1 and 9 had more than 1.5-fold lower parasite densities caused by *P. falciparum* than children not infected with *S. haematobium.* No significant association with *P. falciparum* was found for higher egg loads.

TABLE 2
Schistosoma haematobium egg load and prevalence of urinary schistosomiasis according to sex, age, and village

	S. haematobium egg load						Urinary schistosomiasis prevalence			
	1–9		10–49		≥ 50		n (%)	P	n (%)	P
Year	2002 N = 44	2003 N = 8	2002 N = 20	2003 N = 23	2002 N = 50	2003 N = 66	2002		2003	
Sex (ref = Female)	24	6	7	10	11	18	42 (37)	0.42	34 (35)	0.22
Age (years)										
5–7	15	1	8	4	8	5	31 (27)	0.0005	10 (10)	< 0.0001
8–10	19	7	5	15	29	27	53 (47)		49 (51)	
11–13	10	0	7	4	13	34	30 (26)		38 (39)	
Village (ref = Diohine)	30	6	8	14	34	37	72 (63)	0.21	57 (59)	0.87

TABLE 3

Discordance between measures of *Schistosoma haematobium* egg load in 2002 and 2003

		2003			
2002	Egg load caused by *S. haematobium*	None	1–9	10–49	≥ 50
	None	47	5	2	10
	1–9	20	1	11	12
	10–49	4	0	4	12
	≥ 50	10	2	6	32

We did not find any statistical association between age and *S. haematobium* egg load ($P = 0.11$). The season variable was associated with *P. falciparum* parasitemias ($P < 0.0001$, Table 4).

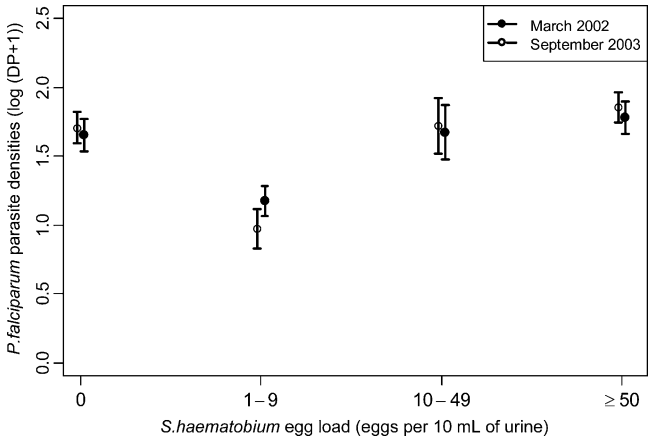

FIGURE 2. *Plasmodium falciparum* parasite densities according to *Schistosoma haematobium* egg load at different times (results adjusted on others factors presented in the Table 4).

DISCUSSION

After a first study of 523 children in Senegal, which suggested a negative interaction between *S. haematobium* and *P. falciparum*,[7] we followed for a second consecutive year 178 of these children, who underwent a total of 10 measures of *P. falciparum* parasite densities and 2 measures of *S. haematobium* egg load.

Our results showed that children with a light *S. haematobium* infection (1–9 eggs/mL of urine) presented lower *P. falciparum* parasite densities (a decrease by 1.5 in this class) than children not infected by *S. haematobium* ($P < 0.04$), thus confirming the findings of the first study. Our methodology was improved compared with the previous work conducted on the same Senegalese children because we considered a longer follow-up with repeated measures on two successive malaria transmission seasons. More precisely, four parasite densities caused by *P. falciparum* and one excreted egg load caused by *S. haematobium* were considered on 523 children in the first study in contrast to 10 malaria measures and two schistosomiasis measures on 178 children in our study. Given the characteristics of helminth infection, which is a chronic disease and the seasonal exposure of children to malaria, individual follow-up over a 2-year period is important to further the understanding of the interaction between the two parasites.

Two typical approaches are usually applied to study the interaction between malaria and helminth infections. Experimental studies have been conducted in animals to explore the immunological mechanisms involved.[1,5] Epidemiological studies have been conducted in humans to show either biological manifestations (biological studies) or to study clinical manifestations.[16]

The results of experimental and epidemiological studies are often contradictory and the nature of the interaction between malaria and helminth infections is under debate.[4–6,17]

In this study, we focused on the interaction between schistosomiasis and malaria infection. Several biological studies have shown a synergistic effect of coinfection,[16,18–21] whereas other studies suggested an acceleration or regulation toward protective profile of the acquired immunity against malaria in children coinfected with malaria and schistosomiasis[9,22] and another study did not find an association.[23] A study on children conducted in Mali in 2002–2003 presented both epidemiological and biological approaches and concluded on a protective effect of infection with urinary schistosomiasis on malaria.[8,9] In contrast, other studies suggested an additive or synergistic effect of coinfection.[11]

Several explanations can be found for such apparently conflicting results. First, the same outcomes were not considered in all studies: parasite densities or clinical symptoms, mild or severe malaria, specific age ranges that may induce specific immune responses. Second, designs differed from

TABLE 4

Relationship between *Plasmodium falciparum* parasite densities and *Schistosoma haematobium* egg load, age, sex, intestinal helminth infection, village, and season by univariate analysis and multivariable analysis*

	Univariate analysis			Multivariable analysis		
	Estimate†	95% IC	*P* value	Estimate*	95% IC	*P* value
Age	–0.0011	–0.058, 0.035	0.63	–0.017	–0.067, 0.034	0.52
Sex (ref = Female)	0.16	–0.027, 0.35	0.092	0.14	–0.057, 0.34	0.16
S. haematobium (ref = 0)						
1–9	–0.37	–0.65, –0.091	0.033	–0.28	–0.52, –0.039	0.10
10–49	–0.038	–0.36, 0.29		–0.018	–0.30, 0.26	
≥ 50	0.0042	–0.22, 0.23		0.0037	–0.22, 0.22	
Intestinal helminth infection (ref = No)	0.0040	–0.21, 0.21	0.97			
Village (ref = Diohine)	–0.083	–0.27, 0.11	0.39			
Season (ref = dry season)	0.45	0.29, 0.60	< 0.0001	0.43	0.28, 0.58	< 0.0001

*Each measure of *P. falciparum* parasite densities and *S. haematobium* egg load was considered and we related the egg load for schistosomiasis measured in March 2002 to the malaria parasite density in June, September, October, November 2002, January, April, and June 2003 and the one measured in September 2003 to the malaria parasite densities in September, October, and December 2003.) Variables with a *P* value < 0.20 in the univariate analysis were selected for multivariate analysis.

†Estimates from a linear mixed-effects model. A positive (respectively negative) significant coefficient indicates a positive (or negative) association between the tested factors and *P. falciparum* parasite densities.

one study to the other. Theoretically, the best way to avoid biases would be a two-arm randomized trial (treatment and control) aiming to suppress one of the two parasites while observing the variations in the other parasite's infection. To our knowledge, four such trials have been conducted. The first two involved children co-infected with *A. lumbricoides* and *P. falciparum* in Madagascar and found a negative interaction between the two parasites,[24,25] contrary to the third conducted in Nigeria that identified a synergistic association of *A. lumbricoides* with *P. falciparum*.[26] The fourth trial aiming to explore the influence of *A. lumbricoides*/hookworm on malaria in Indonesia is still ongoing.[19] Clinical trials are difficult to setup for the purpose of investigating parasitic coinfections, as they imply a long follow-up for a benefit that is not obvious and ethically questionable as it leads to a cure of helminths in only one half of the population.

A good alternative is observational studies that allow adjusting for confounding factors.

In this work, the intensity of infection caused by *S. haematobium* varied with age and was dependent on environmental factors such as, for example, the area of living. In addition to analyses adjusted on covariates, we took into account the statistical correlation between children of the same family and between measures of the same child by using a hierarchical model.

We found an association between a mild *S. haematobium* infection but not moderate or heavy egg counts, and parasite density to *P. falciparum*. We cannot exclude a lack of statistical power because children, who present the highest levels of *S. haematobium* infection, are also the oldest and thus are less infected with malaria. Moreover, to study the effect of age, we conducted a sensitivity analysis considering separate models for each age group (5–7 years; 8–10 years, and 11–13 years). We found significant results in the 5–7 years age group only (–0.59, 95% CI (–1.11; –0.06). Although the results were not significant in the 8–10 and 11–13 age group, we still found negative coefficients (–0.40, 95% CI [–0.95; 0.14]), (–0.35, 95% CI [–0.97; 0.27]). One explanation is that children > 8 years of age probably began to develop anti-malarial immunity, consequently reported *P. falciparum* densities were lower. All children were considered in our work and statistical analyses were adjusted on age to improve study power.

A second year of follow-up better established the *S. haematobium* infection status of the children, only checked once in the previous study,[7] and allowed to confirm its results on a higher number of plasmodial infections. However, there was discordance between the intensity of infection measured in 2002 and in 2003 for 16 children. Schistosomiasis is characterized by an inter-day and intra-day variation of excreted eggs with a peak observed during the hottest hours. In this study, we optimized the *S. haematobium* egg load assessment by collecting two urinary samples between 11 AM and 1 PM. The delay between the two measures was 18 months. We cannot exclude that these 16 children were misclassified. We therefore propose several hypotheses. If the differences correspond to classification mistakes, they were not differential because the filtrations were performed in a blinded manner. A treatment against schistosomiasis could have been given sporadically, however it is unlikely because these children were monitored. Finally, we also cannot exclude that these children had a modification of their immune response modification that reduced the egg load as a result of *S. haematobium*. We decided not to exclude these children from the analysis but we verified that they did not modify the relationship between the two parasites.

To control selection biases of children selected in our study, we compared their characteristics with those of children selected in the previous study. Except for sex, the characteristics were quite similar between the two groups of children.

The antagonistic interaction found in our study and in other studies is supported by physiopathological hypotheses.[9,22,27–30] As to the two antagonistic responses (Th1 and Th2) described in animals and humans, it has been established that the immune response caused by helminth infections is predominantly Th2, leading to a Th1 downregulation and to an exacerbation of Th2-dependent antibody response, which would accelerate the process of parasite clearance, and favor *P. falciparum* elimination with a better control of malaria parasite density.[22] A recent study on malaria–urinary schistosomiasis coinfection, conducted in Senegal, showed that children presenting moderate intensity of urinary schistosomiasis infection produced higher IgG1 and IgG3 responses to whole *P. falciparum* extracts than children not infected with urinary schistosomiasis.[18] Interestingly, IgG1 and IgG3 isotypes are known to be involved in the malaria protective immune response.

These studies and our results suggest the hypothesis that a low intensity of urinary schistosomiasis could improve protective anti-malarial immune response associated with the regulation of specific production of cytokines. However, high infection caused by schistosomiasis could lead to a strong cytokine production that could promote the occurrence of malaria attacks.

The results of these biological studies strengthen the hypotheses of antagonistic interaction between *S. haematobium* and *P. falciparum*, already put forward in epidemiological studies.

From a viewpoint of public health, these results could lead to be caution regarding the implementation of mass treatment against schistosomiasis in endemic areas in children. Supplementary studies should be conducted to measure the impact of mass treatment with Praziquantel on the occurrence of malaria and perhaps consider a systematic anti-malaria treatment at the same time of the anti-helminths treatment. Moreover, the results of this study will be important for the development of a malaria vaccine because we cannot exclude that helminths infection may interfere with vaccine response. In this context, anti- helminths treatment may need to be given before vaccination for children.

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