

Relative Contribution of Schistosomiasis and Malaria to Anemia in Western Kenya

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Abstract. Because anemia is one of the markers of morbidity associated with schistosomiasis, it has been proposed as a potential measure to evaluate the impact of control programs. However, anemia is also a common consequence of malaria, and schistosomiasis and malaria are often co-endemic. To estimate the attributable fraction of anemia due to *Schistosoma mansoni* and *Plasmodium falciparum* infections, we applied a log-binomial model to four studies measuring these parameters of a combined 5,849 children in western Kenya. In our studies, malaria contributed 23.3%, schistosomiasis contributed 6.6%, and co-infection contributed 27.6% of the anemia. We conclude that in areas where *S. mansoni* and *P. falciparum* are co-endemic, the contribution of schistosomiasis to anemia is masked by anemia resulting from malaria, thus limiting anemia as a useful measure for schistosomiasis control programs in these settings.

Schistosomiasis *mansoni* has been associated with subtle morbidities such as anemia, fatigue, malnutrition, and impaired cognitive development as well as more obvious morbidities, such as hepatosplenic disease. Anemia has been proposed as a marker for morbidity reduction in schistosomiasis control programs because it is one of the most easily quantified of the subtle morbidities and is affected by presence and intensity of schistosome infection.¹ However, in many areas where individuals are at risk for schistosomiasis, they are additionally at risk for malaria, which also causes anemia. Furthermore, in Africa, these diseases often overlap geographically. Thus, the effect of co-infection and the potential impact of interaction of schistosomiasis and malaria on anemia may affect the usefulness of anemia as a marker of schistosomiasis morbidity, though this phenomenon is not well understood.^{2–6}

We wished to evaluate the use of anemia prevalence as a morbidity outcome measure in schistosomiasis control programs in an area where malaria is co-endemic with schistosomiasis. To do so, we determined the fraction of anemia attributable to each infection and assessed whether having both schistosomiasis and malaria has a synergistic effect on anemia. Our results may provide a better evidence base for schistosomiasis, malaria, and anemia public health program planning and execution.

We evaluated the attributable fraction of anemia due to schistosomiasis in children in western Kenya, an area where malaria is endemic. For this analysis, four cross-sectional datasets containing measures of anemia, malaria, and schistosomiasis in children in western Kenya were combined.^{7–10} Each of the datasets was generated from studies that were reviewed and approved by the Scientific and Ethical Review Committees of the Kenya Medical Research Institute and at the U.S. Centers for Disease Control and Prevention (CDC) based either on formal reliance on KEMRI human subjects protections, or review by the CDC Institutional Review Board. Data were collected from 2006 to 2011 in children between the ages of 1 and 15. No systematic treatment of schistosomiasis had been implemented in this area before 2012, and a

single mass drug administration of mebendazole for soil-transmitted helminth control was implemented in 2009. Access to datasets was granted by co-investigators, and all datasets were already de-identified before incorporation into the analysis. The datasets are listed in Table 1.

We defined anemia as < 12 g/dL hemoglobin according to Kenyan national guidelines,¹¹ schistosomiasis as ≥ 1 egg seen in any stool sample, and malaria as ≥ 1 parasite seen in any blood smear. We used the World Health Organization guidelines for schistosome infection intensity: 1–99 eggs per gram (epg) is low, 100–400 epg is moderate, and > 400 epg is high.¹²

A log-binomial model was used to estimate the attributable fraction of anemia due to schistosomiasis.¹³ The outcome of anemia was modeled with the presence of schistosomiasis, presence of malaria, and potential confounders (gender, age, season, and body mass index). We also added a schistosomiasis by malaria interaction term to assess how the attributable fraction of anemia due to schistosomiasis varied by malaria status. The calculation of attributable fraction was conducted using Bruzzi et al.'s approach, which consists of 1) calculating an odds ratio (OR) point estimate from a logistic model for the exposure, schistosomiasis, and 2) using that value in the following equation:

$$1 - \left(\frac{1}{N} \times \left[\frac{N_{\text{exp}}}{\text{OR}} + \{N - N_{\text{exp}}\} \right] \right)$$

where N is the total number of people with the disease of interest (anemia), N_{exp} is the number of people with the disease who have the exposure of interest (schistosomiasis), and OR is the previously calculated adjusted odds ratio point estimate from the logistic regression model for the exposure.¹⁴ Whether the attributable fraction of anemia by schistosomiasis varied with malaria status was determined by testing the statistical significance of the interaction variable.¹⁴ We controlled for study by including a categorical study variable in the regression model. Generalized estimating equations were used to control for clustering at the school level.¹⁵

There were 2,461 (42.1%) children with anemia in our combined dataset. The log-binomial model indicated that although schistosomiasis and malaria both contribute to anemia separately, they also contribute to anemia through an

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TABLE 1
Datasets combined for the analysis of attributable fraction of anemia from schistosomiasis and malaria

	Date of study	N	Age range (years)	Study type	Reference
1	June 2006, May 2007	2,745	9–12	School based	7
2	September–December 2007	484	1–15	Community	8
3	February–April 2011	822	7–8	School based	9
4	October 2010–April 2011	1,798	8–12	School based	10

interaction effect. In children without schistosomiasis, the prevalence of anemia was 1.72 (95% confidence interval [CI]: 1.47–2.00; $P \leq 0.001$) times higher in those with malaria than in those without malaria. In children without malaria, the prevalence of anemia was 1.43 (95% CI: 1.16–1.78; $P \leq 0.001$) times higher in those with schistosomiasis than in those without schistosomiasis. In addition, we see that there is an interactive effect of these two infections on anemia. In children with *S. mansoni* infection, the prevalence of anemia in children with malaria was 1.98 (95% CI: 1.57–2.05) times higher than in those without malaria ($P < 0.0001$). In contrast, there was no effect of schistosomiasis on the anemia of children with malaria. In addition, the attributable fraction of anemia from each of these diseases differs considerably. Using Bruzzi et al.'s equations, we found that the attributable fraction of anemia due to malaria is 23.3% (95% CI: 17.8–28.0%), due to schistosomiasis is 6.6% (95% CI: 3.0–9.6%), and due to the interaction of the two diseases is 27.6% (95% CI: 20.3–28.6%).¹⁴

These results suggest that the effect of malaria on anemia may limit the utility of anemia as a measure of schistosomiasis program impact in populations where co-infection is common. The interaction effect found here exemplifies the importance of taking a broad view when assessing public health problems, as infection with more than one pathogen may lead to worse outcomes than might be expected with single infections. However, there are some limitations in the methods used here. Although research is beginning to suggest that anemia due to *S. mansoni* infection results from inflammation,⁷ the biological mechanism that causes the massive cyclical intravascular hemolysis of malaria-associated anemia is not fully understood.¹⁶ This lack of understanding in biological mechanisms prohibits a more granular, directed study of the interaction seen here. In addition, information about other known causes of anemia that may influence these results, such as inadequate nutrition, bacterial or hookworm infection, and presence of sickle cell disease, was not available for inclusion in the analysis.^{17,18} Lastly, these studies were all conducted in western Kenya, near Lake Victoria, so these results may not be generalizable to different locations where co-infection is possible and other species of schistosome are prevalent. Further investigation with other co-morbidities and in other geographic settings is thus required before adopting anemia as a universal marker for progress in programs relating to schistosomiasis.

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