Schistosoma haematobium Infection and Morbidity Before and After Large-Scale Administration of Praziquantel in Burkina Faso

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(See the editorial commentary by King, on pages 653–5.)

Background. In sub-Saharan Africa, 112 million people are infected with *Schistosoma haematobium*, with the most intense infections in children 5–15 years old.

Methods. We describe a longitudinal epidemiological study that evaluates the relationship between *S. haematobium* infection and associated morbidity in children before and after the large-scale administration of praziquantel for schistosomiasis and albendazole for soil-transmitted helminths.

Results. At baseline, higher intensities of *S. haematobium* infection were observed in children with anemia and/or severe microhematuria, but there was no apparent association between the risk of undernutrition and intensity of *S. haematobium* infection. Significant reductions in the prevalence and intensity of *S. haematobium* infection 1 year after treatment were, however, observed. Children who benefited the most from anthelmintic treatment in terms of increased hemoglobin concentrations were those who had anemia at baseline and those with highly positive microhematuria scores at baseline.

Conclusions. This study suggests that even a single round of mass chemotherapy can have a substantial impact on *S. haematobium* infection and its associated morbidity in children.

Improving the health of school-aged children, particularly in developing countries, has emerged as a policy priority in international health [1, 2]. Over the past 2 decades, significant progress has been made in improving child survival, resulting in more children reaching primary school age. However, human infections with 1 of the 5 parasitic helminths of the family Schis-

tosomatidae still represent a significant segment of the global burden of illness, with ~200 million people infected and with the highest intensities in children 5–15 years old [3]. Schistosomiasis causes granuloma formation and both reversible and irreversible damage to the urinary and intestinal tracts [4]. Furthermore, new estimates of schistosomiasis-related disability have indicated the need to reassess priorities for treating this chronic infection in areas where it is endemic [5].

Praziquantel has been established in several controlled trials as a safe and effective drug for the treatment of infection with all human schistosome species [6–9]. The dramatic reduction in its price since 1990—by >90%, from US$4 to treat a person to approximately US$0.30—has led to the resolution of many of the challenges surrounding large-scale chemotherapy campaigns [10]; recently, through the Schistosomiasis Control Initiative (SCI), >20 million treatments were administered in 2005–2006 in 6 sub-Saharan African countries [11, 12]. One of the primary objectives of

Table 1. Baseline characteristics of Burkinabé schoolchildren who were followed up for 1 year or dropped out.

Characteristic	Followed up for 1 year	Dropped out	P
Demographic			
Age, mean, years	9.8 (n = 1131)	11.3 (n = 686)	<.001
Male sex, %	55.0 (n = 1131)	62.0 (n = 686)	.004
Parasitologic			
Infected with *Schistosoma haematobium*, %	53.9 (n = 1124)	54.1 (n = 690)	.953
Infected with *S. mansoni*, %	6.2 (n = 536)	5.8 (n = 432)	.810
Infected with hookworm, %	6.3 (n = 556)	4.3 (n = 418)	.174
S. haematobium intensity, mean (SD), eggs/10 mL	83.6 (229.2)	94.2 (234.6)	.728
S. mansoni intensity, mean (SD), epg	8.0 (73.9)	11.3 (76.1)	.869
Hookworm intensity, mean (SD), epg	12.5 (90.7)	3.3 (21.0)	.158
Hematologic			
Anemia, %	65.8 (n = 1130)	66.4 (n = 687)	.390
Hemoglobin concentration, mean (SD), g/dL	11.0 (1.4)	11.1 (1.4)	.036
Nutritional status			
Wasted, %	32.8 (n = 1131)	100.0 (n = 686)	<.001
Stunted, %	13.3 (n = 1131)	100.0 (n = 686)	<.001
Hemastix test	(n = 1124)	(n = 692)	.460
Negative, %	50.4	53.5	
Trace, %	12.9	10.7	
+, %	6.8	5.6	
++, %	9.3	8.9	
+++, %	20.6	21.4	

NOTE. Anemia was defined (according to World Health Organization guidelines) as a hemoglobin concentration <11.5 g/dL for children 5–11 years old and <12.0 g/dL for children 12–14 years old. Wasting denotes reduced body weight for height, defined as a body-mass-index z score less than -2. Stunted denotes reduced body length in relation to a reference standard, defined as a height-for-age z score less than -2. +, weakly positive; ++, moderately positive; +++, highly positive; epg, eggs per gram of feces.

these SCI-supported control programs is to achieve, and hence also to demonstrate, a quantifiable reduction in schistosome-associated morbidity as a consequence of chemotherapeutic intervention.

The aim of the present study was to evaluate the relationship between *Schistosoma haematobium* infection and associated morbidity in children before and after the large-scale administration of praziquantel and albendazole (against soil-transmitted helminths) by the national Burkinabé helminth control program. A secondary aim was to identify those individuals whom one may predict to show the greatest improvements in nutritional status and hemoglobin (Hb) concentrations after chemotherapy.

SUBJECTS AND METHODS

Control program, study sites, sampling, and cohort design. Both *Schistosoma mansoni* and *S. haematobium* are endemic throughout Burkina Faso [13]. The SCI-supported schistosomiasis control program was implemented during 2004 and had treated 3,322,564 school-aged children in the 13 regions of the country through October 2006. Further details about the na-

tional Burkinabé helminth control program have been described elsewhere [14].

For the present study, parasitological and morbidity data were collected from a cohort of 1727 Burkinabé children 6–14 years old, randomly sampled from 16 schools before and 1 year after chemotherapy (2004 and 2005, respectively). The schools included in these surveys were randomly selected from all schools in 4 Regional Health Directorates known a priori to be places where schistosomiasis is highly endemic. Details concerning sample-size calculations and cohort design have been described elsewhere [15, 16].

Parasitological and morbidity measures. All children enrolled in the study were interviewed by appropriately trained personnel at the Ministry of Health, Burkina Faso. Ethical clearance was obtained from the Ministry of Health and Imperial College London.

Stool examination. A single stool sample was collected from each child, and 41.7 mg was processed to make duplicate Kato-Katz slides for microscopic determination of intestinal helminth infection. Individual egg output was expressed as eggs

Table 2. Health characteristics of children successfully followed up for 1 year (2004–2005), at baseline and after treatment.

Characteristic	2004	2005
Parasitologic		
Infected with *Schistosoma haematobium,* % (*n* = 1124)	53.91 (51.00–56.83)	5.78 (4.42–7.15)
Infected with *S. mansoni,* % (*n* = 536)	6.16 (4.12–8.19)	0.19 (0.00–0.55)
Infected with hookworm, % (*n* = 555)	6.31 (4.28–8.33)	1.62 (0.57–2.67)
S. haematobium intensity, mean, eggs/10 mL	83.55 (70.14–96.96)	0.94 (0.35–1.53)
S. mansoni intensity, mean, epg	8.04 (1.77–14.31)	0.02 (0.00–0.07)
Hookworm intensity, mean, epg	12.47 (4.92–20.03)	0.78 (0.22–1.34)
Hematologic (*n* = 1131)		
Hemoglobin concentration, mean, g/dL	10.97 (10.88–11.05)	11.25 (11.18–11.32)
Anemia	65.75 (62.99–68.52)	61.59 (58.76–64.43)
Microhematuria as diagnosed by Hemastix test (*n* = 1124)		
Negative, %	50.44 (47.52–53.37)	89.50 (87.71–91.29)
Trace, %	12.90 (10.94–14.86)	4.89 (3.63–6.15)
+, %	6.76 (5.29–8.23)	2.31 (1.43–3.19)
++, %	9.34 (7.64–11.04)	1.07 (0.47–1.67)
+++, %	20.55 (18.19–22.91)	2.22 (1.36–3.09)
Nutritional status (*n* = 1131)		
Thinness or wasting, %	32.80 (30.07–35.54)	35.10 (32.32–37.88)
Shortness or stunting, %	13.26 (11.29–15.24)	11.85 (9.96–13.73)

NOTE. Data are means or proportions (95% confidence interval) of children with characteristic, unless otherwise indicated. Sample sizes are provided in parentheses for each examined outcome in the left-hand column. Anemia was defined (according to World Health Organization guidelines) as a hemoglobin concentration <11.5 g/dL for children 5–11 years old and <12.0 g/dL for children 12–14 years old. Wasting denotes reduced body weight for height, defined as a body-mass-index *z* score less than −2. Stunted denotes reduced body length in relation to a reference standard, defined as a height-for-age *z* score less than −2. +, weakly positive; ++, moderately positive; +++, highly positive; epg, eggs per gram of feces.

per gram of feces, calculated as the arithmetic mean of the 2 individual slide counts whenever these were available.

Urine examination. One urine specimen was collected from each child to determine the prevalence and intensity of *S. haematobium* infection by the filtration method. The intensity of *S. haematobium* infection was expressed as the number of eggs per 10 mL of urine. To determine the presence and severity of microhematuria, all urine specimens were tested for presence of detectable blood using urine reagent strips (Bayer Hemastix). The results were recorded semiquantitatively: negative, trace hemolyzed, weakly positive (+), moderately positive (++), and highly positive (+++).

Nutritional assessment. Heights and weights were measured to determine height-for-age *z* scores (HAZ) and body-mass-index *z* scores (BMIZ). All measures were obtained using height poles and electronic balances in the morning, and children were barefoot, wearing only light indoor clothing. A low BMIZ is the index of choice for the assessment of recent undernutrition resulting in thinness or wasting, whereas a low HAZ represents long-term growth and nutritional status resulting in shortness or stunting [17, 18]. *z* scores for each

nutritional index were calculated from Centre for Disease Control (National Center for Health Statistics; year 2000) reference values using EpiInfo (version 2000; US Centers for Disease Control and Prevention) [19].

Anemia assessment. Blood samples for Hb concentrations were obtained from each individual by the fingerprick method using a photometer (Hemocue) [20]. Anemia was defined according to World Health Organization (WHO) guidelines [21].

Statistical analyses. Differences between dropouts and children successfully followed up were tested by univariate analysis using a Wilcoxon 2-sample test for means and a χ^2 test or Fisher's exact test if there was a small value for proportions. SAS software was used (version 8; SAS Institute).

Hierarchical models are often applicable to modeling data from complex surveys of a population, with a hierarchical structure used to explain relations between individual and supraindividual determinants. A 2-level linear hierarchical model assuming normally distributed errors was fitted to the logarithmically transformed baseline *S. haematobium* egg counts ($\ln [\chi + 1]$), using Gibbs sampling for all parameters [22] to quantify any associations with anemia, measures of nutritional

Table 3. Estimates from 2-level hierarchical model for *Schistosoma haematobium* egg counts among 1130 Burkinabé schoolchildren at baseline and after treatment (2004–2005).

Model	Coefficient (95% CI)	P
Fixed effects		
Effect of year 1 follow-up relative to baseline	−52% (−57% to −47%)	<.001
Male sex (reference category: female)	11% (2% to 21%)	.020
Baseline age (reference category: 14 years)		
13 years	9% (−19% to 45%)	.572
12 years	45% (11% to 90%)	.007
11 years	25% (−4% to 63%)	.095
10 years	32% (2% to 72%)	.035
9 years	24% (−4% to 61%)	.106
8 years	22% (−6% to 59%)	.143
7 years	2% (−24% to 37%)	.906
6 years	19% (−27% to 92%)	.488
Baseline anemia (reference category: not anemic)	11% (1% to 21%)	.026
Baseline hematuria (reference category: negative)		
Trace	242% (191% to 302%)	<.001
+	462% (357% to 592%)	<.001
++	1470% (1176% to 1833%)	<.001
+++	4107% (3493% to 4827%)	<.001
Baseline thinness or wasting (reference category: not wasted)	4% (−6% to 14%)	.463
Baseline shortness or stunting (reference category: not stunted)	−13% (−26% to 2%)	.089
	Variance components (SE)	
Random effects		
Level 2 variance (between schools)	0.008 (0.004)	
Level 1 variance (measurement occasions within a child)	0.190 (0.006)	

NOTE. Anemia was defined (according to World Health Organization guidelines) as a hemoglobin concentration <11.5 g/dL for children 5–11 years old and <12.0 g/dL for children 12–14 years old. Wasting denotes reduced body weight for height, defined as a body–mass-index z score less than −2. Stunting denotes reduced body length in relation to a reference standard, defined as a height-for-age z score less than −2. +, weakly positive; ++, moderately positive; +++, highly positive; CI, confidence interval.

status, and microhematuria while adjusting at the same time for demographic factors such as age and sex. In this way, we tested whether children with pathology potentially induced by *S. haematobium* infection had higher *S. haematobium* egg counts before treatment. We used a similar model to quantify changes in *S. haematobium* egg counts from baseline to 1 year of follow-up. Mlwin software (version 2.01; Multilevel Models Project, Institute of Education, University of London) was used. Box plots of the *S. haematobium* egg counts at baseline were used for validation and comparison of the significant findings from the model described above.

Changes in Hb concentration and in HAZ and BMIZ scores over time were evaluated using 2-level linear hierarchical models of raw change scores between baseline and the 1-year follow-up time point. With this approach, we aimed to compare the average change in each of the studied outcomes over the studied period between different groups of children. All of the models presented were also adjusted for age and sex. $P < .05$ was considered to be significant.

An additional 3-level hierarchical linear modeling analysis was performed to determine any change in the children's Hb concentrations. With this model, we aimed to quantify the adjusted overall change in Hb concentration from baseline to follow-up and to quantify average Hb concentrations of different groups of children at baseline as well as to examine whether the intensity of *S. haematobium* infection was associated with lower Hb concentrations. Logistic random-intercepts regression models were fitted to examine whether the intensity of *S. haematobium* infection was associated with an increased risk of thinness and shortness at baseline while adjusting for potential confounders.

RESULTS

A total of 1727 children from 16 schools were recruited at baseline. Of these, 1131 (65%) were successfully retraced at the 1-year follow-up time point, and 321 new children were recruited into the cohort during the second year of the study
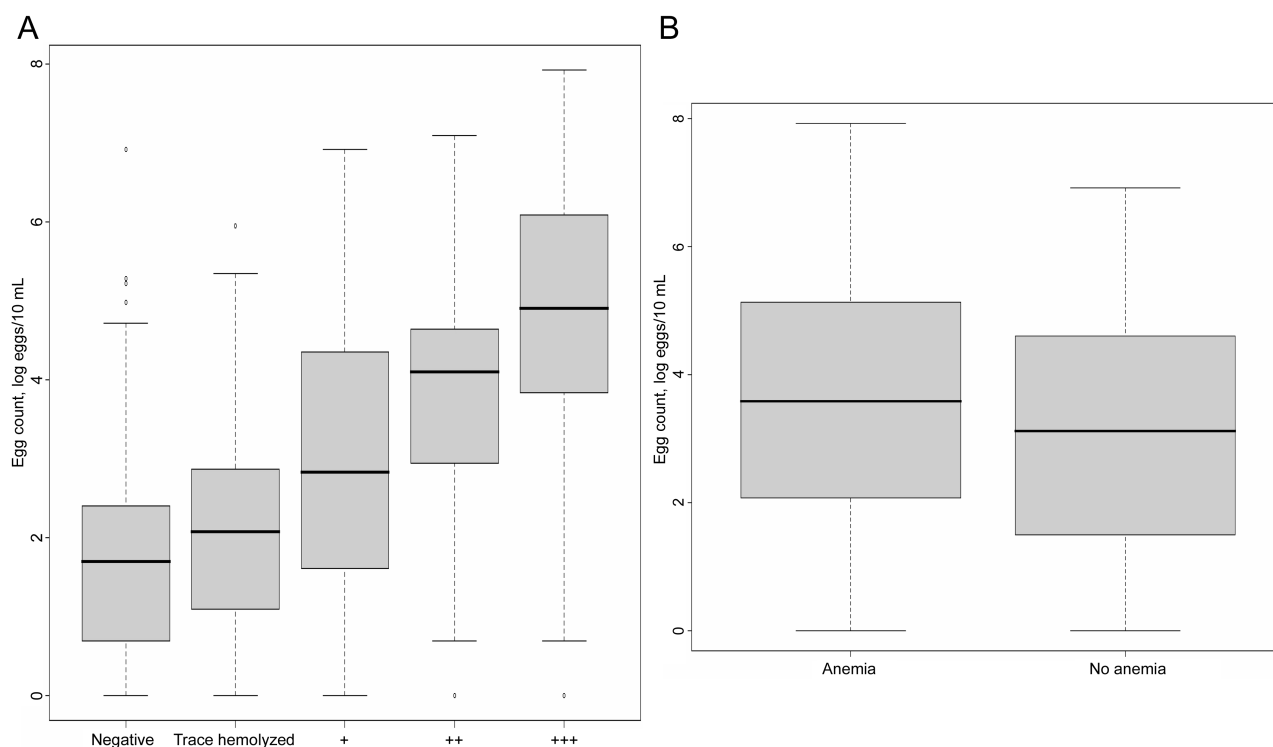
Figure 1. Box plots for the logarithmically transformed (base *e*) *Schistosoma haematobium* egg counts of positive subjects only (*n* = 613 Burkinabé schoolchildren, 2004). *A,* Box plot for log *S. haematobium* egg counts with respect to different microhematuria test scores at baseline. *B,* Box plots for log *S. haematobium* egg counts with respect to anemia status at baseline. Data are smallest observations, lower quartiles (Q1), medians, upper quartiles (Q3), and largest observations. +, weakly positive; ++, moderately positive; +++, highly positive.

(data not shown). There were significant differences between the children who were successfully followed up and the dropouts, according to their demographic characteristics and nutritional status as defined by baseline thinness and shortness as well as by baseline Hb concentrations (table 1). The children who dropped out were of an older mean age than those successfully followed up, and boys proved more difficult to recruit into the cohort during the second year of the study. All children who dropped out were wasted and stunted at baseline and had slightly higher mean Hb concentrations. No other baseline characteristic measured varied significantly between children followed up and those who dropped out.

Table 2 presents the health indicators of children surveyed at baseline and successfully followed up 1 year after treatment. During the 12 months between examinations, the overall prevalences of *S. haematobium, S. mansoni,* and hookworm infections decreased significantly (*P* < .001). For both years examined, *Ascaris lumbricoides* infection was absent, and the prevalence of *Trichuris trichura* infection was estimated to be 1.1% at baseline and totally absent 1 year later. Because prevalences and coinfections with *S. haematobium* were so low for the intestinal helminth species at both time points, such data were not analyzed further here.

A significant increase in mean Hb concentration (*P* < .001)

and a significant decrease in the prevalence of anemia (*P* = .021) were also observed between 2004 and 2005. Finally, the unadjusted observed changes in both recent and chronic undernutrition from baseline to follow-up were not significant (*P* = .135 and *P* = .093, respectively).

Table 3 presents the results of the model of the change in *S. haematobium* egg counts for 1 year after treatment as well as differences in *S. haematobium* egg counts between different groups of children at baseline. This model indicated that, compared with baseline counts, there was on average an overall significant decrease in *S. haematobium* egg counts by 52% 1 year after treatment (*P* < .001). At baseline, only children 10 and 12 years old had significantly higher *S. haematobium* egg counts, compared with those who were 14 years old (*P* = .035 and *P* = .007, respectively) after controlling for sex, nutritional and anemia status, and microhematuria test scores. Children with +++, ++, +, and trace microhematuria scores had on average significantly higher *S. haematobium* egg counts than those of children with negative scores at baseline, by 4107%, 1470%, 462%, and 242%, respectively. Additionally, children with anemia at baseline had significantly higher *S. haematobium* egg counts (by 11%) than children without anemia (*P* = .026). Boys also had significantly higher *S. haematobium* egg counts (by 11%) than girls at baseline (*P* = .020).

Figure 1*A* shows that children with the most severe microhematuria scores harbored higher intensities of *S. haematobium* infection than children who were negative for microhematuria at baseline. Children with anemia at baseline also harbored slightly higher intensities of *S. haematobium* infection than those without anemia (figure 1*B*).

Results from the 2-level logistic regression model for the probability of being wasted did not suggest associations with any baseline characteristics examined other than age. In particular, there was a trend toward younger children being less likely to be wasted, although none of the other odds ratios (ORs), except for those for 10-year-old children, were significantly different from the ORs for 14-year-old children ($P = .022$). Furthermore, the 2-level logistic regression model of the probability of being stunted at baseline suggested a trend toward younger children being less likely to be stunted; the OR for 6–12-year-old children was significantly different from that for 14-year-olds. In addition, children with anemia were almost 1.5 times more likely than those without anemia to be stunted at baseline ($P = .034$; data not shown).

Table 4 contains estimates from the two 2-level linear multilevel models for changes in HAZ and BMIZ during the period studied. The effect for the 14-year-old comparison group was a decrease in BMIZ of 0.519 units, which was of borderline significance ($P = .053$). This suggests that there was no dramatic change over the period studied in this group. However, children who were 7, 8, and 10 years old at baseline had a greater decrease in BMIZ, compared with 14-year-olds. The coefficients of the continuous variables that refer to the baseline HAZ and BMIZ scores indicated that BMIZ increased for wasted children, whereas, BMIZ decreased for stunted children more than that of children with no nutritional problems. These results can be obtained if one multiplies the coefficients of HAZ and BMIZ by -2 (i.e., the cutoff score that defines wasting and stunting, respectively).

The effect for the 14-year-old comparison group was a non-

Table 4. Estimates from 2-level hierarchical model for the change of body-mass-index *z* score (BMIZ) and height-for-age *z* score (HAZ) ($n = 1130$).

Model	Coefficient (95% CI) for change in BMIZ	*P*	Coefficient (95% CI) for change in HAZ	*P*
Fixed effects				
Intercept	−0.519 (−1.003 to −0.035)	.053	0.143 (−0.073 to 0.359)	.214
Baseline intensity of *Schistosoma haematobium* infection (reference category: uninfected)				
Lightly infected	0.060 (−0.133 to 0.253)	.543	0.032 (−0.059 to 0.124)	.490
Heavily infected	0.218 (−0.030 to 0.465)	.085	0.078 (−0.040 to 0.196)	.193
Male sex (reference category: female)	0.011 (−0.100 to 0.122)	.850	−0.066 (−0.119 to −0.013)	.015
Baseline age (reference category: 14 years old)				
13 years	−0.120 (−0.649 to 0.410)	.658	−0.134 (−0.388 to 0.119)	.300
12 years	−0.375 (−0.816 to 0.067)	.097	−0.236 (−0.447 to −0.025)	.029
11 years	−0.396 (−0.835 to 0.043)	.077	−0.177 (−0.386 to 0.033)	.099
10 years	−0.483 (−0.915 to −0.051)	.029	−0.008 (−0.215 to 0.198)	.936
9 years	−0.347 (−0.778 to −0.084)	.115	0.000 (−0.206 to 0.206))	.999
8 years	−0.448 (−0.879 to −0.017)	.042	0.051 (−0.155 to 0.257)	.625
7 years	−0.642 (−1.083 to −0.201)	.004	−0.033 (−0.244 to 0.178)	.757
6 years	−0.483 (−1.051 to 0.085)	.096	0.428 (0.157 to 0.699)	.002
Baseline anemia (reference category: not anemic)	0.005 (−0.114 to 0.123)	.939	−0.041 (−0.098 to 0.015)	.153
Baseline hematuria (reference category: negative)				
Trace	−0.166 (−0.389 to 0.057)	.144	−0.063 (−0.169 to 0.043)	.243
+	−0.147 (−0.416 to 0.123)	.286	−0.014 (−0.142 to 0.114)	.829
++	0.054 (−0.208 to 0.317)	.685	−0.027 (−0.152 to 0.097)	.669
+++	−0.110 (−0.356 to 0.136)	.383	−0.058 (−0.174 to 0.059)	.334
Baseline BMIZ	−0.588 (−0.628 to −0.548)	<.001	0.054 (0.035 to 0.073)	<.001
Baseline HAZ	0.184 (0.135 to 0.232)	<.001	−0.138 (−0.161 to −0.115)	<.001
	Variance components (SE)			
Random effects				
Level 2 variance (between schools)	0.155 (0.065)		0.009 (0.004)	
Level 1 variance (between children within a school)	0.846 (0.036)		0.194 (0.008)	

NOTE. Anemia was defined (according to World Health Organization guidelines) as a hemoglobin concentration <11.5 g/dL for children 5–11 years old and <12.0 g/dL for children 12–14 years old. +, weakly positive; ++, moderately positive; +++, highly positive; CI, confidence interval.

significant ($P = .214$) increase in HAZ of 0.143 units. Compared with 14-year-olds, 6-year-olds had a significantly greater increase, whereas the 12-year-olds had a decrease in HAZ (significantly different from that of 14-year-olds). Boys had a significantly smaller increase in HAZ than girls. Likelihood ratio tests indicated a better fit in both models mentioned above when we included HAZ and BMIZ as explanatory continuous variables and not the relevant categorical ones that would denote wasting and stunting if HAZ or BMIZ was, respectively, less than −2 SD.

Table 5 contains the estimates of two 3-level hierarchical models for Hb concentrations before and after chemothera-peutic treatment, taking into account adjustment and nonadjustment for microhematuria scores. From the former model it was estimated that an overall increase of 0.092 g/dL in Hb concentration after treatment was not significant ($P = .146$). Children with +++ microhematuria scores had significantly lower Hb concentrations (0.318 g/dL; $P = .016$) than micro-hematuria-negative children at baseline. Children who were 6, 7, 8, and 10 years old at baseline had significantly lower Hb concentrations ($P = .024$, $P < .001$, $P = .019$, and $P = .008$, respectively) than those who were 14 years old, after controlling for intensity of *S. haematobium* infection, sex, hematuria, wasting, and thinness. From the alternative model, which did not

Table 5. Estimates from 3-level hierarchical models for hemoglobin concentration before and after treatment, taking into account adjustment and nonadjustment for microhematuria scores ($n = 1124$).

Model	Coefficient (95% CI) with adjustment for microhematuria	P	Coefficient (95% CI) without adjustment for microhematuria	P
Fixed effects				
Intercept	11.473 (11.067 to 11.879)	<.001	11.480 (11.074 to 11.886)	<.001
Effect of year 1 follow-up relative to baseline	0.092 (−0.031 to 0.215)	.146	0.093 (−0.030 to 0.216)	.139
Baseline intensity of *Schistosoma haematobium* infection (reference category: uninfected)				
Lightly infected	−0.107 (−0.311 to 0.097)	.303	−0.079 (−0.238 to 0.080)	.332
Heavily infected	−0.084 (−0.354 to 0.186)	.542	−0.220 (−0.410 to −0.030)	.024
Male sex (reference category: female)	−0.035 (−0.158 to 0.088)	.577	−0.039 (−0.162 to 0.084)	.538
Baseline age (reference category: 14 years old)				
13 years	−0.026 (−0.383 to 0.331)	.888	−0.037 (−0.396 to 0.322)	.838
12 years	−0.136 (−0.489 to 0.217)	.452	−0.138 (−0.493 to 0.217)	.445
11 years	−0.334 (−0.683 to 0.015)	.061	−0.353 (−0.704 to −0.002)	.048
10 years	−0.468 (−0.813 to −0.123)	.008	−0.471 (−0.818 to −0.124)	.008
9 years	−0.296 (−0.643 to 0.051)	.095	−0.290 (−0.639 to 0.059)	.103
8 years	−0.425 (−0.780 to −0.070)	.019	−0.415 (−0.772 to −0.058)	.022
7 years	−0.817 (−1.205 to −0.429)	<.001	−0.816 (−1.206 to −0.426)	<.001
6 years	−0.693 (−1.297 to −0.089)	.024	−0.685 (−1.289 to −0.081)	.026
Baseline hematuria (reference category: negative)				
Trace	0.108 (−0.115 to 0.331)	.344		
+	0.135 (−0.149 to 0.419)	.352		
++	0.229 (−0.063 to 0.521)	.124		
+++	−0.318 (−0.577 to −0.059)	.016		
Baseline thinness or wasting (reference category: not wasted)	−0.042 (−0.162 to 0.078)	.488	−0.042 (−0.162 to 0.078)	.491
Baseline shortness or stunting (reference category: not stunted)	−0.149 (−0.351 to 0.053)	.148	−0.155 (−0.359 to 0.049)	.135
	Variance components (SE) from the model with adjustment for microhematuria		Variance components (SE) from the model without adjustment for microhematuria	
Random effects				
Level 3 variance (between schools)	0.136 (0.056)		0.140 (0.057)	
Level 2 variance (between children within a school)	0.514 (0.051)		0.519 (0.051)	
Level 1 variance (measurement occasions within a child)	1.106 (0.047)		1.116 (0.047)	

NOTE. Wasting denotes reduced body weight for height, defined as a body-mass-index z score less than −2. Stunting denotes reduced body length in relation to a reference standard, defined as a height-for-age z score less than −2. +, weakly positive; ++, moderately positive; +++, highly positive; CI, confidence interval.

adjust for microhematuria scores, estimates of the parameters mentioned previously remained approximately the same, but the effect of *S. haematobium* infection intensity became significant, such that children who were heavily infected with *S. haematobium* at baseline had significantly lower Hb concentrations (0.220 g/dL; $P = .024$) than uninfected children. This suggests that because the variable of microhematuria scores is related to both Hb concentration and the intensity of *S. haematobium* infection, 2 different causal effects of *S. haematobium* infection on Hb concentrations are indicated. Two-way interaction terms were also tested, but because they were not significant, they were omitted from the models presented. Also, variances in all 3 levels of the second model were higher than the corresponding ones in the first model, which implies that

the microhematuria scores explain some of the variability in the studied outcome across all 3 levels of the models presented.

Finally, table 6 contains estimates from the 2-level linear multilevel model for the change in Hb concentration over the course of the period studied. This model suggested that the change varied significantly as a function of the following baseline characteristics: anemic status, +++ microhematuria score, and age. The effect for the comparison group (baseline uninfected, male, 14 years old, not anemic, negative microhematuria score, not wasted, and not stunted) was a decrease in Hb concentration of 0.128 g/dL, which was not significant ($P = .747$). Significant increases in Hb concentration during the period studied were observed among children with anemia at baseline (increase by 1.360 g/dL [that is, 1.488–0.128 g/dL]; $P < .001$)

Table 6. Estimates from a 2-level hierarchical model for changes in hemoglobin concentration ($n = 1130$).

Model	Coefficient (95% CI)	P
Fixed effects		
Intercept	−0.128 (−0.888 to 0.633)	.747
Baseline intensity of *Schistosoma haematobium* infection (reference category: uninfected)		
Lightly infected	−0.081 (−0.350 to 0.187)	.553
Heavily infected	−0.258 (−0.602 to 0.086)	.141
Male sex (reference category: female)	0.050 (−0.105 to 0.205)	.529
Baseline age (reference category: 14 years old)		
13 years	−0.625 (−1.364 to 0.114)	.097
12 years	−0.605 (−1.222 to 0.013)	.055
11 years	−0.435 (−1.049 to 0.179)	.165
10 years	−0.464 (−1.067 to 0.140)	.132
9 years	−0.719 (−1.321 to −0.117)	.019
8 years	−0.284 (−0.886 to 0.318)	.355
7 years	−0.139 (−0.753 to 0.475)	.657
6 years	−0.788 (−1.575 to −0.002)	.050
Baseline anemia (reference category: not anemic)	1.488 (1.323 to 1.653)	<.001
Baseline hematuria (reference category: negative)		
Trace	0.106 (−0.204 to 0.415)	.504
+	−0.029 (−0.404 to 0.345)	.878
++	0.010 (−0.354 to 0.375)	.955
+++	0.361 (0.019 to 0.702)	.039
Baseline thinness or wasting (reference category: not wasted)	−0.057 (−0.226 to 0.112)	.506
Baseline shortness or stunting (reference category: not stunted)	0.004 (−0.225 to 0.234)	.971
	Variance components (SE)	
Random effects		
Level 2 variance (between schools)	0.123 (0.062)	
Level 1 variance (between children within a school)	1.647 (0.070)	

NOTE. Anemia was defined (according to World Health Organization guidelines) as a hemoglobin concentration <11.5 g/dL for children 5–11 years old and <12.0 g/dL for children 12–14 years old. Wasting denotes reduced body weight for height, defined as a body-mass-index *z* score less than −2. Stunting denotes reduced body length in relation to a reference standard, defined as a height-for-age *z* score less than −2. +, weakly positive; ++, moderately positive; +++, highly positive; CI, confidence interval.

and among children with +++ microhematuria scores at baseline (increase by 0.233 g/dL [that is, 0.361–0.128 g/dL]; $P = .039$). Marginally significant decreases in Hb concentration during the same period were observed in children who were 12 years old at baseline; these children had a greater decrease, by 0.733 g/dL (that is, $-0.605–0.128$ g/dL; $P = .055$), in Hb concentration than 14-year-old children. In addition, 9-year-old children had a significantly greater decrease in Hb concentration, by 0.847 g/dL (that is, $-0.719–0.128$ g/dL; $P = .019$).

DISCUSSION

Among the different schistosomes infecting humans, *S. haematobium* is responsible for the largest number of infections. It has been estimated that, in sub-Saharan Africa, 112 million people are infected with *S. haematobium,* compared with 54 million infected with *S. mansoni* [23]. However, *S. haematobium* remains largely unstudied, particularly in comparison to *S. mansoni,* primarily because of the more demanding conditions for its laboratory maintenance. This is also reflected in the paucity of research examining the potential effectiveness of praziquantel against *S. haematobium* under various experimental and clinical circumstances [24]. To our knowledge, the present study represents the first longitudinal study in Africa that reports on the relationship between *S. haematobium* infection and its associated morbidity as a whole, by use of a uniquely detailed large data set from 16 randomly selected schools across the entire national territory of Burkina Faso. Moreover, these data have the potential to provide important evidence characterizing urinary schistosomiasis-associated morbidity, particularly in a population such as that of Burkinabé, where the prevalence of hookworms and other soil-transmitted helminthiasis is estimated to be very low. Although previous studies have tended to focus on the impact of large-scale control programs on intense transmission of *S. haematobium* infection with regard to Hb concentrations and anemia only (Tohon Z, Boubacar Mainassara H, Elhaj Mahamane A, et al., submitted) [25], to parasitological measures only [26, 27], or to *S. haematobium* morbidity indicators before and after treatment [28], the present study examined all these issues together and also adjusted for potential differences in demographic characteristics as well as potential confounders.

We have demonstrated that children with anemia or children with more severe microhematuria scores at baseline had higher *S. haematobium* infection intensities (table 3 and figure 1), which suggests that heavy intensities of *S. haematobium* infection can be associated with anemia and hematuria. We also provide evidence that heavy infections of urinary schistosomiasis are associated with lower Hb concentrations and, as a consequence, with potential anemia, given that the models in table 5 indicate that *S. haematobium* infection might be associated with anemia in 2 different ways. More precisely, he-maturia—which, as demonstrated previously (Tohon Z, Boubacar Mainassara H, Elhaj Mahamane A, et al., submitted) [29], is associated with *S. haematobium* infection—can be an important cause of blood and iron loss, which also may lead to anemia. Our data suggest significant reductions in the prevalence and, more importantly, intensity of infection of *S. haematobium* as well as in the percentages of children with positive microhematuria scores 1 year after treatment (tables 2 and 3).

The children who most benefited from anthelmintic treatment in terms of increased Hb concentration were those with anemia at baseline and those who had +++ microhematuria scores at baseline (table 6), which confirms similar findings presented elsewhere [30, 31]. The mechanisms by which treatment for *S. haematobium* infection allows Hb concentrations to increase in children with anemia may be the decrease in blood in urine that results from a reduction in the intensity of *S. haematobium* infection [32].

Growth and nutritional status have been proposed to represent the most sensitive indicators of health in children [33]. Furthermore, one of the factors emphasized in the World Development Report 1993 is the relationship between parasitic infections and malnutrition [2]. We examined whether greater *S. haematobium* egg counts were associated with increased risks of wasting or stunting at baseline, adjusting for demographic characteristics and other potential predictors such as microhematuria and anemia status. The results of this study did not suggest any significant association between the risk of undernutrition and intensity of *S. haematobium* infection, with only age being revealed as a significant factor. Younger children tended to be less likely to be wasted or stunted than 14-year-old children, which could imply prior malnutrition in these older children, as has been reported elsewhere [1]. In the aforementioned study, the authors also reported that, in Zanzibari boys, the association between microhematuria and poor growth was only marginally significant [1], which is in line with our findings that, in the Burkinabé children, changes in the BMIZ scores depended only on age, whereas changes in the HAZ scores depended on age and sex (table 4). A more plausible explanation for the lack of statistical association between the intensity of *S. haematobium* infection and stunting may relate to dropout bias toward stunted children (table 1); this means that it is difficult to make a definitive conclusion regarding the relationship between urinary schistosomiasis and stunting in our study population [34].

Nevertheless, it must be considered that essential methodological constraints inherent in the present study design—in particular the lack of a control group, which was necessary for ethical reasons—could result in some potential bias toward the estimation of the absolute impact of the treatment, thereby allowing only the relative impact of the treatment in different groups of children to be calculated. However, even though these

data were obtained from a large-scale control program and studies such as ours are generally difficult to execute in terms of design, methodology, and sampling, we believe that the results will be of substantial value in estimating the total benefit that control of schistosomiasis can provide to communities [35].

This study shows that praziquantel can have a substantial impact on *S. haematobium* infection and associated disease when delivered as part of a large-scale control program in a country such as Burkina Faso, which was the first country in the WHO African Region to achieve nationwide coverage with anthelminthic drugs against 3 major neglected tropical diseases: lymphatic filariasis, schistosomiasis, and soil-transmitted helminthiasis [36]. Our findings suggest a dramatic reduction in the prevalence and intensity of *S. haematobium* infection, an improvement in Hb concentration in certain groups of children, and reductions in schistosome-related morbidity in a cohort of Burkinabé schoolchildren, which demonstrate that mass chemotherapy can offer a practical strategy for the control of *S. haematobium* infection and its associated morbidity.

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