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ASSESSMENT OF ULTRASOUND MORBIDITY INDICATORS OF SCHISTOSOMIASIS IN THE CONTEXT OF LARGE-SCALE PROGRAMS ILLUSTRATED WITH EXPERIENCES FROM MALIAN CHILDREN

ARTEMIS KOUKOUNARI,* MOUSSA SACKO, ADAMA D. KEITA, ALBIS F. GABRIELLI, ALY LANDOURÉ, ROBERT DEMBELÉ, ARCHIE C. CLEMENTS, SARAH WHAWELL, CHRISTL A. DONNELLY, ALAN FENWICK, MAMADOU TRAORÉ, AND JOANNE P. WEBSTER

Schistosomiasis Control Initiative, Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College London, London, United Kingdom; Institut National de Recherche en Santé Publique, Ministère de la Santé, Bamako, Mali; Service de Radiologie, Hôpital National du Point G, Bamako, Mali; Programme National de Lutte contre la Schistosomiase et les Géohelminthiases, Direction Nationale de la Santé, Ministère de la Santé, Bamako, Mali; Direction Nationale de la Santé, Ministère de la Santé, Bamako, Mali; Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College, London, United Kingdom

Abstract. We assessed morbidity indicators for both *Schistosoma haematobium* and *Schistosoma mansoni* infections and evaluated the appropriateness of the World Health Organization (WHO) guidelines for ultrasound in schistosomiasis in the context of large-scale control interventions. Abdominal and urinary tract ultrasonography was performed on 2,247 and 2,822 school children, respectively, from 29 randomly selected schools in Mali before the implementation of mass anthelminthic drug administration. Using two-level logistic regression models, we examined associations of potential factors with the risk of having a positive ultrasound global score (morbidity indicative of *S. haematobium* infection), abnormal image pattern scores, dilatation of the portal vein, and/or enlarged liver (morbidity indicative of *S. mansoni* infection). The WHO protocol was found useful for detection of *S. haematobium* pathology but overestimated the risk of portal vein dilatation and left liver lobe enlargement associated with *S. mansoni* infection. We conclude that ultrasonography should be included in large-scale control interventions, where logistics allow, but cautiously.

INTRODUCTION

Schistosomiasis remains one of the most prevalent parasitic diseases in developing countries and has significant economic and public health consequences.[1] Recently, it has been estimated that the urinary type of schistosomiasis, resulting from infection with *Schistosoma haematobium*, causes hematuria in 70 million people and major bladder wall pathologic effects in 18 million people in sub-Saharan Africa.[2] *Schistosoma mansoni*, one of the etiologic agents of the intestinal type of schistosomiasis, is responsible for bloody diarrhea in an estimated 4.4 million people, and an estimated 8.5 million people have hepatomegaly due to the infection. The death rate due to *S. mansoni*-related hematemesis may be up to 130,000 per year in sub-Saharan Africa.[2] King and others have argued convincingly that additional subtle morbidities (i.e. symptoms such as anemia, chronic pain, diarrhea, exercise intolerance, growth stunting, and nutritional and cognitive impairment, which have so far been difficult to quantify and are based on observed association rather than established causality) should be added to these estimates of disease burden.[3]

Since 1984 the World Health Organization (WHO) Expert Committee on the Control of Schistosomiasis has recommended a strategy for morbidity control that is now feasible because of the availability of effective, affordable, and safe single-dose drugs.[4] As a consequence, since 2003, the Schistosomiasis Control Initiative (SCI) has assisted six sub-Saharan African countries to develop and implement schistosomiasis morbidity control programs through the provision of health education and mass treatment, using praziquantel for schistosomiasis and co-administering, where appropriate, albendazole for soil-transmitted helminthiasis. The primary objective of these SCI-supported control programs is to achieve and demonstrate a quantifiable reduction in schistosome-associated morbidity as a consequence of such chemotherapeutic intervention. Inherent within such an objective, it is therefore imperative to both define and characterize pretreatment baseline morbidity levels within the risk populations so that any subsequent changes in morbidity caused by the intervention can be accurately determined.[5] Furthermore, identification of sensitive and specific indicators of schistosome-associated morbidity that may be practically implemented within such large scale-control programs, as distinct from the individual clinical or research-based setting, should also prove invaluable in assisting identification of target populations for ongoing and future intervention.[6] Campagne and others also emphasized the need to validate indirect morbidity indicators to know the development of their predictive value during different stages of a schistosomiasis control program.[7]

Ultrasonography is currently the diagnostic tool of choice for detecting pathologic conditions associated with schistosomiasis, such as dilatation of the renal pelvis, bladder wall lesions, liver fibrosis and enlargement, and dilatation of the portal vein.[8,9] For detection of infection with *S. haematobium*, ultrasonography is an established method for detecting urinary tract pathologic effects not only in the hospital setting,[10–13] but also in field-based studies,[14] with the advantage of being non-invasive, relatively simple to perform, well accepted by communities, and providing a direct image of the pathologic changes.[15] Additionally, ultrasonography provides sensitive and precise measurements of *S. mansoni*-associated pathologic changes[16,17] In the attempt to objectively define and categorize the pathologic changes associated with schistosomiasis and to standardize the different scoring systems used in the past in different disease-endemic areas,[18,19] successive ultra-

* Address correspondence to Artemis Koukounari, Schistosomiasis Control Initiative, Department of Infectious Disease Epidemiology, Imperial College Faculty of Medicine, St. Mary's Campus, Norfolk Place, London W2 1PG, United Kingdom. E-mail: artemis.koukounari@imperial.ac.uk

sound consensus meetings were held in Niamey, Niger in 1996 and Belo Horizonte, Brazil in 1997. These meetings led to the revision of standardized scoring protocols and the development of the WHO-recommended ultrasonography protocol (Niamey-Belo Horizonte protocol).[19] Nevertheless, the prognostic features of individual ultrasonography findings in different disease-endemic situations,[17] as well as whether ultrasonography can be incorporated into a mass chemotherapy program to monitor morbidity, are still to be confirmed.

The aim of this study was to assess indicators of ultrasonography-detectable morbidity caused by infection with both *S. haematobium* and *S. mansoni* in the context of large-scale control interventions targeting school age children in Mali before large-scale administration of praziquantel by the National Schistosomiasis Control Program with support from SCI. In Mali, both *S. haematobium* and *S. mansoni* pose serious public health problems.[20] Fishing, market gardening, and rice cultivation all expose the population to the risk of occupational transmission, and children are regularly exposed through bathing and playing in ponds, streams, and rivers. *Schistosoma haematobium* transmission is more widespread, occurring along river and streams, as well as around ponds and in irrigation schemes.[21,22] The geographic distribution of *S. mansoni* infections is more restricted, mainly occurring in irrigation schemes, such as Office du Niger, Bandiagara, Sélingue, and Baguinéda-Koulikoro.[22,23]

The results obtained here should contribute to evaluate the appropriateness and the role of the full WHO protocol in the context of large-scale schistosomiasis control programs. We also aimed to determine whether the numeric WHO cut-off values, originally derived from a healthy Senegalese population in an area not endemic for *S. mansoni*, contain bias in the estimation of the risk of dilatation of portal vein and enlargement of left liver lobe in a Malian setting. This will be achieved here by comparison with local height-indexing of portal vein diameter (PVD) scores and longitudinal parasternal line scores (PSL), respectively, obtained from children who had normal image patterns as assessed by ultrasonography using the recommendations of King and others.[17]

MATERIALS AND METHODS

Preparation of the survey and selection of schools. The Malian Ministry of Health, through its National Institute of Research in Public Health (Institut National de Recherche en Santé Publique [INRSP]) and its Disease Prevention and Control Division (Direction Nationale de la Santé), was charged with planning and implementing data collection with assistance from the SCI. Baseline data collection was initiated in the Ségou region in late March 2004 and was completed in Bamako in June 2004. Ultrasonagraphic examination based on the WHO protocol was performed on children 7–14 years of age (2,841 for *S. haematobium* and 2,820 for *S. mansoni*) from 29 schools. These schools were randomly selected from all schools in three areas highly endemic for schistosomiasis: Bamako, Ségou, and Baguinéda-Koulikoro (Figure 1). All children enrolled in the study were interviewed by appropriately trained Ministry of Health staff. Ethical clearance was obtained from the Ministry of Health, Mali and Imperial College, London.

Sampling design. In schools from areas known to be endemic for only *S. haematobium*, the estimated sample size was calculated to be 180 persons per sampling unit (usually a school) with 80% power to detect a 70% reduction in *S. haematobium* mean intensity over a two-year period (two annual treatments). The expected reductions of 70% in *S. haematobium* and 60% in *S. mansoni* mean intensities over two annual treatments were calculated using the EpiSchisto software tool (http://www.schoolsandhealth.org/epidynamics.htm). The figure of 180 was selected based on prevalence/intensity data from schools in various African countries with similar age ranges (Table 1). Since the relationship between prevalence and intensity varied between countries, a different k value (an inverse measure of worm aggregation in the host population that was estimated by maximum likelihood estimation using the negative binomial relationship between prevalence and intensity) was estimated separately for each country. Consequently, a different sample size was calculated for each country in Table 1 and the value of 180 was selected because it was the maximum of all values. Calculations were made for the sample size of the entire school so that results were comparable between countries. A simple approach of a paired sample *t*-test with level of type I error = 0.05 for testing the difference between pre-treatment mean intensity and post-treatment mean intensity was followed. Finally, we allowed for an overall dropout rate of 40% over the course of the monitoring period.

Where both *S. haematobium* and *S. mansoni* infections were known *a priori* to be prevalent, the same methodology as for only *S. haematobium* was followed, although the number of surveyed children was increased to 300 per school with 80% power because EpiSchisto simulations showed an expected reduction in mean *S. mansoni* intensity of 60%. Since the difference of the two means became larger compared with that of *S. haematobium* infection, the magnitude of the non-centrality parameter increased the required sample size needed to achieve suitable statistical power. No schools were included in the present study in which only *S. mansoni* infection was prevalent.

Whenever it was difficult to recruit the required number of children in any one school (usually because of the small size of the school), we combined data from two or more adjacent schools provided that they appeared to be ecologically similar (e.g., with the same relative proximity to the nearest supposed focus of transmission). For ethical reasons, it was not appropriate to include any untreated control groups. Further technical details concerning the sample size calculations can be found elsewhere.[24]

Parasitologic examination. From each child, two urine specimens were collected on two consecutive days to determine the intensity of *S. haematobium* infection using filtration method. 10 mL of urine were passed through a Whatman (Brentford, United Kingdom) filter paper (Ø = 25 mm) using a Millipore (Billerica, MA) Swinnex® filter support. Filters were stained with 3% ninhydrin and microscopically examined for eggs. The intensity of *S. haematobium* infection was expressed as number of eggs per 10 mL of urine and the mean intensity of infection was the arithmetic mean of egg counts in the two urine samples. To determine the presence and extent of microhematuria (invisible hematuria), all urine specimens were tested for detectable blood with urine reagent strips (Hemastix®; Bayer, Tarrytown, NY). The results were recorded semi-quantitatively as –, +, ++, and +++. Additionally, two fecal specimens (each 41.7 mg) were screened for *S. man-*

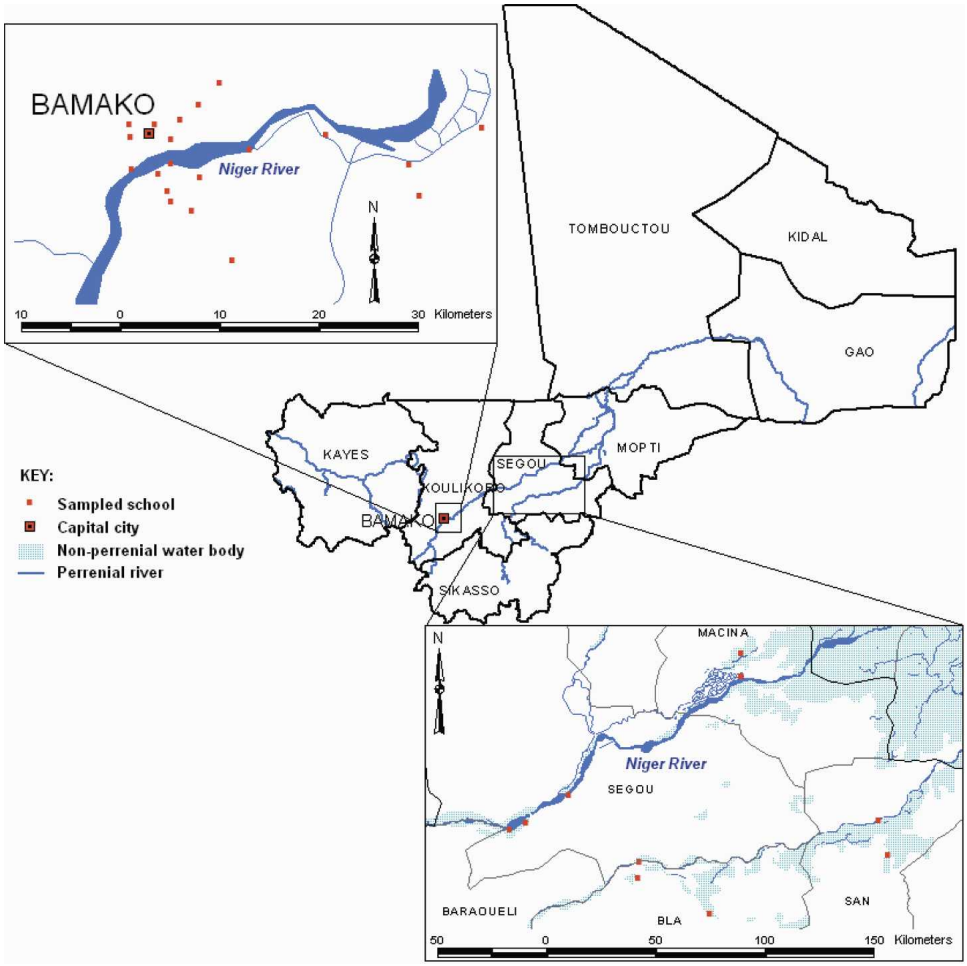

FIGURE 1. Location of sampled schools in Mali. Schools in Bamako and Koulikoro are in the upper box and schools in Ségou are in the lower box.

soni by the Kato-Katz technique.[25–27] Individual egg output was expressed as eggs per gram of faces (epg), which was calculated as the arithmetic mean of the two individual slide counts.

Ultrasound examinations. Utrasonographic assessments were performed with a portable ultrasonography device (SSD-500®; Aloka, Tokyo, Japan). A convex 3.5-Mhz transducer was used to detect pathologic changes associated with both *S. haematobium* and *S. mansoni* infection. All examinations were performed by the same clinician (A.D.K.), who was blind to schistosome infections status of the individual children. Ultrasonographic examinations were performed according to current WHO guidelines.[19]

Pathologic changes caused by *S. haematobium* were assessed by recording the shape of the urinary bladder, defining any lesions detected on the bladder wall, and measuring the degree of dilation of the ureters and renal pelvis. The exact coding of each of these characteristics was made according to the recommendations of Richter and others.[19] Further categorization of pathologic changes was performed by calculating the global score, which serves as an index of severity of morbidity and lesions. Children were provided with water and asked to drink abundantly before having an ultrasonographic examination, which took place only when the bladder was filled. In case of detection of dilatation of the renal pelvis, which is suggestive of hydronephrosis, the child was re-examined after urination to rule out the possibility that such dilatation was caused by bladder and urethral repletion.

To characterize morbidity caused by *S. mansoni*, the size of the left liver lobe was measured in PSL. Measurements of PVD were also performed. Liver patterns were graded from A to F, in order of the severity of the pathologic changes they indicate. B0, B1, and B2 are most often grouped together, as are C1 and C2. It should be noted, however, that the SCI protocol did not include periportal thickening measurements

TABLE 1
Sample data used in the study

Infection	Data used
S. mansoni	Uganda SCI survey, 11,844 children 5–12 years of age from 135 schools
S. mansoni	Uganda SCI baseline survey, 3,689 children 6–12 years of age from 32 sentinel schools in 7 districts
S. mansoni	Busia region, Kenya, 603 children 6–12 years of age from 25 schools
S. haematobium	Tanga region, Tanzania, 1,396 children 8–13 years of age from 41 schools
S. haematobium	Volta region, Ghana, 1,216 children 6–12 years of age from 57 schools

because of concerns about both the reproducibility of measurements[16] and the time-consuming component of the examination. Therefore, interpretation of the final score for morbidity caused by *S. mansoni* infection was based on assessment of image patterns and portal hypertension only. Presence of ascites and portosystemic collaterals was also recorded. Detection of pathologic changes not caused by schistosomiasis was also recorded but is not discussed in the present paper. Persons in need of health care were directed to the nearest medical facility.

Ultrasonography protocol definitions. The WHO protocol states that measurements of organ size and vein diameter should be height-adjusted, using standard reference measurements for healthy members of the same population group.[19] King and others found that the numeric WHO cut-off values derived from a healthy Senegalese population in an area not endemic for *S. mansoni* seriously overestimated the risk of portal vein enlargement in Kenyan and Egyptian patients infected with *S. mansoni*.[17] We have also investigated this issue in a Malian setting because the Niamey workshop members anticipated the refinement of the guidelines through continued use and evaluation, by using alternative height-indexing of PVD scores obtained from all children that had normal image patterns as assessed by ultrasonography (n = 2,719). With reference to the PSL measurement, the liver was considered enlarged, or much enlarged if the height-adjusted value exceeded two or four SD in relation to the normogram produced for a Senegalese population, respectively.[28] In addition, we also calculated local cut-off scores for liver left lobe enlargement and verified if the overestimation also applied to this parameter.

At the end of all examinations, each child enrolled in the survey was treated with the WHO-recommended dose of praziquantel (40 mg/kg) for schistosomiasis and with albendazole (400 mg) for intestinal helminths. Side effects were monitored, and adverse reactions after drug administration were infrequent; when present, these were minimal and transient, and no severe adverse experiences were observed.

Statistical analysis. Data from children with incomplete parasitologic or ultrasonographic records were excluded from our analysis and no replacements were made for missing subjects under the assumption that data were missing at random.[29] Descriptive statistics for subject characteristics and outcomes were calculated using SAS version 8 (SAS Institute Inc., Cary, NC).

To examine *S. haematobium* morbidity, we modeled the probability of a child having a positive individual global score using hierarchical multi-variable logistic regression. Potential predictors included *S. haematobium* infection intensity category (light [< 50 schistosome eggs per 10 mL of urine] or heavy [≥ 50 eggs/10 mL),[24] microhematuria, sex, school-level *S. haematobium* infection prevalence (classified as low [< 10%], medium [11–49%], and high [≥ 50%]), and age. The model structure was a two-level random intercept logistic regression model with level-1 defined as the individual child and level-2 as the school allowing for assessment of the extent of between-school variation in individual global scores. The model had the form

$$\log[\pi_{ij}/(1-\pi_{ij})] = x_{ij}a + w_j b + u_j + e_{ij}$$

where π_{ij} is the probability that child i in school j has a positive individual global score, x_{ij} and w_j are vectors of individual- and school-level characteristics respectively, a and b are vectors of estimated parameter coefficients, u_j (~Normal$(0, \sigma^2)$) is an error term at the school level, and e_{ij} (~Normal$(0, \sigma^2)$) is an error term at individual level.

To study the morbidity of *S. mansoni*, we used three hierarchical multi-variable logistic regression models where we aimed to model 1) the probability of having abnormal image pattern scores, 2) the probability of having dilatation or marked dilatation as assessed by the PVD based on the Malian cut-off scores, and 3) the probability of having enlarged liver as assessed by the PSL measurements based on the Malian cut-off scores. Potential predictors included *S. mansoni* infection intensity category (light [1–99 epg of feces, moderate [100–399 epg], or heavy (≥ 400 epg]),[30] sex, school-level *S. mansoni* prevalence (included in the relevant models as a categorical variable and classified as that of *S. haematobium*), and age. The structure and form of the model used to assess each of these *S. mansoni* morbidity indicators, were identical to those used for evaluation of *S. haematobium*.

All four models were constructed using the Mlwin software (version 2.01; Multilevel Models Project, Institute of Education, University of London, London, United Kingdom). The method of estimation was the second-order, penalized, quasi-likelihood procedure,[31] and first-order marginal quasi-likelihood estimates were used to provide the starting values for the estimation procedure, the stability of the algorithm, and convergence criteria.[32] The model structure was selected because of the hierarchical nature of the dataset, i.e., children were clustered in schools and observations from children within the same school were therefore not independent. Multilevel models account for this dependence by partitioning the total variance in the data into variation between and variation within the higher-level units.[33] Although partitioning of variance is straightforward in models with a continuous dependent variable and with a normally-distributed error at each level of the hierarchy, their extension to models with binary responses is more problematic. For the school effect in each model we calculated the median odds ratio (MOR) to quantify the variation between schools.[34,35] The MOR is always ≥ 1 and directly comparable with fixed-effects odds ratios. More precisely, if the MOR = 1, there is no variation between clusters (no second-level variation). If there is considerable between cluster variation, the MOR will be large.

This quantification of the heterogeneity of the schools is not simply of technical value; the apportioned variances are of substantive interest in much of biomedical research because they give important insights to the level at which the action lies[36] and for epidemiologic reasons (in this case quantification of the importance of the schools for understanding individual health).[35] The percentage of total variation in the ultrasonographic global scores as well as in the liver image patterns, the PVD and the PSL, which are explained by each of the corresponding models presented, was estimated using an R^2 measure developed by Snidjers and Boskers.[37]

RESULTS

Schistosoma haematobium was prevalent in all 29 schools surveyed, and *S. mansoni* was prevalent in 25 of these schools.

Schistosoma haematobium. Ultrasonographic examination was performed on 2,841 children. Of these, parasitologic data were obtained from 2,822 children. In 136 (4.8%) of

2,822, there was no second examination of urine and prevalence and mean intensity calculations were based on one urine filtration result for these children. Overall, *S. haematobium* prevalence of infection was 59% and the arithmetic mean intensity was 43.0 eggs/10 mL of urine. At school level, prevalence of infection ranged from 10.8% to 100.0% and arithmetic mean intensity ranged from 0.7 to 202.5 eggs/10 mL of urine. Girls accounted for 53% of children in the survey and approximately equal numbers of children were recruited in each year group from 7 to 14 years of age. Bladder wall thickening and irregularities, bladder masses, and pseudo-polyps, were found in 6.0% of the children. The prevalence of upper urinary tract (kidney) pathology was estimated to be 3.7%. The prevalence of positive global scores was estimated to be 10.1%, and this prevalence at the school-level ranged from 1.0% to 61.4%.

The odds ratios (ORs) from two-level logistic regression analysis for the probability of having a positive ultrasonographic global score are shown in Table 2. Children with either light or heavy *S. haematobium* infection intensities were more likely to have a positive ultrasonographic global score than uninfected children (light: OR = 2.6, $P = 0.013$ and heavy: OR = 5.7, $P < 0.001$). Children with +, ++, and +++ microhematuria scores were significantly more likely to have positive schistosomiasis ultrasonographic global scores than microhematuria-negative children (OR = 2.4, $P = 0.003$; OR = 3.0, $P < 0.001$; and OR = 5.0, $P < 0.001$, respectively). Boys showed significantly higher ultrasonographic morbidity global scores than girls (OR = 2.0, $P < 0.001$). Age was not a statistically significant indicator of *S. haematobium* morbidity, although there was a trend for older children to be more likely to have a positive schistosomiasis ultrasonographic global score. Schools with high *S. haematobium* prevalence were significantly more likely to have positive global scores than those with medium *S. haematobium* prevalence (OR = 1.7, $P < 0.001$). Since there were no schools with a low prevalence of *S. haematobium* included in the survey, this category does not appear in Table 2. This table also shows that a relatively high MOR (2.2) is associated with between-school variation. Of the total variation in the global ultrasonographic score, 9.4% remained unexplained at the school level and 48.0% remained unexplained at the child level.

Schistosoma mansoni. Both ultrasonographic and parasitologic data were obtained from 2,247 (79.7%) of 2,820 children. Overall prevalence of infection was 27% and the overall arithmetic mean intensity was 119.5 epg. Calculations were based on two fecal smear examinations from all but four children, for whom the second measurement was missing. School-level prevalence of infection ranged from 0.0% to 96.0% and arithmetic mean intensity ranged from 0.0 to 814.9 epg.

A total of 2,820 children were examined by ultrasonography for *S. mansoni*-related pathologic changes. Of these children, 96% had normal livers, as assessed by liver image patterns. Of the children that had abnormal liver image patterns, 84% had grade B patterns and 16% had grade C patterns. Figure 2 shows that using the current WHO cut-off value, 85% of the children had a 0 PVD score. In contrast, 96% of the children had a 0 PVD when the cut-off value derived from the data from the Malian children with normal liver image patterns was used. The difference between these two propor-

TABLE 2

Odds ratios (ORs) with 95% confidence interval (CI) estimates and percentage of variation explained for two-level logistic model of prevalence of positive global score as measured by ultrasound using data set of children with complete parasitologic and ultrasound data on *Schistosoma haematobium* infection (n = 2,822)

Fixed effects				
Variables	Categories	OR	95% CI	*P*
Age	7 years old	1		
	8 years old	1.206	0.636–2.284	0.565
	9 years old	0.928	0.480–1.792	0.825
	10 years old	1.380	0.750–2.538	0.300
	11 years old	1.567	0.853–2.877	0.148
	12 years old	1.252	0.671–2.336	0.480
	13 years old	1.267	0.682–2.355	0.454
	14 years old	1.665	0.888–3.124	0.112
S. haematobium intensity infection	Not infected	1		
	Lightly infected	2.578	1.219–5.451	0.013
	Heavily infected	5.709	2.521–12.927	≤ 0.001
Sex	Female	1		
	Male	2.018	1.483–2.745	< 0.001
Results of Hemastix text	Negative	1		
	Trace hemolyzed	1.578	0.772–3.227	0.212
	+	2.442	1.343–4.441	0.003
	++	3.010	1.722–5.262	< 0.001
	+++	4.973	3.035–8.149	< 0.001
S. haematobium school-level infection prevalence	Medium	1		
	High	4.051	1.824–8.995	< 0.001
Random effects				
School		Median OR		
		2.147		
Variation	%			
Total variance explained	42.640			
Total variance unexplained				
At school level	9.380			
At child level	47.980			

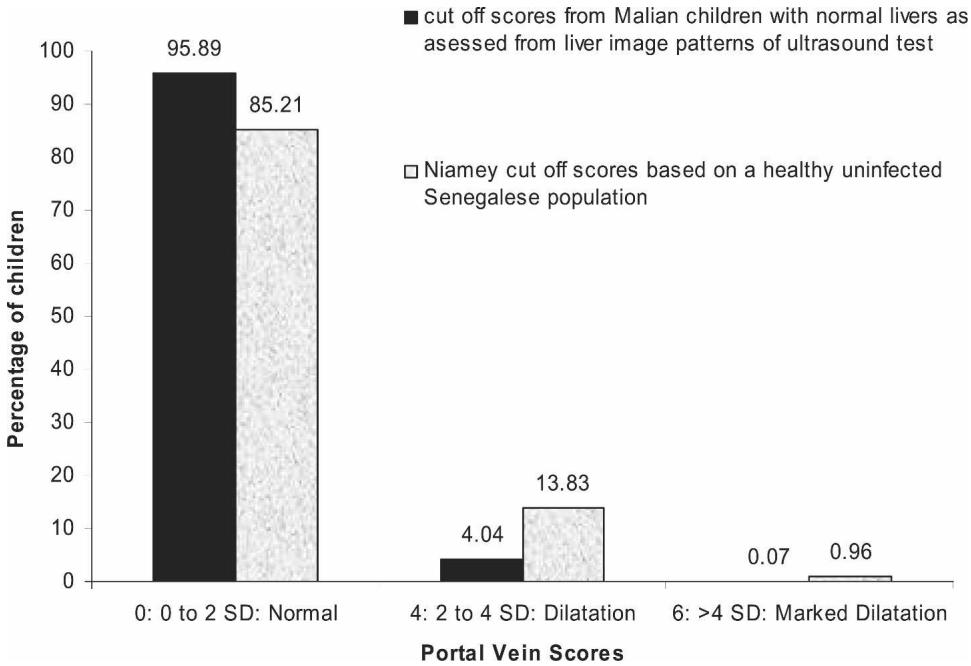

FIGURE 2. Percentages of children with portal veins scores based on different cut-off values.

tions was statistically significant ($P < 0.001$). Statistically significant differences were also found between the proportions of children allocated positive PVD scores of four and six using the two different cut-off values (both $P < 0.001$).

In 99.9% of the children, no collateral vessels were detected and no free fluid was detected in abdomen. Figure 3 shows that 50% of the children in the ultrasonographic cohort had left lobe hepatomegaly as assessed by PSL using the current WHO cut-off value. A total of 41% of the children had an enlarged liver and 8% had a greatly enlarged liver. Conversely, 99% did not have an enlarged liver when the cut-off value derived from the data from the Malian children with normal liver image patterns was used. Statistically significant differences were found between all proportions of children allocated null or positive PSL scores of one and two using the two different cut-off values ($P < 0.001$).

Table 3 shows the ORs from two-level logistic regression analysis for the probability of having abnormal image pattern scores as assessed from ultrasonography for *S. mansoni* infection. Children with light, moderate, or heavy *S. mansoni* infection intensities were more likely to have an abnormal liver image pattern than uninfected children (light: OR = 2.6, $P = 0.023$; moderate: OR = 1.3, $P = 0.62$; and heavy: OR = 3.1, $P = 0.036$). There was a trend for older children to be less

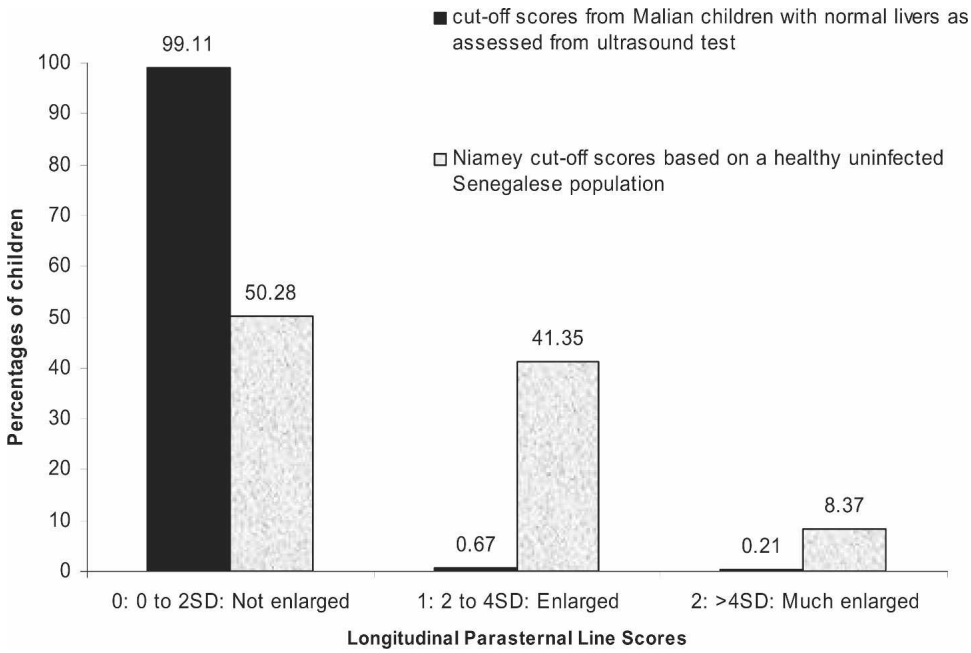

FIGURE 3. Percentages of children with longitudinal parasternal scores based on different cut-off values.

TABLE 3

Odds ratios (ORs) with 95% confidence interval (CI) estimates and percentage of variation explained for two-level logistic model of prevalence of abnormal liver image patterns as measured by ultrasound using data set of children with complete parasitologic and ultrasound data on *Schistosoma mansoni* infection (n = 2,247)

Fixed effects				
Variables	Categories	OR	95% CI	*P*
Age	7 years old	1		
	8 years old	0.550	0.209–1.450	0.226
	9 years old	0.412	0.152–1.120	0.082
	10 years old	0.523	0.202–1.353	0.182
	11 years old	0.305	0.107–0.875	0.027
	12 years old	0.323	0.112–0.926	0.036
	13 years old	0.516	0.189–1.404	0.196
	14 years old	0.224	0.066–0.755	0.016
S. mansoni intensity infection	Not infected	1		
	Lightly infected	2.622	1.144–6.008	0.023
	Moderately infected	1.336	0.423–4.223	0.621
	Heavily infected	3.099	1.080–8.895	0.036
Sex	Female	1		
	Male	1.520	0.873–2.648	0.138
Random effects				
School		Median OR		
		13.444		
Variation	%			
Total variance explained	3.388			
Total variance unexplained				
At school level	66.981			
At child level	29.631			

likely to have an abnormal liver image pattern, but these differences were only significant for 11-, 12-, 13-, and 14-year-old children relative to 7-year-old children (OR = 0.3, $P = 0.027$; OR = 0.3, $P = 0.036$; and OR = 0.2, $P = 0.016$, respectively). When we attempted to include the school-level categorical variable that was representing *S. mansoni* infection prevalence, classified as low, medium, and high, the algorithm did not converge; therefore, we were unable to include this variable in the final model. The same applies to the modeling of the probability of having dilatation or marked dilatation; therefore, this variable was also excluded from the model (Table 4).

Table 3 shows that a high MOR (13.4) was associated with between-school variation. Of the total variation in the liver image pattern, 67.0% remained unexplained at the school level and 30.0% remained unexplained at the child level.

Table 4 shows the ORs from two-level logistic regression analysis for the probability of having dilatation or marked

TABLE 4

Odds ratios (ORs) with 95% confidence interval (CI) estimates and percentage of variation explained for two-level logistic model of prevalence of having dilatation or marked dilatation as assessed by the ultrasound PVD score based on the Malian cut-off scores by using data set of children with complete parasitologic and ultrasound data on *Schistosoma mansoni* infection (n = 2,247)

Fixed effects				
Variables	Categories	OR	95% CI	*P*
Age	7 years old	1		
	8 years old	1.567	0.444–5.525	0.484
	9 years old	3.640	1.159–11.435	0.027
	10 years old	3.245	1.035–10.172	0.043
	11 years old	2.835	0.887–9.064	0.079
	12 years old	1.980	0.586–6.687	0.271
	13 years old	3.647	1.134–11.730	0.030
	14 years old	4.655	1.462–14.826	0.009
S. mansoni intensity infection	Not infected	1		
	Lightly infected	1.402	0.619–3.175	0.418
	Moderately infected	1.408	0.547–3.621	0.478
	Heavily infected	0.774	0.303–1.979	0.593
Sex	Female	1		
	Male	2.250	1.373–3.687	0.001
Random effects				
School		Median OR		
		4.364		
Variation	%			
Total variance explained	6.480			
Total variance unexplained				
At school level	39.360			
At child level	54.159			

dilatation as assessed by ultrasongraphy for *S. mansoni* infection PVD height-adjusted measurements based on the Malian cut-off value. The ORs of having dilatation or marked dilatation as assessed by ultrasonographic PVD measurements for children with light, moderate, or heavy *S. mansoni* infection intensities were not significantly different from those of uninfected children ($P = 0.418$, 0.478, and 0.593, respectively). There was a trend for older children to be more likely to have an increased PVD, but these differences were only significant for 9-, 10-, 13-, and 14-year-old children compared with 7-year-old children (OR = 3.7, $P = 0.027$; OR = 3.3, $P = 0.043$; OR = 3.7, $P = 0.030$; and OR = 4.7, $P = 0.009$, respectively). The MOR to have an increased PVD was 4.364, which has a high OR and is associated with between-school variation. Of the total variation in the PVD, 39.0% remained unexplained at the school level and 54.2% remained unexplained at the child level.

Relative to modeling of the probability of having an enlarged liver as assessed by PSL measurements based on the Malian cut-off scores, the algorithm did not converge. Therefore, we were unable to provide any estimates and establish any associations for this measure.

DISCUSSION

Ultrasonography has become an invaluable extension of the clinical investigation of patients with schistosomiasis and has provided direct evidence of the pathologic changes associated with this infection.[38] This evidence has been well validated in the individual patient clinical setting[39–42] and the relatively small-scale research setting.[43–46] However, the overall aim of this study was to test the suitability of the full WHO-recommended ultrasonography protocol in the context of large-scale schistosomiasis control programs. There is a requirement to elucidate whether ultrasonography could, and indeed should, be incorporated into a mass chemotherapy program to monitor morbidity associated with *S. haematobium* infection and, perhaps in particular, morbidity associated with the often more difficult to characterize *S. mansoni* infections in all but the most severe cases.[47,48]

The current study complements and expands previous ultrasonography-based studies within Africa on a number of issues. First, although previously published surveys[17,49–54] have used ultrasongraphy to measure schistosomiasis-associated morbidity both in children and in adults, which is indicative of long-term chronic infections, we assessed ultrasonography in monitoring schistosomiasis morbidity in control programs focused on children. Although we recognize that measuring only children might be a limitation, if one considers the overall aim of this study, our results still contribute to assessing the suitability of ultrasonography for more recent infections and targeting age groups for future disease control programs. This study should also provide a unique opportunity to clarify the relationship of early lesions to later ones through a subsequent comparison of the baseline findings presented here, particularly where there are identifiable cohorts, over extended periods of time. Moreover, in terms of cohort size, we followed a larger number of persons than previous research or clinical-based studies. Finally, our study has methodologic advantages, particularly since we account for the interdependence of observations by partitioning the total variance into different components of variation due to various cluster levels in the data.

Children are probably the most important age group for ultrasound-detectable morbidity caused by *S. haematobium*, and the results obtained from Mali confirm that the current WHO protocol (Niamey-Belo Horizonte protocol) is a suitable and valid public health tool because its scoring criteria performed acceptably well in defining ultrasound pathology caused by urinary schistosomiasis. Sophisticated statistical models yielded significant associations between global ultrasonography scores from the WHO protocol and several other morbidity predictors. A significant association between the degree of morbidity as defined by ultrasonography global scores and *S. haematobium* infection intensity and microhematuria was demonstrated. Boys had a higher prevalence of morbidity than girls and this has also been observed in studies of Heurtier and others[55] and Keita and others.[56] Our results also indicated that there was considerable variation between schools in the prevalence of positive global scores, thus showing the focal clustering of morbidity caused by urinary schistosomiasis in areas of overall intense transmission. We conclude that ultrasonography global scores and microhematuria scores are likely to be valuable markers in children for morbidity caused by both light and heavy infections with *S. haematobium*. We therefore recommend the inclusion of ultrasonographic examinations in the routine monitoring and evaluation activities of control programs against urinary schistosomiasis whenever resources are available, as in the case of middle-income countries (i.e., North and South Africa and potentially some Middle Eastern countries such as Iraq). In sub-Saharan Africa, such a recommendation should be weighted against additional costs that a subsequent decision would bring (equipment, personnel, training) and the available national or external funds of the control programs.

With regards to intestinal schistosomiasis, the significant associations observed between liver image patterns with *S. mansoni* intensity of infection confirms that these patterns are likely to be valuable markers for morbidity caused by light or heavy infections with *S. mansoni*, as suggested by King and others.[17] However, although our findings suggest that current scoring criteria perform well in defining disease caused by *S. haematobium* infection, they also show, in accordance with those of King and others,[17] that the current WHO cut-off values can lead to serious overestimation of the risk of PVD in patients infected with *S. mansoni*. In addition, our data show that the risk of left liver lobe enlargement may be overestimated by WHO cut-offs values. We therefore agree that cut-off norms should be recalculated at least in each disease-endemic country from a subset of local persons with pattern A prior to the implementation of the WHO protocol, which also fulfills the recommendations included in the Niamey-Belo Horizonte protocol guidelines. Further studies to confirm appropriate cut-off scores for these measurements are therefore required.

Nevertheless, the observation that much of the variability in the liver image pattern remained unexplained, as well as the high MOR, suggest that other variables might be needed to explain the between-school heterogeneity. Another explanation for this high MOR and unexplained variation might be that among children with abnormal liver image patterns, 84% were found to have grade B (coding for the earliest pathologic changes in the liver), which may not be schistosomiasis specific. This same fact might also explains the unexpected finding that older children have less likelihood of abnormal pat-

terns than younger ones compared with other studies of schistosomiasis morbidity. Therefore, liver image patterns of grade B may have represented a confounding factor in our analysis. Further studies are therefore needed to fully elucidate the relationship between liver fibrosis and schistosomiasis, with particular reference to the degree of association between pattern B and *S. mansoni* infection and to the role played by other factors in determining such fibrosis. Likewise, in the case of hepatomegaly, we were unable to distinguish clear associations, which may have been due to the fact that these observed morbidities were likely to have been multifactorial, with *S. mansoni* infection being only one of a number of potential causes.[57] There are often many factors (genetic and possibly most importantly malaria, which is transmitted throughout the year in Mali[58]) other than *S. mansoni* that can cause liver enlargement, and their role and interaction with *S. mansoni* infection also requires further clarification.

Although these data are on children and as such were expected to be less likely to demonstrate ultrasonagraphy-detected morbidity caused by *S. mansoni* infection because of the amount of time of exposure associated with the time taken for fibrosis to build up, in contrast, they show morbidity for this type of infection, suggesting that in these communities children may become infected early in life.[59] We expect that in adults the dynamics of exposure, treatment, and host immunity would show even more ultrasonography-detectable *S. mansoni* morbidity than observed in this study. It might also be important to include the periportal thickening measurement in the ultrasonography examinations when the adult population is examined to evaluate the performance of the protocol. We predict that in adults infected with *S. mansoni*, the comparison between Malian and WHO cut-off values (derived in a similar way as previously described) would show significant differences in the estimations of risk of PVD and left liver lobe enlargement because King and others[17] also observed the same pattern irrespective of age.

For *S. haematobium*, as in high transmission areas like those under study, successive episodes of infection would result in recrudescence of urinary tract abnormalities detected by ultrasonography,[60] and we would expect to observe more severe pathology caused by urinary schistosomiasis in young adults because of continuing reinfection. However, ultrasonography may not be the most appropriate tool to detect and define late-stage morbidity caused by *S. haematobium* infection in older adults because of decreased rates of reinfection in this age group, which leads to decreased development of new inflammatory bladder wall lesions pathognomonic of urinary schistosomiasis. Thus, it would be interesting to conduct a survey on adults from the same communities of children described in this report and investigate up to which age group ultrasonography is a suitable tool to monitor morbidity caused by urinary schistosomiasis in a field setting.

Thus, for both intestinal and urinary schistosomiasis, it will be necessary to obtain longitudinal data to fully elucidate the natural history of morbidity related to infection, with the aim of formulating recommendations for treatment and retreatment based on natural history and evolution of morbidity after large-scale administration of anthelminthic drugs. Such work is currently being conducted by INRSP, SCI, and the National Schistosomiasis Control Program and hopefully will help plan and evaluate sustainable morbidity control.

Conversely, if only parasitologic measurements were incorporated into monitoring of schistosomiasis morbidity of a mass chemotherapy program, the following three issues should be taken into consideration.[15] 1) Diagnosis of infected persons might be missed because of substantial day-to-day variation of egg output in *S. mansoni* infections and then in *S. haematobium* infections. Some persons might not shed eggs at the time of the stool or the urine examination or eggs could be missed. 2) Signs of disease could still be present even in the true absence of egg excretion. Eggs could be trapped in lesions, especially in long-standing infections. Just after treatment, eggs could also be absent, but lesions would still be present. In this case, ultrasonography would still provide detection of irreversible lesions long after treatment. 3) Confounding causes other than schistosomiasis of observed pathologic signs could be excluded by ultrasonography. The epidemiologic importance of confounding causes of uropathy in areas where *S. haematobium* is endemic appears to be small, but information for areas where *S. mansoni* is endemic is still lacking.

In conclusion, the results of this study suggest that the current WHO protocol (Niamey-Belo Horizonte protocol) is a suitable and valid public health tool for urinary schistosomiasis for morbidity control programs focused on children. In detection of morbidity of intestinal schistosomiasis in large-scale control interventions, this same protocol is a useful tool provided local cut-off values are used to define abnormal values and that results are interpreted with caution.

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Authors' addresses: Artemis Koukounari, Albis Francesco Gabrielli, Archie C. Clements, Sarah Whawell, Alan Fenwick and Joanne P. Webster, Schistosomiasis Control Initiative, Department of Infectious Disease Epidemiology, Imperial College Faculty of Medicine, St. Mary's Campus, Norfolk Place, London W2 1PG, United Kingdom, Telephone: 44-20-7594-3820, Fax: 44-20-7262-8140, E-mails: artemis.koukounari@imperial.ac.uk, a.gabrielli@imperial.ac.uk, a.clements@imperial.ac.uk, a.fenwick@imperial.ac.uk, and joanne.webster@imperial.ac.uk. Moussa Sacko and Aly Landouré, Institut National de Recherche en Santé Publique, Ministère de la Santé, Bamako BP 1771, Mali, E-mails: msacko@dblnet.dk and aland@afribonemali.net. Adama D. Keita, Service de Radiologie, Hôpital National du Point G, Bamako BP 333, Mali, E-mail: gadkeita@hotmail.com. Robert Dembelé, Programme National de Lutte contre la Schistosomiase et les Géohelminthiases, Direction Nationale de la Santé, Ministère de la Santé, Bamako BP 232, Mali BP, E-mail: rdembele2000@yahoo.fr. Christl A. Donnelly, Department of Infectious Disease Epidemiology, Imperial College Faculty of Medicine, St. Mary's Campus, Norfolk Place, London W2 1PG, United Kingdom, E-mail: c.donnelly@imperial.ac.uk. Mamadou Traoré, Direction Nationale de la Santé, Ministère de la Santé, Bamako BP 232, Mali BP, E-mail: mstraore@dnsmali.org.

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