Resolution and Resurgence of *Schistosoma haematobium*–induced Pathology After Community-based Chemotherapy in Ghana, as Detected by Ultrasound

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Community-based treatment is recommended for endemic populations with urinary schistosomiasis; however, the optimal target group for treatment and retreatment interval have not been established. Using ultrasound, this study identified subpopulations whose lesions were most likely to respond to treatment and characterized resurgence of pathology. Ultrasound examination of 1202 infected patients was followed by chemotherapy with praziquantel. A sample of 698 patients was followed for 18 months after treatment. Nearly all types of bladder pathologies resolved after treatment, regardless of patient's age or intensity of initial infection. However, many patients' upper urinary tract pathologies (62.5%) did not resolve. During the 18-month follow-up period, reappearance of severe bladder pathologies was rare, and <10% of persons had resurgence of mild bladder pathologies. For this population, retreatment is not needed annually but might be cost effective if given several years later. Confirmation from other areas is required before general policies can be formed.

Schistosomiasis is a widespread parasitic infection affecting 200 million people in 74 endemic countries [1, 2]. Schistosomiasis is currently widespread in Ghana, where *Schistosoma haematobium* is much more common than *S. mansoni* [2, 3]. The current global control strategy is to reduce morbidity; thus, more people living in endemic areas have been treated for schistosomiasis through control programs in recent years [1]. After treatment, lesions generally regress, but determinants of regression and the sequence of regression, reinfection, and resurgence of pathology are not well understood [4, 5]. Understanding the age-specific reduction and resurgence in morbidity following community or school-based intervention is essential in identifying the most appropriate target population for treatment, as well as for formulating a retreatment schedule.

Ultrasound has become a valuable tool with which to assess urinary system pathology associated with schistosomiasis [6]. It is safe, rapid, noninvasive, and acceptable and applicable in field settings, and it enables examinations of large numbers of people at a relatively low cost per capita [7–11]. Ultrasonography is the only technique that is feasible at present for field use to assess the impact of the disease in terms of damage to organs, the regression of lesions after treatment, and the resurgence of pathological lesions due to reinfection [12]. Standardized criteria for ultrasonographic observations for *S. haematobium* infection have been established and are in the process of being refined [6, 13].

The aim of this longitudinal ultrasonographic study was to assess resolution of *S. haematobium*–associated pathological lesions of the lower and upper urinary tract after treatment and to detect the resurgence of pathological signs due to reinfection in relation to age, sex, pretreatment pathology, and intensity of infection, by means of the standard examination protocols for *S. haematobium* recommended by the World Health Organization (WHO) [14].

Methods

Study population and screening laboratory examinations. The study was conducted in 8 rural communities in southern Ghana where *S. haematobium* was known to be common. Infection with *S. mansoni* was not detected in screenings of school children in the study area. These communities are situated approximately 50 km northwest of Accra, and all are along the river Densu. Between August 1992 and June 1993, 2562 (65.5%) of 3912 individuals aged at least 5 years submitted urine samples for examination (popu-

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Informed consent was obtained from all patients or their guardians who participated in this study. The study was approved by the Committee on Human Research at The Johns Hopkins University and by the IRB of the Noguchi Memorial Institute for Medical Research.

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lation census was conducted by the study team in June 1992). Of these, samples from 1453 persons (56.7%) were found to be positive for *S. haematobium* by means of a method using a 12-μm Nucleopore filter (Coster, Cambridge, MA) [15]. Intensity of infection was expressed as the number of eggs per 10 mL of urine for each patient. One pretreatment urine sample (about 200 mL) was collected from each study patient between 10 AM and 2 PM because of the circadian variation of ova output in urine. In addition, we determined macrohematuria by naked eye examination and microhematuria and proteinuria by means of urine chemical reagent sticks (Hemcombisticks; Ames, Miles-Sankyo, Tokyo). Traveling during the collection period and refusal were the main reasons for nonsubmission of urine, and the coverage rates of urine collection did not differ by age group.

Baseline ultrasound examinations. During January–September 1993, all persons identified as infected (1453 patients) were called for ultrasound examinations using a portable ultrasound machine (Aloka SSD-500 with standard convex probe [3.5 MHz]; Aloka, Tokyo). The standard protocol proposed by the WHO workshop was adopted [14]. Bladder shape, wall thickening, wall irregularity, (pseudo)polyps, and masses were recorded. If any abnormality of the kidneys and/or ureters was observed, a postvoiding examination of these organs was done 0.5–1 h later, and the second examination data were recorded and used for the analysis. Bladder wall calcification and kidney fibrosis were also recorded. Of the 1202 baseline patients, 162 (13.5%) were reexamined for a quality control purpose by an expert recommended by the WHO Working Group on Ultrasound in Schistosomiasis-related Pathology.

Estimation of frequency of water contact. To estimate the frequency of water contact, trained community health workers observed community members' water contact behavior at all major water contact sites in the study area for a total of 30 days during a 3-month period in the dry season (when more-intense water contact activities were usually observed). All recorded subjects were matched with population census ID numbers, and study patients were identified. Each individual's total number of visits at water contact sites during the 30-day observation period was then used as an indicator for individual water exposure. The observers were not aware of the patients' infection and pathological statuses. Three monthly frequency categories were used for the level of water contact: 0, 1–29, and >30 times (more than once per day average water contact).

Chemotherapy. All school-aged children (aged 5–16 years) in the study communities were targeted for treatment with praziquantel (40 mg/kg body weight) between August and December 1993. This strategy, in which all school-aged children receive treatment, was recommended by the WHO when the average prevalence among school-aged children is >50% [16] (this strategy is now being reevaluated [2, 17]). For study participants >16 years old, only persons with *S. haematobium* eggs in a urine sample were treated (selective chemotherapy).

Follow-up examinations and sampling strategy. Of the 1202 patients examined by ultrasound at baseline, 698 infected patients were selected for follow-up. This total was stratified to include 140 individuals from each of four pathology-severity categories: (1) no pathology, (2) mild bladder pathology, (3) severe bladder pathology, and (4) ureter and kidney (renal pelvis) dilatation, for each category of children and adults. Irregularity of the bladder inner surface and/or <5 mm thickening at the posterior wall were categorized as mild bladder pathology. Protrusion(s) >1 cm into the lumen, with a broad or narrow stem(s) (masses or polyps) and/or >5 mm posterior wall thickening were categorized as severe bladder pathology. All patients with ureter or kidney dilatation with or without bladder pathologies were grouped as a final category. This sample size was needed to detect differences in pathological resolution or resurgence if the rates differed between groups by 20% (χ^2 approximation for binary outcome measurements, 0.05 for type I and type II error probability, 20% loss to follow-up). All the patients in the severe bladder and upper urinary tract pathology categories were chosen for follow-up examinations, since the numbers of children and adults in these categories were close to or less than the calculated sample size. All adult patients ($\geq$20 years old) in the mild bladder pathology category were also chosen for follow-up, for the same reason. Children (<20 years old) in the mild bladder pathology category were sampled with the proportion 1 to 2 (1:2). The follow-up patients with no pathology were matched with mild bladder pathology patients by age, sex, and community.

We conducted ultrasound and urine examinations 1, 3, 6, 12, and 18 months after treatment, using the same ultrasound criteria as for the first examination. Two urine samples per patient were collected at each follow-up period, and the geometric means of egg counts were calculated, to indicate the intensity of infection. All samples were also tested for macrohematuria, microhematuria, and proteinuria.

Data analysis. All data were recorded onto standardized recording sheets with drawings of the lesions. The codes for pathological grades, as defined by the WHO Cairo Proposals [14], were entered into a microcomputer. Geometric mean of $(x + 1)$ eggs per 10 mL of urine was used for subgroup-specific intensity of infection. For statistical analysis, χ^2 test, Fisher's exact test, Mantel-Haenszel test for linear association (M-H linear association test), and one-way analysis of variance (ANOVA) were used, as appropriate.

We calculated resolution rates by using the subset of the follow-up patients with a particular pathology at baseline that had resolved at follow-up examinations. We calculated resurgence rates by using the subsets of follow-up patients who did not have an initial baseline pathology or whose pathologies had resolved and by examining for subsequent resurgence 12 and 18 months after treatment, respectively. Relative risks (RRs) of the pathology-specific resolution and resurgence were calculated for possible risk factors—for example, age, sex, pretreatment pathologies, pretreatment intensity of infection, and concurrent infection status (egg excretion).

Results

Ultrasound findings before treatment. A total of 1202 (82.7%) of 1453 infected patients participated in ultrasound examination before treatment (participation rates did not differ by sex or age group). The numbers of patients examined at baseline and at each follow-up period are shown by age group in table 1. More than half (52.7%) of the infected patients had abnormalities found by ultrasound. Three hundred nineteen (26.5%) had mild bladder pathologies and 235 (19.6%) had severe bladder pathologies. A majority (78.7%) of the severe

Table 1. Age distribution of patients at baseline and follow-up ultrasonographic examinations.

Age group (years)	No. (%) of patients examined at posttreatment month					
	0 (baseline)	1	3	6	12	18
5–9	288 (24.0)	170 (28.8)	187 (27.8)	198 (30.0)	184 (29.3)	174 (29.2)
10–14	291 (24.2)	141 (23.9)	169 (25.1)	172 (26.1)	164 (26.1)	157 (26.4)
15–19	199 (16.6)	83 (14.0)	95 (14.1)	94 (14.2)	86 (13.7)	83 (13.9)
20–29	186 (15.5)	99 (16.8)	115 (17.1)	101 (15.3)	91 (14.5)	92 (15.5)
30–39	104 (8.7)	48 (8.1)	50 (7.4)	49 (7.4)	50 (8.0)	43 (7.2)
40+	134 (11.1)	50 (8.5)	57 (8.5)	46 (7.0)	53 (8.4)	46 (7.7)
Total	1202 (100)	591 (100)	673 (100)	660 (100)	628 (100)	595 (100)

bladder pathologies were found in patients <20 years old. Eighty (6.7%) of the screened patients had upper urinary tract pathology (all 80 patients had kidney dilatation, and 34 of 80 patients had ureter dilatation). Bladder wall thickening and irregularity of bladder inner surface were significantly associated with ureter dilatation (odds ratio [OR] for bladder wall thickening, 2.4; 95% confidence interval [CI], 1.1–5.1; and OR for irregularity of bladder inner surface, 2.6; 95% CI, 1.2–5.4), and kidney dilatation (OR for bladder wall thickening, 2.3; 95% CI, 1.3–3.8; and OR for irregularity of bladder inner surface, 2.4; 95% CI, 1.5–4.0).

Irregularity of the bladder inner surface and masses or polyps were associated with age, with younger patients having more of these pathologies (M-H linear association test, $P < .001$). Irregularity of bladder inner surface had a peak prevalence among individuals aged 5–9 years, whereas masses or polyps had a peak prevalence among individuals aged 10–14 years. Ureter and kidney dilatation were more frequent in individuals aged 10–14 and 15–19 years than in individuals aged 5–9 or ⩾20 years. Male (χ^2 test, $P < .001$) and heavily infected patients had more pathologies, including irregularity of the bladder inner surface, mass or polyp, and ureter or kidney dilatation. Linear trends were significant for all three pathological changes by baseline intensity of infection level (M-H linear association test, $P < .001$).

Calcification was detected in 18 patients and was associated with increasing age (M-H linear association test, $P < .01$). Only 2 cases of pyelon fibroses were detected among 1173 screened patients (29 of 1202 baseline patients were not screened for pyelon fibrosis; nonparticipation rates did not differ by age, sex, or pathology category).

Resolution of urinary tract pathologies after treatment. Most of the severe bladder pathologies resolved within 1 month, whereas minor irregularity remained for as much as 3 months. Two-thirds (29 [69%] of 42) of the upper urinary tract pathologies were still present at 18 months (figure 1). Overall pathology clearance rates (before resurgence) in the patients aged 5–14 years and in older patients were 95.9% and 89.2%, respectively.

Resolution rates for all types of bladder pathologies did not differ by sex or age group 3 months after treatment. However, for upper urinary tract pathologies, those in school-aged children resolved more completely than did those in older individuals 18 months after treatment (46.7% for individuals aged 5–14 years and 26.9% for those aged ⩾15 years). The resolution rates did not differ by initial intensity of infection or by concurrent infection status (presence of eggs).

Intensity of infection before and after treatment. At baseline, geometric mean egg counts were 31, 71, 80, and 133 eggs per 10 mL of urine for the four pathology categories (no pathology, mild bladder pathology, severe bladder pathology, and upper urinary tract pathology), respectively. More-severe bladder pathologies had higher geometric mean values of egg output (ANOVA, $P < .001$). A peak intensity of infection was observed among individuals aged 10–14 years (137 [95% CI, 96–196], ANOVA by age group, $P < .001$). Mean egg counts were drastically reduced (98.3%) 3 months after treatment. After a 6-month follow-up period, the mean egg count started to increase slowly, and, by 18 months, the overall mean egg count (3) was still low (95.0% reduction from baseline level). A higher intensity of infection at 18 months was significantly associated with younger age (intensity peak in individuals aged 5–9 years: 6 [95% CI, 4–8], ANOVA by age group, $P < .001$). Mean egg counts during the follow-up examinations did not differ by pretreatment pathology-severity category. Although egg counts remained low during follow-up examinations, 224 (37.6%) of the 595 patients had reinfection at 18 months (58.6% for the peak age group [5–9 years]). Mean egg counts did not differ by sex at baseline or at 12 or 18 months after treatment.

Macrohematuria, microhematuria, and proteinuria before and after treatment. Macrohematuria, microhematuria, and proteinuria were observed in 431 (35.9%), 932 (77.5%), and 896 (74.5%) of the 1202 examined patients, respectively, before treatment, all of these findings being most common in individuals aged 10–14 years. All were related to the severity of pathology (M-H linear association test, $P < .001$) and the intensity of infection (M-H linear association test, $P < .001$). All rates decreased to very low levels 6 months after treatment, to 0% (0/660), 14.4% (95/660), and 1.4% (9/660) for macrohematuria, microhematuria, and proteinuria, respectively. Twelve months after treatment, no macrohematuria cases were observed among examined patients. Eighteen months after treatment, 8 (1.3%), 178 (29.9%), and 51 (8.6%) of 595 examined patients had macrohematuria, microhematuria, and proteinuria, respectively.

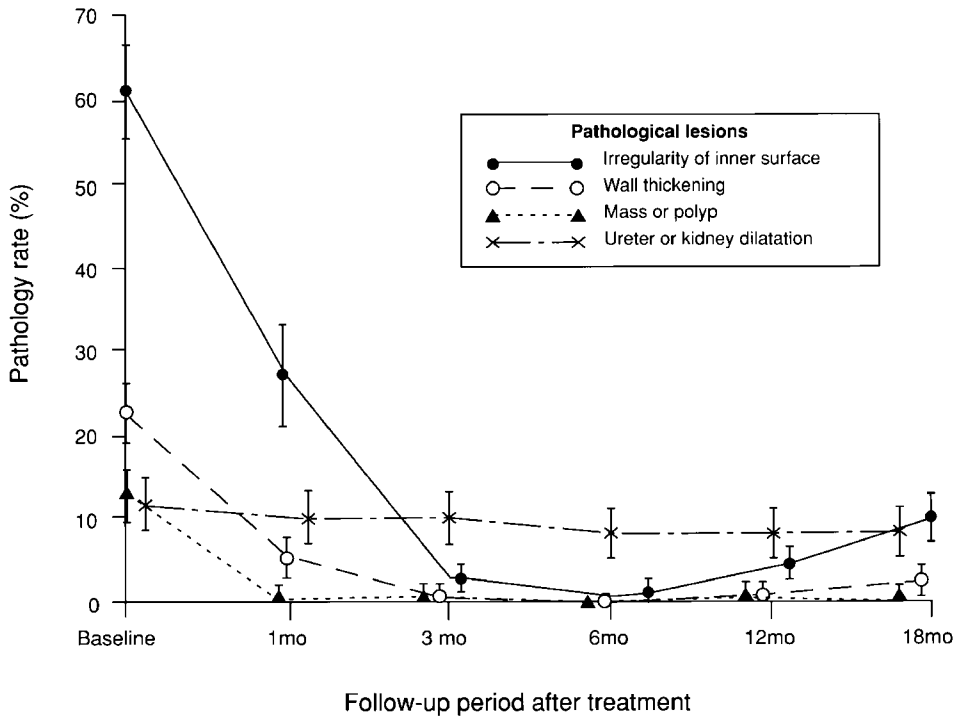

Figure 1. Resolution and resurgence of ultrasound pathologies after treatment among patients who attended all examinations, at baseline, 1, 3, 6, 12, and 18 months after treatment ($n = 363$).

Microhematuria severity level was associated with the severity of bladder pathology resurgence both 12 and 18 months after treatment (M-H linear association test, $P < .001$). Proteinuria was associated with resurgence of bladder pathology only at 18 months after treatment (Fisher's exact test, $P < .01$). Twelve months after treatment, microhematuria occurred most commonly among those aged 5–9 years, whereas 18 months after treatment it occurred most commonly among those aged 10–14 years.

Resurgence of ultrasound pathologies. Mild bladder pathologies (irregularity of the bladder inner surface) reemerged first, followed, at a very low level, by more-severe pathologies, that is, wall thickening. Masses and polyps recurred in only 2 patients 18 months after treatment (figure 1).

Among the patients who did not have an initial pathology or whose pathologies had resolved, 21 (3.4%) of 616 had a reappearance of irregularity of bladder inner surface, 7 (1.1%) of 625 had wall thickening, and 3 (0.5%) of 625 had a mass or polyps 12 months after treatment. At 18 months after treatment, the rates of resurgence were still low, with rates of 9.5% (56/590), 3.2% (19/594), and 0.3% (2/594) for these respective pathologic groups. At 18 months after treatment, younger individuals (aged 5–14 years) showed a higher relative risk of recurrence of bladder inner surface irregularity and wall thickening than did individuals ⩾15 years old (RR for irregularity: 10 [95% CI, 3.8–28.1]; RR for wall thickening: 6.8 [95% CI, 1.6–29.0]). Patients who had pretreatment bladder pathology had a higher relative risk of resurgence of bladder inner surface irregularity and wall thickening than did those who did not have pretreatment pathology (RR for irregularity: 3.7 [95% CI, 1.8–7.7]; RR for wall thickening: 5.4 [95% CI, 1.2–23.3]). The resurgence rate for mild bladder pathology was higher among male (11.4%) than among female (6.5%) patients 18 months after treatment (χ^2 test, $P < .05$). Pretreatment intensity of infection level did not, however, alter the rate of the resurgence of any ultrasound-detected pathologies 18 months after treatment. Those with reinfection 18 months after treatment had a higher relative risk of having resurgence of bladder inner surface irregularity and wall thickening compared with those without reinfection (RR for irregularity: 29 [95% CI, 9.3–92.5]; RR for wall thickening: 14 [95% CI, 3.3–60.2]). A mass or polyp was detected in only 2 patients 18 months after treatment.

Resurgence of bladder pathology by age group, 12 and 18 months after treatment. Figure 2 shows the probability of bladder pathology resurgence 12 and 18 months after treatment for the four age groups. The Mantel-Haenszel test showed a linear association of resurgence decreasing as age increased, both 12 and 18 months after treatment ($P < .001$). At the peak age group (5–9 years), 13 (7.1%) of 184 patients had resurgence of bladder pathologies at 12 months, and 37 (21.3%) of 174 had resurgence at 18 months. Resurgence was not observed in adults at 12 months and was found in only 1 (0.6%) of 179

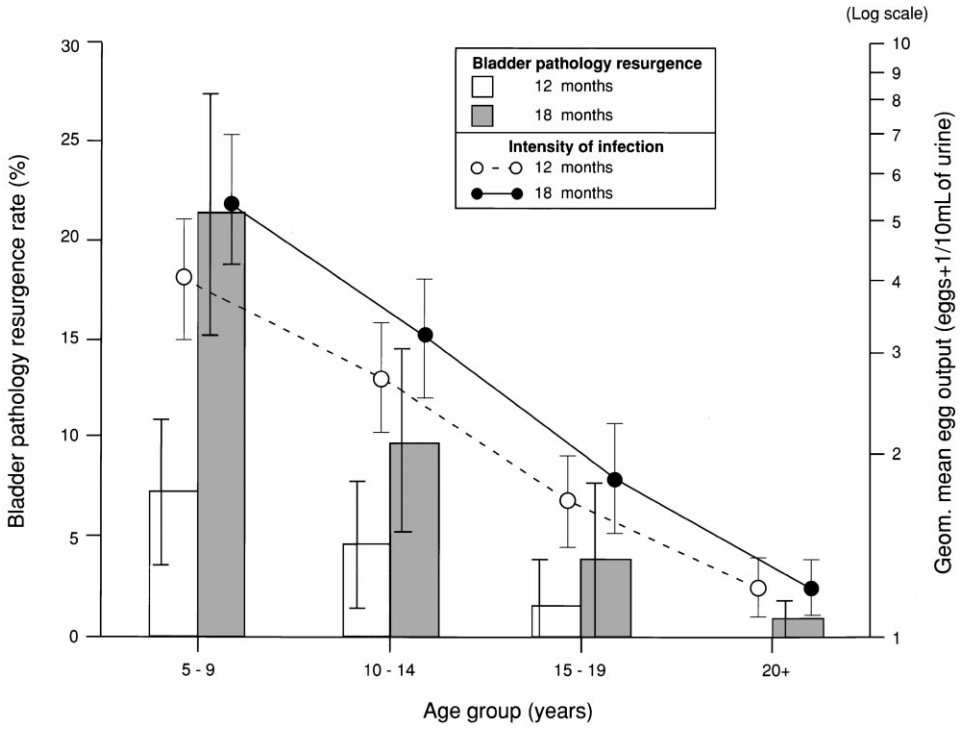

Figure 2. Probability of bladder pathology resurgence and intensity of infection 12 and 18 months after treatment by age group among patients who did not have initial pathology at baseline or whose pathologies had resolved before examinations at 12 and 18 months after treatment ($n = 615$ at 12 months; $n = 590$ at 18 months after treatment).

patients 18 months after treatment. The relative risk of bladder pathology resurgence for the age group 5–14 years versus the ⩾15-year age group was 16.0 [95% CI, 2.2–118] for 12 months and 10.3 [95% CI, 3.8–28] for 18 months after treatment. Figure 2 shows that the intensity of infection decreased with increasing age 12 and 18 months after treatment, respectively.

Resurgence rates 18 months after treatment, by water contact frequency. Figure 3 shows the resurgence rates by water contact and age group at 18 months. Both age and water exposure appeared to be factors in the likelihood of recurrence of urinary pathology, but younger children with frequent water exposure were at highest risk, whereas older individuals appeared to be at low risk regardless of frequency of water exposure. The Mantel-Haenszel test showed a significant linear association of bladder pathology resurgence with water contact level for all ages combined ($P < .01$). There was a borderline significance by the frequency of water contact for the age groups 5–9 and 10–14 years (M-H linear association test, $P < .10$). Intensity of infection was related to water contact level for all ages combined (ANOVA, $P < .001$), for age group 10–14 years (ANOVA, $P < .05$), and for age group ⩾15 years (ANOVA, $P < .10$).

Discussion

Three features distinguish this study of *S. haematobium* infection: (1) study patients were chosen by population-based sampling for baseline and follow-up examinations, (2) a relatively large number of patients with differing pretreatment pathologies were followed longitudinally, and (3) the study allowed observation of the pathological resolution and resurgence after community-based chemotherapy.

The study showed that infected younger children (aged 5–9 years) tended to have milder bladder pathologies and that older children (aged 10–14 years) had more-severe pathology. These findings are consistent with a progression of severity through school-aged children. Furthermore, treatment with praziquantel was nearly universally effective in eliminating bladder pathology from those treated, but older individuals with upper urinary tract disease were more resistant to resolution of their pathologies. Resurgence of pathology did occur but tended to be mild at 18 months after treatment and occurred primarily in individuals aged 5–9 years. Resurgence of severe pathology during the 18-month follow-up period was not observed. Younger children (aged 5–9 years) with frequent water exposure were at highest risk for bladder pathology resurgence, with the highest intensity of infection.

Previous community-based ultrasound studies have indicated that severe bladder pathology occurs in school-aged children and that this group should be targeted for intervention [7–10]. This study showed that there was a peak of minor bladder wall pathology at age 5–9 years but that more-severe bladder le-

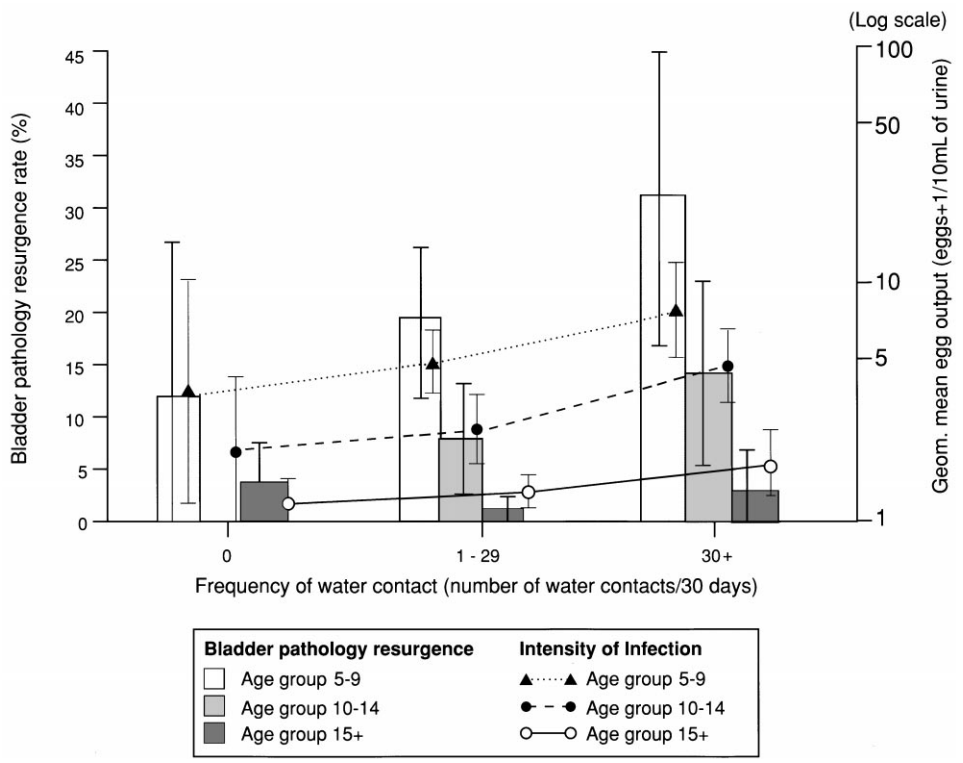

Figure 3. Probability of bladder pathology resurgence and intensity of infection by frequency of water contact and age group 18 months after treatment among patients who did not have initial pathology at baseline or whose pathologies had resolved before examination at 18 months after treatment ($n = 590$).

sions—for example, wall thickening >5 mm and masses or polyps—tended to occur in individuals aged 10–14 years. The previous studies were not able to stratify their results by small age-group intervals because of smaller sample sizes within the different pathology categories.

Although the observation periods after treatment varied, the significant resolution of bladder pathologies within a few months after treatment has been seen previously [5, 10, 18–21]. Doehring et al. [19] observed the disappearance of severe bladder pathologies, that is, wall thickening (>5 mm) and polyps, within 1 month. Devidas et al. [20] reported regression of bladder pathologies 10 months after treatment, with no difference by age, sex, or initial intensity of infection, similar to our results.

Many of the upper urinary tract pathologies did not resolve during the 18-month follow-up period, and only 37.5% of kidney dilatations were resolved. Others have also observed that upper urinary tract pathology is less likely to resolve. King et al. [21] reported delayed clearance of kidney lesions 1 year after treatment in coastal Kenya. By contrast, others have observed resolution of lesions, and improvement rates have ranged from 73% to 95% [10, 18, 20]. The age distribution among the various studies differed, and studies reporting high reversibility included mostly children. Data from the present study suggest that upper urinary tract pathology in younger children is more responsive to treatment than that of older children and adults. This is the expected finding if long-standing pathology results in fibrosis and scarring, a condition less likely to respond to praziquantel.

There are only a few well-designed population-based sample studies using ultrasound to assess the long-term morbidity pattern in the endemic population after community-based chemotherapy. King et al. [22] reported that resurgence rates of urinary tract lesions remained at a very low level even 2 years after discontinuing chemotherapy. A recent longitudinal study showed that some severe pathology requiring treatment appeared at 18 months, and the incidence increased to 11% at 24 months [5]. Some control programs found that annual retreatment was effective for populations at risk [22, 23]. In our study, younger children (aged 5–9 years) showed the highest resurgence rates, and a decreasing trend of resurgence was observed with age. Even for this age group, <10% of the children had resurgence 12 months later, and one-fifth of the children had recurrence of mainly mild bladder lesions 18 months after treatment.

Some studies have argued that water-contact patterns may explain the age-related distribution of schistosomiasis [24, 25]. Our study demonstrates an age-related pattern of water contact. The epidemiological significance of immunity in human schistosomiasis has been the subject of inconclusive debate. Recent

studies have confirmed the importance of protective immunity [26–28]. Therefore, the different resurgence rates among the different age groups observed among study patients suggests that exposed children had a higher risk of bladder lesions 12 and 18 months later, but the older patients had a low risk of resurgence regardless of water exposure, suggesting that these individuals had developed protective immunity.

Microhematuria as detected by urine reagent strips predicts well the severity of pathology both before and after community-based treatment. Gross hematuria and proteinuria are good predictive indicators for pathology in a pretreatment population, but they are less sensitive 12 and 18 months after treatment, when only mild pathologies reappeared. Further studies using these indicators with a predictive potential for direct morbidity (i.e., pathology) should be encouraged, to evaluate the long-term effectiveness and cost-effectiveness of feasible control programs in different endemic areas.

One limitation of our findings is that the study was conducted in one region of Ghana. Transmission of *S. haematobium* in the study area was typical for this parasite, but other geographic areas might have somewhat different transmission patterns. Second, the infected populations in other geographic areas may differ in their immune responses to the parasite, resulting in differing rates of resurgence. Third, strains of *S. haematobium* in other areas could vary in their virulence and their likelihood of inducing resurgent pathology. Thus, confirmation of these results in other areas endemic for *S. haematobium* is needed before general policies can be formed.

With these reservations, the present study suggests that, in areas with high rates of infection, such as this area in Ghana, treatment should be provided to children at the age of admission to primary school (7–9 years). Retreatment may be needed, but annual retreatment is not necessary in this setting. The optimal time for retreatment is not established by the present study, but the low rate of resurgence with severe pathology suggests that retreatment might be given at approximately the time of graduation from primary school (12–15 years). The timing of this treatment schedule is intended to prevent severe pathology, and it emphasizes the importance of preventing schistosomiasis-related disability rather than simply treating infections.

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