LATE BENEFITS 10–18 YEARS AFTER DRUG THERAPY FOR INFECTION WITH *SCHISTOSOMA HAEMATOBIUM* IN KWALE DISTRICT, COAST PROVINCE, KENYA

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Abstract. Late benefits of remote antischistosomal therapy were estimated among long-term residents of an area with high transmission of *Schistosoma haematobium* (Msambweni, Kenya) by comparing infection and disease prevalence in two local adult cohorts. We compared 132 formerly treated adults (given treatment in childhood or adolescence ≥ 10 years previously) compared with 132 age- and sex-matched adults from the same villages who had not received prior treatment. The prevalence of current infection, hematuria, and ultrasound bladder abnormalities were significantly lower among the previously treated group, who were found to be free of severe bladder disease. Nevertheless, heavy infection was equally prevalent (2–3%) in both study groups, and present rates of hydronephrosis were not significantly different. Therapy given in childhood or adolescence appears to improve risk for some but not all manifestations of *S. haematobium* infection in later adult life. Future prospective studies of continued treatment into adulthood will better define means to obtain optimal, community-based control of *S. haematobium*-related disease in high-risk locations.

INTRODUCTION

Urinary schistosomiasis due to *Schistosoma haematobium* is a significant cause of clinical morbidity and disability in disease-endemic countries of Africa and the Middle East, where more than 110 million people are infected.[1] Accumulation of parasite eggs in body tissues leads to acute and chronic injury,[2] and long-term infection is associated with increasing structural urinary tract damage, with consequent bladder and kidney dysfunction, and risk for cancer.[3–5]

In childhood or early adolescence, most forms of *S. haematobium*-associated morbidity are readily reversed by drug treatment.[6,7] However, at this same stage of life, risk for reinfection is at its highest level.[8] Given the interplay of these two competing factors, some policy assessments have suggested that a single praziquantel treatment, given in mid-to-late adolescence (after the period of greatest risk of reinfection), could potentially provide the most cost-effective means of achieving long-term infection-free periods for adult residents. Furthermore, provided morbidity remains reversible at mid-adolescence, such therapy would regress existing morbidity, and consequently reduce levels of late *S. haematobium*-related disease found among the population at large.[9,10] However, the validity of this strategy has not been tested. To estimate its potential utility in areas highly endemic for schistosomiasis, the present study examined late (adult) posttreatment outcomes following implementation of a long-term, school-based *S. haematobium* control program in coastal Kenya. The objective of this observational analysis was to analyze whether one or more past drug treatments, taken in late childhood or early adolescence, was indeed associated with reduced rates of *S. haematobium* infection or morbidity 10–18 years later, when subjects were re-examined as adults.

METHODS

Ethical oversight. All participants provided individual informed consent according to guidelines of the Declaration of Helsinki. The research protocol was reviewed and approved by the Ethical Review Board of the Kenya Medical Research Institute and by the Institutional Review Board for Human Investigation of University Hospitals of Cleveland**.** All subjects infected with *S. haematobium* were treated with standard doses of praziquantel (40 mg/kg) immediately following the morbidity survey.

Location. The study was conducted in the adjoining villages of Marigiza, Milalani, Mabatani, Nganja, and Vindungeni (aggregate population = 4,408) situated in the Msambweni location of Kwale District in the Coast Province of Kenya. This area, which is highly endemic for *S. haematobium*, is 50 km southwest of Mombasa on the Indian Ocean. The area is predominantly rural, and the leading occupations are mixed agriculture and fishing. Children from these villages had previously participated in studies of school-based control of *S. haematobium* during 1983–1992.[11] However, at the time of the present survey (2000–2001), there had been no organized treatment of for eight years, and the overall age profile of area-wide infection prevalence and intensity had reverted to pre-control levels.

Study population. *Inclusion criteria.* To evaluate the potential benefits of previous, remote anti-schistosomal therapy, we examined all available long-term area residents ≥ 22 years of age with a history of treatment ≥ 10 years previously (and without subsequent treatment) for their prevalence of *S. haematobium* infection and infection-related morbidity. Long-term local residency status was defined as continuing membership in a local household group, with primary domicile (sleeping quarters) being in the study area. Such continued residency was established by current interview, and confirmed by reference to the records of community censuses performed in the area for research purposes in 1983, 1984, 1987, 1997, and 2000–2001. Those household members who were not regularly domiciled within the community (e.g., long-term employment out of area) were excluded. After enrollment, the last date of therapy of the included subject was determined by interview, and confirmed by reference to local pharmacy records and records from an area treatment control program that had been active between 1984 and 1992.[11] (No control programs were active in the study area during the

interval from 1992 to the present study.) A total of 132 subjects meeting these entry criteria were enrolled, along with a comparison group of 132 village-, age-, and sex-matched control subjects, who were also long-term residents of the study area, but who had not received therapy. The untreated status of the latter comparison group was determined by detailed subject interview, and confirmed by reference to study and pharmacy records. Because of the (otherwise) very limited availability of antischistosomal drugs in the District until the present time, it was inferred that the comparison group had not received any anti-schistosomal therapy before the present study.

Parasitologic examination for *S. haematobium* infection. All participants provided two urine samples at least 24 hours apart, which were collected at mid-day, i.e., between 10:00 AM and 2:00 PM. The presence of *S. haematobium* eggs was measured by Nucleopore (Pleasanton, CA) polycarbonate filtration as previously described.[12] The average of the two specimens from each individual was used for egg count (infection intensity) analysis.

Prevalence of morbidity. *Hematuria.* Microhematuria was evaluated in semi-quantitative fashion using reagent strips (Hemastix®; Ames, Bie and Bernsten, Copenhagen, Denmark), and results were ranked as negative, trace, 1+, 2+, or 3+, according to the manufacturer's instructions. Macrohematuria was scored as positive when urine samples showed red-brown color or frank blood.

Kidney and bladder disease. Kidney and bladder diseases were detected by ultrasound examination (by EM, HK, and PM) using a standardized World Health Organization protocol.[13] Following this approach, each examination was systematically scored independently by two readers for severity of bladder thickening and irregularity and for severity of renal outflow obstruction (hydronephrosis or hydroureter).

Data analysis. Outcomes for the previously treated and untreated comparison groups were entered and rechecked with the use of desktop computer spreadsheets. Statistical testing was conducted with SAS version 9 statistical software (SAS, Cary, NC).

Comparison of treated and untreated groups. Outcomes data for infection status, infection intensity, hematuria, and ultrasound-detectable urinary tract morbidity were analyzed for group-wise differences by McNemar's test (paired data) of categorical outcomes, and a paired *t*-test for continuous variables. Because of the skewed distribution of subject egg counts, mean infection intensity data were also compared after the standard $\log_{10}$ (egg count + 1) transformation. In further analysis, age-related differences were examined by the chi-square test, and the overall, age-adjusted association of study outcomes with treatment status (i.e., adjusted odds ratio [OR]) was estimated by the Mantel-Haenszel test of age-stratified data.[14] Homogeneity of effects across age strata was tested by the method of Breslow and Day.[15]

Analysis of factors affecting outcomes within the treated group. An exploration of the combined influence of host-specific and treatment factors on the observed *S. haematobium*-associated outcomes was conducted by multivariable logistic regression analysis of data from the treated group only (n = 132). The influence of age, sex, drug regimen (praziquantel, metrifonate, or crossover), multiplicity of treatment, and age at last therapy were assessed by estimation of adjusted ORs of present infection, hematuria, and bladder disease in separate logistic regression models for each outcome. These explanatory variables were included as likely to have a significant biologic effect on risk for reinfection or persistence of infection, and thus, present disease manifestations.[1,8,16] The individual significance, multiply adjusted significance, and potential interaction of these factors was determined in nested models by stepwise multivariable logistic regression analysis.[17]

RESULTS

Prevalence and intensity of *S. haematobium* infection. The demographic features of the two study groups are summarized in Table 1, along with their observed infection and morbidity outcomes. Of note, the current prevalence of infection was significantly lower among those with remote prior therapy (22% for the treated group versus 33% for matched untreated subjects; McNemar's S = 3.92, $P < 0.05$). However, the overall prevalence of persons with heavy infection (eggs counts > 100 eggs/10 mL) was comparable in both groups (2–3%, P = not significant). Egg burden was also not significantly different between the previously treated and untreated

TABLE 1

Comparison of remotely treated and matched untreated individuals from the Msambweni study area for demography and observed prevalence of infection and morbidity outcomes*

	Remotely-treated (n = 132)	Not treated (n = 132)
Male/females	63/69	63/69
Age ± SD, years	29.1 ± 7.5	30.4 ± 8.1
Infection prevalence (95% CI)	22% (16–30%)†	33% (25–42%)
Heavy infection prevalence (egg count ≥ 100 per 10 mL)	2.3% (0.5–6.6%)	3.0% (0.8–7.7%)
Geometric mean egg count	1.8	2.4
Hematuria (95% CI)	38% (30–47%)	41% (32–49%)
Severe hematuria (95% CI)	14% (9–22%)†	23% (17–32%)
Bladder abnormality by ultrasound (95% CI)	0.7% (0.2–4.2%)†	4.5% (1.7–9.8%)
Advanced kidney abnormality by ultrasound (95% CI)	0.7% (0.2–4.2%)	0.7% (0.2–4.2%)
Mean ± SD age at last therapy, years	13.1 ± 3.7	
(range)	(3–23)	–
Mean ± SD interval since last therapy	14.5 ± 2.6	
(range)	(10–18)	–

* CI = confidence interval.
† Significantly different between treated and untreated groups at the $P < 0.05$ level.

adult pairs studied (mean ± SEM difference = −0.53 ± 1.5 eggs per 10 mL of urine; P = not significant).

Prevalence of morbidity. *Hematuria.* At the time of our follow-up examinations, prevalence of hematuria was 40% among the previously treated group and 39% among untreated subjects (P = not significant). Moderate-to-severe hematuria (visible hematuria = 2+ or 3+ by dipstick) was more common among untreated subjects (prevalence = 24%) than among those previously treated (prevalence = 14%), and this difference had borderline statistical significance (McNemar's S = 3.6, P = 0.058).

Bladder abnormalities and hydronephrosis. Ultrasound bladder abnormalities were significantly less common among the previously treated group (1% for treated versus 5% for the untreated group; McNemar's S = 5.0, P = 0.025). There was a total absence of severe grade bladder thickening or irregularity among the previously treated subjects. In contrast, prevalence of adult hydronephrosis was not significantly different between the previously treated and untreated groups (1% for treated versus 1% for untreated; P = not significant).

Effect of current age on prevalence of infection and disease: age-adjusted estimates of the effect of past treatment. In further analysis, the present age status of the subjects was observed to have a significant effect on their current prevalence of infection (for age groups in their 20s, 30s, and > 40, with respective infection prevalences of 35%, 21%, and 0%;

$\chi^2_{infection}$ = 12.0, degrees of freedom = 2, P = 0.0025). To adjust for the effect of this potentially confounding factor, age-stratified analysis was conducted for infection and disease outcomes, and age-adjusted estimates of the overall effect of remote treatment were generated by the Mantel-Haenszel technique. When compared with the untreated cohort, the OR (95% confidence interval [CI]) among the previously treated subjects was 0.71 (0.52–0.96) for infection, 0.69 (0.47–1.00) for moderate-severe hematuria, and 0.26 (0.04–1.62) for bladder disease. Because cases of hydronephrosis were few in number, meaningful statistical comparisons by age group could not be made for this outcome. The age-related impact of remote therapy on current prevalence of *S. haematobium* infection and its related morbidity outcomes is summarized in Figure 1. Of note, prior therapy appeared to have a greater effect on infection prevalence among the youngest adult age group (20–29 years of age), whereas its impact on hematuria and bladder disease was distributed across both younger and older age brackets.

Factors influencing disease outcomes among the previously-treated cohort. In reviewing the range of past treatment experience among the previously treated cohort, several aspects of treatment were suggested as possibly modifying the late treatment outcomes that were observed. To investigate this further, we examined by multivariable analysis whether present age, sex, choice of drug, timing of delivery, or interval since therapy significantly influenced the outcomes among
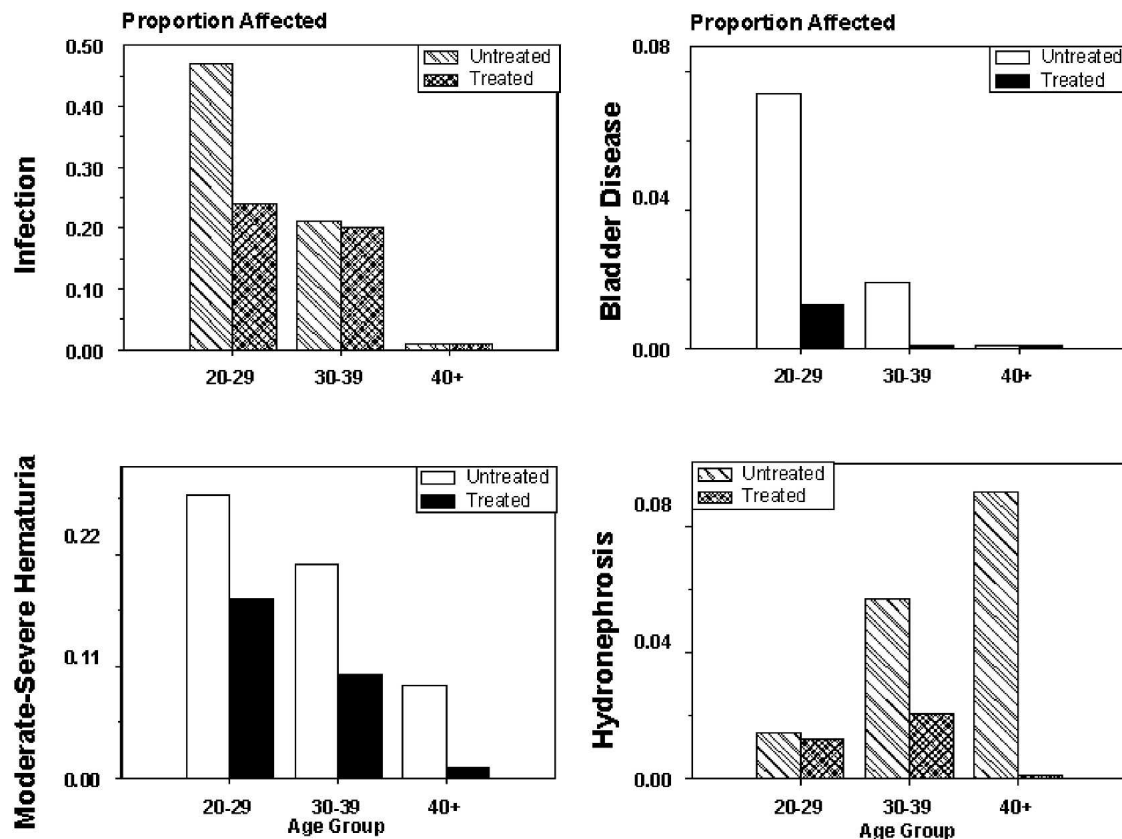

FIGURE 1. Comparison of the current prevalence of *Schistosoma haematobium* infection and morbidity outcomes according to treatment status for the previously treated and untreated groups stratified according to current age group. Age-adjusted estimates of treatment effect were odds ratio (OR) (95% confidence interval) = 0.71 (0.52–0.96) for infection; OR = 0.69 (0.47–1.00) for moderate-severe hematuria; and OR = 0.26 (0.04–1.62) for bladder disease. Cases of hydronephrosis (**lower right**) were too few for meaningful statistical comparison. In each study cohort, respective group sizes were: 20–29 years old, n = 68; 30–39 years old, n = 53; ≥ 40 years old, n = 11.

the remotely treated subjects in our study. Beyond age and sex, the specific factors examined were 1) the cumulative number of times a subject had been treated, 2) the drugs taken (praziquantel, metrifonate, or crossover), 3) the age of the subject at last treatment, and 4) the interval (in years) elapsed since last treatment.

We noted that subjects with a greater number of recorded treatments had a significantly lower prevalence of infection and bladder disease (Figure 2; not shown are the effects multiple treatment, which were not statistically significant for hematuria and kidney disease). After adjustment for age, sex, choice of drug, and interval since last treatment, the impact of multiple therapy remained significant ($P < 0.02$ for infection and $P < 0.03$ for bladder disease). The adjusted OR (95% CI) for infection was 0.67 (0.49–0.92) per treatment given, and the adjusted OR (95% CI) for bladder disease was 0.32 (0.11–0.95) per treatment. No significant interaction was found with the other factors included in the model (Table 2).

In separate analyses, the age at last treatment (4–22.5 years) also had a significant impact on the odds of current infection and of hematuria, but not of bladder disease or other outcomes (Figure 3). This effect remained significant even after adjustment for the time elapsed since last treatment, the sex and current age of the subject, and the number

and type of treatments received (adjusted OR = 0.80, 95% CI = 0.67, 0.94) per year of age at last treatment of infection; for hematuria, OR = 0.90 per year, 95% CI = 0.83–0.98).

As indicated in Table 2, after adjustment for the multiple factors included in the logistic model, current age, sex, choice of drugs given, and interval since last therapy were not significant independent predictors of infection or bladder morbidity among the previously treated group.

DISCUSSION

The results of our long-term follow-up survey, which was conducted 10–18 years after the latest treatment of the subjects for infection with *S. haematobium*, indicate that some benefits of earlier antischistosomal therapy can persist into later life. Nearly all of the remotely treated individuals included in this study had received their therapy as part of a local school-based drug treatment program that had been active between 1984 and 1992, but later suspended due to lack of funds.[6,11] All subjects were long-term residents of the Msambweni area of Kwale District, Coast Province, Kenya, a region that remains highly endemic for urinary schistosomiasis.[18] Among the study subjects, a history of previous remote therapy was significantly associated with reduced risk of present infection and reduced risk of bladder disease (measured as moderate or severe thickening and irregularity on ultrasound examination).[13] In addition, we detected a trend toward reduced risk of severe-grade hematuria among the previously treated group. Although both current infection risk and the treatment effect of remote therapy appeared to vary among age groups (Figure 1), this apparent age-related effect was probably confounded by the varying times elapsed since the prior therapy of the subjects, and by the number of prior treatments they had received. After multivariate adjustment for these effects, both the number of prior annual treatment and the age of the subject at the time of the latest treatment proved to have significant effects on the odds of adult infection, bladder disease, or hematuria in our study (Figures 2 and 3).

In a typical disease-endemic community, children between the ages of 10–16 have the greatest prevalence and the highest intensity of *S. haematobium* infection.[16,19] Concurrent intensity of infection has been associated with acute forms of pathology, such as hematuria and urinary tract granuloma formation, whereas chronic forms of morbidity are also thought to be associated with the long-term duration of infection.[2,3] Policy reviews have suggested that treatment focused on school age children, who carry the heaviest burden of infection in most disease-endemic communities, would serve both to reduce current intensity of infection and to prevent accumulation of long-term injury due to continuing infection, thus subsequently reducing the community burden of disease.[20–22] However, the long-term impact of such a strategy has not been tested. Our present observational results from matched cohorts suggest that the benefits of childhood or adolescent treatment can persist into adulthood, particularly if the therapy is given into adolescence. More recent policy reviews[9] have suggested that due to the high frequency of reinfection during childhood and the relatively high cost of antischistosomal interventions, a single antischistosomal treatment could be given at age 15, which might suffice to
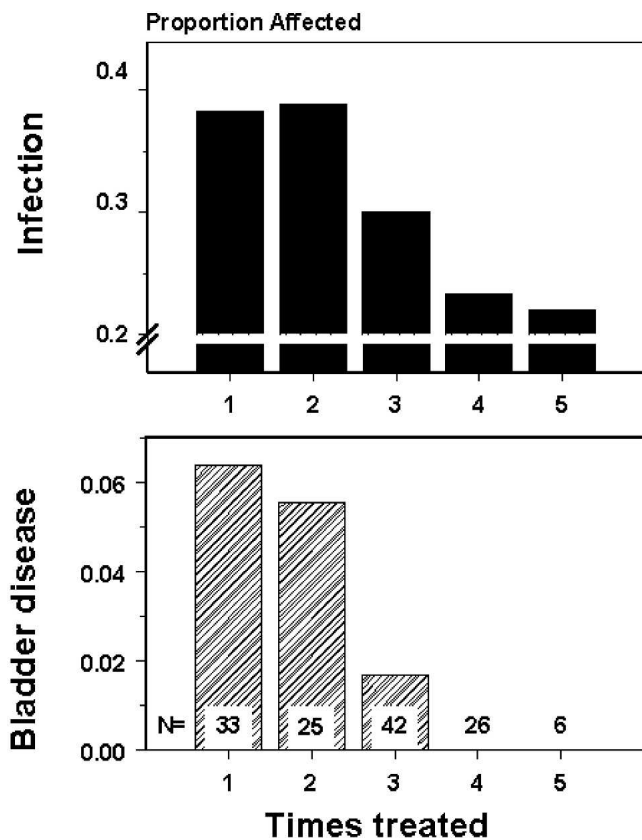

FIGURE 2.   Impact of single or repeated childhood treatments on the prevalence of current *Schistosoma haematobium* infection (**upper panel**) or bladder disease (**lower panel**) among the 132 study subjects with a history of remote prior therapy. Subjects with additional prior treatments had significantly lower prevalence of infection or bladder disease as adults when compared with those with fewer treatments (see text for details). The number of individuals in each group indicated within the bars in the lower panel.

TABLE 2
Multiply-adjusted odds ratio (OR) estimates for the presence of *Schistosoma haematobium* infection, hematuria, or infection-related bladder disease among remotely treated adults surveyed in the Msambweni area of Coast Province, Kenya in 2000–2001

Factor evaluated for effect	Adjusted OR of current infection (95% confidence limits)	Adjusted OR of hematuria (95% confidence limits)	Adjusted OR of current bladder disease (95% confidence limits)
Current age = 21–29 years	1.76 (0.49, 6.28)	1.91 (0.56, 6.56)	3.02 (0.11, 82.7)
Current age = 30–39 years	1.27 (0.54, 2.97)	2.44 (1.09, 5.50)*	1.94 (0.15, 23.9)
Current age ≥ 40 years	(Comparison group)	(Comparison group)	(Comparison group)
Female	1.57 (0.83, 2.98)	1.73 (0.94, 3.16)	0.19 (0.02, 1.84)
Male	(Comparison group)	(Comparison group)	(Comparison group)
Metrifonate treatment	1.52 (0.66, 3.46)	1.62 (0.75, 3.50)	2.03 (0.19, 21.7)
Mixed regimen	2.38 (0.92, 6.16)	1.42 (0.59, 3.43)	3.44 (0.19, 61.2)
Praziquantel treatment	(Comparison group)	(Comparison group)	(Comparison group)
Per treatment effect	0.67 (0.49, 0.92)*	0.84 (0.63, 1.13)	0.32 (0.11, 0.95)*
Interval effect, per year since treatment	0.92 (0.78, 1.08)	0.97 (0.83, 1.13)	0.94 (0.62, 1.42)

* Significantly different from OR = 1.

eliminate the risk of late disease. The results of our study, which indicate greater benefits from repeated therapies, serve to contradict this single-dose recommendation, and suggest that in the face of recurring infection risk, several treatments during the 10–15-year age period would provide better control of disease in endemic areas such as ours. It remains to be determined what further benefits can be obtained by community-based therapy into adulthood.

There are a number of limitations to this study. Both the previously treated and untreated subjects were identified as part of a community-wide survey of household infection risk, and their classification as treated or untreated is based, in part, on their own recollection of any prior therapy. Because routine antischistosomal therapy continues to be rare in local health facilities and clinics, almost all of the previous treatment had been received as part of a 1984–1992 school-based treatment program, and could be confirmed from program records. For most untreated subjects, long-term residence could be confirmed from project census records from the same period. However, not all residence or treatment histories could be independently confirmed, with the possibility of misclassification bias in our analysis. The number of subjects in some subgroup categories was small, which limited our ability to detect small clinical differences that might prove significant in larger studies.[23] This was an observational, retrospective study, which might not have captured important risk factors related to present infection or disease among adult study sub-groups. For example, the earlier willingness (or opportunity) of a subject to take school-based treatment might have reflected a significant difference in his or her risk of re-exposure during the intervening decades, potentially resulting in significant differences in the interpretation of the observed outcomes. Nevertheless, the results of the present study are in accord with an earlier long-term (seven-year) follow-up of area residents treated for structural urinary tract abnormalities.[24] That study, which included a comparison group of subjects from villages outside of the Msambweni treatment area, demonstrated that school-age treatment significantly reduced adolescent and adult urinary tract morbidity despite intervening *S. haematobium* re-infection.

The 264 (132 subject pairs) included in this study were individuals for whom we could be reasonably definite about continued residency status and treatment history. The aspect of confirmed, continuing area residency was believed to be a key factor, in that subject age then similarly reflects the com-
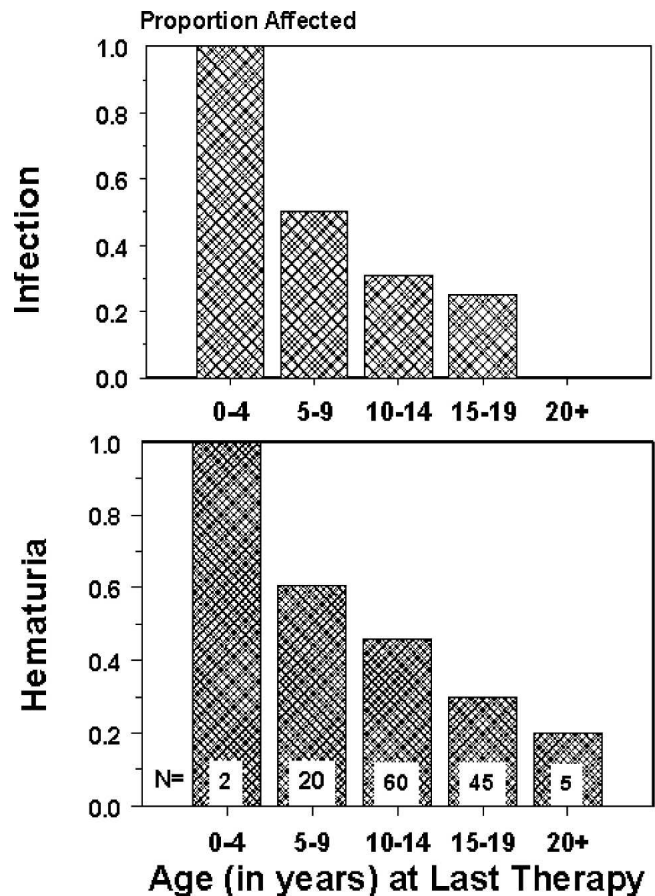

FIGURE 3. Effect of subject age at the time of last treatment on current prevalence of *Schistosoma haematobium* infection (**upper panel**) and related hematuria (**lower panel**). Older age at last treatment was associated with progressively decreasing odds of infection or hematuria among the treated study subgroup (unadjusted odds ratio [OR] = 0.89, 95% confidence interval [CI] = 0.82–0.97 for infection and unadjusted OR = 0.89, 95% CI = 0.82–0.96 for hematuria) for each year of a subject's age at the time of last treatment (see text for adjusted values). Bars indicate current prevalence according to age at last treatment, grouped by five-year age strata, and the number of individuals in each group is indicated within the bars in the lower panel.

plex combination of current exposure risk, past exposure history, as well as exposure-related effects on immunity and disease formation. With matching for stable residency status and for sex and age, study pairs had a shared, secular exposure history for infection and risk of subsequent disease. This was believed to be an important consideration for the meaningful detection of treatment effects. However, the inclusion/exclusion requirements reduced the number of local residents included in the analysis, and thus selection criteria may have unintentionally biased the observed results.

Many schistosomiasis-endemic countries in Africa are now working towards national programs aimed at control of morbidity due to infection, as recommended by the World Health Organization.[25] Current guidelines for community-based morbidity control appropriately focus on school-age treatment in highly disease-endemic communities. However, our present findings suggest that although the adult prevalence of bladder abnormalities is reduced by prior therapy in childhood or adolescence, repeated therapy into adulthood may be required to fully control hematuria and hydronephrosis in high-risk adult populations. Prospective studies of long-term treatment outcomes will be needed to define the optimum number of treatments given after adolescence that are required to obtain the lowest practical levels of community-wide *S. haematobium*-related morbidity.

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