CHAPTER 2

UROGENITAL SCHISTOSOMIASIS IN WOMEN OF REPRODUCTIVE AGE IN TANZANIA'S LAKE VICTORIA REGION.

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Abstract

We conducted a community-based study of 457 women aged 18--50 years living in eight rural villages in northwest Tanzania. The prevalence of female urogenital schistosomiasis (FUS) was 5% overall but ranged from 0 to 11%. FUS was associated with HIV infection (OR = 4.0, 95% confidence interval: [1.2--13.5]) and younger age (OR = 5.5 [1.2--26.3] for age < 25 years and 8.2 [1.7--38.4] for age 25--29, compared to age > 35). Overall HIV prevalence was 5.9% but was 17% among women with FUS. We observed significant geographical clustering of schistosomiasis: northern villages near Lake Victoria had more *S. mansoni* infections ($p < 0.0001$), and southern villages further from the lake had more *S. haematobium* ($p = 0.002$). Our data support the postulate that FUS may be a risk factor for HIV infection, and may contribute to the extremely high rates of HIV among young women in sub-Saharan Africa.

Introduction

Female urogenital schistosomiasis (FUS) is predominantly caused by *Schistosoma haematobium* and has been estimated by the World Health Organization (WHO) to affect up to 45 million women living in sub-Saharan Africa.[1] Adult *S. haematobium* worms inhabit blood vessels surrounding the urinary bladder and female genital tract and lay eggs that migrate through tissue of proximate organs, causing chronic granulomatous inflammation most commonly in the urinary bladder, ureters, cervix, and vagina. Because the urinary and genital tracts are almost always both affected, the WHO has recently renamed this disease "urogenital schistosomiasis," with detection of *S. haematobium* in the urine or genital tract diagnostic.[1]

Chronic female genital tract inflammation caused by *S. haematobium* has been associated with vaginal itching and discharge,[2] postcoital bleeding,[3] genitopelvic discomfort,[4] marital discord,[5] and infertility.[6,7] Genital *S. haematobium* infection has been associated with HIV infection in one cross-sectional study[7] and has been postulated to be a risk factor for HIV infection.[8,9]

Tanzania's Lake Victoria region in northwestern Tanzania borders Kenya, Uganda, and Rwanda and is believed to have among the highest prevalence of *S. haematobium* in the world, with a prevalence of 50--90% reported in young schoolchildren.[10] The prevalence of *S. haematobium* infection has not been quantified in women of reproductive age, the population at risk for increased HIV infection. Therefore, we conducted a study in Tanzania's Lake Victoria region to determine the prevalence and identify risk factors for FUS among women of reproductive age.

Materials and methods

Study sites and subjects. This cross-sectional study was conducted between August 2009 and May 2010 near Lake Victoria in northwest Tanzania in partnership with a cervical cancer screening program being conducted at local health centers. Women who were receiving free cervical cancer screening, were between the age of 18 and 50 years, and who provided written consent were invited to participate in the FUS prevalence study. Women who were menstruating or who refused gynecologic examination were excluded. Pregnant and breastfeeding women were included.

Urine and gynecologic examination. A single urine sample was collected from women between 10am and 2pm and filtered and examined microscopically by a

trained parasitologist for schistosomal ova. A subset of the urine samples were read by two parasitologists for quality control.

Women who provided informed consent underwent a gynecological examination. A swab of vaginal secretions was collected for wet preparation and microscopic examination for diagnosis of Candida (using a potassium hydroxide preparation), *Trichomonas vaginalis* (using warm normal saline), and bacterial vaginosis by Amsel's criteria.[11] Next, a cervical smear was collected using a plastic spatula. Smears were stained with 0.5% Trypan Blue and were examined for schistosomal ova while fresh. Acetic acid was then applied to the face of the cervix, followed by inspection for abnormal areas after one minute. Abnormal cervical lesions were biopsied. Specimens were stained with Hematoxylin and Eosin (H&E) for histopathological examination and with Trypan Blue to examine for schistosomal ova using the "crush technique" previously described.[6,12] Biopsies were not performed on pregnant women.

Female urogenital schistosomiasis (FUS) was defined following WHO criteria as the presence of at least one schistosomal ovum seen in the urine sample, cervical smear, or cervical biopsy.[1]

Other laboratory studies. Single stool samples for *S. mansoni* ova were processed by Kato Katz technique. HIV voluntary counseling and testing was offered to all participants. For those who agreed to be tested, blood was collected and tested using a rapid test (SD Bioline). Testing was performed in the field and patients received their results immediately. Venous blood was also collected and tested for syphilis using the Rapid Plasma Reagin (RPR) test and positive tests were confirmed with the *Treponema pallidum* Particle Agglutination assay (TPPA).

Interview. Women also participated in a 20-minute structured interview about water contact, gynecologic symptoms, sexual history, and depression. The interview was administered by a nurse in Kiswahili. Women were asked to use a 4-point Likert scale to quantify how much, over the past four weeks, they had been bothered by dyspareunia, vaginal discharge, postcoital bleeding, abdominopelvic pain, infertility, menstrual abnormalities, genital itch, and incontinence. Using a 5-point Likert scale to assess sexual dysfunction, women were also asked how much they worried about pain during intercourse, made excuses to avoid intercourse, had experienced decreased frequency or quality of intercourse, and were concerned about partner infidelity. We assessed the responses to these questions as binary variables, where answers of "very much" or "somewhat" were considered positive, while answers of "rarely" or "not at all" were considered negative.

Depression was evaluated using a 9-item depression scale, the PHQ-9, that has been previously translated and validated in Kiswahili in several patient populations.[13,14] The PHQ-9 consists of nine questions, each designed to assess for one of the nine symptoms of depression delineated by the Diagnostic and Statistical Manual-IV (DSM-IV) for depression. These include anhedonia, sleeplessness or excessive sleep, hopelessness, poor or excessive appetite, difficulty concentrating, and feelings of failure. Participants receive between 0 and 3 points on each question, with 0 indicating that they experienced a given symptom "Not at all" and 3 indicating "Nearly every day". A total score of 5--9 has been classified as mild depression, 10--14 indicates moderate depression, 15--19 indicates moderately-severe depression, and above 20 indicates severe depression.[15]

Ethical considerations. The study was explained to women in a large group and subsequently one-on-one by a trained study nurse fluent in the local language. In order to participate in the study, women were asked to provide written informed consent or to place their mark on the consent form. At the local level, permission was obtained from the District Medical Officers and clinicians stationed at participating dispensaries and health centers. Ethical approval was granted by the research ethics committee at Bugando Medical Centre, by the Medical Research Coordinating Committee of the National Institute for Medical Research in Tanzania, and by the Institutional Review Board at Weill-Cornell Medical College.

Women diagnosed with urogenital or intestinal schistosomiasis, syphilis, trichomoniasis, candidiasis, or bacterial vaginosis received free treatment. Women with trichomoniasis were given medication both for themselves and their sexual partners. Women with syphilis and their sexual partners received three intramuscular injections of penicillin at the clinic. Patients diagnosed with HIV were referred to nearby district or regional hospital-based clinics for free care and treatment. Women with cervical dysplasia or cancer were referred to tertiary institutions for further management, and all of them accessed care successfully.

Statistical methods. Data were entered into a REDCap database (Vanderbilt University, Nashville, Tennessee). Continuous variables were summarized by median and interquartile range and categorical variables were summarized by frequency and percentage. Regional disparity of infections was assessed by Fisher's exact test; the association of infection status and region was evaluated using northern versus southern designation (in a 2 x 2 table) as well as individual regions (in a 2 x 8 table). Factors that were associated with the endpoint (i.e., FUS) were examined by multiple logistic regression. Backward elimination was adopted to reach the final parsimonious model that included significant factors

only – starting from a full model with all of the candidate predictors (all factors presented in Tables 1 and 3) and deleting the least significant factor one at a time until only the predictors with p-value < 0.05 remain in the model. We also confirmed that the automatic variable selection procedures (e.g., stepwise, forward, backward selection) yielded the same final model. We analyzed age in two different ways – using a continuous variable and categorized variables (with 25, 30, and 35 as cutoff points, which approximately corresponded to lower quartile, median and upper quartile, respectively).

Association between factors and the endpoint was summarized in odds ratio (OR) along with 95% confidence interval (CI) and the associated p-value. We also computed the area under the receiver-operating-characteristic curve (AUC) to ascertain the discrimination capability of the factors for FUS cases vs. non-cases—AUC of 0.5 means that the discrimination capability is no better than chance, and 1 means perfect discrimination.

SAS 9.2 (Cary, North Carolina) was used for data analyses. Two sided hypotheses/tests were assumed for computation of all confidence intervals and p-values.

Results

Patient Characteristics. Out of 550 eligible women who presented to primary care clinics and were invited to participate in the study, 457 women (83.1%) consented to participate and completed all study procedures. Characteristics of study participants are shown in Table 1. The median age was 30 years (IQR, 24--35 years). The great majority was married, had at least one child, and worked in farming and petty trade. Participants had a median number of 14 contacts with potentially-infectious water per day, and no woman reported zero contacts. One-third reported receiving treatment for schistosomiasis in the past.

Prevalence of *Schistosoma haematobium* and *mansoni* infections. The prevalence rates for *S. haematobium* and *S. mansoni* are presented in Table 2, and a map of the area with the villages where screening took place is shown in **Figure 1.** The prevalence of *S. haematobium* infections was higher among women living in southern inland villages than in northern villages along the shores of Lake Victoria. The prevalence in the south was 13/120 (10.8%) compared with 10/337 (3%) in women who lived in northern lake-side villages (p = 0.002). Of the 23 women with urogenital schistosomiasis included in the analysis, 16 had *S. haematobium* ova detected in the urine only, 6 had *S. haematobium* ova detected in a genital specimen, and one had *S. mansoni* ova visualized on a cervical smear.

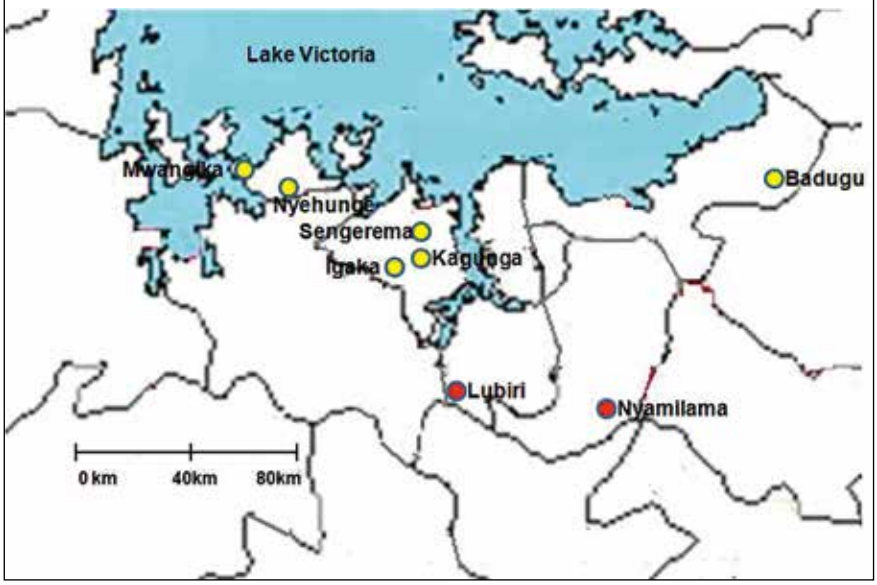
TABLE 1. Baseline characteristics of 457 women attending primary care clinics for schistosomiasis screening in Mwanza, Tanzania.

CHARACTERISTIC	VALUE
Age in years—median (interquartile range)	30 (24--35)
Marital Status—number (percent)	
Single	10 (2.2%)[a]
Living with partner	31 (6.8%)
Married	357 (78.1%)
Divorced	21 (4.6%)
Widowed	7 (1.5%)
Having at least one child—number (percent)	415 (90.8%)
People living in household—number (percent)	
0--4	163 (35.7%)
5--7	150 (32.8%)
8--10	71 (15.5%)
More than 10	56 (12.3%)
Occupation—number (percent)	
Agriculture and/or petty trade	404 (88.4%)
Homemaker	8 (1.8%)
Other	40 (8.7%)
Went to bed hungry in past month—number (percent)	27 (5.9%)
Number of water contacts per day[b]-- median (interquartile range)	14.1 (11.4--17.0)
Ever treated for schistosomiasis—number (percent)	159 (34.8%)
Received an artemesinin-containing medication for malaria in the past 3 years—number (percent)	163 (35.7%)

[a]Percentages were calculated using a denominator of the total sample size, 457. Missing data are present in some variables (with < 7%). Age was missing in 6 women and water contact data was missing in 21 women.

[b]Water contact behaviors combined the following information (swimming, bathing oneself or a child, washing clothes, hands, animals, or dishes, collecting water for use in the home, fishing, using water for crops, wading water to cross it, and cultivating rice) by summing their frequencies and dividing by 30.

Figure 1. Map of Mwanza region in Tanzania's Lake Victoria zone with village locations. Northern villages nearer to Lake Victoria, with lower rates of *S. haematobium* and higher rates of *S. mansoni,* are depicted with yellow dots. Southern villages, with higher rates of *S. haematobium* and no *S. mansoni* infection detected, are depicted with red dots.



S. mansoni infection, by contrast, was only detected among women living in northern villages near the lake. Among 337 women living in northern lake-side villages, 31 (12.2%) were infected with *S. mansoni*, and among 120 women in southern inland villages, none was infected ($p < 0.0001$).

Prevalence of other infections. Of the 457 women examined, 33 had bacterial vaginosis (7.2%), 22 had candidiasis (4.8%), and 15 had trichomoniasis (3.3%). Twenty-seven women were HIV-infected (5.9%), and 33 had reactive syphilis serology (7.2%).

Prevalence of gynecologic symptoms, sexual dysfunction, and depression. Gynecologic symptoms reported most commonly by women included abdominopelvic pain (75.5%), menorrhagia (56.0%), genital itching (54.5%), dysmenorrhea (54.3%), dyspareunia (42.9%), and foul-smelling discharge (31.1%) (Table 3). The majority of women stated that they made excuses to avoid sexual intercourse (66.1%), and 40.9% of women were worried that their partner would have sexual relations outside of the relationship. Notably, 77% of women met

TABLE 2. Prevalence of Schistosomiasis and HIV in Eight Villages in the Mwanza Region of Tanzania's Lake Zone.

VILLAGE	NUMBER ENROLLED	NUMBER WITH HIV INFECTION (%)	NUMBER WITH *SCHISTOSOMA HAEMATOBIUM* INFECTION (%)	NUMBER WITH *S. MANSONI* INFECTION (%)	REGIONAL PREVALENCE OF *S. HAEMATOBIUM*	REGIONAL PREVALENCE OF *S. MANSONI*
					Northern Villages	
Mwangika	67	5 (7.5%)	0	8 (11.9%)	10/337 (3.0%)	41/337 (12.2%)
Nyehunge	75	9 (12%)	6 (8.0%)	12 (16.0%)		
Sengerema town	71	2 (2.8%)	1 (1.4%)	12 (16.9%)		
Kagunga	30	2 (6.7%)	1 (3.3%)	1 (3.3%)		
Badugu	23	4 (17.4%)	0	0		
Igaka	71	3 (4.2%)	2 (2.8%)	8 (11.3%)		
					Southern Villages	
Lubiri	45	0	5 (11.1%)	0	13/120 (10.8%)	0/120 (0%)
Nyamilama	75	2 (2.7%)	8 (10.7%)	0		
P-value[a]			0.01	< 0.0001[b]	0.002	< 0.0001

[a]All p-values were computed by Fisher's Exact Test.
[b]For this specific p-value, Monte Carlo estimation of exact p-values instead of direct exact p-value computation was used due to time and memory problems encountered for exact computations.

criteria for depression based on the PHQ-9 scale. Of the 457 women, 259 (57%) were mildly depressed and 92 (20%) had moderate to severe depression.

Factors Associated with FUS. We examined associations between baseline characteristics, other infectious diseases, and female urogenital schistosomiasis. Younger age was significantly associated with FUS. As a continuous variable, age in years showed an odds ratio of 0.92 (95% CI 0.86--0.98), which may be interpreted as approximately an 8% decrease in odds of disease per one year increase in age. As a categorized variable, age had an odds ratio of 5.5 [95% CI 1.2--26.3] for women who were younger than 25 years old, 8.2 [95% CI 1.7--38.4] for those who were 25--29 years old, and 1.2 [95% CI 0.16--8.4] for those who were

TABLE 3. Prevalence of Gynecologic Symptoms, Sexual Dysfunction, and Depression in 457 women in Mwanza, Tanzania.

	NUMBER (PERCENT)[a]
Gynecologic Symptom:[b]	
Post-coital bleeding	24 (5.3%)
Dyspareunia	196 (42.9%)
Difficulty becoming pregnant	91 (19.9%)
Abdominal/pelvic pain	345 (75.5%)
Irregular menses	180 (39.4%)
Dysmenorrhea	248 (54.3%)
Genital itching	249 (54.5%)
Menorrhagia	256 (56.0%)
Urinary incontinence	41 (9.0%)
Foul-smelling vaginal discharge	142 (31.1%)
Sexual Dysfunction:[c]	
Fearful of pain during sexual intercourse	291 (63.7%)
Makes excuse to avoid sexual intercourse	302 (66.1%)
Decrease in quality or frequency of sexual relations	242 (53.0%)
Worry that partner will have sexual relations outside of relationship	187 (40.9%)
Score on Depression Scale:	
No depression (0--4 points)	48 (10.5%)
Mild depression (5--9 points)	259 (56.7%)
Moderate depression (10--14 points)	85 (18.6%)
Moderately severe or severe depression (≥ 15 points)	7 (1.5%)

[a]Percentages were calculated using a denominator of the total sample size, 457, in order to capture existing symptoms. Depression score was missing for 58 women, while less than 5.5% of data was missing for all other variables.
[b]Includes women that answered they were "somewhat" or "very much" bothered by symptom.
[c]Includes women that answered "I agree" or "I agree completely" that they experience the symptom.

30--34 years old, compared to women who were 35 years old or older (reference group).

HIV was also significantly associated with FUS with an odds ratio of 4.0 [95% CI 1.2--13.5]. Of the 23 women with FUS, 4 (17.4%) were HIV-infected, compared with 23 (5.3%) of the 434 women without FUS. There were no significant differences among women with and without FUS in the overall rates of other vaginal or sexually-transmitted infections including candidiasis, trichomoniasis, bacterial vaginosis, or syphilis, and no other significant differences in other variables. The final regression model with the two risk factors—age and HIV status—resulted in AUC of 0.732 (age as continuous variable) and AUC of 0.72 (age as categorical variable), which are much higher than null value of AUC = 0.5.

Discussion

Female urogenital schistosomiasis affects young women, is associated with HIV infection, and is prevalent in inland villages of the Lake Victoria region of Tanzania. Our study builds on the findings of a previous study in Zimbabwe, which showed an association between HIV infection and *Schistosoma haematobium* detected in cervical specimens with an odds ratio of 2.9 [95% CI 1.2--3.5].[7] The authors of the earlier study postulated that genital schistosomiasis may predispose to HIV infection. Our work extends this finding by demonstrating an association between HIV infection and the newly-expanded WHO case definition of urogenital schistosomiasis. This finding, in light of the high prevalence of FUS in women of reproductive age, may have important public health implications for prevention of HIV infection.

While a causal association between FUS and HIV infection will require a prospective longitudinal study, a number of factors support the hypothesis that the risk of HIV acquisition is augmented by the presence of FUS. First, schistosomal infection is generally acquired during childhood, before the commencement of sexual activity. Second, it has been pointed out that genital schistosomiasis may increase the risk of HIV infection through its disruption of the genital tract epithelium.[8] Third, schistosomiasis can stimulate a Th-2-type immune response similar to other chronic parasitic infections. This produces changes in cytokines and an accompanying upregulation of the HIV coreceptors CC chemokine receptor 5 and CXC chemokine receptor 4 on monocytes and lymphocytes, with an overall shift in the body's immune response away from the Th-1 immunity that provides early initial control in HIV infection.[16,17] Fourth, the inflammatory reaction to schistosomal eggs in genital lesions may increase the numbers of lymphocytes and activated macrophages in the cervical tissue; these

are target cells for HIV infection. Finally, HIV-positive patients with helminth co-infections appear to have higher viral loads than those without co-infections, and thereby may experience both higher rates of HIV transmission and more rapid HIV progression.[17,18] For all of these reasons, the WHO and others have suggested that mass treatment of FUS may be an effective strategy for decreasing HIV transmission in sexually-active women in Africa.[1,9]

The association of FUS with younger age of 18 to 29 years is consistent with the natural history of schistosomiasis and has important public health ramifications. The age of peak prevalence for *Schistosoma haematobium* infection is between 8 and 15 years old, with peaks in the later end of this spectrum occurring in communities with lower prevalence of disease.[19--21] Repeated exposure to the parasite over time leads to the development of at least partial immunity in later adulthood.[19,21] Our findings demonstrate that, in communities in which the prevalence of disease is at least moderate in children [50-90% in a previous study],[10] women continue to have urogenital schistosomiasis throughout their teens and twenties. This is also the age at highest risk for HIV transmission.[22] Women between the ages of 18 and 29 are not a focus of school-based anti-schistosomal treatment campaigns in sub-Saharan Africa, but the substantial burden of FUS in this age group argues strongly for targeted FUS treatment.

Our study suggests that, while *S. mansoni* may be geographically isolated near the Lake shores, *S. haematobium* may be more widespread in inland villages throughout the region, placing more women at risk for urogenital schistosomiasis and, potentially, increased HIV transmission. A school-based survey in central Sudan reported a comparable marked variation in the prevalence and intensity of both infections, even over short distances within the same province.[23] A compilation of over 2000 studies conducted in East Africa between 1980 and 2009 revealed starkly distinct distributions for *S. mansoni* and *haematobium*, including the observations that *S. mansoni* is most prevalent along the shores of large lakes including Lake Victoria.[24] Near Lake Victoria in Tanzania, studies in schoolchildren have similarly found that the prevalence of *S. mansoni* decreased and that of *S. haematobium* increased with increasing distance from the lake.[10,25] Thus although our designation of "Northern" and "Southern" villages was not chosen a priori, our finding of significantly distinct parasite distributions in each of these regions is supported by other studies in the region.

This clustering has been attributed to differences in the ecology preferred by the intermediate snail vectors *Biomphalaria* spp. (for *S. mansoni*) and *Bulinus* spp. (for *S. haematobium*). *Bulinus* snails are capable of aestivation, and are thus able to colonize and survive in temporary water sources that dry up for months of

the year. In contrast, *Biomphalaria* snails do not aestivate and therefore require large permanent bodies of water with at least moderate aquatic vegetation for survival.[26] Because of these characteristics, transmission of *S. haematobium* is generally more widespread than *S. mansoni* but is also more seasonal, with highest transmission occurring after the rainy season when snails are not dormant.[25,26]

Another important finding from this study was the high prevalence of depression among these women in rural villages. We found that 20% of women scored 10 or above on the PHQ-9 scale, consistent with moderate to severe depression. A PHQ-9 score above 10 is 88% sensitive and 88% specific for major depression as defined by the DSM-IV criteria.[15] Other community-based studies in sub-Saharan Africa have reported a similar, though slightly lower, prevalence of major depression by DSM-IV criteria in 5--15% among women, with a higher prevalence in those living in rural settings.[27,28] Thus our findings highlight an additional prevalent healthcare need that affects rural women in sub-Saharan Africa.

This work underscores the significant burden and breadth of diseases—including parasitic, sexually-transmitted, and mental health-related—in women of reproductive age living in rural northwest Tanzania. Due to resource constraints, we relied on single urine and stool samples to estimate prevalence of intestinal and urogenital schistosomiasis. In all likelihood, had we analyzed urine and stool samples on three consecutive days, the prevalence of these infections would have been even higher than those we observed. Schistosomiasis in women of reproductive age is not currently a focus of public health screening or treatment but the infection is common and widespread among this population. It has been pointed out that control of FUS, and possibly the opportunity to curtail new HIV infections, may cost as little as 32 cents per woman.[9]

In conclusion, female urogenital schistosomiasis is a geographically-clustered infection that disproportionately affects women younger than 30 years of age and was significantly associated with HIV infection. These young women, who also have the highest risk for incident HIV infection and in whom genital lesions may be reversible if treated early, should be the focus of public-health interventions aimed to reduce further the prevalence of *Schistosoma haematobium* infection.

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