Schistosomiasis and Infertility in East Africa

Patricia A. Woodall* and Michael R. Kramer

Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia

Abstract. Case reports and pathology series suggest associations of female genital schistosomiasis (*Schistosoma haematobium*) with infertility and ectopic pregnancy. Differential geographic distribution of infertility is not explained by analyses of known risk factors. In this cross-sectional multilevel semi-ecologic study, interpolated prevalence maps for *S. haematobium* and *Schistosoma mansoni* in East Africa were created using data from two open-access Neglected Tropical Diseases Databases. Prevalence was extracted to georeferenced survey sample points for Demographic and Health Surveys for Ethiopia, Kenya, Tanzania, and Uganda for 2000 and 2010. Exploratory spatial analyses showed that infertility was not spatially random and mapped the clustering of infertility and its co-location with schistosomiasis. Multilevel logistic regression analysis demonstrated that women living in high compared with absent *S. haematobium* locations had significantly higher odds of infertility (2000 odds ratio [OR] = 1.5 [confidence interval₉₅ = 1.3, 1.8]; 2010 OR = 1.2 [1.1, 1.5]). Women in high *S. haematobium* compared with high *S. mansoni* locations had significantly higher odds of infertility (2000 OR 1.4 [1.1, 1.9]; 2010 OR 1.4 [1.1, 1.8]). Living in high compared with absent *S. mansoni* locations did not affect the odds of infertility. Infertility appears to be associated spatially with *S. haematobium*.

INTRODUCTION

Published reports of the effects of schistosomiasis on reproductive outcomes are limited to case reports and descriptive series suggesting increased risk of prematurity and of low birth weight,¹ reports of schistosomiasis prevalence in pregnant women,² and many case reports of genital schistosomiasis associated with infertility and with ectopic pregnancy.³ Exploration of the spatial distribution of these outcomes of interest in relation to that of the predominant forms of schistosomiasis is one approach to study these effects.

More than 250 million people are affected by schistosomiasis, more than 90% of these in Africa.⁴ Distribution of human disease is related to that of *Schistosoma* species-specific host snail populations, with local human prevalence extremely high (50–80%) in areas populated by infected snails.⁵ Although one host snail species typically predominates in a given geographic region, no specific habitat factors explain the overall difference in species geographic distribution.⁶ Historically, prevalence surveys have measured egg shedding in urine or feces (measuring presence of reproducing worm pairs) but not disease (organ damage).⁷

Schistosomiasis affects genitourinary (*Schistosoma haematobium*) and digestive organs (primarily *Schistosoma mansoni* and *Schistosoma japonicum*) and has immunologic and other systemic effects.⁸ Female genital schistosomiasis (FGS) occurs when deposition of (primarily) *S. haematobium* eggs leads to granulomas, ulceration, and distortion in ureters, fallopian tubes, and other genitourinary organs, and occurs in 30–75% of women who have urinary schistosomiasis.⁹ The prevalence of upper reproductive tract FGS is unknown because of difficulty of assessment and lack of clinically apparent manifestations, but pelvic ultrasound abnormalities (ovarian cyst, uterine mass, and hydrosalpinx) were seen in 9% of women in one FGS-affected community in Madagascar (baseline unknown).¹⁰ Genital symptoms were already present in 10- to 12-year-old South African girls with urinary

schistosomiasis,¹¹ and genital damage may not regress unless treated early.¹²

Infertility, a common consequence of upper reproductive tract disease, has serious social consequences for women, including divorce, stigma, socioeconomic burden, and presumption of infidelity/sexually transmitted infections (STIs) as the cause.¹³ Combined analyses of more than 300 Demographic and Health Surveys (DHS) and reproductive health surveys have produced global prevalence estimates of 2–4% for primary (never having given birth) and 10–40% for secondary (no subsequent births) infertility, with secondary infertility increasing sharply with age (from 2–5% of 20- to 25-year-old women to 60–70% of 40- to 50-year-old women).¹⁴ Wide variations in infertility prevalence among countries have been found, with highest risk in sub-Saharan Africa.¹⁵ Where medical investigation has occurred, tubal factors account for a much higher proportion of infertility in Africa than in other regions.¹⁶ Where bacteriologic testing has been done, 30–70% of tubal disease was due to *Chlamydia*, 15–50% to gonorrhea, and 6–21% to genitourinary tuberculosis.¹⁷ Other possible etiologies of fallopian tube disease may not be considered, as the diagnosis of tubal distortion or obstruction is often made by radiologic imaging only (hysterosalpingogram) without microbiologic or pathologic testing.¹⁷

Investigations of ethnicity, sexual patterns, STI risk, and age-cohort effects have not successfully explained the geographic differences in infertility.¹⁸ Analyses of African infertility from DHS or World Fertility Surveys have identified associations with urban residence and variation among cultural groups¹⁹ and in Ethiopia suggested an unknown ecological factor.²⁰ High prevalence of infertility in proximity to water bodies was noted in Congo, Tanzania, and Kenya.²¹ Highest regional-level infertility risks in Kenya and Tanzania are in coastal, central plateau, and island (Zanzibar) regions,^{18,19} which are also *S. haematobium*-endemic areas.

The same tubal pathology which causes infertility may lead to ectopic pregnancy, a major but poorly documented contributor to maternal mortality in developing countries. Twenty-five percentage of maternal deaths in an urban slum in Nairobi, Kenya, in 2009–2013 were estimated to be due to ectopic pregnancy,²² and hospital series in Ghana and South Africa

* Address correspondence to Patricia A. Woodall, 66 Apache Plume Dr., Santa Fe, NM 87508. E-mail: pwoodall@tulane.edu

reported 1–4% of pregnancies as ectopic with 53–61% in hypovolemic shock on arrival.^{23,24}

In addition to many case reports,³ two small community-based studies have addressed the possible association of FGS with infertility. In two *S. haematobium*-affected communities in Zimbabwe, 15% of women were infertile, with odds ratio (OR) 3.6 for FGS.²⁵ Subfertility was found in 44% of women in a highly schistosomiasis-endemic area of Coast Province, Tanzania.²⁶

The aim of this study was to explore associations of infertility with schistosomiasis using spatial and regression methods, hypothesizing that infertility is associated with residence in *S. haematobium*-prevalent areas but not in *S. mansoni*-prevalent areas. This hypothesis suggests an effect of FGS rather than a general immunologic or other systemic effect of schistosomiasis.

MATERIALS AND METHODS

This cross-sectional multilevel semi-ecologic study included Ethiopia, Kenya, Tanzania, and Uganda as a contiguous geographic region with clearly delineated distribution of the two *Schistosoma* species of interest and with established DHS programs using the same methodology for collection of outcome data within a 2-year period. We hypothesized that infertility is associated with residence in high compared with low *S. haematobium*-endemic locations, is associated with residence in high *S. haematobium*-endemic compared with high *S. mansoni*-endemic locations, and does not differ with residence in high compared with low *S. mansoni*-endemic locations.

Data sources. The primary exposure data source was the Global Neglected Tropical Diseases Database of the Swiss Tropical and Public Health Institute (www.gntd.org). For this open-access georeferenced database, schistosomiasis prevalence and location data were abstracted from scientific articles and institutional reports (World Health Organization [WHO], government, control programs) published since the year 1900.²⁷ Most studies determined point prevalence based on egg counts using the Kato-Katz stool method for *S. mansoni* and urine filtration for *S. haematobium*. For our study, additional *Schistosoma* prevalence data were obtained from the Global Atlas of Helminth Infection (thiswormyworld.org), a similar database project of the London School of Hygiene and Tropical Medicine.^{28,29} To address areas with sparse data, additional data points were obtained from the WHO 1987 Global Atlas of Schistosomiasis³⁰ and geocoded (using Google Earth) by name of village and approximate map location. To address border issues in interpolation, data for surrounding countries were included with the Ethiopia, Kenya, Tanzania, and Uganda data, to cover an area from 16° N to –12° S latitude and from 28° W to 8° E longitude.

Prevalence maps for each of the two *Schistosoma* species were produced using ArcGIS Geostatistical Analyst extension, testing various interpolation methods and models to map the predicted distribution and prediction error. The empirical Bayesian kriging model produced the lowest prediction error (root-mean-square standardized error 0.95 for *S. haematobium* and 0.97 for *S. mansoni*) (Figure 1). Several studies have used these databases and methods to produce national and regional schistosomiasis prevalence and risk maps.^{31–33}

FIGURE 1. Predicted distribution of *Schistosoma haematobium* and *Schistosoma mansoni* in East Africa. Empirical Bayesian kriging interpolation surface, ArcGIS Pro Geostatistical Analyst. Demographic and Health Surveys (DHS) sample cluster sites. Data sources: Global Neglected Tropical Diseases Database, Global Atlas of Helminth Infection, World Health Organization Global Atlas of Schistosomiasis, and DHS (Measure DHS). This figure appears in color at www.ajtmh.org.

Outcomes and covariates were derived from DHS, a program of the United States Agency for International Development (USAID) supporting collection and analysis of data about women's and children's health, fertility, and social factors, using standard questionnaires and methodologies.^{34,35} Surveys use a two-stage sampling method with nationally representative selection of DHS clusters (modified for rural/urban and regional stratification) followed by probability proportional to size selection of households. All women of reproductive age (15–49) within each selected household are surveyed. For this analysis, surveys were combined for each of two time periods: Ethiopia 2000, Tanzania 1999, and Uganda 2000 (referred to in this report as “2000 survey”) and Ethiopia 2011, Kenya 2008, Tanzania 2010, and Uganda 2011 (“2010 survey”). Data of the 2000 Kenya survey were not georeferenced.

Interpolated schistosomiasis prevalence was extracted to georeferenced DHS data points following DHS guidance relative to its geomasking displacement process.³⁶ Exposure was categorized as high (> 25%), moderate (5–25%), or low (< 5%) for each of the two *Schistosoma* species, based on apparent natural breaks in histograms of the spatial data, commonly used programmatic categorizations, and sample size considerations.

Our study population consisted of women aged 15–49 years, married or in union for at least 5 years, not using a contraceptive, and not presently pregnant. Infertility was defined as no live birth within the last 5 years, including both primary (never having given birth) and secondary (having previously given birth) infertility. Established methods to operationalize these definitions for analysis with demographic survey data were followed.^{37,38}

Ethical review. Review was waived by the Emory University Institutional Review Board. Data use agreements were executed for Measure DHS (USAID), the Global Neglected Tropical Diseases Database, and the Global Atlas of Helminth Infections.

Analysis. Analyses were carried out using SAS 9.4 (SAS Institute Inc, Cary, NC), ArcGIS 10.3 (ESRI, Redland, CA), and GeoDa 1.6.6 (Center for Spatial Data Science, Chicago, IL).³⁹ We followed DHS guidance for spatial and regression modeling of associations between DHS variables and environmental exposures.^{40,41}

In addition to development of interpolated spatial models to quantify exposure (schistosomiasis prevalence), spatial methods (assessment of autocorrelation and cluster analysis) were used to assess spatial distribution of infertility.^{42,43} *Spatial analysis* addresses the questions of whether the data are autocorrelated (not randomly spatially distributed) and where any clustering/aggregation occurs, and suggests spatial factors associated with this clustering. Spatial distribution of infertility was explored analytically (global and local Moran's *I*) and visually (Getis-Ord cluster and hotspot mapping). Possible associations of outcome with exposures were explored visually with map overlay and analytically as Bivariate Local Indicators of Spatial Association (LISA).

ORs were estimated in a weighted multilevel logistic regression model using SAS PROC GLIMMIX (SAS Institute, Inc.). This mixed model included random-intercept effects for country/survey round (third level) and for DHS cluster (second level), and fixed effects at first (individual) and second level. As DHS second-stage sampling is by household with all eligible women in the household included (mean 1.05 women per

household for the study population), inclusion of household as a level was considered, but produced no change in model fit or in estimates.

Indicator variables for the two levels of comparison for each of the two *Schistosoma* species were measured at the second (DHS cluster) level. Covariates included known risk factors of age (first level) and rural/urban status (second level). Estimates were weighted by DHS sample weights adjusted for differing country-level sampling fractions. For each of the two survey rounds, the model tested five parts of the hypothesis, comparing high and moderate levels of each species to its absence as well as high levels of the two species, and controlling for co-endemicity. ORs were also estimated for important subsets: primary infertility, exposure for more than 10 years, and exposure before age 10. Magnitude and precision of estimates were verified in sensitivity analysis, including various age restrictions (minimum 15–20, maximum 45–50), exposure cutoff points (10%, 30%), and combinations of countries (Supplemental Table 1). Associations were considered significant if the 95% confidence interval (CI) of the OR did not include 1. Population attributable fraction (PAF) was reported, to show the magnitude of significant associations.

RESULTS

Descriptive. In each survey round, 13% of the married noncontracepting women were presently pregnant. For each survey round, neither marriage duration nor contraceptive use (selection criteria) nor woman's age was associated with schistosomiasis prevalence (*t* test, *P* < 0.5). For each of the two survey sets, 14% of women lived in areas of high *S. haematobium* prevalence, 48% in moderate, and 38% in low prevalence. Twelve percentage lived in areas of high *S. mansoni* prevalence, 50% in moderate, and 37% in low prevalence. Table 1 shows that 35% of married noncontracepting women in the 2000 survey round were infertile, with the expected age-related increase from 13% of youngest to 69% of oldest groups. Eighty percentage lived in rural locations; urban women had 3.1 times the odds of infertility. Of 17,547 women in the 2010 survey round, 35% were infertile, increasing from 11% of the youngest to 72% of the oldest. Eighty-one percentage lived in rural locations; urban women had 2.5 times the odds of infertility.

Spatial analysis of outcomes. The distribution of infertility was not spatially random (was autocorrelated) for both survey rounds (2000 Moran's *I* = 0.53 and 2010 Moran's *I* = 1.00), suggesting moderate to strong clustering. As shown in Figure 2 (Getis-Ord analysis), in both survey rounds, infertility hotspots were seen in central and eastern Ethiopia; and in coastal, central plateau, southwest lake, southeast lake/coast, and island (Zanzibar) Tanzania. In the 2010 survey, hotspots were also noted in central and coastal Kenya. Many hotspots appeared to overlie major urban centers (central Ethiopia and Kenya, coastal Tanzania) or areas of high *S. haematobium* prevalence (dark background on map).

In Figure 3, Bivariate LISA maps show that high infertility and high *S. haematobium* prevalence are in similar locations in several parts of Tanzania and in coastal Kenya, and *S. mansoni* in a few locations in Tanzania and western Uganda. The large mapped areas of high-high (red) and low-low (dark blue) co-location of infertility with *S. haematobium*

TABLE 1
Study population description

	2000 Survey round				2010 Survey round				
	Ethiopia	Tanzania	Uganda	Total	Ethiopia	Kenya	Tanzania	Uganda	Total
Number of women	8,357	1,747	2,840	12,944	7,314	2,758	3,945	3,530	17,547
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age 15–19	168 (2)	6 (< 1)	2 (1)	200 (2)	92 (1)	13 (1)	9 (< 1)	24 (< 1)	138 (1)
20–29	2,736 (33)	610 (35)	1,295 (46)	4,647 (36)	2,497 (34)	867 (31)	1,125 (29)	1,288 (36)	5,757 (33)
30–39	3,087 (37)	685 (39)	1,050 (37)	4,822 (37)	2,730 (37)	1,045 (38)	1,556 (39)	1,292 (37)	6,634 (38)
40–49	2,366 (28)	457 (26)	652 (23)	3,475 (27)	1,995 (27)	833 (30)	1,255 (32)	926 (26)	5,009 (29)
Rural	6,930 (82)	1,293 (73)	2,543 (78)	10,766 (80)	6,024 (82)	2,146 (78)	3,319 (82)	2,848 (80)	14,237 (81)
Ever lost pregnancy	1,562 (19)	506 (29)	762 (27)	2,830 (22)	974 (13)	457 (17)	1,032 (26)	997 (28)	3,460 (20)
Infertility	2,828 (34)	684 (39)	875 (31)	4,534 (35)	2,600 (36)	1,107 (40)	1,461 (37)	1,015 (28)	6,183 (35)
Total	2,828 (34)	644 (37)	840 (30)	4,312 (33)	2,451 (34)	985 (36)	1,371 (35)	971 (27)	5,831 (33)
Age 15–29	428 (15)	92 (15)	105 (8)	625 (13)	368 (14)	83 (9)	113 (10)	86 (7)	650 (11)
Age 30–39	801 (26)	228 (33)	277 (26)	1,306 (27)	703 (26)	319 (30)	412 (26)	255 (20)	1,689 (25)
Age 40–49	1,599 (68)	324 (71)	458 (70)	2,381 (69)	1,380 (69)	636 (76)	846 (67)	630 (68)	3,492 (72)
Primary	392 (4)	66 (4)	93 (3)	551 (4)	285 (4)	50 (2)	124 (3)	54 (2)	513 (3)

Women aged 15–49 years, married or in union for at least 5 years, not using a contraceptive. Source: Demographic and Health Surveys Ethiopia 2000, Tanzania 1999, and Uganda 2001 (2000 survey round); Ethiopia 2011, Kenya 2009, Tanzania 2009, and Uganda 2011 (2010 survey round). Infertile = no birth within last 5 years. Primary = never given birth.

suggest an association, with fewer such areas seen in the *S. mansoni* maps.

Regression analysis. For the 2000 survey round, intraclass correlation coefficients indicated that 7% of variability in infertility was between DHS geographic clusters, 1% between countries, and 92% between individuals. For 2010 surveys, 11% of variability in infertility existed between DHS clusters, 0.3% between countries, and 89% between individuals.

As shown in Table 2, women living in high compared with absent *S. haematobium* locations had significantly higher odds of infertility in both the 2000 (OR 1.53) and 2010 (OR 1.24) surveys. Women living in moderate compared with

absent *S. haematobium* locations had significantly higher odds of infertility in the 2010 survey (OR 1.31). Women living in high *S. haematobium* compared with high *S. mansoni* locations had significantly higher odds of infertility for both the 2000 (OR 1.41) and the 2010 (OR 1.44) surveys. Living in high or moderate *S. mansoni* locations was not associated with infertility. By PAF, 7% [CI₉₅ 4.3, 9.4] (2000 survey) and 4% [CI₉₅ 1.2, 7.2] (2010 survey) of infertility cases were associated with residence in high *S. haematobium* areas and 11% (2010 survey) with residence in moderate *S. haematobium* areas.

To address possible temporal effects, three subgroups were analyzed. The sample of women with primary infertility

FIGURE 2. Getis-Ord hotspot analysis, infertility in East Africa; overlying *major cities (known risk factor) and *Schistosoma haematobium* prevalence (hypothesized risk factor). ArcGIS Pro (ESRI). Data sources: Demographic and Health Surveys (Measure DHS), Global Neglected Tropical Diseases Database, Global Atlas of Helminth Infection, and World Health Organization Global Atlas of Schistosomiasis. This figure appears in color at www.ajtmh.org.

FIGURE 3. Association of infertility with schistosomiasis, East Africa. Bivariate Local Indicators of Spatial Association, as maps of local-scale associations. GeoDa 1.6.6. Data sources: Demographic and Health Surveys (Measure DHS), Global Neglected Tropical Diseases Database, Global Atlas of Helminth Infection, and World Health Organization Global Atlas of Schistosomiasis. This figure appears in color at www.ajtmh.org.

was small, 551 (2000 survey) and 513 (2010 survey). Table 2 shows that women living in high compared with absent *S. haematobium* locations had significantly higher odds of primary infertility in both the 2000 (OR 1.78) and 2010 (OR 1.53) surveys. Women living in moderate compared with absent *S. haematobium* locations had significantly higher odds of

primary infertility in the 2000 survey (OR 1.47). Women living in high *S. haematobium* compared with high *S. mansoni* locations had significantly higher odds of primary infertility for the 2010 survey (OR 2.83).

As duration of residence at current location was measured in the 2000 survey round, some assessment of temporal

TABLE 2

Association of infertility with schistosomiasis prevalence at residence

	2000 Survey	2010 Survey
Total infertility	OR (95% CI)	OR (95% CI)
S. <i>h</i> high (ref = absent)	1.53 (1.27, 1.85)*	1.24 (1.06, 1.47)*
S. <i>h</i> moderate	1.14 (0.99, 1.32)	1.31 (1.15, 1.49)*
S. <i>m</i> high	1.09 (0.89, 1.33)	0.86 (0.73, 1.02)
S. <i>m</i> moderate	1.01 (0.87, 1.17)	1.02 (0.90, 1.16)
S. <i>h</i> high (ref = S. <i>m</i> high)	1.43 (1.08, 1.90)*	1.44 (1.14, 1.81)*
Primary infertility		
S. <i>h</i> high (ref = absent)	1.78 (1.61, 2.37)*	1.53 (1.05, 2.25)*
S. <i>h</i> moderate	1.47 (1.08, 2.00)*	1.34 (0.99, 1.81)
S. <i>m</i> high	1.12 (0.73, 1.73)	0.54 (0.35, 0.84)*
S. <i>m</i> moderate	1.25 (0.92, 1.70)	1.31 (0.98, 1.75)
S. <i>h</i> high (ref = S. <i>m</i> high)	1.44 (0.82, 2.53)	2.83 (1.60, 5.00)*

* = significant; CI = confidence interval; OR = odds ratio; ref = reference; S. *h* = *Schistosoma haematobium*; S. *m* = *Schistosoma mansoni*; high = > 25%; moderate = 5–25%; absent = < 5%. Women aged 15–49 years, married or in union for at least 5 years, not using a contraceptive. Source: Demographic and Health Surveys, Ethiopia, Tanzania, and Uganda (2000 survey round); Ethiopia, Tanzania, and Uganda (2010 survey round).

factors was possible. Table 3 shows that women living in high compared with absent *S. haematobium* locations for at least 10 years had significantly higher odds of infertility (OR 1.47). Women living in high compared with absent *S. haematobium* locations since before age 10 had significantly higher odds of infertility (OR 1.69). Women living since before age 10 in high *S. haematobium* compared with high *S. mansoni* locations also had significantly higher odds of infertility (OR 1.66).

Sensitivity analysis of various country groupings, exposure prevalence cut points, and age cutoffs consistently found infertility to be associated with residence in high compared with absent *S. haematobium* locations and in high *S. haematobium* compared with high *S. mansoni* locations (Supplemental Table 1).

DISCUSSION

Infertility was significantly associated with residence in areas of high *S. haematobium* prevalence, compared with both *S. haematobium* absence and to equivalent *S. mansoni* prevalence. Infertility was not associated with *S. mansoni* prevalence. This suggests that the association is related not to unmeasured confounders of the presence/absence of schistosomiasis but to the differing clinical manifestations of the two *Schistosoma* species (i.e., the tubal or other urogenital damage of *S. haematobium* rather than the hepatic damage of *S. mansoni*). *Schistosoma mansoni* occasionally causes FGS; residence in co-endemic areas was addressed in the model. There does not appear to be a proportional effect of the exposure, as ORs did not differ proportionally for high and for moderate *S. haematobium* prevalence. The usual prevalence

TABLE 3

Association of impaired fertility with schistosomiasis prevalence of residence and duration of exposure

	Resident > 10 years	Resident before age 10
Infertility	OR (95% CI)	OR (95% CI)
S. <i>h</i> high (ref = absent)	*1.47 (1.19, 1.81)	*1.69 (1.31, 2.17)
S. <i>h</i> moderate	1.13 (0.96, 1.33)	1.18 (0.96, 1.44)
S. <i>h</i> high (ref = S. <i>m</i> high)	1.35 (1.00, 1.83)	*1.66 (1.15, 2.40)

* = significant; CI = confidence interval; S. *h* = *Schistosoma haematobium*; high = > 25%; moderate = 5–25%; absent = < 5%. OR = odds ratio. Women aged 15–49 years, married or in union for at least 5 years, not using a contraceptive. Source: Demographic and Health Surveys Ethiopia, Kenya, Tanzania, and Uganda (2000 survey round).

measure (proportion of sampled schoolchildren excreting eggs on a given day), although useful as a measure of transmission, does not accurately measure the prevalence of disease, which is cumulative and persistent.⁷

Associations, although statistically significant by OR CIs, were not of large magnitude. PAF illustrates the magnitude of effect, with 7% of 2000 infertility cases and 15% of 2010 cases associated with *S. haematobium* exposure.

An inherent limitation of cross-sectional study design is the difficulty assessing temporal factors. Infertility may result from exposures occurring up to 50 years previously.¹¹ Genital schistosomiasis lesions occur within a few years of exposure and may persist despite antihelminthic treatment.¹² Thus, the disease (infertility due to tubal damage) may reflect either remote childhood exposure or more recent migration into an endemic area. Assuming a 5-year lag time between exposure to the parasite and occurrence of tubal disease and an additional lag time of the 5 years' exposure to pregnancy necessary to define infertility, women known to have resided locally for at least 10 years were analyzed. Associations were of similar magnitude to those for the total population. To assess the effect of childhood exposure, women known to have lived in the exposure area since before age 10 were analyzed, also showing associations of similar magnitude to the total population. These two subgroup analyses were only available for the 2000 surveys.

Primary infertility includes women for whom the etiology of infertility was either innate or of onset earlier in life, possibly including those with childhood FGS. Infections acquired after sexual debut (STIs, pregnancy-related infections) contribute more to secondary infertility.¹⁷ For primary infertility, the associations with *S. haematobium* exposure were at least as strong as for total infertility, with higher upper confidence limits.

Temporal factors also may affect the exposure measurement, as schistosomiasis prevalence data were collected over a century. However, maps from various times show no apparent change in the prevalence in the study area.^{30,33} None of the countries in this study had implemented nationwide high-coverage schistosomiasis control programs far enough before the relevant DHS surveys to have affected the outcomes measured in this study.⁴⁴

Exposure was measured not individually but ecologically, based on current residence. Individual exposure to schistosomiasis within an endemic area varies with lifetime water exposure behaviors as well as with focal distribution of infected snails. Schistosomiasis distribution is heterogeneous at local and seasonal scale. Although this local heterogeneity may affect the precision of kriging-generated estimates, the Bayesian methods used best address this uncertainty.³¹ In this study, the prediction error was very low, and mapping demonstrated low standard error except in sparsely populated regions as indicated by few DHS data points (Supplemental Figure 1).

An ideal measure of impaired fertility would include miscarriages, stillbirths, and ectopic pregnancies as well as live births.^{45,46} Pregnancy losses (stillbirths and miscarriages) were not measureable in all surveys and are known to be biased because of under-reporting in DHS surveys.⁴⁷ Survival bias may be a factor if ectopic pregnancy is associated with *S. haematobium* exposure. As DHS surveys only living women, any women who have died of ruptured ectopic

pregnancy would not be counted as either cases or subjects, potentially biasing study results toward the null (i.e., true associations may be stronger). A reliable method of measuring the incidence of ectopic pregnancy, a commonly fatal manifestation of tubal infertility, is needed. Infertility risk can be considered only suggestive of the risk of this major cause of maternal mortality.

This study addressed infertility as a female outcome. Although *S. haematobium* may damage male as well as female reproductive organs,⁴⁸ the role of infertility and exposure status of the male partner was not addressed.

The association with schistosomiasis increases the evidence that impaired fertility may have etiologies other than STIs and should not be equated with stigmatized sexual behaviors. Schistosomiasis contributes to the women's disease burden of infertility, with its social consequences of stigma and family disruption. If infertility can be considered a surrogate measure of ectopic pregnancy, schistosomiasis may also contribute to the burden of maternal mortality in Africa. Women presenting with infertility or ectopic pregnancy should be evaluated and treated for schistosomiasis if geographically appropriate, although this may not reverse established tubal damage. Prevention efforts should ensure inclusion of girls and women in schistosomiasis control programs.

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Authors' addresses: Patricia A. Woodall and Michael R. Kramer, Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, E-mail: pwoodall@tulane.edu and mkram02@emory.edu.

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