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Approval Sheet

Association of Schistosomiasis with Impaired Fertility in East Africa

By

Patricia Woodall

Master of Public Health

Global Epidemiology

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Michael Kramer

Faculty Thesis Advisor

Abstract Cover Page

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Patricia Woodall

BS, Birmingham Southern College, 1975

MD, Vanderbilt University School of Medicine, 1979

MPH, University of Hawaii, 1996

MPHTM, Tulane University School of Public Health and Tropical Medicine, 2009

Faculty Thesis Advisor: Michael Kramer, MMSc, PhD

An abstract of

A thesis submitted to the Faculty of the Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health in Global Epidemiology

2016

Abstract

Association of Schistosomiasis with Impaired Fertility in East Africa

By

Patricia Woodall

Many case reports and pathology series have suggested associations of Female Genital Schistosomiasis of the Fallopian tubes with infertility and ectopic pregnancy. Geographic distribution of infertility (which in Africa is most commonly due to tubal disease) has been reported but not explained. In this cross-sectional study, interpolated prevalence maps for *S. haematobium* and *S. 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 2009-2011 and 1999-2001. Outcomes included primary and secondary infertility (no births) and infecundity (no pregnancies) and history of pregnancy loss. Exploratory spatial analyses of outcomes (Moran's I, univariate and bivariate Local Indices of Spatial Autocorrelation) showed that outcomes were not spatially random and mapped clustering, hotspots, and areas of co-location of outcomes and exposures. Weighted multilevel logistic regression analysis found that women living in high compared to absent *S. haematobium* locations had significantly higher odds of secondary infertility (1999-2001: OR 1.8 [CI_{95} 1.4, 2.3]; 2009-2011: OR 1.23 [1.1, 1.5]) and of primary infertility (1999-2001: OR 1.8 [1.3, 2.7]; 2001-2011: OR 1.58 [1.1, 2.3]). Living in high compared to absent *S. mansoni* locations did not affect the odds of any outcome. Women living in high *S. haematobium* compared to high *S. mansoni* locations had significantly higher odds of secondary infertility (1999-2001: OR 1.7 [1.3, 2.3]; 2009-2011: OR 1.6 [1.1, 2.0]), and of primary infertility (2010: OR 2.7 [1.5, 4.9]). For 1999-2001, history of pregnancy loss was significantly associated with high compared to absent *S. haematobium* (OR 1.3 [1.1, 1.6]) and with high *S. haematobium* compared to high *S. mansoni* (OR 1.4 [1.0, 1.8]). There is increasing evidence of the clinical and public health consequences of schistosomiasis to women's health and the importance of inclusion of girls and women in control strategies.

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ASSOCIATION OF SCHISTOSOMIASIS WITH IMPAIRED FERTILITY IN EAST AFRICA

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SECTION I: LITERATURE REVIEW

The intersection of the tropical infectious diseases with women's reproductive health has drawn limited attention. Increasing recognition that schistosomiasis is a reproductive as well as a urinary pathogen led to the renaming of urinary to urogenital schistosomiasis. This study will contribute to the knowledge base of these reproductive system effects.

SCHISTOSOMIASIS

Schistosomiasis is a group of parasitic diseases of humans characterized by the presence of paired long-lived (up to 25 years) trematode worms in pelvic and mesenteric vascular plexuses, resulting in pathology caused by deposition of eggs in genitourinary (in the case of *Schistosoma haematobium*) and digestive organs (primarily *Schistosoma mansoni* and *S. japonicum*) and in transmission by passage of eggs in human excreta. After cycling through an intermediate snail host, the parasite is acquired by humans via skin penetration in fresh water. *S. haematobium* occurs throughout Africa, *S. mansoni* in Africa and northern South America, and *S. japonicum* in parts of Southeast Asia and China (1). At least 200 to 600 million people are infected, over 90% of these in Africa (2). Distribution is focal, related to water sources and snail populations, with local prevalence extremely high (50-80%) in affected areas (1). Although historically the resulting human morbidities have been considered to be diarrhea, hepatic cirrhosis, and bladder cancer, recently the much broader spectrum of disease has been recognized, encompassing other chronic urinary tract, genital, and hepatic pathology as well as more subtle effects on anemia and

chronic inflammation (3, 4). Clinical diagnosis is by presence of eggs on microscopy of urine or feces (depending on species) or in pathologic specimens. Recently serologic diagnosis of *S. mansoni* has become accepted, but serologic test characteristics remain unproven for *S. haematobium* (5). Exposure occurs where humans have skin contact with fresh water inhabited by the appropriate host snail and in which eggs have been deposited through urine or feces of infected humans. The popular image of young boys exposed during recreational swimming in irrigation ditches is a limited picture. Exposure occurs among all age groups and both sexes during washing and agricultural work in infested lakes, rivers, and canals. Immunologic factors are thought to reduce new infection rates in adults, after death of worms acquired in childhood; however, re-infection does occur (1)

Prevalence surveys measure egg shedding in urine or feces (measuring active presence of reproducing worm pairs), but not disease (organ damage). Although liver damage may regress after antihelminthic treatment or natural worm death, more advanced liver and genitourinary damage do not. Prevalence (of egg shedding) is typically highest among school-age children, but occurs in all ages (1).

Geographic distribution of the *Schistosoma* species is determined by the distribution of the specific snail host species. One species typically predominates in a given geographic region, although species may co-exist. Typical snail habitat is along freshwater bodies in warm, low-altitude, high-rainfall areas (6). Dams and irrigation schemes may increase snail habitat. Although the *Bulinus* snail host of *S. haematobium* tolerates higher temperature and lower or seasonal rainfall than does the *Biomphalaria* snail host of *S. mansoni*, no specific habitat differences explain the overall difference in geographic distribution of the two species (7, 8).

Older environmental methods of disease control by wetland management or snail control gave way to Mass Drug Administration (MDA) with Praziquantel (PZ) in the 1980s. Due to highest prevalence in school-age children, convenience of school-based MDA, limited availability of PZQ, and (until 2003) lack of approval of PZQ in pregnancy (9), control programs

(where they exist) have typically provided annual or semi-annual PZQ, often integrated with other deworming, to school children. Targeting has been based on prevalence surveys of children (10). Expectations that this approach would lead to eventual local elimination of infection have not been fulfilled (11). The school-based approach misses younger children, girls, adolescents, and adults, thus allowing transmission as well as disease to persist. In 2009 it was estimated that only 5% of the infected population were receiving PZQ (12). Recent evaluations have questioned the impact of MDA with PZQ on prevalence, transmission, and long-term pathology (13).

Of the countries addressed in this study, neither Ethiopia (14) nor Kenya (15) had implemented schistosomiasis control programs prior to the relevant DHS surveys. Tanzania (16) and Uganda (17) partially implemented school-based MDA beginning in 2004. Zanzibar and Pemba islands (in Tanzania) implemented MDA with PZQ in the mid-1980s, but with limited coverage until 2004 (18).

The World Health Organization mapped the known distribution of schistosomiasis in 1987 (19). Recently, detailed mapping has been carried out in many affected countries to facilitate planning of control programs, often integrated with mapping for control of other NTDs such as soil-transmitted helminths and lymphatic giardiasis (20-22).*S. mansoni* is distributed widely in Ethiopia and Uganda and more focally in western and southern Kenya, especially along the shores of Lake Victoria. *S. haematobium* is widely distributed in Tanzania, especially coastal areas, south of Lake Victoria, and Zanzibar islands (estimated national prevalence 50%); in coastal Kenya; and focally in Ethiopia (23). (Figure 1).

Schistosomiasis in women

In addition to the hepatic and urinary effects common to both sexes, schistosomiasis has effects unique to the female reproductive system and reproductive functions. Deposition of eggs leads to granulomas, ulceration, and distortion in ureters, bladder, Fallopian tubes, ovaries, cervix

and vagina (24-26). Although documented for *S. mansoni* (27), this predominantly occurs from *S. haematobium.*

Female Genital Schistosomiasis (FGS) has been recognized for over a century by Egyptian physicians, especially as a major cause of vesicovaginal fistula (28). As the reproductive system disease is chronic and not clinically apparent, it received little attention until mounting evidence of its impact and probable association with HIV (29) led to renaming of *S. haematobium* from urinary to urogenital schistosomiasis. Population-based studies in Madagascar (30),Tanzania (31, 32), Malawi (33), and Egypt (34) have confirmed that vaginal/cervical schistosomiasis (sandy patches, ulcers, fungating lesions identified on vaginal/cervical visualization) occurs in 30-75% of women who have urinary schistosomiasis. Among Tanzanian women of reproductive age with 40% prevalence of urinary and 32% prevalence of cervical schistosomiasis, 23% had FGS with no urinary egg excretion (35). Thus urinary egg counts underestimate schistosomiasis in women.

FGS is associated with a variety of gynecologic symptoms. In Madagascar, significantly more women in an endemic village reported miscarriage, irregular menses, pelvic pain and vaginal discharge than in a control village (30). In Tanzania, post-coital bleeding and genital ulceration were more frequently reported in the endemic site, and FGS cases reported more irregular menses and hypermenorrhea than non-cases (32). 35% of pre-pubertal 10 to 12 year old girls in an *S. haematobium*-endemic area of South Africa reported genital symptoms (discharge, itching, sores) (36). The prevalence of upper tract (Fallopian tube) disease is unknown due to difficulty of assessment, but pelvic ultrasound abnormalities (ovarian cysts, uterine mass, hydrosalpinx) were seen in 9% of women in one affected community in Madagascar (37). The effects of schistosomiasis on the male reproductive system have been even less well studied, but pathology studies report anatomic effects and there are case reports of hemospermia and infertility (38).

Schistosomiasis may potentially affect female reproductive function by several mechanisms (Fig. 2). Little has been published regarding effects of schistosomiasis on pregnancy outcomes. Studies reporting prevalence of schistosomiasis in pregnant women in nine African countries were summarized by Salawu (39). Animal studies and small descriptive studies have on crude analysis suggested increased risk of prematurity (40) and of low birth weight (41-43) in offspring of women with schistosomiasis, thought to be associated with increased anemia or with placental infection (44). A meta-analysis of 20 published studies showed a mean hemoglobin deficit of 4 g/L associated with schistosomiasis (primarily *S. mansoni*) (45). Four descriptive studies of anemia in pregnant women with schistosomiasis found no association for *S. mansoni* in Tanzania and Uganda (46, 47) and a 1.2 - 2.4 OR for anemia in *S. haematobium* in Nigeria and Ghana (48, 49). In Uganda, Praziquantel treatment during pregnancy had no effect on maternal anemia, birthweight, perinatal mortality, or congenital anomalies (50).

Although the major causes of maternal mortality (hemorrhage, hypertensive disorder, sepsis) can each hypothetically be linked to schistosomiasis, published information on actual contribution is lacking. Coagulopathy occurs in young adults with hepatic schistosomiasis (51), suggesting possible contribution to maternal hemorrhage. A systematic review of kidney disease in sub-Saharan Africa summarized high prevalence of renal dysfunction and hydronephrosis/hydroureter in children in *S. haematobium*-endemic areas (52), suggesting possible contribution to eclampsia and to prolepsis. Bacteriuria prevalence of 30-50% has been reported in Nigerian children with urinary schistosomiasis (53, 54). Ossai found OR=31 for bacteriuria in children with/without urinary schistosomiasis (55). Bacteriuria in pregnancy is associated with preterm birth and with maternal sepsis. Three case reports of pregnancies in women with hepatic schistosomiasis report significant thrombocytopenia (56-58). One case report describes pre-eclampsia and fetal death in a woman with hepatic schistosomiasis (59).

Fifteen published case reports were identified linking FGS with ectopic pregnancy (Table 1). The extent of death of women from ruptured ectopic pregnancy in Africa is unknown (60), but

it is likely that most affected women die without being diagnosed, treated, or counted as maternal deaths. From surveillance data and verbal autopsy, Olack estimated that 25% of maternal deaths in an urban slum in Nairobi, Kenya 2009-2013 were due to ectopic pregnancy (61). Hospital series in Ghana and South Africa have reported 1-4% of pregnancies as ectopic with 53-61% in hypovolemic shock on arrival (62, 63). 61% of South African women with ectopic pregnancy had a known history of infertility (63). 73% of 145 Gabon women surviving ectopic pregnancy were subsequently infertile, and 10% had a repeat ectopic pregnancy (64). In Mozambique, 3.9% of operated ectopic pregnancies had associated schistosomiasis (65).

Schistosomiasis could be a primary etiology or a co-factor in occurrence of obstetric vesicovaginal fistula. Egyptian writers have long considered schistosomiasis to be the primary etiology of fistulas (28). One small case-control study did not find an association but found that schistosomiasis deterred healing of obstetric fistula (66).

INFERTILITY

Infertility may be studied as demographic variable (affecting overall fertility rates), as a socio-cultural factor (leading to stigma, divorce, abandonment, and socio-economic burden) (67) and as a marker of its underlying biomedical determinants. Infertility may be a rough surrogate for ectopic pregnancy, otherwise difficult to measure in resource-limited settings where it likely results in unattended death.

Terms used (often inconsistently) include *infertility*, *sub-fertility*, *sterility*, and *infecundity*, with the latter two terms typically considering a permanent state (unmeasurable until after a woman has completed her childbearing years) and the former (infertility) referring to a measureable time period (68). *Fecundity* may refer to conception and *fertility* to birth, or vice-versa (69). *Sub-fertility* or *sub-fecundity* may include both failure to conceive and pregnancy losses (miscarriage, stillbirth, ectopic pregnancy), or may refer to not obtaining the desired number of children (70).

Clinical definitions (for individual diagnosis and treatment) typically measure conception and use short intervals (failure to conceive by 12 months). The *epidemiologic definition* (for monitoring and surveillance) of prevalence of infertility is the "percentage of women of reproductive age (15–49) at risk of pregnancy (not pregnant, sexually active, non-contracepting and non-lactating) who report trying for a pregnancy for two years or more" (71) (note that neither conception nor birth is specified - just "a pregnancy"). The *demographic definition* is failure of a sexually active, non-contracepting woman who desires a child to give birth within a specified time period (variously 3 to 7 years, to account for lactational amenorrhea and socio-cultural factors relating to resumption of intercourse and of childbearing) (70). As contraceptive coverage has increased globally, contraceptive use and desire for pregnancy have become more important factors in definitions.

At clinical level, the unit of analysis is the *couple* and infertility is classified as being due to male factor, female factor (tubal, endocrine, other), or unknown. Epidemiologically or demographically, the unit of analysis is the *woman* (for whom data are measured). *Primary infertility* is failure to produce a live birth (thus including women with early pregnancy loss or stillbirth). *Secondary infertility* is failure of a subsequent birth after having given birth. Bongaarts differentiates *natural sterility* (estimated at ~3% globally) and *pathologic sterility*, that due to a disease process (72). The preferred *denominator* is women ever married or in union. Using all Women of Reproductive Age (WRA) is too inclusive of those who are not sexually active. Counting only those currently married or in union excludes those who have been divorced or abandoned due to the infertility (69).

Operationalizing these definitions for analysis is problematic. Demographic surveys were designed to obtain information about fertility and contraceptive practices; few specifically ask about infertility or desire for pregnancy (73). Data are self-reported and variables must be derived from directly reported variables. Various formulas have been used, especially to measure secondary infertility, based on "self-reported infecundity", "behavioral infecundity", the "open

birth interval" or the "subsequently infertile estimator" (73, 74) and various modifications of it (75).These require complex longitudinal analysis methods to provide age-specific estimates. Operational definitions have been proposed for use with DHS data (75-77), and DHS includes an infertility variable designed to estimate population-level infertility risk.

Using data from 47 Demographic and Health Surveys, Rutstein estimated that over 186 million (25%) women in developing countries were infertile, with prevalence of 4% for primary infertility (5% if pregnancy losses are included) and secondary infertility rates increasing sharply with age (from 5% to 62%) (69). From a 2010 analysis of 277 demographic and reproductive health surveys, Mascarenas estimated that 48.5 million couples globally are infertile, with global prevalence of 1.9% for primary and 10% for secondary infertility (78). Both authors found wide variations among countries, with highest rates in sub-Saharan Africa. From 1978-1984 a WHO-sponsored multi-center worldwide study of 5800 infertile couples was carried out. Africa showed a different pattern from other regions; tubal causes predominated, with 3 times the rate of tubal occlusion as other regions, even though tubal disease was likely underestimated due to use of less-sensitive radiographic rather than surgical diagnostic methods (and thus no bacteriologic or histologic tests) (79).

Determinants of Tubal infertility

Where medical investigation has occurred, tubal factors account for a much higher proportion of infertility in Africa than in other regions (79-82). Although tubal-factor infertility is usually attributed to sexually transmitted infections (gonorrhea and chlamydia), this is generally an assumption, as microbiologic or pathologic testing is rarely done, the diagnosis of tubal distortion or obstruction is made by radiologic imaging (hysterosalpingogram, HSG), and other possible etiologies are not considered. Where serologic testing has been done or pathologic specimens obtained during surgical procedures, only 2-20% of tubal disease was due to

chlamydia (83, 84). Six to 21% of tubal infertility cases in South African clinics were due to genito-urinary tuberculosis (85, 86).

Many case reports, case series, and pathology series have identified Fallopian tube distortion and obstruction due to schistosomiasis in association with infertility (Figure 3). Two small community-based studies have addressed the possible association of schistosomiasis with infertility. In two *S. haematobium*-affected communities in Zimbabwe, 15% of women were infertile, with OR 3.6 for FGS among the infertile (87). Sub-fertility was found in 44% of women in a highly schistosomiasis-endemic area of Coast Province, Tanzania (88).

Geographic distribution of infertility

Differential geographic distribution of infertility is noted, usually speculatively attributed to differing marriage patterns or sexual behaviors leading to sexually transmitted infections.

Portions of central Africa (Congo, Central African Republic, Congo, Cameroon, Gabon) have for decades been known as the "infertility belt" with over 20% of women older than 40 childless (89). Romaniuk noted high prevalence of infertility along the Congo and Uele Rivers in Congo, close to Lake Victoria and Lake Tanganyika, on the coastal regions of Tanzania and Kenya, on the Zanzibar islands, and in Tabora district, Tanzania (90). (Note that these Kenya and Tanzania locations reflect the distribution of *S. haematobium*). He noted a pattern of proximity to water, but attributed this to tribal territorial patterns. He also reviewed two clinical and radiographic studies which identified genital tract lesions in 60% and 75% of sterile Congo women (91, 92). These were presumed due to gonorrhea, although this could be identified in only 25%. In 1996, Ericksen estimated infertility across 27 African countries from DHS or World Fertility Surveys, finding prevalence varying from 1-14% for primary and 5-17% for secondary infertility (73). She found associations with urban residence, early sexual debut, and multiple partners. She also found large variation among cultural groups across Africa; suggested that this may be due to different marriage, sexual, and female circumcision customs; but did not consider

geographic distribution as a possible variable (73). In Zambia, regional variation in infertility prevalence was not explained by STI risk (93).

In 2000 Larsen found wide variations in infertility rates by ethnic groups in Kenya and in Cameroon, presuming these to be due to cultural sexual practices affecting STI risk(94). A 1980-81 survey of infertility in rural Ethiopia found highest levels in Ilubabor region in the west (now Gambela), and suggested that ecological factors could be more responsible than ethnicity (95). (Note that this is one of the few *S. haematobium*-endemic areas in Ethiopia.) Larsen analyzed infertility data from DHS surveys for 29 African countries for the 1980s and 1990s to determine regional patterns. For rural Kenya, rates were highest in the Coast and Central regions; for Tanzania, Coast, Tabora Plateau, and South regions. She investigated ethnicity, age-cohort effects and different patterns of marital sex without successfully explaining the geographic differences in infertility (96).From 1991-92 DHS data, Erickson found overall infertility in Tanzania of 11.4%, primary infertility of 4.1%(73). (These regional patterns roughly coincide with *S. haematobium* endemicity). Blacker found highest Uganda infertility prevalence in Teso region (97).

SECTION II: MANUSCRIPT

ABSTRACT

Many case reports and pathology series have suggested associations of Female Genital Schistosomiasis of the Fallopian tubes with infertility and ectopic pregnancy. Geographic distribution of infertility (which in Africa is most commonly due to tubal disease) has been reported but not explained. In this cross-sectional study, interpolated prevalence maps for *S. haematobium* and *S. 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 2009-2011 and 1999-2001. Outcomes included primary and secondary infertility (no births) and infecundity (no pregnancies) and history of 1pregnancy loss. Exploratory spatial analyses of outcomes (Moran's I, univariate and bivariate Local Indices of Spatial Autocorrelation) showed that outcomes were not spatially random and mapped clustering, hotspots, and areas of co-location of outcomes and exposures. Weighted multilevel logistic regression analysis found that women living in high compared to absent *S. haematobium* locations had significantly higher odds of secondary infertility (1999-2001: OR 1.8 [CI_{95} 1.4, 2.3]; 2009-2011: OR 1.23 [1.1, 1.5]) and of primary infertility (1999-2001: OR 1.8 [1.3, 2.7]; 2001-2011: OR 1.58 [1.1, 2.3]). Living in high compared to absent *S. mansoni* locations did not affect the odds of any outcome. Women living in high *S. haematobium* compared to high *S. mansoni* locations had significantly higher odds of secondary infertility (1999-2001: OR 1.7 [1.3, 2.3]; 2009-2011: OR 1.6 [1.1, 2.0]), and of primary infertility (2010: OR 2.7 [1.5, 4.9]). For 1999-2001, history of pregnancy loss was significantly associated with high compared to absent *S. haematobium* (OR 1.3 [1.1, 1.6]) and with high *S. haematobium* compared to

high *S. mansoni* (OR 1.4 [1.0, 1.8]). There is increasing evidence of the clinical and public health consequences of schistosomiasis to women's health and the importance of inclusion of girls and women in control strategies.

INTRODUCTION

Schistosomiasis is a group of parasitic diseases of humans characterized by the presence of paired long-lived (up to 25 years) trematode worms in pelvic and mesenteric vascular plexuses, resulting in pathology caused by deposition of eggs in genitourinary (in the case of *Schistosoma haematobium*) and digestive organs (primarily *Schistosoma mansoni* and *S. japonicum*) and in transmission by passage of eggs in human excreta. After cycling through an intermediate snail host, the parasite is acquired by humans via skin penetration in fresh water. Exposure occurs among all age groups and both sexes during washing and agricultural work in infested freshwater bodies. *S. haematobium* occurs throughout Africa, *S. mansoni* in Africa and northern South America, and *S. japonicum* in parts of Southeast Asia and China (1). Distribution is focal, related to water sources and snail populations, with local prevalence extremely high (50-80%) in affected areas (1). At least 200 to 600 million people are infected, over 90% of these in Africa (2). Although historically the resulting human morbidities have been considered to be diarrhea, hepatic cirrhosis, and bladder cancer, recently the much broader spectrum of disease has been recognized, encompassing other chronic urinary tract, genital, and hepatic pathology as well as more subtle effects on anemia and chronic inflammation (3, 4). Advanced liver and genitourinary damage do not regress after antihelminthic treatment or natural worm death.

Clinical diagnosis is by presence of eggs on microscopy of urine or feces (depending on species) or in pathologic specimens. Prevalence surveys measure egg shedding in urine or feces (measuring active presence of reproducing worm pairs), but not disease (organ damage). Prevalence (of egg shedding) is highest among school-age children (1).One host snail species typically predominates in a given geographic region, with typical snail habitat along freshwater bodies in warm, low-altitude, high-rainfall areas (6).No specific habitat differences explain the overall difference in geographic distribution between the two species (7, 8).

Since the mid 1980s, control has focused on Mass Drug Administration (MDA) with Praziquantel (PZQ). Due to highest prevalence in school-age children, convenience of school-

based MDA, limited availability of PZQ, and (until 2003) lack of approval of PZQ in pregnancy (9), control programs (where they exist) have typically provided annual or semi-annual PZQ, often integrated with other deworming, to school children. In 2009 it was estimated that only 5% of the infected population were receiving PZQ (12). Recent evaluations have questioned the impact of MDA with PZQ on prevalence, transmission, and long-term pathology (13).Of the countries addressed in this study, neither Ethiopia (14) nor Kenya (15) had implemented schistosomiasis control programs prior to the relevant DHS surveys. Tanzania (16) and Uganda (17) implemented school-based MDA in certain locations in 2004 and beginning in the mid 1980s in Zanzibar.

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 (24-26). As the reproductive system disease is chronic and not clinically apparent, it received little attention until mounting evidence of its impact and probable association with HIV (29) led to renaming of *S. haematobium* from urinary to urogenital schistosomiasis. Population-based studies in Madagascar (30),Tanzania (31, 32), Malawi (33), and Egypt (34) have confirmed that vaginal/cervical schistosomiasis occurs in 30-75% of women who have urinary schistosomiasis. The prevalence of upper tract (Fallopian tube) disease is unknown due to difficulty of assessment, but pelvic ultrasound abnormalities (ovarian cysts, uterine mass, hydrosalpinx) were seen in 9% of women in one affected community in Madagascar (37). Pathology studies and case reports suggest that schistosomiasis also affects the male reproductive system (38).

Published reports of effects of schistosomiasis on reproductive outcomes are limited to case reports and descriptive series suggesting increased risk of prematurity (40)and of low birth weight (41-43); reports of schistosomiasis prevalence in pregnant women (39); and many case reports of FGS of the Fallopian tubes associated with infertility and ectopic pregnancy.

Impaired fertility is a common consequence of upper reproductive tract disease, often stigmatizing the woman due to the presumption of sexually transmitted infections as causal (67). The same tubal pathology may lead to ectopic pregnancy. 25% of maternal deaths in an urban slum in Nairobi, Kenya 2009-2013 were estimated to be due to ectopic pregnancy (61). Hospital series in Ghana and South Africa have reported 1-4% of pregnancies as ectopic with 53-61% in hypovolemic shock on arrival (62, 63). It is likely that most affected African women die without being diagnosed, treated, or counted as maternal deaths.

Terms used often inconsistently to describe impaired fertility include *infertility, sub-fertility, sterility,* and *infecundity* (68). *Fecundity* may refer to conception and *fertility* to birth, or vice-versa (69).*Clinical definitions* (for individual diagnosis and treatment) typically measure conception and use short intervals (failure to conceive by 12 months). The *epidemiologic definition* (for monitoring and surveillance) of prevalence of infertility is the "percentage of women of reproductive age (15–49) at risk of pregnancy (not pregnant, sexually active, non-contracepting and non-lactating) who report trying for a pregnancy for two years or more" (71) (note that neither conception nor birth is specified - just "a pregnancy"). The *demographic definition* is failure of a sexually active, non-contracepting woman who desires a child to give birth within a specified time period (variously 3 to 7 years, to account for lactational amenorrhea and socio-cultural factors relating to resumption of intercourse and of childbearing) (70).At clinical level, the unit of analysis is the *couple* and infertility is classified as being due to male factor, female factor (tubal, endocrine, other), or unknown. Epidemiologically or demographically, the unit of analysis is the *woman* (for whom data are measured). *Primary infertility* is failure to produce a live birth (thus including women with early pregnancy loss or stillbirth). *Secondary infertility* is failure of a subsequent birth after having given birth. The preferred *denominator* is women ever married or in union. Using all Women of Reproductive Age (WRA) is too inclusive of those who are not sexually active. Counting only those currently married or in union excludes those who have been divorced or abandoned due to the infertility

(69).Various formulas to operationalize these definitions for analysis have been proposed for use with demographic survey data (75-77).

Using data from 47 Demographic and Health Surveys, Rutstein estimated that over 186 million (25%) women in developing countries were infertile, with prevalence of 4% for primary infertility (5% if pregnancy losses are included) and secondary infertility rates increasing sharply with age (from 5% to 62%) (69). From a 2010 analysis of 277 demographic and reproductive health surveys, Mascarenas estimated that 48.5 million couples globally are infertile, with global prevalence of 1.9% for primary and 10% for secondary infertility (78). Both authors found wide variations among countries, with highest rates in sub-Saharan Africa. Where medical investigation has occurred, tubal factors account for a much higher proportion of infertility in Africa than in other regions (79-82). Although tubal-factor infertility is usually attributed to sexually transmitted infections, this is generally an assumption, as microbiologic or pathologic testing is rarely done, the diagnosis of tubal distortion or obstruction is made by radiologic imaging (hysterosalpingogram, HSG), and other possible etiologies are not considered. Where serologic testing has been done or pathologic specimens obtained during surgical procedures, only 2-20% of tubal disease was due to chlamydia (83, 84). Six to 21% of tubal infertility cases in South African clinics were due to genito-urinary tuberculosis (85, 86). 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 OR 3.6 for FGS among the infertile (87). Sub-fertility was found in 44% of women in a highly schistosomiasis-endemic area of Coast Province, Tanzania (88).

Differential geographic distribution of infertility has been noted, usually speculatively attributed to differing marriage patterns or sexual behaviors leading to sexually transmitted infections. Portions of central Africa have for decades been known as the "infertility belt" with over 20% of women older than 40 childless (89). Romaniuk noted high prevalence of infertility along the Congo and Uele Rivers in Congo, close to Lake Victoria and Lake Tanganyika, on the

coastal regions of Tanzania and Kenya, on the Zanzibar islands, and in Tabora district, Tanzania, noting a pattern of proximity to water but attributing this to tribal territorial patterns (90). (Note that these Kenya and Tanzania locations reflect the distribution of *S. haematobium*). Clinical and radiographic studies in the 1950s identified genital tract lesions in 60% and 75% of sterile Congo women (91, 92). These were presumed due to gonorrhea, although this could be identified in only 25%. In 1996, Ericksen estimated infertility across 27 African countries from DHS or World Fertility Surveys, finding prevalence varying from 1-14% for primary and 5-17% for secondary infertility (73). She found associations with urban residence, early sexual debut, and multiple partners. She also found large variation among cultural groups across Africa; suggested that this may be due to different marriage and sexual customs but did not consider geographic distribution as a possible variable (73). In Zambia, regional variation in infertility prevalence was not explained by STI risk (93). A 1980-81 survey of infertility in rural Ethiopia found highest levels in Ilubabor region in the west (now Gambela), and suggested that ecological factors could be more responsible than ethnicity (95). (Note that this is one of the few *S. haematobium*-endemic areas in Ethiopia.) Larsen analyzed infertility data from DHS surveys for 29 African countries for the 1980s and 1990s to determine regional patterns. For rural Kenya, rates were highest in the Coast and Central regions; for Tanzania, Coast, Tabora Plateau, and South regions. She investigated ethnicity, age-cohort effects and different patterns of marital sex without successfully explaining the geographic differences in infertility (96).

METHODS

This cross-sectional multi-level study explored associations between impaired fertility in East Africa with the geographic distribution and prevalence of *S. haematobium* (associated with Fallopian tubal damage) and of *S. mansoni* (not commonly associated with Fallopian tubal damage). Ethiopia, Kenya, Tanzania and Uganda were included in this study as representing 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 two-year period. Hypotheses are that risks of infertility, infecundity, and subfertility are associated with residence in high versus low *S. haematobium*-endemic locations; are associated with residence in high *S. haematobium*-endemic versus high *S. mansoni*-endemic locations; and do not differ with residence in high versus low *S. mansoni*-endemic locations.

Data Sources

Exposure

The primary exposure data source was the Global Neglected Tropical Diseases Database (www.gntd.org), a georeferenced, open-access database of schistosomiasis prevalence data established within the EU-funded CONTRAST project based in the Swiss Tropical Institute. For this database, prevalence and location data dating from 1900 were abstracted from published scientific articles, institutional reports (WHO, government, control programs), and direct communication with researchers and health staff (98). Most studies determined point prevalence based on egg counts using the Kato-Katz method for *S. mansoni* and urine filtration for *S. haematobium*. Presence data predominated, although absence data were included for some locations. A few studies reported data aggregated at administrative levels.

For this study, additional exposure data were obtained from the Global Atlas of Helminth Infection (thiswormyworld.org and ntdmap.org), a similar database project of the London School of Hygiene and Tropical Medicine, which included some more recent data but lacked open access

to some of the earlier data and did not differentiate by species in the ntdmap.org platform (99, 100). Finally, to address areas with sparse data, additional data points were obtained from the WHO 1987 Global Atlas of Schistosomiasis (19) and geocoded (using Google Earth) by name of village and approximate map location. Where prevalence was reported only as quantiles, midpoints of the quantile were used. Although schistosomiasis distribution is heterogeneous at local and seasonal scale, existing maps show no apparent change in regional distribution over the 60-year time scale included in the database or the 50-year time scale of the measured outcomes. Several studies have used these databases to produce national and regional schistosomiasis prevalence and risk maps (6, 22, 23)

Data for the four countries of interest (Ethiopia, Kenya, Tanzania, and Uganda) were compiled into a single data file. To address border issues in interpolation, data for surrounding countries were also included, to cover an area from 16^0 North to -12^0 South latitude and from 28^0 West to 8^0 East longitude. In exploratory analysis, prevalence for each of the two *Schistosoma* species was mapped in ArcGIS as point prevalence, administrative-level prevalence, and kernel density.

A prevalence map for each of the two species was produced by interpolation using ArcGIS Geostatistical Analyst extension (Figure 3). Various kriging methods and models were tested to map the predicted distribution and prediction error, using half the randomized dataset for model calibration and half for model testing. The Empiric Bayesian Kriging model produced the lowest prediction error (RMS standardized error 0.95 for *S. haematobium* and 0.97 for *S. mansoni*). It is noted that geographic areas of high standard error coincided with areas of low human population (as indicated by few DHS datapoints).

Interpolated schistosomiasis prevalence was extracted to georeferenced DHS datapoints. DHS coordinates are geomasked by displacement of urban clusters up to 2 km and rural clusters up to 5 km, with a randomly selected 1% of rural clusters displaced up to 10 km (101).DHS guidance indicates that point extraction (rather than buffering to account for this displacement) is

acceptable as it has been shown to produce unbiased estimates for interpolated surfaces having moderate to high spatial autocorrelation (in this data, Moran's I = 0.49 for *S. haematobium*, 0.80 for *S. mansoni*) (101). Exposure was categorized as high (>25%), moderate (5-25%) or low (<5%) for each of the two *Schistosoma* species, based on commonly used programmatic categorizations, apparent natural breaks in histograms of the spatial data and sample size considerations, and confirmed in sensitivity analysis using other levels of categorization. Inclusion of Lake Victoria in maps addresses the very high schistosomiasis prevalence among people living on islands within the lake.

Outcomes and Covariates: Demographic and Health Surveys

The Demographic and Health Surveys, a program of the US Agency for International Development (USAID), support a country's collection and analysis of nationally representative data about women's and children's health, fertility, contraception, social factors, malaria, and HIV, using standard questionnaires and methodologies (102, 103). Surveys use a two-stage sampling method with nationally representative selection of DHS clusters (modified for rural/urban and regional stratification) followed by PPS selection of households. All Women of Reproductive Age (15-49) within each selected household are surveyed. Surveys are typically carried out every 5 years. For this analysis and to explore temporal changes, surveys were combined for each of 2 time periods for which data were available: 2009-11 for Ethiopia, Kenya, Tanzania, and Uganda, and 1998-2000 for Ethiopia, Tanzania, and Uganda. (Georeferenced data were not available for the 2000 Kenya survey).

The reproductive factors measurable at individual level from DHS data include infertility and pregnancy loss, although pregnancy loss can only be assessed as a dichotomous variable of limited accuracy due to under-reporting (104). Differentiation of early miscarriage from stillbirth could not be accurately assessed due to large amount of missing data. Other outcomes of interest were not measurable. As women who have died are not sampled, DHS measures maternal

mortality through the sisterhood method, which would not correlate with the individual-level geographic exposure variable. Birth weight data is non-representative (over 50% missing). Urinary incontinence as a proxy for fistula was measured in the 2005 Ethiopia and Uganda DHS, but not in the *S. haematobium*-endemic countries.

Outcome measures used were *total infertility* (married, non-contracepting women who had not given birth within the past 5 years and were not currently pregnant), classified as *primary infertility* (never having given birth) and *secondary infertility* (ever having given birth). Conception rather than livebirth was measured as *total infecundity* (married, non-contracepting women who had neither given birth nor reported a miscarriage or stillbirth within the past 5 years and were not currently pregnant), classified as *primary infecundity* (never having reported a birth, miscarriage or stillbirth) and *secondary infertility* (ever having reported a birth, miscarriage or stillbirth). *Infecundity* measures were only available for the 2009-2011 data, as calendar year of pregnancy losses (miscarriage or stillbirth) was not reported in the 2000 Tanzania survey. Georeferenced data for other known risk factors for infertility (STIs, TB), which are not known to be spatially distributed, were not available.

For spatial analysis, individual outcome (case) data were aggregated as point prevalence at the geocoded DHS cluster locations and as areal prevalence at second administrative district level. Potential covariates derived from the DHS data included age (measured at subject level) and rural-urban status (measured at DHS cluster level). DHS defines "urban" as cities and small towns and "rural" as countryside, based on each country's governmental designation of the cluster location. Mismatch may be high. Comparison to satellite-imagery methods (GRUMP, MODIS) and population-density methods (WorldPop Project) found that most Tanzania DHS urban-defined clusters were classified as rural by other methods, less so for Uganda (106). However, the DHS classification was used in this study.

Guidance for spatial and regression modeling methods is provided by DHS, as well as examples of studies which have used similar methods to analyze associations between DHS variables and environmental exposures including malaria (105, 106).

Ethical review

Review was waived by the Emory University Institutional Review Board. Necessary datause agreements were executed for MeasureDHS (USAID), the Global Neglected Tropical Diseases Database, and the Global Atlas of Helminth Infections.

Analysis

Analyses were carried out using SAS 9.4 (Cary, NC), ArcGIS 10.3 (ESRI, Redland, CA), and GeoDa 1.6.6 (Tempe, AZ) (107). In addition to development of interpolated spatial models to quantify exposure (schistosomiasis prevalence), spatial methods (assessment of autocorrelation, cluster analysis) were used to assess spatial distribution of outcome variables (108, 109). 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 outcomes (measured as point prevalence) was explored analytically (global and local Moran's I) and visually (cluster and hotspot mapping). Possible associations of outcomes with exposures were explored visually with map overlay and analytically (as areal prevalence in GeoDa) with bivariate LISA (Local Indices of Spatial Autocorrelation). Mapping of urban sample points is more affected by displacement (in DHS data), and the inherent high population density tends to mask visualization of prevalence data (109). For these reasons and as both urban status and advanced age are strongly associated with the outcomes in this study, mapping of outcomes for rural women under 40 years of age provided the best visualization of the unconfounded spatial distribution of the outcomes.

Using pseudo-likelihood methods and empirical standard error estimation, odds ratios were estimated in a weighted multilevel logistic regression model. 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 (dummy) variables for the two levels of comparison for each of the two *Schistosoma* species were measured at second (DHS cluster) level. Covariates included age as a continuous variable (first level) and rural/urban status as a dichotomous variable (second level). Estimates were weighted by DHS sample weights adjusted for differing country-level sampling fractions, as recommended in DHS guidance (110). Total infertility/infecundity and history of pregnancy loss were estimated as dichotomous outcome variables. Polytomous estimation methods were used for 3-level outcomes of primary and secondary (which sum to total) and no infertility/infecundity. Analyses were carried out in in SAS proc GLIMMIX using SAS-recommended procedures for multilevel analysis (111, 112). Models included the two *Schistosoma* species simultaneously, controlling for possible co-endemicity, but were also estimated separately for each of the of the two *Schistosoma* species with minimal difference in results. Associations were estimated separately for each of the two survey rounds (1999-2001 and 2009-2011). As sensitivity analysis, associations were estimated for various age restrictions, exposure cut-off points, and combinations of countries.

Model equation: $\text{logit}\ (Y_{ijk}) = \delta_{000} + (\delta_{100}{*}X_{ijk}) + \Sigma(\delta_{0n0}{*}Z_{njk}) + \mu_{0jk} + e_{00k}$

where i = individual (first level), j = DHS cluster (second level), k=country (third level); X=first-level variable (age), Z=second-level variables (n=5; 4 dummy variables for schistosomiasis

exposure and 1 for rural-urban status), μ_{0jk} = random effect (intercept) for cluster, and e_{00k} = random effect (intercept) for country.

RESULTS

2009-2011 surveys (Table 3)

Of 43,772 women surveyed in the 2009-2011 Ethiopia, Kenya, Tanzania and Uganda DHS, 18,052 (41%) met inclusion criteria of married or in union at least 5 years and not using contraception. By t-test, neither marriage duration nor contraceptive use (selection criteria) was associated with schistosomiasis prevalence (exposure). Of the 18,052 at risk of pregnancy, 505 (2.8%) were excluded due to non-geocoded cluster locations (thus no exposure measurement). 16,861households remained, with a mean of 1.04 women per household,

Of 17,547 women analyzed, 13.6% were currently pregnant, 3.2% had never given birth, and 64.8% had given birth within the past 5 years (Table 3). The inclusion criteria limited the total number under 20 years of age to 138; 92 of these were in Ethiopia, reflecting young marriages in that country. This number has decreased since the 1999-2001 survey. 19.7% reported ever have experienced a pregnancy loss (miscarriage or stillbirth). As over half of the data for gestational month of the loss were missing, differentiation by trimester could not be accurately determined.

35.2% of women were classified as infertile and 30.6% as infecund. Secondary infertility increased with age for all countries (7.5% of age 15-29, 22.7% of age 30-39, and 67.2% of age 40-49). Infecundity followed the same pattern at 6.6%, 20.7% and 63.6% by age category. This is the expected age pattern noted by other writers, reflecting natural declines in fertility and in frequency of intercourse. 3.2% of women had never given birth and 2.4% had never been pregnant (primary infertility and infecundity). Risk did not vary widely by age, as is expected of this measure of biological sterility.

81% lived in rural locations. The odds of infertility were higher for urban residents (OR 2.5 [95% CI 2.1, 3.0)], highest for Ethiopia (OR 3.4 [2.5, 4.7]).

1999-2001 surveys (Table 4)

Of 26,642 women surveyed in the 1999-2001 Ethiopia, Tanzania and Uganda DHS, 13,437 (50%) met inclusion criteria of married or in union at least 5 years and not using contraception. By t-test, neither marriage duration nor contraceptive use (selection criteria) was associated with schistosomiasis prevalence (exposure). Of the 13,437 at risk of pregnancy, 493 (3.7%) were excluded due to non-geocoded cluster locations (thus no exposure measurement). 12,197 households remained, with a mean of 1.06 study-eligible women per household.

Of 12,944 women analyzed,12.6% were currently pregnant, 4.5% had never given birth, 65.0% had given birth within the past 5 years (Table 4). The inclusion criteria limited the total number under 20 years of age to 200; 168 of these were in Ethiopia. 21.9% reported ever have experienced a pregnancy loss (miscarriage or stillbirth). As over half of the data for gestational month of the loss were missing, differentiation by trimester could not be accurately determined.

35.0% of women were classified as infertile. Secondary infertility increased with age for all countries (7.2% of age 15-29, 23.6% of age 30-39, and 65.5% of age 40-49). This is the expected age pattern noted by other writers, reflecting natural declines in fertility and in frequency of intercourse. 4.5% of women had never given birth. Risk did not vary widely by age, as is expected of this measure of biological sterility. Infecundity was not measured in the 1999-2001 survey.

80% lived in rural locations. The odds of infertility were higher for urban residents (OR 3.1 [95% CI 2.5, 3.8]), highest for Ethiopia (OR 3.1 [2.4, 4.1]).Duration of residence was measured in the 1999-2001 surveys. 85.2% of subjects had lived at their current residence for at least five years, 91.9% for Ethiopia, 83.3% for Tanzania, and 66.7% for Uganda. Duration of residence was not associated with prevalence of either of the exposures of interest.

Age was not associated with either *S. haematobium* or *S. mansoni* prevalence for either survey set (R^2=0.001). 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. 12% lived in areas of high *S. mansoni* prevalence, 50% in moderate, and 37% in low prevalence. Schistosomiasis prevalence varied somewhat with rural/urban classification, with high and low classifications of both species higher in urban sites. Age and rural/urban status were considered as potential confounders.

Spatial analysis of outcomes

For 2009-2010, Moran's I (inverse distance weighting) for total (0.54), primary (0.24), and secondary (0.39) infertility and for total (0.53), primary (0.24), and secondary (0.42) infecundity indicated that these outcomes were autocorrelated (not randomly spatially distributed). Ever having experienced a pregnancy loss was weakly autocorrelated (Moran's I = 0.13). For 1999-2001, Moran's I for total (1.00), primary (0.30), and secondary (0.78) infertility indicated that these outcomes were autocorrelated (not randomly spatially distributed). Ever having experienced a pregnancy loss was very weakly autocorrelated (Moran's I = 0.07) (Table 5).

Visually, secondary infertility among younger rural women appeared to cluster in western and central Ethiopia; southwestern and south central Kenya; and southwestern, southeastern and island Tanzania. Primary infertility appeared to cluster in western and northern Ethiopia and in southwestern and island Tanzania. Ever having experienced a pregnancy loss appeared to cluster throughout Uganda, in central Ethiopia, and in central, lake, and island Tanzania (Figure 4). Additional maps illustrate the spatial distribution of outcomes as Local Moran's I Cluster and Outlier Analysis (Appendix, Table 6), as quartile or box maps (Appendix, Table 7), and as Univariate LISAs (Appendix, Table 8).

The Bivariate LISA method allows visualization of areas of high or low prevalence of one variable in relation to another. High secondary infertility is co-located with high *S. haematobium* prevalence in southwestern, southeastern, central and coastal Tanzania and coastal

Kenya; and with *S. mansoni* in central and southwestern Tanzania and western Uganda. Primary infertility is co-located with high *S. haematobium* prevalence in lake, southwest, and coastal Tanzania, coastal Kenya, and northeastern Ethiopia; and with *S. mansoni* in lake and southwest Tanzania and western Uganda. History of pregnancy loss is co-located with high *S. haematobium* prevalence in lake, south, and coastal Tanzania and coastal Kenya, and with *S. mansoni* in lake and southwest Tanzania and western Uganda (Figure 5).

Regression analysis

Results are presented in Tables 6 and 7. For brevity, survey rounds 1999-2001 are referred to as "2000" and rounds 2009-2011 as "2010".

For total infertility for 2010, the intraclass correlation coefficient (ICC) for DHS cluster was 0.108 and for country 0.003, indicating that 10.8% of variability in infertility existed between clusters, 0.3% between countries and 88.9% between individuals. For 2000, the intraclass correlation coefficient (ICC) for DHS cluster was 0.073 and for country 0.012, indicating that 7.3% of variability in infertility existed between clusters, 1.2% between countries and 91.5% between individuals.

Women living in high compared to absent *S. haematobium* locations had significantly higher odds of total infertility (2000: [OR 1.53, 95%ci 1.27, 1.85], 2010: [OR 1.24, 95%ci 1.06, 1.47]), of secondary infertility (2000: [OR 1.77, 95%ci 1.43, 2.18], 2010: OR 1.27, 95%ci 1.07, 1.52]), and of primary infertility (2000: [OR 1.61, 95%ci 1.10, 2.37], 2010: [OR 1.53, 95%ci 1.05, 2.25]) for both survey rounds. Women living in moderate compared to absent *S. haematobium* locations had significantly higher odds of total infertility [OR 1.31, 95%ci 1.15, 1.49]), and of secondary infertility [OR 1.27, 95%ci 1.07, 1.52]for 2010 and of primary infertility for 2000: [OR 1.56, 95%ci 1.14, 2.14]. Living in high or moderate *S. mansoni* locations was not associated with the odds of any infertility outcome.

To control for any unidentified confounders relevant to presence or absence of any schistosomiasis (for example, low, warm, humid location compared to high, cooler, dryer location), residence in high *S. haematobium* compared to high *S. mansoni* locations was analyzed, as no relevant variables determining which species is present have been identified (see Introduction). Women living in high *S. haematobium* compared to high *S. mansoni* locations had significantly higher odds of total infertility (2000: [OR 1.41, 95%ci 1.07, 1.85], 2010: [OR 1.44, 95%ci 1.14, 1.81]), of secondary infertility (2000: [OR 1.60, 95%ci 1.17, 2.17], 2010: [OR 1.52, 95%ci 1.18, 1.94]), and of primary infertility for 2010: [OR 2.83, 95%ci 1.60, 5.00]).

Ever having experienced a pregnancy loss was less consistently associated with schistosomiasis exposure status. Significant associations were with high compared to absent *S. haematobium* in 2000 (OR 1.23, 95%ci 1.04, 1.45) and with high *S. haematobium* compared to high *S. mansoni* in 2000 (OR 1.32, 95%ci 1.03, 1.69).

As duration of residence at current location was measured in the 1999-2001 surveys, some assessment of temporal factors was possible. 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 declare infertility, associations were estimated for those locally resident for 5 years and for 10 years(Table 8). Women living in high compared to absent *S. haematobium* locations for at least 10 years had significantly increased odds of total infertility (OR 1.47, 95%ci 1.19, 1.81), of secondary infertility (OR 1.74, 95%ci 1.38, 2.19), and of pregnancy loss (OR 1.32, 95%ci 1.10, 1.59). Women living for at least 10 years in high *S. haematobium* compared to high *S. mansoni* locations had significantly higher odds of total infertility (OR 1.35, 95%ci 1.01, 1.83), secondary infertility (OR 1.55, 95%ci 1.11, 2.18), and of pregnancy loss (OR 1.35, 95%ci 1.03, 1.78).

As age at exposure to schistosomiasis may be a factor in disease occurrence, associations were also estimated for those residing locally since before age 10. Women living in high compared to absent *S. haematobium* locations since before age 10 had significantly increased

odds of total infertility (OR 1.69, 95%ci 1.31, 2.17), of secondary infertility (OR 2.11, 95%ci 1.59, 2.80), and of pregnancy loss (OR 1.38, 95%ci 1.11, 1.73). Women living for at least 10 years in high *S. haematobium* compared to high *S. mansoni* locations had significantly higher odds of total infertility (OR 1.66, 95%ci 1.15, 12.40) and of secondary infertility (OR 2.11, 95%ci 1.39, 3.22).

Other researchers have excluded the youngest (<20) or oldest (45-50) age groups in infertility classifications. Sensitivity analysis of various age restrictions and country groupings consistently found total and secondary infertility and (for 2009-2011) infecundity to be significantly associated with residence in high compared to absent *S. haematobium* locations and in high *S. haematobium* compared to high *S. mansoni* locations. Associations were less consistent for moderate compared to absent *S. haematobium* and for primary infertility, with confidence intervals for some comparisons including 1. (Table 8)

Population Attributable Fraction (PAF) is a measure of excess risk of an outcome in relation to an exposure; use of the term Etiologic Fraction for this measure is avoided due to the implication of causation. By PAF, for 2000, 7.0% [4.3, 9.4] of all infertility cases were associated with residence in high *S. haematobium* and 5.6% [0, 12.0] with residence in moderate *S. haematobium* areas. For 2010,4.5% [1.2, 7.2] of all infertility cases were associated with residence in high *S. haematobium* and 11.0% [6.3, 15.4] with residence in moderate *S. haematobium* areas. For 2000, 7.8% [1.9, 11.8] of primary infertility cases were associated with residence in high *S. haematobium* and 15.2% [3.7, 23.8] with residence in moderate *S. haematobium* areas. For 2009-2011, 8.7% [1.1, 13.8] of primary infertility cases were associated with residence in high *S. haematobium* areas.

DISCUSSION

Risks of primary, secondary, and total infertility (births) and infecundity (conceptions) were significantly associated with residence in areas of high *S. haematobium* prevalence, compared to both *S. haematobium* absence and to equivalent *S. mansoni* prevalence. Levels of *S. mansoni* prevalence were not associated with any impaired fertility outcomes. This suggests that the association is related not to unmeasured confounders of 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*).

There does not appear to be an ordinal effect of the exposure, as odds ratios did not differ proportionally for high and for moderate *S. haematobium* prevalence. When exposure was dichotomized at 5% (or present/absent), odds ratios for total infertility with any *S. haematobium* exposure did not differ markedly from those for the high and moderate categories (1999-2001: OR 1.25, 95%ci 1.09, 1.43; 2009-2011: OR 1.29, 95%ci 1.15, 1.46). This supports the argument that the usual prevalence measure (proportion of sampled schoolchildren excreting eggs on a given day) while useful as a measure of transmission, does not accurately measure prevalence of disease, which is cumulative and persistent.

History of pregnancy losses (stillbirth or miscarriage), which have many possible etiologies other than genital tract disease, was not consistently associated with schistosomiasis exposure status.

Strengths of the study were the regional approach, large sample size, and standardized data collection and analysis methods available by combining national Demographic and Health Surveys. Another strength was the public accessibility of large parasitic disease data compilations supporting generation of highly predictive interpolated spatial models of disease prevalence. The ability to use *S. mansoni* exposure as a negative control for *S. haematobium* exposure was useful, as there may have been unknown environmental factors confounding the comparison only of high to low prevalence within each species.

A limitation inherent to the cross-sectional study design is the difficulty assessing temporal factors. The 1999-2001 surveys included a variable for duration of current residence, allowing some temporal measures of exposure. Associations for those living in high-exposure regions for at least 5 years or 10 years (accounting for lag time from exposure to measured outcome) did not appear to differ meaningfully from those for the total survey population. This could be explained if previous residences were within the same exposure zone, such as neighboring villages. No data were available for exposure classifications of previous residence or of reasons for moves, such as possible urban migration of infertile women. Migration from a high-exposure to a low-exposure location could result in misclassification of exposed as unexposed, although the reverse would not occur, due to the cumulative nature of exposure. Age of exposure may be important; associations for total and secondary infertility were strengthened for those exposed before age 10. The 2009-2011 surveys lacked this temporal exposure measure, but included a variable for calendar time of previous pregnancy losses, allowing inclusion of all pregnancies, not just those resulting in birth, in outcome measures (infecundity as well as infertility).

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 focal distribution of infected snails within an ecologic zone. Urogenital schistosomiasis lesions occur within a few years of exposure and persist even with anti-helminthic treatment. Thus disease (infertility due to tubal damage) may reflect either remote childhood exposure or recent migration into an endemic area.

As exposure was measured by predicted point prevalence using the same interpolation method for each *Schistosoma* species, any misclassification of exposure was unlikely to be differential by type of schistosomiasis. In sensitivity analysis, various categorization cut-points were tested, with variation in significance of results primarily related to smaller sample sizes (Tables 8 & 9). Misclassification of infertility was unlikely, as DHS collects detailed data on all

births and previous studies have assessed the accuracy of this measurement. Infertility, the major outcome assessed, measures livebirths only. Conceptions (livebirths, stillbirths, and miscarriages) would be a more specific indicator of Fallopian tubal disease, but infecundity was measurable in only the 2009-2011 survey round. Misclassification of history of pregnancy losses (miscarriage or stillbirth) or of infecundity (which incorporates pregnancy losses) may be high due to both reporting bias and recognition bias. Possible misclassification of the rural-urban co-variate was previously discussed. However, none of these is likely to be differential by exposure.

Survival bias may be a factor if ectopic pregnancy, the most severe form of tubal disease, is associated with *S. haematobium* exposure. As DHS surveys only living women, any women who have died from ruptured ectopic pregnancy, a highly likely outcome in the study setting, would not be counted as either cases or subjects, potentially biasing study results toward the null.

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

The association with schistosomiasis increases the evidence that impaired fertility may have etiologies other than sexually transmitted infections and should not be equated with stigmatized sexual behaviors. The data sources and methods provide an approach to studying the intersection of two disparate fields: Neglected Tropical Diseases and Maternal-Child Health. These results contribute to the mounting evidence of the adverse effects of schistosomiasis on women's health, supporting the need to ensure inclusion of girls and women in disease control interventions.

SECTION III: PUBLIC HEALTH IMPLICATIONS AND FUTURE DIRECTIONS

These results may be confirmed by applying the same approach to a different region, perhaps West Africa or southern Africa. The approach of combining geo-referenced DHS data with large tropical infectious disease prevalence datasets may be applied to other possibly spatially-distributed DHS-measurable outcomes (anemia, other maternal and child health indicators) and other spatially-distributed infectious diseases (malaria, lymphatic giardiasis, other vector-borne diseases). Other methods should be explored for assessing possible associations of schistosomiasis with important women's reproductive outcomes of maternal mortality or intervening conditions, such as *S. haematobium* with prolepsis and *S. mansoni* with coagulopathy.

TABLES

Table 1. Published reports of infertility associated with schistosomiasis.

Author	Country	Type of study	Species	Number
Adenitis 2001 (113)	Nigeria	pathology series	NS	2 of 7
Bailey 2010 (114)	UK, Africa travel	case reports	Sh	2
Balasko 1995 (115)	Spain ex Nigeria	case report	Sh	1
Billy-Bris sac 1994 (116)	Guadeloupe	case report	Sm	1
Bland 1970 (117)	Rhodesia	path series	Sh	3 of 10
Boulez 1964 (118)	South Africa	path series	NS	14
Furlough 1976 (119)	Malawi	pathology series	Sh	**
Cornier 1981 (120)	France ex Tunisia	case report	Sh	1
Crump 2000 (121)	New Zealand, Africa travel	case report	NS	1
DeMille 1995 (122)	USA ex Liberia	case report	Sh	1
Doug 1973 (123)	Senegal	case series	NS	4
Ekoukou 1995 (124)	France ex Senegal	case report	Sh	1
El-Mahgoub 1982 (125)	Egypt	case series	NS	13
El_maraghy 1982 (126)	Egypt	case series	NS	10
Gilbert 1943 (127)	Southern Rhodesia	case series	Sh	2
Harouny 1988 (128)	Kuwait	case report	Sh	1
Hoffmann 2004 (129)	Germany ex Angola	case report	Sh	1
Krolikowski 1995 (130)	South Africa	case report	NS	1
LeGuyader 1965 (131)	France	case report	Sh	1
Morice 1996 (132)	France ex Africa	case reports	NS	3
Mouktar 1966 (133)	Egypt	case reports	NS	2
Nouhou 1998 (134)	Niger	case series	Sh	6
O'Leary 1994 (135)	USA ex Zimbabwe	case report	Sh	1
Ogunniyi 1994 (136)	Nigeria	case report	Sh	1
Picaud 1990 (137)	Gabon	case report	Si	1
Schanz 2013 (138)	Germany ex Nigeria	case report	NS	1
Schroers 1995 (139)	Germany ex Togo	case report	Sh	1
Sheorey 2004 (140)	Australia, Africa ravel	case report	Sh	1
Swai 2006 (141)	Tanzania	pathology series	NS	4 of 7
Vass 1982 (142)	UK ex Malawi	case report	Sh	1

NS = not specified
Sh = *Schistosoma haematobium*
Si = *S. intercalatum*
Sm = *S. mansoni*
** 57 of 138 infertile had Sh, 6 had Sm; 13 of 42 spontaneous abortions had schistosomiasis

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Table 2. Published reports of ectopic pregnancy associated with schistosomiasis

Author	Country	Type of study	Species	Number
Aminu 2014 (143)	Nigeria	case report	NS	1
Bahrami 2006 (144)	USA ex East Africa	case report	Sh	1
Bland 1970 (117)	Rhodesia	pathology series	NS	6 of 38
Bugalho 1991 (145)	Mozambique	case reports	NS	4
Doug 1973 (123)	Senegal	case report	NS	1
Ekoukou 1995 (124)	France ex Senegal	case report	Sh	1
El-Bedri 1958 (146)	Egypt	case report	Sh	1
Eogan 2002 (147)	Ireland ex Nigeria	case report	Sh	1
Garba 2004 (148)	Niger	case report	Sh	1
Gilbert 1943(127)	Southern Rhodesia	case series	Sh	1
Hassim 1966 (149)	Zambia	case report	Sh	1
Laxman 2008 (150)	UK ex Zambia	case report	Sh	1
Mayat 1959 (151)	South Africa	case report	NS	1
Mohammed 2004 (152)	Nigeria	case report	Sh	1
Okonufua 1990 (153)	Nigeria	case report	Sh	1
Owusu-Bempah 2013 (154)	Ghana	case report	NS	1
Sahu 2013 (155)	India ex Africa	case report	Sh	1
Scheller 1974 (156)	Tanzania	case series	Sh	37 of 93
Schneider 2000 (157)	South Africa	case report	Sh	1
Ville 1991 (158)	Gabon	case reports	Sh	3

NS = not specified
Sh = *Schistosoma haematobium*
***6 of 38 ectopic pregnancies had Sh

Table 3. Population description, Demographic and Health Surveys Ethiopia 2000, Tanzania 1999, Uganda 2001.

1999-2001	Ethiopia	Tanzania	Uganda	Total
Number	8357	1747	2840	12944
	N (%)	N (%)	N (%)	N (%)
Age 15-19	168 (2.0)	6 (0.3)	24 (0.8)	200 (1.5)
20-29	2736 (32.7)	610 (34.9)	1295 (45.6)	4647 (35.9)
30-39	3087 (36.9)	685 (39.2)	1050 (37.0)	4822 (37.3)
40-49	2366 (28.3)	457 (26.2)	652 (22.9)	3475 (26.8)
Currently pregnant	949 (11.4)	232 (13.3)	440 (15.8)	1679 (12.6)
Never given birth	424 (5.1)	71 (4.1)	94 (3.3)	589 (4.5)
Ever had miscarriage or stillbirth	1562 (18.7)	506 (29.0)	762 (26.9)	2830 (21.9)
Infertile (no birth in last 5 years)	2828 (33.8)	684 (39.2)	875 (30.8)	4534 (35.0)
Primary (never given birth)	392 (3.7)	66 (3.8)	93 (3.3)	551 (4.3)
age 15-29	236 (8.1)	27 (4.5)	24 (2.0)	287 (6.2)
age 30-39	94 (3.0)	32 (4.7)	37 (3.5)	163 (3.4)
age 40-49	62 (2.6)	7 (1.5)	32 (4.9)	101 (2.9)
Secondary (previous birth)	2436 (29.1)	578 (33.0)	747 (26.3)	3761 (29.1)
age 15-29	192 (6.6)	65 (10.7)	81 (7.0)	338 (7.2)
age 30-39	707 (22.9)	196 (28.6)	240 (22.6)	1143 (23.6)
age 40-49	1537 (65.0)	317 (69.4)	426 (64.7)	2280 (65.5)
Current residence > 5 years	7679 (91.9)	1456 (83.3)	1895 (66.73)	11030 (85.2)
Rural	6930 (82.4)	1293 (72.8)	2543 (78.1)	10766 (80.1)
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Odds of infertility, urban vs rural	3.6 (3.2, 4.1)	2.3 (1.8, 2.8)	2.4 (2.0, 2.8)	3.0 (2.7, 3.3)

Table 4. Population description, Demographic and Health Surveys Ethiopia 2011, Kenya 2009, Tanzania 2001, Uganda 2011.

2009-2011	Ethiopia	Kenya	Tanzania	Uganda	Total
Number	7314	2758	3945	3530	17547
	N (%)	N (%)	N (%)	N (%)	N (%)
Age 15-19	92 (1.3)	13 (0.5)	9 (0.2)	24 (0.7)	138 (0.7)
20-29	2497 (34.1)	867 (31.4)	1125 (28.6)	168 (35.9)	5757 (32.8)
30-39	2730 (37.3)	1045 (37.9)	1556 (39.4)	1292 (37.2)	6634 (37.9)
40-49	1995 (27.3)	833 (30.2)	1255 (31.8)	926 (26.2)	5009 (28.6)
Currently pregnant	895 (12.2)	347 (12.6)	581 (14.7)	566 (16.0)	2389 (13.6)
Never given birth	313 (4.3)	54 (20.0)	128 (3.2)	59 (1.7)	554 (3.2)
Ever had miscarriage/stillbirth (loss)	974 (13.3)	457 (16.6)	1032 (26.2)	997 (28.2)	3460 (19.7)
Infertile (no birth in last 5 years)	2600 (35.6)	1107 (40.1)	1461 (37.0)	1015 (28.8)	6183 (35.2)
Primary (never given birth)	285 (3.9)	50 (1.8)	124 (3.1)	54 (1.5)	513 (2.9)
age 15-29	152 (5.9)	14 (1.2)	27 (2.4)	14 (1.1)	207 (3.5)
age 30-39	79 (2.9)	20 (1.9)	59 (3.8)	21 (1.6)	179 (2.7)
age 40-49	54 (2.7)	16 (1.9)	38 (3.0)	19 (2.0)	127 (2.5)
Secondary (previous birth)	2166 (29.6)	935 (33.9)	1247 (31.6)	917 (26.0)	5318 (30.3)
age 15-29	216 (8.3)	69 (7.8)	86 (7.6)	72 (5.6)	443 (7.5)
age 30-39	624 (22.9)	299 (28.6)	353 (22.7)	234 (17.8)	1510 (22.7)
age 40-49	1326 (66.5)	620 (74.4)	808 (64.4)	611 (66.0)	3365 (67.2)
Infecund (no birth or loss in 5 years)	2507 (34.3)	970 (35.2)	1232 (31.2)	855 (24.2)	5364 (30.6)
Primary (never conceived)	251 (3.4)	32 (1.2)	88 (2.2)	42 (1.2)	413 (2.4)
age 15-29	136 (5.2)	7 (0.8)	21 (1.8)	9 (0.3)	173 (2.9)
age 30-39	71 (2.6)	14 (1.3)	40 (2.6)	18 (1.4)	143 (2.2)
age 40-49	44 (2.2)	11 (1.3)	27 (2.2)	15 (1.6)	97 (1.9)
Secondary (previous conception)	2256 (28.1)	938 (34.0)	1144 (29.0)	813 (23.0)	4951 (28.2)
age 15-29	199 (7.5)	63 (7.2)	76 (6.7)	53 (4.1)	391 (6.6)
age 30-39	586 (21.5)	274 (26.2)	311 (20.0)	203 (15.5)	1374 (20.7)
age 40-49	1271 (63.7)	601 (72.2)	757 (60.3)	557 (60.2)	3186 (63.6)
Rural	6024 (82.4)	2146 (77.8)	3319 (81.6)	2848 (80.1)	14237(81.1)
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Odds of infertility, urban vs rural	3.4(2.5,4.7)	2.2(1.4,3.6)	2.0(1.5,2.6)	1.9(1.5,2.4)	2.5(2.1,3.0)

Table 5. Measure of autocorrelation of outcome variables (impaired fertility), Moran's I (inverse distance weighting). Demographic and Health Surveys, Ethiopia 2000 & 2011, Kenya 2009, Tanzania 1999 &2001, Uganda 2001 &2011.

	Moran's I*
1999-2001	
Infertility (total)	1.0110
Infertility (primary)	0.2966
Infertility (secondary)	0.7817
Pregnancy loss	0.0674
2009-2011	
Infertility (total)	0.5413
Infertility (primary)	0.2412
Infertility (secondary)	0.3925
Infecundity (total)	0.5251
Infecundity (primary)	0.2438
Infecundity(secondary)	0.4178
Pregnancy loss	0.1276
*all $p < 0.01$	

Table 6. Association of impaired fertility with schistosomiasis endemicity of residence location, women age 15-50, Demographic and Health Surveys Ethiopia 2000, Tanzania 1999, Uganda 2001.

DHS 1999-2001	OR	95%CI	PAF	95%CI
Total infertility				
S. h high (ref=absent)	1.53	1.27, 1.85	0.070	0.043, 0.093
S. h moderate	1.14	0.99, 1.32		
S. m high	1.09	0.89, 1.33		
S. m moderate	1.01	0.87, 1.17		
S. h high (ref= *S. m* high)	1.43	1.08, 1.90		
Secondary infertility				
S. h high (ref=absent)	1.77	1.43, 2.18	0.088	0.061, 0.110
S. h moderate	1.09	0.92, 1.28		
S. m high	1.11	0.87, 1.40		
S. m moderate	0.97	0.82, 1.15		
S. h high (ref= *S. m* high)	1.60	1.17, 2.17		
Primary infertility				
S. h high (ref=absent)	1.78	1.61, 2.37	0.078	0.019, 0.118
S. h moderate	1.47	1.08, 2.00	0.152	0.037, 0.238
S. m high	1.12	0.73, 1.73		
S. m moderate	1.25	0.92. 1.70		
S. h high (ref= *S. m* high)	1.44	0.82, 2.53		
Pregnancy loss				
S. h high (ref=absent)	1.23	1.04, 1.45		
S. h moderate	0.87	0.77, 1.00		
S. m high	0.93	0.81, 1.12		
S. m moderate	0.92	0.81, 1.05		
S. h high (ref= *S. m* high)	1.32	1.03, 1.69		

S. h = Schistosoma haematobium
S. m = Schistosoma mansoni
PAF = Population Attributable Fraction
N = 12944 clusters N = 973 model AIC = 12420
Method: weighted multi-level mixed logistic regression

Table 7. Association of impaired fertility with schistosomiasis endemicity of residence, women age 15-50, Demographic and Health Surveys Ethiopia2011, Kenya2009, Tanzania2001, Uganda2011.

DHS 2009-2011	OR	95%CI	PAF	95%CI
Total infertility				
S. h high (ref=absent)	1.24	1.06, 1.47	0.045	0.012, 0.072
S. h moderate	1.31	1.15, 1.49	0.111	0.063, 0.154
S. m high	0.86	0.73, 1.02		
S. m moderate	1.02	0.90, 1.16		
S. h high (ref= *S. m* high)	1.44	1.14, 1.81		
Secondary infertility				
S. h high (ref=absent)	1.27	1.07, 1.52	0.048	0.014, 0.077
S. h moderate	1.35	1.18, 1.55	0.123	0.072, 0.167
S. m high	0.84	0.70, 1.00		
S. m moderate	0.97	0.85, 1.11		
S. h high (ref= *S. m* high)	1.52	1.18, 1.94		
Primary infertility				
S. h high (ref=absent)	1.53	1.05, 2.25	0.087	0.011, 0.139
S. h moderate	1.34	0.99, 1.81		
S. m high	0.54	0.35, 0.84		
S. m moderate	1.31	0.98, 1.75		
S. h high (ref= *S. m* high)	2.83	1.60, 5.00		
Total infecundity				
S. h high (ref=absent)	1.25	1.05, 1.47	0.045	0.011, 0.0673
S. h moderate	1.35	1.19, 1.54	0.123	0.075, 0.166
S. m high	0.87	0.73, 1.02		
S. m moderate	1.05	0.92, 1.19		
S. h high (ref= *S. m* high)	1.36	1.07, 1.72		
Secondary infecundity				
S. h high (ref=absent)	1.29	1.07, 1.54	0.048	0.014, 0.076
S. h moderate	1.38	1.20, 1.59	0.124	0.073, 0.168
S. m high	0.88	0.73, 1.06		
S. m moderate	1.00	0.87, 1.14		
S. h high (ref= *S. m* high)	1.47	1.14, 1.89		
Primary infecundity				
S. h high (ref=absent)	1.33	0.86, 2.06		
S. h moderate	1.28	0.91, 1.80		
S. m high	0.66	0.40, 1.08		
S. m moderate	1.46	1.05, 2.04		
S. h high (ref= *S. m* high)	2.01	1.06, 3.84		
Pregnancy loss				
S. h high (ref=absent)	1.14	0.97, 1.33		
S. h moderate	0.81	0.72, 0.92		
S. m high	1.00	0.85, 1.18		
S. m moderate	0.88	0.78, 0.99		
S. h high (ref= *S. m* high)	1.13	0.91, 1.41		
S. h = Schistosoma haematobium *S. m = Schistosoma mansoni* PAF = Population Attributable Fraction N = 17547 clusters N = 1827 model AIC=15606 Method: weighted multi-level mixed logistic regression				

Table 8. Association of impaired fertility with schistosomiasis endemicity of residence, Demographic and Health Surveys Ethiopia 2000, Tanzania 1999, Uganda 2001. Sensitivity analysis, various age restrictions and exposure categories.

1999-2001	*S h* high (ref=0)	*S.h* mod	*S.h* high (ref= *S.m* high)
age restricted	OR (95%ci)	OR (95%ci)	OR (95%ci)
total infertility			
<40	1.62 (1.31, 2.01)	1.17 (0.99, 1.39)	1.47 (1.07, 2.01)
>20	1.62 (1.34, 1.97)	1.15 (0.99, 1.34)	1.46 (1.11, 1.94)
20-45	1.69 (1.38, 2.06)	1.20 (1.03, 1.40)	1.54 (1.15, 2.06)
secondary infertility			
<40	2.10 (1.60, 2.75	1.11 (0.89, 1.38)	1.82 (1.22, 2.72)
>20	1.79 (1.45, 2.21)	1.10 (0.93, 1.30)	1.61 (1.18, 2.20)
20-45	1.97 (1.56, 2.48)	1.17 (0.97, 1.41)	1.77 (1.26, 2.48)
primary infertility			
<40	1.97 (1.30, 2.98)	1.48 (1.05, 2.07)	1.66 (0.90, 3.05)
>20	1.88 (1.26, 2.81)	1.54 (1.11, 2.13)	1.56 (0.87, 1.80)
20-45	2.10 (1.39, 3.19)	1.51 (1.07, 2.12)	1.60 (0.87, 2.95)
pregnancy loss			
<40	1.40 (1.15, 1.70)	0.88 (0.76, 1.03)	1.57 (1.18, 2.10)
>20	1.24 (1.05, 1.47)	0.88 (0.77, 1.00)	1.32 (1.03, 1.68)
20-45	1.36 (1.13, 1.63)	0.88 (0.76, 1.02)	1.47 (1.13, 1.92)
exposure cut-points			
total infertility			
30%, 5%	1.32 (1.07, 1.64)	1.21 (1.05, 1.40)	1.16 (0.83, 1.60)
5% (dichot)	1.25 (1.09, 1.43)	NA	1.24 (1.02, 1.52)
S.h alone (no *Sm*)	1.53 (1.27, 1.85)	1.15 (1.00, 1.33)	NA
secondary infertility			
30%, 5%	1.34 (1.05, 1.71)	1.17 (0.99, 1.37)	1.18 (0.82, 1.0)
5% (dichot)	1.22 (1.05, 1.42)	NA	1.30 (1.04, 1.63)
S.h alone (no *Sm*)	1.60 (1.29, 1.97)	1.09 (0.93, 1.28)	NA
primary infertility			
30%, 5%	1.26 (0.84, 1.89)	1.37 (1.05, 1.80)	1.14 (0.62, 2.10)
5% (dichot)	1.35 (1.05, 1.74)	NA	1.22 (0.83, 1.79)
S.h alone (no *Sm*)	1.39 (0.98, 1.98)	1.35 (1.03, 1.77)	NA
pregnancy loss			
30%, 5%	1.23 (1.01, 1.49)	0.90 (0.79, 1.03)	1.28 (0.95. 1.73)
5% (dichot)	0.97 (0.86, 1.10)	NA	1.08 (0.90, 1.30)
S.h alone (no *Sm*)	1.23 (1.04, 1.46)	0.87 (0.76, 0.99)	NA
residence duration			
total infertility			
>10y	1.47 (1.19, 1.81)	1.13 (0.96, 1.33)	1.35 (1.00, 1.83)
>5y	1.47 (1.20, 1.80)	1.11 (0.95, 1.30)	1.36 (1.01, 1.82)
age 1st expos	1.69 (1.31, 2.17)	1.18 (0.96, 1.44)	1.66 (1.15, 2.40)
secondary infertility			
>10y	1.74 (1.38, 2.19)	1.04 (0.86, 1.25)	1.55 (1.11, 2.18)
>5y	1.72 (1.37, 2.16)	1.04 (0.87, 1.24)	1.51 (1.09, 2.10)
age 1st expos	2.11 (1.59, 2.80)	1.09 (0.86, 1.37)	2.11 (1.39, 3.22)

primary infertility			
>10y	1.49 (0.95, 2.34)	1.58 (1.10, 2.27)	1.29 (0.67, 2.46)
>5y	1.74 (1.15, 2.65)	1.49 (1.06, 2.10)	1.76 (0.95, 3.28)
age 1st expos	1.38 (0.82, 2.33)	1.57 (1.03, 2.40)	1.18 (0.55, 2.56)
pregnancy loss			
>10y	1.32 (1.10, 1.59)	0.89 (0.76, 1.03)	1.35 (1.03, 1.78)
>5y	1.28 (1.07, 1.53)	0.86 (0.75, 0.99)	1.29 (1.00, 1.68)
age 1st expos	1.38 (1.11, 1.73)	0.92 (0.77, 1.10)	1.37 (0.98, 1.91)
countries			
total infertility			
Eth + Tanz	1.58 (1.28, 1.95)	1.21 (1.02, 1.45)	1.49 (1.09, 2.03)
Tanz + Uga	1.68 (1.28, 2.19)	1.05 (0.81, 1.36)	1.41 (0.94, 2.13)
Tanz alone	2.10 (1.02, 4.35)	1.39 (0.66, 2.93)	1.77 (0.77, 4.03)
secondary infertility			
Eth + Tanz	1.75 (1.38, 2.22)	1.18 (0.97, 1.44)	1.59 (1.13, 2.25)
Tanz + Uga	1.59 (1.19, 2.11)	1.03 (0.78, 1.36)	1.41 (0.91, 2.18)
Tanz alone	2.15 (0.96, 4.81)	1.48 (0.65, 3.38)	1.86 (0.74, 4.65)
primary infertility			
Eth + Tanz	1.36 (0.91, 2.02)	1.35 (0.97, 1.88)	1.59 (0.88, 2.90)
Tanz + Uga	1.57 (0.94, 2.62)	0.90 (0.53, 1.53)	1.07 (0.50, 2.30)
Tanz alone	1.42 (0.36, 5.52)	0.50 (0.12, 2.14)	1.16 (0.24, 5.59)
pregnancy loss			
Eth + Tanz	1.58 (1.31, 1.90)	1.04 (0.89, 1.21)	1.49 (1.13, 1.96)
Tanz + Uga	0.84 (0.68, 1.04)	0.78 (0.64, 0.96)	1.02 (0.74, 1.41)
Tanz alone	1.25 (0.72, 2.18)	1.21 (0.68, 2.13)	1.50 (0.80, 2.83)

Table 9. Association of impaired fertility with schistosomiasis endemicity of residence, Demographic and Health Surveys Ethiopia2011, Kenya2009, Tanzania2001, Uganda2011. Sensitivity analysis, various age restrictions and exposure categories.

2009-2011	*S h* high (ref=0)	*S.h* mod	*S.h* high (ref= *S.m* high)
age restricted	OR (95%ci)	OR (95%ci)	OR (95%ci)
total infertility			
<40	1.34 (1.11, 1.63)	1.35 (1.16, 156)	1.62 (1.24, 2.12)
>20	1.26 (1.07, 1.49)	1.31 (1.15, 1.49)	1.47 (1.17, 1.86)
20-45	1.25 (1.05, 1.49)	1.24 (1.09, 1.42)	1.52 (1.19, 1.95)
secondary infertility			
<40	1.40 (1.12, 1.75)	1.43 (1.21, 1.70)	1.70 (1.24, 2.32)
>20	1.28 (1.07, 1.52)	1.35 (1.18, 1.54)	1.53 (1.19, 1.96)
20-45	1.27 (1.04, 1.54)	1.28 (1.10, 1.49)	1.54 (1.17, 2.03)
primary infertility			
<40	1.50 (0.98, 2.30)	1.29 (0.92, 1.80)	2.81 (1.48, 5.33)
>20	1.62 (1.10, 2.38)	1.32 (0.97, 1.80)	3.14 (1.76, 5.62)
20-45	1.62 (1.07. 2.45)	1.33 (0.95, 1.84)	3.27 (1.74, 6.14)
pregnancy loss			
<40	1.11 (0.92, 1.33)	0.81 (0.71, 0.94)	1.17 (0.90, 1.50)
>20	1.14 (0.97, 1.33)	0.82 (0.72, 0.92)	1.14 (0.91, 1.41)
20-45	1.10 (0.93, 1.30)	0.80 (0.70, 0.91)	1.16 (0.91, 1.48)
total infecundity			
<40	1.32 (1.08, 1.62)	1.35 (1.16, 1.57)	1.55 (1.16, 2.05)
>20	1.26 (1.07, 1.50)	1.35 (1.18, 1.54)	1.39 (1.10, 1.77)
20-45	1.24 (1.03, 1.48)	1.27 (1.10, 1.46)	1.43 (1.11, 1.86)
secondary infecundity			
<40	1.38 (1.09, 1.74)	1.41 (1.18, 1.69)	1.61 (1.16,2.24)
>20	1.29 (1.08, 1.54)	1.38 (1.20, 1.58)	1.47 (1.14, 1.90)
20-45	1.26 (1.03, 1.54)	1.29 (1.11, 1.51)	1.48 (1.11, 1.06)
primary infecundity			
<40	1.32 (0.81, 2.16)	1.20 (0.82, 1.76)	2.07 (1.00, 4.29)
>20	1.42 (0.91, 2.21)	1.24 (0.88, 1.76)	2.27 (1.18, 4.37)
20-45	1.42 (0.88, 2.29)	1.24 (0.85, 1.80)	2.36 (1.16, 4.81)
exposure cut-points			
total infertility			
30%, 5%	1.20 (1.00, 1.45)	1.33 (1.18, 1.51)	1.54 (1.18, 2.00)
5% (dichot)	1.29 (1.15, 1.46)	NA	1.32 (1.12, 1.56)
S.h alone (no *Sm*)	1.25 (1.06. 1.47)	1.31 (1.16, 1.49)	NA
secondary infertility			
30%, 5%	1.17 (0.96, 1.42)	1.35 (1.19, 1.54)	1.48 (1.12, 1.95)
5% (dichot)	1.30 (1.15, 1.48)	NA	1.32 (1.12, 1.56)
S.h alone (no *Sm*)	1.28 (1.07. 1.53)	1.35 (1.18, 1.55)	NA
primary infertility			
30%, 5%	1.70 (1.17, 2.46)	1.31 (1.00, 1.72)	2.91 (1.62, 5.24)
5% (dichot)	1.35 (1.04, 1.74)	NA	1.25 (0.88, 1.79)
S.h alone (no *Sm*)	1.47 (1.00, 2.16)	1.34 (0.99, 1.81)	NA
pregnancy loss			
30%, 5%	1.08 (0.91, 1.29)	0.84 (0.75, 0.95)	1.05 (0.82, 1.35)
5% (dichot)	0.89 (0.80, 1.00)	NA	1.00 (0.85, 1.17)
S.h alone (no *Sm*)	1.14 (0.98, 1.34)	0.81 (0.72, 0.92)	NA

total infecundity			
30%, 5%	1.21 (1.00, 1.46)	1.37 (1.20, 1.55)	1.43 (1.09, 1.87)
5% (dichot)	1.32 (1.17, 1.49)	NA	1.30 (110, 1.54)
S.h alone (no *Sm*)	1.25 (1.05, 1.47)	1.35 (1.19, 1.54)	
secondary infecundity			
30%, 5%	1.18 (0.97, 1.44)	1.39 (1.22, 1.59)	1.39 (1.05, 1.84)
5% (dichot)	1.34 (1.18, 1.52)	NA	1.36 (1.14, 1.63)
S.h alone (no *Sm*)	1.29 (1.08, 1.54)	1.38 (1.20, 1.59)	NA
primary infecundity			
30%, 5%	1.58 (1.04, 2.39)	1.25 (0.93, 1.69)	2.31 (1.21, 4.43)
5% (dichot)	1.28 (0.96, 1.70)	NA	1.07 (0.72, 1.59)
S.h alone (no *Sm*)	1.26 (0.81, 1.96)	1.29 (0.91, 1.81)	NA
countries			
total infertility			
Ken + Tanz + Uga	1.49 (1.24, 1.79)	1.50 (1.28, 1.76)	1.58 (1.22, 2.05)
Eth + Tanz + Uga	1.26 (1.06, 1.50)	1.23 (1.07. 1.42)	1.50 (1.17, 1.92)
Tanz alone	1.27 (0.81, 1.99)	1.18 (0.75, 1.86)	1.64 (1.01, 2.65)
secondary infertility			
Ken + Tanz + Uga	1.41 (1.17, 1.71)	1.50 (1.28, 1.77)	1.44 (1.10, 1.89)
Eth + Tanz + Uga	1.26 (1.05. 1.51)	1.23 (1.06, 1.42)	1.46 (1.12, 1.89)
Tanz alone	1.24 (0.78, 1.96)	1.19 (0.75, 1.89)	
primary infertility			
Ken + Tanz + Uga	2.41 (1.54, 3.76)	1.69 (1.10, 2.57)	3.36 (1.76, 6.42)
Eth + Tanz + Uga	1.38 (0.98, 1.94)	1.33 (1.01, 1.76)	2.21 (1.32, 3.71)
Tanz alone	1.94 (0.66, 5.75)	1.62 (0.54, 4.83)	3.23 (1.04, 9.99)
pregnancy loss			
Ken + Tanz + Uga	0.91 (0.77, 1.06)	0.73 (0.64, 0.84)	0.87 (0.70, 1.09)
Eth + Tanz + Uga	1.12 (0.95, 1.33)	0.85 (0.74, 0.97)	1.19 (0.94, 1.51)
Tanz alone	0.89 (0.63, 1.27)	0.86 (0.61, 1.22)	0.90 0.62, 1.31)
total infecundity			
Ken + Tanz + Uga	1.51 (1.26, 1.82)	1.53 (1.30, 1.80)	1.52 (1.16, 1.97)
Eth + Tanz + Uga	1.28 (1.07, 1.52)	1.25 (1.08, 1.45)	1.41 (1.10, 1.82)
Tanz alone	1.39 (0.89, 2.17)	1.20 (0.77, 1.88)	1.59 (0.99, 2.58)
secondary infecundity			
Ken + Tanz + Uga	1.45 (1.20, 1.75)	1.53 (1.30, 1.81)	1.42 (1.09, 1.87)
Eth + Tanz + Uga	1.29 (1.07, 1.56)	1.25 (1.07, 1.46)	1.40 (1.07, 1.83)
Tanz alone	1.37 (0.87, 2.17)	1.23 (0.77, 1.95)	1.54 (0.94, 2.53)
primary infecundity			
Ken + Tanz + Uga	2.26 (1.37, 3.74)	1.51 (0.93, 2.45)	2.51 (1.23, 5.19)
Eth + Tanz + Uga	1.26 (0.84, 1.88)	1.35 (0.98, 1.86)	1.91 (1.05, 3.49)
Tanz alone	1.83 (0.57, 5.93)	1.21 (0.37, 3.98)	2.18 (0.64, 7.43)

FIGURES

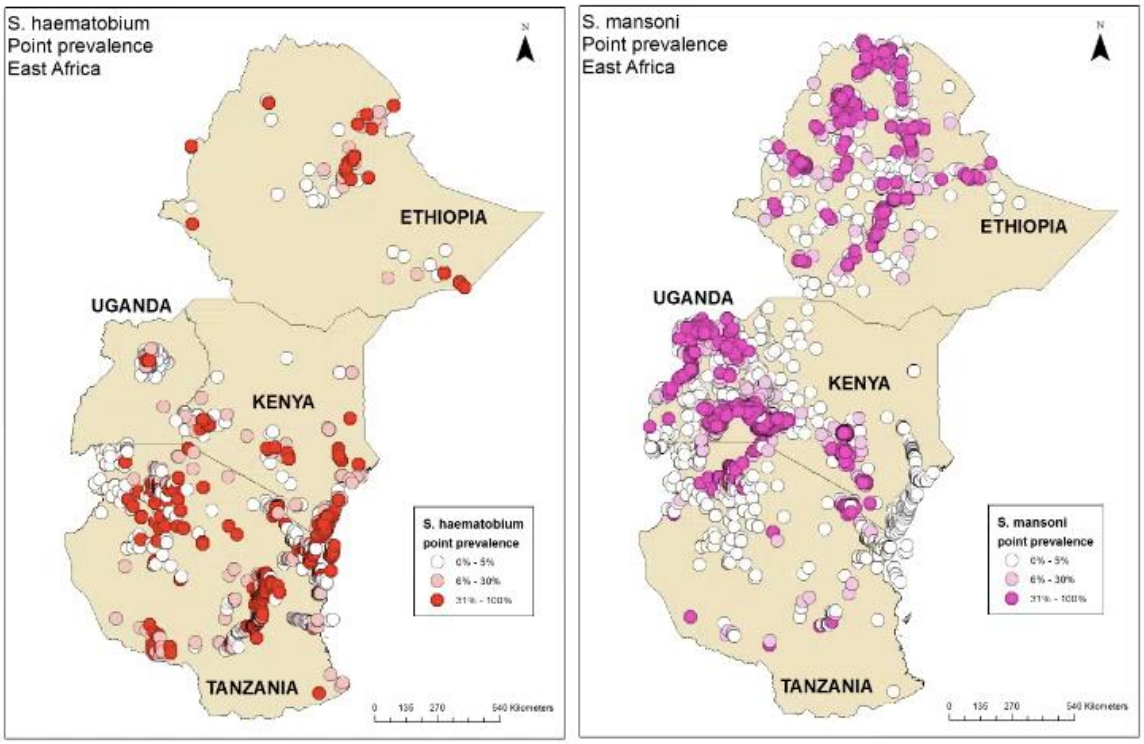


Figure 1: Map of schistosomiasis distribution in East Africa

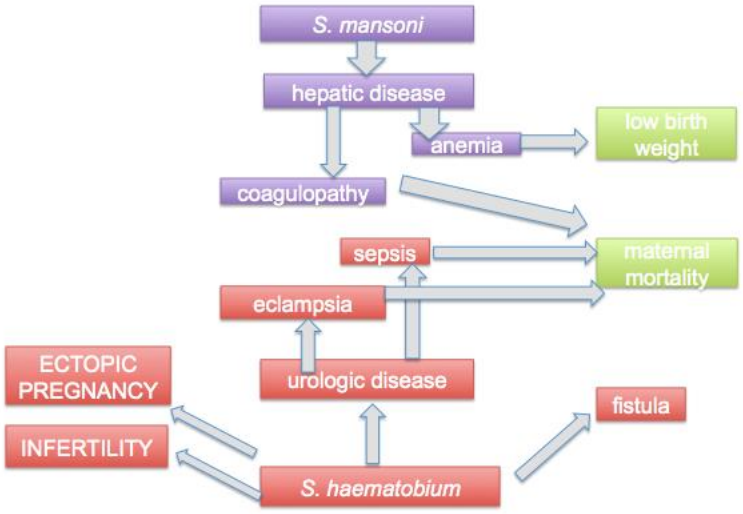


Figure 2: Potential effects of schistosomiasis in pregnancy.

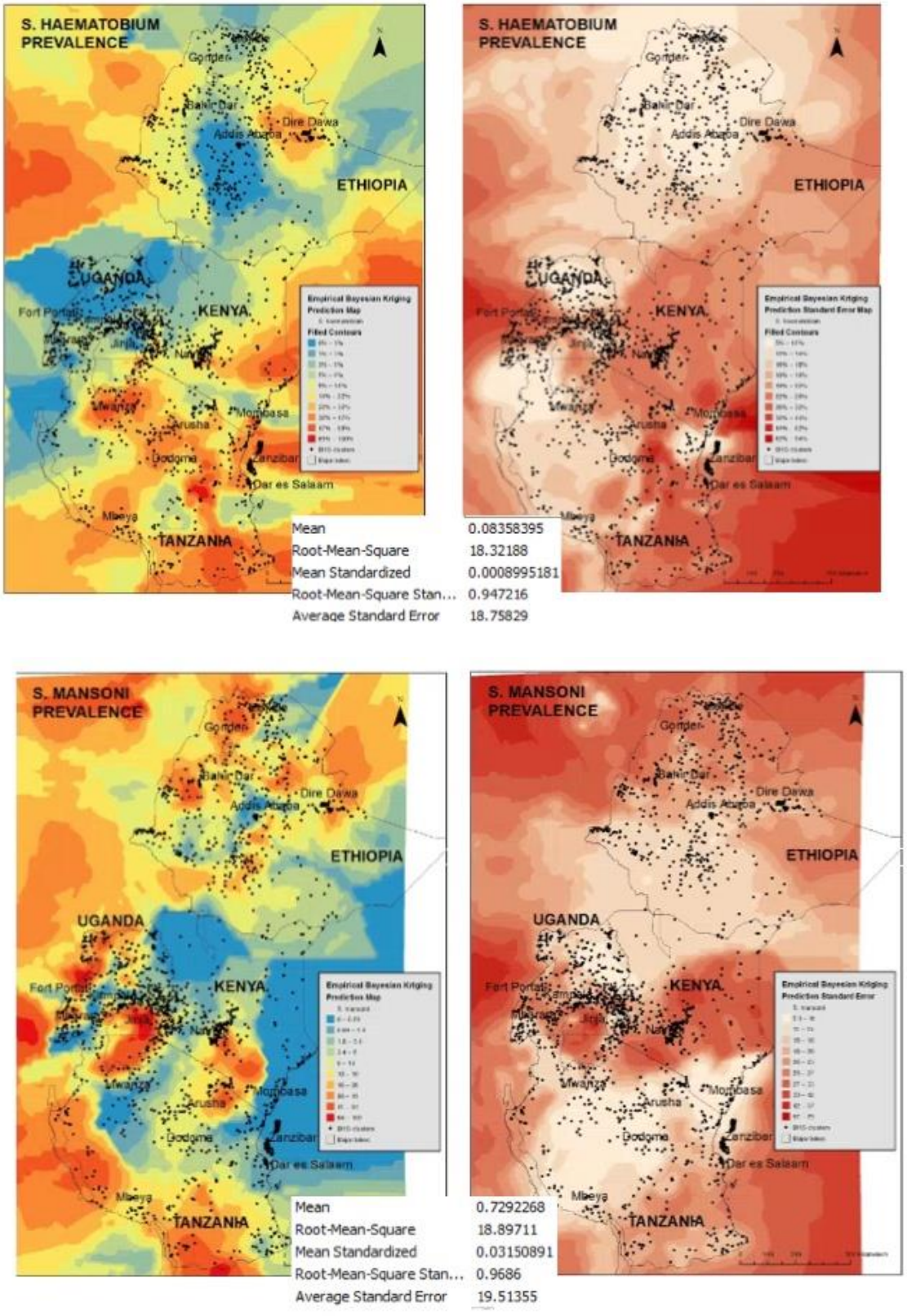
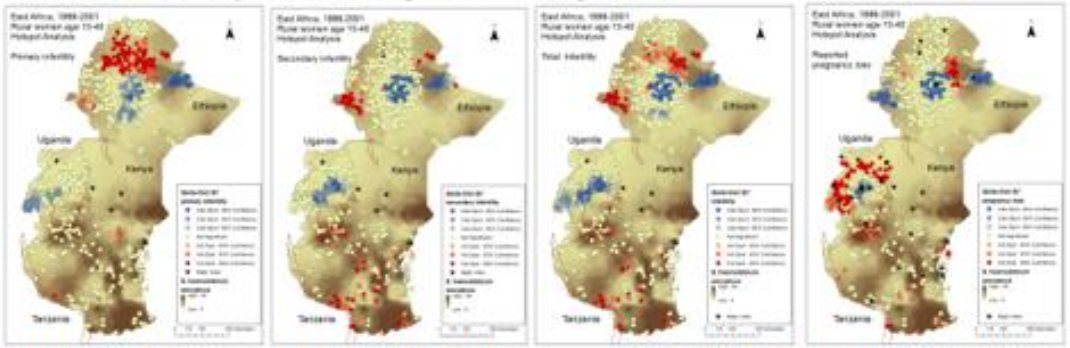


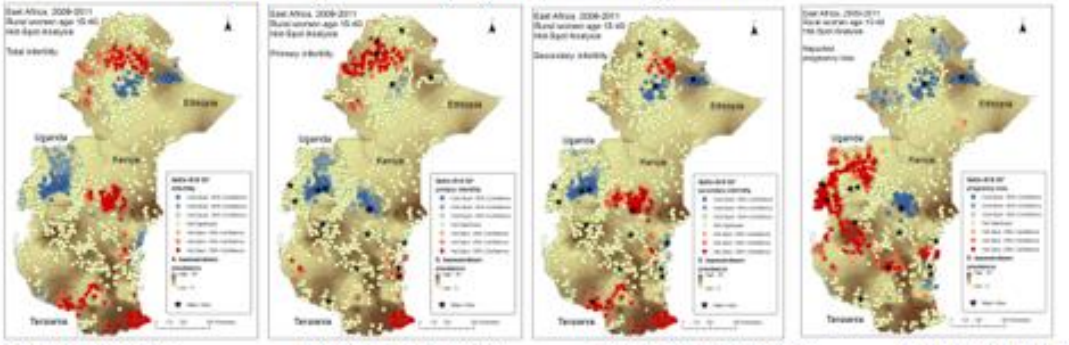
Figure 3. Predicted schistosomiasis distribution in East Africa, surface interpolated by Empirical Bayesian Kriging. Prediction maps (left), prediction standard error (right).

Getis-Ord Gi* cluster analysis
1999-2001 DHS Ethiopia, Tanzania, Uganda, women age 15-50

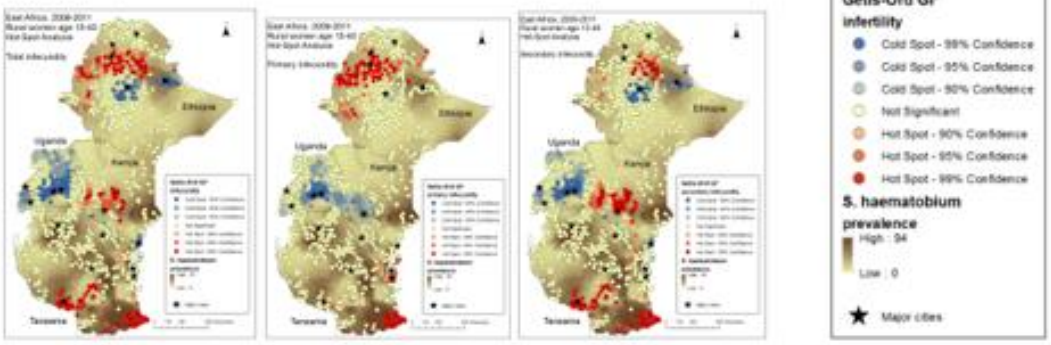


Total Infertility | Primary Infertility | Secondary Infertility | Pregnancy Loss

2009-2011 DHS Ethiopia, Kenya, Tanzania, Uganda, women age 15-50



Total Infertility | Primary Infertility | Secondary Infertility | Pregnancy Loss

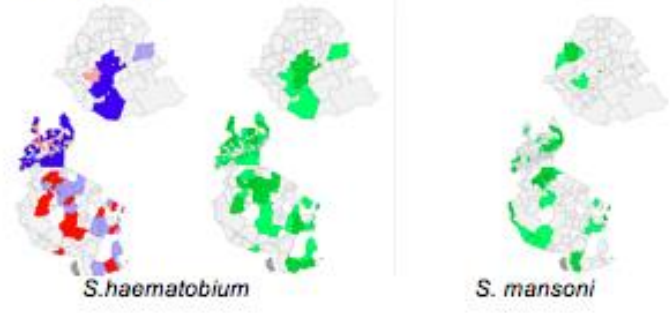


Total Infecundity | Primary Infecundity | Secondary Infecundity

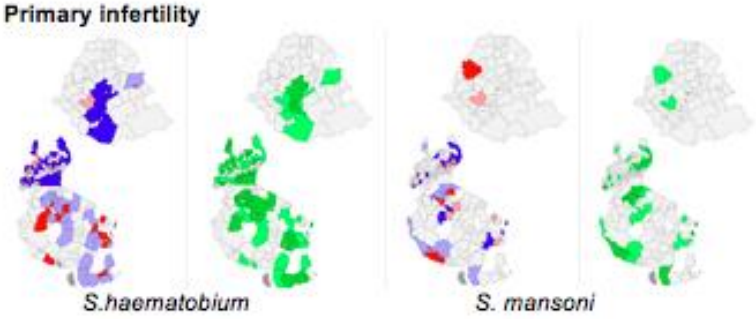
Figure 4. Local clustering of impaired fertility outcomes by Getis-Ord Gi* hotspot analysis. Rural women under age 40, Demographic and Health Surveys Ethiopia, Kenya, Tanzania, Uganda

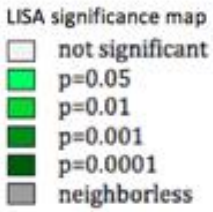
1999-2009 Demographic and Health Survey Ethiopia, Tanzania, Uganda, women age 15-50

Total infertility

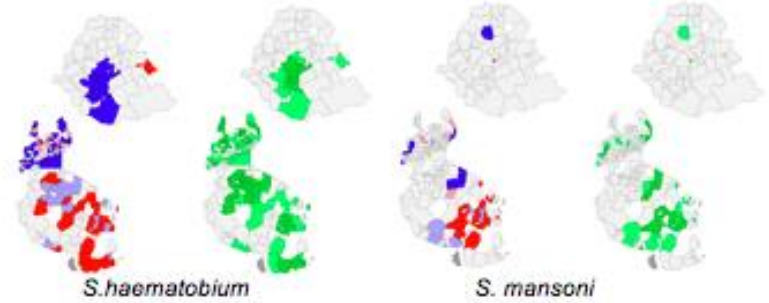


Primary infertility

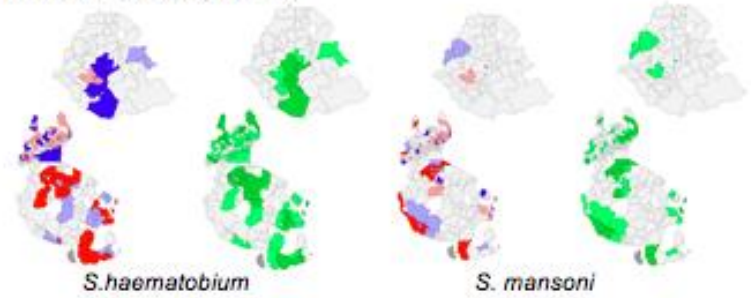




Secondary infertility

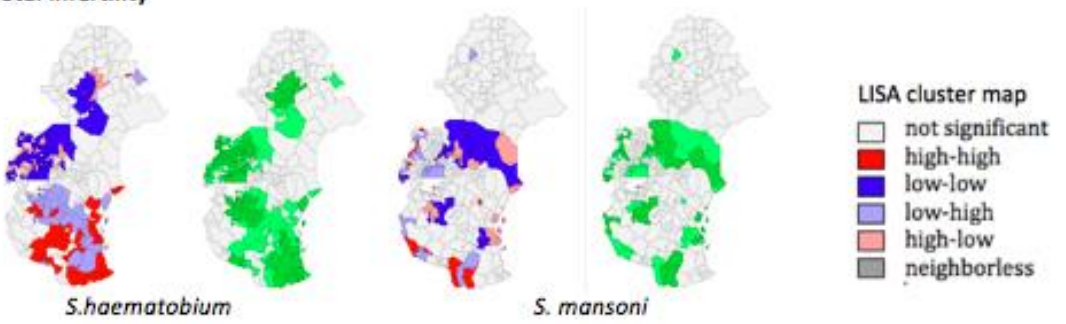


History of pregnancy loss



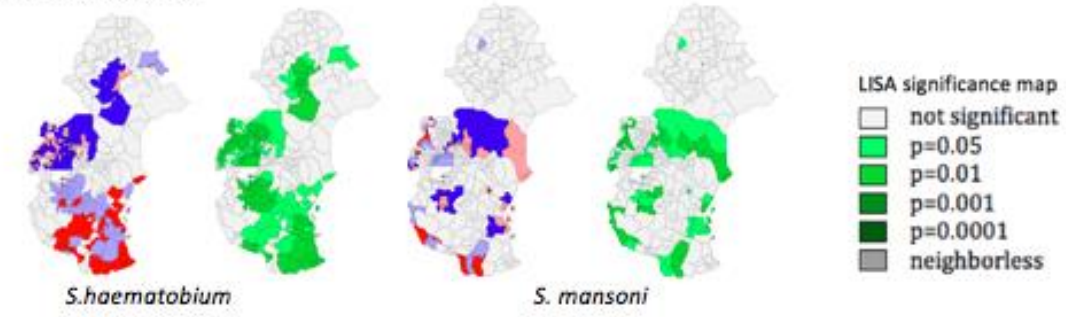
2009-2011 Demographic and Health Survey Ethiopia, Kenya, Tanzania, Uganda, women age 15-50

Total infertility



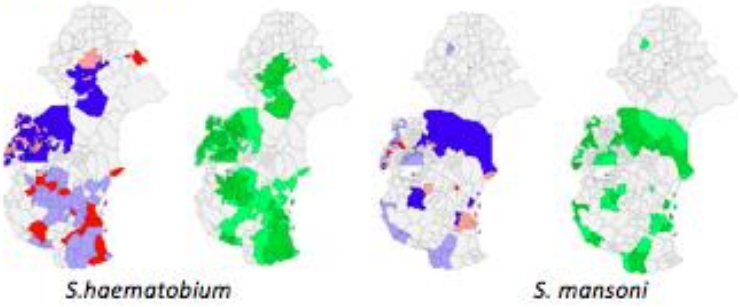
S.haematobium *S. mansoni*

Secondary infertility



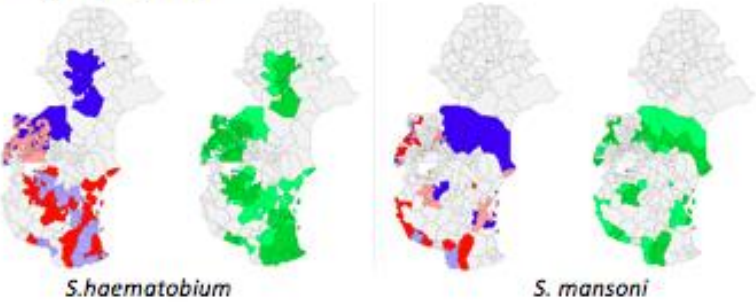
S.haematobium *S. mansoni*

Primary infertility



S.haematobium *S. mansoni*

History of pregnancy loss



S.haematobium *S. mansoni*

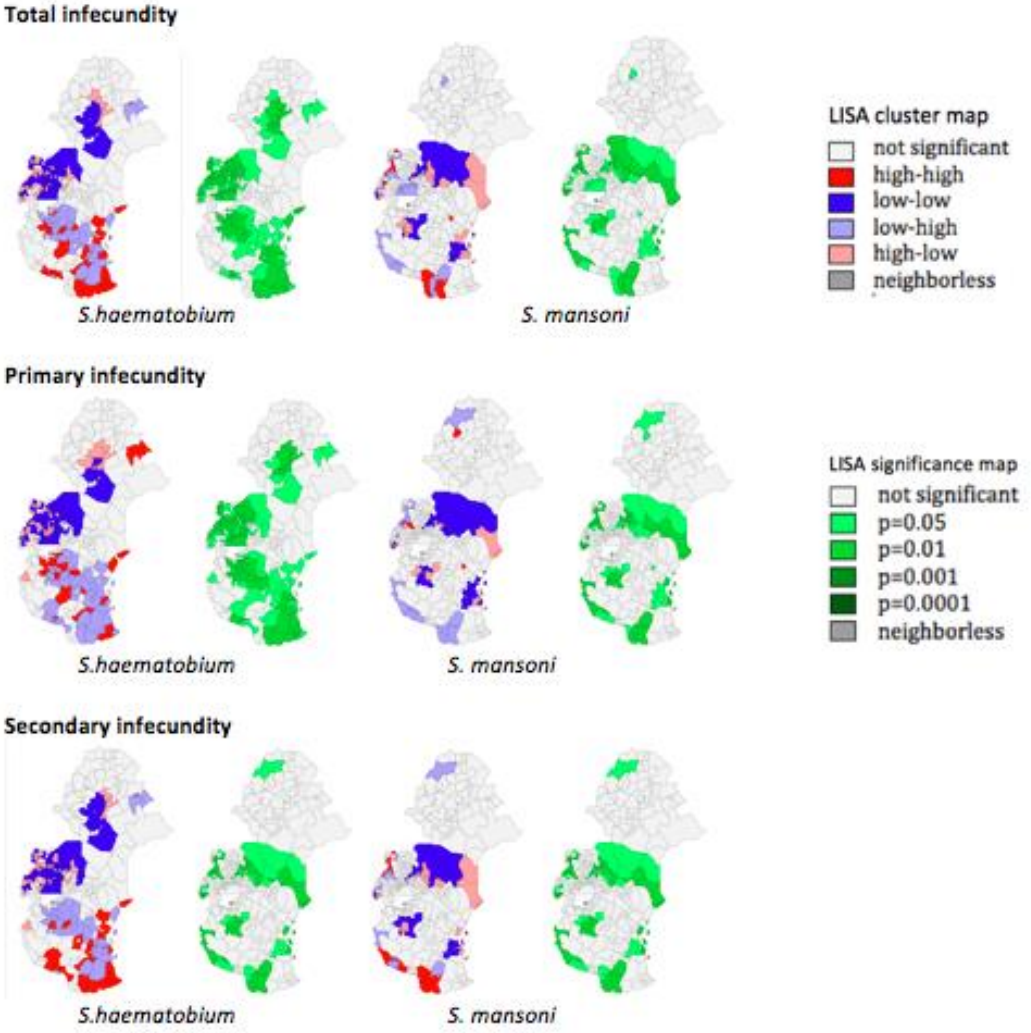


Figure 5. |Measures of fertility impairment: Bivariate Local Indices of Spatial Autocorrelation (LISA). Visual exploration of associations of high and low clustering of outcomes with areas of high and low prevalence of *Schistosoma haematobium and S. mansoni*

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APPPENDIX: ADDITIONAL MAPS

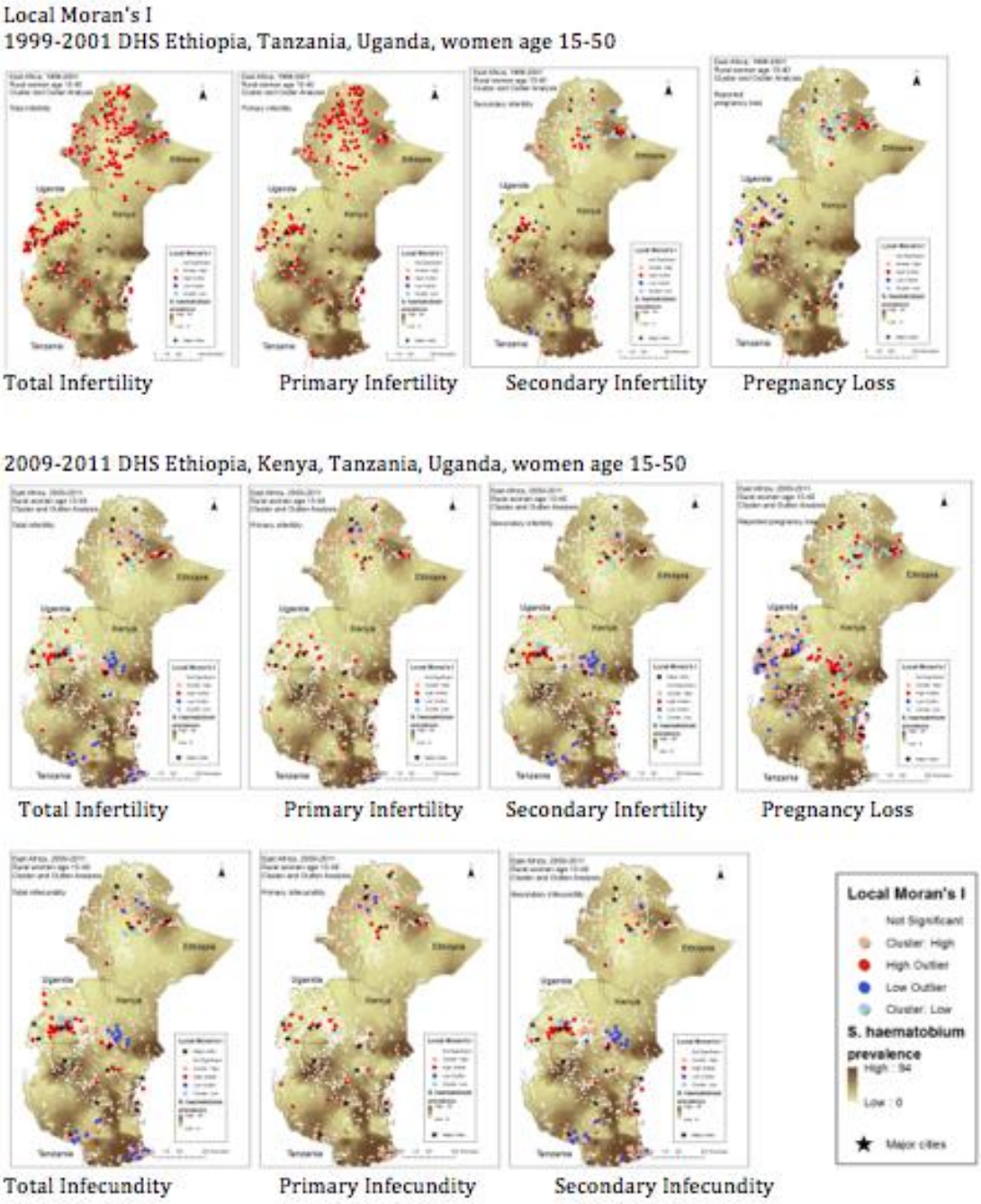


Figure 6. Local clustering of impaired fertility outcomes by Local Moran's I Cluster and Outlier Analysis. Rural women under age 40, Demographic and Health Surveys Ethiopia, Kenya, Tanzania, Uganda

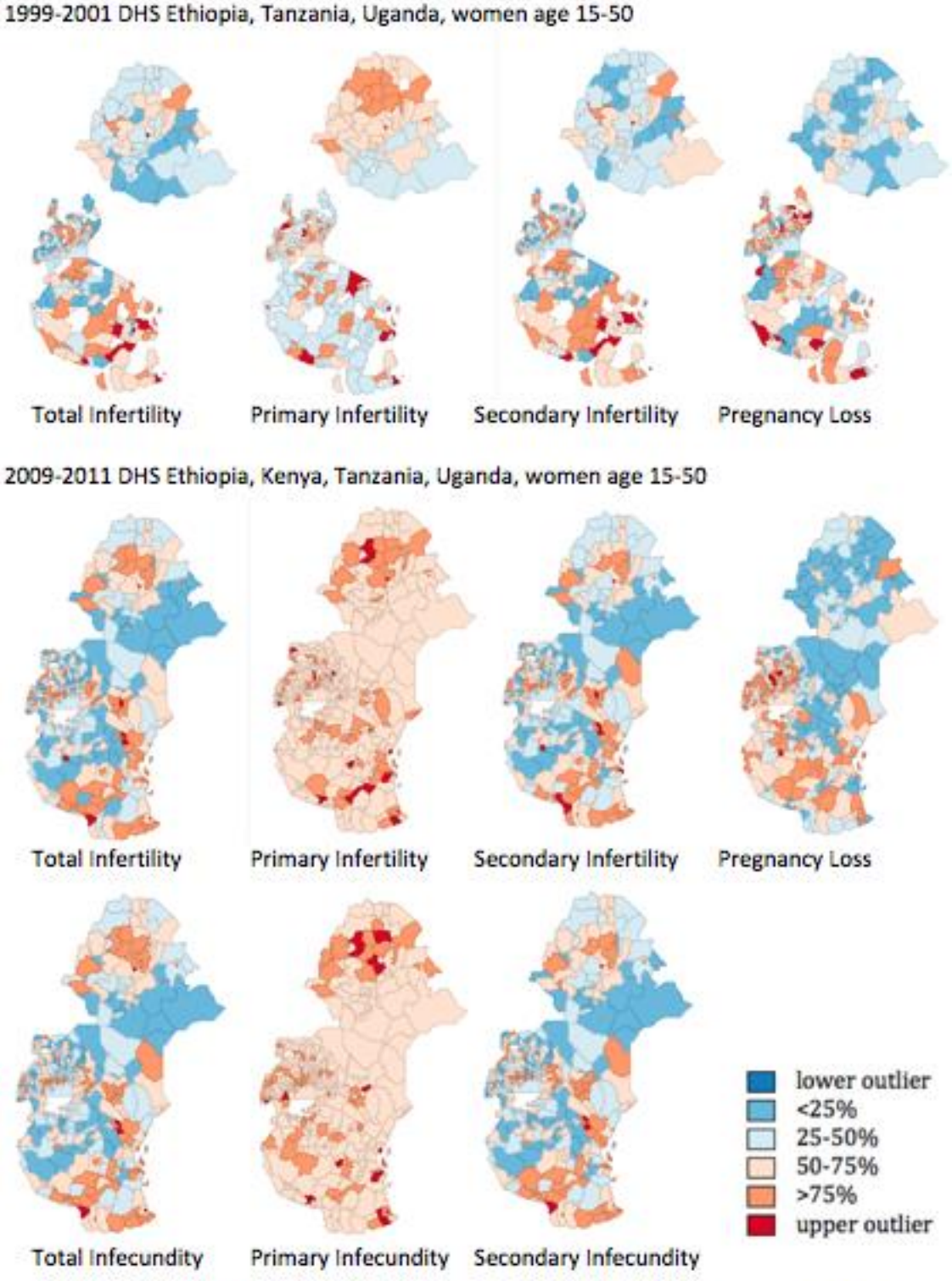
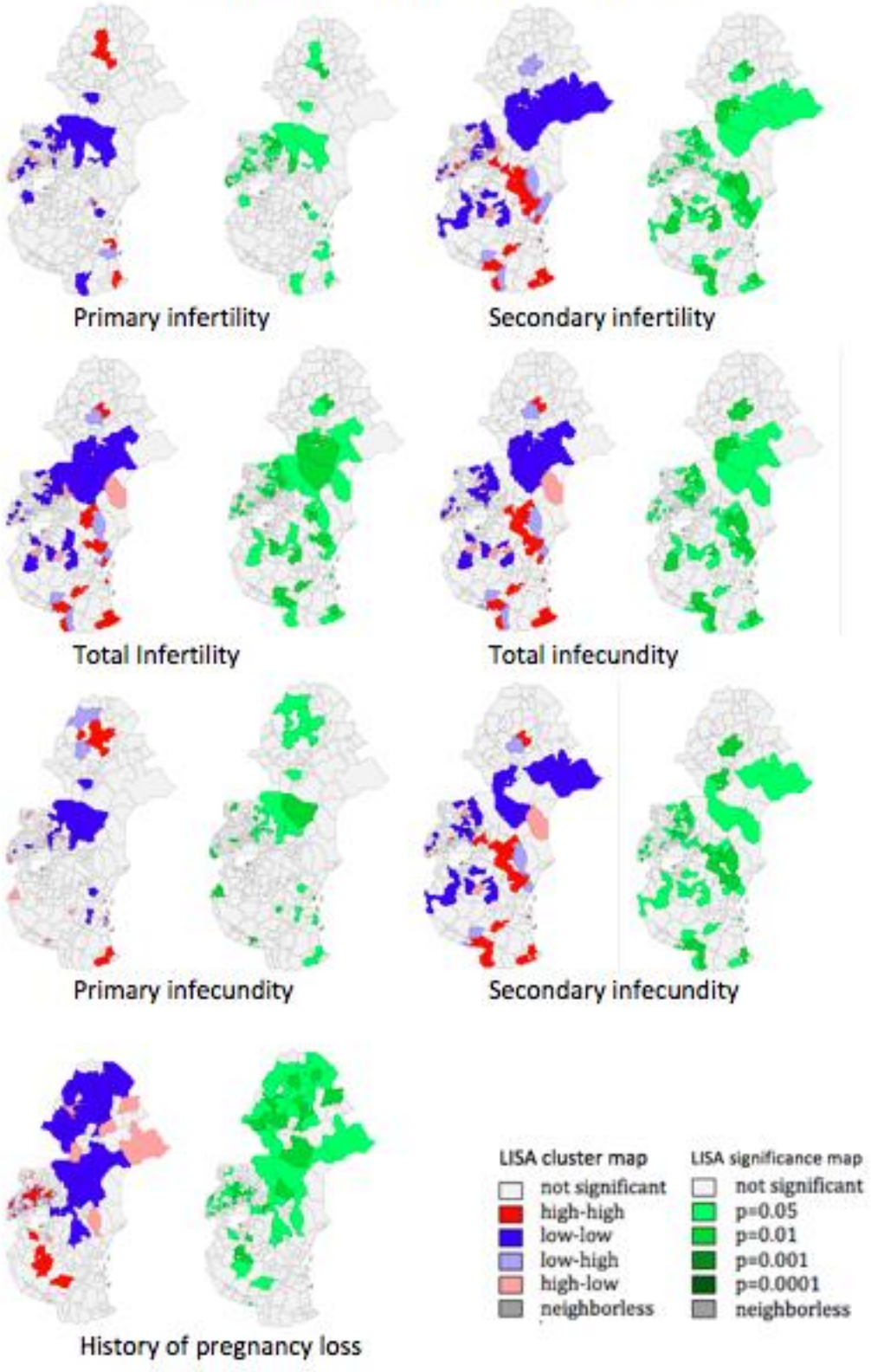


Figure 7. Measures of fertility impairment as box maps (quartiles, non-parametric data). Women age 15-50, Demographic and Health Surveys.

2009-2011 DHS Ethiopia, Kenya, Tanzania, Uganda, women age 15-50



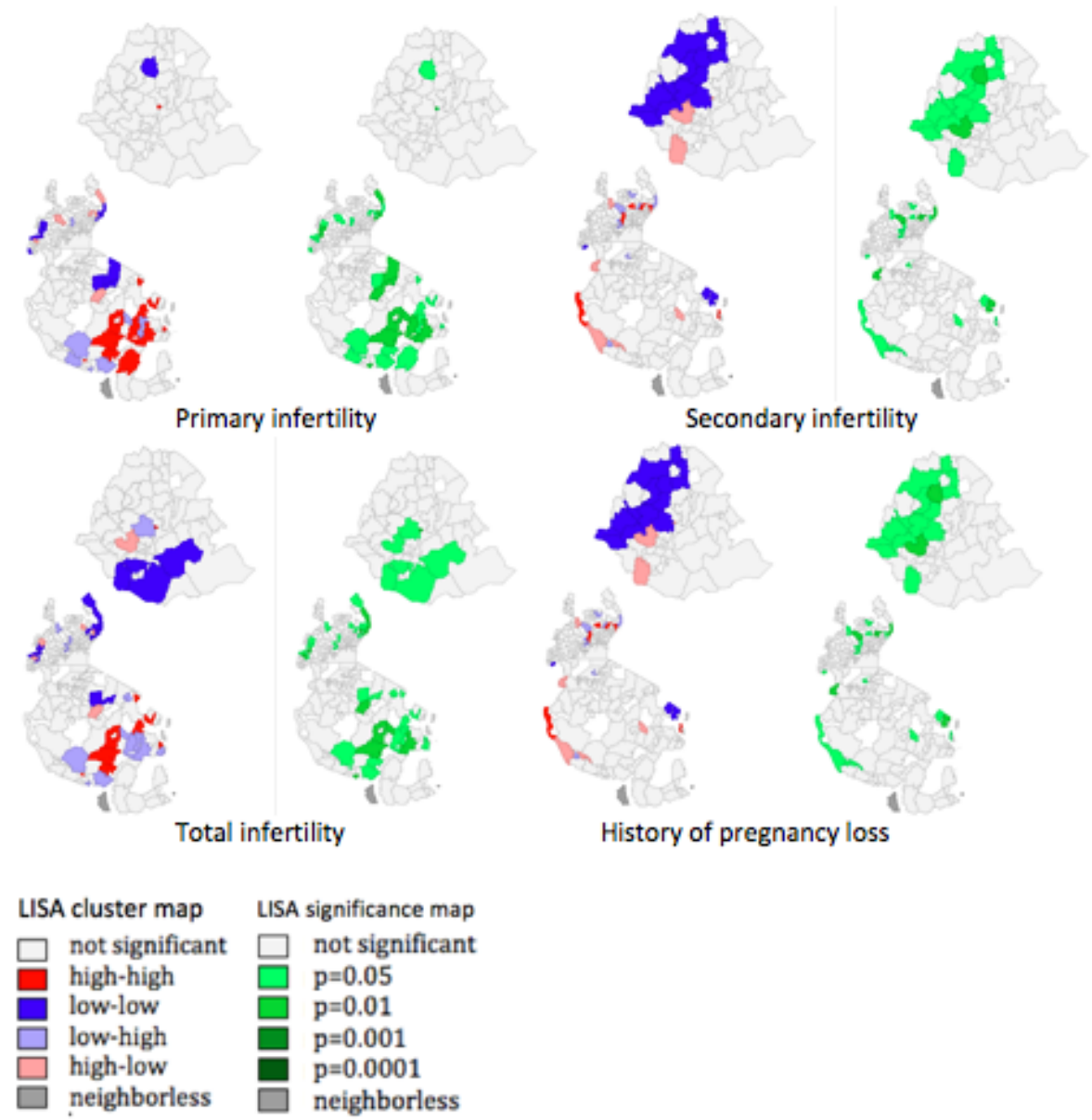


Figure 8. Measures of fertility impairment: Local Indices of Spatial Autocorrelation (LISA)