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Helminth infection and treatment among pregnant women in the Democratic Republic of Congo: An examination of associated risk factors, co-morbidities, and birth outcomes

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in Epidemiology

by

Adva Gadoth-Goodman

2019

ABSTRACT OF THE DISSERTATION

Helminth infection and treatment among pregnant women in the Democratic Republic of Congo: An examination of associated risk factors, co-morbidities, and birth outcomes

by

Adva Gadoth-Goodman

Doctor of Philosophy in Epidemiology

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Professor Anne W. Rimoin, Chair

Helminth infections have an extremely high burden of disease, infecting over a billion people globally. Yet helminthiases remain heavily neglected in research and intervention efforts, especially in women of childbearing age. The exclusion of pregnant and breastfeeding women from preventive chemotherapy campaigns has exacerbated the problem in places like the Democratic Republic of Congo (DRC), a resource-poor, helminth endemic country with a high national fertility rate. The overarching aim of this dissertation is to better describe the landscape of helminthiases in DRC's pregnant population, elucidating effects of prenatal infection on both maternal and neonatal health. Chapter 1 provides a summary of disease pathogenesis, prevention and control strategies for schistosomiasis and soil-transmitted helminths. Chapter 2 describes the prevalence, risk factors, and symptoms associated with urogenital schistosomiasis in a cross-sectional survey of women attending antenatal clinics in southeastern DRC; poor symptom

recognition and a three-fold increase in the odds of sexually transmitted co-infections were identified amongst mothers harboring *S. haematobium*. Chapter 3 utilizes causal inference methods to examine the longitudinal effects of prenatal schistosomiasis on downstream offspring health, finding no distinction in the risk of adverse birth outcomes between mothers with treated infection and uninfected controls. Chapter 4 explores predictors and birth effects of prenatal anthelminthic use at scale, finding that in a nationally representative survey of mother-child pairs in DRC, indiscriminate anthelminthic drug use is unevenly distributed across sociodemographic lines and associated with significantly reduced odds of neonatal death. The findings of this dissertation reiterate the vulnerability of mothers and their offspring to unmitigated helminthiases, as well as the neutral or beneficial effects imparted by prenatal deworming. Given the evidence amassed herein, expansion and institutionalization of preventive chemotherapy at the national level—including the systematic incorporation of pregnant women in mass drug administration campaigns throughout DRC— is warranted.

The dissertation of Adva Gadoth-Goodman is approved.

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2019

To my incredible family, both blood and chosen. Thank you for your unwavering love and support.

It takes a village.

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Chapter 1. Introduction and Background

1.1 Helminthiases

General Information

Helminths are a broad class of large, multicellular parasitic worms which include nematodes and trematodes capable of infecting human hosts. Over one billion people in sub-Saharan Africa, Asia, and the Americas are infected with at least one helminth species, and reinfection is common, as many risk factors for infection are environmentally and economically driven.[1-3] Helminthiases are usually long-lasting, and concentrated amongst already marginalized communities encumbered by poor nutrition, substandard living conditions, inadequate sanitation, and close contact with the animal vectors and reservoirs that carry infectious pathogens. Polyparasitisms and coinfections are common, exacerbating the burden of helminth-related morbidity in resource-poor settings around the globe.[2] Helminthiases cost developing economies billions of dollars each year in direct health care costs and indirect lost working days, impaired cognitive and physical development, and reduced productivity that result from disease-related morbidities.[3, 4] In this way they help perpetuate a vicious cycle of poverty amongst the world's poorest and most vulnerable populations, dampening productivity and socioeconomic development. Better understanding the geospatial, demographic, and behavioral dynamics of helminth disease transmission, as well as effective means for their prevention and control therefore provide an impactful means for improving human welfare in low and middle-income countries (LMIC).

In their 2012 technical report, the WHO Disease Reference Group on Helminth Infections (DRG4) has called for a refocusing of research priorities in regards to helminthiases, with more

money and resources to be devoted to the following areas: updating mapping of disease prevalence, monitoring and evaluation of control interventions, assessing drug efficacy and promptly detecting signs of drug resistance, and developing appropriate research and programming policies in disease-endemic countries, among others.[3] This proposed dissertation aims to shed some light on these priority topics in the context of schistosomiasis and soil-transmitted helminth infections in a sensitive and oft-overlooked sub-population of the Democratic Republic of Congo (DRC).

Preventive Chemotherapy and Mass Drug Administration

Control of helminthiases in endemic countries focuses on reducing disease via periodic, large-scale population treatment with anthelminthics, commonly known as mass drug administration (MDA) campaigns. The strategy of applying treatment to whole communities or subpopulations to stop transmission, without requiring diagnostic testing to discern currently infected individuals from their non-infected peers, is known as preventive chemotherapy (PC). PC is recommended by WHO for use in helminth-endemic countries, with the aim of halting the widespread and long-term consequences of morbidity associated with helminthiases.[1] In order to succeed, delivery of quality drugs to as many eligible members of an endemic community as possible is required, with special attention paid to capturing the young.[5] Successful campaigns are characterized by 75% coverage and above, yet this goal remains difficult to achieve in many endemic settings where road access and remote village contact remain low. In the Democratic Republic of Congo for instance, praziquantel coverage for schistosomiasis in 2015 was only 30%, and albendazole/ mebendazole coverage for geohelminthiases only reached 23%.[6]

[1] World Health Assembly (WHA) resolution 54.19 (endorsed 2001) recommends regular chemotherapy for school-age children and women to reduce morbidity due to schistosomiasis and soil transmitted helminths.

Population-based chemotherapy requires political commitment and strong health systems to be maximally effective and impactful, two things which are often lacking in LMIC that host the majority of global helminthiases.[2, 7] Nevertheless, PC remains an effective and straightforward means of disrupting transmission in places where diagnostic testing is impractical—due to prohibitive expense; lack of qualified administrators, testing equipment, and facilities; and large numbers of continuously re-infected individuals—because of the excellent safety records of antihelminth drugs, regardless of infection status.[5] PC campaigns are frequently targeted at school-aged children (SAC): an easy to capture population at high risk of disease, long-term morbidities, and associated adverse developmental outcomes. MDAs focused on reaching this vulnerable subpopulation therefore present a prime opportunity for interventions against helminthiases in resource-poor and logistically-challenging countries. Unfortunately, financial and infrastructural constraints that restrict resource allocation primarily to SAC often pass over other groups harboring infection. This disparity in drug coverage creates an unaddressed burden of disease amongst non-SAC and an overlooked reservoir for continued disease transmission in endemic communities. Another concern with MDA campaigns is the potential for accelerated drug resistance.[8] Because anthelminthics are being consistently used in two capacities, both as communal prophylactics and as individual treatment, certain populations living in helminth-endemic areas may be exposed to these drugs two or more times per year. Repeated periodic exposures to the same drugs over the span of early life, and often even beyond, may nurture the evolution of parasitic worms capable of surviving treatment; a threat which should be taken seriously given the dependence of public health strategies on these drugs for both prevention and treatment of helminthiases.

1.2 Schistosomiasis

Global impact

Schistosomiasis, also known as bilharziasis, is a parasitic disease caused by infection with one or more distinct schistosome trematode (fluke) species and manifesting in two major forms of clinical disease: intestinal schistosomiasis and urogenital schistosomiasis. Schistosomiasis afflicts more than 250 million people worldwide, 85% of whom reside in Africa. An estimated 700 million more people living in 76 endemic countries are at risk of infection and require coverage by prevention and control programs.[9, 10] The distribution of disease across the globe is severely skewed; over 90% of at-risk persons requiring preventive treatment live in Africa.[9] The Global Burden of Disease study estimates that schistosomiasis was responsible for 2.47 million years lived with disability (YLD) in 2015—second only to malaria amongst all other neglected tropical diseases.[10] Significant declines (-23.5%, 95% CI: -32.5%, -4.4%) have been made in the global prevalence of disease between 2005 and 2015, owing in large part to preventive chemotherapy campaigns.[10] Yet despite the success of large-scale interventions, schistosomiasis continues to go understudied and underfunded, afflicting marginalized communities already struggling with poverty, malnutrition, and poor sanitation.

Epidemiology

The most important risk factors for contraction of schistosomiasis are age, environmental exposures to contaminated waterways, and poor sanitation and hygiene.[11] The risk of schistosomiasis tends to peak in adolescence (10-19 years of age), with risk remaining elevated in the third decade of life before tapering off later in adulthood.[12, 13] Part of this increased risk is hypothesized to be attributable to certain play and recreational habits, such as swimming, which

tend to cluster in school-aged children.[13, 14] Occupations that increase frequency and duration of dermal exposure to infested freshwater bodies, including agricultural work, fishing, mining, and domestic chores (water collection, dish and clothes washing, etc.) also increase the risk of schistosome acquisition.[15]

Geographic distribution and parasitic lifecycle

Six distinct species of schistosomal worms responsible for two forms of human schistosomiasis are distributed differentially across the globe and result in distinct physiologic outcomes: *S. haematobium, S. mansoni, S. intercalatum, S. guineensis*, *S. japanicum*, and *S. mekongi*.[9] Of these, only three species are endemic to DRC: *S. haematobium*, which covers large portions of Africa and the Middle East and leads to urogenital schistosomiasis; *S. intercalatum*, which is found only in the rainforest regions of Central Africa, most notably in the Congo River Basin, and results in intestinal disease; and *S. mansoni* which is spread throughout Africa, the Middle East, the Caribbean and parts of South America, and causes intestinal pathology.[9, 162]

The varied presence of these species in different parts of the world are attributable to the factors that constitute suitable habitats for schistosomes' intermediate hosts—freshwater snails. Snails of the *Bulinus* genus, which harbor *S. haematobium* and *S. intercalatum* larvae, are widespread throughout freshwater bodies in Africa and the Middle East. Snails of the *Biomphalaria* genus, which harbor *S. mansoni* larvae, originated in the Americas but have since spread to colonize waterways in Africa and the Middle East.[17] Both of these snail genera, unlike their schistosome-hosting counterparts in Asia (*Oncomelania*), are completely aquatic and

[2] Although these species tend to follow a specific physiologic route, schistosome eggs may spread throughout the body via the bloodstream to cause lesions in usually-unaffected organ systems.

incapable of surviving outside of the water.[17] Freshwaters snails can take up residence in almost all types of freshwater bodies, from small temporary ponds and streams to large lakes and river systems. Genera that host schistosomes tend to congregate in shallow waters near the shores and banks of the marshes, ponds, rivers, streams, lakes, and irrigation channels that serve as their home: a convenient ecologic feature which schistosomes have evolved to exploit in order to maintain close proximity to their human hosts.[17] Snail densities vary significantly by season, with sensitivities to rainfall patterns, water level, altitude and temperature.[17]

People become infected with schistosomiasis after dermal exposure to freshwater contaminated with both schistosomal larvae and their intermediate snail hosts. Following urination or defecation (species dependent) of infected persons into snail-residing waters, *Schisotsoma* eggs are released from human waste into freshwater media. The eggs then hatch and release miracidia which can penetrate appropriate snail intermediate hosts. Miracidia next undergo three stages of development within the snail, eventually forming infective cercariae which are released from the intermediate snail host and swim to penetrate the skin of a human contacting water. Inside the human, cercariae develop further, migrating through several tissues until settling in the portal blood of the liver and maturing into adults. Adult worms then pair, mate, and release eggs in different locations throughout the human corpus depending on their species: *S. mansoni* and *S. intercalatum* adults tend to move to the mesenteric venules of the bowel/ rectum, laying eggs that circulate to the liver and shed in stools; *S. haematobium* adults opt for the venous plexus of the bladder, where eggs circulate to the kidney/ bladder and shed in urine.[18] Of importance, only about half of the eggs produced by adults over their average 5-year lifespan in the human host are actually eliminated in feces or urine; the rest remain embedded in various tissues of the body where they elicit immune responses and can cause organ damage.[17]

Clinical disease and evidence for health impacts

Schistosomiasis can cause both acute and chronic illness, but commonly remains asymptomatic.[19] Infection with schistosomes becomes serious when parasitic eggs deposited by adult worms do not find their way to an excretable fluid, but rather become lodged in bodily tissues. Immune reactions to trapped eggs can lead to inflammation and fibrosis, with clinical symptoms related to both the number and location of deposited eggs.[19] Intestinal schistosomiasis develops slowly, leading to intestinal damage caused by progressive enlargement of the liver and spleen (respectively referred to as hepatomegaly and splenomegaly), which in rare circumstances can be fatal, as well as intestinal damage caused by fibrotic lesions that form around trapped eggs.[11] In some cases, hypertension of the abdominal blood vessels may also occur, and can lead to fatal bloody stools when repeated.[17] Other common outcomes include chronic growth faltering and anemia, especially in developing children.[11, 17, 20] Urogenital schistosomiasis classically presents as hematuria (bloody urine) and dysuria (pain during urination) following egg-related damage to the urinary tract.[11] Over time however, progressive damage to the bladder, ureters, and kidneys can manifest in more serious outcomes such as bladder obstruction, renal failure, and urinary tract ulcers.[20]

As noted earlier, some complications arising from schistosomal infection occur in other parts of the body via aberrant egg deposition. A common secondary target of schistosome eggs, most frequently *S. haematobium* eggs that have penetrated the urinary tissues, is the female genital tract. Female genital schistosomiasis (FGS) is a common manifestation of disease in schistosomiasis-endemic settings and can cause a host of symptoms including dyspareunia (pain during intercourse) and assorted granulomas in the uterus, fallopian tube, and ovaries.[21] These genital tract lesions appear to lend infected women a propensity for acquisition and transmission

HIV.[22] Additionally, FGS may be responsible for a yet undetermined percent of infertility, abortions, and ectopic pregnancies experienced by women of reproductive age in schistosomiasis-endemic regions where FGS is likely highly prevalent, yet under-diagnosed.[21, 23]

Prevention and control

Schistosomiasis infection can be easily, safely, and effectively treated with a single dose of the anthelminthic drug praziquantel (40 mg/kg), which is employed as both a treatment and communal prophylaxis in the control of disease.[5, 11] [Please see Chapter 1.1 for more.] Vaccines are not yet available, and present an unlikely future intervention strategy. A more comprehensive approach to disease control and prevention includes a holistic look at freshwater treatment, intermediate snail host removal (molluscuscides), and increased access to potable water and improved sources of sanitation, coupled with good hygiene practices.

1.**3 Soil-transmitted helminthiases**

Global impact

Soil-transmitted helminth (STH) infections, also known as geohelminth or intestinal nematode infections, are among the most common morbidities on the globe, infecting over 1.5 billion people: the equivalent of almost a quarter of the entire human race.[2, 24] The 2015 Global Burden of Disease study estimates these infections to be distributed between roundworm, whipworm, and hookworm at 46%, 28%, and 26%, respectively.[10] Widespread throughout virtually every continent, STH infections cause intestinal parasitic disease with high levels of morbidity, but relatively low mortality. Interestingly, although ascariasis (roundworm infection) ranks highest in global prevalence at 46% of all STH infections, hookworm disease accounts for the majority of nematode-induced disability.[10] Complications arising from STH infection,

including anemia, were estimated to collectively account for 3.17 million years lived with disability (YLD) in 2015, with statistically significant percentage reductions in age-standardized rates of YLD from 2005 across all three categories of disease.[10]

Despite this positive advancement in morbidity reduction, asymptomatic infections are common (94% of all roundworm and whipworm infections, 82% of all hookworm infections) and the prevalence of all three soil transmitted helminths remains high.[10] For this and other reasons, STH prevalence has remained virtually unchanged in Central Africa between 1990 and 2010. According to analyses conducted by Pullan and colleagues using pooled data from the Global Atlas of Helminth Infections (GAHI), prevalence of any STH infection in sub-Saharan Africa (SSA) dropped by less than 5% over the course of those 20 years (from 36.8% of population infected by at least one STH in 1990 to 32.2% in 2010), with overall prevalence in Central SSA in 2010 estimated at 19.7% for hookworm infection (95% CI: 16.6 – 22.6), 21.4% for Ascariasis (95% CI: 18.1 – 25.2), and 16.9% for Trichuriasis (95% CI: 13.9 – 20.5).[25] Despite its enormous global impact, STH infections remain understudied and underfunded in public health programming.

Epidemiology

The most important risk factors for contraction of soil transmitted helminths are poor personal hygiene and poor sanitation, including low access to sanitary infrastructure.[24] Places where public defecation is common are therefore frequently locales of high STH incidence and prevalence, as are communities where human feces are intentionally mixed with soil for use as fertilizer.[7] Improper washing or cooking of foodstuffs are also risk factors for infection, as contaminated soil residues may be consumed. Similarly, pica and hand-to-mouth activity increase the risk of nematode contraction, especially amongst children.[3] In the case of hookworm, barefoot activity which exposes the skin to larval worm penetration is also associated with infection.[26]

Geographic distribution and parasitic lifecycle

Three species of STH infect and cause illness in humans: roundworm (*Ascaris lumbricoides*; estimated 807-1,221 million infected), whipworm (*Trichuris trichiura*; estimated 604-795 million infected), and hookworms (*Necator americanus* and *Ancylostoma duodenale*; estimated 576-740 million infected).[27] All three STH parasites are found in the tropics and subtropics, where optimal soil conditions for worm development exist (warm, moist, shaded), and are differentially geographically distributed by species, with Latin America, sub-Saharan Africa, and Southeast Asia each carrying a very large burden of disease.[3] Ascariasis is the most common and widespread of the diseases, with an estimated 21 million persons infected in Central SSA alone, accounting for 21.4% of the region's population, followed by hookworm infection (19.3 million infected, 19.7% of population).[25]

Soil-transmitted helminths are all contracted from soil and spread in one of two ways: *Trichuris* and *Ascasris* via fecal-oral transmission following consumption of improperly cleaned food or water, and hookworms via dermal penetration that resembles schistosomiasis contraction. Ascaris and whipworm eggs that are passed in the feces of infected humans embryonate and develop in contaminated soil, becoming infective after two or more weeks depending on environmental conditions. After ingestion of egg-laced soil through improperly cooked or cleaned food or direct hand-to-mouth contact, the eggs hatch and their larvae invade the intestinal mucosa (*Ascaris*) or small intestine (whipworm), eventually making their way to the lumen of the small intestine (*Ascaris*) or the colon (whipworm) where they mature into adult worms.[28, 29] Adult worms then begin to oviposit several weeks after initial infection and, over the course of their 1-2 year lifespan, release anywhere from 3,000 to 200,000 eggs per day in their human host's feces.[28, 29]

Hookworm eggs are also passed in the stool and hatch in favorable soil conditions after one or two days.[26] After molting in the feces/ soil, third stage infective larvae are produced which can survive for up to four weeks in the earth. Upon contact with human skin, most frequently following barefoot activity, these larvae penetrate the dermis and are carried through the body into the lumen of the small intestine where they mature into adult worms.[26] Infection by *A. duodenale* likely also occurs by oral exposure to contaminated soil, but *N. americanus* requires the transpulmonary migration phase that follows dermal absorption into the bloodstream in order to be swallowed into the gastrointestinal tract.[26] Adult worms can reside in the human host for several years, leaching blood and nutrients while attached to the intestinal walls.[26]

Clinical disease outcomes

STH infections cause chronic illness, with morbidity directly related to worm burden— the heavier the infection (the greater the sheer number of worms residing in the gut of the host), the greater the severity of disease.[2] While light infections tend to remain asymptomatic—a problem for continued transmission of infection—heavy infections can be very painful. Importantly, intestinal parasites produce a number of symptoms that severely impair the nutritional status of infected persons and may lead to death in more serious or prolonged cases of infection. Specifically, loss of appetite, diarrhea and dysentery, reduced absorption of micronutrients into the bloodstream, and intestinal bleeding are common.[7] All of these can lead to serious health problems that have both acute and long-term developmental effects on the body, including severe micronutrient deficiencies, dehydration, anemia (especially well documented as an effect of hookworm infections), and physical and cognitive growth impairments.[7] Simultaneous infection with other parasite species, collectively known as polyparasitism, is also frequent and may further degrade the overall nutritional status and gastrointestinal pathology of unfortunate hosts.[2, 30, 31]

Sometimes secondary complications such as intestinal blockage by heavy adult worm load and rectal prolapse from continued stool passing may require surgical intervention.[7] These clinical manifestations of disease often result in school and work absenteeism in STH-endemic regions, as morbidities keep children, adolescents, and adults from their daily tasks and spill over into the economic sphere, perpetuating cycles of poverty that are the hallmark of neglected tropical diseases (NTDs).[3]

Prevention and control

As with schistosomiasis and other helminth infections, intestinal parasites can be easily and effectively treated with a short regimen (1-3 days) of an anthelminthic drug, usually albendazole (400 mg/day) or mebendazole (500 mg/day).[5] Disease control and management of STHs in endemic communities therefore focus around the same structure of periodic, communal MDA campaigns that are used to target schistosomiasis. This may lead to some of the same concerns regarding imperfect or incomplete coverage rates, potential future drug resistance, and parasitic reservoir formation in groups neglected by SAC-focused chemotherapy operations. [Please see Chapter 1.1 for more.]

Prevention strategies to combat continued STH transmission focus around improving sanitation sources and hygiene practices, including handwashing behaviors, proper food preparation, reduction of outdoor defecation (latrine construction, etc.), and building effective sewage disposal systems.[7] Reduced reliance on manure-based fertilizers and diminished barefoot activities are also important means of disrupting STH transmission.[24]

1.4 Prenatal helminthiases

Background

There is evidence that helminth infections, beyond their normal ability to induce morbidities, may be particularly deleterious during pregnancy. Through potential effects on maternal physiology and downstream fetal exposure to an altered placental environment and maternal blood/nutrient supply, *in utero* exposure to helminthiases have been linked to adverse birth outcomes including potential immunomodulatory effects.[32] Based on preliminary evidence, prenatal exposure of the fetus are hypothesized to impact long-term responses to helminth and non-helminth antigens, and may lead to non-specific effects on the immune system, impacting offspring susceptibility to diseases mediated by inflammation.[32]

Interestingly, patterns of schistosomiasis and STH infections seem to be inverted: the prevalence of hookworm generally increases with age, while the prevalence of schistosomiasis generally decreases with age (although prevalence peaks in school-aged children, it remains high amongst young adults in endemic communities before dropping off in later age).[33, 34] These trends converge on women of childbearing age, yielding a high double burden of helminth infection in an already sensitive subpopulation at increased risk for malaria, anemia and nutritional stress, and creating a worrisome opportunity for helminthiases to exert their effects on mother and child.[35-38]

Studying helminth infections during pregnancy presents challenges because normal pregnancy is characterized by myriad physiologic changes, many of which mimic those accompanied by helminthiases. In a sense, the fetus can be thought of as a parasite: both helminths and developing fetuses inhabit the maternal body as foreign, immunologically distinct organisms. Additionally, both helminths and pregnancy influence immunologic shifts towards the production of type 2 T-cell (Th2) responses, which increase the body's tolerance to immunologically distinct organisms.[39-42] In non-human mammals, susceptibility to helminths and to helminth egg production increases around parturition, which may be attributable to reductions in circulating

cortisol or protein deficiencies.[43, 44] The evidence in humans is conflicting, with studies showing increased or comparable infection intensities between pregnant and nonpregnant women.[37, 45]

Physiological effects

Observational studies in humans suggest that maternal infection with helminths during the pregnant period may result in adverse outcomes for offspring including low birthweight, and perinatal and infant mortality.[46-51] From a mechanistic biological perspective, it appears that some or all of these observed outcomes in offspring may be mediated by maternal anemia. Indeed, numerous human subjects studies have shown certain helminthiases to be correlated with maternal anemia, and it is now considered one of the most common side effects of schistosome and geohelminth infections.[52-56] Hookworm and *T. trichiura* appear to be particularly harmful in this regard, especially in the case of severe infections.[57] While helminthiases alone are rarely associated with severe anemia, nutritional deficits and coinfection with malaria—common to helminth-endemic regions of LMIC—may act synergistically to exacerbate iron deficiencies.[58, 59]

Normal pregnancy is frequently accompanied by hemodilution, whereby total blood plasma volume increases significantly during the first and second trimesters, and the number of erythrocytes and accompanying hemoglobin per volume of blood appears to decline.[60, 61] However, drops in hemoglobin concentration beyond normal expectations, defined by WHO as a hemoglobin concentration below 11 g/dL for pregnant women (7 g/dL considered severe anemia in this group), may be deleterious to the success of the pregnancy and infant health.[5, 62] Severe anemia during pregnancy has been associated with increased risk of maternal mortality,[63] preterm birth and low birth weight,[61, 64, 65] and even neonatal anemia.[61, 66] These findings appear to be supported by studies of helminthiases in mice models. A series of generational experiments by Odiere and colleagues indicate that gastrointestinal nematode infection during pregnancy may harm the

developing mouse fetus, specifically via reductions in fetal linear growth and *in utero* growth of lymphoid tissues and bone.[67, 68]

Immunologic effects of helminthiases on the fetus

Long-term outcomes in offspring are of high concern when discussing helminth infections during pregnancy. Maternal infection has shown both worm-specific and nonspecific modulation of fetal immune responses frequently characterized by increases in Th2 responses to helminth antigens and decreases in Th1 responses to non-helminth antigens.[69] There is evidence that intrauterine exposure to helminth infections including onchocerciasis,[69] lymphatic filariasis,[70, 71] schistosomiasis,[72] and soil-transmitted helminthiases[73] increases the susceptibility of the child to later infection with the same parasitic worms by promoting tolerance to worm antigens and reducing inflammation-induced pathologies. Additionally, observational studies have suggested that *in utero* parasitic exposures can alter the offspring's response to unrelated antigens, including infectious diseases (both naturally acquired and through vaccination) and allergens. For example, a Kenyan study found that infants prenatally sensitized to *W. bancrofti* or *S. haematobium* showed a Th2 bias in their immune responses to BCG vaccine; evaluated following antigen challenge 10-14 months after vaccination, T cell type 1 IFNɣ production was 26-fold higher amongst non-sensitized children compared with subjects who experienced *in utero* sensitization.[74] These results indicate that helminth-specific immune responses acquired during gestation may reduce immunization efficacy against a broad range of infectious diseases in the developing world. In a trial of albendazole and praziquantel amongst pregnant women in Uganda, researchers found treatment to be associated with an increased incidence of eczema in infancy and during the first five years of life.[75, 76] Simultaneously, maternal hookworm infection showed a significant inverse association with childhood eczema in offspring, which increased with parasite load.[77] Taken

together, these findings suggest that prenatal exposure to maternal helminthiases may protect against allergy-related disease outcomes both immediately following delivery, and later in life.

Evidence for adverse birth outcomes

In general, the evidence supporting adverse outcomes such as preterm birth, small infant size at birth, and perinatal mortality are weaker than for other areas of research on the effects of maternal helminth infection. Helminth infections were associated with low birth weight in a study of HIV-positive pregnant women in Tanzania, and with lower birth weight in a study of Nigerian women, however HIV status was not taken into account in the second study, and the impacts of HIV infection alone and in potential synergy with helminthiases cannot be teased apart.[78, 79] In women with anemia, helminth-malaria coinfection was associated with preterm delivery, low birth weight, and small weight for gestational age, but the relative contribution of helminth infection specifically to these effects appears to be small.[53] Other studies of helminthiases alone have found no association between infection and birthweight, and more work needs to be done to investigate this possible outcome. When it comes to exploring the reversibility of effects with treatment, observational studies in Nepal and Sri Lanka found that children of pregnant women taking anthelminthics had reduced odds of abortion, stillbirth or perinatal death.[47, 48] However treatment with various deworming drugs in three randomized control trials had no significant effect on infant mortality.[80-82]

1.5 Dissertation setting: The Democratic Republic of Congo

General country context

Straddling the equator, the Democratic Republic of Congo's climate is humid and tropical, providing an environment extremely conducive to harboring neglected tropical diseases.[10] DRC is

comprised of 11 traditional provinces, which were subdivided into 26 new provinces in 2006, although government operations did not begin to formally adopt new province distinctions until 2015.[83] A formal census has not been conducted in the country since 1980, but population extrapolations estimate over 81 million residents today, making it the 18th most populous country in the world.[84]

More than 70% of the population lives in relative isolation in rural areas, with little road access or connectivity. Agricultural activities, hunting, fishing, and artisanal mining are the most common occupations.[83] Despite being extremely rich in coveted natural resources, and often as a direct result of the conflict these resources leave in their wake, the DRC remains severely underdeveloped ranking 176th out of 187 countries in the United Nation's 2015 Human Development Index (HDI) and lacking in basic health and power infrastructure.[85] Half of the population lives without access to safe drinking water sources or improved sanitation facilities.[86]

Women's health: reproduction, fertility, and nutrition

DRC has an overall fertility rate of 6.6 children per woman, ranging from 5.4 amongst urban women to 7.3 for rural women.[87] In contrast to most fertility trends in sub-Saharan Africa, the national fertility rate actually increased from an average of 6.3 children per woman in 2007 to the current rate measured in 2014.[87] DRC has a high rate of teen pregnancy: 27% of women aged 15-19 in DRC are already mothers or are currently pregnant. The median age at first sex reported by women aged 20-49 is 16.8 years, and the median age at first birth reported by women aged 25-49 is 19.9 years.[87]

Over one third (38%) of all women 15-49 years in DRC are anemic, and an even higher percentage of pregnant women are anemic (43%) with prevalence varying from a provincial

minimum of 21% in Nord- Kivu to a maximum of 55% in Bas Congo.[87] Eighty eight percent of women receive antenatal care from a skilled provider, and 80% of births are delivered in a health care facility.[87] Child mortality is still high in the country at 58 infant deaths per 1,000 live births and under-five mortality resting at 104 deaths per 1,000 live births; in both cases, the mortality rate is higher amongst rural children than urban children.[87]

National helminth landscape

In their 2009 review of NTDs in sub-Saharan Africa, Hotez and Kamath estimated that DRC had the second highest prevalence of any country in the region for hookworm infection and trichuriasis (31 million cases and 26 million cases, respectively), and ranked third in prevalence for schistosomiasis and ascariasis (15 million cases and 23 million cases, respectively).[1] Per WHO's 2015 country data, DRC remains a schistosomiasis endemic country requiring preventive chemotherapy for over 13 million residents annually; just over 1.6 million individuals received this prophylaxis in 2015, accounting for a national drug coverage of 12%.[88] It is also an STH endemic nation, requiring preventive chemotherapy for over 16.8 million school-aged children, 3.8 million of whom received ivermectin + albendazole combination therapy in 2015, and 242,000 of whom either received a combination therapy of albendazole with praziquantel or received only albendazole, accounting for 24.32% coverage of SAC.[89] No data on non-SAC were available, as national drug administration campaigns for STHs cover only pre-SAC and SAC.

Schistosomiasis has been known to be present in certain provinces of Congo for over a century, with the first cases of disease recorded in 1897.[90] Early reports of schistosomiasis during the colonial period were collected and reviewed by Gillet and Wolfs in 1954.[91] Since independence however, DRC has suffered from a dearth of up-to-date, reliable estimates of national schistosomiasis and soil transmitted helminth prevalence, and until 2014, had never conducted

national surveys to this end. Schistosomiasis and STHs are not routinely tested for in DRC, and are not considered reportable diseases, excluding them from both active and passive national surveillance systems. As a result, most of what we know about the helminthic landscape in DRC is a result of pieced-together data from several surveys scattered across space and time which are restricted to small areas and generally to school-aged children. Most utilize discordant methodologies and diagnostic procedures, making it hard to build a national picture of schistosomiasis and STH prevalence in the country. The Global Atlas of Helminth Infection has 75 records of *S. haematobium*, 185 records of *S. mansoni*, 66 records of *Ascaris* and *Trichurus*, and 12 records of hookworm estimates collected in various surveys across the DRC from 1980 – 2012.[92] All of these surveys included sampling of both sexes, but only included school-aged children.

In 2015, Madinga and colleagues published the first and only review of schistosomiasis in DRC since independence, which included only 30 studies published between January 1955 (following the last extensive review of the subject by Gillet and Wolfs) and January 2015.[90] Several trends were noted, namely an overall persistence of disease in the country, a spread of schistosomiasis to formerly non-endemic areas (likely due to absence of control activities and migration patterns attributed to work and war displacements), and an increase in prevalence in rural endemic areas accompanied by a decrease in urban and peri-urban spaces of Kinshasa. The authors also note that because of the piecemeal nature of the small-scale surveys scattered throughout the country, most regions remain unmeasured, leaving their schistosomiasis presence and burden a mystery.[90] No similar reviews of surveys on soil transmitted helminths (by individual helminth class or grouped together) were found.

Until very recently, no country-level mapping of schistosomiasis or STHs had been conducted by the government or outside bodies to determine nationwide burden and distribution of disease. In 2016 the National Neglected Tropical Disease Unit of the Ministry of Health of DRC released estimates for schistosomiasis and STH prevalence amongst school-aged children for 511 out of 515 total health zones nationwide [Coordination Nationale des Maladies Tropicales Négligéés de la RDC (National Coordination of Neglected Tropical Diseases of the DRC), unpublished data]. These data are the first of their kind to give a current, holistic picture of the national landscape of schistosomiasis and STH burden in DRC, despite several shortcomings (no distinction between schistosome species; only school-aged children included in surveys), but remain unpublished and inaccessible to the public.

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Chapter 2. Urogenital schistosomiasis and sexually transmitted co-infections amongst pregnant women in a schistosome-endemic region of the Democratic Republic of Congo

2.1 Abstract

Schistosomiasis afflicts more than 250 million people worldwide. With mounting evidence of adverse impacts to women's health resulting from urogenital schistosomiasis, further research on disease epidemiology specific to women of childbearing age is warranted. Identifying comorbidities between schistosomiasis and sexually transmitted infections (STI) that have negative implications for maternal and fetal health are of special interest. Between October 2016 and March 2017, we conducted a cross-sectional study examining the prevalence of urogenital schistosomiasis and its association with STIs amongst pregnant women visiting antenatal clinics in Kisantu Health Zone, Democratic Republic of Congo (DRC). An extensive sociodemographic and medical history survey was administered to consenting participants, and urine samples and vaginal swabs were collected to deduce active infection with schistosomiasis and STIs, respectively. In total, 17.4% of expectant mothers were infected with *Schistosoma haematobium*. Local risk factors of disease including age, and period of study enrollment were identified. Women infected with urogenital schistosomiasis were also at significantly increased odds of harboring a *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), or *Trichomonas vaginalis* (TV) infection (aOR= 3.0, 95% CI: 1.5, 6.0) than those uninfected, but reports of urogenital symptoms were low. Laboratory-based schistosomiasis and STI testing provided objective evidence of disease in a cohort with low symptomology where syndromic management may not suffice. Shedding light on local risk factors and associated co-infections of urogenital schistosomiasis can identify unique intervention opportunities for prenatal care practices in trematode endemic regions and aid in reducing adverse pregnancy outcomes resulting from both schistosomiasis and STIs.

2.2 Introduction

The Democratic Republic of the Congo (DRC) bears a tremendous burden of neglected tropical diseases, and is estimated to hold the third highest schistosomiasis case rate in Africa.[1, 2] Schistosomiasis most commonly results in morbidities of the kidneys, bladder, and genital tract—collectively designated as urogenital schistosomiasis—following infection with the *S. haematobium* trematode which inhabits the renal, sacral, and pelvic vessels of human hosts.[3] In addition to several well understood symptoms and morbidities, urogenital infection commonly results in an underdiagnosed manifestation of disease known as female genital schistosomiasis, or FGS. New estimates suggest that FGS may occur in as many as 150 million African girls and women, defining this infection as one of the most common and emergent gynecologic conditions in sub-Saharan Africa.[4]

Female genital schistosomiasis results from schistosome egg deposition in the genital tract of infected women, causing granulomatous inflammation often described as "sandy patch lesions" in the vagina and cervix, and commonly accompanied by dyspareunia and contact bleeding.[5, 6] More serious outcomes may also result from egg deposition in the upper genital tract, including infertility, ectopic pregnancy, and abortion.[5, 7] Recent epidemiological studies suggest that genital infection with *S. haematobium* may also increase the risk of HIV acquisition in young women due to local genital pathology and systemic immunologic effects.[8-10] Additionally, schistosomal co-infection may accelerate HIV disease progression, lower the effectiveness of antiretroviral therapy (ART), and facilitate HIV transmission to sexual partners and unborn fetuses.[11, 12] Several modes of action have been proposed for these observed effects, including: increased viral shedding due to schistosomal lesions in the cervix or vagina, chronic immune activation of lymphocytes and

associated inflammation, induction of Th2 bias, and differential expression of chemokine receptors that serve as co-receptors for viral cellular entry.[9, 11, 13-15]

While the prevalence of HIV in the DRC is relatively low (1.2% amongst the general adult population; provincial rates ranging from 1.6 – 8% amongst screened pregnant women), the prevalence of other sexually transmitted infections (STIs), which may similarly be prone to increased susceptibility and severity with concurrent schistosomiasis, remains unknown.[16] We hypothesize that it is biologically plausible that bacterial and protozoan STIs could exploit a schistosome-positive physiological environment via many of the same pathways proposed to be at play in HIV co-infections; namely, via impaired barrier function of the genital epithelium, or exploitation of Th2-skewed cellular phenotypes (including release of anti-inflammatory cytokines) and general immune modulation or suppression. Pregnancies, which require immunomodulation towards a Th2 CD4+ phenotype in order to prevent maternal rejection of the fetus, may further exacerbate immunologic shifts caused by chronic helminth infections like schistosomiasis, increasing concern over potential impacts to STI susceptibility and severity in parous women.[17, 18] Unfortunately, screening for schistosomiasis and STIs other than HIV is not a part of routine prenatal care in most of the developing world, including DRC, where access to diagnostic testing is limited due to financial and other logistic constraints on the health system.[19, 20]

This study provides an assessment of the prevalence of chlamydia, gonorrhea, trichomoniasis, and urogenital schistosomiasis in a group of pregnant women living in a schistosome-endemic district of DRC—the first estimates of their kind in the country, to our knowledge. Furthermore, we examine the relationship between urogenital schistosomiasis and sexually transmitted infections traditionally excluded from routine antenatal care (ANC) testing to determine whether *S. haematobium* infection might increase the propensity for further infection of

the genital tract with additional pathogens. Local risk factors for prenatal urogenital schistosomiasis and associated symptoms are also identified, with implications for regional public health programming.

2.3 Methods

Study site and population

From October 2016 – March 2017, 367 pregnant women were recruited from one of three ANC clinics in Kisantu Health Zone, Kongo Central (formerly, Bas-Congo) province, DRC: Kintanu Etat clinic (n=223), Ngeba clinic (n=63), and Lemfu clinic (n=81) [Figure 2.1]. The study enrolled participants from all three ANC sites throughout the full study period. Eligible participants were 18 years of age or older and between 4-35 weeks pregnant. Women who were past 35 weeks of gestation, were not residents of Kisantu Health Zone, had a history of allergy to praziquantel, or had an AIDS-defining illness were excluded from participation in the study. Due to high illiteracy rates in the DRC, women meeting the eligibility criteria were asked to provide oral informed consent (recorded via thumbprint) prior to study enrollment. Ethical approval for the study, including use of oral consent practices, was provided by institutional review boards at both UCLA (ref. 14-000830-AM-00006) and the Kinshasa School of Public Health (ref. ESP/CE/034/2016).

Study design and procedures

Enrolled participants were asked to respond to a questionnaire and provide biological samples for infection assessment over the course of three days: at enrollment (questionnaire administration, initial urine and vaginal swab specimen collection), and for the two following days (second and third urine collection). All women took part in the survey and 362 (99%) provided

both urine and vaginal swab samples; 353 CT/NG (98%) and 359 TV (99%) swabs were available for final laboratory analysis following a few instances of misplaced or contaminated samples. Those testing positive for *S. haematobium* and/or any STI were notified on site during their clinic visit in order to share test results and provide chemotherapeutics; follow-up testing for STI+ women was performed 4-8 weeks later to ensure disease clearance. Survey administration, sample collection, and disease counseling were performed by local clinic staff trained in study procedures.

Questionnaires: Participants were administered a questionnaire covering basic demographic data, water supply and sanitation, sexual practices, and medical history—including clinical symptoms—of schistosomiasis and STIs. Questionnaires were completed in a private, one-on-one setting.

Biological specimen collection and laboratory testing: Over three consecutive days, beginning with the baseline clinic visit, participants were asked to provide a urine sample to their health care provider. *S. haematobium* exhibits diurnal variation with peak egg excretion around noon daily; as such, attempts were made to collect urine samples from each participant between the hours of 10am and 3pm.[3] After thorough mixing of fresh urine samples, filtration, and staining with Lugol's iodine, specimens were examined by light microscopy at 10x magnification, with results expressed as the number of *S. haematobium* eggs per 10 ml of urine. A senior laboratory technician re-examined 5% of samples for quality control. Due to the inconsistent release of schistosome ova by adult worms into host urine (limiting the sensitivity of urine microscopy), a single positive urine sample was considered sufficient for schistosomiasis positive classification.[21] A trained clinician also collected vaginal swab specimens from each participant at baseline to test for STIs of interest (Xpert® CT/NG and TV kits; Cepheid, Sunnyvale, CA). All vaginal swab specimens were analyzed for *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Trichomonas vaginalis* (TV) via DNA assay (also known as nucleic acid amplification test, or NAAT) using a

GeneXpert® machine (Cepheid, Sunnyvale, CA). Results from HIV tests were also recorded via patient recall or medical records, although serology was not performed as part of this study.

Treatment and follow-up testing. Women testing positive for *S. haematobium* were administered a single dose of 40mg/kg oral praziquantel on site at their clinic visit.[22] Women positive for CT, NG, or TV were provided treatment for themselves and their untested sexual partners in accordance with WHO guidelines,[23-25] and were followed up for tests of cure 4-8 weeks later.

Statistical analysis

Data from this study were analyzed to assess the epidemiology of urogenital schistosomiasis, STIs, and their co-infection in pregnant women in DRC, including important risk factors and symptoms of disease. Descriptive statistics of the study population were calculated and chi-square tests of proportions were conducted to describe any demographic differences between women infected and uninfected with urogenital schistosomiasis. Logistic regression models were performed to examine the association and magnitude of various risk factors of *S. haematobium* infection during pregnancy, as well as the relationship between schistosomiasis and various STI infections. HIV-positive women (n= 2) were excluded from analysis of CT, NG, and TV correlations with schistosomiasis to control for confounding associated with HIV's distinct mode of action and severe immunocompromising pathology. Complete case analysis was implemented for all statistical tests. Finally, symptom frequency was tabulated for all single and co-infections of interest. SAS® software, version 9.4 (SAS Institute Inc., Cary, NC) was used to conduct all statistical analyses for this study.

2.4 Results

General enrollment information

In total, 367 women between 4 and 34 weeks gestational age provided urine samples for *S. haematobium* diagnosis and completed a standardized questionnaire. A majority of study participants were either married or cohabitating with a steady partner (70%), and had experienced at least one previous pregnancy (69%); half were in their third trimester [Table 2.1].

Risk factors of S. haematobium *infection*

Sixty-four women (17.4%) were infected with *Schistosoma haematobium* and displayed a mean infection intensity of 10.8 eggs/10 ml urine; heavy infection (> 50 eggs/ 10 ml urine) was seen in 6.3% of infected women. Age and civil status were significant risk factors of infection amongst our study cohort, with the highest proportion of schistosomiasis cases occurring in 18-24 year-olds. Health center location and enrollment period were also associated with disease; higher schistosomiasis prevalence was noted between February and March, coinciding with the end of the rainy season in Southwestern DRC. Women involved in farming were less likely to test positive for *S. haematobium* than women involved in other occupations (OR= 0.4, 95% CI: 0.2, 0.8), although this relationship was not significant after adjustment for age, education level, civil status, and ANC clinic location (aOR= 0.6, 95% CI: 0.3, 1.1) [Table 2.2]. Differential water sourcing for general household use, laundry, and bathing did not appear to have a significant or distinguishable impact on schistosomiasis outcomes, nor did reports of house flooding events in the year proceeding the questionnaire. Women indicating prior schistosome infection appeared to be at increased odds of current urogenital schistosomiasis (aOR= 2.5, 95% CI: 0.6, 10.7) [Table 2.2].

STI prevalence and comorbidities

In sum, 65 women were found to be positive for at least one STI at the time of interview: 11 women with chlamydia, 5 with gonorrhea, and 52 with trichomoniasis. Thirty-three percent of

STI positive women had concordant *S. haematobium* infection; reciprocally, 33% of schistosomiasis positive women presented with STI [Table 2.3]. Women with a schistosomiasis infection were at substantially increased odds of NG and TV co-infection. After adjusting for age, educational attainment, civil status, and risky sexual behavior (defined as having a primary sex partner who is actively engaged with one or more additional sex partners), those presenting with any STI (CT, NG, or TV) had three times the odds of concurrent schistosomiasis (aOR= 3.0, 95% CI: 1.5, 6.0) [Table 2.3].

Overall, the presence of symptoms was extremely low amongst study participants diagnosed with any urogenital disease. Only 14% of schistosomiasis-positive participants presented with dyspareunia, and 9% or less reported dysuria, gross hematuria, abnormal vaginal discharge, or genital wounds or discomfort—common clinical indicators of urogenital infection. Amongst the 16 participants with CT/NG infection, only two (13%) reported dysuria, dyspareunia, or abnormal discharge; amongst the 52 with TV infection, the most commonly reported symptoms were abnormal discharge and genital itching or discomfort (15%). Finally, amongst those women harboring a schistosomal co-infection, 14% noted dyspareunia or genital itching, 10% painful urination or abnormal discharge, and 5% genital lesions. No incidents of gross haematuria (bloody urine) were disclosed by schistosomiasis/STI co-infected women [Figure 2.2].

When compared with urine microscopy and NAAT laboratory methods, syndromic diagnostics showed sub-optimal specificity and extremely low sensitivity for all disease types. Women NAAT-positive for CT/NG infection were three times as likely to be categorized as false negatives than to be correctly identified as infected on the basis of reported symptoms (sensitivity= 25%). Similarly, the sensitivity of symptom-based diagnoses for TV and *S. haematobium* fell

below the probability of correct diagnosis by chance (less than 50%) when compared to a gold standard NAAT or urine microscopy test, respectively [Table 2.4].

2.5 Discussion

In this study, we estimate the prevalence of *S. haematobium*, the most commonly implicated causal agent in cases of urogenital schistosomiasis and FGS, and elucidate local risk factors of disease amongst a pregnant cohort in Kisantu Health Zone, DRC. We also present previously unreported estimates of CT, NG, and TV prevalence for this area—STIs omitted from routine antenatal care screenings nationwide and throughout much of the developing world. Our results demonstrate a high prevalence of both STIs and urogenital schistosomiasis, as well as a strong association between the two in this population. Specifically, *N. gonorrhoea* and *T. vaginalis* were significantly associated with concurrent *S. haematobium* infection, supporting our hypothesis that *S. haematobium* infection likely increases host susceptibility to progressive infection of the female genital tract. This research represents, to the best of our knowledge, only the second study to describe the relationship between laboratory-confirmed urogenital schistosomiasis and sexually transmitted bacterial and protozoan agents,[26] as well as the first study to show this phenomenon during the prenatal period. Other reports of *S. haematobium* and STIs co-existing within the same population have also been undertaken,[27, 28] however they do not provide estimates of association between these diseases, as presented here.

Our results reiterate the importance of studying both schistosomiasis and STIs in vulnerable and often overlooked adult populations of trematode-endemic residence. We find that in a cross-sectional snapshot of the Kisantu health zone, almost one fifth of participating pregnant women carry active *S. haematobium* infection. Notably, the Congo Basin is home to two additional trematodes, *S. mansoni* and *S. intercalatum*, that commonly manifest in humans as intestinal

schistosomiasis and likely contribute to a higher total schistosome burden amongst pregnant Congolese women than is captured here.[2, 29] The infected women in our study range in gestational age from 6 to 32 weeks, signaling schistosomiasis-induced threats to healthy pregnancy at every stage of *in utero* development. The lack of association found between urogenital schistosomiasis and trimester of pregnancy further reinforces this point, and raises concerns about impacts to maternal physiology during sensitive periods of embryonic and fetal development.

In concert with previous literature on schistosomiasis risk, younger women were more likely to be infected with *S. haematobium* in this population.[26, 30] Environmental determinants of schistosomiasis also appeared to play a role, with infection prevalence spiking at the end of the rainy season (26% in Feb-March compared with 9% in Oct-Dec), suggesting disease seasonality. A statistically significant difference in the distribution of schistosomiasis amongst women visiting different ANC clinics across Kisantu, likely according to location of residence, also indicates potential geographic disparities in environmental trematode reservoirs around the health zone. Unexpectedly, women listing high-risk water contact occupations like fishing and farming were found to have a lower burden of *S. haematobium* infection than women holding other positions. This may be a result of low statistical power, or could indicate that frequent water contact associated with domestic chores, recreation, and personal hygiene is a more important driver of schistosomiasis than occupational freshwater exposure in this population. Alternatively, myriad jobs with low water contact frequency or duration may be unintentionally captured in our survey as farming,[31] thereby diluting or masking the observed effect of agricultural work with high water contact on infection status. Regardless, our results underline the importance of studying local risk factors of disease uniquely tailored to specific populations and geographies, which may be vital to the implementation of effective public health interventions.

Beyond identifying local determinants of schistosomiasis, we found moderate prevalence of poorly characterized STIs amongst pregnant women of Kisantu, and show that these diseases are significantly associated with *S. haematobium* infection. Indeed, the odds of harboring CT, NG or TV infection were three times higher amongst those with microscopically identifiable schistosomiasis in urine. The prevalence of STI in the sub-group of pregnant women with urogenital schistosomiasis (33%) was also consistent with that reported by Leutscher and colleagues (2008) who found concordant STI in 35% of non-pregnant Madagascan women aged 15-49 years with *S. haematobium* infection.[26] With evidence of increased co-infection of pregnant women established for all three STIs of interest, these results hold important implications for maternal, fetal, and infant health.

In many low-resource settings, diagnosis of STIs primarily occurs through the syndromic approach whereby assessment of the clinically symptomatic patient is used to detect markers of disease as a proxy for diagnostic testing.[19, 32] A lack of user-friendly, affordable diagnostic technologies and limited availability of trained laboratory personnel have led to continued reliance on this approach in DRC, where current national protocol does not include genital *C. trachomatis*, *N. gonorrhoeae*, or *T. vaginalis* testing as a part of routine antenatal care.[20, 33] Unfortunately, schistosomiasis, CT, and NG frequently manifest asymptomatically in women.[5, 33, 34] Even when urogenital symptoms do appear, many are shared by both STIs and FGS,[27] and some commonly arise during normal pregnancy; this further hinders clinical distinction between infection types, and highlights the importance of laboratory diagnosis during gestation when genital tract infections may be mischaracterized as common side effects of pregnancy.[34, 35] Myriad cases of urogenital schistosomiasis and STIs thus go undetected or differentially diagnosed, masking the true burden

of disease in endemic regions, hindering treatment programs, and perpetuating an unmitigated risk to pregnant women and their children.

Beyond issues of mischaracterization, low recognition of symptoms may limit women's ability to manage urogenital infections. Notably, almost no schistosome-positive women in our study had bloody or painful urine at the time of positive test, classic indicators of urogenital infection which are frequently substituted for egg-based testing in resource-scarce environments.[36] Indeed, if we use common measures of diagnosis for urogenital schistosomiasis and STIs alone, this study suggests that we are liable to miss nearly 70% of cases in similar groups. The few symptoms reported in our cohort align well with other investigations of self-reported and clinically-verified *S. haematobium* and STI symptomology in regions of endemic schistosomiasis, which describe low or insignificant rates of abnormal vaginal discharge, lower abdominal pain, dyspareunia and contact bleeding in women with urogenital infection.[6, 27, 28] Taken together, our results indicate that urogenital schistosomiasis and STIs are likely severely underdiagnosed where syndromic testing is relied upon exclusively, especially in trematode-endemic settings where co-infection may exacerbate STI incidence. Automated laboratory testing, including the use of NAAT systems like the GeneXpert®, offer solutions for improved STI confirmation and control in resource-limited settings. Such diagnostic tools should be considered for broader use in low and middle-income countries following cost effective analyses and assessment of other contextual considerations.

Limitations

Several limitations of this study should be noted. First, the sample size of our cohort (N=367) may have been insufficient for capturing rare risk factors of schistosomiasis or STI infection. Second, urinary *S. haematobium* egg excretion was used as a proxy indicator of general

urogenital schistosomiasis. Although most FGS cases are caused by *S. haematobium*,[5] they may result from other schistosome species, and can only be officially pathologically diagnosed—often with invasive biopsy or other logistically prohibitive tissue extractions, which were beyond the capabilities of this study. Despite this, urinary excretion of schistosome ova has been significantly associated with genital ova deposition,[27] and up to 75% of women displaying urinary *S. haematobium* ova also exhibit genital egg deposition,[37] thereby presenting urine analysis as a suitable tool for identification of urogenital schistosomiasis for the purposes of this study.

While urine microscopy remains a standard of urogenital schistosomiasis diagnosis exhibiting high specificity, egg excretion must align with urine sample collection in order to detect infection accurately.[3, 21] For this reason, we attempted to collect urine samples during peak excretion at midday. Furthermore, a 5-7 week prepatent period separates actual infection with *S. haematobium* cercariae and diagnosable manifestation of disease, hindering test sensitivity during early infection.[30] Finally, women with schistosomiasis were recently shown to be less likely than men to excrete eggs during active infection.[38] Hence, it is likely that non-differential misclassification (under-detection) of schistosomiasis occurred in our cohort, downwardly biasing estimates of disease prevalence and rendering the associations discovered herein conservative estimates. Selection bias is also of potential concern since women with symptomatic schistosomiasis or STI may be more likely to visit antenatal clinics than uninfected or asymptomatically infected women. However, this is unlikely as the women in our study attended regular prenatal check-ups, and a majority were symptom-free, suggesting that physical discomfort was not an important driver of care seeking behaviors.

Finally, we are limited by the cross-sectional design of this study in determining the temporality of infection amongst women harboring a schistosomiasis/STI co-infection. Based on

the trematode lifecycle, a biological mechanism by which having an STI could increase one's risk of water contact remains improbable, however, and we make no claims about the causality of the associations noted here. Further research to characterize the incidence of urogenital schistosomiasis and STIs in adult and pregnant women—including an assessment of the longitudinal progression of co-infection—is warranted. Nonetheless, this study is novel in its examination of a panel of urogenital co-infections amongst pregnant women, and lays the groundwork for further work on this topic.

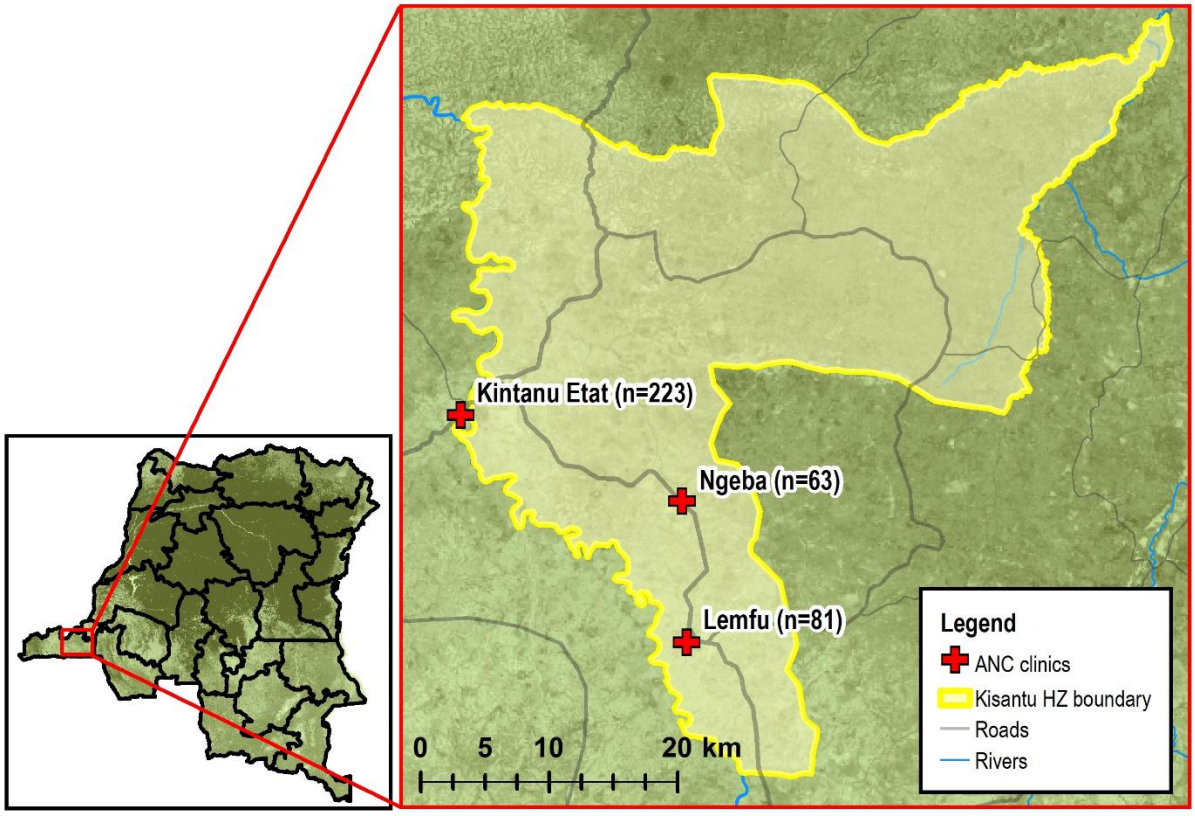
Conclusions

In this study, we expand upon the very limited evidence of association between urogenital schistosomiasis and bacterial and protozoan STIs, specifically chlamydia, gonorrhea, and trichomoniasis. We demonstrate that these infections are highly correlated in a cohort of pregnant women living in DRC, and occur across the entire gestational term. We also show that syndromic diagnoses of schistosomiasis and STIs may be insufficient to recognize or correctly identify most cases of infection during pregnancy. Symptoms of urogenital schistosomiasis may differ substantially for adult and pregnant women compared with school-aged children, upon whom many clinical diagnostic tools for schistosomiasis are designed and implemented.[26] We recommend adjusting schistosomiasis management strategies to better account for prevention and control of asymptomatic infection—whether via expansion of mass drug administration campaigns to the communal level, or by targeted praziquantel distribution to patients visiting ANC clinics in the prenatal period. We also argue for the importance of diagnosis and treatment of STIs as a part of routine adult care, especially in pregnant women vulnerable to deleterious downstream effects to mother and fetus.[38, 39] Investment in expanded prenatal care that includes urogenital

schistosomiasis and broad-spectrum STI screening will be essential to curbing the substantive communal and health systems costs caused by these infections during pregnancy.

Tables and Figures

Figure 2.1. Study sites: Kintanu Etat, Ngeba, and Lemfu antenatal clinics, Kisantu Health Zone, Kongo Central province, DRC.



Legend: Clinic GPS points collected by study authors. Basemap,[40] roads and rivers layers,[41] and Kisantu Health Zone boundary layer[42] all sourced from open access imagery data. Map generated with ArcMap 10.6 software (Esri, Redlands, CA).

Table 2.1. Demographic characteristics of pregnant women in Kisantu Health Zone by *S. haematobium* infection status (October 2016 – March 2017).

	***S. haematobium* status**		
	Positive (%)	**Negative (%)**	**p-value***
Age group			
18-24	41 (22.2)	144 (77.8)	0.03
25-34	15 (10.9)	123 (89.1)	
35+	8 (18.6)	35 (81.4)	
Education			
Some primary or less	13 (18.6)	57 (81.4)	0.12
Completed primary	37 (21.0)	139 (79.0)	
Secondary & beyond	14 (11.8)	105 (88.2)	
Civil status			
Married/ cohabitating	36 (14.0)	222 (86.0)	< 0.01
Not in a union	28 (25.9)	80 (74.1)	
Pregnancy history			
Primigravid	23 (21.3)	85 (78.7)	0.08
Multigravid	33 (13.8)	206 (86.2)	
Current pregnancy**			
First trimester	9 (28.1)	23 (71.9)	0.20
Second trimester	27 (18.0)	123 (82.0)	
Third trimester	28 (15.1)	157 (84.9)	
Clinic site			
Kintanu Etat	54 (24.2)	169 (75.8)	< 0.01
Ngeba	3 (4.8)	60 (95.2)	
Lemfu	7 (8.6)	74 (91.4)	
Total	**64**	**303**	

* p-values calculated using Wald chi-square tests.

** First trimester defined as 0-12 weeks; second trimester 13-27 weeks; third trimester 28+ weeks.

Table 2.2. Environmental risk factors for *S. haematobium* infection among pregnant women in Kisantu Health Zone.

	SCH Positive		Crude		Adjusted*	
	n	%	OR	95% CI	OR	95% CI
Season/ enrollment date**						
Oct-Dec 2016	18	9.3	1		1	
Feb-March 2017	46	26.4	3.5	(2.0, 6.4)	4.6	(2.4, 8.9)
Occupation						
Other	37	24.5	1		1	
Fishing	3	15	0.5	(0.2, 1.9)	0.7	(0.2, 2.5)
Farming	24	12.3	0.4	(0.2, 0.8)	0.6	(0.3, 1.1)
Main HH water source						
Piped	31	21.4	1		1	
In-ground (groundwater)	13	25	1.2	(0.6, 2.6)	1.3	(0.6, 2.9)
Well	20	12.1	0.5	(0.3, 0.9)	1.3	(0.5, 3.0)
Surface	0		n/a	(excluded due to empty cell)		
Laundry water source						
Piped	29	21.5	1		1	
In-ground (groundwater)	14	20.3	0.9	(0.5, 1.9)	2	(0.8, 4.6)
Well	13	14.1	0.6	(0.3, 1.2)	1.3	(0.5, 3.1)
Surface	8	11.4	0.5	(0.2, 1.1)	0.6	(0.3, 1.7)
Bathing water source						
Piped	28	20.1	1		1	
In-ground (groundwater)	14	19.7	1	(0.5, 2.0)	1.9	(0.8, 4.5)
Well	13	14	0.6	(0.3, 1.3)	1.4	(0.6, 3.6)
Surface	9	14.3	0.7	(0.3, 1.5)	1	(0.4, 2.5)
Primary HH water collection						
Other family member	7	12.3	1		1	
Interviewee	57	18.4	1.6	(0.7, 3.7)	1.5	(0.6, 3.6)
Proximity to main water source						
Within 500m	47	19.3	1		1	
Further than 500m	17	13.8	0.7	(0.4, 1.2)	1.3	(0.6, 2.6)
House flooding events, past year						
No	54	16.8	1		1	
Yes	10	21.7	1.4	(0.6, 2.9)	1.4	(0.6, 3.2)
Prior SCH infection, past year						
No	60	17.2	1		1	
Yes	3	21.4	1.3	(0.4, 4.8)	2.5	(0.6, 10.7)

Abbreviations: SCH, schistosomiasis; OR, odds ratio; CI, confidence interval; Oct - Dec, October to December; Feb - March, February to March; HH, household.

* Adjusted for age, education level, civil status, and ANC clinic location.

** The rainy season runs from October to March in Southwestern DRC.

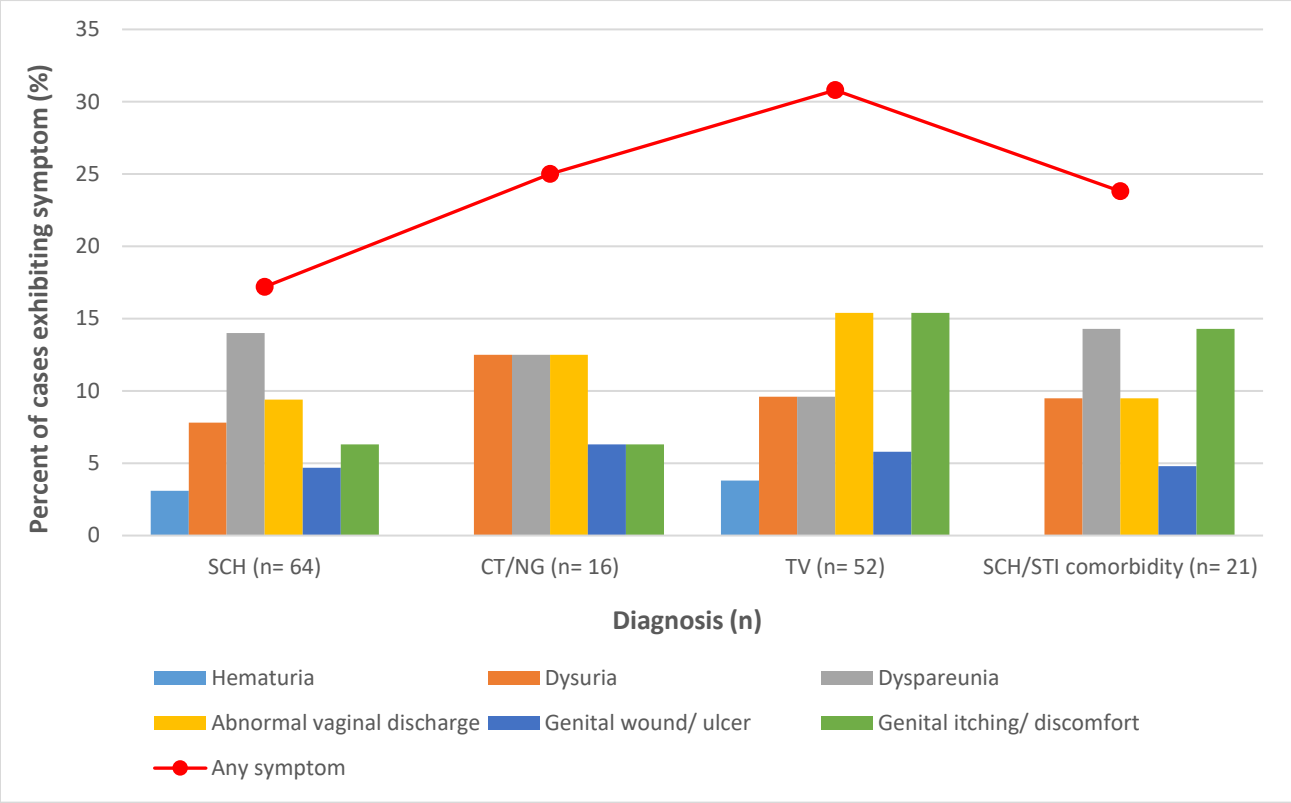
Table 2.3. Increased odds of sexually transmitted infections among pregnant women with urogenital schistosomiasis.

	No. Tested	SCH+ (%)	SCH- (%)	OR (95% CI)	aOR (95% CI)
CT	351	2/62 (3.2)	9/289 (3.1)	1.0 (0.2, 4.9)	
NG	351	4/62 (6.5)	1/289 (0.3)	19.9 (2.2, 180.9)	
CT/NG	351	6/ 62 (9.7)	10/289 (3.5)	3.0 (1.0, 8.6)	2.7 (0.9, 8.3)
TV	357	15/63 (23.8)	37/294 (12.6)	2.2 (1.1, 4.3)	2.3 (1.1, 4.8)
Any STI	359	21/63 (33.3)	44/296 (14.9)	2.9 (1.6, 5.3)	3.0 (1.5, 6.0)

Abbreviations: SCH, schistosomiasis (*S. haematobium*); OR, odds ratio; aOR, adjusted odds ratio; CT, chlamydia (*C. trachomatis*); NG, gonorrhea (*N. gonorrhoeae*); TV, trichomoniasis (*T. vaginalis*); STI, sexually transmitted infection.

SCH tested via urine microscopy, STIs via nucleic acid amplification testing (NAAT, GeneXpert®). All but five women (362/367= 99%) underwent two vaginal swabs for STI determination. An additional 9 CT/NG and 3 TV swabs were misplaced or contaminated prior to laboratory analysis, and 2 HIV+ women were excluded from all STI analyses (see Methods). Only one woman had missing laboratory results for both of her completed swabs. aORs not calculated individually for CT or NG infections due to sparse data. aORs adjusted for participant age, educational attainment, civil status, and sharing of primary sexual partner with other concurrent partners.

Figure 2.2. Symptomology of disease outcomes, by case percentage.



Abbreviations: SCH, schistosomiasis (*S. haematobium*); CT, chlamydia (*C. trachomatis*); NG, gonorrhea (*N. gonorrhoeae*); TV, trichomoniasis (*T. vaginalis*); STI, sexually transmitted infection.

Table 2.4. Sensitivity and specificity of syndromic diagnoses for STIs and urogenital schistosomiasis.

	CT/NG			**TV**			***S. haematobium***		
	NAAT+	**NAAT-**	**Total**	**NAAT+**	**NAAT-**	**Total**	**Urine+**	**Urine-**	**Total**
Symptomatic	4	75	79	16	65	81	11	72	83
Asymptomatic	12	260	272	36	240	276	53	231	284
Total	16	335	**351**	52	305	**357**	64	303	**367**
Sensitivity	(4/16) = 25%			(16/52) = 31%			(11/64) = 17%		
Specificity	(260/335) = 78%			(240/305) = 79%			(231/303) = 76%		

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Chapter 3. Treatment of urogenital schistosomiasis during pregnancy: a prospective analysis of birth outcomes in the Democratic Republic of Congo

3.1 Abstract

An estimated 40 million women of childbearing age suffer from schistosomiasis, a neglected tropical disease concentrated primarily in sub-Saharan Africa. Animal models indicate harmful effects of prenatal schistosomiasis on both mother and child, however a small evidence base in humans paints a conflicting portrait of disease-related assaults to pregnancy, and their potential reversibility with treatment. In this prospective cohort study, we examine the impacts of praziquantel-treated prenatal *S. haematobium* infection on a host of adverse pregnancy outcomes in the endemic region of Kisantu, Democratic Republic of Congo (DRC), utilizing inverse probability of treatment weighting methods. We found that, compared with uninfected mothers, those harboring and treated for urogenital schistosomiasis during their pregnancies showed no difference in delivery rates of premature (RR= 1.13; 95% CI= 0.53, 2.43), low birthweight (RR= 0.64; 95% CI= 0.22, 1.87), or microcephalic (RR= 1.11; 95% CI= 0.58, 2.11) infants. Further, no distinction in the proportion of these birth outcomes was found according to the trimester of discovered and treated schistosomiasis, and no effect modification by treatment of concurrent sexually transmitted infections (STIs) was demonstrated. Our results indicate no significant relationship between treated prenatal urogenital schistosomiasis and adverse birth outcomes in this cohort of women from a schistosome-endemic region of Central Africa. Future studies should be undertaken to better parse out the implications of urogenital schistosomiasis and its treatment during all stages of pregnancy.

3.2 Introduction

Schistosomiasis is endemic in 76 countries, with the three primary species of trematode—*S. haematobium*, *S. mansoni*, and *S. japonicum*—infecting an estimated 230 million people, including 40 million women of childbearing age.[1] While disease pathology and resultant morbidity are well understood in the general population, the impact of schistosomiasis on human pregnancy and parturition, including disease treatment in the prenatal period, are more sparse. Schistosomiasis has been shown to contribute to the burden of anemia in pregnant women,[2] and urogenital schistosomiasis, caused primarily by infection with *S. haematobium* cercariae, has been shown to increase the risk of HIV acquisition, disease progression, and transmission.[3, 4] In pregnant women, urogenital schistosomiasis may also increase rates of vertical (mother to child) transmission of HIV, and has been associated with other sexually transmitted infections (STIs) as well, including chlamydia, gonorrhea, and trichomoniasis (Chapter 2).[5]

Schistosomiasis infection during pregnancy may also impact fetal development and delivery. In a mouse model of *S. mansoni*, maternal schistosomiasis resulted in decreased offspring birthweight, and higher rates of spontaneous abortion, maternal and neonatal death.[6, 7] Limited studies in humans also suggest *S. mansoni* as a risk factor for abortion, preterm delivery and low birthweight (LBW) infants;[8] and *S. japonicum* as a risk factor for prematurity and LBW;[9-11] but evidence of *S. haematobium* as a risk factor for low birthweight is mixed.[12, 13] Finally, *in utero* exposure to schistosomiasis may increase the susceptibility of offspring to later schistosome infections,[14] and can lead to altered immune responses to unrelated antigens, including infectious diseases[15] and allergens.[16]

Schistosomiasis can be safely and effectively treated with a single dose of the anthelminthic drug praziquantel, however pregnant and lactating women have traditionally been

excluded from communal drug administration campaigns, and prenatal disease treatment remains controversial.[7, 17-19] Despite a World Health Organization (WHO) recommendation that these women be treated for their infections,[20] as well as several observational studies and decades of post-market surveillance demonstrating treatment safety,[21-23] many schistosomiasis endemic countries have refrained from adopting official policies regarding prenatal praziquantel use.[17] In DRC for instance, pregnant women may incidentally receive praziquantel as part of a communal drug administration campaign, although the Ministry of Health does not recommend routine schistosomiasis screening or treatment during antenatal clinic visits. Additionally, health care workers may continue to deny their patients treatment over concerns for fetal health or misleading information on praziquantel packaging.[24] The omission, purposeful or accidental, of pregnant and lactating women from access to praziquantel is especially concerning given that many women at risk for schistosomiasis spend up to 25% of their reproductive lives cycling through gestation and up to 60% breastfeeding.[20]

Thus, it is essential that we gain better insight into schistosomal impacts on pregnancy and the proper management of prenatal disease. Currently, only two randomized control trials of prenatal praziquantel have been undertaken, neither of which includes treatment of mothers during the first trimester of pregnancy. In a large, four-arm trial in Uganda (endemic for *S. mansoni*), mothers treated with praziquantel or praziquantel plus albendazole in the second or third trimester were found to have no significant difference in infant birthweight, perinatal mortality or congenital abnormalities compared with those in a placebo group; this outcome held even when restricted to only those mothers with stool-confirmed *S. mansoni* infection.[25] In a pharmacokinetic trial in the Philippines conducted amongst *S. japonicum*-infected pregnant women, praziquantel administered

in the second trimester was found to have no significant effect on birthweight, prematurity, or intrauterine growth restriction.[26]

In the following study, we build upon the existing body of evidence to explore how selective treatment of prenatal, laboratory-confirmed *S. haematobium* infection impacts downstream fetal health and parturition in a group of women from the endemic Kisantu health zone in the Democratic Republic of Congo (DRC). Given the current evidence of praziquantel's safety and effectiveness during the prenatal period, we hypothesized that offspring of mothers with treated disease would demonstrate similar rates of adverse birth outcomes to mothers without urogenital schistosomiasis, but that concurrent exposure to STIs might modify that relationship (given the higher total disease burden on the mother and resultant immunologic stress, localized inflammation or fibrosis of the genital tract, and STI's own relationship with adverse birth outcomes). Below, we utilize causal inference methods to examine how schistosomiasis treatment effects the risk of preterm birth, low birthweight, small size for gestational age, and microcephaly when administered between weeks 4 and 34 of pregnancy.

3.3 Methods

Study site and population

This prospective cohort study—originally designed to examine the relationship between urogenital schistosomiasis and STIs during pregnancy—was carried out in two phases, baseline enrollment and post-delivery follow-up, from October 2016 to December 2017. The study took place in Kisantu Health Zone, Kongo Central (formerly Bas-Congo) province in southwestern DRC—a region endemic for three strains of schistosomiasis, including *S. haematobium*.[27]

The study population consists of expectant mothers and their children born over the course of the study period. As previously described, pregnant women were recruited during regular visits to antenatal clinics, tested for urogenital schistosomiasis, treated if infected, and followed through birth (see Chapter 2). Briefly, pregnant women 18 years of age or older and between 4-35 weeks gestation were invited to participate in the study while visiting one of three antenatal clinics in the health zone during regular prenatal check-ups—Kintanu Etat, Ngeba, or Lemfu—from October 2016 to March 2017 (study baseline). Consenting participants were administered an extensive sociodemographic and medical history questionnaire, and were screened for urogenital schistosomiasis, CT, NG, and TV. Participants presenting with any of these infections were contacted for treatment and tests of clearance, including partner treatment where appropriate. Finally, all participants were followed through delivery for determination of birth outcomes.

Those beyond 35 weeks gestation at the time of study enrollment, and those with a history of allergy to praziquantel were excluded from participation. Only singleton live births were eligible for inclusion in the follow-up analysis, to allow for complete infant categorization by gestational age, size and weight.

Determination and treatment of S. haematobium and sexually transmitted infections

Biological sample collection is described thoroughly in Chapter 2. Briefly, urine samples were collected midday over three consecutive days, beginning at study baseline. Determination of *S. haematobium* infection was performed via microscopic inspection of 10 mL samples of midstream urine that had been filtered and stained with Lugol's iodine. Women were classified as infected if schistosome ova were found in any of the urine samples provided, and were treated with a single 40 mg/kg dose of praziquantel immediately following positive infection determination.

Consenting participants were also screened at baseline for *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Trichomonas vaginalis* (TV). Trained clinic staff collected vaginal swabs (Xpert®CT/NG and TV kits; Cepheid, Sunnyvale, CA), which were analyzed via nucleic acid amplification test (NAAT) using an automated GeneXprt® machine (Cepheid, Sunnyvale, CA). Those testing positive for CT and/or NG were treated with 1g single oral dose of azithromycin, and those positive for TV were treated with 2g single oral dose of metronidazole. Results from HIV tests, a standard of prenatal care in DRC provided free of charge at antenatal clinics, were also recorded via patient recall or medical record, although serology and antiretroviral treatment were not performed as part of this study.

Study variables and birth outcome definitions

Participants were administered both a baseline and follow-up questionnaire. The baseline survey recorded expectant mothers' demographic information, including age and basic anthropometry such as height, weight, and middle-upper arm circumference (MUAC) measured by trained clinic staff. MUAC was measured in lieu of BMI as a preferred method for maternal weight assessment which reduces residual confounding from normal and healthy prenatal weight gain.[28, 29] Participants were also interviewed about their experiences with food insecurity using the United Nations' validated household food insecurity and access survey (HFIAS).[30] The follow-up survey was conducted via participant recall to assess birth outcomes and delivery characteristics, with answers verified by medical record.

The primary study endpoints of interest were defined as the proportion of adverse birth outcomes amongst schistosomiasis infected and uninfected women. Specifically, preterm, LBW, preterm and LBW, small size for gestational age (SGA), and microcephaly were measured after delivery and examined for their association with schistosomiasis infection and treatment during

pregnancy. Gestational age of each infant was calculated at baseline (and then followed through the delivery date) as the number of days between the first day of the last menstrual period (LMP) and the interview date. For those women unable to recall the exact date of their LMP, including those at later stages of pregnancy at study baseline, tape-measured symphysis-fundal height was used as an alternative dating method. The standard definition for preterm birth is delivery prior to 37 weeks of gestation; however, we added a correction factor of two weeks and conservatively defined preterm birth as delivery prior to 35 weeks in order to account for imprecise LMP dating on account of irregular periods and mid-cycle bleeding.

LBW was defined as birth weight below 2500 grams, and determined at delivery using calibrated non-digital scales. Offspring were designated as preterm and LBW if they met both definitions—an indication of potential issues with intrauterine growth restriction. Infants whose weight fell below the 10th percentile of a standard, international birth cohort for their sex and gestational age groups were recorded as small for gestational age (SGA).[31] The INTERGROWTH-21st computer application was used to calculate size for gestational age on a moving percentile scale (INTERGROWTH-21st Newborn Size application, University of Oxford). Finally, microcephaly was defined as having a head circumference falling below the third percentile of the same standard cohort for each offspring's sex and gestational age group, also calculated using the INTERGROWTH 21st application.

Statistical analyses

Maternal characteristics, as well as infection status for *S. haematobium*, *C. trachomatis*, *N. gonorrhoeae,* and *T. vaginalis* were tallied from baseline questionnaires. Chi-square tests were used to compare proportions of newborns with birth outcomes of interest by each mother's prenatal infection status and trimester of detected maternal infection.

Propensity scores were created by regressing schistosomiasis and STI status at baseline by confounding variables of the respective schistosomiasis or STI relationship with our birth outcomes of interest, determined *a priori* via literature review. These two confounder sets included both maternal MUAC and HFIAS scores as complimentary measures of participant nutritional status (the two were significantly but weakly correlated, underscoring a lack of collinearity). Other covariates in the confounder sets included clinic site, maternal age, education level, and civil status.

Next, stabilized inverse probability of treatment weights (IPTWs) were created for both schistosomiasis and STI exposures, as follows:

- Numerator: The probability of treatment = $P_{tx}(schistosomiasis)$ or $P_{tx}(STI)$
- Denominator: The probability of treatment, given confounding covariates (aka: the propensity score for each exposure, as outlined above) = $P_{tx}\ (disease)|\ confounders$

Note that the probability of treatment was equivalent to the probability of infection for both schistosomiasis and STIs, as all women diagnosed with infection were treated immediately following positive test determination. Stabilized schistosomiasis and STI weights were multiplied together to create a single inverse probability weight, which was then applied to our final regression analyses in order to create an artificially "random" analytic sample in which the distribution of measured maternal covariates has been rendered independent of our participants' urogenital schistosomiasis/ STI exposures. IPTW diagnostics were performed to verify covariate independence across treatment groups, a signal of proper confounder control; our final stabilized weight also had a mean of 1, indicating correct specification of the propensity score model.[32, 33]

Using IPTW weighting, log binomial regression models were then run to measure the impact of prenatal schistosomiasis treatment on the relative risk of individual birth outcomes of

interest, including analysis of effect modification by STI treatment and joint effects of dual infection and treatment regimens. Preterm + LBW and SGA outcomes were not modeled individually due to low outcome cell counts in the schistosomiasis and STI treatment groups. Instead, a combined measure of any adverse birth outcome was modeled in order to summarize our findings and maximize statistical power. SAS software version 9.4 (Cary, NC) was used to perform all statistical analyses.

Ethical considerations and informed consent

All women meeting the eligibility criteria were offered enrollment in the study and asked to provide oral informed consent, recorded via thumbprint to accommodate high illiteracy rates. All biological testing, treatment, and survey components of the study were voluntary. Ethical approval for this study, including the use of oral consent practices, was provided by institutional review boards at UCLA (IRB# 14-000830-AM-00006) and the Kinshasa School of Public Health (IRB# ESP/CE/034/2016).

3.4 Results

A total of 367 pregnant women were enrolled at study baseline and 362 women (99%) provided both urine samples for *S. haematobium* screening and vaginal swabs for STI screening. Of those women with complete specimen procurement, a final count of vaginal swabs from 359 women were available for final laboratory analysis. Follow-up survey and medical record data were available for 347 pregnancies resulting in live births (95% of those enrolled), all of which were singletons. Following restriction to participants with complete disease screening and survey information (both baseline and follow-up), our final analytic sample for the adjusted risk analysis consisted of 329 mother-child pairs.

Of the women returning for follow-up, a majority were married or cohabitating with a primary partner (71%) and had had at least one previous pregnancy (69%). About half fell between ages 18-24 and were in their third trimester of pregnancy at the time of enrollment (51%). Almost three quarters of women had a MUAC of 23 cm or greater (73%), indicating a healthy pregnancy weight, but 43% had experienced some food insecurity or access issue in the 4 weeks prior to baseline survey administration; MUAC and HFIAS score were weakly but significantly and negatively correlated (rho: -0.25, $p < 0.001$). Sixteen percent of women were infected with *S. haematobium*, and 19% with a diagnosable STI (CT, NG, or TV) [Table 3.1]. Only one woman in our final analytic sample had a positive HIV test noted in her medical record.

Of live births verified at follow-up, 41% had some health outcome of interest: 15% of infants were classified as preterm deliveries, 26% had small head circumference classifiable as microcephaly, 14% were LBW, and 4% were SGA. None of the adverse outcomes examined showed different rates of occurrence across categories of prenatal maternal infection, although SGA was more common amongst infants born to STI-infected and treated mothers [Table 3.2]. Amongst women screening positive for schistosomiasis, no single or combined birth outcome was associated with the trimester of maternal disease detection and treatment [Figure 3.1].

Inverse probability of treatment weighted regression analysis indicated no significant change in the risk of an adverse pregnancy outcome between mothers with treated prenatal *S. haematobium* infection and those without (adjusted risk ratio [RR]= 1.07, 95% CI: 0.70, 1.63). No significant effect modification of the relationship between schistosomiasis disease/treatment and individual birth outcomes was observed by STI status [Figure 3.2]. However, the relative risk of LBW was higher amongst the subset of women undergoing simultaneous STI treatment compared to those with no underlying STI (RR= 1.30 v. 0.64). The joint effect of concurrent schistosomiasis

and STI exposures was not significant for all birth outcomes, although the relative risk of LBW was moderately increased when both diseases were detected and treated at baseline (joint effect RR= 1.55, 95% CI= 0.71, 3.39).

3.5 Discussion

This investigation represents the first prospective cohort study of prenatal praziquantel treatment in the DRC, a country endemic for several schistosome species. Using causal analytic methods, we found no change in the risk of adverse birth outcomes between women infected with and treated for *S. haematobium,* and those unexposed to both disease and treatment. Furthermore, no association between the trimester of detection/ treatment and downstream birth outcomes was noted amongst schistosomiasis-positive women. As one of only a handful of studies which include treatment of infected women in the first trimester of pregnancy,[21-23] this analysis corroborates a small but growing body of evidence that suggests praziquantel administration is safe, and perhaps even beneficial to maternal and fetal health, at all stages of pregnancy.[17]

Our study design is unique in that we selectively treated participants based on their schistosomiasis status, comparing diseased and treated women to an uninfected and untreated reference group. Previous teams performing praziquantel studies in pregnant populations have opted to select treatment groups independent from infection status to mimic communal drug campaigns,[25] compare treatment plans amongst infected women only,[26] or withhold treatment until pregnancy completion (aligning with local standards) in order to assess the effects of untreated infection.[13] Rather than take one of these approaches, we treated only mothers with active *S. haematobium* infection in alignment with WHO recommendations, collective evidence of praziquantel safety, and an ethical duty to prevent morbidity amongst the infected.

Because we have no direct means of comparing the effects of treatment to nontreatment independent of participant schistosomiasis status, interpretation of our results remains complex. It is impossible to determine, for instance, whether these findings result from a dearth of negative effects of *S. haematobium* on pregnancy outcomes, or from a mitigating effect of treatment on any deleterious effects incurred by infection. Regardless, the lack of statistically significant differentiation between our treatment groups suggests at minimum an absence of serious adverse events resulting from prenatal praziquantel treatment, and potentially even a protective effect of praziquantel on neonatal health. This finding corroborates the results of both randomized control trials of praziquantel,[25, 26] and extends these analyses by including two additional outcomes (SGA and microcephaly). Our results held across a combined assessment of any adverse birth event, as well as individual outcomes of interest. Given that all results were already null, we abstained from corrections for multiple outcomes, which would have simply reiterated these findings.

This study also provides some preliminary, albeit insufficient, evidence of first trimester drug safety by showing no distinction in adverse birth events by trimester of schistosomiasis treatment. Unfortunately, our sample size of women recruited, screened, and treated in their first trimester was too small to make more assertive claims on this front; nearly all cases of urogenital schistosomiasis were detected amongst women in their second or third trimester, likely due in part to low recognition of early pregnancy. Despite this limitation, a series of Sudanese studies of coincidental praziquantel treatment in first trimester mothers seem to support this safety finding.[21-23] Future studies should attempt to follow women throughout the entire pregnancy to glean more nuanced information about how the length and timing of *S. haematobium* infection impacts gestation, as well as how the timing of prenatal praziquantel treatment relative to the onset of infection alters the risk of adverse birth outcomes.

While the focus of our investigation was not on STI treatment, it is unique in its assessment of simultaneous trematode and STI treatment, the first of its kind to our knowledge. Notably, we find that exposure to STI infection and treatment may modify the effect of schistosomiasis and its treatment on the risk of LBW. While this evidence cannot be fully illuminated here, this data extends the limited evidence of praziquantel use in pregnancy to include the impact of co-administered chemotherapies. Further studies of drug interactions with prenatal praziquantel use are warranted.

Several features of this study restrict the interpretation of our results. Primary amongst them is the potential misclassification of gestational age, upon which many birth outcomes are based. The rate of preterm birth in our cohort using the standard definition of < 37 weeks was more than twice as high as national estimates,[34] suggesting likely underestimation of gestational age by menstrual dating. While LMP dating is a valid estimation method commonly used in low resource settings, recall uncertainty, menstrual cycle variations, and potential conflation of non-menstrual bleeding can result in inaccurate estimates of the true gestational age at delivery.[35, 36] For this reason, we restricted our preterm definition to those children born before 35 weeks of pregnancy to reduce noise from measurement error; this two-week correction factor aligned our preterm birth rate much closer to the national estimate of 12%.[34]

Another limitation comes in the form of potential selection bias. As study participation was predicated on voluntary visitation of antenatal clinics, the women in our study may have been more highly educated, in better general health, and/or possessing greater agency over their healthcare decisions than perhaps the general population of pregnant women in Kisantu. However, differential loss to follow-up, a frequent source of concern for longitudinal studies, is unsuspected here as the demographic distribution between baseline and follow-up samples remained

unchanged. Only one maternal demographic—history of miscarriage—differed substantially for women missing from follow-up, who were 12 times as likely to have experienced a prior abortion than those in the baseline and post-delivery follow-up groups. This suggests that perhaps most women missing from follow-up were lost because of an unintended pregnancy termination.

Finally, due to limitations of sample size and variation, we were unable to determine the impacts of schistosome infection intensity on the relationship between praziquantel use and adverse birth outcomes. If treatment is differentially beneficial for women with high intensity infections, for instance, those results may be masked here by women harboring lower worm burdens. A better understanding of infection and treatment along the intensity continuum requires further investigation and should be a priority of future research and surveillance efforts.

Despite these limitations, this study boasts many strengths, including a prospective cohort design, causal analytic methods, and holistic approach to understanding prenatal praziquantel use in tandem with other drugs. By including women in their first trimester of pregnancy in our cohort, this study was also able to assess urogenital schistosomiasis treatment across all phases of gestation. Furthermore, we address broad maternal nutritional status in our analysis, rather than relying solely on anthropometric measurements of health to better control for confounding by maternal nutrient deficiencies. Finally, we included birth outcomes not previously considered in studies of prenatal praziquantel use, including SGA and microcephaly—outcomes especially important to understanding first trimester treatment and sensitive periods of fetal development. Public health research must continue to build an evidence base for the safety and potential benefits of praziquantel treatment during pregnancy which includes assessment of early gestational administration, co-administration with other drugs—especially those indicated in antenatal standards of care—and a broad range of birth outcomes which have long-term effects on health

and development. We hope this study will pave the way for others to continue understanding trematode treatment amongst pregnant women: a severely underserved and understudied population frequently excluded from pharmaceutical research and interventions.[37]

Tables and Figures

Table 3.1. Maternal characteristics, urogenital schistosomiasis, and STI status of study participants during pregnancy: a comparison of baseline demographics between the original, follow-up, and missing from follow-up cohorts.

	Original cohort (n= 367)		Returned for FU (n= 347)		Missing from FU (n= 20)	
	n	%	n	%	n	%
Age group						
18-24	185	50.6	177	51.2	8	40.0
25-34	138	37.7	130	37.6	8	40.0
35+	43	11.7	39	11.3	4	20.0
Education						
None - some primary	70	19.2	65	18.8	5	25.0
Finished primary	176	48.2	168	48.7	8	40.0
Secondary & beyond	119	32.6	112	32.5	7	35.0
Civil status						
Married/ cohabitating	258	70.5	244	70.5	14	70.0
Not in a union	108	29.5	102	29.5	6	30.0
Gravidity						
Primigravid	108	31.1	102	31.2	6	30.0
Multigravid	239	68.9	225	68.8	14	70.0
Term of pregnancy						
First trimester	32	8.7	32	9.2	0	0.0
Second trimester	150	40.9	137	39.5	13	65.0
Third trimester	185	50.4	178	51.3	7	35.0
Prior miscarriage						
Yes	28	7.6	27	7.8	19	95.0
No	339	92.4	320	92.2	1	5.0

Clinic enrollment site						
Kintanu Etat	223	60.7	207	59.7	16	80.0
Ngeba	63	17.2	61	17.6	2	10.0
Lemfu	81	22.1	79	22.8	2	10.0
MUAC						
< 23 cm	99	27.0	95	27.4	4	20.0
>= 23 cm	268	73.0	252	72.6	16	80.0
HFIAS score*						
0	257	57.4	197	56.8	10	50.0
1-9	87	19.4	66	19	3	15.0
10-18	104	23.2	84	24.2	7	35.0
***S. haematobium* infection**						
Yes	64	17.4	57	16.4	7	35.0
No	303	82.6	290	83.6	13	65.0
STI status						
CT, NG, or TV	65	18.0	61	17.9	4	20.0
None	296	82.0	280	82.1	16	80.0

Abbreviations: FU, follow-up; MUAC, mid-upper arm circumference; HFIAS, household food insecurity and access survey; STI, sexually transmitted infection; CT, Chlamydia trachomatis; NG, Neisseria gonorrhoeae; TV, Trichomonas vaginalis.

* Although the HFIAS scale ranges from 0 – 27, nobody in this cohort had a HFIAS score above 18.

Table 3.2. Individual and aggregated birth outcomes of interest, by maternal infection status.

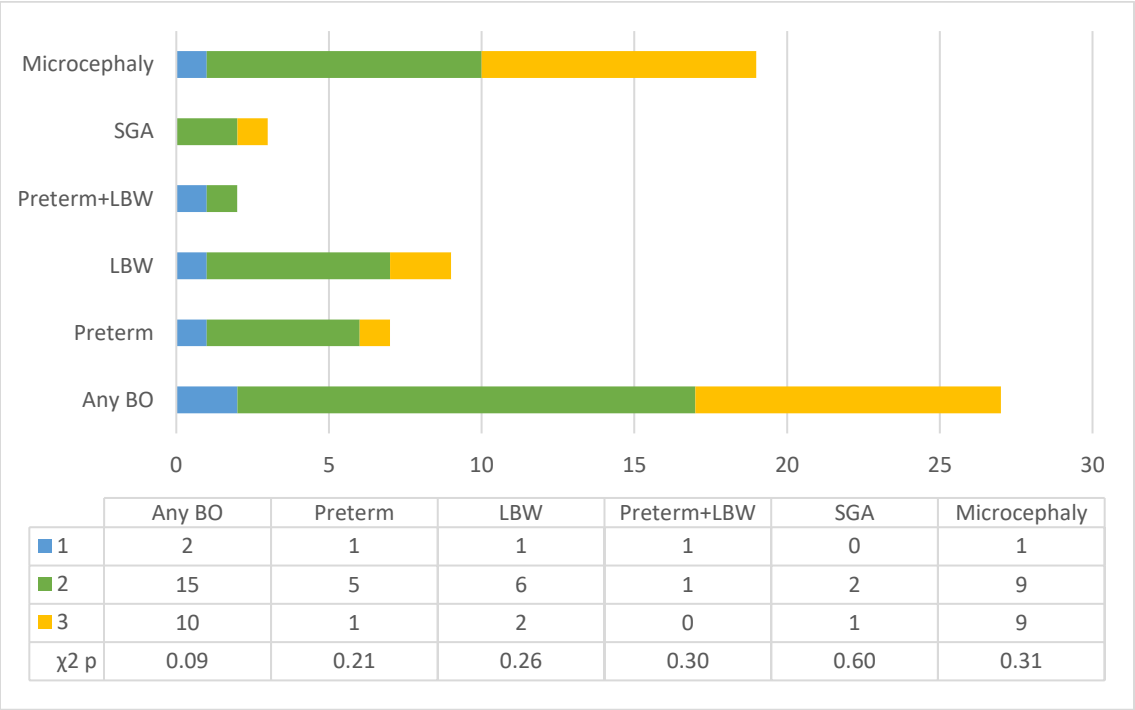
			Schistosomiasis			STI		
Birth outcome	**n**	**%**	**D + Tx, n (%)**	**Control, n (%)**	**χ2 p-value**	**D + Tx, n (%)**	**Control, n (%)**	**χ2 p-value**
Preterm	142	40.9	19 (33.3)	123 (42.4)	0.20	21 (34.4)	120 (42.9)	0.23
Preterm corrected	53	15.3	7 (12.3)	46 (15.9)	0.49	10 (16.4)	43 (15.4)	0.84
LBW	50	14.4	9 (15.8)	41 (14.1)	0.75	10 (16.4)	40 (14.3)	0.67
Preterm + LBW	22	6.3	2 (3.5)	20 (6.9)	0.34	2 (3.3)	20 (7.1)	0.27
SGA	13/345	3.8	3 (5.3)	10 (3.5)	0.52	5 (8.3)	8 (2.9)	0.05
Microcephaly	87/339	25.7	19 (33.3)	68 (24.1)	0.15	19 (31.7)	65 (23.8)	0.20
Any adverse birth outcome	142	40.9	27 (47.4)	115 (39.7)	0.28	30 (49.2)	109 (38.9)	0.14
Total sample	347		57	290		61*	280*	

Abbreviations: D + Tx, disease and appropriate treatment; LBW, low birthweight; SGA, small for gestational age; wks, weeks.

Preterm birth without correction defined as birth prior to 37 weeks of gestation; with correction defined as birth prior to 35 weeks of gestation. Preterm with correction was used in all subsequent definitions for "preterm + LBW" and "any" birth outcomes.

* Note: 6 women missing STI results.

Figure 3.1. Adverse birth outcomes among *S. haematobium*-infected women (n= 57), according to trimester of disease detection and treatment.

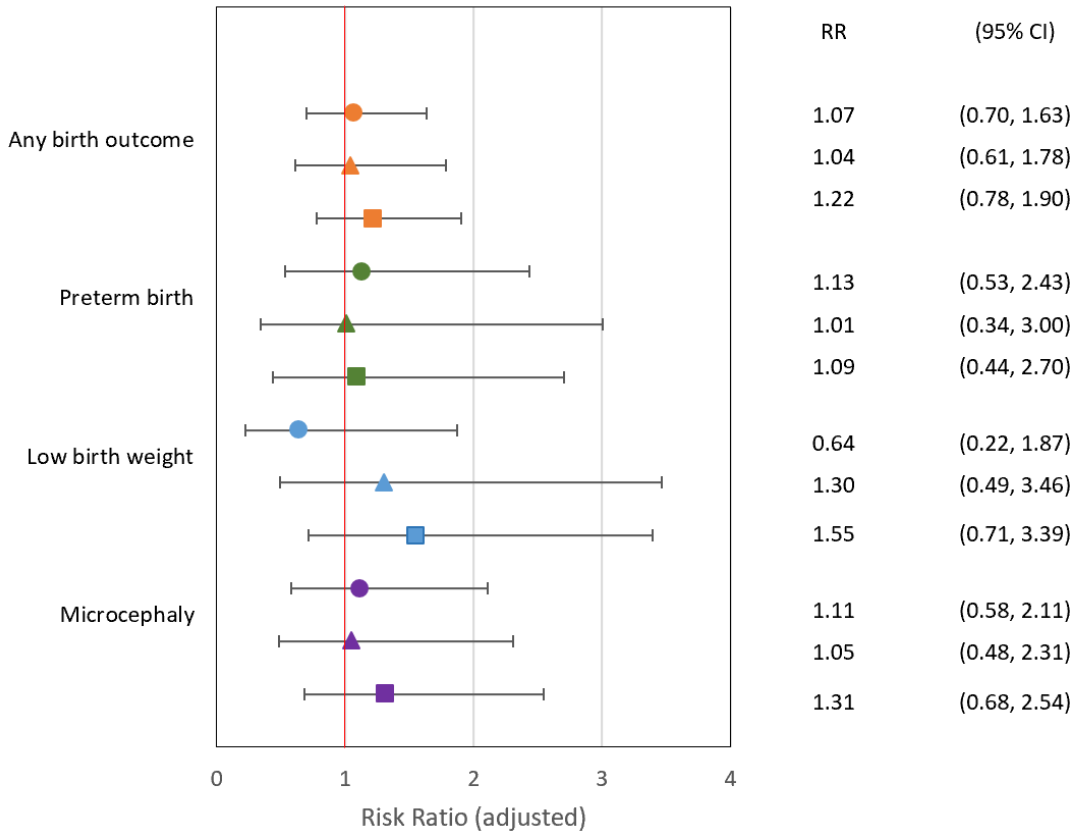


	Any BO	Preterm	LBW	Preterm+LBW	SGA	Microcephaly
1	2	1	1	1	0	1
2	15	5	6	1	2	9
3	10	1	2	0	1	9
χ2 p	0.09	0.21	0.26	0.30	0.60	0.31

Abbreviations: BO, birth outcome; LBW, low birthweight; SGA, small for gestational age.

X-axis displays the number of cases observed for each adverse birth outcome of interest. Wald chi-square p-values are reported, examining differences in the rate of each birth outcome of interest across trimester of schistosomiasis diagnosis and treatment initiation.

Figure 3.2. Effects of prenatal exposure to urogenital schistosomiasis treatment (single 40 mg/kg dose of praziquantel) as a function of concurrent STI treatment.



Abbreviations: STI, sexually transmitted infection; RR, risk ratio; CI, confidence interval.

Circles denote the adjusted RR for schistosomiasis + praziquantel exposure, among those without STI. Triangles denote the adjusted RR for schistosomiasis + praziquantel exposure, among those with concurrent STI disease and treatment. Squares denote the adjusted RR for joint exposure to schistosomiasis and STI disease and treatment.

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Chapter 4. Predictors and birth effects of prenatal anthelminthic drug use in the Democratic Republic of Congo

4.1 Abstract

Despite the endemicity of intestinal parasitic infections to the Democratic Republic of Congo (DRC), national preventive chemotherapy (PC) efforts have thus far neglected coverage for pregnant women due to concerns over drug effects in the prenatal period. While anthelminthic drug safety has been recognized by public health authorities, the effectiveness of these drugs in clearing prenatal disease and improving health outcomes for children exposed to helminthiases *in utero* are less well understood. Using data from DRC's 2013-2014 Demographic and Health Survey, we assessed drug use patterns amongst 10,984 recent mothers, as well as the association between prenatal anthelminthic use and downstream infant health at the national level. Anthelminthic use was reported by 56% of mothers during their most recent pregnancy, and was significantly more prevalent among older, wealthier, and more educated mothers, as well as those reporting increasingly higher numbers of antenatal care visits. Conversely, prenatal drug use was less common among mothers residing in rural areas (adjusted OR= 0.77, 95% CI: 0.58, 1.00), especially those distant from the capital province of Kinshasa. Deworming during pregnancy was also significantly associated with reduced neonatal mortality for offspring exposed as fetuses (adjusted OR= 0.59, 95% CI: 0.36, 0.98), but had no significant effect on their birthweight status. These findings suggest that prenatal anthelminthic use, independent of maternal infection status, may improve neonatal health at scale. The expansion of national drug administration programs to target pregnant women in DRC would likely improve use rates across the country and reduce disparities related to access.

4.2 Introduction

Intestinal parasites, including intestinal schistosomiasis (caused by trematode worms of the *Schistosoma* genus) and soil-transmitted helminthiases [STH; caused by the nematodes *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm (*Ancylostoma duodenale and Necator americanus*)], afflict over a billion people globally, accounting for over 4 million years lived with disability in 2016.[1] Schistosome and STH parasites impair the nutritional status of their hosts through several mechanisms including chronic intestinal blood loss, malabsorption of/ competition for micronutrients, and loss of appetite.[2] As a result, these infections can result in severe impairments to growth and physical development if left untreated.

Due to the safety and affordability of deworming medicines, the World Health Organization (WHO) recommends preventive chemotherapy (PC) consisting of periodic administration of anthelminthic drugs to at-risk populations in regions of high parasitic endemicity.[3] Although pregnant and breastfeeding women have historically been excluded from PC,[4] mounting evidence of the negative health effects of prenatal helminth infections, including increased risk of low birth weight offspring or perinatal death, have informed the integration of this vulnerable population into targeted treatment and mass drug administration (MDA).[4-6] Recently, the WHO began conditionally recommending PC with albendazole or mebendazole for pregnant women in regions with a baseline prevalence of 20% or higher for hookworm and/or Trichuriasis, and an anemia prevalence of 40% or higher.[3] They also advocate for the inclusion of pregnant and lactating women in MDAs for praziquantel across schistosomiasis-endemic regions.[7]

Unfortunately, these recommendations were made largely based on evidence of safety rather than efficacy (WHO themselves refer to these recommendations as being of "moderate-quality evidence"[3]), and are informed by conflicting data, impeding their adoption in many

helminth endemic countries including the Democratic Republic of Congo.[5, 6, 8-10] Recent meta-analysis and Cochrane reviews conclude that prenatal antihelminth treatment has no clear overall effect on maternal anemia, low birth weight, or perinatal mortality.[11-13] Deworming trials during pregnancy have also produced inconclusive results.[8, 10, 14-21] A randomized control trial (RCT) of antenatal mebendazole in Peru that examined anthelminthic use in tandem with iron supplementation versus iron alone showed reduction of very low birthweight, but no difference in maternal anemia in the third trimester between test groups.[15] Alternatively, in an RCT on antenatal ivermectin and albendazole in western Uganda, treatment with both drugs individually and in combination was associated with reduced maternal anemia.[16] No trials have yet shown praziquantel's benefits in combating maternal anemia or impacting birth outcomes such as abortion, intrauterine growth, birthweight, prematurity, perinatal mortality, and congenital abnormalities.[8, 22]

Non-experimental evidence on antenatal deworming from observational studies have demonstrated several benefits of parasitic treatment during pregnancy.[6, 9, 23-25] Two separate studies in Sri Lanka showed a significant positive, synergistic effect of anthelminthics on hemoglobin and serum ferritin levels in pregnant women also taking iron-folate supplementation, as well as reduced odds of stillbirths and perinatal deaths amongst women taking mebendazole specifically.[9, 23] In Nepal, women taking albendazole in the second trimester had lower rates of severe anemia in late pregnancy compared with women who had not taken albendazole; their children were also born at higher birthweights and experienced a 41% reduction in the risk of 6-month mortality.[24]

To date, only one observational study on deworming has been conducted amongst pregnant women in the DRC (Chapter 3), a country highly endemic for schistosomiasis, STH, and a host of other helminth infections. Despite ranking first or second in Africa for case load of several different

worm infections,[26] and qualifying for prenatal preventive chemotherapy per WHO's conditional PC eligibility criteria (anemia is greater than 40% in pregnant women;[27] hookworm prevalence estimated at 38%, Trichuriasis prevalence at 32%;[26] *Schistosoma mansoni* and *intercalatum*, two causal agents of intestinal schistosomiasis, are both endemic), DRC has no national antenatal treatment strategy in place for trematode and nematode infections. Indeed, current PC efforts in the country target school-aged children,[28] leaving women of childbearing age vulnerable to disease and assaults on healthy gestation. Given the high fertility rate of the country, large variances in nutritional stress, MDA coverage, and adherence to anthelminthic use guidelines in ANC settings, it is of great public health importance to gain an understanding of the distribution and effects of antenatal deworming at scale. Furthermore, given the variety of inconsistent outcomes observed from trials and observational studies in other settings, a country-specific examination of the effects of prenatal drug use in the DRC context is warranted.

This study aims to provide insight into the prevalence of prenatal anthelminthic drug use in the DRC, and to elucidate the impacts of preventive chemotherapy on birth outcomes at the national level, with implications for deworming campaigns and antenatal care policies.

4.3 Methods

Data source and study population

This study uses data from the women's questionnaire and linked geographic data points of the DRC Demographic and Health Survey (DHS), conducted between November 2013 and February 2014.[29] A nationally representative, population-based survey, the 2013-2014 DRC DHS includes completed questionnaires from 18,827 women aged 15-49 years old in 536 geographic clusters throughout the country.[29] All women reporting at least one pregnancy within the past five

years resulting in a live birth answered a series of questions on maternity and antenatal care for the most recent of these pregnancies. In total, 10,987 women fit this definition and definitively answered (yes/ no) a question asking if they had taken drugs for intestinal parasites over the course of this most recent pregnancy; each mother-child pair therein served as the base study population for this analysis.

Statistical analysis

The analysis was split into two parts: first, we describe the demographics of all women in in the base population and examine predictors of maternal anthelminthic drug use throughout the country via logistic regression (Part I). Next, we explore the crude and adjusted relationship between prenatal deworming and two child health outcomes of interest, low birth weight and neonatal mortality, also using logistic regression (Part II). To account for DHS survey design, including over- and under-sampling of various geographic areas throughout DRC, we applied individual-, stratum-, and cluster-level weights to produce unbiased estimates and confidence intervals (CIs).[29] SAS software version 9.4 (SAS Institute, Cary, NC) was used to conduct statistical analyses utilizing the appropriate survey commands. We also created national maps of drug use distribution using ArcMap version 10.6 GIS software (Esri, Redlands, CA).

Birth outcomes of interest

As noted, two child health outcomes of interest were examined to determine if some of the effects of prenatal deworming described by other trials and observational studies held in the DRC context: low birth weight (LBW) and neonatal mortality. Children were classified as being of normal (≥ 2500 g) or low birth weight (< 2500 g) based on delivery information provided by maternal recall during the survey interview or copied from the child's health card. All children

who died within the first 30 days of life were recorded as neonatal deaths, with all those surviving the first month postpartum classified as survivors. Although we were also interested in examining other common birth indicators such as prematurity and size for gestational age, no information was available through DHS regarding the timing of delivery.

Covariate selection

Covariate selection for both sets of analyses was based on *a priori* knowledge of potential confounders identified in the literature. All maternal demographics which were not significantly associated with prenatal anthelminthic use in Part I of the analysis were dropped from the birth outcomes models in Part II, as was residence by province, which created sparse data issues in the birth outcomes models. In addition to well-understood confounders of drug use and birth outcomes, including maternal demographics such as age, residence, socioeconomic status, and education, several indicators of prenatal care were also included for adequate model adjustment in Part II of the analysis.

First, the number of antenatal care (ANC) visits made by each mother was included. The WHO recommends that all women conduct at least 8 ANC visits over the course of their pregnancy.[30] These visits may influence the likelihood of receiving PC or targeted helminth treatment, and can also serve as a proxy of general prenatal care seeking and access. In order to control for common polyparasitism between schistosomiasis, STH, and malaria,[31, 32] the use of malaria drugs over the course of the pregnancy was also included as a covariate in our birth effects models. Although malaria testing of adults was not included in the DRC DHS files, antimalarial medication may serve as a proxy indicator of maternal drug use behaviors, and a potential modifier of the effectiveness of other drugs, including our anthelminthics of interest. Indeed, intermittent preventive treatment against malaria in pregnancy (IPTp) with mefloquine exhibits anti-

schistosome activity in addition to acting as a hematinic.[14, 18] As such, a binary variable indicating the use of any anti-malarials in the prenatal period was included in the model, including sulfadoxine/ pyrimethamine (brand name Fansidar), chloroquine, and quinine drugs.

Anthelminthic drugs, where they have shown benefits to maternal and child health, are hypothesized to act via reduction of blood and micronutrient losses, maintaining hemoglobin or ferritin levels.[10, 12, 13] Therefore, nutritional indicators and maternal anemia status or hemoglobin count were not included as covariates in the regression analysis, as these are considered mediators in the anthelminthic – birth outcome relationship.[33] Unfortunately, sample sizes for birth outcomes of interest did not allow for a stratified analysis by maternal anemia or nutritional status. Instead, antenatal iron supplementation was modeled in order to control for maternal drug use behaviors and potential alteration of anthelminthic drug effectiveness due to underlying micronutrient or blood-iron levels.[15, 25]

4.4 Results

Of the 10,987 women included in our study base population (see definition above), only 3 were missing information on our covariate set of interest. Another 2,642 women were missing birth weight information for their most recent pregnancy in the past five years, and could not be included in the LBW outcome analysis in Part II. In order to conduct unbiased analysis through proper application of normalized DHS survey weights, we therefore created two separate analytic sets of women using the domain feature in SAS. The larger set (n= 10,984) included all women in the base population who had complete prenatal care and demographic information available. This analytic set serves as the population for all analyses except the LBW birth outcome analysis in Part II. The smaller set (n= 8,342) of women in the LBW analysis includes only those women from the base population without missing birth weight information.

Part I: Maternal demographics and predictors of prenatal deworming

In this nationally-representative cohort, a majority of mothers fitting our inclusion criteria resided in rural clusters (68.4%), were currently partnered or cohabitating with a male (84.3%), were multigravid (64.4%), and had attended at least one ANC visit over the course of their most recent pregnancy (90.0%). Almost half of all women fell between the ages of 25 – 34 during their most recent delivery (43.7%), and only 18% reported no education. The two most highly represented provinces in this national sample were Bandundu (16.9%) and Equateur (14.2%), with the fewest women interviewed from Maniema (3.5%) and Bas-Congo (4.9%) provinces.

In total, 56.3% of women reported anthelminthic drug use over the course of their most recent pregnancy in the past five years. Maternal age, residence, education, wealth, and antenatal visit frequency were all significant predictors of prenatal deworming, with the adjusted odds of drug use increasing in a positive, monotonic fashion with successive levels of each ordinal characteristic [Table 4.1]. As mothers got older, attained greater educational levels, fell into higher socioeconomic quadrants, and attended more ANC visits over the course of their most recent pregnancy, their odds of anthelminthic use increased. Mothers living in rural clusters of DRC were less likely to have taken medication for intestinal parasites than those living in urban centers (aOR= 0.77, 95% CI: 0.58, 1.00). Partnership status and the number of prior pregnancies were not predictive of maternal drug use during the most recent viable pregnancy.

Women living anywhere outside of Kinshasa province, the capital region of DRC, were also at significantly reduced odds of prenatal drug use, ranging from 0.18 times the odds in Katanga in, to 0.80 times the odds in Bandundu [Table 4.1]. Indeed, a clustering of high anthelminthic coverage in western DRC was noted, fanning out from Kinshasa (87% coverage during the most recent pregnancy) to Orientale, Maniema, and Katanga (36-40% coverage) in the east [Figure 4.1].

A majority of mothers residing in Nord- and Sud-Kivu provinces on the far eastern border also recounted prenatal drug use (55-59%), albeit with lower prevalence than their western counterparts.

Part II: Impact of prenatal deworming on birth outcomes

The odds of having a LBW child were decreased with maternal use of anthelminthic drugs in both crude (cOR= 0.74, 95% CI: 0.48, 1.14) and adjusted (aOR= 0.63, 95% CI: 0.36, 1.09) regression analyses, although neither relationship was significant [Table 4.2]. Similarly, maternal age was inversely associated with LBW offspring, with mothers aged 35 and above exhibiting the lowest odds of LBW children (aOR= 0.52, 95% CI: 0.33, 0.84). The odds of LBW were also associated with the number of ANC visits in the prenatal period, but were only significantly reduced amongst mothers attending WHO's recommended 8 visits or more over the course of their pregnancy (aOR= 0.23, 95% CI: 0.06, 0.88). No other relationships with LBW were significant.

Prenatal deworming significantly reduced the odds of neonatal death following control for other prenatal care and maternal demographic variables (aOR= 0.59, 95% CI: 0.36, 0.98) [Table 4.3]. As with LBW, the only other factors significantly associated with neonatal death were maternal age (25-34 years aOR= 0.43, 95% CI: 0.23, 0.79) and ANC visits (1-7 visits aOR= 0.23 – 0.41, 95% CI: 0.10, 0.87).

4.5 Discussion

In this paper, we show that prenatal anthelminthic use is differentially divided across demographic and geographic lines of the DRC, with potential consequences for maternal and offspring health. Additionally, we show that in a setting with an overlapping burden of two species of intestinal schistosomiasis and three species of STH, prenatal PC appears to significantly lower

the odds of a pregnancy concluding in neonatal death, with no effect on child birth weight. To our knowledge, this is the first such examination of the distribution of prenatal deworming at the national level in DRC, and the first study to describe associated birth outcomes for the country.

As expected, women attaining some degree of secondary education and falling into higher wealth brackets had greater odds of prenatal drug use than those of lower socioeconomic status. Older mothers were also more likely to have taken the drugs, as were those attending one or more ANC visits, suggesting that access to PC for adult women in the DRC occurs primarily through contact with conventional health care facilities and providers, rather than school-based or community-wide MDAs. This finding aligns with WHO reports on DRC's deworming activities for 2007-2014—the full range of possible pregnancy periods for all mother-child pairs in the base population—which show sporadic albendazole and mebendazole MDAs for STH control targeting preschool and school-aged children, and almost no praziquantel campaigns in country for schistosomiasis control, with the exception of 2014.[28] No national deworming activities in this time period covered adults.

Those residing in urban centers, especially in the capital of Kinshasa, were also significantly more likely to report anthelminthic use during pregnancy, pointing to potential issues with drug access that are related to geographic drug distribution and availability. Indeed, maternal residence appears to play a larger, more significant role in dictating prenatal anthelminthic use in DRC than one's education level or family structure. Thus, our findings suggest that increased use of deworming drugs amongst pregnant women may require changes to supply chain management or other logistics impacting drug distribution across the country, rather than interventions targeting behavioral change.

In addition to gaining a better understanding of the drivers of anthelminthic uptake in pregnant women of DRC, this study adds to the literature describing downstream health effects of prenatal deworming. After controlling for a host of other indicators of prenatal care and maternal demographics, we find that anthelminthic use increases neonatal survival, but has no appreciable effect on LBW. Given the smaller sample size of mother-child pairs in the LBW analysis, statistical power may not have been sufficient to detect significant differences in birthweight based on prenatal drug use. Alternatively, antihelminth treatment might only aid in preventing LBW amongst women with very high parasite burdens, dietary insufficiencies, or both.[5] Finally, these results may simply indicate that anthelminthic use improves neonatal health through mechanisms unrelated to fetal growth.

This study has several limitations. Chief amongst them is our reliance on a question regarding prenatal drug use for intestinal parasites as our central outcome (Part I) or exposure (Part II) of interest—the only question of its kind available in the DRC DHS. While we interpreted this question as referring specifically to anthelminthic use, "intestinal worm" could also refer to non-helminth parasites which exist in DRC and are treated with other medications, such as *Giardia* and *Cryptosporidium,* although these exhibit very low prevalence in country, even within immunocompromised subpopulations (< 10%).[34] No detail was provided in the questionnaire as to the type of drug taken, at what point during pregnancy it was taken, the frequency of drug use, or the context of this use (MDA v. PC as a part of an antenatal drug regimen v. targeted treatment to cure infection). As such, some non-differential misclassification is expected and we are unable to make claims about medication timing, spacing, or dosing on birth outcomes. However, given the overwhelming helminth burden of DRC, and the exclusion of all other intestinal parasites in the country from PC and MDA interventions, we believe anthelminthic use is being adequately

captured. Notably, the lack of specificity surrounding the parameters of drug use in the questionnaire may actually strengthen this analysis, as women are more likely to correctly recall a binary account of their prenatal drug use than to identify exact medication names or circumstances. The generality of the question also allows for a broad view of the effects of maternal drug use on fetal and perinatal health which is not restricted to a single parasitic species or associated medication; this is important to places like DRC where a multitude of infections burden the population simultaneously.

We were also limited by the small number of adverse birth outcomes in our base population, which did not allow for thorough sensitivity analysis, for instance of the odds of LBW amongst only children with a delivery weight recorded on their health card. Finally, while recall bias of drug use is less likely to have occurred in our cohort given the binary nature of the main question and the antenatal questionnaire's restriction to births occurring within the past 5 years, social desirability may have influenced responses to prenatal care inquiries.

Despite these limitations, this study represents a first step towards understanding the prenatal deworming landscape of the DRC, and may be used to help target gaps in anthelminthic distribution to women in rural and extra-capital geographies. While the DHS utilizes a cross-sectional study design, we were still able to retroactively assess temporal relationships from prenatal exposures to post-delivery health outcomes. This study also adds to the growing yet inconsistent evidence base demonstrating the null or advantageous effects of deworming on birth outcomes. Our analysis is strengthened by its use of a nationally representative dataset on maternal and child health, and offers a model for replication in other countries with periodic DHS surveillance. Extending this investigation beyond DRC may help illuminate different cultural and social determinants of drug use across helminth-endemic regions, and might offer insights into the

disparate effects of prenatal deworming currently described in meta-analyses which rely on patchworked data from studies across the globe. Future studies should undertake DHS investigation of prenatal deworming as a first step in guiding programmatic and policy interventions for pregnant women in countries with different underlying worm burdens. Such preliminary studies can be used as benchmarks and continued with each successive DHS to track changes in anthelminthic use and access over time.

Inconclusive results of previous studies on anthelminthic drug use have stymied prevention and control efforts for pregnant women in helminth endemic countries. Heterogeneity of treatment plans in these studies may be contributing to the inconsistent results highlighted by Cochrane reviews and meta-analyses on the subject, as well as the resultant confusion about the suitability of prenatal medication. Specifically, the mixed inclusion of studies examining MDAs (treatment administered indiscriminately to all participants, regardless of infection status) with studies of selective treatment for patients with confirmed helminthiases in current reviews of the anthelminthic literature have been hypothesized to mask the true effects of deworming in aggregate studies. In this study, we lump all deworming strategies together and show that broad PC without identifiable or parse-able stratification by frequency or timing of treatment in pregnancy, type of drug administered, or infection status of mothers may still have a net positive impact on reducing neonatal mortality in areas of parasitic endemicity. Combined with international guidelines and indications of drug safety, our findings suggest that indiscriminate maternal deworming should be included as a standard of prenatal care in the DRC (and potentially in similar environs internationally).

Tables and Figures

Table 4.1. Predictors of anthelminthic drug use during each mother's most recent pregnancy in the past five years resulting in live birth (n= 10,984).

	Prenatal drug use				Measure of association			
Characteristics	**No. positive (%)**		**No. negative (%)**		**cOR**	**95% CI**	**aOR**	**95% CI**
Maternal age at birth								
15-24	2218	35.8	1972	41.1	ref		ref	
25-34	2807	45.4	1995	41.6	1.25	(1.12, 1.40)	1.26	(1.08, 1.47)
35+	1162	18.8	830	17.3	1.25	(1.09, 1.42)	1.33	(1.10, 1.61)
Residence								
Urban	2399	38.8	1077	22.5	ref		ref	
Rural	3788	61.2	3720	77.5	0.46	(0.37, 0.56)	0.77	(0.58, 1.00)
Education level								
None	848	13.7	1128	23.5	ref		ref	
Primary	2338	37.8	2316	48.3	1.34	(1.11, 1.63)	1.21	(0.99, 1.48)
Secondary or greater	3001	48.5	1353	28.2	2.95	(2.33, 3.74)	1.81	(1.40, 2.32)
Wealth index								
Poorest	1072	17.3	1322	27.6	ref		ref	
Poorer	1261	20.4	1115	23.2	1.4	(1.18, 1.65)	1.21	(1.01, 1.44)
Middle	1213	19.6	1036	21.6	1.44	(1.21, 1.72)	1.23	(1.01, 1.49)
Richer	1194	19.3	838	17.5	1.76	(1.45, 2.14)	1.24	(0.98, 1.58)
Richest	1447	23.4	486	10.1	3.68	(2.77, 4.89)	1.57	(1.10, 2.23)
Civil/ partnership status								
Never in a union	394	6.4	258	5.4	ref		ref	
Current union/ cohabitation	5182	83.8	4081	85.1	0.83	(0.67, 1.03)	0.88	(0.70, 1.10)
Former union/ cohabitation	611	9.9	458	9.5	0.87	(0.64, 1.18)	1.02	(0.74, 1.41)

Pregnancy order								
Primigravid	1171	18.9	875	18.2	ref		ref	
Secundigravid	1026	16.6	834	17.4	0.92	(0.78, 1.08)	1.01	(0.84, 1.22)
Multigravid	3990	64.5	3088	64.4	0.97	(0.84, 1.11)	1.10	(0.92, 1.32)
Total ANC visits								
None	224	3.6	870	18.1	ref		ref	
1-3 visits	2493	40.3	2046	42.7	4.74	(3.62, 6.19)	3.99	(3.03, 5.26)
4-7 visits	3250	52.5	1748	36.4	7.23	(5.57, 9.39)	5.22	(4.01, 6.78)
8 or more	220	3.6	133	2.8	6.42	(4.58, 9.00)	5.36	(3.80, 7.58)
Province								
Kinshasa	766	12.4	114	2.4	ref		ref	
Bandundu	1296	20.9	559	11.7	0.35	(0.24, 0.49)	0.80	(0.53, 1.21)
Bas-Congo	337	5.4	205	4.3	0.25	(0.17, 0.36)	0.49	(0.31, 0.77)
Equateur	894	14.4	661	13.8	0.20	(0.14, 0.29)	0.53	(0.34, 0.80)
Kasai-Occidental	402	6.5	376	7.8	0.16	(0.11, 0.24)	0.39	(0.24, 0.61)
Kasai-Oriental	562	9.1	572	11.9	0.15	(0.10, 0.21)	0.34	(0.24, 0.50)
Katanga	418	6.8	730	15.2	0.09	(0.06, 0.12)	0.18	(0.13, 0.26)
Maniema	154	2.5	227	4.7	0.10	(0.05, 0.19)	0.22	(0.11, 0.42)
Nord-Kivu	490	7.9	347	7.2	0.21	(0.13, 0.34)	0.43	(0.27, 0.70)
Orientale	408	6.6	636	13.3	0.10	(0.06, 0.14)	0.22	(0.15, 0.34)
Sud-Kivu	460	7.4	370	7.7	0.19	(0.11, 0.31)	0.43	(0.24, 0.79)
TOTAL	6187		4797					

Abbreviations: cOR, crude odds ratio; aOR, adjusted odds ratio; ANC, antenatal care.

Figure 4.1. Geographic coverage of prenatal anthelminthic drug use in DRC at the provincial level, by prevalence of maternal report.

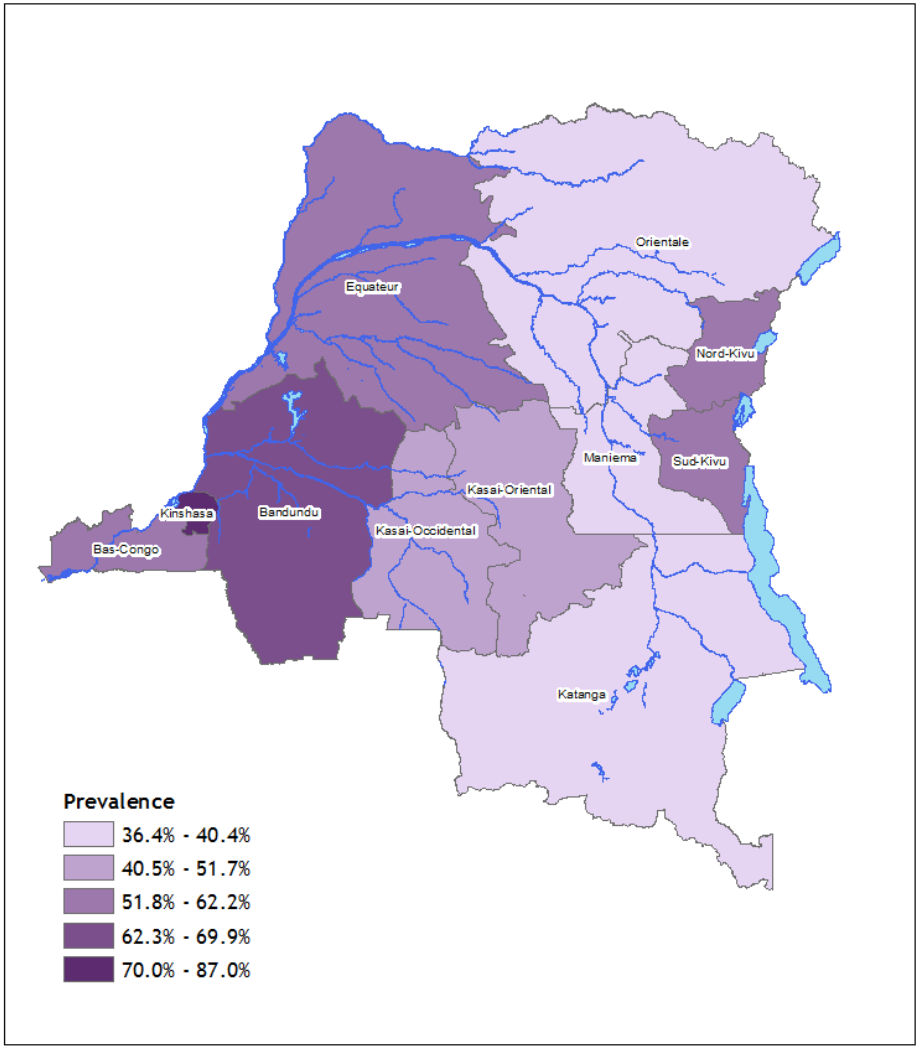

Table 4.2. Predictors of low birth weight (LBW) amongst most recent live birth deliveries in the past five years (n= 8,342).

	LBW status				Measure of association with LBW			
	No. positive (%)		No. negative (%)		cOR	95% CI	aOR	95% CI
Pretnatal care								
Intestinal parasitic drugs (anthelminthics)								
No	210	39.0	2977	38.2	ref		ref	
Yes	329	61.0	4826	61.8	0.74	(0.48, 1.14)	0.63	(0.36, 1.09)
Any malaria drug								
No	268	49.7	3929	50.4	ref		ref	
Yes	271	50.3	3874	49.6	1.32	(0.90, 1.95)	1.48	(0.98, 2.23)
Iron supplementation								
No	168	31.2	2594	33.2	ref		ref	
Yes	371	68.8	5209	66.8	1.30	(0.85, 1.98)	1.33	(0.88, 2.03)
ANC visits								
None	22	4.1	308	3.9	ref		ref	
1-3 visits	244	45.3	3236	41.5	0.84	(0.35, 2.04)	0.67	(0.27, 1.66)
4-7 visits	260	48.2	4010	51.4	0.73	(0.28, 1.92)	0.55	(0.21, 1.42)
8 or more	13	2.4	249	3.2	0.27	(0.07, 1.01)	0.23	(0.06, 0.88)
Maternal demographics								
Maternal age at birth								
15-24	257	47.7	2908	37.3	ref		ref	
25-34	215	39.9	3478	44.6	0.58	(0.36, 0.96)	0.58	(0.37, 0.93)
35+	67	12.4	1417	18.2	0.52	(0.31, 0.85)	0.52	(0.33, 0.84)
Residence								
Urban	231	42.9	3057	39.2	ref		ref	
Rural	308	57.1	4746	60.8	0.98	(0.68, 1.42)	1.09	(0.65, 1.84)

Education level								
None	75	13.9	1144	14.7	ref		ref	
Primary	201	37.3	3094	39.7	0.90	(0.60, 1.35)	0.90	(0.60, 1.34)
Secondary or greater	263	48.8	3565	45.7	1.08	(0.65, 1.81)	1.00	(0.57, 1.76)
Wealth index								
Poorest	85	15.8	1296	16.6	ref		ref	
Poorer	81	15.0	1506	19.3	0.72	(0.40, 1.28)	0.76	(0.42, 1.38)
Middle	105	19.5	1554	19.9	1.26	(0.73, 2.18)	1.26	(0.74, 2.14)
Richer	140	26.0	1671	21.4	1.30	(0.87, 1.95)	1.31	(0.82, 2.11)
Richest	128	23.7	1776	22.8	1.02	(0.61, 1.71)	1.12	(0.54, 2.34)
TOTAL	539		7803					

Abbreviations: LBW, low birth weight; ANC, antenatal care; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

Table 4.3. Predictors of neonatal death amongst most recent live birth deliveries in the past five years (n= 10,983).

	Neonatal death				Measure of association with neonatal death			
	No. positive (%)		No. negative (%)		cOR	95% CI	aOR	95% CI
Pretnatal care								
Intestinal parasitic drugs (anthelminthics)								
No	113	50.4	4684	43.5	ref		ref	
Yes	111	49.6	6075	56.5	0.56	(0.33, 0.92)	0.59	(0.36, 0.98)
Any malaria drug								
No	140	62.5	6131	57.0	ref		ref	
Yes	84	37.5	4628	43.0	0.78	(0.45, 1.34)	0.94	(0.53, 1.66)
Iron supplementation								
No	97	43.3	4405	40.9	ref		ref	
Yes	127	56.7	6354	59.1	0.95	(0.58, 1.57)	1.68	(0.99, 2.84)
ANC visits								
None	37	16.5	1056	9.8	ref		ref	
1-3 visits	84	37.5	4456	41.4	0.26	(0.13, 0.54)	0.23	(0.10, 0.51)
4-7 visits	90	40.2	4907	45.6	0.48	(0.25, 0.95)	0.41	(0.19, 0.87)
8 or more	13	5.8	340	3.2	0.35	(0.10, 1.27)	0.32	(0.09, 1.20)
Maternal demographics								
Maternal age at birth								
15-24	116	51.8	4074	37.9	ref		ref	
25-34	62	27.7	4741	44.1	0.40	(0.23, 0.71)	0.43	(0.23, 0.79)
35+	46	20.5	1944	18.1	0.78	(0.40, 1.52)	0.79	(0.40, 1.59)
Residence								
Urban	59	26.3	3417	31.8	ref		ref	
Rural	165	73.7	7342	68.2	1.29	(0.75, 2.23)	0.93	(0.50, 1.74)

Education level								
None	35	15.6	1941	18.0	ref		ref	
Primary	96	42.9	4557	42.4	1.27	(0.59, 2.73)	1.30	(0.61, 2.76)
Secondary or greater	93	41.5	4261	39.6	1.33	(0.61, 2.91)	1.71	(0.73, 4.01)
Wealth index								
Poorest	44	19.6	2350	21.8	ref		ref	
Poorer	51	22.8	2325	21.6	1.18	(0.57, 2.44)	1.27	(0.59, 2.72)
Middle	63	28.1	2186	20.3	1.09	(0.52, 2.29)	1.16	(0.51, 2.64)
Richer	41	18.3	1990	18.5	1.08	(0.52, 2.00)	1.11	(0.49, 2.48)
Richest	25	11.2	1908	17.7	0.50	(0.20, 1.24)	0.47	(0.15, 1.44)
TOTAL	224		10759					

Abbreviations: ANC, antenatal care; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

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Chapter 5. Conclusions and Implications

5.1 Summary of research context, findings, and associated recommendations

Despite the persistent endemicity of schistosomiasis and soil-transmitted helminths in the Democratic Republic of Congo (DRC), national prevention and control measures to combat these diseases remain exclusive of pregnant women. Almost all country-level campaigns for mass chemotherapy over the past decade have been targeted specifically at school-aged children, leaving women of childbearing age outside the main mode of anthelminthic drug delivery. And while pregnant women may be incidentally offered treatment by their health providers, no national strategy exists to systematically distribute deworming medications as a part of routine antenatal care.

This dissertation describes the potential benefits of expanding prenatal anthelminthic drug coverage in DRC. In general, deworming interventions during pregnancy may reduce the downstream risk of neonatal mortality. For urogenital schistosomiasis specifically, targeted treatment with praziquantel appears socially acceptable, safe, and potentially mitigating of the harmful fetal effects of prenatal disease. As such, we recommend that pregnant women infected with schistosomiasis be treated upon diagnosis, and that general preventive chemotherapy (PC) with anthelminthics be expanded and institutionalized at the national level to systematically incorporate pregnant women in DRC. The central findings of this report reinforce or extend overarching conclusions of the current helminth literature to support these recommendations, namely:

1. The treatment of helminth infections is an efficacious and cost-effective means of reducing chronic morbidities in pregnant women. Praziquantel, albendazole, and mebendazole are

safe for use by adults and children alike, with mounting evidence to support safety across all trimesters of pregnancy, and only a small number of doses required for disease clearance. As demonstrated in Chapters 2 and 4, deworming medication is also a socially acceptable means of disease control in Congolese society, even during the prenatal period.

2. Prenatal anthelminthic treatment may help reduce the incidence and transmission of associated comorbidities. Helminthiases serve as risk factors for other parasitic agents (polyparasitism) as well as HIV, and their treatment can therefore serve as an indirect control method for these diseases. In Chapter 2, we show that the odds of CT, NG, and TV infections are significantly increased in the presence of prenatal *S. haematobium* infection as well, indicating that anthelminthic administration may help reduce or prevent the spread of STIs beyond HIV which pose threats to healthy pregnancy and fetal development.
3. Prenatal deworming appears to impart neutral or beneficial effects to children exposed *in utero*. This held true in both targeted treatment settings and in the context of preventive chemotherapy which occurs independent of one's infection status. In Chapter 3 we show that offspring of *S. haematobium*-infected and treated mothers were no more likely to be born low birth weight, preterm, or microcephalic than their counterparts born to uninfected mothers. In Chapter 4, we show at scale that neonates of mothers reporting prenatal anthelminthic use at any point in their pregnancy had reduced odds of death during the first month of life.
4. Under the current, non-institutionalized mode of anthelminthic distribution in DRC, expectant mothers experience differential exposure to these drugs according to their socioeconomic status and place of residence. Over half of mothers nationwide reported prenatal deworming over the course of their most recent pregnancy, as noted in Chapter 4;

yet women from the poorest quantile of Congolese society and those living far from Kinshasa have the lowest odds of drug use, likely stemming from access issues. Updating national policy to systematically provide anthelminthics as a part of routine antenatal care would likely improve country-wide drug coverage and reduce disparities.

Practical challenges and prevailing research practices which exclude pregnant women from health research continue to hamper our understanding of helminthiasis detection, progression, and management in the prenatal period. Specifically, more evidence on the timing, frequency, and dosage of medications is required to better guide medical decisions about safe and effective treatment for pregnant women globally. This dissertation was written with the aim of filling some of these urgent research gaps. Future investigations should continue to elucidate the specific challenges faced by pregnant populations in order to better guide disease prevention and management in a context-specific, logistically feasible, and socially acceptable manner. Only with inclusive research frameworks may we adequately address issues of maternal and fetal safety, and expand access to beneficial medications as a matter of health justice and equity.