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Exploring the Link between Sociocultural Variables and Schistosomiasis in Minas Gerais, Brazil

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By

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University of South Florida
2019

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Abstract

Exploring the Link between Sociocultural Variables and the

Prevalence of Schistosomiasis in Minas Gerais, Brazil

By Morgan Toth

Background and Goals: Human schistosomiasis caused by the subspecies *Schistosoma mansoni* is prevalent in Brazil, specifically in the southeastern state of Minas Gerais; despite this, control strategies are incohesive and insufficient to eliminate schistosomiasis in the state. In comparison to other schistosomiasis endemic areas, Minas Gerais has high coverage of adequate sanitation services. Access to sanitation is widely believed to reduce schistosomiasis, implying other factors are contributing to the prevalence in Minas Gerais. The goal of this study was to determine if other sociodemographic factors and knowledge or awareness of the disease may contribute to the prevalence of schistosomiasis in the area. **Methods:** Data were collected in Minas Gerais between June 2016 and December 2018 as part of a case-control study investigating schistosomiasis and leprosy co-infections. Participants (cases of leprosy and controls) ages 3 and older were recruited and tested for schistosomiasis by a multiplexed beaded assay identifying serum antibody response to soluble egg antigen (SEA). Post-hoc analyses focusing on schistosomiasis alone compared antibody reactivity to demographic, socioeconomic, and WASH variables of interest. Descriptive and bivariate analyses were performed, followed by logistic regression models that compared infection status to the explanatory variables of interest. **Results:** Of the 256 participants enrolled, 66 (30%) tested positive for S. mansoni IgG. Of these participants, 38 (58%) did not report a history of schistosomiasis. While most (96%) participants had access to improved sanitation services, having a latrine instead of a toilet was significantly associated with schistosomiasis infection, as was participating in freshwater activities. Being unaware of schistosomiasis infection (reporting no history but testing positive) was found to be positively associated with age and marital status. Awareness of schistosomiasis infection (reporting a history of schistosomiasis and testing positive) was found to be significantly associated with urban residence and lower education. **Conclusions and future directions:** Findings surrounding WASH factors support water contact and poor sanitation services as risk factors for schistosomiasis. Subsequent models suggested that sociocultural factors and educational attainment may influence knowledge of schistosomiasis, with concern that many people continue to unknowingly have infection. More research is needed to explore the relationship between sociocultural factors, especially unmeasured ones, and the continued transmission of schistosomiasis in Minas Gerais.

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Chapter I: Introduction

Schistosomiasis is a neglected tropical disease (NTD) caused by parasitic worms of the genus *Schistosoma* (Gryseels et al., 2006). Infection occurs when individuals come in direct contact with fresh water that is contaminated with schistosomes. Larval forms of the parasites swim freely in fresh water and burrow through the skin of individuals who come in direct contact with contaminated water. Three species of schistosomes are responsible for the majority of human schistosomiasis; of these, only *S. mansoni* is present in the Americas (Gryseels et al., 2006). While global prevalence has decreased as a result of widespread control efforts, it is estimated that at least 140 million people worldwide are currently infected with schistosomiasis (Deol et al., 2019). Brazil experiences a high burden of disease caused by *S. mansoni,* estimated to account for 95% of schistosomiasis cases in the Region of the Americas (World Health Organization, 2013). The southeastern state of Minas Gerais is endemic for schistosomiasis and experiences some of the highest cases in the country (Katz, 2018).

Although an estimated 200,000 deaths are attributed to schistosomiasis yearly, the disease is more likely to cause severe chronic morbidity than death (Gunda et al., 2020). Symptoms of untreated chronic schistosomiasis infection include anemia, chronic inflammation, gastrointestinal pain, and diarrhea. Untreated infections in young children can lead to cognitive defects (Colley et al., 2014). Schistosomiasis can be debilitating and can significantly contribute to loss of productivity in high-prevalence areas. Thus, effectively controlling schistosomiasis is a critical public health issue in Brazil.

Despite the public health importance of schistosomiasis in Brazil, surveillance and control efforts in the country have been historically incohesive and disorganized (Drummond et al., 2010). While a countrywide action plan that included schistosomiasis control efforts was introduced in Brazil in 2011, there is still a need to improve control strategies (Ministério da Saúde, 2012a). Because schistosomiasis is relatively easy to prevent, educational programs aimed at increasing knowledge of transmission have the potential to greatly reduce the burden of disease in endemic areas like Minas Gerais.

This study investigated the gap between self-reported history of schistosomiasis infection and seroreactivity for schistosomiasis to look for factors that may be associated with a lack of awareness of the infection. Schistosomiasis infection and self-reported history of infection were compared to key demographic variables, such as education level, financial status, age, and sex, to determine what factors may impact infection status.

<u>Chapter II: Literature Review</u>

Schistosomiasis

Biology

Schistosomiasis is a disease caused by blood flukes of the genus *Schistosoma* (Gryseels et al., 2006; Maldonado-Moll, 2020). Schistosomes are pale-colored, cylindrical flatworms that measure between 7-20 millimeters in length (Gryseels et al., 2006). Three primary species of schistosomes cause the majority of disease in humans; these are *S. mansoni, S. haemotabium,* and *S. japonicum* (Gryseels et al., 2006). *S. mansoni* is the only species prevalent in the Americas and is of particular importance in Brazil.

Schistosomes have two distinct sexes and reproduce sexually (Gryseels et al., 2006; Maldonado-Moll, 2020). Adult female schistosomes are long and slender, fitting within a groove on the male schistosome's body. The flukes remain permanently paired within the venous plexus of vertebrate hosts (Gryseels et al., 2006); *S. mansoni* "prefers to live in the inferior mesenteric vein of the lower bowel, particularly the branches of the sigmoid and rectum" (Maldonado-Moll, 2020). Paired schistosomes produce around 300 eggs per day (Lambertucci, 2010).

Life Cycle

Schistosoma mansoni eggs exit the body via fecal matter. These eggs must reach a fresh water source within seven days to continue the life cycle (Gryseels et al., 2006). Eggs that reach fresh water within the seven day period of viability hatch and release miracidia, the first larval stage of the life cycle (Gryseels et al., 2006). In order to survive and reproduce, miracidia must enter the body of a freshwater snail. *S. mansoni* exclusively infects snails of the species *Biomphalaria.* Once inside the body of the snail, the miracidia reproduce asexually and eventually mature into cercariae, the second larval stage. After 4-6 weeks, cercariae leave the body of the snail and free float in the water for up to 72 hours until they are able to locate a host. Once a host is located, cercariae enter through the skin, losing their bifurcated tails and becoming schistosomulae. Schistosomulae make their way into the bloodstream and travel to the inferior mesenteric vein, where they pair with an adult worm of the opposite sex (Centers for Disease Control, 2019; Gryseels et al., 2006; Maldonado-Moll, 2020). Egg laying occurs approximately 25-30 days after pairing (Lambertucci, 2010).

Clinical Symptoms

In some cases, the site where cercaria enter the skin becomes inflamed and irritated, causing a rash known as cercarial dermatitis. Because the rash is typically mild, many individuals who present with cercarial dermatitis do not seek medical treatment and thus many cases likely go undiagnosed (Lambertucci, 2010).

Acute schistosomiasis, sometimes referred to as Katayama fever or Katayama syndrome, occurs when the body mounts a strong immune response to the schistosomulae traveling within the body. Symptoms of acute schistosomiasis include dry cough, angioedema, and high eosinophil counts. The severity of symptoms varies depending on the number of cercariae that enter the body (Jauréguiberry et al., 2010). Acute schistosomiasis typically manifests within two to 12 weeks post-exposure, with symptoms often lasting several weeks (Leshem et al., 2008). While acute schistosomiasis is relatively common in travelers with no prior exposure to schistosomiasis, acute cases are rarely seen in individuals living in endemic areas (Leshem et al., 2008).

Morbidity associated with chronic schistosomiasis, the most common form of the disease in endemic areas, is a result of schistosome eggs and not the actual worms (Colley et al., 2014). *S. mansoni* eggs that are unable to exit the body via fecal matter become lodged in the lower gastrointestinal tract or liver, inducing an immune response from the host and causing granulomas to form around the eggs (Colley et al., 2014). The formation of granulomas results in chronic inflammation, causing symptoms that include "non-specific intermittent abdominal pain, diarrhea, and rectal bleeding" (Colley et al., 2014). Additionally, since schistosomes are blood flukes that feed on the hosts' bloodstream, patients with high parasite loads often experience anemia. Chronic anemia can in turn lead to fatigue and limited ability to work and actively participate in normal day-to-day activities. Other clinical symptoms of chronic schistosomiasis include malnutrition and cognitive impairment, especially in children (Colley et al., 2014).

Diagnosis

There are three primary means of diagnosing schistosomiasis infections: Direct parasitological diagnosis; immunological diagnosis; and nucleic acid-based amplification techniques. In direct parasitological diagnosis, schistosome eggs are detected in stool samples (Siqueira et al., 2015). The most common form of direct parasitological test is the Kato-Katz technique. Kato-Katz requires a fresh stool sample, but is inexpensive, highly specific, and easy to use. The Kato-Katz technique is currently the diagnostic tool recommended by the World Health Organization (WHO). However, Kato-Katz has low sensitivity and does not always detect low-intensity infections (Enk et al., 2008).

Immunological diagnostic tests detect antibodies or antigens. One of the most common antigen tests for schistosomiasis is the soluble egg antigen (SEA) IgG, which tests for IgG antigens to schistosome eggs. These tests are more sensitive than direct diagnostic tests and are thus more useful to detect early infections and light parasite burdens. These tests are useful in children and in travelers who are likely to have only infrequent exposures and where antibody reactivity is more likely to represent active infection. However, because antibodies remain in the body post-infection, antibody tests cannot distinguish between current and past infections. Furthermore, while they are capable of detecting light parasite burdens, they are unable to distinguish between heavy and light parasite burdens (Graeff-Teixeira et al., 2021; Pinheiro et al., 2012).

Nucleic acid-based amplification techniques detect genetic material of schistosomes. These tests are highly accurate, making them especially useful for fieldwork requiring precise diagnosis. However, these tests are also extremely costly and are less realistic in low-resource settings (Taman & El-Beshbishi, 2019).

In endemic countries like Brazil, a combination of diagnostic methods are often recommended (Silva-Moraes et al., 2019). While the Kato-Katz method may not be ideal due to its low sensitivity, studies have shown that performing multiple Kato-Katz tests across multiple days can significantly improve the sensitivity of the technique (Enk et al., 2008; Rabello et al., 1992). Additionally, Siqueira et al. found that performing multiple Kato-Katz tests on one stool sample could increase the accuracy of the tests (Siqueira et al., 2015). Because antibody tests are incapable of distinguishing between current and past infections, they are not ideal in endemic areas like Brazil. Overall, while Kato-Katz tests are currently commonly used, there is a need for more accurate tests to diagnose schistosomiasis in Brazil (Silva-Moraes et al., 2019).

Minas Gerais

Minas Gerais is a state in Southeastern Brazil. With a population of about 21.4 million, it is the second largest state in Brazil in terms of population (Brazilian Institute of Geography and Statistics, n.d.) and the fourth largest in terms of geographical land area (Meyer, 2010).

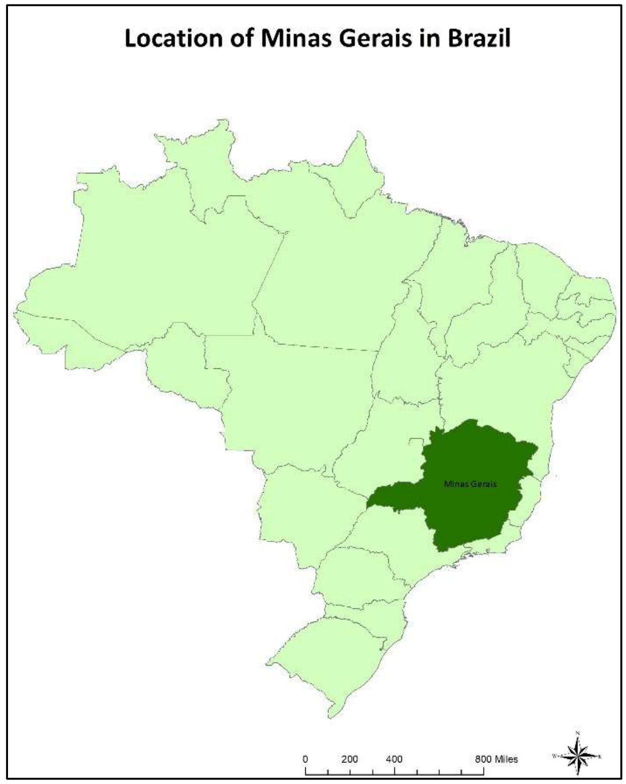


Figure 1: Location of Minas Gerais in Brazil. Shapefile from Instituto Brasileiro de Geografia e Estatística, 2010.

In 2010, Brazil accounted for approximately 95% of all schistosomiasis cases in the Region of the Americas (World Health Organization, 2013). The state of Minas Gerais experiences a high burden of disease (Katz, 2018). A study conducted between 2014-2015 found an overall prevalence of about 52% in indigenous peoples living in rural Maxakali villages in the northeastern part of Minas Gerais (Nacife et al., 2018). Additional studies have also found that individuals in rural areas have higher rates of infection compared to those living in more urban areas (Gazzinelli et al., 1998). A 2016 study found that the prevalence of schistosomiasis infection in preschool aged children in a rural municipality of Minas Gerais was 62.5% (Zoni et al., 2016). However, a statewide study published in 2018 found an overall prevalence closer to about 4% (Katz, 2018).

S mansoni was first described in Brazil in 1908, and is still considered a "major public health problem" today (Drummond et al., 2010). The first major schistosomiasis control program in Brazil was implemented in 1975, when the Brazilian Ministry of Health employed the Special

Schistosomiasis Control Program (PECE). This program remained a “high priority” in the Ministry until 1988, when it was demoted to the Schistosomiasis Control Program (PCE), a more generalized and lower-priority program. The PCE was eventually phased out in 1993 (Drummond et al., 2010). Schistosomiasis surveillance and control was relatively disorganized and was not prioritized by the Brazilian Ministry of Health until recently. In 2011, a new infectious disease action plan was published by the Ministry of Health in Brazil that aimed to eliminate schistosomiasis as a public health problem by 2015. This plan outlined surveillance and control strategies for several infectious diseases, including schistosomiasis (Ministério da Saúde, 2012b). However, at the conclusion of the action plan, studies showed that disability-adjusted life years (DALYs) attributed to schistosomiasis remained virtually unchanged (Martins-Melo et al., 2018).

Little information currently exists on the presence of schistosomiasis-specific educational programming throughout Minas Gerais. A 2016 study found high levels of awareness of schistosomiasis amongst school-aged children, but also found that behaviors considered “high-risk” for schistosomiasis infection were prevalent (Cabello et al., 2016). A qualitative study aiming to identify factors related to schistosomiasis awareness and knowledge found that “information on both community and individual specific causes of schistosomiasis infection, modes of transmission, and prevention needs to be especially promoted” (Gazzinelli et al., 1998).

Case Study: A Comparison of Brazil and Sierra Leone, two *S mansoni* endemic countries

Brazil is an interesting case in terms of schistosomiasis prevalence because there are some demographic and sociocultural differences compared to other schistosomiasis endemic countries. *S. mansoni* is most prevalent on the African continent, specifically in sub-Saharan Africa, which includes some of the poorest nations in the world (*Schistosomiasis: Epidemiology*

& Risk Factors, 2019). To better exemplify the differences between Brazil and other schistosomiasis-endemic countries, a comparison can be drawn between Brazil and Sierra Leone, a country with a comparable prevalence of schistosomiasis.

Brazil has a far higher human development index (HDI) compared to Sierra Leone. In 2019, Brazil's HDI was 0.765, which ranked the country in the high human development category (United Nations Development Programme, 2020a). Sierra Leone's HDI in 2019 was 0.452, placing the country in the low human development category (United Nations Development Programme, 2020b). Approximately 87.6% of Brazilians live in urban areas, with an annual rate of urbanization equaling about 0.87% ("Brazil," 2022). Despite suffering from a major recession in 2015, Brazil currently has the eight largest economy in the world. Only about 4.2% of Brazilians live below the poverty line ("Brazil," 2022). On the other hand, Sierra Leone is considered "extremely poor", with nearly 57% of the population living below the poverty line ("Sierra Leone," 2022). Only about 43% of Sierra Leoneans live in urban areas, with an annual urbanization rate of approximately 3.02% ("Sierra Leone," 2022).

Water, sanitation, and hygiene (WASH) factors have long been recognized as a critical aspect of schistosomiasis transmission and control. Because the parasite is contracted via contact with contaminated water, increasing access to sanitation services and safe water in turn reduces incidence of schistosomiasis (J. E. T. Grimes et al., 2014). Unlike most other waterborne diseases, schistosomiasis is contracted via direct contact with infected water rather than via consumption of infected water. Thus, increasing access to safe sanitation, which prevents fecal contamination of fresh water, is more important to control schistosomiasis than increasing access to safe drinking water (J. E. Grimes et al., 2015).

A unique aspect of schistosomiasis in Brazil is that Brazil has relatively high WASH coverage, especially in comparison to other *S. mansoni* endemic countries. Approximately 61% of people living in urban areas of Brazil have access to sanitation systems, though only 53% of the total population has sanitation coverage (Narzetti & Marques, 2020). Interestingly, Minas Gerais has much higher sanitation coverage than many other Brazilian states (Ferreira et al., 2021). About 92% of municipalities in Minas Gerais have access to some sort of sewage service (Oliveira, 2015). In comparison, Sierra Leone has a comparable prevalence of schistosomiasis but has total sanitation coverage of only 13.2% (Alagidede & Alagidede, 2016). Figures 3 and 4 show sanitation service levels in Brazil and Sierra Leone, respectively, using sanitation service levels defined by the Joint Monitoring Programme. Each level is defined as follows: safely managed service refers to private facilities that allow for safe disposal and treatment of human feces; basic service refers to improved private facilities; limited service refers to improved facilities that are shared amongst at least two households; unimproved includes pit latrines, hanging latrines, and bucket latrines; and open defecation refers to the total absence of any sanitation facilities (Joint Monitoring Programme, n.d.).

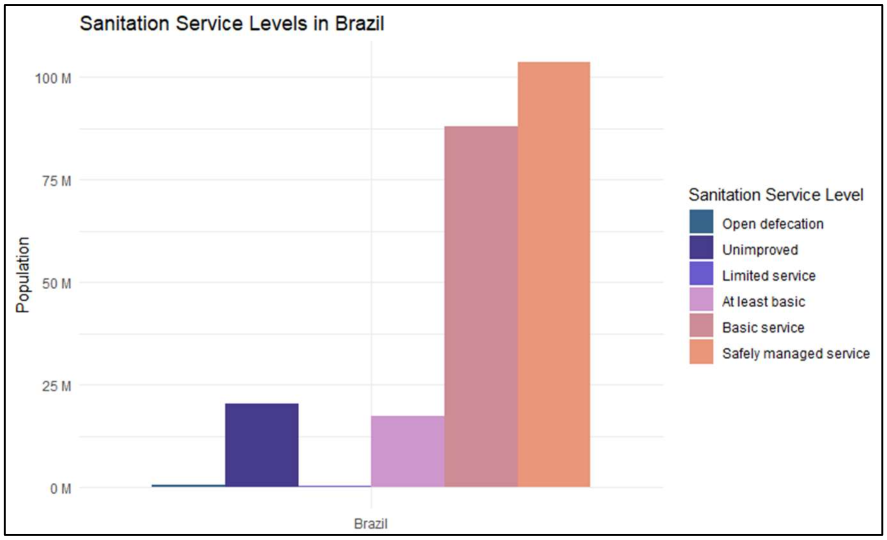


Figure 2: Number of people in Brazil with access to sanitation services. Data was collected in 2020 and provided by the Joint Monitoring Programme (n.d.)

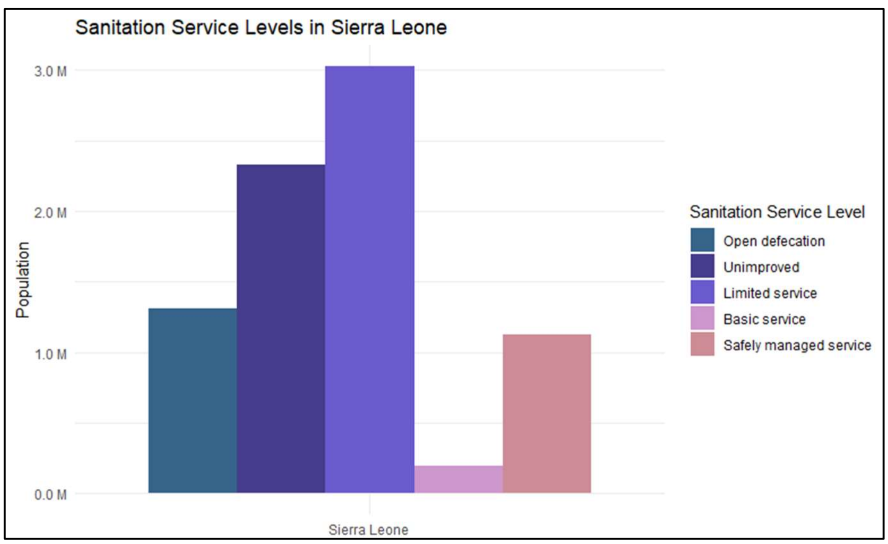


Figure 3: Number of people in Brazil with access to sanitation services. Data was collected in 2020 and provided by the Joint Monitoring Programme (n.d.).

The stark differences between schistosomiasis prevalence in Brazil and other endemic countries suggests other differences may be at play. It is likely that some of the high burden of *S. mansoni* infections in Brazil can be attributed to lack of mass drug administration (MDA) programs in the country. Additionally, it is possible that low knowledge or understanding of *S. mansoni* in Brazil may influence transmission.

Chapter III: Manuscript Formatted for the Journal

Abstract

Background and Goals: Human schistosomiasis caused by the subspecies *Schistosoma mansoni* is prevalent in Brazil, specifically in the southeastern state of Minas Gerais; despite this, control strategies are incohesive and insufficient to eliminate schistosomiasis in the state. In comparison to other schistosomiasis endemic areas, Minas Gerais has high coverage of adequate sanitation services. Access to sanitation is widely believed to reduce schistosomiasis, implying other factors are contributing to the prevalence in Minas Gerais. The goal of this study was to determine if other sociodemographic factors and knowledge or awareness of the disease may contribute to the prevalence of schistosomiasis in the area. **Methods:** Data were collected in Minas Gerais between June 2016 and December 2018 as part of a case-control study investigating schistosomiasis and leprosy co-infections. Participants (cases of leprosy and controls) ages 3 and older were recruited and tested for schistosomiasis by a multiplexed beaded assay identifying serum antibody response to soluble egg antigen (SEA). Post-hoc analyses focusing on schistosomiasis alone compared antibody reactivity to demographic, socioeconomic, and WASH variables of interest. Descriptive and bivariate analyses were performed, followed by logistic regression models that compared infection status to the explanatory variables of interest. **Results:** Of the 256 participants enrolled, 66 (30%) tested positive for S. mansoni IgG. Of these participants, 38 (58%) did not report a history of schistosomiasis. While most (96%) participants had access to improved sanitation services, having a latrine instead of a toilet was significantly associated with schistosomiasis infection, as was participating in freshwater activities. Being unaware of schistosomiasis infection (reporting no history but testing positive) was found to be positively associated with age and marital status. Awareness of infection (reporting a history of schistosomiasis and testing positive) was found to be significantly associated with urban residence and lower education. **Conclusions and future directions:** Findings surrounding WASH factors support water contact and poor sanitation services as risk factors for schistosomiasis. Subsequent models suggested that sociocultural factors and educational attainment may influence knowledge of schistosomiasis, with concern that many people continue to unknowingly have infection. More research is needed to explore the relationship between sociocultural factors, especially unmeasured ones, and the continued transmission of schistosomiasis in Minas Gerais.

Background

Schistosomiasis is a parasitic infection caused by blood flukes of the genus *Schistosoma.* Of the three species responsible for most human infections, the subspecies *S. mansoni* is the only species found in the region of the Americas (Gryseels et al., 2006). Adult worms of the subspecies *S. mansoni* infect the mesenteric vein of the lower bowel, where females can produce upwards of 300 eggs per day (Lambertucci, 2010). These eggs can become trapped in the intestinal walls and cause severe chronic inflammation. Because adult worms feed on the bloodstream of their host, schistosomiasis can also cause anemia, chronic fatigue, and in children can lead to cognitive deficiencies (Colley et al., 2014). While schistosomiasis is typically not associated with high mortality, it is responsible for chronic morbidity and loss of productivity.

Brazil accounts for approximately 95% of human schistosomiasis cases in the Region of the Americas (World Health Organization, 2013). In Brazil, the southeastern state of Minas Gerais experiences the highest burden of disease. Minas Gerais is unique to other schistosomiasis endemic areas because it has much higher water, sanitation, and hygiene (WASH) coverage relative to other endemic regions. Approximately 61% of people living in urban areas and 53% of the total population of Brazil have access to sanitation services (Narzetti & Marques, 2020). Minas Gerais has even higher sanitation coverage than many other Brazilian states (Ferreira et al., 2021). Despite this, the prevalence of schistosomiasis in Minas Gerais remains high, with some studies estimating prevalence in rural areas to be greater than 50% (Nacife et al., 2018; Zoni et al., 2016). Because WASH coverage is widely believed to lower the prevalence of schistosomiasis, it is likely that other factors are at play in Minas Gerais (J. E. T. Grimes et al., 2014).

Despite the prevalence of schistosomiasis in Brazil, surveillance and control strategies in the state have historically been incohesive (Drummond et al., 2010). A national action plan to address neglected tropical diseases, including schistosomiasis, was enacted in 2011 that aimed to eliminate schistosomiasis as a public health problem by 2015 (Ministério da Saúde, 2012a). However, a 2016 study found that the number of disability-adjusted life years (DALYs) attributed to schistosomiasis did not significantly decrease during the time period specified in the action plan (Martins-Melo et al., 2018).

We hypothesized that lack of knowledge or awareness of schistosomiasis may impact the prevalence in Minas Gerais. This study aimed to investigate the gap between self-reported history of schistosomiasis infection and seroreactivity for schistosomiasis to assess the potential benefits of educational programs. The purpose of this study was to determine what, if any, demographic factors may influence awareness of the disease.

Methods

Study Site and Population

The data used in this study was collected between June 2016 and December 2018 as part of a case control study by Dennison et al. analyzing leprosy and helminth co-infections in Minas Gerais (Dennison et al., 2021). Individuals at least three years old were recruited for the study investigating the prevalence of schistosomiasis in leprosy cases and controls in an endemic area of Minas Gerais; pregnant women were excluded. The study was conducted in the municipalities of Governador Valadares and Mantena; participants were recruited from a clinic in Governador Valadares and from surrounding rural communities. The present study uses a post-hoc approach to identify factors associated with schistosomiasis in this study sample.

Schistosomiasis was evaluated by both Kato Katz stool examination and by seroreactivity, with the understanding that seroreactivity would include both current and past infections (Katz & Chaia, 1968). Antibodies (IgG) to soluble egg antigen (SEA) were identified via multiplexed beaded assay serum test at the Centers for Disease Control (CDC), methods as previously described (Cooley et al., 2016). Additionally, a survey was conducted to collect information on participants' socioeconomic status and sociocultural characteristics. WASH variables of interest included participants' water source, sewage system, and treatment of household water, as well as whether participants reported participating in activities in fresh water. Demographic variables of interest included age, sex, race, location of household (either urban or rural), completed education, and marital status. Variables related to socioeconomic status included occupation, whether the participant was considered below or above minimum wage, and the participants' monthly income.

Data Analysis

Post-hoc analyses were conducted using antibody reactivity to SEA to designate history or current presence of schistosomiasis. Descriptive statistics using t-tests and chi-square tests were conducted as appropriate to compare schistosomiasis negative and schistosomiasis positive respondents to the variables of interest. Tables were generated to compare schistosomiasis infection status against the available demographic variables, socioeconomic variables, and WASH variables of interest. Additional tables were constructed to show the number of respondents who self-reported a history of parasitic infections and what type of parasite they reported having.

Three logistic regression analyses were completed. The first model compared schistosomiasis infection status with WASH variables of interest. The second model compared respondents with an unknown schistosomiasis infection to the demographic variables. Unknown infection was determined by combining those who self-reported no previous history of parasites with those who tested positive for schistosomiasis; i.e., these were individuals who were not aware of a current or past schistosoma infection. Lastly, a model was created to compare participants who self-reported a history of schistosomiasis and tested positive via an anti-SEA antibody test to the demographic variables. To complete this analysis, a new binary variable was created that combined participants who self-reported a history of schistosomiasis with those who tested positive with the antibody test. Participants who both self-reported a history of schistosomiasis and tested positive for schistosomiasis were referred classified as a 1. Participants who either did not self-report a history of schistosomiasis but tested positive or who did self-report a history but tested negative were classified as a 0. Participants who both did not self-report a history of disease and tested negative were excluded from the model.

Logistic regression was used for all three models. Dummy variables were created for each analysis, and factor variables were tested against a specified reference level. Reference levels for variables with more than two levels are defined alongside each model. Final models were presented with odds ratios, associated 95% confidence intervals, and p-values. P-values ≤ 0.05 were considered significant. All analyses were completed with RStudio.

Data Mapping

Data on schistosomiasis cases reported in 2017 were obtained from the Brazilian Ministry of Health (Ministério da Saúde, 2012a). All data was collected at the municipality level within Minas Gerais. Of the 890 municipalities in Minas Gerais, schistosomiasis cases were reported in 184. Cases were mapped by municipality with ArcGIS (v10.8.1) using a publicly available shapefile of Minas Gerais from the Brazilian Institute of Geography and Statistics (n.d.). Counts of cases per municipality were calculated within ArcGIS and displayed as a choropleth map.

Results

In total, 256 participants between the ages of 5 and 85 were recruited. Of these, 155 tested negative for schistosomiasis via a multiplexed beaded assay serum test identifying IgG response to SEA and 66 tested positive. The remaining 35 participants did not provide a serum sample. Stool examinations were collected from 241 participants; of these, 16 (6.6%) tested positive for schistosomiasis using the Kato-Katz technique.

The primary goal of the analysis was three-pronged. First, we aimed to confirm that lack of access to safe water and sanitation did not fully account for the prevalence of schistosomiasis in Minas Gerais. Second, we aimed to determine what demographic factors contributed to lack of awareness of schistosomiasis infection. Third, we aimed to identify factors that may be associated with a lack of general understanding of schistosomiasis. In sum, the findings of these analyses may be able to inform future control strategies.

Descriptive Statistics

Table 1 shows a comparison of SEA positive and negative participants to the demographic variables of interest. Based on descriptive statistics alone, schistosomiasis negative and positive participants seemed to be similar in age. More males than females were positive (51.7% versus 48.3%, respectively), though this difference was not significant at $p \leq 0.05$. The majority of participants in the study identified as mixed race (56.2%) or white (24.3%). Differences in schistosomiasis infection status by race were not significant ($p = 0.441$). As expected, significantly more respondents living in rural areas tested positive for schistosomiasis compared to those living in urban areas (68.3% versus 31.7%, $p = 0.006$). Education was also significantly associated with infection status ($p = 0.005$); infection status appeared to vary based on level of education. Most of the study participants reported being single (33.5%) or married (55.7%). Marital status was not significantly associated with infection status (p = 0.575).

Table 1: Demographic characteristics of participants and their schistosomiasis infection status. 185 of the original 221 observations were included after assessing for missingness of the descriptive variables.

Demographic Variables and Schistosomiasis Infection Status					
Variable	**Level**	**Total**	**SEA Negative**	**SEA Positive**	**p-value**
n		185	125	60	
Age (mean (SD))		40.57 (20.54)	41.33 (20.80)	39.00 (20.08)	0.472
Sex (%)	F	95 (51.4)	66 (52.8)	29 (48.3)	0.68
	M	90 (48.6)	59 (47.2)	31 (51.7)	
Race (%)	White	45 (24.3)	29 (23.2)	16 (26.7)	0.441
	Black	33 (17.8)	20 (16.0)	13 (21.7)	
	Asian	3 (1.6)	3 (2.4)	0 (0.0)	
	Mixed	104 (56.2)	73 (58.4)	31 (51.7)	
Education (%)	High School	10 (5.4)	3 (2.4)	7 (11.7)	0.005
	Middle School	32 (17.3)	27 (21.6)	5 (8.3)	
	Elementary School	122 (65.9)	78 (62.4)	44 (73.3)	
	No Schooling	21 (11.4)	17 (13.6)	4 (6.7)	
Residence Type (%)	Rural	98 (53.0)	57 (45.6)	41 (68.3)	0.006
	Urban	87 (47.0)	68 (54.4)	19 (31.7)	
Marital Status (%)	Single	62 (33.5)	43 (34.4)	19 (31.7)	0.575
	Married	103 (55.7)	70 (56.0)	33 (55.0)	
	Divorced	12 (6.5)	6 (4.8)	6 (10.0)	
	Widowed	8 (4.3)	6 (4.8)	2 (3.3)	

Table 2 shows a comparison of schistosomiasis positive and negative participants to demographic variables related to occupation and socioeconomic status (SES). Infection status was relatively similar across participant occupations, though those who reported being businesspeople were more likely to test positive for schistosomiasis (23.4% tested positive while 9.3% tested negative). However, this association was not significant (p = 0.056). Significant differences in infection status were not observed based on participant income level (p = 0.345) or SES (p = 0.647).

Table 2: Socioeconomic characteristics of participants and their schistosomiasis infection status. 214 of the original 221 observations were included after assessing for missingness of the descriptive variables.

Socioeconomic Variables and Schistosomiasis Infection Status					
Variable	**Level**	**Total**	**SEA Negative**	**SEA Positive**	**p-value**
n		214	150	64	
Occupation (%)	Hourly worker	18 (8.4)	16 (10.7)	2 (3.1)	0.056
	Agriculture	35 (16.4)	24 (16.0)	11 (17.2)	
	Domestic	24 (11.2)	17 (11.3)	7 (10.9)	
	Student	38 (17.8)	24 (16.0)	14 (21.9)	
	Businessperson	29 (13.6)	14 (9.3)	15 (23.4)	
	Retired	35 (16.4)	26 (17.3)	9 (14.1)	
	Does not work	14 (6.5)	11 (7.3)	3 (4.7)	
	Other	21 (9.8)	18 (12.0)	3 (4.7)	
Monthly Income (%)	1 to 3 times minimum wage	77 (36.0)	52 (34.7)	25 (39.1)	0.345
	3 to 5 times minimum wage	127 (59.3)	89 (59.3)	38 (59.4)	
	>5 times minimum wage	10 (4.7)	9 (6.0)	1 (1.6)	
Socioeconomic Status (%)	> Minimum wage	137 (64.0)	98 (65.3)	39 (60.9)	0.647
	< Minimum wage	77 (36.0)	52 (34.7)	25 (39.1)	

Table 3 compares participant infection status to WASH variables of interest. The majority of participants reported having access to improved sanitation systems, with 70.4% reporting having access to a piped sewer system. Of the remaining participants, 25.4% reported having access to a latrine, 3.3% had sewage without plumbing, and 0.9% had no sewer system. Schistosomiasis infection status was significantly associated with the type of sanitation system a participant had (p = 0.006). More participants with plumbing were schistosomiasis negative, while more participants with a latrine were schistosomiasis positive. Similarly, most participants reported having access to running water, with 67.6% reporting using piped water and 27.2% reporting using well water. Only 0.9% of participants reported using a stream as their primary water source. The difference between infection status based on water source was not significant (p = 0.412). Water treatment was also not significantly associated with infection status (p = 0.988). Because so few participants utilize unimproved WASH services, it is difficult to compare infection status between those with improved versus unimproved water and sanitation. The most important WASH variable seemed to be reported water activities. About 38.5% of schistosomiasis positive respondents reported participating in water activities, while only 18.2% of schistosomiasis negative respondents reported participating in water activities (p = 0.003).

Table 3: Participants' access to WASH services and their infection status. 213 of the original 221 observations were included after assessing for missingness of the descriptive variables.

WASH Variables and Schistosomiasis Infection Status					
Variable	**Level**	**Total**	**SEA Negative**	**SEA Positive**	**p-value**
n		213	148	65	
Sewer System (%)	Piped sewer	150 (70.4)	114 (77.0)	36 (55.4)	0.006
	Sewer without plumbing	7 (3.3)	4 (2.7)	3 (4.6)	
	No sewer system	2 (0.9)	2 (1.4)	0 (0.0)	
	Latrine	54 (25.4)	28 (18.9)	26 (40.0)	
Water Source (%)	Piped	144 (67.6)	105 (70.9)	39 (60.0)	0.412
	Stream	2 (0.9)	1 (0.7)	1 (1.5)	
	Well	58 (27.2)	37 (25.0)	21 (32.3)	
	Other	9 (4.2)	5 (3.4)	4 (6.2)	
Water Treated (%)	No	126 (59.2)	87 (58.8)	39 (60.0)	0.988
	Yes	87 (40.8)	61 (41.2)	26 (40.0)	
Activities in Water (%)	No	161 (75.6)	121 (81.8)	40 (61.5)	0.003
	Yes	52 (24.4)	27 (18.2)	25 (38.5)	

Self-Reported Schistosomiasis Infection

All participants were asked if they had a history of parasitic infections. Regardless of self-reported parasite history, a multiplexed beaded assay serum test identifying IgG response to SEA was used to confirm schistosomiasis infection. Table 4 shows the number of participants who self-reported a history of schistosomiasis versus the number of participants who actually tested positive for schistosomiasis.

Table 4: The number of study participants who self-reported a history of schistosomiasis versus the number who tested positive via a SEA test.

	SEA Negative (N=155)	SEA Positive (N=66)	Total (N=256)
Self-Reported History of Schistosomiasis			
No Reported Schistosomiasis	108 (70.1%)	38 (57.6%)	171 (67.3%)
Reported Schistosomiasis	46 (29.9%)	28 (42.4%)	83 (32.7%)

Of the 256 study participants, 168 self-reported a history of parasitic infection. The majority of these participants reported having either roundworm or schistosomiasis. Tables 5 and 6 summarize the self-reported parasite history of the study participants.

Table 5: First possible parasite self-reported by participants.

Characteristic	N = 256[1]
Self-Reported History of Parasite	168 (69%)
Missing	11
Possible Parasite 1	
Roundworm	75 (30%)
Schistosomiasis	61 (24%)
Hookworm	1 (0.4%)
Tapeworm	3 (1.2%)
Pinworm	5 (2.0%)
Giardia	5 (2.0%)
Amoeba	4 (1.6%)
Other	1 (0.4%)
Not Applicable	82 (32%)
No Response	17 (6.7%)
Missing	2

[1] n (%)

Table 6: Second possible parasite self-reported by participants.

Characteristic	N = 256[1]
Self-Reported History of Parasite	168 (69%)
Missing	11
Possible Parasite 2	
Roundworm	0 (0%)
Schistosomiasis	23 (9.1%)
Hookworm	2 (0.8%)
Tapeworm	3 (1.2%)
Pinworm	16 (6.3%)
Giardia	13 (5.1%)
Amoeba	3 (1.2%)
Other	5 (2.0%)
Not Applicable	171 (67%)
No Response	18 (7.1%)
Missing	2

[1] n (%)

Multivariable Analysis

The first multivariable model compared schistosomiasis infection status with all WASH variables considered risk factors for schistosomiasis, along with age and sex. Because only six covariates were considered in the model, the full model is presented here rather than a reduced model. Reference levels used were female sex for the sex variable; piped water for the water source variable; and piped sewage for the sewer system variable. Of the six covariables, only two were found to be significant. Respondents who reported using a latrine had increased odds of schistosomiasis infection (OR = 4.38 p = 0.006), as did respondents who reported participating in fresh water activities (OR = 2.68, p = 0.005). Water activities reported by participants included swimming; fishing; wading; and unspecified leisure activities. Results of the first model are shown in Table 7.

Table 7: Multivariate Model 1, with positive SEA test as the intercept and WASH factors as predictors.

	Multivariable Model 1: WASH Factors		
Predictors	*Odds Ratios*	*95% CIs*	*p-values*
Intercept	0.25	0.10 – 0.56	**0.001**
Age	1.00	0.98 – 1.01	0.655
Sex: Male	1.16	0.62 – 2.19	0.644
Water Source: Stream	1.19	0.03 – 47.24	0.921
Water Source: Well	0.62	0.21 – 1.65	0.361
Water Source: Other	0.61	0.11 – 3.31	0.573
Water is Treated	1.19	0.61 – 2.30	0.606
Sewer System: Sewage Without Plumbing	3.23	0.53 – 18.29	0.180
Sewer System: Latrine	4.38	1.59 – 13.19	**0.006**
Does Activities in Water	2.68	1.34 – 5.37	**0.005**
Observations	211		
R^2 Tjur	0.104		

The second model compared study participants who reported no history of parasites but tested positive for schistosomiasis to the remaining participants (those who tested negative and reported no history, those who tested positive but were aware of the history, and those that reported a history but tested negative). In the full model, education, occupation, and monthly income were not significant at $p < 0.05$ and also introduced error into the model due to small observations. These variables were subsequently removed. Results of the reduced model are shown in Table 8. Unmarried status was used as a reference level for the marital status variable. Of all of the demographic variables, only age and marital status were considered significant. Unknown schistosomiasis infection seemed to be associated with being married (OR = 7.84, p = 0.015) and previously married (OR = 31.85, p = 0.003). The designation of previously married included all participants who reported being widowed or divorced. A boxplot was created to further assess the relationship between age and unknown schistosomiasis infection.

Table 8: Multivariable Model 2, with unknown schistosomiasis infection as the intercept and demographic variables as predictors.

	Multivariable Model 2: Unknown Schistosomiasis Infection		
Predictors	*Odds Ratios*	*95% CIs*	*p-values*
Intercept	0.27	0.05 – 1.23	0.105
Age	0.94	0.90 – 0.98	**0.009**
Sex: Male	1.15	0.41 – 3.29	0.785
Residence Type: Urban	0.53	0.16 – 1.54	0.255
Marital Status: Married	6.15	1.21 – 35.17	**0.033**
Marital Status: Previously Married	31.85	3.52 – 329.66	**0.003**
SES: < Minimum Wage	0.64	0.20 – 1.90	0.440
Observations	197		
R^2 Tjur	0.066		

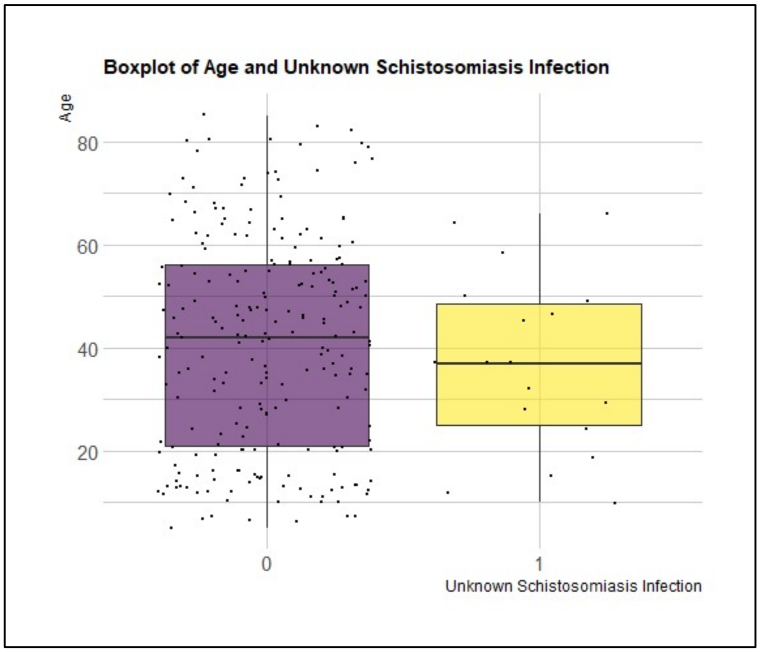


Figure 4: Boxplot of Age and Unknown Schistosomiasis Infection, where 1 indicates participants who self-reported no history of schistosomiasis but tested positive and 0 indicates participants who either self-reported no history and tested negative; self-reported a history and tested positive; or self-reported a history and tested negative.

The third multivariable model aimed to determine what demographic factors contribute to awareness of schistosomiasis infection. Awareness of infection was defined as self-reporting a history of schistosomiasis and testing positive for schistosomiasis via anti-SEA test. Lack of awareness was defined as either self-reporting a history of schistosomiasis and testing negative for schistosomiasis or self-reporting no history of schistosomiasis and testing positive. Participants who both did not self-report a history of schistosomiasis and tested negative were excluded.

In the full model, occupation and monthly income were not significant at $p < 0.05$ and introduced error into the model; these variables were removed. The reduced model used high school education or higher as the reference for the education variable and unmarried status as the reference for the marital status variable. Results of the reduced model are shown in Table 9. Of all of the demographic variables, only urban residence, middle school education, and elementary school education were significant at $p < 0.05$. Awareness of schistosomiasis infection seemed to be negatively associated with urban residence type (OR = 0.17, p = 0.027), as well as with education. Participants who had only completed middle school were less likely to be aware of their infection (OR = 0.05, p = 0.028), as were those who had only completed elementary school (OR = 0.07, p = 0.006).

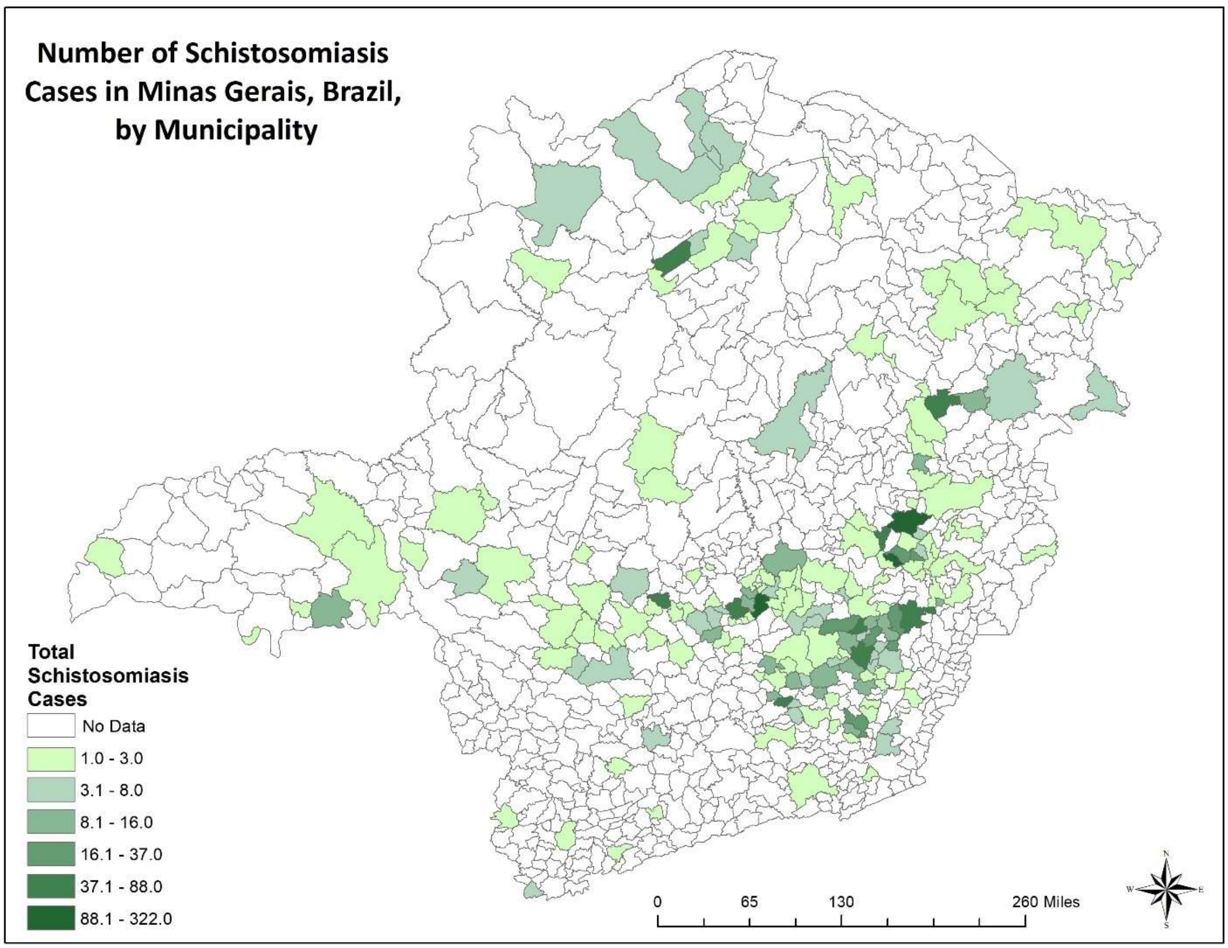
Table 9: Multivariable Model 3, showing awareness of schistosomiasis infection and the demographic variables of interest.

	Multivariable Model 3: Awareness of Infection		
Predictors	*Odds Ratios*	*95% CIs*	*p-values*
Intercept	3.97	0.39 – 50.27	0.259
Age	0.98	0.93 – 1.03	0.414
Sex: Male	2.82	0.90 – 9.67	0.083
Race: Non-White	1.30	0.32 – 5.93	0.720
Residence Type: Urban	0.17	0.03 – 0.70	**0.027**
Education: Middle School	0.05	0.00 – 0.56	**0.028**
Education: Elementary School	0.07	0.01 – 0.42	**0.006**
Education: No Schooling	0.33	0.02 – 4.00	0.390
Marital Status: Married	0.72	0.10 – 5.26	0.746
Marital Status: Previously Married	1.94	0.15 – 26.55	0.610
SES: < Minimum Wage	2.17	0.57 – 8.72	0.260
Observations	104		
R^2 Tjur	0.253		

Data Mapping

The GIS study showed cases spread across the state of Minas Gerais, with a concentration of cases in the southeastern region of Minas Gerais. The municipality with the highest reported schistosomiasis cases was Ipatinga, with 322 cases. Most municipalities had a relatively low case count; the mean number of cases per municipality was 11, with a standard deviation of 32.88. In total, 1,937 cases were reported throughout the state. Results of the GIS study are shown in Figure 6.

Figure 5: Map of schistosomiasis cases in Minas Gerais by municipality.



Discussion

It is widely accepted that WASH factors, especially sanitation infrastructure and water source, are important determinants of schistosomiasis prevalence (J. E. T. Grimes et al., 2014). A systematic review of literature studying increased sanitation as a control strategy for schistosomiasis found that the odds of *S. mansoni* infection in Brazil significantly decreased as sanitation improved (overall OR = 0.79) (J. E. Grimes et al., 2015). As expected, our analyses showed that participating in water activities increased odds of schistosomiasis infection. Participants who tested positive for schistosomiasis were 2.68 times more likely to participate in water activities compared to participants who tested negative for schistosomiasis. Likewise, schistosomiasis positive participants were 4.38 times more likely to use a latrine (as opposed to a toilet with plumbing) than schistosomiasis negative participants. While a sewer system without plumbing was also associated with schistosomiasis infection, this result was not significant at $p \leq 0.05$. This is likely because the sample of participants who reported using a sewage system without plumbing was very small; less than 3% of all participants reported using a sewer system without plumbing. This statistic also aligns with current knowledge that sanitation coverage in Minas Gerais is high (Ferreira et al., 2021). Water source and water treatment were not found to be significantly associated with schistosomiasis infection. This was expected, as schistosomiasis is acquired through direct contact with infected water and not through consumption of infected water. While the results of this analysis were in line with our expectations given current knowledge of schistosomiasis, the Tjur R^2 value of 0.1 suggests that this model has low explanatory power and other factors are likely at play.

Because Brazil has high WASH coverage this is overall likely not a major risk factor in endemic areas of Brazil. Therefore, we hypothesized that knowledge of schistosomiasis (or lack thereof) may influence the prevalence of schistosomiasis in Minas Gerais. Younger age seemed to be significantly associated with unknown schistosomiasis infection (defined as not reporting a history of schistosomiasis but testing positive). Interestingly, participants who were married, divorced, or widowed had higher odds of having an unknown schistosomiasis infection, with a relationship status of single as the reference level. These results are unusual, as a systematic review of schistosomiasis in sub-Saharan Africa found that married women had significantly higher knowledge of schistosomiasis compared to unmarried women (Sacolo et al., 2018). The association between unknown infection and marital status that we found here may be indicative of other underlying sociocultural factors that are currently unknown or a reflection of the small sample size of this study.

To further explore the hypothesis that knowledge of schistosomiasis affects prevalence, awareness of schistosomiasis infection was compared to the demographic variables of interest. Participants who were aware of a schistosomiasis infection had slightly lower odds of living in an urban area, with living in a rural area as a reference point ($OR = 0.17$, $p < 0.027$). This may be because schistosomiasis is more common in rural areas, so participants living in rural areas may have a greater awareness of the disease than participants in urban areas (Gazzinelli et al., 1998). There are local municipality health centers that may conduct programs for schistosomiasis education and surveillance. In fact, at one of the study sites, the lead nurse kept reports of annual schistosomiasis diagnoses in the catchment area. Additionally, participants who were aware of a schistosomiasis infection had lower odds of completing middle school, elementary school, or having no schooling, with completing high school as the reference point. These findings support our hypothesis, as we would expect those with higher educational attainment to have a greater understanding of schistosomiasis. Studies have shown that educational attainment can be utilized as a predictor for schistosomiasis infection, with higher educational attainment being associated with lower odds of schistosomiasis (Sacolo et al., 2018). While children were included in this study and may have a higher risk of schistosomiasis, and lower education attainment at the time of testing, age was not associated with the outcome in any of the models.

It is important to note that anti-SEA tests only give reliable test results for about three months after exposure to schistosomiasis (Sarhan et al., 2014). Thus, it is possible that participants who self-diagnosed a history of schistosomiasis and were treated could have tested negative in the infection was a long time prior. However, the Brazilian Ministry of Health currently focuses on early identification and treatment of disease, rather than mass drug administration (Cabello et al., 2016). Thus, infections that go undiagnosed are unlikely to be treated, and continued infection in endemic areas is likely. Further limitations include the post-hoc nature of the analysis and an overall small sample size which may have limited detection of significant findings.

It is also possible that sociocultural factors other than general knowledge or awareness of schistosomiasis are at play here. The availability of medical facilities or diagnostic tools for schistosomiasis may limit ability to receive an accurate diagnosis. Additionally, lack of physician awareness of schistosomiasis or its associated symptoms may inhibit being diagnosed. One study of utilization of schistosomiasis-related healthcare services in a rural area of Minas Gerais found that only about 40% of patients who reported schistosomiasis symptoms were asked to provide a stool sample (Reis et al., 2010).

Conclusions

Unlike in other schistosomiasis-endemic areas, WASH factors alone are less likely to play a major role in the prevalence within Minas Gerais, although we did find expected outcomes of water activities and latrine use associated with schistosomiasis. Based on subsequent models, it is possible that a lack of knowledge of schistosomiasis could contribute to the high prevalence in the region. Of the 66 participants who tested positive for schistosomiasis, 38 (nearly 58%) reported that they had never had schistosomiasis. It is also possible that lack of diagnostic tools, challenges accessing medical care, or lack of physician awareness of schistosomiasis could contribute to patients' unawareness of their infection.

Other findings support our hypothesis that lack of knowledge surrounding schistosomiasis may influence the prevalence of the disease. We expected higher educational attainment to correspond with awareness of infection, which does appear to be the case as demonstrated in Model 3. We also expected a higher prevalence of schistosomiasis in rural areas, which may explain why participants in urban areas have lower knowledge of schistosomiasis.

However, some results of our models were unexpected and remain unclear. Marital status, especially divorced and widowed status, appear to significantly impact participants' lack of knowledge around schistosomiasis infection, despite literature indicating that the opposite should be true (Sacolo et al., 2018). Overall, it is evident that further research is needed to explore the influence of sociocultural factors on schistosomiasis prevalence in Minas Gerais.

Chapter IV: Public Health Implications

Schistosomiasis remains a critical public health issue in Minas Gerais, Brazil. Many of the factors traditionally associated with schistosomiasis, namely poor sanitation infrastructure and lack of access to piped water, are not significant issues in Brazil (Ferreira et al., 2021; J. E. T. Grimes et al., 2014; Narzetti & Marques, 2020). Despite this, Brazil maintains the highest prevalence of schistosomiasis in the Americas and the Caribbean (World Health Organization, 2013).

Our findings suggest that lack of knowledge of schistosomiasis and ineffective screening and testing may contribute to increased prevalence in Minas Gerais. These findings would make sense within the context of Brazil, as there are currently no cohesive control strategies or educational programs specifically targeting schistosomiasis in the country (Drummond et al., 2010). Thus, increasing schistosomiasis-specific educational programming in the region may be a cost-effective solution. A 2018 study of schistosomiasis in sub-Saharan Africa found that health education was a critical component of schistosomiasis control programs and could positively impact participants' knowledge and behaviors surrounding risk factors for the disease (Sacolo et al., 2018). Likewise, additional schistosomiasis-specific health education targeted at healthcare providers may increase the likelihood of patients being tested for and accurately diagnosed with schistosomiasis.

Additionally, there appears to be underlying sociocultural factors that influence awareness of schistosomiasis. It remains unclear how these factors influence knowledge of the disease or what their overall impact may be. Additional research and exploration in this area may be beneficial to understanding the cultural and contextual factors that influence the prevalence of schistosomiasis in Minas Gerais.

Finally, it remains possible that environmental factors not accounted for in this study are critical components of disease in Minas Gerais. Schistosomiasis is inextricably linked to the environment, as the parasite relies on intermediate snail hosts to reproduce (Centers for Disease Control, 2019; Colley et al., 2014; Gryseels et al., 2006). Because schistosomiasis is more prevalent in Minas Gerais than in other Brazilian states, environmental studies comparing Minas Gerais to surrounding low-endemicity areas may provide key information to inform future control programs.

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