SOIL-TRANSMITTED HELMINTH INFECTIONS IN HONDURAS

SOIL-TRANSMITTED HELMINTH INFECTIONS IN HONDURAS:

MAPPING INFECTION PREVALENCE AND IMPLICATIONS FOR HEALTH CARE REGIONALIZATION

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ABSTRACT

Soil-transmitted helminth (STH) (*A. lumbricoides*, *T. trichiura* and hookworm) infections are a significant public health concern in Honduras. These infections are treatable using inexpensive anthelmintic medications, however long-term control and eradication will require large investments in public and private sanitation infrastructure. Importantly, both types of interventions are targeted towards high-risk populations and regions rather than individuals. The goal of this thesis is to contribute to improving the efficiency of soil-transmitted helminth control efforts in Honduras. In our first study, we use multiple regression analyses to identify determinants of STH infections and generate estimates of *A. lumbricoides*, *T. trichiura* and hookworm infection prevalence, as well as recommended deworming frequencies, for each of Honduras' 298 municipalities. Our estimates suggest that prevalence of all three infections has declined over time, however 75% of municipalities still require annual or semi-annual deworming. In our second study, we quantify how the type of region used for measuring prevalence and allocating resources can impact the success and efficiency of public health programs. More specifically, we compare administrative regions to alternative zoning schemes at the same geographic scale. Our findings suggest that regions designed to be homogeneous with respect to prevalence can be more efficient than existing municipalities (at the same scale) for distributing resources. This research has implications on future control efforts.

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CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

1.1.1 Introduction

Soil-transmitted helminths (STH), including *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm species' *Necator americanus* and *Ancylostoma duodenale*, are parasites that infect the gastrointestinal tract of human hosts. Such infections, collectively referred to as STH infections, affect an estimated two billion people worldwide (Savioli & Albonico, 2004; Montresor, 2002; Pullan, Smith, Jasrasaria & Brooker, 2014) and are endemic in low and middle-income countries with tropical and subtropical climates (Hotez et al., 2006; Sanchez et al., 2014). Case-fatality rates are low, however chronic infections can cause a number of serious metabolic problems including malnutrition and anemia, as well as physical and cognitive stunting (Bethony et al., 2006; Bundy & Cooper, 1996; Center for Disease Control, 2015; Center for Disease Control, 2013a; Center for Disease Control, 2013b; Eberhard, Cabrielli, Montresor & Savioli, 2015; Deming & Eberhard, 2015a; Deming & Eberhard 2015b). STH infections have also been associated with reductions in productivity, school attendance (de Silva et al., 2003; Miguel & Kremer, 2004), school performance (Hotez et al., 2008) and wage-earning capacity in adults (Bleakley, 2007; Reviewed in Guyatt, 2000).

1.1.2 Transmission

Humans acquire STH infections through contaminated soil, either by ingesting infectious eggs (*A. lumbricoides*, *T. trichiura*) or via direct skin contact with mature larvae (hookworm). Immature larvae of these species then migrate throughout the host's body before developing into sexually mature adults within the intestine (CDC 2015; CDC, 2013a; CDC, 2013b; Deming & Eberhard, 2015a; Deming & Eberhard, 2015b; Eberhard et al., 2015). Once in the gastrointestinal tract, female parasites are fertilized and begin producing eggs, which are subsequently shed through feces. Fertilized eggs mature into infectious ova (*A. lumbricoides* and *T. trichiura*) or larvae (hookworm) after incubating in warm, moist and shaded soil for a period of time, ranging from days to weeks depending on the species. As a result, STH infections cannot be directly communicated between hosts or from fresh feces. Rather, *Ascaris lumbricoides* and *Trichuris trichiura* infection occur via ingestion of their respective embryonated eggs, while hookworm eggs hatch in the external environment, releasing motile larvae that, upon maturation, can actively penetrate the skin (CDC 2015; CDC, 2013a; CDC, 2013b; Deming & Eberhard, 2015a; Deming & Eberhard, 2015b; Eberhard et al., 2015). Thus, transmission of these parasites is highly dependent on a number of environmental and behavioural factors that influence (i) parasite survival, (ii) the degree to which the environment is contaminated with infectious stages, and (iii) the amount of contact between human hosts and polluted soil.

1.1.3 Treatment

STH infections are treatable with oral administration of antiparasitic drugs such as albendazole and mebendazole, which are inexpensive, have few side effects and can be administered *en masse* by trained community members (Pan American Health Organization, 2011). These medications are an important tool for the short-term control of STH infections, and rather than attempting to diagnosis individual cases, mass drug administration (MDA) is typically targeted towards groups of people at elevated risk of infection, or geographic regions where risk of infection is high. This strategy is recommended for keeping the worm burden below levels associated with disease, reducing individual morbidity and mortality and, in doing so, improving large-scale economic productivity and the success of other public health programs (e.g., feeding and nutritional programs) (PAHO, 2011). Although it would be financially feasible to treat whole populations, a targeted approach is preferred due to growing fears of drug-resistance developing in these parasites.

Despite the many benefits of deworming interventions, there are some important limitations. In particular, deworming medications have limited efficacy against both hookworm and *T. trichiura* species (Horton, 2000; Adams, Lombard, Dhansay, Markus & Fincham, 2004; Albonico et al., 1994; Levecke et al., 2014); although single-dose albendazole is highly effective in curing ascariasis (95% mean cure rate, 67 studies), treatment resolves fewer than half of *T. trichiura* infections (47% mean cure rate, 56 studies) (Horton, 2000; Bennett & Guyatt, 2000). Additionally, deworming does nothing to combat existing contamination; the soil remains an active reservoir of infection for as long as eggs and larvae survive in the environment, which can be months or years if conditions remain favourable (CDC, 2015; Deming & Eberhard, 2015). Thus, while MDA is relatively effective and economical (Utzinger & Keiser, 2004), anthelmintic drugs only reduce transmission temporarily (Campbell et al., 2014). Reinfection rates are high, and both prevalence and infection intensity rapidly rebound to pre-treatment levels (Jia et al., 2012; Campbell et al., 2014; Karagiannis-Voules et al., 2015). As a result, World Health Organization guidelines recommend yearly and twice-yearly treatment in regions with prevalence rates between 20 and 50% and exceeding 50%, respectively (World Health Organization, 2006). Regular deworming is important to combat high reinfection rates and maintain the worm burden below levels associated with disease.

In the long-term, sustainable control and eventual elimination of these infections will require significant poverty reduction and, importantly, large investments in public and private sanitation infrastructure.

1.2 RESEARCH OBJECTIVES

1.2.1 Research Questions

Much of the existing research in this field has sought to identify or improve our understanding of the determinants associated with STH infections. Importantly, elucidating these risk factors allows policymakers to better identify and target at-risk populations, but also enables the creation of public health programs designed to alter high-risk behaviours and/or environments.

Another important objective of these investigations has been mapping the distribution and prevalence of infection at different geographic scales. For example, microbiological and laboratory analyses have measured infection prevalence in schools, communities and municipalities, and researchers in epidemiology and geography have compiled this data to map and model prevalence at increasingly larger scales. Importantly, this collaboration allows us to predict prevalence in areas where it has not yet been measured, identify priority areas for resource allocation and recommend how often deworming should be administered for each region.

Less attention has been paid to other important research questions, including the role of treatment accessibility in explaining the distribution and relative magnitude of infection prevalence, as well as the implications of using different sets of regions on the efficiency of public health interventions These questions represent an important gap in knowledge that we aim to address in this thesis.

In this study, we model municipal *A. lumbricoides, T. trichiura* and hookworm infection prevalence in Honduras, identify associated risk factors specific to the study region, and attempt to determine the role of accessibility to treatment in explaining STH prevalence distribution. We then quantify how the *type* of region used for allocating resources can impact the success and efficiency of public health programs. More specifically, we compare existing administration regions such as municipalities to alternative zoning schemes at the same geographic scale.

1.2.2. Study Site

The Republic of Honduras ("Honduras") was chosen as the setting for this research. Like most of Latin America, Honduras is characterized by large disparities in income, consumption levels, access to education, land, basic services, and other socioeconomic variables (Gasparini, Cruces & Tornarolli, 2011). There is great regional variability in climate throughout Honduras, however the entire country lies within the tropics and experiences adequate precipitation and warmth for free-living STH ova and larvae to mature to infectivity. As a result, the natural, built and social environments in Honduras are optimal for the survival, maturation and transmission of *A. lumbricoides*, *T. trichiura* and hookworm species.

Nearly one hundred independent studies and surveys conducted between 2001 and 2012 have established prevalence estimates throughout the country, however few efforts have sought to explain the geographic variability in infection rates. These isolated reports demonstrate that STH infections are endemic in Honduras, however a deeper and more complete understanding of the risk factors associated with infection, as well as the distribution and magnitude of infection prevalence throughout the country would have important benefits for both individual and public health in Honduras.

1.3 CHAPTER OUTLINE

1.3.1 Summary

This thesis includes four chapters. The introductory chapter (Chapter 1) provides context for the remainder of the manuscript and outlines the purpose of each subsequent chapter. The body of the research is then presented in Chapters 2 and 3, which are formatted as independent papers that seek to answer different, but related, research questions. Finally, Chapter 4 summarizes the results of these investigations and discusses policy implications and recommendations related to their respective findings.

1.3.2 Chapter Two

In Chapter 2, we use multiple linear regression analysis to (i) identify risk factors associated with soil-transmitted helminth infection prevalence in Honduran municipalities and (ii) predict infection burden in areas where it has not been measured previously. We map these prevalence estimates and the recommended deworming frequency for each municipality, as informed by prevalence rates and World Health Organization (WHO) guidelines. Finally, we comment on the estimated distribution of infection, including how it appears to have changed over time, and make recommendations for future researchers.

1.3.3 Chapter Three

In Chapter 3, we compare the relative efficiency of allocating resources using different regionalization schemes. We start by aggregating small-scale prevalence rates (as estimated using models created in Chapter 2) into twenty different sets of regions at a similar geographic scale. In each case, an optimization algorithm aggregates smaller scale "zones" into the same number of regions as there are mainland municipalities in Honduras. Regions are delineated to minimize within-region variability in prevalence and maintain relatively compact shapes, subject to minimum and maximum population constraints. We then measure the efficiency of distributing resources to existing municipalities versus the best alternative regionalization scheme and determine what, if any, benefits are associated with using this scheme to measure/predict prevalence and allocate resources. We comment on our findings and discuss future applications for this work.

1.3.4 Chapter Four

Chapter 4 reiterates the primary findings of both Chapters 2 and 3 and reflects upon the implications of these results on public health policy in Honduras.

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CHAPTER TWO: PREDICTIVE MODELS OF SOIL-TRANSMITTED HELMINTH INFECTION PREVALENCE IN HONDURAS

2.1 INTRODUCTION

2.1.1 Background

Soil-transmitted helminth (STH) species *Ascaris lumbricoides, Trichuris trichiura* and hookworm (*Necator americanus* and *Ancylostoma duodenale)* represent a significant public health concern in low and middle income countries with tropical and subtropical climates. These nematodes infect an estimated 2 billion people worldwide (Montresor, 2002; Savioli & Albonico, 2004; Pullan, Smith, Jasrasaria & Brooker, 2014) and produce a burden of disease exceeding that of malaria and tuberculosis (Hotez, Bottazzi, Franco-Paredes, Ault & Periago, 2008a). Although severe infections can cause death, case fatality rates are low (less than 0.08% (Montresor, 2002)) and acute clinical effects (i.e. intestinal obstruction, gastrointestinal perforation and rectal prolapse) are relatively rare; of those infected, it is estimated that less than 1% are at risk of these complications (de Silva, Chan & Bundy, 1997). Rather, it is the metabolic consequences associated with chronic infections, including malnutrition and anemia, as well as the resulting physical and cognitive stunting that pose the greatest threat to human health and the economic success of afflicted populations (Guyatt, 2000).

Immature larvae of these nematodes species first migrate throughout the host's body before developing into sexually mature adults within the intestine. Female parasites are then fertilized and begin producing eggs, which are then expelled from the host's body in feces. Though initially innocuous, fertilized eggs mature into infectious ova (*A. lumbricoides* and *T. trichiura*) or larvae (hookworm) after incubating in warm, moist and shaded soil for a period of time, ranging from days to weeks depending on the species of parasite (Center for Disease Control, 2015; Center for Disease Control, 2013a; Center for Disease Control, 2013b). As a result, STH infections cannot be directly communicated between hosts or from fresh feces.

Infection with *Ascaris lumbricoides* and *Trichuris trichiura* are caused by ingestion of their respective embryonated eggs, while hookworm eggs hatch in the external environment, releasing motile larvae that can actively penetrate the skin (CDC, 2015; CDC, 2013a; CDC, 2013b). The unique transmission dynamics of hookworm compared to the other STH species has important implications for their relative determinants, risk factors and resulting geographic distribution.

Importantly, STH infections can be treated using anthelmintic drugs (e.g. albendazole), which are inexpensive and effective, particularly against *A. lumbricoides* (Horton, 2000; Bennett & Guyatt, 2000; Adams, Lombard, Dhansay, Markus & Fincham, 2004; Albonico et al., 1994; Levecke et al., 2014). These medications are an important tool for short-term control of STH infections; regular treatment keeps the worm burden below levels associated with disease, reduces individual morbidity and mortality and, in doing so, improves large-scale economic productivity and the success of other public health programs (e.g. feeding and nutritional programs) (Pan American Health Organization, 2011).

Due to the low cost of treatment and relatively high cost of diagnosis, interventions tend to be targeted towards groups of people thought to be at elevated risk of infection, or geographic regions where risk of infection is high, rather than specific individuals who have tested positive for infection or whole populations. Although it would be financially feasible to treat whole populations, a targeted approach is preferred due to growing fears of drug-resistance developing in these parasites (as observed in livestock-infecting nematodes) (Bethony et al., 2006; Albonico, 2003; Albonico, Engels & Savioli, 2003; Geerts, Coles & Gryseels, 1997; Jackson & Coop, 2000; Humphries et al., 2011; Humphries, Nguyen, Boakye, Wilson & Cappello, 2012; Vercruysse et al., 2011; World Health Organization, 2011). Additionally, re-infection rates are high, necessitating regular deworming (Jia et al., 2012; Campbell et al., 2014; Karagiannis-Voules et al., 2015).

2.1.2 Objectives and Rationale

The World Health Organization (WHO) currently advocates for regular deworming of pre-school and school-aged children through vaccination programs or school-based interventions. More specifically, these guidelines recommend annual and twice annual mass drug administration (MDA) when prevalence amongst these populations exceeds 20% and 50%, respectively (WHO, 2011; Bundy, Kremer, Bleakley, Jukes & Miguel, 2009). However, establishing baseline prevalence rates at the school or municipality level requires collecting a large number of stool samples and conducting timely laboratory analysis, which is prohibitively time-consuming and expensive, particularly in the resource-poor regions most vulnerable to infection. Despite these challenges, many researchers have conducted isolated investigations to establish STH prevalence rates of small-scale study sites. These prevalence estimates have then been used to develop predictive models that can generate location-specific estimates of prevalence. This approach can then be used to predict prevalence in areas where infection burden has never been measured, and also forecast how prevalence may respond to changing social, built and natural environments.

The primary objective of this chapter is to model and generate small-scale predictions of ascariasis, trichuriasis and hookworm infection prevalence in Honduras. This will enable us to determine the risk factors associated with infection, identify the regions where prevalence is highest and provide recommendations on where treatment should be targeted. A secondary aim of this work is to assess the role of accessibility to treatment as a correlate of infection prevalence.

2.2 METHODS

2.2.1 Study Area

The Republic of Honduras ("Honduras") is a Central American country bordered by Guatemala to the west, El Salvador to the southwest, and Nicaragua to the southeast. It is also flanked by the Gulf of Honduras, a large inlet of the Caribbean Sea, to the north, and the Gulf of Fonseca of the Pacific Ocean to the south.

Honduras is divided into 18 departments, 298 municipalities and contains three topological zones: an extensive and rugged mountainous interior representing about 80% of the total land area, and two narrow lowland regions along the coastlines (Humanitarian Data Exchange, 2017; Merrill, 1995). Although the entire country lies within the tropics, there is great regional variability in climate; conditions tend to be temperate in the interior highlands, hot and humid in the lowlands and temperature is closely, and negatively, correlated with elevation (Merrill, 1995; Clegern, Moncada & Woodward, 2016). Precipitation also varies regionally; the lowlands along the northern coastline have rainfall distributed fairly evenly throughout the year, while the interior and Pacific lowlands experience distinct wet and dry seasons (Merrill, 1995; Clegern et al., 2016).

Honduras is home to approximately 9 million people, the majority of whom live in the western part of the interior highlands and Caribbean lowlands (The World Bank, 2016; Clegern et al., 2016). The eastern region of the country is sparsely settled, largely due to La Mosquitia, a large undeveloped lowland jungle in the northeast.

Like most of Latin America, Honduras is characterized by large disparities in income, consumption levels, access to education, land, basic services, and other socioeconomic variables (Gasparini, Cruces & Tornarolli, 2011). In fact, Honduras has the highest income inequality in the region, with a GINI coefficient of 50.64, compared to 48.66, 41.84, and 47.05 in the neighbouring countries of Guatemala, El Salvador and Nicaragua, respectively (The World Bank, 2014). Within Honduras, poverty rates are generally lowest in the north and central regions, where the majority of industry and infrastructure is concentrated, and highest in the south, west, along the eastern border and among rural and indigenous populations (Gasparini, Cruces & Tornarolli, 2011).

The Honduran people suffer from high rates of malnutrition and infant and child mortality as well as several neglected tropical diseases (NTDs) including ascariasis, trichuriasis and to a lesser degree, hookworm (Merrill, 1995; Sanchez et al., 2014;

Sanchez et al., 2016). These infections are intimately related to poverty and are associated with reduced productivity, school attendance (de Silva et al., 2003; Miguel & Kremer, 2004), school performance (Hotez et al., 2008a) and wage-earning capacity in adults (Bleakley, 2007; Reviewed in Guyatt, 2000), as well as physical and cognitive stunting (Bethony et al., 2006). This likely contributes to the maintenance of poverty and reduced economic development observed in Honduras.

Prevalence data from nearly one hundred independent studies and surveys suggests that infection risk varies significantly between Honduran communities (Sanchez et al., 2014). At the municipality level, prevalence of ascariasis, trichuriasis and hookworm range between 0-74.4%, 1.7-91.1% and 0-42.2%, respectively, however this geographic variability has yet to be explained.

2.2.2 Study Design

This paper employs an ecological study design conducted at the municipality level. Linear, robust and logistic regression analyses were run (where appropriate) to model prevalence of ascariasis, trichuriasis and hookworm infection using data from 64 Honduran municipalities. These models were then used to generate predictions of infection prevalence for all 298 municipalities.

2.2.3 Data Collection

2.2.3.1 Dependent Variables: Prevalence.

Infection prevalence (represented as a proportion between 0 and 1) for ascariasis, trichuriasis and hookworm infections were collected from 97 community or school-based studies conducted in Honduras between 2001 and 2012 (process described in Sanchez et al., 2014). Importantly, all of these surveys were conducted among children $\leq$ 15 years of age using the Kato Katz method for stool examination (Sanchez et al., 2014). Sixty-four municipalities were represented in this data set.

Studies were classified by time period, where those conducted before or during 2006 were assigned as time "0" (38 studies conducted in 28 municipalities) and those conducted after 2006 were assigned as time "1" (59 studies in 47 municipalities). In the cases where more than one study was conducted in the same municipality during the same time period (10 in time "0" and 12 in time "1"), sample-size weighted averages of their respective prevalence rates were calculated. 28 municipalities had a measured prevalence in time "0", 47 in time "1" and 11 municipalities were represented in both time periods; therefore, a total of 75 (sample-size weighted) prevalence rates representing 64 municipalities were used in the regression analysis. Due to the large number of municipalities where no cases of hookworm were observed (prevalence = 0), hookworm prevalence was also coded as a dichotomous variable, where 0 and 1 represented zero and non-zero infection prevalence, respectively.

2.2.3.2 Independent Variables: Natural Environment

Climate. Free-living ova and larvae require warm, moist soil to mature to infectivity in the external environment (Brooker, Clements & Bundy, 2006a; Beer, 1976; Brooker et al., 2003; Udonsi & Atata, 1987; Smith & Schad, 1989). Thus, climate variables such as temperature and precipitation might be expected to explain, in part, the observed geography of these infections and were therefore included in the preliminary analysis. Mean temperature and annual precipitation data were retrieved from Hijmans et al. (2005) “Very high resolution interpolated climate surfaces for global land areas”.

Ground Cover. Vegetation distribution was a significant explanatory variable in models of *A. lumbricoides* and *T. trichiura* infection in both sub-Saharan Africa (Brooker et al., 2006a; 2006b) and Southeast Asia (Brooker et al., 2003), and studies have reported increased hookworm prevalence in forested areas (Raso et al., 2006; Riess et al., 2013). It is thought that the dense vegetation characteristics of forested areas contributes positively to STH maturation by helping maintain relatively consistent soil moisture, preventing heavy rainfall from waterlogging soil or washing away contaminated feces and reducing soil evaporation (Raso et al., 2006). Remotely-sensed forest cover data were retrieved from the MODIS Land Cover Type product (MCD12Q1), available from the US Geological Survey (USGS) Land Processes Distributed Active Archive Center (LP DAAC) (NASA USGS, n.d). These data were aggregated to the municipality level based on the proportion of total land area classified as “Evergreen Needleleaf forest”, “Evergreen Broadleaf forest”, “Deciduous Needleleaf forest”, “Deciduous Broadleaf forest” or “Mixed forest”.

In addition to forest cover, the proportion of land classified as cropland was collected from Ramankutty, Evan, Monfreda and Foley (2010) database of “Global Agricultural Lands: Croplands”, made available on NASA’s Socioeconomic Data and Applications Center (SEDAC). These data combine several different imagery systems as well as an agricultural inventory to quantify agricultural land cover. The proportion of land classified as cropland was then calculated for each municipality in QGIS. Cropland is considered in this analysis because agricultural work is thought to increase the risk of hookworm infection; higher prevalence rates have been noted in farming households compared to non-farming households in Man, Cote d'Ivoire (Matthys et al., 2007), perhaps because agricultural work increases exposure of the hands and feet to potentially contaminated soil and/or night soil, a fertilizer comprised primarily of human excreta associated with increased intensity of hookworm infection (Behnke et al., 2000; Hotez & Ferris, 2006; Humphries et al., 1997).

Altitude and Terrain Ruggedness. Average altitude and mean terrain ruggedness index (TRI) (Riley et al., 1999), an index quantifying topographic heterogeneity, were both considered in this analysis. Evidence suggests that prevalence varies with altitude (Chammartin et al., 2013; Raso et al., 2006), perhaps because elevation is correlated with climatic variables known to influence STH survival (temperature, precipitation, ground cover). However, we are aware of no previous investigations into the relationship between TRI and prevalence. We consider that high elevations and increased variability in elevation (high TRI values) might also influence the availability of deworming resources, and thus prevalence, by physically isolating municipalities from the organizations that donate chemotherapy drugs and/or impeding foot and vehicular traffic to the institutions where these medications are made available to the public. Altitude data was retrieved from a 10 km digital elevation model (DEM) collected using ASTER (Advanced Spaceborne Thermal Emission and Reflection Radiometer) technology (GDEM V1) (Abrams, 2000). QGIS was used to determine the municipal-level average of both these variables.

Soil Composition: Clay Content. Research suggests that sandy soils and non-loamy soils are associated with increased hookworm infection (Saathoff et al., 2005; Brooker & Michael, 2000; Augustine & Smillie, 1926; Mabaso, Appleton, Hughes & Gouws, 2003) and reduced STH prevalence rates (Ahmed et al., 2011), respectively. It is thought that soil-type and porosity influences hookworm prevalence by facilitating (sandy soil) or inhibiting (high clay content) vertical migration of larvae, which alters their ability to actively avoid desiccation, solar radiation and rising water levels (Udonsi, Nwosu & Anya, 1980; Saathoff et al., 2005; Brooker & Michael, 2000). Clay content of soil was extracted from the Harmonized World Soil Database, a 30-arc second raster database available from the Food and Agriculture Organization of the United Nations, and included in this analysis (Nachtergaele et al., 2008). Data had not been aggregated at the municipality level, so a spatial merge was conducted in QGIS; for each municipality, an inner centroid was calculated and the clay content (%) of the corresponding soil area was then assigned to the municipality.

2.2.3.3 Independent Variables: Built Environment.

Poor housing construction, inadequate building materials and lack of well-maintained sanitation facilities have been identified as important small-scale risk factors for STH infection (Hotez, 2008). For example, households with dirt or sand floors tend to have higher levels and more intense STH infections than those finished with vinyl/asphalt strips, carpeting, concrete or cement (Gamboa et al., 2009; Hotez, 2008; Quintero et al., 2012; Anderson, Zizza, Leche, Scott & Solomans, 1993; Holland et al., 1988; Raso et al., 2006; Sanchez et al., 2016, Pullan et al., 2008; Narain, Rajguru &

Mahanta, 2000; Raso et al., 2005; Worrell et al., 2016). Similarly, living in a cement home has been identified as protective against infection (Holland et al., 1988; Raso et al., 2005) and rudimentary wall materials are associated with significantly higher prevalence of ascariasis, trichuriasis, intense trichuriasis, and intense hookworm reinfection following treatment (Cundill et al., 2011; Quintero et al., 2012; Holland et al., 1988; Alvarado & Vásquez, 2006). With respect to sanitation facilities, access to latrines has been associated with decreased prevalence and intensity of STH infections (Strunz et al., 2014; Esrey, Potash, Roberts & Shiff, 1991) and persons lacking a latrine in their home were significantly more likely to suffer from moderate-to-heavy helminthiases (Ahmed, 2011) and multiple-species infections (Sanchez et al., 2016). Well-maintained sanitation infrastructure reduces infection risk and severity by minimizing indiscriminate, open-field defecation, which is independently associated with increased risk of STH infection (Quihui et al., 2006; Narain et al., 2000).

Municipal-level data describing the proportion of homes constructed with various floor (earth, cement sheet, cement brick) and wall (cement/concrete, adobe) materials, as well as the proportion of homes without a toilet were retrieved for all 298 municipalities from both the 2001 and 2013 Honduras census (Instituto Nacional de Estadistica, 2001; Instituto Nacional de Estadistica, 2013). For each of the 75 prevalence rates measured in time 0 and time 1, these housing and population variables were populated with data from the 2001 and 2013 census, respectively. The sources of these data and additional information including comprehensive, pre-translation Spanish naming for each variable are included in Appendix A. We predict that municipalities with a higher proportion of homes with earthen floors and no toilets will have increased prevalence estimates, while the opposite is expected for municipalities with a greater proportion of homes with cement brick floors and concrete/cement walls.

Population Density. In addition to housing quality, there is evidence to suggest that settlement (Saathoff et al., 2005) and population density (Riess et al., 2013) are associated with increased hookworm infection. Similarly, household overcrowding has been associated with increased ascariasis (Holland et al., 1988) and STH infection prevalence more generally (Gamboa et al., 2009; Anuar, Salleh & Moktar, 2014). All else being equal, increased population density at both the family and community scale would be expected to increase the concentration of free-living infectious forms in the environment, particularly in the absence of adequate sanitation infrastructure. For the purposes of this analysis, population density was calculated using population count data from the Center for International Earth Science Information Network (2016) and area was calculated in QGIS.

Road Density. An index describing road density was calculated in QGIS using a map of Honduras' roadways retrieved from the Humanitarian Data Exchange (2015). For each municipality, the length of all mapped roadways were summed and then divided by the region's area. This index was included in the model as a proxy for treatment accessibility, based on the assumption that a more complete, dense road system would be expected to facilitate the distribution of treatment resources and the ability for those at risk to access them.

2.2.3.4 Independent Variables: Social Environment

Human Development Index and Income. STH infections are associated with poverty and inequality at national and international scales (Hotez et al., 2006; Gazzinelli, Correa-Oliveira, Yang, Boatin & Kloos, 2012; de Silva et al., 2003), while low socioeconomic status (Matthys et al., 2007; Holland et al., 1988; Pullan et al., 2008), material disadvantages (Alvarado & Vásquez, 2006; Quihui et al., 2006; Anuar et al., 2014) and high unemployment rates (Quihui et al., 2006) are associated with increased STH prevalence and intensity (Holland et al., 1988; Sanchez et al., 2016) in communities. In Honduras specifically, a literature review conducted by Sanchez et al. (2014) reported a significant negative association between Human Development Index (HDI) scores (a composite index of life expectancy, education and income) and STH prevalence, which suggests that a relationship between social inequities and infection distribution exists in our study area.

As such, estimates of income and relative development were both included in the initial analysis; municipal estimates for average per capita income (US$ PPP) based on the “Instituto Nacional de Estadistica” (INE) database of permanent multiple household survey from May 2009, and HDI from 2002 and 2009 were retrieved from the 2011 Human Development Report Honduras, To Reduce Inequity: An Urgent Challenge (“Informe Sobre Desarrollo Humano Honduras 2011, Reducir la inequidad: un desafío impostergable”) (United Nations Development Program (UNDP) Honduras, 2012). HDI data from 2002 was assigned to prevalence rates measured in time 0, and data from 2009 was assigned to those measured in time 1.

Literacy Rate and School Attendance Rates. School attendance and literacy rates are likely proxies for social/economic development and represent direct and indirect measures of school attendance, respectively. These variables are particularly important for modelling STH prevalence, given that deworming programs are typically administered through existing educational infrastructure and thus increased school attendance and literacy rates might also reflect more comprehensive treatment coverage. There is also evidence that comprehensive school-based health education reduces risk of infection (Xu et al., 2000; Bieri et al., 2013; Gyorkos, Maheu-Giroux, Blouin & Casapia, 2013) and researchers have noted significant inverse correlations between maternal education level and STH infection prevalence (Holland et al., 1988; Alvarado & Vásquez, 2006; Quihui et al., 2006) and intensity (Naish, McCarthy & Williams, 2004) in children.

Similarly to the housing materials and sanitation variables described previously, the literacy rate of persons over 3 years of age was retrieved for all 298 municipalities from both the 2001 and 2013 censuses (INE, 2001; INE, 2013). For prevalence rates measured during time 0, literacy rate was pulled from the former, while the latter was used for observations from time 1. Additionally, a time-invariant estimate of municipality-level school attendance rate as a percentage of individuals 7 years and older was retrieved from the 2011 Human Development Report Honduras, To Reduce Inequity: An Urgent Challenge ("Informe Sobre Desarrollo Humano Honduras 2011, Reducir la inequidad: un desafío impostergable"). Estimates were based on the INE database of the permanent multiple household survey from May 2009 (United Nations Development Program (UNDP) Honduras, 2012).

2.2.4 Analysis

The R-programming language and R-studio ecosystem were used to generate descriptive statistics including mean, median, standard deviation, maximum and minimum values for all variables (Appendix B.1 and Appendix B.2). Simple regression analyses were then conducted to assess the relationship between each independent variable and the three prevalence rates - *A. lumbricoides* (Table 1.A), *T. trichiura* (Table 1.B) and hookworm (Table 1.C). For each infection, independent variables significant at the 0.05 level were tested for multicollinearity; when correlations exceeded 0.5, one (or both) variables were removed based on their relative significance levels and our existing understanding of risk-factors as identified in previous investigations. The remaining (significant) variables were retained for inclusion in the multiple regression analysis.

Multiple linear regression analysis was then used to produce three predictive models for each of the infections - a main effects model, a main effects model with the addition of the dichotomous time variable, and a third model containing a literacy rate-time interaction term. All three models were then re-run using robust regression analysis; these results were compared with the least squares regression output to ensure that the latter was not affected by outliers or overly influential observations. Due to the large number of communities with a prevalence of 0, the presence/absence of hookworm was also modeled using logistic regression.

Final regression models were assessed using several diagnostic tools. Firstly, variance inflation factors (VIF) were calculated to test for multicollinearity in the independent variables. The square root of the VIF indicates how many times larger the standard error is than it would be if that variable were uncorrelated with the other predictor variables in the model. Recommended maximum VIF values of 4, 5 and 10 have been cited in the literature (Pan & Jackson, 2008; Rogerson, 2001; Hair, Anderson, Tatham & Black, 1995; Kennedy, 1992; Marquardt, 1970; Neter, Wasserman & Kutner, 1989).

The Moran's I tool was then used to assess for spatial autocorrelation amongst the models' residuals. For this analysis, the null hypothesis is that the residuals vary randomly over space. Conversely, the alternative hypothesis states that spatially proximate municipalities will have similar residuals, resulting in clusters of predictions that are similarly close or similarly far from observed prevalence levels. In this context, the presence of spatial autocorrelation would likely suggest that there could be some important predictive variable excluded from the model that is also characterized by a clustered geography (whereby close regions are more similar than those separated by increasingly large distances). This is especially likely given that the municipalities included in this analysis are relatively far apart and thus direct disease transmission between municipalities is probably relatively insignificant.

Heteroskedasticity, a condition whereby the variance of the errors from a regression model are dependent on the value of independent variables, was assessed using the Breusch-Pagan Test (bptest {lmtest}). This technique fits a linear regression model to the residuals of the multiple regression models, and the null hypothesis of homoskedasticity is rejected when the test statistics p-value falls below an established threshold (<0.05).

Finally, the multiple regression models were used to generate and map predicted infection prevalence in time 0 and time 1. In accordance with WHO guidelines, prevalence was then used determine recommended treatment frequency, which was also mapped.

2.3 RESULTS

2.3.1 *Ascaris lumbricoides*

Sample-size weighted *A. lumbricoides* prevalence varied between 0% and nearly 75%, with mean and median prevalence of 21% and 27%, respectively. Summary statistics describing ascariasis prevalence are included in Appendix B (Appendix B.2).

The simple regression analyses indicated that the proportion of homes with cement brick floors (p value: 0.0363), literacy rate (0.00046), average per capita income (0.00981), schooling rate (0.013) and HDI (0.000275) were significantly and negatively associated with ascaris lumbricoides infection, while the proportion of homes without a toilet (0.00124) and forest cover as a percent of total land (0.0232) were significantly and positively associated with prevalence. The results of this preliminary analysis are displayed in Table 1A, 1B and 1C (see purple section).

Table 1.A: Simple Linear Regression Output: BUILT ENVIRONMENT (Household and Community Characteristics)

		A. lumbricoides					***T. trichiura***					**Hookworm**				
	Model Variables	**Estimate**	**Std. Error**	**T value**	**Pr (>|t|)**	**Multiple R-squared**	**Estimate**	**Std. Error**	**T value**	**Pr (>|t|)**	**Multiple R-squared**	**Estimate**	**Std. Error**	**T value**	**Pr (>|t|)**	**Multiple R-squared**
	i. Floor Material (source: Census)															
1	Intercept	0.213549	0.048744	4.381	3.89e-05	0.02645	0.464851	0.051863	8.963	2.18e-13	0.07052	0.0453529	0.019875	2.282	0.0254	0.002638
	Earth	0.001696	0.001204	1.408	0.163		**-0.00302**	0.001281	-2.353	**0.0213**		-0.000216	0.000491	-0.439	0.6617	
2	Intercept	0.331112	0.036373	9.103	1.19e-13	0.05865	0.411767	0.039993	10.30	7.25e-16	0.04024	0.0463694	0.015043	3.083	0.0029	0.007841
	Cement Brick	**-0.00568**	0.002662	-2.133	**0.0363**		-0.005120	0.002926	-1.75	0.0844		-0.000836	0.001101	-0.760	0.4500	
	ii. Wall Material (source: Census)															
3	Intercept	0.286634	0.037795	7.584	8.49e-11	0.003147	0.301038	0.040221	7.485	1.3e-10	0.04789	0.0261807	0.015142	1.729	0.088	0.01392
	Cement/ Concrete	-0.00058	0.001207	-0.480	0.633		0.002460	0.001284	1.916	0.0593		0.0004908	0.000483	1.015	0.313	
4	Intercept	0.257764	0.046483	5.545	4.44e-07	0.002031	0.506782	0.046379	10.93	< 2e-16	0.1621	0.0658409	0.018338	3.590	0.0006	0.04281
	Adobe	0.000341	0.000885	0.385	0.701		**-0.00332**	0.000883	-3.758	**0.00034**		-0.000631	0.000349	-1.807	0.07488	
	iv. Sanitation System (source: Census)															
5	Intercept	0.170857	0.038145	4.479	2.72e-05	0.1339	0.336783	0.044511	7.566	9.17e-11	0.005488	0.0006516	0.015583	0.042	0.96676	0.1093
	No Toilet	**0.00491**	0.001460	3.360	**0.00124**		0.001081	0.001703	0.635	0.528		**0.001785**	0.000596	2.993	**0.0038**	
	v. Population Density															
6	Intercept	0.297608	0.031212	9.535	1.86e-14	0.02189	3.640e-01	3.44e-02	10.60	<2e-16	0.0006848	4.490e-02	1.26e-02	3.551	0.00068	0.01115
	Pop. Density	-0.00021	0.000167	-1.278	0.205		-4.11e-05	1.8344	-0.224	0.824		-6.140e-05	6.77e-05	-0.907	0.36732	
	vi. Road Density															
7	Intercept	0.27527	0.06051	4.549	2.1e-05	2.473e-05	0.44080	0.06506	6.775	2.71e-09	0.02519	0.04691	0.02435	1.926	0.0579	0.002299
	Road Dens.	-13.6657	321.6479	-0.042	0.966		-474.9862	345.8149	-1.374	0.174		-53.08137	129.424	-0.410	0.6829	

Table 1.B: Simple Linear Regression Output: NATURAL ENVIRONMENT (Land Cover, Topography, Climate, Soil Composition)

		A. lumbricoides					***T. trichiura***					**Hookworm**				
	Model Variables	**Estimate**	**Std. Error**	**T value**	**Pr (>|t|)**	**Multiple R-squared**	**Estimate**	**Std. Error**	**T value**	**Pr (>|t|)**	**Multiple R-squared**	**Estimate**	**Std. Error**	**T value**	**Pr (>|t|)**	**Multiple R-squared**
i. Land Cover																
1	Intercept	0.20204	0.03882	5.205	1.72e-06	0.0686	0.22418	0.03893	5.759	1.87e-07	0.2102	0.01462	0.01583	0.923	0.359	0.04522
	Forest (%)	**0.24324**	0.10490	2.319	**0.0232**		**0.46360**	0.10518	4.408	**3.5e-05**		0.07955	0.04278	1.860	0.067	
2	Intercept	0.31312	0.04424	7.077	7.49e-10	0.0161	0.50300	0.04416	11.39	< 2e-16	0.1735	0.06070	0.01768	3.434	0.0010	0.03221
	Cropland (%)	-0.21221	0.19415	-1.093	0.278		**-0.75864**	0.19377	-3.915	**0.00020**		-0.12090	0.07757	-1.559	0.1234	
ii. Topography																
3	Intercept	2.222e-01	5.213e-02	4.262	5.96e-05	0.01639	4.928e-01	5.44e-02	9.053	1.48e-13	0.09581	7.175e-02	2.07e-02	3.468	0.0009	0.04529
	Avg. Altitude	6.184e-05	5.607e-05	1.103	0.274		**-1.63e-04**	5.85e-05	-2.781	**0.00689**		-4.141e-05	2.23e-05	-1.861	0.0668	
4	Intercept	2.686e-01	7.183e-02	3.739	0.000365	5.764e-05	0.528100	0.075329	7.011	9.96e-10	0.07245	0.0632838	0.02876	2.200	0.0309	0.01206
	TRI	1.775e-05	2.736e-04	0.065	0.948457		**-0.00069**	0.000287	-2.388	**0.0195**		-0.000103	0.00011	-0.944	0.3482	
iii. Precipitation																
5	Intercept	1.267e-01	1.060e-01	1.195	0.236	0.02681	4.425e-03	1.09e-01	0.041	0.96771	0.1331	-6.121e-02	4.16e-02	-1.471	0.1456	0.0757
	Avg. ann. precip.	9.105e-05	6.420e-05	1.418	0.160		**2.21e-04**	6.60e-05	3.348	**0.00129**		**6.163e-05**	2.52e-05	2.445	**0.0169**	
iv. Temperature																
6	Intercept	0.619059	0.225982	2.739	0.00773	0.03149	-0.14058	0.24302	-0.578	0.5647	0.05539	-0.093368	0.09120	-1.024	0.309	0.02787
	Avg. temp	-0.015359	0.009969	-1.541	0.12771		**0.02218**	0.01072	2.069	**0.0421**		0.005820	0.00402	1.447	0.152	
v. Soil Composition																
7	Intercept	0.170726	0.057461	2.971	0.00401	0.05001	0.12393	0.05656	2.191	0.0316	0.2237	-0.008475	0.02299	-0.369	0.7134	0.06318
	Clay (%)	0.004620	0.002357	1.960	0.05377		**0.01064**	0.00232	4.586	**1.8e-05**		**0.002092**	0.00094	2.219	**0.0296**	

Table 1.C: Simple Linear Regression Output: SOCIAL CONDITIONS & DEVELOPMENT (Literacy Rate, Schooling Rate, Estimated Per Capita Income, Human Development Index)

		A. lumbricoides					***T. trichiura***					**Hookworm**				
Model Variables		**Estimate**	**Std. Error**	**T value**	**Pr (>|t|)**	**Multiple R-squared**	**Estimate**	**Std. Error**	**T value**	**Pr (>|t|)**	**Multiple R-squared**	**Estimate**	**Std. Error**	**T value**	**Pr (>|t|)**	**Multiple R-squared**
i. Literacy Rate (source: Census)																
1	Intercept	0.994156	0.197905	5.023	3.48e-06	0.1557	0.628547	0.232375	2.705	0.0085	0.0183	0.211452	0.084315	2.508	0.0144	0.05561
	Literacy	**-0.00977**	0.002662	-3.669	**0.00046**		-0.00365	0.00313	-1.167	0.2472		**-0.00235**	0.001134	-2.073	**0.0417**	
ii. Estimated Per Capita Income (US$ PPP) (source: INDH 2011)																
2	Intercept	4.072e-01	5.589e-02	7.286	3.07e-10	0.08788	3.449e-01	6.370e-02	5.414	7.52e-07	0.0008561	5.281e-02	2.349e-02	2.248	0.0276	0.006766
	Income	**-4.91e-05**	1.853e-05	-2.652	**0.00981**		5.281e-06	2.112e-05	0.250	0.803		-5.492e-06	7.789e-06	-0.705	0.4829	
iii. Schooling Rate(% of 7 years and older) (source: INDH 2011)																
3	Intercept	0.588554	0.126238	4.662	1.38e-05	0.08154	0.459151	0.142942	3.212	0.00196	0.006885	0.091756	0.052672	1.742	0.0857	0.01468
	Schooling Rate	**-0.007058**	0.002772	-2.546	**0.013**		-0.002233	0.003139	-0.711	0.47911		-0.001207	0.001157	-1.043	0.3004	
iv. Human Development Index (HDI) (source: INDH 2011)																
4	Intercept	1.186	0.240	4.943	4.74e-06	0.1668	0.5199	0.2857	1.820	0.0729	0.00435	0.2024	0.1041	1.943	0.0558	0.03336
	HDI	**-1.422**	0.372	-3.823	**0.000275**		-0.2501	0.4428	-0.565	0.5740		-0.2562	0.1614	-1.587	0.1168	

Literacy rate and no toilet were highly correlated, as were all four social and developmental variables (literacy rate, estimated per capita income, schooling rate and HDI) (see Appendix B.3). Although HDI exhibited the most significant relationship with prevalence, we were less interested in the combined effect of social and health inequalities than the specific consequences of education and school attendance on the risk of ascariasis via school-based treatment programs. Unfortunately, school attendance rates were only available for one point in time, so we opted to include literacy rate in the multiple regression analysis instead. Similarly, the no toilet variable was omitted from the multiple regression analysis in favour of retaining literacy rate.

As a result of this preliminary analysis, cement floor, proportion forest and literacy rate were included in the main effects multiple linear regression model (Table 2.A.I). A second model was then run with the addition of the dichotomous time variable, and the final model, which expanded on the previous iteration by adding a literacy rate-time interaction, was assessed for multicollinearity, heteroskedasticity and spatial autocorrelation in residuals.

Although there was no signs of either multicollinearity or heteroskedasticity in the final model, the Moran's I assessment indicated spatial autocorrelation of model residuals (see Appendix B.6). To address this, residuals were mapped (blue representing over predictions, red representing under-predictions) (Figure 1) and compared with climate maps of Honduras (Figure 2). Clusters of positive and negative residuals appeared to coincide with areas of similar temperatures, so average temperature was added to the main effects, main effects plus time and interaction term). Spatial autocorrelation was no longer observed in the residuals.

Table 2.A.I: *Ascaris lumbricoides*: Multiple Linear Regression I												
	Main Effects (Model 1)				Main Effects + Time (Model 2)				Main Effects + Interaction (Model 3)			
	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)
Intercept	0.9162	0.1973	4.643	1.53e-05	0.7073	0.2096	3.373	0.00122	0.0408	0.2449	0.167	0.868213
floor_cementbrick	-0.0003	0.0029	-0.120	0.90501	-0.0042	0.0032	-1.312	0.19397	-0.0051	0.0029	-1.763	0.082259
prop_forest	0.2347	0.1067	2.199	**0.03111**	0.2063	0.1039	1.985	0.05104	0.2735	0.0945	2.894	**0.005086**
literacy_rate	-0.0096	0.0028	-3.459	**0.00092**	-0.0050	0.0033	-1.499	0.13831	0.0046	0.0037	1.240	0.219331
Time	N/A				-0.1374	0.0569	-2.412	**0.01848**	1.4740	0.3826	3.852	**0.000259**
literacy_rate*time	N/A				N/A				-0.0221	-0.0221	-4.249	**6.59e-05**
Multiple R-squared	0.2226				0.2822				**0.4311**			
Adjusted R-squared	0.18979				0.2412				**0.3899**			

Table 2.A.II: *Ascaris lumbricoides*: Robust Regression with Huber assumption I												
	Main Effects (1)				Main Effects + Time (2)				Main Effects + Interaction (3)			
	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)
Intercept	1.1141	0.1906	5.8460	<0.00001	0.8512	0.2009	4.2364	0.00007	-0.0948	0.2412	-0.3932	0.695531
floor_cementbrick	0.0011	0.0028	0.3839	0.7022	-0.0029	0.0031	-0.9628	0.33886	-0.0051	0.0028	-1.7970	0.076712
prop_forest	0.3117	0.1030	3.0254	**0.00345**	0.2572	0.0996	2.5827	**0.01190**	0.2903	0.0931	3.1180	**0.002655**
literacy_rate	-0.0129	0.0027	-4.8072	**<0.00001**	-0.0073	0.0032	-2.3080	**0.02396**	0.0062	0.0037	1.6907	0.095407
time	N/A				-0.1469	0.0546	-2.6921	**0.00888**	1.6101	0.3769	4.2717	**0.000061**
literacy_rate*time	N/A				N/A				-0.0238	0.0051	-4.6558	**0.000015**
Residual St. Error	0.1631 on 71 degrees of freedom				0.1462 on 70 degrees of freedom				**0.1589 on 69 degrees of freedom**			

Figure 1: *A. lumbricoides* "Model 3" Residuals

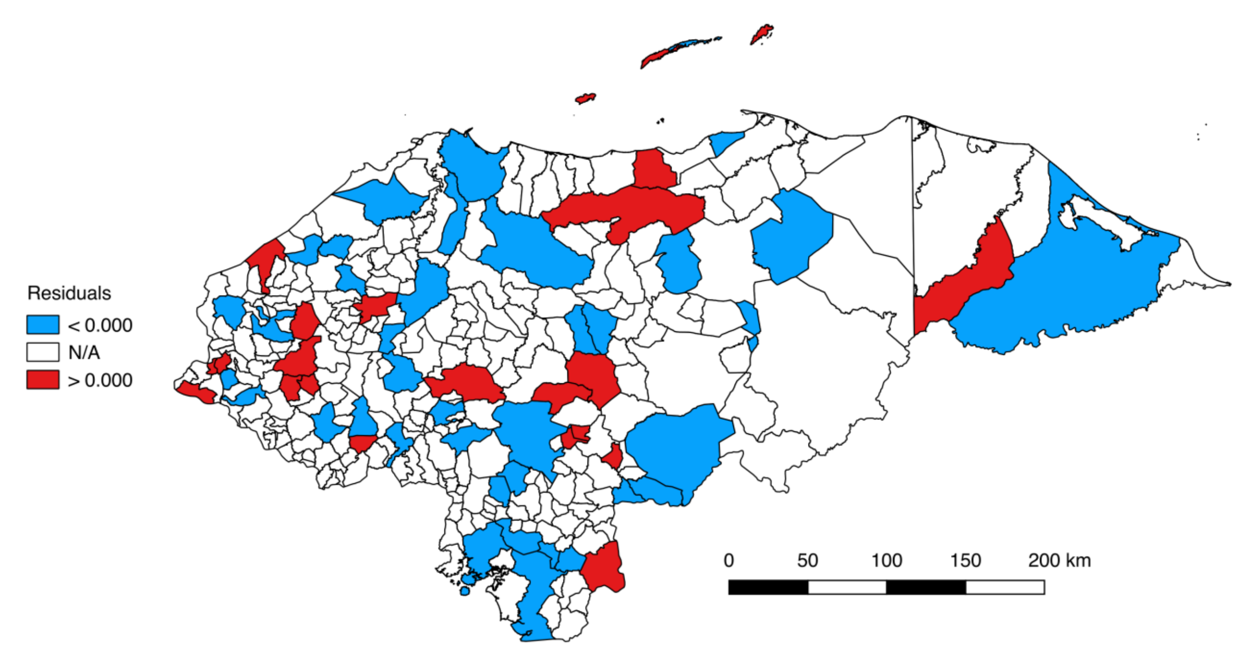


Figure 2: Average Mean Temperature, Honduras

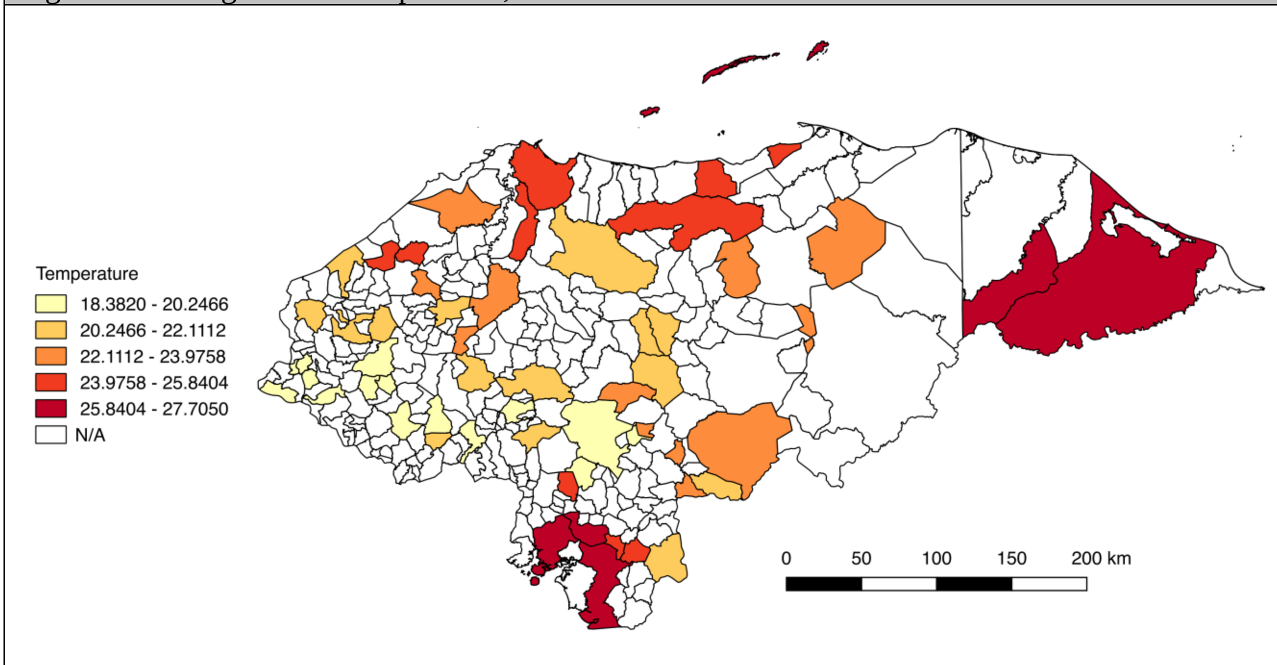


Table 2.A.III: *Ascaris lumbricoides*: Multiple Linear Regression II (with temperature added)

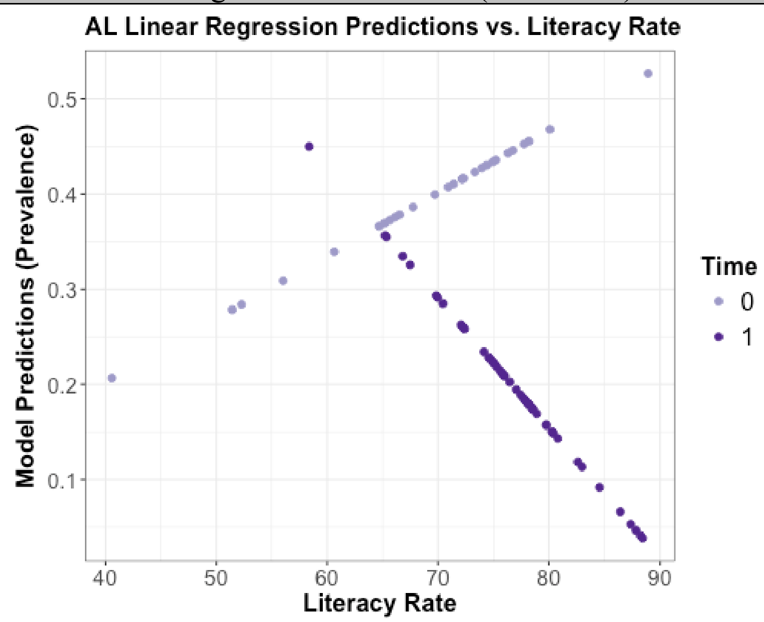
	Main Effects (1)				Main Effects + Time (2)				Main Effects + Interaction (3)			
	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)
Intercept	1.2229	0.2553	4.790	9.04e-06	1.0899	0.2438	4.470	2.99e-05	0.4044	0.2792	1.448	0.152123
floor_cementbrick	-0.0016	0.0029	-0.562	0.57591	-0.0072	0.0032	-2.233	**0.02880**	-0.0075	0.0029	-2.543	**0.013280**
prop_forest	0.2627	0.1060	2.478	**0.01564**	0.2384	0.1000	2.383	**0.01991**	0.2943	0.0917	3.210	**0.002025**
Avg_temp	-0.0178	0.0096	-1.848	0.06882	-0.0260	0.0094	-2.757	**0.00745**	-0.0211	0.0086	-2.448	**0.016934**
literacy_rate	-0.0082	0.0028	-2.920	**0.00471**	-0.0015	0.0034	-0.456	0.65015	0.0066	0.0037	1.797	0.076759
time	N/A				-0.1799	-0.1799	-3.180	**0.00221**	1.3118	0.3754	3.495	**0.000840**
literaacy_rate*time	N/A				N/A				-0.0203	0.0051	-4.011	**0.000153**
Multiple R-squared	0.2587				0.3535				0.4772			
Adjusted R-squared	0.2164				0.3066				0.4311			

Table 2.A.IV: *Ascaris lumbricoides*: Robust Regression with Huber assumption II (with temperature added)

	Main Effects (1)				Main Effects + Time (2)				Main Effects + Interaction (3)			
	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)
Intercept	1.3303	0.2558	5.1998	<0.00001	1.1203	0.2471	4.5338	0.000024	0.2799	0.2904	0.9637	0.338611
floor_cementbrick	-0.0007	0.0029	-0.2485	0.80486	-0.0057	0.0033	-1.7445	0.085613	-0.0070	0.0031	-2.2901	**0.025129**
prop_forest	0.3109	0.1062	2.9267	**0.004617**	0.2732	0.1014	2.6949	**0.008836**	0.3039	0.0953	3.1875	**0.002169**
Avg_temp	-0.0160	0.0097	-1.6582	0.101793	-0.0225	0.0095	-2.3607	**0.021056**	-0.0183	0.0090	-2.0376	**0.045442**
literacy_rate	-0.0106	0.0028	-3.7552	**0.000355**	-0.0035	0.0034	-1.0168	0.312706	0.0072	0.0038	1.8671	0.066199
time	N/A				-0.1746	0.0574	-3.0446	**0.003293**	1.3993	0.3905	3.5836	**0.000632**
literacy_rate *time	N/A				N/A				-0.0214	0.0053	-4.0540	**0.000132**
Residual St. Error	0.1936 on 70 degrees of freedom				0.1671 on 69 degrees of freedom				0.166 on 68 degrees of freedom			

Proportion forest (p-value: 0.01564) and literacy rate (p-value: 0.00471) were the only variables to remain significant in the main effects multiple linear regression analysis (Model 1); forested areas were associated with increased prevalence, while high literacy rates and increased temperatures were associated with reduced levels of *A. lumbricoides* infection (Table 2.A.III). The second iteration of the model (Model 2) saw the addition of a dichotomous time variable, which, along with cement floor (p-value: 0.02880) and average temperature (0.00745), was strongly associated with reduced infection (p-value: 0.00221). Conversely, proportion forest (0.01991) was positively correlated with prevalence (Table 2.A.III). The final model (Model 3), which included a literacy rate-time interaction term (p-value: 0.000153), was able to explain nearly 50% of variability in *A. lumbricoides* infection prevalence (multiple R-squared: 0.4772) (Table 2.A.III). The relationship between time, literacy rate and prevalence is shown in Figure 3; the model predicts a positive association between literacy and prevalence in time period 0 (before or during 2006) and a negative association in time period 1 (after 2006).

Figure 3: *A. lumbricoides* Regression Predictions (“Model 3”) versus Literacy Rate (%)



The results of the robust regression closely mirrored those of the linear regression analyses, however cement floor was no longer significant following the addition of the time variable in Model 2 (Table 2.A.IV). For the main effects (Model 1) and interaction models (Model 3), findings were comparable to those described above (Table 2.A.IV).

The final model was used to generate municipal prevalence rates for both time periods. These predictions are mapped in Figure 4. During time 0 (2001-2006) (Figure 4.A), ascariasis prevalence was lowest in the south and highest along the northern coast and an inland corridor in the west. Although a similar distribution was observed in time 1 (2001-2012) (Figure 4.B), prevalence decreased significantly between the two time periods; on average, prevalence was 15% lower in time 1 than time 0, and infection rates were predicted to decline in 86% of municipalities. Finally, recommended treatment frequency is mapped in Figure 4.C; annual deworming is recommended in 171 municipalities (prevalence between 20% and 50%), and twice yearly administration is recommended in 15 municipalities (prevalence exceeds 50%).

Figure 4: *A. lumbricoides* Predicted Prevalence & Recommended Treatment Frequency

Figure 4.A: Predicted Prevalence, Time 0 (2001-2006)

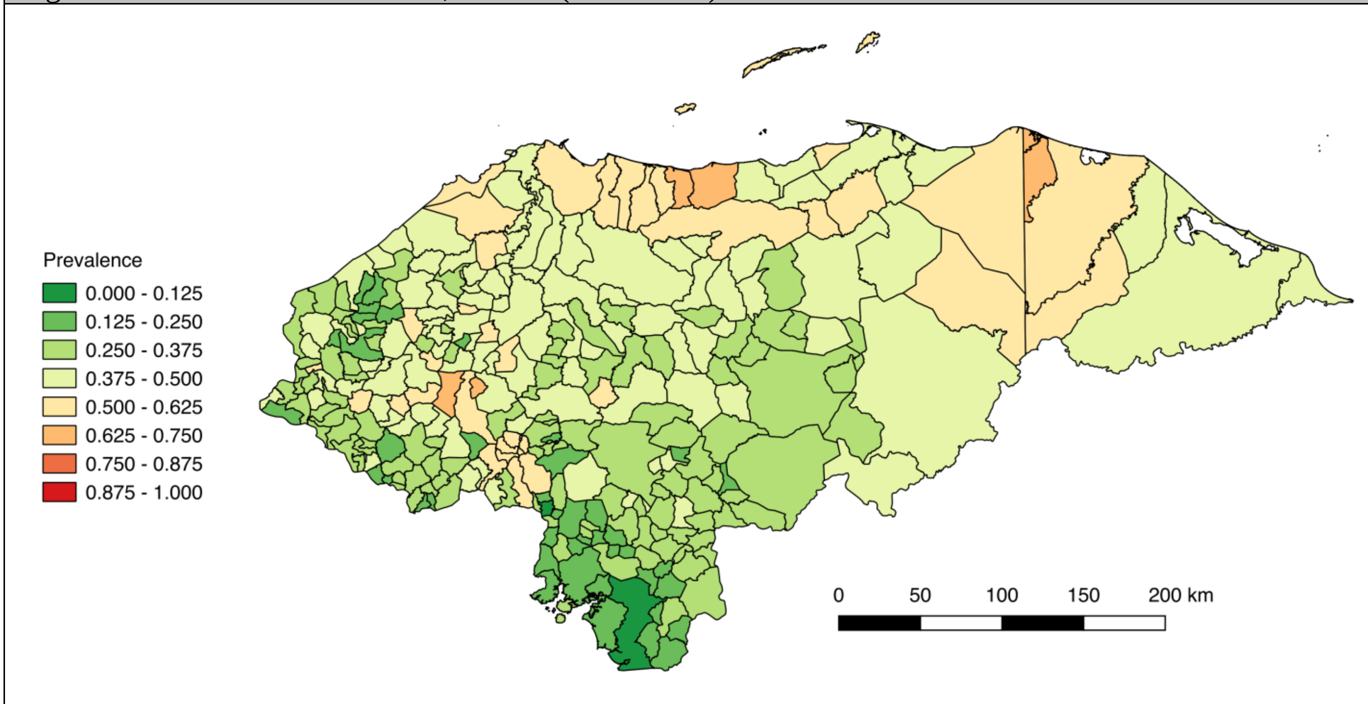


Figure 4.B: Predicted Prevalence, Time 1 (2007-2012)

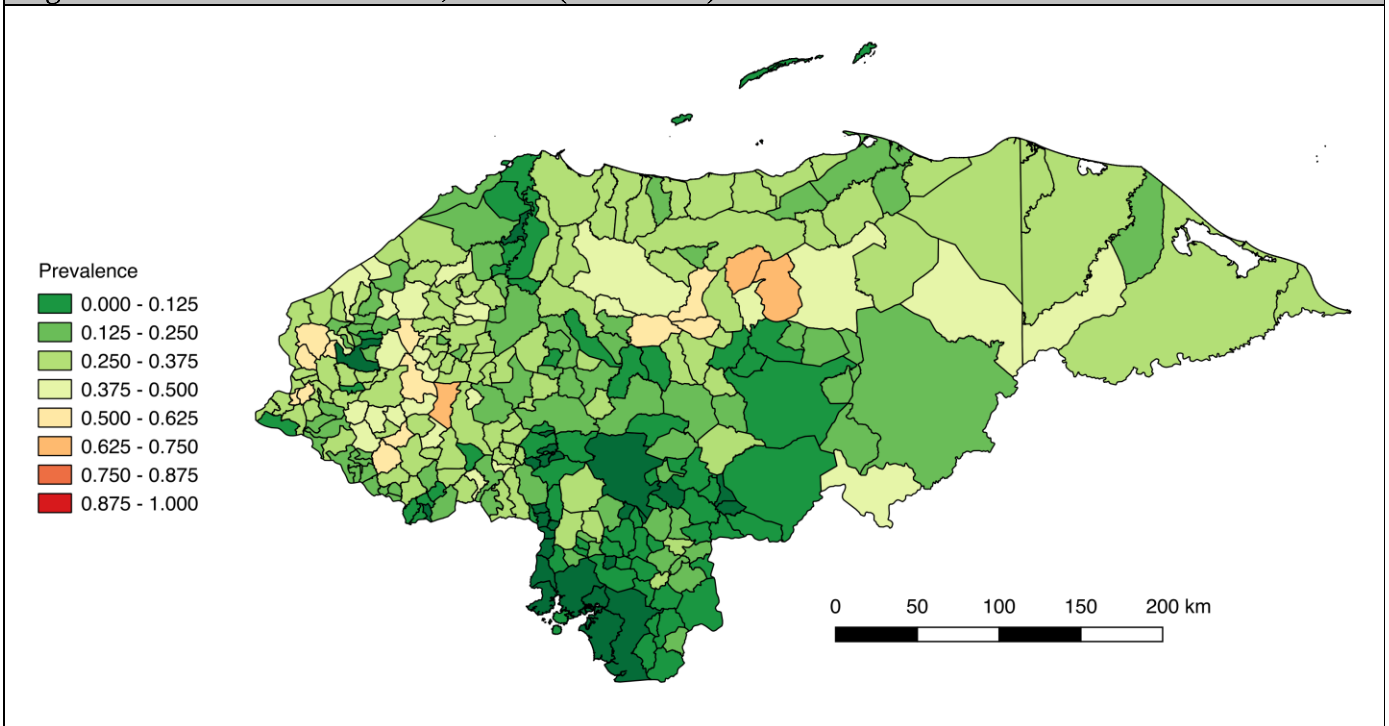
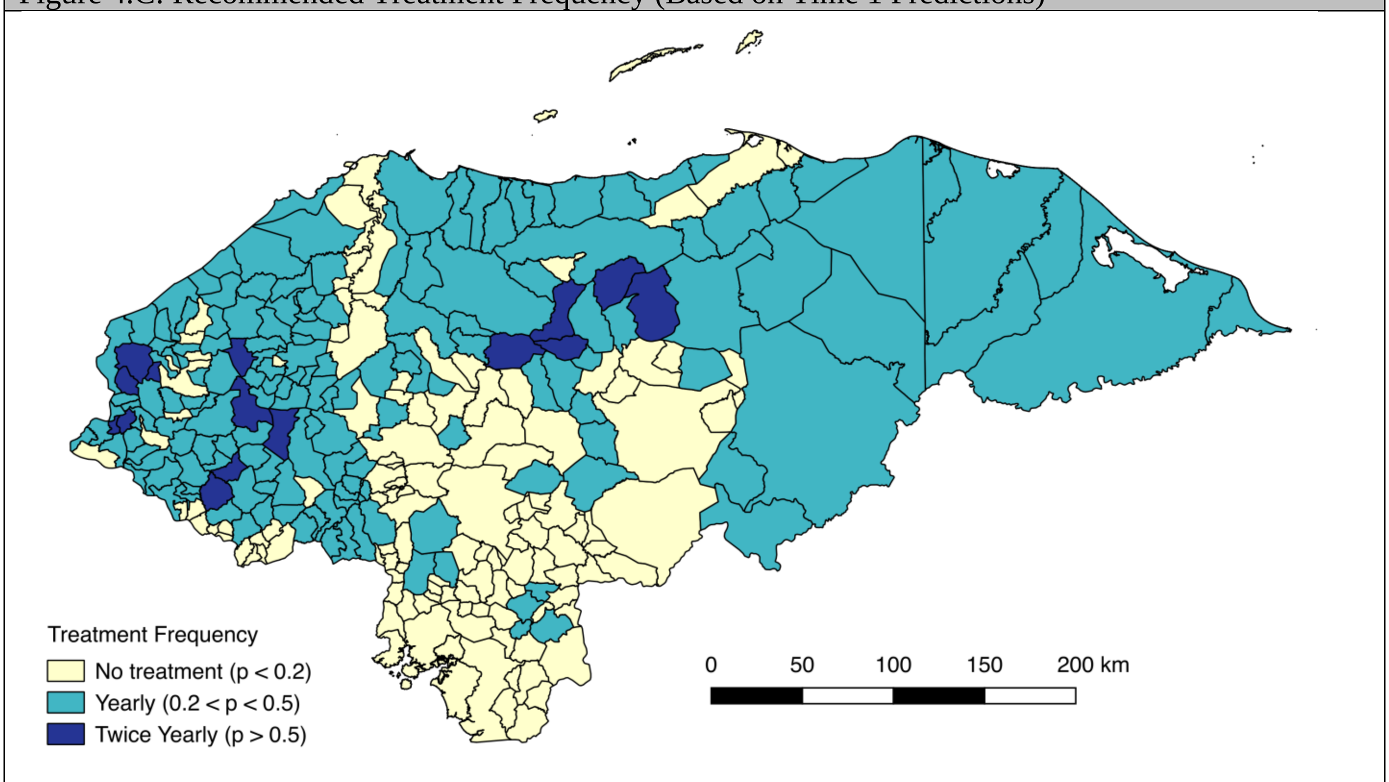


Figure 4.C: Recommended Treatment Frequency (Based on Time 1 Predictions)



2.3.2 *Trichuris trichiura*

Sample-size weighted *T. trichiura* prevalence varied between 2% and 92%, with mean and median prevalence of 32% and 36%, respectively. Based on these metrics, whipworm was, on average, the most prevalent STH infection in Honduras. Summary statistics describing trichuriasis prevalence are included in Appendix B (Appendix B.2).

A total of nine variables were identified as significant predictors of *T. trichiura* prevalence in the simple regression analyses: earth floor (p-value: 0.0213), adobe wall (0.00034), cropland (0.00020), average altitude (0.00689) and TRI (0.0195) were negatively associated with infection prevalence, while forest cover (3.5e-05), average annual precipitation (0.00129), average temperature (0.0421) and clay content (1.8e-05) were positively associated with infection prevalence (Table 1A, 1B and 1C, see orange section). Several of these variables were highly correlated with one another, including adobe walls, cropland, average altitude and average temperature (Appendix B.4). These four variables were omitted from the multiple regression analysis, leaving earth floors, forest cover, TRI, average precipitation and percent clay in the model.

In the main effects multiple linear regression analysis (Model 1), forest cover (0.00871), TRI (0.00750), and percent clay (0.00146) remained significant (Table 2.B.I). With the exception of TRI, each of these variables was associated with increased infection prevalence. This main effects model had a moderate model fit, as described by a multiple R-squared of 0.3881. When the dichotomous time variable was added (0.000172) (Model 2), all three variables remained significant and the multiple R-squared rose to 0.4565. Similarly to *A. lumbricoides,* the literacy-time interaction term added in

Model 3 was a highly significant predictor of *T. trichiura* prevalence (p-value: 4.61e-05) (Table 2.B.I); prevalence predictions were positively associated with literacy during time 0, and negatively associated with literacy in time 1 (Figure 5). This final model was able to explain close to two-thirds of the variability in *T. trichiura* prevalence (multiple R-squared: 0.6019) (Table 2.B.I), and no signs of multicollinearity (Appendix B.4), spatial autocorrelation of residuals (Appendix B.6) or heteroskedasticity (Appendix B.7) were observed in diagnostic assessments.

No remarkable differences were noted between the findings reported in the multiple linear regression and robust regression analyses; effect sizes were comparable, and the same variables remained significant when both techniques were used (Table 2.B.II).

Table 2.B.I: *Trichiura trichuris*: Multiple Linear Regression

	Main Effects (Model 1)				**Main Effects + Time (Model 2)**				**Main Effects + Interaction (Model 3)**			
	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)
Intercept	2.307e-01	1.541e-01	1.497	0.13888	3.140e-01	1.490e-01	2.107	0.03880	5.315e-01	3.932e-01	1.352	0.181067
floor_earth	9.184e-04	1.298e-03	0.708	0.48147	-5.708e-04	1.333e-03	-0.428	0.66975	-3.528e-03	1.792e-03	-1.969	0.053196
prop_forest	3.300e-01	1.222e-01	2.700	**0.00871**	3.141e-01	1.162e-01	2.704	**0.00864**	3.415e-01	1.079e-01	3.164	**0.002352**
TRI	-7.980e-04	2.897e-04	-2.755	**0.00750**	-6.088e-04	2.825e-04	-2.155	**0.03469**	-6.824e-04	2.474e-04	-2.758	**0.007521**
Avg_precip	1.251e-05	7.319e-05	0.171	0.86483	3.596e-05	6.994e-05	0.514	0.60878	5.753e-06	6.125e-05	0.094	0.925450
percent_clay	7.991e-03	2.411e-03	3.315	**0.00146**	6.880e-03	2.320e-03	2.966	**0.00416**	5.325e-03	2.090e-03	2.548	**0.013177**
time	N/A				-1.376e-01	4.700e-02	-2.927	**0.00464**	1.446e+00	3.599e-01	4.018	**0.000153**
literacy_rate	N/A				N/A				6.664e-05	4.254e-03	0.016	0.987549
literacy_rate *time	N/A				N/A				-2.120e-02	4.859e-03	-4.363	**4.61e-05**
Multiple R-squared	0.3881				0.4565				0.6019			
Adjusted R-squared	0.3437				0.4086				0.5537			

Figure 5: *T. trichiura* Regression Predictions ("Model 3") versus Literacy Rate (%)

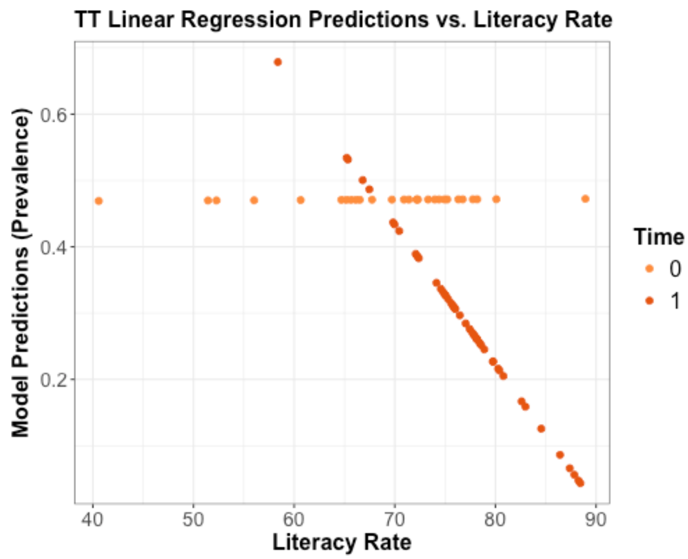


Table 2.B.II: *Trichiura trichuris*: Robust Regression

	Main Effects (1)				**Main Effects + Time (2)**				**Main Effects + Interaction (3)**			
	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)
Intercept	0.2089	0.1574	1.3274	0.188752	3.5168e-01	0.1387	2.5362	0.013508	6.0056e-01	0.4476	1.3417	0.184291
floor_earth	0.0008	0.0013	0.5899	0.557185	-1.2870e-03	0.0012	-1.0378	0.302947	-3.8514e-03	0.0020	-1.8880	0.063423
prop_forest	0.3380	0.1248	2.7076	**0.008536**	3.2416e-01	0.1081	2.9989	**0.003783**	3.5634e-01	0.1229	2.8999	**0.005065**
TRI	-0.0008	0.0003	-2.5857	**0.011824**	-5.3587e-04	0.0003	-2.0386	**0.04534**	-7.0379e-04	0.0003	-2.4984	**0.014989**
Avg_precip	0.000015	0.0001	0.1941	0.846668	2.2111e-05	0.0001	0.3397	0.735129	-5.2686e-07	0.0001	-0.0076	0.993641
percent_clay	0.0081	0.0025	3.2821	**0.001619**	6.5581e-03	0.0022	3.0382	**0.003375**	4.9302e-03	0.0024	2.0719	**0.042186**
time	N/A				-1.7394e-01	0.0437	-3.9766	**0.000172**	1.4274e+00	0.4097	3.4841	**0.000882**
literacy_rate	N/A				N/A				-4.9607e-04	0.0048	-0.1024	0.919066
literacy_rate *time	N/A				N/A				-2.0946e-02	0.0055	-3.7867	**0.000332**
Residual St. Error	0.1877 on 69 degrees of freedom				0.1351 on 68 degrees of freedom				0.1478 on 66 degrees of freedom			

Model 3 was used to generate predictions of prevalence for time 0 (Figure 6.A) and time 1 (Figure 6.B). Although prevalence was notably high along the northern border and in the easternmost third of the country, infection rates were quite low in the south and southwest. This distribution was largely unchanged over time.

Like *A. lumbricoides, T. trichiura* infection rates decreased significantly between the two time periods, however reductions were more modest*;* on average, prevalence was 7% lower in time 1 than time 0, and infection rates were predicted to decline in 71% of municipalities. Based on predictions from the most current time period, once and twice yearly deworming is recommended for 160 and 45 municipalities, respectively (Figure 6.C).

Figure 6: *T. trichiura* Predicted Prevalence & Recommended Treatment Frequency

Figure 6.A: Predicted Prevalence, Time 0 (2001-2006)

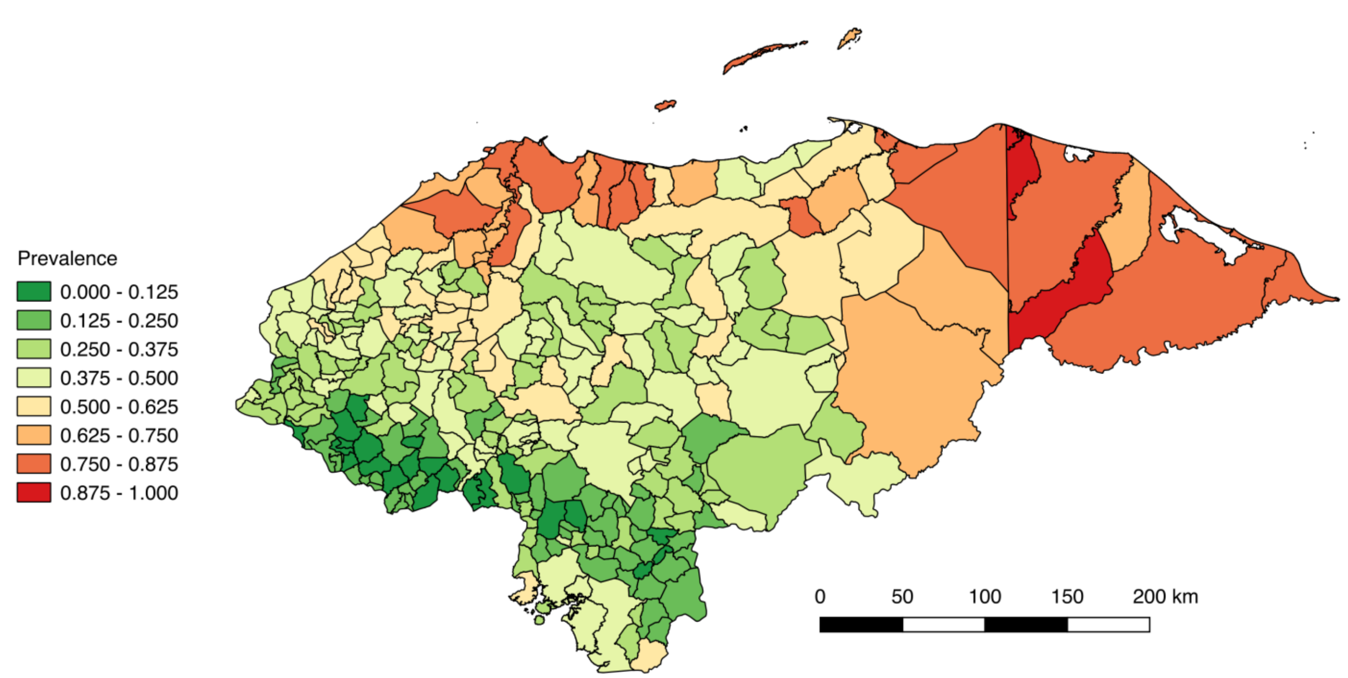


Figure 6.B: Predicted Prevalence, Time 1 (2007-2012)

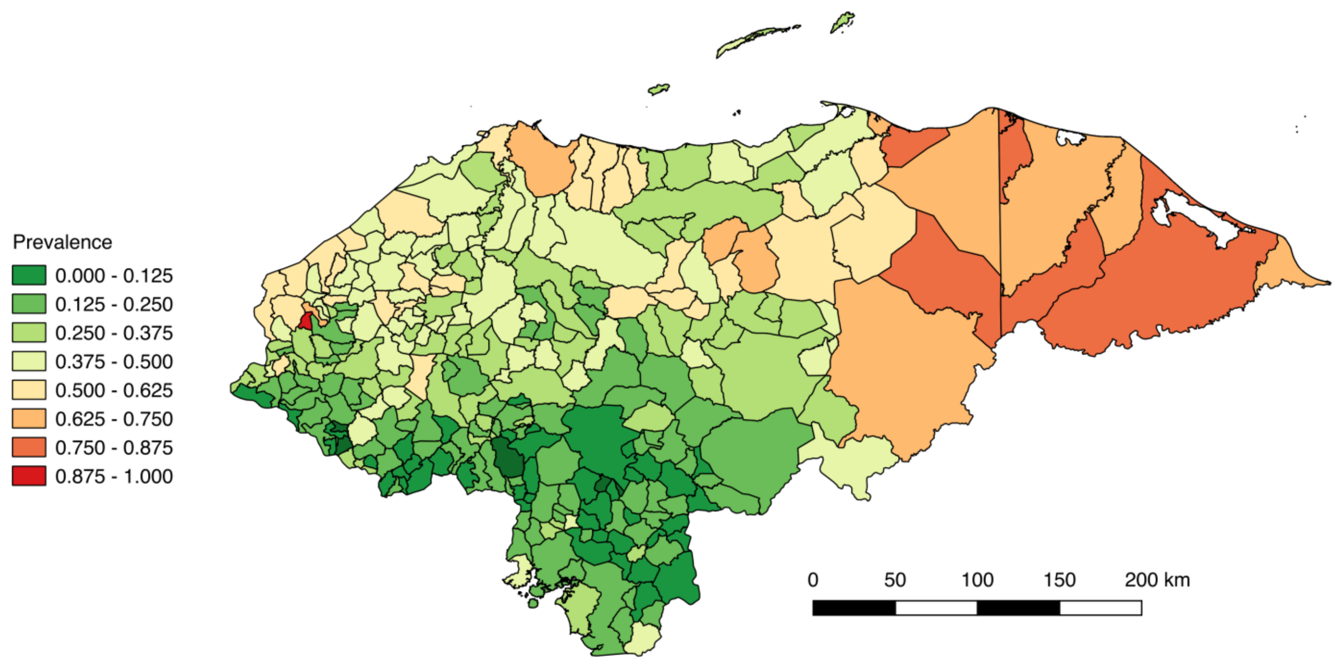
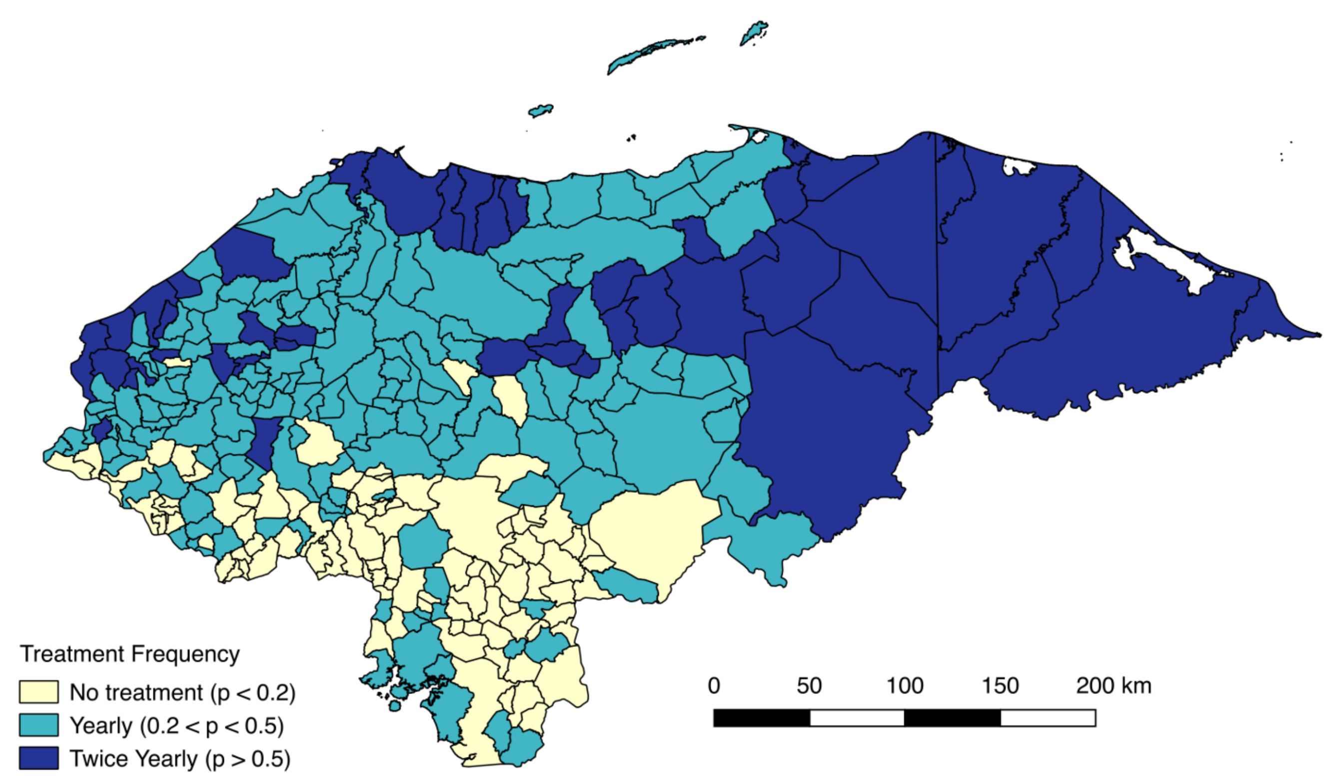


Figure 6.C: Recommended Treatment Frequency (Based on Time 1 Predictions)



2.3.3 Hookworm

Sample-size weighted hookworm prevalence rates varied between 0% and 47%, with mean and median prevalence rates of 0% and 4%, respectively. On average, hookworm was the least prevalent STH infection in Honduras. Summary statistics describing hookworm prevalence are included in Appendix B (Appendix B.2).

No toilet (0.0038), average annual precipitation (0.0169), clay content of soil (0.0296) and literacy rates (0.0417) were the only independent variables significantly associated with hookworm prevalence in simple regression analyses; increased literacy rate was associated with reduced infection prevalence, while the other three variables had the opposite effect on risk of infection (Table 1.A, Table 1,B and Table 1.C). Literacy rate and no toilet were highly correlated (-0.84512), however the sanitation variable was retained for further analysis because hookworm is transmitted transdermally and the absence of latrines is associated with increased open-field defecation (Narain, Rajguru & Mahanta, 2006; Quihui et al., 2006).

In the main effects multiple linear regression, all three variables were positively associated with infection prevalence, however only no toilet (p-value: 0.00217) and average annual precipitation (0.04594) were significant at the 0.05 level (Table 2.C.I). When time was added in the second model (Model 2), both time (p-value: 0.00109) and precipitation (0.00710) were significant; the former was associated with a reduction in prevalence, while the latter was associated with increased prevalence (Table 2.C.I). This model explained slightly over one third of the variability in the dependent variable (multiple R-squared: 0.3303), and the addition of a literacy-time interaction in Model 3 (p-value: 0.4530) only conferred a marginal improvement in model fit (multiple R-squared: 0.3371). Although VIFs were low (Appendix B.5) and no spatial autocorrelation was detected in model residuals (Appendix B.6), heteroskedasticity in errors was observed (Appendix B.7).

Both Model 1 and 2 were re-run using robust (Table 2.C.II) and logistic regression techniques (Table 2.C.III); although the results of the robust and logistic regressions were similar to each other, they differed quite substantially from the linear regression output. The linear regression model (Model 2) was used to generate predictions of hookworm prevalence, however maximum infection rates were 20.6% and 12.9% for time 0 and time 1, respectively. Based on the WHO treatment guidelines and prevalence estimates from the more current time period, no municipalities require deworming on the basis of hookworm prevalence alone.

Table 2.C.I: Hookworm: Multiple Linear Regression

	Main Effects (Model 1)				**Main Effects + Time (Model 2)**				**Main Effects + Interaction (Model 3)**			
	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)
Intercept	-1.147e-01	4.156e-02	-2.759	0.00737	-6.417e-02	4.149e-02	-1.546	0.12650	-2.057e-01	2.074e-01	-0.992	0.3248
toilet_none	1.801e-03	5.662e-04	3.182	**0.00217**	6.448e-04	6.277e-04	1.027	0.30783	1.245e-03	1.267e-03	0.983	0.3290
Avg_precip	4.987e-05	2.454e-05	2.032	**0.04594**	6.462e-05	2.330e-05	2.774	**0.00710**	6.190e-05	2.472e-05	2.504	**0.0147**
percent_clay	1.576e-03	9.120e-04	1.728	0.08833	1.317e-03	8.539e-04	1.542	0.12757	1.452e-03	8.934e-04	1.625	0.1087
time	N/A				-7.085e-02	2.078e-02	-3.409	**0.00109**	5.894e-02	1.716e-01	0.343	0.7324
literacy_rate	N/A				N/A				1.788e-03	2.524e-03	0.708	0.4812
literacy_rate*time	N/A				N/A				-1.727e-03	2.288e-03	-0.755	0.4530
Multiple R-squared	0.2192				0.3303				0.3371			
Adjusted R-squared	0.1862				0.2921				0.2787			

Table 2.C.II: Hookworm: Logistic Regression								
	Main Effects (1)				**Main Effects + Time (2)**			
	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)
Intercept	-1.898e-01	2.471e-01	-0.768	0.4451	0.07829	0.25088	0.312	0.75591
toilet_none	9.563e-03	3.367e-03	2.840	**0.0059**	0.00342	0.00380	0.902	0.37039
Avg_precip	8.382e-05	1.460e-04	0.574	0.5676	0.00016	0.00014	1.151	0.25352
percent_clay	1.218e-02	5.423e-03	2.246	**0.0278**	0.01081	0.00516	2.093	**0.03998**
time	N/A				-0.37618	0.12566	-2.994	**0.00381**
Dispersion parameter	0.2123961				0.1909808			
Null deviance	18.187 on 74 degrees of freedom				18.187 on 74 degrees of freedom			
Residual deviance	15.080 on 71 degrees of freedom				13.369 on 70 degrees of freedom			
AIC	102.53				95.498			
#of Fisher scoring iterations	2				2			

Table 2.C.III: Hookworm: Robust Regression								
	Main Effects (1)				**Main Effects + Interaction (2)**			
	Estimate	Std. Error	T value	Pr (>|t|)	Estimate	Std. Error	T value	Pr (>|t|)
Intercept	0.05667	0.0198	2.8559	0.005624	0.04041	0.0228	1.7708	0.080947
toilet_none	-0.00075	0.0003	-2.9317	**0.00453**	-0.00040	0.0003	-1.2915	0.200951
Avg_precip	-0.00702	0.0107	-0.6590	0.512027	-0.00056	0.0119	-0.0472	0.962647
percent_clay	0.00058	0.0002	2.4318	**0.017549**	0.00058	0.0003	2.2196	**0.029688**
time	N/A				-0.01696	0.0055	-3.0667	**0.003082**
Residual St. Error	0.01745 on 71 degrees of freedom				0.01519 on 70 degrees of freedom			

2.4 DISCUSSION

2.4.1 Summary of Methods and Findings

Our models predict that more than 75% of Honduran municipalities have at least one STH prevalence rate above 20% and thus qualify for MDA based on WHO guidelines (2006; 2011). Of these regions, 50 municipalities have prevalence rates greater than 50%, thus necessitating twice yearly treatment administration. Figures 4.C and 6.C illustrate the recommended treatment frequency for each municipality as informed by ascariasis prevalence and trichuriasis prevalence, respectively. The majority of municipalities that qualify for semi-annual deworming are located in the easternmost third of the country and do so on the basis of elevated trichuriasis prevalence rates.

Our results also suggest that STH prevalence rates are declining in Honduras. Ascariasis and trichuriasis prevalence rates were, on average, 15% and 7% lower in 2007-2012 compared to the earlier time period, and reduced infection rates were predicted in 86% and 71% of municipalities, respectively. Moreover, the dichotomous time variable was significantly associated with reduced infection for all three parasites, suggesting that *A. lumbricoides*, *T. trichiura* and hookworm prevalence were lower in time 1 (2007-2012).

Reduced prevalence rates in Honduras are probably the result of environmental, social and/or behavioural change that was not quantified or accounted for in our independent variables. One likely hypothesis is that these declines are attributable to successful control programs, as observed in several Asian and Latin American countries (de Silva et al., 2003). Although organized control efforts started in the 1990s, nation-wide deworming programs targeting school-age children were introduced in 2001 (WHO, 2012) and have continued to expand in the intervening years. Based on the limited data available, treatment coverage in the first and second time periods averaged 41.92% and 58.74%, respectively (WHO PCT database, 2017), and national coverage rates of around 70% were reported between 2009 and 2011 (Sanchez et al., 2014). As treatment programs have become more pervasive and comprehensive, prevalence of ascariasis and, to a lesser, trichuriasis, have declined significantly.

Perhaps unsurprisingly, our model also predicted a shift in the relative distribution of these two infections. Trichuriasis prevalence exceeded that of ascariasis in slightly over half (154) of Honduras' 298 municipalities during the first time period, however it was the leading infection in 71% of municipalities (212/298) in 2007-2012. This is likely a by-product of the previous observation - ascariasis prevalence has declined more significantly and in more areas, leaving trichuriasis as the leading infection in the majority of the country.

Although hookworm was the least prevalent infection in both time periods, with maximum predicted prevalence of 20.6% and 12.9% for time 0 and time 1, respectively, our models likely underestimate the burden of hookworm due to the selection criteria of the original dataset (Sanchez et al., 2014). For example, all 97 studies used to generate our models were conducted in children ≤ 15 years of age, however hookworm prevalence peaks in adulthood (Anderson et al., 1993; Bethony et al., 2002; Behnke et al., 2000; Brooker et al., 2004; Brooker et al., 2006a). This is in contrast to *A. lumbricoides* and *T. trichiura*, which are most prevalent among pre-school and school aged children (Anderson et al., 1993; Anuar et al., 2014; Bethony et al., 2006; Hotez et al., 2006; Quintero et al., 2012). As a result, it is likely that the prevalence rates used to generate our hookworm models were lower than if the studies also considered adults, while the opposite would be expected for the other two infections. Additionally, all of the original surveys used the Kato Katz method for stool examination, which has low sensitivity for identifying hookworm eggs (Tarafder, Carabin, Joseph, Balolong, Olveda, & McGarvey, 2010).

Our findings are consistent with several recent studies that have identified *T. trichiura* as the dominant STH species in Honduras (Torres et al., 2014; Sanchez et al., 2014; Gabrie et al., 2014). As described by these researchers, the most likely explanation for this observation is the low efficacy of single-dose albendazole for treating trichuriasis (Horton, 2000; Adams et al., 2004; Albonico et al., 1994; Levecke et al., 2014). Although it is highly effective in curing ascariasis (95% mean cure rate, 67 studies), single-dose albendazole resolves fewer than half of *T. trichiura* infections (47% mean cure rate, 56 studies) (Horton, 2000; Bennett & Guyatt, 2000). Perhaps unsurprising, trichuriasis is now relatively more common in many regions where mass administration of albendazole has been employed (Sanchez et al., 2016). By extension, geographic variability in ascariasis prevalence is likely related to municipal-level differences in access and availability of deworming resources.

Importantly, this might explain why the risk factors predictive of ascariasis and trichuriasis infections differed so significantly in the simple regression analysis. *A. lumbricoides* and *T. trichiura* thrive in similar environmental conditions and are transmitted via the same mechanism, so we expected that the prevalence of these infections would be associated with many of the same determinants. However, determinants identified as significant predictors of *A. lumbricoides* in simple regression analyses differed from those identified for *T. trichiura.* All seven determinants describing characteristics of the natural environment (average mean temperature, average annual precipitation, clay content of soil, altitude, TRI, forest and agricultural cover) were significant for the latter infection, while only one (forest cover) was significant for the former. Conversely, ascariasis prevalence was highly correlated with social and developmental metrics including HDI, literacy rate, income and school attendance, none of which were significant for trichuriasis.

We hypothesize that these social and developmental metrics are correlated with ascariasis prevalence because they explain variability in treatment accessibility; access to health services is frequently lowest amongst the poor (Peters et al., 2008), and poor children are less likely to enrol in school (Ainsworth & Filmed, 2002; Case, Paxson & Ableidinger, 2004). Because deworming programs are administered through the educational system, the poorest municipalities, as well as those with low literacy and school attendance rates, are likely to have lower treatment coverage than regions where all children are able to attend school. As a result, it is unsurprising that *A. lumbricoides* infection prevalence was negatively correlated with all four of these variables.

Improved social and economic development might protect against infection via other mechanisms, however none of these factors were significant predictors of trichuriasis prevalence in simple or multiple regression analysis. If the associations between ascariasis prevalence and HDI, income, school attendance and literacy rates were due to reduced environmental contamination and/or decreased transmission in wealthier/more developed areas, we'd expect that these determinants would be negatively correlated with both species. The fact that these relationships are only observed for *A. lumbricoides* suggests that their effects are mediated by albendazole administration.

In multiple regression analyses, these effects were less striking; trichuriasis prevalence was significantly associated with clay content of soil and terrain ruggedness, while ascariasis was correlated with proportion of homes with cement floors and average temperature. Additionally, forest cover, time and the literacy rate-time interaction term were significant for both infections. Hookworm infection was associated with average precipitation and time. Models of ascariasis, trichuriasis and hookworm prevalence were able to account for 47%, 60% and 33% of variability in prevalence rates.

We hypothesize that much of the unexplained variability in prevalence rates, particularly for ascariasis, is attributable to differential treatment accessibility. Future researchers should include explicit measures of deworming history and access to treatment in their regression analyses to control or better understand these effects. Existing information regarding geographic coverage of control programs is relatively poor (Torres et al., 2014) so establishing and maintaining accurate, up-to-date records of where and what proportion of children have been treated should continue to be a priority for organizations administering deworming programs. Ultimately, treatment should be administered to areas where prevalence is highest, however it is important to consider that these areas will change depending on where treatment has been made available in the past.

2.4.2 Limitations

One of the primary limitations of this study concerns the ecological fallacy; the results of ecological analyses might depend on how the populations have been grouped, and thus cannot be used to infer about the nature of individuals (Piantadosi, Byar &

Green, 1988). While this certainly limits the application of our results to other settings, it does little to detract from our objectives; deworming programs are administered at national and sub-national scales so understanding municipal-level correlates of infection is more valuable than explaining how risk varies between individuals.

A second important limitation involves our prevalence data, which was compiled from independent samples collected and analyzed by different researchers over a twelve-year period. However, this is a common strategy in the field (Karagiannis-Voules et al., 2015; Chammartin et al., 2013; Brooker et al., 2003; Brooker et al., 2006b) because establishing prevalence rates is extremely expensive and time-consuming. As a result, our findings are limited in much the same way as other comparable national and sub-national investigations.

Using these data would have been less of an issue if our independent variables were year-specific, however annual data was difficult to obtain, particularly for developmental and census metrics. Similarly, no behavioural variables were included in our analysis despite being significant in other research (Bethony et al., 2006; Anuar et al., 2014; Hohmann, Panzer, Phimpachan, Southivong & Schelp, 2001; Belyhun et al., 2010; Strunz et al., 2014; Alelign, Degarege & Erko, 2015; Balen et al., 2011; Alemu et al., 2011; Xu et al., 2000; Bieri et al., 2013; Gyrokos et al., 2013; Naish, McCarthy & Williams, 2004; Holland et al., 1988; Alvarado & Vásquez, 2006; Quihui et al., 2006). These variables, such as propensity to wash hands, wear shoes and defecate outdoors are difficult to measure and are not typically included in large-scale data collection devices, such as the national census.

Similarly, we did not consider parasite or host variables that might explain differences in vulnerability to infection between individuals. Although these biological confounders might be important for explaining infection distribution at small scales, they are unlikely to explain differences between municipalities unless they themselves vary between these regions. Furthermore, many of our natural variables vary at the microenvironmental scale, however we were unable to capture these differences because data was aggregated at the municipality level. Parasite, host and microenvironmental variables are examples of important small-scale factors that should be considered in surveys conducted at a finer spatial resolution.

Finally, our treatment recommendations are based on either ascariasis or trichuriasis prevalence, depending on which is higher. However, it is not necessarily the same proportion of the population infected with both infections; thus, it is likely that the proportion of municipal populations suffering from "any STH infection" is higher than either of these predictions. In addition to modeling ascariasis, trichuriasis and hookworm, future investigations should analyze the distribution of any STH infection, as it is more valuable for informing treatment distribution and resource allocation.

2.5 CONCLUSION

In this study we model *A. lumbricoides*, *T. trichiura* and hookworm prevalence and illustrate the geographic distribution of each infection at two periods of time. Although prevalence of all three infections has declined significantly, more than 75% of municipalities still require annual or semi-annual deworming. Reductions in prevalence are likely related to deworming campaigns, however unmeasured inequities in treatment accessibility represent a challenge for modeling infection prevalence. We suggest that including an explicit measure of access to treatment in future analyses will be necessary to determine how differential access contributes to variability in the distributions of *A. lumbricoides* and *T. trichiura* specifically.

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Sanchez, A. L., Gabrie, J. A., Rueda, M. M., Mejia, R. E., Bottazzi, M. E. & Canales, M. (2014). A Scoping Review and Prevalence Analysis of Soil-Transmitted Helminth Infections in Honduras. *PLOS Neglected Tropical Diseases, 8*(1):e2653.

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APPENDIX A: SOURCES OF DATA

I. Dependent Variables: Prevalence Rates

Methods used for retrieving prevalence data are described in:

Sanchez, A. L., Gabrie, J. A., Rueda, M. M., Mejia, R. E., Bottazzi, M. E. & Canales, M. (2014). A Scoping Review and Prevalence Analysis of Soil-Transmitted Helminth Infections in Honduras. *PLOS Neglected Tropical Diseases, 8*(1):e2653. Retrieved at http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002653

II. Independent Variables:

A. Natural Environment.

1. Forest Cover.

NASA, USGS Land Processes Distributed Active Archive Center (LP DAAC). (n.d). MODIS Land Cover Type product (MCD12Q1), Land Cover Type Yearly L3 Global 500m SIN Grid (2001-2013). Retrieved at https://lpdaac.usgs.gov/dataset_discovery/modis/modis_products_table/mcd12q1

2. Agricultural Land.

Ramankutty, N., Evan, A. T., Monfreda, C., & Foley, J. A. (2010). Global agricultural lands: Croplands, 2000. *Data distributed by the NASA Socioeconomic Data and Applications Center (SEDAC)*. Retrieved from http://sedac.ciesin.columbia.edu/data/set/aglands-croplands-2000

3. Average Altitude.

Abrams, M. (2000). The Advanced Spaceborne Thermal Emission and Reflection Radiometer (ASTER): data products for the high spatial resolution imager on NASA's Terra platform. *international Journal of Remote sensing*, *21*(5), 847-859. Retrieved from https://asterweb.jpl.nasa.gov/gdem.asp

4. TRI.

Riley, S. J. (1999). Index That Quantifies Topographic Heterogeneity. Intermountain Journal of Sciences, 5(1–4), 23-27

5. *Temperature & Precipitation.*

Hijmans, R. J., Cameron, S. E., Parra, J. L., Jones, P. G., & Jarvis, A. (2005). Very high resolution interpolated climate surfaces for global land areas. *International journal of climatology*, *25*(15), 1965-1978.

6. Clay Content of Soil.

Nachtergaele, F. O., van Velthuizen, H., Verelst, L., Batjes, N. H., Dijkshoorn, J. A., van Engelen, V. W. P., ... & Prieler, S. (2008). *Harmonized world soil database (version 1.0)*. Food and Agric Organization of the UN (FAO); International Inst. for Applied Systems Analysis (IIASA); ISRIC-World Soil Information; Inst of Soil Science-Chinese Acad of Sciences (ISS-CAS); EC-Joint

Research Centre (JRC). Retrieved from http://www.fao.org/soils-portal/soil-survey/soil-maps-and-databases/harmonized-world-soil-database-v12/en/

B. Built Environment.

1. Floor Material. "Material predominante en el Piso"(2001) and "Material del piso" (2013) quantify the proportion of homes in each municipality with each of 8 different floor materials: "Tierra" (earth); "Plancha de cemento" (cement sheet); "Madera" (wood); "Ladrillo de cemento" (cement brick); "Ladrillo de terrazo o granito" (terrazzo or granite brick) ; "Ladrillo de barro" (clay brick); "Cerámica" (ceramic) and "Otro" (other).

Data Sources: Floor Material

-2001 ("Material predominante en el Piso"):

Instituto Nacional de Estadistica. (2001). Honduras Population and Housing Census, 2001. Retrieved from http://170.238.108.227/binhnd/RpWebEngine.exe/Portal?BASE=CPVHND2001&lang=ESP

-2013 ("Material del piso"):

Instituto Nacional de Estadistica. (2013). Honduras Population and Housing Census, 2013. Retrieved from http://170.238.108.227/binhnd/RpWebEngine.exe/Portal?BASE=CPVHND2013NAC&lang=ESP

2. Wall Material. Similarly, "Material predominante en las Paredes Exteriores" (2001) and "Material de pared" (2013) describe the proportion of homes with each of 9 different wall materials, including "Ladrillo rafón" (brick); "Piedra rajada o cantera" (stone burst or quarry); "Bloque de cemento o concreto" (concrete block or cement); "Adobe"; "Madera" (wood); "Bahareque"; "Palo o caña" (stick or cane); "Material de desecho" (waste material) and "Otro" (other).

Simple regression was conducted on earth, cement sheet and cement brick floor variables, and cement brick/concrete and adobe wall variables for each of the three STH infections.

Data Sources: Wall Material

-2001 ("Material predominante en las Paredes Exteriores"):

Instituto Nacional de Estadistica. (2001). Honduras Population and Housing Census, 2001. Retrieved from http://170.238.108.227/binhnd/RpWebEngine.exe/Portal?BASE=CPVHND2001&lang=ESP

-2013 ("Material de pared"):

Instituto Nacional de Estadistica. (2013). Honduras Population and Housing Census, 2013. Retrieved from http://170.238.108.227/binhnd/RpWebEngine.exe/Portal?BASE=CPVHND2013NAC&lang=ESP

3. Sanitation Type. In the 2001 census, home ("hogar") sanitation type ("Servicio Sanitario") was classified into 5 categories: "Inodoro conectado a red de alcantarillado" (toilet connected to a sewage system); "Inodoro conectado a pozo séptico" (toilet connected to septic tank); "Inodoro con descarga a rio, quebrada, laguna, mar o lago" (toilet with discharge to river, ravine, lagoon, sea or lake); "Letrina de pozo simple" (single pit latrine); and "No tiene" (does not have). For the 2013 census, "Tipo de Sanitario" was classified by the same 5 variables plus "Letrina con cierre hidráulico" (latrine with hydraulic closure) and "Otro" (other). For this study, "no tiene" (does not have) was retained for analysis

Data Source: Sanitation Type

-2001 ("Servicio Sanitario"):

Instituto Nacional de Estadistica. (2001). Honduras Population and Housing Census, 2001. Retrieved from http://170.238.108.227/binhnd/RpWebEngine.exe/Portal?BASE=CPVHND2001&lang=ESP

-2013 ("Tipo de Sanitario"):

Instituto Nacional de Estadistica. (2013). Honduras Population and Housing Census, 2013. Retrieved from http://170.238.108.227/binhnd/RpWebEngine.exe/Portal?BASE=CPVHND2013NAC&lang=ESP

4. Population Density.

Center for International Earth Science Information Network - CIESIN - Columbia University. (2016). Gridded Population of the World, Version 4 (GPWv4): Population Count. Palisades, NY: NASA Socioeconomic Data and Applications Center (SEDAC). http://dx.doi.org/10.7927/H4X63JVC. Accessed 04, 03, 2017.

5. Road Density.

Humanitarian Data Exchange. (2015). Honduras – Roads (Zipped Shapefile). Retrieved from https://data.humdata.org/dataset/honduras-roads

C. Social Environment.

1. Literacy Rate. The census variable "Sabe leer y escribir", coded as either "Si" (yes) or "No" (no) measures the proportion of the population that can read and write.

Data Sources: Literacy Rate

-2001 ("Sabe Leer y Escribir"):

Instituto Nacional de Estadistica. (2001). Honduras Population and Housing Census, 2001. Retrieved from http://170.238.108.227/binhnd/RpWebEngine.exe/Portal?BASE=CPVHND2001&lang=ESP

-2013 ("Sabe Leer y Escribir"):

Instituto Nacional de Estadistica. (2013). Honduras Population and Housing Census, 2013. Retrieved from http://170.238.108.227/binhnd/RpWebEngine.exe/Portal?BASE=CPVHND2013NAC&lang=ESP

2. Income, Schooling Rate and HDI.

United Nations Development Program (UNDP) Honduras. (2012). Human Development Report Honduras 2011. Reduce inequity: an imperative challenge. Retrieved from http://www.undp.org/content/dam/honduras/docs/publicaciones/INDH2011Completo_sin%20anexos.pdf

APPENDIX B: EXTRA TABLES AND FIGURES

Appendix B.1: Descriptive Statistics: Independent Variables											
	Min.	Median	Mean	Max.	Std. Dev.		Min.	Median	Mean	Max.	Std. Dev.
A. BUILT ENVIRONMENT											
i. Floor Material						iii. Sanitation System					
Earth	1.200	33.95	35.01	88.59	20.45	No toilet	0.30	16.78	20.81	72.34	15.91
Cement Brick	0.110	7.43	10.25	37.57	9.098	iv. Population Density					
ii. Wall Material						Pop. per km^2	3.132	78.79	115.6	755.0	147.7
Cement/Concrete	1.010	18.62	23.67	83.93	20.65	v. Road Density					
Adobe	0.380	45.76	44.43	93.63	28.17	Road Densi.	0.000	1.87×10^{-4}	1.72×10^{-4}	4.14×10^{-4}	7.76×10^{-5}
B. NATURAL ENVIRONMENT											
i. Ground Cover						iii. Precipitation					
Forest (%)	0	0.296	0.291	0.878	0.230	Avg. Ann. Precip.	946.9	1516	1607	2614	383.5
Cropland (%)	0	0.182	0.189	0.531	0.128	iv. Temperature					
ii. Topography						Avg. Temp	18.38	21.92	22.54	27.71	2.464
Average Altitude	6.515	928.1	819.9	1584	441.5	v. Soil Composition					
TRI	7.001	255.4	246.3	470.0	91.22	Clay Content (%)	12	24	22.12	49	10.32
C. SOCIAL CONDITIONS											
i. Literacy Rate						iii. Schooling Rate (% of 7 years and older)					
Literacy Rate	40.58	75.21	73.84	88.94	8.614	Schooling Rate	21.21	44.88	44.72	64.39	8.628
ii. Estimated Per Capita Income						iv. Human Development Index (HDI)					
Income (US$ PPP)	1057	2465	2732	6876	1286	HDI	0.5010	0.646	0.642	0.787	0.061

Appendix B.2: Descriptive Statistics: Dependent Variables					
	Minimum	Median	Mean	Maximum	Standard Deviation
A. lumbricoides Prevalence	0.00000	0.21154	0.27292	0.74359	0.2132475
T. trichiura Prevalence	0.01724	0.32184	0.35928	0.92157	0.2322107
Hookworm Prevalence	0.00000	0.00000	0.03780	0.47059	0.08590375

Appendix B.3: Multicolinearity Assessment - *Ascaris lumbricoides*

Correlation between independent variables

	floor_cementbrick	toilet_none	prop_forest	Avg_temp	literacy_rate	income	school_rate	HDI	time
floor_cementbrick	1	-0.2471139	-0.392441	-0.2357978	0.3315109	0.4514748	0.554811	0.3648516	-0.2858021
toilet_none	-0.2471139	1	-0.059840	-0.0798911	-0.86904	-0.576760	-0.6377755	-0.7952859	-0.5340289
prop_forest	-0.3924411	-0.0598403	1	0.248634	-0.009089	0.0712768	0.02614146	0.1150948	0.1021107
Avg_temp	-0.2357978	-0.0798911	0.248634	1	0.1753889	0.1728588	0.09416321	0.1997969	0.00743421 6
literacy_rate	0.3315109	-0.86904	-0.009089	0.1753889	1	0.6783146	0.8439348	0.8981941	0.4254612
income	0.4514748	-0.5767604	0.07127679	0.1728588	0.6783146	1	0.7362017	0.8689491	0.05194025
school_rate	0.554811	-0.6377755	0.02614146	0.09416321	0.8439348	0.7362017	1	0.8354721	0.07079115
HDI	0.3648516	-0.7952859	0.1150948	0.1997969	0.8981941	0.8689491	0.8354721	1	0.3514158
time	-0.2858021	-0.5340289	0.1021107	0.00743422	0.4254612	0.0519403	0.07079115	0.3514158	1

Note: *"toilet_none" variable was removed from the model due to the high correlation between "toilet_none" and "literacy_rate". Similarly, "income", "school_rate" and "HDI" were removed from the model because they were highly correlated with each other and "literacy_rate". See* ***Results*** *for rationale.*

Variance Inflation Factors

	floor_cementbrick	toilet_none	prop_forest		literacy_rate	income	school_rate	HDI	time
	1.803805	N/A	1.221123		1.734801	N/A	N/A	N/A	1.649012

Appendix B.4: Multicolinearity Assessment - *Trichuris trichiura*

Correlation between independent variables

	floor_earth	wall_adobe	prop_forest	cropmean	Avg_altitude	TRI	Avg_precip	Avg_temp	percent_clay	time
floor_earth	1	0.7325576	-0.360607	0.4613422	0.4563031	0.4014766	-0.4066903	-0.4025161	-0.2659864	-0.3405102
wall_adobe	0.7325576	1	-0.5617076	0.6006608	0.6834245	0.4169006	-0.5413432	-0.6467647	-0.3357984	-0.04928164
prop_forest	-0.360607	-0.5617076	1	-0.6537348	-0.3046861	0.01992842	0.4730708	0.248634	0.4440337	0.1021107
cropmean	0.4613422	0.6006608	-0.6537348	1	0.5343921	0.2714371	-0.4026611	-0.4824093	-0.3563198	-0.1194375
Avg_altitude	0.4563031	0.6834245	-0.3046861	0.5343921	1	0.5250622	-0.5394784	-0.9861042	-0.2144441	-0.01802303
TRI	0.4014766	0.4169006	0.01992842	0.2714371	0.5250622	1	-0.3817684	-0.483432	0.0372327	0.01645602
Avg_precip	-0.4066903	-0.5413432	0.4730708	-0.4026611	-0.5394784	-0.3817684	1	0.458773	0.28988	0.1453724
Avg_temp	-0.4025161	-0.6467647	0.248634	-0.4824093	-0.9861042	-0.483432	0.458773	1	0.1443981	0.007434216
percent_clay	-0.2659864	-0.3357984	0.4440337	-0.3563198	-0.2144441	0.0372327	0.28988	0.1443981	1	-0.02591843
time	-0.3405102	-0.04928164	0.1021107	-0.1194375	-0.01802303	0.01645602	0.1453724	0.00743421 6	-0.02591843	1

Note: *"wall_adobe", "cropmean", "Avg_altitude" and "Avg_temp" were removed from the model due to high correlations with each other and several other variables.*

Variance Inflation Factors

	floor_earth	wall_adobe	prop_forest	cropmean	Avg_altitude	TRI	Avg_precip	Avg_temp	percent_clay	time
	1.723349	N/A	1.651017	N/A	N/A	1.540451	1.669251	N/A	1.330189	1.215651

Appendix B.5: Multicolinearity Assessment - Hookworm

Correlation between Independent Variables

	literacy_rate	**toilet_none**	**Avg_precip**	**percent_clay**	**time**
literacy_rate	1	-0.86904	0.1162217	-0.07003552	0.4254612
toilet_none	-0.86904	1	-0.00709848	-0.007561723	-0.5340289
Avg_precip	0.1162217	-0.00709848	1	0.28988	0.1453724
percent_clay	-0.07003552	-0.007561723	0.28988	1	-0.02591843
time	0.4254612	-0.5340289	0.1453724	-0.02591843	1

Note: *"literacy_rate" variable was removed from the model due to the high correlation between "toilet_none" and "literacy_rate"*

Variance Inflation Factors

	literacy_rate	**toilet_none**	**Avg_precip**	**percent_clay**	**time**
	N/A	1.412943	1.130815	1.100491	1.450822

Appendix B.6: Spatial Autocorrelation (Moran's I)

		$observed	**$expected**	**$sd**	**$p.value**
A. lumbricoides Multiple linear regression with interaction	**Observed Prevalence**	0.09707627	-0.01351351	0.0197237	2.059232e-08
	Predicted Prevalence	0.05060004	-0.01351351	0.01968832	0.001128246
	Model Residuals	0.04938193	-0.01351351	0.01961551	**0.001344007**
A. lumbricoides Multiple linear regression + interaction, Avg_temp	**Predicted Prevalence**	0.09624451	-0.01351351	0.01971265	2.578312e-08
	Model Residuals	0.008339185	-0.01351351	0.01966842	0.2665445
T. trichiura Multiple linear regression with interaction	**Observed Prevalence**	0.1128722	-0.01351351	0.01969119	1.377265e-10
	Predicted Prevalence	0.120197	-0.01351351	0.01957621	8.476553e-12
	Model Residuals	0.005627928	-0.01351351	0.01968615	0.3308863
Hookworm Multiple linear regression, no interaction	**Observed Prevalence**	0.007566695	-0.01351351	0.01821022	0.2470259
	Predicted Prevalence	0.0335617	-0.01351351	0.01968018	0.01675631
	Model Residuals	-0.02442563	-0.01351351	0.01891896	0.5640869

Appendix B.7: Heteroskedasticity Assessment

	I. Breush Pagan Test via "lmtest::bptest(model)"			**II. Non-constant Variance Score Test via "car" package**		
	BP	**df**	**p-value**	**Chisquare**	**Df**	**p**
A. lumbricoides	9.4157	5	0.09359	1.451585	1	0.2282738
T. trichiura	6.8046	8	0.5579	3.630856	1	0.05671764
Hookworm	19.782	4	**0.0005515**	65.44852	1	**5.965199e-16**

CHAPTER THREE: HEALTH CARE REGIONALIZATION IN HONDURAS:

The modifiable areal unit problem and a case for regionalization based on soil-transmitted helminth infection prevalence rates

3.1 INTRODUCTION

3.1.1 Background

Soil-transmitted helminth (STH) infections are neglected tropical diseases (NTDs) characterized by the presence of adult parasitic worms, namely *Ascaris lumbricoides, Trichuris trichiura* and hookworm (*Necator americanus* and *Ancylostoma duodenale*), in the digestive tract of human hosts (Bethony et al., 2006). Fertilized eggs are expelled from the host's body in feces and mature to infectivity in warm, moist and shaded soil. *A. lumbricoides* and *T. trichiura* infections are transmitted via ingestion, while hookworm can actively penetrate the skin (Center for Disease Control, 2015; Center for Disease Control, 2013a; Center for Disease Control, 2013b).

Like other NTDs, STH infections thrive in areas with high levels of poverty, economic disadvantage, inadequate sanitation infrastructure and irregular or limited access to clean water (World Health Organization, 2011). These conditions facilitate helminth transmission by increasing the degree to which soil is contaminated with human feces, and the amount of contact between potential hosts and polluted soil (Narain, Rajguru & Mahanta, 2000; Quihui et al., 2006; Strunz et al., 2014; Esrey et al., 1991;

Ahmed et al., 2011; Sanchez et al., 2016; Hohmann, Panzer, Phimpachan, Southivong & Schelp, 2001; Anuar, Salleh & Moktar, 2014; Belyhun et al., 2010; Balen et al., 2011; Alemu et al., 2011). Thus, eradication of these infections will require significant poverty reduction and, importantly, large investments in public and private sanitation infrastructure.

Major reductions in poverty and investments in sanitation are not be realistic short-term solutions in the impoverished countries where STH infections are endemic, however immediate and sustainable control is essential because of the significant burden these infections pose to both individuals and public health. While case-fatality rates are low, STH infections are associated with malnutrition, and anemia, physical and cognitive stunting (Bethony et al., 2006; Bundy & Cooper, 1996; CDC, 2015; CDC 2013a; CDC, 2013b; Eberhard, Cabrielli, Montresor & Savioli, 2015; Deming & Eberhard, 2015a; Deming & Eberhard 2015b), decreased school attendance (de Silva et al., 2003; Miguel & Kremer, 2004) and performance (Hotez et al., 2008), impaired literacy (Bleakley et al., 2007) as well as reduced productivity and wage-earning capacity in adults (Bleakley et al., 2007; Reviewed in Guyatt, 2000). These effects contribute to the cycle of poverty and subsequently increase vulnerability to future infection (Hotez et al., 2008).

Importantly, STH infections are treatable with oral administration of benzimidazole antiparasitic drugs such as albendazole and mebendazole, which, when used properly, are a powerful tool for short-term control of STH infections. These medications are inexpensive, have few side effects and can be administered *en masse* by trained community members (Pan American Health Organization, 2011). Additionally, regular administration helps maintain the worm burden below levels associated with disease, reduce individual morbidity and mortality and, in doing so, improve large-scale economic productivity and the success of other public health programs (i.e. feeding and nutritional programs) (Pan American Health Organization, 2011).

Due to the low cost of treatment and relatively high cost of diagnosis, interventions tend to be targeted towards groups of people thought to be at elevated risk of infection, or geographic regions where risk of infection is high, rather than specific individuals who have tested positive for infection or whole populations. Although it would be financially feasible to treat whole populations, a targeted approach is preferred due to growing fears of drug-resistance developing in these parasites (as observed in livestock-infecting nematodes) (Bethony et al., 2006; Albonico, 2003; Albonico, Engels & Savioli, 2003; Geerts, Coles & Gryseels, 1997; Jackson & Coop, 2000; Humphries et al., 2011; Humphries, Nguyen, Boakye, Wilson & Cappello, 2012; Vercruysse et al., 2011; World Health Organization, 2011). Current World Health Organization (WHO) guidelines suggest that deworming interventions should target the highest risk communities, as determined by the prevalence of STH infections among school-age children (WHO, 2006). When prevalence of any STH infection is less than 20%, large-scale preventive chemotherapy is not recommended, however all school-age children should be dewormed once and twice yearly in low-risk (20-50%) and high-risk communities (>50%), respectively. The goal of each administration is to cover at least 75% of at risk-populations (PAHO, 2011).

The same strategy applies for more costly interventions such as improved water, hygiene and sanitation infrastructure. Investments are generally targeted towards high-risk groups or regions, rather than individuals, in part due to the logistics of building such infrastructure, but also because it is likely that these changes need to be pervasive to have any significant effect on reducing community-wide environmental contamination and transmission. Thus, scarce resources are allocated to groups or regions based on estimates of infection burden, such as average regional prevalence rates.

3.1.2 Objectives and Rationale

A key challenge to implementing these guidelines is demarcating continuous geographic space into regions useful for efficiently administering interventions. One recommendation is to stratify countries or districts into ecologically homogenous areas ('agro-ecological zones') and determine average infection prevalence from a small sample of 5-10 schools in each area (WHO, 2006; WHO, 2011). This estimate is then used to determine treatment frequency for the entire area, which can be quite large and heterogeneous, containing rural, urban and peri-urban subregions (Davis et al., 2014). Prevalence has been found to differ between these types of settlements (Pullan & Brooker, 2012; Raso et al., 2004; Matthys et al., 2007; Brooker et al., 2006; Karagiannis-Voules et al., 2015; Crompton & Savioli, 1993; Cundill, et al., 2011; Gamboa et al., 2009; Davis et al., 2014), so using large sampling units likely results in the loss of important small scale variability in prevalence. Measuring prevalence via parasitological and laboratory assessment is also time and resource-intensive; for each school, stool-samples need to be collected and processed in a timely manner, making it difficult to collect large, high-quality and representative samples. As a result, rural, urban and peri-urban schools can potentially represent each other, and the few schools sampled might be a poor reflection of the range of prevalence across the entire region.

An affordable alternative involves estimating infection prevalence from models of environmental and social determinants of infection. However, this strategy may be limited by the scale and boundaries employed by the producers of secondary data (Schuurman et al., 2007). Common examples include political administrative regions and census reporting areas. While it is practical to use these geographic areas for predicting prevalence rates, it is unlikely that the risk of infection is defined by these same boundaries (Flowerdew et al., 2008).

The borders of agro-ecological zones and municipalities are not drawn to reflect regions of homogeneous prevalence; thus, it is likely that these areas contain variability in prevalence rates, especially since STH infections have been observed to cluster at even the smallest geographic scales (e.g. households) (Hotez et al., 2006; Davis et al., 2014; Sturrock, Yiannakoulias & Sanchez, 2017). Importantly, this small-scale heterogeneity in prevalence is lost when data are aggregated, so neither is an ideal strategy for defining zones where uniform frequency of deworming is appropriate. The question, then, is how *should* these areas be defined, and perhaps more importantly, how dependent are the resulting prevalence estimates on the partitioning strategy employed?

This is the essence of the modifiable areal unit problem (MAUP), a well-known problem in geography where the interpretation of data can vary significantly when the data are aggregated into different zones or at different scales (Openshaw and Taylor, 1979; Wong, 2009). This is particularly important in the context of STH infections because prevalence rates averaged at regional scales are used to inform policy decisions and deworming interventions. Thus, choosing how to demarcate endemic countries into discrete spatial units could have implications on treatment recommendations.

There are two sub-problems of the MAUP; (i) the scale problem and (ii) the zoning problem. The scale problem refers to the tendency for different findings to be obtained when the same data is aggregated at different spatial resolutions (Openshaw & Taylor, 1979). Alternatively, the zoning problem describes analytical differences resulting from how a study area is divided up, even at the same scale (Openshaw & Taylor, 1979; Flowerdew et al., 2008).

Thus, the scale at which data are aggregated and the zoning technique used to delineate regions can influence the results and interpretation of analyses. As a result, the ways in which we define regions might alter regional STH prevalence estimates and, as a result, lead to different recommendations for allocating resources. For example, if infection burden or risk of infection varies drastically within a region, the average prevalence rate is unlikely to be representative of infection burden across that area. Since this metric is used to determine recommended deworming frequency, it is likely that small pockets of particularly low or high prevalence rates will be over and undertreated, respectively. However, if prevalence is measured at smaller scales or we redefine sampling units such that regional boundaries reflect areas of relatively homogenous prevalence, average prevalence estimates might be more representative; fewer healthy individuals will be dewormed unnecessarily, and fewer infected individuals will go untreated. Thus, creating regions defined by homogenous prevalence rates might improve the efficiency of treatment and resource delivery.

Goal of this study. The primary objective of this chapter is to assess the efficiency of allocating resources using Honduras' existing administrative boundaries compared to an alternative scheme that maximizes within-region homogeneity in STH prevalence rates.

3.2 METHODS

3.2.1 Study Area

The Republic of Honduras ("Honduras") is a central American country divided into 298 municipalities within 18 larger departments; the vast majority of these municipalities are on the mainland (294), and four are located on the Bay Islands in the Gulf of Honduras, an inlet of the Caribbean sea which forms much of the nation's northern border. As of 2016, Honduras had a population of approximately 9 million people (The World Bank, 2016).

While departments represent the country's largest administrative and geographic subdivisions, municipalities are the only sub-national government unit recognized by Honduran law. Municipalities have been classified as a distinct level of government since 1927, however local-level decisions and services were controlled by the national government until enactment of the Municipal Reform Law in 1990. This granted municipalities with increased autonomy and identified local services and small-scale infrastructure as a priority of local government. These changes were accompanied by substantial electoral reform, including the introduction of democratic mayoral elections

(Lippman & Pranke, 1998; The Organisation for Economic Co-operation and Development (OECD), 2016). However, implementation of these changes was targeted towards larger, more populous municipalities and, as of 1998, little progress had been made with respect to developing autonomous and democratic local governments in smaller, poorer and more isolated jurisdictions. Since the law was first introduced, a number of reforms have been launched to strengthen decentralization but implementation has been poor and estimates suggest that fewer than 10% of municipalities have substantive administrative capacity to assume greater responsibilities (OECD, 2016). Thus, decisions regarding resource allocation, policy and infrastructure development remain under the control of national government for many regions.

Like most of Latin America, Honduras is characterized by large disparities in income, consumption levels, access to education, land, basic services, and other socioeconomic variables (Gasparini, Cruces & Tornarolli, 2011). In fact, Honduras has the highest income inequality in the region, with a GINI coefficient of 50.6, compared to 48.7, 41.8, and 47.0 in the neighbouring countries of Guatemala, El Salvador and Nicaragua, respectively (The World Bank, 2014). Within Honduras, poverty rates are generally lowest in the north and central regions, where the majority of industry and infrastructure is concentrated, and highest in the south, west, along the eastern border and among rural and indigenous populations (Gasparini, Cruces & Tornarolli, 2011).

Soil-transmitted helminth infections are endemic in Honduras. Based on a sample of 97 studies, municipal prevalence rates range from 0-74.4%, 1.7-91.1% and 0-42.2% for ascariasis, trichuriasis and hookworm, respectively (Sanchez et al., 2014; Chapter 2).

Additionally, regression models predict that *A. lumbricoides* and *T. trichiura* infection prevalence rates exceed 20% in 156 and 160 municipalities, respectively (Chapter 2). Because of the significant distribution and endemicity of STH infections in Honduras, it is important that scarce resources are allocated as efficiently as possible.

3.2.2 Data Collection and Preparation

Creating Zones. First, Honduras was partitioned into 2568 “zones”. This was done by creating a uniform grid of 2240 10 km x 10 km cells, which was then overlaid by the municipality boundary file in a GIS and clipped with Honduras’ national borders, leaving approximately 1200 cells within the country’s boundaries. We then combined the two layers using a spatial union operation, meaning the uniform cells were subdivided or split along administrative borders. This process is illustrated in the appendix (Appendix A.1). We used this method so the resulting zones could be re-aggregated into existing administrative divisions such as departments and municipalities.

Calculating Zonal Statistics. We then calculated a number of statistics, including population and prevalence, for each zone. The number of people living within each zone was summed from a population density raster available from the Center for International Earth Science Information Network (2016) and zonal prevalence rates of both ascariasis and trichuriasis were estimated using regression models developed in a previous analysis (see Chapter 2). Most of the independent variables used to generate these predictions, including forest cover as a proportion of land area, terrain ruggedness index (TRI), average annual precipitation, average mean temperature and clay content of soil, were retrieved from raster datasets and aggregated up to the zone scale. The remaining independent variables were collected from the 2013 population and housing census and were only available at the municipal scale; thus, data for each municipality was attributed to their respective constituent zones. A detailed description of the sources and collection of these data is provided elsewhere (see Chapter 2). Once ascariasis and trichuriasis prevalence rates were generated for each zone, a singular estimate of prevalence was calculated by taking the average of these two values. This metric will be referred to as "zonal prevalence" and is distinct from municipal and regional prevalence rates.

Regionalization. We then used a multicriteria regionalization tool to aggregate these zones into 294 regions. We chose to generate the same number of regions as there were mainland municipalities in Honduras (294) because we wanted to understand how efficiency varies when zones are re-aggregated at the *same scale* as the administrative plan (zoning problem of the MAUP). Island municipalities were excluded from this analysis because they were not connected/contiguous with the rest of the country.

Our algorithm used a tabu search heuristic, similar to that developed by Bozkaya, Erkut & Laporte (2003) and implemented by Yiannakoulias and Bland (2016), to generate a regionalization scheme that optimizes some objective outlined in a cost function. In this application, the goal was to produce regions with as homogenous prevalence rates as possible. This was done because average prevalence rates, which guide resource allocation, should be more representative for homogeneous versus heterogeneous regions; thus, the proportion of uninfected individuals treated or targeted unnecessarily should be lower when resources are allocated using a more homogeneous regionalization scheme. The general steps involved in the regionalization algorithm are as follows.

Starting plan. The algorithm begins by creating a feasible starting plan where contiguous zones are aggregated into the same number of regions as desired in the solution. This starting plan is generated by first selecting 294 random starting zones. Other adjacent zones are then agglomerated to these zones in a stepwise fashion. These are the regions that comprise the starting regionalization plan, and the agglomeration continues until all zones have been added to a region.

Changing the regionalization plan. The algorithm then identifies all the zones which can be moved from their existing region into an adjacent region without making any region discontiguous, thereby creating an inventory of "feasible moves". After inventorying all possible moves, the algorithm moves the zone that most minimizes the value of the cost function. Weights are assigned to each term in the function to establish their respective importance and to instruct the algorithm on how to prioritize conflicting objectives. The algorithm continues in this manner for a maximum number of iterations specified by the user.

This regionalization algorithm is classified as a "greedy" algorithm because it makes immediately best choices; for every turn, the algorithm inventories all possible zone moves and moves a zone from one region to another that seems best at that moment. However, a weakness of greedy algorithms is that the list of feasible moves is dependent on the initial starting plan. As a result, a poor starting plan will limit the tool's ability to identify the true, globally optimal solution, even though it yields locally optimal solutions (or the best solution given the constraints of the starting plan). To solve this problem, we used a tabu search that forces the algorithm to explore other parts of the problem domain/search space (Glover, 1986; Bozkaya, Erkut & Laporte, 2003; Yiannakoulias & Bland, 2016). Specifically, if a zone is "cycled", or moved into a region and then out again twice in a row, movement of that zone becomes forbidden or "tabu" for a set number of turns. This limits the algorithm's options, forcing it to explore other moves and leads to a better solution (that more closely approximates the true, global solution) than what would be produced by the greedy algorithm alone.

Application. In our study, we applied the algorithm to five different starting plans (A, B, C, D, E) and four versions of the cost function (1, 2, 3, 4), generating a total of twenty unique solutions. All four versions of the cost function contained two elements: 1) within-region standard deviation of zonal prevalence, and 2) region connectivity (a computationally efficient proxy for compactness (Yiannakoulias et al., 2007)) as well as a constraint prohibiting the creation of regions with populations greater than 400,000 or less than 3000, but differed with respect to the weighting of each term. Cost function 1 represented one extreme, where homogeneity in prevalence was assigned a weight of 100% and connectivity weight was set to 0, while cost function 4 assigned the terms in the cost function an equal weight. Cost function 2 and 3 fell between these extremes, placing progressively more weight on connectivity. The algorithm was then run for 4000 iterations, however a provision was included to automatically stop the tool if no improvements were made (the value of the cost function did not decrease) for 1500 consecutive turns. The length/size of the tabu list was set at/to 20-100, meaning that cycled zones were forbidden for a random number of turns between these two values.

We calculated each plan's mean within-region standard deviation of prevalence and the value of their respective cost functions after the 4000th turn. The solution that most minimized both metrics was identified as the "best" regionalization scheme.

3.2.3 Analysis

Purpose and Plan. The primary purpose of this analysis was to determine if, and to what degree, a regionalized plan is more efficient than existing municipalities for allocating preventative and treatment resources. Because some types of treatment resources are scarce, efficient distribution is very important; interventions should be directed towards areas where the need is greatest, while aiming to minimize waste of effort and/or expense. In this context, we assess efficiency in terms of the proportion of individuals treated or targeted by interventions whom were actually infected with STH parasites.

To quantify this, we considered a situation where municipalities and regions were each prioritized from highest to lowest prevalence, and resources were allocated to both sets of areas in that sequence. We then calculated and compared their efficiencies, as described above, for 294 scenarios; we started where investments were supplied to only the highest priority region or municipality (scenario 1) and in each subsequent scenario, we added (in a cumulative manner) the region or municipality with the next highest prevalence. In this way, the number of the scenario (1 through 294) also represents the number of regions or municipalities targeted by intervention at that time (1 through 294).

For example, the second scenario compares the efficiency of allocating resources to the two highest priority municipalities versus the two highest priority regions, as ordered by prevalence rates, while the fifth scenario compares the efficiency of allocating resources to all 5 of the highest prevalence municipalities and regions, respectively. We can then compare the relative efficiency of these two plans, for an investment of varying size.

Steps. We started by quantifying the efficiency of allocating resources using (i) existing municipalities and (ii) our "best" regionalization scheme, as identified previously.

We first calculated the average prevalence rate, population count and the total number of infected individuals living in each of the 294 municipalities and sorted them from highest to lowest prevalence. This was done to reflect the order in which municipalities would be targeted by interventions; areas with the highest burden of infection would be the first priority when allocating resources, while the areas with the lowest prevalence would be the last.

Once the municipalities were ordered, the cumulative sum of infected individuals was calculated; starting from the highest prevalence area, we added up the infected population step-by-step, where each subsequent "step", or scenario, represented the addition of the next highest prevalence area. Thus, the value of this parameter for any region is equivalent to the sum of the infected individuals in that region, plus all other regions that came before it in the series. We then calculated cumulative population in the same manner.

Finally, we divided the cumulative number of infected individuals by cumulative population to create an estimate of "efficiency" for the 294 scenarios which each contained one more municipality than the previous. For example, the "efficiency" of scenario 2 was the sum of infected individuals in municipality 1 and 2 divided by the total population of both regions. Similarly, the efficiency of scenario 200 was calculated by summing the infected individuals in municipalities 1 through 200, divided by the total population of these 200 regions. This metric measures the proportion of targeted populations who were actually infected, where higher values indicate higher efficiency.

This entire procedure was then repeated for the regionalized plan, beginning with calculating regional statistics (population, prevalence and infected individuals), sorting the regions from highest to lowest prevalence and concluding with calculating the efficiency metric.

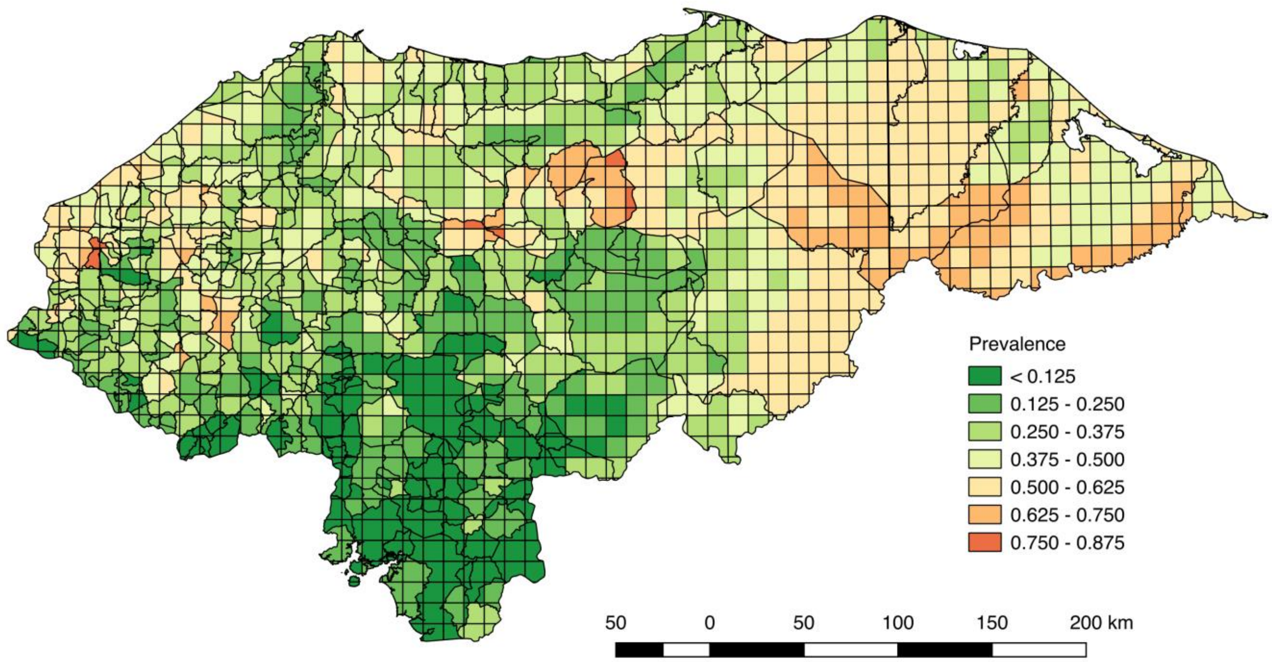
For each scenario or "step", the efficiency of the regionalized plan was divided by that of the municipality plan to create an efficiency ratio; values above 1 indicated that the regionalized plan was more efficient than the municipality plan, while values below 1 suggested the opposite.

3.3 RESULTS

Zones. We created 2568 zones with population counts and average prevalence rates ranging from 1 to 361085 and 0% to 86%, respectively. These zones and their respective prevalence rates are mapped in Figure 1.

Figure 1: Map of Zonal Prevalence

Mean soil-transmitted helminth infection prevalence in 2568 zones created using a union of the municipal boundary file and a uniform grid



Regionalization Procedure and Solutions. We then generated 20 regionalization solutions. As expected, within-region standard deviation of prevalence was lowest for those solutions generated using the first cost function (0.0439-0.0457) and increased as successively more weight was given to the connectivity term (0.0440-0.0476, 0.0465-0.0495 and 0.0599-0.064 for cost function 2, 3 and 4, respectively) (Table 1). However, regions in all twenty plans were more homogenous than the municipalities (0.06785992), even when prevalence and connectivity were assigned an equal weight in the cost function. Within-region standard deviation of prevalence rates was lowest in solution A1 (0.0440).

Table 1: Within-Region Standard Deviation of Prevalence – 20 algorithm-generated solutions versus municipalities

(a) Mean Within-Region Standard Deviation for 20 Algorithm-Generated Solutions

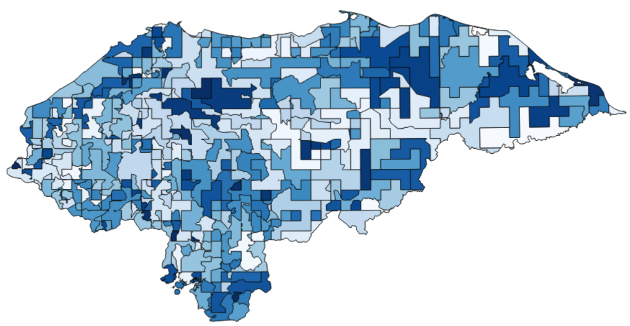
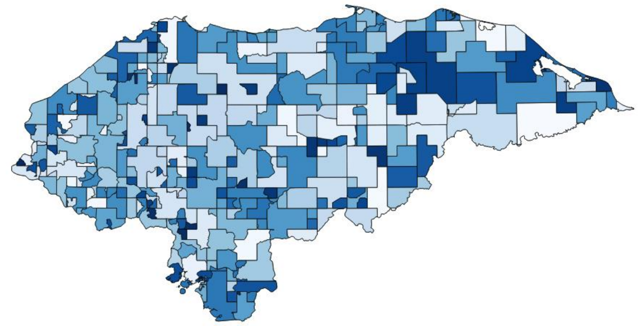
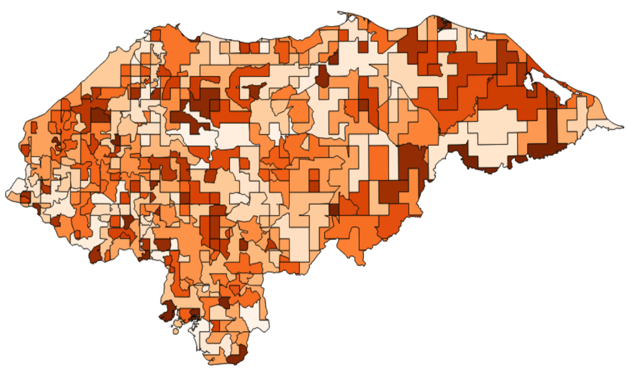
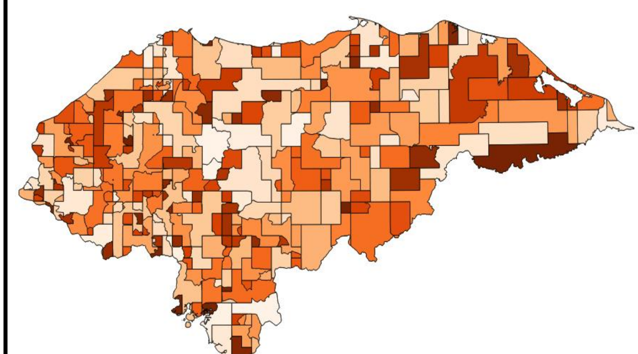
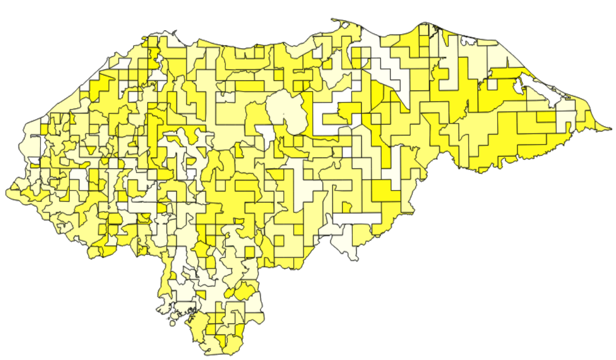
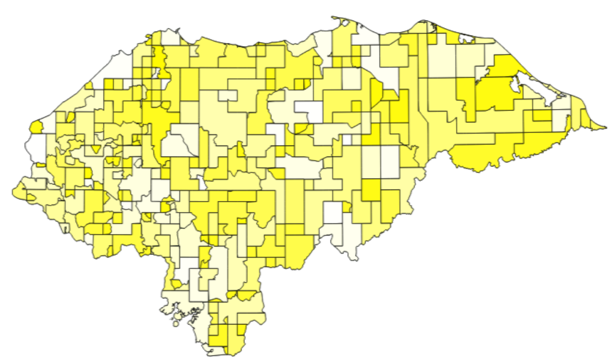
		Starting Plan					
		A	B	C	D	E	Average
Version of Cost Function	**1**	**0.04392**	0.04525	0.04549	0.04567	0.04442	0.04494
	2	0.04405	0.04760	0.04434	0.04436	0.04473	0.04502
	3	0.04655	0.04692	0.04946	0.04889	0.04714	0.04779
	4	0.05988	0.06234	0.06376	0.06392	0.06396	0.06277
	Avg.	0.04860	0.05053	0.05076	0.05071	0.05006	

(b) Mean Within-Region Standard Deviation for Existing Municipalities

Municipalities	0.06786

We then mapped the solutions generated using cost functions 1 and 4. These figures are included in Table 2, where maps are colour-coded based on starting plan. Qualitative inspection of Table 2 suggests that that similar solutions were yielded when different starting plans were regionalized using the same cost function. Panels A1, B1, C1, D1 and E1 (Table 2, left column) look relatively similar to each other but different than A4, B4, C4, D4 and E4 (Table 2, right column), which are all characterized by more regular, geometric regions. Quantitatively, the value of the cost function at its 4000th iteration was comparable for all starting plans when the same cost function was used (See Row 1 and Row 4 in Table 3). The value of the cost function at the 4000th iteration was lowest for plan E1.

Table 2: Comparison of Solutions Generated using Cost Function 1 and 4 (starting plans A-E)

	Cost Function 1: *Minimize within-region std. dev. of prevalence**	Cost Function 4: *Also considers connectivity of regions**
A		
	Within-region SD of prevalence: **0.04392018**	Within-region SD of prevalence: **0.05988345**
B		
	Within-region SD of prevalence: **0.0452468**	Within-region SD of prevalence: **0.06233982**
C		
	Within-region SD of prevalence: **0.04549101**	Within-region SD of prevalence: **0.06376078**

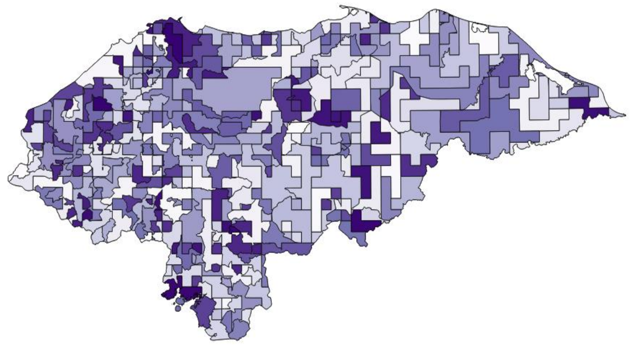
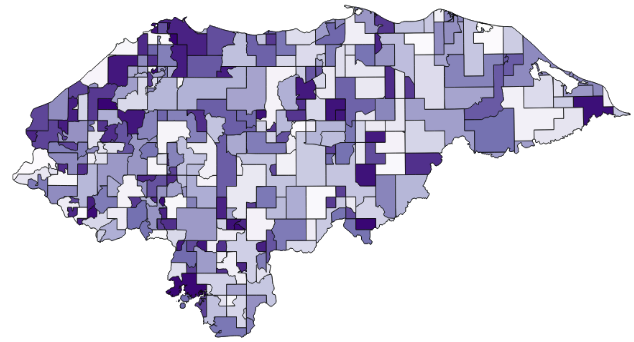
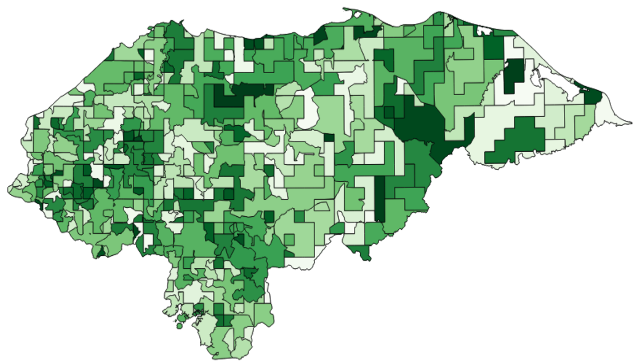
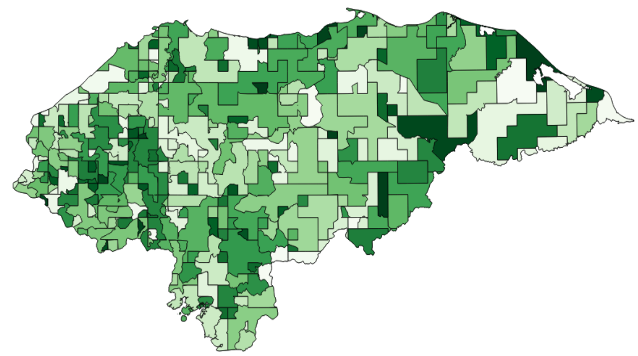
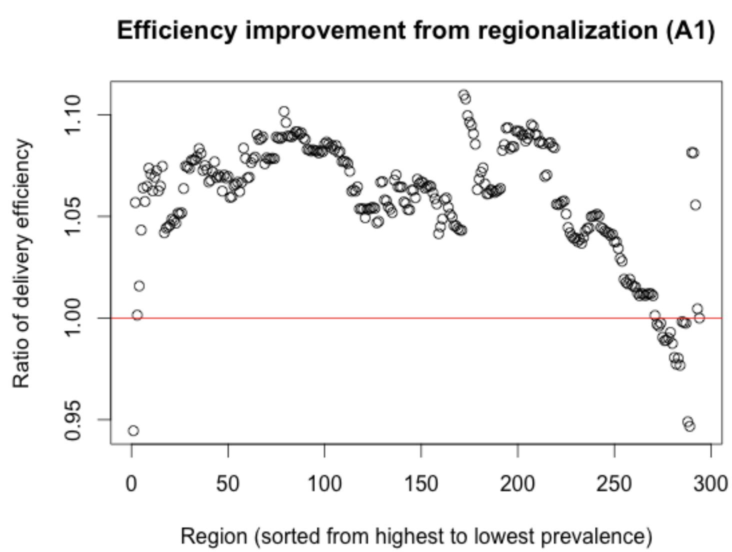
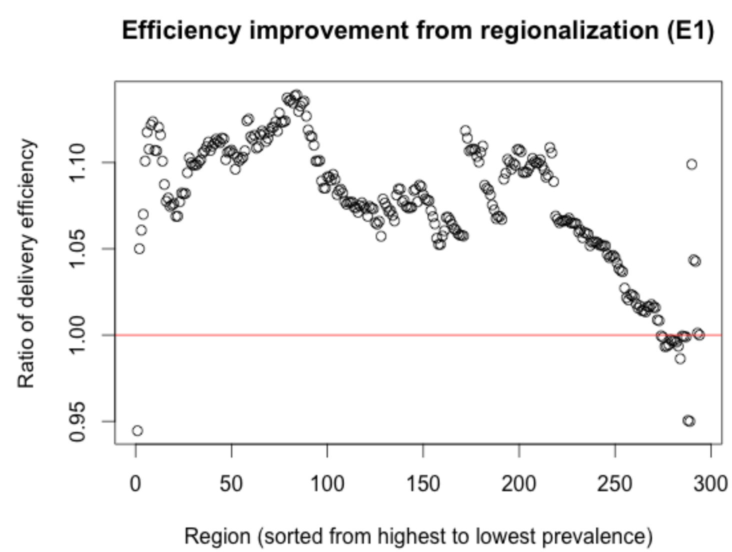
D		
	Within-region SD of prevalence: **0.04566596**	Within-region SD of prevalence**: 0.06392241**
E		
	Within-region SD of prevalence: **0.04442174**	Within-region SD of prevalence: **0.06396176**
	**Note: Both cost functions also include a hard constraint on population which prevented regions with more than 400,000 and less than 3000 people*	

Table 3: Value of Cost Function at the 4000th Iteration for 20 Different Solutions						
		A	B	C	D	E
Version of Cost Function	**1**	**54630570**	56686671	57805746	56357536	54251139
	2	**63067865**	68053858	65283926	63451910	63672567
	3	137539087	**131082412**	139775373	136427618	135835742
	4	767525264	**761289020**	803242760	842662634	830841794

Solutions A1 and E1 were therefore identified as the “best” solutions. For both solutions, we calculated and plotted the efficiency ratio as described in the methods. These graphs are included in Table 4, which also contains maps and summary statistics.

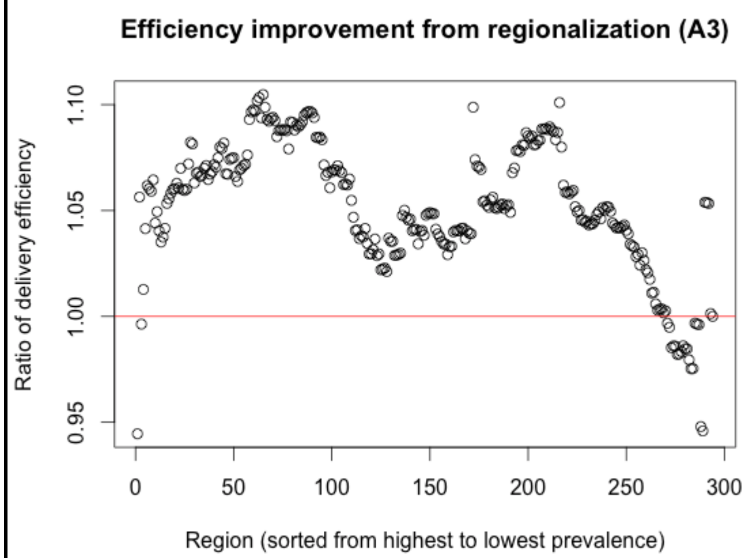
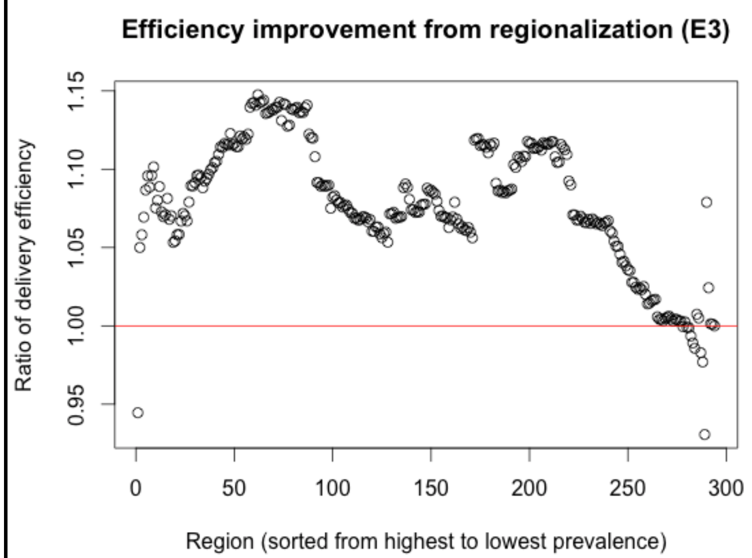
On average, the A1 plan was more efficient than the municipality plan; the minimum value of the efficiency ratio was 0.9445764, however the maximum and mean efficiency ratios were 1.109767 and 1.057931, respectively**.** This suggests that the municipality plan is more efficient in at least one scenario, however the regionalized plan is, on average, more efficient. The minimum value of the efficiency ratio for E1 was the same as A1 (0.9445764), however the maximum and mean values were higher at 1.139183 and 1.076818, respectively. Thus, the E1 regionalized plan was nearly 14% more efficient than the municipal plan, compared to A1, which exhibited an 11% efficiency improvement over existing administrative regions.

As observed in Figure 2 and Figure 3 the municipality plan is more efficient than either A1 or E1 when treatment and investments in infrastructure are only targeted towards the region with the single highest prevalence; however, the regionalized solutions are superior when interventions are expanded to additional high-risk regions. The municipal plan also appears to be more efficient than the regionalized solution for the last 17-19 scenarios (Table 4, Figures 2 and 3), however this is because the cumulative number of infected people and cumulative population are equal for the municipal and regionalized plans, and begin to converge on these value in the final scenarios; any extra individuals treated in the regionalized plan in previous scenarios are being recouped in the municipal plan as total population approaches that of the country as a whole.

<table>
<tr><th colspan="3">Table 4: Comparison of Solutions: A1 and E1</th></tr>
<tr><th></th><th>A1</th><th>E1</th></tr>
<tr><td rowspan="2">Efficiency Plot
A plot of the efficiency ratio for each municipality-region comparison, where both were sorted by descending prevalence and efficiency was calculated by dividing cumulative counts of infected individuals by cumulative population</td><td>Figure 2: Efficiency Plot – A1</td><td>Figure 3: Efficiency Plot – E1</td></tr>
<tr><td>
</td><td>
</td></tr>
<tr><td>Minimum</td><td>0.9445764</td><td>0.9445764</td></tr>
<tr><td>Maximum</td><td>1.109767</td><td>1.139183</td></tr>
<tr><td>Mean</td><td>1.057931</td><td>1.076818</td></tr>
<tr><td>Standard Deviation</td><td>0.02956083</td><td>0.03679206</td></tr>
<tr><td>Efficiency Ratio <1</td><td>19/294 (~6.5%)</td><td>17/294 (~5.8%)</td></tr>
</table>

Although A1 and E1 were identified as the "best" solutions, many of their regions were irregularly shaped (Table 2). As a result, allocating and distributing resources using these regions would be less efficient than if the plan had also aimed to maximize regional connectivity. Thus, we also generated efficiency ratios for A3 and E3. We opted to use the solutions generated using the third cost function, rather than the fourth, because the latter offered very little benefit over the municipal plan with regards to homogeneity in prevalence (see Table 1; within-region standard deviation of prevalence rates were 0.04714036 for E3, 0.06396176 for E4 and 0.06785992 for the municipality plan).

The A3 and E3 solutions are compared in Table 5. Similarly to the solutions generated using cost function 1, E3 had a higher maximum and mean efficiency ratio than A3, and the efficiency ratio was lowest for the first municipality-region comparison in both solutions. Interestingly, the E3 plan was also more efficient, on average, than the E1 plan. This was surprising given that less emphasis was placed on maximizing homogeneity in prevalence in the former than the latter. Otherwise, the general patterns observed in Figure 4 and 5 were similar to those illustrated in Figure 2 and 3 for A1 and E1, respectively; the municipal plan was superior for the first scenario and towards the end of the series, however the regionalized solution was more efficient more often.

Table 5: Comparison of Solutions: A3 and E3		
	A3	E3
	Figure 4: Efficiency Plot – A3	Figure 5: Efficiency Plot – E3
Efficiency Plot *A plot of the efficiency ratio for each municipality-region comparison, where both were sorted by descending prevalence and efficiency was calculated by dividing cumulative counts of infected individuals by cumulative population*		
Minimum	0.9445764	0.9306448
Maximum	1.104727	1.147487
Mean	1.052199	1.078207
Standard Deviation	0.03038941	0.0403041
Efficiency Ratio < 1	21/294 (~7.1%)	10/294 (3.4%)

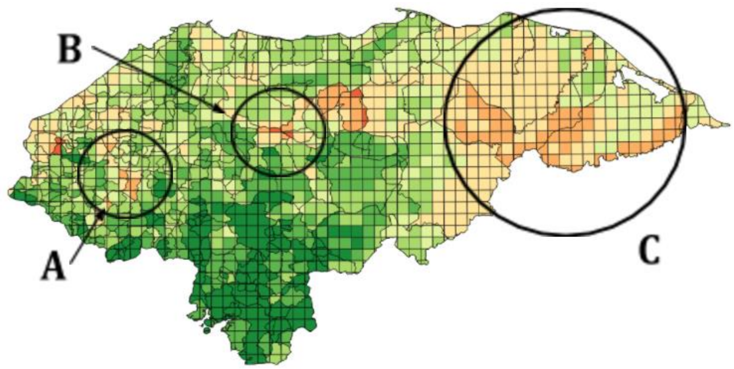
Finally, we mapped zonal, municipal and regional (E3) prevalence in Table 6 panels I, II and III, respectively, to illustrate the effects of aggregating prevalence using two different regionalization schemes. We highlighted three areas where zonal prevalence was relatively high, labelled A, B and C, and found that the regionalized plan was much better at retaining small geographic hot spots of prevalence. Conversely, aggregating prevalence at the level of the municipality obscured the significant burden of infection in these areas. Using aggregated prevalence rates, we then mapped the twenty highest prevalence municipalities, and regions, in panels IV and V, respectively. In these maps, the colour represents the order in which municipalities (IV) and regions (V) should be prioritized to receive resources; zones shaded red represent the municipality/region with the highest prevalence which should be the highest priority for treatment, while shades of purple represented the municipality/region with the lowest priority (of the 20 municipalities/zones where STH infections were most prevalent). Although there is significant overlap between these two figures, there are importance differences in the priority of several regions. In particular, many of the small pockets of high prevalence areas from Table 6, panel I such as area B are a higher priority in the regionalized plan (yellow) (Table 6, Panel IV) than the municipality plan (purple) (Table 6, Panel V).

Table 6: Comparison of Municipal and Regionalized Plans

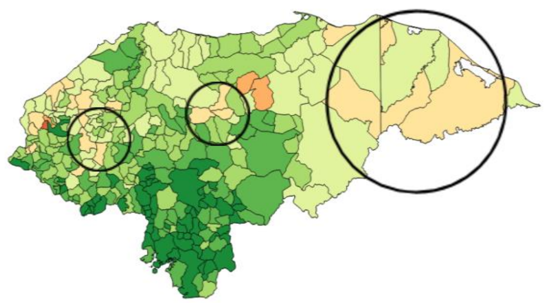
Legend

- < 0.125
- 0.125 - 0.250
- 0.250 - 0.375
- 0.375 - 0.500
- 0.500 - 0.625
- 0.625 - 0.750
- 0.750 - 0.875
- 0.875 - 1.00

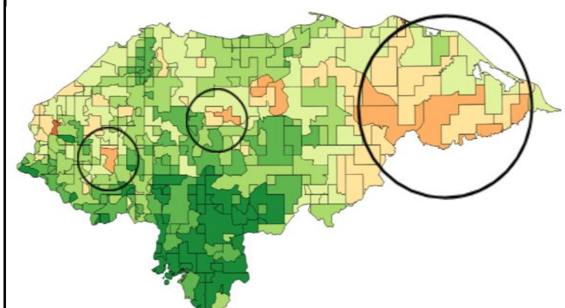
I. Prevalence: **ZONES**



II. Prevalence: **MUNICIPALITIES**



III. Prevalence: **REGIONS (E3)**

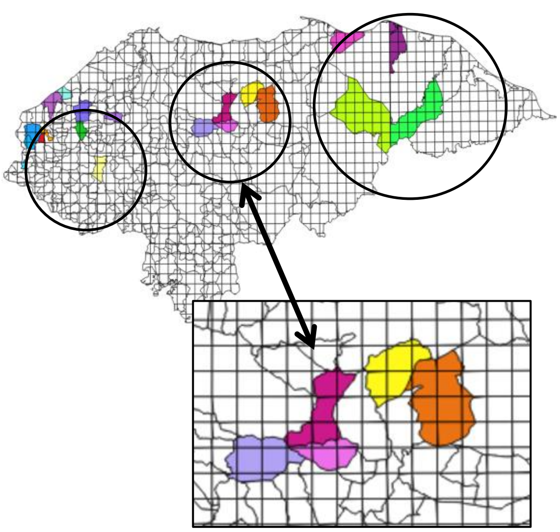


REGIONS PRIORITIZED FROM HIGHEST TO LOWEST PREVALENCE

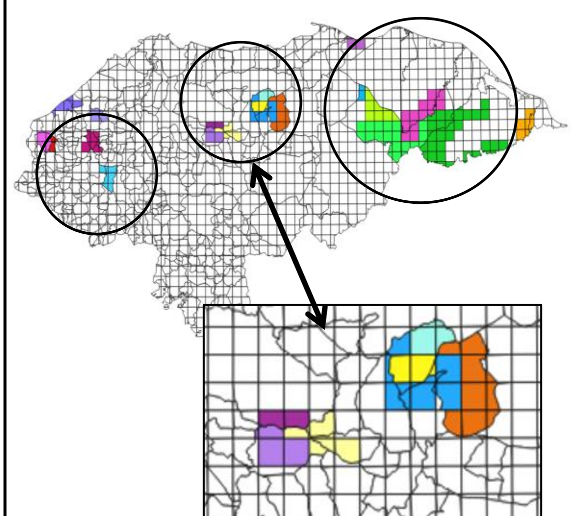
Legend

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- > 20

IV. **MUNICIPALITIES**



V. **REGIONS (E3)**



3.4 DISCUSSION

3.4.1 Summary of Methods and Findings

Soil-transmitted helminth infections represent a significant public health concern in much of the developing world. Inexpensive anthelmintic drugs are an important resource for maintaining worm burdens below the threshold associated with disease, however long-term control and eventual eradication of these infections is dependent on improved water and sanitation infrastructure.

Due to the high cost of diagnosis, the ubiquity of these parasites in endemic regions and the significant public health consequences of infection, both treatment and preventative resources are targeted towards at-risk regions or groups, rather than individuals who have tested positive for infection. The World Health Organization recommends that treatment frequency be guided infection prevalence, however less attention has been paid to how, and at what scale, geographic areas should be regionalized for the purposes of establishing prevalence and thus allocating resources. Importantly, the results of analyses can vary when the same data is aggregated into different regions or at different scales, a common analytical problem called the modifiable areal units problem (MAUP). As a result, it is reasonable to assume that prevalence of infection, and thus allocation of resources, might look different if regions are aggregated in different ways.

In this study, we quantified the effects of using different regionalization schemes on the efficiency of resource allocation. More specifically, we assessed the benefits of administering interventions to regions that were delineated to reflect areas of homogenous prevalence, rather than arbitrary administrative regions such as municipalities. To do this, we divided Honduras into 2568 zones and aggregated them into 294 relatively compact regions characterized by minimal variability in prevalence. We then calculated and compared the efficiency of this plan and the municipality plan for 294 scenarios; each scenario “X” simulated a situation where resources were distributed to “X” number of municipalities, ordered from highest to lowest prevalence. In the first scenario, only the highest prevalence region or municipality received resources, and each subsequent scenario saw resources distributed to the areas considered in the previous scenario, plus the next highest prevalence municipality or region.

Method of regionalization matters - an example of the modifiable areal units problem. As expected, aggregate prevalence estimates varied depending on the method used to regionalize Honduras. As illustrated in Table 6 panels I, II and III, the regional plan retains more small-scale variability than the municipal plan, which contains higher within-region heterogeneity in prevalence rates and sees a greater loss of information upon calculating average prevalence rates (see hot-spots of infection such as A, B and C after aggregating zonal prevalence using regionalized and municipal plans). As a result, these two plans provide different recommendations regarding how to prioritize regions for resource allocation (Table 6 panels IV and V). For example, the municipal plan places a lower priority on areas A, B and C than the regionalized plan, owing to the fact that high prevalence zones in these areas were grouped with, and subsequently averaged out by, lower prevalence zones in the same municipality. This was less of an issue for the alternative scheme since boundaries were deliberately drawn to define areas where variability in zonal prevalence rates was minimal. In this way, our study provides a contemporary example of the modifiable areal units problem in infectious disease research; the results of our analysis and the recommendations that stem from these findings are dependent on the method used to subdivide Honduras. Future researchers should consider these effects when interpreting results or planning spatially targeted interventions.

Homogenous regions are better sampling units for estimating prevalence. As described previously, the World Health Organization recommends stratifying nations into zones characterized by relatively homogeneous prevalence rates. A small number of samples are taken from 5-10 schools in each region, and the average prevalence is assumed to be representative of the entire area. One option is using agro-ecological zones, however previous researchers have cited problems with this strategy, particularly because they are delineated at a larger geographic scale and may contain urban, rural and peri-urban subregions (Davis et al., 2014). Thus, generating regions specifically for the purposes of measuring prevalence and allocating resources accordingly has important and practical implications.

In this study, we divided Honduras into regions that were more homogenous with respect to prevalence than existing administrative units at the same scale. Importantly, stratified sampling using homogeneous units reduces the variance of the sampled quantity being measured (Williams, 1978). Thus, our regions represent a better sampling unit than municipalities because they are explicitly defined to reduce within-region variability in prevalence. Future attempts to quantify STH prevalence using a small sample of schools should consider using a stratified sample of more homogenous units, such as our regions, rather than arbitrary administrative regions or larger scale agro-ecological zones.

Allocating resources using regionalized schemes can be more efficient. Perhaps most importantly, our analysis suggests that regionalized plans are more efficient than existing administrative boundaries for allocating resources. For investments of varying sizes, a higher proportion of those treated or otherwise targeted by resources were actually infected in the regionalized plan compared to the municipal plan. As a result, fewer resources were misdirected towards uninfected individuals when the regionalized plan was used to guide distribution.

Efficient allocation of anthelmintic medications is important to prevent the waste of scarce resources and stave off the development of drug-resistant parasites, a likely consequence of indiscriminate over-treatment (Bethony et al., 2006; Geerts, Coles & Gryseels, 1997; Humphries et al., 2011). Similarly, investments in infrastructure are expensive and difficult to coordinate, particularly in resource-poor countries. Therefore, it's important that their implementation be strategically targeted towards those regions that have the most to benefit.

3.4.2 Limitations

Although efficiency improvements were noted for regionalization schemes generated using different cost functions (i.e. A1, A3) and starting plans (i.e. A1, E1), these improvements were relatively small. Based on our “best” solution, the highest improvement was 15%, and the average was less than 8% (Table 5).

Another potentially important factor that we failed to account for was the intangible or hard-to-measure benefits of administering resources to existing administrative or government units, including infrastructure. Much of the infrastructure required to administer deworming is under the authority of local governance, so it might make more sense to target municipalities, rather than synchronize efforts between adjacent communities. However, not all municipalities are autonomous from central government with respect to financial decisions, and for those that are, mayors and their councils can use zonal prevalence estimates (Figure 1) to determine how to prioritize efforts within their jurisdiction, even if the aggregate regions are not used for administering larger-scale programs.

Additionally, municipalities might also be more compact than our regions, many of which are relatively irregularly shaped despite placing equal weight on maximizing within-region homogeneity in prevalence and between-region connectivity.

Other important limitations stem from our use of prevalence as the sole proxy of infection burden. Firstly, the models used to generate these predictions were only able to explain 60% and 47.7% of variability in *T. trichiura* and *A. lumbricoides* prevalence, respectively (see Chapter 2). Better and more accurate predictions of prevalence are necessary to generate solutions that will yield real-world benefits.

Finally, we did not consider infection intensity in our cost function. Infection intensity is difficult to measure accurately, however prevalence alone is insufficient for planning public health interventions; although a population might have a very high prevalence rate, the individual and public health consequences of infection are negligible when the worm burden, or intensity, is below the level associated with disease (Bethony et al., 2006; Chan et al., 1994; Hotez et al., 2008). Furthermore, small numbers of heavily infected individuals represent a significant source of environmental contamination and should be a higher priority for treatment programs compared to larger groups of people each harbouring a small number of parasites. As a result, regions should be prioritized on the basis of the proportion of heavily infected individuals in a population, rather than prevalence alone.

3.5 CONCLUSION

In spite of these limitations, our results suggest that alternative regionalization schemes could improve the efficiency of allocating resources. Our estimates of these benefits seem low, however they are highly conservative; we only used five randomly generated starting plans, and although their respective solutions were qualitatively similar, we almost certainly could have generated a better plan if the algorithm had been left to run tens or hundreds of times using different parameters. As a result, the actual benefits of using a regionalized plans, rather than an administrative plan for measuring prevalence and subsequently allocating resources likely exceeds what we have illustrated in this study. In our findings, we indicate that a regionalized plan is more efficient for allocating resources than an administrative plan at the same scale. In the future, these procedures should be conducted comparing the efficiency of agro-ecological zones and regionalized plans at larger geographic scales. These estimates would be less conservative and perhaps more useful for allocating less expensive resources such as anthelmintic treatments.

Even though our solution doesn't greatly improve the efficiency of allocating and delivering resources, the regions we generated are a better sampling unit for estimating prevalence at regional scales. In particular, increased within-region prevalence of STH infections prevents small-pockets of high-risk from being obscured by lower prevalence zones in the same municipality or region. This is important for preventing under-treatment of small populations where risk of infection is very high.

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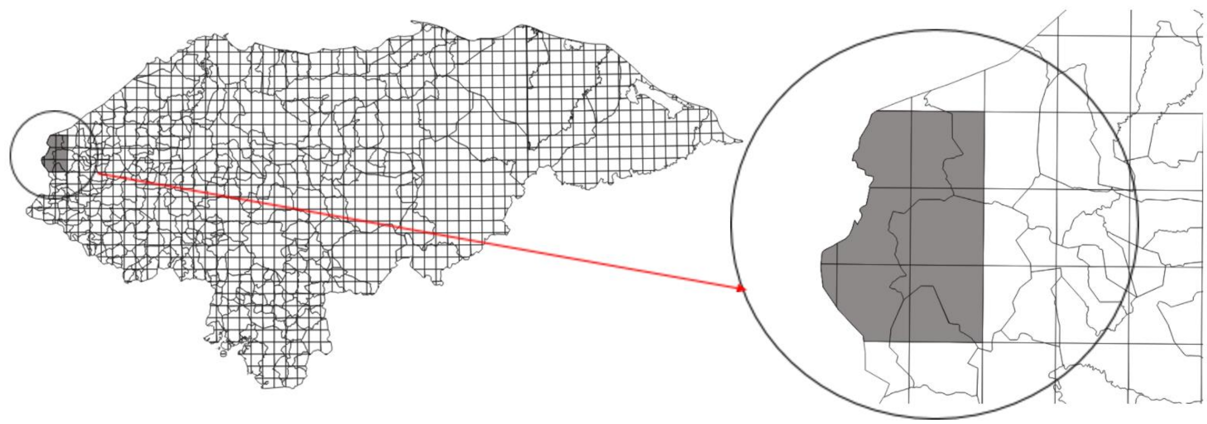
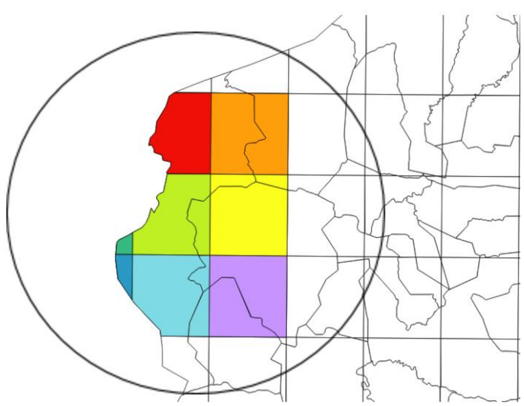
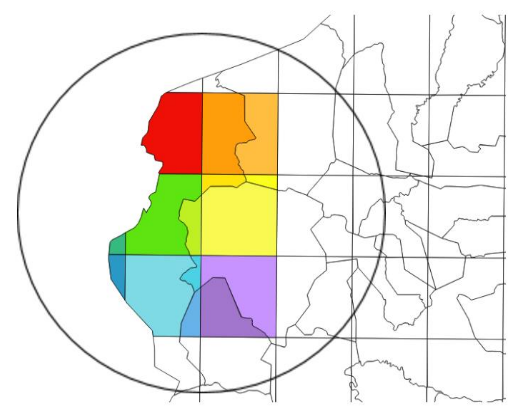
APPENDIX A

<table>
<tr><th colspan="2">Appendix A.1: Methods Used to Create Zones</th></tr>
<tr><td colspan="2">STEP 1: Overlay uniform grid over municipal boundary file</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2">STEP 2: Split cells along municipal boundaries (a “union” of both layers)</td></tr>
<tr><td>Starts with 8 uniform <u>cells.</u></td><td>Split cells along administrative borders to create 15 <u>zones.</u></td></tr>
<tr><td></td><td></td></tr>
</table>

CHAPTER FOUR: CONCLUSION

4.1 INTRODUCTION

The goal of this research was to improve our understanding of soil-transmitted helminth epidemiology in Honduras.

In the second chapter, we identified risk factors associated with STH infections in Honduran municipalities, modelled prevalence rates of ascariasis, trichuriasis and hookworm at this geographic scale, and offered recommendations for where, and how frequently, deworming should be administered. We also investigated the role of accessibility to treatment in explaining the geographic distribution of these infections. Many researchers have used similar methods to answer similar research questions, however few efforts have been made to model municipal prevalence rates across Honduras.

Our third chapter describes an example of the modifiable areal units problem (MAUP), where results and interpretation of analyses vary depending on the scale, and zoning technique, used to aggregate the same data. More specifically, we assess the efficiency of allocating resources using Honduras' existing administrative boundaries compared to an alternative scheme that maximizes within-region homogeneity in STH prevalence rates.

4.2 SUMMARY OF MAJOR FINDINGS

4.2.1 Chapter Two

Our multiple linear regression analysis identified several significant risk factors associated with *A. lumbricoides* prevalence in Honduran municipalities, including the proportion of homes with cement floors, forest cover, average mean temperature, time and the literacy rate-time interaction variable (Chapter 2, Table 2.A.IV). Similarly, trichuriasis prevalence was predicted by forest cover, terrain ruggedness index, clay content of soil, time and the literacy rate-time interaction (Chapter 2, Table 2.B.II), and hookworm was associated with average annual precipitation and time (Chapter 2, Table 2.C.I).

Our results also suggest that municipal prevalence of ascariasis, trichuriasis and hookworm infection have declined significantly between the time periods considered in this study (2001-2006 and 2007-2012). Reductions were greatest for *A. lumbricoides* and more modest for *T. trichiura*, leaving the latter as the dominant parasite in 70% of municipalities between 2007 and 2012 (compared to 50% in time 0). This is consistent with several recent investigations that have identified trichuriasis as the most prevalent STH infection in Honduras (Sanchez et al., 2014; Torres et al., 2014; Gabrie et al., 2014).

These declines are likely related, in part, to improved availability and accessibility of anthelmintic medications. Furthermore, the more drastic improvements observed for ascariasis compared to trichuriasis might be due to the differential efficacy of anthelmintics against these species. This might also explain why prevalence of ascariasis and trichuriasis were associated with different variables in simple regression analysis; determinants of the former might simply be correlated with improved accessibility to treatment. Thus, unmeasured inequities in treatment accessibility represent a challenge for modeling infection prevalence. We suggest that including an explicit measure of access to treatment in future regression analyses will be necessary to determine how differential access contributes to variability in the distributions of *A. lumbricoides* and *T. trichiura* specifically.

These regression models serve as an important tool for estimating prevalence in areas where it has not yet been measured, predicting the effects of environmental and social change on municipal prevalence rates and planning public health interventions and resource allocation strategies.

4.2.2 Chapter Three

Our results suggest that the method of regionalization used to aggregate small-scale prevalence rates has implications on regional prevalence estimates and subsequent recommendations for planning STH control programs and allocating medications and investments. More specifically, these findings suggest that regions designed to be homogeneous with respect to prevalence rates can be more efficient than existing municipalities (at a similar geographic scale) for distributing resources. Even though our best regionalized plan only conferred a 15% efficiency benefit, this estimate is probably conservative.

Future attempts at quantifying the advantages of regionalized schemes should compare the efficiency of agro-ecological zones and regionalized plans at larger geographic scales. These estimates would be less conservative and perhaps more useful for allocating less expensive resources such as anthelmintic treatments. Furthermore, policymakers and government officials should consider using stratified samples of more homogenous units, such as our regions, for measuring prevalence rates. These regions are likely a better sampling unit than arbitrary administrative regions or larger scale agro-ecological zones and may produce a smaller error estimation than would be produced by a simple random sample of the same size (Williams, 1978).

4.3 CONCLUSIONS

In this study, we generate the first municipal-level estimates of STH prevalence rates in Honduras and provide a contemporary example of the modifiable areal units problem in the context of infectious disease epidemiology and public health. Our results suggest that, despite improvements in prevalence over time, STH infections remain endemic in Honduras. We also identify previously underexplored issues associated with existing control programs, such as the potential consequences of using different zoning techniques on prevalence estimates, resource-allocation recommendations and how regions are prioritized. These findings should be particularly valuable for policymakers, government officials, non-governmental organizations and future researchers who are tasked with identifying where to prioritize control efforts, and how to improve the efficiency of public health programming.

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