USING KERNEL DENSITY INTERPOLATION TO VISUALIZE THE EFFECTS OF MASS TREATMENT WITH IVERMECTIN ON HELMINTH PREVALENCE IN RURAL NORTHEAST BRAZIL

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Abstract

Kernel density estimation is an effective tool to identify high-risk areas within point patterns of disease incidence by producing a smooth, continuous surface that defines the level of risk for that area (Bithell, 1990). In addition, kernel density estimation represents a powerful way to conduct hot spot analysis and easily visualize trends over large areas (Levine, 2007). It can be used in public health research to target areas of high concentrations of disease for control and to target areas at higher risk for prevention (Arden, 2008; Arden & Leitner, 2008).

The spatial 'evolution' of parasitic infections in a community over time is a rarely studied topic. However, studies such as the one by Heukelbach et al. (2004b) provide a unique opportunity to visualize the spatial dynamics of infection over time as they reappear in a population. Using techniques of disease mapping, this study identified several key points about the spatial variability of parasitic infections during mass treatment of a community with an antiparasitic drug: 1) helminth burdens are localized to specific 'niches' in the community, and are not evenly distributed; 2) treatment with ivermectin does not produce the same spatial 'effect' with all of the helminth diseases; and 3) the way that re-infections appear can be a clear indication that the areas of reappearance represent either significant points of transmission or environmental 'foci' of infection.

Because many of the parasites examined in this study appear in some areas of Balbino, a rural community in northeast Brazil, and not others, there is already evidence that there are underlying geographical factors in their distribution and abundance. With the geohelminths, it is evident that particular areas of the village are more suited for their environmental life cycles than others. For instance, *Trichuris* and *Ascaris* are both prevalent in greater numbers as distance from the beach and the mangroves decreases. This could be because the soil type near the beach and mangroves is not conducive to these parasites' growth and development. *Strongyloides*, on the other hand, seems to have village-wide distribution, indicating that it is perhaps a hardier organism whose environmental life cycle can tolerate more soil types.

The spatial effects seen in this study reflect the fact that the effectiveness of ivermectin to certain parasites is variable. Though this fact has already been addressed through non-spatial techniques (Heukelbach et al., 2004b), the use of disease mapping and kernel density interpolation provides a novel way at visualizing this process. In addition, disease mapping may also provide a way to visually associate effectiveness with different environmental and/or demographic characteristics of the community—a point that may wish to be addressed in future studies.

Using the kernel density interpolation routine in this study was useful for visualizing the community-wide effects of antiparasitic treatment, but would have been inappropriate for a micro analysis. Determining the effects of treatment on the disappearance and re-appearance of infections within households, for instance, would require different geospatial techniques such as spatial description or cluster analysis.

It is evident from this study that a full understanding of the exact mechanisms of parasite distribution in Balbino will not come until further investigations using subsequent geographical data are initiated. With the current advances in remote sensing, it is possible to integrate satellite-derived data on vegetation (normalized difference vegetative index), soil type, altitude, distance from ocean and roads, topography, wetness indices, temperature, and average rainfall with health data (Albert et al., 2000). These environmental variables can be analyzed to better our understanding of the environmental life cycles of these parasites, with implications on their control and/or eradication. In addition, confounding variables, such as socio-economic status and access to hygiene need to be taken into account when performing geographical analysis.

Introduction

Within the realm of human parasitology and public health, geographical information systems (GIS) has the potential to become a valuable tool used 1) to capture, map, and analyze disease data for use in parasite atlases; 2) to model the spatial structure of infection relative to environmental variables (like those obtained through remote sensing (RS) technologies); 3) to predict the effects of density-related factors in disease distribution; and 4) to focus and drive parasite control programs by improving the identification of endemic areas and populations at risk (Brooker, et al., 2000). With such implementation, disease mapping and spatial analysis can play a vital part in disease epidemiology (Wen et al., 2006).

This research employs kernel density interpolation to view the changes in helminth infection associated with mass treatment with ivermectin. Kernel density interpolation generalizes incident locations over an entire area (Levine, 2007). This approach to spatial modeling thus proves more useful than spatial descriptors when trying to visualize the effects of ivermectin pharmacotherapy over the entire community. In addition, most other interpolation techniques such as kriging, trend surfaces, and local regression models are not suitable for individual point-level data, making kernel density estimation the only suitable interpolation technique for this data (Bailey & Gatrell, 1995).

The objectives of this study were to use kernel density to visualize four parasitic helminth infections during three distinct time periods: 1) pre-treatment with ivermectin; 2) 1 month post-treatment; and 3) 9 months post-treatment. Because this study analyzes data over time, it is able to demonstrate the geographic variability of infection as a measure of treatment efficacy by providing visual displays of 'hot spot' densities that not only show where infections disappear after treatment, but also where they reappear—a direct indicator of the importance of certain geographic areas of Balbino that are particularly prone to infection. These helminth foci can then in turn be ecologically analyzed to determine the specific variables that make them more susceptible areas for infection. Such information is extremely useful in both the control and prevention of helminth infections.

Background to Helminth Infections

Parasitic diseases are a major concern in both tropical and temperate biomes around the world. Endoparasites, namely the intestinal geohelminths, infect more than a billion people worldwide, while skin parasites (ectoparasites) infect hundreds of millions (Heukelbach, et al., 2004b). Global parasitic disease burden is especially high in developing nations and among children. Though rarely acknowledged as a public health problem, human parasitism can lead to significant morbidity, growth inhibition, mental deficiencies, and impaired physical performance in people who are already resource-deprived (Heukelbach, et al., 2006). In the developing nations, this leads to decreased productivity for individuals who are already struggling to subsist. The four human parasitic geohelminth infections considered in this study are *Ascaris lumbricoides*, *Strongyloides stercoralis, Trichuris trichuria*, and hookworm.

Ascaris lubricoides is the causative agent of ascariasis, one of the most common worm infections of humans estimated to infect 644 million to 1 billion people worldwide (PAHO, 2003). *Ascaris* is a nematode intestinal parasite that grows to 20 to 35 centimeters and usually spends most of its life in the intestine of its host. Transmission of the disease occurs through ingestion of infective eggs located in contaminated soil, water, and edible plants. The ingested eggs contain infective larvae that hatch within the intestine. Larvae invade the mucosa of the cecum and colon, then migrate to the liver via the portal circulation. Larvae are carried through the bloodstream to the heart and lungs. In the lungs, larvae break through the pulmonary capillaries, enter the alveoli, and migrate through the bronchial tubes and trachea into the pharynx, where they are swallowed and carried to the lumen of the small intestine. Larvae develop into male and female adults within the intestine. Females can lay up to 200,000 single-cell eggs a day which pass through the digestive tract into the feces. Once in the environment, infective third-stage larvae develop within the eggs after around three weeks and can survive in the soil for up to 20 years.

The disease ascariasis is due to: 1) large numbers of worms competing for nutrients; 2) worms penetrating the gut wall; 3) aberrant or 'wandering' worms lodging in the wrong places (i.e., brain); and 4) larvae migrating through the lungs (PAHO, 2003). High parasite burdens may cause vague abdominal discomfort, colic, diarrhea, and vomiting. Respiratory symptoms can include fever, irregular/asthmatic breathing, spasmodic coughing, and pulmonary infiltration. The disease may cause stunted growth and slow weight gain in children. The most serious complication in children is intestinal obstruction by large masses of parasites. Each year, around 20,000 people die from *Ascaris* infection usually due to intestinal complications (PAHO, 2003). *Ascaris* is most prevalent in rural areas where contamination of the soil is common and in hot, humid areas that favor egg maturation. Children have the highest rates of infection because of lower hygiene levels and naïve immunity. In the U.S., infection is rare but most common in rural areas of the southeast.

Diagnosis of ascariasis is made by demonstration of eggs in the feces, coughing, or passing of worms. Treatment is pharmacotheraputic and includes the anti-nematode drugs pyrantel, mebendazole, and albendazole. Because *Ascaris* infection is related to standard of living and hygiene, control and prevention of the disease involves massive and periodic treatment of the human population to stop environmental contamination, proper or improved sanitary waste disposal, provisioning of potable water, and health education that instills personal hygiene habits (PAHO, 2003).

Strongyloides stercoralis is an enteric helminthic parasite that infects an estimated 100 to 200 million people in 70 countries worldwide (Rose, 2008). The disease is endemic in many tropical and subtropical countries of sub-Saharan Africa, South and Southeast Asia, Central America, South America, and parts of Eastern Europe, where prevalence ranges from 2 to 20%. The transmission of *Strongyloides* is similar to that of *Ascaris*, with several exceptions: 1) filariform larvae matured in the soil can directly enter the skin upon contact; 2) *Strongyloides* eggs can hatch and mature into rhabditiform larvae within the intestine; and 3) it has the ability to avoid the environmental cycle and can directly re-infect its host via filariform larvae. The autoinfectious cycle can be accelerated in immunocompromised patients or drug or disease-related defects in cellular immunity, leading to a hyperfection that carries a mortality rate of 60 to 85%. In addition, autoinfection allows the parasite to persist within its host for decades. Strongyloidiasis is diagnosed by examination of feces for larva, which usually can be seen around one month after initial skin penetration, or, in more advanced settings, can be diagnosed with ELISA serology. Ivermectin and Thiabendazole are the preferred methods of treatment. Prevention includes normal hygiene precautions, such as wearing shoes and defecating in appropriate locations (Rose, 2008).

Trichuris trichiuria, or whipworm, is another common intestinal helminth infection that is estimated to infect over a quarter of the world population (Donkor, 2006). Whipworms get their name from their whip-like shape. Male worms are around 30 to 45 millimeters in length, while females are 35 to 50 millimeters. Usually, these worms burry themselves into the intestinal mucosa of the cecum and colon and feed on tissue secretions. Infection by whipworm is characterized by a lack of a tissue migration phase, unlike Strongyloides and Ascaris, and a relative lack of symptoms. Transmission is through the fecal-oral route, associated with poor hygiene, and usually greatest in children. Eggs mature in the soil after around 10 to 14 days, are ingested, hatch in the small intestine, and mature into adults in approximately three months. Female worms can live in the intestines and produce eggs for up to five years. Diagnosis of whipworm is made by fecal examination, which shows 'tea-tray' shaped eggs. Serology usually reveals eosinophilia, but rarely anemia. The drug of choice for whipworm infection is Mebendazole or Albendazole. Prevention involves strict maintenance of hygiene and avoiding the fecal-oral route of contamination (Donkor, 2006).

Hookworm disease is commonly caused by two species of intestinal helminth worms, *Ancyclostoma duodenale* and *Necator americanus* (Tam, 2008). Hookwork disease is found in over 740 million people around the world, and, like many of the other intestinal helminths, is usually asymptomatic. Male worms are 8 to 11 millimeters long, and females are around 10 to 13 millimeters. Larvae hatch in soil from eggs after 24 hours of being laid in stool. Approximately 24 hours later, the worms molt into infective filariform larvae that are capable of penetrating intact skin. Transmission to humans usually occurs through bare feet on contaminated soil, and once penetrated the worms migrate and develop in human tissues in a method similar to Ascaris and Strongyloides. Adult worms reside in the intestine and feed on the blood of the host. Adult worms can consume around 0.3 to 0.5 ml of blood each day, which can lead to anemia and impaired nutrition in the host. Worms can live in the human intestine for one to five years. Suspicion of infection is taken from patient history and clinical signs like eosinophilia, and diagnosis is made through visualization of eggs and parasites in the feces. The drugs of choice for hookworm are mebendazole, albendazole, and pyrantel pamoate. Like the other helminth infections, hookworm infection can be prevented through appropriate hygiene control (Tam, 2008).

Materials and Methods

Study Area and Population

This study examines the prevalence of helminth infection in Balbino, Brazil. Balbino is divided into at least two different ecological environments: 1) an area with homes built on sand dunes adjacent to the beach; and 2) an area built on sand dunes located next to a mangrove swamp. The population of Balbino is mostly poor: the village has no paved streets, and most of the houses are built with sand floors (Heukelbach, et al., 2004a). Inhabitants live in compounds, typically larger than those found in urban slums. The village has no sheep or goats, but does have a number of cats and dogs and a few pigs. Only 75% and 84.1% of homes have electricity and latrines, respectively, and a little more than 84% have private bore water wells (Heukelbach, et al., 2004b). During field data collection, it was observed that many of the households raised pigs that were fed garbage and were allowed to roam free around the house sites. There is no doubt that ecological, socioeconomic, and hygienic conditions in Balbino Village contribute to the high helminth prevalence.

Data Collection

This study considered pre-treatment prevalence as well as two post-treatment prevalence periods for helminth infection. These two periods include a one and nine month post-treatment follow-up of epidemiological data collection using methods similar to the pre-treatment data collection phase. The treatment used was ivermectin, an antiparasitic drug developed in the 1980's whose efficacy was shown to reduce parasite burden in Balbino by 94% (Speare & Durrheim, 2004). All members of households with at least one person with parasite infection were treated except those with contraindications for administration (younger than 5 years old, weighing less than 15 kilograms, being pregnant or breastfeeding, or having renal/hepatic disease) (Heukelbach, et al., 2004b). Those with contraindications were treated with mebendazole or albendazole antiparasitic drugs. Prevalence of helminth infection one and nine months after treatment was subsequently determined. Advanced statistical analysis on crude, non-spatial prevalence has already been calculated in previous studies (Heukelbach, et al., 2004b).

Exploratory Data Analysis

Geographic coordinates of household locations were imported into ArcView GIS Version 3.2 (ESRI, 1999). Epidemiological data on individual prevalence was imported into the GIS in database format and merged with household coordinates using family number as the merge variable. Prevalence was then displayed in disease maps as event themes systematically divided by the type of helminth infection and time of data collection (pre-treatment, one month post-treatment, and nine months post-treatment).

In order to get an idea of the type of approximate bandwidth (i.e., search radius) to use in preparation for kernel density calculation, Moran correlograms were produced for each helminth at each time interval and for total population. Selecting bandwidths at which the Moran correlograms level off, or approach the global I value, leads to an estimation that minimizes spatial autocorrelation and maximizes the capture of major trends in the dataset (Bailey & Gatrell, 1995). For example, for pre-treatment hookworm incidence global I values begin to level off around a bin distance of 125 meters. Therefore, in calculation of kernel densities for pre-treatment hookworm incidence, a bandwidth of 125 meters was chosen.

Spatial Analysis

ArcView GIS Version 3.2 was used to develop density maps of helminth infection and population. The single kernel density routine offered through the spatial analyst extension was used to estimate density values for each household. Resultant bandwidth estimation taken from the Moran Correlograms produced in CrimeStat were used to select an optimal bandwidth and a 'uniform distribution' for the type of kernel used in the single kernel interpolation. Visual presentation of the single kernels was obtained by scaling density values in a choropleth map such that higher densities are shown in darker tones and lower densities in lighter tones.

Results

Statistical analysis of the data indicate that at pre-treatment the incidence of helminth infections in Balbino was 60.1% (N = 548). Only 9.7% (N = 154) of households were complete free of helminth infection. Figure 1 shows the results of the kernel density estimations.

Ascaris infection occurred with a 17.1% incidence (N = 88). The geographical distribution of *Ascaris* was mostly confined to the northwest corner of Balbino and appeared to be limited by proximity to both the beach and the mangrove swamp. Of the four most prevalent helminths, *Ascaris* has the smallest geographical range in Balbino village. Ascariasis in the short term appeared to be affected by ivermectin treatment the most of all the parasitic infections investigated in this study. As shown in Figure 1, prevalence was limited mostly to the center but occurred throughout the southern two-thirds of Balbino village at baseline. Four weeks after treatment, prevalence was drastically diminished to include only two focal points of infection located in the south and east of the village. After nine months, infection returns to the center of the village, but disappears from the foci found at the four week interval.

Of the 516 people tested for *Strongyloides*, 57 (11%) tested positive for the disease. Spatially, the incidence of *Strongyloides* correlates with population density (see Figure 1) rather than geographical location, as cases were generally located in a northwest-southeast band on and off the beach and around the mangrove swamp. Strongyloidiasis showed the strongest long-term effect to ivermectin treatment out of all of the helminths in this study. At baseline, this disease was prevalent throughout Balbino, with most cases occurring in the center along a diagonal axis to the northwest. Unlike ascariasis, strongyloidiasis occupied the northern two-thirds of Balbino during this time. Four weeks after treatment, a dramatic reduction in prevalence can be seen, with two foci of infection occurring near the center-east of Balbino. After nine months, only one focal point of infection remains, located in the southeast-center portion of the village.

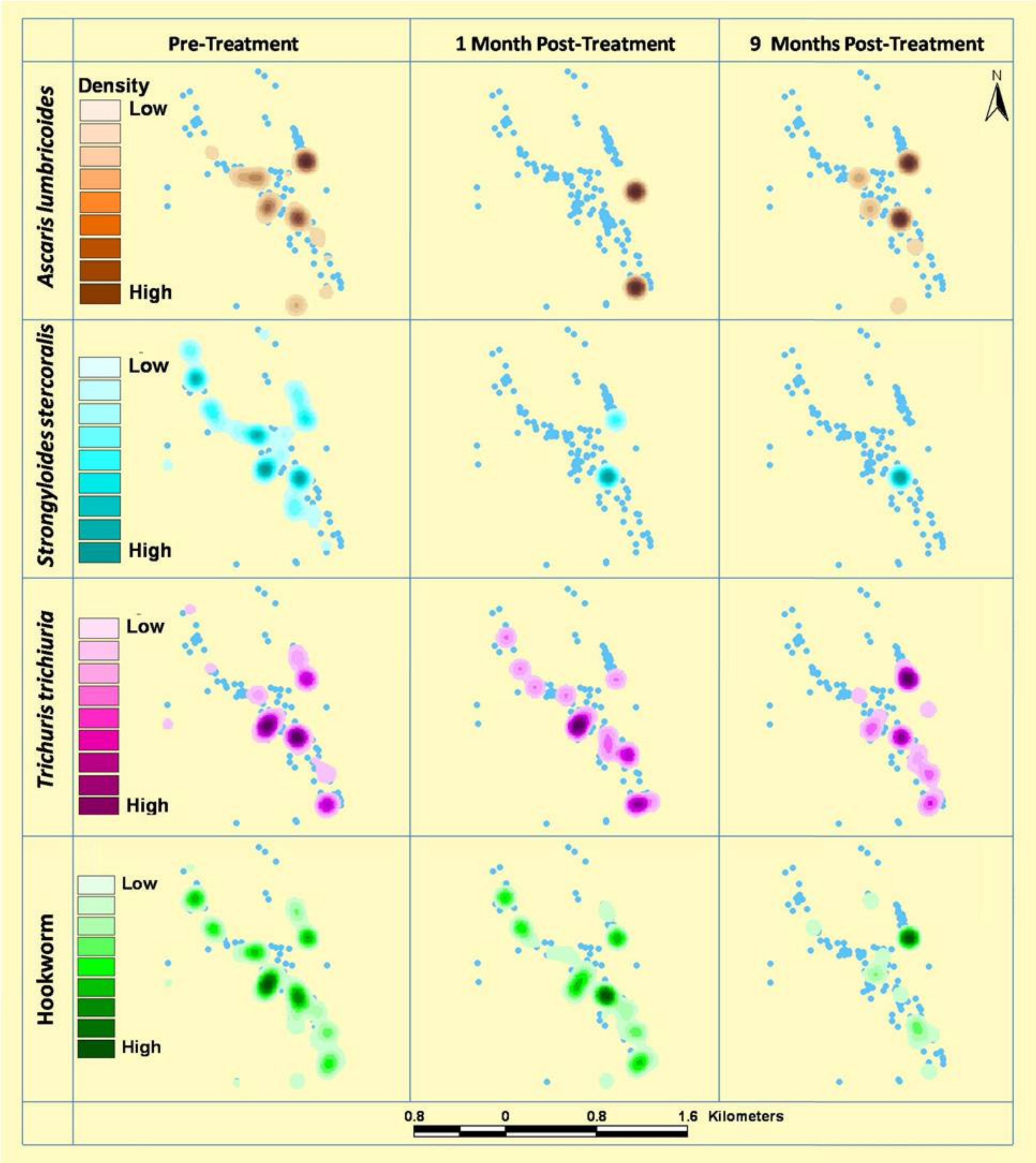

Figure 1: Kernel density interpolation of helminth infection in Balbino, Brazil

Infection with *Trichuris trichiura* (whipworm) occurred in 16.5% (N = 85) of the tested population. Kernel densities calculated from this incidence indicate that whipworm infection was generally centered around the northwest area of Balbino, away from the mangrove swamp and not on the beach. As viewed in Figure 1, the effects of ivermectin treatment on trichuriasis in Balbino are less apparent than with the other endoparasitic infections. At baseline, the majority of infection is present along the southeastern portion of Balbino. Ironically, prevalence increases during the first follow up, spatially moving more northward in the village. At nine months, however, infection disappears from the new areas seen at the first follow-up, and resumes a distribution similar to that at baseline.

Ancyclostoma (hookworm) infections were found in 28.5% (N = 147) of the population. The geographic range of this disease appeared to be more spread out than that of whipworm, with a northwest-southeast distribution that even borders the mangrove swamp. Like whipworm, however, this infection seems to have been limited by proximity to the beach. The disappearance of hookworm disease, like strongyloidiasis, occurred more in the long-term after drug treatment than in the short-term. This trend is evident in Figure 1. In this figure, it can be seen that the baseline and first follow-up periods have nearly identical spatial distributions of hookworm prevalence throughout Balbino, whereas during the second follow-up most of this prevalence disappears from the western portion of the village. One strong foci of infection is evident during this period in the center-east of Balbino, which is surrounded by smaller points of infection.

Discussion

Kernel density estimation is an effective tool to identify high-risk areas within point patterns of disease incidence by producing a smooth, continuous surface that defines the level of risk for that area (Bithell, 1990). In addition, kernel density estimation represents a powerful way to conduct hot spot analysis and easily visualize trends over large areas (Levine, 2007). It can be used in public health research to target areas of high concentrations of disease for control and to target areas at higher risk for prevention.

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Conclusions

Using the kernel density interpolation routine in this study was useful for visualizing the community-wide effects of helminthic treatment, but would have been inappropriate for a micro analysis. Determining the effects of treatment on the disappearance and re-appearance of infections within households, for instance, would require different geospatial techniques such as spatial description or cluster analysis.

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