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Medical geography in public health and tropical medicine: case studies from Brazil

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MEDICAL GEOGRAPHY IN PUBLIC HEALTH AND TROPICAL MEDICINE: CASE STUDIES FROM BRAZIL

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As always,

Dedicated to my family and friends around the world:

“First for Virtue, and then the Crown”

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PREFACE

As a fourth-grader, I used to spend my spare class time reading a set of *National Geographic* magazines that someone donated to my elementary school. What fascinated me was the depth and scope of knowledge presented to me in these magazines: on one page I could read about the demise of the white rhino on the Serengeti of East Africa; on the next page read about Sir Edmund Hilary's 1953 trek across the Himalayas and Mount Everest; and yet on the next page read about the thousand year old art of sheep farming in Wales. The fact of the matter was that I could pick up any issue, open it to nearly any page, and be completely entranced by whatever article would appear. Though not the end-all or be-all of geographic literature, it was from *National Geographic* that I not only gathered my definition of geography, but also was introduced to all the facets of knowledge that exist around the world.

My interest in human health, however, did not come from a magazine. Rather, they came from childhood stories of notable imperial physicians. My favorite stories were about the English Bush doctors of Kenya and South Africa during colonial times, who traveled from village to village in their khaki shorts with brown leather medicine kits strapped over their shoulders. Working as philanthropists as much as physicians, these doctors would refuse the natives' offerings of chickens and goats as payment for medical services. These people practiced the *art* of medicine, gained knowledge of the world and its cultures, and served humanity. In my mind, these people (though sometimes fictionally embellished I'm sure) were the epitome of nobleness.

It thus seems highly appropriate that the topic of my dissertation, tropical medicine and medical geography, encompass both of these childhood experiences. In the last decade, I have expanded my curiosity for geography by traveling the world and seeing for myself what I used to

read in magazines, and have pursued my aspiration to augment human health and humanity by studying and choosing a profession in the health sciences. It seems that when I was collecting my data for this dissertation in Brazil, amongst the poorest of the poor diseased children of the Brazilian slums, I had become the person that I used to so admire as a child. I hope that through my fortune of accomplishing these feats that I can somewhat give back to those around me through the fruits of this dissertation, and continue to aspire to be that notable "bush" philanthropist of my childhood dreams.

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ABSTRACT

Within the last few decades, the multitude of infrastructural and environmental changes associated with population growth, human migration, and economic development have catalyzed the emergence and re-emergence of many infectious diseases worldwide. The morbidity and mortality associated with these diseases have in turn led to an increased and renewed impetus to gain a better understanding of the etiology, epidemiology, prevention, and control of these diseases in order to achieve better health and well-being, especially for underprivileged populations. Two traditionally separate fields, medical geography and tropical medicine, have recently seen complex and radical paradigm shifts in response to this global situation: medical geography has been developing many new and sophisticated methods of data collection, data manipulation, and spatial analysis that make it more suited for the study of health-related problems; and tropical medicine has been revisiting the fundamental notion that disease is intimately linked to the physical and cultural geographic environments in which humans live. As a result, concepts of medical geography are being more readily employed within tropical disease research, and tropical medicine is embracing geographic methods as a central mainstay in the control, management, and prevention of tropical diseases. As the associations between these two fields continue to grow, a clearer understanding of how they compliment each other will be needed in order to better define their interrelated roles in augmenting human health.

This dissertation examines the multifarious relationships that have developed between the fields of medical geography and tropical medicine in recent years by presenting the reader with a brief history of their common origins and a comprehensive review of the techniques and methodologies in medical geography that are frequently employed in tropical disease research. Following this background information, several case studies are investigated that provide

examples of how geographic methods can be easily and effectively employed in the analysis of several tropical diseases, including tungiasis, intestinal helminthes, leprosy, and tuberculosis. These case studies demonstrate some of the advantages and disadvantages of current geographic methods employed in health research, and offer a framework for readers who are interested in applying basic geographic concepts to analyze questions of health.

CHAPTER 1. INTRODUCTION

In the two decades preceding the start of the new millennium, geography as a discipline witnessed an innovative revolution that completely reorganized the traditional boundaries of this field. Building upon its established strengths and embracing the novel ideas and perspectives brought about by the technological boom of the late 1980s, geography has expanded into a more robust, recognized, marketable, unified, and diversified scientific discipline (Gaile & Willmott, 2003). Increasingly, geographers are applying new concepts and research methods to approach more complex spatial questions in a growing number of sister fields (NRC, 1997).

One of the fastest growing fields in geography is medical geography, or the study and application of geographic concepts and techniques to health-related problems (Barrett, 2000a). Like its mother field, medical geography has seen major shifts in its ideology, approach, methodology, and scope in the last few decades. The traditional perspective of medical geography, the implementation of geographical concepts and techniques to study health and disease, has remained the same to this day (Meade & Earickson, 2000). However, the field has recently grown to integrate novel principles of the social, physical, and biological sciences as well as to embrace recent technological developments in computing power. Increasingly, medical scholars are seeking the assistance of geographers while geographers are venturing into the realms of health research (Johnston & Williams, 2003).

The application of geographic concepts in medicine—and indeed many other disciplines—has led to many meaningful clues about the world in which we live: finding out *where* events happens often leads to some indication of *why* these events happen (Waller & Gotway, 2004). In medicine, the identification of many diseases' distribution patterns has led to a better understanding of their epidemiology and ultimately their control with direct implications

for health outcomes (Meade & Earickson, 2000). For instance, the distribution of onchocerciasis, a parasitic disease found in West Africa that causes blindness, depends on an area's proximity to turbulence in a river, which in turn is influenced by regional variation in rainfall and climate (Aron & Patz, 2001). This epidemiological information, which has been vital to the control and reduction of onchocerciasis in recent years, would not have been discovered had it not been for geographic methods that correlate patterns of meteorological and hydrologic data with patterns of case incidence data. As such, the application of geographic methods in medical research has—and continues to have—a significant impact on both local and global health (Gatrell & Loytonen, 1998).

This dissertation focuses on the applications of medical geography within the realm of tropical medicine, specifically providing case studies that examine several tropical diseases present in the country of Brazil. It is hypothesized that through the use of concepts in spatial analysis and medical geography that disease patterns specific to Brazil can be underpinned. It is the goal of this research to identify spatial patterns of disease that may contribute to the risk of disease.

This dissertation is structured so that a general background of medical geography and tropical medicine precede several case studies. Chapter 2 begins as an introduction to the fields of geography and tropical medicine, reviewing how the fields originated, how they are related, and what future directions they are taking. Chapter 3 is an introduction and review of the methods used in medical geography—namely the technologies and techniques that are applied to questions of health and space. Chapter 3 is meant to give some background to the reader in preparation for the techniques and methods used in subsequent case studies. Chapter 4 is designed both as a literature review and an examination into the interrelated fields of tropical

medicine and medical geography. Specifically, Chapter 4 investigates the role of geographic information systems in tropical disease research by quantifying the number of articles published in several leading tropical medicine journals. Chapter 5 is the first case study presented in this dissertation and employs some of the basic concepts used in spatial analysis to determine the spatial structure of the ectoparasitic disease tungiasis in a small fishing community of northwest Brazil. Chapter 6 is a continuation of Chapter 5, and examines the spatial structure of endoparastic helminth infections using a common routine known as *kernel density estimation*. Chapter 7 gives readers a thorough introduction to Hansen's disease, or leprosy, and the challenging road to leprosy elimination—including a brief history of leprosy elimination, the current global situation of leprosy, and future expectations for leprosy elimination. Chapters 8 and 9 are continuations of the case studies, and investigate the clustering of leprosy within two ecologically and demographically distinct regions of Brazil—Ceará, a dry, arid state in the northwest of Brazil, and Rondonia, a wet, tropical state in the western Brazilian Amazon. Chapter 10, though dealing with leprosy in Rondonia State, introduces the potential of a new methodology into public health spatial analysis—the use of adjusted disease rates in the calculation of disease clusters. Chapter 11 is the last case study presented in this dissertation, and is a spatial examination of tuberculosis in Ceará State. Chapter 11 was designed to show how the spatial structure of tuberculosis differs from that of leprosy over a similar region and time period. Chapter 12 begins with a light-hearted photo journey through Fortaleza that describes some of the experiences of the author while collecting data in Brazil. Chapter 13 is the conclusion of this dissertation, reviews the results and conclusions herein, and gives insight into the potential future of medical geography, public health, and tropical medicine.

CHAPTER 2. THE FORMAL BEGINNINGS AND PROGRESS OF MEDICAL GEOGRAPHY AND TROPICAL MEDICINE

The unification of health and geography dates as far back as when humans first realized that their health was linked to the environment in which they lived. Though there is no concrete date for this realization, it seems likely that as long as there has been a consciousness for health there has been a consciousness for health geographics—after all, nearly every source of disease is attributable to some aspect of the cultural or physical environment in which we live. In fact, it has been the identification and modifications of these environments that have allowed modern medicine to progress from simple theories of miasmatic disease origin to such complex discoveries as the identification of specific host cell ligands and receptors that allow entry of Human Immunodeficiency Virus (HIV) into lymphocytes (Kumar et al., 2004).

Though we may take for granted the position of modern medicine and health today, the path to improving human health through scientific investigation has not been easy or brief. It was the ancient Greek physician Hippocrates who first formally described and documented in 400 B.C. what he thought was a distinct relationship between human culture, disease, and environment (Hippocrates, 1886). Occurring almost two and a half millennia ago, this realization laid what was to become the beginnings of modern medicine. However, it would take nearly 1900 more years for medical investigators to push through the quagmire of theories and public perception of miasmas, spontaneous generation of infectious particles, and divine resolution of disease to determine that germs were the origin of most disease and that these germs came from the environment surrounding us.

The discovery of the “germ theory” in the early nineteenth century was so profound that it enabled physicians and scientists of the time to enter into a new world of medical investigation

that was to fatefully change and alter the course of human health (Haynes, 2001). This discovery was accompanied by two interrelated events that precipitated a renewed vigor of thought and discovery that subsequently led to the development of what we know today as the fields of medical geography and tropical medicine. The first event was the outward expansion and increase of European powers through colonization and migration, which sent ship after ship of steadfast imperialists into never-before 'discovered' corners of the globe. The second event, which in some ways is a result of the first, was the sharing, mixing, and introduction of new forms of disease into both the 'new' and 'old' worlds. The result of these two events was a marked challenge to human health: the diseases brought back to Europe were ravaging the 'home' population in massive epidemic waves (not to mention the indigenous populations of the 'conquered' lands), and the diseases encountered in the newly claimed lands were inhibiting colonization and hence the growth of European power and might. The reaction to this problem in the minds of Europeans was to launch an all-out attack on these strange diseases to determine the who, what, when, and why of how they existed, laying the preliminary and rudimentary foundation of what was contemporarily coined "imperial medicine" (Farley, 1991). Because of the importance of maintaining health in the face of colonization (health meant wealth for colonizers), imperial medicine was considered the "queen of medical sciences" during the nineteenth century, and it formed the epicenter of applied science of the time (Haynes, 2001; Rupke, 2000).

It was through the enthusiasm for imperial medicine that the fields of medical geography and tropical medicine developed (Speare & Leggat, 2006). Unlike today, in its formal materialization near the turn of the nineteenth century medical geography was pioneered by the endeavors of physicians rather than geographers. These physicians, prompted by the emergence

and re-emergence of epidemic diseases like cholera (which during the start of the nineteenth century had spread from India to Europe in a series of pandemics), began a whole series of medical inquiry that was fundamentally based on the geography of these diseases. One of the earliest accounts of this era was a map of global disease distribution produced by the Prussian Physician L.L. Finke in 1792 (Barrett, 2000b). Following Dr. Finke's work was the American physician Daniel Drake's publication *The Principal Diseases of the Interior of North America* in 1850, the first description of disease occurrence in North America as it relates to geography (Barrett, 1996). In 1859, the German physician August Hirsch published his two-volume *Handbuch der Historischen-Geographischen Pathologie,* a monumental attempt to describe the world distribution of disease (Johnston & Williams, 2003). However, the pivotal point in the course of medical geography came in 1854 when the renowned English physician John Snow pioneered the idea that ecological phenomena can be cartographically matched to health events, correlating cases of cholera to water supply structures within London using maps (Newsom, 2006). Snow was simply applying the concepts of medical geography to control a disease based directly on the results of a spatial analysis. Because his work showed for the first time that geography can play a primary rather than supportive role in the explanation of many diseases, he is considered the father of modern medical geography (Barrett, 1996).

Tropical medicine, like medical geography, also arose out of the confines of early nineteenth century imperial medicine (Speare & Leggat, 2006). As mentioned above, tropical medicine began when colonists and soldiers of European origin were expanding into tropical regions of the planet and encountered unique diseases not found in temperate zones. Most of these diseases, but not all, were communicable in origin, and to control them colonial physicians had to develop a greater understanding of infectious disease epidemiology. In 1851 the German

chief of surgery at the Kasr-el-Aini Medical School of Cairo, Egypt, Theodor Bilharz, was the first to discover and describe *Schistosoma haematobium*, the cause of schistosomiasis (Speare & Leggat, 2006). In 1900 the Cuban scientist Carlos Finlay confirmed American physician Walter Reed's hypothesis that mosquitoes were the vector of the viral disease yellow fever. In 1901, while examining bodies in the Indian Medical Service, the British medical officer Lieutenant-General Sir William Leishman discovered that the protozoan *Leishmania donovani* was the cause of kala azar (visceral leishmaniasis) (Murray et al., 2000). These discoveries were only the beginning of the foundation of what was to become tropical medicine.

It is from their common root of origin in nineteenth century imperial medicine that tropical medicine and medical geography formally developed as distinct yet parallel fields of study (Brown & Moon, 2004). Today, medical geography has progressed more in the realm of academic research, lying mostly in the social sciences but occasionally venturing into the realm of medical practice. Tropical medicine, on the other hand, has progressed mainly in clinical practice but because of its use of medical investigation frequently ventures into the realm of academic research (Murray et al., 2000).

Medical geography was first recognized as a formalized academic sub-discipline of geography in 1952, when the Commission on Medical Geography (Ecology) of Health and Disease gave its first report to the International Geographic Union (Meade & Earickson, 2000). This report came just a few years before Jaques May, the father of disease ecology, published *The Ecology of Human Disease* (1958), a book whose concepts were to turn disease ecology into the fundamental core of medical geography. It was also during the 1950s that the field began to see a paradigm shift from the traditional notion that medical geography was focused on the understanding of the spatial distribution of disease to the wider notion that it should incorporate a

range of approaches to understand the relationship between space and the broader idea of health and well-being (Cummins & Milligan, 2000; Rosenberg, 1998). This shift came nearly a decade after the World Health Organization (WHO) redefined the concept of health to include not only the absence of disease but also the state of complete physical, mental, and social well-being (WHO, 1946). This ideological shift fundamentally changed the focus of medical geography to include both disease ecology and healthcare delivery, using disease mapping and spatial analysis as its technique (Gaile & Willmott, 2003). Today, medical geography is one of the fastest growing sub-disciplines of geography, and refinements in technology promise to continue to impact the field (Glass, 2000; Kamel Boulos et al., 2001).

Tropical medicine, like medical geography, has witnessed some paradigm shifts in response to current global health definitions and demands. It is no longer considered the medicine of colonizers, but rather has grown to encompass the medicine of indigenous residents of the tropics (Speare & Leggat, 2006). In essence, this transition has made tropical medicine not only the medicine practiced in the tropics, but, more specifically, the medicine of developing countries and populations in transition. A contemporary working definition of tropical medicine is given by Speare & Leggat (2006) as "a branch of medicine that deals with the health problems that occur either uniquely in tropical and subtropical regions of the planet or are either more widespread or are more difficult to control in the tropics." The dilemma of defining tropical medicine in a contemporary context is the fact that 'tropical' diseases are not static in location. In fact, many diseases that are considered 'tropical' today were once endemic to countries located in temperate and even arctic zones—these include leprosy, cholera, malaria, hookworm, and many others. In other regards, tropical diseases are not confined exclusively between the Tropic of Capricorn and the Tropic of Cancer, and are often times found outside of these latitudes (this

phenomenon has led to the development of a relatively new branch of tropical medicine, travel medicine, that deals exclusively with the management and prevention of tropical diseases such as malaria or schistosomiasis in travelers and migrants). Because many of the diseases studied in tropical medicine are confined to certain areas or populations, this field is sometimes called "geographic" medicine (Eddleston et al., 2008).

Tropical medicine is also intimately linked with public health, which is the study of managing the health of populations (Speare & Leggat, 2006). Public health and tropical medicine share a unique relationship because many of the approaches used to control tropical diseases are population-based. Whether this is due to the infectious nature of the disease or because of the status of the population can be debated.

The purpose of grouping medical geography and tropical medicine together in this chapter is not only to express their common origins, but also to express the fact that they share much of their content and objectives and what they have to learn from each other. Today, the fields of tropical medicine and medical geography operate under different spheres of influence: one being run under the confines of the medical sciences and the other being run under the confines of the social sciences and geography. However, both disciplines with a few exceptions concentrate on the relationship between human disease and human environments.

One of the great milestones in the development of the association between medical geography and tropical medicine came during the 1980's, when several new technologies including geographic information systems (GIS), global positioning systems (GPS), and remote sensing (RS) were introduced into the fields (Kitron et al., 2006). These technologies, combined with the increased availability and power of computing systems and software that deal with spatially explicit data, led to an explosion of research and a renewed interest in the capabilities of

these two fields (Glass, 2000). Compared to the rudimentary procedures used by early investigators like Snow and Leishman, these technologies are the 'new' arsenal of medical geography and tropical medicine. This topic is further explored in the following chapter.

CHAPTER 3. THE ARSENAL OF MEDICAL GEOGRAPHY: GIS, REMOTE SENSING, GPS, AND METHODS OF SPATIAL ANALYSIS

3.1 Introduction

Some of the main advances in the study of spatial phenomena in recent years have been the developments and improvements seen with geographic information systems (GIS), remote sensing (RS), global positioning systems (GPS), and spatial statistics (Cano et al., 2007). However, compared to traditional applications of spatial analysis, the application of these technologies to the study of health-related problems is relatively new and in its early stages (Kitron, 2000; Leibhold et al., 1993). Nonetheless, the number of studies employing these technologies within medical geography over the last few years has increased staggeringly, making it one of the fastest growing areas in geographic research (Oppong, 2006). This chapter is designed as a general introduction and overview of these technologies and methods with a few brief examples of their applications in health research, and is meant to provide some background for the subsequent studies examined by this dissertation.

3.2 Geographic Information Systems

Geographic information systems (GIS) are computer-based sets of procedures that capture, store, manipulate, edit, retrieve, analyze, model, and display data with spatial characteristics (Aronoff, 1989). GIS enable users to interactively query datasets, analyze spatial information, and present the results of these operations in maps, tables, and organized datasets. The uses of GIS extend into academic research, resource management, environmental impact assessment, urban planning, cartography, criminology, geographic history, logistics, and marketing—just to name a few (Wikipedia, 2008a). GIS have become a mainstay in many of these applications because they incorporate so many techniques and data types into a single

analysis, making the handling of complex data sets faster, cheaper, and more effective (Aron & Patz, 2001). In addition to its practical applications, GIS have also brought geography into many academic fields of research where it did not exist before, thus increasing the appreciation of geography and its tools in solving spatial problems (Gatrell, 2002).

In all the applications that use GIS, perhaps one of the most valuable has been its use in medical research. Specifically, medical geography has embraced GIS as a remarkable tool for understanding how health is related to space, in forms such as uncovering disease distribution to the allocation of health resources across communities. As mentioned before, one of the biggest advantages to using GIS is its capability to analyze both temporally and spatially complex data sets—and in geospatial health research these have grown to include demographic, political, environmental, ecological, topographical, hydrological, climactic, land-use, public infrastructure, transportation, health infrastructure, and epidemiological data—to name a few (Kamel Boulos et al., 2001; Kistemann et al., 2002). Indeed, GIS has been used to capture, map, transform, and analyze data for use in disease atlases; to model disease in relation to environmental variables; to predict the effects of density-related factors in disease distribution; and to focus and drive infection control programs by identifying areas of endemic disease or populations at risk (Brooker et al., 2000).

The importance of GIS in health research is exemplified by the amount of literature published within medical geography in the last few years—especially in infectious disease research of viruses, bacteria, and parasites. For example, recent research in virology has grown to include using GIS to document the emergence and geographic spread of Barmah Forest virus in Queensland, Australia (Tong et al., 2005); to assist in real-time surveillance of dead birds killed by West Nile Virus in Canada (Shuai et al., 2006); and to model the temporal-spatial distribution

of a dengue outbreak in Puerto Rico (Morrison et al., 1998). Within bacteriology, GIS has been used to identify wells and homesteads associated with enteric disease in Mexico City (Cifuentes et al., 2002); to analyze the health impact of water sources on diarrhea in Nigeria (Njemanze et al., 1999); to identify risk factors for Lyme disease in Baltimore (Glass et al., 1995); and to document access to community-based treatment for tuberculosis in Hlabisa, South Africa (Wilkinson & Tanser, 1999).

The use of GIS in medical geography has witnessed its greatest growth in research involving parasitology—as mentioned earlier especially in the realms of tropical medicine and the developing world. Within these two areas, GIS has been used to map the national distribution of lymphatic filariasis in Nepal (Sherchand et al., 2003); to formulate risk maps of lymphatic filariasis in Africa based on climactic variation (Lindsay & Thomas, 2000); to unmask the profound heterogeneity of malaria risk in magisterial districts of South Africa (Booman et al., 2000); to predict the spatial distribution of schistosomiasis in Tanzania for use in a national mass drug treatment control program (Clements et al., 2006); to model patterns of African trypanosomiasis in southern Cameroon (Muller et al., 2004); to develop models incorporating tsetse flies, livestock biomass, clinical disease, farming systems, and land use for the control of African trypanosomiasis (Hendricks et al., 2001); to determine the spatial pattern of African trypanosomiasis in Cote D'Ivoire using GPS and ground-collected information on households, agriculture, and vegetation (Courtin et al., 2005); to predict community prevalence of onchocerciasis in the Amazon (Carabin et al., 2003); to map the global distribution of trachoma and trichiasis (Polack, Brooker et al., 2005); to identify areas of high risk for giardiasis in Canada (Odoi et al., 2003); and to construct a disease atlas of helminth infection in sub-Saharan

Africa (Brooker, Rowlands et al., 2000). There is no doubt that the use of GIS in virology, bacteriology, and parasitology will continue to increase in the next few years.

3.3 Remote Sensing

Remote sensing (RS), in a general sense, is the small or large-scale acquisition of data on an object or phenomenon by the use of recording or real-time sensing devices that are not in physical or direct contact with the object or phenomenon being studied (Campbell, 2002). Using this definition of remote sensing, observation satellites, oceanographic and atmospheric weather buoys, magnetic resonance imaging (MRI), positron emission tomography (PET), and even ultrasound used to monitor pregnancy are all examples of remote sensing. Within the context of geography, however, remote sensing generally refers to the use of imaging sensor technologies such as electromagnetic radiation to obtain and record environmental attributes (Patterson, 1998). This sub-category of remote sensing is often divided into two kinds of remote sensing—those that use sensors to detect passive, natural ration that is emitted or reflected by the object being observed, and those that actively emit radiation in order to scan objects and then record the radiation that is reflected or bounces off of the target (Campbell, 2002).

The use of remote sensing in geography presents several advantages over classical techniques of data collection. For example, remote sensing makes it possible to obtain data from inaccessible locations or those that present too much danger for humans to collect the data in person, such as in the Amazon Basin or during the flooding of New Orleans after hurricane Katrina (Wikipedia, 2008b). Remote sensing can also be used to record environment change over time, such as the monitoring of El Niño in the Pacific or on a larger scale the measuring of global climate change by NASA's Earth Observing System (Williams, 2008). These advantages

make remote sensing a highly valuable tool in comprehensive research and enable the study of locations and spatial phenomenon that would otherwise be impossible.

In medical geography, when such problems as the identification of endemic areas of disease, the estimation of populations at risk, and the assessment of environmental information in areas that lack baseline data or cannot be accessed arise, the use of remote sensing, especially in conjunction with other technologies such as GIS, provides an efficient and effective method of data capture (Guo-Jing et al., 2005). For example, satellites such as Landsat's Multispectral Scanner (MSS) and Thematic Mapper (TM), the National Oceanic and Atmospheric Administration (NOAA)'s Advanced Very High Resolution Radiometer (AVHRR), and France's Système Pour l'Observation de la Terre (SPOT), can provide information about vegetation cover, landscape, structure, and water bodies in almost any region of the globe—information that can be extremely valuable in health research that examines environmental factors in disease dissemination (Beck et al., 2000).

The importance of remote sensing in medical geography is evident through the amount of literature published each year that exemplifies its applications. For example, remote sensing has been used to predict cholera outbreaks in Bangladesh that are based on large-scale oceanic algal blooms (Ali et al., 2002); to identify snail habitat for schistosomiasis control in China (Guo-Jing et al., 2002; Zhou et al., 2001); to predict the distribution of urinary schistosomiasis in Tanzania using land surface temperature (LST) and the normalized difference vegetation index (NDVI) (Brooker, 2002; Brooker et al., 2001); to map the distribution of intestinal schistosomiasis in Uganda using AVHRR (Kabatereine et al., 2004); to construct a household-GIS database for health studies in Karachi, Pakistan, using high resolution IKONOS imagery where GPS receivers failed because of structural barriers such as tall buildings (Ali et al., 2004); to quantify areas of

reduced risk of hantavirus pulmonary syndrome in the United States using Landsat Thematic Mapper imagery (Glass et al., 2000); to predict intestinal schistosomiasis infection in school children in the Côte d'Ivoire (Raso et al., 2005); to risk map visceral leishmaniasis in Sudan using NDVI and climate data (Elnaiem et al., 2003); to forecast malaria outbreaks in sub-Saharan Africa using climactic variables to predict vector habitat (Rogers et al., 2002); to determine small-area clustering of malaria in Nandi District, Kenya, based on landcover types retrieved from the Digital Landsat Enhanced Thematic Mapper (ETM+) (Brooker et al., 2004); and to identify environmental factors that could predict *Ascaris* infections in South Africa (Saathoff et al., 2005).

3.4 Global Positioning Systems

Hand-held global positioning systems (GPS) are a technology developed by the United States Department of Defense that use a constellation of 24 to 32 medium earth orbiting satellites to pinpoint a user's location, speed, direction, and time (King, 1997; Strom, 2002). Re-developed for civilian use under the issue of Ronald Reagan in 1983, GPS today is utilized in a variety of geospatial applications, from advanced computer cartography to on-board consumer automobile navigation systems (Pellerin, 2006).

GPS technology works through the synchronized timing of signals sent through a known array of satellites continually in orbit above the earth's atmosphere (Pellerin, 2006). These satellites transmit data that include the time the transmission was sent, the orbital path position, or ephemeris, and the rough orbital position of all GPS satellites, or the almanac. The GPS receiver, on the other hand, uses the arrival time of each data signal to measure the distance to its respective satellite source. By using signals and calculating the distance from several satellites, each receiver can determine its own position in space and time using geometric and

trigonometric algorithms in a process known as trilateration (Daly, 1993). The results of trilateration are converted to into user-friendly formats such as latitude and longitude or the location on a map.

The accuracy of a GPS is dependent on both natural and intentional errors (USCGNC, 2008). Natural errors that disrupt the exact calculation of position include atmospheric effects that distort signals as they travel through the atmosphere, multipath effects caused by the reflection of signals off surrounding terrain, ephemeris errors that include noise and clock drift phenomena, and sources of signal interference that can include solar flares, geomagnetic storms, and even metallic sources such as car window tinting films (USCGNC, 2008). GPS models used in military applications can be accurate to several centimeters and even millimeters; however, for civilian use the accuracy of a GPS receiver can be altered using a feature called Selective Availability (SA) that introduces intentional random errors into publicly available navigation systems for purposes of national security (USCGNC, 2008). Despite these errors, civilian GPS receivers are still considered to be accurate in most instances up to 100 meters for inexpensive models, within a few meters for more complex receivers, and within centimeters and millimeters for units with differential correction (King, 1997).

The applications of GPS have grown from military uses, such as target tracking, missile guidance, search and rescue, and reconnaissance, to an array of civilian uses that require absolute location, relative movement, or time transfer (Pellerin, 2006). One of the practical civilian uses of GPS that has gained considerable attention within the last few years has been the use of GPS in health research (Dwolatzky et al., 2006). Although the value of GPS in health research has only been relatively recently identified, its use and application continues to grow (Cano et al., 2007). Some examples of recent research that utilized GPS include Wiehe et al. (2008)'s

examination of the travel patterns of adolescents by giving them GPS-enabled cell phones that allowed them to track and to better understand adolescent environments and how they are related to high-risk health behaviors, such as smoking; Allpress et al. (2008)'s use of GPS to determine exact positions of households within GIS and remote-sensing derived maps in order to prospectively examine pesticide exposure in Illinois; Tran et al. (2008)'s use of GPS to identify and map larval and adult populations of *Anopheles hyrcanus* to examine the potential of re-emergence of malaria in Southern France; Zeilhofer et al. (2007)'s identification of habitat suitability of *Anopheles darlingi*, a vector of malaria, with GPS around hydroelectric plants in Mato Grosso State, Brasil; and Dwolatzky et al. (2006)'s implementation of GPS into a personal digital assistant (PDA) in order for health care workers to locate remote home sites of tuberculosis cases in support of a tuberculosis control program in South Africa .

3.5 Basic Theory of Spatial Analysis

When dealing with problems of space, the step beyond simple cartography and mapping is spatial analysis, which in geographic research is the tool used to compare the spatial distribution of a set of features to a hypothetically-based random spatial distribution (Mitchell, 2005). These spatial distributions, or patterns, are of interest to many areas of geographic research because they can help identify and quantify patterns of features in space so that the underlying cause of the distribution can be determined (Fotheringham et al., 2002). The process of identifying unique spatial distributions, or *statistical pattern recognition*, can range from simply "eye-balling" features on a map to complex computer-based spatial algorithms that can detect very minute differences on a surface (Mitchell, 2005).

There are many approaches to the analysis of spatial data. However, as Wilson & Fotheringham (2007) suggest, the typical method to approaching spatial analysis is: 1) create

adjusted rate maps of disease events; 2) use spatial statistics to determine whether or not the rates are spatially autocorrelated; 3) detect and identify the locations of clusters, hot-spots, cold-spots, and outliers; and 4) to assess why clusters, hot-spots, cold-spots, and outliers exist where they do.

In health research, spatial analysis is used to detect and quantify patterns of disease distribution that may offer insight into a disease's epidemiology (Srividya et al., 2002; Waller & Gotway, 2004). Spatial analysis is designed to detect 'clusters' of health events that demonstrate significant areas of either high or low disease risk. Although spatial analytical techniques rarely give reasons *why* spatial patterns occur, they do identify *where* spatial patterns occur. Within the realms of health research, this provides a useful means by which to hypothesize about health outcomes or to identify spatial issues that need to be investigated in further detail (Wen et al., 2006). However, spatial analysis is only part of the approach to answering geographic questions in health research, as it takes spatial analysis *in addition to* a strong understanding of biological processes before underlying clues about health problems can be inferred (Malone, 2005).

The fundamental concept behind the use of spatial analysis in health research is the idea of *spatial autocorrelation*. This concept is based on the idea that observations that are located near each other are influenced by each other and not distributed in space or time by random chance alone (Meade & Earickson, 2000). Positive spatial autocorrelation occurs when events of similar value are adjacent to each other, while negative spatial autocorrelation occurs when high values are located adjacent to low values (Gatrell, 2002). General examples of spatial autocorrelation would include the diffusion of a communicable disease where the presence of an infected individual would lead to increased susceptibility for surrounding individuals, or distance-decay risk associated with a toxic point-source exposure. In both these examples,

observations located adjacent to either the infected individual or the point source would have an abnormal relative risk for disease manifestation.

Most health research using spatial analysis begins with a study region that is partitioned into a number of small areas (Glass, 2000). Each small area, or unit, is correlated to a disease *rate* that is indicative of a disease outcome compared to the population at risk in that unit (Rothman & Greenland, 1998). Under the *null hypothesis*, the disease rate in each area has a nominal Poisson distribution with the expected number of cases equal to the mean of the Poisson process (Glass, 2000; Waller & Jacquez, 1995). The *reference distribution* is the distribution of the spatial test statistic under the conditions of a true null hypothesis (Fotheringham et al., 2002). The reference distribution is generated using a *null spatial model* that can be based on randomization techniques, such as the Monte Carlo, or on simple distribution theory. The *alternative hypothesis*, on the other hand, is a prediction of the spatial pattern that is to be detected based on an expected distribution of the spatial test statistic (Fotheringham et al., 2002). A *spatial test statistic*, such as an autocorrelation statistic or spatial cluster statistic, is used to quantify each unit's spatial pattern and compare that value to the one predicted by the null hypothesis (Goovaerts & Jacquez, 2004). Areas of positive or negative clustering are identified when their values deviate from the null hypothesis by showing increased variability in disease rates (Elliott et al., 1996). The end result, therefore, is the identification of how unlikely an observed spatial pattern is under the null hypothesis (Gustafson, 1998).

Complete Spatial Randomness (CSR) is the null hypothesis used by most spatial analyses in health research (Goovaerts & Jacquez, 2004). Using CSR can be problematic, however, when dealing with ecological or biological systems because complete spatial randomness rarely occurs in the natural world and "background" patterns can exist even under conditions described by the

null hypothesis. These patterns increase the probability for false positives (e.g., Type I error) and can lead to an over-identification of clusters (Goovaerts & Jacquez, 2004). However, there are a number of statistical tests used in health research that can reduce the problem of *background noise* when identifying significant disease clusters (Song & Kulldorff, 2003). Many of these tests use alternative null hypotheses, such as the "neutral model" suggested by Fotheringham et al. (2002), that provide more plausible null patterns that account for background variation.

One of the most prevalent methods of spatial analysis is called exploratory spatial data analysis (ESDA) (Mitchell, 2005). ESDA consists of a variety of spatial-statistical techniques designed to describe and visualize spatial distributions, identify unusual locations or outliers, discover clusters, and suggest hypotheses without pre-conceived notions about disease transmission (Munch et al., 2003). The key to ESDA, as opposed to spatial data or process models, is that it attempts to assess non-random spatial patterns *rather than trying to prove or disprove an explicit hypothesis about a health outcome* (Gatrell, 2002). As such, ESDA is considered the primary step in the spatial analysis of disease. Though they will not be discussed here, logistical regression analysis and spatial data process models are used as secondary approaches to health research, after particular hypotheses can be inferred from ESDA (Jacquez, 2004).

3.5.1 Spatial Statistics and Cluster Detection

Spatial autocorrelation is quantified in spatial analysis through the use of spatial statistics. Spatial statistics are used to detect patterns of spatial autocorrelation that represent areas of either high or low disease risk (Waller & Gotway, 2004). These patterns, which often represent areas of significant excess or deficit of disease activity, are referred to as *clusters*. Many spatial statistics that detect clusters also describe *cluster morphology*, which can be the geographic size

and shape of the cluster, the locations of spatial outliers, the descriptions of boundary shapes, and the magnitude of the excess or deficit (Fotheringham et al., 2002). The advantage to detecting clusters is to identify spatial patterns that are unique and different than what could be expected in the absence of the phenomenon being studied—in this sense, clustering is a measure of an area's abnormality relative to a null expectation (Fotheringham et al., 2002).

The primary purpose of cluster detection and other descriptors of spatial patterns (i.e., outliers, hotspots, cold spots, trends, and boundaries) is first to identify the locations, magnitudes, and shapes of statistically significant pattern events (Fotheringham et al., 2002). The secondary purpose, and the more useful, is the generation of significant and testable explanations and hypotheses about the processes that produced the pattern events. Within disease research, the detection of clusters through spatial analysis can offer insight into a disease's causation and can lead to the identification of potential risk factors (Khan & Ehreth, 2003; Srividya et al., 2002).

3.5.2 Types of Spatial Statistics Employed in Health Research

Cluster detection within a spatial analysis can be undertaken using a variety of spatial statistical tests, many of them characterized as *global, local, or focused* (Glass, 2000). As a general rule, global and local statistics are used to identify areas of clustering in studies that do not have a pre-determined hypothesis about where clusters may be located, while focal statistics are used to test whether or not events are clustered around a suspected location (Lawson, 2001).

Global cluster statistics detect patterns that depart from the null hypothesis and occur anywhere in the study area (Fotheringham et al., 2002). One of the first measures of global spatial autocorrelation to be developed was Moran's I, a statistic used to measure the strength of correlation between events as a function of the distance separating them (Oliveau & Guilmoto,

2005). Moran's I is similar to Pearson's coefficient in that its numerator is a covariance while its denominator is a sample variance. The value of Moran's I can range from -1, indicating a strong negative spatial autocorrelation, to +1, indicating a strong positive spatial autocorrelation. A value near 0 would indicate a spatially random pattern. Moran's I can be calculated at various levels of distance, using contiguity and other distance matrixes to define the concept of 'neighboring observations'. Because of this user-defined variation, Moran's I test can lead to results that identify some variables as significant over short distances and others that are significant over long distances. Moran's I is a useful statistic to use because of its simplicity, but its downfall is that it tends to average local variations in the strength of spatial autocorrelation, sometimes ignoring spatial outliers or areas of local clustering (Oliveau & Guilmoto, 2005).

Geary's C, like Moran's I, is a measure of global autocorrelation. The value of Geary's C is based on paired comparisons between juxtaposed events (Sawada, 2004). Ranging from 0 to 2, this value can represent positive spatial autocorrelation (0 to 1), negative spatial autocorrelation (1 to 2) or no spatial autocorrelation (1). Both Geary's C and Moran's I require further tests such as randomization or normal approximation to determine significance.

Perhaps the most well-understood and employed statistic for identifying areas of global spatial autocorrelation is the *K-function* (Wilson & Fotheringham, 2007). Unlike intensity functions, which use first-order properties of events (i.e., using the mean), the K-function is a measure of interrelationship *between* events, or second-order properties (Waller & Gotway, 2004). Simply stated, the K-function assesses a location based on the values of events within a specified distance (Vazquez-Prokopec et al., 2005). To determine whether or not clustering is occurring, the value of the K-function is compared to that expected by CSR. By definition,

therefore, the traditional K-function detects clustering across all events in the study region rather than identifying a particular set of events as a cluster (Waller & Gotway, 2004).

Indicators of global spatial autocorrelation, including Moran's I, Geary's C, and the K-Function, though they can identify whether or not clustering is occurring, cannot specify the location of clusters or how spatial dependency can vary from one place to another (Fotheringham et al., 2002).

Local spatial statistics are used to quantify clustering within smaller areas of a larger study area, and in many instances can be seen as smaller partitions of the global spatial statistical analysis (Fotheringham et al., 2002). For example, Anselin (1995)'s local indicator of spatial autocorrelation (LISA), is a type of spatial statistic that when summed and scaled across all the smaller areas of a larger study area, produces Moran's I. In essence, LISA is a test for "hot spots" in the presence of global autocorrelation (Ord & Getis, 2001). LISA works by calculating the similarity of a location's value to that of its neighbors and testing this association for significance. The values that emerge from LISA indicate pockets of high values ("hot spots"), low values ("cold spots"), spatial outliers, or no significant local autocorrelation (Oliveau & Guilmoto, 2005). LISA values, however, must be interpreted correctly, taking into account the degree of global autocorrelation to reduce Type I error (Ord & Getis, 2001). The limitation of using LISA is that it does not correct for multiple comparisons when testing for spatial autocorrelation, a problem that can lead to up to 5% of areas being identified by random chance variation (Odoi et al., 2003).

Getis and Ord's (1992) local spatial autocorrelation statistics, G_i[d] and G_i*[d], like LISA, were developed in response to the impracticality of global statistics to search for regional patterns. Like LISA, these two statistical procedures are used to detect 'hot spots' amid global

spatial autocorrelation. Both statistics are a measure of the weighted sum of the values in a neighborhood as a proportion of the sum of values for the whole study region (Wilson et al., 2003). G_i*[d] includes the value of the study location while G_i[d] does not. Both of these statistics only identify positive spatial autocorrelation, and, like LISA, need to be interpreted with care in the presence of global spatial autocorrelation. There are several variations of this procedure, including the one proposed by Zhang et al. (2000) that implements k-order neighbors into the G_i computation.

The spatial scan statistic, a method developed by Kulldorf (1997), uses a circular window with a user-defined maximum radius that is systematically moved throughout the study area to identify areas of significant case clustering (Tiwari et al., 2006). For each location and size of the scanning window, a likelihood ratio is computed to test whether or not there is an elevated disease rate within the window when compared to outside the window (Brooker et al., 2004). The location and window size with the maximum likelihood is then defined as a cluster. The smallest likelihood of this clustering by chance and the associated p-value are determined through Monte Carlo hypothesis testing. The limitation to this method, and indeed most spatial statistics, is its inability to detect space-time clustering (i.e., time-dependent spatial clusters). However, this problem has been overcome with a space-time statistic that uses the same approach as described above in a cylindrical form, with a three-dimensional window whose base represents space and whose height represents time (Odoi et al., 2004). Tango & Takahashi (2005) have adapted the spatial scan statistic so that it can detect noncircular hot-spot clusters. Both the spatial scan statistic and the space-time statistic are integrated into the SaTScan software developed by Kulldorf (2006), and are discussed in further detail in subsequent chapters.

Local spatial statistics, such as LISA, and G_i[d], G_i*[d], and the spatial scan statistic, can thus reveal the nature of spatial dependency in small localities (Fotheringham et al., 2002). They can determine whether or not patterns are statistically different from that predicted by the null hypothesis, whether these patterns represent clusters of low or high values, or whether the patterns are simply spatial outliers (Wilson & Fotheringham, 2007).

Focal spatial statistics are unique from global and local spatial statistics in that they quantify clustering around a specific feature or location called a *focus* (Mitchell, 2005). An example of a focal spatial statistic is the k-function, which, although a global spatial statistic, can be altered to detect focal clustering so that it measures the distance from the tested location to where cases begin to appear (nearest neighbor distance), the distance to which clustering is maximized, and the distance at which clustering is statistically significant (Getis & Franklin, 1987). In health research, focal statistics such as the K-function, Diggle's method (Diggle, 1990), G_i[d] and L_i[d], can be useful for detecting whether vectors or disease cluster around a suspected source (Cromley & McLafferty, 2002).

With the choice of global, local, and focused statistics, many researchers often wonder which is the most suitable for their research—though in many instances the spatial resolution of data and the nature of the alternative hypothesis will give some indication of which spatial statistic to use. As can be imagined, however, the choice of spatial statistic can dramatically influence the results of a study—for example, studies that rely on only a single spatial statistic will result in clusters that only that statistic is designed to identify (i.e., global or local) (Jacquez, 2004). As Fotheringham et al. (2002) explain, however, researchers should not look for a specific, single suitable cluster statistic because in order to do so would require researchers to have a prior knowledge of cluster morphology (which would not be known until after a cluster

analysis was performed). Thus, in order to overcome these problems, many studies employ a variety of spatial statistical methods to identify different types of spatial distributions that would not be possible using a single statistical method (Jacquez, 2004).

Today, spatial statistics, despite their variety and specificities, are widely used in a number of geospatial applications. Within health research, for instance, are innumerous studies that use spatial statistics for a number of applications and from a number of different perspectives. For example, Ruiz et al. (2004) used a local variation of Moran's I to identify areas of focal clustering of West Nile Virus transmission in Chicago during an outbreak in 2002; Jeffery et al. (2002) used local G statistics to investigate spatial autocorrelation of mosquito vectors for Ross River and Barmah Forest Viruses in Queensland; Wen et al. (2006) used LISA to identify spatial clustering within a 2002 dengue fever epidemic in Taiwan; Dangendorf et al. (2002) used Moran's I to determine global spatial autocorrelation of enteritis and water supply structures in the Rhine-Berg District of northwest Germany; Hinman et al. (2006) used the G_i*[d] statistic to identify local clustering of typhoid fever in Washington, D.C., during 1906-1909; Cecere et al. (2006) used both global (weighted K-function) and local (LISA) spatial statistics to detect clustering of *Triatoma infestans*, the vector for Chagas disease, within two communities of north-central Argentina; Vazquez et al. (2005) and Kitron et al. (2006) used a K-function and G_i[d] statistic to link focal clustering of *Triatoma* to sylvatic environments and wood piles within a rural village of Argentina; Clennon et al. (2004) used a focal derivative of G_i[d] to identify clustering of schistosomiasis cases in Kenyan children; Polack et al. (2005) used the spatial scan statistic to detect household clustering of trachoma in Tanzania; and Ozenderol et al. (2005) compared clustering of low birth weight resulting from the spatial scan statistic and spatial filtering techniques. As is evident by the literature, spatial statistics play a

key role in the investigation of disease, and are a vital part of the armamentarium of medical geography.

3.6 Conclusions

This chapter has been designed as both an introduction and review of the technologies and methods often employed in medical geography. As can be guessed, it is the combination of both technologies and methods in medical geography that make it such a strong and useful tool in the evaluation of spatial health problems (Anselin et al., 2006). As technologies improve and new methods of spatial analysis are developed, no doubt medical geography will grow in its applications. Already, with improved methods of health surveillance, routine remote sensing and environmental modeling, and increased access to computer-based geographic methods, medical geography has seen unpronounced growth as a field. However, as these technologies and methods continue to evolve, so will medical geography and its place in both the health sciences and geography.

CHAPTER 4. DEFINING TROPICAL MEDICINE THROUGH GEOGRAPHY: A SURVEY OF LEADING TROPICAL MEDICINE JOURNALS AND PUBLICATIONS EMPLOYING GEOGRAPHIC INFORMATION SYSTEMS

4.1 Introduction

The geographic distribution of publications as an indication of the direction of current research within academic and clinical fields has recently become a topic of growing interest (Tutarel, 2002). Historically, this topic has included the research outputs of individuals (Powner & Kellum, 2001), countries (Sorrentino et al., 2000; Weisinger & Bellorin-Font, 1999), and single specialties (Maleck et al., 2001). This type of literature meta-analysis can be useful in determining which countries are the most influential within the chosen field, who are the important opinion formers within academic discussions, and where current research trends within a given field lie (Tutarel, 2002).

As mentioned in the previous chapter, both medical geography and tropical medicine are relatively new disciplines. New advances in spatial technology and methodology, namely the development of geographic information systems (GIS), have blurred the boundaries of traditional geography as their applications are increasingly applied in many unrelated disciplines. Few studies to date have attempted to define these trends based on the geographic distribution of publications, but doing so will no doubt lead to valuable insight about how these two disciplines interact.

4.1.1 GIS in Tropical Medicine

A growing interest in tropical medicine, especially from the developed world, has led to a surge in three key areas of tropical disease research (TDR): 1) a better understanding of the basic microbiology, pathogenesis, and host defenses associated with tropical diseases; 2) expanded knowledge of their epidemiology; and 3) newer approaches to their clinical management,

control, and surveillance (H.W. Murray et al., 2000). With this new interest has come a better appreciation of the role that GIS can play in tropical disease research. Indeed, recently GIS has been included in all three areas of TDR. For example, Moonan et al. (2004) used GIS to examine the strain distribution of tuberculosis within a population; Brooker et al. (2004) identified risk factors for malaria in Kenya by comparing case clustering with data on household construction, exposure factors, and socio-economic status; and Andrade et al. (2004) have implemented a GIS-based surveillance system for monitoring pediatric pneumonia in Brazil. These are only a few examples of the wide range of GIS applications that exist in tropical medicine.

Despite the widespread use of GIS in tropical medicine, the nature in which GIS and tropical medicine interact and the direction in which they are conjointly heading are still unclear. Several key questions can be asked regarding this dilemma. For instance, are researchers in TDR maximizing the capabilities of GIS in their research? Are the results of their research ending up in the right places (i.e., in journals read by clinicians in the field rather than geographers and in international journals available to developing countries)? Does technological impairment inhibit researchers in the developing world from using computer-based GIS? Or is the use of GIS in TDR being imperialized by developed-world researchers and research interests?

In an attempt to gain a better understanding of these questions and identify current trends regarding GIS and tropical medicine, this study reviewed articles published by the ten leading tropical medicine journals that utilized GIS in their methodologies. The objectives of this study were to: 1) quantify the number of published studies in these journals that utilize GIS; 2) determine the geographic distribution of study locations; 3) examine the ratio of articles whose first authors are affiliated with developing versus developed countries; 4) identify the nature of

diseases that tend to be analyzed using GIS; and 5) review the temporal trend of articles being published that utilize GIS.

4.2 Materials and Methods

4.2.1 Tropical Medicine Journals and Their Impact Factor

In the 2006 Journal Citation Reports-Science Edition (ISI, 2006), ten journals are listed in the subject category "tropical medicine." These journals include *Malaria Journal, Tropical Medicine and International Health, the American Journal of Tropical Medicine and Hygiene, Acta Tropica, the Transactions of the Royal Society of Tropical Medicine and Hygiene, Memorias do Instituto Oswaldo Cruz, the Annals of Tropical Medicine and Parasitology, the Annals of Tropical Pediatrics, Leprosy Review, and the Journal of Tropical Pediatrics*. These ten international journals are the top journals in the field of tropical medicine in terms of impact factor. The *impact factor* of a journal is calculated by taking the number of times an article from the journal was cited in the two preceding years and dividing that amount by the total number of citable items published in indexed journals in the two preceding years; in short, the impact factor is a measure of the intensity of publication or citation of a particular journal (JCR, 2007). The *immediacy index* is the number of citations the articles in a journal receive in a given year divided by the number of published articles (ISI, 2006). Though the impact factor is not a measure of the quality of a journal, it can be used as an indication of the most trafficked journals in a given field. Thus, these ten journals were chosen as the top ten tropical medicine journals for use in this study. Table 4.1 is a summary of the journals chosen by this study and their associated citation reports as reported by the 2006 Journal Citation Report (JCR, 2007).

Table 4.1: Leading international tropical medicine journals and their impact factors

Journal Title	Total Cites	Impact Factor	Immediacy Index	Total Articles, 2000-2006
Malaria Journal	566	2.748	0.366	421
Tropical Medicine & International Health	3,275	2.595	0.502	1,338
American Journal of Tropical Medicine and Hygiene	11,532	2.546	0.448	2,392
Acta Tropica	2,851	2.211	0.248	1,068
Transactions of the Royal Society of Tropical Medicine and Hygiene	6,319	2.03	0.593	1,360
Memorias do Instituto Oswaldo Cruz	2,858	1.208	0.115	1,592
Annals of Tropical Medicine and Parasitology	2,450	1.191	0.308	751
Annals of Tropical Pediatrics	566	0.934	0.0037	412
Leprosy Review	472	0.847	0.13	447
Journal of Tropical Pediatrics	802	0.592	0.126	767

4.2.2 Search Methodology

The search engine PubMed (http://www.ncbi.nlm.nih.gov) was used to search the U.S. National Library of Medicine's publication database, MEDLINE. Each of the ten selected journal titles was entered into the "Journal" field, and advanced search options including date (2000 to 2006) were used to limit the search. The search was further refined by including only articles that included the boolean "geographic" in their titles, abstracts, or keywords. Because GIS is almost always referred to as "geographic" information systems (or science), it was expected that this search boolean would lead to a high sensitivity in detecting articles that contained GIS. Results of the boolean search were displayed in MEDLINE format. In order to improve specificity, each article was further retrieved as a .pdf file and scanned to determine whether or not it employed GIS in its methodology. The journal name, the country of affiliation of the first and corresponding authors, the disease(s) under investigation, and the study location of articles positively identified as employing GIS were recorded into a spreadsheet. Data was compiled and analyzed using ArcView GIS Version 3.2 (ESRI, 1999).

4.3 Results

From 2000 to 2006, a total of 10,548 articles were published in the ten searched journals. Of these articles, 108 (1.024%) were positively identified as having employed GIS in their methodology (Figure 4.1). These 108 articles included first authors from 29 countries (Figure 4.2) and were conducted in a total of 51 countries (Figure 4.3). Studies on malaria, schistosomiasis, dengue, chagas, leishmaniasis, Ross River virus, Lyme disease, African trypanosomiasis, West Nile virus, tuberculosis, plague, hantavirus, and diarrhea were the most common and comprised 95 of the 108 total articles, or 85% (Figure 4.4). The total number of articles published each year that employed GIS is shown in Figure 4.5.

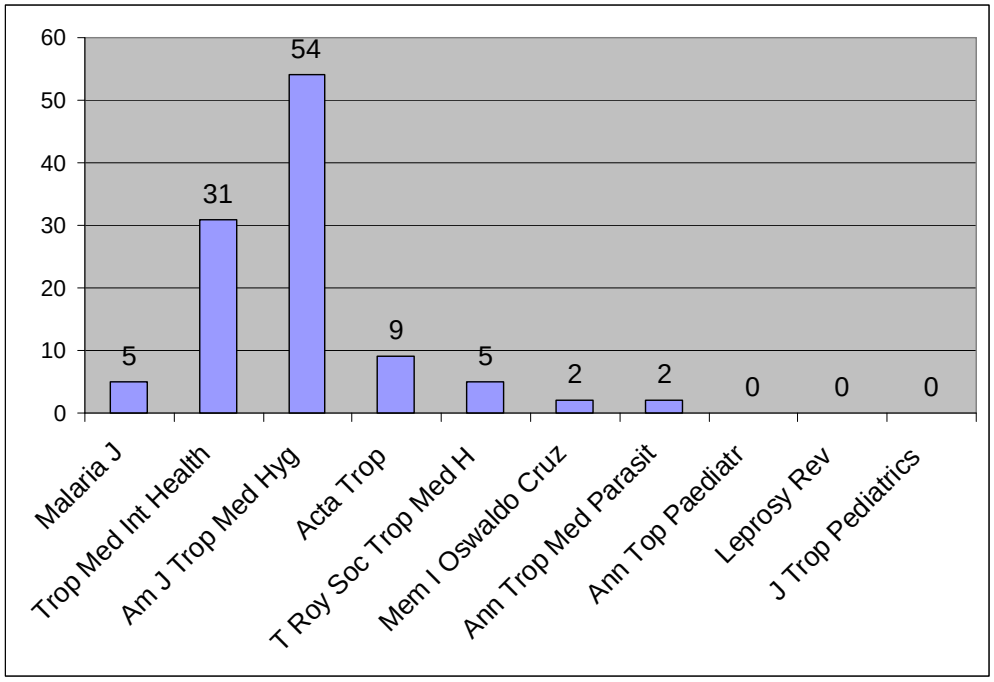

Figure 4.1: Number of articles published utilizing GIS by journal

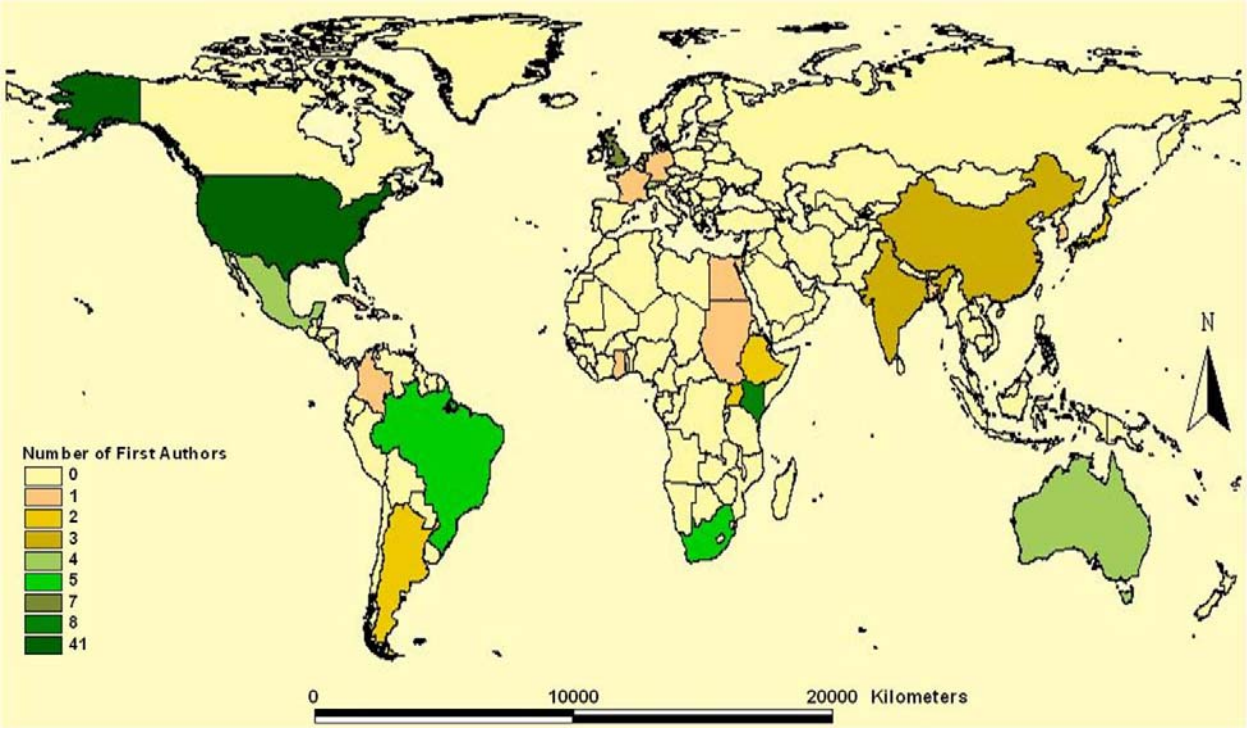

Figure 4.2: Locations and number of articles published by country of affiliation of first author

First authors from the United States and Europe (defined as members of the European Union) represented 54% of articles, whereas 65% of articles included first authors from developed countries (defined as "high income countries" by the World Bank (WB, 2008)). First authors from developing tropical countries (those countries located between the Tropics of Cancer and Capricorn and not included in the developed countries list) were found in 37% of examined articles. Seventy-three articles, or 68%, included authors from English-speaking countries. Fifty-seven articles, or 53%, had first authors affiliated with the country in which the investigated disease occurred. The research of eighty-six articles, or 80%, was conducted in developing tropical countries.

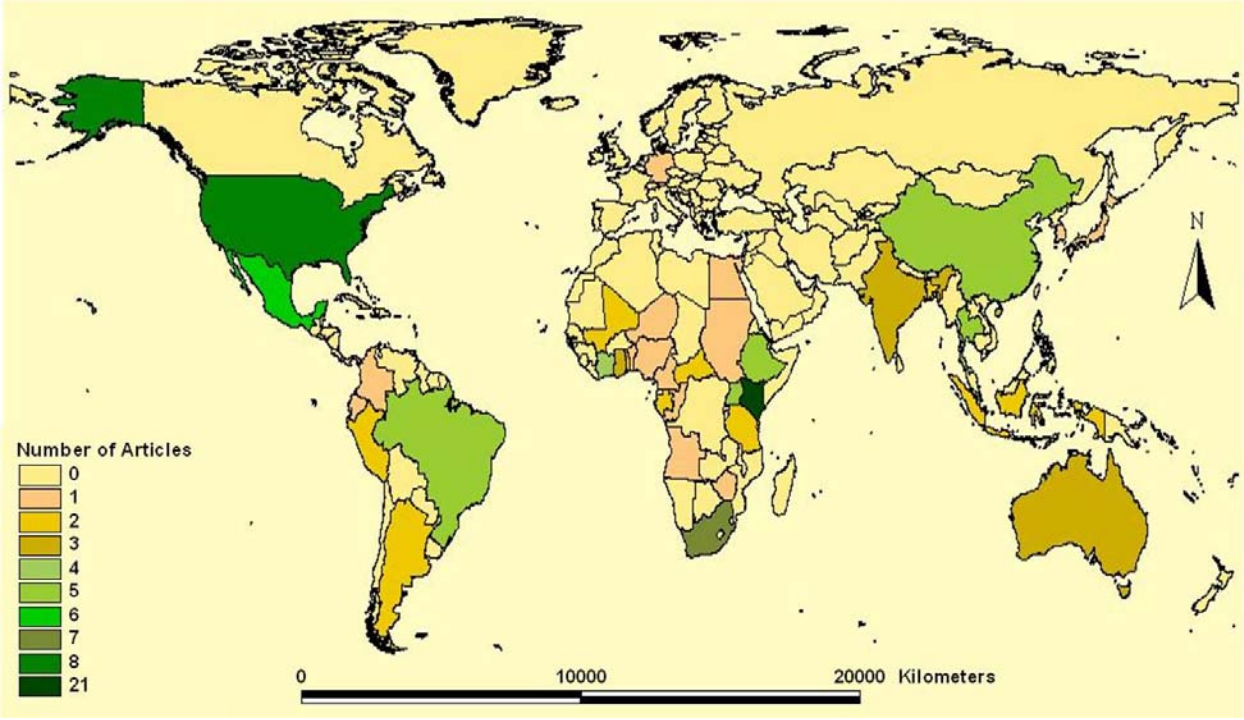

Figure 4.3: Locations and number of articles by study location

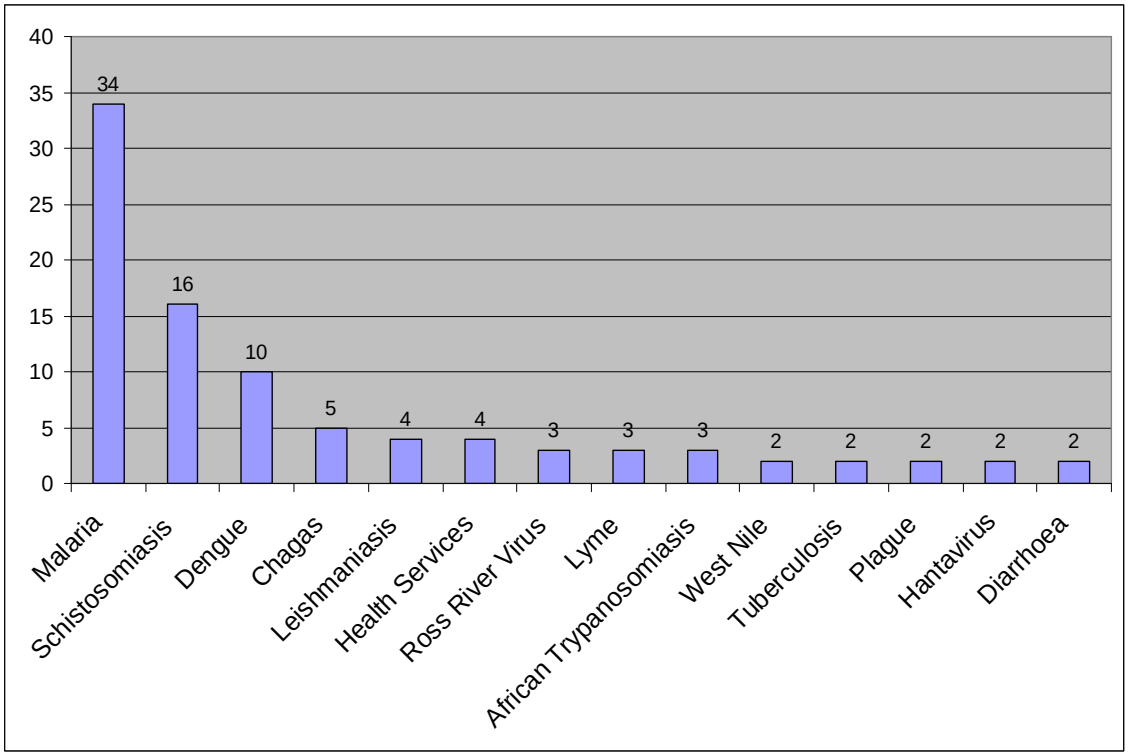

Figure 4.4: Most common diseases under investigation

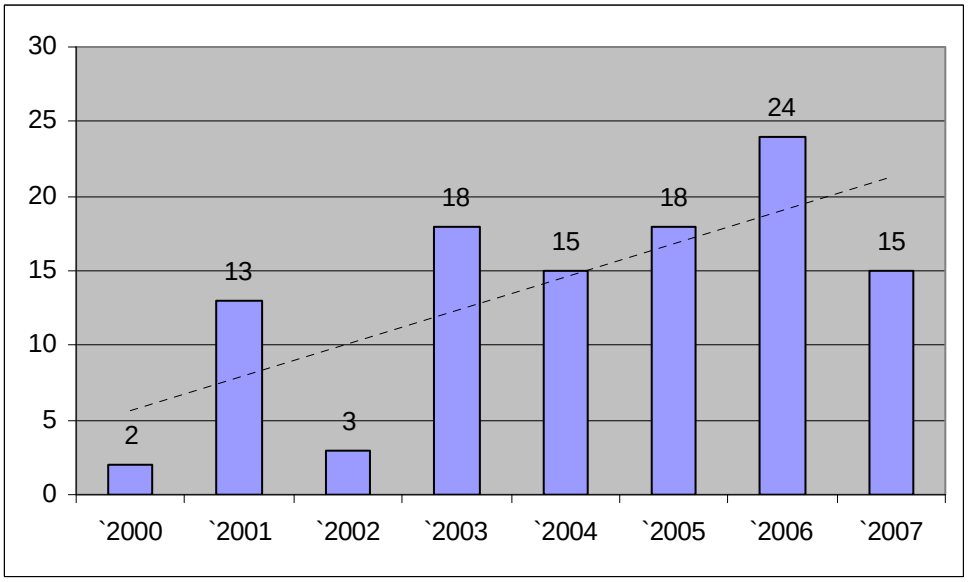

Figure 4.5: Number of articles in the top 10 tropical medicine journals utilizing GIS by year

4.4 Discussion

This study investigated the trends of GIS use in tropical medicine by examining the geographic distribution of publications that employ GIS in the ten leading tropical medicine journals. Specifically, the study locations, the diseases under investigation, and the contribution of individual countries to these journals were quantified.

When compared to the major diseases of the developed world (i.e., heart disease, diabetes, obesity, cancer, etc.), the major diseases of the tropics are almost entirely communicable. This is due to the fact that the major burden of ill health in tropical nations is attributable to communicable diseases. The World Health Report of 1995, for instance, iterates this point: malaria kills about 1 million children in the tropics each year; diarrheal disease kills about 3 million children; 7,000 adults die each day from tuberculosis; hepatitis B kills about 1 million; over 5 million children in the tropics are infected with HIV; and more than 4 million children in developing nations under 5 die each year of acute respiratory infections, especially pneumonia (WHO, 1995). To further this point, the World Bank estimates that communicable diseases cause nearly 71% of death and disability in developing countries and about 10% in developed countries, while non-communicable diseases cause 19-58% of death and disability in developing countries and 78% in developed countries (WB, 2002). The major diseases of developing countries, as a general rule, tend to cause more disability and death than the major diseases of developed countries, and a much greater percentage of these diseases are infectious (Speare & Leggat, 2006). It is appropriate, therefore, that this study found that the majority GIS-tropical medicine articles concerned these diseases.

Despite the growing value of GIS in health research, it seems surprising that such a small number (1.024%) of total articles published in the ten leading tropical medicine journals employed GIS. This phenomenon could be explained by the fact that many articles involving GIS are not selected for publication by health journals but rather geographic journals. In this case, a follow-up study would be required to investigate the ratio of articles using GIS in tropical medicine journals versus geographic journals such as *Annals of the Association of American Geographers, Transactions of the Institute of British Geographers, Social Science and Medicine, the International Journal of Health Geographics*, etc. (An important point to make here is that health practitioners, who implement the findings of many of these studies, are more likely to read or be exposed to articles in health journals than geographic journals.) The problem with such a study, however, would be defining articles that are tropical-medicine related rather than GIS-related. In addition, a future study may wish to expand to include other geographic methods such as spatial analysis its query for articles. Another interesting standpoint for analysis would be the professional affiliation of the authors—whether they are geographers, physicians, or public health workers.

Another explanation to scant amount of GIS-related tropical medicine publications could be that the application of geographic methods in health research has not developed to the point to be confidently accepted as routine publication in health journals. Indeed, geographic methods still have a way to go before being standardized to the point where their implementation is efficient and practical in health research (Ward & Carpenter, 2000). However, as is indicated by this study and Figure 3.5, the implementation of GIS into tropical medicine journals shows a promising increase.

Ironically, the study locations for the articles examined in this study include a fair amount of countries that are located more in temperate zones than the tropics. The United States, for instance, was the second most frequent study location after Kenya. This fact elucidates the impact of the United States on international tropical medicine journals. Nonetheless, it would be expected that more articles would have their study locations in tropical countries, especially in Africa. This may be an indication that international collaboration is not as strong as it could be, or that research groups in tropical countries have a harder time publishing in international journals and are more likely to publish in journals affiliated with their own countries and language (Tutarel, 2002).

Another surprising finding is that over half of all articles were published by a first author in either the United States or Europe. Like study location, first author affiliation once again points to the fact that international tropical medicine journals are dominated by the developed world. This trend has been found in studies of other international health journals, including medical education (Tutarel, 2002) and reproductive medicine (Kremer et al., 2000).

Finally, there appears to be more articles that use GIS with certain tropical diseases than others. Nearly a third of all examined articles, for instance, examined malaria. This is not too surprising considering that GIS can be applied more readily to diseases with certain epidemiological features (i.e., those that are dependent on environmental or demographic factors). However, this does not mean that GIS is not applicable to other diseases; it is only an indication that researchers prefer to use current methodologies in GIS with some diseases more than others.

4.5 Conclusions

This study examined the basic trends of recent articles published in tropical medicine journals that employ GIS. Though the field of GIS has only recently entered the world of health research, it would be preferable to see more articles that utilize this technology published in tropical medicine journals. Although this study was able to identify some basic trends in GIS use in tropical medicine, it was unable to explain the reasons for these trends. Future studies may wish to examine the distribution of articles in more detail using expanded search criteria.

CHAPTER 5. USING SPATIAL DESCRIPTOR, K-FUNCTION, AND HOT SPOT ANALYSES TO DETERMINE CLUSTERING OF *TUNGA PENETRANS* IN THE SMALL FISHING VILLAGE OF BALBINO, BRAZIL

5.1 Introduction

Tungiasis is a zoonotic skin disease caused by the female sand flea *Tunga pentrans*. Embedding under the skin, this parasite causes substantial morbidity in its host. Most cases of tungiasis occur throughout economically disadvantaged communities of South America, sub-Saharan Africa, and the Caribbean (J. Heukelbach, S. Franck et al., 2004). Prevalence rates reign high in these areas, sometimes reaching as much as 80% (J. Heukelbach, S. Franck et al., 2004).

Tungiasis is a disease of the poor. As such, it receives little attention from investigators and medical personnel. In Ceará State, Brazil, it was thought that tungiasis was unknown until a 2001-2003 epidemiological study proved otherwise (Wilcke et al., 2002). In actual fact, tungiasis is hyperendemic in *favelas* (shantytowns) of Ceará State, with prevalence rates ranging from 16% to 55% (J. Heukelbach, S. Franck et al., 2004). Because resource-poor favelas like these are so common throughout northeast Brazil, it is now assumed that tungiasis is a frequent problem in these underprivileged communities (Wilcke et al., 2002).

The impact of tungiasis is centered on its severely debilitating pathogenesis. The disease is associated with substantial morbidity, including chronic inflammation, lymphoedema, ulcerations, fissures, nail loss, difficulty walking, and difficulty grasping or using the hands (Feldmeier, Heukelbach et al., 2003). In addition, superinfections with pathogenic bacteria almost always occur concomitantly with tungiasis lesions. In many instances, tungiasis lesions serve as entry points for *Clostridium tetani*, rendering un-immunized individuals susceptible to tetanus infections (Muehlen et al., 2006). In Sao Paulo State, tungiasis was found to be responsible for 10% of tetanus cases (Feldmeier, Eisele et al., 2003).

Besides the physical strain inflicted by tungiasis morbidity, the disease also causes considerable social strain. In some favela communities, it is estimated that on average 15 new flea penetrations occur per individual per week; with families that average three or four children who cannot remove the fleas themselves, parents would have to remove between six and nine fleas per night in order to avoid infection accrual (Feldmeier, Eisele et al., 2003). Removal is extremely painful, and takes about three minutes. It requires great precision, skills, and patience along with adequate light and a sharp instrument—items that normal families cannot afford. Even motivated caregivers can be daunted by such a task. Lack of motivation and the conditions of the favela explain why parasite burden and morbidity in these communities is so high.

Because tungiasis is so common in these resource-poor communities, inhabitants often assume that the disease is linked to everyday life and that it is 'normal'—there is absolutely no social stigma in these communities associated with tungiasis infection (Heukelbach et al., 2003). This, in turn, makes individuals unaware or unconcerned about the infections that they carry. As a result, infestations continue because the life cycle of *Tunga penetrans* progresses without interruption, increasing morbidity in the host.

In addition, it is a well-known fact that inhabitants of poorer communities are less likely to actively seek medical services than individuals of higher socio-economic groups (J. Heukelbach, S. Franck et al., 2004). This matter is made worse by health care services in northeast Brazil that are not particularly oriented to poverty-associated public health issues, like ectoparasites. Though serving a population that is hyperendemic for tungiasis, many health care workers usually neglect this disease—it is rarely diagnosed by the Primary Health Care Center (PHCC), and usually *only* if pointed out by the patient (Heukelbach et al., 2003). In addition, patient attitudes towards health care services may also be a barrier to health care provisions.

Because the PHCC does not provide medical treatment or surgical removal of tungiasis lesions, many people do not bother presenting (only 3 out of 55 patients with tungiasis sought medical assistance in a health-care seeking study (Heukelbach et al., 2003)).

To determine the attack rates of tungiasis in these communities, one study transported infected residents to a tungiasis-free resort 40 km away from Fortaleza for a period of two weeks (J. Heukelbach, S. Franck et al., 2004). When they were allowed to return, all the subjects were all clear of parasites. This allowed an accurate measure of the attack rate of tungiasis in their homes. Re-infestation occurred at an alarming rate: after the first 3 days, about one-fifth of the group showed imbedded fleas; after 9 days 55%; and after 21 days of returning home 100% were re-infected. This data shows that tungiasis infection follows site-specific risk factors, presumably that stem from the home.

Animal reservoirs play a vital role in tungiasis transmission. Dogs, cats, pigs, and rats, common animals found in these communities, act as amplifying hosts for *Tunga penetrans*. In Fortaleza, 67% of dogs, 59% of captured rats, and 50% of cats showed parasite infestation (Heukelbach, 2005). In Morro de Sandras, a favela of Fortaleza, 49.6% of cats and 67.1% of total animals were infected (J. Heukelbach, A.M.L. Costa et al., 2004). In Balbino, 30.9% of dogs and 32.4% of cats were infected. The infection rates of tungiasis in animals presumably play a significant role in the attack rate of humans, especially considering that 95% of the families in Balbino have domestic animals (Muehlen et al., 2003).

Muehlen et al. (2003) examined a range of potential demographic, behavioral, and environmental characteristics in northeast Brazil to determine risk factors related to heavy tungiasis infestation. Their study found that tungiasis is a disease strongly correlated to poor housing conditions, poor hygiene/health education, and association with other zoonotic hosts of

Tunga penetrans. The specific risk factors investigated included housing construction, house location, family size, use of traditional remedies on wounds, spraying insecticides, waste disposal, sewage disposal, and animals on the compound (Muehlen et al., 2003).

Though many of the studies mentioned above attempt to determine epidemiological risk factors for tungiasis based on environmental and behavioral factors, none examine tungiasis prevalence based on a purely geographic, or spatial, perspective. In an effort to add to the knowledge of the epidemiology of tungiasis, this study examined the prevalence of this disease in Balbino using geographic rather than epidemiological methods. A geographic information system (GIS) was implemented for Balbino, and a spatial analysis was conducted. The purpose of investigating tungiasis prevalence in Balbino using geographic methods was: 1) to determine the community structure of disease; 2) to determine whether or not tungiasis was spatially autocorrelated; 3) to determine whether or not the disease was clustered; and 4) to show the value of using geographic methods in disease research and how it could be used in public health prevention and control of tungiasis.

5.2 Materials and Methods

5.2.1 Study Area

Data for this study was collected in Balbino, a rural community located near Cascavél municipality, about 60 km south of Fortaleza, Ceará State, northeast Brazil, on the Atlantic coast. At the time of data collection, Balbino was inhabited by 154 family units comprised of a total population of 620 people. The majority of the villagers live through traditional fishing (Muehlen et al., 2003). Most inhabitants are born in the village and there is little influx of new people from outside the village, keeping the population stable. Balbino was chosen as a study area because of

the pre-existing health infrastructure located there and the familiarity of the community with research collaborators in this project.

Homes are located close to the ocean, with some built directly on the beach and others built on sand dunes adjacent to the beach. A mangrove swamp (dark green region at centre right, Figure 1) acts as a geographical divide between the population living on the beach and the population living on sand dunes.

The population of Balbino is mostly poor: the village has no paved streets, and most of the houses are built with sand floors (J. Heukelbach, A.M.L. Costa et al., 2004). 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 (J. Heukelbach, B. Winter et al., 2004).

Many ectoparasitic diseases are hyperendemic in Balbino, including scabies, pediculosis, and cutaneous larval migrans. Tungiasis is also considered hyperendimc in Balbino, with an estimated prevalence of 51% (Muehlen et al., 2006; Wilcke et al., 2002). Prevalence of tungiasis versus age follows an s-shaped curve in Balbino, being high in younger age groups, decreasing significantly in ages above 15, and then sharply increasing again in ages over 60 (Wilcke et al., 2002). In addition, parasite load varies unevenly across individuals—only 8% of individuals carry 55% of parasite burden. This trend seems to indicate that risk is associated with the home, as these age groups frequent these premises more than their working parents or siblings. The high prevalence in infants (15.8%) seems to back up this argument, as infants generally do not spend much time away from the home. However, children also tend to walk barefoot more frequently than adults, increasing their risk (they have less keratinization of their feet, too).

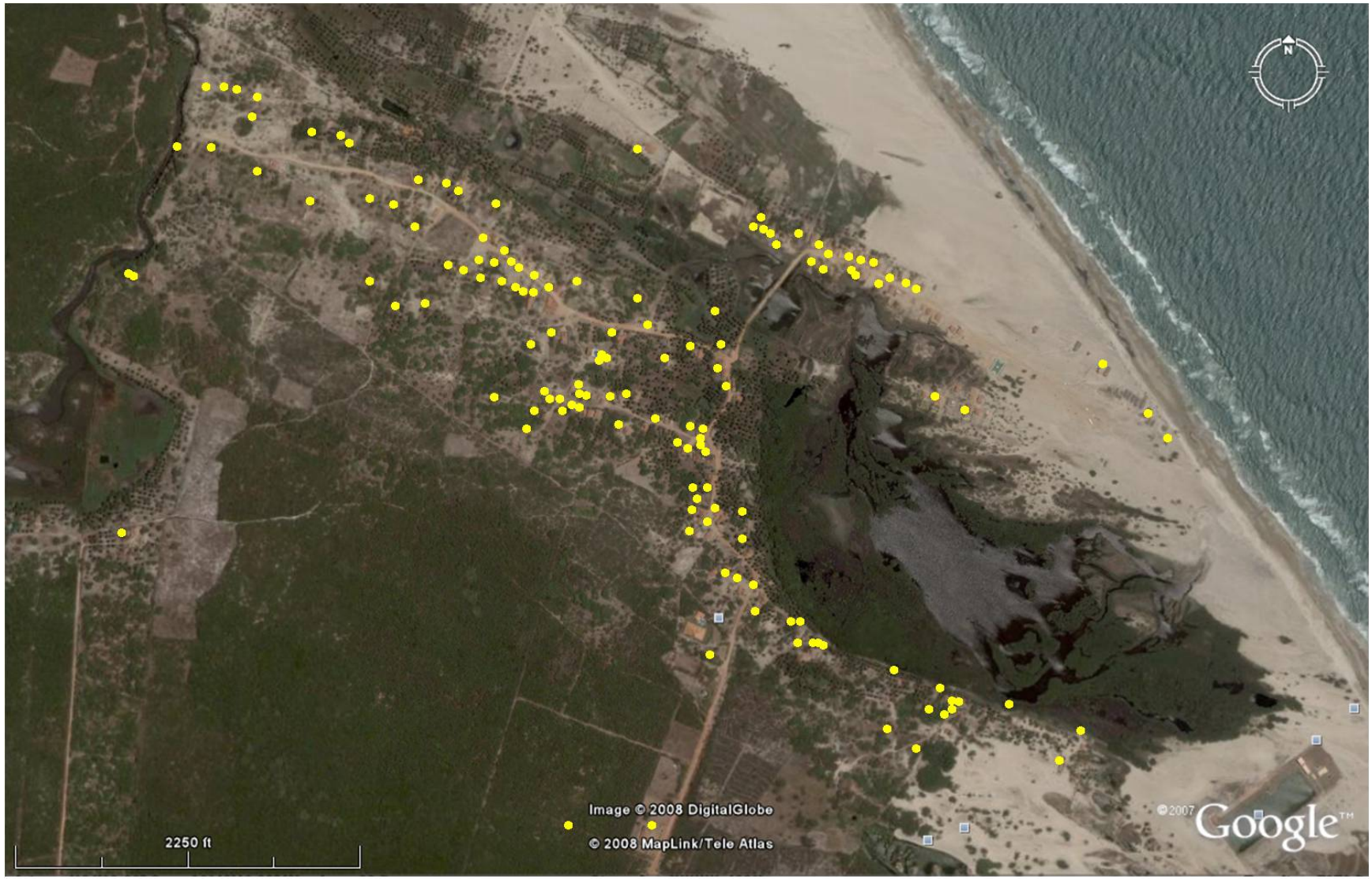

Figure 5.1: Satellite imagery of Balbino (Study Sites Marked as Yellow Dots) [Image obtained from Google Earth™]

In addition, children are not trained to remove fleas and depend on adults for this task. Girls were also found to have both a lower prevalence rate and a lower number of manipulated (excised) lesions. Because girls do not demonstrate a higher number of manipulated lesions, it can be assumed that their lower prevalence is due to less exposure rather than different health behavior, such as excising fleas (Wilcke et al., 2002).

In Balbino, people seek medical care through a medical caregiver provided by the Family Health Program (Programa de Saude de Familia) (Muehlen et al., 2006). Balbino employs these health workers to actively, rather than passively, seek health issues in these communities. In Balbino, two health agents are employed, one for children and the other for the general population, who are responsible for health education and patient referrals to the major health clinic in the nearby town of Cascavel (Muehlen et al., 2006). However, as mentioned previously, these health programs often ignore tungiasis and are more concerned with more immediate life-threatening conditions.

5.2.2 Epidemiological Data

Baseline epidemiological data for tungiasis prevalence used in this investigation (and helminth prevalence used in the following chapter—both are described here) was initially collected throughout the summer of 2001 by a team of scientists comprised of Jorg Heukelbach, Benedikt Winter, Thomas Wilcke, Marion Muehlen, Stephan Albrecht, Fabiola Araujo Sales de Oliveira, Ligia Regina Sansigolo Kerr-Pontes, Oliver Liesenfeld, and Hermann Feldmeier. This data has been used in several published reports, including some on tungiasis (Jorg Heukelbach et al., 2004; J. Heukelbach, A.M.L. Costa et al., 2004; J. Heukelbach, S. Franck et al., 2004; Muehlen et al., 2006; Muehlen et al., 2003; Wilcke et al., 2002) and some on the use of

ivermectin in mass treatment campaigns (J. Heukelbach, B. Winter et al., 2004). The author would thus like to acknowledge these people for the use of this data in this report. The following description is a summary of data collection protocol derived from the above mentioned sources.

In preparation for this study, the investigators contacted community leaders and held meetings with local organizations to explain the objectives of the study (Muehlen et al., 2006). They were informed that participation in the study was completely voluntary and that those who did not participate would be at no disadvantage. Those eligible for the study must have spent on average at least four days per week in the village in the prior three months. Data was collected using a door to door survey. If members of a family were absent during the visit, the family was revisited two further times. If individuals were missing on all three visits, then they were invited to present at the health center. Those who did not present at the center and were missing from the home visits were not included in the survey.

Data were collected between June 20th and July 30th, 2001 (Muehlen et al., 2006). Each individual was examined for tungiasis and each lesion, if appropriate, was staged using a method developed by Muehlen et al. (2003). So that no lesions could be overlooked, the whole body except the genital region was examined. Diagnosis of tungiasis was made using the criterion defined by Heukelbach et al. (2004).

In addition to examination for ectoparasites, each participant was given a plastic vial for stool specimen collection for fecal examination of endoparasites (J. Heukelbach, B. Winter et al., 2004). To account for the variability of egg secretion, three stool samples were collected from each person at three to four day intervals. Samples were examined for intestinal helminthes on the same day as collection in a field laboratory without the use of preservatives using the method outlined in Heukelbach et al. (2004).

The study design and objectives were reviewed by the Ethical Committee of the Cascavél Municipality Board (Muehlen et al., 2006). This committee comprised health professionals, administrative authorities, and community representatives. Individuals who participated in the study or their legal guardian in the case of children must have given informed oral consent to be enrolled. All participants were informed that all data would be handled confidentially. At the end of the study, because more than 50% of the inhabitants were thought to have an intestinal helminth and/or ectoparasitic infection, all villagers were offered free antihelminthic treatment.

5.2.3 Geographic Data

During the epidemiological survey, each individual was given not only an 'individual' number but also was assigned a family number. The family number corresponded to the family and household in which the individual belonged and lived. During the month of December, 2006, W.B. Arden visited Balbino along with the help of two family health care workers assigned to the area. The purpose of this visit was 1) to record GPS locations of each residence (matched to each family number); 2) to photograph and get a general view of the social and environmental layout of the village; and 3) to see cases of tungiasis first-hand. GPS data was collected using a Magellan eXplorist 500 TM receiver. Latitude and longitude were both recorded for each location manually on paper and within the physical memory of the receiver. The accuracy of each recording was checked by importing the coordinates into Google Earth™ to see if they cartographically matched the satellite image.

5.2.4 Implementing a GIS and Spatial Analysis

Epidemiological data included each patient's individual number, family number, and whether tungiasis was present or absent during examination. This data were imported into

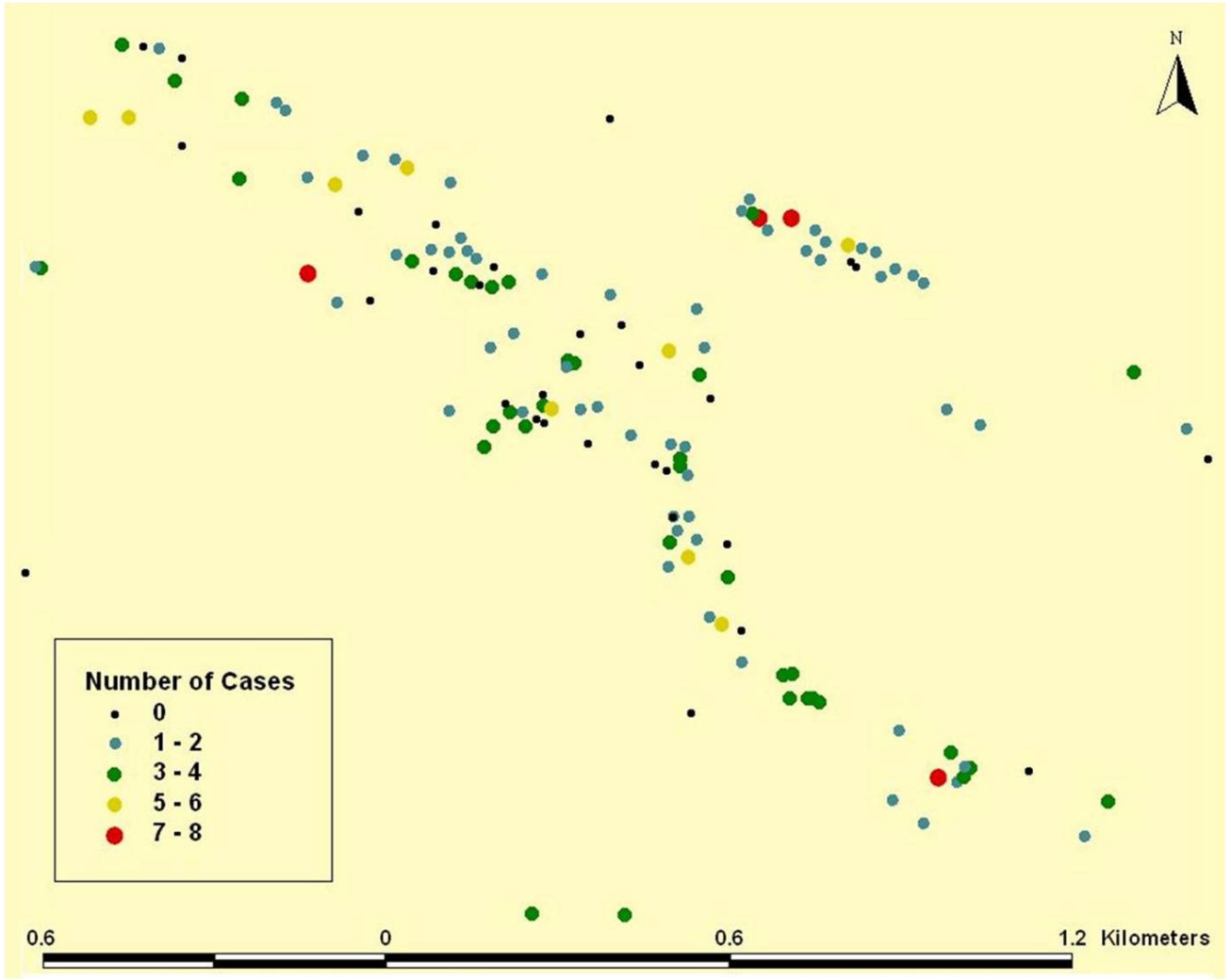

Figure 5.2: Prevalence of tungiasis per household, Balbino, Brazil

ArcView GIS Version 3.2 (ESRI, 1999) in database format. Geographic data, which included the geographic coordinates for each household, was also imported into ArcView.

Epidemiological data was merged with the geographic data so that each individual was assigned geographic coordinates according to his or her respective family number. Counts were made so that each family was assigned both a population—the total number of people living at that site—and a count of the number of members with tungiasis infection (infection was not quantified per individual in this study). This data were kept in ArcView and disease maps were produced of tungiasis prevalence per household (Figure 5.2). The spatial-epidemiological data were also exported in database format from ArcView for use in the spatial analysis.

Spatial analysis of tungiasis prevalence in Balbino was completed using Crimestat III, a free spatial analysis program offered through the National Institute of Justice by Ned Levine and Associates (2007). Though originally designed to examine crime incident locations, this software allows the user to reference and analyze any data with X and Y coordinates, intensity, weight, and time as variables. CrimeStat allows the computation of spatial descriptions (mean center, standard deviation, median center, and convex hulls), distance analyses (nearest neighbor indices, Ripley's K statistics, and distance matrices), hot spot analyses (Hot Spot Analysis I and II), and spatial models (kernel density interpolation and space-time analysis). In this study, CrimeStat was used to calculate all spatial descriptions of tungiasis prevalence in Balbino, including spatial distribution, distance analysis, and hot spot statistics.

5.2.4.1 Spatial Distribution

For the spatial distribution, two indices of spatial autocorrelation were calculated, Moran's I and Geary's C statistics. Both of these indices are considered 'global' or first-order

(Levine, 2007). As mentioned in Chapter 3, Moran's I is determined by calculating a mean for observations and then comparing the value of each incident with the value at all other locations (Levine, 2007). CrimeStat uses an inverse distance weight to calculate Moran's I. Because distances in Balbino are small, adjustments for small distances were made through CrimeStat. Values of Moran's I above the theoretical mean, or E(I), indicate that there is spatial autocorrelation of the data, whereas values of Moran's I below E(I) indicate negative spatial autocorrelation. Geary's C is similar to Moran's I except that Geary's C compares deviations in intensities of each observation location with one another rather than the cross-product of deviations from the mean—as such, Geary's C is more sensitive to differences in smaller areas than Moran's I (Geary, 1954). Values of Geary's C can fall between 0 and 2, where values less than 1 indicate positive spatial autocorrelation, 1 indicates the 'expected' value, and values greater than 1 indicate negative spatial autocorrelation (Levine, 2007). Testing of the significance of Moran's I and Geary's C was also calculated by CrimeStat, which outputs Z-values and p-values for normality and randomization assumptions. For this study, the total sample size included 144 sites (prevalence was aggregated per site and was defined as the intensity variable), and no spatial weights were used. In addition to calculating Moran's I for tungiasis prevalence, these indices were also calculated in the same manner for overall population as a comparison.

5.2.4.2 Distance Analysis

The distance analysis calculates statistics that are based not only on the location of points, but on the distances between points. Because this is used to identify the *degree* of clustering of points, it is sometimes called a local, or 'second-order,' analysis (Levine, 2007). The two local statistics used in this study were the nearest neighbor index (NNI) and Ripley's K.

Like the global spatial descriptors, the nearest neighbor analysis calculates a NNI that approximates whether points are more clustered or dispersed than would be expected by chance alone (Levine, 2007). The index is computed by dividing the average distance of the nearest other event case with a spatially random expected difference. Values less than 1 indicate that observed values are closer than expected, suggesting clustering. Values close to 1 indicate that the observed average distances are about the same as the mean random distance. Values greater than 1 indicate that observed values are farther apart than expected, suggesting dispersion. Testing of significance of the NNI is done by a Z-test proposed by Clark and Evans (1954). The number of nearest neighbors to be computed was one. Because the nearest neighbor analysis does not normally adjust for underestimation of tungiasis near the boundaries of Balbino (edge effects), a circular border adjustment was used that assigned events that were closer to the border than their nearest neighbor with an index that uses the distance to the border rather than the empirical nearest neighbor distance as the numerator.

Ripley's K statistic, or L(t), is a measure of spatial autocorrelation at different scale values—it is a modification of the nearest neighbor statistic providing a test of autocorrelation for every distance from each observed event (Ripley, 1981). Unlike the NNI, Ripley's K examines not just first order spatial autocorrelation but all orders cumulatively. In addition, because it uses circles of increasing radii to examine the number of observed versus expected events, it applies to all distances up to the limit of the study area. As such, the results of Ripley's K statistic are usually graphed against distance and transformed by a square root function to make it more linear (Levine, 2007). Values of L(t) farther away from zero (CSR) on the graph represent distances where spatial autocorrelation is occurring. Because tungiasis incidence is

most likely not random but perhaps dependent on some baseline population, the K statistic was calculated using population as a weighting variable.

5.2.4.3 Hot Spot Analysis

Hot spots are concentrations of incidents within a limited geographic area that appear over time (Levine, 2007). Detecting hot spots is a valuable method of identifying areas with larger or smaller than expected concentrations of events. When dealing with health events, hot spots are indicative of a particular area or environment that is particularly prone to disease. Health prevention, therefore, can target efforts to these areas knowing that they will achieve a positive result in reducing disease with limited resources. Hot spots are, however, arbitrary boundaries and do not exist in reality—they are mere spatial representations of a perceptual construct (Levine, 2007).

CrimeStat allows several different methods of hot spot analysis including point-location, hierarchical, partitioning, density, clumping, and risk-based clustering techniques (Levine, 2007). Point-location techniques identify areas with the most number of incidents as hot spots and include the Mode and Fuzzy Mode detection techniques. Hierarchical cluster detection involves grouping incidents by nearest neighbor according to certain user-defined criteria and includes the Nearest Neighbor Hierarchical Clustering (NNHC) routine and the Spatial and Temporal Analysis. Partitioning techniques assign points into groups for cluster detection and include the K-means technique. Density techniques identify clusters based on concentrations of incidents. Clumping techniques are similar to the partitioning techniques but allow overlap of cluster membership. Risk-based techniques detect clusters based on an underlying risk variable such as population, socioeconomics, property value, etc. This study used a hybrid-based method

available in CrimeStat known as the Risk-adjusted Nearest Neighbor Hierarchical Clustering routine (RaNNHC).

The RaNNHC routine is a modification of the NNHC routine that includes adjustment of clusters based on an identified variable (in this case population) and kernel density interpolation techniques (Levine, 2007). The RaNNHC routine detects clusters by identifying points that are closer together than a user-defined threshold distance. However, because the concentrations of events could be due to higher population densities, this technique dynamically adjusts the threshold distance based on the underlying population of that area, therefore making it a risk measure rather than a volume measure. Statistical significance is simulated for the RaNNHC routine through Monte Carlo-approximated confidence intervals (Levine, 2007).

For this routine, epidemiological data that included geographic coordinates and the number of cases per site were used as the primary file. Demographic data that included the population for each site was used as the secondary file. A normal distribution was used as the method of interpolation, and an adaptive bandwidth with a minimal sample size of six was used because this number represents the average number of members per family. Output units were set to meters, and population was used as the intensity variable. More information about these parameters and their effects on interpretation can be found in Levine (2007). Results were saved as convex hull shapefiles that were imported into ArcView for visualization.

5.3 Results

5.3.1 Spatial Descriptions

Moran's I, the classic indicator of spatial autocorrelation, was calculated for tungiasis prevalence at -0.006639. The spatially random, or E(I), I was -0.007143, and the standard deviation was 0.007265. The significance test of I under the assumption of normality (Z-test)

was 0.069331 and was not significant. The significance test of I under the assumption of randomization was 0.069332 and was also not significant. Because the value of Moran's I was greater than the expected I, this test indicates that the prevalence of tungiasis is clustered and not dispersed; however, the significance tests indicate that the difference between these two values is not significantly greater than what would be expected by chance alone. Moran's I for total population was calculated at -0.004939, with E(I) being the same as that calculated for tungiasis prevalence.

Geary's C was calculated to be 0.992319. The spatial random, or expected, C was 1.0 with an associated standard deviation of 0.009155. The significance test of C under the assumption of normality (Z-value) was -0.838930 and was not significant. Geary's C for total population was calculated at 0.99672 with a Z-value of -0.035806 ($p < 0.001$). These results are further reviewed in the discussion.

5.3.2 Distance Analysis

Results of the nearest neighbor analysis for tungiasis are shown in Table 5.1. The NNI, which is less than one, indicates a significant amount of local clustering in Balbino. Ripley's K statistics for tungiasis are shown in Figure 5.3. It can be noted from this figure that the maximum value of L(t) occurred at 300 meters, and that the K statistic for population is nearly identical to that for tungiasis.

5.3.3 Hot Spots

Two first-order risk-adjusted nearest neighbor hierarchical clustering hot spots were detected in this analysis. These hot spots are depicted in Figure 5.4. As can be seen in this figure, the two hotspots were located near the center of Balbino. The hot spot located in the north-central portion of Balbino contained 15 cases of tungiasis out of a population of 46, or

approximately 33% prevalence. The hot spot located in the south-central portion of Balbino contained 27 cases out of a population of 46, or approximately 59% prevalence.

Table 5.1 Nearest Neighbor Statistics for Tungiasis in Balbino

Mean nearest neighbor distance	40.35 meters
Standard deviation of NN distance:	52.08 meters
Nearest neighbor index:	0.54287
Standard error:	3.27 meters
Test statistic (Z):	-10.3843
p-value (one tail):	0.0001
p-value (two tail):	0.0001

5.4 Discussion

Using two global indicators of spatial autocorrelation, Moran's I and Geary's C, it was found that tungiasis was weakly positively spatially autocorrelated. However, finding positive spatial autocorrelation with Moran's I and Geary's C for tungiasis prevalence is not surprising considering that the population of Balbino is concentrated both in location and within families. Comparing Moran's I for tungiasis prevalence (-0.006639) to that of the population (-0.004939) suggests that tungiasis infections are slightly less concentrated than what could be expected on the basis of population distribution. This hypothesis can be tested using an approximate test suggested by Levine (2007) :

$$Z(I) = (I_t - I_p)/S_{E(I)}$$

where I_t and I_p are Moran's I for tungiasis and prevalence, respectively, and $S_{E(I)}$ is the standard deviation of I under the assumption of normality. The low Z-value produced through this

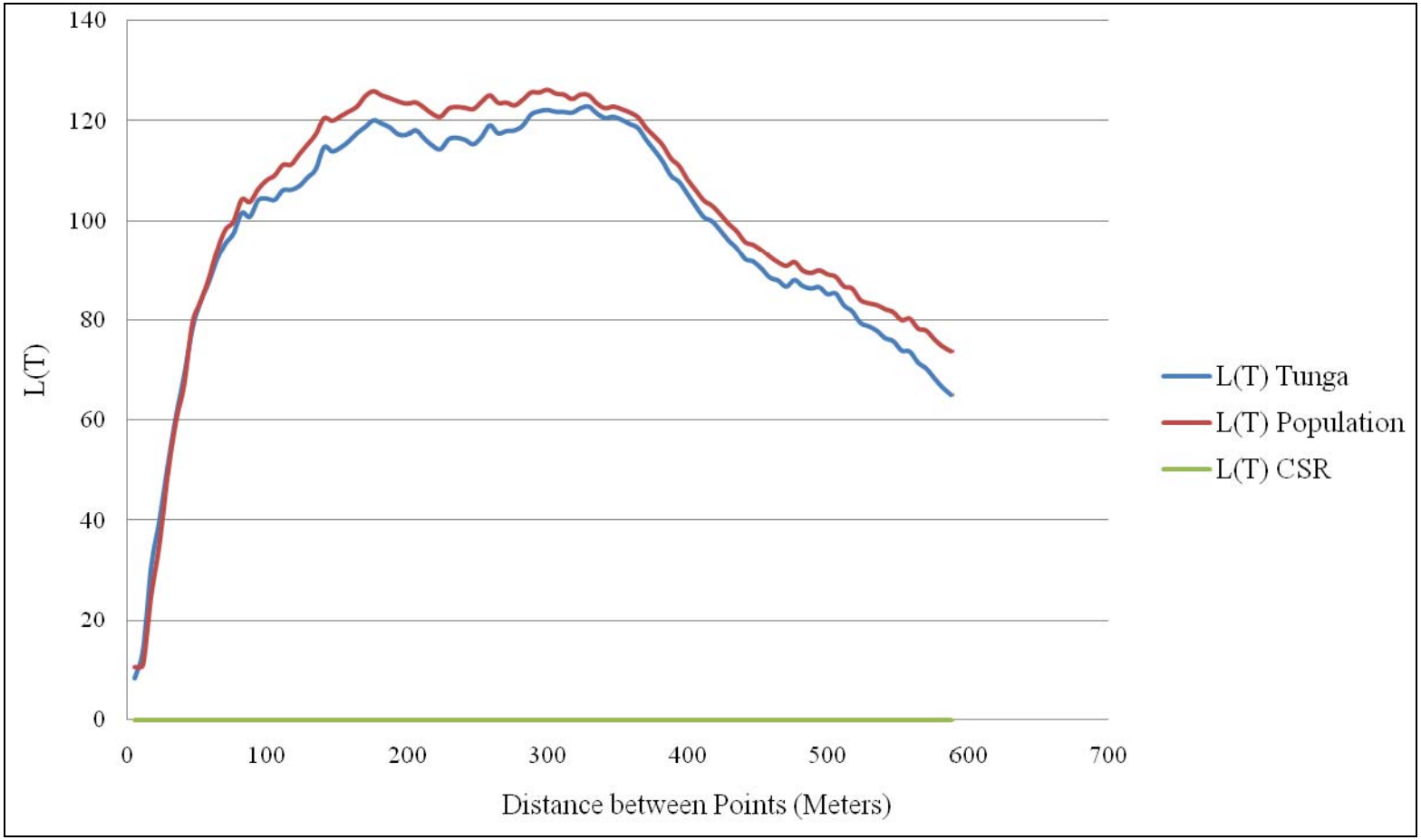

Figure 5.3: "K" Statistic for Tungiasis Compared to Population and CSR Distributions

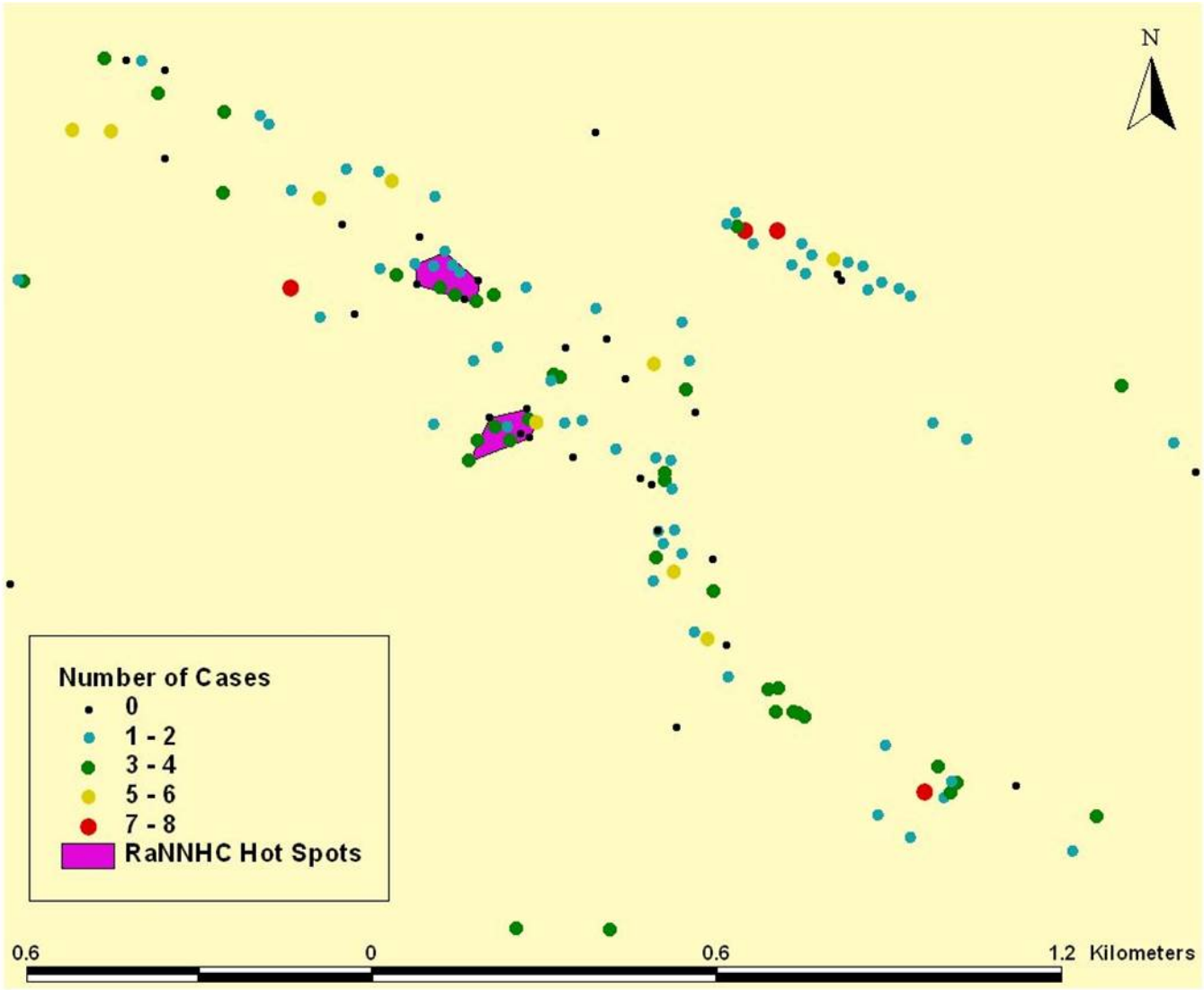

Figure 5.4: Tungiasis Cases and Risk-adjusted nearest neighbor hierarchical clusters in Balbino

test (-0.233998) thus suggests that tungiasis prevalence is no more clustered than the clustering of the population. When Geary's C for tungiasis (0.992319) is compared to Geary's C for population (0.99672), it appears that both tungiasis and population are weakly positively spatially

autocorrelated—backing up the hypothesis proposed by Moran's I. What Moran's I and Geary's C could thus be suggesting for tungiasis is that concentration of infection is perhaps most related to population concentration, and not necessarily related to local environmental factors or specific individual behaviors. Because Geary's C is more sensitive to local clustering than Moran's I, and because both Geary's C and Moran's I indicate that tungiasis is only weakly positively correlated, this may suggest that there is little difference between global (first-order) and local (second-order) spatial autocorrelations. The major limitation to using these two indices in this study is that they only give indication that spatial autocorrelation exits, not *where* it exists.

Unlike global indicators of spatial autocorrelation that represent the dominant pattern of overall distribution, local indicators represent 'neighborhood' patterns in the overall distribution (Levine, 2007). The two local indicators used in this analysis were the nearest neighbor and Ripley K's indices. Both of these indices confirmed the findings of the global statistics that spatial autocorrelation was occurring, but they also gave further information about the nature of spatial autocorrelation: 1) that significant spatial autocorrelation occurs at an average distance of 40.35 meters, and 2) spatial autocorrelation of tungiasis is strongest around 300 meters. Though both of these indices are powerful tools for testing spatial autocorrelation, they are subject to edge biases and sample size issues. Edge bias was controlled for in this study by using circular correction (which in its own rights can produce skewed results if the study area is not circular). Levine (2007) also cautions that the precision of the K function is inaccurate for small sample

sizes, indicating that this study's sample size of 141 may produce some unavoidable inaccuracy in the K function statistic. In addition to this caution, there is also a caution of scale. Data sets with dominant first-order properties, such as those that are correlated with population concentrations, are likely to have 'shadowed' second-order effects, making it unclear whether clustering is due to primary or secondary clustering. As determined by this study, the NNI and K statistic detected spatial autocorrelation, but these indices provide little other information about the nature of first and second order clustering.

Cluster analysis offers a reliable means of detecting abnormally high concentrations of tungiasis. However, when deciphering detected clusters several factors must be considered (Levine, 2007): how the cluster was defined—whether it is a discrete grouping of events or a continuous variable; how distance is measured and geometry is used; the number of clusters to be detected as defined by the user; the scale of cluster detection; whether clusters are initially identified by mathematical or user-defined means; the algorithms used to adjust cluster locations; and the way in which clusters are displayed.

The two clusters detected in this study are no doubt subject to the criteria listed above. Altering the bandwidths, the minimum number of cases to be included in a cluster, and the search radius are all variables that could manipulate the size, shape, and even number of clusters detected. However, these variables are user-determined and must be chosen based on the objectives of the study. For this analysis, the parameters based on household size and the nearest neighbor indices identified in the spatial description analysis were adequate enough to produce clusters.

Using the Risk-adjusted NNHC technique provides a useful method of detecting clusters of disease. Compared to a NNHC analysis, this technique provides the user to integrate a

dependency variable (population) into the computations of clusters. In disease research, where such variables as population or socioeconomics play such a great role, this type of method seems the most appropriate.

The methods used in this study were only able to detect clusters, not give reasons on why they are located where they are. However, it can be guessed that these clusters are located in areas of Balbino that are at particularly high risk for tungiasis infection. With further ecological or demographic study, the reason for these clusters could be identified. However, at this point, it would be safe to hypothesize that concentrating preventative and clinical measures in the households that lie within the clusters would probably lead to more focused resource management and higher efficacy of tungiasis control.

5.5 Conclusions

This study has provided a framework for a routine spatial examination of epidemiological data using geographic methods. Starting with spatial descriptors and finishing with hot spot analyses, this study showed that tungiasis prevalence in Balbino is spatially autocorrelated both locally and globally, and that hot spots of disease do occur. Though the reasons for spatial autocorrelation and clustering are not discussed here, future geographic studies of tungiasis may wish to examine how such variables as demographics, socioeconomics, soil types, animal reservoirs, and other spatially explicit data play a role in the spatial distribution of case prevalence. The results of these studies could no doubt aid in the control and prevention of tungiasis in Balbino and other resource-deprived communities throughout Brazil and the developing tropical world.

CHAPTER 6. USING KERNEL DENSITY INTERPOLATION TO VISUALIZE THE EFFECTS OF MASS TREATMENT WITH IVERMECTIN ON HELMINTH PREVALENCE IN BALBINO, BRAZIL

6.1 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, Michael et al., 2000). With such implementation, disease mapping and spatial analysis can play a vital part in disease epidemiology (Wen et al., 2006).

In the previous chapter, spatial distribution, distance analysis, and hot spot detection were used to describe the spatial structure of tungiasis in Balbino. This chapter takes a different spatial methods approach by employing kernel density interpolation to view the changes in helminth infection associated with mass treatment with ivermectin. Whereas the techniques used in the previous chapter provide statistical summaries for specific disease incidents, the 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.

6.1.1 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 (J. Heukelbach, B. Winter et al., 2004). 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).

6.2 Materials and Methods

6.2.1 Study Area and Population

This study examines the prevalence of helminth infection in Balbino, Brazil. The location and population of this community is described in the previous chapter on tungiasis. In addition to what is included in that chapter, it would also be useful to reiterate some information about Balbino that is related to helminth infection. 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 (J. Heukelbach, A.M.L. Costa et al., 2004). 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 (J. Heukelbach, B. Winter et al., 2004). 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.

6.2.2 Data Collection

The baseline epidemiological and geographic data used in this study were also described in the previous chapter on tungiasis. However, as the previous study only considered pre-treatment prevalence of tungiasis, 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) (J. Heukelbach, B. Winter et al., 2004). 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 (J. Heukelbach, B. Winter et al., 2004).

6.2.3 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). Figure 6.1 is a sample Moran correlogram for pre-treatment hookworm incidence used in bandwidth estimation. As can be seen in this figure, 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.

6.2.4 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.

6.3 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 completely

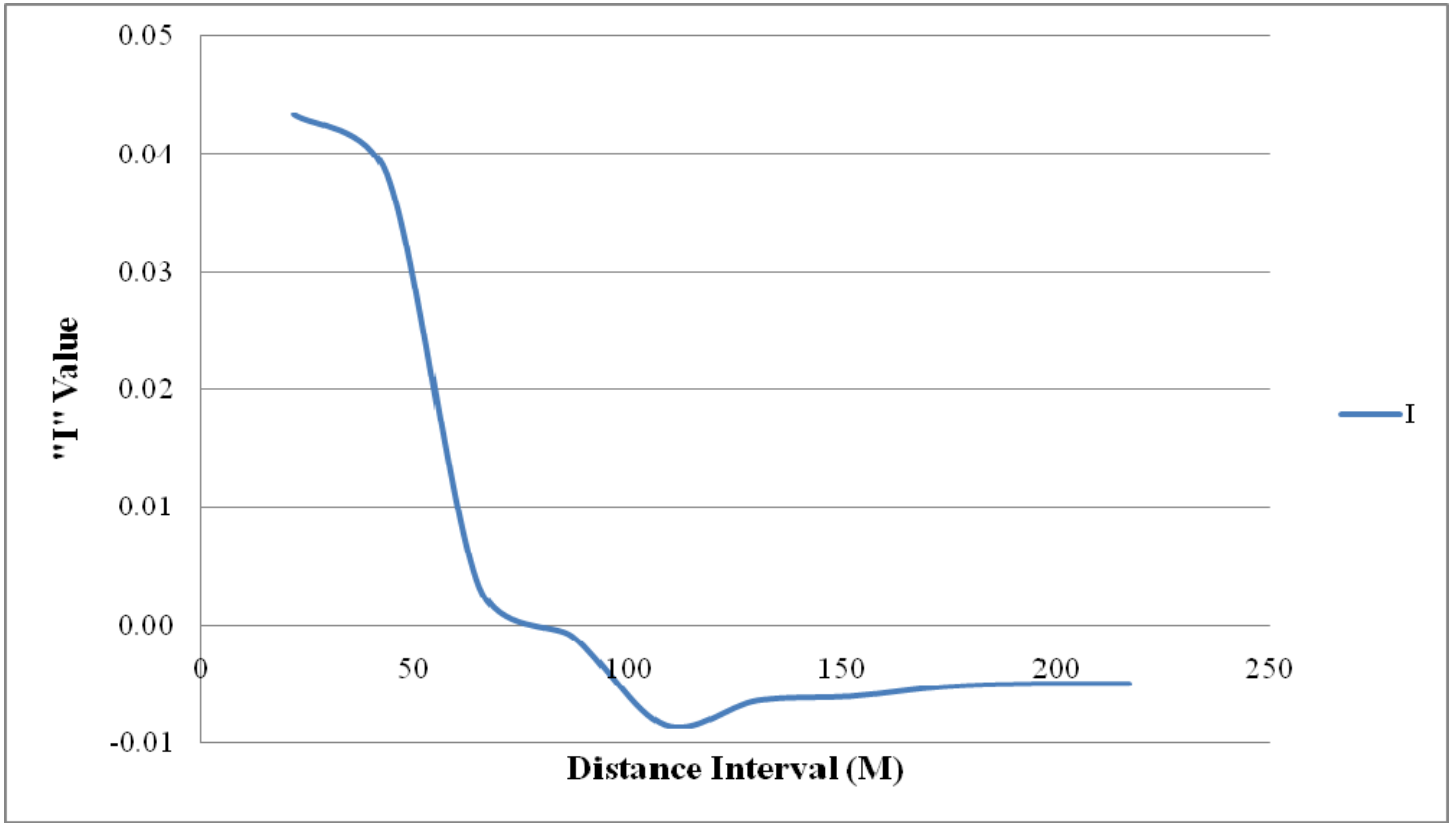

Figure 6.1: Moran's Correlogram for Pretreatment Hookworm Incidence

free of helminth infection. Figure 6.2 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 6.2, 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 6.2) 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.

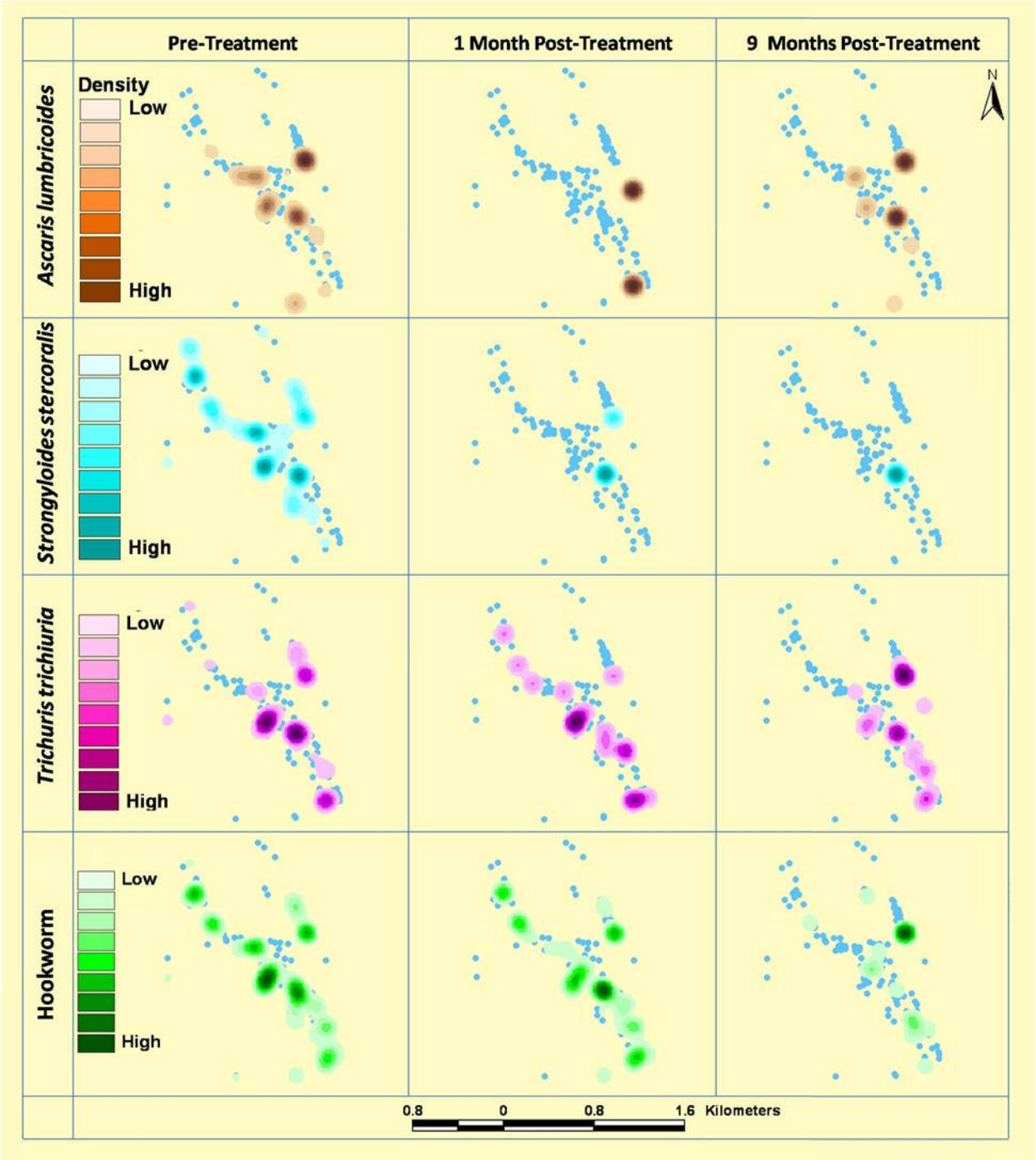

Figure 6.2: Kernel density interpolation of helminth infection in Balbino, Brazil

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 6.2, 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 6.2. 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.

6.4 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.

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. (2004) 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 infections 'reappear' 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 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 (J. Heukelbach, B. Winter et al., 2004), 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.

6.5 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.

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.

CHAPTER 7. THE GEOGRAPHY OF LEPROSY ELIMINATION

7.1 Introduction

The course to leprosy elimination in endemic countries has continued to endure despite nearly two decades of intense elimination efforts and failure to reach set national elimination targets. Leprosy thus still remains a legitimate global health concern and continues to be an important topic in tropical disease research. The objectives of the next three chapters are as follows: 1) to give the reader an introduction and review of leprosy; 2) to examine the role of geography in leprosy elimination in Brazil; 2) to determine what geographic level is most useful in examining leprosy distribution in Brazil; and 3) to pinpoint how GIS and other geographic technologies could be used to help reach leprosy elimination targets in Brazil and other countries where the disease still persists.

7.2 Leprosy: An Ongoing Struggle

When most people today think of leprosy they are reminded of the pitiful disease thrown upon Judah's mother and sister in the movie *Ben Hur*—the disease that turns them both into disfigured beggars who are ridiculed and shunned from biblical society—or of the infliction depicted through Robert the Bruce's crippled and deranged father in *Braveheart*. Although most people's experience with leprosy is limited to Hollywood's depiction of this disease, the fact still remains that leprosy is a *real* disease that affects *real* people. In addition, and also contrary to popular notion, especially in Western countries, leprosy is a disease that continues to infect people mainly in developing countries but also in places like the United States. Indeed, although leper colonies such as the ones in Carville, Louisiana, or in Kalaupapa, Hawaii, are closed and have been turned into tourist attractions, they still do remain as reminders of not only the intense

suffering of the colonies' inmates and missionaries, but also of the need to continue to fight for elimination of leprosy across the globe.

Leprosy, or *Hansen's disease*, is a complex chronic infectious disease caused by the acid-fast bacillus *Mycobacterium leprae* (Yawalker, 2002). Leprosy is one of the oldest diseases of humankind—in fact, this disease is so ancient that the earliest records of its existence can be traced back to around 600 B.C. Indeed, leprosy was a well recognized and documented disease in almost all of the great ancient civilizations, including Egyptian, Chinese, and Indian (F. S. Lewis, 2007). By 300 A.D., leprosy had spread along trade routes to nearly every corner of the Old World, including the European subcontinent, where incidence of the disease peaked along with the Black Plague in the 13th century. During this time, leprosaria, or leper colonies, begin to appear across Europe, numbering near an estimated 19,000 by the end of the 14th century (TCE, 1913). These colonies served as quarantine 'prisons' for lepers who were seen to exist in a place somewhere between life and death: cursed with what was considered by many medieval sources as going through Purgatory on earth (Brody, 1974). Unfortunately, there is historical argument over whether or not many of the people placed in leper colonies who were presumed to have leprosy had, in fact, syphilis (Wills, 1996). Leprosy was introduced to the New World not long after Columbus's discovery of the Americas in 1492, and the disease spread rapidly among the indigenous people. In 1873, the Norwegian physician Armauer Hansen discovered that the causative agent for leprosy was *Mycobacterium leprae*, making it the first bacillus to be associated with a human disease (F. S. Lewis, 2007). However, it was not until 1946 that a real promise to control the disease emerged, when the creation of the first sulfa drugs designed to treat leprosy, Promin, Diasone, and Promizole, were successfully trialed at the U.S.'s only leprosarium in Carville, Louisiana (Matcham, 1946).

Although leprosy has been intimately associated with humans throughout history, even today little is known about its pathogenesis, course, treatment, and prevention relative to other infectious diseases (F. S. Lewis, 2007). It is not considered a highly infectious disease, contrary to popular belief, and it is thought to be transmitted from human to human by aerosol spread through an infected individual's nasal secretions that come in contact with a susceptible individual's exposed nasal and oral mucosa (van Beers et al., 1999). Because of the way leprosy is transmitted, all of an infected individual's household, neighbors, and social contacts are at increased risk of contracting leprosy—with an inverse relationship between physical distance from the patient and the risk of infection (Moet et al., 2006; van Beers et al., 1999). Leprosy is generally not spread by means of direct skin contact, although there is suspicion that foci may exist in infected soil and that the disease can be spread through insect vectors (F. S. Lewis, 2007). Though humans are the primary reservoir of *M. leprae*, animal reservoirs exist in three other animal species: 9-banded armadillos, chimpanzees, and mangabey monkeys. Though there is a common notion that leprosy can be contracted from armadillos, the risk of acquiring the disease through this zoonotic reservoir is unknown (Truman, 1992).

Leprosy, which is derived from the Greek *lepros* and *lepein*, meaning "scales on a fish" and "to peel" respectively, is probably best known for the intense morbidity suffered by its victims—one that is so stigmatizing that it has made leprosy without a doubt one of the most notorious diseases in the human repertoire (Kane et al., 1997). In fact, leprosy is known as a granulomatous disease, caused by bacteria that can incubate for six months to 40 years in patients before producing symptoms (F.S. Lewis, 2007). The bacillus tends to lodge in cooler parts of the body such as superficial peripheral nerves, skin, mucous membranes of the upper respiratory tract, the anterior chambers of the eyes, and the testes. Tissue damage results from

the reaction caused by cell-mediated immunity to the bacillus (i.e., lepra reactions) which leads to a chronic inflammatory reaction in affected areas. Cutaneous lesions in the skin usually manifest as hypopigmented macules with raised borders. Because of the bacillus's affinity for macrophages and Schwann cells (whose perineurium undergoes ischemia, fibrosis, and axonal death), tissue damage almost always involves the peripheral nervous system. Morbidity results from skin necrosis and loss of sensory/nervous stimulation that can lead to secondary trauma and further bacterial superinfection. Generally, temperature is the first sensation to be lost followed by light touch, pain, and finally deep pressure. These losses are usually localized to the hands and feet, and the chief complaint when patients present to a clinic is usually a burn or ulcer localized on an anesthetic extremity (caused by burning of hands when cooking, for instance). It is the skin lesions and deformities associated with sensory and motor damage of peripheral nerves that historically have been responsible for the traditional stigma associated with the disease (F.S. Lewis, 2007).

Clinical disease manifests and is classified along a spectrum that has tuberculoid leprosy (TL) at one end and lepromatous leprosy (LL) at the opposite end (Bakker et al., 2004; F.S. Lewis, 2007). The strength of the host's immune system usually dictates the clinical form of the disease and where along the spectrum the individual lies: strong cell-mediated immunity and a weak humoral response generally lead to milder forms of leprosy, whereas a relatively void cell-mediated immunity and strong humoral response leads to widespread lesions, extensive skin and nerve involvement, and high bacterial loads indicative of LL. Infection with the human immunodeficiency virus (HIV), which alters immune status, has not been identified as a risk factor for acquiring leprosy, increasing virulence of *Mycobacterium leprae*, or worsening clinical symptoms (Bakker et al., 2004). Diagnosis of leprosy is a fairly straightforward process

that usually begins with a general physical evaluation of the patient's cutaneous neuropathies and the eyes (F.S. Lewis, 2007). Confirmation of clinical suspicion is made in the lab with tissue smears or slit-skin smears, histamine testing, and methacholine sweat testing. These methods of diagnosis lead to high sensitivity (97%) and specificity (98%) for leprosy (F.S. Lewis, 2007).

Once diagnosed, leprosy patients are managed medically through pharmacotherapy and physical therapy, and mentally with social and psychological rehabilitation (F.S. Lewis, 2007). The most important element of leprosy treatment is drug therapy, which is designed to stop the infection, arrest transmission, reduce morbidity, and prevent complication. Since 1981, pharmacotherapy has involved multi-drug therapy (MDT) including dapsone, rifampin, ofloaxin, and clofazimine. In patients with profound inflammation or extensive nerve damage, surgery can be performed to improve function, drain abscesses, or cosmetically restore damaged areas. Early diagnosis and effective antimicrobial treatment can arrest transmission, reduce pathogenesis, and even cure the disease. However, one of the challenges presented by treatment is its long and arduous duration, which can last from six months to two years and often is not completed by patients (F.S. Lewis, 2007).

Leprosy can occur in any race, in any age group, and in any gender (F.S. Lewis, 2007). Demographically, however, TL tends to occur more predominantly in Africans and LL occurs more predominantly in light-skinned races and Chinese individuals. LL is more common in adult men than women in a ratio of 2:1, while in children TL predominates with no preference for sex. Leprosy incidence generally peaks between the ages of 10-14 and 35-44. However, children are the most susceptible to infection. Women usually show increased morbidity because they tend to be delayed in their presentation and thus are diagnosed at more advanced stages (F.S. Lewis, 2007).

Currently, leprosy affects between two and three million people worldwide and continues to be one of the world's leading causes of physical disability (Yawalker, 2002). Most infected individuals live in the tropics and subtropics, making leprosy rank at the top of important tropical diseases. However, leprosy still presents in developed, non-tropical countries. The United States, for instance, has approximately 6,000 patients and 200-300 new cases each year usually within small endemic foci in Texas, Louisiana, and Hawaii—though ninety-five percent of these cases are thought to have been contracted in developing countries (F.S. Lewis, 2007). The greatest number of cases worldwide occurs in India, followed by Brazil, Burma, Madagascar, Mozambique, Tanzania, and Nepal (WHO, 2005a). At the start of 2008, the Democratic Republic of the Congo and Mozambique reached the leprosy elimination goal, while Brazil, Nepal, and Timor-Leste had yet to reach the elimination goal (WHO, 2008). As can be seen in Figure 7.1, the majority of new case detection continues to be in the tropical developing countries of Asia, Africa, and South America.

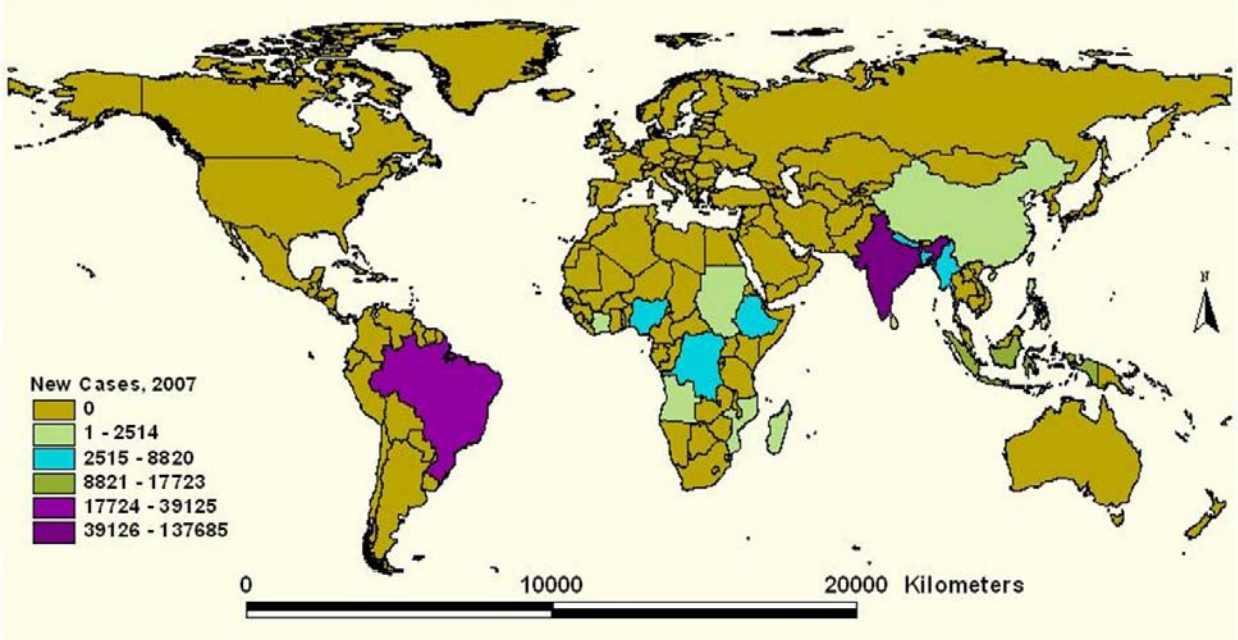

Figure 7.1: Countries reporting >1,000 new cases of leprosy during 2007 [Data source: WHO Weekly Epidemiological Record 2008]

7.3 Leprosy Elimination: Is It Possible?

In 1991, the Forty-fourth World Health Assembly (WHA) adopted a resolution to eliminate leprosy as a global health problem by the year 2000 (WHA, 1991). "Elimination" was defined as attaining prevalence below one case per 10,000 population. Because this target reflected a dynamic global average and did not consider disease rates in specific countries, areas, or populations, the target was reached by the end of 2000. However, attaining this goal did not mean that leprosy had been eliminated or that it was under suitable control where it was most severe. Despite reaching the *global* elimination target and a resulting decrease in global prevalence by more than 90%, leprosy continued to persist beyond acceptable levels in five endemic countries: India, Brazil, Madagascar, Mozambique, and Nepal (WHO, 2003). As a result, the WHO set another target to eliminate leprosy at the *national* level by 2005—a move that was proposed by the "Final Push" in 1999 and backed by the creation of the Global Alliance for Elimination of Leprosy (GAEL). Unlike the goal set in 2000, the push to eliminate leprosy by 2005 at the national level was not achieved. As a result, leprosy continues to exist as a significant health problem in endemic countries like India, Brazil, Madagascar, Mozambique, and Nepal. Today, the leprosy burden in these five countries alone accounts for 83% of prevalence and 88% of detection worldwide—indicating that the disease has taken on national foci that reflect either endemic clusters or failures in specific national programs designed to eliminate leprosy (WHO, 2007).

When assessing a disease's candidacy for elimination, many factors must be considered in order to determine the practicalities of elimination, as not all diseases are suitable for elimination (Speare & Leggat, 2006). Small pox, for instance, was a disease that was only found in humans, had a suitable vaccine, and precipitated such a substantial global effort that it was, in

effect, ‘eliminated’ and then eradicated from the planet (except in the few laboratories around the globe that claim to still have the virus in storage). On the other hand, diseases such as yellow fever and encephalitis, though vaccines exist, are not ‘eligible’ for elimination because of the complications that arise with sylvatic vectors and viral transgenicity. Therefore, in order to make the assessment of disease elimination more organized, the WHO (2003) has proposed certain criteria for diseases that help to determine whether or not elimination should be sought for a specific disease:

1) *Only one source of infection*.
2) *Simple and practical ways to diagnose the disease.*
3) *An effective intervention to interrupt transmission*.
4) *Incidence is kept low such that prevalence declines to non-sustainable levels.*
5) *No other diseases exist that can adversely affect the disease marked for elimination*.

Because of the specificity of these criteria, it is rare to find a disease that meets all the requirements for elimination. However, leprosy, like small pox, is nearly an ideal disease to target for elimination: transmission is believed to occur only from human to human, with zoonotic or environmental transmission negligible (if at all possible); leprosy can be diagnosed based on clinical signs alone; it can be treated with multi drug therapy (MDT), which renders infected individuals non-infectious; widespread applications of MDT for several years has led to significant decline in the annual new case detection rates; and leprosy (unlike tuberculosis) does not appear to be adversely affected by other diseases such as HIV. The possibility of achieving global elimination of leprosy, therefore, is a very real practicality.

It is important to remember, however, that elimination of a disease does not mean eradication. Whereas eradication is complete removal of the disease from a population so that no new cases develop, elimination is merely reaching a certain set target of prevalence and incidence. In the case of leprosy, the strategy behind setting the global target at a prevalence of

less than one case per 10,000 population is based on the assumption that detecting and treating all active cases will reduce transmission to such an extent that the number of new cases gradually decreases (WHO, 2003). In this way, a negative feedback loop is created that hopefully would eventually lead to such low prevalence that incidence approaches zero, until finally the disease is 'eradicated.'

In most instances, setting elimination targets has proven much easier than actually reaching them. To reach elimination for leprosy, for instance, all active and new cases of leprosy would have to be rapidly and aggressively detected, diagnosed, and treated with MDT. This fact only begins to hint at the complications that arise in developing countries like India and Brazil and in some ways explains why leprosy still persists at such levels in these countries to this day. For instance, the major complication that has been encountered in leprosy elimination has been the availability of MDT to leprosy patients. Although the WHO has offered MDT to any leprosy patient around the world since 1995, the obstacle has been *getting* the drugs to patients, especially to those located in areas with weak health care infrastructures or those that are difficult to access geographically, socially, economically, and culturally (WHO, 2003). In addition, leprosy diagnosis and treatment are highly centralized activities dependent on specially trained staff that is not always accessible or available—and in some instances patients will not present because of the intense fear and stigmatization that still exist. These complications in leprosy elimination reveal that the major setbacks are operational (i.e., organizational) in nature rather than technical (i.e., pharmaceutical) (F.S. Lewis, 2007). In fact, the biggest challenges to face leprosy control programs are maintaining services—especially in peripheral areas—and sustaining political support for leprosy control—two operations that were setback further when the global elimination target was reached (WHO, 2008).

Despite these critical downfalls, organizations continue to strive for leprosy elimination in endemic countries. Setting targets, such as the 2005 WHO target, have been important in showing leprosy endemic countries that the disease need not be regarded as a permanent and unsolvable problem, that the disease can be effectively treated with MDT, and that leprosy can be controlled through its definitive acceptance as a real yet solvable public health problem (WHO, 2007). In order to make elimination possible, however, countries like India and Brazil will have to continue to deliver sustainable diagnosis and treatment regimens, improve the quality control of case management, recording, and reporting of cases in endemic areas, develop procedures and tools in aggressive home/community based public health campaigns, and finally strengthen collaboration efforts between international groups advocating leprosy eradication (WHO, 2005b).

7.4 The Geography of Leprosy Elimination

At this point, it is important to consider the role that geography can play in leprosy elimination. Obviously, geography has strongly influenced the epidemiology of leprosy through physical and cultural space, and in part can be used to explain the statistical distributions and risk factors that are included in the disease's etiology. However, as mentioned above, the major setbacks to achieving leprosy elimination in endemic countries have not been technical in nature but operational—reflecting the possibility of a different role for geography in leprosy elimination. Specifically, geography can be used to augment operational procedures as a "valuable management tool in the elimination program, strengthening national, regional and sub-regional capacities in surveillance and monitoring" (WHO, 2007). Specifically, geography has the potential to be used in leprosy elimination in the following ways: 1) to view, analyze, and display geographic variation in leprosy distribution; 2) to integrate remotely sensed data with

case data to examine environmental causality; 3) to detect spatial clustering of leprosy to determine areas of unusual case occurrence; 4) to utilize demographic and socioeconomic data to model leprosy dynamics both spatially and temporally; and 5) to focus elimination efforts and resources on areas of unusually high transmission (Argaw et al., 2006; Fine, 2007; Lapa et al., 2006).

Despite the great potential for the use of geography in leprosy elimination, little has been done to integrate geographic methods into both the research and clinical sides of leprosy elimination (Lapa et al., 2006). In many respects, the potential of geography as a tool to better understand this disease has only begun to be realized by researchers, clinicians, and government programs. However, in endemic countries, the use of geography in leprosy elimination has been limited by technological development, funding, and lack of training (Durrheim, 2003). What is needed, therefore, are ways in which to strengthen geography's role in leprosy elimination. These may include defining new parameters in spatial analyses and statistics for leprosy epidemiology, developing geography-based leprosy surveillance, integrating environmental and demographic data into geographic models of leprosy distribution, and, most importantly, increasing collaborative efforts between countries with 'developed' methods of geographic investigation, like the United States, and countries with less sophisticated geographic-technological development, like India and Brazil.

7.5 Brazil as a Model

As mentioned previously, the country of Brazil has the world's second largest case load of leprosy, accounting for nearly 16.3 % and 21.5% of worldwide incidence and prevalence, respectively, at the beginning of 2008 (WHO, 2008). The fifth largest country in the world by land area, Brazil has been struggling for the last two decades to reach national WHO leprosy

elimination targets. Though prevalence of leprosy in Brazil has declined dramatically in the last decade, detection rates have remained relatively stable, indicating that ongoing transmission of *Mycobacterium leprae* is still occurring (Penna & Penna, 2007). However, in early 2006, the Brazilian Ministry of Health announced that it had achieved a reduction of 24.3% in the number of newly diagnosed leprosy cases over the previous two years. In order to keep this trend moving in the same direction, Brazil will undoubtedly have to aggressively increase its efforts to detect and treat leprosy patients (Durrheim, 2003). Reaching the elimination target too quickly, however, may not be Brazil's prime objective. Some critics would argue that once leprosy is 'eliminated' in Brazil, leprosy programs and their inclusion in health policy would suddenly come to end (Penna & Penna, 2007). Critics on the opposite side say that if Brazil wants to meet leprosy elimination targets, it could through "artful manipulation of the definition of leprosy and by avoiding active case detection" (Mudur, 2005). Luckily for the patients who suffer with the disease, the Brazilian Ministry of Health has chosen a middle path that slows down the race to elimination but also increases the thoroughness and quality with which patients are treated.

Because of its highly irregular geographic distributions of leprosy, Brazil is an ideal setting for the application of geographic methods to leprosy research and surveillance (Montenegro et al., 2004). However, because of the sheer size of Brazil, determining the geographic level of analysis for this research is more difficult than it seems. For instance, a geographic analysis can detect spatial patterns at the state level (Figure 7.2), municipality level (Figure 7.3), or even at the barrios (suburb) level (Figure 7.4).[1] At all of these levels, heterogeneity of leprosy distribution can be seen.

[1] Datasource for figures: DataSUS (2007)

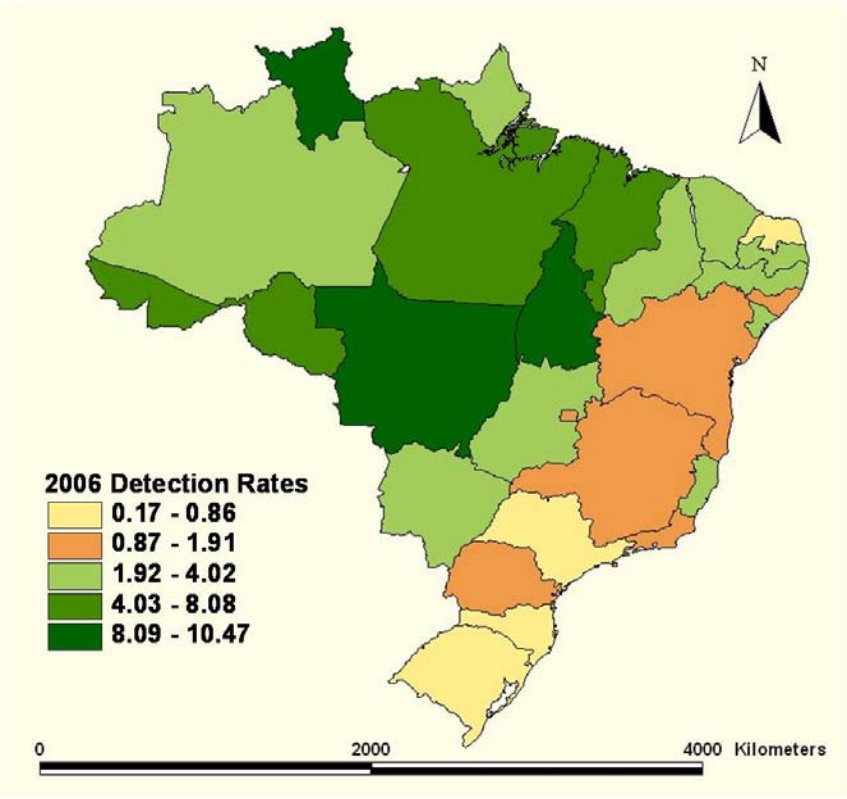

Figure 7.2: Leprosy detection rates (new cases per 10,000 population per year) across Brazilian states, 2006

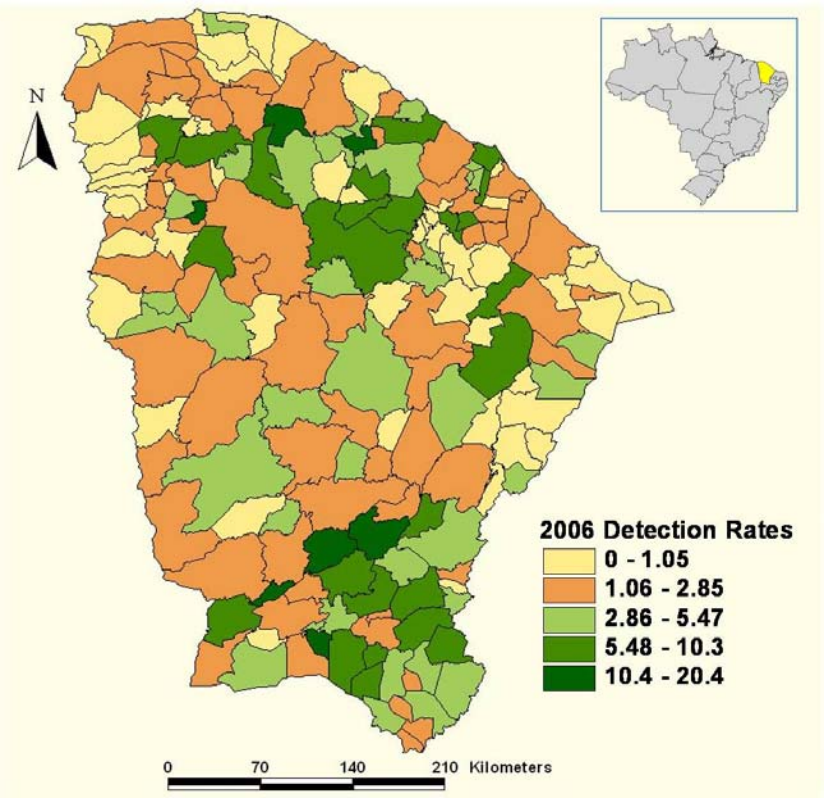

Figure 7.3: Leprosy detection rates (new cases per 10,000 population per year) across municipalities of Ceará State, Brazil, 2005

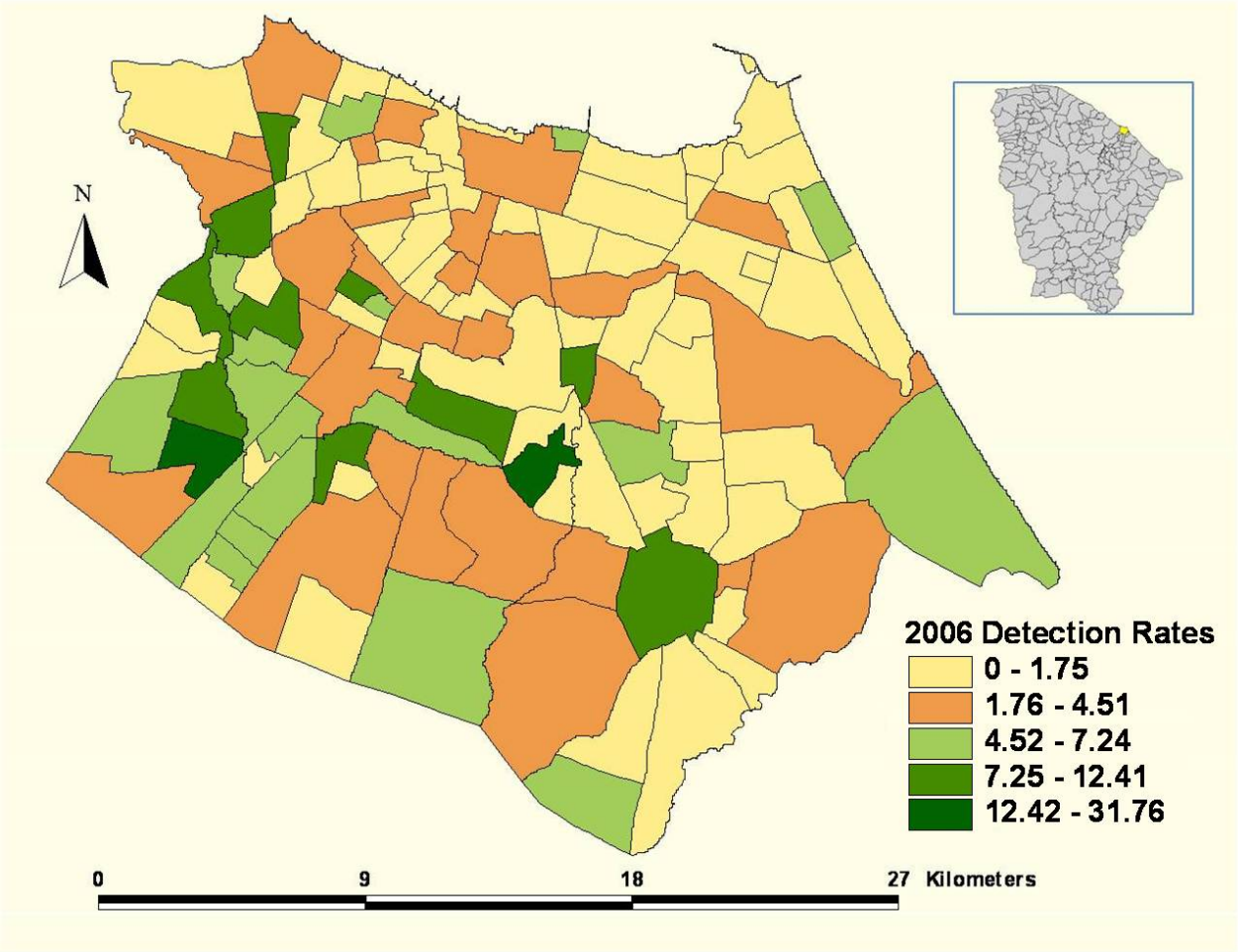

Figure 7.4: Leprosy detection rates (new cases per 10,000 population per year) across barrios of Fortaleza, Ceará State, Brazil

Without a doubt, significant spatial clusters could be detected at the state, municipality, and barrios levels. However, detecting clusters at the state-level may provide too variable of a region for a proper ecological analysis, while detection of clusters at the barrios level is made difficult because of the obstacle of obtaining data at this spatial resolution. For now, it seems appropriate to use the municipality as the level of geographic analysis because of the quality and availability of data at this spatial resolution.

In order to gain a better understanding of both the applicability of geographic techniques in leprosy research and to provide publishable accounts of the leprosy situation in Brazil, Chapters 8 and 9 examine the distribution of leprosy in Ceará and Rondonia States at the municipality level. In these chapters, the methodology was chosen so that the results of the spatial analyses could be compared across Ceará and Rondonia States. Chapter 10 continues with a spatial analysis of Rondonia State; however, this chapter employs the use of rate-adjustment in order to compare the results to those obtained in Chapter 9. Chapter 11 follows Chapter 8 in that it is a spatial analysis of Ceará State, this time dealing with the distribution of tuberculosis rather than leprosy.

CHAPTER 8. SPATIAL AUTOCORRELATION OF LEPROSY IN CEARA STATE, BRAZIL, FROM 1995-2005

8.1 Introduction

Prior to the 1980s, data on the prevalence of leprosy in Brazil were not sufficient enough to represent the real situation of case occurrence, distribution, and transmission within this endemic country (Opromolla et al., 2006). However, after the introduction of multidrug therapy in 1981 and the promise that an effective treatment could cure current patients and arrest the transmission to new patients, a renewed interest in the epidemiology of this disease and methods for its control were developed (WHO, 1982). In 1991, the World Health Organization set out a proposal to eliminate leprosy as a global health problem by the year 2000 (WHO, 1998). Reaching their goal of achieving less than 1 per 10,000 case-population ratio at the global scale, WHO then decided to target leprosy at the national level with a "Final Push" to eliminate this dreaded disease from all corners of the planet (Durrheim, 2003). Several countries, however, have not been able to reach this target, among which is Brazil. In 2005, in an effort to reach international standards on leprosy elimination, Brazil forged a new commitment to rearrange its control tactics for leprosy, delaying elimination in this country until the newly proposed date of 2010 (WHO, 2005b).

Despite the organizational difficulties of reaching elimination targets in Brazil, leprosy prevalence in the country has been declining dramatically since the 1980s. In 1985, prevalence levels were around 16.4 cases/10,000 population, whereas in 2003 this number dropped to 4.52 per 10,000 (Opromolla et al., 2006). In some areas of Brazil, however, detection rates have actually increased. Andrade (1996) proposes that these increases in detection rates across Brazil are not only due to epidemiological factors, but could also be due to operational factors that lead

to increased identification and notification of leprosy, such as increased coverage of control programs, training of personnel for treatment and detection, decentralization of health agencies, and increased public awareness. In actuality, therefore, these increased rates would more closely represent the true situation of leprosy across Brazil, and would be a strong indication that control programs are doing what they are supposed to do.

Despite the optimistic forecast of leprosy in Brazil, the fact remains that this disease is still a significant public health problem in many parts of the country. Ceará State appears to be approaching a pre-elimination phase, even though the pattern of leprosy occurrence still represents a heterogeneous distribution with some areas of high endemicity (Montenegro et al., 2004). The complex nature of the factors involved in reaching the elimination target in Ceará State are reflected through the inequalities and spatial distributions in case incidence across municipalities (refer back to Figure 7.2). For the year 2005, some municipalities had incidence rates of less than 0.16, while others had rates as high as 20.4. It also appears that municipalities with high incidence rates tend to be surrounded by others with high or intermediate incidence—a fact that is also seen with prevalence (Tavares, 1997). The apparent existence of these 'clusters' of similar incidence allude to the fact that the spatial distribution of leprosy within Ceará State may be influenced by geographic and/or environmental variables.

As mentioned in the previous chapter, many factors influence the risk of leprosy from physiological conditions such as immunological status to demographic and socioeconomic factors such as race, age, poverty and overcrowding. These factors vary in their spatial distributions relative to the geographic area being studied. Because public health and disease are extensively influenced by the spatial patterns of these factors, the incorporation of spatial analysis into health research and surveillance is justified (Barcellos et al., 2002). With this in

mind, combined with the need to implement and structure new strategies for leprosy control and surveillance, spatial analysis could play a useful tool in assessing the situation of leprosy in Ceará State.

Tiwari et al. (2006) set the foundation for how a spatial analysis could be developed for a region such as Ceará State. According to these authors, a spatial analysis of disease distribution should include the identification of areas of exceptionally high or low (abnormal) disease rates, test the statistical significance of these areas, and lead into an investigation of why abnormal disease rates are occurring (Tiwari et al., 2006). In order to meet these criteria, the spatial scan statistic developed by Martin Kulldorf (1997) can both detect and provide inference into spatial and space-time disease clusters. Integrated into the freeware SaTScan (Kulldorf, 2006), the spatial scan statistic offers many advantages over other cluster detection techniques, namely the implementation of a temporal element into cluster analysis. It has been used to detect and evaluate clusters of cancer (Hsu et al., 2004; Pollack et al., 2006),dengue (Nisha et al., 2005), trachoma (Polack, Solomon et al., 2005), filariasis (Washington et al., 2004), and many other diseases.

The scan statistics were designed to test for geographic clusters and to identify their approximate locations (Kulldorf, 1997). These statistics can be used with either point level data with precise geographic coordinates or with data aggregated to larger areas, such as census blocks, municipalities, or states. This method of cluster detection uses a mobile circular window that includes different sets of neighboring areas at different positions. The radius of the circular window varies from zero to a maximum radius at each position such that the window never includes more than 50% of the total population at risk. This method allows detection that is flexible in both location and size (Onozuka & Hagihara, 2007).

The scan statistic tests the null hypothesis that cases are distributed through complete spatial randomness against the alternative hypothesis that the probability of a case inside the window is greater than it being outside the window (Kulldorf, 1997). Each zone that rejects the null hypothesis is further likelihood tested for statistical significance. Large datasets are adjusted for multiple testing using the *Monte Carlo* method such that each case time and location are shuffled randomly within the dataset and the most likely cluster is calculated for each simulated set in the same way it is for the real data. Only a small number of possible clusters are tested to minimize false positives. For each identified cluster, the output includes a list of geographic subdivisions, numbers of observed and expected cases, population, relative risk (RR), and *p*-value. (Relative risk is a measure of the risk of developing a disease and reflects the ratio of the probability of the disease occurring in the exposed individuals versus non-exposed individuals.)

In purely spatial analyses that examine data over long time periods, it is less likely that the scan statistic will detect recently emerging clusters (Onozuka & Hagihara, 2007). In analyses of data with short time periods, low to moderate excess risk that is present over a long period of time could be missed. These problems are solved using a combined space-time scan statistic that uses a three-dimensional cylindrical window whose base represents space and whose height represents time. As with the purely spatial scan statistic mentioned above, the space-time scan statistic uses a likelihood ratio constructed through a computational algorithm to test each window, this time in three dimensions rather than two (Kulldorf, 1997).

The detection of spatial clustering of leprosy incidence for the years 1991 to 1999 in Ceará State was initially undertaken by Montenegro et al. (2004). Their study examined the large and small scale variations of incidence rates using *Moran's I* as an indicator of significant spatial autocorrelation. Their results identified three regions of high incidence during this period and

showed that high incidence rates of leprosy tend to cluster on a north-south axis in the middle of the state (Montenegro et al., 2004).

The objective of this study was to analyze the spatial patterns of leprosy case occurrence in Ceará State through the identification of clusters that represent either high or low risk for leprosy and to map probable transmission risk as calculated through spatial statistical methods. This study was designed as a partial continuation of the Montenegro (2004) study, with several key differences: 1) a new study period, from 1995 to 2005, was examined, which in theory should show how cluster distribution has changed over the last decade and give an indication of elimination progress; 2) a different spatial statistical methodology is employed that uses the scan statistic, allowing purely spatial clusters of the entire 10 year period to be detected as one unit; 3) a temporal element is added to the statistical analysis in order to see how time influences clusters; and 4) a control for the confounding of age and gender in case detection was included in a separate analysis for comparison.

8.2 Materials and Methods

The study area for this analysis is Ceará State, located in the semi-arid, drought-prone region of northeast Brazil (Figure 8.1). Covering an area of about 148,000 km^2,Ceará State is one of the least developed and poorest regions of Brazil (Montenegro et al., 2004). Ceará State's population has grown considerably in the last decade, from 6.7 million in 1995 to over 8.3 million in 2007(IBGE, 2008).In recent years, poor environmental and socioeconomic conditions have led to a massive migration of the rural poor into urban areas in search of work, creating new disease dynamics in many of Ceará State's urban favelas.

Case data on patients diagnosed with leprosy in Ceará State for the period of 1 January 1995 to 31 March 2006, was obtained from the ongoing national population-based surveillance system

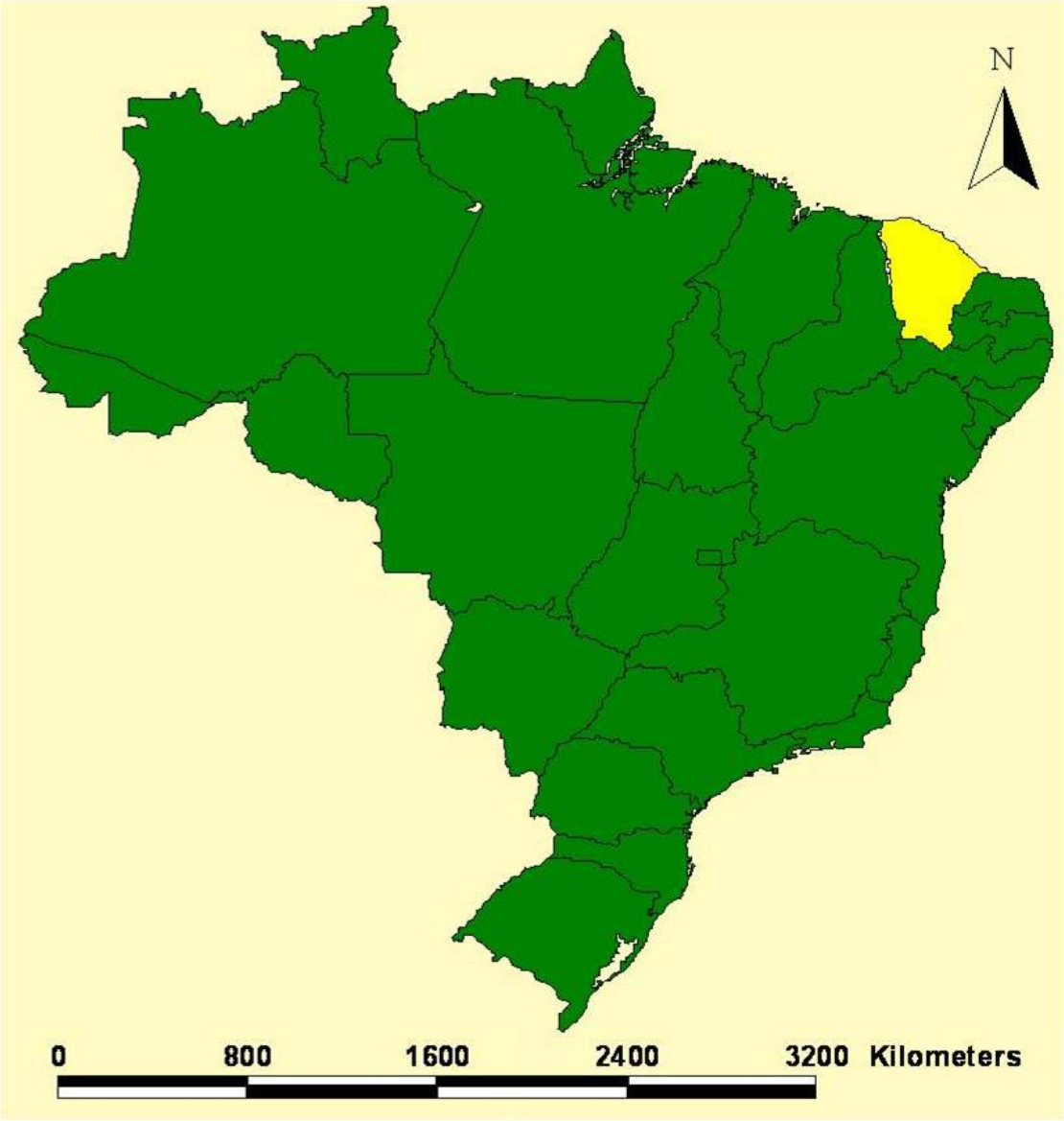

Figure 8.1: Location of Ceará State (yellow), in the northeastern region of Brazil

for leprosy, the Brazilian Ministry of Health's Sistema de Informação de Agravos de Notificação, or SINAN. This database contains an active registry for diagnosed cases of leprosy, and includes demographic, geographic, and clinical information for each patient. Access to this database was made available through collaboration with the Ceará coordinator for leprosy control at the Department of Community Health in the Faculty of Medicine at the Federal University of Ceará.

Population data for each municipality of Ceará State for use in the calculation of incidence rates was obtained from the Sistema IBGE de Recuperação Automatica (SIDRA, 2007). Spatial data for each municipality (n=184), including associated shapefiles, were obtained from the Instituto Brasileiro de Geografia e Estatística (IBGE, 2008).

Detection of clusters was carried out using the scan statistic in the SaTScan suite of software (Kulldorf, 2006). As mentioned earlier, this method of cluster detection uses a mobile circular window that includes different sets of neighboring areas at different positions. The radius of the circular window varies from zero to a maximum radius at each position such that the window never includes more than 50% of the total population at risk. This method allows detection that is flexible in both location and size (Onozuka & Hagihara, 2007). For this study, a retrospective spatial analysis was performed using the *Poisson* probability model, scanning for areas of either high or low rates. To test for statistical significance, the number of *Monte Carlo* replications was set to 9999, and only clusters with a statistical significance of $p < 0.05$ were reported. Two separate cluster detection analyses were run through SaTScan to produce two sets of clusters and relative risks: 1) a purely spatial analysis using the spatial scan statistic; and 2) a temporal-spatial analysis using the space-time scan statistic.

Results from each of the cluster detection analyses were imported into a GIS using the ArcView suite of software (ESRI, 1999). Clusters and relative risks were cartographically depicted and displayed using choropleth maps.

8.3 Results

Table 8.1 is a summary of clusters detected by the purely spatial analysis. Figure 8.2 is a cartographic depiction of these clusters. In total, the purely spatial analysis detected three clusters. The most likely cluster included 11 municipalities and contained 6,782 observed cases and 2,399 expected cases (RR = 2.827, $p = 0.0001$). Two secondary clusters were detected: the first including 120 municipalities containing 9,157 observed cases and 14,598 expected cases (RR = 0.473, $p = 0.0001$), and the second containing one municipality with 11,633 observed cases and 9,031 expected cases (RR = 1.288, $p = 0.0001$). Figure 8.3 is a choropleth map of the relative risks for each municipality as calculated by the spatial scan statistic.

Table 8.1: Significant high and low rate purely spatial clusters for leprosy in Ceará State, 1995-2006

Cluster	No. of Municipalities in Cluster	Observed Cases in Cluster	Expected No. of Cases	Cluster Relative Risk	High or Low Risk	P-value
1	11	6,782	2,399	2.827	High	0.0001
2	120	9.157	14,598	0.473	Low	0.0001
3	1	11,633	9,031	1.288	High	0.0001

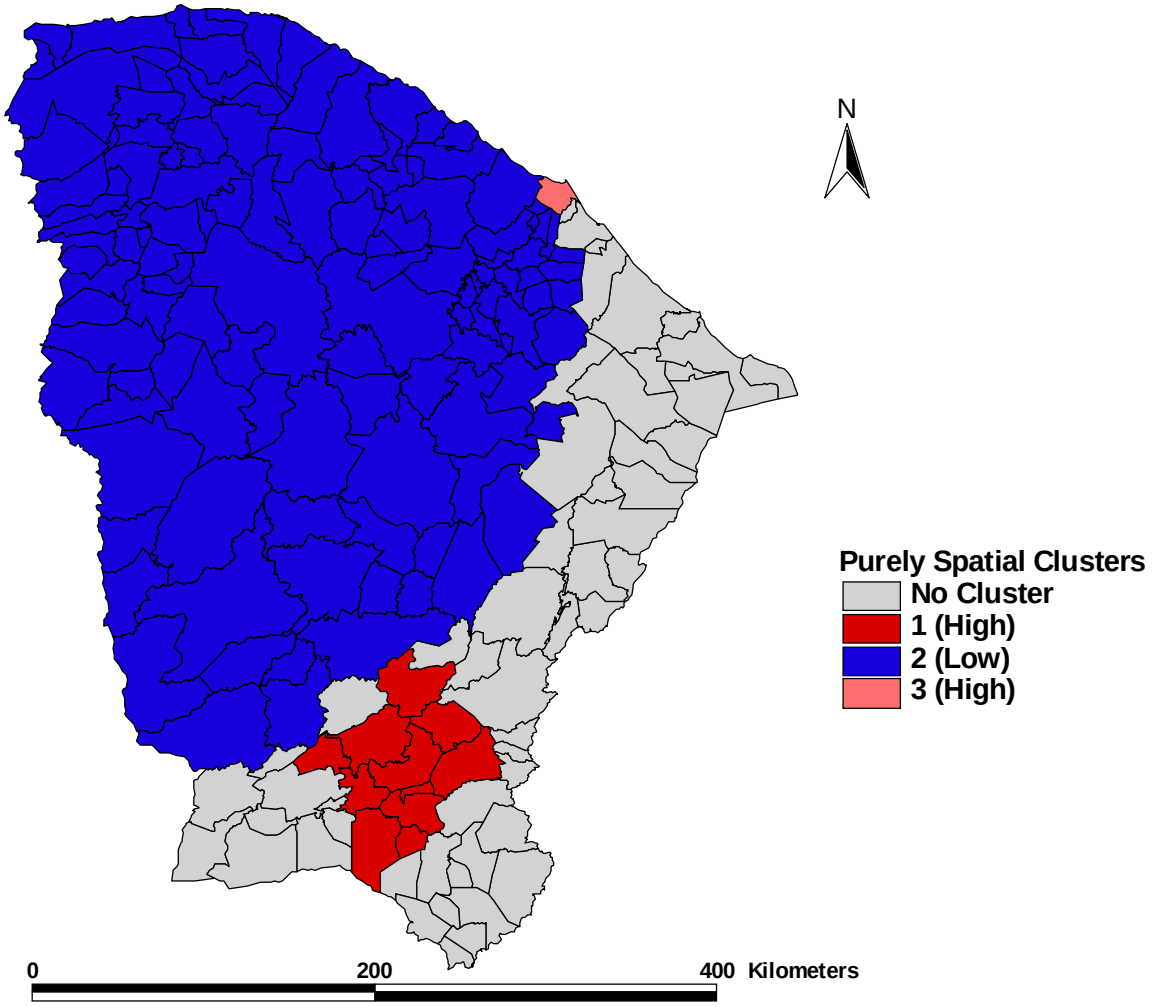

Figure 8.2: Purely spatial clusters of leprosy, Ceará State, Brazil, 1995-2006

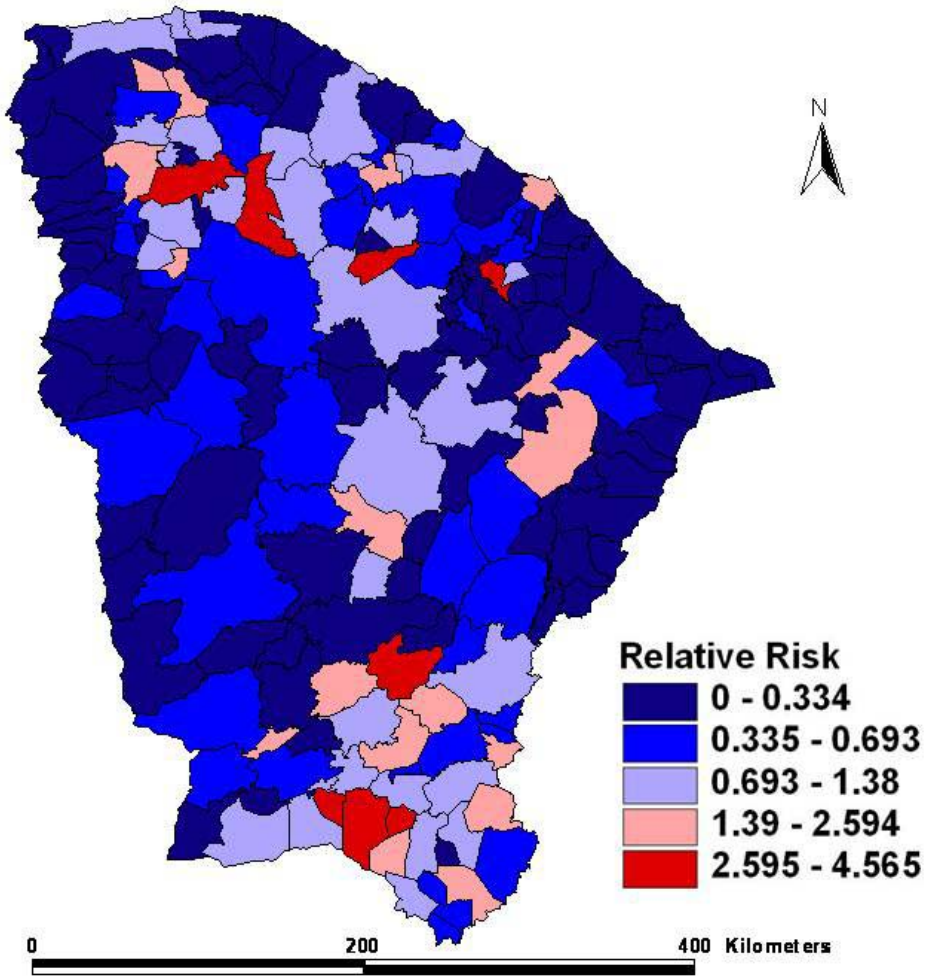

Figure 8.3: Relative Risk of Leprosy by municipality of Ceará State, Brazil, as calculated by the purely spatial scan statistic

Table 8.2 is a summary of clusters detected by the temporal-spatial analysis. Figure 8.4 is a cartographic depiction of these clusters. In total the temporal-spatial analysis detected four clusters. The most likely cluster included 3 municipalities from April 1995 to March 2000 and contained 2,546 observed cases and 579 expected cases (RR = 4.702, $p = 0.0001$). Three secondary clusters were detected: the first including one municipality from April 1995 to March 2004 and containing 1,349 observed cases and 300 expected cases (RR = 4.660, $p = 0.0001$); the second containing 71 municipalities from April 1995 to April 2000 with 1,794 observed cases and 3,863 expected cases (RR = 0.432, $p = 0.0001$); and the third containing a single municipality from April 2000 to March 2005 with 5,603 observed cases and 4,187 expected cases (RR = 1.412, $p = 0.0001$). Figure 8.5 is a choropleth map of the relative risks for each municipality as calculated by the spatial scan statistic.

Table 8.2: Significant high and low rate temporal spatial clusters for leprosy in Ceará State, 1995-2006

Cluster	No. of Municipalities in Cluster	Observed Cases in Cluster	Expected No. of Cases	Cluster Relative Risk	High or Low Risk	P-value
1	3	2,546	579	4.702	High	0.0001
2	1	1,349	300	4.660	High	0.0001
3	71	1,794	3,863	0.432	Low	0.0001
4	1	5,603	4.187	1.412	High	0.0001

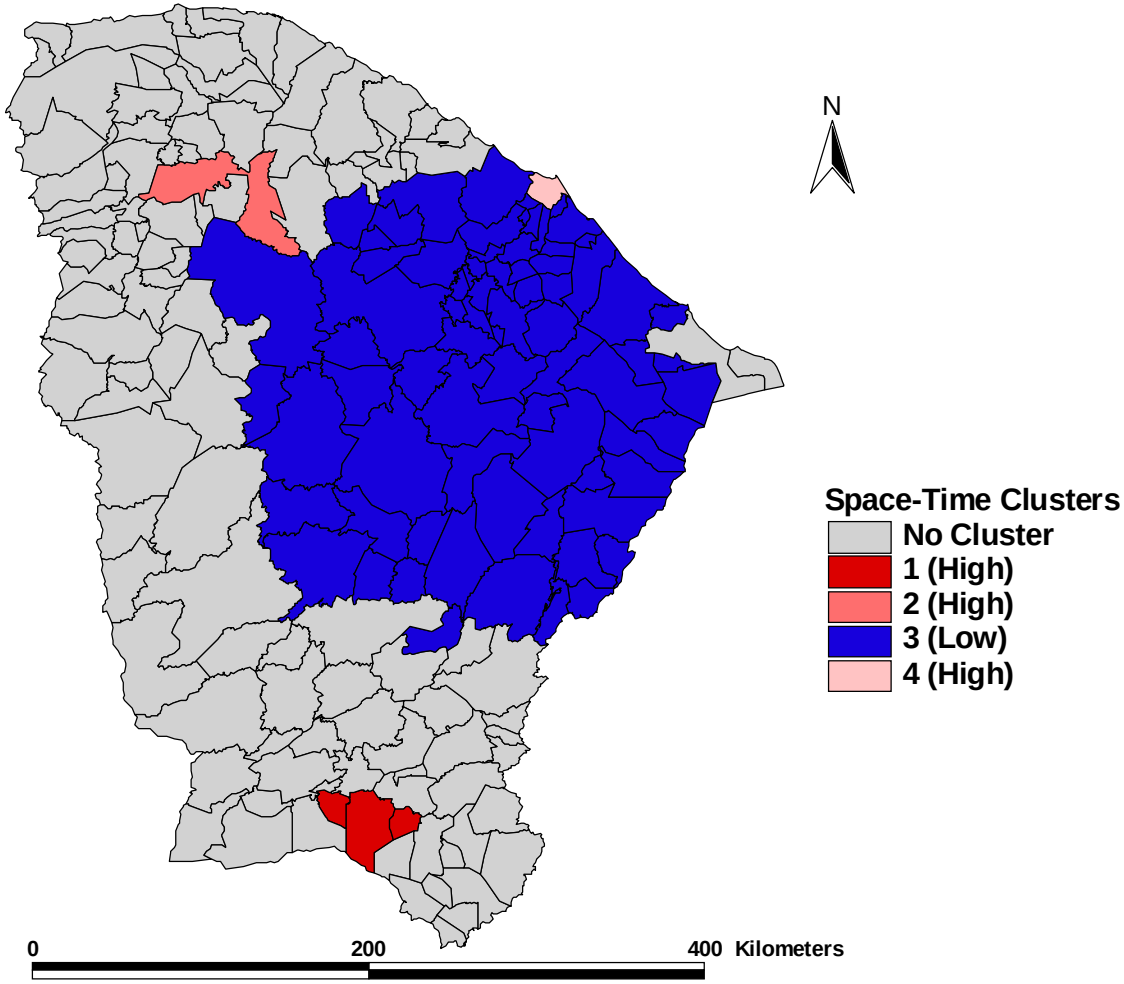

Figure 8.4: Spatial-temporal clusters of leprosy within Ceará State, Brazil, 1995-2006

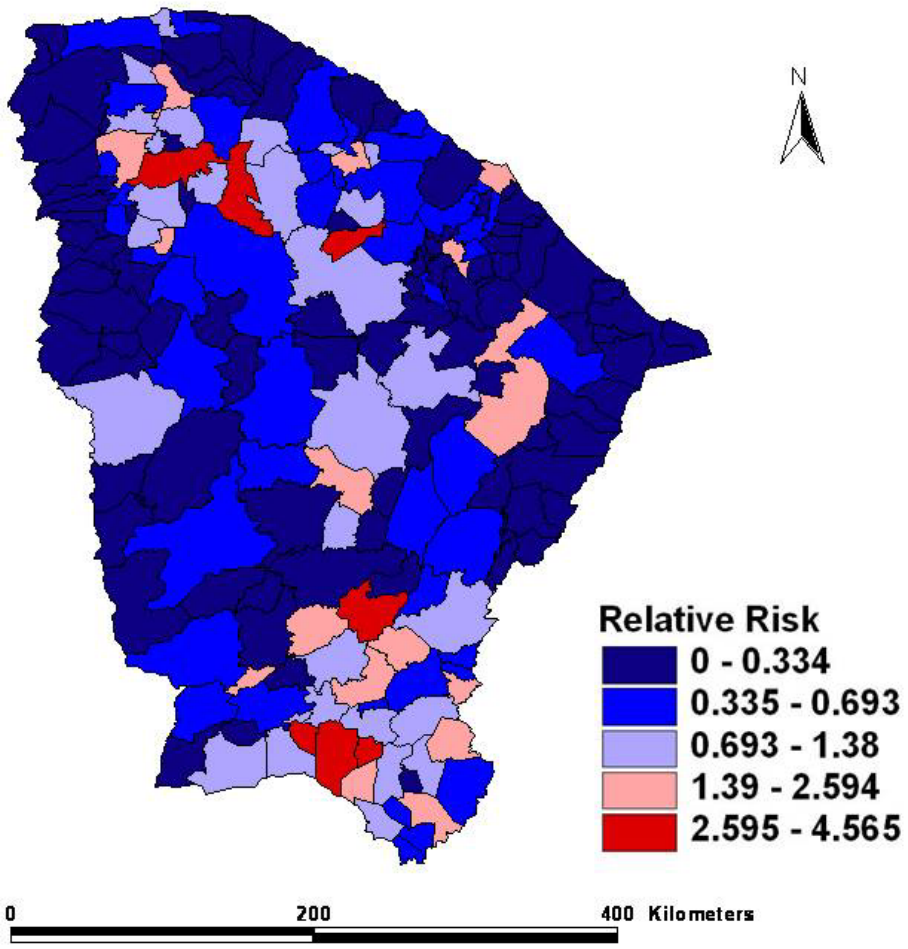

Figure 8.5: Relative risk for leprosy within municipalities of Ceará State, Brazil, as calculated by the space-time scan statistic

8.4 Discussion

This study has confirmed the findings by Montenegro et al. (2004) that the spatial distribution of leprosy in the state of Ceará is extremely heterogenous. Through the use of the spatial scan statistic, this study was able to identify clusters of high incidence rates in the northeastern municipality of Fortaleza and in the south-central municipalities of Nova Olinda, Crato, and Juazeiro do Norte. With the inclusion of a space-time analysis, additional clusters of high incidence in the north-central municipalities of Sobral and Paramoti and in the south-central municipality of Iguatu were found.

In comparison to the study by Montenegro et al. (2004), which examined clustering of leprosy incidence in Ceará State for cases diagnosed between 1991 and 1999, this study found nearly identical clustering around the south-central and north-central portions of the state. This study, however, has also identified Fortaleza as a hot spot. The fact that this study overlapped Montenegro's by five years, also included the following five years, and found similar results could be evident that the progress to leprosy elimination in Ceará State is proceeding at a slow rate or that strategies of control programs have not changed drastically in the last decade to illicit geographic variation in incidence.

For the highly populated municipalities of Fortaleza and Juazeiro do Norte, spatial clustering of cases may be occurring because of the link between leprosy and crowding, social inequality, or the urban environment—or could be due to better access to health services in urban areas (Kerr-Pontes, 2004). Another explanation for the clustering of cases around population centers is the massive urban migration that has been occurring in Ceará within the last two decades (Montenegro et al., 2004). These population movements contribute to suburban shantytowns, or favelas, that tend to maintain some characteristics of rural areas such as poor

housing, lack of sanitation, growing gardens, and keeping animals. These environments are thought to provide a setting suitable for *Mycobacterium leprae* and hold an increased number of individuals susceptible to infection. In order to better understand this phenomenon, it may be necessary to employ spatial analysis at smaller scales (i.e., within barrios or favelas) to determine whether or not clustering is occurring within certain urbanized areas (Lapa et al., 2006).

The heterogeneous distribution of cases and subsequent clustering may also be due to differences in municipal surveillance systems of varying quality (Montenegro et al., 2004). Municipalities that are at economic advantages over others tend to have better health services and consequently detect new cases of leprosy more efficiently.

The inclusion of a temporal component to this study allowed the identification of an additional 'hot spot' that was not identified in the purely spatial analysis. Relative risks, however, remained the same in both the temporal-spatial and purely spatial analysis. Most leprosy studies that use a temporal component in their analysis do so with caution because of the difficulty with operational issues that makes the temporal component of leprosy reporting somewhat skewed. Nonetheless, geospatial analyses and surveillance should try to make the best use of temporal data, as it has the potential to provide valuable clues about the changes in incidence over time as a result of the alteration of control program strategies over time.

The use of spatial analysis and GIS in the detection of disease clusters warrants more attention from public health control programs. No doubt as these technologies develop, they will become more suited for application in the field (i.e., by healthcare workers), their interpretation will become more user-friendly, and access to them will become more readily available.

CHAPTER 9. SPATIAL AUTOCORRELATION OF LEPROSY IN RONDONIA STATE, 1996-2005

9.1 Introduction

Located in the far southwestern region of the Brazilian Amazon (Figure 9.1), Rondonia State has been the repeated subject of many recent studies because of its quickly changing environmental and demographic landscapes (De Barris Ferraz et al., 2006). Rondonia has been targeted by researchers who are interested in determining the effects of deforestation, increased carbon flux, degrading water quality, and deteriorating socioeconomic conditions (De Barris Ferraz et al., 2006). There is little doubt that increased development and human migration into this state is having a detrimental effect on the land, its flora and fauna, and its human inhabitants.

One area of particularly burgeoning research in Rondonia focuses on the effects of anthropogenic change on human health (Camargo et al., 1996; Camargo et al., 1999; Oliveira et al., 2003). In Rondonia, environmental change due to anthropogenic activities within the last 40 years have caused unprecedented increases in disease incidence in both rural and urban areas of the state (Takken et al., 2003). In particular, incidence of vector-borne diseases such as malaria, leishmaniasis, and Chagas has risen dramatically—a phenomenon most likely due to both increased migration and environmental changes such deforestation and urban development.

Leprosy is hyperendemic in Rondonia State, with detection rates for 2006 well above the national average at 8.08 cases per 10,000 population (DATASUS, 2007). Like many other diseases in Rondonia, leprosy has witnessed a dramatic rise in incidence in the last three decades, despite aggressive control programs. Seemingly far away from achieving elimination targets, Rondonia is in desperate need of new applications and strategies for the detection, treatment, and sustained surveillance of leprosy.

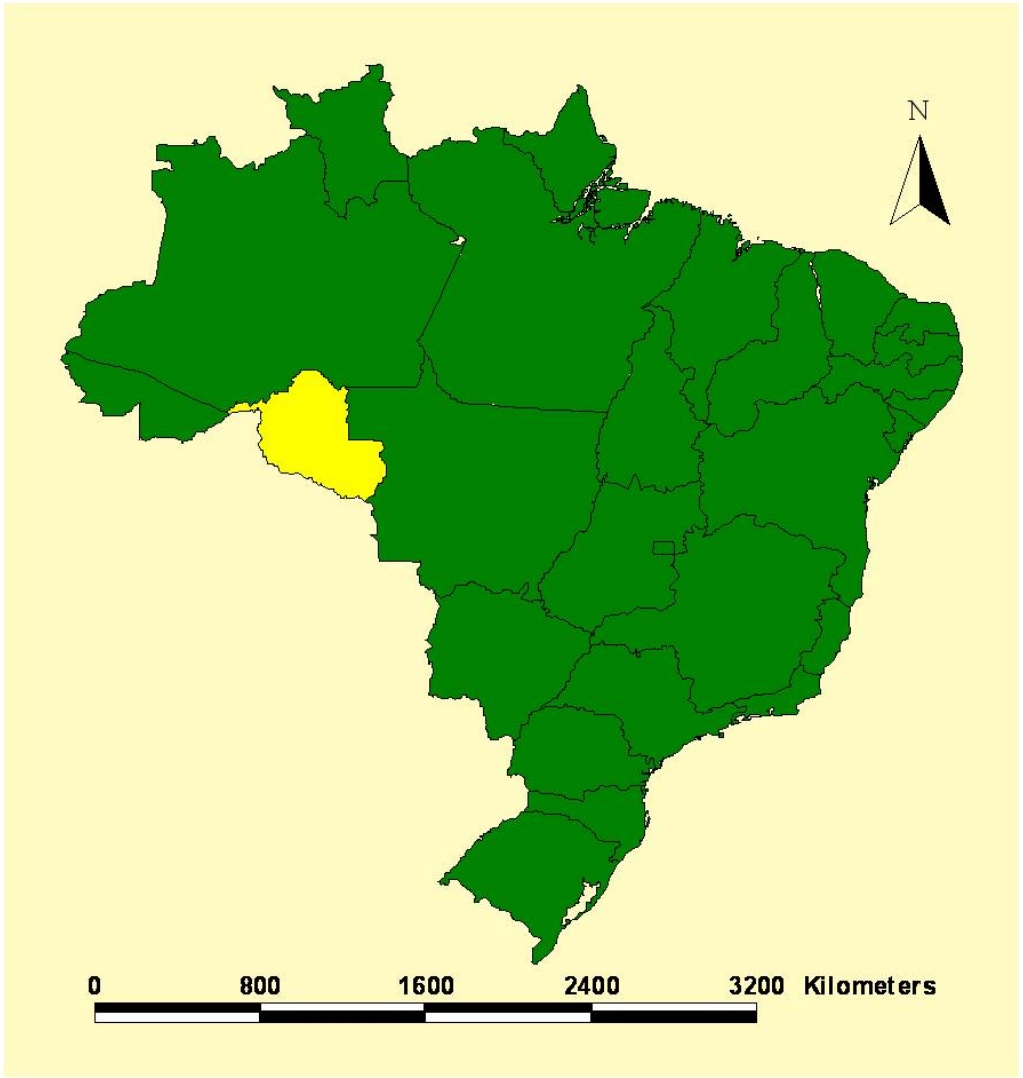

Figure 9.1: Rondonia State (yellow), located in the tropical southwestern Amazon region of Brazil

Similar to what is seen in Ceará State, Rondonia's pattern of leprosy incidence represents a heterogeneous distribution with areas of high and low endemicity (Figure 9.2). However, the heterogeneous nature of this distribution is more apparent in Rondonia than Ceará; low-incidence municipalities have rates around 0.54 cases/10,000 population and high-incidence municipalities have rates around 53 cases/10,000 population.[2] There is no doubt that these variations in rates are attributable to various heterogeneously distributed geographic and demographic factors.

In a method similar to the previous chapter's, this study's objectives were to detect and quantify spatial patterns of leprosy incidence in Rondonia State through the identification of clusters that represent either high or low risk for leprosy and to map probable transmission risk as calculated through spatial statistical methods. Two methods were used to identify clusters in this study: 1) a purely spatial analysis that does not take time into consideration; and 2) a space-time analysis that considers the effects of space as well as time on leprosy incidence.

9.2 Materials and Methods

As mentioned previously, Rondonia is one of the nine states of the Amazonian region of Brazil, located in the southwestern part of the region near the Bolivian border and covering an area of 237,576, 167 km^2 (CIA, 2006). The state is divided into 52 municipalities, and has a total population of about 1,534,594 people, a number that has grown substantially in recent years because of migration into the state (IBGE, 2008; Ichii et al., 2005).

Case data on patients diagnosed with leprosy in Rondonia State for the period of 1 January 1996 to 31 December 2005, was obtained from the ongoing national population-based

[2] It should be noted that incidence rates calculated by this study, which used private case-specific notifications for leprosy, are about 3-10% higher than those given to the public through DataSUS.

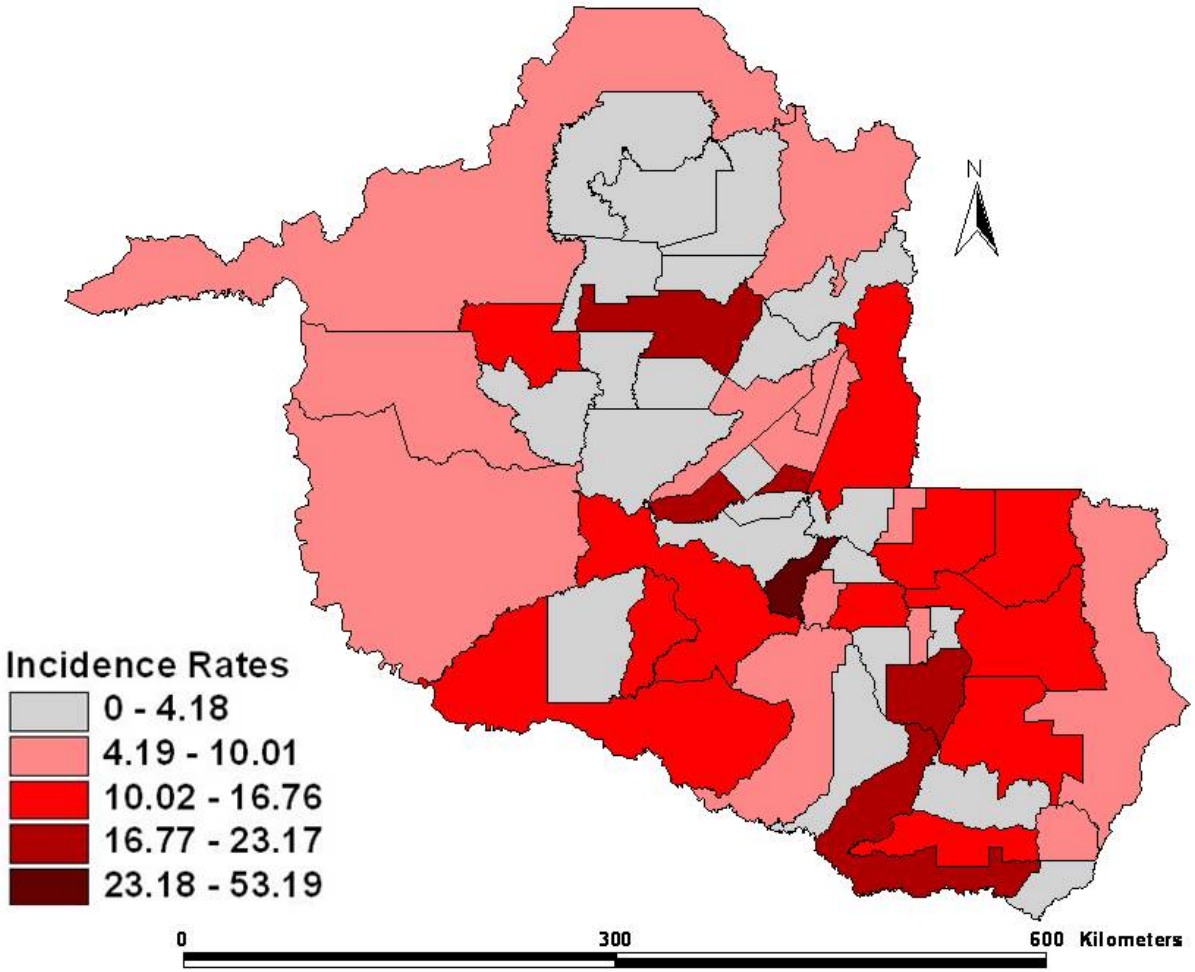

Figure 9.2: Leprosy incidence rates for Rondonia State, 2005. Grey municipalities represent those below the leprosy elimination target.

surveillance system for leprosy, the Brazilian Ministry of Health's Sistema de Informação de Agravos de Notificação, or SINAN. This database contains an active registry for diagnosed cases of leprosy, and includes demographic, geographic, and clinical information for each patient. Access to this database was made available through collaboration with the coordinator for leprosy control for Rondonia State at the Department of Community Health in the Faculty of Medicine at the Federal University of Ceará.

Population data for each municipality of Rondonia for use in the calculation of incidence rates was obtained from the DataSUS (DATASUS, 2007). Spatial data for each municipality (n=52), including associated shapefiles, were obtained from the Instituto Brasileiro de Geografia e Estatística (IBGE, 2008). Detection of clusters was carried out using the scan statistic and the SaTScan suite of software (Kulldorf, 2006) in a similar method to that defined in the previous chapter.

9.3 Results

In total the purely spatial analysis detected four clusters within Rondonia State. The most likely cluster included a single municipality and contained 2,155 observed cases and 795 expected cases (RR = 3.015, $p = 0.0001$). The second cluster included six municipalities and contained 2,303 observed cases and 3,899 expected cases (RR = 0.512, $p = 0.0001$). The third cluster included 13 municipalities and contained 5,366 observed cases and 3,858 expected cases (RR = 1.626, $p = 0.0001$). The fourth cluster included four municipalities with 377 observed cases and 820 expected cases (RR = 0.445, $p = 0.0001$). Table 9.1 is a summary of clusters detected by the purely spatial analysis. Figure 9.3 is a cartographic depiction of these clusters. Figure 9.4 is a choropleth map of the relative risks for each municipality as calculated by the spatial scan statistic.

The space-time analysis detected four clusters within Rondonia State. The most likely cluster included a single municipality from 1 January 1999 to 31 December 2003, and contained 1,152 observed cases and 394 expected cases (RR = 3.070, $p = 0.0001$). The second cluster included six municipalities from 1 January 2001 to 31 December 2005, and contained 1,069 observed cases and 2,117 expected cases (RR = 0.512, $p = 0.0001$). The third cluster included six municipalities from 1 January 1996 to 31 December 2000, and contained 1,055 observed cases and 524 expected cases (RR = 2.094, $p = 0.0001$). The fourth cluster included 20 municipalities from 1 January 2000 to 31 December 2004, with 1,083 observed cases and 1,777 expected cases (RR = 0.577, $p = 0.0001$). Table 9.2 is a summary of clusters detected by the space-time analysis. Figure 9.5 is a cartographic depiction of these clusters. Figure 9.6 is a choropleth map of the relative risks for each municipality as calculated by the spatial scan statistic.

9.4 Discussion

This analysis was able to confirm and quantify the heterogeneous spatial structure of leprosy incidence in Rondonia State, Brazil, through spatial analysis and the detection of significant clusters. Two analyses were performed: one that used the spatial scan statistic to detect purely spatial clusters, and the other that used the space-time scan statistic to detect temporal-spatial clusters. Both methods detected two hot spots and two cold spots of leprosy incidence. However, the spatial locations of these hot spots differed between the two analyses. The purely spatial analysis identified hot spots in the northern center and eastern regions of the state and cold spots in the western and northern regions of the state. The space-time analysis identified hot spots in the south-center and northeast regions of the state and cold spots in the north-center and southeast regions of the state. Compared to the purely spatial analysis, relative risk for leprosy was seen to slightly increase in all regions when calculated by the space-time analysis.

Table 9.1: Significant high and low rate purely spatial clusters for leprosy in Rondonia State, 1996-2005

Cluster	No. of Municipalities in Cluster	Observed Cases in Cluster	Expected No. of Cases	Cluster Relative Risk	High or Low Risk	P-value
1	1	2,155	795	3.015	High	0.0001
2	6	2,303	3,899	0.512	Low	0.0001
3	13	5,366	3,858	1.626	High	0.0001
4	4	377	820	0.445	Low	0.0001

Table 9.2: Significant high and low rate purely spatial clusters for leprosy in Rondonia State, 1996-2005

Cluster	No. of Municipalities in Cluster	Observed Cases in Cluster	Expected No. of Cases	Cluster Relative Risk	High or Low Risk	P-value
1	1	1,152	394	3.070	High	0.0001
2	6	1,069	2,117	0.512	Low	0.0001
3	6	1,055	524	2.094	High	0.0001
4	20	1,083	1,777	0.577	Low	0.0001

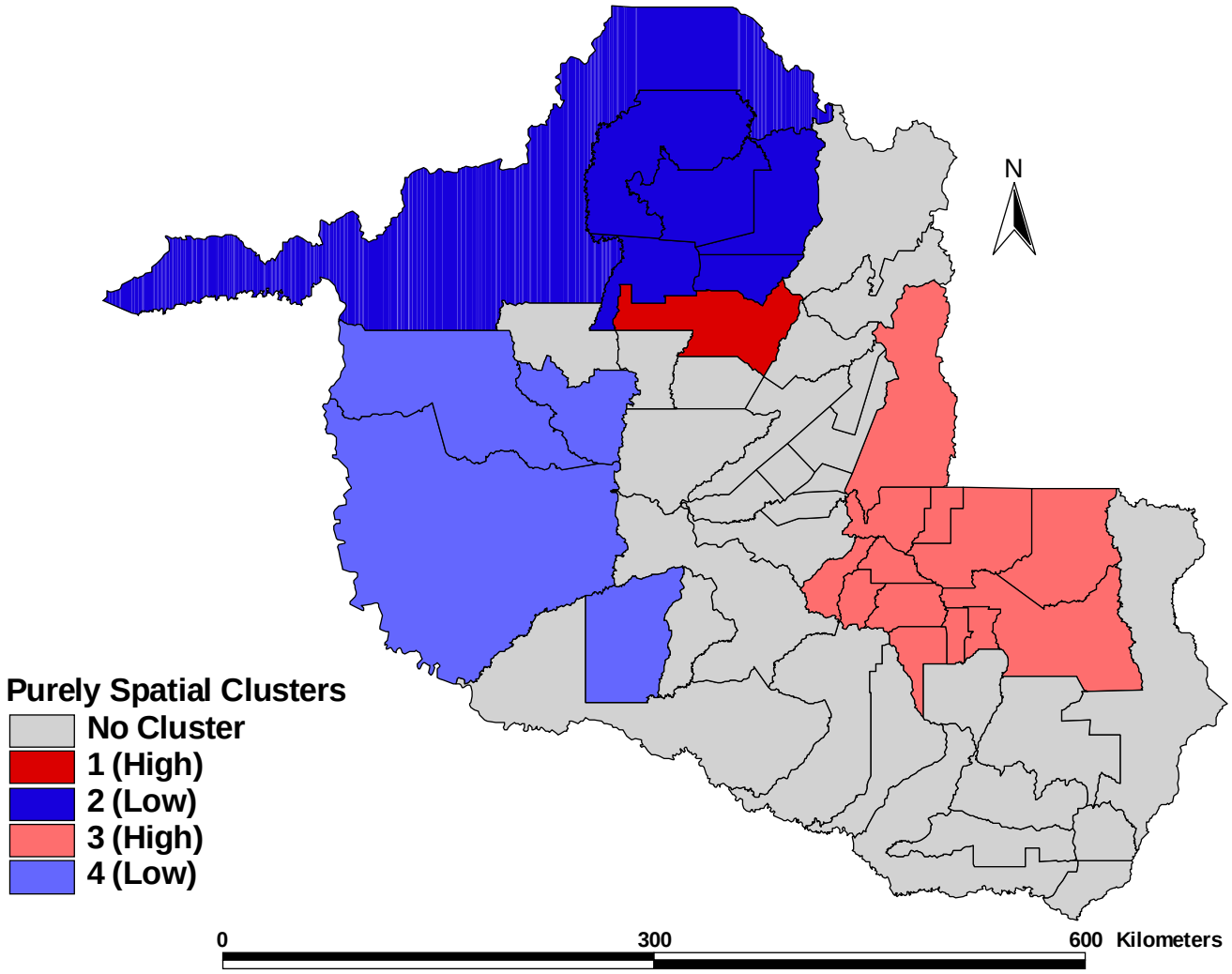

Figure 9.3: Purely spatial clusters of leprosy, Rondonia State, Brazil, 1996-2005

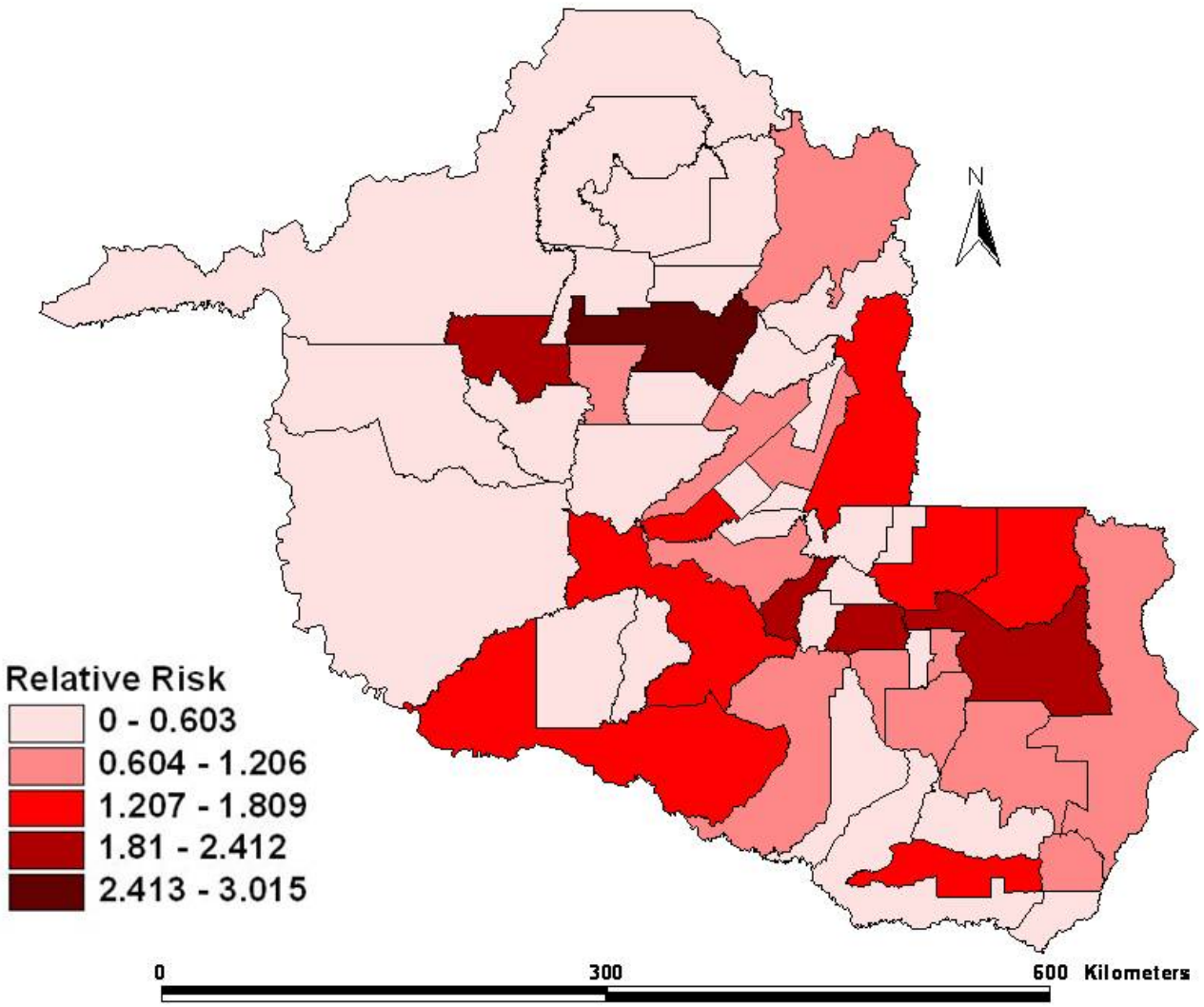

Figure 9.4: Relative risk for leprosy within municipalities of Rondonia State, Brazil, as calculated by the purely spatial scan statistic

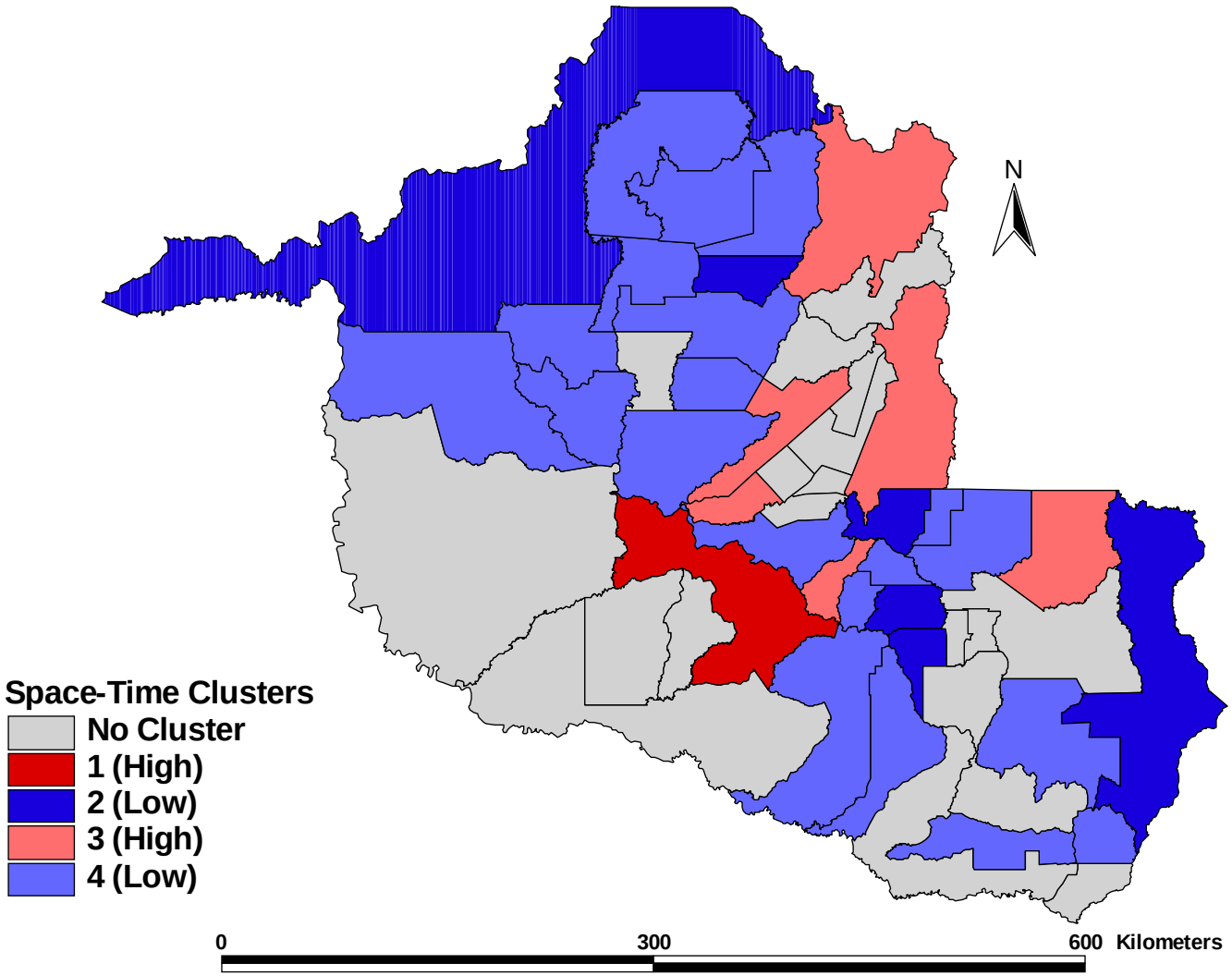

Figure 9.5: Space-time clusters of leprosy, Rondonia State, Brazil, 1996-2005

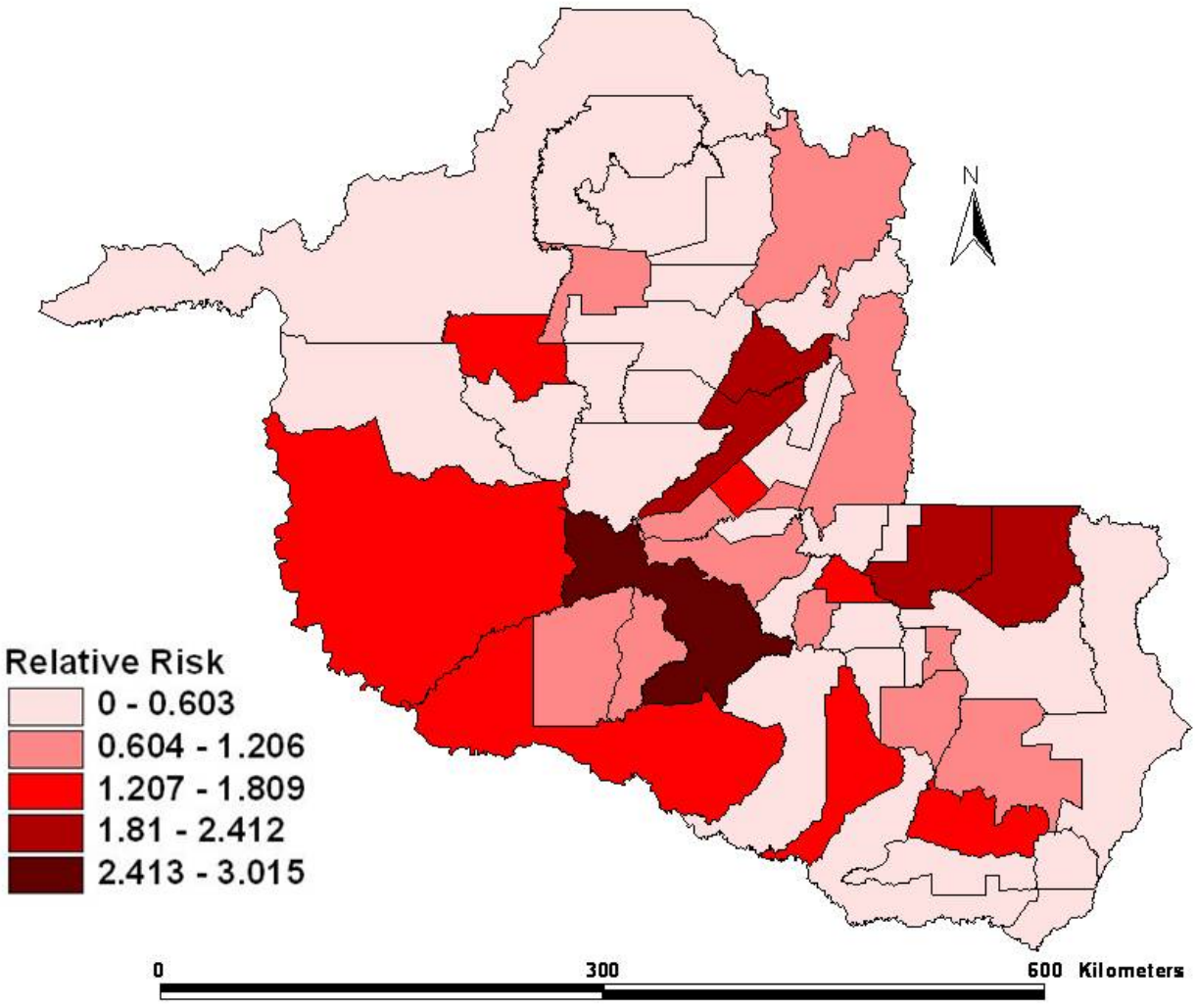

Figure 9.6: Relative risk for leprosy within municipalities of Rondonia State, Brazil, as calculated by the space-time spatial scan statistic

Because of the differences between these two analyses, it can be inferred that time plays a key role in the spatial distribution of leprosy incidence in Rondonia State, a fact that has also been eluded to in studies of leprosy incidence in other Brazilian states (Matos, 2004; Moet et al., 2006; Montenegro et al., 2004).

9.5 Conclusions

This chapter has detected spatially significant clustering of leprosy in Rondonia State using the scan statistics offered through SatScan (Kulldorf, 2006). Comparing the results to those found in Chapter 8, the distribution of leprosy incidence in Rondonia appears to be less heterogeneous than that in Ceará State, and leprosy clusters in Rondonia appear to be larger with more regular, non-dispersed shapes. The reasons for these differences can be: 1) demographic—the population of Ceará State is much larger and therefore reflects different densities, age structures, and socioeconomic variation; and 2) environmental—the geography of Rondonia is nearly opposite from Ceará State ecologically. Both states, however, have witnessed large changes in both environment and demographics in recent years through human migration and climate change.

One of the limitations of this study is that it did not employ covariate analysis to associate risk factors with the spatial distributions. Because of this, no ecological assumptions about the epidemiology of leprosy except for basic space and time inferences can be made by this study. Future studies may wish to utilize the vast quantities of remotely sensed data or demographic data obtained by other studies to integrate into a GIS and spatial analysis for the purpose of ecological-epidemiological investigation (De Barris Ferraz et al., 2006).

There is no doubt that more research is needed to determine factors that influence the transmission of leprosy and the impact that interventions play in its epidemiology (Visschedijk et al., 2000). Rondonia State, with its dynamic environmental and demographic landscape, provides a unique opportunity to examine the effects of massive anthropogenic change on leprosy incidence. Future studies should build on the methods and results of this study in order to better understand the factors associated with the heterogeneous spatial structures of leprosy in Rondonia State. No doubt that such information, combined with geospatial techniques like the ones used in this study, would aid in the surveillance and control of leprosy in Rondonia State.

CHAPTER 10. USE OF OBSERVED VERSUS STATE AND NATIONAL-LEVEL ADJUSTED INCIDENCE RATES TO DETECT SPATIAL CLUSTERS OF LEPROSY IN RONDONIA STATE, BRAZIL, FROM 1996-2005

10.1 Introduction

As previously mentioned, since the attainment of global elimination of leprosy to a level below one case per 10,000 population worldwide in 2000, the World Health Assembly has proposed a "Final Push" to achieve the same prevalence at the national level (WHA, 1991). This is particularly relevant for the five endemic countries that now contain over 90% of leprosy prevalence worldwide—Brazil, India, Madagascar, Mozambique, and Nepal (WHO, 2003). However, at the end of 2006, Brazil still had not come close to the WHA's elimination target for leprosy, with a national incidence rate of 2.11 cases per 10,000 population. This number sounds near to the elimination target, but it must be remembered that it is an average—and therefore does not reflect geographic variation in incidence rates. When considering that the country of Brazil covers a land area of around 8,511,965 km^2 (only slightly smaller than the United States) and has a population of over 190 million, this number becomes more meaningless when trying to determine how close Brazil is to meeting elimination targets.

At a smaller scale than national, rates vary dramatically from the north region (5.77) to the central-west (4.57) to the northeast (2.95) to the southeast (0.96) to the south (0.65) (DATASUS, 2007). When viewed within regional subdivisions, the southern temperate regions of Brazil have met elimination targets, while the northern tropical regions are well above. As expected, when continuing to compare rates at smaller and smaller subdivisions, such as state, municipality, or even barrios-levels, incidence rates become even more variable, with clear cut spatial variation in areas that are below and above the elimination target. For instance, in Ceará

State, Brazil, some municipalities have incidence rates less than 0.1/10,000, while others have rates as high as 25/10,000 (Montenegro et al., 2004).

No matter what the spatial subdivision, the demographic and geographic structures of any population will vary considerably from one area to another. These structures can include age, gender, race, education, and socio-economics. When investigating health outcomes, these elements of a population structure can influence the relative risk of a population for developing a disease. For instance, as discussed earlier, age, race, and poverty can be important indicators of leprosy incidence (Kerr-Pontes, 2004). As can be concluded, a portion of observed leprosy incidence may then be contributed to demographic and geographic variation across areas. How, therefore, can differences in rates be compared across different geographic areas?

One method frequently used in public health research when reporting data is to standardize or 'adjust' rates for demographic variation (Liu et al., 2006). For instance, in the United States cancer mortality rates are often age-adjusted so that rates of cancer can be compared across communities with different age structures (NYSDH, 2007). This process makes sense considering that a community with a higher number of older individuals will have higher rates of cancer than one with a higher number of younger individuals. If a comparison between these two communities only involved observed rates, then the association between exposure and disease would be confounded by age. Adjusting rates is one way to statistically remove this type of confounding.

Rates are usually adjusted to a standard population, which for the United States usually involves the Standard Million Distribution of the total population, figures that are based on the 1940, 1970, or 2000 U.S. censuses (PDH, 2007). Other standard populations include the WHO-issued World Standard Population, the Canadian Standard Population for 1991 and 1996, and the

European Standard Population (NCI, 2007). Within these population datasets, each demographic or geographic category is listed with its respective population. Age-adjustments are calculated by first multiplying the category-specific observed rate by the standard population for that category (PDH, 2007). The resultant number is the number of cases that are 'expected' to occur in each category if the specific death rates had prevailed within the standard population per unit time. Adjusted rates are then found by summing the number of expected deaths and dividing by the total standard population.

This study investigated the variation in leprosy clustering at the municipality level of Rondonia State, Brazil, when observed and adjusted rates were used in the calculation of clusters. Rates in this study were adjusted for age, gender, education, and zone (urban/rural) using both a national (Brazilian) standard population and a state-level (Rondonian) standard population. The purpose was to determine whether or not rate adjustment plays a role in cluster detection, and whether or not such a process should be used in routine spatial comparisons of rates across various geographic subdivisions in the public health surveillance of leprosy.

10.2 Materials and Methods

The study area of Rondonia is described in the previous chapter. Data on incidence of leprosy for each municipality of Rondonia (n=54) were derived from an ongoing national population-based surveillance system for leprosy, the Brazilian Ministry of Health's Sistema de Informação de Agravos de Notificação, or SINAN. This database contains an active registry for diagnosed cases of leprosy, and includes demographic, geographic, and clinical information for each patient (n=13,841). Though non-specific aggregated data is available through the world wide web, specific data with the respective desired variables (municipality of residence, age, gender, education, and zone) for each case was made available through collaboration with the

leprosy coordinator for Rondonia State at the Department of Community Health in the Faculty of Medicine at the Federal University of Ceará.

Observed incidence for each municipality was calculated by counting the number of cases that occurred per municipality per year and dividing by the respective municipality's population for that year. Municipality population data for incidence calculation was obtained from DATASUS (2007).

Two standard populations were used to calculate two adjusted rates for each municipality. The first was a Brazilian Standard Population, based on the 2000 Brazilian census, and the second was a Rondonian Standard Population, also based on the 2000 Brazilian census. This information can be accessed by the public via the web through the Sistema IBGE de Recuperação Automática (SIDRA, 2007).

Spatial data for use in GIS relating to the 54 municipalities of Rondonia were obtained from the Instituto Brasileiro de Geografia e Estatística (IBGE, Brazilian Institute of Geography and Statistics database).

Categories for adjustment included age, gender, education, and zone. To limit the size of datasets for this study, each municipality's population was divided into four age groups (<20, 20-39, 40-59, and 60<), two genders (M/F), six education levels according to years of instruction (<1, 1-3, 4-7, 8-11, >11, and unknown) and two zones (U/R). This requires that datasets for the Brazilian and Rondonian Standard Populations have 96 (=4 X 2 X 6 X 2) categories, while the dataset containing incidence information for each municipality be divided into 5,184 (=54 X 4 X 2 X 6 X 2) categories. Both Excel and ArcView GIS were used to calculate adjusted rates. Calculation of adjusted rates proceeded as shown in Table 10.1.

Table 10.1: Example of Method of Rate Adjustment for Ariquemes Municipality

Municipality (n=54)	Category	Category-Specific Incidence Rate (per 10,000)		Standard Population (Brazil)		Expected Cases in Standard Population
Ariquemes	MUAA[3]	10.78	X	2,815,620	=	3,035
Ariquemes	MUAB	8.56	X	4,176,905	=	3,575
.	.	.		.		.
.	.	.	.	.		.
Total:					∑	**1,500,176**
Adjusted Rate = 1,500,176 / 169,799,170 = 0.0884 * 10,000 = 8.84						

Spatial clusters for observed, state-adjusted, and national-adjusted rates were calculated using the SaTScan software (Kulldorf, 2006). Results from SaTScan were imported into ArcView and merged with the associated shapefile in order to create cartographic depictions of clusters. In addition to mapping the detected clusters, choropleth maps showing relative risks for each municipality were created.

10.3 Results

When using observed leprosy rates, the SaTScan software detected four clusters.[4] The most likely cluster contained one municipality with 2,037 observed cases and 789 expected cases (RR = 2.855, $p = 0.0001$). The second cluster contained six municipalities with 2,215 observed

[3] MUAA = **M**ale, **U**rban, Age group **A** (<19), Education level **A** (<1 year)
[4] These clusters will vary from those detected in the previous chapter because this study was dependent on a more complete dataset that had to include age, gender, education, and zone for each case.

cases and 3,724 expected cases (RR = 0.518, $p = 0.0001$). The third cluster contained 13 municipalities with 5,221 observed cases and 3,765 expected cases (RR = 1.621, $p = 0.0001$). The final cluster contained three municipalities with 298 observed and 712 expected cases (RR = 0.406, $p = 0.0001$). These clusters are summarized in Table 10.2 and depicted in Figure 10.1. Relative risks per municipality as calculated by observed incidence rates are shown in Figure 10.2

When using incidence rates adjusted to the Rondonia State Standard Population, the SaTScan software detected five clusters. The most likely cluster contained seven municipalities with 4,252 observed cases and 1,032 expected cases (RR = 4.121, $p = 0.0001$). The second cluster contained 20 municipalities with 2,582 observed cases and 5,463 expected cases (RR = 0.352, $p = 0.0001$). The third cluster contained one municipality with 1,522 observed cases and 414 expected cases (RR = 4.005, $p = 0.0001$). The fourth cluster contained seven municipalities with 558 observed cases and 1,699 expected cases (RR = 0.328, $p = 0.0001$). The fifth cluster contained three municipalities with 1,957 observed cases and 1,260 expected cases (RR = 1.645, $p = 0.0001$). These clusters are summarized in Table 10.3 and depicted in Figure 10.3. Relative risks per municipality as calculated by state-adjusted incidence rates are shown in Figure 10.4.

When using incidence rates adjusted to the Brazilian (National) Standard Population, the SaTScan software detected five clusters. The most likely cluster contained seven municipalities with 469,849 observed cases and 117,724 expected cases (RR = 5.355, $p = 0.0001$). The second cluster contained 20 municipalities with 263,232 observed cases and 580,028 expected cases (RR = 0.338, $p = 0.0001$). The third cluster contained one municipality with 168,889 observed cases and 47,664 expected cases (RR = 3,866, $p = 0.0001$). The fourth cluster contained seven municipalities with 60,936 observed cases and 181,816 expected cases (RR = 0.307, $p = 0.0001$).

Table 10.2: Significant purely spatial clusters for leprosy in Rondonia State using observed incidence rates, 1995-2006

Cluster	No. of Municipalities in Cluster	Observed Cases in Cluster	Expected No. of Cases	Cluster Relative Risk	High or Low Risk	P-value
1	1	2,037	789	2.855	High	0.0001
2	6	2,215	3,724	0.518	Low	0.0001
3	13	5,221	3,765	1.621	High	0.0001
4	3	298	712	0.406	Low	0.0001

Table 10.3: Significant purely spatial clusters for leprosy in Rondonia State using state-adjusted incidence rates, 1995-2006

Cluster	No. of Municipalities in Cluster	Observed Cases in Cluster	Expected No. of Cases	Cluster Relative Risk	High or Low Risk	P-value
1	7	4,252	1,032	4.121	High	0.0001
2	20	2,582	5,463	0.352	Low	0.0001
3	1	1,522	414	4.005	High	0.0001
4	7	558	1,699	0.328	Low	0.0001
5	3	1,957	1,260	1.645	High	0.0001

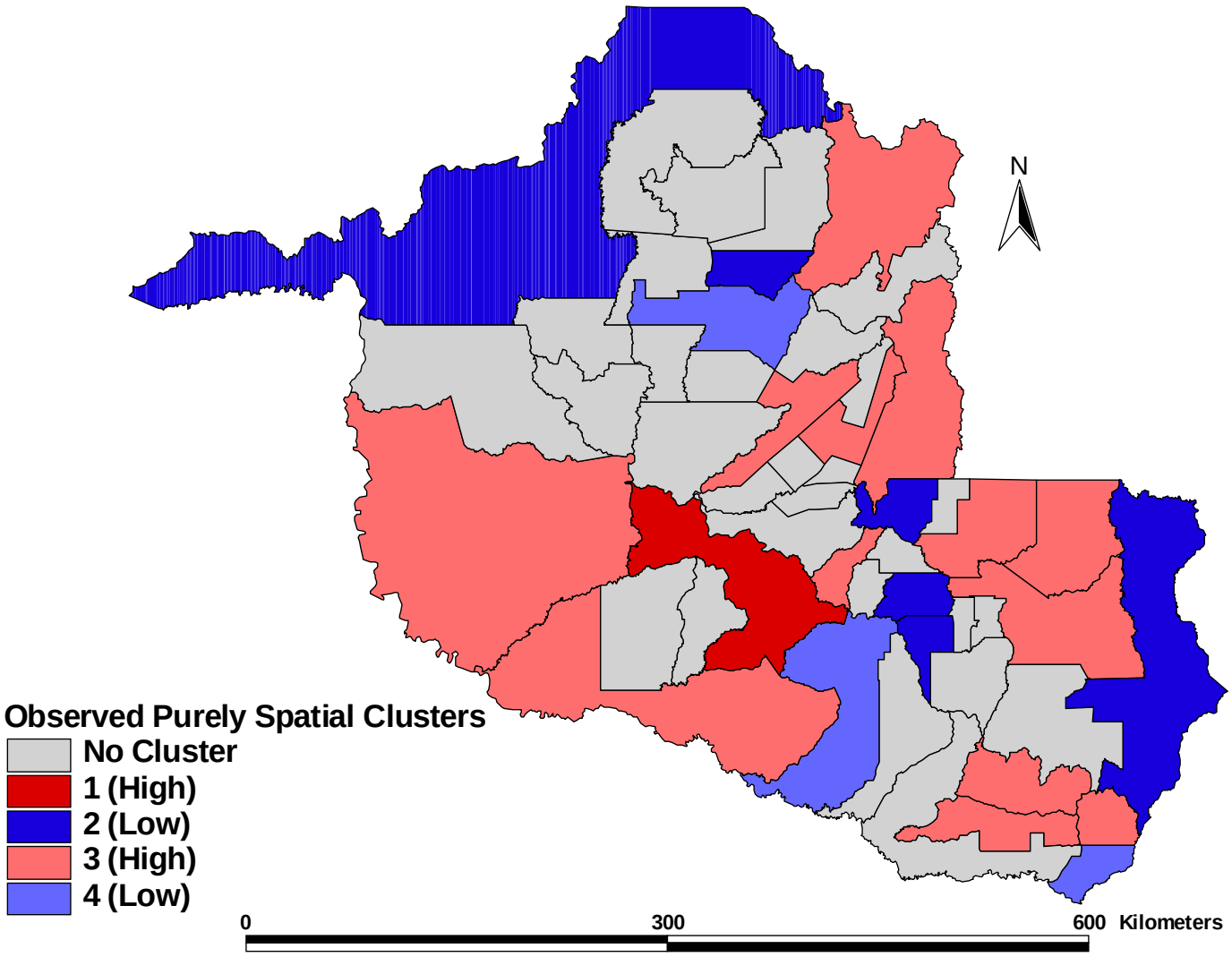

Figure 10.1: Clusters detected using the purely spatial scan statistic and observed incidence rates for leprosy, Rondonia State, Brazil, 1996-2005

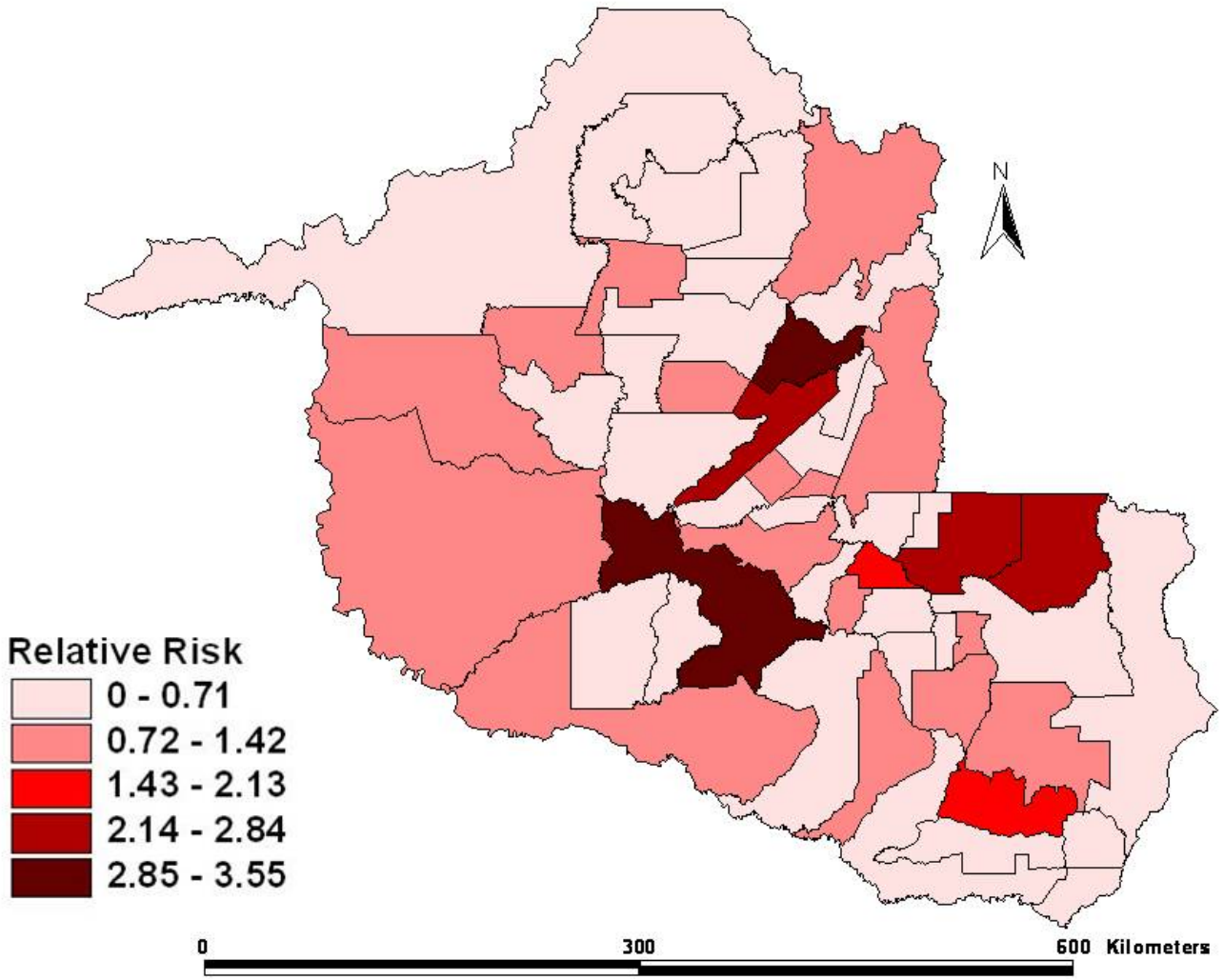

Figure 10.2: Relative risk for leprosy in Rondonia State as calculated using observed incidence rates, 1996-2005

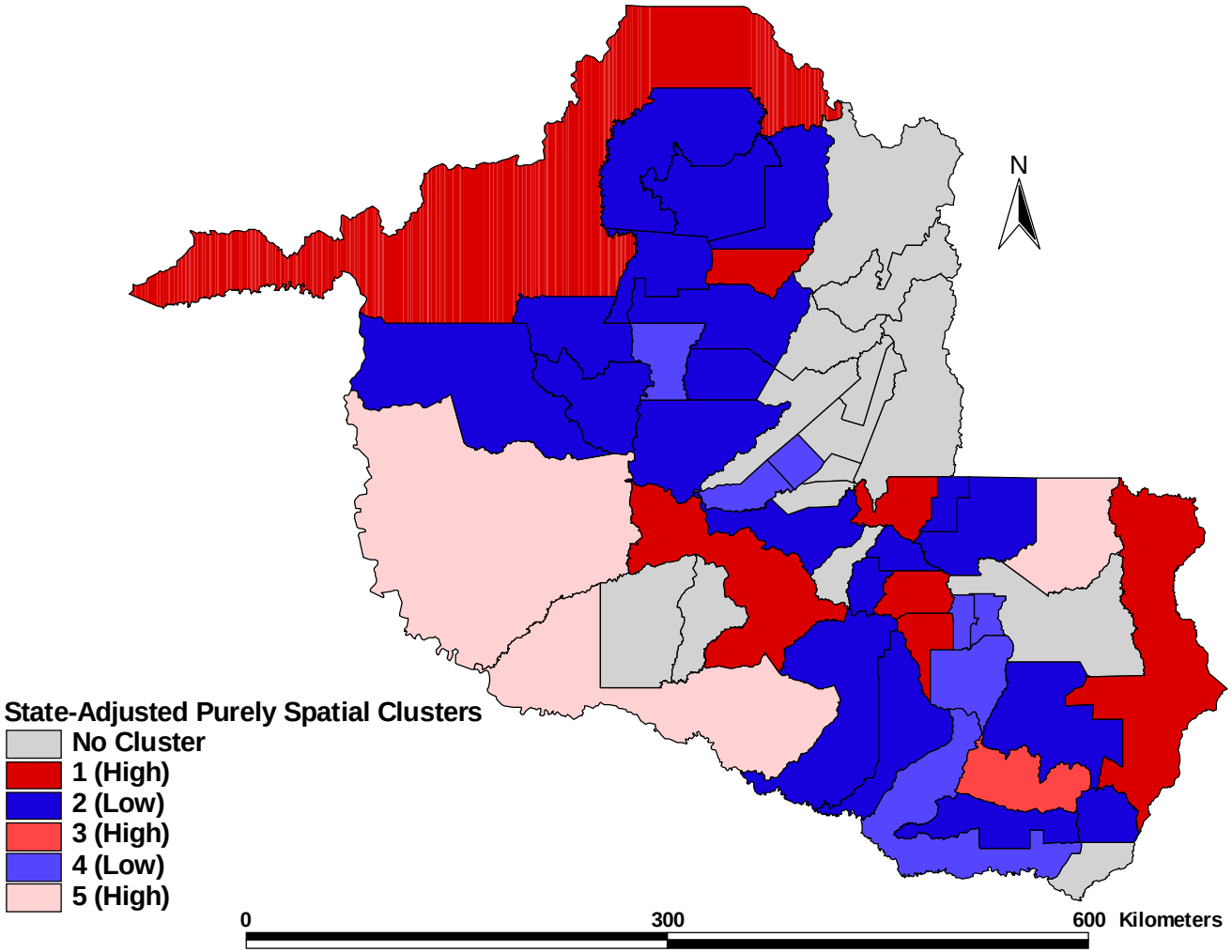

Figure 10.3: Clusters detected using the purely spatial scan statistic and state-adjusted incidence rates for leprosy, Rondonia State, Brazil, 1996-2005

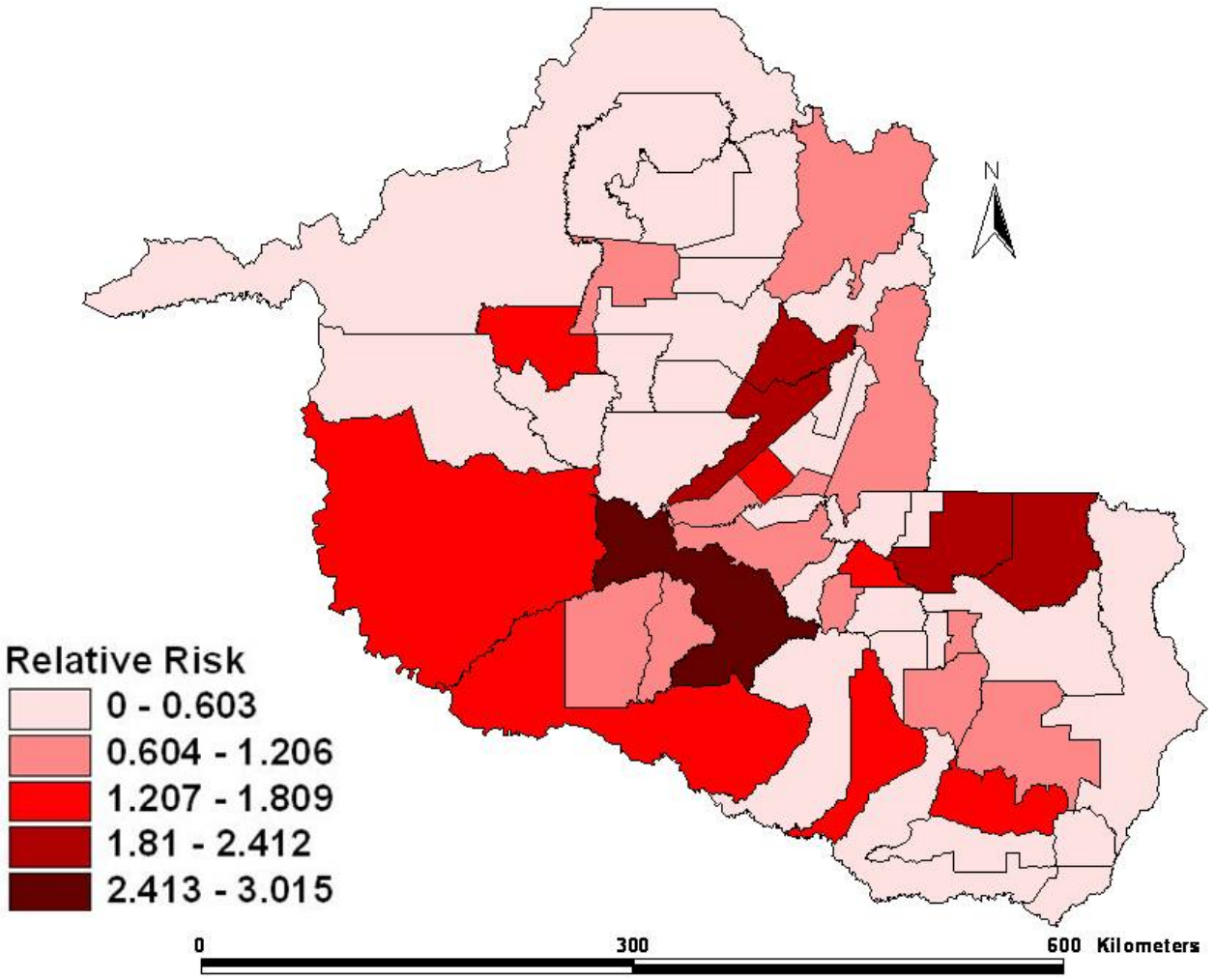

Figure 10.4: Relative risk for leprosy in Rondonia State as calculated using state-adjusted incidence rates, 1996-2005

The fifth cluster contained one municipality with 104,079 observed cases and 49,120 expected cases (RR = 2.202, $p = 0.0001$). These clusters are summarized in Table 10.4 and depicted in Figure 10.5. Relative risks per municipality as calculated by state-adjusted incidence rates are shown in Figure 10.6.

10.4 Discussion

Though rate adjustment is a common practice in public health to compare incidence across different geographic regions, its utility in spatial analysis is still not well understood (Liu et al., 2006). Through the implementation of spatial analysis to three variations of the same dataset, this study was able to quantify the resulting geospatial distributions of leprosy in Rondonia State in order to compare the effects of adjusted rates on cluster detection. This analysis used two different populations for rate adjustment, one based on a Rondonian standard population and the other based on a Brazilian standard population. Though clusters detected

Table 10.4: Significant purely spatial clusters for leprosy in Rondonia State using nationally-adjusted incidence rates, 1995-2006

Cluster	No. of Municipalities in Cluster	Observed Cases in Cluster	Expected No. of Cases	Cluster Relative Risk	High or Low Risk	P-value
1	7	4,252	1,032	4.121	High	0.0001
2	20	2,582	5,463	0.352	Low	0.0001
3	1	1,522	414	4.005	High	0.0001
4	7	558	1,699	0.328	Low	0.0001
5	3	1,957	1,260	1.645	High	0.0001

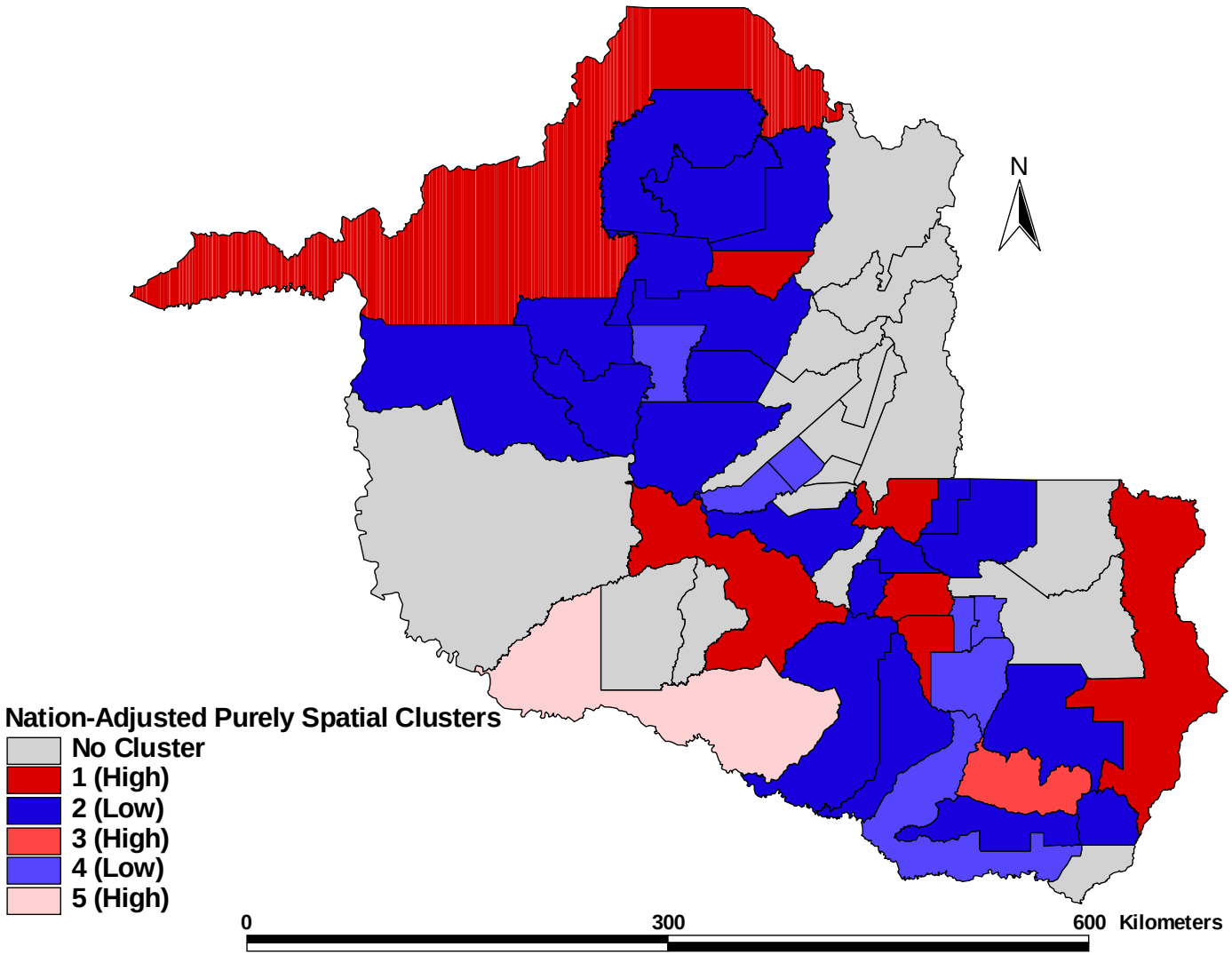

Figure 10.5: Clusters detected using the purely spatial scan statistic and nationally-adjusted incidence rates for leprosy, Rondonia State, Brazil, 1996-2005

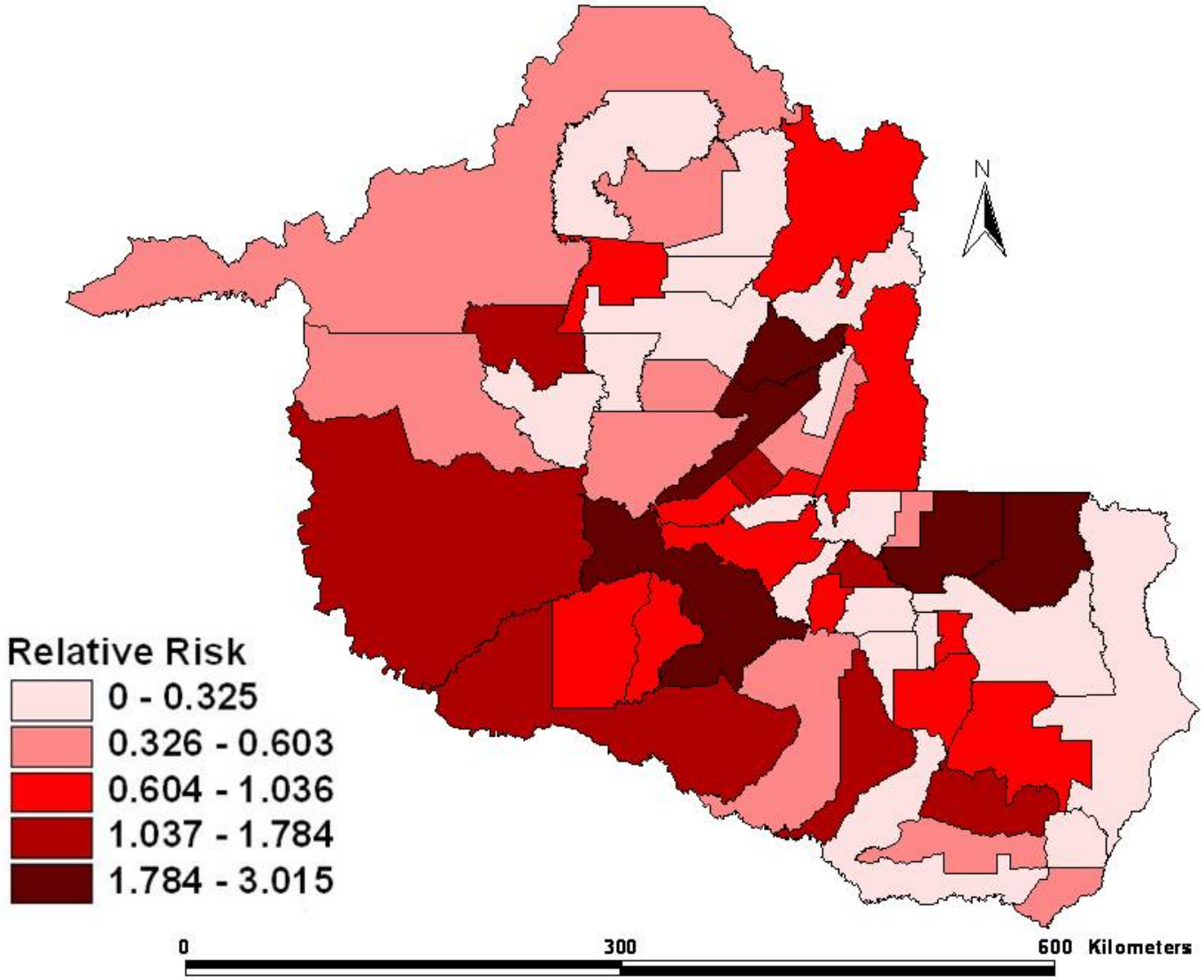

Figure 10.6: Relative risk for leprosy in Rondonia State as calculated using nationally-adjusted incidence rates, 1996-2005

using both sets of adjusted rates were relatively similar, they differed considerably from those detected by using actual observed rates.

When reviewing the changes between observed, state, and national cluster maps, several changes can be noted. The capital municipality and the most populated, Sao Miguel do Guaporé, remains a high cluster throughout all maps. Two peripheral municipalities, Porto Velho and Vihena, change from low clusters using the observed rates to high clusters using the adjusted rates. Municipalities to the northeast of Rondonia change from being high clusters to no cluster. Municipalities away from the periphery towards the center portion of the state on a north-south axis change from being no cluster to cold clusters. Comparing the state-adjusted clusters to the national-adjusted clusters, it can be noted that the large municipality of Guajará-Mirim changes from a high cluster to no cluster. When comparing the maps produced of relative risk, it becomes apparent that when going from observed to state to national rates the relative risks become more evident in contrast—a useful result when trying to emphasize the variations in risk across municipalities.

The trends observed during rate adjustment indicate that the clusters change substantially between observed rates for leprosy and adjusted rates. Trends between state-adjusted and national-adjusted rates vary much less. This fact brings to light a key point: that adjusting rates will lead to different results in spatial analysis of leprosy incidence. However, the question remains: which set of clusters are a more accurate representation of the leprosy situation in Rondonia? To answer this question would require a detailed statistical analysis of the demographic and clinical data that is beyond the scope of this dissertation. However, it can be hypothesized from looking at the demographic data that the cluster changes noted from

adjustment are more likely to account for population bias than those found through observed rates alone.

10.5 Conclusions

This study has examined the effects of using adjusted rather than observed rates on the detection of clusters in leprosy incidence in Rondonia State. It was found that adjusting incidence for demographic variables substantially altered the clusters detected through spatial analysis. It can be concluded that rate adjustment may offer superior results when trying to compare or model clusters across larger geographic areas (Bailey et al., 2005), such as between municipalities or states, but that these clusters may not offer suitable results when quantifying leprosy incidence in specific or localized areas.

Rate adjustment, though commonly used in reporting epidemiological data, has a long way to go before being routinely used in spatial analysis. No doubt there is a greater role for rate adjustment in the geospatial aspects of leprosy surveillance, especially in large, demographically diverse countries such as Brazil and India. However, more research is needed to determine exactly how rate adjustment affects spatial analysis and how these effects can be interpreted by health care practitioners and geographers.

CHAPTER 11. INVESTIGATING SPATIAL AND TEMPORAL-SPATIAL CLUSTERS OF TUBERCULOSIS IN CEARA STATE, BRAZIL, USING GIS AND THE SCAN STATISTIC

11.1 Introduction

Within the last few decades, tuberculosis (TB) has reemerged as a major global public health problem. Ranked as the world's seventh worst morbidity-causing disease, TB is present in an estimated 2 billion people globally, or approximately one-third of the earth's population (WHO, 2006). Every year, nearly 8.9 million new people contract the disease, and almost 3 million people die from TB-related illness (Li & Brainard, 2006). When the global impact of the disease is measured using disability-adjusted life-years (DALYs), TB ranks second globally (Murray & Lopez, 1997). Approximately 99.8% of the world's TB burden falls on developing countries (Daniel, 2004).

Despite the work of aggressive public health control programs, global TB incidence continues to rise each year (Munch et al., 2003). Lack of knowledge of the disease, acute subjective responses to TB treatment, travel barriers, stigma, adverse effects of medication, and overburdened TB control programs have all hampered control efforts to contain the disease (Dwolatzky et al., 2006). The worst barrier to controlling TB within the last couple of decades, however, has been the relationship that has emerged between HIV and TB, especially with the presence of a new multi-drug resistant strain of TB in southern Africa (Vendramini et al., 2005).

TB is an airborne-spread infectious disease caused by the acid-fast bacillus *Mycobacterium tuberculosis.* TB transmission dynamics are complex, with many interrelated factors contributing to risk including unemployment, overcrowding, poverty, unequal distributions of wealth, and accelerated urbanization (Munch et al., 2003; Vendramini et al., 2005). TB tends to affect adults more than children, and adults play a greater role in the disease's

transmission (Lienhardt et al., 2003). In most instances, however, it has been impossible to model the exact nature of TB epidemiology because of the inability to determine exactly when and where transmission occurs (Munch et al., 2003).

Brazil ranks sixteenth in the world in TB prevalence and accounts for over half of all TB cases in Latin America (Souza et al., 2005; USAID). In 1998, in response to a national TB crisis in Brazil, the Ministry of Health established the National Tuberculosis Control Plan (NTCP) with the goal of involving 100% of municipalities in the program, identifying 92% of the existing cases by 2001, curing 85% of cases, and reducing incidence by 50% and mortality by 66% by 2007 (Ruffino-Neto & Souza, 2001). Not only has this plan set to standardize the identification, diagnosis, treatment, and control of tuberculosis across municipalities, but it has also set out to improve the country's TB surveillance system through the collection of higher quality data. However, major setbacks have included the lack of political commitment, lack of epidemiological data representative of the TB situation in Brazil, and lack of understanding of local (territory) levels of disease dynamics. As a result, the NTCP has not achieved its 2007 goal for TB control, and the number of TB cases in Brazil continues to rise (Vendramini et al., 2005).

Ceará State, located in the northeast corner of Brazil, is not only one of the poorest and least-developed states within Brazil, but is also the state with the highest level of income inequality (Montenegro et al., 2004). These demographic traits no doubt contribute to the relatively high prevalence and transmission rates of TB seen within Ceará State (Facanha, 2006).

Recent applications of geographic methods (namely GIS) in TB research has led not only to a better understanding of TB transmission dynamics and epidemiology, but also to a wider understanding of the important role that these methods can play in disease surveillance and cluster detection. Moonan et al. (2004) related clustering of TB cases with genotyped isolates of

TB in Dallas, Texas, to determine that TB transmission was occurring at focal points of transmission rather than wider, more randomized points of transmission. Munch et al. (2003) integrated census block data with clinical TB data in Capetown, South Africa, to investigate the possibility of TB transmission within and around various shebeens (pubs). Tiwari et al. (2006) used geographic analyses to detect clusters of TB within Almora district, India, in order to clarify and quantify the health burden of TB in this area. Onozuka & Hagihara (2007) and Nunes (2007) used a geographic temporal-spatial analysis to identify space-time clusters of TB within Japan and Portugal, respectively. Vendramini et al. (2005) analyzed the variance in standardized incidence of TB in São José do Rio Preto, São Paulo State, Brazil, using demographic and socioeconomic data to show that TB incidence was directly correlated to socioeconomic level. In Olinda, Pernambuco, Brazil, Souza et al. (2005) also analyzed the spatial distribution of TB in relation to several demographic and socioeconomic variables, finding a relationship between the number of household inhabitants and TB incidence. (It should be noted that all of these studies involved intense collaboration between clinicians with epidemiological data and geographers with the capability of using advanced spatial analyses.)

To date, there have been no studies that detect statistically significant clusters of TB in Ceará State, Brazil. Using the spatial scan statistic (Kulldorf, 2006) and GIS, this study investigated the spatial clustering of registered cases of TB and identified the areas of abnormal risk of TB within Ceará State, Brazil, from January 1995 to August 2006. The results of this study can be used to help clarify and quantify the burden of TB in Ceará State in an effort to improve its control.

11.2 Materials and Methods

This study analyzes data from Ceará State, Brazil, a location that is described in detail in Chapter 8. Data relevant to TB incidence for Ceará State, was obtained from both demographic and clinical databases. Clinical data on each TB case diagnosed between 1 January 1995, and 31 August 2006, including date of diagnosis, municipality of residence, gender, and birth date, were obtained from the Brazilian Ministry of Health's national registry of TB cases (Sistema de Informação de Agravos de Notificação, or SINAN) through collaboration with clinicians in the Department of Community Health in the Faculty of Medicine at the Federal University of Ceará.

Demographic data were obtained from the Sistema IBGE de Recuperação Automatica (SIDRA, 2007). This database, derived from the 2000 Brazilian Census, allows users to aggregate data at various spatial scales (i.e., state, municipality, or barrios level) within certain parameters (i.e., gender, urban/rural, age group, education, etc.). This functionality allows the calculation of different strata of the population—for instance the number of males living in rural areas between the ages of 20 and 25 who have 5-8 years of total education. Population data for each of the 184 municipalities were extracted from this database, including total population for each year between 1995 and 2006 and gender/age group data for the year 2000. For the purpose of this study, the population was divided into four age groups: 0-19, 20-39, 40-59, and >60. The number of males and females for each of the four age groups and for each of the 184 municipalities was aggregated into a population file.

Geographic data, which included shapefiles containing spatial information for each of the 184 municipalities of Ceará, were obtained online from the Brazilian Institute of Geography and Statistics (IBGE, 2008).

11.3 Exploratory Spatial Data Analysis

Before deciding on the type of spatial analysis to perform for this study, an initial basic exploratory spatial data analysis was used to examine case trends of TB data within Ceará State. Incidence rates aggregated to the municipality level were visualized using a choropleth map (Figure 11.1). As can be seen from this figure, there appears to be clustering of high rates in three epicenters of Ceará State: the central-north, the center-east (Fortaleza), and the southeast. However, spatial analysis was required to determine whether or not these epicenters were true clusters and whether or not they were significant.

By plotting the number of cases detected per month, it can be seen in Figure 11.2 that incidence rates have remained relatively stable from 1995-2006, with only a minor decline in incidence. Also evident from this figure are temporal detection 'spikes' that hint at a possible seasonality for TB detection (whether physiological or bureaucratic). With this information, it seemed appropriate to thus apply a temporal component to the spatial analysis.

In addition to temporary trends observed with exploratory data analysis, demographic trends within Ceará State also became evident through the exploratory data analysis. Figure 11.3 depicts the number of cases detected by age between January 1995 and August 2006. From this figure it can be seen that the majority of cases of TB are detected between the ages of 20 and 39. Gender is also a factor in TB detection, with more males being detected than females (Figure 11.4). With this information, it was decided to add a covariate temporal-spatial analysis to this study that took into consideration the underlying age and gender structure of the Ceará population.

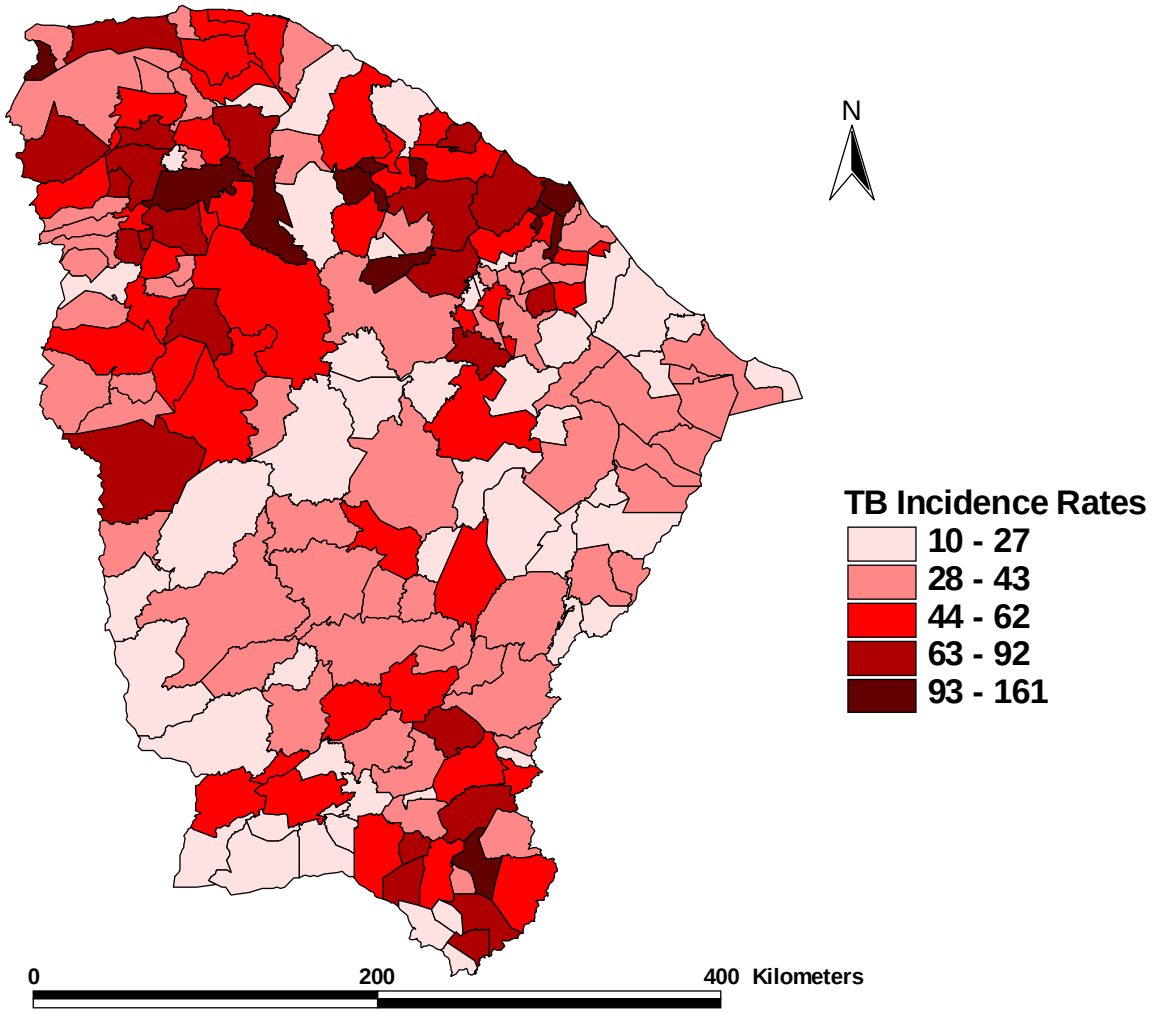

Figure 11.1: Average yearly incidence rates of tuberculosis for Ceará State, Brazil, between January 1995 and August 2006

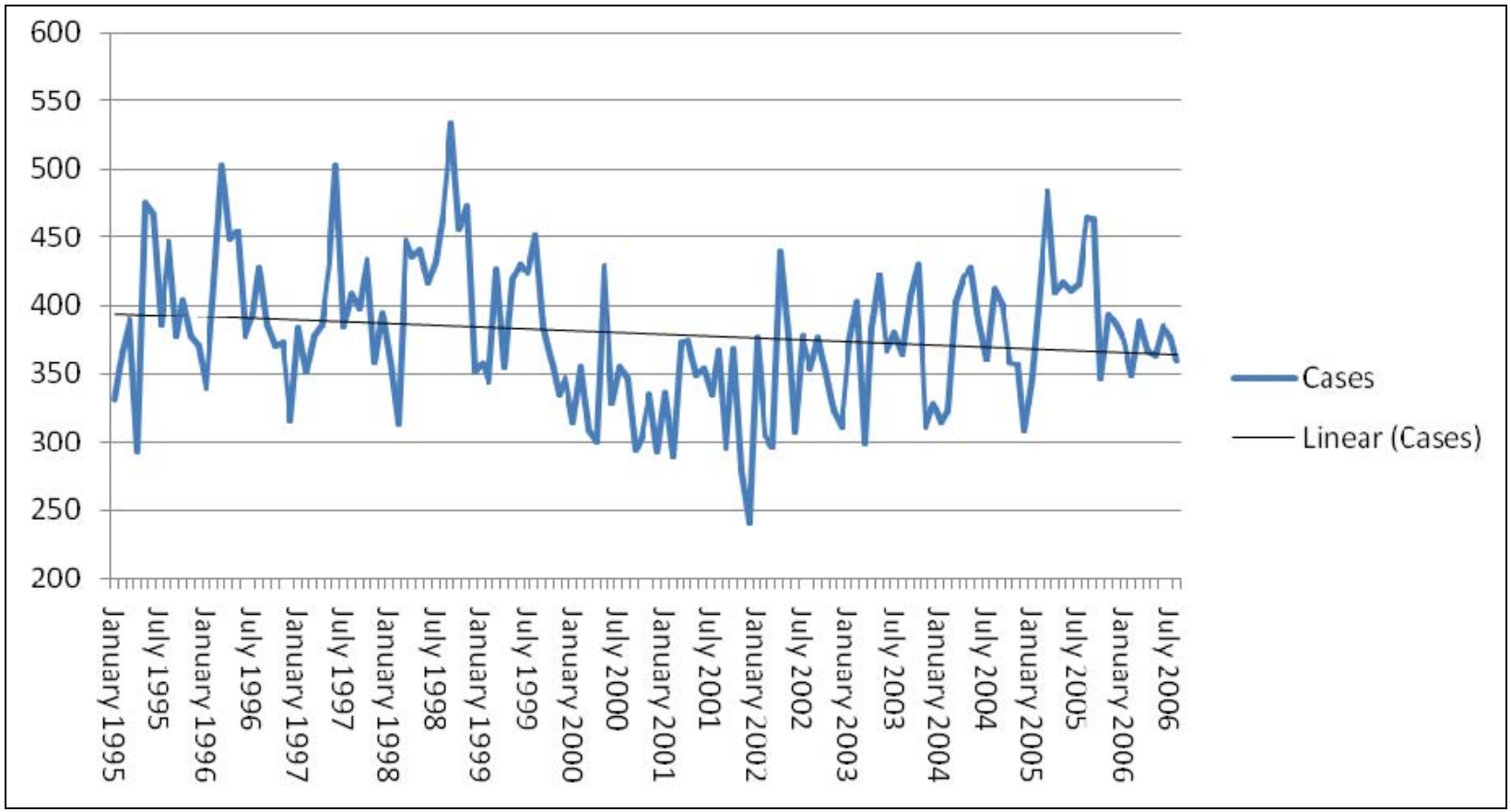

Figure 11.2: Monthly incidence of TB cases in Ceará State, Brazil, from January 2005 to August 2006

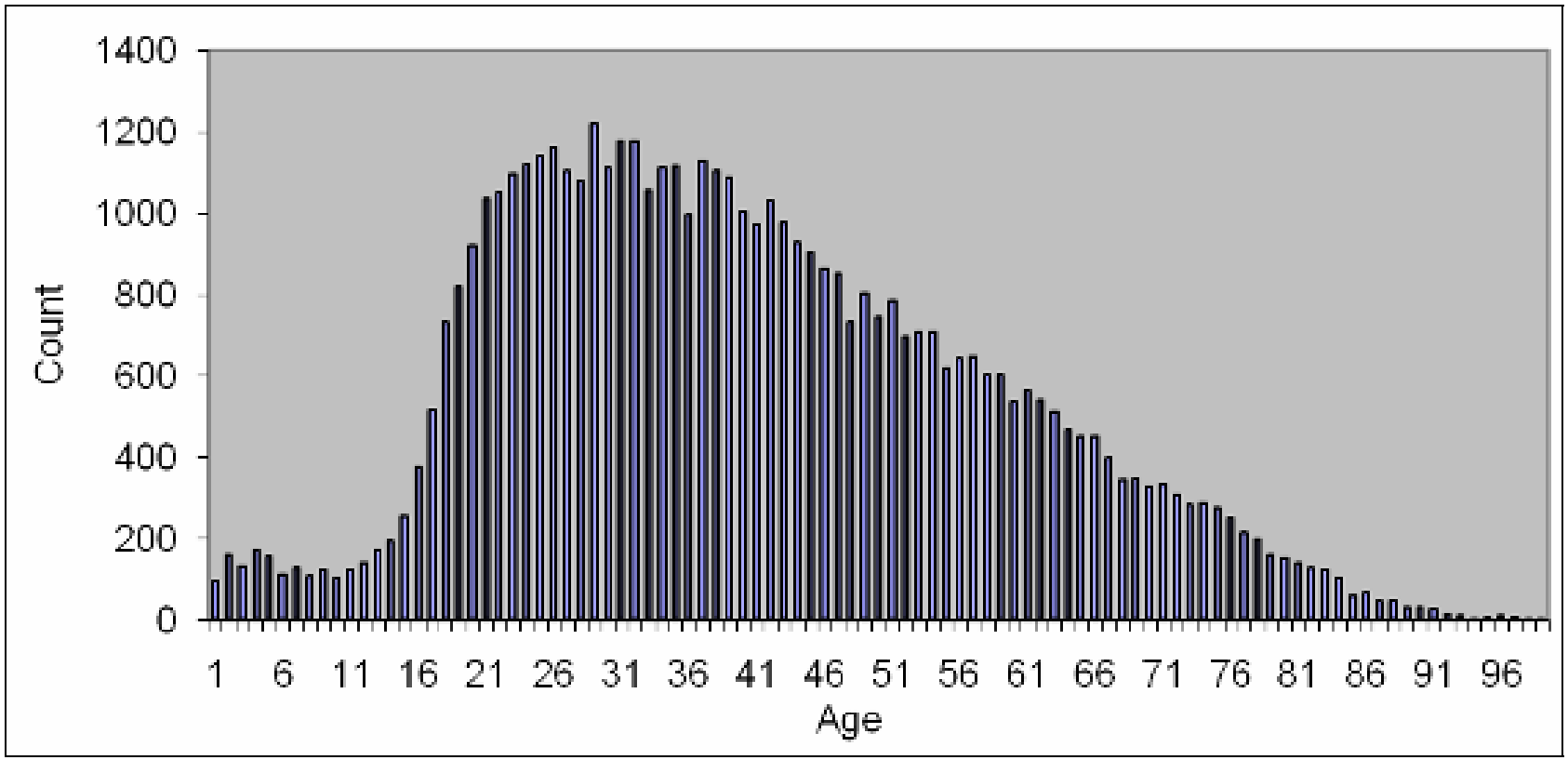

Figure 11.3: Age at time of detection for tuberculosis cases, Ceará State, from January 1995-August 2006

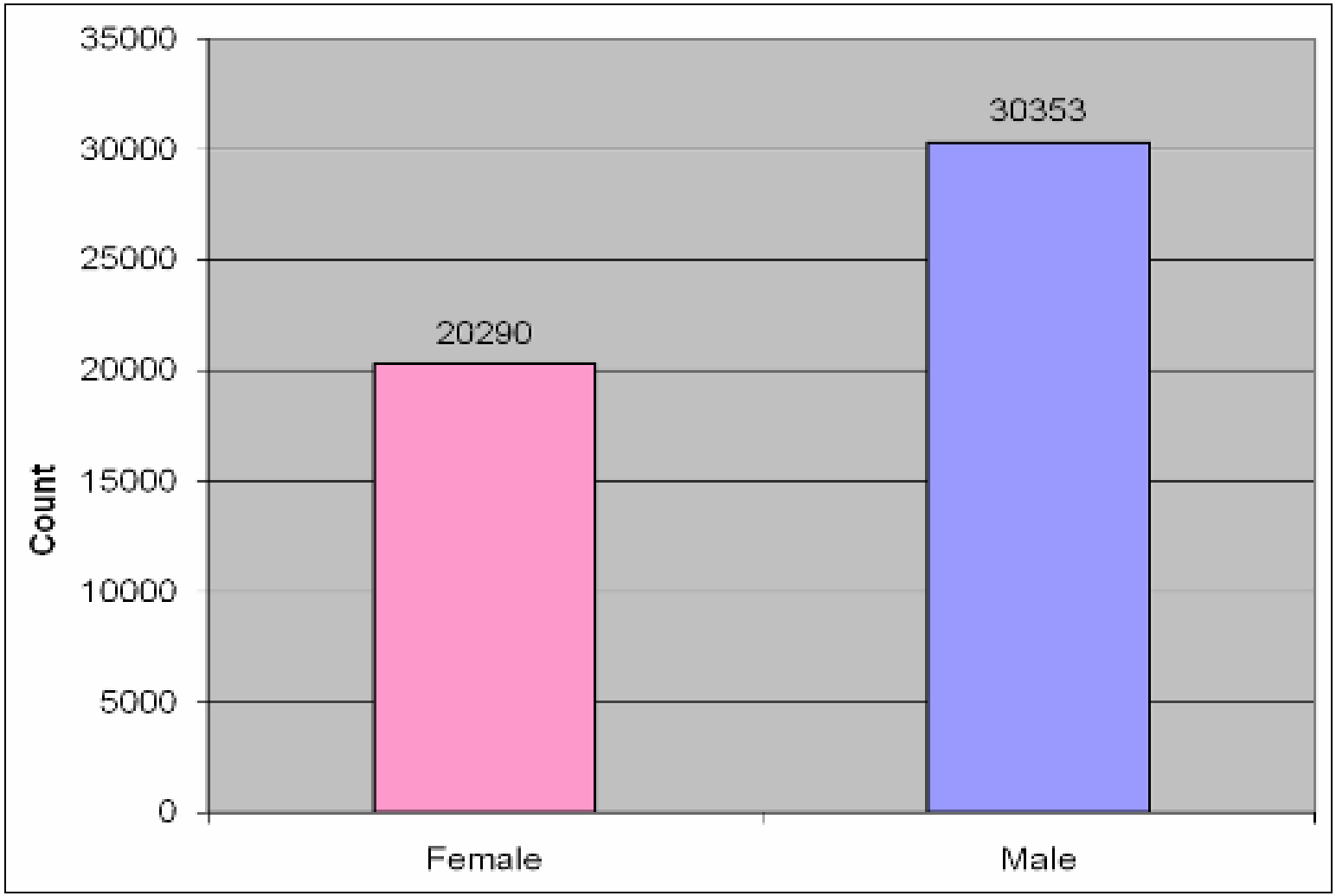

Figure 11.4: Gender of tuberculosis cases reported between January 1995 and August 2006, Ceará State, Brazil

11.4 Data Analysis

Based on the results of the exploratory data analysis, it was decided that three separate analyses should be performed: 1) a purely spatial analysis of total population and cases without covariates to detect simple clustering of high and low rates; 2) a space-time analysis of cases and total population with no covariates to assess the role temporal clusters associated with spatial clustering; and 3) a space-time analysis of aggregated cases and population with the covariates gender and age to assess the role of these demographic factors in cluster detection. The purpose of using three separate analyses was to compare the nature of the clusters detected by each.

Clusters of TB were identified in Ceará State at the municipality level using the scan statistic in the software SaTScan (Kulldorf, 2006). A retrospective space-time analysis was performed using the *Poisson* probability model, scanning for areas of unusually high or low rates. Maximum cluster size was set to 50% of the total population at risk and 50% of the study period. To ensure sufficient statistical power, the number of *Monte Carlo* replications was set to 9999, and only clusters with a statistical significance of $p < 0.05$ were reported. Each municipality's cluster data was merged with its associated shapefile in ArcView GIS (ESRI, 1999) to produce cartographic maps of TB clusters. In addition to depicting clusters, each municipality's relative risk was displayed on a choropleth map in order to visualize areas of high and low risk.

11.5 Results

The results of the purely spatial analysis of TB data from January 1995 to August 2006 with no covariates are shown in Table 11.1 and Figures 11.5 and 11.6. The most likely cluster for this analysis included three municipalities with 28,202 observed cases and 17,349 expected cases (RR = 2.294, $p = 0.0001$). Four secondary clusters were detected: the first containing 134

municipalities with 15,278 observed cases and 25,464 expected cases (RR = 0.445, $p = 0.0001$); the second containing one municipality with 2,505 observed cases and 1136 expected cases (RR = 2.263, $p = 0.001$); the third containing 21 municipalities with 2481 observed cases and 3969 expected cases (RR = 0.607, $p = 0.0001$); and the fourth cluster containing 2 municipalities with 720 observed cases and 424 expected cases (RR = 1.709, $p = 0.0001$).

The results of the space-time analysis of TB data from January 1995 to August 2006 with no covariates are shown in Table 11.2 and Figures 11.7 and 11.8. The most likely cluster for this analysis included three municipalities with 11,789 cases from 1 January 1995, to 31 August 1999. The expected number of cases within this cluster was 6,516 (RR = 2.032, $p = 0.0001$). Four secondary clusters were detected: the first containing 134 municipalities, 6244 observed cases, and 11,311 expected cases (RR = 0.494, $p = 0.0001$) from 1 September 2001 to 31 August 2006; the second containing one municipality, 1259 observed cases, and 421 expected cases (RR = 3.041, $p = 0.001$) from 1 January 1995 to 31 August 1999; and the third containing 20 municipalities, 969 observed cases, and 1738.98 expected cases (RR = 0.549, $p = 0.0001$) from 1 September 2001 to 31 August 2006.

The results of the space-time analysis with gender and age as covariates are summarized in Table 11.3 and Figures 11.9 and 11.10. The most likely cluster for this analysis contained two municipalities with 11,059 observed cases and 6,611 expected cases (RR = 1.861, $p = 0.0001$) and occurred from 1 January1995 to 31 August 1999. This analysis identified four secondary clusters: the first containing 134 municipalities with 4490 observed cases and 8199 expected cases (RR = 0.504, $p = 0.0001$) occurring from 1 September 2001 to 31 August 2006; the second containing a single municipality with 995 observed cases and 412 expected cases (RR = 2.443, $p = 0.0001$) occurring from 1 January 1995 to 31 August 1999; the third containing fifteen

Table 11.1: Significant high and low rate tuberculosis spatial clusters in Ceará State, 1995-2006

Cluster	No. of Municipalities in Cluster	Observed Cases in Cluster	Expected No. of Cases	Cluster Relative Risk	High or Low Risk	P-value
1	3	28,202	17,349	2.294	High	0.0001
2	134	15,278	25,464	0.445	Low	0.0001
3	1	2,505	1,136	2.263	High	0.0001
4	21	2,481	3,969	0.607	Low	0.0001
5	2	720	424	1.709	High	0.0001

Table 11.2: Significant high and low rate tuberculosis temporal-spatial clusters in Ceará State, 1995-2006

Cluster	No. of Municipalities in Cluster	Time Period	Observed Cases in Cluster	Expected No. of Cases	Cluster Relative Risk	High or Low Risk	P-value
1	3	1/1/1995-31/8/1999	11,789	6,516	2.032	High	0.0001
2	134	1/9/2001-31/9/2006	6,244	11,311	0.494	Low	0.0001
3	1	1/1/1995-31/8/1999	1,259	421	3.041	High	0.0001
4	20	1/9/2001-31/8/206	969	1,738	0.549	Low	0.0001

Table 11.3: Significant high and low rate temporal-spatial clusters of tuberculosis using covariate analysis, Ceará State, 1995-2006

Cluster	No. of Municipalities in Cluster	Time Period	Observed Cases in Cluster	Expected No. of Cases	Cluster Relative Risk	High or Low Risk	P-value
1	2	1/1/1995-31/8/1999	11,059	6,611	1.861	High	0.0001
2	134	1/9/2001-31/9/2006	4490	8199	0.504	Low	0.0001
3	1	1/1/1995-31/8/1999	995	412	2.443	High	0.0001
4	15	1/1/1995-31/8/2000	491	870	0.560	Low	0.0001
5	2	1/9/2002-31/8/2006	314	129	2.436	Low	0.0001

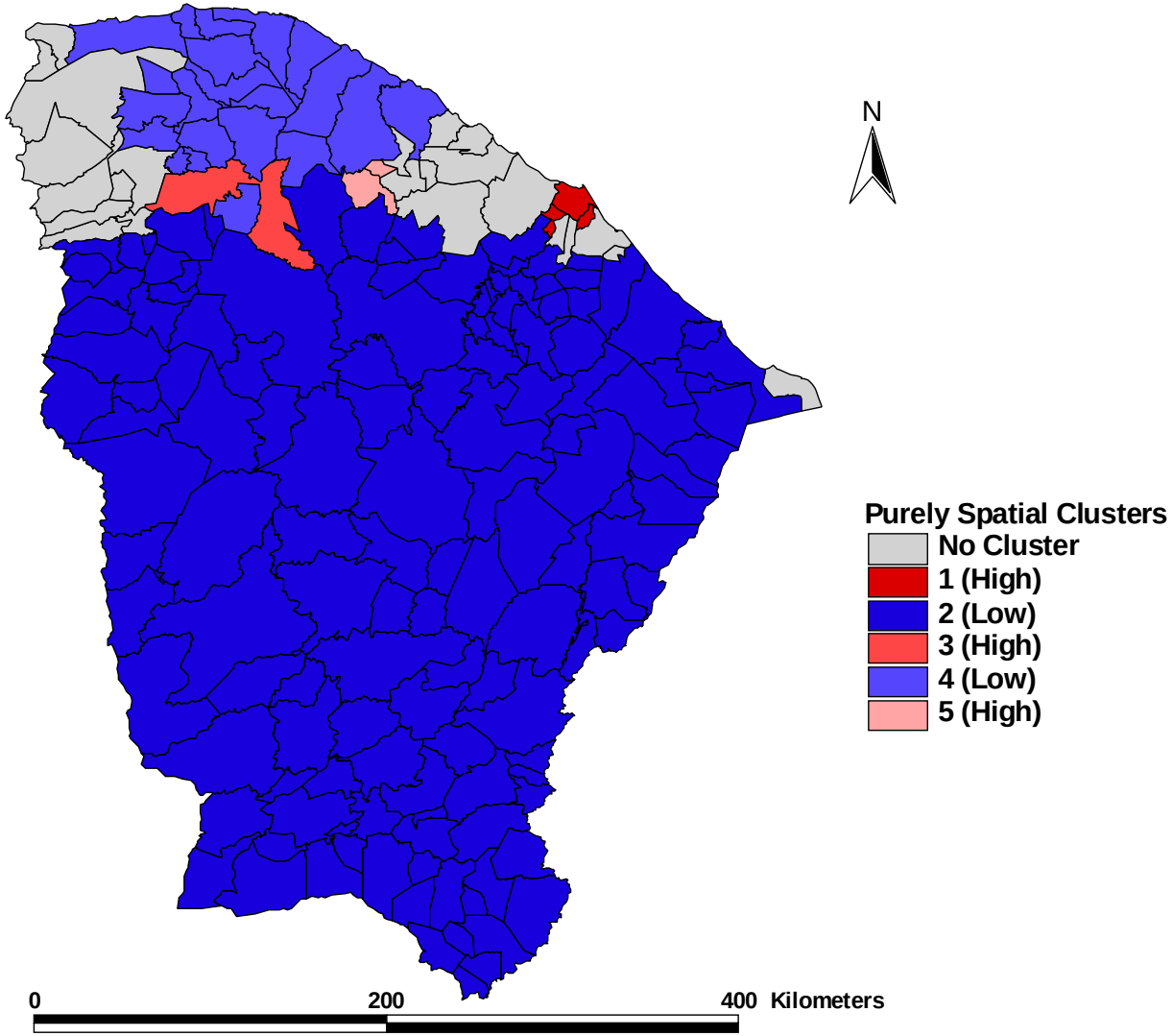

Figure 11.5: Purely spatial clusters of TB within Ceará State, Brazil

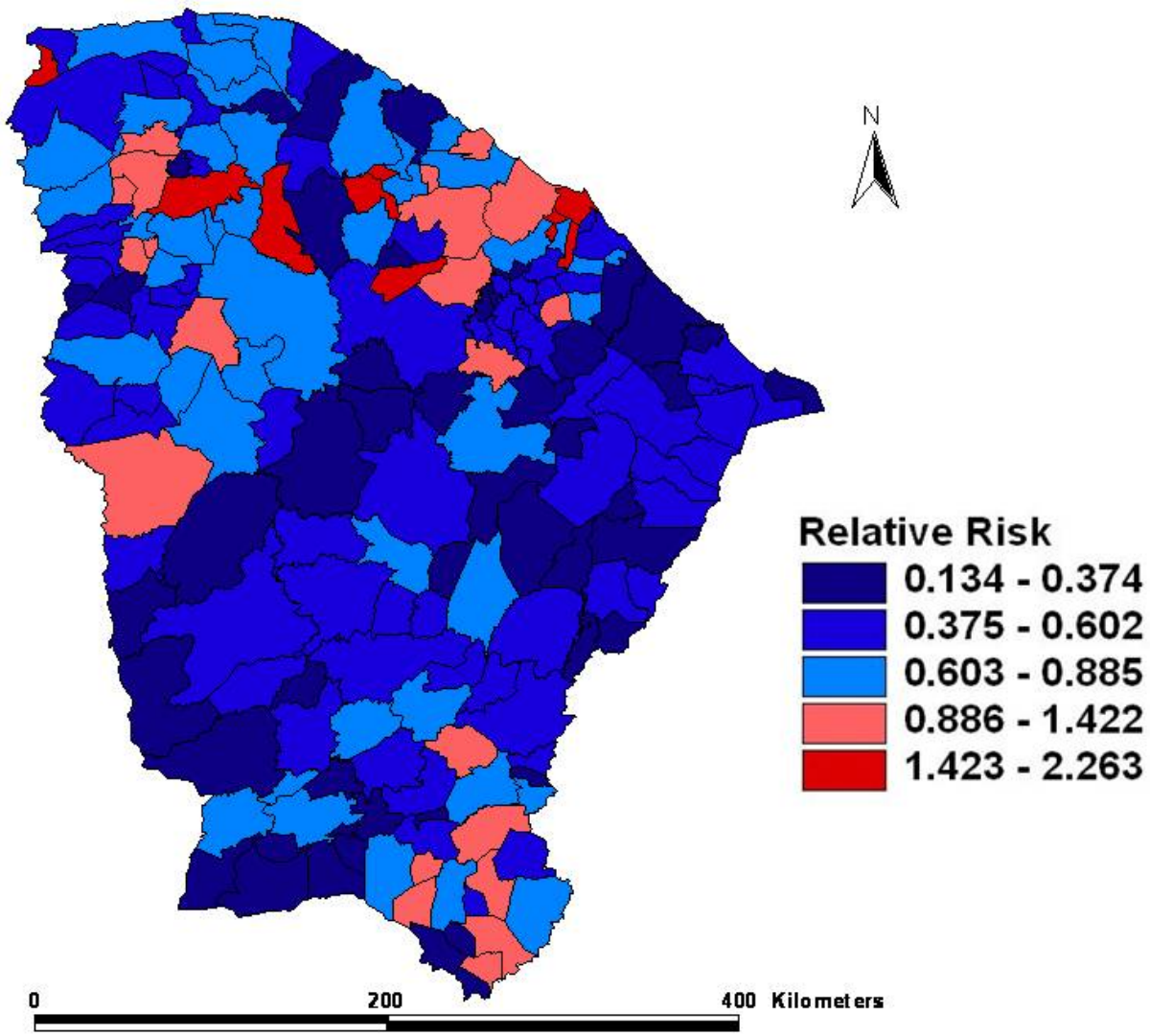

Figure 11.6: Relative risk of TB in Ceará State, Brazil, as predicted by the purely spatial scan statistic

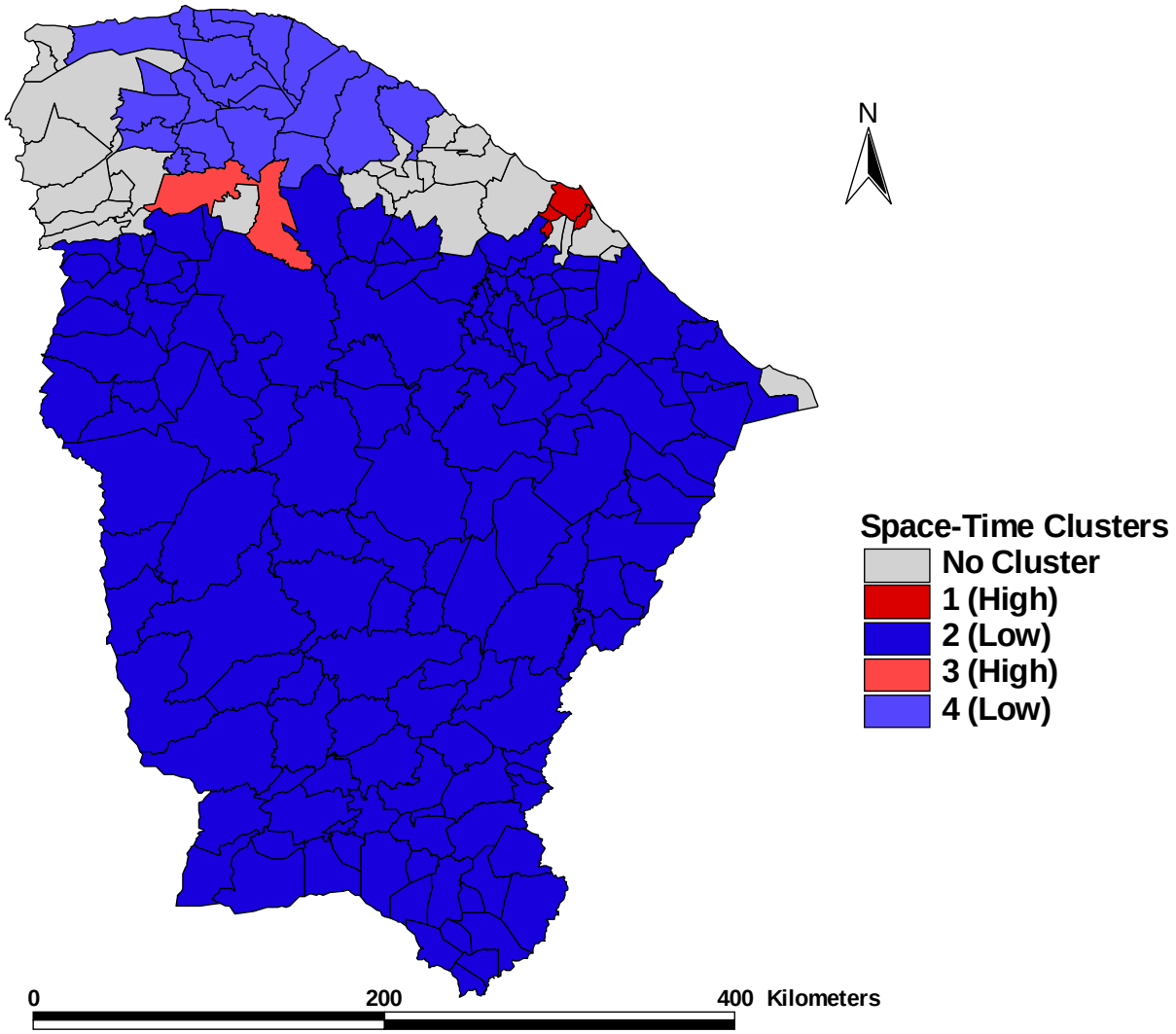

Figure 11.7: Space-time clusters of TB within Ceará State, Brazil

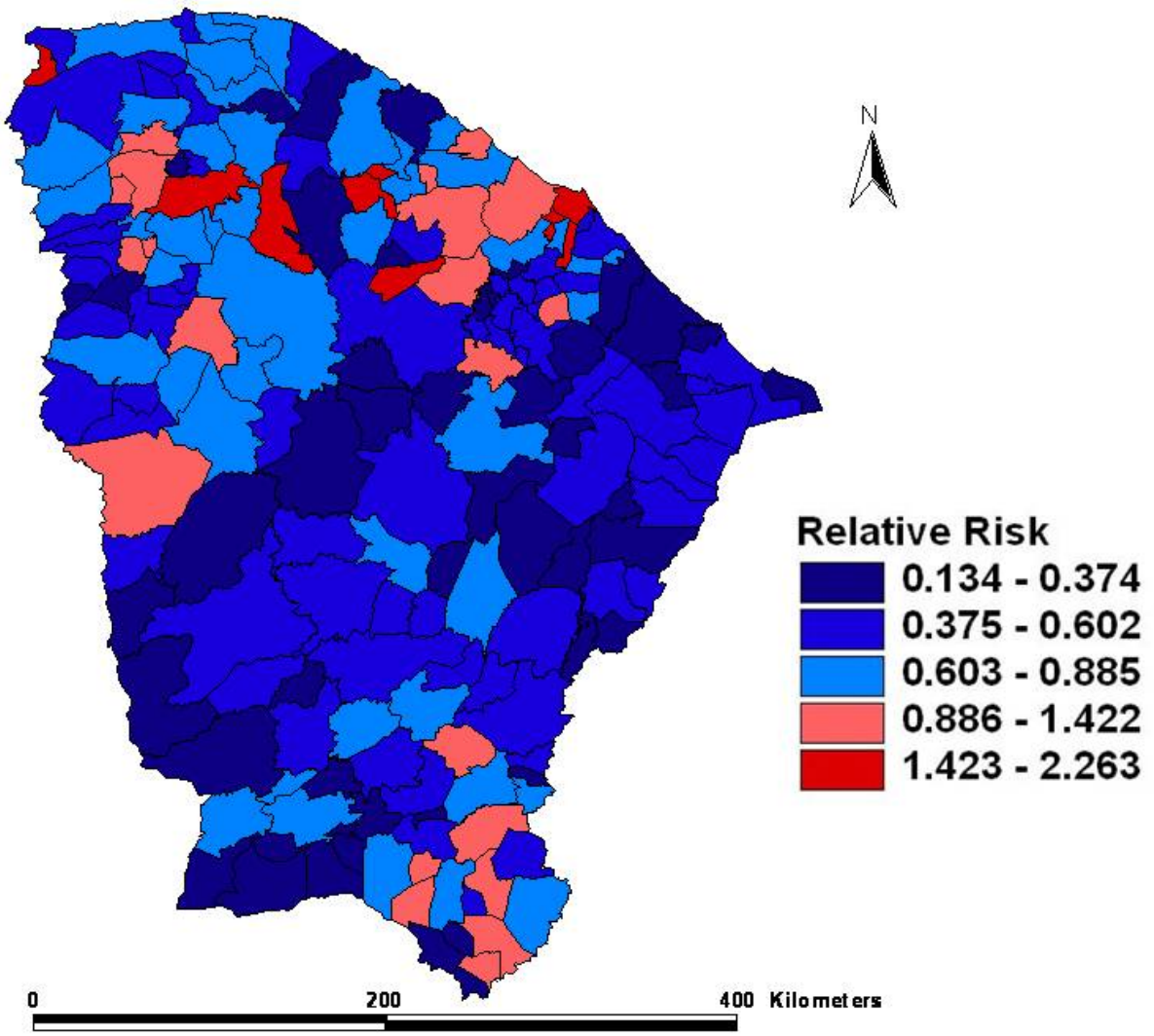

Figure 11.8: Relative risk of TB in Ceará State, Brazil, as predicted by the space-time scan statistic

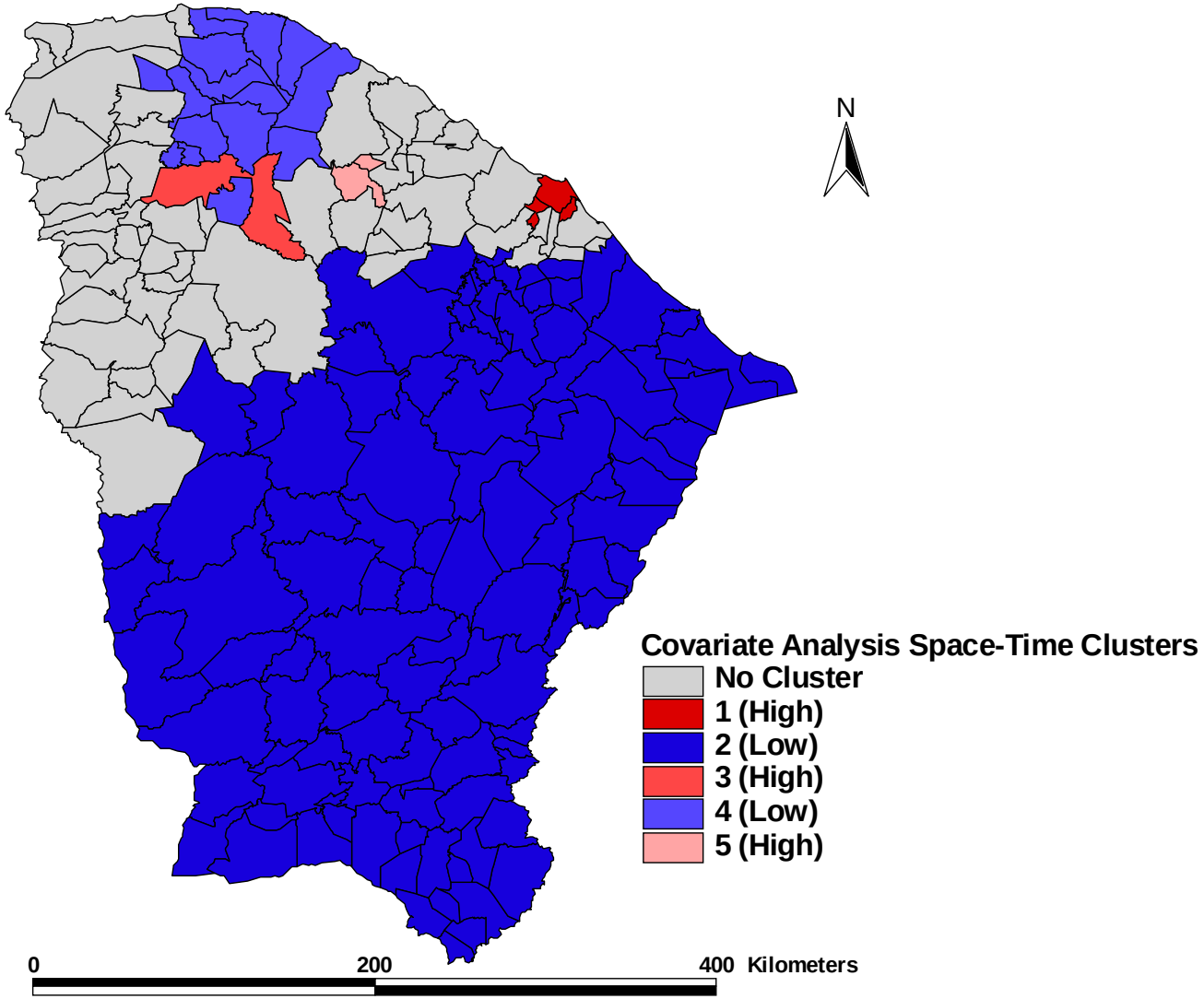

Figure 11.9: Space-time clusters of TB in Ceará State, Brazil, detected with age and gender as covariates

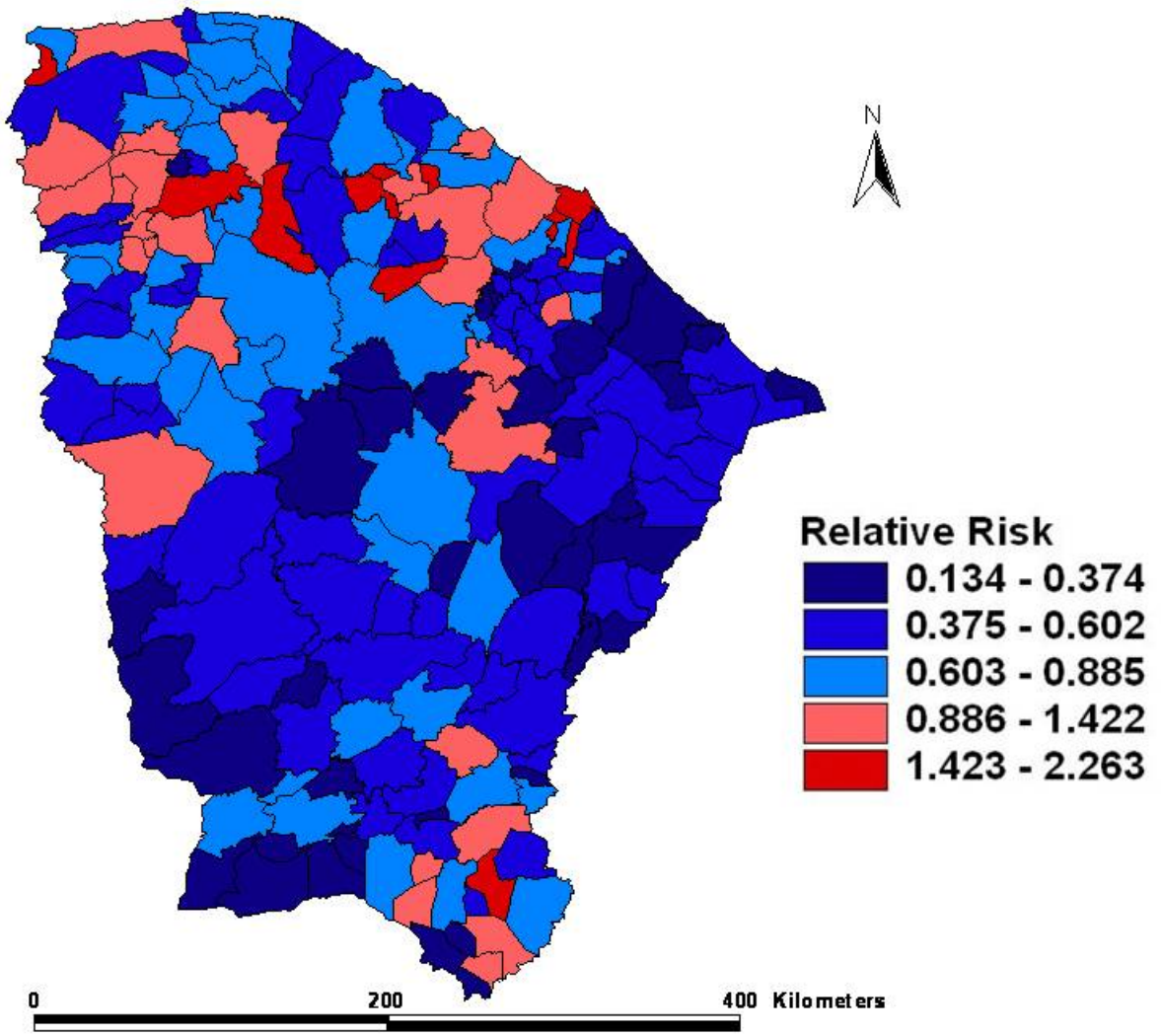

Figure 11.10: Relative risk of TB in Ceará State, Brazil, as detected by the space-time scan statistic with age and gender as covariates

municipalities with 491 observed cases and 870 expected cases (RR = 0.560, p = 0.0001) occurring from 1 January 1995 to 31 August 2000; and the fourth containing two municipalities with 314 observed cases and 129 expected cases (RR = 2.436, p = 0.0001) occurring from 1 September 2002 to 31 August 2006.

11.6 Discussion

The purely spatial analysis identified three hot spots in Fortaleza, Sobral, and Itapage municipalities. These three cluster groups lie on an east-west linear axis in the north of Ceará State. The entire southern region of Ceará was identified through this analysis as a cold spot, which is in contrast to what was seen with leprosy in the previous chapters. In the temporal-spatial analysis, only two hot spots were detected, in Fortaleza and Sobral municipalities. Itapage, located between Fortaleza and Sobral, was not identified as a hot spot when the temporal component was added to the analysis. In addition, the temporal-spatial analysis also resulted in the disappearance of two municipalities from cold spots when compared to the purely spatial analysis. In the space-time analysis with age and gender as covariates, there was no change in hot spot detection compared to the purely spatial analysis. However, like with the temporal-spatial analysis, many municipalities disappeared from cold spots in the northern region of the state.

No change in relative risks for TB was seen between the purely spatial and temporal-spatial analyses. However, in the temporal-spatial analysis with covariates, there was a slight increase in relative risk in several municipalities in the north of Ceará.

11.7 Conclusions

In this study, three different methods were used to analyze clusters of TB incidence in Ceará State, Brazil. All three methods identified ‘hot spots’ along an east-west line in the north

central portion of the state, while ‘cold spots’ existed in the southern and far-north regions of the state. This analysis provides empirical evidence that TB is heterogeneously dispersed and that risk of TB is clustered in Ceará State. Compared to the distributions of leprosy determined in Chapter 8, however, TB seems to show less state-wide heterogeneity. This trend may be attributable to TB’s predilection for urban areas and leprosy’s predilection for rural areas.

The major limitation of this analysis is that it used minimal assumptions about underlying factors associated with TB transmission to calculate clusters. Age and gender, which are both heavily associated with TB risk, appeared to play a minimal role in cluster detection, indicating that perhaps other geo-demographic factors are involved in the spatial heterogeneity of TB risk. The results, however, do not contradict the importance of demographics in TB transmission (Vendramini et al., 2005). Because no other covariates were examined, no other ecological assumptions about TB transmission were made.

The SaTScan software used in this analysis proved to be an efficient method for TB cluster detection. Results files of the analysis are easily integrated into GIS software, and clusters are readily mapped using this information. In addition, this software integrates statistical significance testing into the cluster detection such that only statistically significant clusters are reported. One limitation to using this software with covariate analysis, however, is that it gives no quantifiable or statistical information about the relationship between independent variables (covariates) and dependent variables (risk). Nonetheless, the user-friendly functionality and cost effectiveness of SaTScan make it an ideal software for use in public health surveillance and disease control programs both in the developed and developing worlds.

From the point of cluster detection, several paths could be taken in follow-up studies to further examine the spatial distributions of TB in Ceará State. In this study, the municipality was

used as the unit of analysis. However, future studies may wish to look at different spatial scales to determine whether or not differences in clustering exist (i.e., to examine the effects of the Modifiable Areal Unit Problem) (Odoi et al., 2003). In addition, future studies may also wish to examine 'hot spots' using smaller area units in order to identify potential risk factors. This type of study would be complemented by the use of remotely sensed data (Lienhardt et al., 2003). Because the relation of TB to urban settings, future studies may also wish to consult urban geographers in order to assess the specific risks associated with TB transmission in urban landscapes (Facanha, 2006; Munch et al., 2003). Finally, to address the need of more standardized geographic methods in public health research, future studies may wish to investigate the variation produced by different spatial statistics and software. This analysis, for instance, showed that variation in clustering results with different types of analyses even within a single family of spatial statistics. Studies that examine differences in geographic techniques will in the long run assist epidemiologists and statisticians in improving current methodological issues (Ward & Carpenter, 2000).

The use of geographic techniques in health research no doubt provides a vital part of epidemiological research and disease control. Disease mapping and cluster detection like the ones examined in this study can be used to target high-risk areas or plan for future control programs for TB. In addition, the results of this study and similar ones can be used to assess the effectiveness of past and current TB control programs in Ceará State. Despite the limitations of this study, the detection of clusters of TB in Ceará State has demonstrated that risk of TB is not homogenously distributed throughout the state and that there are underlying geographic and demographic factors involved in TB transmission that deserve further attention.

CHAPTER 12. A PHOTOJOURNEY THROUGH THE FIELD

The research presented in this dissertation in the preceding chapters is the product of a two-month data-collecting field trip into the poorest and driest region of Brazil, Ceará State. My path to Brazil actually started in Australia, where I was studying Public Health and Tropical Medicine at the Anton Brienl Centre (ABC) at James Cook University in Townsville, Queensland. It was here that I met a guest lecturer who was giving a presentation on a little known human flea parasite in poor tropical regions of Brazil and Mozambique called *tunga*. I was so intrigued by the description of this little bug that after class I immediately went to introduce myself to the lecturer, Dr. Jorg Heukelbach. While chatting with Jorg, Dr. Richard Speare, the director of the ABC, came up and mentioned to Jorg that I was a graduate student at LSU interested in medical geography. Upon hearing this, Jorg practically jumped in the air, as he had been looking for someone who could begin to spatially analyze the oodles of epidemiological data that he had been collecting over the past few years! Jorg had read of the advances of geographic methods in the health sciences, but did not have the time or experience to implement them into his own research. Jorg therefore mentioned that he would be *more* than happy for me to come over to Brazil to meet with his research associates and collect data for use in my dissertation.

The following section presents some of the photos that I took while in Brazil that have special descriptive meaning or that illustrate some key points during my data collection in Fortaleza. In breaking with the serious format of the preceding chapters, this photo journey is offered as a light-hearted trip through an eye-opening and amazingly intriguing part of Brazil. Each photo is accompanied by a short narrative that describes its significance during my field research phase in Ceará State.

Figure 12.1: Aerial view of Fortaleza, Brazil

After twenty-six hours of airplanes and airports, I arrived in Fortaleza, Brazil, just at the start of their hot, dry, and windy November summer. The first thing that I noticed from the plane was the amount of housing per city block, defined by the rustic clay shingle roofs. From the plane, I could see stray dogs chasing a group of flip-flop wearing teenagers down the street, school children playing soccer in a dirt field, and men fishing in what looked like an extremely tepid city drainage pond. This was not the United States or Europe. In fact, what I was seeing was just an early indication of what I was to experience nearly the whole time while I was in Fortaleza, and ironically what I had come to Brazil to study. These were communities of ultra-poor, ultra-displaced, and ultra-diseased Brazilians trying to scratch a living in an unbelievably harsh and degraded environment. This was the actuality behind the etiological and epidemiological disease theory that I had learned over prior several years. I was finally seeing it first-hand.

Figure 12.2: Teacher removing *Tunga* lesions from child in Foundation Kindergarten

My research collaborator, Jorg, as a physician and researcher in public health, took it upon himself to assist the poor in Fortaleza as much as he could. Having raised thousands of Euros in his home country of Germany, Jorg established a Foundation Kindergarten for underprivileged kids in one of Fortaleza's poorest *favelas*, Morro do Sandros. This foundation is the only place where these kids have the opportunity for a clean shower, a decent meal, and a basic education. In addition, the foundation removes the kids from the drug and sex trafficked corners of the favela and gives them a safe haven in which to grown and learn.

This picture shows the kindergarten teacher removing tungiasis lesions from a child (one whom I found out later was very boisterous and loved to have her picture taken). Unfortunately, these children are so overburdened with these parasites that the teacher must spend the majority of her time removing the lesions—a task that parents generally do not consider because they are too busy scraping a living or dealing with more 'important' matters—basic survival.

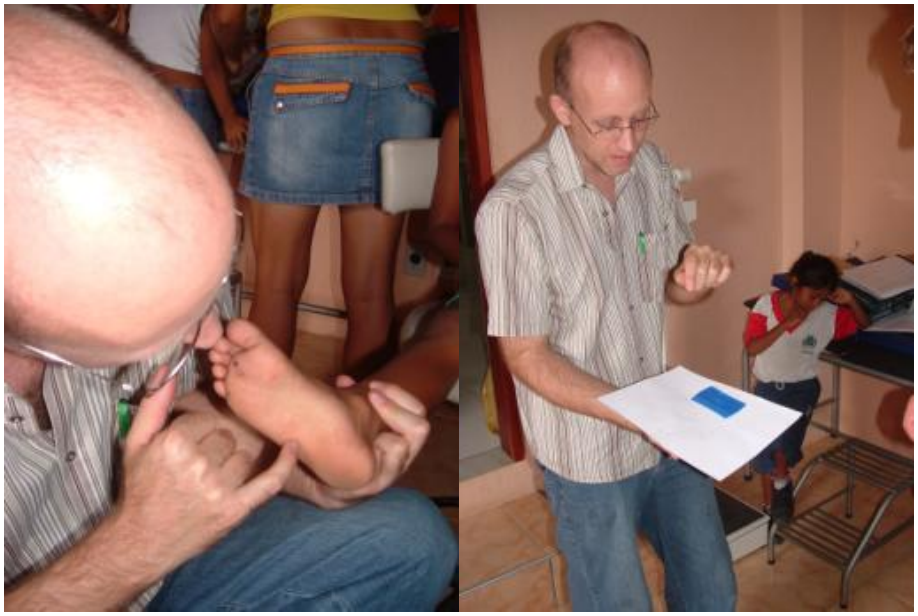

Figure 12.3: Jorg demonstrating tungiasis and pediculosis (head lice)

The reality of the setting of these favelas is that they are incubators for the development of so many diseases simply because of the socioeconomic-associated hygiene practices of the people that live in them. Tungiasis, which Jorg is pointing out here on the left, can be simply managed by wearing shoes, applying bug repellant, and clearing established lesions. However, these 'simple' public health measures prove too great even for these people—they cannot afford shoes or repellant (though they use home remedies like coconut oil and battery acid), and the parasite burdens are too large for them to keep up with. The one child in the left picture had several visible lesions at different stages on the bottom of his foot. To further illustrate the poor conditions of the favela, Jorg pulled a random girl from the kindergarten class and passed a single comb stroke through her hair. We counted 12 head lice from that one pass (in the right picture)! Control of pediculosis is relatively impossible here because treating a single child will just lead to re-infection from her classmates. These parasites lead to an array of spiraling conditions including superinfections, anemia, and impaired learning—just to name a small few.

Figure 12.4: Kindergarten children loved their pictures taken

One of the quirks of being in Fortaleza that I had to get use to was being the odd person out. As a tall blond Caucasian, I rarely matched the darker skinned and haired people around me. As such, I stuck out to such a degree that I was like a celebrity—at least among the children. They particularly loved my camera, not only because it was an electronic device (which they have few of) but it was also a way that they could pose and see themselves on screen (the LCD was equivalent to a big screen TV in their minds). Something I never came to understood was their use of finger 'signs' as they posed. Walking around the favela was actually very dangerous for a foreigner, especially one toting a laptop, GPS, and a camera. However, I used the fact that all eyes-were-on me as a tactic to deter potential thieves—which must have worked as I returned home with all the equipment that I brought. As a general rule, I found people to be extremely helpful and kind, especially in situation where I obviously had no idea what I was doing!

Riding the city bus was the main means by which I traveled around the city. It amazed me that there were New York-level traffic jams in Fortaleza, but that the jams were caused by city buses rather than taxis. I was disheartened at the amount of diesel fumes emitted by the buses and even acquired an air-quality-induced respiratory irritation while in Fortaleza.

Figure 12.5: Touring the favela

The realities of life are harsh in the favela. During my first day in Morro do Sandros, as Jorg was showing a German medical student and me around, we walked a young kindergarten boy whose father had been killed in an accident with a city bus a few hours earlier to his makeshift home (left picture). This was disastrous for his family, as his mother (who was a prostitute with several kids) now had the added burden of only having a single income to support her family.

One of the 'homes' we visited was occupied by a rather worn looking woman in her late 40's (right picture). Jorg explained to me that this woman has had a total of 20 kids during her life, many of different fathers, and that half of them had already died. Indeed, the reason we were visiting this family was because her newest 6-month old had severe fever. Their home absolutely astounded me with its sand floors, makeshift furniture, and lack of electricity. However, there was a wonderful amateur painting of the Virgin Mary on the wall.

Figure 12.6: Morro do Sandros

Morro do Sandros is one of the poorest favelas in Fortaleza. However, it is located next to one of the most famous and wealthy beach-suburbs of the city. As can be seen in this photograph, the tall skyscrapers of the beach upper-class are just a stone's throw from the urban slum of Morro do Sandros. The contrast between rich and poor is such an evident feature in Ceará State and across Brazil.

Trash collection is not a feature of the favelas. As evidenced here, many of the residents just throw their trash right outside of their homes. This rubbish acts as suitable homes for stray dogs, cats, rats, fleas, and other harbingers of disease. Plastic, with its ability to withstand decomposition for years, is found scattered around every corner of Fortaleza. To a Westerner, this seems untidy—but to the resident, this trash rolling in the wind is a natural part of the landscape. I have often times wondered that if I were in this situation, sitting around all day in the shade unemployed, if I might be induced to try to clean up all the rubbish around me, or if I simply would be so overwhelmed by it that I would casually ignore it.

Figure 12.7: Diseased stray dog in Morro do Sandros

While touring the favela, we came across many stray animals that were extremely shy and diseased. This dog had immediately noticeable scabies, an ectoparasitic disease that is often transmitted to humans. Scabies is highly contagious and from a public health standpoint is one of the most difficult ectoparasitic infections to treat. Though I did not directly see many people with scabies in the favelas, there is little doubt in my mind that the disease is endemic in human populations here as well as in animal populations.

Stray animals are a sad sight in Fortaleza and provide a reflection of the conditions suffered by humans as well. Just as these animals struggle to survive, so do their human counterparts. Many of the diseases that I encountered while in Brazil are shared between humans and animals that both live a co-existence in deprived conditions.

Figure 12.8: Stray dogs collected by the Fortaleza Department of Zoonotic Diseases

One of the places I visited while in Fortaleza was the city's Department of Zoonotic Diseases, which not only tracks communicable disease conditions in animals but also in humans. This department is responsible for controlling diseases by controlling their animal reservoirs and vectors. The department had a very large dog containment facility that catches around 50 stray dogs a day (right picture). Many of the dogs are tested for zoonotic infections, and all unclaimed dogs are put to sleep several days later. Extensive paper data records are kept recording the locations of collected animals and the presence of disease.

I met some veterinary students at the department that were dissecting some of the dogs to examine them for parasites. They showed me examples of active disease in several animals, including a dog (left picture) with a serious case of visceral leishmaniasis (an ulcerating disease transmitted to humans from animal reservoirs by sandflies).

Figure 12.9 Jorg pointing out cases of rabies in Fortaleza on a pin map

Coming from a computerized world of GPS and GIS, it was a shock to me to find out that the city of Fortaleza still used physical maps and pins to determine the structure of disease in the city. Jorg had taken me to meet the head of the Department of Zoonotic Diseases so that I could obtain some of the city's disease data for a spatial analysis. The head of the department explained to me that he had all the data on his computer, but the hard drive failed and he lost it all. The only data remaining for the past 4 years was a room full of blown-up street maps filled with pins representing the various diseases. Settling with this, I took high-quality photographs of the maps hoping I could extract what I needed from the photographs. I was able to crudely digitize the leptospirosis, leishmaniasis, and rabies cases onto a map in GIS, but was unable to go further because I could not match the case data with the spatial data simply because of the incompleteness of the publically available street shapefiles for Fortaleza. This was a disappointment, because data for leprospirosis and rabies rarely exists in such magnitude suitable for spatial analysis.

Figure 12.10: Research collaborators including Germans, Brazilians, and an American

The acquisition of data in Brazil comes in two ways: 1) the direct collection of data from the field; and 2) through collaboration with those who have already collected the data. What is unique about geography is that it can use data from other sources that were collected for purposes other than spatial analysis. In my case, I was on the hunt for spatial data and epidemiological data. Depending on the scale, I could obtain spatial data from the internet or collect it in the field with a GPS. Without qualifications, I could not collect epidemiological data directly, however, and had to rely on collaboration with healthcare workers to get this information. In most instances, this involved Jorg introducing me to his colleagues who worked in various capacities such as the Director of Leprosy Elimination in Rondonia or simply as a general physician at the local health clinic. In most instances, these people were enthralled that I was interested in their data and happily agreed to let me use it in my research. One of the disturbing factors about this process, however, was how easy it was to obtain confidential disease data! In countries like the United States, obtaining epidemiological data is a drawn out process that requires approval from a variety of third-party sources. However, in Brazil, the need for people to analyze such data has made its acquisition much easier to the researcher.

Figure 12.11: Breakfast with German medical students

In one of my more relaxing field trips, a group of German medical students and I took a bus to the famous coastal town of Lagoania, northwest of Fortaleza for the weekend. These students came to Fortaleza via Jorg to do observing and participate in research. One of them, Daniel, was explaining to me that he came to Fortaleza to do research in the Obstetrics ward, where he was learning to deliver babies with HIV+ mothers. Liana (to my right) was the only Brazilian among us, and she was assigned to be my 'assistant' while I was in Brazil. She was one of Jorg's graduate students who had recently been awarded a scholarship to research tungiasis in Mozambique. Originally, Liana and I were going to work on a project that was to involve a mini-GIS spatial analysis of the predilection sites for tungiasis on the human body.

Liana proved to be a great asset during my time in Fortaleza, showing me around and translating for me in most of the instances where I could not. We had a very relaxing weekend in Lagoania eating local seafood and doing a bit of swimming and surfing in the Atlantic.

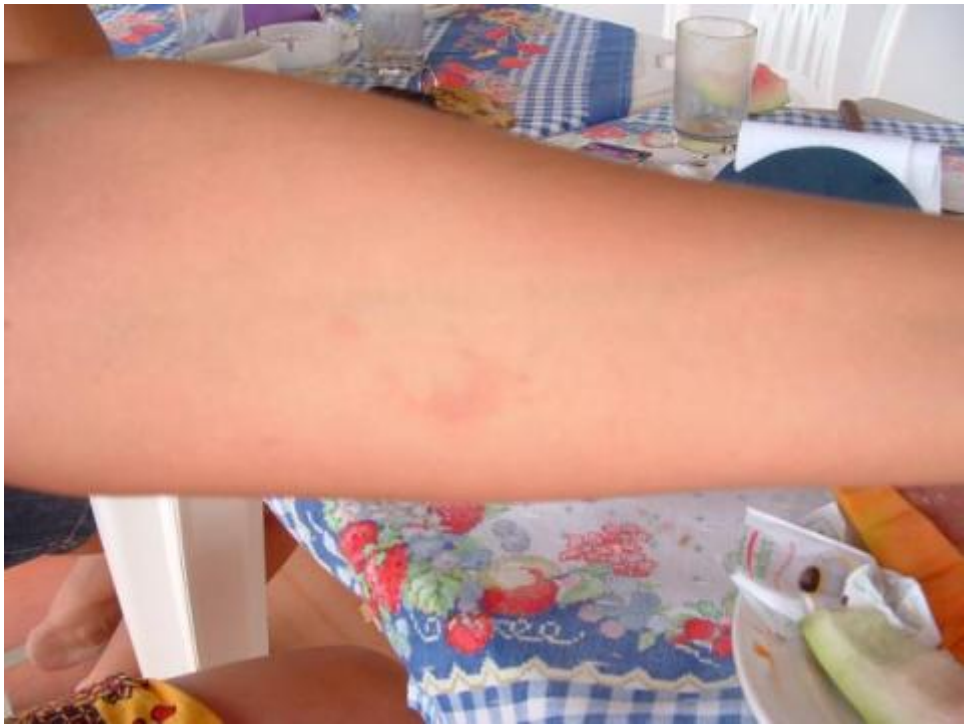

Figure 12.12: Cutaneous larval migrans on a German medical student's arm

When studying tropical diseases in the field, there is always the chance of contracting the diseases you are studying. While eating breakfast in Lagoania, I happened to notice a red macular lesion on one of the German medical student's arms. Asking her about it, I found out that it was cutaneous larval migrans (CLM). CLM can be caused by several zoonotic parasitic helminthes of animals that accidently invade the human body and crawl around inside a bit before dying. I was told in Australia that many aboriginal people present with large cuts in their arms because they were trying to "cut out the worm." In reality, these worms burrow through to the subcutaneous layer and usually hours to days later an immune reaction occurs causing these red macular lesions. However, by the time the lesions appear the worm has moved on. Simple hygiene is a control for these, as they are transmitted through animals' fecal material left as an environmental contaminant. The number one rule for tropical disease field research, therefore, is do not put anything in your mouth that is not clean and do not walk barefooted!

Figure 12.13: Views of typical home sites in Balbino

One of my primary objectives while in Brazil was to collect GPS coordinates of households in Balbino, a small village on the southeast outskirts of Fortaleza. The reason I chose Balbino as a study area was because Jorg had done several very thorough epidemiological studies that included disease data for nearly the entire village's population. Balbino was shocking to me because it was a community practically carved out of sand dunes and swamps—a seemingly unlikely choice to set up a community. The houses were very basic, usually made out of wood sticks and palm fronds, and had rudimentary kitchens set apart out the back so that fire was not an issue with the main dwelling. Most of these people drank from bore water, which when I had visited had recently been contaminated causing Balbino to import truckloads of potable water from Fortaleza. A jean factory had recently moved into Balbino, creating a mini-economy in the village and giving hope to the people who were traditionally working in the failing fishing industry (on Google Earth images of shrimp farms can be seen around Balbino—which have led to an enormous amount of salt water invasion and coastal destruction). Despite the factory, the socioeconomic future of Balbino remains uncertain.

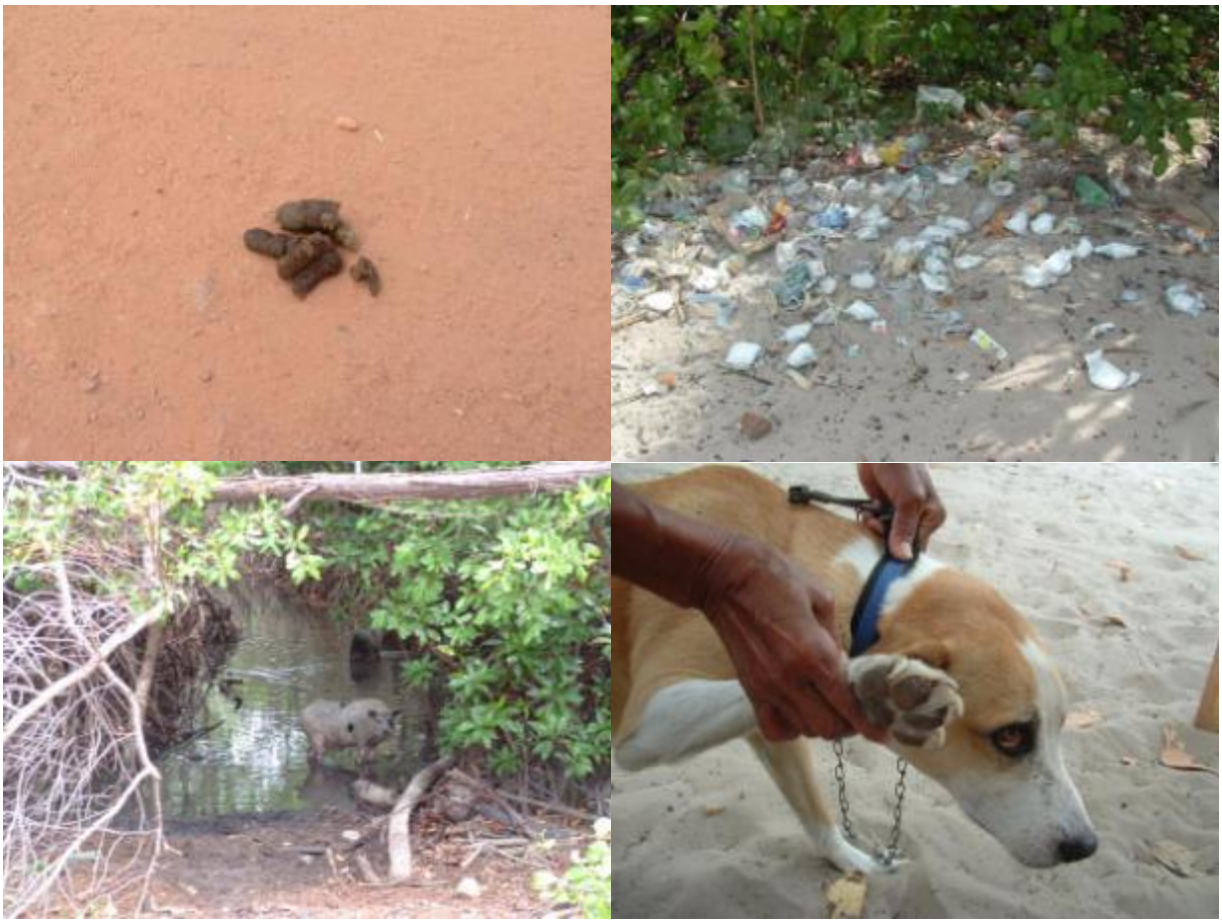

Figure 12.14: Some of the causes of zoonotic disease spread in Balbino

While walking through Balbino, several lessons that I had learned in public health training about the lack of hygiene practices that lead to disease became apparent. As discussed earlier, many zoonotic diseases are transmitted to humans via fecal contaminants that contain either eggs or infective worms. It was common while walking around Balbino to find animal dung on the walking paths—and equally common to find villagers walking around barefooted. In one house we visited, the residents were disposing of their baby diapers in an enclave behind their house that double d as a pig pen. Obviously the pigs were eating the diapers, which may or may not have been contaminated with helminthes that in turn were infecting the pigs. One lady gladly showed us her pet dog, which reluctantly allowed us to look at its tungiasis lesions.

Figure 12.15: Lady offering cashew apples to research passers-by

I had always eaten cashews at parties and at home, but never really comprehended where they came from. In Brazil I found the answer: they grew on large shady trees and hung off the bottoms of these fruits that tasted like apples. It was an odd arrangement of a kidney-bean-looking nut handing off of a bell-pepper-looking fruit.

I was instantly flabbergasted and ecstatic the first time I saw a cashew hanging on the tree, as I tried to imagine how many fruits it would take to fill a box of nuts. I was told by many of the Brazilians that I came across that the fruit was nice to eat and its juice sweet, but that I should not eat the cashew nut raw. Come to find out, the raw nut contains cyanide that must be roasted out before it can be eaten—a process that added to the complexity of processing these nuts. Every time I see or eat a cashew now, I am reminded of where they came.

Figure 12.16 The curse of plastic in the developing world

Even in rural communities like Balbino one can find rubbish strewn about over the landscape. Plastic seems to be a curse for the developing world, with a strong penchant for shopping bags and water bottles to resist decomposition and remain as permanent fixtures. I saw a similar problem in North Africa, where people find ways of recycling just about everything except for plastic shopping bags. Balbino was not an exception and in just about any part of the village was littered with residual plastic items. Fortunately, plastic rubbish tends not to be directly associated with being a fomite for disease, but is an indication that a community is not practicing effective garbage collection. It is saddening to see such beautiful areas littered so badly, especially considering what little effort it takes to keep things tidy.

Figure 12.17: Relaxing during data collection in Balbino

Balbino in mid-December is hot, windy, dry, and dusty. Fortunately for me, I was use to the heat and walking around the village for a few days did not prove to be overwhelming. My two companions, Liana and Maria, were equally use to the heat. Most of the people in Balbino did not have electricity or air conditioning, so they sat out in the shade during the heat of the day making it easy to chat with them. Although the heat can be a deterrent to most people, I did not mind it, especially considering that most of the mosquitoes and sand flies were not active during the hottest parts of the day.

Liana was able to find us local food to eat during our fieldwork and often times we were invited in to eat with families—this gave me ample opportunity to see not only the inside of the homes but also to learn a few new culinary techniques. The most memorable item that I ate while in Balbino was a stew made of manna ray that was eaten with rice. It was a bit stringy, but very tasty. I have to say that the food in Brazil is very unique, being a blend of local products and western presentation. I did have to adjust to the eating schedule of Brazilians, which includes a light breakfast, a very heavy lunch, and a light supper late at night. The large lunches nearly incapacitated me for a couple of hours, but gave me a good understanding of the necessity of siesta.

Figure 12.18: Christmas time in the favela

I was fortunate enough to be in Fortaleza around Christmas time so that I could share in the special activities that Jorg had planned for the children in Morro do Sandros. As a fundraiser for the activities, the children made Christmas cards from their own recycled paper, and Jorg sent the cards to Germany to be sold to raise money. With the funds, Jorg bought the children Christmas presents which happened to be delivered by Santa himself! The children had also prepared several Christmas songs, which they very eagerly sung to the group of German medical students and me. Afterwards was a feast for the kids that included hot dogs—something that I would normally consider 'junk' food but was actually quite a positive augmentation of these kids' diets. In addition to the presents given to the children, the German medical students and I donated money to buy baskets of rice and beans for each child's family.

Figure 12.19: Learning to speak the language

I have learned through experience that learning a language is a lot easier if thrown into it rather than having to study it independently. Before going to Brazil, I bought several Portuguese language books to learn the basics in grammar and syntax and a few useful vocabulary words. While there, however, I was amazed to find that people would speak to me in English by preference. This was especially true for all of the academics and students that I met—come to find out learning English is a big priority for them because English is considered critical in getting publications.

In a somewhat comical event, one of Jorg's friends in the Kindergarten Foundation came up to me and started rattling off in Portuguese at me, to which I simply continued to nod and smile. I believe he talked to me for about five minutes and in that time I think that I understood maybe five or six words that he said. However, I do not think he ever realized that I did not speak Portuguese.

Figure 12.20: Future opportunities in Fortaleza

During my two-month field research campaign in Brazil, I was able to meet many wonderful people who showed me both the best and worst aspects of their country. I left Brazil not only with valuable research data, but also with experiences that I will never forget. Before I left Fortaleza, I took a picture of a dental chair located in the Kindergarten Foundation to serve as a reminder that someday I may be able to return to Brazil with an increased capacity to directly help the people that I once researched.

CHAPTER 13. CONCLUSION

The health landscape of most of the world today is an amalgamation of disparities, contrasts, complexities, and opportunities. These challenges are intricate outcomes of the extraordinary interplay between human physical and cultural environments that reflect the vast multitude of spatial 'uniqueness' that exists around the globe. In essence, these differences are all products of *geography*—and since the dawn of time one key principle has dominated and guided the pursuit of medical inquiry: that health is fundamentally and intimately linked to geography.

There is perhaps no greater place on earth where geography—both physical and cultural—plays such a prominent role in health outcomes as in the tropical developing world. It is here that literally billions of people suffer and die from easily curable or preventable diseases that exist because of a range of factors that scale from issues of hygiene that cause diseases like dracunculiaisis to complex host-vector-agent interactions that result in deadly infestations with diseases like falciparum malaria. It is also in the tropical developing world where the greatest social and economic inequalities exist. In terms of health, this means diverging from the standard medical practices of the developed world to create new and innovative ways to find, detect, and treat disease as well as sustaining adequate health in populations and communities—not just individuals. The challenge in developing these new approaches over the last three hundred years, since the dawn of 'tropical' medicine, has been to identify those geographic factors unique to the tropics that result in such disproportionate amounts of disease in these populations. It has thus been necessary to develop an array of tools, technologies, and methodologies within geography that can be used to gain a better understanding of the etiology, epidemiology, and control of tropical diseases.

Despite the complementary natures of medical geography and tropical medicine, these two disciplines have only recently begun to realize the potential of each other. Indeed, since they both diverged from imperial medicine around the middle of the nineteenth century, medical geography and tropical medicine have both developed as separate and independent entities within the social and health sciences, respectively. It has only been recently, since the development of several key technologies and methodologies in medical geography and the emergence and re-emergence of several key tropical diseases, that we have seen the reunification and increased communication between these two fields.

The unprecedented growth in medical geography over the last two decades is partially attributable to an increase in demand for health-related research, but the main push forward for medical geography has been the advances seen in geographic technologies and methods. Geographic information systems, developed in the 1980's, have proven to be by far the greatest impetus and asset to the growing field of medical geography. This technology, which enables the capturing, storage, analysis, and display of complex sets of many different data types, has revolutionized not only the field of geography but also the multitude of sister fields that use GIS as a tool for spatial research. To complement the applications of GIS in geographic research, several other key technologies have also emerged in the last few decades including remote sensing and global positioning systems. Remote sensing has enabled the acquisition of data in areas of the globe that was previously impossible and has enabled the continuous recording of large amounts of environmental data over time—with direct implications for research dealing with global trends over long periods, such as the study of climate change on human health. Global positioning systems, which use trilateration to determine a user's position in space and time, have also transformed geographic research. This technology over the past decade has

become increasing user-friendly, affordable, and widespread such that its applications have extended far beyond academic research to be included in many parts of everyday life, such as in vehicle navigation. GIS, remote sensing, and GPS have thus enabled a degree of geographic analysis and application that is larger than anything seen in geography's history, and promise to continue to revolutionize the field as more sister fields recognize its great potential.

One of the features of medical geography that has made it so useful in health research is statistical spatial analysis, which enables the quantification and qualification of health events in comparison to a hypothetical distribution. There are a variety of spatial statistics, including global, local, and focal statistics that can be used in spatial analysis. In health research, spatial statistics are usually taken a step further to include cluster detection. Cluster detection has increased the capacity of spatial analysis in health research because it enables the rapid identification of areas that represent either high or low disease risk. Once these areas are identified and determined to be statistically significant, hypotheses can be made about the underlying processes that produce the patterned events—hypotheses that can lead to insight into a disease's causation or to the discovery of potential risk factors. As such, the spatial statistical methods offered in medical geography are extremely valuable tools in health research.

Medical geography, with its powerful armamentarium of technologies and methods, has expanded into a variety of niches across a variety of disciplines. One field that has embraced medical geography in recent years is tropical medicine, or the study of health problems that occur more frequently or are more difficult to control in the tropics. The relationship between medical geography and tropical medicine is evident in the literature, especially in social science and geographic literature, but is less evident in tropical medicine literature. Because many of the people who would implement the results of spatial analysis into the field are more likely to read

or come across articles in tropical medicine journals rather than geography journals, it becomes vital to understand the trends of use and publishing of geographic articles within tropical medicine journals.

In an examination of tropical medicine journals, it was found that only a little more than one percent of published articles actually contained geographic analyses that utilized GIS. Fifty-four percent had first authors from the United States and Europe, while thirty-seven percent had authors from tropical developing countries. A little more than half of the articles, or fifty-three percent, had authors affiliated with the country in which the investigation was undertaken. Most of the articles examined three key tropical diseases: malaria, schistosomiasis, and dengue. What these trends indicate is that mainstream tropical disease research is still dominated by non-tropical developed countries and that the applications of GIS are still only applied to specific tropical diseases with propensity for spatial analysis. One apparent trend discovered by this research is that the number of articles with GIS published over time in tropical disease journals has substantially increased over the past seven years. With increased awareness of the capabilities of medical geography within tropical disease research, there is no doubt that this trend will continue. What is needed, however, is increased cooperation between developing and developed world research groups so that the results of such studies can be more effectively applied in the field—namely in tropical developing countries. This means engaging more scientists from the tropical developing world, encouraging more publications from this part of the world, and undertaking more studies that utilize geographic methods in tropical developing countries. With these goals in mind, geographers and clinicians will be more equipped to develop the relationship between medical geography and tropical medicine, with direct consequences for the improvement of health in these parts of the world.

With a clearer understanding of the role that medical geography can play within the fields of tropical medicine and public health, this dissertation further examined six case studies that implemented the methods of geographic analysis into several sets of health data. These case studies were all based on data collected in the field in Brazil, a country that has proven to be an ideal setting for this research because of the prevalence of tropical diseases, the quantity and quality of health data collected by the Brazilian Ministry of Health, the vigor of Brazilians to want to use up-to-date geographic technologies and methods, and their urgent need to focus resources on several diseases and underprivileged communities across the country.

The first case study presented herein utilized several basic and fundamental concepts in spatial analysis to determine the spatial structure of the human flea disease tungiasis in a rural fishing village of northeast Brazil. Using spatial descriptors, the K-function, and hot spot analysis, it was determined that tungiasis is weakly spatially autocorrelated in Balbino, though no more than population itself. These results indicate that the disease tungiasis, though dependent on an environmental cycle, is more likely to be correlated with population rather than environmental risk factors. This conclusion is in agreement with several qualitative clinical hypotheses for tungiasis such as variable in-home attack rates dependent on individual family member parasite burden. Tungiasis, a disease that is rarely investigated in medical literature despite its high prevalence in underprivileged communities, deserves further attention from both medical geographers and clinicians in order to more effectively illicit its control and prevention.

The second case study presented in this dissertation examined the spatial structure of four intestinal helminths over time in Balbino. The unique feature of this study was that it utilized epidemiological data collected during three periods before and after mass treatment with the anti-helminthic drug Ivermectin. This enabled the visualization of parasite re-appearance after

treatment that potentially could correspond to areas where these parasites are most prone to infect. The geographic method used to determine this visualization was kernel density interpolation, a relatively quick and easy technique that produces choropleth maps of parasite density. Results of this case study indicated that each of the four parasites is likely to show environmental niche-partitioning and that Ivermectin is likely to induce varied effects on the spatial structure of each parasite. Two of the parasites, *Strongyloides* and *Ascaris*, showed definite propensities of infection in certain areas of the village that correspond to sandy and swampy regions despite the fact that they are transmitted through larva and egg stages, respectively. This case study, though easily analyzed using GIS, shows how methods of geographic analysis can complement the results of an epidemiological study and enable quick visualization of parasite trends over time.

The third and fourth case studies, in an effort to augment the leprosy elimination effort in Brazil, examined spatial autocorrelation of leprosy incidence in two ecologically and demographically distinct regions of Brazil, Ceará and Rondonia states. The methods used in both of these case studies were identical, allowing direct comparison of the results across the two states. A freeware software program, SatScan, and the Kulldorf space-time scan statistic were implemented in order to quantify the spatial autocorrelation of leprosy. Results indicated that leprosy was both positively and negatively spatially autocorrelated in both states. In Ceará, positive autocorrelation tended to be within the most populated municipalities—a fact that reflects the recent mass migration of rural communities into the urban areas of Ceará because of drought and lack of employment. In Rondonia, positive autocorrelation tended to be more generalized and included larger areas of the state—reflecting the rural nature of Rondonia and perhaps a less developed health infrastructure system for leprosy detection. Methods of spatial

autocorrelation like the ones demonstrated in these two studies have the potential to be utilized in leprosy surveillance programs across Brazil in order to effectively assess detection trends, treat and control cases, and manage health resources.

The fifth case study in this dissertation presented a novel method of data adjustment in order to more effectively analyze epidemiological trends across demographically variable regions. Rate adjustment, though frequently employed to report epidemiological trends in tables, is rarely employed in geographic analyses and to the author's knowledge has never been employed in order to examine its effects on spatial autocorrelation. Using the same data examined in the fourth case study in Rondonia state, this case study adjusted leprosy incidence rates to both state and national population estimates according to four demographic variables. Results show that adjusting rates dramatically alters the results of spatial analysis, but that the results of rate adjustment are more likely to reflect the true underlying situation of leprosy incidence across regions with complex demographic variation. This topic deserves more attention from statisticians and researchers, as it could be used to more accurately portray the leprosy situation across Brazil and other hyper-endemic countries when spatial analysis is employed.

The sixth and final case study presented in this dissertation is comparable to the third case study on leprosy autocorrelation in Ceará State, except that this case study considered the spatial autocorrelation of tuberculosis. Though these diseases lie within the same bacterial family, their niches within communities is known to be almost polar opposites. The results of the spatial analysis confirm this idea, with cold spots and hot spots appearing in different areas than what were seen with leprosy. However, Fortaleza, the most populated municipality of Ceará, was a hot spot for both leprosy and tuberculosis in both analyses. Fortaleza, which has

witnessed unprecedented growth and migration in recent years even for Brazilian standards, is deserving of closer analyses that examine smaller scales of autocorrelation. Though the location of transmission of leprosy and tuberculosis is almost impossible to identify, spatial analyses on city-level scales would be able to give clues as to the dynamics of detection, treatment, and management of these two diseases.

This dissertation thus presented several case studies that demonstrate how geographic methods common to medical geography can be applied to epidemiologic data sets that deal with tropical medicine. Though not all geographic analyses of health problems are identical, the basic framework for approaching these problems is consistent and the case studies presented here can be used to get an idea of how to organize such an analysis. For many health professionals, the idea of approaching geographic methods and analyses on their own is daunting; however, many health professionals do not realize the abundance of free geographic software designed specifically to analyze epidemiological data from geographic perspectives—the results of which are easily interpretable by non-geographers. The ideal situation, however, is for health professionals and geographers to work together in their research so that both analysis and interpretation can be taken to higher academic levels. This cooperation will no doubt continue to solidify the role that geography plays in health research, and lead to more effective and efficient disease control and prevention strategies with direct consequences for global human health.

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VITA

Born and raised into two Welsh families, William Brennan Arden, 27, graduated from the Louisiana School for Math, Science, and Arts, in Natchitoches, Louisiana, in May of 1999. While a student at LSMSA, he was a member of the National Physics Olympiad Team, was awarded at graduation for his accomplishments in math and music, and was one of 15 students to earn a "Graduation with Distinction" for his research into the lives of classical composers Chopin and Rachmaninoff that culminated in a seminar and senior recital.

In the fall of 1999, Arden began his undergraduate studies at Louisiana State University in Baton Rouge, where he was a member of the Honors College, the College of Basic Sciences, and the College of Arts and Sciences. Arden continued his study of music at LSU under the direction of Dr. Jennifer Hayghe, and worked as a supplemental instructor in biology, a research assistant in marine physiology and genetics, and a bird specimen preparer in LSU's Museum of Natural Sciences. He was a member of the Honors College Advocates as well as an Honors Fellow of the Intercollegiate Studies Institute. In the fall of 2001, Arden participated in a LSU reciprocal exchange at the University of Essex, Colchester, England. In 2003, he was initiated in the oldest honor society in America, Phi Beta Kappa. Arden graduated from LSU in 2003 with 196 credit hours and three bachelor's degrees in international studies, history, and biological sciences.

Arden began his post-undergraduate studies in the fall of 2003, enrolled in the School of Medicine Class of 2007 at the University of Texas Medical Branch in Galveston, Texas. In the Fall of 2004, Arden decided to discontinue his study of medicine and began graduate school in the Department of Geography and Anthropology at LSU. During the Spring of 2005, Arden studied abroad as a graduate student at the University of Fribourg, Switzerland, in the Faculté de

Science's Département des Géosciences. In the Fall of 2005, Arden continued graduate studies in the LSU Department of Geography and Anthropology, completing his thesis research entitled "Urban Yellow Fever Diffusion Patterns and the Role of Micro-Environmental Factors in Disease Dissemination: A Temporal-Spatial Analysis of the Memphis Epidemic of 1878." In December of 2005, Arden graduated with a Master of Arts in geography from LSU.

In January of 2006, Arden was awarded a Rotary International Ambassadorial Scholarship from Rotary District 6200 to attend James Cook University in Townsville, Queensland, Australia. Hosted by the Mundingburra Rotary Club of District 9550, Arden pursued graduate studies at James Cook University's Anton Brienl Centre School of Public Health and Tropical Medicine, where he was first formally introduced to the story of alleviating tropical diseases in the developing world. Finishing requirements for his degree in late October 2006, Arden graduated in March of 2007 with the degree of Master of Public Health and Tropical Medicine.

While at the Anton Brienl Centre, Arden was introduce to Dr. Jorg Heukelbach, a German research physician who managed a slum-based public health clinic in the *favelas* of Fortaleza, Brazil. After discussing potential research topics, Arden decided to travel to Brazil in November of 2006 in order to collect data for his doctoral research. Returning in January 2007, Arden resumed studies in the LSU Department of Geography and Anthropology, and took the position of instructor for GEOG 1001, the Geography of the Americas and Europe.

In July of 2007, Arden entered the Dental School Class of 2011 at the University of Texas Health Science Center at San Antonio, where he is currently pursuing a Doctor of Dental Surgery degree. Besides being a keen pursuer of academic degrees, Arden also enjoys three solid

hobbies: piano and classical music, swimming, and traveling. Since the beginning of his travel career in 2001, Arden has visited and explored countries on every continent except Antarctica. It is his hope to continue traveling and one day settle into a philanthropic professional career.