A MULTISCALAR ANALYSIS OF BURULI ULCER IN GHANA: ENVIRONMENTAL
AND BEHAVIORAL FACTORS IN DISEASE PREVALENCE

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Buruli ulcer (BU), an infectious disease caused by *Mycobacterium ulcerans*, is the third most common mycobacterial disease after leprosy and tuberculosis and a WHO-defined neglected tropical disease. Despite years of research, the mode of transmission of BU remains unknown.

This master’s thesis provides an integrated spatial analysis of disease dynamics in Ghana, West Africa, an area of comparatively high BU incidence. Within a case/matched control study design, environmental factors associated with BU infection and spatial behaviors are investigated to uncover possible links between individual daily activity spaces and terrains of risk across disturbed landscapes. This research relies upon archival and field-collected data and analyses conducted with geographical information systems (GIS).
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CHAPTER 1
INTRODUCTION

Buruli ulcer (BU), an infectious disease caused by *Mycobacterium ulcerans* (MU), has become an international public health concern. In 1998, the World Health Organization (WHO), with support from many international partners, established the Global Buruli Ulcer Initiative to address this growing problem. In the Yamoussoukro Declaration, which resulted from a conference held later that year, participants stated that due to “the increasing number of cases and the associated health complications, Buruli ulcer could hinder efforts to improve the economic and social development of the communities most affected” (WHO 1998).

On October 14, 2010, WHO released its first global report on neglected tropical diseases. Neglected tropical diseases are characterized as receiving little attention from the general public and the public health community due to the fact that they usually occur in areas of poverty and conflict, places vulnerable to the spread of infectious disease (WHO 2010). According to the WHO, more than a billion people suffer from neglected tropical diseases, or about one-sixth of the global population (WHO 2010). Buruli ulcer disease is one of these seventeen neglected tropical diseases.

Research has yet to identify a definitive mode of transmission for BU, yet many potentially critical associations, including proximity to natural bodies of
water and landscape disturbance, have been identified with risk of contracting Buruli ulcer (Merritt et al. 2010, WHO 2010). Additionally, human behavioral factors have been linked to possible interaction with these spaces across MU environments. Building upon this body of literature concerning the possible etiology of BU and ecological components of its disease dynamics, this research analyzed archival and field-collected datasets from the Upper Denkyira East district in Central region of Ghana in an attempt to investigate the relationship between Buruli ulcer incidence and these environmental and behavioral factors at individual and community levels.

Implications of Research

This study is part of a larger project funded by the National Science Foundation (CNH Award #0909447: Research and Education on Buruli ulcer, Inundations, and Land Disturbance – ReBUild, rebuildghana.org) involving geographers, earth scientists, medical professionals, and education specialists from several US and Ghanaian universities and other research partners. The goal of this transdisciplinary investigation is to evaluate socio-ecological complexities of BU disease dynamics and environmental and behavioral risk factors for MU interaction, as well as provide public health education and cultural exchange in primary schools in Ghana and the US. The collaborative nature of the project as well as the broad spectrum of expertise of the team supports the framework and approach to this complex health issue. The specific contribution to the project from this research is to provide an approach to delineating daily
activity spaces in order to analyze human movement across the landscape and identify potential interactions with areas thought to be high-risk for MU exposure. These data and methodology, in conjunction with additional quantitative and qualitative data collected through the ReBUild Project, may provide insights into BU disease dynamics, as well as overall understanding of the microgeographies of BU.

**Research Questions**

In preliminary analyses investigating associations of 1999 national BU prevalence to land cover, clusters of BU disease were found in certain districts within the Central, Western, and Ashanti regions of Ghana. The national-level patterns of infection rates from these analyses correspond with earlier findings within the BU literature concerning relationships of disease prevalence to environmental factors. The results of that work led to the following research questions, the core focus of this study. The questions are addressed through several methodologies, drawing upon earlier work and incorporating archival and field-collected data from the case study area in the Upper Denkyira East district in Ghana.

*What is the microgeography of BU prevalence in Ghana?*

BU risk factors and prevalence have been examined in endemic areas around the globe, many times at the national level. (Amofah et al. 2002, Debacker et al. 2006, Sopoh et al. 2007, Brou et al. 2008, Wagner et al. 2008b) These studies yielded important information concerning the overall relationships
of BU disease patterns of infection, environmental factors, socio-demographic and behavioral variables. However, the results of these broader investigations indicate that examinations of the patterns of BU at local scales may provide important insights into possible modes of transmission and prevalence.

*How do microgeographies of local environment, landscape disturbance, and spatial behavior relate to BU prevalence?*

The study of spatial patterns of BU prevalence has identified environmental (Aiga et al. 2004, Brou et al. 2008, Wagner et al. 2008a), landscape disturbance (Duker et al. 2004) and behavioral factors (Raghunathan et al. 2005, Sopoh et al. 2010, Quek et al. 2007, Pouillot et al. 2007) which relate to infection rates and patterns. This research evaluated how these factors may contribute to BU prevalence at an individual and community level, through employment of daily activity space analysis.

*Does the spatial distribution of BU disease vary at multiple scales?*

Research into BU at local scales (Pouillot et al. 2007, Williamson et al. 2008) has provided insights into the spatial patterns of BU infection. This research investigated patterns of BU prevalence at the individual and community levels, and then attempt to evaluate these analyses within a broader context.
Buruli Ulcer Epidemiology

Buruli ulcer is the third most common mycobacterial disease after leprosy and tuberculosis (Sopoh et al. 2010). The infections begin as painless nodules underneath the skin that, if untreated, can progress to large ulcers (Figure 3), resulting in massive tissue loss (WHO 2008). If identified in the early stages of
the disease, successful treatment has been accomplished with antibiotics. In a study of three hundred patients in West Africa, a 50 percent success rate of treatment was attained solely through the use of antibiotics (WHO 2010).

Mortality rates for BU are relatively low, but delaying treatment can result in long lasting effects. (WHO 2010) In these cases surgical removal of infected tissue, sometimes requiring multiple skin grafts to treat the ulcerated tissue, can lead to severe disfigurement. This is particularly troubling due to the fact that children under the age of 15 constitute 75 percent of all cases of the disease worldwide (WHO 2007), potentially permanently affecting future productivity and quality of life.

Early treatment is key, as delays in diagnosis and treatment necessitate more invasive treatment procedures. Due to issues surrounding the expense of BU treatment and mistrust of Western-style medicine, among other factors, many people turn to alternative sources of care, such as traditional healers, or avoid treatment altogether. As most of those affected by Buruli ulcer are children, this can mean facing a lifetime of hardship living with the resulting disability and social stigma (Grietens et al. 2008).

Although previously described in the late 19th century in the Buruli area of Uganda, it was not until 1948 that the causative agent for BU was identified in Australia as *Mycobacterium ulcerans* (MU) (WHO 2007). MU is an environmental mycobacterium that has an optimal growth temperature range from 30-32°C (86-90°F) in tropical and subtropical areas (WHO 2010). In 1998, after many
decades of attempts to isolate the causative agent from nature, researchers identified Strain 00-1441, which “represents the first fully characterized culture of the agent of BU from an environmental source” (Poertaels et al. 2008). This culture, derived from an aquatic insect, supports research identifying an environmental nidus for MU (Poertaels et al. 2008).

Since the mid-twentieth century, there has been a marked increase in the number of cases of BU disease globally (WHO 2010). It has now been reported in over thirty countries, mainly in tropical and subtropical regions, from West Africa to Asia to Central and South America (Walsh et al. 2008). (Figure 2) West Africa has experienced a comparatively greater increase in BU prevalence. This is particularly true in Côte d’Ivoire (24,000 cases reported from 1978 and 2006), Benin (7000 cases), and Ghana with 11,000 cases since 1993, which represents almost one-fifth of the global disease burden (WHO 2010). A total of 5,619 patients were reported during a national case search in 1999 (Amofah et al. 2002). However, because of widespread underreporting, misdiagnosis due to insufficient knowledge of symptoms, distance from treatment centers, and the serious social stigma associated with the disease, estimating BU prevalence accurately is difficult (WHO 2010). The challenges of clinical treatment of the disease underscore the importance of education campaigns, both for medical professionals and the general public, in stemming the spread of infection.
**Figure 2** 2009 Worldwide *Buruli ulcer* incidence (Merritt et al. 2010).

**Figure 3** Active *Buruli ulcer* infection.

**Figure 4** Potential BU vectors: semi-aquatic hemiptera (Johnson et al. 2005).
The infection pathway of BU remains unclear, but possible modes of vectored and environmentally-sourced transmission have been identified in recent decades. MU has been found in the saliva of certain aquatic insects that may serve as a vector for the disease (Marsollier et al. 2002, Johnson et al. 2005, Portaels et al. 2008, Marion et al. 2010). (Figure 4) A recent study in Cameroon identified several species of water bugs that tested positive for MU. The density of these potential vectors was ten times higher in areas known to be endemic for BU than non-endemic areas (Marion et al. 2010). In addition, potential reservoirs for MU have been identified in Australian terrestrial mammals, including koalas, possums, and alpacas (Portaels et al. 2001, Fyfe et al. 2010). Other investigated potential MU reservoirs include mosquitoes and sand flies (Johnson et al. 2007), fish (Eddyani et al. 2004), snails and mollusks (Marsollier et al. 2002), and certain amphibian species (Drancour et al. 2002). It has also been posited that MU is part of the normal microbial flora, or biofilms on aquatic plants (Merritt et al. 2005). The complex role potentially played by reservoirs and vectors in MU exposure dynamics complicates the challenge of identifying BU infection etiology (see Merritt et al. 2010 for a discussion).

Environmental and Behavioral Factors

Many variables have been shown to have an influence on the prevalence of Buruli ulcer. If we view the disease dynamics of Buruli ulcer through the lens of the human ecology model, which describes the continuum of population, environment, and behavior as the main determinants in disease ecology, we can
identify specific elements which contribute to BU infection rates and spatial distribution. Notwithstanding important elements of the genetic component of the disease ecology of Buruli ulcer, the behavioral and environmental factors are the main focus of this research, with a much greater emphasis on the natural, built, and social structures of the environment.

One important variable in the ecology of Buruli ulcer is age. Children under the age of 15 constitute 75 percent of all cases of the disease worldwide (WHO 2007). Although no difference exists in disease prevalence amongst boys and girls of this age group, in adult cases women are more likely than men to contract the disease (WHO 2010). Another factor that has been shown to possibly influence vulnerability to Buruli ulcer is family history. Statistical analysis of Buruli ulcer patients in Benin resulted in an odds ratio of greater than 5 for contracting the disease if there was a history of Buruli ulcer infection in the family (Sopoh et al. 2010).

Land use/land cover many times represents the most critical impact on the spread of infectious disease. This is particularly true in the case of a disease that is caused by an environmental agent such as *Mycobacterium ulcerans*. The ecology of Buruli ulcer is therefore integrated into the natural environment, and alternating patterns of land cover affect its spatial distribution patterns (Meade and Emch 2010). For example, research has indicated that Buruli ulcer infection rates are positively correlated with the percentage of agricultural land surrounding a village and negatively correlated with percentage of urban land.
use surrounding a village (Wagner et al. 2008b). In addition, land use changes, such as agricultural intensification, development of mining operations and transportation infrastructure, etc., can result in drastic changes in the disease patterns of vectored or naturally occurring infectious diseases (Meade and Emch 2010).

In studies of land use/land cover and associated Buruli ulcer prevalence in West Africa, certain characteristics have been shown to increase probability of infection. Villages at a low elevation, located in areas with variable moisture patterns due to drainage, and surrounded by forest land cover have been shown to exhibit higher rates of Buruli ulcer infection (Wagner et al. 2008b). Additionally, Duker et al. (2004) report a positive correlation between arsenic-enriched agricultural lands and drainage basins and increased Buruli ulcer prevalence. Arsenic can suppress the immune system, resulting in greater success of infectious diseases such as Buruli ulcer. Landscape change due to agricultural development or mining operations can increase the level of arsenic contamination, and therefore may influence the spatial distribution and prevalence of Buruli ulcer. Similarly, irrigated agricultural lands, especially for rice production, and spatial proximity to dams used for agricultural irrigation purposes, are high risk factors for Buruli ulcer disease (Brou et al. 2008). This illustrates the role that landscape disruption can play in the overall spatial patterns of Buruli ulcer.
The seemingly clearest and exhaustively researched environmental factor of Buruli ulcer prevalence is association with water bodies. Studies in endemic areas of Buruli ulcer have examined relationships with a variety of water sources at differing geographic scales. Despite slight variations, there exists an overarching agreement on this vital connection (WHO 2008). Sopoh et al. (2010) found that in Benin 73 percent of Buruli ulcer cases had daily contact with natural water sources, resulting in a 2.31 odds ratio for relative risk. Certain types of water bodies have been shown to possibly present a higher risk. Aiga et al. (2004) observed that the use of river water associated with a significantly greater risk of disease when compared to other water sources, such as a piped water supply or well source. In general, it has been established that proximity to water bodies resulted in higher risk of Buruli ulcer infection (Merritt et al. 2010).

In addition to proximity to water sources, certain activities associated with water sources have been shown to increase the likelihood of coming in contact with *Mycobacterium ulcerans* and becoming infected with Buruli ulcer disease. Raghunathan et al. (2005) identified wading in streams and rivers in Buruli ulcer disease endemic areas as a risk factor for the disease. The odds ratio from multivariate modeling based on data collected for that study was 2.69 for this type of activity as a risk factor for contracting Buruli ulcer disease. The researchers concluded that the data supported their hypothesis that Buruli ulcer disease is an environmentally acquired infection related to exposure to natural
bodies of water, such as rivers and streams in tropical climates (Raghunathan et al. 2005).

From this review of the current literature, it is clear that the disease ecology of Buruli ulcer, as is the case with many infectious diseases, is associated with critical behavioral and environmental factors. This body of research illustrates that many questions - definitively identifying the etiology of BU, the impact of landscape dynamics and disturbances, and the role human behavior plays in infection patterns - remain unanswered. The following section outlines the framework used to approach this complex problem, linking human health with the environment and daily activity spaces, in order to identify critical exposures and potentially result in more effective public health interventions to address this debilitating disease.
CHAPTER 2
THEORETICAL FRAMEWORKS

Frameworks of Human Health

Human health is inextricably linked to environmental health. A central theme of health and medical geography research is the investigation of the complex coupled dynamic that exists between humans and their environment. There is a growing recognition of the complexity and interrelatedness of the many physical and social systems that impact the concentration and diffusion of disease and the importance of new approaches in addressing this phenomenon (Allotey et al. 2010). Human dimensions of environmental change, whether through development for agriculture, mining, or housing, can result in drastic changes in health outcomes (Meade 1976, Daszak 2001, Connor et al. 2004, Meade and Emch 2010). This may occur through creation of new “space” for emerging or reemerging infectious diseases, changes to habitat for vectors and reservoirs of disease, or altered dynamics of environmentally sourced diseases (Mayer 2000, Vasconcelos et al. 2001, Connor et al. 2004, Derraik and Slaney 2007, Pimentel et al. 2007, Jones et al. 2008). New approaches are needed to investigate and better understand changes in disease patterns resulting from anthropogenic impacts on the environment. The following section establishes the framework for this research, derived from literatures of medical geography and spatial (and spatio-temporal) analysis of activity spaces.
Emerging infectious diseases such as Buruli ulcer (BU) are addressed from varying perspectives within the sub-discipline of medical geography. Mayer (2000) identifies the social and ecological components contributing to the spread of emerging infectious diseases, particularly changes to the human-environment relationship. Previously unrecognized and underreported diseases may be driven by changing ecological conditions, such as suburbanization, and impacts of climate change. Interdisciplinary approaches to investigating emerging infectious disease dynamics may provide critical insights into these complex systems. The human ecology model situates health at the nexus of population (human physiology, gender, age), behavior (socio-cultural practices, political and economic forces), and habitat (natural and built physical and social environments) in engaging human health (Meade and Emch 2010). This model provides an overarching perspective into the geographies of human health, allowing connections between these factors to be identified and explored.

An ecosystem approach to disease focuses on the “understanding of interrelationships among factors that produce ill health and ecosystem disruption” (Spiegel and Veiga 2005, 365). This framework uses a hierarchy of human health as its underlying structure and incorporates the social, cultural, economic, and environmental factors which influence health outcomes at each level (Nielson 2001, Mergler 2003). Disparities in health outcomes have also been investigated from the environmental justice perspective, evaluating environmental hazard exposure differentials and resulting disease burdens in certain populations.
(Pearce et al. 2010). The investigation of health impacts from environmental
degradation has identified important links to rates of infectious disease such as
Buruli ulcer (Duker et al. 2006, Kibadi et al. 2008), malaria (Barbieri et al. 2005),
and HIV (Gilgen et al. 2001), among others.

The link between environmental health and human health serves as a
starting point from which divergent conceptualizations of drivers of infectious
disease have emerged. Eisenberg et al. (2007) present a framework of
environmental determinants of infectious disease consisting of three main
components, applicable in investigating diseases related to dynamic
environmental factors. Environmental change includes anthropogenic and
naturally occurring changes to the physical environment, resulting in direct and
indirect changes to patterns and infection rates of disease. Transmission cycles,
which vary between categories of infectious disease (i.e. human-to-human,
zoontic, vectored, etc.), are nonetheless all mitigated by the biophysical
environment. Finally, by creating external conditions that influence distribution
and disease rates, such as impacts on food resources due to climate change or
social upheaval resulting from excessive resource extraction, environmental
change can indirectly influence disease patterns and burden. These three
elements within the environmental determinants of infectious disease (EnvID)
framework emphasize the connectedness of human health and changing
landscapes. Lambin et al. (2010) identify dynamic principles of pathogenic
landscapes, including landscape attributes, habitat connectivity, land use/tenure,
and human behavior, among others. This approach allows for a more comprehensive and nuanced framework of environment and human health, incorporating landscape determinants of disease transmission at multiple scales.

Albrecht et al. (1998) argue for an approach to investigations of health disparities that explores non-linear relationships and provides multi-level explanations for the observed phenomena. The authors propose a trans-disciplinary approach to research, which incorporates the dynamic systems (social, environmental, political, economic, etc.) that interact at varying scales. This method seeks to incorporate not only a few inter-connected fields, but provides a framework for collaboration across many disciplines, resulting in a more holistic perspective and novel solutions (Albrecht et al. 1998). This is an important concept in the investigation of infectious diseases – a seamless integration of various fields into a multi-faceted understanding of the socio-cultural environment and its reciprocal relationship to human health.

Although the impact of human-environment interactions on health has been acknowledged since the time of Hippocrates, the work of John Snow during the cholera outbreak of 1854 in London began a new era in the investigation of this complex relationship (Meade and Emch 2010). Jacques May, recognized as the “father” of medical geography in the US, identified not only the critical relationship between the physical environment and human health, but recognized that culture plays an equally important role in this dynamic (May 1960). Current areas of research in medical geography, including emerging and re-emerging
infectious diseases, would benefit from the deeper understanding resulting from a synthesis of social and ecological impacts in the health and medical geography context (Mayer 2000). Incorporating socio-cultural elements of environment change linking to human health outcomes can provide an additional perspective into infectious disease dynamics.

Medical geography and the application of spatial and spatio-temporal methodologies are critical approaches to examining issues of health access and outcome disparities. From examinations of socio-cultural dimensions of health (Curtis and Rees Jones 1998, Cutchin 2007) to increasingly robust spatial visualization and analytical tools, including geographic information systems (GIS) (Meliker and Sloan 2011), the application of geographical principles can provide critical perspectives into disease dynamics. Indeed, an appreciation of the need to explore critical intersections within complex infectious diseases systems – biophysical, social, environmental, and climatic – is continuing to grow from multiple academic and institutional sectors (Mayer 2000, Wilcox and Colwell 2005, Allotey et al. 2010). These perspectives from health and medical geography and spatial epidemiology provide an underlying structure to engaging Buruli ulcer disease dynamics. The next section will address activity space analysis of daily movements as a means of identifying individual and community-level environmental and behavioral factors in BU infection.
Activity Spaces

In order to understand how individuals interact with the environment, and where they might be exposed to *Mycobacterium ulcerans* (MU) across terrains of risk, this research focuses upon daily activity spaces. Activity space analysis incorporates identification of territory and delineation of movement in the environment (Golledge & Stimson, 1998). Previous analyses of patterns of individual movements and exposure to infectious disease demonstrate the efficacy of this technique (Kloos et al. 1998, Seto et al. 2007, Vazquez-Prokopec et al. 2009). Kwan (2000) highlights recent advancements in technology, including new developments in the ability to visualize and analyze human spatial behavior within GIS. Additionally, the development of methodologies to geo-reference spatial data through global positioning systems (GPS) as well as remotely-sensed information has contributed to increasingly sophisticated representations of built and natural environments (Kwan 2000). The convergence of these new tools and insights present the opportunity for precise measures and analyses of individual patterns of movement and associations with health burdens.

A variety of methodologies are employed in constructing, visualizing, and analyzing daily activity patterns, density, and extent (Rainham et al. 2010). Spatial and temporal data concerning human movement can be derived from a spectrum of quantitative and qualitative data. Point pattern analysis of nodes of activity and travel routes can be represented by spatial deviation ellipses (Figure...
5), road network buffers, and time travel polygons among others (Sherman et al. 2005). In addition to places of residence, activity spaces, or the nodes of activity and movement which constitute daily routine movement, are critical to understanding health disparities (Cromley and McClafferty 2002). Schools, workplaces, supermarkets, and churches are examples of spaces of potential risk for exposure to disease. As any parent with a young child in public school can attest, interactions with individuals and places outside of the home can have a strong influence on health outcomes. Exposure to social and environmental determinants of disease infection can be viewed through a lens of these daily patterns.

Stoddard et al. (2009) present a conceptual model of multi-scale frameworks of human movement and methodologies for examining the role of individual activity spaces in disease exposure patterns. The authors highlight research illustrating the importance of human movement in disease dynamics, specifically mosquito-vectored dengue. The importance of daily human movements and vector behavior drives interactions leading to disease exposure is illustrated using a framework of temporal and spatial scales of human movements and vector-borne disease. In addition, a spatio-temporal lifeline activity space model is employed in the study, representing nodes of activity, velocities of human movement, and dengue vector activity.
By modeling individual potential exposure to dengue for various locations and offering descriptions of differing methods of human movement capture, the authors conclude that effective interventions can be designed by identifying these nodes of interaction through human movements and vector behavior (Stoddard et al. 2009) This approach is employed in the current study in describing and delineating terrains of BU risk for communities and peoples across the pathogenic landscapes of central Ghana.

Figure 5 Geo-referenced points, tracks, and spatial deviation ellipses.
Seto et al. (2007) created hourly activity maps from data logs of GPS units attached to vests worn by project participants to identify interaction with water sources. Interviews were carried out following the activity to investigate perceptions and spaces of routine daily events and differing activities and locations were identified for possible connection to potential disease exposure. Several limitations of this methodology were identified, including issues with participants wearing the vest, GPS accuracy, and representative sampling. Kloos et al. (1998) examined the microgeography of water contact behavior, exposure, and risk for schistosomiasis in several small communities in Egypt, Kenya, and Brazil. Frequency of contact with water sources, as well as duration at the site and distance from home yielded significant relationships to risk for contracting schistosomiasis, a vectored infectious disease. The study highlights the impact of social and behavioral networks on disease burden and how they might be employed in identifying potential exposure to high-risk areas.

The development of spatio-temporal analyses of human movement through activity spaces has resulted in increasingly sophisticated representations of these phenomena (Kwan 2004, Yu and Shaw 2008). Sherman et al. (2005) highlight spatial deviation ellipses as traditionally employed measures of patterns of movement. Employing access to primary health care services in North Carolina as a case study, the authors illustrate the utility of incorporating the existing transport infrastructure and temporal data in these measures, resulting in models including road network buffers, thirty-minute standard travel time
polygons, and relative travel time polygons. Including these elements of the physical environment can result in a more nuanced perspective into local spatial phenomenon influencing movement, and resulting interaction with certain environments. Indeed, activity spaces in general offer advantages over single, point-based analyses (geocoded home address, administrative centroid, etc.) in presenting a more clearly defined and delineated representation of daily movement.

Due to difficulties in reconciling human activity patterns and environmental exposures linked to human health within spatial and spatio-temporal analyses, relatively few of these studies have been conducted (Meliker and Sloan 2011). To address this limitation in the study of Buruli ulcer disease, a case/control study design provides a framework to identify differential exposures to risk factors among individuals. Potential points of contact with MU environments are identified by geo-referencing activity spaces, micro-scales of distribution and direction of daily movements, and individual nodes of activity. This approach seeks to uncover the individual and community-level behavioral characteristics that may produce variations of spatial behavior and connections to BU infection. The application of this framework and methodological approach in the case study area to address the research questions are described in the next section.
CHAPTER 3
STUDY AREA, DATA, AND METHODOLOGY

Study Area

The study area for this research is located in Ghana, a country in West Africa, which has experienced comparatively high rates of Buruli ulcer (BU) in recent decades. Ghana has reported close to 11,000 BU cases since 1993, which represents almost one-fifth of the global Buruli ulcer disease burden (WHO 2010). Located on the Gulf of Guinea, bordered by Côte d’Ivoire, Burkina Faso, Mali, and Togo, (Figure 6), Ghana is divided into ten regional and 138 district administrative units. (Figure 1) The country experiences a tropical climate, and is dominated by low plains, with high plateaus bisecting the country across the south-central region (Naylor 2000). The south-central and the western portions of Ghana contain the basins of four major rivers, the Densu, the Tano, the Ankobra, and the Pra. This region of Ghana serves as a major drainage area for the country, specifically the Uplands further north in the Ashanti region (LOC 1994). As the elevation drops from the highlands of the Ashanti region towards the border with Côte d’Ivoire to the west and the Atlantic Ocean to the south, this broad area of lower elevation levels results in the potential for increased exposure to flooding, because this part of Ghana receiving the heaviest annual rainfall levels, from 1,000 to 2,150 millimeters (LOC 1994).
The study area for this research consists of three localities along the Offin River in the Upper Denkyira East District of the Central Region of Ghana. (Figure 1) The three localities within this region, Study Areas A, B, and C consist of two, four, and five towns and villages, respectively. The predominately Akan residents of the region grow subsistence crops including yam, cassava, plantain, as well as cash crops such as cocoa and palm oil (Naylor 2000). However, landscape degradation resulting from the conversion of secondary forest and agricultural lands to artisanal gold mining, or galamsey, operations have significantly impacted these practices (Hilson 2002, Hilson and Potter 2005). Maps of the 1999 national BU prevalence (Figure 6) and 2008 regional BU incidence (Figure 7) confirm that these three localities lie within the area of Ghana experiencing the highest burden of BU infection.

Data Sources

This research relies upon many data sources, both archival and field-collected, at a variety of scales. All spatial data, points and polylines, were captured or created using the WGS 84 datum and projected into Universal Transverse Mercator (UTM) Zone 30N for analysis. Transformation, organization, creation and analyses of spatial data for this research were conducted using ESRI geographic information systems (GIS) software (ArcGIS 9.3, ArcGIS 10, and ArcScan 10). Additional spatial data manipulation was completed using Geospatial Modeling Environment (Version 0.5.3 Beta). In addition, smoothed
disease rates were computed using WebDMAP, a web-based GIS software (http://www.webdmap.com).

Archival

District-level BU infection rates in Ghana were calculated from a 1999 national case search, conducted in collaboration with the United States Centers for Disease Control and Prevention (CDC), which resulted in the identification of 5,619 BU patients and a national rate of 20.7 per 100,000 (Amofah et al. 2002). (Figure 6) The 1999 national case search was conducted following the launch of the Global Buruli Ulcer Initiative and the Yamoussoukro Declaration (WHO, 1998) to directly address issues of underreporting and misdiagnosis associated with Buruli ulcer. BU infection rates are also derived from clinical data provided by the National Buruli Ulcer Control Program, and cover the years 2005 to 2010 (Klutse 2010). (Figure 7)

It should be noted that the methodologies for data collection of the BU disease data from 1999 and 2005-2010 differ in representation of disease burden. Disease prevalence refers to all cases within an identified population at any given time, regardless of start or total duration of infection or illness. Disease incidence provides the number of new infections or illnesses in a population over a specified period of time, usually one year (Meade and Emch 2010). This is an important distinction, as differing epidemiological study frameworks depend upon these varying methodologies of disease data collection. Demographic data are
derived from the 2000 Population and Housing Census conducted by the Ghana Statistical Service.

Figure 6 1999 national Buruli ulcer prevalence in Ghana.

Administrative boundaries and point data used as base layers within the GIS to orient collected and archival data are drawn from Maplibrary.org. In calculating disease rates based upon the available BU case data from the national case search in 1999, adjustments were made to account for the creation of 28 new administrative districts in 2006, bringing the total number of districts in Ghana to 138 from 110 (Figure 1). Landsat 7 Enhanced Thematic Mapper (ETM+) imagery (LE71940562001092EDC00) used to classify land cover types
via supervised classification in the study area was downloaded from USGS/EROS.

![Prospective Small-scale Gold Mining and 2008 Buruli ulcer Incidence](image)

**Figure 7** 2008 regional Buruli ulcer incidence in Ghana.

Quickbird 4-Band Pansharpened imagery (February 14, 2011; 10300100091B3800) was acquired from eMap International and provides high-resolution (2.4 m) coverage for Study Area A. National-level land cover classification was drawn from the Food and Agriculture Organization of the United Nations GeoNetwork GlobCover Project (www.fao.org/geonetwork).

Digitized hydrological and topographic layers used in spatial analyses of
BU disease for this study were derived from topographic maps created by the survey departments of the Ministry of Lands and Forestry and Ministry of Minerals in Ghana. Colleagues from the University of Mines and Technology in Tarkwa, Ghana acquired the digitized coverage layers of these datasets. Three grids from these surveys, 0603D, 0602C, and 0502A provide complete coverage of the study area. These map layers were created in the War Office/Clarke 1880 datums, Ghana National Grid projection and were first re-projected into WGS 84 UTM Zone 30N to spatially reconcile the data with base layer information, field-collected activity space, and other data. Neat line layer files provided in the coverage datasets were utilized in order to spatially adjust the layers to account for alignment error of 3 to 6 meters. These layers were then merged and subsequently spatially dissolved into a single layer dataset to prevent the redundancy of spatial information overlap in creating biases during analyses.

Due to the proximity of the study area to the convergence of three grid quadrants, the neat lines created for spatial adjustment were then deleted to prevent the introduction of further error. Arc10 GIS software interprets neat line borders as rivers or streams within the hydrological layer and includes these line segments in the interpolation of polylines in the creation of digital elevation models (DEM). This DEM was then used to analyze elevation changes within collected daily activity spaces. This task was completed using the ‘Topo to Raster’ interpolation tool within the 3D Analyst toolbox in Arc10, resulting in a 20
x 20 meter raster grid, with an elevation range of 9.78 meters below to 622.07 meters above sea level.

Field-Collected Data

ReBUild project team members and research partners collected the individual daily activity space data during fieldwork conducted in July of 2011 in the study areas. IRB approval for research involving human subjects was gained through Penn State University and the University of North Texas (National Science Foundation CNH Award #0909447). Initial surveys within the ten communities of the study areas identified previously infected or currently active BU cases. A case-control framework is used in this study, which involves grouping people into categories of cases (experiencing a disease or health related event) and controls (those who do not experience the disease or health related event) an examining the experiences or exposures (i.e. smoker/non-smoker and lung cancer) to look for differences between the groups (Merrill 2010). The resulting measure of risk from this study is an odds ratio, which measures the relative occurrence of the disease or health related event in each of these groups based upon exposure to a certain risk factor (Cromley and McLafferty 2002). Additionally, matching within a case-control study design involves controlling for confounding factors such as age and gender (Merrill 2010). In this study of BU, community members included in the study as cases have previously been infected or are currently infected with BU. Family members or neighbors, as closely matching the BU cases in gender and age were
identified as a matched control for eventual comparative analysis within the case/control study design. The longitudinal nature of the case/control epidemiological study design allows for continual enrollment of newly discovered cases and matched controls into the study.

By the completion of the field season in July 2011, 80 cases and matched controls comprised the overall study sample. Of these, a sample of active cases or those diagnosed in the past three years, along with their matched controls (n = 48) were selected for geo-referencing of activity spaces. These cases and matches were selected to reduce recall biases in behavioral patterns and daily movements. Of this cohort identified for geo-referenced activity space data collection, a total of 30 samples (GPS tracks and points) were collected in July 2011. Travel, illness, disruption of workday, among other reasons, precluded the collection of activity space data for the remaining 18 cases and matched controls. While the 30 samples collected do not represent a complete data set (i.e. 15 cases and their matched controls), it allows a detailed analysis of the cases (n = 17) and controls (n = 13) in the context of environmental and behavioral factors related to BU infection.

Various ReBUIld project team members collaborated with local project participants in collecting daily activity spaces data for the cases and matched controls during July 2011 in the study area. Project team members, including community research partners, accompanied enrolled BU cases and matched and geo-referencing nodes of daily activities. (Figure 8)
Figure 8 Geo-referenced activity spaces of case and matched control.

These spaces may have included, but were not limited to: compounds, water sources (bathing, washing, cooking, drinking), place of employment, farms, schools, and points of contact with natural bodies of water. (Figure 9)

The geo-referenced activity space data points were collected using GPS units (Garmin eTrex Legend, Garmin 60CSx, Trimble Juno SB). Daily activity paths were created using the “tracks” GPS feature, automatically capturing a point every 10 meters. These files were then converted from multiple feature point files into polylines in Arc10 GIS software. GPS-derived activity space points
and tracks were downloaded periodically in the field using DNRGarmin (version 5.4) software, developed by the Minnesota Department of Natural Resources, due to GPS internal memory constraints for storing geo-referenced track information and also to validate data. Additional activity space points were collected in field notes containing reference ID, description of location, coordinates, and elevation. Copies of all field notes taken by team members collecting activity space data were incorporated into spreadsheets representing all geo-referenced case and matched control data, including accompanying spatial information, date, and description upon return from the field (Appendix A).

Due to GPS data collection limitations and other extenuating circumstances, several daily activity tracks were created or digitally manipulated within Arc10 GIS software, using the Editor toolkit. All geo-referenced points taken for a case or matched control were joined by shortest distance to the nearest point or track polyline, based upon field notes. These polylines were then merged and dissolved into one continuous track for further analysis. All daily tracks, field recorded or reconstructed from geo-referenced points, were converted into 3-D polylines to investigate overall elevation differentials and variability across space (Appendix C). Elevation data were extracted for each daily case and matched control by converting these tracks into three dimensional features, using the digital elevation model created from the detailed study area topographic information described above.
In order to create standard deviation ellipses used to represent the extent of daily activity space, all case and matched control track polylines were first converted into point files, due to the fact that a minimum of three features are required to create the standard deviation ellipse polygons. These points, created with the Construct Points feature of the Editor toolkit in Arc10, were placed at 10 meter intervals, equaling the data capture setting used in the GPS units when collecting geo-reference activity space data in the field. Standard deviation ellipses as measures of daily activity spaces were then created using the Spatial Analyst toolkit in Arc10. Ellipses were created for each case and matched control at one, two, and three standard deviations, resulting in approximately 68, 95, and 99 percent coverage of all points, respectively. (Appendix B) Spatial deviation ellipses representing three standard deviations were employed in analyses of environmental exposures associated with BU infection as three standard deviations of geo-referenced point distribution and dispersion provides close to complete coverage of all point locations.
Figure 9 Examples of geo-referenced daily activity spaces: (A) Mixed cassava & corn farm adjacent to galamsey gold mining operation, (B) Swampy area on path to farm, (C) Galamsey mining operation, (D) GPS recording of swampy area.
Data Limitations

There are many limitations of both the archival and field collected datasets. Buruli ulcer, classified as a "neglected disease" by the World Health Organization (WHO) is subject to problems of underreporting and misdiagnosis (Johnson et al. 2005, Sizaire et al. 2006, Wainsbrough-Jones and Phillips 2006). This critical issue was addressed in the WHO Global Buruli Ulcer Initiative of 1998 (WHO 1998). This problem exists in Ghana, and therefore the 1999 national case search data, as well as the infection rate information provided by the National Buruli Ulcer Control Program of the Ministry of Health in Ghana should not be considered a complete representation of BU disease burdens.

Population data is based upon the 2000 census, due to the fact that population estimates at the community and district level from the 2010 survey were not available at the time of the study. Expanded mining operations and related economic activities may have produced new demographic trends in these areas, also leading to issues of changing disease burdens as a result of local environmental interaction.

Additionally, activity spaces constructed for this research should not be viewed as inclusive of every location visited by project participants, both cases and controls, but rather an estimation of the relative extent of the home range for each individual. Some cases and matched controls are represented by the same measures of daily activity spaces, as they share identical nodes of activity. Possible means of parsing individual exposures within these spaces through the
analyses of additional behavioral data will be discussed in the next section. Incomplete descriptive data for several of these samples prevents a detailed analysis of all interactions with environmental features or areas of landscape disturbance which may increase risk for exposure to MU and therefore susceptibility to BU infection.

Exposure Identification

Previous research investigating potential environmental drivers of BU infection has determined that exposure to natural bodies of water, represented here as total river/stream length, number of river/stream crossings (daily track), and percent land cover classified as water body, constitutes a risk factor for Buruli ulcer (Aiga 2004, Merritt et al. 2005, Ragathunan et al. 2005, Pouillot et al. 2007, Williamson et al. 2008, Sopoh et al. 2010). Also, percent of land cover closed forest (Pouillot et al. 2007, Brou et al. 2008, Wagner et al. 2008a), percent mosaic forest/croplands lands (Wagner et al. 2008b), and elevation (Wagner et al. 2008a, Wagner et al. 2008b) are associated with increased BU infection rates.

Table 1 Correlation of 1999 National Buruli ulcer rates and Landcover Classifications

<table>
<thead>
<tr>
<th>Land cover Classification</th>
<th>Mosaic Forest/Croplands</th>
<th>Open Broadleaved Deciduous Forest</th>
<th>Closed to Open Shrubland</th>
<th>Open Grassland</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999 Buruli ulcer rate</td>
<td>Pearson Correlation</td>
<td>.317</td>
<td>-.201</td>
<td>-.234</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.000</td>
<td>0.018</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>138</td>
<td>138</td>
<td>138</td>
</tr>
</tbody>
</table>
Using the 1999 BU case search data, the relationship of BU rates and landcover type is presented in Table 1. A mosaic of forest and croplands are positively correlated with BU infection rates. These results, along with factors identified in the BU literature referenced above, will be analyzed using daily activity spaces of cases and matched controls. The statistical tests presented in the next section will evaluate individual and community-level interactions within specific landscapes to identify associations between these factors and BU infection based upon daily patterns of movement.
CHAPTER 4
ANALYSIS AND RESULTS

Statistical analyses of the environmental variables and behavior data delimited by the activity space extents described in the previous section were conducted to identify significant differences between cases and matched controls. Wilcoxon signed-rank tests, the non-parametric alternative to the paired t-test, are used to measure relative environmental exposure levels within paired cases and matched controls. Mann-Whitney U tests provide nonparametric measures of difference among overall cases and controls, as well as within and across study areas, to provide insights into Buruli ulcer (BU) disease dynamic patterns at individual and community scales. In addition, a logistic regression model was developed in order to calculate odds ratios for BU infection based upon exposure to environmental factors and levels of individual interaction with these phenomena (Hosmer and Lemeshow, 2000; Kleinbaum and Klein, 2010). All statistical analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS Statistics version 20).

In order to analyze the paired case/matched control exposures to the six environmental variables determined by the delimited individual activity spaces, the Wilcoxon signed ranks test is employed, using 11 paired samples. The remaining samples \( n = 8 \) are excluded because they lack associated cases or matched controls, due to limitations in field collection of activity space data.
addressed in the previous section. No significant differences were calculated for any of the six variables in the Wilcoxon signed ranks test ($p = 0.109 - 0.655$).

(Table 2) Additional statistical analyses will examine the exposure levels within the entire case/control sample of geo-referenced activity spaces.

**Table 2 Wilcoxon Signed Ranks Test**

<table>
<thead>
<tr>
<th>Wilcoxon Signed Ranks Test</th>
<th>River/Stream Length (km)</th>
<th>River/Stream Crossings</th>
<th>Elevation (m)</th>
<th>% Mosaic Forest/Agriculture</th>
<th>% Water</th>
<th>% Closed Forest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z</td>
<td>-1.604&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-1.633&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-1.604&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-1.604&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.447&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.535&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Asymp. Sig. (2-tailed)</td>
<td>.109</td>
<td>.102</td>
<td>.109</td>
<td>.109</td>
<td>.655</td>
<td>.593</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on positive ranks

Similarly, disease dynamics within the overall case/control geo-referenced sample indicate no statistically significant difference in exposure levels to environmental variables hypothesized to have association with Buruli ulcer infection. Resulting levels of exposure to these environmental variables (Appendix A) are compared at various scales and in order to identify differences at the individual and community scales ($n = 30$). Cases exhibited an overall higher level of exposure to the environmental variables (Table 3) compared to controls. However, none of these differences were statistically significant. The exposure levels of the cases ($n = 17$) was about 20 percent higher than the controls ($n = 13$).
Percent mosaic forest/agriculture dominated both the cases and controls in overall land cover classification within defined spatial deviation ellipse activity spaces. This may be attributed to the rural context of the study area, located within Ghana’s highly productive agricultural south, and the local dependence upon subsistence agriculture. Moreover, the percent water classification may not reflect an accurate estimate of total surface water comprising points of potential risk within the local “terrain of risk” for MU interaction. Due to the coarseness of available satellite imagery, small streams or other bodies of water, as well as swampy areas under closed forest (Figure 11C) may not be accurately represented. Based on field observation during July 2011, including semi-structured interviews and informal conversations, exposure to these smaller natural bodies of water can vary substantially. Interaction with ephemeral bodies of water tied to seasonal rainfall patterns, periodic flooding, and landscape disturbance in the form of deforestation and artisanal gold mining may not be captured in these analyses.

**Table 3** Overall Case/Matched Control Median Exposure Levels

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>River/Stream Length (km)</td>
<td>3.055</td>
<td>2.859</td>
<td>0.711</td>
</tr>
<tr>
<td>River/Stream Crossings</td>
<td>1.000</td>
<td>1.000</td>
<td>0.621</td>
</tr>
<tr>
<td>Δ Elevation (m)</td>
<td>34.812</td>
<td>19.449</td>
<td>0.198</td>
</tr>
<tr>
<td>% Mosaic Forest/Agriculture</td>
<td>80.400</td>
<td>75.90</td>
<td>0.563</td>
</tr>
<tr>
<td>% Water</td>
<td>0.1</td>
<td>0.1</td>
<td>0.902</td>
</tr>
<tr>
<td>% Closed Forest</td>
<td>8.900</td>
<td>6.800</td>
<td>0.300</td>
</tr>
</tbody>
</table>
In comparing community level differences, activity space-derived exposure levels are compared for all samples from two study areas (Table 4) and cases and controls from the same two study areas (Table 5). Nonparametric comparisons between Study Area A (n = 9) and Study Area B (n = 17), result in statistically significant differences between number of river/stream crossings (p = 0.005), percent land cover classified as water (p = 0.013), and percent land cover classified as closed forest (p = 0.006). The median exposure levels for environmental variables in Study Area A cases and controls are higher in total river/stream length, number of river/stream crossings, percent land cover classified as water. Study Area B exhibits higher rates of exposure in change in elevation and percent land cover classified as mosaic forest/agriculture and closed forest.

The overall increase in exposure to environmental variables in three of the six categories (Table 4) can be viewed through the lens of overall population and BU infection rates. Based upon the 2007-2010 National Buruli Ulcer Control Program individual case-level data and 2000 census, Study Area A, with a population of 5,777 and BU infection rate of 311.58 per 100,000 could reasonably be expected to exhibit lower environmental exposure levels compared to Study Area B, with a population of 2,242 and overall rate of 624.44 per 100,000. Additionally, Study Area A is made up of two towns, whereas Study Area B is comprised of four. The combination of higher concentrations of populations and lower BU infection rates would seem to support the conclusion
that Study Area B would exhibit higher exposure rates to the identified environmental variables. However, as shown in Table 4, this is not the case.

**Table 4 Overall Study Area Median Exposure Levels**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study Area A</th>
<th>Study Area B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>River/Stream Length (km)</td>
<td>3.964</td>
<td>2.859</td>
<td>0.164</td>
</tr>
<tr>
<td>River/Stream Crossings</td>
<td>3.000</td>
<td>1.000</td>
<td>0.005</td>
</tr>
<tr>
<td>$\Delta$ Elevation (m)</td>
<td>18.845</td>
<td>34.812</td>
<td>0.287</td>
</tr>
<tr>
<td>% Mosaic Forest/Agriculture</td>
<td>75.200</td>
<td>78.600</td>
<td>0.597</td>
</tr>
<tr>
<td>% Water</td>
<td>0.600</td>
<td>0.000</td>
<td>0.013</td>
</tr>
<tr>
<td>% Closed Forest</td>
<td>6.600</td>
<td>10.100</td>
<td>0.005</td>
</tr>
</tbody>
</table>

These seemingly disconnected relative exposure levels are reinforced in comparisons of cases and matched controls across Study Areas A and B (Table 5). There are two statistically significant differences between cases from Study Area A (n = 4) and Study Area B (n = 7). These two environmental exposure variables are number of river/stream crossings ($p = 0.04$) and percent land cover classified as closed forest ($p = 0.013$). The analysis did not result in any statistically significant differences in matched control exposure variables across the study areas.
Table 5 Median Exposure Levels of Cases/Matched Controls by Study Area

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases</th>
<th>Controls</th>
<th>(p)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study Area A</td>
<td>Study Area B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>River/Stream Length (km)</td>
<td>3.964</td>
<td>2.956</td>
<td>0.679</td>
<td>5.851</td>
</tr>
<tr>
<td>River/Stream Crossings</td>
<td>3.000</td>
<td>1.000</td>
<td>0.040</td>
<td>2.500</td>
</tr>
<tr>
<td>△ Elevation (m)</td>
<td>18.845</td>
<td>34.985</td>
<td>0.859</td>
<td>17.744</td>
</tr>
<tr>
<td>% Mosaic Forest/Agriculture</td>
<td>75.200</td>
<td>80.450</td>
<td>0.679</td>
<td>74.900</td>
</tr>
<tr>
<td>% Water</td>
<td>0.600</td>
<td>0.000</td>
<td>0.099</td>
<td>0.800</td>
</tr>
<tr>
<td>% Closed Forest</td>
<td>6.600</td>
<td>10.250</td>
<td>0.013</td>
<td>4.800</td>
</tr>
</tbody>
</table>

A binary logistic regression model was developed to calculate odds ratios for the environmental exposures analyzed above. These exposure variables are transformed (Appendix A) in order to prevent bias resulting from the inclusion of varying scales of continuous variables. This analytical tool has been widely used in epidemiological case/control studies investigating multiple factors, categorical or interval, in the prediction of health outcomes and is represented in the following equation:

\[
\text{logit } \left[ \theta(x) \right] = \log \left[ \frac{\theta(x)}{1-\theta(x)} \right] = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_i x_i
\]

where \( \text{logit } [\theta(x)] \) represents the likelihood ratio that the dependent variable is a BU infection outcome (Peng et al. 2002). In the present case study, this outcome is the presence or absence of BU disease (i.e. case or matched control). Therefore the model will identify the impact of each factor in determining the
probability of BU infection. The odds ratios statistic (Exp(B) in Table 6) generated by this model represents the measure of association between exposure and this probability, including 95 percent confidence intervals.

<table>
<thead>
<tr>
<th>Logistic Regression Model</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% C.I. for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>River/Stream Crossings</td>
<td>.281</td>
<td>.571</td>
<td>.242</td>
<td>1</td>
<td>.623</td>
<td>1.324</td>
<td>0.432, 4.056</td>
</tr>
<tr>
<td>Δ Elevation (m)</td>
<td>.616</td>
<td>.777</td>
<td>.627</td>
<td>1</td>
<td>.428</td>
<td>1.851</td>
<td>0.403, 8.49</td>
</tr>
<tr>
<td>% Water</td>
<td>.318</td>
<td>1.141</td>
<td>.078</td>
<td>1</td>
<td>.781</td>
<td>1.374</td>
<td>0.147, 12.87</td>
</tr>
<tr>
<td>River/Stream Length (km)</td>
<td>.006</td>
<td>.812</td>
<td>.000</td>
<td>1</td>
<td>.994</td>
<td>1.006</td>
<td>0.205, 4.945</td>
</tr>
<tr>
<td>% Closed Forest</td>
<td>.248</td>
<td>.630</td>
<td>.155</td>
<td>1</td>
<td>.693</td>
<td>1.282</td>
<td>0.373, 4.408</td>
</tr>
<tr>
<td>% Mosaic Forest/Agriculture</td>
<td>.237</td>
<td>.694</td>
<td>.116</td>
<td>1</td>
<td>.733</td>
<td>1.267</td>
<td>0.325, 4.937</td>
</tr>
<tr>
<td>Constant</td>
<td>-3.161</td>
<td>4.652</td>
<td>.462</td>
<td>1</td>
<td>.497</td>
<td>0.042</td>
<td>N/A, N/A</td>
</tr>
</tbody>
</table>

The results of this test are not unexpected, based upon the results of the previous statistical analyses above. All exposure variables resulted in odds ratios above one, indicating that an increase in one unit exposure to river/stream crossings, overall river/stream length, change in elevation, and percent water, closed forest, or mosaic forest/agriculture results in an individual 1.324, 1.006, 1.851, 1.374, 1.282, and 1.267 times more likely to become infected with BU, respectively. However, none of these environmental exposure variables resulted
in statistically significant results, with an effective overall model $R^2$ of 0.08. This model may be vastly improved through future research and data collection within the ReBUild project, described in the next section.
CHAPTER 5
DISCUSSION AND CONCLUSIONS

The results of the activity space analyses presented in the previous section, although exhibiting higher overall levels in each category tested for cases over matched controls, do not indicate a statistically significant difference in environmental exposures amongst Buruli ulcer (BU) cases and controls. However, the overall increased exposure levels in cases, as well as the uniform pattern of odds ratios greater than one, with the exception of “river/stream length (km),” indicate that previously identified associations warrant further exploration at individual and community scales. These results may be further refined through the inclusion of additional behavioral and environmental data. This may also result in a more robust binary logistic regression model. Buruli ulcer is a complex disease. Many agents and unknown processes converge in space and time to create the opportunities for exposure to *Mycobacterium ulcerans* (MU) in the landscape. New approaches are required in order to understand BU disease dynamics and develop appropriate policies and public health interventions to address this problem.

The measures of daily activity spaces utilized in this research improve upon previous methodologies such as the use of environmental spatial buffers and arbitrary measures of potential range and movements, or reliance upon studies tied to a single location or areal unit. However, this approach can
nonetheless be improved. Compared with other measures (i.e. home range, buffered networks, and point based analyses) standard deviation ellipses provide a comparatively less biased measure of activity space at this small scale. An expanded sample of cases and matched controls may aid in uncovering these spatial patterns. In addition to further expansion and enhancement of the case/matched control epidemiological design and analysis, spatial analyses of BU cases and controls may provide another perspective into the relationship of environment and potential MU interaction.

Future data collection should include temporal components to improve the representations of activity spaces and individual daily patterns of movement. (Figure 10) The analytic potential in studies of health and human movements are greatly improved with the inclusion of time geographies into modeling frameworks (Jacquez 2000, Rainham et al. 2009, Meliker and Sloan 2010). Whereas purely spatial representations of movement illustrate direct and potential interactions with certain spaces and localized environments, temporal data recontextualizes those interactions. The standard deviation ellipses created and analyzed in this research are measures of daily average spatial range. Information concerning time spent at certain nodes of activity including places of residence and work may produce more sophisticated individual space-time measures of these ranges. Many critical details of daily activity spaces, including daily movements bypassing road networks, for example, can be included into these new measures. Similarly, information concerning mode of transportation,
incorporated in travel time polygons (Sherman et al. 2005), hotspot kernel
density estimations (Rainham et al. 2009), or a combination of these
methodologies may produce clearly defined, multidimensional representations of
human movement.

Figure 10 Geographic information systems (GIS) framework.

In addition to temporal data, community-sourced local spatial knowledge,
gained through participatory methods such as activity mapping (Kesby 2007,
Pretty et al. 1995) could be used to further refine these analyses and models.
Specific landscape characteristics may be linked (Figure 11) to spaces of
interaction and movement seasonally throughout the year, as well as historically.
Figure 11 Potential MU environments: (A) Galamsey pit, (B) Borehole adjacent to gold washing operation, (C) Natural water source in study area.
This process may also involve incorporating information gained through participatory historical land-use mapping and other ethnographic data reflecting local spatialities of MU ecological systems. Key behavioral data from other data collection activities, such as the administration of annual surveys, may also provide information essential to delineating spatio-temporal patterns, motivation, and negotiations of daily movements. Pain (2004) highlights the efficacy of employing spatial participatory methods in examining geographies that are context-specific and benefit from local knowledge. In moving forward with this research, these representations and analytical frameworks of activity spaces may be improved by incorporating a mixed-methods approach, reflected in the diversity of collected quantitative and qualitative datasets. These data may be visualized and analyzed in a qualified GIS, combining local spatial knowledge and perceptions, mapped individual and community-level patterns of movement, along with environmental sampling and other data (Elwood 2006). Triangulating individual and household-level interactions of human behavior and environmental contact (Merritt et al. 2005) may be critical to understanding susceptibility to BU.

In addition to the continuing lack of a clear understanding of the socio-ecological conditions conducive to MU exposure or a definitive mode of transmission, as well as critical issues related to disease reporting, misdiagnosis, social stigma, and treatment, BU remains a neglected disease. Further research, both at the individual and population levels, are needed to address this growing issue. New approaches to these studies must address issues related to a lack of
comprehensive disease reporting in countries such as Ghana, as well as the need to focus on local contexts to uncover critical elements of BU mode(s) of transmission.

The future directions in data collection and methodologies described above are reflective of the many new questions emerging from this research surrounding spatial behavior and infectious disease, as well as critical to addressing aspects of the original research questions that remain unanswered. Many unknowns remain in connection with the microgeography of BU prevalence in Ghana. Issues related to BU misdiagnosis and deficiencies in official reporting complicate estimations of BU incidence. The lack of recent high resolution imagery prevents accurate estimates of highly localized landscape disturbance. This study illustrates that engaging purely spatial patterns of movement and broad environmental categories are not sufficient to address BU disease dynamics. Future work, in addressing these concerns, may provide new insights into varying scales of spatial patterns of BU infection.

Conclusion

The analysis of activity spaces in representing multiscaled patterns of daily movement holds great promise in further investigation of BU disease dynamics. Merritt et al. (2010) make the call for further research to address murky questions concerning Buruli ulcer disease and its mode of transmission. Human behavior in BU endemic villages warrants further examination. While these behaviors are central to the questions surrounding exposure to MU
environments, in order to fully understand interactions with terrains of risk, these behaviors must be spatialized. Through representations of daily movements based upon spatial (and ideally temporal) field-collected data, human behavior patterns can be tied not only to general categories of disturbed landscapes or land cover/land use typologies, but also to specific local contexts. This holds greater potential of revealing new links within the complex BU ecological system.

This research illustrates the utility of the activity space methodology and incorporates individual, intra-community, and community-level data in studies of infectious disease. This approach to investigating BU disease ecology may be valuable to research of other rare or complex diseases within socio-environmental networks. The coupled dynamic of human disease and environment will continue to be a central focus of research in health and medical geography. Human dimensions of environmental change, manifested in landscape degradation, disruption of traditional farming practices, pollution, social upheaval, and migration will play a critical role in emerging and re-emerging infectious diseases. New approaches are needed to better understand and spatialize changes in disease patterns linked to culture, political economy, vectors and reservoirs and mitigated by anthropogenic and natural environmental shifts as well as human patterns of human behaviors and daily movement.
APPENDIX A

CASE/MATCHED CONTROL EXPOSURE DATA AND TRANSFORMED VARIABLES
### Transformed Exposure Variables

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<th>Case/Control</th>
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Daily Activity Spaces

- Geo-Referenced Points
- River/Stream Intersections
- S21 + S21M
- SD1
- SD2
- SD3

Daily Activity Spaces

- Geo-Referenced Points
- River/Stream Intersections
- S23 + S23M
- SD1
- SD2
- SD3

Elevation (meters)
- 90 - 105
- 106 - 120
- 121 - 135
- 136 - 150
- 151 - 165
- 166 - 180
- 181 - 195
- 196 - 210
- 211 - 225
- 226 - 240
- 241 - 255

Distance Scale:
- 0 250 500 1,000 Meters

Distance Scale:
- 0 150 300 500 Meters
APPENDIX C

INDIVIDUAL ELEVATION PROFILES
REFERENCES


doi:10.1016/j.jag.2005.06.013


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Wagner, T., Benbow, M., Burns, M., Johnson, R., Merritt, R., Qi, J., & Small, P. (2008a). A landscape-based model for predicting mycobacterium ulcerans


