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Mary Claire Worrell 4/16/2015

Tuberculosis in Fulton County, Georgia, 2008-2014:
Risk Markers for Isoniazid Monoresistance and
a Pilot Study of Novel Spatial Methods

By

Mary Claire Worrell

Degree to be awarded: MPH

Global Epidemiology

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Michael R. Kramer

Faculty Thesis Advisor

____

Neela Goswami

Field Thesis Advisor

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By

Mary Claire Worrell

Bachelor of Science in Microbiology and Immunology

McGill University

2010

Faculty Thesis Advisor: Michael R. Kramer, PhD

An abstract of

A thesis submitted to the Faculty of Epidemiology
Rollins School of Public Health of Emory University in partial fulfillment of the
requirements for the degree of
Master of Public Health
in Global Epidemiology

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Abstract

Tuberculosis in Fulton County, Georgia, 2008-2014:
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Background: Tuberculosis (TB) continues to cause morbidity and mortality in the United States (US), particularly in poor and transient populations. Disease transmission, particularly in homeless populations, can occur in multiple locations, and practical approaches are needed to understand the geographic characteristics of transmission.

Objective: (1) Identify the effect of homelessness on isoniazid (INH) monoresistant TB in Fulton County, Georgia. (2) Pilot novel spatial analysis techniques for disease surveillance that includes transient populations.

Methods: In Fulton County, Georgia, two separate TB outbreaks were recorded since 2008. A random sample of active TB cases diagnosed between 2008 and 2014 was selected from Fulton County Department of Health records. Disease and demographic indicators and all addresses and locations of interest were abstracted from charts. Logistic regression was used to understand the relationship between INH resistance and homeless status and various covariates. Kernel density methods were used to characterize the distribution of reported cases when using a single residential address compared to using multiple addresses, adding additional residences, work, school, and hangout spots. Activity space analysis evaluated the intersection of cases with particular traits.

Results: Homelessness was highly related to INH resistance; the odds of INH resistance in homeless cases was 3.3 times higher than the odds of INH drug resistance in the non-homeless population when controlling for year of diagnosis, excessive alcohol use, HIV status, history of incarceration, age, and sex (CI: 1.22-9.14). Greater dispersion of cases was found when utilizing all addresses for each case for kernel density interpolation compared to using a single address. Activity spaces of homeless and INH resistant cases overlapped with other homeless and INH resistant cases respectively more than non-homeless and INH susceptible cases ($p<0.0001$ and $p<0.0001$ respectively).

Conclusion: INH resistant TB remains a major problem in Fulton County; 50% of this study's TB cases diagnosed in 2014 were INH resistant. Alternative spatial methods offer insight into the spatial context of TB and provide information for cases without permanent addresses. Activity space analysis, prominent in exposure science and chronic disease, can provide insight into the investigation of infectious disease and should be utilized alongside standard epidemiologic methodologies.

Keywords: tuberculosis, isoniazid monoresistance, activity space, spatial analysis

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Chapter 1: Extended Background and Literature Review

Tuberculosis

Microbiology and Transmission

While great strides have been made in reducing the rate of tuberculosis (TB) in the United States (US), outbreaks of TB continue to occur and cause concern for public health authorities. TB infection is caused by acid-fast bacilli bacteria from the *mycobacteria* genus, particularly the *Mycobacterium tuberculosis* complex (MTBC). The MTBC includes the eight TB-causing bacteria: *M. tuberculosis*, *M. bovis*, *M. africanm*, *M. canetti*, *M. caprae*, *M. pinnipedii*, *M. mungi*,and *M. microti*. *M. tuberculosis* causes the majority of TB cases in the US. The bacteria are transmitted on airborne particles, or infectious droplet nuclei, which are produced by persons with active pulmonary TB disease. Transmission occurs when the infectious droplet nuclei is inhaled and reaches the alveoli of the lung. Macrophages in the alveoli ingest the bacteria killing a majority, but a few may survive and replicate. Using the lymphatic channels or bloodstream, these bacteria can spread to other tissues in the body including lymph nodes, kidneys, bone, and brain; this type of infection is called extra-pulmonary TB. Extra-pulmonary TB disease is typically not infectious unless the person also has pulmonary disease or the extra-pulmonary site of infection is located in the oral cavity or larynx or the site is an open abscess or lesion with extensive or aerosolized drainage (1).

Active v. Latent TB Infection

M. tuberculosis can infect people without causing TB disease, resulting in latent tuberculosis infection (LTBI). These individuals cannot spread TB to others, and therefore are not considered cases of TB. For individuals with LTBI, the body's immune response is able to kill or encapsulate the majority of the *M. tuberculosis* bacilli into a granuloma. With active TB, the body's immune response is unable to suppress the bacteria, resulting in replication and disease progression (1). The active state of TB is diagnosed by a positive smear or culture for tuberculosis or sufficient radiographic, clinical, or laboratory evidence of disease (2). Approximately 5% of people infected with *M. tuberculosis* will develop active TB disease within the first two years after infection with an additional 5% developing disease later in life (1).

People with LTBI can develop TB disease when the bacteria multiply past the control of the immune system. Factors, such as human immunodeficiency virus (HIV) infection or presence of other diseases affecting the immune system, increase risk of conversion from LTBI to active TB disease(1). The lifetime risk of development of TB disease for persons with LTBI alone is 10% compared to the 5-15% yearly risk for persons with TB/HIV co-infection (1,3–5). Additional risk factors for progression of LTBI to TB disease includes age of less than 5 years, treatment with immunosuppressive therapy, diabetes, particular cancers, cigarette smokers, and history of drug and/or alcohol abuse (1).

Symptoms

Symptoms of pulmonary TB disease include: cough lasting two weeks or longer, hemoptysis (coughing up blood), chest pain, loss of appetite, unexplained weight loss, night sweats, fever, and fatigue. Symptoms of extrapulmonary TB disease depends on the site of infection; for instance, TB meningitis may cause headaches or confusion or TB of the spine may cause back pain (1).

Testing

Various methods are available for testing patients for tuberculosis infection. Depending on clinical symptoms and test availability, different test may be performed to determine TB infection and disease.

The Mantoux tuberculin skin test (TST) is a screening test used to determine if a person is infected with TB; however, LTBI or TB disease may still occur with a negative result. For the TST, a purified protein derivative (PPD) from tuberculin is injected under the skin. Most people who have TB infection will react to PPD with a T-cell mediated delayed-type hypersensitivity reaction. False negative results can occur in people who have been administered the Bacillus Calmette- Guérin (BCG) anti-TB vaccine in addition to a variety of other situations including co-infection with HIV or other viruses, bacteria or fungi, stress, or chronic renal failure (1).

The Interferon-gamma release assay (IGRA) tests for the presence of an anti-TB immune response using whole blood. Similar to TSTs, IGRAs cannot distinguish LTBI and active TB disease, so additional tests are needed to diagnose or exclude TB disease. In some situations, IGRA testing is preferred over TST, for example, in individuals who have received prior BCG vaccination (1).

Bacteriologic examination of clinical specimens is performed for persons suspected of TB disease. The main type of clinical specimen for investigation of TB disease is sputum, mucus from the lower airways. Depending on the site of infection, other specimens may be connected for testing. First, specimen smears (AFB smears) are stained, acid-washed, and examined microscopically to determine presence of mycobacteria. However, AFB smears cannot differentiate between M. tuberculosis and other acid-fast bacilli. Further, a negative AFB smear cannot exclude TB disease, because subsequent cultures may be positive. The specimens are then incubated and cultured to determine if there is growth of MTBC bacteria. Incubation time can range from 4 days to 12 weeks. Positive culture results confirms the diagnosis of TB disease, while negative culture results does not rule out TB disease, since the bacteria may be growing in other specimens and/or other sites within the body. After diagnosis, bacteriologic examinations are performed at monthly intervals until a pattern of negative specimens is established (1).

Initial *M. tuberculosis* isolates from clinical specimens are tested for susceptibility to the first-line anti-TB drugs: rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE).

Clinicians use the results of the susceptibility testing to choose the best treatment regimen for the patient (1).

Genotyping can be used to analyze the DNA of a particular isolate of *M. tuberculosis*. By looking at genetic difference between strains, clinicians and researchers can identify TB transmission between individuals, groups, or outbreaks of TB (1).

Treatment

As of 2013, USA Food and Drug Administration (FDA) has approved 11 medications for use in treatment of TB. These medications are divided into two sub-groups: first-line drugs and second-line drugs. First-line drugs include: isoniazid (INH), rifampin (RIF), Pyrazinamide (PZA), and Ethambutol (EMB). Second-line drugs include: Streptomycin (SM), Cycloserine, Capreomycin, ρ-Aminosalicylic acid, Ethionamide, and Bedaquiline Fumarate (Sirturo) (1,6,7). Approved in 2012, Bedaquiline Fumarate is the most recent addition to the list of available treatments, and it is the first drug to be approved for treatment of MDR TB (6,8,9). Further, numerous non-FDA approved drugs are commonly used to treat TB, including fluoroquinilones (levofloxacin, moxifloxacin, and gatifloxacin) and some aminoglycoside drugs (amikacin and kanamycin) (7).

The standard initial treatment regimen for TB patients includes RIF, INH, PZA, and EMB, also known as RIPE. After susceptibility testing, the regimen is evaluated and changed if necessary. Standard treatment regimens can be 6-9 months in length depending on the individual case with medications that need to be taken daily (1). Strict adherence to the treatment regimen is necessary to cure TB and to prevent development of resistant strains. Lack of compliance and treatment interruption are common among TB patients. Therefore, TB case management includes the use of directly observed therapy (DOT), wherein a health care worker or other designated individual watches and documents the patient’s ingestion of the anti-TB medication for each dose prescribed. CDC recommends that all patients undergo DOT with particular emphasis on patients with drug resistant TB, patients receiving intermittent therapy (non-daily doses), and patients with high risk of nonadherence, which includes patients with a history of nonadherence, children, homeless persons, patients with mental, emotion, or physical disabilities who are unable to take medication on their own, and persons abusing alcohol or illicit drugs (10).

INH Monoresistant, Multi-drug Resistant, and Extensively-drug Resistant TB

INH monoresistant is the most common type of drug resistance for TB. Four main studies have been conducted investigating INH monoresistance; risk factors common to all of these studies include history of TB or TB treatment, being foreign-born (for US-based studies), and HIV co-infection. Characteristics such as race, ethnicity and age differed between all of the studies, suggesting that context is particularly important (11–14).

Multi-drug resistant TB (MDR-TB) occurs when the *M. tuberculosis* isolates are resistant to at least both first-line drugs: INH and RIF. Extensively drug resistant TB (XDR-TB) occurs when there is resistance to both INH and RIF in addition to being resistance to any fluoroquinolone and at least one of the injectable second-line drugs (amikacin, kanamycin, or capreomycin) (1,15). In the 2000s, there were numerous reports of resistant strains found in Italy, Iran, and India that were resistant to all TB drugs. These findings have lead some authors to coin the terms extremely resistant TB (XXDR-TB) and totally resistant TB (TDR-TB); however, the WHO does not recommend defining and utilizing these terms yet (16) .

MDR-TB and XDR-TB pose a major problem to eliminating TB. The CDC has classified drug-resistant tuberculosis, including INH-resistance, at serious hazard level, meaning that there are significant resistance threats that will worsen and become urgent with out public health intervention. About 10% of all TB cases in the US in 2011 were reported resistant to antibiotics. Resistance to INH and first-line antibiotics has been increasing since 2011. In order to prevent multi drug-resistant TB, the CDC recommends implementation of “effective infection control procedures to limit exposure to known drug-resistant TB patients in settings such as hospital, prisons, or homeless shelters” (17). In the past three decades, the discovery and approval of new antibiotic compounds has been steadily decreasing; from 2008-2012 only two antibacterial drugs were approved compared to the 1983-1987 time period when about 16 antibacterial drugs were approved (17–19).

Epidemiology

Tuberculosis in the United States

In 2013, the TB incident case rate for the US was 3 per 100,000 persons compared to 52.6 cases per 100,000 persons in 1953, a 17-fold decrease (20). In 2011, 536 deaths were attributed to TB. The percentage of cases occurring in foreign-born individuals continues to increase and contributes to 65% of the cases in the US. Of the cases occurring in US-born persons, blacks or African Americans represented 37% of cases in 2013 (20). Outbreaks of TB occur in low-resource communities (21), prison populations (22–24), and homeless populations (20,25,26). In 2013, 5.7% of all US TB cases occurred in cases reporting being homeless and 88% of TB cases were HIV positive (20).

Tuberculosis in Georgia

In 2013, Georgia reported 340 cases of TB, representing 3.5% of all of the diagnosed TB cases in the United States (including Territories). Georgia is ranked 5th in the country for total number of TB cases and 8th for case rate (3.4 cases per 100,000). Within the state of Georgia, the four counties reporting the highest number of TB cases reside in the Atlanta metropolitan area: DeKalb, Fulton, Gwinnett, and Cobb Counties. In 2012, these counties reported 50% of all of the TB cases in the state of Georgia, but these counties contain only 32% of the total population of Georgia. Further, the metropolitan Atlanta area has 74% of the state's population who have TB/HIV co-infection (27). The State of Georgia reported 8.3% of cases all reported cases were homeless and 12.7% of all reported cases with known HIV status were HIV positive. Metropolitan Area (Atlanta, Sandy Springs, Roswell, GA) reported 202 cases in 2013, 8.4% reported as being homeless (20).

Population at Risk: Homeless

A 2013 cross-sectional homeless survey found that in the state of Georgia, on a single night (January 28), there were 16,947 homeless persons, about half of whom were unsheltered, not in an Emergency Shelter or Transitional Housing; about 35% (6,434 persons) of the state's total number of homeless persons were in Fulton County. The 2013 count shows a 15% reduction in homeless persons compared to the count in 2009. The transitional or emergency shelters in Fulton County have limited capacity, and could only accommodate about three quarters of the homeless population (4,622 available beds). Thirty percent of respondents who were homeless had been homeless for more than one year. The amount of support needed to become stably housed is positively associated with the amount of time homeless; so the longer a person is homeless, the more support they will need. Additionally, 38% of respondents self-reported having at least one disability. Among the reported disabilities were chronic medical conditions, physical disabilities, HIV, mental illness and addictive diseases. While there are benefits through federal and state programs targeted at the homeless population, the application process can be very difficult for homeless persons (28,29).

A 2003 cross-sectional study of 200 clinics supported by the US Health Care for the Homeless (HCH) Program found that twice as many individuals from overall US population obtained preventative care compared to the HCH homeless users. Further, self-reported health status of both populations showed that twice as many individuals identified as excellent or very good in the US population compared to HCH users. Health problems, including asthma, diabetes, hypertension, stroke, HIV/AIDS, tuberculosis, substance abuse, and mental health program, were found at a much higher prevalence among the HCH users compared to the general population. The survey found 3.1% of HCH users had tuberculosis compared to 2007 figures from CDC of 0.0004% of individuals within the US population. Further, homeless persons typically received little or fragmented care, and thus, they were more likely to visit emergency rooms and other costly hospital services. The goal of the HCH program is to increase the number of persons with “usual source of health care”, which can prevent or ameliorate chronic health problems, decrease medical costs, and cause an overall increase in health status (30).

TB has been declining in the general population; however, these gains may not be reflected within the homeless population. Higgs et al. has shown that TB incidence in the homeless population in San Francisco has remained relatively stable (31).

Geospatial Analysis Methods

Geospatial methods have been used in a variety of public health studies from infectious disease to chronic disease to environmental exposures(21,31–47). Various methods can be applied to geolocated data in order to understand spatial patterns, autocorrelation, and spatial risk factors. An understanding of these factors helps epidemiologists and public health practitioners understand disease transmission, create effective surveillance systems, target disease screening and prevention activities, and target interventions (36).

Numerous studies have shown that TB cases form clusters in space. Goswami and Cegielski have both used GIS methods to target TB screening programs in North Carolina and Texas respectively (21,37,46) . Spatial statistical methods have been used to detect and analyze TB outbreaks (31,38,41). Various methods have been used to analyze TB cases spatially. Kistemann et al. utilized a chi square test to investigate spatial heterogeneity (48). Global spatial autocorrelation of TB cases using Moran's I statistic has been used to determine clustering of cases (45,49). Local spatial autocorrelation using the Getis G^*_i statistic has been used to determine clusters or hotspots of TB infections(49). Kuldorff's SatScan statistic and variations on the statistics have been successfully used to investigate TB outbreaks, determine geographic predictors of disease, and for surveillance activities in a variety of contexts including USA(21,31,37,50,51), Canada(52), Brazil(40,53), China (45,49,54), Madagascar (55), Peru (56), Germany (48), Mexico (57), Uganda(58), and India (43). Kammerer et al. compared the effectiveness of three statistical methods in detecting tuberculosis outbreaks: county-based log-likelihood ratio, cumulative sums, and Kuldorff's SatScan statistic. The three methods were found to be comparable and showed the potential to detect outbreaks before local public health authorities detect the outbreak (38).

These methodologies are important tools in understanding the spatial context of TB disease; however, a large sample size is needed in order to use these tools and show a statistically sound effect. Further, all of these analyses utilize one address per case. The use of a single address to define areas of disease transmission for a person is shortsighted, because it assumes that humans are stationary. However, people are mobile; individuals move around in order to go to work, socialize, run errands, etc. This concept has been previously described as spatial polygamy, "the simultaneous belonging or exposure to multiple nested and non-nested, social and geographic, real, virtual and fictional, and past and present contexts" (59). Matthews and Yang utilize methods to understand spatial polygamy in order to understand the neighbourhood context, which cannot be simply distilled down to zip code or even census track (59). Spatial polygamy is particularly important for investigating transient populations, who are highly mobile. Many spatial analyses exclude homeless cases due to their transient status or ignore homelessness as an important issued for collecting spatial data (21,37,52); other studies have included homeless cases in spatial analyses, but have only included a single address for analysis (31). Many homeless individuals circulate among a variety of locations, including homeless shelters and hangout spots. Additional areas of transmission are neglected with a one-address analysis. Identifying these areas is important to allocate resources for screening and prevention activities.

The use of the activity space, a multidimensional space that represents spatial movement of people in their day-to-day lives (60), could provide a simple but useful framework for analysis. Activity space analyses are commonly used for chronic disease and health care access studies (60,61). Analysis of activity in space and time has been performed using a simulation to model the transmission of infectious disease in an urban setting. The simulation included a variety of parameters including movements to and from the home, movements to regular activity locations, including work and social events, and movement around these regular activity locations (62). While this modeling approach may be able to create a picture of disease transmission, the complexity and amount of information required to perform this analysis renders it unfeasible for general application.

Since TB outbreaks continue to occur across the country, strategies are needed to evaluate both drug resistance and spatial context of disease. Context has been shown to be an important factor in understanding and controlling TB outbreaks. Strategies and new methodologies need to be developed in order to assess important exposures and the areas in which these exposures occur. The results of this analysis can inform case finding and resource allocation. Further, due to the low-prevalence nature of the disease, these techniques need to be useful with a small sample size.

Chapter 2: Manuscript

Background

While great strides have been made in reducing the rate of tuberculosis (TB) in the United States (US) (20), outbreaks of TB continue to occur and cause strain on public health resources (63). Since 1993, there has been a 38% reduction in TB cases in the US; however, the percentage of all TB cases that have resistance to one of the first-line medications, isoniazid (INH), has remained steady around 6% in the same time period (20). Research on multi-drug resistant (MDR) TB, TB that is resistant to at least INH and rifampin (RIF) (1), is extensive; however, there is limited research on risk factors for INH monoresistance. Four main studies have been conducted investigating INH monoresistance; risk factors common to all of these studies include history of TB or TB treatment, being foreign-born (for US-based studies), and HIV co-infection. Characteristics such as race, ethnicity and age differed between all of the studies, suggesting that local context is particularly important (11–14).

Numerous outbreaks of TB have been reported across the US (22,23,25,64–67) A recent study of source case-patients from 26 TB outbreaks in the US from 2002-2011 found that the "largest outbreaks involved source case-patients who were incarcerated or had been homeless" (63). Further, source cases shared many characteristics, including alcohol abuse and prolonged infectious periods (63). Of the four main studies on INH monoresistance (11–14), only one included a stratified analysis on homeless status concluding that INH resistance was associated with homelessness (12). Evaluation of homelessness as a correlate of INH resistance remains a major gap in the literature.

Spatial context of disease is important for all infectious disease. Geospatial methods have been used in a variety of public health studies and programs from infectious disease to chronic disease to environmental exposures (21,31–47). Various analytical methods have been applied to geolocated TB case data in order to understand spatial patterns and clusters, space-time clustering, autocorrelation, and spatial risk factors (21,31,37,38,41,43,45,46,48,49,52,56). An understanding of these factors helps epidemiologists and public health practitioners understand disease transmission, create effective surveillance systems, target disease screening and prevention activities, and target interventions (36).

These methodologies are important tools in understanding the spatial context of TB disease; however, a large sample size is typically needed in order to identify statistically significant patterns with these tools. Further, typical analyses utilize one address per case. The use of a single address to define areas of disease transmission for a person is limited, because it assumes that humans are stationary. However, people are mobile; individuals move around in order to go to work, socialize, run errands, etc. This concept of spatial polygamy, "the simultaneous belonging or exposure to multiple nested and non-nested, social and geographic, real, virtual and fictional, and past and present contexts", has be previously been described as a way to understand the neighbourhood context, which cannot be simply distilled down to zip code or census track (59). Spatial polygamy is particularly important for investigating transient populations, who are highly mobile. Many spatial analyses exclude homeless cases due to their transient status or ignore homelessness as an important issue when collecting spatial data (21,37,52); other studies have included homeless cases in spatial analyses, but have only included a single address for analysis (31). Many homeless individuals circulate among a variety of locations, including homeless shelters and hangout spots; therefore, additional areas of transmission are neglected with a one-address analysis. Identifying these areas may be important for allocating resources for screening and prevention activities.

The use of the activity space, a multidimensional space that represents spatial movement of people in their day-to-day lives (59,60), could provide a simple but useful framework for analysis. Activity space analyses are typically used for chronic disease and health care access studies (59–61). Analysis of activity in space and time has been performed using simulation to model the transmission of infectious disease in an urban setting. The simulation included a variety of parameters including movements to and from the home, movements to regular activity locations, including work and social events, and movement around these regular activity locations (62). While this modeling approach may be able to create a picture of disease transmission, the complexity and amount of information required to perform this analysis renders it unfeasible for general application.

Since TB outbreaks continue to occur across the country, strategies are needed to evaluate both drug resistance and spatial context of disease. Context has been shown to be an important factor in understanding and controlling TB outbreaks. Strategies and new methodologies need to be developed in order to assess important exposures and the areas in which these exposures occur. The results of this analysis can inform case finding and resource allocation. Further, due to the low-prevalence nature of the disease, these techniques need to be useful within relatively small sample sizes.

Methods

Fulton County Outbreak:

In January 2014, an outbreak of TB was discovered centering in several homeless shelters within Fulton County, Georgia. As of August 2014, 47 cases, including two shelter volunteers, and three deaths were identified and linked to the outbreak (68,69). Further spread of the outbreak was anticipated during the winter months due to the increased use of emergency shelters during winter weather. A similar outbreak occurred in 2008/2009 with the identification of 12 confirmed cases and an additional four probable cases of TB. Georgia Department of Health with the support of the Centers for Disease Control and Prevention, thoroughly investigated both of these outbreaks. The two outbreaks share many features, including high incidence of INH resistance and confirmed transmission within homeless shelters. Genotypic similarities between the 2008/2009 and the 2014 outbreaks indicate that transmission has continued in the interim period (70).

The outbreak in Fulton County is of particular concern for many reasons. First, the outbreak is occurring in a highly transient population with lower linkage to health services. Secondly, the outbreak strain is resistant to one of the standard treatment antibiotics, isoniazid (INH). Thirdly, outbreaks of TB continue in Atlanta, particularly the homeless community, meaning that there are still major gaps. A better understanding of the situation in Atlanta is needed in order to bring more awareness to clinicians and government officials. The association of homelessness with TB cases, particularly INH resistance cases, is known; however, the strength of this association and the confounders mediating this relationship have not been reported.

Study:

We performed a retrospective pilot study involving spatial and risk factor data from a random sample of diagnosed cases of active TB in Fulton County. The study population included persons 18 years and older diagnosed with active TB disease between January 1, 2008 and October 31, 2014 and who were reported to Fulton County Department of Health. Data for this study was abstracted from medical charts at the Fulton County TB Clinic and a database of TB cases from Grady Hospital. From January 2008 to December 2014, there were about 431 cases of active TB reported from the Fulton County Department of Health to the Georgia Department of Health (27,71,72). A randomly selected subset of 198 active TB cases, 44% of the total reported in the time period, was used for this study.

Due to random sampling, the percentage of cases sampled per year changes; the highest percentage of cases sampled for the study was from 2010 (61% of all reported TB cases), while the lowest percentage of cases sampled for the study was from 2014 (22% of all reported TB cases). The number of cases reported to Georgia Department of Health, and number of cases sampled and sampling percentages from each year for the study can be found in Figure 1.

Modeling

The primary objective of the study was to determine the risk factors associated with INH resistant TB infection in Fulton County. INH resistance status was collected from laboratory reports. For modeling purposes, INH resistance was categorized in two different ways. First, INH resistance was categorized with INH resistant and INH sensitive; cases' whose TB strain was not tested for drug resistance were excluded from analysis. Secondly, for clinical relevance, we included the TB strains that were not tested in the INH sensitive group. TB strains are typically not tested because the patient improves before a bacterial isolate can be tested; therefore, clinically, INH treatment was successful and the strain is not resistant.

Risk factors of interest include sex, age, year of diagnosis, race, ethnicity, country of origin, homelessness, history of incarceration, employment status, excessive alcohol use, and HIV status. Risk factor data was collected through standard health department contact tracing processes as well through clinic physician intake and recorded in the patient's chart. As such, most risk factor data, including homelessness, history of incarceration, employment status, and excessive alcohol use, were based upon self-classification by the patient. Sex, ethnicity, country of origin, homelessness, history of incarceration, excessive alcohol use were all coded as binary variables with unknown status denoted as a missing value. Age was calculated by subtracting date of birth (DOB) from the date of first positive TB culture or date of hospital admission/clinic visit (for clinical cases). Employment status was coded with four categories, employed, not employed, student, and unknown. For analysis, the student category was added into the employed category, as it shares the same purpose. Unknown employment status was coded as a missing value. Year of diagnosis was calculated from the date of first positive TB culture or date of hospital admission/clinic visit (for clinical cases). For analysis purposes, the year of diagnosis variable was divided into three categories, 2008-2009, 2010-2012, and 2013-2014, to represent the two periods of outbreak and the interim time period.

SAS 9.4 (SAS institute, Cary, NC) was used for data cleaning and analysis. Correlation of INH-resistance and homelessness was evaluated using the Mantel-Haenszel Chi Square test using a cut-off p-value of 0.05. Logistic Regression was used to evaluate homeless status as an exposure and INH resistance (INH Resistant or INH Susceptible), as the outcome. Due to sample size, interaction assessment was not performed. Confounders were evaluated using the all-possible models approach; all possible combinations were produced using a macro in Microsoft Excel and imported into SAS to iteratively run the models with the TB study data. Models producing Odds Ratios (ORs) falling within +/- 10% range of the gold standard OR (model including homelessness and all possible covariates) were considered. Precision and number of variables in the model were also considered for model selection.

Spatial Analyses

The secondary objective of the study was to understand the spatial distribution of TB infections in relation to particular risk factors in Fulton County. We were particularly interested in whether there are significant hotspots of TB in Fulton County. Further, we wanted to describe not only the primary addresses of cases, but multiple locations reported by individuals. Most spatial analyses are performed on primary, sleeping addresses; however, individuals spend time significant time in locations other than their homes. Disease transmission can occur at work, school, and other social spaces, and therefore, should not be excluded from analysis. This technique is particularly important for mobile populations, such as homeless persons, who may move sleeping spots regularly.

All addresses associated with a patient were collected from information within each chart and from the database provided to us by Grady Hospital. Addresses collected included home addresses, work addresses, school addresses, activity place addresses (for instance, church or volunteer work), and hangout spots. Addresses were collected from a variety of locations within each chart, including addresses given during registration at the Fulton County Department of Health, addresses submitted to state surveillance program, addresses reported through contact tracing, addresses reported from further investigations. Thus, a list of addresses was collected for each patient, then a primary address was designated for each patient; this primary address was typically the address sent to the Georgia Department of Health's SendSS TB reporting system. If multiple addresses were sent to the Georgia DoH, then the first address (most recent) was used as a primary address. Geocoding of addresses collected for the TB cases was performed using ArcGIS 10.2.2 (ESRI, Redlands, CA, USA) using reference data from Topologically Integrated Geographic Encoding and Referencing (TIGER)/Line shapefiles (www.census.gov). Locations without street addresses were identified using Google Earth, and latitude and longitude were recorded and mapped in ArcGIS. Further, we used Google Earth to geolocate addresses that were not found using the TIGER dataset. Shapefiles were projected into the UTM 17N projection for analyses.

A chloropleth map was created using geolocated primary address and census block data from the TIGER database. In order to evaluate disease prevalence, addresses were spatially joined to census block shapefiles that contained population information from the 2010 Census. Chloropleth maps were created to show the number and prevalence of TB in Fulton County. Homeless shelter addresses were extracted from the Homeless Shelter Directory (http://www.homelessshelterdirectory.org/cgi-bin/id/city.cgi?city=Atlanta&state=GA) and then geolocated using TIGER Road reference files.

Additionally, kernel density methods were used to identify variation between the densities of TB case locations when using primary addresses and the comprehensive list of all of the patients' addresses. The optimized bandwidth for the primary addresses, 242 m^2, was used for generating the density maps for both the primary and all area maps.

For the activity space analysis, addresses were subsetted to include only TB cases with 3 or more addresses (n=50). First, in ArcGIs and QGIS, polygons were created for each case using the three address (or more) points as vertices. These polygons represent the space in which each case is active, or activity space. Three addresses were considered to be outliers as they were far outside the greater Atlanta area, and therefore, these addresses were excluded for some of the analyses. Risk factor attributes were then joined to the activity space polygon shapefiles. For this analysis, INH resistance classification excluded cases where INH drug resistance was not tested.

Activity space analysis was split into two methods, area and overlay analyses. For the area analysis, the area of each polygon (km^2) was calculated using ArcGIS; this area represents the space in which people live and move. People who live, work, and hangout in close proximity have a smaller area, while those who live, work, and hangout farther away will have a larger area. The activity area data was right-skewed, since more cases tended to have smaller activity spaces. Thus, for analyses, the data was log-transformed to produce a normal distribution. Two-sample t-tests with a threshold p-value of 0.05 were used to evaluate the difference between the mean areas of polygons stratified on homeless status and INH resistance.

Secondly, the degree of overlap between polygons was assessed. A ternary classification was used to classify polygon overlap: no overlap, intersection at a point (but polygon does not overlap), and overlap at more than a point. Polygons were visually inspected to determine overlap and intersection with all other polygons in the dataset; a matrix of overlap and intersection indicators was created. Percentage overlap was calculated for each polygon dividing the number of polygons that overlapped or intersected with the polygon of interest divided by the total number of polygons (n=50). A percentage overlap was calculated including and excluding the intersection points. Two-sample t-tests with a threshold p-value of 0.05 were used to evaluate whether differences in percentage overlap based upon features of the patient, including homeless status and INH drug susceptibility.

Ethics Statement:

The Emory University Institutional Review Board approved the study protocol, and the Fulton County Department of Health approved the use of records for the study.

Results

The demographic characteristics for the 198 TB cases included in this study can be found in Table 1. Demographic characteristics were stratified by homeless status; 30% of the cases were identified as homeless, 68% were not identified as homeless, and 2% had unknown homeless status. Homeless TB cases were predominantly black, non-Hispanic males, while the non-homeless TB cases showed higher prevalence of many of the risk factor characteristics including history of incarceration, excessive alcohol use, and HIV positivity. Further, the homeless group showed a higher percentage of USA-born cases (89%) compared to the non-homeless group (59%).

TB disease characteristics of the cases for this study can be found in Table 3. INH resistance was found in 18% of all TB cases. Among the homeless group, 38% of TB cases had INH resistance compared to 10% in the non-homeless cohort. India accounts for the highest percentage of foreign-born TB cases from the study with 27%. INH resistant strains of TB occurred in 8% of the foreign-born TB cases; no single country of origin had more than on case of INH resistance (Table 2).

Nineteen percent of TB cases in the study were resistant to the drug INH; when stratified by homeless status, 41% of homeless patients' TB was resistant to INH, while 10% of the non-homeless patients' TB was resistant to INH. The highest yearly count of TB cases for the study was diagnosed in 2009 (n=40), while the lowest count of TB cases (n=20) occurred in 2012 and 2014. From 2008 to 2014 there appears to be a slightly decreasing trend of non-homeless case counts, while homeless case counts declined until 2013 when the counts started to increase (Table 3).

The percentage of INH drug resistant TB cases in our study mirrors the percentage of homelessness in our study over time. Both proportions peak in 2014, where about 65% of study cases were identified as homeless and 50% of cases had INH resistant TB. This rise represents a major increase in the percentage of homeless cases and INH resistance cases, even higher than the previous outbreak in 2008/2009, which had about 40% of cases identified as homeless and about 30% with INH resistant TB (Table 3).

Correlation between homeless status and INH resistance was significant for the entire cohort (Mantel-Haenszel Chi-square=0.43, p-value <0.0001). When stratified by year, only two of the seven years (2008 and 2010) showed statistically significant correlation between homeless status and INH resistance. No correlation analysis could be performed for 2011 because none of the study TB cases in that year had INH resistance. (Table 4)

Model

Multivariable logistic regression models were used to assess the association between homeless status and INH drug resistance. (Table 5) The unadjusted odds of INH drug resistance in homeless cases was 7.4 times higher than the odds of INH drug resistance in the non-homeless population (95% CI: 3.3-16.4). To investigate possible confounders, we used the all-possible models approach, generating possible 1,023 models from one exposure variable, homeless status, and twelve possible confounders. The Gold Standard (GS) model containing all of the possible covariates had an OR for homelessness of 3.41 (95% CI: 1.2-9.7). Of the 1,023 models generated models, 113 models generated ORs for homelessness within 10% of the GS model. Through this analysis, we identified year of diagnosis, excessive alcohol use, sex, employment status, and HIV status as possible confounders of homeless status. The final best-adjusted model chosen included confounders of year of diagnosis, excessive alcohol use, history of incarceration, age, and sex. The best-adjusted model showed a strong positive relationship between homeless status and INH drug resistance (OR= 3.33, 95% CI: 1.22-9.14).

The same analysis was performed including INH not tested in the INH sensitive category. The unadjusted odds ratio for INH drug resistance with homeless status was 5.92, and the fully adjusted odds ratio for INH drug resistance with homeless status and all possible confounders was 2.76. The best-adjusted model had an odds ratio of 2.90 for INH resistance with homeless status as the exposure and included homeless status, year of diagnosis, excessive alcohol use, HIV status, history of incarceration, employment status, and sex as confounders (Table 6).

Mapping

TB cases can be found throughout Fulton County; however, TB cases appear to concentrate in the downtown Atlanta area. When normalized by census population, the concentration of TB cases in downtown Atlanta becomes more prominent (Map 1). In downtown Atlanta, there are 13 locations that provide services for homeless persons. Nine of the 13 locations (69%) reside within census tracts with TB rates of greater than 65 cases per 100,000 people (Map 2).

The kernel density map of the primary address of TB cases shows a high density of cases in the central region of the county, specifically in the city of Atlanta. When all locations for the TB cases, not just the primary addresses, were smoothed using kernel density, there was greater dispersion of the density of cases compared to the kernel density of the primary addresses alone. With all addresses, areas of high density in the central region were wider, and additional high-density areas in the northern region of the county are depicted (Map 3). The homeless shelters reside in area of high density of TB cases in Atlanta. When using single address for the kernel density, six of the thirteen (46%) of the shelters reside in the area of highest density; when using all addresses for the kernel density, eleven of the thirteen (85%) reside in one of the areas with the highest density of TB cases in Atlanta (Map 4-5).

Activity Space

The demographic characteristics of the 50 cases used for the activity analysis can be found in Table 7. The areas (km^2) of activity space did not statistically differ based on homeless status or INH drug susceptibility status (p=0.87 and p=0.41, respectively). However, there was a statistically significant difference in the overlap or intersection of the activity spaces (Table 8). On average, homeless TB cases overlapped with 68% of all activity spaces, while non-homeless TB cases overlapped with 30% of all activity spaces ($t=5.89$, $p<0.001$). On average, INH resistant TB cases overlapped with 68% of all activity spaces, while INH susceptible TB cases overlapped with 46% of all activity spaces ($t=-3.25$, $p=0.0025$) (Table 9). Further, we found that homeless cases' activity spaces overlapped with on average 86% of the other homeless cases' activity spaces, while non-homeless cases' activity space overlapped on average 29% with other non-homeless cases ($t=-9.03$, $p<0.0001$). Similarly, INH susceptible cases' activity spaces overlapped with on average 38% of the other INH susceptible cases' activity spaces, while INH resistant cases' activity spaces overlapped with on average 81% of other INH resistant cases ($t=-6.9$, $p<0.0001$) (Table 10).

Discussion

TB remains a major public health problem within Fulton County, Georgia. In Fulton County, Georgia, INH drug resistant TB cases continue to affect the homeless community. The percentage of INH drug resistant TB cases in our study mirrors the percentage of homelessness in our study from 2008 to 2014. In 2014, the proportion of TB cases with INH drug resistance in Fulton County (50%) is over 30 percentage points higher than the percentage of INH resistant TB at the US national level in 2013 (16%) (20). Such a large increase in the percentage of INH drug resistance is a cause for concern. Further, since the resistance corresponds with an increase in the percentage of TB cases being identified as homeless, there is an urgent need to improve spatial and other surveillance approaches appropriate for transient populations.

The characteristics of INH resistant TB cases differ from previous studies, including a national study of INH resistant TB in the US from 1993 to 2005. In the national study, they found the highest proportions of INH resistant cases for each demographic category were foreign-born, Asian/Pacific Islander individuals, and ages 25 to 44, while the highest proportions of INH susceptibility occurred in Black, non-Hispanic persons (11). In our study, the highest proportions of INH resistant cases for each demographic category were US-born, Black, non-Hispanic and an average age of 50 years. Thus, risk markers for INH resistant TB are not fixed, and prevention and surveillance efforts need to utilize epidemiologic techniques to evaluate each outbreak and its local context. Further, this demonstrates that there is on-going transmission of INH resistant TB within the United States, and thus, is not limited to importation.

Our goal was to understand if being homeless was truly the exposure for the disease or if other factors are confounding the relationship of homelessness and INH resistant TB. We found a strong positive association between homelessness and INH resistance. A strong association remained once the model was adjusted for suspected confounders. The results from model selection when cases where INH resistance wasn't tested were added to the INH sensitive category showed similar results; the unadjusted effect of homelessness was much lower when including untested INH cases, but the fully adjusted models for both classifications has similar odds ratios. Confounders common to the best-adjusted model and the three most parsimonious models from both model selection strategies include year of diagnosis and excessive alcohol use. Due to the outbreaks of TB disease at separate points in time, creating an indicator time variable was important to represent times of outbreak and times of low disease incidence. The need to control for this in a logistic model would be situational. Other confounds including excessive alcohol use, history of incarceration, sex, age, HIV status, country of origin, and employment status have all been investigated previously as confounders.

Since about a third of TB cases in this study were found in homeless individuals, the need to understand the spatial context is particularly important. Typically, studies exclude homeless patients from spatial analyses due to the complexity of utilizing spatial data for transient populations or studies distill the experience of homeless cases down to a single address (21,37,41,47). However, excluding homeless cases or only reporting one address for those cases would not provide a sufficient picture of the location of TB cases in

Fulton County. This also holds true for non-homeless TB cases. While people spend a large time at their place of residence, they also spend time in other locations, including work, school, hangout locations, and church. Using kernel density smoothing, we found that primary address of TB cases have the highest density in the central, downtown region of Atlanta. However, when we perform kernel density including all reported address, for instance residential, work, and hangout areas, we found a more dispersed spatial pattern. Thus, people with TB move within a larger area than can be described using primary address alone. These additional locations, particularly work and school, are already targeted for contact tracing purposes; thus, including all locations is a feasible way to describe the spatial context. From this pilot study analysis, we recommend that the same analysis should be performed on the entire active TB case cohort in Fulton County and this methodology could be transferred to other settings.

Activity spaces based upon homeless status and INH drug resistance status was not significantly different. However, we found the homeless cases' activity space overlapped with a higher percentage of cases' activity space compared to non-homeless cases. Thus, while homeless and INH resistant cases show the same distribution in the area enclosed by key activity locations, homeless and INH resistant cases' activity spaces overlap more than non-homeless and INH susceptible activity spaces, suggesting there is potential to describe transmission patterns within these spaces for some. Locations overlapped by homeless persons with TB activity spaces are likely locations servicing this population, such as homeless shelters and hangout areas, while INH resistance activity spaces could suggest areas where transmission of INH resistant TB occurs. Since, public health authorities are still struggling in containing the transmission of TB, understanding the areas where people can come into contact with persons with TB or persons with INH resistant TB is extremely important. Further analysis of the activity space data could identify additional locations, which are currently being neglected, and target screening and prevention activities. Knowing these areas of high transmission is important for case finding and scaling prevention activities.

Strengths:

Drug resistance is an important issue in the control of tuberculosis; scientific literature concentrates on MDR TB, but mostly ignores INH monoresistant TB. Our study provides insight into the relationship between homelessness and INH resistant TB and the various risk markers, which may confound this relationship. Activity space methods were utilized in this study in order to better understand the geographic distribution and context of TB outbreaks in Fulton County from 2008 to 2014.

Limitations:

TB cases from 2014 were undersampled for the study. Since data collection started in December 2014, many of the 2014 TB cases were still active and unable to be abstracted. Further, some 2014 TB cases were diagnosed after the start of the study, and thus, were not included in our sampling. Since only 22% of the 2014 TB cases were included in our analysis, the results may not be valid for that year.

Further, we were limited by the data collected by the physician or contact tracer. For many indicators, including excessive alcohol use and homelessness, cases self-reported their status; this data collection method can suffer from information bias, specifically social desirability bias. In the same way, address collection was based upon information from the chart. Numerous addresses had to be excluded due to insufficient information to geolocate the address; thus, many addresses could not be identified in the TIGER database or on Google Earth. Additionally, some addresses lacked directionality or other portions of the address, which meant that addresses could not be distinguished and thus were excluded. For locations, particularly for the homeless cases, lack of detailed description of locations often meant that addresses were excluded. For instance, "sleeping under a bridge" was a common location; however, without identification of the particular bridge, the location could not be geolocated.

Conclusion

INH resistant TB remains a major problem in Fulton County, GA. The fact that INH resistant TB is highly associated with homelessness means that alternative methodologies are necessary for investigating outbreaks. Using geographic as well as traditional epidemiologic analyses provides important demographic and spatial contextual information about TB within Fulton County. Utilization of multiple addresses or activity spaces for the study of TB is paramount to understand the full spatial context. Further, study of the entire cohort of TB cases from Fulton County using this methodology could provide additional information about outbreak and its trend over time. The application of these methods can be utilized in counties or states across the United States. Further, this methodology is transferable and can be used to investigate other infectious diseases and their possible areas of transmission. The results of this study will be presented to the Fulton County TB Taskforce and used to demonstrate the utility of spatial analyses for surveillance and the need to accurately collect multiple addresses for TB cases.

Tables, Figures, and Maps

Tables

Table 1. Demographics of Study Population, Active Tuberculosis Study Cases in Fulton County, GA, 2008-2014 (n=198)

Demographics	Total (N=198)	Homeless (N=63)	Not Homeless (N=131)	Unknown Homeless Status (N=4)
	N (%) or Mean (SD)	N (%) or Mean (SD)	N (%) or Mean (SD)	N (%) or Mean (SD)
Age (years)	47 (15)	50 (9)	45 (18)	53 (16)
Sex				
Male	133 (67%)	54 (86%)	76 (58%)	4 (100%)
Female	63 (32%)	9 (14%)	53 (40%)	0
Missing	2 (1%)	0	1 (1%)	0
Race				
Black	134 (68%)	51 (81%)	80 (61%)	3 (75%)
White	36 (18%)	11 (17%)	24 (18%)	1 (25%)
Asian	28 (14%)	1 (2%)	27 (21%)	0
Ethnicity				
Hispanic	22 (12%)	5 (8%)	17 (13%)	0
Non-Hispanic	176 (88%)	58 (92%)	114 (87%)	4 (100%)
History of Incarceration				
Yes	23 (12%)	13 (21%)	10 (8%)	0
No	171 (86%)	49 (78%)	121 (92%)	1 (25%)
Unknown	4 (2%)	1 (2%)	0	3 (75%)
Country of Origin				
USA	139 (70%)	57 (90%)	78 (60%)	4 (100%)
Not USA	58 (29%)	6 (10%)	52 (40%)	0
Unknown	1 (1%)	0	1 (1%)	0
Employment Status				
Employed	61 (31%)	6 (10%)	54 (41%)	1 (25%)
Not Employed	125 (63%)	56 (89%)	67 (51%)	2 (50%)
Student	8 (4%)	0	8 (6%)	0
Unknown	4 (2%)	1 (2%)	2 (2%)	1 (25%)
Excessive Alcohol				
Yes	36 (18%)	20 (32%)	15 (12%)	1 (25%)
No	152 (77%)	38 (60%)	112 (85%)	2 (50%)
Unknown	10 (5%)	4 (6%)	4 (3%)	1 (25%)
HIV Status				
Positive	52 (26%)	23 (37%)	29 (22%)	0
Negative	138 (70%)	38 (60%)	96 (73%)	4 (100%)
Unknown	8 (4%)	2 (3%)	6 (5%)	0

Table 2: Top Four Countries of Origin of Foreign-born Tuberculosis Study Cases in Fulton County, GA. from 2008-2014

Country	Total (N=60)	INH Resistant (N=5)	INH Susceptible (N=44)	Not Tested (N=10)
	N (%)	N (%)	N (%)	N (%)
India	16 (27%)	0	13 (29%)	3 (30%)
Mexico	11 (18%)	1 (20%)	9 (20%)	1 (10%)
Democratic Republic of Korea	3 (5%)	1 (20%)	1 (2%)	0
Ethiopia	3 (5%)	0	1 (2%)	2 (20%)

Table 3. Tuberculosis Disease Characteristics, Active Tuberculosis Study Cases in Fulton County, GA from 2008-2014 (n=198)

Tuberculosis Disease Characteristics	Total (N=198)	Homeless (N=63)	Not Homeless (N=131)	Unknown Homeless Status (N=4)
	N (%) or Mean (SD)	N (%) or Mean (SD)	N (%) or Mean (SD)	N (%) or Mean (SD)
Isoniazid (INH) Susceptibility				
Sensitive	128 (65%)	25 (40%)	100 (76%)	2 (50%)
Resistant	38 (19%)	26 (41%)	13 (10%)	0
Test Not Performed	31 (16%)	12 (19%)	17 (13%)	2 (50%)
Unknown	1 (1%)	0	1 (1%)	0
Year of Diagnosis				
2008	37 (19%)	14 (22%)	23 (18%)	0
2009	40 (20%)	15 (24%)	23 (18%)	2 (75%)
2010	33 (17%)	7 (11%)	26 (20%)	0
2011	23 (12%)	3 (5%)	19 (15%)	1 (25%)
2012	20 (10%)	3 (5%)	17 (13%)	0
2013	25 (13%)	8 (13%)	16 (12%)	1 (25%)
2014	20 (10%)	13 (21%)	7 (5%)	0
Diagnosis				
Culture Positive	170 (86%)	52 (80%)	115 (88%)	3 (75%)
AFB Smear Positive Only	3 (2%)	0	3 (2%)	0
Clinical*	25 (13%)	11 (20%)	13 (10%)	1 (25%)
Documented Death within 12 months of Diagnosis	23 (12%)	5 (%)	18 (14%)	0
TB-related	7	2	5	0
Not TB-related	12	2	10	0
Unknown	4	1	3	0

*Clinical Diagnosis is defined as sufficient radiographic, clinical, or laboratory evidence of tuberculosis disease

Table 4: Association of INH Resistance and Homeless Status in Fulton County, GA, 2008 to 2014

Excluding INH susceptibility not tested (n=164)		
Year of Diagnosis	**Mantel-Haenszel Chi Square**	**p-value**
All Years	27.6119	<0.0001*
2008	9.5895	0.0020*
2009	0.5134	0.4737
2010	20.1923	<0.0001*
2011	NA**	NA**
2012	0.4832	0.487
2013	0.0294	0.8638
2014	3.7778	0.0519
Including INH susceptibility not tested as INH Sensitive (n= 193)		
Year of Diagnosis	**Mantel-Haenszel Chi Square**	**p-value**
All Years	23.5219	<0.0001*
2008	7.8478	0.0051*
2009	0.6128	0.4276
2010	11.8857	0.0006*
2011	NA**	NA**
2012	0.8839	0.3471
2013	0.1437	0.7046
2014	3.141	0.0763

* Statistically significant
** No INH resistant cases occurred for our study cases during 2011

Table 5: Logistic Regression Models for Isoniazid Drug Resistance of Study Tuberculosis Cases in Fulton County, GA, 2008-2014 (n=164)

Model	Variables in the Model	Variables Dropped	# Var	OR	95% CI
Unadjusted	Homeless status	All	1	7.40	3.33-16.41
Fully Adjusted	Homeless status Year of Diagnosis Country of Origin Excessive Alcohol use Race Ethnicity HIV status History of Incarceration Age Employment Status Sex	None	13	3.41	1.20-9.73
Best Adjusted Model	Homeless status Year of Diagnosis Excessive Alcohol Use HIV status History of Incarceration Age Sex	Country of Origin Race Ethnicity Employment Status	8	3.33	1.22-9.14
Most Parsimonious	Homeless status Year of Diagnosis Excessive Alcohol Use Employment Status Sex	Country of Origin Race Ethnicity HIV Status History of Incarceration Age	6	3.49	1.31-9.29
	Homeless status Year of Diagnosis Excessive Alcohol Use History of Incarceration Employment Status	Country of Origin Race Ethnicity HIV Status Age Sex	6	3.68	1.42-9.52
	Homeless status Year of Diagnosis, Country of Origin, Excessive Alcohol Use Employment Status	Race Ethnicity HIV Status History of Incarceration Age Sex	6	3.53	1.34-9.26

Table 6: Logistic Regression Models for Isoniazid Drug Resistance with Not Tested INH Cases Classified as INH Sensitive of Study Tuberculosis Cases in Fulton County, GA, 2008-2014 (n=193)

Model	Variables in the Model	Variables Dropped	# Var	OR	95% CI
Unadjusted	Homeless status	All	1	5.92	2.76-12.71
Fully Adjusted	Homeless status Year of Diagnosis Country of Origin Excessive Alcohol use Race Ethnicity HIV status History of Incarceration Age Employment Status Sex	None	13	2.76	1.03-7.39
Best Adjusted Model	Homeless status Year of Diagnosis Excessive Alcohol Use HIV status History of Incarceration Employment Status Sex	Country of Origin Race Ethnicity Age	8	2.90	1.11-7.54
Most Parsimonious	Homeless status Year of Diagnosis Excessive Alcohol Use Employment Status Sex	Country of Origin Race Ethnicity HIV Status History of Incarceration Age	6	2.96	1.17-7.51

Table 7. Demographics of Activity Space Study Sub-Population, Active Tuberculosis Study Cases in Fulton County, GA, 2008-2014 (n=50)

Demographics	Total (N=50)	Homeless (N=34)	Not Homeless (N=16)
	N (%) or Mean (SD)	N (%) or Mean (SD)	N (%) or Mean (SD)
Age (years)	46 (12)	49 (9)	38 (14)
Sex			
Male	38 (76%)	29 (85%)	9 (56%)
Female	12 (24%)	5 (15%)	7 (44%)
Race			
Black	38 (%)	28 (82%)	10 (63%)
White	10 (%)	6 (18%)	4 (25%)
Asian	2 (%)	0	2 (13%)
Ethnicity			
Hispanic	7 (14%)	3 (9%)	4 (25%)
Non-Hispanic	43 (86%)	31 (91%)	12 (75%)
History of Incarceration			
Yes	13 (26%)	11 (32%)	2 (13%)
No	36 (72%)	22 (65%)	14 (88%)
Unknown	1 (2%)	1 (3%)	0
Country of Origin			
USA	40 (80%)	31 (91%)	9 (56%)
Not USA	10 (20%)	3 (9%)	7 (44%)
Employment Status			
Employed	12 (24%)	2 (6%)	10 (63%)
Not Employed	38 (%)	32 (94%)	6 (38%)
Excessive Alcohol			
Yes	18 (36%)	14 (41%)	4 (25%)
No	31 (62%)	20 (59%)	11 (69%)
Unknown	1 (2%)	0	1 (6%)
HIV Status			
Positive	19 (38%)	12 (35%)	7 (44%)
Negative	31 (62%)	22 (65%)	9 (56%)
Isoniazid (INH) Susceptibility			
Sensitive	22 (44%)	9 (26%)	13 (81%)
Resistant	21 (42%)	20 (59%)	1 (6%)
Not Tested/Unknown	7 (14%)	5 (15%)	2 (13%)
Year of Diagnosis			
2008	11 (22%)	8 (24%)	3 (19%)
2009	11 (22%)	8 (24%)	3 (19%)
2010	11 (22%)	6 (18%)	5 (31%)
2011	3 (6%)	1 (%)	2 (13%)
2012	3 (6%)	3 (9%)	0
2013	4 (8%)	2 (6%)	2 (13%)
2014	7 (14%)	6 (18%)	1 (6%)

Table 8: Area of Activity Spaces of a Subset of the Fulton County Tuberculosis Study Cases, 2008-2014 (n=47)

Activity Space Area Analysis	**Activity Space Area (km-squared)**					**2 Sample T-test**	
	n (%)	**Mean**	**Min**	**Max**	**SD**	**T**	**p-value**
Total	47	48.3	0.0005	692.9	107.6		
Not Homeless	16 (34%)	45.2	1.3	242.1	67.2	-0.17	0.87
Homeless	31 (66%)	49.9	0.0005	692.9	124.5		
INH Susceptible	22 (47%)	58.4	0.02	692.9	146.6	0.84	0.41
INH Resistant	20 (43%)	30.9	0.0005	168.6	39.9		

Table 9: Proportion of All Activity Spaces with Intersection or Overlap for Each Activity Space Area, Fulton County Tuberculosis Study, 2008-2014 (n=50)

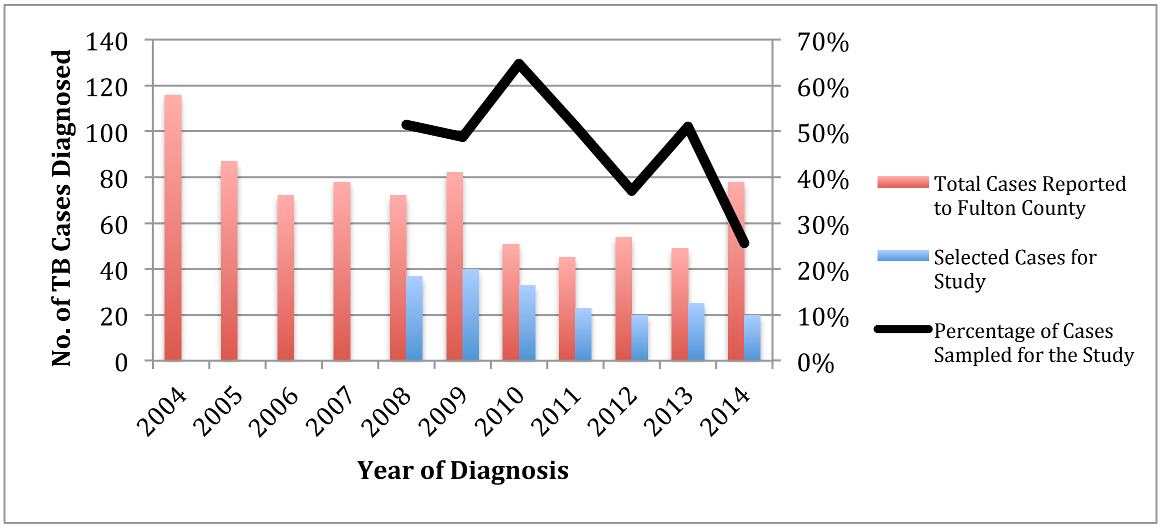
Activity Space Overlap and Intersection	**Proportion of All Activity Spaces with Intersection or Overlap for Each Activity Space Area**					**2-Sample T-test**	
	N	**Mean**	**SD**	**Min**	**Max**	**T**	**p-value**
All	50	0.56	0.25	0	0.84	-	-
Not Homeless	16	0.30	0.24	0	0.66	5.89	<0.0001
Homeless	36	0.68	0.15	0.30	0.84		
INH Susceptible	22	0.46	0.25	0	0.84	-3.25	0.0025
INH Resistant	21	0.68	0.18	0.07	0.84		

Table 10: Proportion of Activity Spaces with Intersection or Overlap within Each Classification (Homelessness and INH Resistance), Fulton County Tuberculosis Study, 2008-2014 (n=50)

Activity Space Overlap and Intersection	Percent of All Activity Spaces with Intersection or Overlap for Each Activity Space Area					2-Sample T-test	
	N	**Mean**	**SD**	**Min**	**Max**	**T**	**p-value**
Not Homeless	16	0.29	0.22	0	0.75	-9.03	<0.0001
Homeless	34	0.86	0.17	0.41	1		
INH Susceptible	22	0.38	0.22	0	0.8	-6.9	<0.0001
INH Resistant	21	0.81	0.19	0.10	1		

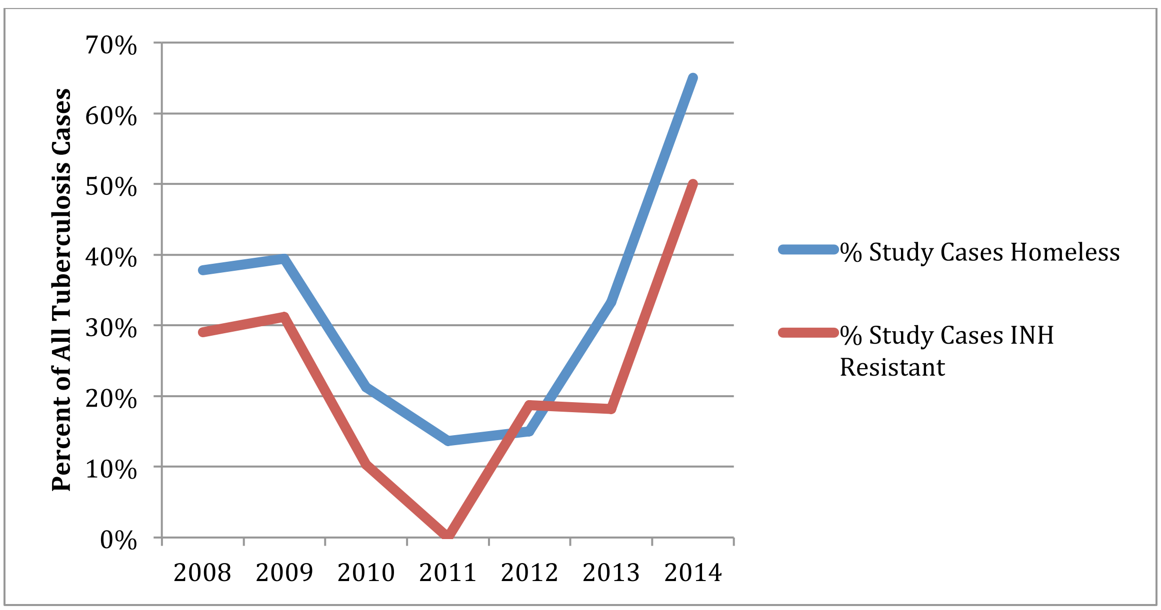
Figures:

Figure 1: Total Active TB Cases in Fulton County, Georgia and Percent of Cases Sampled for the Study, 2008-2014



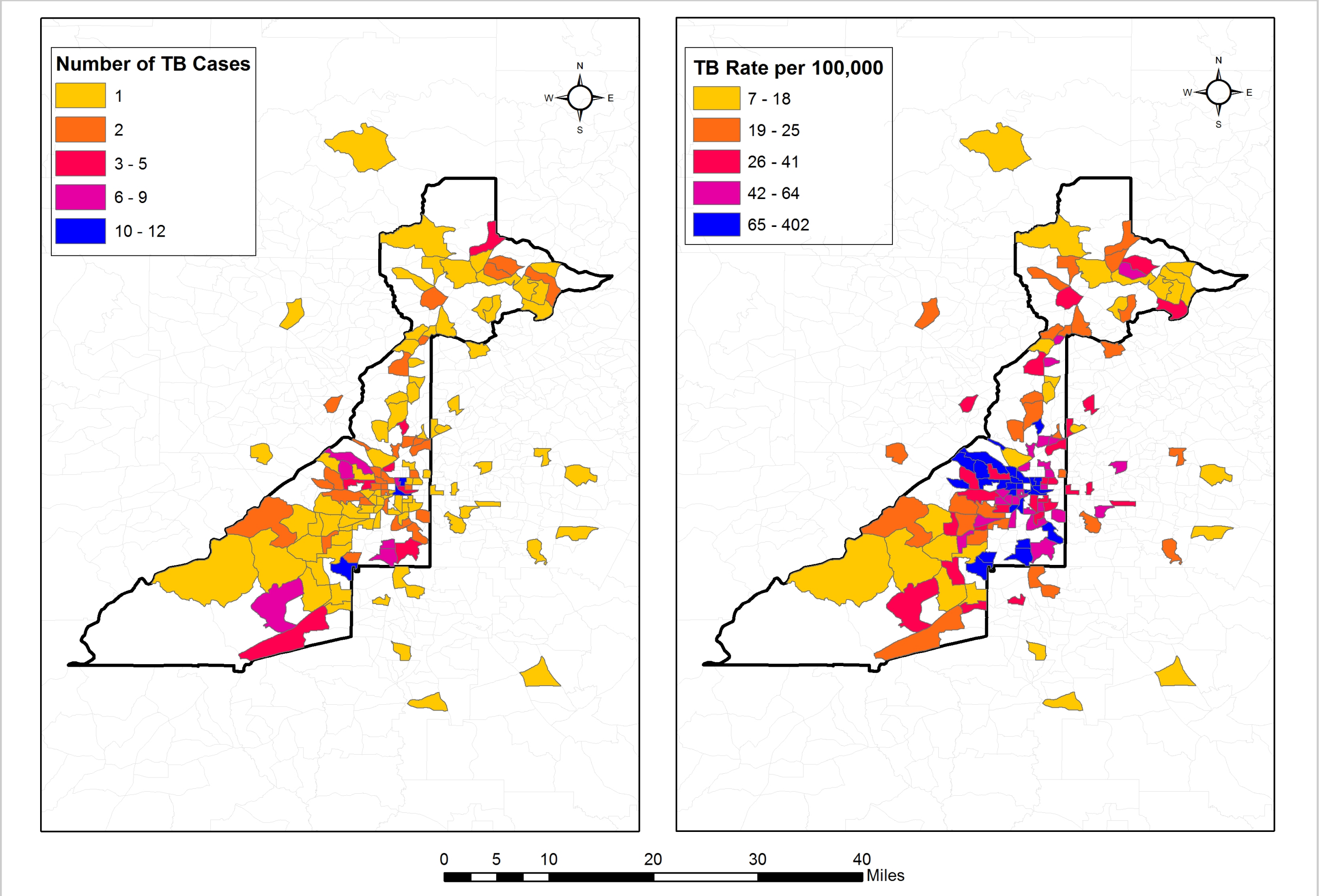
* Sources: Georgia Department of Health Tuberculosis Reports (27,71,72)

Figure 2: Percentage of Study Cases Identified as Homeless and Percentage of Study Cases with Isoniazid Resistant Tuberculosis by Year in Fulton County, Georgia, 2008-2014



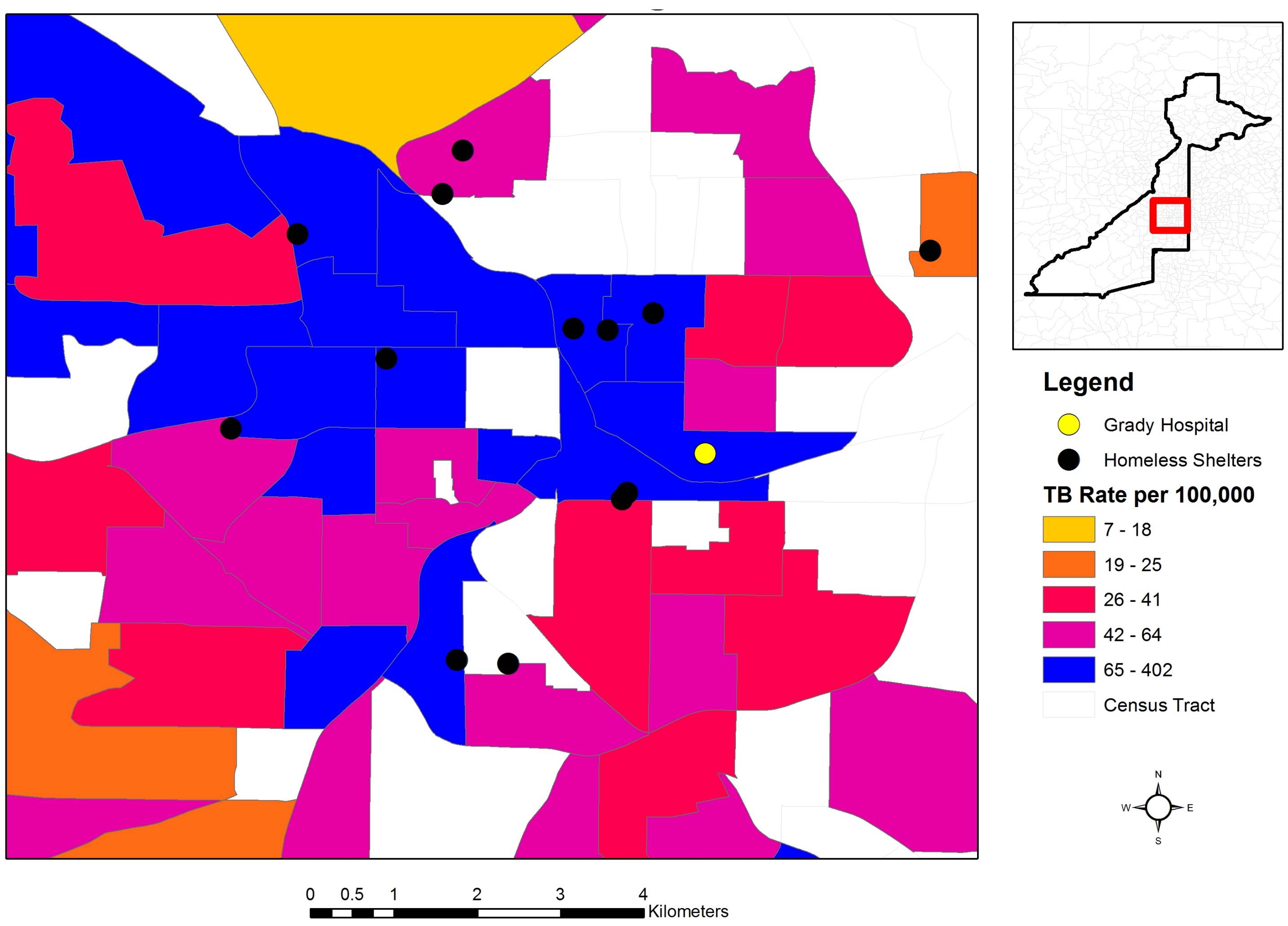
Maps:

Map 1: Tuberculosis Cases and Case Rate per 100,00 people in a Fulton County, Georgia Study, 2008-2014

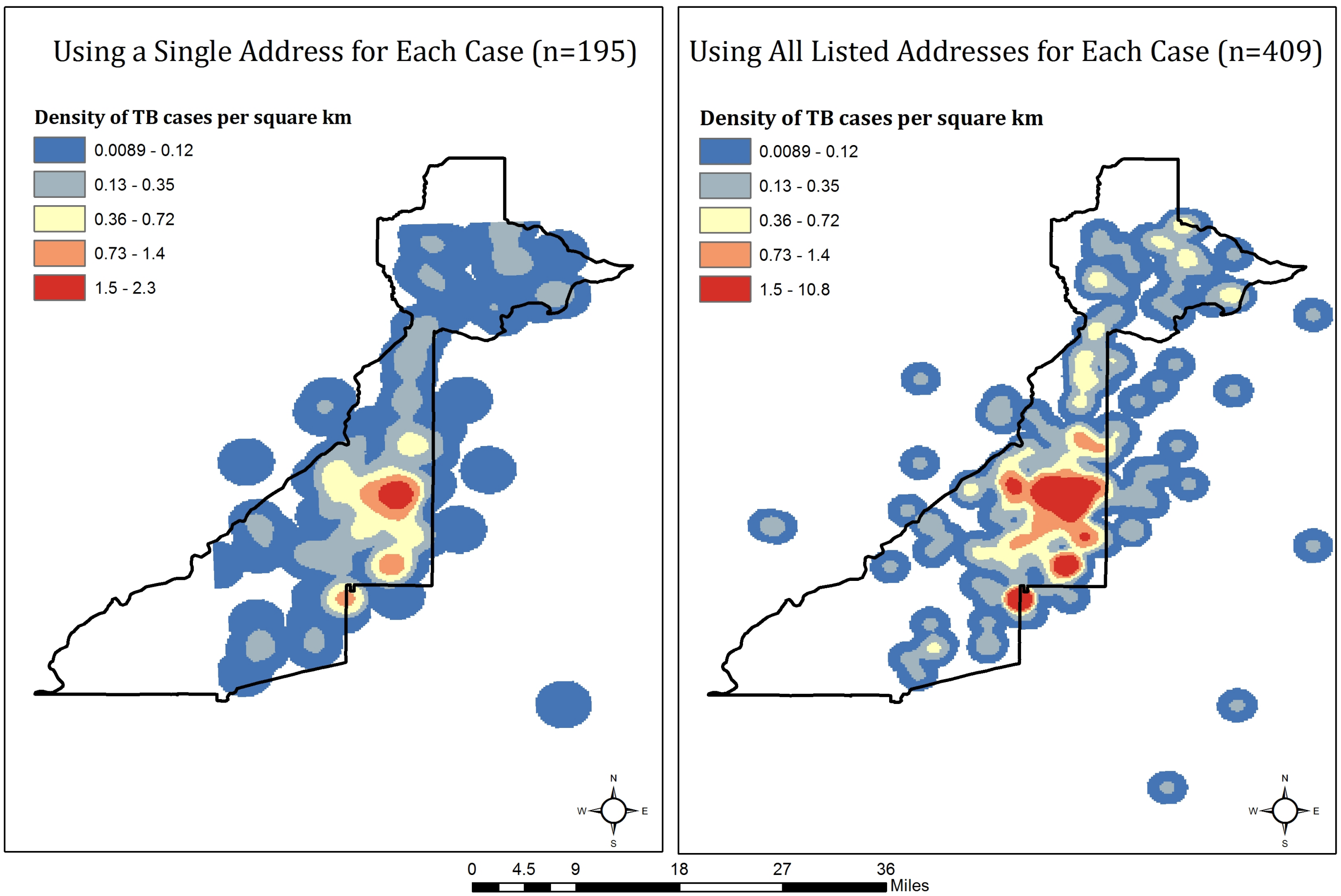


*Classification using quintiles was used to create both maps

Map 2: Tuberculosis Study Case Rate per 100,00 people with Locations of Homeless Shelters in Atlanta, Georgia Study, 2008-2014

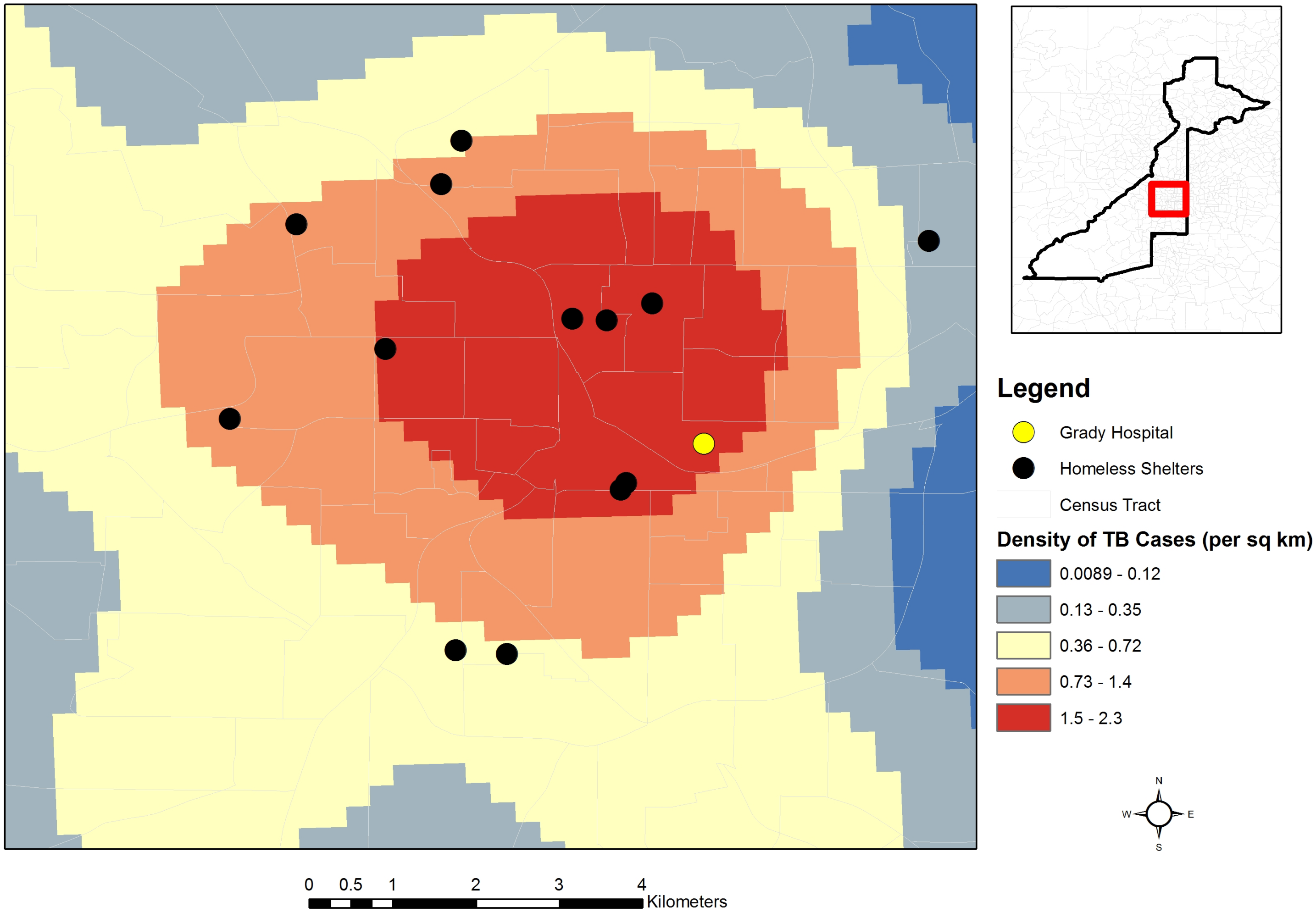


Map 3: Difference in Density of Tuberculosis Cases when using a Single Address versus Multiple Address for Each Case, Fulton County, Georgia, 2008-2014

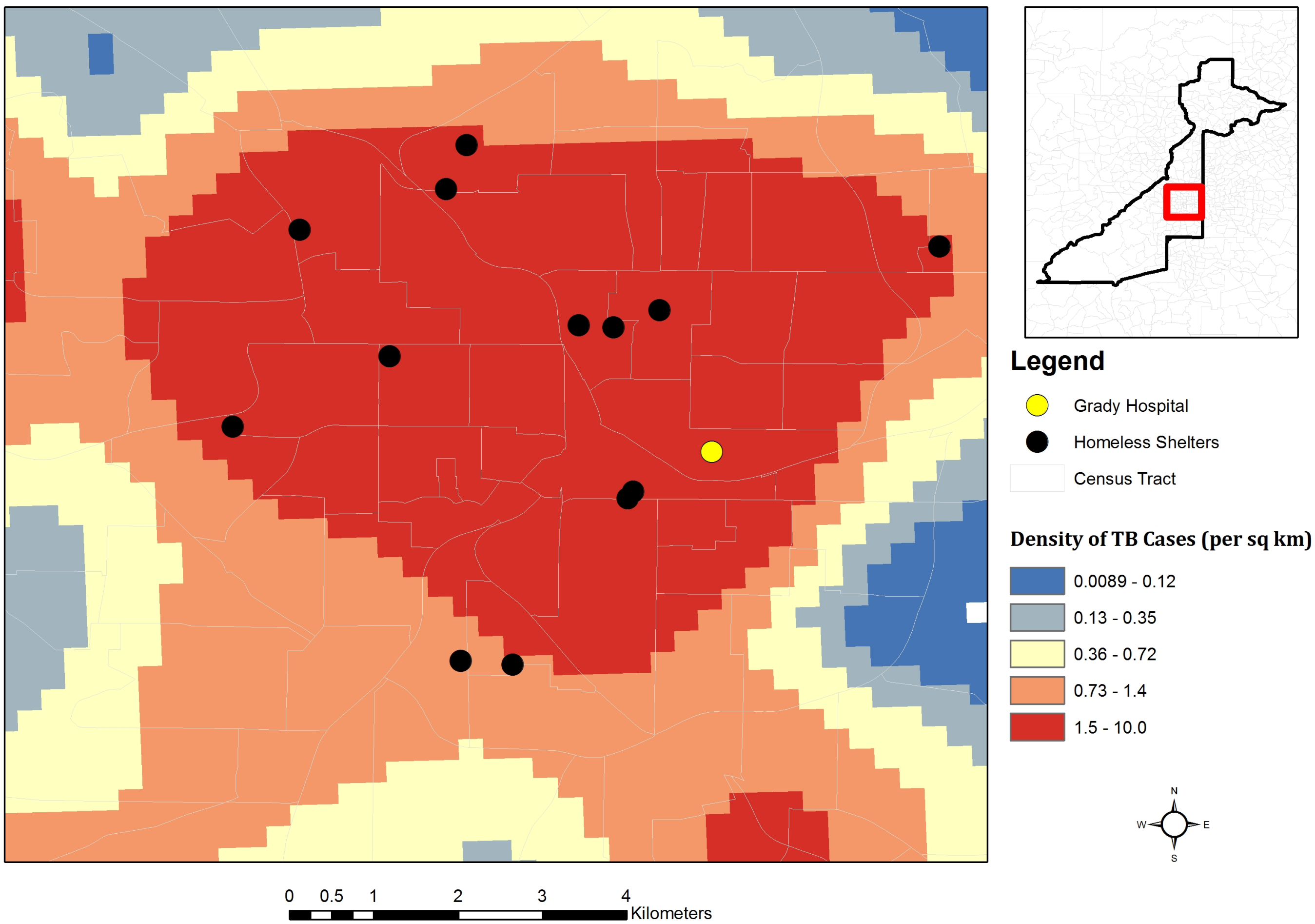


*Single address classification created using quintiles, and multiple address classification was matched to the single address classification increasing the final category to include values up to the maximum.

Map 4: Density of Tuberculosis Cases when using a Single Address with Locations of Homeless Shelters, Atlanta, Georgia, 2008-2014



Map 5: Density of Tuberculosis Cases when using All Addresses with Locations of Homeless Shelters, Atlanta, Georgia, 2008-2014



Chapter 3: Public Health Implications

INH resistant TB remains a major problem in Fulton County, GA, and remains a steady proportion of TB cases in the US. The epidemiology of INH monoresistance is not well studied, since MDR TB dominates the literature. The proportion of TB with multi-drug resistance has decreased in the US, while the proportion of TB with INH monoresistance has not decreased. Therefore, further investigation of INH resistance is crucial. In Fulton County, INH resistant TB is highly associated with homelessness, while INH resistance often is associated with cases of foreign origin. Thus, INH resistance is likely circulating within the US and within homeless populations. During our investigation, we found that using multiple addresses for each case provides a better picture of the possible areas of transmission than utilization of a single address, the standard technique. Standard approaches for spatially analyzing TB outbreaks, such as spatial autocorrelation, require a large number of cases and accurate addresses for cases. Further these analyses, neglect the diverse experience of human movement by including only a single address. Therefore, alternative methodologies are necessary for the investigation of TB outbreaks. Further, we found that both homeless cases and INH resistant cases were more likely to have an overlap in activity space compared to their non-homeless and INH susceptible counterparts. These findings support the idea that people with similar characteristics are active within the same area; homeless people with TB are active in the same areas as other homeless with TB people, and INH resistance cases are active. Further analysis of the activity space data could identify additional locations of concern that can be targeted for screening and prevention activities. Understanding the breadth of area where transmission may occur can help control and prevent outbreaks, since previous prevention and control efforts have failed to fully stop transmission. Using GIS analysis methods alongside statistical analyses provides important demographic and spatial contextual information about TB within Fulton County. Utilization of multiple addresses or activity spaces for the study of TB is paramount to understand the full spatial context. Further, study of the entire cohort of TB cases from Fulton County using this methodology could provide additional information about outbreak and its trend over time. Additionally, broadening the geographical scope to include the other counties in metro Atlanta would provide a more complete picture of TB. As seen by our analyses, people who live in Fulton County also move throughout the area including other counties, and the opposite may be true, yet these people are not included in our analyses.

The application of these activity space methods can also be utilized in other counties or states across the US for TB surveillance and outbreak investigation. Further, this methodology is transferable and can be used to investigate other infectious diseases and their possible areas of transmission. As technology improves, our ability to collect more information, which can also be geolocated, also increases. Leveraging technology can allow for a more data and better data will allow for increased sophistication of these methodologies.

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Appendix

List of Acronyms:

Tuberculosis (TB)
United States of America (US)
Mycobacterium tuberculosis complex (MTBC)
Latent tuberculosis infection (LTBI)
human immunodeficiency virus (HIV)
Mantoux tuberculin skin test (TST)
purified protein derivative (PPD)
Bacillus Calmette- Guérin (BCG)
isoniazid (INH)
rifampin (RIF)
Pyrazinamide (PZA)
Ethambuton (EMB)
Rifapentine (RPT)
Interferon-gamma release assay (IGRA)
USA Food and Drug Administration (FDA)
Department of Health (DoH)
Date of birth (DOB)