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THE SOCIAL DETERMINANTS OF MULTIDRUG RESISTANT TUBERCULOSIS
IN THE UNITED STATES BETWEEN 2005 AND 2009

By

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B.A., History

GEORGIA STATE UNIVERSITY

A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment

of the

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THE SOCIAL DETERMINANTS OF MULTIDRUG RESISTANT TUBERCULOSIS
IN THE U.S. BETWEEN 2005 AND 2009

by

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ABSTRACT

INTRODUCTION: Multi-drug resistant tuberculosis (MDR-TB) poses a great threat to the eradication of TB. In the US, MDR-TB is faced with inadequate diagnostic tools and long and expensive treatment regimens. Therefore, preventing the disease is the key to saving lives and resources. Social and behavioral variables play a big part in this prevention. It is important to determine the social factors that may lead to MDR-TB in order to set up prevention programs and more efficient treatment regimens.

AIM: This study was conducted to ascertain the social determinants of MDR-TB in the US between the years of 2005 and 2009 to better equip public health officials to deal with this growing threat.

METHODS: This study used the Centers for Disease Control and Prevention (CDC) Online Tuberculosis Information System (OTIS) database to find associations between certain social variables and MDR-TB. The variables that were tested were whether or not the individual had lived in a correctional facility for the past year; HIV status; homelessness; whether or not the individual had an occupation; and whether the individual was foreign-born or US-born. An unadjusted odds ratio (OR) was calculated to find this association. The variables were then stratified with age; sex; race; age and race; age and sex; and age, sex, and race to see whether or not the strata were confounders.

RESULTS: The variables of having lived in a correctional facility and homelessness were found to be associated with MDR-TB. However, all of the strata were found to be confounders for this relationship. Having HIV and being US-born were not found to be associated with MDR-TB. All of the strata for HIV were found to be confounders. But for place of birth, stratifying by age, sex, and both age and sex were not confounders. The rest of the strata were. The OR for occupation versus MDR-TB was almost at 1, meaning that those with a job and those without a job had almost equal odds of having MDR-TB. Effect modification was present for the strata in all variables, meaning that the risk of having MDR-TB varied with each different age, sex, and racial group.

DISCUSSION: Results from this study showed which variables were more likely to be associated with MDR-TB in the US between the years of 2005 and 2009. However, when compared to the literature that exists, the results showed that more research needs to be done to properly ascertain this relationship. Using this study, public health officials can identify which populations to focus prevention efforts on.

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CHAPTER 1

INTRODUCTION

The eradication of tuberculosis (TB) has been made much more difficult with the emergence of multidrug-resistant TB (MDR-TB). The World Health Organization (WHO) estimated 650,000 cases of MDR-TB around the world in 2010 (Walter, Strong et al. 2012). The actual number of cases may be a lot greater since surveillance for MDR-TB is inadequate because of the lack of laboratory resources around the world for testing drug sensitivity. This is a problem that not only affects developing nations, but is a threat to the control of TB in developed nations.

Public Health Importance

MDR-TB is a growing threat to the United States (US). In 2011, it was reported by the Centers for Disease Control and Prevention (CDC) that 9.2% of TB cases in the US were resistant to one first-line TB drug and 1.3% was resistant to more than one drug (ALA 2013). The number of MDR-TB cases in the US is increasing each year. This study will help to determine associations between MDR-TB and some of its social and behavioral risk factors. It is important to look at the social risk factors for MDR-TB because they help us better understand the behaviors of individuals that lead to the disease and how these behaviors can be altered. The CDC tracks many of these variables in their Online Tuberculosis Information System (OTIS) Database. Literature also shows these variables to be the ones associated with higher rates of MDR-TB elsewhere in the world. Therefore, it would be ideal to focus on how these variables are associated with

MDR-TB. The aim is to find the variables associated with MDR-TB in order to set up prevention programs for the future. This study hopes to be the first step in that process.

1a. Study Objective

Developed nations, such as the United States, have set procedures and resources that help control tuberculosis. However, MDR-TB is a threat to these TB control measures. This study will look at the social determinants of MDR-TB compared to those of TB in the United States from 2005 to 2009. This association has not been one that has been explored before. The study will look at the association of MDR-TB with the variables of occupation; place of birth; HIV status; homelessness in the past year; and whether or not the person lived in a correctional facility and stratify them with age, sex, race, and a combination of the three. These specific variables are tracked annually by the CDC. If associations are found, public health officials can focus on specific behaviors related to these variables and set up programs that better prevent MDR-TB.

1c. Research Question

Is there an association between specific risk factors and the rates of multidrug resistant tuberculosis in the United States?

Can the analysis of the data provide a model to predict multidrug resistant rates in the United States?

How can the answers to the previous two questions be used to formulate interventions and possibly come up with solutions to the problem of multidrug resistant tuberculosis in the United States?

CHAPTER 2

LITERATURE REVIEW

2a. Background of TB

Tuberculosis (TB) is a disease that is caused by the bacterium *Mycobacterium tuberculosis*. It usually manifests as a respiratory illness, but can present in other areas of the body as well such as joints, kidneys, and the brain. If it is not treated properly, it can be fatal.

TB is a highly contagious disease that is spread through the air. One must inhale the infectious droplets to become infected. However, TB is not spread through person-to-person physical contact, sharing bodily fluids, or touching infected surfaces.

Tuberculosis is an ancient disease that can be traced back to the time before humans. The genus *Mycobacterium* is thought to have originated more than 150 million years ago during the Jurassic period (Daniel 2006). Reports show that an early predecessor of *M. tuberculosis* may have infected early hominids as far back as 3 million years ago in present East Africa. However, modern strains of *M. tuberculosis* are thought to have originated about 20,000-15,000 years ago (Daniel 2006). Knowing the mutation rate of *M. tuberculosis*, scientists have concluded that a lot of present diversity among the strains of this bacterium came about between 2,500-1,000 years ago. Egyptian mummies from more than 5,000 years ago show skeletal abnormalities typically associated with tuberculosis. The art from this era also depicts the ailments associated with tuberculosis. However, there are very limited written records of tuberculosis in ancient Egypt. The

Bible also mentions tuberculosis using the ancient Hebrew word “schachepeth.” Peruvian mummies show archaeological evidence of tuberculosis in the Americas. During the middle ages, though written records of tuberculosis became hard to find, the phenomenon of the “royal touch” became widespread in Europe. The royal touch consisted of monarchs touching individuals with tuberculosis in hopes of curing them (Daniel 2006).

During the Renaissance, knowledge of tuberculosis began to change. René Théophile Hyacinthe Laennec clarified the pathogenesis of the disease, unified the concept of pulmonary and extrapulmonary TB, and described the physical symptoms of it (Daniel 2006). Laennec’s exposition pioneered the modern understanding of tuberculosis. During this era, tuberculosis had reached epidemic levels across Europe and society began romanticizing the disease. People with TB were said to be interesting and melancholy. Many authors of the time, such as Emily Brontë, described their tuberculosis characters as, “young and fresh.” Many other examples of this romanticism of TB can be found in the works of Charles Dickens and Lord Byron and in the descriptions of important figures of the time.

On March 24, 1882, the history of tuberculosis changed when Hermann Heinrich Robert Koch made his famous presentation, *Die Aetiologie der Tuberculose*. His presentation identified his famous postulates, known as the Koch-Henle postulates, which are still the standard for identifying infectious disease causality. In 1909, pediatrician Clemens Freiherr von Pirquet introduced the term “latent tuberculosis,” when he

published a study of tuberculin reactions that showed positive tuberculin reactions in children who did not have symptoms of tuberculosis. Charles Mantoux introduced the use of needles and syringes to inject tuberculin into the skin. Florence Seibert was the one who developed purified protein derivative (PPD) in 1908 in fundamentally the same form it is used today. PPDs were used to establish the commonality of latent TB infection in the United States. In 1921, Albert Calmette and Camille Guérin developed a vaccine for tuberculosis called the BCG (Bacille Calmette-Guérin). Over the next decade, the vaccine was used to protect hundreds of thousands of children from TB infection. However, BCG was not widely used in the United States, where treatment of latent infection was more emphasized (Daniel 2006). The 1950s brought about the biggest advances in tuberculosis with the development of treatment drugs. In 1950, the British Journal of Tuberculosis and Diseases of the Chest reported the first case of streptomycin as treatment. The first oral anti-tuberculosis drug, Isoniazid, followed in 1952, with rifamycin in 1957. Tuberculosis control entered a new era with the introduction of these treatments. The next section will describe the symptoms of TB, along with the treatments in the new era.

Once a person becomes infected with the TB bacteria, they develop one of two conditions: latent TB infection and active TB disease. Latent TB infection is when *M. tuberculosis* lives in the body without causing any symptoms. The infected person is not infectious and cannot spread TB during this phase and is said to have Latent TB Infection (LTBI). But, the TB bacteria can become active at any time and cause active TB disease. When a person has active TB disease, the *M. tuberculosis* is actively spreading through

their body. The site of the infection determines the symptoms that a person experiences. For pulmonary TB, the symptoms include a bad cough lasting three weeks or more, chest pain, weight loss, weakness or fatigue, loss of appetite, blood or sputum in the cough, chills, fever, and night sweats.

There are many ways to diagnose tuberculosis. The most common is a TB skin test, often referred to as a TST or PPD. It is performed by injecting a small amount of the liquid tuberculin under the skin in the forearm. The patient must then wait between 48-72 hours to have their area checked by a health professional. The healthcare worker checks to see the reaction the person has had. The area is checked for a hard raised area and then measure the diameter of the area, if present. Whether or not the result is positive depends on the size of the induration. An induration greater than 10 mm is indicative of a positive diagnosis. The diagnosis is influenced by a person's age and their risk for contracting TB. A positive test means the person either has active or latent TB infection and further tests need to be done to determine which. A negative skin test means that the person's body did not react to the test, and it is unlikely that they are infected with TB (CDC, 2012). However, in some cases, these people may still be infected with TB and must be diagnosed using their symptoms. These people are referred to as anergic.

Tuberculosis may also be diagnosed with a blood test, called interferon-gamma release assays or IGRAs. This test is a blood test that measures how the immune system reacts to the TB bacteria. Like the TSTs, a positive test means the person is likely infected with active or latent TB and further tests need to be done to determine exactly

which one. A negative IGRA means it is not likely the person is infected with TB disease. IGRAs are preferred to TSTs in the case that a patient has received bacille Calmette-Guérin (BCG), which is a TB vaccine, or a patient is not able to return to have their TST evaluated (CDC, 2012).

Treatment for tuberculosis is based on the type of TB a patient has. The goal of latent TB treatment is to prevent the patient from developing active TB disease. Latent TB infections are treated with one of four regimens suited to meet their needs. All four of the regimens include different variations of the medications isoniazid (INH), rifampin (RIF), and rifapentine (RPT) for various durations (CDC, 2012).

Treatment for active tuberculosis is more extreme since these people have significantly greater numbers of TB bacteria in their bodies. Currently, there are 10 drugs on the market that are approved for the treatment of TB. However, the main four that are used as the front-line drugs are isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA). The treatment regimens last 6-9 months, with the first two months known as the initial phase, followed by a continuation phase lasting from 4 to 7 months. It is imperative that patients complete their drug regimens because failing to do so can lead to re-infection or drug resistance (CDC, 2012).

2b. Background of MDR-TB

MDR-TB is caused by strains of *Mybacterium tuberculosis* that are resistant to at least isoniazid and rifampicin, two of the most powerful first-line drugs to combat TB (Migliori, D'Arcy Richardson et al. 2009). Molecular epidemiological techniques have shown that the *M. tuberculosis* strain known as the “Beijing,” is responsible for MDR-TB outbreaks in countries with lower rates of TB, such as the United States (Drobniewski, Balabanova et al. 2005). In addition to the great global threat that the disease poses, it can also lead to the more deadly extensively drug-resistant TB (XDR-TB). XDR-TB is caused by *Myobacteria* that meet the same requirements as MDR-TB, but are also resistant to any fluoroquinolone and to at least 1 of 3 anti-TB injectable drugs: capreomycin, amikacin, or kanamycin (Migliori, D'Arcy Richardson et al. 2009). As is to be expected, the mortality for both of these forms of TB is high. Among XDR-TB patients, mortality rates are similar to the pre-antibiotic era (Ershova, Kurbatova et al. 2012).

MDR-TB and XDR-TB can occur for many different reasons. First, it may be due to the providers. They may prescribe inadequate drug regimens for patients, whether it be not enough doses, not enough drugs, the incorrect drugs, or a too short treatment time. The second reason may come down to the patients. They may not follow their drug regimens as prescribed. Third, the drugs used to treat TB may not be of good quality (Migliori, D'Arcy Richardson et al. 2009).

The second reason listed above, patients not following their drug regimens as prescribed, will be the focus of this study. Finding out the factors that hinder patients from correctly taking their medication is imperative. Once those factors are known, steps can be taken to help in those situations and prevention programs can be set up. As will be explained later, prevention is a key factor in the fight against MDR-TB in this nation.

MDR-TB and XDR-TB are either primary or acquired. Primary drug resistance takes place when MDR-TB or XDR-TB is directly transmitted from one individual to another. Acquired drug resistance may happen through the incorrect use of TB drugs. (Migliori, D'Arcy Richardson et al. 2009).

The issue of drug resistance to TB was first realized shortly after streptomycin was introduced in 1944. The first reported death from a drug-resistant strain of TB was reported by the British Medical Research Council in 1948. This led to the discovery in the late 1940s that combination therapy with both streptomycin and *para*-aminosalicylic acid was an effective treatment for the emerging drug-resistant strains. However, the duration of this treatment regimen was markedly long. Beginning in 1952, the introduction of INH, RIF, EMB, and PZA kept the problem in check until the 1980s. In the early 1990s, however, there began several outbreaks of MDR-TB, particularly among Human Immunodeficiency Virus (HIV)-infected patients, that brought this problem back to the forefront as a major global public health issue (Nguy, Shui et al. 2009). The most well-known of these outbreaks was a cluster that took place in one Florida hospital and three New York City hospitals from 1990 to 1992. These outbreaks had mortality rates

between 72% and 83% among HIV positive patients. These outbreaks led to an overhaul in the way MDR-TB was reported on in the country and allowed for population-based analysis of the disease (Migliori, D'Arcy Richardson et al. 2009).

Multidrug resistant tuberculosis is diagnosed using drug susceptibility testing (DST). DST is a difficult procedure to perform and standardize because it requires the knowledge of the origins of the drug resistance and the conditions surrounding it; potency and stability of drugs in the lab; antimycobacterial activity of the drugs in different testing mediums; and reading interpretation of the results. From start to finish, the test takes one month to complete and may only be done once a TB diagnosis has been established. It also requires a live growing organism. DST must also be done for first- and second-line drugs separately (CDC 2010). DST is a long, complicated, and expensive process and usually only given to patients of high priority (Manjourides, Lin et al. 2012). Therefore, prevention is key when it comes to MDR-TB.

2c. Treatment of MDR-TB

Treatment of MDR-TB is an arduous and expensive process. It can take up to two years to treat with drugs that are less potent and more toxic than regular TB drugs (Jenkins, Zignol et al. 2011). The drug regimen for treating drug-resistant TB depends on the exact drugs the patient is resistant to. The drugs that can be used as part of the treatment regimen are isoniazid (INH); rifampin (RIF); pyrazinamide (PZA); ethambutol (EMB); streptomycin (SM); ciprofloxacin or ofloxacin or moxifloxacin or gatifloxacin

(FQ); injectable agents like SM or kanamycin or amikacin or capreomycin or viomycin; and second-line drugs such as rifabutin, ethionamide, prothionamide, *para*-amino salicylic acid, D-cycloserine and thiacetazone. Treatment regimens can include anywhere from three to many of these drugs at a time and last anywhere from six months to over two years (Ahmad, Suhail et al. 2010). Patients must be closely monitored to ensure they follow the treatment regimen exactly. The outcome of the treatment depends on the type of drug-resistance, the availability of the previously listed drugs, and the patient's adherence to the therapy (Migliori, D'Arcy Richardson et al. 2009).

In extreme cases, surgical resection of the infected lung tissue has been used as treatment. This treatment method is only used in cases with severe drug resistance with a high probability of medication therapy failing, localized disease with good postoperative expectations for lung function, and ample activity of TB drugs to ensure proper healing of the surgery stump. Surgical measures should only be offered after medication treatment has been tried for at least three months (Migliori, D'Arcy Richardson et al. 2009).

2d. Risk Factors for MDR-TB

There are many different risk factors for multi-drug resistant TB. A survey done by Casal, et. al. identified immigration, aging, HIV infection, population mobility, living in communities, and drug abuse as possible factors in Western European countries (Casal, Vaquero et al. 2005).

HIV

When tuberculosis drugs became available in the 1950s, the disease began a steady decline in Western countries. However, TB re-emerged with the advent of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) (Breathnach, de Ruyter et al. 1998). Shenoj et al. estimated that as of 2009, there were 12-14 million people coinfecting with HIV and *M. tuberculosis*. They also stated that TB is the most common opportunistic infection among HIV patients (Shenoj, Heysell et al. 2009). The CDC states that as of July 2012, a quarter of all HIV/AIDS deaths can be attributed to TB (2012). HIV lowers an individual's ability to fight off infection, making them more susceptible to not only regular TB, but MDR-TB and XDR-TB as well. HIV/AIDS has been associated with the malabsorption of TB drugs, which may contribute to higher rates of drug-resistance (Andrews, Shah et al. 2010). A cross-sectional, country-wide study done in Estonia found that HIV-infected patients are three times more likely to develop extensively drug-resistant tuberculosis than those not infected with HIV (Kliiman and Altraja 2009). In Ukraine, it was found that HIV patients are at a higher risk for developing multidrug-resistant TB during their first occurrence of TB, which differs from non-HIV patients (Shenoj, Sheela et al. 2009).

Patients infected with HIV are not only more likely to develop MDR-TB; they also have higher rates of mortality from the disease. Between the years 1993 and 2007, 26 deaths occurred from XDR-TB in the U.S. Out of these deaths, 21 were confirmed HIV-positive cases (Migliori, D'Arcy Richardson et al. 2009). Mortality rates in North

America have ranged from 70-90% with a median survival time ranging from 4-6 weeks from diagnosis to death (Kelleher, Coakley et al. 1996).

One of the biggest issues facing the coinfection of multidrug-resistant TB and HIV is the inability to get a rapid TB diagnosis and then subsequently determine drug susceptibility. The patients must wait for a diagnosis, and in the meantime, they not only spread disease but they also are given inadequate treatment. In South Africa, most patients with XDR-TB die before their results come back and even before they have had a chance to be tested for drug resistance (Shenoi, Sheela et al. 2009). This issue is mainly one in developing nations, but can affect the developed world in areas where adequate TB diagnostic tools do not exist.

Co-infection of MDR/XDR TB and HIV can also have a great impact on the HIV epidemic. Shenoi et al. listed ten ways drug-resistant TB can affect HIV:

- 1) higher risk of drug-resistant TB compared to patients not infected with HIV;
- 2) higher mortality rates for co-infected individuals;
- 3) potential side effects from combining secondline TB drugs and antiretrovirals (ARVs);
- 4) hospital-related transmission of drug-resistant TB to HIV patients;
- 5) risk to healthcare workers dealing with HIV patients;
- 6) strain on national TB and DOT programs;
- 7) demand exceeding the amount of available laboratory services and specialized treatment referral;
- 8) competition for resources between TB and HIV programs;
- 9) greater stigma for co-infected patients;

10) general undoing of gains made in HIV epidemic from ARVs (Shenoi, Sheela et al. 2009).

The evidence for an association between MDR-TB and HIV is strong. However, no study has measured the association within the same parameters and the same time frame that this study will.

Previous TB Infection

A well-established risk factor of multidrug-resistant TB is prior TB infection (Andrews, Shah et al. 2010). One study put the rate of acquired resistant as high as 20% for previous cases, with 4-10% going on to develop full-fledged MDR-TB (Casal, Vaquero et al. 2005). According to a study done by Tracy Dalton across Estonia, Latvia, Peru, the Philippines, Russia, South Africa, South Korea, Thailand, and Taiwan, a history of TB was the strongest risk factor for MDR-TB, with the overall value of 93.8% probability (Hoffner). The risk only increases the more times a person is treated for TB (Zhao, Xu et al. 2012) or the longer their treatment regimen lasts (Migliori, D'Arcy Richardson et al. 2009). These results show the importance of programs such as directly observed therapy (DOT), where patients are monitored while they take TB medications to ensure the regimen is being followed correctly and having the desired outcomes. DOT helps cure most cases and prevents the development of chronic cases, which can go on to become drug resistant (Casal, Vaquero et al. 2005). Many of the variables studied in this

thesis are not only risk factors for MDR-TB; they are also risk factors for regular TB.

This, as this section states, is itself a risk factor for MDR-TB.

US-born versus Foreign-born

Global migration and travel have had an immense impact on TB in the United States. It was reported that between 2001 and 2008, 54.6% (62,364) of the new TB cases in the U. S. were diagnosed among foreign-born patients. Of this, 249 cases were MDR-TB cases (Liu, Painter et al. 2012). More recent statistics state that foreign-born cases are now responsible for 80% of the MDR-TB cases in the U.S. (Migliori, D'Arcy Richardson et al. 2009). Table 1 provides the exact statistics from 1993. A recent study reported that active pulmonary TB was diagnosed in 7.0% of refugees and immigrants in the United States when these same patients had smear-negative diagnoses before arrival to the country (Liu, Painter et al. 2012). Therefore, it can be concluded from this study that at least some immigrants and refugees are acquiring the disease upon entering the country. Finding this association is important because then, the reasons behind the association can be explored.

Table 2.1 Incidence of MDR-TB in the United States among new cases according to place of birth, 1993-2007

Year	New MDR-TB Cases		
	Total	United States-born (%)	Foreign-born (%)
1993	407	301 (74)	103 (26)
1994	353	238 (67)	110 (33)
1995	254	169 (67)	85 (33)
1996	207	105 (51)	101 (49)
1997	155	76 (49)	79 (51)
1998	132	55 (42)	76 (58)
1999	127	39 (31)	88 (69)
2000	120	38 (32)	82 (68)
2001	118	34 (29)	84 (71)
2002	130	36 (28)	94 (72)
2003	92	24 (26)	68 (74)
2004	102	26 (25)	76 (75)
2005	98	19 (19)	78 (81)
2006	94	17 (18)	77 (82)
2007	98	20 (20)	78 (80)

Adapted from : (Migliori, D'Arcy Richardson et al. 2009)

Hospitalization

Some studies have shown hospitalization as a risk factor for MDR-TB. A study conducted in South Africa by Andrews, Shah, et al concluded that a prolonged hospital stay is associated with a 3-fold increase in the risk of contracting MDR-TB (Andrews, Shah et al. 2010). Another recent study suggested that MDR-TB patients that were treated with first-line drugs were responsible for the majority of TB spread in a tuberculosis ward of the hospital (Escombe, Moore et al. 2008). Gandhi, Weissman et al. used social network analysis to study XDR-TB and concluded that rather than an outbreak starting from a single patient, there is a high degree of interconnectedness among hospital patients. The study also stated that the long delay in diagnosing XDR-TB patients contributed to transmission since it gave unrecognized patients time and opportunity to infect others in congregation areas. (Gandhi, Weissman et al. 2013).

Poverty

As stated earlier, homelessness has been associated with MDR-TB and XDR-TB. The homeless live in poor conditions and are usually malnourished from reduced access to food. They also have reduced access to healthcare. This prolongs their period of infectiousness, increasing their risk of transmission to their peers. The homeless also have higher rates of defaulting from their treatment, thus increasing their risk for drug-resistant TB (Migliori, D'Arcy Richardson et al. 2009). Poverty is also linked to higher rates of incarceration. Prisons have reported higher rates of drug-resistant strains of tuberculosis

due to overcrowding and the inability to isolate the resistant cases (Migliori, D'Arcy Richardson et al. 2009).

Race

Many studies have linked race to multidrug resistant TB. A study conducted in Texas stated that US-born blacks are more likely than US-born whites to not only have drug-resistant forms for tuberculosis; they are also more likely to have a lot of the risk factors for MDR-TB (Serpa, Teeter et al. 2009). The study went on to explain that socioeconomic characteristics are linked to race and therefore explain the disparity in TB rates.

Age

Age may be a risk factor for MDR-TB. A disproportionate number of older adults are affected by all forms of TB due the weakening of their immune systems with age. They are also more likely to be afflicted with illness such as diabetes mellitus, renal disease, and silicosis, which increases the risk of progressing from LTBI to active TB disease. Certain medications taken by older adults, such as corticosteroids and transplant suppression drugs, also accelerate the progression to active disease (Pratt, Winston et al. 2011). Also, just being older and being around peers who are more susceptible to TB increases risk. With increased risk of TB comes increased risk of drug resistant forms.

The literature shows that all of the previously listed variables may be associated with higher rates of MDR-TB. Therefore, it was important for this study to include as many of them as possible in data analysis and test the associations for the sample population. The next chapter will explain the methodology of this data analysis.

CHAPTER 3

METHODS

The main objective of this study was to find the association between certain social determinants and multidrug-resistant tuberculosis in the United States. The variables that were examined were whether or not the patient lived in a correctional facility at the time of diagnosis; HIV status; homelessness; whether or not the patient had an occupation; and place of birth (US-born or foreign born), all between the years of 2005 and 2009. Each variable was cross-tabulated with MDR-TB to find the crude odds ratio (OR). Each crude OR was then each stratified by age; sex; race; age and race; age and sex; and age, sex, and race to find if any of the strata were confounders between the variable in question and MDR-TB.

3a. Data Sources

All of the data were obtained from the CDC Online Tuberculosis Information System (OTIS). OTIS contains information on verified TB cases as reported to the CDC by state health departments, the District of Columbia, and Puerto Rico from 1993 to 2010. The data is extracted using the CDC national TB surveillance system. This database is updated annually and includes data for 26 variables that can be cross-stratified. Users can obtain charts, graphs, and tables and extract the data for the available variables.

3b. Study Population

The study population was the US population, including all 50 states and the District of Columbia. All races/ethnicities, genders, and ages were incorporated.

3c. Statistical Analysis

The OTIS database does not allow for raw data to be extracted. Therefore, it was impossible to use statistical analysis software to examine the data. Instead, each variable was cross-tabulated with MDR-TB and then stratified by race/ethnicity, sex, and age. First, each association was stratified by age; then sex, then race independently; then by both age and race; then by both age and sex, and lastly by age, sex, and race. The race/ethnic groups the data were classified in are Non-Hispanic Whites; Hispanics; Non-Hispanic Blacks or African Americans; and Other, which included Non-Hispanic Native Americans and Non-Hispanic Asians and/or Pacific Islanders. The sexes were classified into male and female. The ages were grouped by 0-24 years of age and 25 and above. For all of the variables, only the Yes/No results were used. Therefore, only the variables that could be put into a 2x2 Yes/No table were able to be included. All of the indeterminate and not reported data were ignored. The stratification was done in OTIS, after which the data were transferred to Microsoft Excel (version 2010). From there, the data were put into 2x2 tables to calculate odds ratios and Mantel-Haenszel odds ratios to find associations between the variables and MDR-TB and to decipher if any of the variables were confounded by the different stratifications of age, sex, and race.

CHAPTER 4

RESULTS

The main purpose of this study was to find the social determinants of multidrug-resistant tuberculosis in the United States. To find the association, if any, between certain variables and MDR-TB, the Mantel-Haenszel odds ratio (OR_{mh}) was calculated. Below are the results for each of the following variables as tested against MDR-TB:

- 1) Whether or not the patient was in a correctional facility
- 2) HIV Status
- 3) Homelessness
- 4) Whether or not the patient had an occupation
- 5) Place of birth

Correctional Facility vs. MDR-TB

Table 4.1 Results of Correctional Facility vs. MDR-TB

EXPOSURE	OR_{MH}	EFFECT MODIFICATION
Crude OR = 1.757	-----	-----
Age	1.793 Negative Confounding	Present
Sex	1.581 Positive Confounding	Present
Race	1.436 Positive Confounding	Present
Age, Race	1.442 Positive Confounding	Present
Age, Sex	1.612 Positive Confounding	Present
Age, Sex, Race	1.361 Positive Confounding	Present

These calculations were testing the association between living in a correctional facility and having MDR-TB. The crude OR for this association is 1.757, meaning that those that resided in a correctional facility in the past year have a 75% increase in the odds of developing MDR-TB than those who did not reside in a correctional facility in the past year. However, as this association was further stratified, it showed different results. Age was shown to be a negative confounder for the association between living in a correctional facility and having MDR-TB. Negative confounding means that the OR is falsely lowered. Further stratification by sex; race; age and race; age and sex; and age, sex, and race showed that these strata are positive confounders for the association between living in a correctional facility and having MDR-TB. Positive confounding means that the OR is falsely elevated. All of the strata showed effect modification; meaning that the different groups (i.e. different age groups, different racial groups, males

and females) had different risk estimates for the association between living in a correctional facility and having MDR-TB.

HIV Status vs. MDR-TB

Table 4.2 Results of HIV Status vs. MDR-TB

EXPOSURE	OR_{MH}	EFFECT MODIFICATION
Crude OR = 0.764	-----	-----
Age	0.692 Positive Confounding	No Effect Modification
Sex	0.741 Positive Confounding	Present
Race	0.569 Positive Confounding	Present
Age, Race	0.522 Positive Confounding	Present
Age, Sex	0.678 Positive Confounding	Present
Age, Sex, Race	0.511 Positive Confounding	Present

The crude OR for the association between HIV and MDR-TB showed a surprising result. It showed that those with HIV were about 25% less likely to have MDR-TB than those without HIV. Each stratification showed positive confounding, meaning that when stratified with those variables, the ORs were falsely elevated and should have been lower. Effect modification was present in all of the strata except age, meaning that the risk estimates for age were the same but were different for all of the other strata.

Homeless vs. MDR-TB

Table 4.3 Results of Homeless vs. MDR-TB

EXPOSURE	OR_{MH}	EFFECT MODIFICATION
Crude OR = 1.157	-----	-----
Age	1.086 Positive Confounding	Present
Sex	1.052 Positive Confounding	Present
Race	0.864 Positive Confounding	Present
Age, Race	0.811 Positive Confounding	Present
Age, Sex	1.004 Positive Confounding	Present
Age, Sex, Race	0.783 Positive Confounding	Present

This set of calculations tested the association between being homeless and having MDR-TB. The crude OR showed the homeless are 15% more likely to have MDR-TB than those that are not homeless. However, all of the strata showed positive confounding and effect modification.

Occupation vs. MDR-TB

Table 4.4 Results of Occupation vs. MDR-TB

EXPOSURE	OR_{MH}	EFFECT MODIFICATION
Crude OR = 0.990	-----	-----
Age	1.004 Negative Confounding	Present
Sex	0.957 Positive Confounding	Present

Race	1.050 Negative Confounding	Present
Age, Race	1.056 Negative Confounding	Present
Age, Sex	0.970 Positive Confounding	Present
Age, Sex, Race	1.030 Negative Confounding	Present

The crude OR for the association between having an occupation and having MDR-TB was 0.990. Since this OR is so close to 1, it means that both groups (those with an occupation and those without) have almost the same odds of getting MDR-TB. The different strata showed various results. When this association was further stratified by age; race; age and race; and age, sex, and race, these strata were shown to be negative confounders, meaning that the OR was falsely lowered. However, stratification by sex and by both age and sex showed these respective strata to be positive confounders, meaning they falsely elevated the OR. Effect modification was present for all of the strata.

Place of Birth vs. MDR-TB

Table 4.5 Results of Place of Birth vs. MDR-TB

EXPOSURE	OR_{MH}	EFFECT MODIFICATION
Crude OR = 0.292	-----	-----
Age	0.299 No Confounding	Present
Sex	0.296 No Confounding	Present
Race	0.413 Negative Confounding	Present
Age, Race	0.377 Negative Confounding	Present
Age, Sex	0.299 No Confounding	Present
Age, Sex, Race	0.400 Negative Confounding	Present

When calculating the association between place of birth and having MDR-TB, the crude OR was 0.292. This means that those that were US-born were about 70% less likely to have MDR-TB than those that were foreign-born. When further stratified by age, sex, and by both age and sex, there was no confounding. Meaning that these three strata were not confounders in the relationship between place of birth and having MDR-TB. When stratifying by race; age and race; and age, sex, and race, there was negative confounding, showing that the OR was falsely lowered. Effect modification was once again present in all strata.

CHAPTER 5

DISCUSSION

The main objective of this study was to find the social determinants of multidrug resistant TB in the US. The variables that were examined and tested against the rates of MDR-TB were whether or not the patient was in a correctional facility; HIV status; homelessness; occupation; and place of birth. These variables were then stratified by race, sex, and age to find associations. The specific research questions asked were:

Is there a correlation between specific risk factors and the rates of multidrug resistant tuberculosis in the United States versus drug-treatable tuberculosis?

Can the analysis of the data provide a model to predict multidrug resistant rates in the United States?

How can the answers to the previous two questions be used to formulate interventions and possibly come up with solutions to the problem of multidrug resistant tuberculosis in the United States.

Confounding is a difficult phenomenon to understand and explain. A confounding variable is usually related to both the independent and dependent variables, thus affecting the relationship between the variables. There could be several reasons why a certain characteristic is a confounder. The next section will attempt to explain the disparities in the results as each variable was tested against MDR-TB.

When looking at the association between having lived in a correctional facility in the past year and MDR-TB, the unadjusted odds ratio showed that those who have lived in a correctional facility in the past year are 75% more likely to have MDR-TB than those who did not live in a correctional facility. A study done by Dalton et al. reinforced this result. The study was a prospective cohort study evaluating the prevalence and the risk factors of MDR-TB in eight different countries. They concluded that resistance to second-line injectable TB drugs was associated with imprisonment (Dalton, Cegielski et al.). Internationally, TB prevalence in prisons is high; as is transmission of resistant strains. This could be explained by prison overcrowding and the inability of these prisons to isolate the resistant cases (Migliori, D'Arcy Richardson et al. 2009). However, all of the strata were shown to be confounders for the association between living in a correctional facility and having MDR-TB, meaning that the MDR-TB could be due to either living in a correctional facility or due to age, sex, race, or a combination of the three. Future studies would have to control for these variables when testing the relationship between living in a correctional facility versus having MDR-TB.

With a crude OR of 0.764, the association between HIV and MDR-TB was shown to be protective. Those with HIV were shown to be 25% less likely to have MDR-TB than those without HIV. This was surprising since most of the literature suggested the opposite. Some of the literature even went as far as to suggest that there is an epidemic of HIV and MDR-TB coinfection (Shenoi, Heysell et al. 2009). It may be that the unusual results that were achieved pertain only to the sample population. In a study done in the country of Georgia, it was found that HIV and AIDS both were not associated with the development of drug-resistant TB (Vashakidze, Salakaia et al. 2009). Another case-control study about the risk factors for MDR-TB in four European countries also concluded that HIV status did not prove to be a statistically significant risk factor for MDR-TB at the European level. Suchindran et al. also state that not a single study from Africa showed an association between HIV and MDR-TB and that results from other regions were also conflicting (Suchindran, Brouwer et al. 2009). Again, further studies would have to be conducted in the United States to ascertain if HIV and MDR-TB are associated or not.

When looking at the association between homelessness and MDR-TB, the results showed that homeless people were 15% more likely to have MDR-TB than those that were not homeless. Literature showed an association between being homeless and having XDR-TB, but not MDR-TB. However, since XDR-TB is a more severe form of MDR-TB, the explanations for the associations can be similar. Homeless people live in poor conditions and are often malnourished. They have less access to healthcare and are more

likely to default from treatment. Homelessness is also associated with alcohol abuse, which has been shown by many studies to be associated with higher rates of MDR-TB (Migliori, D'Arcy Richardson et al. 2009). Kliiman et al. also found homelessness to be an independent risk factor for MDR-TB (Kliiman and Altraja 2009).

The unadjusted OR for the relationship between having an occupation and having MDR-TB was 0.990. This OR was so close to 1 that it means both groups, those with an occupation and those without, have about the same risk for getting MDR-TB. While the literature did not mention having or not having an occupation as a risk factor for MDR-TB, it did mention poor living conditions as a factor. Poor living conditions usually come about when one does not have a source of income, i.e. a job.

The last variable that was tested was place of birth versus MDR-TB. The crude OR showed that the US-born were about 70% less likely to get MDR-TB than those that were foreign-born. TB rates among foreign-born that have recently arrived to the US continue to remain very high (Liu, Painter et al. 2012). A study done in California found that most MDR-TB cases in the US are related to the migration of those who have already been infected with MDR-TB (Metcalf, Kim et al. 2010). These results show that better screening procedures and treatment options should be made available for newly arrived persons to the US.

Limitations

There were several limitations to this study. The main limitation was the database that was used. The OTIS database did not provide raw data. The lack of these data did not allow for full testing of association. The testing that was done had to be done by hand. Therefore, human error should also be taken into account. The data did not provide information on other social determinants such as socioeconomic status, alcohol abuse, hospitalization, etc. that would have been helpful in explaining MDR-TB rates. The study was also limited by its use of secondary data, as opposed to primary data.

Conclusions and Recommendations

The study tested five variables against MDR-TB to find association measures according to age, sex, and race. The evidence showed these three strata and combinations of the three to be confounders for the separate variables and MDR-TB.

The results of the calculations and the literature showed that it is important to control and strive to improve the situation of MDR-TB. Further testing of the variables that lead to MDR-TB should be done in the sample population and expanded populations to help find ways to prevent the disease. Improved treatment regimens for MDR-TB that include less toxic drugs, shorter treatment durations, and generally more efficient drugs should be developed (Walter, Strong et al. 2012). Studying the mechanism of mutation to develop drugs that are more targeted to treated resistant strains of *M. tuberculosis* would help with this endeavor (Walter, Strong et al. 2012). New anti-TB drugs should be

developed for all forms of TB and randomized control trials should be used to evaluate them (Walter, Strong et al. 2012). Better ways of testing for tuberculosis should be established that provide faster diagnoses (Walter, Strong et al. 2012). Another factor that would help improve MDR-TB rates would be to increase drug resistance testing before treatment begins (Zhao, Xu et al. 2012). Making sure TB treatment is completed is also imperative. Directly observed therapy programs should be in place to ensure patients are completing their drug regimens. All of these suggestions would help WHO of achieving its goal of eradicating all forms of TB by the year 2050.

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