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An Examination of The Distribution of Diabetes Mellitus Among TB Patients with Pulmonary Tuberculosis and Drug Resistant Tuberculosis In The State Of Florida, USA.

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An Examination of The Distribution of Diabetes Mellitus Among TB Patients with Pulmonary Tuberculosis and Drug Resistant Tuberculosis In The State Of Florida, USA.

by

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Public Health Department of Global Health with a concentration in Global Communicable Diseases College of Public Health University of South Florida

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DEDICATION

This thesis is a dedication to my loving mother, Mrs. Nomsa Mkhontfo. She is an extraordinary sweet woman whose unconditional love, support and teachings have made me the proud gentleman I am today. To my late dad who died before I became a man, I know he is smiling down on me for my achievements and the great that is yet to come. From his dedication and commitment to success I learnt that things worth having are worth working hard for. To my siblings, Nokuthula and Mnetisi Mkhontfo for being the best family in the world, I know how much they look up to me as a brother and I’m certain there is so much greatness in the universe for both of them to embrace, they should just stay focused and their big brother loves them. This is also dedicated to my wife and kids for their love and support gave me hope and were a voice of reason that kept me going and focused throughout my study.
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ABSTRACT

Background: Pulmonary Tuberculosis (PTB) is considered a disease of the past but it remains a major cause of mortality among immune compromised patients and continues to be a significant threat to public health globally. Notably, the prevalence of diabetes mellitus (DM) has increased over the years. The biological link of TB and DM has been reported in numerous literature with DM attributed to three folds increase in the risk of TB and linked to Drug Resistant TB, especially amongst aged diabetic patients. The aim of the study was to examine the distribution of DM among TB patients and explore the risk of Drug resistant TB in Diabetics infected with TB.

Methods: The study employed a retrospective cross-sectional descriptive case based study involving 3638 patients diagnosed with pulmonary TB in the State of Florida, USA, 2009-2014. A comparative analysis of TB cases with DM and cases without DM adjusted for age was conducted. The risk of Drug resistant TB associated with DM was estimated through logistic regression analysis. Odds Ratios of TB/DM comorbidity were calculated and adjusted for Age using 5-year intervals from 40 years to above 70 years. Ninety-five percent (95%) confidence intervals were used and the accepted level of error was 0.05.

Results: There were 3836 cases of Pulmonary TB in Florida for the period of 2009-2014. The majority of cases (65%) were males and likely unemployed (59.1%). The prevalence of DM was
12 % but when adjusted for age the prevalence of DM was 3.9% amongst patients aged below 40 years and 16.7 % in patients aged above 40 years. An estimated 469 cases had TB/DM comorbidity (12.2%). The majority of TB/DM cases were above 40 years amongst the patients with DM, 44/469 (9.4%) had drug resistant TB and a majority were resistant to Rifampin. Population density did not influence the distribution of TB in this study.

**Conclusion:** Diabetes Mellitus, Aging, and low immunity are linked with increased rates of progressing from latent TB infection to active disease. To achieve the goal of TB elimination it is important to fully understand and identify known TB comorbidities for proper diagnosis and early initiation to care. There is a positive correlation between high DM burden and increased TB prevalence. Therefore, it is recommended that prevention of DM, hyperglycemia and comprehensive management of DM be intensified to prevent TB, improve TB treatment outcomes and reduce the risk of drug resistant TB in Florida, USA.
1. CHAPTER ONE: INTRODUCTION

1.1. Background

Tuberculosis (TB) is a significant cause of mortality among immune compromised patients and continues to be a significant threat to humans globally[1]. The Center for Disease Control and prevention (CDC) defines TB as a bacterial infection caused by Mycobacterium Tuberculosis. TB has been recognized by the World Health Organization (WHO) as the most common cause of death among people with Human Immune Deficiency Virus (HIV), responsible for a reported 25% mortality of global Acquired Immune Deficiency Syndrome (AIDS) death in 2013 [2]. Notably, the prevalence of Diabetes Mellitus (DM) has increased in countries with a high burden of TB [3]. The physiological link between the two epidemics has been recognized throughout history [4].

Diabetes is a group of metabolic disorders marked by high blood glucose levels. It is entirely dependent on how insulin is produced, regulated or both. There are two types of DM, type 1, formerly known as insulin dependent diabetes mellitus and type 2 DM, formerly known as non-insulin dependent DM (WHO). They both present with a similar range of complications, however, the significant difference is their time of onset or diagnosis [3]. This research focused on diabetes mellitus without disaggregating the type among patients with TB, exploring their characteristics as well as their risk of drug resistant TB. Type 2 DM accounts for 90-95% of all DM
diagnosed cases and the most observed in TB/DM comorbidity. It is associated with old age, obesity, lifestyle practices and race. Blacks and Hispanics are most at risk [3]

1.2. Problem statement

The United States reported 9421 cases of TB in 2014 [5]. According to CDC, the prevalence of TB as of 2014 was 9.6/100 000 persons. TB is considered a disease of the past but it is still a major cause of mortality in developing countries and Asia [5]. CDC and the WHO estimate that 2 billion people globally are infected with mycobacterium tuberculosis [5]. The United States saw a resurgence of the disease in 1985 due to multiple factors including increased prison population, homelessness, injection drug use, overcrowding of houses, and an increase of populations in long term care facilities. Immigration of people from endemic countries has been cited as a contributing factor to TB transmission. Further fueling factors are HIV and DM. TB kills 2-3 million people annually worldwide and is the leading cause of death among young adults [1]. Most concerning is that 4% of TB cases are resistant to at least more than one anti-TB drug, however, drug resistant TB is rare in the United States [2]. Medical interventions, improved diagnostics and treatment have rendered TB curable but proper treatment and adherence to treatment is not easily attainable. The prevalence of TB among diabetics is high and has been since ancient history as documented by Root H in 1934 13 [6]. This article observed that TB is much more common amongst patients whose diabetes is poorly managed [6].

In Philadelphia, Kelly E Dooley and Richard E Chaisson, cited a study where there was an observed two-fold increase in TB prevalence among diabetics. A dose-response pattern was also
observed in patients with diabetes who needed increased insulin units per day as they were
double the risk of TB compared to patients who required lower doses [7]. A major limitation
amongst the growing body of studies looking at the association between TB and Diabetes is the
use of active TB cases in studies compared to latent TB infection which may either overestimate
of underestimate the strength of association between TB and DM. The interactions between
Diabetes and TB is most critical at analyzing TB/DM comorbidity. It is known that diabetes
increases the severity of TB and negatively affects treatment outcomes amongst patients taking
anti TB drugs [4]. Research highlights that diabetes lowers a patients’ immunity and subsequently
results in increased incidents of relapse following treatment and prolonged culture conversion
rates [8].

A study in Turkey observed longer sputum conversion rate of 67 days amongst people with
diabetes compared to 55 days amongst patients without diabetes [9]. Diabetes further influences
treatment success among TB patients. In Egypt, TB patients with diabetes were estimated at 3.9
increased risk of treatment failure [10]. To support this observation, an Indonesian study
observed that there was 22.2 % of positive sputum cultures among TB patients with diabetes as
compared to 6.9 % in TB patients at 6 months’ sputum culture.

Most significantly, a 41 % treatment failure in TB/DM comorbidity was observed compared to
only 13 % of patients without Diabetes [7]. On a global scale, the risk of TB death amongst
diabetics is estimated at 6.5-6.7 which is evident that the risk is a public health threat [11].
Deaths and treatment failure are common in TB/DM comorbidity. Poorly managed diabetes increases susceptibility to TB. This is attributable, amongst other factors, to hyperglycemia which is a major diabetes complication that affects cellular immunity, in particular, the macrophages [12]. Macrophages are significant in mycobacterium TB containment and their ability to physiologically function is impaired by diabetes [3, 13].

Despite the high prevalence of TB among people with diabetes, the pathological relationship remains understudied. Estimates show that 180 million people are suffering from DM and this is likely to double by 2030 [14]. The observed correlation between TB and diabetes could have a negative impact on TB control programs [15]. Patients with diabetes have a weak immunity and are prone to getting infections including TB which dents global TB control initiative [3].

1.3. Hypothesis
Aging is associated with diminished immunity. Macrophages, which play a pivotal role in the first line defense of pathogen invasion, have their endocytosis and lysosomal action delayed as people age. The capacity, therefore of alveolar macrophages to kill Mycobacterium tuberculosis is significantly compromised in aging populations. DM tends to lower a persons’ immunity as evident in many studies [Nuria et al], hence, the hypothesis of this study was that the prevalence of DM is higher amongst TB patients and there is an increased risk of drug-resistant TB with age among diabetic patients.
1.4. **Study goals and objectives**

The Primary goal of the study was to examine the distribution of DM among TB patients and explore the risk of Drug-resistant TB in Diabetics who are also infected with TB in Florida, USA. The Florida department of health TB control program aims to eliminate TB in the state through TB care initiative, a Florida system of Tuberculosis care formed by a partnership between the Florida Department of Health (FDOH) and the public health system statewide to ensure availability of effective TB management program, an aim in line with the global plan to stop TB 2016-2020 adopted by WHO has a post 2015 strategy to eliminate TB as a global epidemic by 2035. The research aimed to gain in-depth understanding of TB and drug-resistant TB risk associated with DM in aging populations to initiate collaborative TB/DM control initiatives throughout the state of Florida as well as identify counties with the highest risk of disease through spatial analysis and in doing so, contribute to the body of evidence in the state and country available for decision making and planning.

**1.4.1 Main objective**

The Primary goal of the study was to examine the distribution of DM among TB patients and explore the risk of Drug-resistant TB in Diabetics in Florida, USA using secondary data sources from the Florida department of health, American diabetes association, Florida TB control program and the Center for Disease Control.

**1.4.2. Specific objectives**

a. To describe the characteristics of TB patients co-infected with DM

b. To determine if Drug Resistant TB is associated with DM among Patients with Pulmonary
c. To determine whether level of urbanization, using population density as a proxy, is positively associated with increased rates of TB/DM Comorbidity in the state of Florida counties.

1.5. Public health significance

The double burden of TB and DM is a significant Public health threat, understandably so because of the increase in diabetic patients among countries where TB is endemic [3, 7]. Individually TB and DM each present a burden on any public health system, however, together they form a significant public health threat that warrants urgent interventions[3]. In the beginning of the 19th century one in seven Americans were killed by TB, however with the development of highly effective TB drugs in the 1940’s, there was a decline in TB cases [16]. With the emergence of the HIV epidemic in the 1980’s, there was a noticeable rise in TB cases in the US as with the rest of the world (CDC). HIV is not the only risk factor for TB disease, other causes of immunosuppression increase the risk for TB disease such as DM. DM is becoming an epidemic attributed to diet, sedentary lifestyles and genetics (WHO). In countries with TB epidemics and a rising DM prevalence, control of TB has become tenuous and unless collaborative control efforts are implemented, the world will continue to struggle with eliminating TB disease. The TB/DM dual burden has recently received attention due to the recent spike of TB amongst diabetics in the Middle East and has been classified as a dual burden due to the negative impact on the health systems in countries with an already high TB incidence [3].

TB/DM comorbidity is a major public health problem because global efforts pioneered by WHO and CDC in controlling TB are undermined by the increased TB risk posed by DM. DM increases TB risk by three folds which is a major drawback to public health [17]. DM does not only increase
the risk of progressing from latent TB infection to active TB disease but makes TB disease more severe and negatively impacts on TB treatment outcomes with a risk of 1.89 for dying and a risk of 1.69 for treatment failure and dying combined [18]. Relapse following treatment is estimated at 3.89 amongst diabetics putting them at higher risk of developing Multi Drug Resistant TB (MDR-TB) which causes, increased costs of managing TB [18]. This makes TB control efforts harder and unless all possible control interventions are explored people will continue dying from the deadly but preventable and curable disease. Interesting findings from a recent study point out that by 2035 there will be an 8.8% cumulative increase in the incidence of TB by if the diabetes prevalence continues to increase at the current rate [19]. This study looked at TB transmission in 13 countries and used epidemiological models to estimate the burden of TB that can be reduced through various DM prevention scenarios. According to their models, if the prevalence of diabetes could be lowered by 6.6-13.8 % TB incidence would decline by 11.5-25.2 (Absolute level) and subsequently mortality to TB would decline by 8.7 – 19.4 %. This translates to 6 million incident cases prevented and 1.1 million deaths to TB. Hence, by 2035, 7.8 million cases of TB would be prevented and 1.5 million deaths prevented. These projections present empirical data that if synergies between infectious and non-infectious disease control programs are established unwarranted deaths can be prevented and morbidity to TB controlled in the United States and globally [20].
2. CHAPTER TWO: LITERATURE REVIEW

Data from the CDC show a decline in national TB cases in the United States since 1993 but TB control efforts have not resulted in the goal of elimination [21]. In 2014, WHO estimated that there were 9.6 million new cases of TB with a reported 1.5 million deaths globally [2] and in the United States alone, 9,412 cases of TB were reported in 2014, with an incidence rate of 3.0/100,000 persons, a decrease of 2.2% from 2013 [5]. The total numbers of TB cases continue to decline, however, this is the smallest percentage decrease in over a decade [5].

HIV has been for years the leading risk factor for mortality but the attributable proportion of HIV to TB mortality in 2014 was 0.4 million out of 1.5 million deaths [5, 22]. This is indicative of other key players increasing the risk of mortality besides HIV, such as diabetes. The biological and physiological links between TB and DM are not novel concepts since this association has been recognized from ancient history but with medical advancement, insulin introduction for DM coupled with Streptomycin discovery for TB substantially reduced cases of TB and DM [23].

This study aimed to examine the distribution of DM among TB patients and explore the risk of Drug resistant TB in Diabetics who are also infected with TB in Florida, USA, using age as an effect modifier. Florida population has a median age of 41 years with the aging population representing 39.1 % of the population according to Florida population estimates. The American diabetes association, CDC and WHO have indicated that as people get older there is an increased risk of type 2 DM [3, 24]. This age group has a double risk of aging and immune suppression that
makes them hypothetically at an increased risk of opportunistic infections like TB particularly when they are diabetic [3].

Other literature have shown that the comorbidity of these diseases increases the severity of the other in infected persons [25]. There is a growing body of literature that supports the association between TB and DM [3], however, results have been inconsistent. It is without a doubt that TB/DM comorbidity complicates TB control and treatment outcomes [23]. A population based study that was conducted in California observed that Diabetes accounts for a 3.5 times risk increase of TB as compared to persons without diabetes [21]

The study further pointed out that the risk of TB caused by diabetes varies by age group with the old age posing a lower risk. These findings are an antagonist to other research particularly a meta-analysis study conducted in Mexico which observed that risk of TB increases with age amongst diabetics [26]. WHO suspects that the increased burden of Diabetes undermines global TB control efforts [2]. A temporal association has been suggested between increased TB incidence and rapid industrialization and urbanization which could be plausibly explained by the increased TB transmission associated with migration, population density, emergence of non-communicable diseases like diabetes and overcrowding observed during the peak transmission in Great Britain between the 17th and 18th Century [27]. Rural or urban settlement has been implicated in various diseases and the prevalence of diabetes has been reported to be high in urban developments compared to rural [28].
Additionally, TB interacts with DM with a reported three times higher risk of progression to MDR-TB in these patients. Evidence further shows that TB and DM drugs counteract each other complicating the conditions even further[25]. A study was conducted in Egypt to study predictors of treatment failure among people undergoing TB treatment utilizing the DOTS strategy and it was observed that diabetes confers an estimated 3.9 times increased risk of treatment failure [29].

TB infection and disease are biologically complicated. The disease progresses quickly from TB infection to acute TB infection in people with weakened immune system. In most instances, the body’s immune system initially fights off infection and contain the disease as latent TB infection [17].

An estimated one-third of the world’s population has latent TB infection [29]. About 90 % of diabetes cases are type 2 diabetes mellitus which explains why most of TB/DM comorbidity has a high proportion of people with Type 2 diabetes [30]. In Tanzania D. Faurholt-Jepsen et al reported that diabetes is strongly associated with increased mortality amongst TB patients especially after starting TB treatment [31]. His findings indicate DM as a stronger predictor of death since it negatively affects treatment outcomes. Multiple studies as indicated by D. Faurholt et al report more advanced pulmonary TB amongst patients with DM since DM is associated with delayed sputum conversion which further affects TB diagnosis and subsequently reduction in treatment success rate. An explanation for this phenomenon is the biologically plausible fact that DM affects the absorption and metabolism of TB drugs such as rifampicin. Diabetes is a known immune suppressor exposing patients with latent TB to fast progression to active TB.

TB just like HIV weakens the immune system, though the immunological defects have not been characterized, the effect of diabetes on the immune system cannot be cast to doubt. In persons
without compromised immunity, the body initially fights off infection and contain the disease as latent TB infection, however, when the immune system gets compromised the body’s ability to fights off disease is limited. Alarmingly, A third of the world’s population has latent TB and is at an explosive risk of progressing to active TB if DM continues to be poorly managed [17].

Despite the observed association between TB and DM, the role of DM in TB risk has not been fully studied. The link between TB and DM has long been established yet diabetes continues to complicate TB control efforts [3]. DM is much likely to complicate the TB problem further as there is a global increase in DM cases. Like HIV, Diabetes weakens the immune system and permits progression of Latent TB infection to active TB. TB symptoms in TB/DM coinfection are convoluted complicating the identification and treatment resulting in lower case detection rates, misdiagnosis and poor treatment outcomes [32].

There is evidence of interaction between Rifampicin and insulin which are the drugs of choice for TB and Diabetes which exert strain on TB case management [4], Rifampicin is also known to induce hyperglycemia which affects the control of diabetes. There is a global need to study and greater understand TB/DM comorbidity to effectively manage DM and prevent an increase in TB cases [33]. Further evidence highlights that TB might not only worsen glycaemic control but could also predispose patients to DM since Rifampicin which is the first line drug for TB causes hyperglycemia and has been associated with hyperinsulinemia not only in diabetic patients but non-diabetics as well [7].
2.1. Epidemiology of TB

The incidence rate of TB in the United States was at 3.0 / 100000 people in 2014. The CDC highlighted this as a decline, however, this is the smallest decline in prevalence in a decade [5]. A strategic plan for TB control was developed by the CDC in 1989 and a goal to eliminate TB from the USA in 2015 was established and this initiative lead to a decline of TB cases from 1993 to current date. Statistics periodically indicate a substantive decline in TB cases but cases are still reported [5]. It is, therefore, important to understand state and county epidemiology of TB to monitor disease trends in the population.

TB counts and prevalence rates have declined nationally among US-born people, however, the total number of cases have steadily increased among foreign born individuals. According to the CDC, foreign-born persons were 13.4 times more likely to have TB than US-born persons in 2014. During the same reporting year, 2014, minority groups, blacks, Asians and Hispanics continued to record the highest number of TB cases. Asians had the highest rate and were 28.5 times more likely to have TB than whites. Four states in the US (California, Florida, Texas and New York) housed about 50 % of the national TB cases in 2014. These states were noted to have higher numbers of foreign born persons ranging from 16-26 % of the total population. In a broader view, the Hispanics remained largely affected while a decline in rates was observed in other groups particularly the whites [5].
Figure 1. Number and rate of newly diagnosed TB cases among US and foreign born persons by year, 2002-2014; Source: National TB Surveillance System: Morbidity and Mortality Weekly Report (MMWR) Tuberculosis Trends

2.2. Drug Resistant TB epidemiology

For the period of 2010-2013, there were a reported 9% TB cases that were, at least, resistant to one of the four major TB drugs. TB cases had declined nationally by 2014 but the proportion of drug resistant TB cases have remained high especially Isoniazid which increased from 7.9 % in 2000 to an estimated 9 % in 2013. Drug resistant TB was mostly observed in persons of foreign origin compared to US born persons. As a result, by 2013, about 90% of MDR-TB cases were recorded in persons born outside the USA. Anti-TB drug resistance is a growing health problem in the United States and globally and it is a major threat to TB control initiatives. Drug resistant TB is very rare in the United States as compared to Asia and Sub-Saharan Africa [5].
2.3 Aging and TB/DM

Aging is a complicating factor for chronic diseases in most population and warrants further investigation in TB/DM comorbidity. Type 1 and type 2 diabetes are pathologies along the same spectrum of disease and complications. Type 2 DM risk increases with age and poses a much larger threat at population level since TB patients with DM are largely older than TB patients without Diabetes, the double jeopardy of aging and the setting of type 2 diabetes complicates an already complex problem [4].

Conclusive pathophysiological cascade is not clear how DM is a risk factor for TB. Suggestively it is attributable to compromised cellular immunity and deficiency in alveolar macrophages response to tubercle bacilli [25]. In an effort to understand host susceptibility to TB, Qu et al, conducted a longitudinal diabetes study in a Hispanic cohort to analyze their gene expression of TB gene candidates to explore the molecular cascades in the associated TB risk in diabetics [34]. This was the Hispanic population that another study found that persons with diabetes aged 35-years to 64 years accounted for about 50% of the TB cases [35]. Qu et al over a period of three years profiled sampled genes of RNA. The study showed reduced expression and genes that play an important role in macrophage function particularly Gene H2K which mediates aerobic glycolysis known to be a source of energy for macrophages [34]. This could in part explain the reduced function of macrophages in Diabetics predisposing patients to TB.

A study in India highlighted the intensity of TB/DM comorbidity [36]. In a similar study Baker et al conducted a systemic review of 33 studies and discovered that DM does not only increase the risk of TB but also its severity [12]. In a prospective cohort study in Mexico of TB, an OR of 1.51 was observed for delayed sputum conversion and an OR of 2.93 for treatment failure in
diabetics [32] indicating that DM increases the risk of treatment failure amongst people on anti-TB treatment. Christie Y Jeon and Megan B Murray conducted a systematic review of 13 studies that studied TB and DM comorbidity mainly to provide a summary of existing evidence showing association and to further assess the quality of the studies conducted paying particular attention to the methodologies implemented [17]. Their review and conclusion didn’t fall far from existing studies and findings. Their meta-analysis is corroborated in Demlow et al. study of 2015 which found that diabetes was much more common in people with TB [21].

The researchers conducted a retrospective study of TB cases in California for the years 2010-2012 and observed that the overall risk of TB among diabetics was 3.5 [21]. Christie Y Jeon and Megan B Murray further concluded that DM was responsible for 67% of pulmonary TB cases among people with DM. This was based on the Mexico border study assuming a Relative Risk of 3 and 6% prevalence in Mexico [17]. Another interesting study found that the death rate is 6 times higher among TB DM co-infected patients receiving anti-TB treatment. Many critical questions remain unanswered indicating a need for further research [37]. Epidemiologic models in India indicated that diabetes accounts for 14.8% of pulmonary TB. DM prevalence in urban places is associated with 15.2% incidence in smear positive Pulmonary TB as compared with rural population [36]. In Tanzania, 1990, a study found that DM is four times more common in patients with TB. Inconsistent findings reveal that the connection between DM and TB is much higher than HIV/AIDS and TB, which is by far a well-known and established comorbidity. In a retrospective study in Mexico, DM/TB comorbidity exceeded HIV/TB comorbidity. A similar study in Brazil showed consistency with the Mexico study revealing a DM/TB comorbidity of 16% of death compared to 11% death in TB/HIV comorbidity [35].
3. CHAPTER THREE: METHODOLOGY

3.1. Research design

The study employed a retrospective cross-sectional descriptive case based study design involving patients diagnosed with pulmonary Tuberculosis between 2009 -2014. Diabetes mellitus and drug-resistant TB and other known risk factors were analyzed. The purpose was to determine the association, if any, of DM and Drug-resistant TB in the state of Florida comparing population below 40 years and above 40 years. This objective included identifying the risk of association between drug resistant TB and DM among TB patients to determine any causal relationship as cited by other studies. The study further explored county TB/DM comorbidity to identify counties at highest risk of TB and finally established if levels of urbanization using population density as a proxy had a correlation with the prevalence rate of TB/DM in the different counties.

Therefore, a population-based cross-sectional retrospective study of patients with TB diagnosis in Florida was employed. Patients with TB are recorded in the Florida TB registry which was the principal source of data. DM as a risk was not recorded as a risk factor for TB until 2009. This study reviewed retrospective data collected in the Florida state TB registry.

Data collected between 2009 and 2014 were selected to allow for the inclusion of the DM variable. However, the data did not categorize DM by type and all cases were recorded as DM without stating the type. The registry is formed by data collected by health professionals in the TB control program from medical records.
### 3.2 Study population

The study population was all adult TB patients in the registry. However, the sample population was all pulmonary TB patients reported between January 2009 and December 2014. Florida has low TB rates, just like the rest of the US when compared with Africa and Asia and a comparative risk between young population and old was considered important for TB control in the state. Ideally, patients with TB under 40 years would have been excluded from the study, but for the purpose of comparison they were not excluded and all individuals fulfilling the required criteria were all included. The registry was queried for known risk factors for TB and diabetes, the patient’s age, ethnicity, country of origin and gender amongst other variables.

### 3.3 Inclusion criteria:

- People diagnosed with Pulmonary TB regardless of age
- People diagnosed with either type 2 DM or Type 1 DM
- Florida residents

### 3.4 Exclusion criteria:

- Meeting all the above criteria but not a Florida resident. Each study participant was screened for study eligibility prior to enrollment

### 3.5 Study setting

Florida is the 26th largest state in the US measuring 53997sq miles and an estimated population of 20271272 according to The United States Census Bureau. There are 67 counties consisting of highly urbanized and farmlands. Some counties are large farm lands, but the majority is urbanized. As of 2013, 19.4 % of the population were foreign-born which is higher than the
national average of 12.9 %. Foreign-born population held the highest risk of TB in the state at 62% according to Health management systems 2014.

3.6. Data collection

Data access was granted by the Florida department of health. The data were de-identified for ethical concerns and zip code analysis was not feasible which posed as a limitation. The dataset was received in Microsoft excel format and exported to SAS for analysis. The dependent variable was drug resistant Pulmonary TB and all enrolled subjects had TB. The key independent variable was Diabetes Mellitus, which was captured by TB risk factors in the registry. In addition to the key variable of DM, the research collected and analyzed data on the following variables; Age, Sex, gender, born or not born in the USA, country of origin, ethnicity, Race and other socio-economic factors including homelessness and occupation. The date of TB diagnosis was captured, but DM diagnosis was not captured by the registry. This was a major limitation for establishing causality because the date of diagnosis or onset of DM would have strengthened the causal relationship in this study. In most literature, however, DM is usually diagnosed before TB, which forms the assumption that DM is the risk factor for TB.

Population with diabetes was based on Florida charts estimates for the corresponding years of 2009-2014. Florida charts is a state managed information system that is periodically updated to provide information on disease trends and statistics. Both adults aged above 40 years and those below 40 years formed the TB and DM estimates at the population level. These statistics were crucial in odds ratios for known risk factors.

Data quality checks were performed to ensure each field was accurately and completely recorded. Aggregated data were verified for plausibility and interpretability. Trial runs for analysis were
implemented to observe for data anomalies such as missing variables. Statistically, outliers that could indicate heteroscedasticity were modified for good model fit. Data cleaning mainly manually was done to remove duplicates and account for missing values. Data access was limited to persons directly involved in the study to maintain confidentiality. There was no sensitive information in the data sets but further confidentiality measures were ensured to ensure that the data was not shared beyond the limits the research.

3.7. Data analysis

Data were received in excel spreadsheets and exported to SAS 9.4 for analysis. 95 % confidence intervals were obtained using SAS. The acceptable level of error was 00.5 and P-values of <0.05 were significant when at two-tailed T-Test was applied for the continuous variables. Since two significant groups were analyzed, the TB/DM group and TB without DM only group, a chi-square test was performed for the categorical variables. The prevalence of TB in Florida, just like most of the states is not alarmingly high, and the analysis of the odds ratios was not different from risk ratios, but we chose to report the odds ratio in this study since it talks directly to the study objectives. Data were summarized using descriptive statistics. For country of birth, the data were categorized into two places of origin; US born and those born outside the US and Canada were classified as foreign born. Since diabetes is not a notifiable disease, the state of Florida does not have a diabetes surveillance registry and in that regard, we were not able to make a causal relationship analysis but simply explored the characteristics of TB patients with DM. To account for this discrepancy, the data were stratified into age categories with 5-year intervals; (40-45, 46-50, 51-55, 56-60, 61-65, 66-70 and 71 years and above). Using TB prevalent cases, annual TB incidence was calculated for the patients with and without diabetes to estimate
the rate per 100 000 population. Prevalent cases from the Florida charts formed the denominator for analysis and the numerator was obtained from the recorded cases of TB and DM from the Florida TB registry. Continuous variables were expressed as mean or median with standard deviation and proportions used for categorical variables.

3.8. GIS and geo-spatial analysis

Researchers have employed GIS in several TB studies to geospatially examine trends and clusters of the disease. In this study, we overlay descriptive epidemiological analysis of two epidemics, TB and DM to provide a spatial summary of their divergence and occurrence throughout the state of Florida.

This study determined spatial patterns of TB/DM comorbidity through the application of negative binomial regression for more precision and establishment of high disease prevalent counties, normally presented as hot spot analysis. For geographic analysis of the two disease patterns, prevalence maps were created through Esri’s Arc Map 10.3. Population density figures were used as a proxy for urbanization. This was aimed at analyzing the level of urbanization which is known to have a positive correlation with both diseases. Choropleth maps downloaded from open source diva-GIS to designate boundaries.
3.9. Ethical considerations

The principal concern of this research was privacy and confidentiality of patient’s data, but there were no identifiers since the lowest landmark was county level not patient level outcome. The study relied entirely on secondary data, hence, no social or psychological harm were experienced by study subjects. Specifically, all data obtained from the state health department were de-identified before release and the department granted permission to use the information because of the potential to inform TB program planning. Names, addresses, phone numbers, social security numbers and any other information that renders one capable of identifying specific individuals were not included.
4. CHAPTER FOUR: RESULTS

4.1. Characteristics of TB patients enrolled in the study

The study reviewed de-identified data of 3836 Pulmonary TB patients. The results are presented as a comparison of patients with DM and those without DM. The eligibility of patient records reviewed fulfilled the inclusion criteria of the site of TB infection being pulmonary diagnosed either through case definition by a clinician or laboratory confirmed. Laboratory confirmed cases of TB were 82% and 18% were diagnosed by the provider through case definition. The majority of the cases were males (64.6%) and 35.4% were females. Homeless persons in the year preceding diagnosis accounted for 9.4% of the TB cases. Equal proportions were observed for country of birth, broadly classified as USA born or Foreign born, 51.5% and 48.5% respectively amongst >40 patients with DM. The proportion of TB cases reported per year did not vary much with a mean of 639 cases reported a year. The highest disease frequencies were recorded in 2009 and 2010: 19% and 18% respectively (see Figure 1). A slight decline of cases was noted in 2014 compared to previous years (See figure 2). Most of the TB patients were non-Hispanic/Latino (72%). Approximately 50% were racially white and 37% were black. Miami-Dade was the state with the highest proportion. Unemployed patients were 59.1%, employed 24.84% and retired were 2.29%. There were 72.76% patients that were HIV negative and 12.25% of the cases were HIV positive. Homeless patients accounted for 9.38% of the study population. Alcohol intake in the year preceding diagnosis was reported by 19.9% of the population.
Table 1: Demographic characteristics of pulmonary TB by DM status in the state of Florida, USA, 2009-2014

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with DM</th>
<th>Patients without DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>(%)</td>
</tr>
<tr>
<td>All</td>
<td>469</td>
<td>12.23</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>320</td>
<td>8.34</td>
</tr>
<tr>
<td>Female</td>
<td>149</td>
<td>3.88</td>
</tr>
<tr>
<td><strong>Age Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=40 years</td>
<td>52</td>
<td>1.36</td>
</tr>
<tr>
<td>&gt;40 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-45</td>
<td>47</td>
<td>1.23</td>
</tr>
<tr>
<td>46-50</td>
<td>52</td>
<td>1.36</td>
</tr>
<tr>
<td>51-55</td>
<td>59</td>
<td>1.54</td>
</tr>
<tr>
<td>56-60</td>
<td>60</td>
<td>1.56</td>
</tr>
<tr>
<td>61-65</td>
<td>47</td>
<td>1.23</td>
</tr>
<tr>
<td>66-70</td>
<td>39</td>
<td>1.02</td>
</tr>
<tr>
<td>70 and above</td>
<td>113</td>
<td>2.95</td>
</tr>
<tr>
<td><strong>Race and Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>136</td>
<td>3.55</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>2437</td>
<td>63.53</td>
</tr>
<tr>
<td>Black</td>
<td>174</td>
<td>4.54</td>
</tr>
<tr>
<td>White</td>
<td>231</td>
<td>6.02</td>
</tr>
<tr>
<td>Asian</td>
<td>59</td>
<td>1.54</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>County of birth</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>203</td>
<td>5.29</td>
</tr>
<tr>
<td>Foreign Born</td>
<td>266</td>
<td>6.93</td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>99</td>
<td>2.59</td>
</tr>
<tr>
<td>Unemployed</td>
<td>328</td>
<td>8.55</td>
</tr>
<tr>
<td>Retired</td>
<td>46</td>
<td>1.04</td>
</tr>
<tr>
<td><strong>Alcohol Consumption</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol Past year</td>
<td>66</td>
<td>1.72</td>
</tr>
<tr>
<td>No alcohol past year</td>
<td>403</td>
<td>10.51</td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>35</td>
<td>0.91</td>
</tr>
<tr>
<td>Negative</td>
<td>352</td>
<td>9.18</td>
</tr>
<tr>
<td>Unknown</td>
<td>82</td>
<td>2.14</td>
</tr>
<tr>
<td><strong>TB Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory confirmed</td>
<td>420</td>
<td>10.95</td>
</tr>
<tr>
<td>Case definition</td>
<td>49</td>
<td>1.28</td>
</tr>
</tbody>
</table>
Figure 2. Proportion of TB cases per year, 2009-2014

Figure 2 above indicates Proportions of PTB cases, 2009-2014. The years 2009 and 2010 recorded the highest proportions, 20.65% and 18.22 % respectively. A gradual decline in the trends was observed from 2009 until 2014 with 2014 recording 14.23 % of the Total TB cases.

4.2. TB patients with Diabetes Mellitus

The study further profiled TB cases according to DM status. The prevalence of DM in this population of TB patients was 12% (469/3836), in the < 40 years it was 3.9% (52/1345) while in those older than 40 years it was 16.5 % (417/2513). TB patients with DM infection were more likely to be old, above 40 years, Mantel-Haenszel Crude Odds Ratio of 4.99; 95% Confidence interval [3.7-6.7] (P <.0001). Using the white race as a reference group, black people had an OR 1.4 to be TB patients with DM [CI 1.132-1.835; P-value 0.003. Foreign born patients had an OR
5.09; [CI 3.4-7.6] P-Value 0.02. There was an observed pattern where OR increased with age among TB patients to have DM. Age category 70 years and above had an OR 8.59 with CI [5.93-12.44] p-value <.0001.

**Table 2.** Age adjusted Odds Ratios for TB cases with DM by age category, Florida, USA, 2009-2014

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-45</td>
<td>3.64</td>
<td>2.40-5.53</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>46-50</td>
<td>4.51</td>
<td>2.98-6.81</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>51-55</td>
<td>5.09</td>
<td>3.40-7.62</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>56-60</td>
<td>6.36</td>
<td>4.25-9.50</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>61-65</td>
<td>6.50</td>
<td>4.22-10.02</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>66-70</td>
<td>6.85</td>
<td>4.33-10.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>70 and above</td>
<td>8.59</td>
<td>5.93-12.44</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

**Table 3.** Analysis of DM associated risks among TB patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>0.589</td>
<td>0.437-0.795</td>
<td>0.0005</td>
</tr>
<tr>
<td>Race/Black</td>
<td>1.441</td>
<td>1.132-1.835</td>
<td>0.0030</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>5.09</td>
<td>3.40-7.62</td>
<td>0.0195</td>
</tr>
<tr>
<td>HIV Positive</td>
<td>0.501</td>
<td>0.340-0.739</td>
<td>0.0005</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.236</td>
<td>0.936-1.631</td>
<td>0.1351</td>
</tr>
<tr>
<td>Gender/Sex</td>
<td>1.150</td>
<td>0.921-1.435</td>
<td>0.2168</td>
</tr>
<tr>
<td>Unemployed</td>
<td>0.805</td>
<td>0.624-1.040</td>
<td>0.0970</td>
</tr>
</tbody>
</table>

An analysis of association was conducted for drug resistant TB and DM among patients diagnosed with TB. From the total of 3686 pulmonary TB cases, 275 (7.4%) patients had drug resistant TB and the majority (87.3%) were resistant to Isoniazid. Unadjusted Drug resistance OR was 1.4; CI [1.002-1.971]. Patients with Diabetes had an adjusted OR 1.5, CI [0.52 – 4.4] which indicate an association that was not significant. Alcohol consumption, African American and
native people born in the United States indicated a positive association between DM and drug resistant TB among patients with TB using age as an effect modifier (see table 4 below).

Table 4. Analysis of DR-TB risk among Diabetics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>Resistant (n)</th>
<th>OR</th>
<th>95% CI</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>469</td>
<td>44</td>
<td>1.41</td>
<td>1.002</td>
<td>1.97</td>
</tr>
</tbody>
</table>

The odds ratio of DR-TB amongst diabetics was 1.41, 95% CI [1.002, 1.97] p-value 0.047. The odds ratio seems to be low but significant showing an association of drug resistant TB and DM.

Table 5. Crude Odds Ratio for Drug Resistant TB associated risks

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ODDS RATIO 95%</th>
<th>Confidence Limits</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>1.34</td>
<td>0.99</td>
<td>1.97</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.45</td>
<td>1.05</td>
<td>2.00</td>
</tr>
<tr>
<td>Black Race</td>
<td>0.73</td>
<td>0.53</td>
<td>0.99</td>
</tr>
<tr>
<td>Foreign Born</td>
<td>0.45</td>
<td>0.33</td>
<td>0.61</td>
</tr>
<tr>
<td>HIV positive</td>
<td>1.37</td>
<td>0.93</td>
<td>2.01</td>
</tr>
<tr>
<td>HIV unknown</td>
<td>0.75</td>
<td>0.50</td>
<td>1.12</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.67</td>
<td>0.49</td>
<td>0.93</td>
</tr>
<tr>
<td>Un-employment</td>
<td>0.88</td>
<td>0.66</td>
<td>1.16</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.2</td>
<td>0.92</td>
<td>1.60</td>
</tr>
</tbody>
</table>
Table 6. Adjusted Odds Ratio by age >40 years for Drug Resistant TB associated risks

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ODDS RATIO</th>
<th>95% Confidence Limits</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>1.502</td>
<td>0.517</td>
<td>4.362</td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td>2.192</td>
<td>1.158</td>
<td>4.149</td>
</tr>
<tr>
<td>Black Race</td>
<td>0.522</td>
<td>0.296</td>
<td>0.922</td>
</tr>
<tr>
<td>Born in the USA</td>
<td>0.434</td>
<td>0.249</td>
<td>0.756</td>
</tr>
<tr>
<td>HIV positive</td>
<td>1.16</td>
<td>0.524</td>
<td>2.566</td>
</tr>
<tr>
<td>HIV unknown</td>
<td>0.662</td>
<td>0.295</td>
<td>1.486</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.604</td>
<td>0.354</td>
<td>1.03</td>
</tr>
<tr>
<td>employment</td>
<td>0.878</td>
<td>0.544</td>
<td>1.418</td>
</tr>
<tr>
<td>Sex</td>
<td>0.915</td>
<td>0.577</td>
<td>1.45</td>
</tr>
</tbody>
</table>

There was no observed association between the development of drug resistant TB amongst TB patients with Diabetes when adjusted for age > 40 years and the results were insignificant in this analysis.
4.3. TB and Diabetes prevalence rates by County

Figure 3. TB prevalence rates by county, Florida, USA, 2012
Figure 4. Diabetes Mellitus prevalence rates by county, Florida, USA, 2012
**Table 7.** Analysis of population density as a risk factor for increased TB/DM comorbidity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Wald 95% Confidence Limits</th>
<th>Wald Chi-Square</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1</td>
<td>-10.5418</td>
<td>0.2367</td>
<td>-11.0057 -10.0779</td>
<td>1983.94</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pop_Density</td>
<td>1</td>
<td>-0.0008</td>
<td>0.0002</td>
<td>-0.0012 -0.0004</td>
<td>15.46</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total TB Cases</td>
<td>1</td>
<td>0.0079</td>
<td>0.0015</td>
<td>0.0048 0.0109</td>
<td>26.21</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Dispersion</td>
<td>1</td>
<td>1.4380</td>
<td>0.3547</td>
<td>0.8867 2.3321</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Population density, a proxy used for urbanization did not seem to influence the distribution of TB positively. A negative binomial regression analysis indicated a significant protective effect (P-Value 0.008) whereby for each one unit increase in Population Density the expected log count of TB/DM comorbidity cases decreased by 0.001 and this is probably attributed to the omission of other risk factors in the model. Further studies would need to be done to test this association since it can provide pivotal information for TB control programs. The model was tested and it was a good fit with R-Square 0.9.
5. CHAPTER FIVE

5.1. Discussion

Diabetes Mellitus is associated with TB. This is a known phenomenon that has been established and recorded in numerous literature. In this retrospective cross-sectional population based study of TB cases in Florida, USA, the characteristics of TB patients with DM and drug resistant TB were explored. Age was used as an effect modifier when evaluating the association between DM and Drug resistant TB amongst patients with Pulmonary TB. The association between DM and TB was not feasible to establish because of secondary data limitations which was a huge methodology issue but nonetheless, the study was able to explore known TB risk factors amongst diabetics to evaluate the characteristics of patients co-infected with TB and DM. The results did not show causality pattern or risk of developing TB amongst diabetics but the evaluation of the characteristics and known risks are empirical to draw hypotheses that will influence further research in the field.

This study analyzed the prevalence of DM amongst the TB patients and it observed that the prevalence increased with age. The overall prevalence was 12% but when categorized by age, in the < 40 years category, the prevalence of DM was 3.9% compared to 16.7% amongst those aged above 40 years. The results are not significantly different from a study that was conducted in India that recorded a diabetes prevalence of 15.3 % among TB patients in India. These findings show the influence age has on TB/DM comorbidity. The majority of TB patients with DM in this study were older, > 40 years in keeping with findings from studies exploring the convergence of the two epidemics, [17]. Logistic regression analysis comparing the odds ratios for the <40 years
and > 40 years group indicated that the ratio was high amongst the older category, reaching 8.6 amongst those aged 70 and above with a CI [6.0 – 12.2]. The odds ratio increased every 5 units of age category symbolizing a dose-response pattern by age. Since this study did not warrant causality, it is prudent to investigate further the role of aging in DM attributable risk to TB especially Type 2 diabetes in the aged population. Such research will be important in Florida particularly since the mean age of the population is 41 years signifying that most people are older and prone to diabetes and subsequently TB. Findings from such a study would reveal the risk and number of people needed to treat to prevent further TB infections as well as providing information as to whether it would be beneficial to start preventive therapy in the aged population. Analyzing TB treatment outcomes in the older age group would have provided further pertinent information for program use.

This study further examined the association between drug resistant TB and DM amongst the patients. Studies have shown that TB and DM confluence each other and the relationship could be reciprocal. TB can inversely impact DM control by inducing glucose intolerance and poor glycemic control among diabetics thus complicating DM control further. Likewise, DM interferes with TB treatment, particularly rifampin. The study concluded that increasing age, black race and non-US born persons are at an increased TB/DM comorbidity. These study findings are not different from Viswanathan et al study in India that found out that age, diabetes history and non-active occupation were the most identified risk factors for DM among patients with TB. Alcohol consumption was found to have a higher association with diabetic in patients with TB and these results corroborate study findings by Raghuraman et al which found similar output following
logistic regression analysis of DM risks in TB patients [38]. With DM on the increase in the United States and globally, this study magnifies the emerging threat to TB control initiatives.

High DM prevalence was observed in TB patients however attributable risk ratios would have provided better information on causal effects of DM on TB but this analysis was not possible in this study. As a result, it would be plausible to conduct a population based retrospective cohort study enrolling newly diagnosed DM patients and follow them over years to determine the risk of developing TB.

Faurholt-Jepsen et al in their earlier studies reported that DM has no clinical significance in the presentation of TB [31]. However, a similar study was carried out by the same researchers in Tanzania and they documented that DM negatively affects TB treatment outcomes [31]. Several studies have provided evidence that TP patients have much more severe TB when they have DM since DM is associated with reduced cure rate and resistance to treatment [39]. Evidence further shows that DM complicates absorption of anti-TB drugs which could explain in part why, though not significant, our study found that diabetes is associated with drug resistant TB. This could have resulted in part due to the small numbers of drug resistant TB. It is convincing to hypothesize that different populations would yield different results while applying the same research methodology. Unlike the USA, where the rates of TB are low and DM control is well coordinated, other parts of the world with limited resources like Africa and Asia have high disease prevalence for both DM and TB, and the control program for these diseases are not well coordinated, resulting in poor disease control and treatment outcomes. This would partly account for the positive association presented by Restrepo et al in Tanzania, 2007, [15].
Seven point two percent (7.2%) of the TB cases were drug resistant to mainly rifampin which literature has cited as a DM metabolism effect on rifampin absorption, therefore, resulting in reduced drug availability leading to the development of resistance over time. Significantly true, this study did not evaluate the effect of DM on treatment outcomes among TB patients or mortality thereof but we can learn from other studies [11] that DM has detrimental effects on treatment success and mortality. Faurholt-Jepsen et al in their study observed that out of 6 patients with TB, one had DM and about 50% of reported death occurred in the first 60 days of initiating treatment amongst diabetics due to treatment failure [31].

In this analysis, population density, a proxy used for urbanization did not seem to influence the distribution of TB. A negative binominal regression analysis indicated a protective effect with and this is probably attributed to the omission of other risk factors in the model. Further studies would need to be done to test this association since it can provide pivotal information for TB control programs.

5.2. Limitations
1. The study implemented a retrospective cross-sectional study design and as a result, the causality or sequence of events could not be established. All persons had the dependent variable, but the study could not establish which was diagnosed first between TB and DM, hence, causality could not be inferred.

2. Data sources and unavailability of DM data from available sources was a major limitation. The State of Florida does not routinely report on DM. To establish causal relationship TB cases
and Data cases needed to be merged according to unique identifiers and followed over time to establish the rates at which cases developed the disease. A prospective cohort study would have been more ideal for this research.

3. It would have been more informative to have patient-level data to determine clusters based on transmission or the occurrence of TB. Patient-level cluster analysis would have provided the precise location beyond county or zip code analysis, but the lack of such identifiers in the data set received limited this analysis.

5.3. **Conclusion**

Diabetes Mellitus, aging, low immunity and several other medical conditions are linked with the risk of progressing from latent TB infection to active disease. To achieve the national goal of TB elimination, it is important to fully understand and identify known comorbidities among patients with TB to facilitate proper diagnosis and early initiation into care. In numerous circumstances, the high prevalence of diabetes in TB populations have been demonstrated and this study shared the same findings. The rates of TB and Drug resistant TB in the US are not alarmingly high as the rest of the world but the increase in DM poses a greater threat in the future. It is therefore recommended that prevention of DM, management of hyperglycemia and comprehensive care of diabetes is made a priority for stakeholders involved in the prevention of both communicable and non-communicable diseases.
REFERENCES


APPENDIX 1: Communication with the Florida Department of Health

Per our discussion yesterday I’m sending you the TB data from 2000-2014. (Please note the data is derived from two different sources and contained on two worksheets.) If known, the HIV status is documented for each case. However, additional risk factors, such as diabetes, weren’t collected for TB cases until 01/01/2009. Please note the following:

1. We have provided you with a de-identified data set without zip codes.
2. We do ask if any publication is to be done that we are notified as a courtesy.

Please let me know if you have questions about the data.

Lori Johnston
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DOH Mission: To protect, promote and improve the health of all people in Florida through integrated state, county and community efforts.

**Please Note: Florida has a very broad public records law. Most written communications to or from state officials regarding state business are public records available to the public and media upon request. Your email communications may therefore be subject to public disclosure.

From: Mkhontfo, Mandzisi [mailto:mandzisim@health.usf.edu]
Sent: Thursday, September 24, 2015 3:36 PM
To: Johnston, Lori A. <Lori.Johnston@flhealth.gov>
Cc: Novak, Robert <rnovak@health.usf.edu>
Subject: TB, HIV and Diabetes data for Florida

Dear Lori Johnson

My name is Mandzisi Mkhontfo. I am a Master of Public Health Student at the University of South Florida. I am working with Dr. Robert Novak and Dr. Benjamin Jacobs on a Tuberculosis research. The purpose of the research is to compare the odds of developing pulmonary tuberculosis amongst people with Diabetes and those with HIV, with the hypothesis that the risk of disease is much higher amongst aged population with diabetes as compared to HIV. The study will be based on the state of Florida.
Part of the objective is to evaluate the risk of disease based on population distribution and spatial analysis. This is aimed at developing a predictive model to predict which areas will require urgent public health intervention to prevent the spread of TB.

In that regard, I am requesting your department to provide me with Tuberculosis, Diabetes and HIV data for the past 15 years, preferably from year 2000 to 2014. I am interested in all the variables you collect for each of the disease, when the cases were diagnosed for TB, HIV and Diabetes. The data will help me test the hypothesis and evaluate it against known risk factors.

I am willing to engage in a telephonic discussion with you in case you need more clarity.

Thank you

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