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Kristen Renneker Date

# Diabetes Mellitus among Persons with Tuberculosis in the United States, 2009–2011

By

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Master of Public Health

Epidemiology

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By

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Bachelor of Science
The University of Texas at Austin
2011

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An abstract of
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in Epidemiology
2013

# Abstract


Diabetes Mellitus among Persons with Tuberculosis in the United States, 2009–2011

By
Kristen Renneker

**Background:** Both tuberculosis (TB) and diabetes mellitus (DM) remain major public health problems, and their association has been the topic of much research. Several studies have provided evidence that DM increases the risk of TB; however the risk factors involved in this relationship are less well-known.

**Objectives:** The purpose of this study was to analyze important risk factors in the relationship of TB and DM using United States' TB surveillance data.

**Methods:** Data collected from 2009–2011 as part of the National Tuberculosis Surveillance System (NTSS) was used to compare cases of TB with and without DM. Logistic regression was used to model characteristics of TB cases with and without DM in univariate and multivariate analyses.

**Results:** From 2009 to 2011, there were 28,611 cases of reported TB in the United States, 13.8% (n=3,951) of which also had reported DM. As age at TB diagnosis increased, the odds of having TB-DM vs. no DM increased in a dose-response pattern, with cases aged 65 and over having an odds of TB-DM 98.3 times greater than the 5–14 year old age group (95% CI 24.4, 225.8). Native Hawaiian/Pacific Islanders (OR: 5.5, 95% CI 3.7, 8.2) and Hispanics (OR: 3.2, 95% CI 2.9, 3.7) were the racial/ethnic groups with the highest odds of having DM compared to non-Hispanic whites. TB cases with end-stage renal disease (ESRD) had 3.5 higher odds of also having DM compared to TB cases without ESRD (95% CI 3.0, 4.2).

**Conclusion:** Several risk factors, including higher age, non-white race/ethnicity, and comorbid ESRD were positively associated with TB-DM. TB program workers should be aware of certain risk factors on the TM-DM relationship to tailor care, screening, and treatment for TB-DM cases.

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# Chapter I: Literature Review

## Tuberculosis

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. TB is primarily a disease of the lungs but can infect other parts of the body, such as the spine, kidney, and brain. TB is spread person-to-person through the air when a person with active TB coughs, sneezes, or otherwise emits respiratory fluids into the air. Approximately one-third of the world's population is infected with TB (1). However, only a small proportion of those infected become sick from TB (2). Thus, two TB-related conditions exist, latent TB infection (LTBI) and active TB disease. A person with LTBI, who has no symptoms and cannot spread TB bacteria to others, needs treatment to prevent latent TB from developing into active TB (2). People with LTBI have a 10% lifetime risk of developing active TB (1). However, for those with compromised immune systems such as HIV-infected individuals, this risk is much higher. According to the WHO, the risk of developing TB is estimated to be 20–37 times greater among people infected with HIV compared to those without HIV infection (3).

## Worldwide burden of TB

The worldwide incidence of TB was 8.7 million in 2011, with most of these cases occurring in developing countries (1). Ninety-five percent of TB deaths occur in low- and middle-income countries (1). Rates of TB incidence and death vary widely across the globe. The World Health Organization identifies countries with TB rates higher than 40 per 100,000 as "high-incidence" countries (4). For perspective, in 2011, Italy had one of the world's lowest rates of TB at 2.8 per 100,000, while Swaziland had the world's highest rate at 1,317 cases per 100,000 (4). Regionally, the burden of TB is highest in

Asia and Africa. India and China combined account for almost 40% of the world's TB incidence (5). While the global burden of TB remains enormous, progress toward global health targets for reductions in TB cases and deaths continues. The rates of new cases have been falling worldwide for several years, with a reduction of 2.2% between 2010 and 2011 (5). TB prevalence and mortality are falling slowly, thus the Millennium Development Goal of halting and reversing the TB epidemic by 2015 is on track (6). However, the need for continued awareness and surveillance of TB persists even as overall rates of incident TB cases drop.

**Tuberculosis in the United States**

In the United States in 2011, 10,521 total new cases of tuberculosis were reported, an incidence of 3.4 per 100,000 (7). This is the lowest rate reported since national reporting began in 1953, and represents a 6.4% decrease from the rate reported in 2010 (7). While rates of TB decreased in both U.S.-born and foreign-born persons, foreign-born persons and racial/ethnic minorities continue to have a disproportionately high burden of TB. The rate of incident TB cases is 12 times higher in foreign-born than in U.S.-born populations (7). In 2011, non-Hispanic Asians had the highest rate of incident TB among racial/ethnic groups. Among racial/ethnic groups (regardless of origin of birth), the incident TB rate was 25 times greater for non-Hispanic Asians than for non-Hispanic whites (7). The greatest racial disparity among U.S.-born cases occurred between non-Hispanic blacks and non-Hispanic whites, with the former having a rate of incident TB six times higher than the latter (7).

Although in 2011, the number and rate of TB cases in the foreign-born population in the U.S. decreased, the difference between the proportion of U.S.-born and foreign-

born persons diagnosed continued to increase from 2010 to 2011. In 2011, 62.5% of all cases of known origin were foreign-born (n=6,546) (7). The rate of incident TB cases in the foreign-born population was 17.3 per 100,000, while the rate in the U.S.-born population was 1.5 per 100,000. In 2011, 50.4% of foreign-born cases of TB originated from five countries: Mexico, the Philippines, Vietnam, India, and China (7).

If the United States wishes to achieve its goal of TB elimination (less than 0.1 cases per 100,000) (8), addressing the growing disparity in TB rates between U.S.-born and foreign-born persons is of critical importance (7). Control and treatment of LTBI will be an important factor in lowering cases and rates of TB among foreign-born persons in the U.S., because a large percentage (78.8%) of foreign-born incident cases were diagnosed after at least 2 years of residence in the U.S. (7); this is consistent with the reactivation of LTBI acquired abroad (9). In 2007, CDC issued updated technical instructions for screening and treating of prospective U.S. immigrants. The updated technical instructions delineate a new TB classification[1] specific to LTBI cases from high-incidence TB countries, as well as updated rigorous screening and treatment regimens (10). Furthermore, CDC recently recommended a shorter course of therapy for LTBI cases, consisting of one drug administration weekly for 12 weeks (10). As high-burden countries increasingly adopt these new technical instructions and recommended shorter LTBI treatment regimen, the rates of LTBI might decrease, having the effect of lowering case counts and rates of incident TB among the foreign-born U.S. population (7).

[1] Class B: Latent TB Infection Needing Evaluation for Treatment

**Drug resistant TB**

Drug-resistant strains of TB are a major public health problem and threaten to diminish progress made in combating TB worldwide. Drug resistant TB can be either primary or acquired. Resistance is primary when a case, who has received no previous TB treatment, is infected with a drug resistant strain (11). In contrast, cases with acquired drug resistance developed resistance to anti-TB drugs during the course of therapy (11). Once resistance emerges, drug-resistant organisms can spread from person-to-person. Multi-drug resistant (MDR) TB is defined as an isolate of *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampin, the most effective anti-TB drugs (12). Persons diagnosed with MDR TB must be treated for up to 2 years with a regimen of drugs that are less potent, more expensive, and have greater side-effects. TB bacteria that are MDR TB are widespread and found in all countries surveyed by the WHO (13). In 2012, WHO estimated 220,000 to 400,000 cases of MDR TB globally, equating to 3.7% of all incident TB cases (13). Almost half of all MDR TB cases are diagnosed in China and India (12). In 2008, MDR TB caused an estimated 150,000 deaths worldwide (12).

In the U.S., 124 cases of MDR TB were reported in 2011, the most recent year for which complete data were available. Among the culture-confirmed cases tested for drug susceptibility (95.7%), 1.7% were found to be MDR TB (14). Cases with a history of TB are more likely to have MDR-TB: 1.3% of cases without a previous TB history have MDR TB, while cases with a previous history of TB are proportionally 6 times more likely to have MDR TB (7.8%). In 2011, 85.5% of the MDR-TB cases were among foreign-born persons (14).

**Risk Factors**

TB risk factors include chronic illnesses which impair the function of the immune system (such as HIV and end-stage renal disease), lifestyle factors such as alcohol and drug use, and demographic factors such as where one works or lives (e.g., long-term healthcare facility). In 2011, 4.3% of U.S. TB cases were among those who lived in correctional facilities, 5.8% of cases were homeless, and 2.3% were residents of long-term care facilities (15). The percent of reported TB cases that reported use of injection drugs, non-injection drugs, or excess alcohol were 1.5, 7.6, and 12.4%, respectively. Being unemployed, a healthcare worker, a correctional employee, a migrant worker, retired, or not seeking employment also puts one at an increased risk of developing TB. Over 7 percent (7.7%) of cases were HIV-positive among those with known HIV status (82.5%) (15).

**Diabetes Mellitus**

Diabetes mellitus (DM) is a group of chronic metabolic diseases in which either the pancreas does not produce enough insulin or the body does not effectively use the insulin it produces. Because insulin is a hormone that controls blood sugar, both the first type, in which the body does not produce enough insulin (Type 1 DM) and the second type, in which the body is resistant to its own insulin (Type 2 DM) result in an increase in the body's blood glucose (hyperglycemia). Type 1 DM (formerly called "juvenile-onset" DM) is not preventable and has an unknown etiology. Type 2 DM (formerly called "adult-onset" DM) comprises 90% of the total diabetes cases globally. Unlike Type 1 DM, Type 2 DM is largely preventable, and is known to be caused, in part, by high excess body weight and a sedentary lifestyle. Uncontrolled diabetes can, over time, lead

to serious damage, especially to the nervous and vascular systems. Diabetes increases the risk of cardiovascular disease, foot ulcers, limb amputation, retinopathy, and renal failure. A study using U.S. data found that the rate of death in diabetic compared to non-diabetic persons was significantly higher in all age groups, ranging from a rate ratio of 1.5 ($p<0.001$) in persons aged 65–74 to a rate ratio of 3.6 ($p<0.001$) in persons aged 25–44 (16).

**Worldwide burden**

Worldwide, 347 million people are estimated to have DM (17). In 2010, an estimated 3.4 million people died from complications of diabetes (17). While DM prevalence is similar in high- and low-income countries, more than 80% of these deaths occur among people in low- and middle-income countries (17). According to WHO estimates, if current trends continue, DM will be the 7$^{th}$ leading cause of death worldwide by 2030 (a prevalence increase of 50%) (18). Diabetes is the 4$^{th}$ or 5$^{th}$ leading cause of death in most high-income countries, and there is substantial evidence that it is a growing epidemic in developing countries (19). The International Diabetes Federation divides the world into seven regions. Of these regions, the Western Pacific region has the highest number of people with DM, an estimated 132 million cases (19). Looking at prevalence rates rather than total number of cases, however, shows that 11% of adults in the Middle East and North Africa region have diabetes, the highest percentage in the world (although followed closely by the North America and Caribbean region at 10.7%) (19).

**Diabetes mellitus in the U.S.**

In 2010, an estimated 18.8 million people had diagnosed DM in the United States (20). This number has been rising sharply in every state since 1990, even after age-

adjustment. During 1995–2010, the estimated age-adjusted prevalence of self-reported diagnosed diabetes increased in every reporting area (all 50 states, the District of Columbia, and Puerto Rico), with a median increase of 4.5% to 8.2% (20). In 2010 the reported diabetes prevalence ranged from 6.0% to 11.7% by state. The remarkable increase in DM prevalence (at least 50% increases in every state, with 18 states showing increases greater than or equal to 100% from 1995–2010) can be due to both improved survival of people with DM, and to an increase in the incidence of DM. Data suggest that mortality of persons with DM has decreased substantially during this time period, including decreased rates of complications and improved quality of healthcare for diabetic cases (20). However, the major reason for the increase in DM prevalence from 1995–2010 is the increased incidence of DM since 1990 (20). While this increase may be due, in part, to increased detection of previously undiagnosed DM and demographic changes to the population of the U.S., the steep increase in diagnosed DM does coincide with the increase in obesity prevalence in the U.S., as well as an observed increase in the prevalence of risk factors for obesity (20).

**Risk factors for DM**

The percentage of the population with diagnosed and undiagnosed DM increases with age. In the U.S., 3.7% of adults aged 20–44, 13.7% of adults aged 45–64, and 26.9% of adults aged 65 and over have diagnosed or undiagnosed DM (20). It has been shown that the aging-related decrease in mitochondrial function is associated with increased muscle insulin resistance, which can lead to diabetes (21). While the risk of diabetes increases with age, in the United States, the number of new cases diagnosed is highest for those aged 45–64 (n=1,052,000), over twice the number of new diagnoses for

adults aged 20–44 (n=465,000) and 65 and over (n=390,000) (22). An analysis of U.S. National Health Survey data shows that the odds of having DM increases with age, and those aged 65 and older have 3.8 times greater odds of having DM than those younger than 65 (23).

After adjusting for age, recent national data show that 16.1% of American Indians and Alaska Natives age 20 and over who received care from the Indian Health Service have diagnosed DM. During the period 2007–2009, national survey data show that among people aged 20 and over, 7.1% of non-Hispanic whites, 8.4% of Asian Americans, 11.8% of Hispanics, and 12.6% of non-Hispanic blacks had diagnosed diabetes (22). This trend holds among juvenile (age 10–19) rates of Type 2 diabetes from 2002-2005 data: American Indians have the highest rate, followed by non-Hispanic blacks. Hispanics and Asians/Pacific Islanders had similar rates, followed by non-Hispanic whites with the lowest rate of diagnosed Type 2 DM in juveniles aged 10–19 (22).

Among those who are foreign-born, the odds of having DM are associated with length of time in the United States; in an age-adjusted model of diabetes in the U.S., foreign-born survey respondents in the United States for 15 or more years had significantly increased odds of having diabetes by 13% compared to foreign-born respondents in the United States for less than 1 year (23). The aORs increased in each of the remaining cohorts (based on time in United States) but this increase was not significant (compared to those in the United States less than 1 year, the aOR for 1-4 years in the United States is 0.76, the aOR for 5-9 years in the United States is 0.78, and the aOR for 10-14 years in the United States is 0.96) (23).

**Increased susceptibility to infection**

Clinicians and public health practitioners have long noted that people with DM have an increased susceptibility to infection (24). Previous studies show that immune function in DM patients is compromised (24). Diabetes mellitus increases the risk of comorbidities that may increase susceptibility to infection, such as foot ulcers. Diabetes mellitus also can influence the outcome of an infection, such that infectious disease mortality is increased among DM cases compared to cases without DM (RR 2.0, 95% CI 1.2–3.2) (25). Furthermore, one study found that the risk ratio for acquiring an infectious disease was 1.21 (99% CI 1.20–1.22) for diabetic compared to non-diabetic cases (26). The risk of hospitalization for an infectious disease increased more than two-fold in these groups, and the risk of death attributable to infection was 1.92 times higher for diabetic than non-diabetic cases (26). People with DM are at a higher risk of developing and dying from an infectious disease than people without DM.

**Comorbid TB and DM**

Comorbid DM and TB have existed for thousands of years, with their association being noted “even in Roman times” (27). The introduction of effective therapies for these two conditions, insulin in 1920 and antibiotics in the 1940s, substantially lowered case mortality rates for cases with either DM or TB (28). As such, the association between TB and DM “became less…relevant” as the two diseases were rarely ever endemic to the same areas (27). However, this situation has changed dramatically in the last decade as a result of transitioning lifestyles in low- and middle-income countries towards greater intake of calories and increasingly sedentary lifestyles coupled with continued high rates of TB in these same countries (29). As populations at risk for both DM and TB

increasingly overlap, the confluence of these two epidemics represents a worldwide health threat.

A 2008 study by Jeon et al conducted a meta-analysis of observational studies that quantified the association between active TB and DM. This analysis, which included 13 age-adjusted studies, found that DM increases the risk of TB, regardless of study design, background TB incidence, geographic location of study, or underlying medical conditions of the population (30). In the cohort studies included in the analysis, DM was associated with an increased risk of TB (RR 3.11, 95% CI 2.27–4.26) (30). The strength of the association between DM and TB was significantly higher in Central America (RR=6.00), Europe (RR= 4.40), and Asia (RR=3.11) than in North America (RR=1.46) (30).

**Demographic risk factors**

The TB-DM association may be dependent on demographic factors such as sex, age, and ethnicity. The relationship of TB, DM, and age can be looked in two separate ways. A large Korean prospective cohort study of the incidence of TB among diabetics found that the RR of TB-DM decreases with age (30–39 years: RR 9.98, 95% CI 6.8–14.5; >60 years: RR 1.76, 95% CI 1.07–2.9) (31). Alternatively, looking at the prevalence of DM among people with TB, it has been shown that diabetic cases with tuberculosis are relatively older (32),(33). In summary, the risk of a person with DM acquiring TB decreases as age increases, while the odds of a person having DM given already having TB increases as age increases.

The association between TB, DM, and sex is less clear. A 2003 study in Mexico found that there is a stronger association between TB and DM in men than women, but that there is a progressive shift toward female predominance as age increases (for

example, at age 40–49 74% of TB-DM cases are male, at age 70–99, this percentage is 27%) (34). For reference, the same study found that males comprised well over 50% of TB cases without DM at all age groups (34). Restrepo et al found that most TB-DM cases were males (and most TB cases were males), but there was a significantly higher proportion of females among those with TB-DM compared to those with TB only (33). However, the proportion of females was only significant in one of the populations (Mexico), not the other (Texas), although this could be due to reduced access of care in Mexico, as well as lack of data availability to adjust for certain possible confounders in the Mexican population (33).

In North American studies, the strength of the association between TB and DM was higher among Hispanics than non-Hispanics (RRs of 2.69 and 1.23, respectively) (30). This increased risk may be due to the increased incidence of LTBI among Hispanics (28). Among Hispanic people aged 25–54 years, the TB risk attributable to DM was 25.2%, equivalent to that of HIV (25.5%) (35).

**Clinical characteristics**

The clinical presentation of TB and comorbid DM may differ from standard TB in many ways. Many studies have found an association between DM and the smear positive form of TB. A 2007 study of Turkish hospital patients found that DM was an independent risk factor for sputum smear positivity (36). Another study found that cases with TB-DM were significantly more likely to have a positive smear at diagnosis than cases without DM (aOR 1.8, 95% CI 1.3–2.4) (33). Increased presentation of sputum smear-positive TB may be due to DM accelerating the progression from smear-negative infections and latent infections to smear-positive disease (37). TB-DM cases were also

more likely to have a significantly greater sputum bacterial concentration (38), consistent with this hypothesis (37).

Whether or not DM increases the severity of TB disease, as measured by lung cavitation, remains controversial. Some studies suggest that TB-DM cases are more likely to present with cavitary TB. For example, a 2003 study of Saudi Arabian hospital patients found that 50.8% of TB-DM patients while only 39.0% of TB patients presented with lung cavitation ($p=0.005$) (39). A small but significant increased likelihood of cavitary disease was found among TB-DM cases on the Texas-Mexico border (aOR 1.1, 95% CI 1.1–1.2) (33). Other studies have found similar results, as well as an increased likelihood of infection in multiple lung lobes and involvement of the lower lung field (both indicators of increased TB severity) (40),(41). However, other studies have found no evidence of a radiological difference. A retrospective study in Malaysia found no difference in lung cavitation, with cavitation being present in 89% and 91% in the TB-DM and non-diabetic groups, respectively (42).

Likewise, the results of studies assessing the relationship between TB-DM and MDR TB are also heterogeneous. One study found that after controlling for age, gender, alcohol and drug abuse, HIV infection, and a history of previous TB infection, cases with diabetes did have a statistically significant higher odds of MDR TB than cases without diabetes (OR 2.14, 95% CI 1.10–4.17) (43). Furthermore, of cases with a previous history of TB, those with TB-DM were more likely to have MDR TB than cases without DM (OR 3.0, 95% CI 1.1–8.2) (43). A retrospective case-control study of hospital patients found a strong association between DM and MDR-TB; the aOR of having MDR-TB in patients with and without DM was 5.3 (95% CI 1.9–14.7) (44). A recent study in

Taiwan assessed the association between drug resistance and DM in TB cases with and without a previous history of TB. This study found that in both groups, the odds of INH-resistance was significantly higher in cases with DM, while the odds of MDR-TB was not significant in either group (45). Other studies have likewise found the risk of MDR-TB among TB-DM cases to not be significant (38, 42, 46). The biological mechanism by which DM would lead to preferential infection with MDR-TB is unclear at this time (28). However, the possibility of pharmacological issues in the co-management of DM and TB necessitates a clear understanding of the effects of common antibacterial drugs and DM. The common anti-TB drug rifampicin can cause hyperglycemia, and isoniazid is a possible risk factor for peripheral neuropathy in diabetic cases (28). A systematic review of the relationship between drug resistant TB and DM would be beneficial to make more definite conclusions about this association.

The outcomes of treatment for TB cases with DM cannot be assumed to be the same as for cases with TB only. The WHO offers definitions of several possible treatment outcomes. A “relapse” describes the event wherein a case who has been previously treated for TB, and for whom treatment completed successfully, is later diagnosed with bacteriologically-positive (sputum smear or culture) TB. A “failure” describes a treatment outcome wherein a case is still sputum-smear positive at and beyond 5 months of treatment (47). A 2012 prospective cohort study in southern Mexico found that cases with TB and DM have more severe clinical manifestations, take longer to exhibit sputum conversion, and have a higher probability of treatment failure and relapse (48). This study found that the risk of treatment failure as an outcome associated with DM was 2.93 (95% CI 1.18–7.23) (48). While this is higher than other studies have

suggested, few studies isolate treatment failure as an outcome (many studies look at failure and death combined), and this study has a larger sample size and is in an area with a high burden of TB. A systematic review of 33 different studies estimated that the risk ratio for death among cases with TB and DM compared to just TB was 1.89 (95% CI, 1.52–2.36) (49). This risk ratio increased to 4.95 (95% CI, 2.69–9.10) when studies that adjusted for confounding were included (49). The authors argue that even this estimate is probably too conservative, due to loss to follow-up and competing risks among cases with DM (49). Studies assessing sputum culture conversion are largely heterogeneous, with risk ratios that range from 0.79 to 3.29 (49). DM is also associated with an increased risk of relapse (RR 3.89; 95% CI 2.43–6.23) (49). A prospective cohort study from Taiwan found that the risk of relapse increased for cases TB-DM, even after adjustment (OR 1.65, 95% CI 1.02–2.63).The use of *M. tuberculosis* fingerprinting has provided evidence that TB cases with DM are much more likely to experience a recurrent infection caused by the same bacteria as the previous episode as opposed to an exogenous reinfection (48).

# Chapter II: Manuscript

## Introduction

Roughly one-third of the world's population is infected with tuberculosis (TB) (1). The worldwide incidence of TB in 2011 was 8.7 million, with most of these cases occurring in developing countries (1). In the United States in 2011, 10,521 total new cases of tuberculosis were reported, an incidence of 3.4 per 100,000 (7). Worldwide, 347 million people are estimated to have diabetes mellitus (DM) (17). In 2010, an estimated 3.4 million people died from complications of diabetes (17). According to WHO estimates, if current trends continue, DM will be the 7$^{th}$ leading cause of death worldwide by 2030, a prevalence increase of 50% (18).

Comorbid DM and TB have existed for thousands of years, with their association being noted in Roman times (27). The introduction of effective therapies for these two conditions, insulin in 1920 and antibiotics in the 1940s, substantially lowered case fatality rates for cases with either DM or TB (28). As such, the association between TB and DM "became less…relevant" as the two diseases were rarely ever endemic to the same areas (27). However, this situation has changed dramatically in the last decade as a result of transitioning lifestyles in low- and middle-income countries towards greater intake of calories and increasingly sedentary lifestyles coupled with continued high rates of TB in these same countries (29). As populations at risk for both DM and TB increasingly overlap, the confluence of these two epidemics represents a worldwide health threat.

A 2008 systematic review found that having diagnosed DM roughly triples the risk of developing TB (30). Many previous studies have quantified the association between DM and TB in different populations, however, few studies have used nation-

wide TB surveillance data, and no study has looked at the Center for Disease Control and Prevention's (CDC) National Tuberculosis Surveillance System (NTSS) data. A previous multistate study found that 99.5% of U.S. TB cases are reported to NTSS (50). This study assesses the TB-DM relationship with respect to demographic and clinical risk factors in the United States, and uses data from CDC's TB surveillance system, and as such is representative of every reported TB case in the United States.

## Methods

### Study Population/Data Source

The study population in this analysis is all cases with TB disease reported to CDC's NTSS. All NTSS data was collected using the Report of Verified Case of Tuberculosis (RVCT) form. The RVCT is a standardized collection form recording demographic, clinical, laboratory, and outcome information on all verified cases of TB in the United States (51). RVCT forms are submitted electronically to CDC's Division of Tuberculosis Elimination (DTBE) by 60 reporting areas (the 50 states, the District of Columbia, New York City, Puerto Rico, and 7 other jurisdictions in the Pacific islands and the Caribbean). In 2009, the RVCT was expanded to include additional information including a current comorbid diagnosis of DM. Data from 2009–2011 was used in this study.

### Inclusion/Exclusion Criteria

Only data from the 50 states, the District of Columbia, and New York City was used in this study. While the new, expanded RVCT was released in 2009, not all states had electronic reporting systems capable of reporting the new risk factors, including presence of DM, until 2010. For this reason, the data of 10 states that used systems without the

capacity of DM reporting were excluded for the year 2009. The state of Missouri was excluded as they did not report information on DM comorbidity to NTSS during the study period. Cases were excluded from analysis if they did not meet the definition of a verified case of tuberculosis, if they were not a countable case, or if the reason therapy was stopped was because the case did not have TB. In the logistic regression analysis, patients who were not alive at diagnosis of TB were also excluded.

**Outcome Variables**

The outcome of interest is a case with verified TB with or without reported DM. To meet the definition of verified TB for this study, the case must meet one of the following verification criteria: culture positivity, nucleic acid amplification test (NAAT) positivity, acid-fast bacilli smear positivity, clinical case definition,[2] or provider diagnosis[3] (51). For the DM reporting in the RVCT, the question instructs the data collector to "select all that apply" for a range of possible risk factors, one of which is diabetes mellitus.

**Predictor Variables**

Both sociodemographic and clinical variables, collected on the RVCT, were used in the analysis. These included variables for : sex; age group; race/ethnicity; reported substance abuse in the past year including injection drug use, non-injection drug use, and excessive alcohol use; residence of a correctional facility; long-term care facility residence; homelessness; history of TB; primary occupation; origin of birth (U.S.-born or foreign-born), country of birth among foreign-born persons; years in United States among

[2] Persons must meet all of the following criteria to meet the clinical case definition for TB: Evidence of TB infection based on a positive test (tuberculin skin test or interferon gamma release assay) and either 1) signs and symptoms compatible with TB disease or 2) clinical evidence of current disease, and must be receiving current treatment with at least 2 anti-TB medications.

[3] "Provider diagnosis" is not a component of the case definition for TB, but CDC reports have traditionally included all TB cases that are considered verified by reporting areas, without a requirement that cases meet the case definition.

foreign-born persons; vital status (alive or dead) at diagnosis; case verification criteria; primary reason evaluated for TB disease; HIV status; chest radiographic findings from both via x-ray and CT scan; sputum smear result; disease site (pulmonary, extrapulmonary, or both); documented culture conversion; first-line drug resistance (resistance to isoniazid, rifampin, pyrazinamide, or ethambutol); multidrug resistant (MDR) TB (resistant to at least isoniazid and rifampin); reason therapy was stopped; cause of death (related to TB disease, related to TB therapy, or unrelated to TB disease); directly-observed therapy (DOT) (totally self-administered, totally directly observed, or both); provider type (management by health department, by private/other care, or both); other risk factors including contact with an MDR-TB case, contact with an infectious TB case, missed contact (2 years or less), incomplete LTBI therapy, tumor-necrosis factor alpha (TNF-α) therapy, post-organ transplantation, end-stage renal disease (ESRD) , and/or immunosuppression not due to HIV infection.

**Data analysis**

All data analysis was done using SAS version 9.3. A descriptive analysis of the data was performed by computing the proportion of TB cases with and without DM for each of the included potential predictors. A univariate analysis was performed to calculate unadjusted odds ratios to determine which potential predictors were significantly associated with TB-DM. An alpha of 0.05 was used to determine significance.

Variables found to be significant in the univariate analysis were included in the multivariate linear regression models. Four models were constructed, each through the method of backwards selection; removing non-significant variables in a stepwise manner until all remaining variables in the model were significant. Model 1 included all data

from 2009 to 2011, but did not contain outcome variables. Model 2 included data from 2009 only and included outcome variables.[4] The variables for origin of birth (U.S-born or foreign-born), country of birth, and years in the United States showed collinearity, therefore 2 distinct models were created to separate the data based on origin of birth. Model 3 is restricted to U.S.-born cases and Model 4 is restricted to foreign-born cases. Models 3 and 4 use data from 2009–2011, thus do not contain outcome variables. Model 4 contains variables that only apply to foreign-born persons (country of origin and years in the United States). Each logistic regression model was used to calculate adjusted odds ratios to determine the strength of any associations between the predictor and outcome variables.

**Results**

From 2009 to 2011, there were 28,611 cases of reported TB in the United States, 13.8% (n=3,951) of which also had reported DM. Population characteristics of TB cases with and without DM are presented in Table 1. Of all the TB cases in the U.S. in this time period, 61.1% (n=17,471) were male and 50.7% (n=14,504) were age 45 or over. The proportions of TB cases by race/ethnicity were non-Hispanic American Indian (1.22%), non-Hispanic Asian (27.4%), non-Hispanic Black (24.8%), Hispanic (28.7%), non-Hispanic multiple races (0.3%), non-Hispanic Native Hawaiian/Pacific Islander (0.8%), and non-Hispanic White (16.4%).

**Univariate Associations**

Unadjusted odds ratios and 95% confidence intervals for the association between each predictor variable and the outcome are presented in Table 1. At least one level of the

[4] Reporting areas have up to 2 years to collect data on the outcomes of TB treatment, therefore, data for cases incident after 2009 is not complete with regard to follow-up variables.

values for the variables for sex, age group, race/ethnicity, non-injection drug use, excessive alcohol use, residence of a correctional facility, long term care facility residence, homelessness, occupation, origin of birth (U.S.-born or foreign-born), country of origin (among foreign-born persons), years in the United States (among foreign-born persons), vital status (alive or dead) at TB diagnosis, TB case verification criteria, reason evaluated for TB, HIV status, chest radiograph findings, CT scan findings, sputum smear result, disease site, reason therapy stopped, directly observed therapy status, and other risk factors were found to be significantly associated (either positively or negatively) with the risk of having reported DM. Among those who died during therapy, the cause of death was significantly more likely to be due to TB disease (rather than unrelated to TB) for TB cases with DM vs. without DM (OR: 1.82, 95% CI 1.03–3.23).

**Modeling**

The results of each of the 4 logistic regression models are presented in Tables 2–5, respectively. In all models, older age, non-white race, cavitary disease detected by a CT scan, sputum smear positivity, and ESRD were factors significantly more likely to occur in TB-DM cases than in non-DM cases. In all models, excessive alcohol use, residence in a correctional facility, and HIV positivity were factors significantly less likely to occur in TB-DM cases than in non-DM cases. In the follow-up model (Model 2, Table 3) a case being lost to follow-up (as a reason therapy stopped) was significantly more likely to occur in TB-DM cases. No other outcome was found to be significantly associated with reported DM. In the model restricted to foreign-born persons (Model 4, Table 5), a person with TB-DM was significantly more likely to be from Mexico, the Philippines, or

India (compared to all other countries), and significantly less likely to be from China (compared to all other countries).

## Discussion

### Age

In the univariate analysis and all of the models, older age was a risk factor for TB-DM comorbidity. Furthermore, as age increased, the odds of having TB-DM vs. no DM increased in a dose-response pattern, with cases aged 65 and over having an odds of having TB-DM that were 98.3 times greater than the 5–14 year old age group (Model 1, 95% CI 24.4–225.8). It has been well-established that the risk of DM increases with age. An analysis of U.S. National Health Survey data shows that the odds of having DM increases with age, and those aged 65 and older have 3.8 times greater odds of having DM than those younger than 65 years of age (23). It has also been shown that diabetic cases with tuberculosis are relatively older (32); one study found that, among TB-DM cases in Texas, the odds of being age 70 or older was 3.4 (95% CI 2.1–5.3) times the odds of being younger than age 70 (33). So, while the observed increase in aORs of TB-DM compared to TB without DM as age increases is not unusual, the magnitude of the observed effect in this analysis is quite large.

### Race/Ethnicity

In every analysis, TB cases of non-white race/ethnicity were significantly more likely to have DM compared to non-Hispanic white cases. This is not surprising, given that non-White race and Hispanic ethnicity are associated with higher rates of both TB and DM separately. Native Hawaiian/Pacific Islanders were at particularly elevated odds in all analyses (from the 2009–2011 model, OR: 5.50, 95% CI 3.69–8.18). One study of

the prevalence of DM among Asian-American subgroups found that Native Hawaiian and Pacific Islanders (NHPI) had the highest adjusted risk ratio of DM when compared to whites out of any Asian-American sub-population (RR 2.35, 95% CI: 2.23–2.48) (52). Hispanics also showed a high odds of TB-DM compared to non-Hispanic whites (from the 2009–2011 model, OR: 3.24, 95% CI 2.87–3.66), which is supported by several studies, (30),(35) with one study explaining this higher odds as possibly due to a higher risk of LTBI among Hispanics (28).

**Risk of End Stage Renal Disease**

TB-DM cases were at significantly higher odds of having ESRD than TB cases without DM (from the 2009–2011 model, OR: 3.94, 95% CI 2.96–4.23). The aOR for this relationship was 3.54 (95% CI 2.96–4.23) in Model 1. It has long been known that DM is a significant predictor of ESRD. More specifically, diabetic nephropathy is associated with a higher risk of progression towards ESRD (53). Therefore, it is not surprising that this relationship would also be evident among people with TB. However, an increase in screening for ESRD among TB-DM cases may be beneficial.

**Strengths/Limitations**

A major strength of this study is its data source; CDC's TB surveillance data is comprehensive of every reported case of TB in the United States. This also had the added benefit of having a large sample size, which increased precision of the effect estimates. Furthermore, using surveillance data hopefully avoids Berkson's bias, because unlike many previous studies, this study was not limited to hospital patients with TB, who may, by definition, be more likely to have severe complications (such as DM) that would lead to hospitalization.

A major limitation is the lack of ability of the data collection instrument (RVCT) to discern TB cases without DM from TB cases that were not assessed for DM. For this analysis, the dichotomous DM variable is given either the value of "DM reported" or "DM not reported," consistent with this limitation of the survey instrument. While we cannot know for certain the true number of TB cases without DM, all but one state was reporting this variable by 2010. We also have no reason to suspect that grouping the variable responses in this way would result in any differential bias. TB surveillance data is also limited to persons who have TB, therefore we could not make comparisons to the non-TB population with and without DM using these data.

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## Tables

Table 1: Univariate associations of demographic and clinical risk factors for TB cases with and without DM

| Characteristic | | with DM reported | | DM not reported | | unadj. OR | lower CI | upper CI |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | n | % | n | % | | | |
| Sex | | | | | | | | |
| Male | 17471 | 2543 | 14.6 | 14928 | 85.4 | 1.18** | 1.10 | 1.26 |
| Female | 11126 | 1407 | 12.6 | 9719 | 87.4 | 1.00 | | |
| Unknown | 14 | 1 | 7.1 | 13 | 92.9 | 0.53 | 0.07 | 4.07 |
| Age (years) | | | | | | | | |
| 0–4 | 990 | 0 | 0.0 | 990 | 100.0 | | | |
| 5–14 | 651 | 2 | 0.3 | 649 | 99.7 | 1.00 | | |
| 15–24 | 3019 | 46 | 1.5 | 2973 | 98.5 | 5.02** | 1.22 | 20.74 |
| 25–44 | 9436 | 637 | 6.8 | 8799 | 93.2 | 23.49** | 5.85 | 94.35 |
| 45–64 | 8783 | 1822 | 20.7 | 6961 | 79.3 | 84.94** | 21.18 | 340.66 |
| ≥65 | 5721 | 1443 | 25.2 | 4278 | 74.8 | 109.46** | 27.28 | 439.15 |
| Unknown | 11 | 1 | 9.1 | 10 | 90.9 | 32.45** | 2.72 | 387.64 |
| Race/Ethnicity[5] | | | | | | | | |
| American Indian/Alaska Native | 344 | 58 | 16.9 | 286 | 83.1 | 1.69** | 1.25 | 2.27 |
| Asian | 7835 | 1227 | 15.7 | 6608 | 84.3 | 1.55** | 1.38 | 1.73 |
| Black | 7092 | 706 | 10.0 | 6386 | 90.0 | 0.92 | 0.82 | 1.04 |
| Hispanic | 8218 | 1379 | 16.8 | 6839 | 83.2 | 1.68** | 1.50 | 1.87 |
| Multiple Races[6] | 97 | 17 | 17.5 | 80 | 82.5 | 1.77** | 1.04 | 3.01 |
| Native Hawaiian/Pacific Islander | 232 | 46 | 19.8 | 186 | 80.2 | 2.06** | 1.47 | 2.88 |
| White | 4687 | 503 | 10.7 | 4184 | 89.3 | 1.00 | | |
| Unknown | 106 | 15 | 14.2 | 91 | 85.8 | 1.37** | 0.79 | 2.39 |
| Substance abuse | | | | | | | | |

[5] Race/ethnicity: Race and ethnicity are separate variables that are combined for analysis purposes. "Hispanic or Latino" regardless of race is grouped into "Hispanic," and all other races are understood to be non-Hispanic.

[6] Indicates 2 or more races reported for a person.

Table 1: Univariate associations of demographic and clinical risk factors for TB cases with and without DM

| Characteristic | | with DM reported | | DM not reported | | unadj. OR | lower CI | upper CI |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | n | % | n | % | | | |
| Injection drug use[7] | | | | | | | | |
| Yes | 418 | 49 | 11.7 | 369 | 88.3 | 0.82 | 0.61 | 1.11 |
| No | 27626 | 3844 | 13.9 | 23782 | 86.1 | 1.00 | | |
| Unknown | 567 | 58 | 10.2 | 509 | 89.8 | 0.71 | 0.54 | 0.93 |
| Non-injection drug use[8] | | | | | | | | |
| Yes | 2007 | 192 | 9.6 | 1815 | 90.4 | 0.64** | 0.55 | 0.74 |
| No | 25998 | 3697 | 14.2 | 22301 | 85.8 | 1.00 | | |
| Unknown | 606 | 62 | 10.2 | 544 | 89.8 | 0.69** | 0.53 | 0.90 |
| Excessive alcohol use[9] | | | | | | | | |
| Yes | 3480 | 437 | 12.6 | 3043 | 87.4 | 0.88** | 0.79 | 0.98 |
| No | 24599 | 3457 | 14.1 | 21142 | 85.9 | 1.00 | | |
| Unknown | 532 | 57 | 10.7 | 475 | 89.3 | 0.73** | 0.56 | 0.97 |
| Correction facility residence | | | | | | | | |
| Yes | 1271 | 58 | 4.6 | 1213 | 95.4 | 0.29** | 0.22 | 0.37 |
| No | 27132 | 3879 | 14.3 | 23253 | 85.7 | 1.00 | | |
| Unknown | 208 | 14 | 6.7 | 194 | 93.3 | 0.43** | 0.25 | 0.75 |
| Long term care facility residence | | | | | | | | |
| Yes | 628 | 138 | 22.0 | 490 | 78.0 | 1.78** | 1.47 | 2.16 |
| No | 27878 | 3801 | 13.6 | 24077 | 86.4 | 1.00 | | |
| Unknown | 105 | 12 | 11.4 | 93 | 88.6 | 0.82 | 0.45 | 1.49 |
| Homelessness | | | | | | | | |
| Yes | 1530 | 157 | 10.3 | 1373 | 89.7 | 0.70** | 0.59 | 0.83 |
| No | 26805 | 3772 | 14.1 | 23033 | 85.9 | 1.00 | | |
| Unknown | 276 | 22 | 8.0 | 254 | 92.0 | 0.53 | 0.34 | 0.82 |
| History of TB[10] | | | | | | | | |

[7] Within past year.
[8] Within past year.
[9] Within past year.
[10] Patient has received a previous diagnosis of TB.

Table 1: Univariate associations of demographic and clinical risk factors for TB cases with and without DM

| Characteristic | | with DM reported | | DM not reported | | unadj. OR | lower CI | upper CI |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | n | % | n | % | | | |
| Yes | 1277 | 161 | 12.6 | 1116 | 87.4 | 0.89 | 0.75 | 1.06 |
| No | 27076 | 3774 | 13.9 | 23302 | 86.1 | 1.00 | | |
| Unknown | 258 | 16 | 6.2 | 242 | 93.8 | 0.41 | 0.25 | 0.68 |
| Occupation[11] | | | | | | | | |
| Health Care Worker | 958 | 110 | 11.5 | 848 | 88.5 | 0.99 | 0.80 | 1.22 |
| Migrant/Seasonal Worker | 379 | 49 | 12.9 | 330 | 87.1 | 1.13 | 0.83 | 1.54 |
| Retired | 3706 | 964 | 26.0 | 2742 | 74.0 | 2.68** | 2.43 | 2.95 |
| Not Seeking Employment | 4721 | 484 | 10.3 | 4237 | 89.7 | 0.87 | 0.78 | 0.98 |
| Correctional Facility Employee | 48 | 7 | 14.6 | 41 | 85.4 | 1.30 | 0.58 | 2.91 |
| Other Occupation | 9087 | 1055 | 11.6 | 8032 | 88.4 | 1.00 | | |
| Unemployed | 8502 | 1169 | 13.7 | 7333 | 86.3 | 1.21** | 1.11 | 1.33 |
| Unknown | 1210 | 113 | 9.3 | 1097 | 90.7 | 0.78 | 0.64 | 0.96 |
| U.S.-Born | | | | | | | | |
| Yes | 11230 | 1312 | 11.7 | 9918 | 88.3 | 1.00 | | |
| No | 17301 | 2629 | 15.2 | 14672 | 84.8 | 1.35** | 1.26 | 1.45 |
| Unknown | 80 | 10 | 12.5 | 70 | 87.5 | 1.08 | 0.56 | 2.10 |
| Foreign-Born Top 5[12] | | | | | | | | |
| Mexico | 3869 | 845 | 21.8 | 3024 | 78.2 | 2.44** | 2.20 | 2.71 |
| Philippines | 1853 | 489 | 26.4 | 1364 | 73.6 | 3.13** | 2.76 | 3.55 |
| Vietnam | 1363 | 201 | 14.7 | 1162 | 85.3 | 1.51** | 1.28 | 1.78 |
| India | 1406 | 162 | 11.5 | 1244 | 88.5 | 1.13 | 0.95 | 1.35 |
| China | 840 | 99 | 11.8 | 741 | 88.2 | 1.16 | 0.93 | 1.45 |
| all other foreign-born | 7970 | 833 | 10.5 | 7137 | 89.5 | 1.00 | | |

[11] Primary occupation within past year.

[12] Top 5 countries of origin, by number of TB-DM cases in the U.S. Restricted to foreign-born cases.

Table 1: Univariate associations of demographic and clinical risk factors for TB cases with and without DM

| Characteristic | Total Cases | with DM reported | | DM not reported | | unadj. OR | lower CI | upper CI |
|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | | | |
| Years in U.S.[13] | | | | | | | | |
| <1 year | 4519 | 540 | 11.9 | 3979 | 88.1 | 1.00 | | |
| 1-4 | 3248 | 215 | 6.6 | 3033 | 93.4 | 0.52** | 0.44 | 0.62 |
| 5-9 | 2639 | 284 | 10.8 | 2355 | 89.2 | 0.89 | 0.76 | 1.04 |
| 10-19 | 3192 | 540 | 16.9 | 2652 | 83.1 | 1.50** | 1.32 | 1.71 |
| >=20 | 3702 | 1049 | 28.3 | 2653 | 71.7 | 2.91** | 2.60 | 3.27 |
| Vital status | | | | | | | | |
| Alive at diagnosis | 27953 | 3827 | 13.7 | 24126 | 86.3 | 1.00 | | |
| Dead at diagnosis | 649 | 122 | 18.8 | 527 | 81.2 | 1.46** | 1.20 | 1.78 |
| Unknown/ Missing | 9 | 2 | 22.2 | 7 | 77.8 | 1.81 | 0.38 | 8.69 |
| Verification Criteria | | | | | | | | |
| Culture positive | 21809 | 3360 | 15.4 | 18449 | 84.6 | 1.00 | | |
| NAAT[14] positive | 305 | 40 | 13.1 | 265 | 86.9 | 0.83 | 0.59 | 1.16 |
| Smear positive | 173 | 14 | 8.1 | 159 | 91.9 | 0.48** | 0.28 | 0.84 |
| Clinical diagnosis | 4726 | 371 | 7.9 | 4355 | 92.1 | 0.47** | 0.42 | 0.52 |
| Provider diagnosis | 1598 | 166 | 10.4 | 1432 | 89.6 | 0.64** | 0.54 | 0.75 |
| Reason Evaluated | | | | | | | | |
| Symptoms of TB | 15917 | 2438 | 15.3 | 13479 | 84.7 | 1.00 | | |
| Abnormal chest radiograph | 5861 | 839 | 14.3 | 5022 | 85.7 | 0.92 | 0.85 | 1.01 |
| Contact Investigation | 1385 | 72 | 5.2 | 1313 | 94.8 | 0.30** | 0.24 | 0.39 |
| Targeted testing[15] | 1300 | 110 | 8.5 | 1190 | 91.5 | 0.51** | 0.42 | 0.62 |
| Health Care Worker | 94 | 9 | 9.6 | 85 | 90.4 | 0.59 | 0.29 | 1.17 |
| Emp/Admin testing[16] | 194 | 11 | 5.7 | 183 | 94.3 | 0.33** | 0.18 | 0.61 |
| Immigration med exam[17] | 546 | 38 | 7.0 | 508 | 93.0 | 0.41** | 0.30 | 0.58 |

[13] Among foreign-born persons.
[14] Nucleic Acid Amplification Test
[15] Case tested due to specifically being considered high-risk.
[16] Test required by employer, or primary or secondary school as part of routine testing.

Table 1: Univariate associations of demographic and clinical risk factors for TB cases with and without DM

| Characteristic | | with DM reported | | DM not reported | | unadj. OR | lower CI | upper CI |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | n | % | n | % | | | |
| Incidental lab result | 2416 | 350 | 14.5 | 2066 | 85.5 | 0.94 | 0.83 | 1.06 |
| Unknown | 898 | 84 | 9.4 | 814 | 90.6 | 0.57** | 0.45 | 0.72 |
| HIV status | | | | | | | | |
| Positive | 1863 | 118 | 6.3 | 1745 | 93.7 | 0.43** | 0.35 | 0.52 |
| Negative | 19904 | 2727 | 13.7 | 17177 | 86.3 | 1.00 | | |
| Total Unknown | 6844 | 1106 | 16.2 | 5738 | 83.8 | 1.21** | 1.13 | 1.31 |
| Chest radiograph findings | | | | | | | | |
| Cavitary | 5934 | 1140 | 19.2 | 4794 | 80.8 | 1.58** | 1.46 | 1.71 |
| Noncavitary | 16516 | 2157 | 13.1 | 14359 | 86.9 | 1.00 | | |
| Unknown | 6161 | 654 | 10.6 | 5507 | 89.4 | 0.79** | 0.72 | 0.87 |
| CT scan findings | | | | | | | | |
| Cavitary | 4575 | 995 | 21.7 | 3580 | 78.3 | 1.76** | 1.60 | 1.95 |
| Noncavitary | 6644 | 905 | 13.6 | 5739 | 86.4 | 1.00 | | |
| Unknown | 17392 | 2051 | 11.8 | 15341 | 88.2 | 0.85** | 0.78 | 0.92 |
| Sputum smear result | | | | | | | | |
| Positive | 10029 | 1880 | 18.7 | 8149 | 81.3 | 1.71** | 1.59 | 1.84 |
| Negative | 13352 | 1584 | 11.9 | 11768 | 88.1 | 1.00 | | |
| Unknown/not done | 5230 | 487 | 9.3 | 4743 | 90.7 | 0.76 | 0.69 | 0.85 |
| Disease site | | | | | | | | |
| Pulmonary | 19376 | 2945 | 15.2 | 16431 | 84.8 | 1.00 | | |
| Any Extrapulmonary | 8388 | 878 | 10.5 | 7510 | 89.5 | 0.67** | 0.62 | 0.73 |
| Unknown | 17 | 1 | 5.9 | 16 | 94.1 | 0.38 | 0.05 | 2.84 |
| Culture Conversion* | | | | | | | | |
| Yes | 3144 | 438 | 13.9 | 2706 | 86.1 | 1.00 | | |
| No | 539 | 76 | 14.1 | 463 | 85.9 | 1.01 | 0.78 | 1.32 |
| Unknown | 38 | 4 | 10.5 | 34 | 89.5 | 2.06 | 0.21 | 19.84 |
| First Line Drug Resistance*[18] | | | | | | | | |

[17] Testing was part of the immigration application process.

[18] Resistance to isonaizid, rifampin, pyrazinamide, or ethambutol.

Table 1: Univariate associations of demographic and clinical risk factors for TB cases with and without DM

| Characteristic | | with DM reported | | DM not reported | | unadj. OR | lower CI | upper CI |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | n | % | n | % | | | |
| Yes | 571 | 65 | 11.4 | 506 | 88.6 | 0.84 | 0.64 | 1.10 |
| No | 4874 | 648 | 13.3 | 4226 | 86.7 | 1.00 | | |
| MDR* | | | | | | | | |
| Yes | 65 | 7 | 10.8 | 58 | 89.2 | 0.79 | 0.36 | 1.74 |
| No | 5236 | 694 | 13.3 | 4542 | 86.7 | 1.00 | | |
| Unknown | 13 | 2 | 15.4 | 11 | 84.6 | 0.60 | 0.33 | 1.08 |
| Reason therapy was stopped* | | | | | | | | |
| Completed therapy | 6078 | 673 | 11.1 | 5405 | 88.9 | 1.00 | | |
| Moved | 2 | 0 | 0.0 | 2 | 100.0 | 0.00 | | |
| Lost | 145 | 25 | 17.2 | 120 | 82.8 | 1.67** | 1.08 | 2.59 |
| Died | 395 | 72 | 18.2 | 323 | 81.8 | 1.79** | 1.37 | 2.34 |
| Other/unknown | 311 | 33 | 10.6 | 278 | 89.4 | 0.95 | 0.66 | 1.38 |
| Directly Observed Therapy (DOT)* | | | | | | | | |
| Totally Self-Administered | 429 | 30 | 7.0 | 399 | 93.0 | 0.55** | 0.38 | 0.81 |
| Totally Directly Observed | 4607 | 553 | 12.0 | 4054 | 88.0 | 1.00 | | |
| Both SA[19] and DOT | 1828 | 216 | 11.8 | 1612 | 88.2 | 0.98 | 0.83 | 1.16 |
| Unknown | 67 | 4 | 6.0 | 63 | 94.0 | 0.47 | 0.17 | 1.28 |
| Provider Type* | | | | | | | | |
| Health Department | 5411 | 618 | 11.4 | 4793 | 88.6 | 0.94 | 0.79 | 1.13 |
| Private/Other | 1419 | 171 | 12.1 | 1248 | 87.9 | 1.00 | | |
| Both | 38 | 8 | 21.1 | 30 | 78.9 | 1.95 | 0.88 | 4.32 |
| Unknown | 89 | 2 | 2.2 | 87 | 97.8 | 0.62 | 0.28 | 1.37 |
| Other Risk Factors | | | | | | | | |
| MDR Contact | 50 | 5 | 10.0 | 45 | 90.0 | 0.69 | 0.28 | 1.75 |
| unknown | 28561 | 3946 | 13.8 | 24615 | 86.2 | 1.00 | | |
| Infectious TB | 2552 | 159 | 6.2 | 2393 | 93.8 | 0.39** | 0.33 | 0.46 |

[19] Self-administered

Table 1: Univariate associations of demographic and clinical risk factors for TB cases with and without DM

| Characteristic | | with DM reported | | DM not reported | | unadj. OR | lower CI | upper CI |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | n | % | n | % | | | |
| contact | | | | | | | | |
| unknown | 26059 | 3792 | 14.6 | 22267 | 85.4 | 1.00 | | |
| Missed contact | 180 | 14 | 7.8 | 166 | 92.2 | 0.52** | 0.30 | 0.91 |
| unknown | 28431 | 3937 | 13.8 | 24494 | 86.2 | 1.00 | | |
| Incomplete LTBI therapy | 860 | 80 | 9.3 | 780 | 90.7 | 0.63** | 0.50 | 0.80 |
| unknown | 27751 | 3871 | 13.9 | 23880 | 86.1 | 1.00 | | |
| TNF-α therapy | 128 | 18 | 14.1 | 110 | 85.9 | 1.02 | 0.62 | 1.68 |
| unknown | 28483 | 3933 | 13.8 | 24550 | 86.2 | 1.00 | | |
| post organ-transplant | 129 | 40 | 31.0 | 89 | 69.0 | 2.82** | 1.94 | 4.11 |
| unknown | 28482 | 3911 | 13.7 | 24571 | 86.3 | 1.00 | | |
| End Stage Renal Disease | 684 | 297 | 43.4 | 387 | 56.6 | 5.10** | 4.37 | 5.95 |
| unknown | 27927 | 3654 | 13.1 | 24273 | 86.9 | 1.00 | | |
| Immunosuppression | 1281 | 227 | 17.7 | 1054 | 82.3 | 1.37** | 1.18 | 1.58 |
| unknown | 27330 | 3724 | 13.6 | 23606 | 86.4 | 1.00 | | |
| Other | 6106 | 850 | 13.9 | 5256 | 86.1 | 1.01 | 0.93 | 1.10 |
| unknown | 22505 | 3101 | 13.8 | 19404 | 86.2 | 1.00 | | |

*2009 data only, ** significant at alpha <0.05

Table 2: Demographic and Clinical Characteristics of Results of Model 1 (Year 2009-2011, no outcome variables), Adjusted Odds Ratios

| Demographic Characteristic | Point Estimate | 95% Wald Confidence Limits | |
|---|---|---|---|
| | | | |
| Sex | | | |
| Male | 1.15 | 1.06 | 1.25 |
| Female | 1 | | |
| Unknown | 0.65 | 0.08 | 5.18 |
| Age (years) | | | |
| 0–4 | <0.001 | <0.001 | >999.999 |
| 5–14 | 1 | | |
| 15–24 | 4.07 | 0.98 | 16.89 |
| 25–44 | 23.64 | 5.86 | 95.46 |
| 45–64 | 92.20 | 22.87 | 371.70 |
| ≥65 | 98.26 | 24.35 | 396.44 |
| Unknown | 18.10 | 1.45 | 225.83 |
| Race/Ethnicity | | | |
| American Indian/Alaska Native | 2.46 | 1.78 | 3.41 |
| Asian | 2.10 | 1.86 | 2.36 |
| Black | 1.45 | 1.27 | 1.65 |
| Hispanic | 3.24 | 2.87 | 3.66 |
| Multiple Races | 2.75 | 1.53 | 4.92 |
| Native Hawaiian/Pacific Islander | 5.50 | 3.69 | 8.18 |
| White | 1.00 | | |
| Unknown | 1.98 | 1.06 | 3.70 |
| Excessive Alcohol Use | | | |
| Yes | 0.70 | 0.62 | 0.79 |
| No | 1.00 | | |
| Unknown | 0.98 | 0.70 | 1.38 |
| Correction facility residence | | | |
| Yes | 0.42 | 0.32 | 0.55 |
| No | 1 | | |
| Unknown | 0.52 | 0.29 | 0.96 |
| Homelessness | | | |
| Yes | 0.69 | 0.57 | 0.83 |
| No | 1 | | |

| | | | |
|---|---|---|---|
| Unknown | 0.79 | 0.47 | 1.33 |
| Occupation | | | |
| Health Care Worker | 1.31 | 1.05 | 1.63 |
| Migrant/Seasonal Worker | 0.86 | 0.61 | 1.21 |
| Retired | 1.38 | 1.21 | 1.58 |
| Not Seeking Employment | 1.31 | 1.14 | 1.49 |
| Correctional Facility Employee | 1.69 | 0.71 | 4.04 |
| Other Occupation | 1.00 | | |
| Unemployed | 1.18 | 1.07 | 1.30 |
| Unknown | 0.86 | 0.68 | 1.08 |
| Clinical Characteristic | | | |
| | | | |
| | | | |
| HIV status | | | |
| Positive | 0.53 | 0.43 | 0.65 |
| Negative | 1 | | |
| Total Unknown | 1.05 | 0.96 | 1.15 |
| Chest radiograph findings | | | |
| Cavitary | 1.35 | 1.22 | 1.49 |
| Noncavitary | 1 | | |
| Unknown | 1.02 | 0.92 | 1.14 |
| CT scan findings | | | |
| Cavitary | 1.52 | 1.34 | 1.71 |
| Noncavitary | 1 | | |
| Unknown | 0.98 | 0.90 | 1.08 |
| Sputum smear result | | | |
| Positive | 1.44 | 1.32 | 1.57 |
| Negative | 1 | | |
| Unknown/not done | 0.89 | 0.79 | 1.02 |
| Disease site | | | |
| Pulmonary | 1 | | |
| Any Extrapulmonary | 0.87 | 0.79 | 0.96 |
| Unknown | 1.25 | 0.15 | 10.17 |
| Other Risk Factors | | | |
| Infectious TB contact | 0.76 | 0.64 | 0.91 |
| unknown | 1 | | |
| incomplete LTBI ther | 0.75 | 0.58 | 0.97 |
| unknown | | | |
| End-Stage Renal Disease | 3.54 | 2.96 | 4.23 |

| | | | |
|---|---|---|---|
| unknown | 1 | | |

Table 3: Demographic and Clinical Characteristics of Results of Model 2 (year 2009 only, includes outcome variables), Adjusted Odds Ratios

| Demographic Characteristic | OR | Lower CI | Upper CI |
|---|---|---|---|
| Sex | | | |
| Male | 1.2 | 1.007 | 1.429 |
| Female | 1 | | |
| Unknown | 1.951 | 0.227 | 16.779 |
| Age (years) | | | |
| 0–4 | <0.001 | <0.001 | >999.999 |
| 5–14 | 1 | | |
| 15–24 | 2.095 | 0.267 | 16.46 |
| 25–44 | 11.242 | 1.532 | 82.493 |
| 45–64 | 44.295 | 6.062 | 323.685 |
| ≥65 | 52.157 | 7.112 | 382.498 |
| Unknown | 18.615 | 0.886 | 390.987 |
| Race/Ethnicity | | | |
| American Indian/Alaska Native | 3.251 | 1.619 | 6.531 |
| Asian | 1.787 | 1.386 | 2.302 |
| Black | 1.317 | 1.023 | 1.695 |
| Hispanic | 2.807 | 2.194 | 3.592 |
| Multiple Races | 2.42 | 0.744 | 7.87 |
| Native Hawaiian/Pacific Islander | 7.883 | 3.769 | 16.486 |
| White | 1 | | |
| Unknown | <0.001 | <0.001 | >999.999 |
| Excessive alcohol use | | | |
| Yes | 0.768 | 0.607 | 0.972 |
| No | 1 | | |
| Unknown | 1.136 | 0.494 | 2.61 |
| Correction facility residence | | | |
| Yes | 0.36 | 0.202 | 0.639 |
| No | 1 | | |
| Unknown | 0.805 | 0.089 | 7.286 |

| | | | |
|---|---|---|---|
| Occupation | | | |
| Health Care Worker | 1.581 | 0.983 | 2.543 |
| Migrant/Seasonal Worker | 0.618 | 0.252 | 1.517 |
| Retired | 1.326 | 0.983 | 1.787 |
| Not Seeking Employment | 1.4 | 1.06 | 1.849 |
| Correctional Facility Employee | 2.35 | 0.552 | 10 |
| Other Occupation | 1 | | |
| Unemployed | 1.094 | 0.888 | 1.349 |
| Unknown | 0.253 | 0.075 | 0.853 |
| Clinical Characteristic | | | |
| HIV status | | | |
| Positive | 0.693 | 0.482 | 0.996 |
| Negative | 1 | | |
| Total Unknown | 0.952 | 0.759 | 1.195 |
| Chest radiograph findings | | | |
| Cavitary | 1.501 | 1.224 | 1.839 |
| Noncavitary | 1 | | |
| Unknown | 1.002 | 0.794 | 1.265 |
| CT scan findings | | | |
| Cavitary | 1.37 | 1.043 | 1.8 |
| Noncavitary | 1 | | |
| Unknown | 1 | 0.806 | 1.24 |
| Sputum smear result | | | |
| Positive | 1.45 | 1.204 | 1.748 |
| Negative | 1 | | |
| Unknown/not done | 1.003 | 0.774 | 1.298 |
| Reason therapy was stopped | | | |
| Completed therapy | 1 | | |
| Moved | <0.001 | <0.001 | >999.999 |
| Lost | 2.219 | 1.357 | 3.628 |
| Died | 0.821 | 0.605 | 1.115 |
| Other/unknown | 0.583 | 0.271 | 1.251 |
| End-Stage Renal Disease | 4.805 | 3.197 | 7.222 |
| unknown | 1 | | |

Table 4: Demographic and Clinical Characteristics of Results of Model 3 (year 2009-2011, restricted to U.S.-born only), Adjusted Odds Ratios

| Demographic Characteristic | OR | 95% Wald Confidence Limits | |
|---|---|---|---|
| Age (years) | | | |
| 0–4 | <0.001 | <0.001 | >999.999 |
| 5–14 | 1 | | |
| 15–24 | 11.16 | 1.50 | 82.78 |
| 25–44 | 53.56 | 7.45 | 384.97 |
| 45–64 | 114.14 | 15.91 | 819.03 |
| ≥65 | 144.29 | 20.11 | >999.999 |
| Unknown | <0.001 | <0.001 | >999.999 |
| Race/Ethnicity | | | |
| American Indian/Alaska Native | 2.33 | 1.68 | 3.23 |
| Asian | 1.10 | 0.63 | 1.92 |
| Black | 1.45 | 1.25 | 1.68 |
| Hispanic | 3.53 | 2.95 | 4.24 |
| Multiple Races | 1.76 | 0.66 | 4.72 |
| Native Hawaiian/Pacific Islander | 4.41 | 2.89 | 6.74 |
| White | 1.00 | | |
| Unknown | <0.001 | <0.001 | >999.999 |
| Excessive alcohol use | | | |
| Yes | 0.65 | 0.55 | 0.76 |
| No | 1 | | |
| Unknown | 0.77 | 0.43 | 1.37 |
| Correction facility residence | | | |
| Yes | 0.58 | 0.41 | 0.84 |
| No | 1 | | |
| Unknown | 0.64 | 0.22 | 1.86 |
| Homelessness | | | |
| Yes | 0.72 | 0.57 | 0.92 |
| No | 1 | | |
| Unknown | 0.79 | 0.32 | 1.97 |
| Clinical Characteristic | | | |
| HIV status | | | |
| Positive | 0.46 | 0.35 | 0.61 |

| | | | |
|---|---|---|---|
| Negative | 1 | | |
| Total Unknown | 1.00 | 0.85 | 1.17 |
| CT scan findings | | | |
| Cavitary | 1.41 | 1.17 | 1.70 |
| Noncavitary | 1 | | |
| Unknown | 1.01 | 0.86 | 1.18 |
| Sputum smear result | | | |
| Positive | 1.20 | 1.04 | 1.38 |
| Negative | 1 | | |
| Unknown/not done | 0.97 | 0.81 | 1.17 |
| Infectious TB contact | 0.74 | 0.58 | 0.95 |
| unknown | 1 | | |
| End-Stage Renal Disease | 2.75 | 2.06 | 3.68 |
| unknown | 1 | | |

Table 5: Demographic and Clinical Characteristics of Results of Model 4 (year 2009-211, restricted to Foreign-born), Adjusted Odds Ratios

| Demographic Characteristic | OR | 95% Wald Confidence Limits | |
|---|---|---|---|
| | | | |
| Sex | | | |
| Male | 1.21 | 1.09 | 1.35 |
| Female | 1 | | |
| Unknown | <0.001 | <0.001 | >999.999 |
| Age (years) | | | |
| 0–4 | <0.001 | <0.001 | >999.999 |
| 5–14 | | | |
| 15–24 | 1.81 | 0.24 | 13.65 |
| 25–44 | 13.29 | 1.85 | 95.61 |
| 45–64 | 57.98 | 8.07 | 416.63 |
| ≥65 | 54.69 | 7.60 | 393.37 |
| Unknown | 20.03 | 1.13 | 355.47 |
| Race/Ethnicity | | | |
| American Indian/Alaska Native | 2.80 | 0.21 | 38.10 |
| Asian | 1.56 | 1.20 | 2.03 |
| Black | 1.49 | 1.12 | 1.99 |
| Hispanic | 1.53 | 1.16 | 2.02 |
| Multiple Races | 2.76 | 1.27 | 6.01 |
| Native Hawaiian/Pacific Islander | 4.40 | 1.76 | 11.02 |
| White | 1.00 | | |
| Unknown | 2.54 | 1.26 | 5.14 |
| Excessive alcohol use | | | |
| Yes | 0.78 | 0.64 | 0.93 |
| No | 1.00 | | |
| Unknown | 0.84 | 0.54 | 1.30 |
| Correction facility residence | | | |
| Yes | 0.28 | 0.18 | 0.44 |
| No | 1 | | |
| Unknown | 0.36 | 0.15 | 0.89 |
| Long term care facility residence | | | |
| Yes | 1.80 | 1.28 | 2.53 |
| No | 1 | | |

| | | | |
|---|---|---|---|
| Unknown | 3.16 | 1.16 | 8.65 |
| Occupation | | | |
| Health Care Worker | 1.21 | 0.92 | 1.59 |
| Migrant/Seasonal Worker | 0.75 | 0.51 | 1.10 |
| Retired | 1.50 | 1.26 | 1.79 |
| Not Seeking Employment | 1.38 | 1.16 | 1.64 |
| Correctional Facility Employee | 0.81 | 0.09 | 7.05 |
| Other Occupation | 1 | | |
| Unemployed | 1.33 | 1.17 | 1.52 |
| Unknown | 0.97 | 0.73 | 1.28 |
| Foreign-Born Top 5 | | | |
| Mexico | 2.26 | 1.90 | 2.70 |
| Philippines | 2.10 | 1.76 | 2.50 |
| Vietnam | 1.00 | 0.81 | 1.23 |
| India | 1.37 | 1.10 | 1.71 |
| China | 0.67 | 0.51 | 0.87 |
| all other foreign-born | 1.00 | | |
| Years in U.S. | | | |
| <1 year | 1 | | |
| 1-4 | 0.89 | 0.73 | 1.07 |
| 5-9 | 1.11 | 0.93 | 1.32 |
| 10-19 | 1.30 | 1.12 | 1.51 |
| >=20 | 1.45 | 1.27 | 1.66 |
| | | | |
| Clinical Characteristic | | | |
| | | | |
| | | | |
| HIV status | | | |
| Positive | 0.55 | 0.40 | 0.74 |
| Negative | 1 | | |
| Total Unknown | 1.03 | 0.92 | 1.15 |
| Chest radiograph findings | | | |
| Cavitary | 1.46 | 1.29 | 1.66 |
| Noncavitary | 1 | | |
| Unknown | 0.98 | 0.84 | 1.13 |
| CT scan findings | | | |
| Cavitary | 1.65 | 1.41 | 1.93 |
| Noncavitary | 1 | | |
| Unknown | 0.98 | 0.87 | 1.11 |

| | | | |
|---|---|---|---|
| Sputum smear result | | | |
| Positive | 1.60 | 1.43 | 1.79 |
| Negative | 1 | | |
| Unknown/not done | 0.84 | 0.71 | 1.00 |
| Disease site | | | |
| Pulmonary | 1 | | |
| Any Extrapulmonary | 0.79 | 0.69 | 0.90 |
| Unknown | <0.001 | <0.001 | >999.999 |
| Other Risk Factors | | | |
| Infectious TB contact | 0.75 | 0.57 | 0.98 |
| unknown | 1 | | |
| incomplete LTBI therapy | 0.63 | 0.43 | 0.93 |
| unknown | 1 | | |
| End-Stage Renal Disease | 3.93 | 3.11 | 4.96 |
| unknown | 1 | | |
| immunosuppression | 0.78 | 0.62 | 0.97 |
| unknown | 1 | | |

## Chapter III: Conclusion

This study found several risk factors both positively and negatively associated with TB-DM among TB cases in the United States. TB cases with higher age, non-white race, and ESRD were consistently found to have significantly higher odds of having comorbid DM in all models analyzed. Steps should be taken to develop adequate care and treatment regimens for TB cases with DM.

Future studies should look to confirm the relationships between risk factors studied here with populations that include cases without TB and with or without DM. Done prospectively, such studies could provide evidence for the directionality of the TB-DM relationship. The effectiveness of screening vulnerable TB cases for DM should also be assessed.

EMORY UNIVERSITY | Institutional Review Board

November 5, 2012

**RE: Determination: No IRB Review Required**
**"Tuberculosis among persons with Diabetes Mellitus in the United States 2009–2011"**

Dear Kristen Renneker:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition(s) of "research" involving "human subjects" or the definition of "clinical investigation" as set forth in Emory policies and procedures and federal rules, if applicable.

Based on the information included in the submission, you will be analyzing a data set that was collected by the CDC about tuberculosis and diabetes mellitus afflicted individuals in the United States. This data set, while not publically available, also contains no identifiers. Also, note that access to this data set should be approved by your thesis advisor/committee and no attempt should be made to identify any subjects within the data set. As such, this project does not represent "human subjects" based research, and the IRB has determined that this study does not constitute "human subjects research" under the foregoing definition.

This determination could be affected by substantive changes in the study design or subject population. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Aric Edwards, BA
IRB Analyst Assistant
*This letter has been digitally signed*