INCIDENCE, RISK FACTORS AND DIAGNOSTIC TEST PERFORMANCE FOR TUBERCULOSIS AMONG IMMIGRANTS IN GEORGIA

by

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(Under the Direction of Mark H. Ebell)

ABSTRACT

BACKGROUND: The proportion of active tuberculosis (TB) cases occurring in foreign-born persons has been increasing since 1993 in the United States (U.S.). Foreign born persons have accounted for the majority of TB cases in the U.S. every year since 2001. In 2010, 60% of TB cases occurred in foreign born persons. This study measured the annual incidence rate for TB disease among the immigrant population in Georgia and identified risk factors for latent TB infection.

METHODS: Georgia Department of Public Health (GDPH) data from 2004 to 2016 and National Health and Nutrition Examination Survey (NHANES) data from 1999-2000 and 2011-2012 were analysed. The Kaplan-Meier (KM) method was utilized to assess time to diagnosis rates and the median time. The effect of Bacille Calmette Guerin (BCG) vaccination on latent tuberculosis infection (LTBI) diagnosis was assessed. Kappa statistics

and mixture method analysis were used to analyze the data for tuberculin skin tests (TST) results.

RESULTS: GDPH data included 5,315 TB cases from 2004 to 2016. There were 2,240 (42.2%) immigrants in the dataset. Immigrants were more likely to be diagnosed with TB disease compared to non-immigrants (IRR= 6.9; 95%CI: 6.8 - 6.9) in Georgia for the years 2004 to 2016. Median time in years for immigrants from date of entry in to the U.S. to diagnosis was 8.4 years (n=1,652; 95% CI: 7.7 - 9.2). There was no significant risk reduction for long term to be diagnosed with TB infection by receiving BCG vaccination (RR=2.78, 95%CI: 2.21 – 3.50). Immigration status and age were confounding variables. There was moderate overall agreement beyond that expected by chance alone between Quantiferon and TST test when used in diagnosis of LTBI (Kappa statistic= 0.447; 95%CI: 0.395 - 0.498).

CONCLUSION: The results showed that immigrant status/location of origin is associated with an increased risk of TB/LTBI in the U.S. population. This was confirmed from three different datasets for different time periods. Results revealed the need for better surveillance and control methods to eradicate this global epidemic.

ABSTRACT WORD COUNT: 329/350

INDEX WORDS: Tuberculosis, M. tuberculosis, tuberculin skin test, mixture modelling, immigration, epidemiology, tuberculin test

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DEDICATION

I dedicate this work to my loving wife, Daison, my daughter, Amita, my son, Austin, my father, late Mr. Joshua, my mother, Thankamma, my brothers Paul, Jacob, Varghese, sister Suja, families, relatives, and friends who have been a constant source of encouragement.

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CHAPTER 1

INTRODUCTION

It is estimated that nearly one third of the world's population, 2 billion people, are infected with tuberculosis (TB) bacteria, *Mycobacterium tuberculosis (Mtb)*. In 2014, 9.6 million people around the world became sick with TB disease. There were 1.5 million TB-related deaths worldwide according to data from Centers for Disease Control (CDC) based in Atlanta, U.S. and the World Health Organization (WHO) [1]. Research shows that active TB disease is a leading cause of death among people who are infected with human immunodeficiency virus (HIV). TB typically exhibits itself in the patient's lungs which is known as pulmonary TB. However, extra pulmonary TB can live effectively anyplace in the body [2]. Active TB or TB disease was used interchangeably in the literature for active tuberculosis disease (TB). Latent Tuberculosis infection (LTBI) is defined as the TB infection stage where the infection is contained in a granuloma and not progressed to active TB disease.

The primary mode of TB transmission is airborne through infected droplet nuclei which are expelled when someone breathes, coughs, sings or otherwise exhales. The immune system will attack the *Mtb* upon inhalation. Depends on the health of the person combined with the virulence of the

inhaled bacteria and the frequency of exposure, the bacteria may reach the lungs' alveoli and infect the individual. The bacteria may travel to other parts of the body and/or will be attacked by the immune system forming a granuloma. A granuloma is a small area of inflammation in tissue. Granulomas occur in the lungs as the result of an infection and the granuloma is the pathologic hallmark of TB. The primary cellular component of the granuloma is the macrophage. A spectrum of granuloma types is observed in both active and latent TB in human TB. If the infection is contained in a granuloma, the individual is said to have a latent TB infection (LTBI). This infection may remain latent for the duration of the individual's life or may progress to active TB disease [3]. TB was one of the leading cause of death in the early 19th century in Europe and earned the name, "the white plague". Economic development in the world led to better nutrition and easing of crowding, which helped to reduce TB incidence rates [4].

In 2015, an estimated 10.4 million people around the world fell ill with TB disease, including 1.2 million cases among people with HIV, according to the WHO. Most people who are infected with *Mtb* have LTBI and they harbour the bacterium without symptoms and some will develop active TB disease. It is estimated that approximately 10% of people who are with LTBI will develop active TB at some time in their lives [6]. The risk of developing active disease after infection is greatest in the first year. Also, active disease may not occur until many years later. TB incidence rates vary by well-known

factors such as age, race and ethnicity, and country of origin. Minorities are affected disproportionately by TB. TB occurs more often among foreign-born individuals than among people born in the U.S. This is partially because they were more likely to be exposed to *Mtb* in their country of origin before moving to the U.S. [7].

TB threatens HIV-infected patients before and after start of antiretroviral therapy (ART). TB is challenging to diagnose and quickly fatal when it is drug resistant. Traditional TB diagnostic tests are less sensitive and specific for patients with advanced immune suppression. The consequences of poor diagnostic tests for TB prevention and control are immense because a large number of TB patients may remain undiagnosed and untreated. Drug interactions between rifampin and HIV nonnucleoside reverse transcriptase inhibitors and protease inhibitors create the greatest challenge in the choice of ART regimen for HIV-infected patients with TB [8].

The proportion of total TB disease cases occurring in foreign-born persons has been increasing since 1993 in the U.S. In 2010, 60% of TB cases occurred in foreign-born persons, compared with 34.2% in 1992 [9]. Foreign-born persons have accounted for the majority of TB cases in the U.S. every year since 2001. Moreover, according to the CDC, in 2010 the incidence rate among foreign born persons was approximately 11 times higher than among U.S. born persons [10].

TB Incidence in the U.S.

The annual incidence rate of TB in the U.S. remained approximately 3.0 cases per 100,000 persons during the years of 2013 to 2015. Preliminary data reported to the National Tuberculosis Surveillance System (NTSS) indicated that TB incidence among foreign-born persons in the U.S. (15.1 cases per 100,000 persons per year) has remained approximately 13 times higher the incidence among U.S. born persons (1.2 cases per 100,000 persons per year). Health departments in the 50 states and District of Columbia (DC) electronically report verified TB cases to the NTSS. This is based on the guidelines that meet the CDC and Council of State and Territorial Epidemiologist's (CSTE) case definition [10].

According to the CDC, 11,182 TB cases (a rate of 3.6 cases per 100,000 persons per year) were reported in the U.S. in 2010. Both the number of TB disease cases reported and the incidence rate decreased, representing a 3.1% and 3.8% decline compared to those of 2009. According to the Georgia Department of Public Health (GDPH), 2014 Georgia Tuberculosis Report, published in October 2014, active TB disease is a reportable disease in Georgia. Georgia reported 334 new TB disease cases in 2014, a rate of 3.3 cases per 100,000 persons per year. This represents a 1.1% decrease from 339 TB disease cases reported in 2013. There were 321 new TB cases in 2015 in Georgia, a rate of 3.1 cases per 100,000 persons per year [11].

In many individuals, LTBI is the initial infection. The disease may remain dormant within the body with the immune system capable of containing the infection. There is reactivation of the infection when the immune system weakens for some reason (e.g. HIV infection, diabetes, renal disease etc.). When immunity is suppressed, the risk of this reactivation rises. People with simultaneous HIV infection have an increased risk of reactivation of tuberculosis of 10% per each year of infection. Some predictors of a poorer prognosis include age and other medical conditions which will increase the risk of TB disease. Risk of TB is increasing with age but children are at high risk if they have contact with active TB disease case. Medical conditions include infection with HIV, diabetes mellitus, low body weight, head or neck cancer, leukaemia, Hodgkin's disease, medical treatments including corticosteroids and autoimmune disease, and respiratory disease like silicosis. In Africa, TB mainly affects young adults and teenagers and in some developed countries such as U.S. and Britain, TB mainly affects the elderly [12].

U.S. born Person Definition

Persons born in U.S. are defined as persons born in the U.S., American Samoa, the Federated States of Micronesia, Guam, the Republic of the Marshall Islands, the Commonwealth of the Northern Mariana Islands, Puerto Rico, the Republic of Palau, the U.S. Virgin Islands, U.S. minor outlying islands, or persons born elsewhere to a U.S. citizen. Race and

ethnicity is self-identified. Persons of Hispanic and non-Hispanic ethnicity might be of any race or multiple races. The CDC calculates state and overall national TB incidence by using July 1st midyear population estimates from the U.S. Census Bureau [13, 14].

In 2015, most U.S. born persons diagnosed with TB were either non-Hispanic blacks (1,144 cases) or non-Hispanic whites (991 cases). Among U.S.-born non-Hispanic blacks, TB incidence was at an all-time low (3.3 cases per 100,000 persons per year). TB incidence among U.S. born non-Hispanic whites remained the lowest (0.5 cases per 100,000 persons per year). Although U.S. born Hispanics had the third highest case count (661 cases), they had the second lowest annual incidence rate (1.8 cases per 100,000 persons per year). U.S. born Native Hawaiians/other Pacific Islanders had the highest incidence (12.7 cases per 100,000 persons per year), followed by U.S. born American Indians/Alaska Natives (6.8 cases per 100,000 persons per year). A total of 344 TB cases occurred among U.S. born persons aged <15 years (0.6 cases per 100,000 persons per year), representing 10.7% of all U.S. born persons reported as having incident TB in 2015 [11].

TB in Foreign-born Persons in the U.S.

As per a CDC report, in 2015, among foreign-born persons with reported TB cases in the U.S., Asians had both the highest case count (3,007 cases) and highest incidence (28.2 cases per 100,000 persons per year). The top five countries of origin for foreign-born persons with TB were Mexico

(1,250; 19.7%), the Philippines (819; 12.9%), India (578; 9.1%), Vietnam (513; 8.1%), and China (424; 6.7%). Together, these countries represent 45.2% of the foreign-born population in the U.S., but accounted for 56.6% (3,584 cases) of all TB disease cases among foreign-born persons [11].

Two thirds of all U.S. TB disease cases occur among foreign-born persons within less than three years after arrival. This is consistent with disease progression following years of untreated LTBI. Epidemiologic modelling shows that eliminating the threat of TB in the U.S. will require additional strategies to reduce TB in the countries of origin. Also, it will require expanded treatment of LTBI among the foreign-born immigrants in the U.S. Despite recent declines in TB incidence among foreign-born persons, these persons continue to have a higher risk for TB. It is necessary to intensify the global fight against TB and execute interventions to screen and treat U.S.-bound immigrants and refugees for TB disease. TB elimination will require global interventions, as well as improvement in identification and treatment of LTBI among foreign-born persons living in the U.S. This approach is consistent with CDC's strategic plan for the national elimination of TB in the U.S. [10, 15].

The U.S. Immigrant Population

According to the U.S. Census Bureau's 2014 American Community Survey (ACS), the U.S. documented immigrant population stood at more than 42.4 million, or 13.3%, of the total U.S. population of 318.9 million in

2014. Between 2013 and 2014, the foreign-born population increased by 1 million, or 2.5%. Documented immigrants in the U.S. and their U.S.-born children number approximately 81 million people, or 26% of the overall U.S. population. In 2014, 1.3 million foreign-born individuals moved to the U.S., an 11% increase from 1.2 million in 2013. In 2014, India was the leading country of origin for new immigrants, with 147,500 arriving, followed by China with 131,800, Mexico with 130,000, Canada with 41,200, and the Philippines with 40,500[5].

TB disease cases among persons born outside of the U.S. accounted for 45% of TB cases identified in Georgia in 2014 compared to 51% in 2013. Most foreign-born cases reported in 2014 were diagnosed in immigrants from Mexico (19%), Vietnam (16%), and India (10%), all countries where TB is an endemic disease. Among 150 TB cases identified in Georgia among foreign-born TB cases, 43 (29%) were diagnosed in the first five years of their arrival in the U.S [16].

BCG Vaccine

The BCG vaccine was first used in 1921 and is still the only vaccine currently available against TB. It is a live weakened strain of *Mycobaterium bovis*. The effect of BCG immunization on tuberculin reactivity varies with age and has a tendency to be more prominent for young adults. This population is likely to be most at risk for a positive TST result not related to *Mtb* infection but to BCG vaccination. BCG is not an ideal vaccine and has

two major limitations. BCG exhibits highly variable effectiveness against the development of TB both in pediatric and adult populations and can cause disseminated BCG disease in immunocompromised individuals [17, 18].

Latent TB Infection

Latent TB infection (LTBI) is a state of persistent immune response to stimulation by *Mtb* antigens without evidence of clinically manifested (symptomatic) active TB disease. A direct measurement tool for *Mtb* infection in humans is currently unavailable. One-third of the world's population is estimated to have LTBI. They do not have active TB disease but may develop it in the near or remote future, a process called "TB reactivation." [19]

TB Disease Diagnosis

In some people, TB bacteria overcome the defences of the immune system and begin to multiply, resulting in the progression from LTBI to active TB disease. People with active TB disease usually have symptoms and may spread TB bacteria to others. TB bacteria most commonly grow in the lungs, and can cause symptoms such as a bad cough that lasts 3 weeks or longer, pain in the chest, and coughing up blood or sputum from the lungs. Other symptoms of TB disease may include weakness or fatigue, weight loss, no appetite, chills, fever, sweating at night [20].

There are two types of tests that are used to detect TB bacteria in the body. They are TB skin test (TST) and TB blood tests. A positive TB skin test or positive TB blood test only reveals that a person has been infected

with TB bacteria. The TST is also called the Mantoux tuberculin skin test. A TB skin test requires two visits with a health care provider. The test is placed on the first visit and on the second visit 48 to 72 hours later the health care provider reads the test. It does not indicate whether the person has LTBI or has progressed to TB disease. Additional tests are needed to determine if the person has LTBI or TB disease. Active TB disease is diagnosed by medical history, physical examination, chest x-ray, a sample of sputum, and other laboratory tests [21].

TB Screening

The primary priority to prevent the spread of TB infection is the treatment of persons with active TB disease. A secondary priority is the identification and treatment of persons with LTBI, particularly in developed countries where there is a lower incidence of the disease. The goal of screening for LTBI is to detect individuals who are at increased risk for developing TB infection and who would benefit from treatment of the infection. Some of the groups who will benefit from TB screening are immigrants, persons infected with HIV, healthcare workers who had recent contact with someone has active TB, patients with underlying medical conditions such as diabetes mellitus and lymphomas. It is necessary to make a decision before testing for TB to treat the individuals who may tested positive [22, 23].

TB Blood Tests

TB blood tests are also called interferon-gamma release assays (IGRAs). Two TB blood tests are approved by the U.S. Food and Drug Administration (FDA) and are available in the U.S. They are the QuantiFERON®–TB Gold In-Tube test (QFT-GIT) and the T-SPOT®.TB test (T-Spot). For QFT, FDA approved overall sensitivity is 94% and specificity is 98% [24]. For T-SPOT, sensitivity is 95.0% and 99.0% specificity after exclusion of borderline results [25]. Positive TB blood test means that the person has been infected with TB bacteria. It is necessary to conduct additional tests to determine if the person has latent TB infection or TB disease. A negative TB blood test means that the person's blood did not react to the test and that LTBI or TB disease is not likely. TB blood tests are the preferred TB test for people who have received the TB vaccine BCG and people who have a difficult time returning for a second appointment to look for a reaction to the TST. If a person has TB symptoms, but a negative test result, they should still be evaluated for TB disease using chest X-ray and sputum [23, 26-28].

TB Control Methods

Diagnosing TB cases as early as possible during the illness will allow earlier airborne precautions and curative treatment to interrupt transmission. This will help to control the TB effectively. Also, an early diagnosis of a patient with active TB allows a timely contact investigation to

detect and prevent additional TB cases. Children with recently infected contacts benefit significantly from treatment to avoid progression to active TB. TB prevention, timely diagnosis, and treatment completion are necessary for all age groups. This method is more important for groups disproportionally affected by TB. Since 2003, TB incidence among Native Hawaiians/other Pacific Islanders and American Indians/Alaska Natives has remained high despite declining incidence among Hispanics and non-Hispanic Asians, whites, and blacks [11].

Table 1: Five Steps for Patient Management to Prevent Transmission of TB in Health Care Settings (WHO guidelines) [29]

Step	Action	Description
1	Screen	Early identification of TB suspects or confirmed TB patients can be achieved by assigning a health worker to screen patients for prolonged cough immediately they arrive at the facility. TB suspects or patients on TB treatment should be separated from other patients.
2	Educate	Instruct all patients with chronic cough on cough hygiene i.e. covering the nose and mouth when coughing or sneezing, o Where possible provide face masks or tissues to assist them in covering their mouths. Educate on safe sputum disposal methods
3	Separate	TB suspects and patients must be separated from other patients Keep them in a separate well ventilated waiting area, Where possible provide face masks or tissues to cover their mouths and noses while waiting.
4	Investigate for TB or refer	TB diagnostic tests should be done onsite or, if not available, the facility should have an established link with a TB diagnostic center to which symptomatic patients can be referred. Each facility should have a linkage with a TB treatment center to which those who are diagnosed with TB can be referred.
5	Monitor and evaluate	Monitor and evaluate the TB prevention plan

A collective effort of infection prevention control practices is required for the prevention of TB in the community and hospitals. Isolating TB patients from others those who do not have disease is necessary in this prevention effort. It is crucial to strengthen infection prevention because despite the patients being isolated, there are people who constantly come into contact with the TB patients. TB Patients should be managed on outpatient basis in the hospital whenever possible. This should apply to all TB patients including those who are not too sick to require hospitalization [30].

TB is preventable, treatable, and curable, and its elimination would have widespread health, economic, and social benefits. TB incidence reduction will require more comprehensive public health approaches, both globally and nationally. These include increasing case detection and cure rates globally, reducing TB transmission in institutional settings such as health care settings and correctional facilities, and increasing detection and treatment of pre-existing LTBI among the U.S. populations most affected by TB. More emphasis should be placed on interrupting the relatively limited, but persistent, ongoing TB transmission among persons experiencing homelessness in the U.S. Also, continuing research on better methods to diagnose, treat, and prevent TB infection and disease is vital [31].

The overall goal of this study was to assess the burden of TB disease among the immigrant population in Georgia within 5 years of their arrival to the U.S., and determine the risk factors for active TB disease in this

population. The first aim was to determine the active TB disease incidence among the immigrant population in Georgia. The second aim was to determine the risk factors of incident active TB disease among the immigrant population in Georgia. The third aim has two parts. The first part was to determine whether BCG vaccination affects the results or interpretation of TST for LTBI in the U.S. population. The second part of aim three was to assess LTBI in the U.S. population using TST measurement and QFT.

SPECIFIC AIMS, OBJECTIVES

Research Question

What is the incidence rate of active TB disease among the immigrant population in Georgia, and what are the distribution of known risk factors for active TB disease in this population?

Specific Aims

1. To determine the annual incidence rate for active TB disease in the immigrant population in Georgia after their arrival to the U.S.

   H_0: There is no difference in the annual incidence rate for active TB disease between immigrants and non-immigrants in Georgia.

   H_1: There is a difference in the annual incidence rate for active TB disease between immigrants and non-immigrants in Georgia.

2. To describe the distribution of known risk factors for incident active TB disease among the immigrant population compared to non-immigrants in Georgia.

   H_0: The distribution of known risk factors does not differ between immigrants and non-immigrants with active TB disease in each group.

   H_1: The distribution of known risk factors does differ between immigrants and non-immigrants with active TB disease in each group.

3. To assess latent tuberculosis infection (LTBI) in the U.S. population.

a). To determine whether bacille Calmette-Guerin (BCG) vaccination affects the results of the tuberculin skin test (TST) for LTBI in the U.S. population.

   H_0: BCG vaccination is not associated with the results of TST for LTBI in the U.S. population.

   H_1: BCG vaccination is associated with the results of TST for LTBI in the U.S. population.

b). To compare TST and Quantiferon diagnostic measurements for LTBI in the U.S. population

   H_0: There is no difference between TST and Quantiferon diagnostic accuracy in assessing LTBI in the U.S. population.

   H_1: There is a difference between TST and Quantiferon diagnostic accuracy in assessing the LTBI in the U.S. population.

Table 2: Aims, Objectives, Data Sources, and Methods

Aim	Objectives	Data Sources	Methods
1	To determine the annual incidence rate for active TB disease in the immigrant population in Georgia after their arrival to the U.S.	Georgia Department of Health	Secondary data analysis. Estimate the incidence of TB disease among immigrants by calculating the proportion with a positive diagnostic test.
2	To describe the distribution of known risk factors for incident active TB disease among the immigrant population compared to non-immigrants in Georgia.	Georgia Department of Health	Secondary data analysis. Relative risks and odds ratios. Stratified analysis by region/country of origin and logistic regression. Kaplan-Meir survival analysis.
3	To assess latent tuberculosis infection (LTBI) in the U.S. population. a). To determine whether bacille Calmette-Guerin (BCG) vaccination affects the results of the tuberculin skin test (TST) for LTBI in the U.S. population. To compare TST and Quantiferon measurements for LTBI in the U.S. population	NHANES Data 1999-2000 and 2011-2012 data	Secondary data analysis. Descriptive statistics will be used to present the characteristics of the participants. Percent agreement and Kappa method will be used to determine the concordance between the Quantiferon Test and TST test. Mixture method analysis will be used to analyse the TST results.

REFERENCES

1. CDC. Reported tuberculosis in the United States, 2014. Atlanta, GA: US Department of Health and Human Services, CDC; 2015. http://www.cdc.gov/tb/statistics/reports/2014/default.htm
2. Lee JY. Diagnosis and treatment of extra pulmonary tuberculosis. *Tuberc Respir Dis (Seoul)*. 2015;78(2):47-55.
3. Ehlers S, Schaible UE. The granuloma in tuberculosis: dynamics of a host-pathogen collusion. *Front Immunol*. 2013;3:411. Published 2013 Jan 7. doi:10.3389/fimmu.2012.00411.
4. .Falzon D, Ait-Belghiti F. What is tuberculosis surveillance in the European Union telling us? Clin Infect Dis. 2007; 44 (10):1261–7. doi: 10.1086/514343.
5. Jie Zong, Jeanne Batalova. Frequently Requested Statistics on Immigrants and Immigration in the United States. http://www.migrationpolicy.org/article/frequently-requested-statistics-immigrants-and-immigration-united-states. Accessed on October 2016.
6. Global Tuberculosis Report 2015. (20th edition) (2015; 204 pages); http://apps.who.int/medicinedocs/en/d/Js22199en/. Accessed on October 1, 2016

7. Talbot, EA & Moore, M & McCray, E & J Binkin, N. (2001). Tuberculosis Among Foreign-Born Persons in the United States, 1993-1998. JAMA: the journal of the American Medical Association. 284. 2894-900.

8. Chamie G, Luetkemeyer A, Charlebois E, Havlir DV. Tuberculosis as part of the natural history of HIV infection in developing countries. *Clin Infect Dis*. 2010;50 Suppl 3(Suppl 3):S245-54.

9. Morbidity and Mortality Weekly Report (MMWR). February 8, 2002 / 51(05);101-4. Accessed on July 20, 2019. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5105a3.htm

10. Stewart RJ, Tsang CA, Pratt RH, Price SF, Langer AJ. Tuberculosis — United States, 2017. MMWR Morb Mortal Wkly Rep 2018;67:317–323. DOI: http://dx.doi.org/10.15585/mmwr.mm6711a2

11. Salinas JL, Mindra G, Haddad MB, Pratt R, Price SF, Langer AJ. Leveling of Tuberculosis Incidence — United States, 2013–2015. MMWR Morb Mortal Wkly Rep 2016;65:273–278. DOI: http://dx.doi.org/10.15585/mmwr.mm6511a2. Accessed on March, 2016.

12. American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000; 161:1376–95.

13. Oren E, Winston CA, Pratt R, Robison VA, Narita M. Epidemiology of urban tuberculosis in the United States, 2000-2007. *Am J Public Health*. 2011;101(7):1256-63.

14. Immigration Policy at the Edges: International Migration to and Through the U.S. Island Territories. Accessed on December 2016. https://cis.org/Report/Immigration-Policy-Edges-International-Migration-and-Through-US-Island-Territories.

15. Parmer J, Allen L, Walton W. CE: Tuberculosis: A New Screening Recommendation and an Expanded Approach to Elimination in the United States. *Am J Nurs*. 2017;117(8):24-34.

16. 2014 Georgia Tuberculosis Report. Accessed on March 2016. https://dph.georgia.gov/sites/dph.georgia.gov/files/2014%20GA%20TB%20Report%20FINAL3.pdf

17. Bacille Calmette Guerin (BCG) Vaccine. http://www.cdc.gov/tb/publications/factsheets/prevention/bcg.htm. Accessed on October 1, 2016

18. BCG Vaccine. Accessed on October 1, 2016. https://www.cdc.gov/tb/publications/factsheets/prevention/bcg.htm

19. Kiazyk S, Ball TB. Latent tuberculosis infection: An overview. *Can Commun Dis Rep*. 2017;43(3-4):62-66. Published 2017 Mar 2.

20. Tuberculosis (TB) Disease: Symptoms and Risk Factors. Accessed on October 1, 2016. https://www.cdc.gov/features/tbsymptoms/index.html.

21. Testing for Tuberculosis (TB). Accessed on October 1, 2016. https://www.cdc.gov/tb/publications/factsheets/testing/tb_testing.htm.

22. Jin J. Screening for Latent Tuberculosis. *JAMA.* 2016;316(9):1004. doi:10.1001/jama.2016.12212

23. Ayub A, Yale SH, Reed KD, Nasser RM, Gilbert SR. Testing for latent tuberculosis. *Clin Med Res*. 2004;2(3):191-4.

24. Accessed on July 20, 2019. https://www.who.int/tb/areas-of-work/preventive-care/ltbi/mk.pdf?ua=1.

25. Accessed on July 20, 2019. http://www.oxfordimmunotec.com/international/products-services/patients/why-choose-t-spot-tb/.

26. QuantiFERON-TB Gold (QFT). http://www.quantiferon.com/us/products/quantiferon-tb-gold. Accessed on April 4, 2018.

27. T-SPOT.TB TEST. http://www.tspot.com. Accessed on April 4, 2018.

28. Mazurek GH, Jereb JA, Vernon A, LoBue P, Goldberg S, Castro KG. Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection, United States, 2010. MMWR Recomm Rep. 2010;59(RR05);1–25

29. Tuberculosis Infection Control in the era of Expanding HIV care and Treatment. Addendum to WHO Guidelines for the Prevention of Tuberculosis in Health Care Facilities in Resource-Limited Settings,

1999. http://www.who.int/tb/publications/2006/tbhiv infectioncontroladdendum.pdf. Accessed September 19, 2018)

30. Implementing the WHO Stop TB Strategy: A Handbook for National Tuberculosis Control Programmes. Geneva: World Health Organization; 2008. 6, Infection control in health-care settings. Available from: https://www.ncbi.nlm.nih.gov/books/NBK310742/. Accessed on March, 2016.
31. Hargreaves JR, Boccia D, Evans CA, Adato M, Petticrew M, Porter JD. The social determinants of tuberculosis: from evidence to action. *Am J Public Health*. 2011;101(4):654-62.

CHAPTER 2

LITERATURE REVIEW

Almost 2 billion people, equal to one third of the world's population, are thought to be infected with the TB bacteria, *Mycobacterium tuberculosis (Mtb)*. In 2014, 9.6 million people around the world became infected with TB disease. There were also 1.5 million TB related deaths worldwide according to Centers for Disease Control (CDC) and World Health Organization (WHO) [1 - 3]. Prior research shows that TB is a leading cause of death for people who are co-infected with HIV.

Active TB disease results from infection caused by *Mtb*. It usually reveals itself in the patient's lungs, known as pulmonary TB disease. TB disease located anywhere in the body outside the lungs is called extra pulmonary TB disease. TB disease was a leading cause of death in the early 19th century in Europe and earned the name, "the white plague". Economic development 20th century in most part of the world led to improved nutrition and easing of crowding, and TB infection rates began to fall globally [4].

In 2010, an estimated 8.8 million people infected with TB disease, including 1.1 million cases among people with HIV, according to the WHO. Research shows that one in ten people who are infected with *Mtb* will develop in to active TB disease at some time in their lives. The risk of

developing active TB disease is greatest in the first year after infection, but active disease often does not occur until many years later. TB disease incidence rates vary by well-known risk factors such as age, race, ethnicity, and country of origin. In the U.S, the incidence of TB disease is higher in persons born in foreign countries than among people born in the U.S. [5]. The next sections of this chapter will address the epidemiology of TB disease globally, in the U.S, and in the state of Georgia.

Global Epidemiology of TB

TB remains a major public health concern worldwide even though there has been a regular slow decline in incidence over the last decade. An estimated 8.6 million new cases and 1.3 million deaths have occurred in 2012. TB is a poverty-related disease, mainly affecting the most vulnerable populations in the poorest countries worldwide. One of the major challenges for TB control is the presence of multidrug-resistant strains of *Mtb* in most countries with high prevalence. Early TB case detection in resource-constrained settings and in marginalized groups remains a challenge. It is estimated that about 3 million people remain undiagnosed or not notified and are therefore untreated worldwide. WHO has launched a new global TB strategy for the "post-2015 era" aimed at "ending the global TB epidemic" by 2035. This strategy is based on the three pillars that give emphasis to patient centered TB care and prevention, prioritize bold policies and supportive systems, and push intensified research and innovation [1, 6].

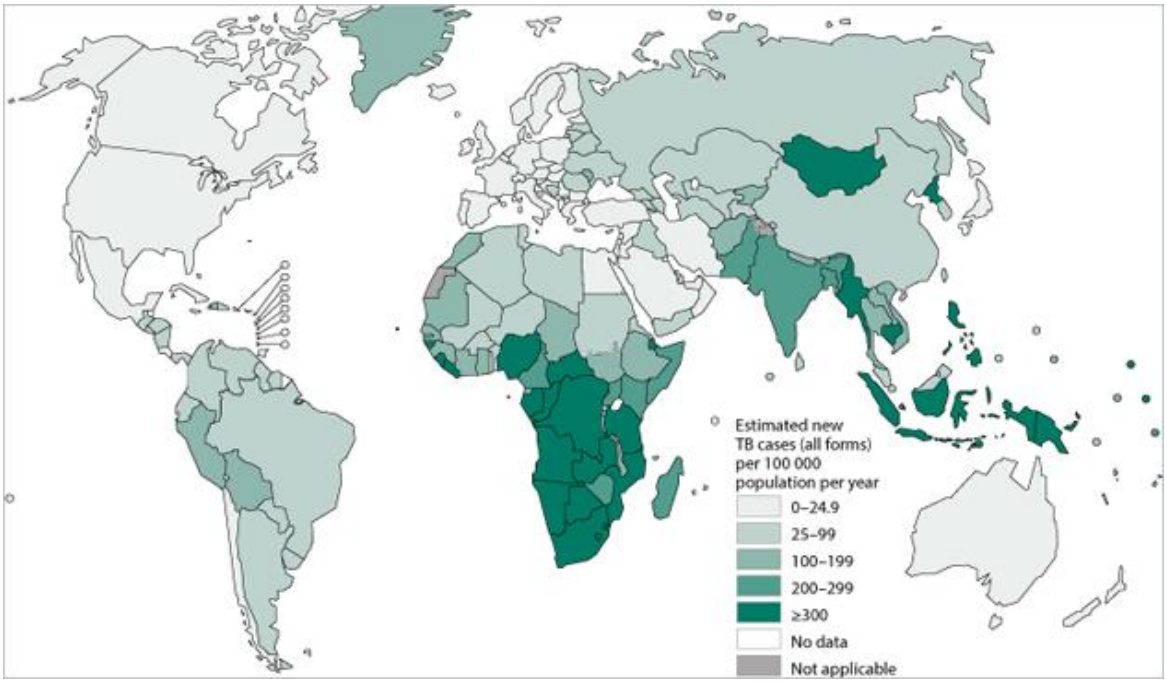

Figure 1: Global TB report 2016: Map of TB incidence; WHO [7]

According to the WHO, about 8.6 million cases (8.3–9.0 million) were estimated to have occurred in 2012 globally, approximately 2.9 million of whom were in women. Figure 1 is taken from the WHO global report 2016 that shows the global active TB incidence. Most cases are estimated to be in Asia and Africa, 58% and 27% respectively, with the highest incidence in India (2.0–2.4 million) and China (0.9 −1.1 million), together accounting for 38% of the total number of cases. The global TB incidence rate slowly declined from 1997 to 2001, with an increase in 2001 due to the rising number of cases among HIV-infected patients in Africa. Subsequently, 1.3% per year average reduction rate has been observed since 2002, reaching 2.2%

between 2010 and 2011. The absolute number of cases is also currently decreasing, though this declining trend only began in 2006 [1, 7].

The 20th global report on TB was published by WHO in 2015, part of a series that began in 1997 [1]. It provides a comprehensive and up-to-date assessment of the TB epidemic and progress in implementing and financing TB prevention, care, control and research at global, regional and country levels. Data reported by more than 200 countries that account for more than 99% of the world's TB cases were used in this assessment. Particular attention was given to the assessment of whether 2015 global TB targets set in the context of the Millennium Development Goals (MDGs) were achieved worldwide and at regional and country levels. Using data from 205 countries and territories, this global TB report documents advances in prevention, diagnosis and treatment of the disease. It also detects areas where efforts can be reinforced or improved [1, 7 - 9].

According to WHO's report, overall TB disease mortality worldwide has fallen 47% since 1990 when the MDGs were set, with nearly all of that improvement taking place from the year 2000 onward. Effective diagnosis and treatment of TB saved an estimated 43 million lives between 2000 and 2014. The aim of the MDGs to decrease active TB disease incidence has been achieved on a worldwide basis, in each of the six WHO regions and in 16 of the 22 high-burden countries that collectively account for 80% of TB cases. Globally, TB disease incidence has fallen by an average of 1.5% per year

since 2000 and is in 2015, 18% lower than the level in 2000. The 2015 report describes higher global totals for new TB disease cases than in previous years, but these reflect increased and improved national data rather than any increase in the spread of the disease. Despite these advances and despite the fact that nearly all cases can be cured, TB remains one of the world's leading threats among infectious diseases. In 2014, TB killed 1.5 million people globally of whom 1.1 million were HIV-negative and 0.4 million were HIV-positive. This include 890,000 men, 480,000 women and 140,000 children and shows the seriousness of the TB disease burden globally [1, 7].

TB now ranks alongside HIV as a leading cause of death worldwide. HIV's death toll in 2014 was estimated at 1.2 million, which included the 0.4 million TB deaths among HIV positive persons. Worldwide, 9.6 million people were estimated to have infected with TB disease in 2014. This include 5.4 million men, 3.2 million women and 1.0 million children. Globally, 12% of the 9.6 million new TB cases in 2014 were HIV-positive. Detection and treatment gaps must be addressed, funding gaps must be closed and new tools must be developed to reduce this disease burden. The quality of care for people in the undiagnosed category is unknown. It was estimated that 480,000 cases of MDR-TB occurred in 2014, but that only about a quarter of these (123,000) were detected and reported [1, 7].

The number of HIV-positive TB patients on antiretroviral therapy (ART) increased in 2014 to 392,000 people equivalent to 77% of notified TB

patients known to be co-infected with HIV. This number was approximately one third of the estimated 1.2 million people living with HIV who developed TB in 2014. All HIV-positive TB cases are eligible to receive ART. Funding gaps for implementation of existing interventions amounted to an estimated $ 1.4 billion in 2015. Current estimate of the annual funding gap for research and development is about $ 1.3 billion [1].

Since 2016, the goal has been to end the global TB disease burden by implementing the 'End TB Strategy'. The "End TB strategy" was adopted by the World Health Assembly in May 2014 and with targets linked to the newly adopted Sustainable Development Goals (SDGs), the strategy serves as a blueprint for countries to reduce the number of TB deaths by 90% by 2030 compared with 2015 levels. The goal is to decrease new TB cases by 80% and ensure that no family is burdened with higher costs due to TB disease and life events related to the disease [1].

Epidemiology of TB in the U.S.

Health departments in the 50 states and the District of Columbia (D.C.) electronically report verified TB cases to the NTSS. This was based on the guidelines from the CDC and Council of State and Territorial Epidemiologists (CSTE) case definition [10]. TB incidence in the U.S. remained approximately 3.0 cases per 100,000 persons during the years 2013 to 2015. Preliminary data reported to the National Tuberculosis Surveillance System (NTSS) show that TB incidence among foreign-born persons in the

U.S. was 15.1 cases per 100,000. This was approximately 13 times the incidence among U.S.-born persons, which was reported as 1.2 cases per 100,000 persons per year [10]. Figure 2 was published by CDC with TB case rates in U.S.

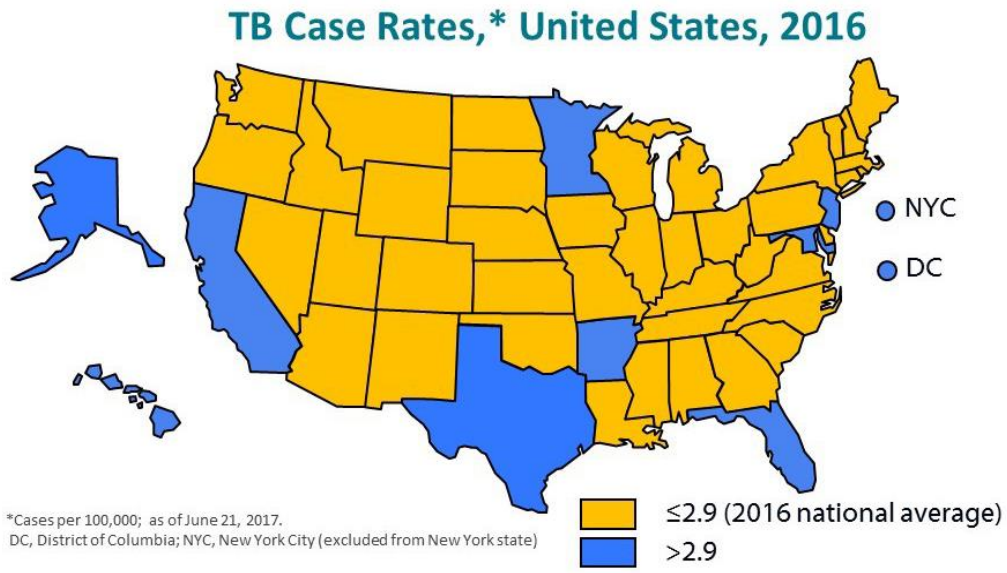

Figure 2: TB Cases Rates in the United States in 2016: CDC [11]

U.S.-born Person Definition

U.S.-born persons are defined as persons born in the U.S., American Samoa, the Federated States of Micronesia, Guam, the Republic of the Marshall Islands, the Commonwealth of the Northern Mariana Islands, Puerto Rico, the Republic of Palau, the U.S. Virgin Islands, and minor

outlying islands, or persons born elsewhere to a U.S. citizen. Race and ethnicity are self-identified. Hispanic and Non-Hispanic persons are categorized by race. July 1 midyear population estimates from the U.S. Census Bureau is used by the CDC to calculate state and overall national TB incidence [12].

U.S. States with Majority of TB Cases

CDC in its report states that California, Florida, New York, and Texas reported greater than 500 cases each in 2015. These four states accounted for 4,839 TB cases, or approximately 50.6% of all reported cases of a total of 9,563 TB cases in 2015. State-specific annual incidence ranged from 0.5 cases per 100,000 persons in West Virginia to 9.1 TB cases per 100,000 persons in Alaska. The highest TB incidence was reported in the Middle Atlantic, West South Central, and Pacific census divisions. The largest increases in TB incidence from 2014 to 2015 occurred in the East North Central, New England, Mountain, and West South Central divisions. Among the 9,563 TB cases reported during 2015, 3,201 (33.5%) occurred among U.S.-born persons. This rate corresponds to an annual TB incidence of 1.2 per 100,000 persons. The 6,335 TB cases among foreign-born persons in the U.S. accounted for 66.2% of the total U.S. cases and corresponded to an annual TB incidence of 15.1 per 100,000 persons [13].

The CDC states that in 2015, most U.S.-born persons reported with TB were either non-Hispanic blacks (1,144 cases) or non-Hispanic whites (991

cases) [13]. Among U.S.-born non-Hispanic blacks, TB incidence was at an all-time low (3.3 cases per 100,000 persons). TB incidence among U.S.-born non-Hispanic whites remained the lowest (0.5 cases per 100,000). Although U.S.-born Hispanics had the third highest case count (661 cases), they had the second lowest incidence (1.8 cases per 100,000). U.S.-born Native Hawaiians/other Pacific Islanders had the highest incidence (12.7 cases per 100,000), followed by U.S.-born American Indians/Alaska Natives (6.8 cases per 100,000). A total of 344 TB cases occurred among U.S.-born persons under the age of 15 years (0.6 cases per 100,000). This incidence represented 10.7% of all U.S.-born TB cases in 2015 [13].

Epidemiology of TB in Georgia

According to the CDC, 11,182 TB cases with a rate of 3.6 cases per 100,000 persons were reported in the U.S. in the year 2010. The number of active TB cases reported and the incidence rate declined representing 3.1% and 3.8% respectively in 2010, compared to 2009. According to the Georgia Department of Public Health (GDPH), 2014 Georgia Tuberculosis Report published in October 2014, TB is a reportable disease in Georgia [14]. Georgia reported 334 new TB cases (3.3 per 100,000 persons) in 2014. This represents a 1.1% decrease from 339 TB cases reported in 2013. In 2015, there were 321(3.1 per 100,000 persons) new cases reported in Georgia [14].

Active TB disease case numbers in Georgia have decreased 63% since 1991. The TB case rate in Georgia decreased from 3.4 cases per 100,000

persons per year population during 2013 to 3.3 cases per 100,000 persons per year in 2014, slightly higher than the U.S. TB disease incidence rate in 2014 of 3.0 cases per 100,000 persons per year. Even though active TB disease incidence rate per year seems somewhat stable in those years, Georgia ranked fifth highest in the U.S. for the number of newly reported active TB cases in 2014 and had the seventh highest active TB disease case rate among the 50 reporting states [14].

Four Counties in Metro Atlanta Area

Among the 159 counties in Georgia, the four large counties (Fulton, DeKalb, Gwinnet, and Cobb) in the metropolitan Atlanta area reported the highest number of TB cases in 2014 and accounted for 59% of TB cases in Georgia. Fulton reported 76 cases, DeKalb with 60, Gwinnet with 35, and Cobb with 25 TB cases. In 2014, TB in Georgia occurred mainly among males (66%), compared to females (34%). The highest proportion of TB cases by age group occurred among persons 25 to 44 years old (36%). TB disproportionately affects racial and ethnic minorities in Georgia. In 2014, non- Hispanic blacks, Asians and Hispanics, accounted for 47%, 22%, and 17% of TB cases in Georgia respectively. They represent 30.7%, 3.7% and 9.3% of Georgia's population, respectively [14].

History of TB

The organism causing tuberculosis, *Mycobacterium tuberculosis (Mtb),* existed 15,000 to 20,000 years ago [15]. It has been found in relics from

ancient Egypt, India, and China. Archaeologists detected spinal tuberculosis among Egyptian mummies, known as Pott's disease. Many different names were used to identify TB such as consumption, phthisis, scrofula, Pott's disease, and the "White Plague" throughout the history. In 2014, results of a new DNA study of a tuberculosis genome reconstructed from remains in southern Peru suggested that human tuberculosis is less than 6,000 years old. Researchers theorize that humans first acquired TB in Africa about 5,000 years ago [15]. They also found that it is related most closely to a tuberculosis strain in seals, and have theorized that these animals were the mode of transmission from Africa to South America [16]. Evidence of TB of the cervical lymph nodes or lymph nodes of the neck termed *scrofula* was found in the middle ages. It was termed as the "king's evil" and was widely believed that the kings of England and France could cure scrofula simply by touching those affected [17].

Koch's Bacillus

In the 18th century TB reached its peak with a prevalence as high as 900 deaths per 100,000 in Western Europe. Poorly ventilated and overcrowded housing, primitive sanitation, malnutrition and other risk factors are thought to have contributed to the rise in TB incidence. The term "White plague" emerged around this time because of the unhealthy pale whiteness appearance of the TB patients. *Tubercle bacilli*, the causative organism of TB disease, was identified by Robert Koch in 1882. He showed

that the organism's unique protein coat made it difficult to visualize earlier until a specific stain called the Zeihl Neelson stain was discovered. The bacteria was called Koch's bacillus and since it took up the red acidic dye, it was called acid fast bacilli or AFB. Koch was awarded the Nobel Prize in 1905. In 1895 Wilhelm Roentgen developed X- rays, which further advanced diagnostics of TB. This allowed early diagnosis and isolation of TB infected individuals [17 - 19].

TB Sanatorium

The concept of keeping TB patients isolated in a sanatorium began in the 19th century. It initially started in Silelsia in Poland in 1859 by Hermann Brehmer, after which the idea caught on. In 1884, Edward Livingston Trudeau started the first sanatorium in the U.S. Infectious TB persons were isolated from society and treated with rest and improved nutrition [17 – 19]. In the 1880s Louis Pasteur began the concept of development of vaccines against anthrax, chicken cholera, and, later, rabies. In 1908, the French scientists Albert Calmette and Camille Guerin grew Koch's bacillus in several mediums to decrease their virulence and increase the capacity to produce immunity. This led to the vaccine called BCG (Bacillus Calmette – Guerin) named after the two founders [20].

TB Disease and Natural History

It is recognized that clinical TB disease may follow shortly after initial infection, or many years thereafter through either reactivation or after

reinfection. The risks of developing TB disease are age-dependent, and reflect infection risks which may change overtime. The effectiveness or ineffectiveness of any therapeutic or preventive measure is impossible to determine with accuracy unless the natural history of a lifetime disease is better understood [21]. Figure 3 shows the natural history of TB infection.

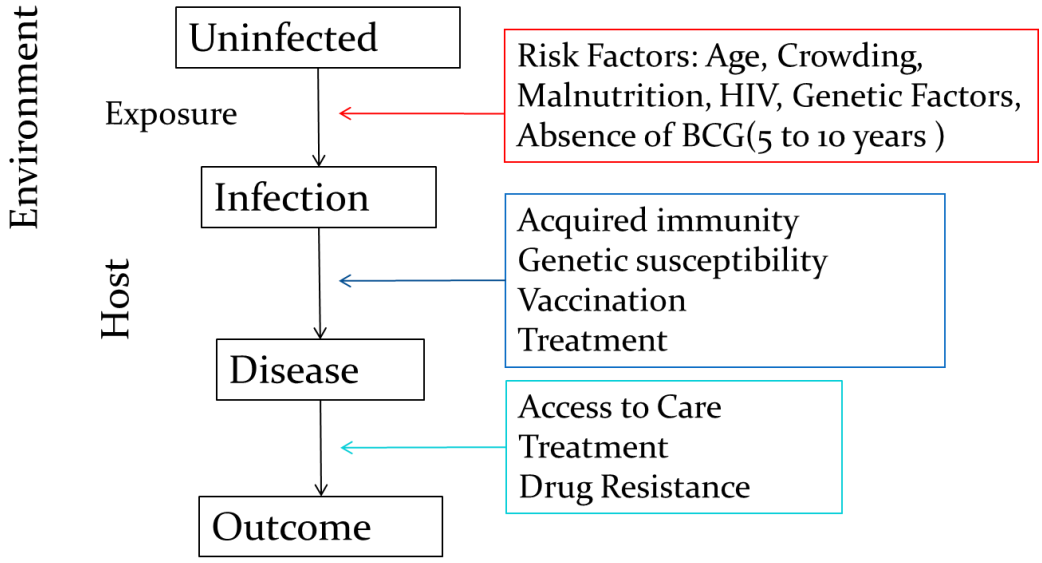

Figure 3: Natural history of TB infection (Dr. Whalen's class notes, UGA, Athens. With permission)

TB begins with primary lesions, which usually subside without causing serious illness or much destruction of tissues. Dependable immunity does not develop. In many cases, active TB disease usually do not appear until years and even decades after the initial infection with *Mtb*. BCG vaccination was introduced for tuberculin negative 13 year old children in

England and Wales in 1954. Small numbers of other individuals with contacts of cases had also been vaccinated. Vaccination was assumed to be approximately 77 % effective against TB disease at that time [22].

Spread of TB Infection

TB is a chronic bacterial infection. It spreads through the air and usually infects the lungs. Also, other organs and parts of the body can be infected as well. Most people who are infected with *Mtb* harbor the bacterium without symptoms called latent TB infection, but some will develop active TB disease. The bacteria that cause TB are spread through the air from person to person. The TB bacteria are put into the air when a person with TB disease coughs, sneezes, speaks, or sings. People nearby may breathe in these bacteria and become infected. In most people who breathe in TB bacteria and become infected, the body is able to fight the bacteria to stop them from growing. If TB bacteria become active in the body and multiply, the person will go from having latent TB infection to being sick with TB disease [23].

Small droplets containing tubercle bacilli disseminate in to the air when an infectious TB patient coughs. These tiny droplet nuclei float in air and the fluid evaporates, the living tubercle bacillus may remain air-born for long periods. Another individual who inhales the organism may become infected. The duration of disease is the time from onset of disease till the individual is cured or dies. There is a rapid inflammation with

polymorphonueclear leukocytes at the alveolar site in the beginning where the tubercle bacillus is deposited. This inflammatory reaction does not usually decrease the growth of the organism, instead it increases and spreads the local reaction. Tubercle bacilli drain through lung lymphatics to the hilar lymph nodes, to the thoracic duct and ultimately may gain entry to the systemic venous circulation. From there, they re-circulate to the lungs and can cause additional local foci of infection [24, 25].

The cellular immune reaction provides the basis for the tuberculin skin test (TST), and for the characteristic pathologic lesion, the granuloma, that is typical of tuberculous infection. Extra pulmonary foci may progress promptly, or they may remain dormant throughout life most often, or may exacerbate many years after the initial infection. Cellular immunity directed to the tubercle bacillus develops after a period of 6 to 12 weeks following the initial infection. Stimulated by antigens from the organism, T-lymphocytes become specifically sensitized and activated. This may activate macrophages that become capable of antibacterial action against the tubercle bacillus [26].

To determine exactly when TB disease started is not possible, as patients may remain asymptomatic or have very mild symptoms after getting the disease. Moreover, the number of individuals cured is hard to measure as relapses are common. Also, establishing who has been cured in untreated TB patients requires extensive medical investigations. Duration of disease can be estimated indirectly from the ratio of prevalence to mortality. Previous

studies show that the duration of active TB disease from start to cure or death is approximately 3 years [27].

Rontgen discovered X-rays in 1895 and chest radiographs became widely available in the Western world after the First World War. This enabled the diagnosis of childhood TB more efficiently. The first TB drugs became available after the Second World War with more effective drugs following in the early 1950s. Many observational studies were conducted during this time with long term follow-up of patients. Large cohorts of children were carefully monitored for the development of disease following primary infection with *Mtb*. This provided detailed descriptions of disease presentation and progression [28, 29].

A Model of Causation for TB Infection

In 1976 Ken Rothman, proposed a conceptual model of causation known as the "sufficient component cause model". The purpose of this attempt was to provide a practical view of causation with a theoretical basis. The model was similar to the "web of causation" theory which simultaneously provides a general model for the conditions necessary to cause or prevent disease in a single individual. This model helped in the epidemiological study of the causes of disease among groups of individuals. Rothman recognized that disease outcomes have multiple contributing determinants that may act together to produce a given instance of disease. Rothman defined a sufficient cause as "a complete causal mechanism" that "inevitably produces disease."

Accordingly, a "sufficient cause" is not a single factor, but a minimum set of factors and circumstances that, if present in a given individual, will produce the disease [30, 31].

Each component in a sufficient cause is called a component cause. Epidemiologists incline to refer to the components as "causes" because the outcome will not occur by that pathway if any one of the components is missing within a given sufficient cause model. Also, it is not necessary to identify all of the component causes in order to prevent the disease outcome. There may be a number of sufficient causes for a given disease or outcome. A component cause that must be present in every sufficient cause of a given outcome is referred to as a necessary cause [30 - 32].

Based on this model, exposure to TB disease does not necessarily result in the occurrence of active TB disease. Other sufficient causes are needed for the disease to occur. The determinants that cause TB in one individual may not be the same conditions in others for the TB disease to occur [30 - 32]. The component needed to complete the causation of TB in an individual with AIDS and poor nutrition would be exposure to the TB bacillus. Absence of BCG vaccination, age, crowded living conditions, poor ventilation, and poor nutrition are examples of other sufficient causes to produce the disease [30 - 32].

Devolopment of BCG

Before antibiotics were found effective against TB, surgical treatment of TB was common and often lifesaving. Dr. James Carson, a Scottish physician, began treatment in 1821 by draining pleural effusion from around the lungs and found that surgery helped prolong life. Various techniques evolved but due to the lack of efficacy faded away after the advent of anti-tubercular drugs. Antibiotics were used against tuberculosis for the first time in 1944 after the discovery of streptomycin. Use of this agent alone led to antibiotic resistance that is still a major problem. Better results followed the development of Para-Aminosalicyclic Acid (PAS). PAS was an oral agent unlike streptomycin. Thereafter, more effective drugs like isoniazid (INH) came in the 1950's and treatment with rifampicin followed [33, 34].

Mtb is a tough and robust microorganism altered to sustained habitation in its human host. Tubercle bacilli are protected against foreign chemicals shielded by a waxen cell wall that protects against lethal enzymes expounded by the body's antibacterial defences. Those foreign chemicals include gold, arsenic, mercury, calcium, iodine, quinine, creosote, turpentine, cod liver oil, and chaulmoogra oil, which are some of the many substances of historical interest that had been used in an effort to stop or reverse the progress of consumption [19].

BCG Vaccines against TB Infection

BCG was introduced by French bacteriologists Albert Calmette and Camille Guerin who named the product Bacillus Calmette-Guerin in 1921. The BCG vaccine was first used in 1921 and is still the only vaccine currently available against TB. It is a live weakened strain of *Mycobaterium bovis*. The effect of prior BCG vaccination on tuberculin reactivity has been known for a long time. This effect varies with age and has a tendency to be more prominent for young adults. This population is therefore most at risk for a false positive TST result not related to *Mtb* infection but to BCG vaccination. BCG is not an ideal vaccine and has two major limitations. BCG exhibits highly variable effectiveness against the development of TB both in pediatric and adult populations and can cause disseminated BCG disease in immunocompromised individuals [20].

BCG comprises a number of sub-strains that are genetically distinct. Whether and how these genetic differences affect BCG efficacy remains largely unknown. BCG has been most effective in protecting children against TB. Because of the variable effectiveness (ranging from 0 to 80%) of the vaccine against adult pulmonary TB, and the vaccine's potential interference with TST reactivity, it is rarely used in the U.S. Although, BCG is generally considered very safe, there is a substantially higher risk of disseminated BCG disease in children with primary immune deficiencies or HIV infection.

However, this risk with BCG is thought to be outweighed by the potential benefit of TB prevention in high risk populations (WHO, 2010) [20].

Currently, the BCG vaccination is recommended by WHO for three main groups of people. The first group are infants born in areas where the incidence rate of TB is high and in those infants with one or more parents or grandparents born in countries with a high rate of TB. The Mantoux skin test or TST is not required beforehand while giving BCG vaccine to an infant. The second group that needs BCG vaccine includes children under 16 years of age who have one or more parents or grandparents born in countries with a high rate of TB and have not been vaccinated as infants. Children under 16 who have been in close contact with someone with TB or have lived for at least three months in a country with a high rate of TB are also vaccinated with BCG after getting a Mantoux test. The third group that requires BCG vaccination are those in high risk occupations, which includes people under 35 years of age whose occupations expose them to TB infected persons [20, 35].

Risk Factors of TB Infection

There are a number of major risk factors for TB infection. High risk factors for TB infections are HIV/AIDS, close contacts with TB, organ transplant recipients, chronic renal failure patients who require dialysis, TNF-alpha blockers users, and Silicosis. Moderate risk factors are fibro nodular disease on chest x-ray, immigrants from high TB prevalence

countries, health care workers, prisoners, homeless persons, and illicit drug users. Low risk factors are diabetes mellitus, smoking, use of corticosteroids, and underweight. High risk factors contribute to TB reactivation rate significantly. Patients with high risk factors should undergo screening and treatment for LTBI even if they live in countries with a low TB disease prevalence [36, 40].

TB is one of the leading cause of morbidity and mortality among people with HIV/AIDS worldwide. In the year 2000, of the estimated 8.3 million new cases of TB worldwide, 9% were attributable to co-existing HIV infection. This proportion was much higher (31%) in African continent [37]. TB is predominantly a disease of the poor and marginalized, although HIV infection is another major driver of the epidemic in certain areas like Africa. Other risk factors like travel to or emigration from an area where TB is endemic, homelessness, shelter dwelling, and incarceration need to be included in the TB control methods [7].

Increased Risk Factors

Persons with recent close contact with persons known to have active TB disease are at higher risk for TB infection. Children under the age of 4 years old and increase in induration of at least 10 mm on TST within a 2 year period are other risk factors. Foreign born persons from Asia, Africa and Latin America where the prevalence of TB is high; homeless persons; and persons living or working at nursing home, prison,

healthcare facility are also at higher risk for TB infection. Other risk factors include HIV disease, intravenous drug use, end stage renal disease, silicosis, diabetes mellitus, immunosuppressive therapy, haematological malignancy, poverty, malnourishment, gastrectomy, and jejunoileal (JIB) bypass [38].

Clinical Manifestation of TB Disease

Accurate case definition of TB revolves mainly around the ability to differentiate latent infection from active disease. The clinical manifestations of TB are dependent on a number of factors. They include age, immune status, co-existing diseases, immunization status to BCG, virulence of the infecting organism, and host-microbe interaction. Approximately 85% of reported TB cases were pulmonary only before the advent of the HIV epidemic. The remaining 15% were extra-pulmonary or both pulmonary and extra-pulmonary sites. Extra-pulmonary involvement tends to increase in frequency with worsening immune compromise. TB disease involving any site may produce systemic or non-organ specific symptoms. The frequency of fever ranges from 37 to 80%. Loss of appetite, weight loss, weakness, night sweats, and malaise are also common symptoms [39].

The most common haematologic indicators are increases in the peripheral blood polymophonuclear leukocyte count and anaemia. Cough is the most common symptom. Initially it may be non-productive, but sputum is produced as inflammation and tissue necrosis ensue. Haemoptysis is

occasionally a presenting symptom but usually results from previous disease and may not indicate active TB. It may arise from tuberculous bronchiectasis, rupture of a dilated vessel in the wall of a cavity also known as Rasmussen's aneurysm, bacterial or fungal infection, especially Aspergillus mycetoma, in a cavity or erosion into an airway called as broncholithiasis [39, 40].

Inflammation of the lung parenchyma adjacent to a pleural surface may cause pleuritic pain. Dyspnoea is unusual unless there is extensive disease and may result in respiratory failure. Rales or crackles may be heard in the area of involvement and bronchial breathing indicating consolidation. Tuberculous lymphadenitis usually presents as painless swelling of one or more lymph nodes. The nodes most commonly involved are those of the posterior or anterior cervical chain or those in the supraclavicular fossa [39, 40].

The natural history of disease demonstrates that progression to disease is indicated by the onset of persistent, non-remitting symptoms, referred to as the breakpoint of clinical significance. The complete absence of symptoms usually indicates good organism containment. The natural history of disease demonstrates that age is the most important variable that determines the risk to progress to disease following primary *Mtb* infection [22].

Cough, weight loss/anorexia, fever, night sweats, hemoptysis, chest pain, and fatigue are the classical clinical features associated with active pulmonary TB. Chest pain in patients with TB can also result from tuberculous acute pericarditis. Pericardial TB can lead to cardiac tamponade or constriction. Elderly individuals with TB may not display typical signs and symptoms of TB infection, because they may not mount a good immune response. Active TB infection in this age group may manifest as non-resolving pneumonitis. Laboratory findings of extra pulmonary TB may be nonspecific. They can include leukocytosis, anemia, and hyponatremia due to the release of antidiuretic hormone (ADH) like hormone from affected lung tissue [41].

Patients with tuberculous meningitis may present with a headache that has been either intermittent or persistent for 2 to 3 weeks. Over a period of days to weeks, subtle mental status changes may progress to coma. Fever may be low grade or absent. The most common site of skeletal TB involvement is the spine which is known as Pott's disease. Symptoms of that include back pain or stiffness. Lower-extremity paralysis occurs in up to half of patients with undiagnosed Pott's disease. Tuberculous arthritis usually involves only one joint. Although, any joint may be involved, the hips and knees are affected most commonly, followed by the ankle, elbow, wrist, and shoulder. Pain may precede radiographic changes by weeks to months [41].

Symptoms of genitourinary TB may include flank pain, dysuria, and frequent urination. In men, genital TB may noticeable as a painful scrotal mass, prostatitis, orchitis, or epididymitis. In women, genital TB may mimic pelvic inflammatory disease. TB is the cause of approximately 10% of sterility cases in women worldwide and 1% in industrialized countries. Any site along the gastrointestinal tract may become infected too [41].

Symptoms of gastrointestinal TB are referable to the infected site and include non- healing ulcers of the mouth or anus. There may be difficulty swallowing with esophageal disease and abdominal pain mimicking peptic ulcer disease with stomach or duodenal infection. Also, malabsorption with infection of the small intestine, pain, diarrhoea, or hematochezia with infection of the colon [41].

LTBI or Infection Stage

LTBI is a state of persistent immune response to stimulation by *Mtb* antigens without evidence of clinically established active TB disease. One third of the world's population is estimated to have LTBI. Individuals with LTBI do not have active TB disease but may develop it in the near or remote future. This process is called "TB reactivation."[42]

Persons with LTBI do not feel sick and do not have any symptoms. They are infected with *M. tuberculosis*, but do not have TB disease. The only sign of TB infection is a positive reaction to the TST or TB blood test. Persons with LTBI are not infectious and cannot spread TB infection to others. The

lifetime risk of reactivation for a person with documented LTBI is estimated to be 5 to10%. A majority of them develop TB disease within the first five years after initial infection [42]. However, the risk is considerably higher in the presence of predisposing factors.

TB Disease or Infectious Stage

People with TB disease usually have symptoms and may spread TB bacteria to others. TB bacteria most commonly grow in the lungs, and can cause symptoms such as a bad cough that lasts 3 weeks or longer, pain in the chest, and coughing up blood or sputum (mucus from deep inside the lungs). Other symptoms of TB disease may include weakness or fatigue, weight loss, no appetite, chills, fever, sweating at night. In some people, TB bacteria overcome the defences of the immune system and begin to multiply, resulting in the progression from latent TB infection to TB disease [23].

TB disease may develop in some people soon after infection. For others with TB infection, TB disease may develop later when their immune system becomes weaker. Persons with TB disease are considered infectious and may spread TB bacteria to others. If TB disease is suspected, persons should be referred for a complete medical evaluation. If it is determined that an individual has TB disease, then the recommended treatment is therapy. TB disease is a serious condition and can lead to death if not treated [23].

Diagnosis of LTBI and Active TB Disease

Active TB disease is diagnosed by medical history, physical examination, chest x-ray, sputum for acid-fast bacillus (AFB) and other laboratory tests. There are two kinds of tests that are used to detect TB bacteria in the body: the TB skin test (TST) and TB blood tests. A positive TB skin test or TB blood test only reveals that a person has been infected with TB bacteria. It does not indicate whether the person has LTBI or has progressed to TB disease. Other tests, such as a chest x-ray and a sample of sputum, are needed to see whether the person has TB disease. The TB skin test is also called the Mantoux tuberculin skin test (TST). A TB skin test requires two visits with a health care provider. On the first visit the test is placed and on the second visit the health care provider reads the test [23].

The TB skin test is performed by injecting a small amount of fluid (called tuberculin) into the skin on the lower part of the arm. A person given the TST must return within 48 to 72 hours to have a trained health care worker look for a reaction on the arm. The result depends on the size of the raised, hard area or swelling. A positive TST means the person's body was infected with TB bacteria, while a negative TST means the person's body did not react to the test, and that latent TB infection or TB disease is not likely. False negative tests may occur in immunosuppressed persons, though. A TB skin test can be repeated. If repeated, the additional test should be placed in

a different location on the body (e.g., other arm). The TB skin test is the preferred TB test for children under the age of five [23].

TB blood tests are called interferon-gamma release assays (IGRAs). Two IGRAs are approved by the U.S. Food and Drug Administration (FDA) and are available in the U.S.: the QuantiFERON®–TB Gold In-Tube test (QFT-GIT) and the T-SPOT®.TB test (T-Spot). As with the TST, positive TB blood test means that the person has been infected with TB bacteria. Additional tests are needed to determine if the person has LTBI or TB disease. Negative TB blood test means that the person's blood did not react to the test and that LTBI or TB disease is not likely. TB blood tests are the preferred TB test for people who have received the TB vaccine (BCG) and people who have a difficult time returning for a second appointment to look for a reaction to the TST. If a person has symptoms, but a negative TB test result, they should still be evaluated for TB disease [43-46].

Science of Testing for LTBI

A large number of new active TB cases are developed from the patients with LTBI. Screening and treating LTBI cases is an important public health measure. This approach will prevent interpersonal spread of TB infection and active TB occurring in individuals. Immigrants, persons infected with HIV, healthcare workers who had recent contact with someone has active TB, patients with underlying medical conditions such as diabetes mellitus and lymphomas are some of the groups who will benefit from TB screening. A

decision must be made before testing to treat the individuals who tested positive [45, 46]. There are two tests available to confirm a diagnosis of LTBI: TST and IGRAs.

TB screening tests based on PPD cannot differentiate between TB infection, BCG vaccination, or exposure to environmental mycobacteria. PPD is a crude and poorly defined mixture of mycobacterial antigens containing both secreted and somatic proteins. Researchers were investigating alternatives to skin testing for many years. An in vitro diagnostic test for *Mycobacterium bovis* infection in cattle was developed, based on the detection of gamma interferon (IFN-γ) liberated in whole blood cultures incubated in vitro with PPD in 1990. In 1994, a variation of this test was developed for the diagnosis of *Mtb* and *Mycobacterium avium* infection in humans, again using PPD-type antigens [47].

The BCG vaccine is with different strains with very different properties. There are different genotypes within strains. There were 3924 open reading frames (ORFs) in the genome of *Mycobacterium tuberculosis* H37Rv when the genome was sequenced. Advances in genomic research resulted in the discovery of a genomic region of difference (RD1) that is absent in BCG but present in *Mtb*, which led to the development of in vitro T-cell-based immunodiagnostics measuring Interferon-gamma (IFN-γ) release in response to the RD1-encoded immunodominant antigens ESAT-6 and CFP-10 [47].

The identification of regions of the *M. tuberculosis* genome that were missing from BCG and most NTM provides an opportunity for the development of new diagnostic tools. A 9.5-kb section of DNA called region of deletion 1 (RD1) is present in virulent *Mtb* strains but is deleted in all attenuated Mycobacterium bovis BCG vaccine strains. Due to natural deletion event, the 9455-bp region of RD1 of M. tuberculosis is absent in all attenuated Mycobacterium bovis BCG vaccine strains. RD1 region encodes the T-cell antigen ESAT-6, which was originally isolated from a highly stimulatory low-molecular-mass fraction of *Mtb* culture filtrate. RD1 region was found by utilizing the availability of the genome sequences approach of *Mtb* and BCG by applying principles of comparative genomics to the identification of species-specific antigens. CFP10 and ESAT-6 are strong T- and B-cell antigens and it is presently not known if any of the other *Mtb* RD1 proteins are expressed in vivo. CFP10 and ESAT-6 are the best studied RD1 proteins. The combination of ESAT-6 and CFP10 is highly specific for *Mtb*, with a low reactivity in BCG-vaccinated individuals responsive to PPD [48 - 52].

Diagnoses of LTBI

TST and IGRAs are the main tests currently available for the diagnosis of LTBI. The diagnosis is based on a positive result of either a TST or IGRA test indicating an immune response to *Mtb* in a patient without clinical signs and symptoms of disease and negative sputum tests. These

tests have limitations as they cannot distinguish between latent infection with viable micro-organisms and healed/treated infections. They also poorly predict who will progress to active TB. The risk of progression to active disease is considerably higher in infected individuals who belong to specific high risk populations [3, 11, 21, 35].

Diagnosis of Active TB Disease

Many medical evaluation methods are used to confirm the diagnosis of active TB disease. A chest X-ray shows the lesion within the lungs. The lesion more often lies in the lungs in pulmonary tuberculosis. There may be a scarred appearance of the lungs. Primary tuberculosis usually appears in the central upper portion of the lungs with a pleural effusion or collection of fluid around the lungs. In severe disease, there may be a picture like millet seeds over the X-ray plate of the lungs. This is called *milliary* tuberculosis. The phlegm or mucus is collected from the patient and placed onto a glass slide and stained with a special dye called the *Ziehl-Neelson* stain and then viewed under the microscope. The tubercle bacilli will show up as tiny red thread like organisms. At least 3 spontaneous sputum samples need to be examined for culture and microscopy for examination of sputum. Sputum is cultured on a medium called the *Lowenstein-Jensen* slope which takes 4-8 weeks due to slow bacterial growth. Samples should include at least one early morning sample. In the case of children, or in those who cannot produce a sputum or phlegm sample, the washings of the bronchus and air passages are taken

using bronchoscopy, lavage and gastric washings. These samples are then tested for the bacteria. Samples need to be taken before starting treatment or within 7 days of starting [3, 11, 21, 35].

In patients with TB disease suspected outside the lungs, which is called extra-pulmonary tuberculosis, several tests are suggested. A computerized tomography (CT) scan or a magnetic resonance imaging (MRI) scan of the part of the body affected or of the whole body to look for other focus of the disease. An ultrasound scan of the abdomen and other hollow parts of the body that may be affected may also give clues. Series of routine and special blood tests to detect tuberculosis. Urine tests for the bacteria if the urinary tract is affected. Biopsy of the affected tissues and parts of the body and examination of the sample under the microscope helps detects the presence of the disease [3, 11, 21, 35].

Those with suspected tuberculosis of the nervous system or of the brain and meninges (layers of cells that cover the brain and the spinal cord) also need a lumbar puncture. This involves taking a small sample of cerebrospinal fluid (CSF) from the base of the spine. This CSF is a clear fluid that bathes and surrounds the brain and the spinal cord. The fluid is checked under the microscope of using biochemical tests to detect tuberculosis. Other diagnoses that need to be ruled out while confirming tuberculosis include cancers, lymphoma, Pneumonia, fibrotic lung disease, and diabetes.

TB Diagnosis Methods

The goal of testing for any disease is to identify persons with a particular disease who are at high risk and who would benefit from treatment of the disease. TB disease prevention can be achieved through targeted diagnosis and treatment of persons with TB disease. The majority of new cases are diagnosed from LTBI cases, so it is important to identify latent TB cases and treat them. This will prevent the spread of TB infection and reduce the incidence of TB disease. There are many methods available now [3, 11, 21, 35].

TST

Tuberculin Skin Test (TST) was first introduced in the 1800s and went through continual improvement in its making, standardization and dosage. Also, the interpretation and indication went through changes. Practical TST testing first started in 1909. The American Thoracic Society/CDC guidelines [3, 11, 21, 35, 47] highlight that administering a TST implies a guarantee to provide treatment if latent TB infection is diagnosed. An important limitation of TST is the likelihood of false positives in BCG vaccinated individuals.

TST, Purified Protein Derivative (PPD) and Mendel-Mantoux test are often used interchangeably. Mantoux refers to the technique for administering the test. Tuberculin, also called purified protein or PPD, is the solution used in this test. The preferred term for this test is TST. TST is an intradermal injection of 0.1 ml of tuberculin on the inner surface of the

forearm. The skin test reaction should be read between 48 and 72 hours after administration. Another TST should be administered if the test is not read within 72 hours unless the amount of induration is greater than or equal to 10mm within 7 days. A palpable, raised, hardened area or swelling should be measured in millimeters of induration [3, 11, 21, 35, 47].

Table 3: TST and induration and interpretation (CDC guidelines 2017) [3, 11, 21, 35, 47]

Step	Induration	Interpretation
1	>=5 mm is classified as positive if	• Persons who have had recent close contact with persons who have active TB • Persons who have human immunodeficiency virus (HIV) infection or risk factors for HIV infection but unknown HIV status • Persons who have fibrotic chest radiographs consistent with healed TB
2	>=10 mm is classified as positive if	• Injecting-drug users known to be HIV seronegative • Persons who have other medical conditions that have been reported to increase the risk for progressing from latent TB infection to active TB. • Residents and employees of high-risk congregate settings • Foreign-born persons recently arrived (i.e., within the last 5 years) from countries having a high prevalence or incidence of TB • Some medically underserved, low-income populations, including migrant farm workers and homeless persons • High-risk racial or ethnic minority populations, as defined locally • Children <4 years of age or infants, children, and adolescents exposed to adults in high-risk categories.
3	>=15 mm is classified as positive if	• persons who do not meet any of the above criteria

The degree of induration on skin testing is assessed differently in high risk populations. Individuals with HIV infection, those with recent contact with active TB, prior TB cases, or individuals who are immunosuppressant users are advised for latent TB treatment if the induration is 5 mm or above. Foreign-born immigrants, intravenous drug users, individuals who suffer from alcoholism, those residing or working in high risk areas, those employed in a mycobacteriology laboratory, those with certain medical conditions, or children less than 4 years of age should get treatment for latent TB if the induration is 10 mm or above. 15 mm induration or above is eligible for latent TB treatment if they are with unknown risk factors [54].

C-TB Skin Test

The C-TB skin test (Statens Serum Institute, Copenhagen, Denmark) is based on ESAT-6 (early secretory antigen of *Mycobacterium tuberculosis*-6) and CFP10 (culture filtrate protein-10) antigens. This test is a skin test designed to combine the operational advantages of the TST with the specificity of IGRAs for the diagnosis of TB infection. C-TB tests generate similar indurations compared to TSTs. Also, have similar diagnostic specificity and sensitivity in comparison to QuantiFERON-TB Gold In-Tube test ([QFT], QIAGEN N.V., Netherlands]. The TST and C-TB agents are clear, colourless solutions. C-TB is administered intradermally and induration is measured in 48 to 72 hours, similar to the TST [55, 56].

IGRAs

Interferon gamma release assays (IGRAs) are in-vitro diagnostic alternatives to the TST and C-TB. These tests are based on the highly immunogenic antigens ESAT-6 and CFP10, which are specific to *M tuberculosis*, and overcome the issues of the interaction with BCG vaccine and infection with non-tuberculous mycobacteria seen with the TST. Two IGRA tests are commercially available, QuantiFERON-TB Gold In-Tube test ([QFT] [QIAGEN N.V., Netherlands], which uses whole blood, and the T-SPOT.TB test[Oxford Immunotec Ltd, Oxford, U.K. Marlborough, Massachusetts], which uses purified peripheral blood mononuclear cells. IGRAs are more complex and labor intensive than the TST and C-TB, and need a laboratory infrastructure and skilled staff. Interpretation of the results of IGRAs are more objective and simple compared to the TST and C-TB. IGRAs, the TST, and C-TB have low positive predictive value for the development of active tuberculosis. IGRAs are used in adults and assessment in young children is unclear [43, 44, 57].

Xpert MTB/RIF

The Xpert MTB/RIF assay is a new test that is revolutionizing TB control by contributing to the rapid diagnosis of TB disease and drug resistance. WHO recommended the use of the rapid test, Xpert MTB/RIF in 2010 and more than 100 countries used this test in 2016. The test simultaneously detects Mycobacterium tuberculosis complex (MTBC) and

resistance to rifampin (RIF) in less than 2 hours. This test is recommended by WHO as the initial diagnostic test in all persons with signs and symptoms now. In comparison, standard cultures can take 2 to 6 weeks for MTBC to grow and conventional drug resistance tests can add 3 more weeks. The information provided by the Xpert MTB/RIF assay aids in selecting treatment regimens and reaching infection control decisions quickly. Diagnosing multi-drug resistance early on is very important in readjusting medications to treat TB [58].

C-TAB

A polymerase chain reaction (PCR) test based on insertion sequence IS1081 was developed to detect *MTBC* organisms in the peripheral blood. The abbreviation stands for the DNA purification (cetyltrimethylammonium bromide, C-TAB). DNA amplification using PCR has allowed rapid and accurate diagnosis of infections in microbiology. The method was applied to blood samples from immunocompetent individuals with localized pulmonary tuberculosis. The method is mostly applied to blood samples from immunocompetent individuals with localized pulmonary tuberculosis [58].

Differences between QFT and T-SPOT

The CDC Guidelines recommend the use of IGRAs in all situations in which the TST was historically used, with IGRAs being the preferred test for persons who have been BCG vaccinated or are unlikely to return for TST

reading [59]. Table given below give the differences between QFT and T-SPOT.

Table 4: Differences in Currently Available IGRAs [59]

	QFT-GIT	T-SPOT
Initial Process	Process whole blood within 16 hours	Process peripheral blood mononuclear cells (PBMCs) within 8 hours, or if T-Cell Xtend® is used, within 30 hours
M. tuberculosis Antigen	Single mixture of synthetic peptides representing ESAT-6, CFP-10 & TB7.7.	Separate mixtures of synthetic peptides representing ESAT-6 & CFP-10
Measurement	IFN-g concentration	Number of IFN-g producing cells (spots)
Possible Results	Positive, negative, indeterminate	Positive, negative, indeterminate, borderline

IGRA interpretations are based on the amount of IFN-g that is released or on the number of cells that release IFN-g. Both the standard qualitative test interpretation (positive, negative, or indeterminate) and the quantitative assay measurements (Nil, TB, and Mitogen concentrations or spot counts) should be reported.

As with the TSTs, IGRAs should be used as an aid in diagnosing infection with *Mtb*. A positive test result suggests that *Mtb* infection is likely. A negative result suggests that infection is unlikely. An indeterminate result

indicates an uncertain likelihood of *Mtb* infection. A borderline test result (T-SPOT only) also indicates an uncertain likelihood of *Mtb*.

A diagnosis of LTBI requires that TB disease be excluded by medical evaluation. This should include checking for signs and symptoms suggestive of TB disease, a chest radiograph, and, when indicated, examination of sputum or other clinical samples for the presence of *Mtb*. Decisions about a diagnosis of *Mtb* infection should also include epidemiological and historical information [57].

The Replacement Principle of Tuberculosis

New cases of TB come from two sources in the population, recently infected contacts and remote infections. Recently infected contacts are often called progressive primary disease, and remote infections are called reactivation disease. Unrecognized TB cases cause continuous transmission of disease and latent TB infections cause reactivation disease. The replacement principle of TB is evident when one index case is replaced by one or more cases of the same disease. To prevent new cases, it is necessary to reduce or interrupt transmission through early case detection and treatment [42].

Challenges and Strategy

Social determinants of health in the TB infectious disease area are poverty and high risk populations. Addressing those two areas through meaningful interventions can reduce and eliminate the worldwide TB

epidemic. The largest burden of disease is in the poorest and socially excluded groups of people. This does not mean the rich are excluded from this epidemic. In developing countries, there are several servants who work inside and outside of the homes of individuals with high socioeconomic status. Mostly, these people are coming from slums and poor living conditions. They may test positive for TB disease and they can spread the disease within the homes of high income people unknowingly. Essentially, TB is not the disease of the poor anymore. When people are getting wealthier, they may recruit people to do work in their homes. In India, most of the middle-income or above families have servants or maids as part of their family. In India, middle class means 'not poor'. Most of the time, the servants are unemployed, illiterate individuals. This may be true for other developing countries, too. This setting contributes to the spread of infectious diseases like TB in a rapid speed [60, 61].

Spread of Multidrug-resistance TB

The spread of multidrug-resistance TB is another challenging area in TB control methods. This area needs special attention and further research to find newer methods in diagnostics, new drugs, and vaccines. The WHO started the end-TB strategy in 2014 with seventeen sustainable development goals. The goal is to achieve 90% reduction in TB-related mortality and TB-incidence by 2030. Since it is a worldwide goal, many government agencies and non-government agencies will work together and there may be

challenges in bringing all these agencies together.

Another area of concern is the HIV infected high risk population. HIV is the strongest risk factor for TB and TB is the leading cause of death among people living with HIV. The majority of these deaths occur in the African continent where the HIV burden is very high. Diabetes mellitus, smoking, and alcohol abuse are other major risk factors contributing to the development of TB disease from latent TB.

The Millennium Declaration by the United Nations General Assembly in September 2000 was a historical resolution [61]. Eight goals were identified in that resolution and three of them were dedicated to health issues. TB, HIV/AIDS, and malaria were the three world epidemics that were given priority. One area of concern is the number of missing cases in the data. There may be millions of cases missing in the world wide data due to care and transmission problems. Technical support may be missing in rural areas and remote places where TB incidence may be high. There must be better methods to capture all TB cases and their outcome with treatment.

Treatment for LTBI

People with latent TB infection do not have symptoms, and they cannot spread TB bacteria to others. However, if TB bacteria become active in the body and multiply, the person will go from having latent TB infection to being sick with TB disease. For this reason, people with latent TB infection are often prescribed treatment to prevent them from developing TB

disease [54]. Treatment of latent TB infection is essential for controlling and eliminating TB in the United States. LTBI can be effectively treated in order to prevent progression to active TB, thus resulting in a substantial benefit for both the individual and the community. Currently available treatment options allow individuals to reduce the risk of developing active TB by at least 60%. However, safety concerns exist, mainly related to the development of hepatotoxicity. Regimens recommended by WHO for the treatment of LTBI are 6 or 9 month isoniazid daily, 3 month rifapentine plus isoniazid weekly, 3 or 4 month isoniazid plus rifampicin daily, and 3 or 4 month rifampicin alone daily [54].

People with a positive IGRA result or a TST reaction of 5 or more millimeters who are HIV-infected persons, recent contacts of a TB case, persons with fibrotic changes on chest radiograph consistent with old TB, organ transplant recipients, or persons who are immunosuppressed for other reasons should be given high priority for LTBI treatment [54]. Also, people with a positive IGRA result or a TST reaction of 10 or more millimetres who are recent immigrants immigrated within 5 years from high-prevalence countries, injection drug users, residents and employees of high-risk congregate settings like correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities, mycobacteriology laboratory personnel, or children under 4 years of age, or children and

adolescents exposed to adults in high-risk categories should be treated with high priority [54].

Persons with no known risk factors for TB may be considered for treatment of LTBI if they have either a positive IGRA result or if their reaction to the TST is 15 mm or larger. However, targeted TB testing programs should only be conducted among high-risk groups. All testing activities should be accompanied by a plan for follow-up care for persons with TB infection or disease [54].

Treatment for TB Disease

When TB bacteria become active by multiplying in the body and the immune system cannot stop the bacteria from growing, it is TB disease. People with TB disease may spread the bacteria to people with whom they are in contact, with the likelihood of transmission depending on factors such as the duration, intimacy, and frequency of exposure. It is very important that people who have TB disease are treated, finish the medicine, and take the drugs exactly as prescribed. If they stop taking the drugs too soon, disease may occur. If they do not take the drugs correctly, the TB bacteria that are still alive may become resistant to those drugs. TB that is resistant to drugs is harder and more expensive to treat. Taking several drugs for 6 to 9 months can treat TB disease. There are 10 drugs currently approved by the U.S. Food and Drug Administration (FDA) for treating TB. Of the approved drugs, the first-line anti-TB agents that form the core of treatment

regimens are isoniazid (INH), rifampin (RIF), ethambutol (EMB), pyrazinamide (PZA) [62]. See table 5 for detailed information on treatment regimens.

Table 5: Regimens for treating TB disease (CDC Guidelines 2017) [62]

	INTENSIVE PHASE		CONTINUATION PHASE				
Regimen	**Drugs[a]**	**Interval and Dose[b] (minimum duration)**	**Drugs**	**Interval and Dose[b,c] (minimum duration)**	**Range of Total Doses**	**Comments[c, d]**	**Regimen Effectiveness**
1	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) *or* 5 days/week for 40 doses (8 weeks)	INH RIF	7 days/week for 126 doses (18 weeks) *or* 5 days/week for 90 doses (18 weeks)	182 to 130	This is the preferred regimen for patients with newly diagnosed pulmonary TB.	Greater
2	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) *or* 5 days/week for 40 doses (8 weeks)	INH RIF	3 times weekly for 54 doses (18 weeks)	110 to 94	Preferred alternative regimen	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 weeks)	INH RIF	3 times weekly for 54 doses (18 weeks)	78	Use regimen with caution in patients with HIV and/or cavitary disease.	
4	INH RIF PZA EMB	7 days/week for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 weeks)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear positive and/or cavitary disease.	Lesser

Abbreviations: DOT = directly observed therapy; EMB = ethambutol; HIV = human immunodeficiency virus; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin.

[a] Other combinations may be appropriate in certain circumstances; additional details are provided in the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis*.

[b] When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered less than 7 days per week.

[c] Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.

[d] Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (e.g., pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

[e] Alternatively, some U.S. TB control programs have administered intensive-phase regimens 5 days per week for 15 doses (3 weeks), then twice weekly for 12 doses.

TB Regimens for treating drug- susceptible TB disease have an intensive phase of 2 months, followed by a continuation phase of either 4 or 7 months (total of 6 to 9 months for treatment). Regimens used are daily INH, RIF, PZA, and EMB for 40-56 doses (8 weeks), daily INH, RIF, PZA, and EMB for 14 doses (2 weeks), then three-times-weekly for 18 doses (6 weeks), and three-times-weekly INH, RIF, PZA, and EMB for 24 doses (8 weeks).

A continuation phase of once-weekly INH/rifapentine can be used for HIV-negative patients who do not have cavities on the chest film and who have negative acid-fast bacilli (AFB) smears at the completion of the intensive phase of treatment. Treatment completion is determined by the number of doses ingested over a given period of time [62].

Drug-resistant TB is caused by TB bacteria that are resistant to at least one first-line anti-TB drug. Multidrug-resistant TB (MDR TB) is resistant to more than one anti-TB drug and at least isoniazid (INH) and rifampin (RIF). Extensively drug-resistant TB (XDR TB) is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs like amikacin, kanamycin, or capreomycin. Treating and curing drug-resistant TB is complicated. Inappropriate management can have life-threatening results. Drug-resistant TB should be managed by or in close consultation with an expert in the TB disease. Patients on treatment for LTBI or TB disease

should report any signs and symptoms of adverse drug reactions to their health care provider [62].

Prognosis of TB Disease

Tuberculosis is a curable disease. Progress of TB from infection to active TB disease involves the bacteria overcoming the immune system defences. T- cells are immune cells which play an important role in protecting against TB disease. Particular T - cells that recognise antigens or peptides resulting from *Mtb* must multiply to increase their numbers and reach the lungs. During a TB infection, it takes an extensive time to generate a protective T-cell response. *Mtb* achieve a higher level of infection during this time, unchecked. It takes an estimated six weeks for T-cells to recognize the *Mtb* in the human body. It takes approximately seven to ten days to detect T-cell responses. Delayed response of T-cells in TB infection is an area of interest for TB scientists.

Some studies in mice show that T-cell response does not start for eleven to fourteen days after *Mtb* infection. *Mtb* must be inhaled in to the lungs and then it is phagocytized by a cell called a macrophage. *Mtb* reproduces within the macrophage and spills the bacteria when it dies. Other cells will eat this bacteria and the cycle will continue until a cell called a dendritic cell eats the bacteria. The dendritic cell carries the bacteria to a lymph node in nine to eleven days post infection. Specific T-cells recognize bacterial antigens on the surface of the infected dendritic cell. At this stage,

T-cells will be initiated in the lymph node. T-cells specific to *Mtb* must proliferate and migrate to lung and produce cytokines that help the macrophage to kill or control the growth of *Mtb*. This process is a slow process and it may take at least three weeks. It usually takes 4 weeks to peak in numbers post-infection [62].

Once diagnosed, with effective, adequate and appropriate therapy with anti-tubercular drugs, treatment is possible and so is a cure. In primary TB, which makes up around 1 to 5% of all cases, the progression of the infection to frank disease occurs soon after infection. In many individuals, the initial infection is LTBI. The disease may remain dormant within the body with the immune system capable of containing the infection. When the immune system weakens for some reason (e.g. HIV infection, diabetes, renal disease etc.) there is reactivation of the infection. The risk of this reactivation rises when immunity is suppressed. For example, those with concomitant HIV infection have an increased risk of reactivation of tuberculosis of 10% each year of infection.

Some predictors of a poorer prognosis include extreme ages and other medical conditions. In Africa, tuberculosis mainly affects young adults and teenagers. In some developed countries, however, tuberculosis mainly affects the elderly. Another risk factor that increases the risk of poor prognosis includes smoking more than 20 cigarettes a day, which raises the risk of

tuberculosis by two to four times. Diabetes also worsens the prognosis and outcome of tuberculosis.

People with healthy immune systems can fight the infection at the early stages and not become ill with TB disease. A person with a positive TB skin test and normal X-ray is not sick with contagious TB disease and they don't spread the TB disease to others. TB medications can kill the bacteria at that stage and prevent the development of disease in those people in the future [63]. The TB bacteria may grow in people with LTBI who did not take antitubercular medications and they may become active disease cases. Constant cough that lasts two or more weeks, chest pain, weakness, and loss of appetite are some of the symptoms for active TB cases. Those individuals with active TB disease are contagious and cause infection in other people. Chances of infection are high for people who interact with TB disease cases in close contact. TB disease in the lungs and larynx are infectious TB disease [64].

Persons with recent close contact with person known to have TB disease are at higher risk for TB infection. Children under 4 years old with a tuberculin induration increase of at least 10 mm on TST within a 2 year period are also at high risk. Foreign-born persons from Asia, Africa and Latin America where prevalence of TB are high, homeless persons, or persons living or working at nursing home, prison, healthcare facility are also at higher risk for TB infection. Other risk factors include persons

with HIV, intravenous drug abusers, end stage renal disease, silicosis, diabetes mellitus, immunosuppressive therapy, haematological malignancy, poverty or malnourished, and gastrectomy or jejunoileal bypass [64].

The U.S. Immigrant Population

The U.S. immigrant population stood at more than 42.4 million, or 13.3%, of the total U.S. population of 318.9 million, according to the U.S. Census Bureau's 2014 American Community Survey (ACS). Twelve percent of the 42.4 million foreign born in the United States in 2014 entered in or after 2010, 29% between 2000 and 2009, and the majority (59%) before 2000 [65, 66].

TB Among U.S. Immigrants

TB cases among persons born outside of the U.S. accounted for 45% of TB cases in Georgia in 2014. Most foreign born cases reported in 2014 came from Mexico (19%), Vietnam (16%), and India (10%) countries where TB is an endemic disease. Among 150 foreign born cases, 43 (29%) were diagnosed in the first five years of their arrival in the U.S [67, 68].

Although Mexico born persons accounted for the largest proportion of foreign born persons reported with TB, their TB incidence in the United States (10.4 cases per 100,000) was lower than that among persons born in China (24.9 cases per 100,000), India (23.9 cases per 100,000), Philippines (46.9 cases per 100,000), and Vietnam (47.8 cases per 100,000). From 2014 to

2015, the number of TB cases among Philippines born persons grew from 755 to 819 (8.5% increase), and the number of TB cases among India born persons grew from 479 to 578 (20.7% increase). The Philippines born population in the U.S. grew from 1,639,286 to 1,747,287 (6.6% increase), and the India born population grew from 2,166,930 to 2,421,795 (11.8% increase). Ninety six TB cases occurred among foreign born persons aged <15 years (6.0 cases per 100,000), representing 1.5% of all foreign born persons reported as having incident TB in the U.S. in 2015 [69 - 72].

All TB patients need to be tested for HIV infection because TB treatment may change when antiretroviral therapy for HIV is given, and active TB often accelerates the natural progression of HIV infection. Among 311 TB cases in Georgia with known HIV status in 2014, 37 (12%) were HIV positive compared to 13% in 2013. Among 37 HIV co-infected TB cases in 2014, 76% were non-Hispanic blacks, 78% were male and 54% were 25-44 years old. HIV status was reported in 93% of TB cases in Georgia in 2014 compared to 92% in 2013. In the high-risk age group of adults 25-44 years of age, 98% reporting of HIV was achieved in 2014 [10, 13, 14].

In the U.S. in 2015, Asians had both the highest TB case count reported (3,007 cases) and highest incidence (28.2 cases per 100,000 persons) among foreign born persons. The top five countries of origin for foreign born persons with TB were Mexico (1,250; 19.7%), the Philippines (819; 12.9%), India (578; 9.1%), Vietnam (513; 8.1%), and China (424; 6.7%). These

countries together represent 45.2% of the foreign born population in the U. S. and accounted for 56.6% (3,584 cases) of all TB cases among foreign born persons [73 - 76].

Two thirds of all U.S. TB cases occur after years of arrival among foreign born persons, which is consistent with disease progression following years of untreated LTBI. Epidemiologic modelling indicates that eliminating the threat of TB in the U.S. will require additional strategies to reduce TB in the countries of origin and expand treatment of LTBI among the foreign born population. Despite recent declines in TB incidence among foreign born persons, these persons continue to have a higher risk for TB. This implies the urgency of further strengthening the worldwide fight against TB. Also, it is important to screen and treat U.S. bound immigrants and refugees for TB disease. TB elimination will require both global interventions and a substantial improvement in larger scale identification and treatment of LTBI among foreign born persons living in the U.S., which is consistent with CDC's strategic plan for the national elimination of TB [14].

Among immigrants, Mexican immigrants are primarily concentrated in the West and Southwest, and more than half live in California or Texas. In 2014, the top five states in which Mexican immigrants resided were California (37% of all Mexican immigrants), Texas (22%), Illinois (6%), Arizona (4%), and Florida (2%). About 69% of the 11.3 million immigrants from Mexico ages 16 and older were in the civilian labor force in 2014. This

rate is slightly higher than the labor force participation of the overall foreign born population ages 16 and older (66% of 40.4 million immigrants) and the native born population ages 16 and older (62% of 213.1 million U.S. born). In 2014, approximately 53% of immigrants in the U.S. had private health insurance compared to 68% of the native born and 27 percent had public health insurance coverage compared to 34 percent of the native born. Slightly more than one quarter (27%) were uninsured, compared to 9% of the native born [14].

Effect of the Health Insurance Status

Health insurance coverage of immigrants particularly non-citizens at a greater rate than the U.S. born population improved access to health care for immigrants. The improvement in coverage for immigrants is a result of an increase in both private coverage (from 50% to 53%) and public coverage (from 24% to 27%). Among the foreign born, non-citizens witnessed a larger drop in the uninsured rate (from 46% to 40%) than naturalized citizens (from 16% to 11%). The top five countries of birth for new lawful permanent residents (LPRs) in 2014 were Mexico (13%), India and China (8% each), and the Philippines and Cuba (5% each). Approximately 385,000 new LPRs were from one of these top five countries of birth, accounting for about 38% of all persons who received LPR status in 2014 [14].

According to the Department of Homeland Security (DHS) Office of Immigration Statistics (OIS), an estimated 11.4 million unauthorized

immigrants resided in the U.S. as of January 2012 compared to 11.5 million in January 2011[73]. These results suggest no major change in the unauthorized immigrant population from 2011 to 2012. About 7.8 million unauthorized immigrants present in the U.S. in the 2009 to 2013 period (71% of the total unauthorized population) were born in Mexico and other Central American countries. About 1.5 million (14%) were from Asia, 690,000 (6%) from South America, 423,000 (4%) from Europe, Canada, or Oceania 342,000 (3%) from Africa, and 260,000 (2%) from the Caribbean [73].

Unauthorized Immigrants

The top five countries of birth for unauthorized immigrants were Mexico (56%), Guatemala (6%), El Salvador (4%), and Honduras and China (3% each) in 2012. TB is brought into the U.S. from Mexico and Central America in three ways: 1) persons with active TB disease move northward across the border; 2) persons with LTBI experience active disease after arrival in the U.S.; or 3) the U.S. residents touring Mexico, including immigrants, acquire TB disease after returning to the U.S. After a person with TB enters the U.S., further transmission might occur, which contributes to TB morbidity in the U.S. directly from source patients and indirectly from their contacts [75, 76].

Many factors contribute to higher TB incidence and complicate TB control efforts along the U.S. Mexico border. Mexico's higher TB rate of approximately 27 cases per100,000 population, compared with that of the

U.S. (3 cases per 100,000 population), and the migratory flow across the border result in elevated TB incidence in the geographic areas most affected by cross border immigration. Low socioeconomic status, crowded living conditions, and limited access to health care increase the risk for TB transmission on both sides of the border. Frequent bilateral border crossings and movement within the U.S. contribute to delays in TB diagnosis and impede treatment completion. Language and sociocultural differences also contribute to delays in seeking care and influence adherence to treatment.

Coordinating TB case management across an international border is complicated, and among certain TB patients, outcomes are compromised. Ultimately, lowering TB rates in the border area and reducing racial and ethnic disparities of TB disease depend on identifying and treating infected persons on both sides of the border until patients are cured. TB prevention and control efforts along the U.S.-Mexico border require the cooperation of local, state, and national TB control programs in both countries, including strategies for coordinated interventions and funding to ensure that adequate resources are available [77, 78].

The U.S. Mexico Border

The U.S.-Mexico border is approximately 2,000 miles long and separates four U.S. states (California, Arizona, New Mexico, and Texas) from six Mexican states (Baja California Norte, Sonora, Chihuahua, Coahuila, Nuevo Leon, and Tamaulipas). Approximately 1 million persons cross the

U.S. Mexico border daily. Major metropolitan areas span the border, including San Diego-Tijuana (population is 4 million persons), El Paso-Ciudad Juarez (1.9 million), Laredo-Nuevo Laredo (0.4 million), Brownsville-Matamoros (0.5 million), and Harlingen/McAllen-Reynosa (1 million). Two of these areas, San Diego-Tijuana and El Paso-Ciudad Juarez, account for 40% of daily border crossings. Although they are legally separate cities, these sister cities have become closely integrated with bi-national and bi-cultural communities by sharing social, environmental, and economic interests and problems [71 - 73].

Counties along the U.S.-Mexico border are among the poorest economically in the U.S. Approximately 33% of U.S. border families live at or below the poverty line compared with a national average of 11%. An estimated 400,000 persons live in the U.S. along the Texas border in semirural communities without access to public drinking water or wastewater systems. Unemployment rates in the border area are approximately threefold higher than those in the rest of the U.S. A total of 10 of 24 counties evaluated along the U.S.-Mexico border are medically underserved and of low socioeconomic status. Communicable diseases similar to brucellosis, measles, hepatitis A, hepatitis B, mumps, pertussis, salmonellosis, and shigellosis occurred at higher rates in the U.S. border counties than in non-border counties. Diabetes, which increases the risk for

TB, is also more common among Hispanics and American Indians compared with non-Hispanic whites [76, 77].

TB continues to be a concern for border areas in both Mexico and the U.S. Both countries report approximately 15,000 cases of all forms of TB on a yearly basis. In 2005, the TB incidence rate in Mexico was 15 per 100,000, while the U.S. reported a rate of 4.7 (3.0 in 2015) incident TB cases per 100,000 population. The U.S. - Mexico border states reported a TB incidence rate higher than the national average in 2015, with rates of 7.9 in U.S. border states and 26.3 in Mexican border states. In 2015, the total population in Mexico was 127 million and the TB incidence rate was 27 (compared to 3.0 in the U.S.) per 100,000 as per WHO's TB report. Data shows the TB risk in the immigrant population, mainly in Mexican immigrants considering the large numbers [73, 76, 77].

Resuming progress towards TB elimination in the U.S. will require intensification of efforts both in the U.S. and globally, including increasing U.S. efforts to detect and treat LTBI. Also, strengthening systems to interrupt TB transmission in the U.S. and globally, accelerating reductions in TB globally, particularly in the countries of origin for most U.S. TB cases. The reasons for the resurgence are complex, but four factors have generally been implicated. They were arrival and spread of HIV infection, immigration of people from high-prevalence countries, the development of "hot spots" (e.g.,

hospitals, shelters, prisons) where TB flourishes, and the deterioration of TB control.

LTBI in Immigrants

The rate of incident TB cases among foreign born persons in the U.S. was 12 times greater than among U.S. born persons in 2011. Addressing differences between TB rates in foreign and the U.S. born persons is necessary for TB elimination in the U.S. Consistent with reactivation of LTBI acquired abroad, there were approximately 80% of foreign born persons diagnosed with TB after being in the U.S. for more than two years. Most of these cases result from reactivation of LTBI, as immigrants are screened for active TB disease prior to leaving their country of origin [78]. A critical component of any national effort toward TB elimination in low incidence countries such as the U.S. must include effective strategies for the detection and treatment of LTBI amongst the foreign born individuals. This health undertaking anticipated to require extensive resources. Most immigrants to the U.S. originated from the regions of the world where TB is highly endemic. Also, TB infection prevalence are very high in those regions.

It is estimated that approximately 4% of the total U.S. population has LTBI. The rate among newly arriving immigrants has been well described. An estimated 12% of the children arriving in the U.S. were diagnosed with LTBI during the pre-immigration LTBI screening in 2010. Although TB was decreasing overall in the U.S., there was a disproportional increase in TB in

foreign born individuals. Following the approval by the U.S. Food and Drug Administration of two IGRAs, the CDC recommendation was revised in 2010 to state that IGRAs were the preferred initial test for persons who are likely to have received BCG vaccine [77 - 79].

Further Research

To improve efficiency of TB control methods in Georgia and the U.S., it is necessary to assess the TB incidence among immigrants in Georgia and LTBI prevalence in the U.S. Effective strategies for the detection and treatment of LTBI amongst the foreign born individuals would appear to be an essential component of any national effort toward TB elimination. This is very important for countries such as the U.S., with low TB incidence. LTBI screening programs should be targeted toward groups with high prevalence of infection or risks for reactivation to improve efficiency. It is necessary to have the accurate information to target specific populations.

Active TB disease incidence rates among foreign born individuals in the U.S. are increasing disproportionally, even though TB rates in the U.S. born individuals is continuing to decline. This study looked in to the TB incidence in Georgia among foreign born and the U.S. born population. This research provides the information on TB incidence and risk factors among immigrants in Georgia. Also, this study analysed the NHANES data for the years 1999-2000 and 2011-2012. NHANES data used to assess the BCG vaccination effects and interpretation of TST results for LTBI. LTBI in the

U.S. population using TST measurement and Quantiferon was also assessed using NHANES data.

It is necessary to provide TB screening tests considering the false positive tests in BCG vaccinated people. A positive reaction to a TB skin test may be due to the BCG vaccine itself or due to infection with TB bacteria. TB blood tests (IGRAs), unlike the TB skin test, are not affected by prior BCG vaccination and are not expected to give a false positive result in people who have received BCG. TB blood tests are the preferred method of TB testing for people who have received the BCG vaccine. This study looked in to whether BCG vaccination affects the results or interpretation of TST for LTBI in the U.S. population.

REFERENCES

1. World Health Organization. Global Tuberculosis Report 2015. Accessed on March 2018. https://www.who.int/news-room/fact-sheets/detail/tuberculosis.
2. Zaman K. Tuberculosis: a global health problem. *J Health Popul Nutr*. 2010; 28(2):111-3.
3. CDC. Reported tuberculosis in the United States, 2014. Atlanta, GA: US Department of Health and Human Services, CDC; 2015. http://www.cdc.gov/tb/statistics/reports/2014/default.htm
4. European Center for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance in Europe 2009. Stockholm: European Centre for Disease Prevention and Control; 2010.
5. Padmapriyadarsini C, Narendran G, Swaminathan S. Diagnosis & treatment of tuberculosis in HIV co-infected patients. *Indian J Med Res*. 2011;134(6):850-65.
6. Abarca TB, Pell C, Bueno CA, Guillen SJ, Pool R, Roura M. Tuberculosis in migrant populations: a systematic review of the qualitative literature. PLoS One. 2013;8(12):e82440. doi: 10.1371/journal.pone.0082440.
7. World Health Organization. Global Tuberculosis Report 2016. Accessed on March 2018. http://apps.who.int/medicinedocs/en/d/Js23098en

8. Coker R. Tuberculosis screening in migrants in selected European countries shows wide disparities. Eur Respir J. 2006;27(4):801–7. doi: 10.1183/09031936.06.00104305.14.
9. Alvarez GG, Gushulak B, Abu Rumman K, Altpeter E, Chemtob D, Douglas P, et al. A comparative examination of tuberculosis immigration medical screening programs from selected countries with high immigration and low tuberculosis incidence rates. BMC Infect Dis. 2011;11:3. doi: 10.1186/1471-2334-11-3
10. Stewart RJ, Tsang CA, Pratt RH, Price SF, Langer AJ. Tuberculosis — United States, 2017. MMWR Morb Mortal Wkly Rep 2018;67:317–323. DOI: http://dx.doi.org/10.15585/mmwr.mm6711a2. Accessed March 2018.
11. Centers for Disease Control and Prevention. Tuberculosis Data and Statistics 2017. https://www.cdc.gov/tb/statistics/default.htm. Accessed on March 2018.
12. U.S. Code § 1401. Nationals and citizens of United States at birth. https://www.law.cornell.edu/uscode/text/8/1401. Accessed on March 2018.
13. Salinas JL, Mindra G, Haddad MB, Pratt R, Price SF, Langer AJ. Leveling of Tuberculosis Incidence — United States, 2013–2015. MMWR Morb Mortal Wkly Rep 2016;65:273–278. DOI: http://dx.doi.org/10.15585/mmwr.mm6511a2. Accessed on March 2018.

14. Georgia Department of Public Health, 2014 Georgia Tuberculosis Report, Atlanta, Georgia, October 2016. Accessed on October 31, 2016. https://dph.georgia.gov/sites/dph.georgia.gov/files/2014.pdf.
15. Barberis I, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. *J Prev Med Hyg*. 2017;58(1):E9-E12.
16. Carl Zimmer, "Tuberculosis Is Newer Than Thought, Study Says", New York Times, 21 August 2014, Accessed 11/20/16
17. McHenry LC, Keith RM. Samuel Johnson's Childhood Illness and the King's Evil. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1033643/pdf/medhist00149-0084.pdf. Accessed dated 11/20/16.
18. History of Tuberculosis. http://www.hektoeninternational.org/Schwartz_TB.htm. Accessed dated 11/120/16
19. Murray JF. A Century of Tuberculosis. American Journal of Respiratory and Critical Care Medicine. https://www.atsjournals.org/doi/full/10.1164/rccm.200402-140OE. Accessed dated 11/120/16
20. Bacille Calmette Guerin (BCG) Vaccine. http://www.cdc.gov/tb/publications/factsheets/prevention/bcg.htm. Accessed on October 1, 2016

21. Testing for Tuberculosis Infection and Disease. CDC. https://www.cdc.gov/tb/education/corecurr/pdf/chapter3.pdf. Accessed on October 1, 2016
22. E. Vynnycky, P. E. M. Fine. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. Epidemiol. Infect. (1997), 119, 183-201. 1997 Cambridge University Press
23. The Difference between Latent TB Infection and TB Disease. CDC. https://www.cdc.gov/tb/publications/factsheets/general/ltbiandactivetb.htm. Accessed on October 1, 2016.
24. World Health Organization. The Natural History of Pulmonary Tuberculosis. Accessed on March 2018. https://apps.who.int/iris/bitstream/handle/10665/66906/WHO_CDS_CPE_SMT_2001.11.pdf;jsessionid=3DAF0BAC0B61ACDB3EFFF952A99D057B?sequence=1
25. Hunter RL. Pathology of post primary tuberculosis of the lung: an illustrated critical review. *Tuberculosis (Edinb)*. 2011;91(6):497-509.
26. Cooper AM. Cell-mediated immune responses in tuberculosis. *Annu Rev Immunol*. 2009;27:393-422.
27. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic

review. *PLoS One*. 2011;6(4):e17601. Published 2011 Apr 4. doi:10.1371/journal.pone.0017601

28. Weisz G, Cambrosio A, Keating P, Knaapen L, Schlich T, Tournay VJ. The emergence of clinical practice guidelines. *Milbank Q*. 2007;85(4):691-727.
29. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis—A critical review of the pre-chemotherapy literature. Int J Tuberc Lung Dis. 2004;8: 392–402.
30. Parascandola Mark;The epidemiologic transition and changing concepts of causation and causal inference, Revue d'histoire des sciences 2/2011 (Tome 64) , p. 243-262
31. Rothman KJ. Causes. Am J Epidemiol 1976; 104: 587–92.
32. Parascandola M. The Epidemiologic Transition and Changing Concepts of Causation and Causal Inference. URL : www.cairn.info/revue-d-histoire-des-sciences-2011-2-page-243.htm. Accessed October 1, 2016
33. Hawgood BJ (2007) Albert Calmette (1863–1933) and Camille Guerin (1872–1961): the C and G of BCG vaccine. J Med Biogr 15: 139–146.
34. Crofton J. The MRC randomized trial of streptomycin and its legacy: a view from the clinical front line. *J R Soc Med*. 2006;99(10):531-4.
35. Questions and Answers About Tuberculosis. CDC. https://www.cdc.gov/tb/publications/faqs/pdfs/qa.pdf. Accessed on October 1, 2016

36. Ai JW, Ruan QL, Liu QH, Zhang WH. Updates on the risk factors for latent tuberculosis reactivation and their managements. *Emerg Microbes Infect*. 2016; 5(2):e10. Published 2016 Feb 3. doi:10.1038/emi.2016.10

37. Dye C, Harries AD, Maher D, et al. Tuberculosis. In: Jamison DT, Feachem RG, Makgoba MW, et al., editors. Disease and Mortality in Sub-Saharan Africa. 2nd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2006. Chapter 13. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2285.

38. Ayub A, Yale SH, Reed KD, Nasser RM, Gilbert SR. Testing for latent tuberculosis. *Clin Med Res*. 2004;2(3):191-4.

39. Heemskerk D, Caws M, Marais B, et al. Tuberculosis in Adults and Children. London: Springer; 2015. Chapter 3, Clinical Manifestations. Available from: https://www.ncbi.nlm.nih.gov/books/NBK344404/

40. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. *Pulm Med*. 2013; 2013: 828939.

41. Tuberculosis (TB) Clinical Presentation. https://emedicine.medscape.com/article/230802-clinical. Accessed March 2016.

42. Whalen CC. The Replacement Principle of Tuberculosis. Why Prevention Matters. Editorial in American Journal of Respiratory and Critical Care

Medicine Volume 194 Number 4 | August 15 2016. Accessed on April 5. www.atsjournals.org.

43. T-SPOT.TB TEST. http://www.tspot.com. Accessed on April 4, 2018.
44. QuantiFERON-TB Gold (QFT). http://www.quantiferon.com/us/products/quantiferon-tb-gold. Accessed on April 4, 2018.
45. Geiter L. Ending neglect: the elimination of tuberculosis in the United States. Washington, D.C.: National Academy Press; 2000. [June 30, 2004]. Available at:http://books.nap.edu/books/0309070287/html/R1.html.
46. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med. 2000; 161((4 Pt 2)):S221–S247.
47. Laurens A. H. van Pinxteren, Pernille Ravn, Else Marie Agger, John Pollock, Peter Andersen. Diagnosis of Tuberculosis Based on the Two Specific Antigens ESAT-6 and CFP10. Published in Clinical and Vaccine Immunology Journal. Mar. 2000, p. 155–160; DOI: 10.1128/CDLI.7.2.155-160.2000

48. S.T. Cole, R. Brosch, J. Parkhill, T. Garnier, C. Churcher, D. Harris, et al. Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence, Nature 393 (1998) 537–544.

49. J.C. Camus, M.J. Pryor, C. Medigue, S.T. Cole, Re-annotation of the genome sequence of Mycobacterium tuberculosis H37Rv, Microbiol.148 (2002) 2967–2973.

50. S. Ahmad, H.A. Amoudy, J.E.R. Thole, D.B. Young, A.S. Mustafa, Identification of a novel protein antigen encoded by a Mycobacterium tuberculosis-specific RD1 region gene, Scand. J. Immunol. 49 (1999) 515–522.

51. Doherty TM, Demissie A, Olobo J, Wolday D, Britton S, Eguale T, Ravn P, Andersen P. Immune responses to the Mycobacterium tuberculosis-specific antigen ESAT-6 signal subclinical infection among contacts of tuberculosis patients. J Clin Microbiol 2002; 40:704–6. 26

52. Lalvani A, Nagvenkar P, Udwadia Z et al. Enumeration of T cells specific for RD1-encoded antigens suggests a high prevalence of latent Mycobacterium tuberculosis infection in healthy urban Indians. J Infect Dis 2001; 183:469–77

53. Schluger NW. Tuberculosis and nontuberculous mycobacterial infections in older adults. *Clin Chest Med*. 2007;28(4):773-81, vi.

54. Deciding When to Treat Latent TB Infection. CDC http://www.cdc.gov/tb/topic/treatment/decideltbi.htm. Accessed 11/20/16

55. Ayub A, Yale SH, Reed KD, Nasser RM, Gilbert SR. Testing for Latent Tuberculosis. *Clinical Medicine and Research*. 2004; 2(3):191-194.

56. Maloney SA, Fielding KL, Laserson KF, Jones W, Nguyen TN, Dang QA, et al. Assessing the performance of overseas tuberculosis screening programs: a study among US-bound immigrants in Vietnam.Arch Intern Med. 2006;166(2):234–40. doi: 10.1001/archinte.166.2.234.

57. Laurens A. H. van Pinxteren, Pernille Ravn, Else Marie Agger, John Pollock, Peter Andersen. Diagnosis of Tuberculosis Based on the Two Specific Antigens ESAT-6 and CFP10. Published in Clinical and Vaccine Immunology Journal. Mar. 2000, p. 155–160; DOI: 10.1128/CDLI.7.2.155-160.2000

58. Honore-Bouakline, S., Vincensini, J. P., Giacuzzo, V., Lagrange, P. H., & Herrmann, J. L. (2003). Rapid Diagnosis of Extrapulmonary Tuberculosis by PCR: Impact of Sample Preparation and DNA Extraction. Journal of Clinical Microbiology, 41(6), 2323–2329. http://doi.org/10.1128/JCM.41.6.2323-2329.2003

59. Interferon-Gamma Release Assays (IGRAs) – Blood Tests for TB Infection. CDC.GOV. https://www.cdc.gov/tb/publications/factsheets/testing/igra.htm. Accessed on April 4, 2018.

60. Raviglione, M., & Sulis, G. (2016). Tuberculosis 2015: Burden, Challenges and Strategy for Control and Elimination. Infectious Disease

Reports, 8(2), 6570. http://doi.org/10.4081/idr.2016.6570

61. United Nations General Assembly. United Nations Millennium Declaration, Resolution Adopted by the General Assembly, 2000, A/RES/55/2. Available from: http://www.refworld.org/docid/3b00f4ea3.html.

62. Treatment for TB Disease. CDC. https://www.cdc.gov/tb/topic/treatment/tbdisease.htm. Accessed March, 2018

63. Jing-Wen Ai, Qiao-Ling Ruan, Qi-Hui Liu, Wen-Hong Zhang (2016) Updates on the risk factors for latent tuberculosis reactivation and their managements. Emerg Microbes Infect. 2016 Feb; 5(2): e10. Published online 2016 Feb 3. doi: 10.1038/emi.2016.10

64. Revisiting Rates of Reactivation Tuberculosis: A Population-based Approach. C. Robert Horsburgh, Jr., Max O'Donnell, Sandra Chamblee, Janet L. Moreland, Johnny Johnson, Bryan J. Marsh, Masahiro Narita, Linda Scoles Johnson, C. Fordham von Reyn. Am J Respir Crit Care Med. 2010 Aug 1; 182(3): 420–425. Published online 2010 Apr 15. doi: 10.1164/rccm.200909-1355OC. PMCID: PMC2921602

65. Jie Zong, Jeanne Batalova. Frequently Requested Statistics on Immigrants and Immigration in the United States. http://www.migrationpolicy.org/article/frequently-requested-statistics-immigrants-and-immigration-united-states. Accessed on October 2016.

66. Miramontes R, Pratt R, Price SF, Jeffries C, Navin TR, Oramasionwu GE. Trends in Tuberculosis- United States, 2011. Morbidity and Mortality Weekly Report. 2012; 61(11).

67. US Census Bureau. The DataWeb: DataFerret. Washington, DC: US Department of Commerce, US Census Bureau; undated. http://dataferrett.census.gov. Accessed October 1, 2016.

68. U.S. Department of Justice/Immigration and Naturalization Service. Annual report: legal immigration, fiscal year 1998. Washington DC: U.S. Government Printing Office, 1999. Available at <http://www.ins.usdoj.gov:80/graphics/publicaffairs/newsrels/98Legal.pdf >. Accessed October 1, 2016.

69. U.S. Department of Justice/Immigration and Naturalization Service. 1997 statistical yearbook of the Immigration and Naturalization Service. Washington, DC: U.S. Government Printing Office, 1999. Available at <http://www.ins.usdoj.gov:80/graphics/aboutins/statistics/1997YB.pdf>. Accessed October 1, 2016.

70. Georgia Department of Public Health, 2014 Georgia Tuberculosis Report, Atlanta, Georgia, October 2014. Accessed on October 1, 2016

71. Jasmer RM, Ponce de Leon A, Hopewell PC, et al. Tuberculosis in Mexican-born persons in San Francisco: reactivation, acquired infection and transmission. Int J Tuberc Lung Dis 1997; 1:536--41.

72. Chin DP, DeRiemer K, Small PM, et al. Differences in contributing factors to tuberculosis incidence in U.S.-born and foreign-born persons. Am J Respir Crit Care Med 1998; 158:1797-- 803.

73. Office of Immigration Statistics. https://www.dhs.gov/office-immigration-statistics. Accessed on October 1, 2016

74. Tornieporth NG, Ptachewich Y, Poltoratskaia N, et al. Tuberculosis among foreign-born persons in New York City, 1992--1994: implications for tuberculosis control. Int J Tuberc Lung Dis 1997;1: 528--35.

75. Lobato MN, Hopewell PC. Mycobacterium tuberculosis infection after travel to or contact with visitors from countries with a high prevalence of tuberculosis. Am J Respir Crit Care Med 1998;158:1871--5.

76. Ailinger RL, Dear MR. Adherence to tuberculosis preventive therapy among Latino immigrants. Public Health Nurs 1998;15:19--24.

77. Doyle TJ, Ellinas P, Bryan RT. Infectious disease morbidity in the U.S. region bordering Mexico [Abstract]. International Conference on Emerging Infectious Diseases; March 8--11, 1998, Atlanta, GA.

78. Ricks PM, Cain KP, Oeltmann JE, Kammerer JS, Moonan PK. Estimating the burden of tuberculosis among foreign-born persons acquired prior to entering the U.S., 2005–2009. PLoS One. 2011;6 (11):e27405. doi: 10.1371/journal.pone.0027405.

79. Kamper-Jorgensen Z, Andersen AB, Kok-Jensen A, Kamper-Jorgensen M, Bygbjerg IC, Andersen PH, et al. Migrant tuberculosis: the extent of

transmission in a low burden country. BMC Infect Dis. 2012;12:60. doi: 10.1186/1471-2334-12-60.

CHAPTER 3

METHODOLOGY

Methodology for Specific Aim One

1. To determine the annual incidence rate for active TB disease in the immigrant population in Georgia after their arrival to the U.S.

   H_0: There is no difference in the annual incidence rate for active TB disease between immigrants and non-immigrants in Georgia.

   H_1: There is a difference in the annual incidence rate for active TB disease between immigrants and non-immigrants in Georgia.

Study Population and Setting

The study was conducted using secondary data analysis of the Georgia Department of Health (GDPH) active TB disease database. GDPH data was collected through U.S. Department of Health and Human Services, Division of Centers for Disease Control (CDC) and Prevention. The Tuberculosis Surveillance Data Report of Verified Case of Tuberculosis (RVCT) was used for the data collection of the first aim. In order to address the first aim, all active TB disease cases from the years 2004 to 2016 reported to GDPH were included as a fixed convenience sample. All participants gave written informed consent given at the time of data collection. An IRB application was submitted to GDPH which was approved.

RVCT Data Collection

RVCT data collection instructions and modules were prepared by the branches within the Division of Tuberculosis Elimination (DTBE) at the CDC. A U.S. national surveillance system was established in 1953 to collect information on new cases of active TB. Since 1985, all states have been reporting TB cases to the CDC using RVCT, the national TB surveillance form. Data are collected by state and local TB programs and submitted electronically to DTBE. These data are used to monitor national and state TB trends, identify priority needs, and create the DTBE annual surveillance report. National guidelines require and recommend state health departments to use the RVCT forms for all verified cases of TB case reporting.

Exclusion Criteria

There was no exclusion of TB disease cases since the study plan was to include all cases from 2004 to 2016 in the analysis.

Study Design

This aim used a retrospective cohort study design for analysis. Data was already collected based on national and state guidelines regarding notifiable disease.

Data Collection

A data request was submitted to GDPH for TB data for the years 2004 to 2016. Immigrants were defined as people born outside the U.S. and not born to a U.S. citizen based on the information given in GDPH database.

Birth country data was used to create 5 locations named South America, Asia, Africa, Europe, and the U.S. Number of immigrants in Georgia is approximately 10% of the population which is estimated to be 1 million people.

Study Outcome

The outcome of this aim was active TB disease using GDPH data.

Exposure

The exposure in this analysis was country of origin and year of immigration to the U.S. Immigrants were defined as people born outside U.S and not born to a U.S. citizen. Birth country data was used to create 5 locations: America other than the U.S, Asia, Africa, Europe, and the U.S. Time was calculated from date of entry in to the U.S. to date of diagnosis of active TB disease.

Sample Size Estimations

We considered a fixed sample size for this study since we planned to analyse secondary data from GDPH. There estimated that there were 5,315 cases in GDPH database from the years 2004 to 2016. A sample size calculation was done to assess the required minimum sample size. We estimated an effect size of 0.1 with a sample size of 5,315, which was a small effect size for rare diseases. The overall sample size was dependent on the sample size requirements to detect variations in the effect of a risk factor. The sample size was calculated on the basis of the following parameter

specifications: (a) Total sample size=5,315; (b) beta/alpha ratio=1; (c) effect size=0.1. A sample size of 1,300 with a degree of freedom=1 will provide a power of 0.95. Figure 4 given below shows the sample size and effect size calculation.

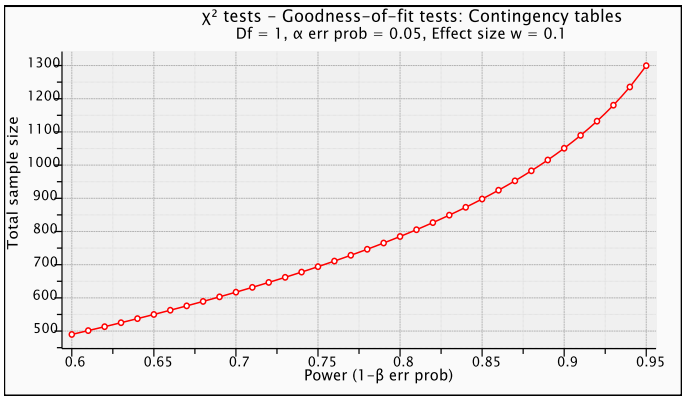

Figure 4: Total sample size and Effect size

Analytic Strategy for Aim One

General Approach

In general, we started with cleaning and editing of the dataset. Item analysis was conducted for descriptive data. Pearson and Spearman Correlation analysis was used to assess the relationship between variables since there were continuous and discreet variables. Univariate analysis was conducted on explanatory and outcome variables to assess the central tendency (mean, mode and median) and dispersion: range, variance, maximum, minimum, quartiles (including the interquartile range), and

standard deviation. A chi-square test was used to assess the association between each variable and the likelihood of TB disease with binary data.

Descriptive statistics were used to present the characteristics of the participants. Adjustment for age was necessary since almost all diseases or health outcomes occur at different rates in different age groups. TB may occur in different rates in young and old people. The output/code/data analysis for this paper was generated using SAS software. Copyright © [2018] SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Incidence is a measure of disease to determine a person's probability of being diagnosed with a disease during a given period of time. Incidence proportion (cumulative incidence) is the probability of developing disease over a stated period of time. Incidence proportion doesn't distinguish when a disease occurs as long as it is within the follow up period.
Incidence Rate = number of new case over the particular period of time x 100,000/size of the population at risk.

To address this aim, we estimated the annual incidence rate of TB disease among immigrants in Georgia by calculating the proportion with a positive diagnostic test. This was done as a crude analysis. The estimated annual incidence of TB disease in the Georgia immigrant population was calculated by examining the total TB cases in immigrants between the years

2004 to 2016 from the GDPH TB cases database. Incidence rate ratios (IRR) with 95% confidence interval was calculated for state and counties with 4 or more TB incidence cases between immigrants and non-immigrants.
An immigrant is defined as an individual born in countries in America other than the U.S including Mexico, Guatemala, and Canada, Asia, Africa, and Europe based on the information given in the GDPH database. The total cases for 13 years were calculated and an estimate for one year was applied to find the cumulative incidence.

The overall population in Georgia for 2010 was 9,688,680 and the total documented immigrant population was 920,381. The overall population in Georgia for 2016 was 10,310,371 and the total immigrant population was 1,038,312. The years 2010 and 2016 were chosen since the U.S. Census Bureau maintained data on Georgia's immigrant population for those years. An average incidence for TB cases in Georgia was calculated from 2004 to 2016 and applied to the 2016 population number to find the overall incidence rate per 100,000 for the overall population. The lack of availability of the actual documented immigrant population per year from 2004 to 2016 led to the decision to not calculate annual incidence per every year. Due to this decision, 2010 and 2016 were chosen as the median and latest years. Using estimated numbers of immigrants for the denominator may not provide the most accurate interpretation for rare diseases.

Methodology for Specific Aim Two

2. To describe the distribution of known risk factors for incident active TB disease among the immigrant population compared to non-immigrants in Georgia.

   H_0: The distribution of known risk factors does not differ between immigrants and non-immigrants with active TB disease in each group.

   H_1: The distribution of known risk factors does differ between immigrants and non-immigrants with active TB disease in each group.

Study Population and Setting

The study was conducted using secondary data analysis of data received from GDPH for cases of active TB disease cases in the state of Georgia. GDPH data was collected through the CDC Tuberculosis Surveillance Data Report of Verified Case of Tuberculosis (RVCT). The data used for this aim included all active TB disease cases reported to the GDPH from the years 2004 to 2016. All participants in the database gave written informed consent at the time of data collection for these datasets.

RVCT data collection instructions and modules were prepared by DTBE, a branch within CDC. A U.S national surveillance system was established in 1953 to collect information on new cases of active TB. Since 1985, all states have been reporting TB cases to the CDC using RVCT, the national TB surveillance form. Data were collected by state and local TB programs and submitted electronically to DTBE. These data are used to

monitor national TB trends, identify priority needs, and create the DTBE annual surveillance report. National guidelines require and recommend state health departments to use the RVCT forms for all verified cases.

Exclusion Criteria

There was no exclusion of active TB disease cases since the study plan was to include all cases from 2004 to 2016 in the analysis.

Study Design

This aim used a retrospective cohort study design for analysis. Data were already collected using national guidelines.

Data Collection

A data request was submitted to the GDPH for TB data from the years 2004 to 2016. The immigrants were defined as people born outside the U.S. and not born to a U.S citizen based on the information given in DPH database. Birth country data was used to create 5 locations: America other than the U.S including Mexico, Guatemala, and Canada, Asia, Africa, Europe, and the U.S. Sex, diabetes, HIV status, TB contact, LTBI treatment status, immunosuppressant status, and alcohol use were gathered by GDPH and were used in the analysis as risk factors. The time in years from entry in to the U.S. to the diagnosis of active TB disease were used for survival analysis.

Study Outcome

The outcome of the aim two was active TB disease using GDPH data.

Exposure

The exposure in this analysis was country of origin and time in years of immigration to the U.S. The immigrants were defined as people born outside the U.S. and not born to a U.S. citizen. Time was calculated from the date of entry in to the U.S. to the date of diagnosis of TB disease.

Effect Modifier/Interaction

Interactions between risk factors were assessed. Interaction is the variation in the magnitude of the measure of effect across levels of a third variable. Effect modification is not a bias, but useful information and happens when an odds ratio or relative risk is different between subgroups or strata of a population.

Confounders

Confounding is a distortion in the estimated measure of association that occurs when the primary exposure of the interest is mixed up with some other factor that is associated with the outcome. By definition, a confounding variable must be associated with both the risk factor of interest and the outcome must be distributed unequally among the groups being compared, and cannot be an intermediary step in the causal pathway from the exposure of interest to the outcome of interest. There are three methods to identify confounders. One method is to compare the estimated measure of association before and after adjusting for confounding. If the difference between the two measures of association is 10% (an arbitrary value) or more, then

confounding is present. If there is a clinically meaningful relationship between the variable and the risk factor and between the variable and the outcome, regardless of statistical significance, one should perform formal statistical tests of hypothesis to assess the association (Figure: 5, 6).

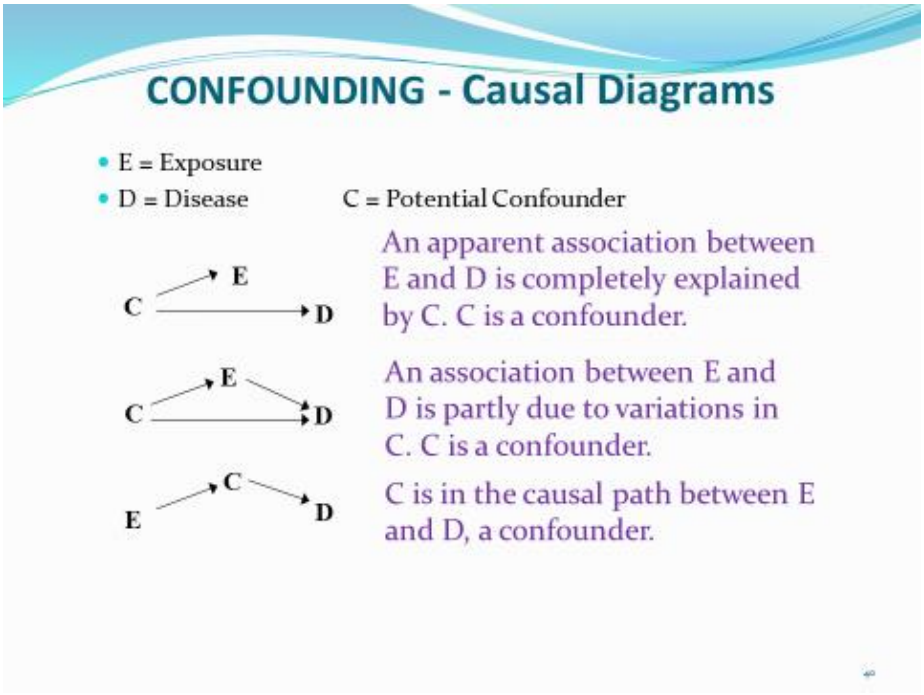

Figure 5: Confounding causal diagrams
(EPI 809/Spring 2008;http://www.msu.edu/~fuw)

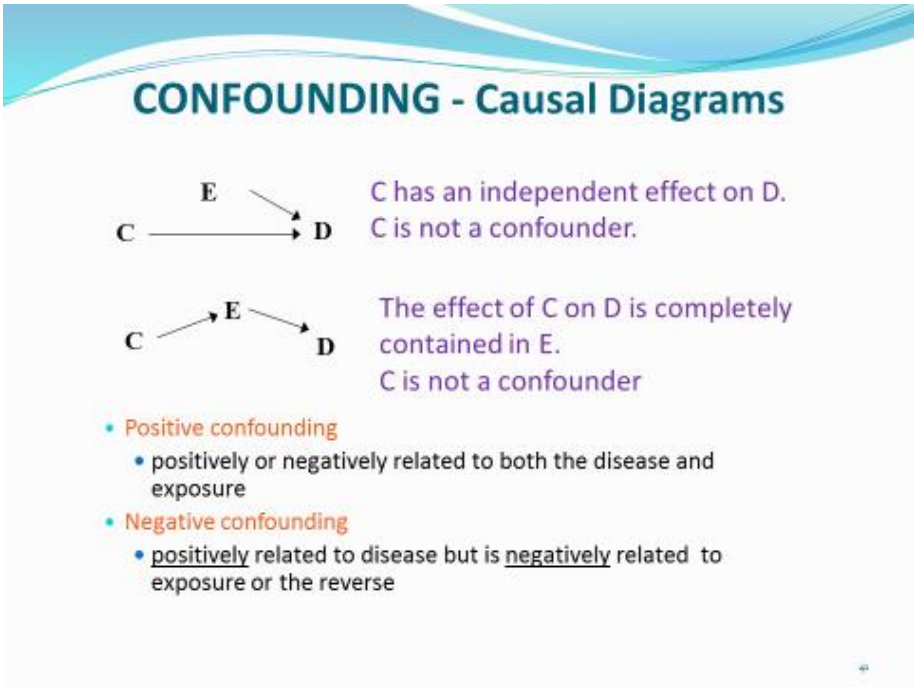

Figure 6: Confounding causal diagrams
(EPI 809/Spring 2008;http://www.msu.edu/~fuw)

The main confounder for this analysis was age. Age is a potential confounder because it is likely associated with both immigration into the U.S. and with active TB disease. Using the CMH test, the adjusted odds ratios were obtained and the difference was calculated from crude odds ratios. The CMH method produces a single, summary measure of association, which provides a weighted average of the odds ratios across the different strata of the confounding factor.

Covariates

Immigration status, sex, diabetes, HIV status, TB contact, LTBI treatment status, immunosuppressant status, and alcohol use were used in

the analysis as risk factors. Time from entry in to the U.S. to diagnosis of TB disease were used for survival analysis. Diabetes Mellitus was categorized from the additional TB risk factors in the dataset. Additional TB risk factors in the dataset included TB contact, LTBI incomplete therapy, immunosuppression, and excess alcohol use data were used to create categorical data for those covariates. HIV status information was also included in the dataset. TB case information was calculated from the case verification variable which includes NAA positive case, positive culture, and positive smear/Tissue methods. Median age was used to categorise the age variable.

Sample Size Estimations

We considered a fixed sample size for this study aim two as given for aim one above since we planned to analyse secondary data from GDPH.

Analytic Strategy for Specific Aim Two

General Approach

In general, we started with cleaning and editing of the dataset. Item analysis was conducted for descriptive data. Pearson and Spearman Correlation analysis was used to assess the relationship between variables since there were continuous and discreet variables. Univariate analysis was conducted on explanatory and outcome variables to assess the central tendency (mean, mode and median) and dispersion: range, variance, maximum, minimum, quartiles (including the interquartile range), and

standard deviation. A chi-square test was used to assess the association between each variable and the likelihood of TB disease with binary data.

A stratified analysis using Cochran-Mantel-Haenszel method (CMH) was used to assess the relationship with explanatory variables and outcome variables. A stratified analysis using the CMH method was used to assess the relationship with explanatory variables and outcome variables. Also, descriptive statistics were used to present the characteristics of the participants. Adjustment for age is necessary since almost all diseases or health outcomes occur at different rates in different age groups. TB may occur in different rates in young and old people. This was a secondary data analysis; dataset was obtained from GDPH located in Atlanta, Georgia. An IRB application was submitted to GDPH. The main outcome of the aim was TB disease. The output/code/data analysis for this paper was generated using SAS software. Copyright © [2018] SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

To address this aim, we performed a stratified analysis by region/country of origin and risk factors in the model. Data was recoded to find the number of people born outside the U.S. and number of years were calculated from the data. A chi-square test was used to assess the association between the variables with binary data and TB disease. Interaction was tested using the Breslow-Day test for homogeneity between strata. Odds

ratios were calculated for each explanatory variable with TB disease, and the difference between crude odds ratios and stratums were calculated to assess confounding. A stratified analysis using CMH method were used to assess the relationship between explanatory variables and TB disease. A logistic regression analysis was conducted, too.

Independent variables were origin of country and time in years entered in to the U.S. Survival times were calculated using the Kaplan-Meier (KM) method to assess survival rates and the median survival time. KM curves were plotted for subjects with TB disease and other variables. The KM estimate is the simplest way of computing the survival over time in spite of difficulties associated with subjects or situations. The survival curve can be created assuming various situations. It involves computing the probabilities of occurrences of events at a certain point of time and multiplying these successive probabilities by any earlier computed probabilities to get the final estimate. The log-rank test was used to test whether the difference between survival times between two groups is statistically different or not.

The log-rank test was used to test whether the difference between survival times between two groups is statistically different or not, but this method does not allow testing of the effect of the other independent variables. The survival probability at any particular time is calculated by the formula given below:

$$S_t = \frac{Number\ of\ subjects\ living\ at\ the\ start - Number\ of\ subjects\ died}{Number\ of\ subjects\ living\ at\ the\ start}$$

The two survival curves can be compared statistically by testing the null hypothesis (i.e. there is no difference regarding survival among two interventions). This null hypothesis was statistically tested by another test, known as the log-rank test and Cox proportional hazard test. In the log-rank test we calculate the expected number of events in each group (i.e. E1 and E2 while O1 and O2 are the total number of observed events in each group, respectively). The test statistic is:

$$Log - rank\ test\ statistic = \frac{(O_1 - E_1)^2}{E_1} + \frac{(O_2 - E_2)^2}{E_2}$$

Methodology for Specific Aim Three

3. To assess latent tuberculosis infection (LTBI) in the U.S. population.

a). To determine whether bacille Calmette-Guerin (BCG) vaccination affects the results of the tuberculin skin test (TST) for LTBI in the U.S. population.

H_0: BCG vaccination is not associated with the results of TST for LTBI in the U.S. population.

H_1: BCG vaccination is associated with the results of TST for LTBI in the U.S. population.

b). To compare TST and Quantiferon diagnostic measurements for LTBI in the U.S. population

H_0: There is no difference between TST and Quantiferon diagnostic accuracy in assessing LTBI in the U.S. population.

H_1: There is a difference between TST and Quantiferon diagnostic accuracy in assessing the LTBI in the U.S. population.

Study Population and Setting

The study was conducted using secondary data analysis of National Health and Nutrition Examination Survey (NHANES) data. NHANES data for the years 1999-2000 was used for addressing the third aim, part (a) and NHANES data for the years 2011-2012 was used for addressing the third aim part (b).

National Health and Nutrition Examination Survey

The National Health Survey Act to provide the legislative authorization for a continuing survey to provide current and detailed statistical data on the amount, distribution, and effects of illness and disability in the U.S. was passed in 1956. Three sources were recognised for data collection efforts; direct interview from people; laboratory data and physical examinations from sample persons (SPs); from health care settings. NHANES surveys data were obtained from the U.S. population. Data were collected by direct interviewing participants at their homes and at mobile examination centers (MECs). Fifteen survey locations per year were used to

conduct the examination component of the NHANES survey. A 2-year cycle is used to release NHANES data. TB skin-testing component of NHANES is handled by CDC. Testing for TB infection are offered for all participants aged 6 years or older.

NHANES Data Collection Methods

NHANES data are obtained using a complex, multistage, probability sampling design. Exclusion criteria was applied for persons residing in nursing homes, members of the armed forces, institutionalized persons, or the U.S. nationals living abroad. A four step process was used to collect data. In stage one, primary sampling units (PSUs) from single counties or groups of contiguous counties were selected. In stage two, PSUs were divided in to segments. In stage three, a sample is randomly drawn from households within each segment. From each households, individuals were drawn at random within subdomains of age, sex, race, and ethnicity in the fourth stage. Each SP is assigned a sample weight to produce an unbiased national estimate [1, 2].

Inclusion Criteria

NHANES data for the year 1999-2000 and 2011-2012 were included in the analysis for the study aim three, part a and part b. All participants in the database gave written informed consent at the time of data collection for these datasets.

Exclusion Criteria

There was no exclusion of cases since the study plan is to include all cases in the dataset.

Data Collection

Data from the NHANES website were downloaded for the years 1999-2000 and 2011-2012. NHANES data is publicly available in small datasets for different variables groups.

For part a, an analysis-ready dataset for the years 1999-2000 was created by merging NHANES datasets of demographics, TB TST results, blood pressure, body mass index, HIV, and glycohemoglobin. BCG information based on scarring was available for immigrant participants in this dataset.

For part b, an analysis-ready dataset for the year 2011-2012 was created by merging NHANES datasets for demographics, TB TST results, TB Quantiferon test results, blood pressure, body mass index, exhaled nitric oxide concentration, HIV, vitamin D, and glycohemoglobin. There was no BCG information collected for immigrants in this dataset.

Study Design

A retrospective cohort study design was used for aim three.

Study Outcome

Diagnosis of LTBI was the outcome for aim three, using NHANES data sets.

Exposure

The exposure in this analysis was country of origin and BCG vaccination. Immigrants were defined as people born outside the U.S. and not born to a U.S. citizen. Birth country data was used to create 5 locations: South America, Asia, Africa, Europe, and the U.S. and then combined as a variable for immigrants. BCG information was collected on the visual confirmation of a scar for immigrant participants in this dataset.

Effect Modifier/Interaction

Interaction between risk factors were assessed. Interaction is the variation in the magnitude of the measure of effect across levels of a third variable. Effect modification is not a bias but useful information and happens when odds ratio (or relative risks) are different between subgroups or strata of a population. This will help to identify a subgroup with lower or high risk and help to formulate public health actions. Interaction occurs when the incidence rate of disease in the presence of two or more risk factors differs from the incidence rate expected to result from individual effects. The effect can be greater than would be expected, which is called positive interaction or synergism, or less than would be expected, which is known as negative interaction or antagonism. If there is an association, first confirm if it is due to confounding. If not, look for differences between strata formed on the basis of the third variable. If there are differences present between strata, then interaction or effect modification is present. Otherwise, no interaction or

effect modifier is present. The Breslow –Day test for homogeneity/interaction can test the odds ratio between explanatory variable and outcome amongst different levels of the variable of interest using CMH. Interaction is confirmed if the p-value is less than 0.10. Cox proportional hazards regression analysis can be used to test the interaction using the -2log likelihood approach, which uses the main model as the reference.

Confounders

Confounding is a distortion in the estimated measure of association that occurs when the primary exposure of interest is mixed up with some other factor that is associated with the outcome. By definition, a confounding variable must be associated with both the risk factor of interest and the outcome, must be distributed unequally among the groups being compared, cannot be an intermediary step in the causal pathway from the exposure of interest to the outcome of interest. There are three methods to identify confounders. First compare the estimated measure of association before and after adjusting for confounding. If the difference between the two measures of association is 10% (an arbitrary value) or more, then confounding is present. If there is a clinically meaningful relationship between the variable and the risk factor, and between the variable and the outcome, regardless of statistical significance, perform statistical formal tests of hypothesis to assess the association.

The main confounders for this analysis are likely to be age and BCG vaccination. Age is a potential confounder because it is likely associated with immigration into the U.S. and associated with TB disease. BCG may cause a false positive TST reaction. Using CMH Test, adjusted odds ratios were obtained and the difference were calculated from the crude odds ratio. The CMH produces a single, summary measure of association which provides a weighted average of the odds ratio across the different strata of the confounding factor.

Covariates

Sex, number of people living in same household (crowding), BCG scar, HIV status, BMI, income, TB TST results, TB Quantiferon test results, blood pressure, cholesterol, HDL cholesterol, HIV positive or negative status, LDL cholesterol, triglyceride, exhaled nitric oxide concentration, vitamin D, length of time in the U.S., and glycohemoglobin were the covariates in this analysis. Sex includes males and females. Crowding was calculated based on the number of people in the same household. In this analysis, crowding was defined as a household with more than four people. This definition was an arbitrary selection for analysis since there was not a defined number for crowding available. The BCG scar was noted in the dataset, and it was collected based on the observation of a scar on the participant's body.

BMI measurement was provided in the dataset as a continuous variable and it was used to calculate obesity. If BMI was greater than or

equal to 30, then that individual was considered obese as per the National Institutes of Health (NIH) definition. An income less than $25,000, an arbitrary selection, was considered as poverty status. TST data was continuous and is used to create the latent TB variable. If the TST reading was greater than or equal to 10 then it was considered as latent TB infection diagnosis, based on the CDC guidelines for immigrants who are from countries with high incidence of TB disease.

The degree of induration on skin testing in high risk populations is assessed differently. Individuals with HIV infection, recent contact with active TB, prior TB cases, or immunosuppressant persons are advised for latent TB infection treatment if the induration is 5 mm or above. Immigrants, intravenous drug users, alcoholic individuals, persons spending time in high risk areas, mycobacteriology laboratory workers, medical conditions with weak immune systems, or young children aged 4 years of age or younger should get latent TB treatment if the induration is 10 mm or above. Persons with unknown risk factors with 15 mm induration or above should get latent TB treatment.

The TB Quantiferon test results were noted as positive, negative, or indeterminate in the 2011-2012 data only for part b of the aim three. Cholesterol was considered high if it is greater than or equal to 200, LDL was high if it is greater than or equal to 100, HDL was low if it is less than or equal to 50, and triglyceride was high if it is greater than or equal to 100 as

per the NIH guidelines. Time in the U.S. was calculated using the given variables for immigrants. Blood pressure was high if Systolic BP is greater than 120 or diastolic BP is greater than 90, as per the NIH guidelines.

In addition to the above, 2011-2012 dataset contain exhaled nitric oxide (FeNO) concentration and vitamin D measurements. If the FeNO concentration is greater than 0.35 ppb then that individual was considered to have higher inflammation of airways according to American Thoracic Society. FeNO is a biomarker of airway inflammation in mild to moderate asthma. Vitamin D is considered deficient if it was less than 100 nmol/L.

Statistical Considerations

Sample Size Estimations

We considered a fixed convenient sample size for this study since we plan to analyse secondary data from NHANES datasets. Since this was a secondary analysis, we did not need to calculate the sample size but the NHANES dataset for 1999-2000 has an estimated 9,965 observations. For the year 2011-2012, there were an estimated 9,756 observations.

The overall sample size is dependent on the sample size requirements to detect variations in the effect of a risk factor. The sample size is calculated on the basis of the following parameter specifications: (a) Total sample size=9,965 and 9,756; (b) beta/alpha ratio=1; (c) effect size=0.1. A sample size of 1,300 with a degree of freedom=1 will provide a power of 0. 95. Figure 7 given below is showing the sample size and effect size calculation.

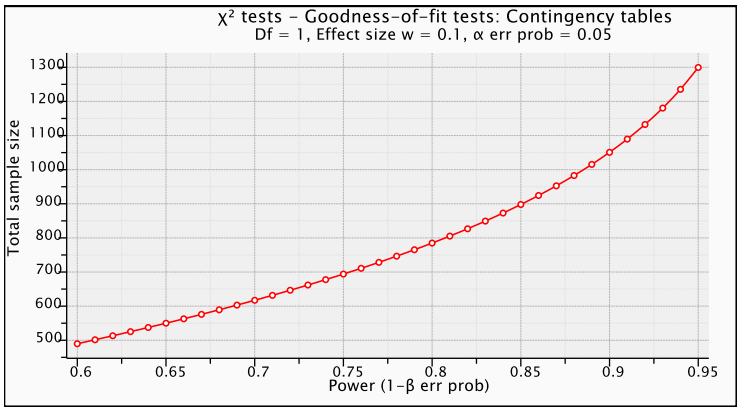

Figure 7: Power analysis

Analytic Strategy for Specific Aim Three

General Approach

In general, we started with cleaning and editing the dataset. Item analysis was conducted for descriptive data. Pearson and Spearman correlation analysis was used to assess the relationship between variables, since there were continuous and discreet variables. Univariate analysis was conducted on explanatory and outcome variables to assess the central tendency (mean, mode and median) and dispersion (range, variance, maximum, minimum, quartiles, including the interquartile range, and standard deviation). A chi-square test was used to assess the association between the variables with binary data. A stratified analysis with CMH

method was used to assess the relationship with explanatory variables and outcome variables. Also, descriptive statistics was used to present the characteristics of the participants. Adjustment for age is necessary since almost all diseases or health outcomes occur at different rates in different age groups. TB may occur in different rates in young and old people. The output/code/data analysis for this paper was generated using SAS software.

The main outcome of this aim is diagnosis of LTBI. LTBI was determined using the TST measurements. The exposure of interest was country of origin outside of the U.S. BCG vaccination may act as a confounder and assessed on all participants. Other covariates were taken from the dataset. It was used to determine whether BCG vaccination affects the diagnosis of LTBI.

To address this aim, we performed a stratified analysis by region/country of origin and risk factors in the data. Data were recoded to find the number of people born outside of the U.S. BCG vaccination information was available only in the 1999-2000 dataset for part a. A chi-square test was used to assess the association between the variables with binary data and LTBI- status. Interaction was tested using Breslow-Day-test for homogeneity between strata.

Prevalence ratios were calculated and the difference with crude odds ratio and stratums were calculated to assess the confounding. If the RR is 1 (or close to 1), it suggests no difference or little difference in risk of LTBI (incidence in each group is the same) based on immigrant status. A risk ratio greater than 1 suggests an increased risk of LTBI in the immigrants. A risk ratio less than 1 suggests a reduced risk in the immigrant group. When the RR is greater than 1; the percent increase = (RR - 1) x 100, increase in risk of LTBI. When the RR is less than 1; the percent decrease = (1 - RR) x 100, decrease in risk of LTBI. Those who exposed to BCG vaccination may have a certain percentage of reduction in risk of TB infection, LTBI, compared to those who did not take BCG vaccination.

A stratified analysis using CMH method was used to assess the relationship among explanatory variables and LTBI. The independent variables were BCG vaccination and country of origin. We used percent agreement and the Kappa method to determine the concordance between the TST and Quantiferon test for LTBI for part b.

Mixture method analysis was used to analyze the data for TST results. Non-specific causes may interact with distributions of TB infection. This method will help to separate non-specific causes from underlying component distributions of TB infection. A finite mixture model is a mixture of K component factors drawn from populations. Mixture models may help to

capture the heterogeneity in the TST induration if TST cross react with non-Tuberculosis Mycobacterium infection. Let λ_i represent the proportion of the total population that the i^{th} component population constitutes and let $f_i(x)$ represent the probability density function for the i^{th} component population. If the measure of TST induration is X which is a random variable from sample space *w,* the probability density function will be $g(x)=\lambda_1 f_1(x)+\ldots\ldots+\lambda_k f_k(x)$, $x \in w, 0 \leq \lambda_i \leq 1; \lambda_{1+\ldots\ldots+}\lambda_{k=1,}$ where i= 1….k, then we say g(x) is a finite mixture of k components. The parameters $\lambda_{1\ldots\ldots}\lambda_k$ are called missing proportions representing the proportion of the population in each component. $f_1(x)\ldots\ldots f_k(x)$ are the probability density functions of the random variable X in each component [3]. We looked in to 2, 3, and 4 component factors and selected the 2 component factor as the best model. SAS software The 'PROC FMM' procedure within SAS software was used to fit the model.

Ethical Considerations

This study was submitted to the Institutional Review Boards (IRBs) of the Georgia Department of Health, Augusta University, and the University of Georgia for permission. We received permission from all three IRBs to conduct this study. We took utmost care to meet HIPAA regulations and patient safety. The methods we used don't identify the cases and with minimum risks to participants. We will report the results to the government agencies as per laws. This study will help the participants as well as the community.

REFERENCES

1. International Journal of Tuberculosis and Lung Disease 7, S29–S37.
2. NHANES:https://www.cdc.gov/nchs/tutorials/nhanes/surveydesign/sampledesign/info1.htm. Accessed April 11, 2018
3. Titterington DM, Smith AF, Makov UE. Statistical analysis of finite mixture distributions. Wiley; 1985

CHAPTER 4

RESULTS

This study was conducted as a secondary data analysis of two databases, the Georgia Department of Health (GDPH) and the National Health and Nutrition Examination Survey (NHANES). GDPH data was collected through U.S. Department of Health and Human Services Division of Centers for Disease Control and Prevention (CDC) Tuberculosis Surveillance Data Report of Verified Case of Tuberculosis (RVCT), which were used for the first two study aims. NHANES data for the years 1999-2000 and 2011-2012 were used for addressing the third aim with two parts.

RESULTS FOR SPECIFIC AIM ONE

1. To determine the annual incidence rate for active TB disease in the immigrant population in Georgia after their arrival to the U.S.

   H_0: There is no difference in the annual incidence rate for active TB disease between immigrants and non-immigrants in Georgia.

   H_1: There is a difference in the annual incidence rate for active TB disease between immigrants and non-immigrants in Georgia.

Characteristics of Immigrant and Non-Immigrants with TB Disease

The dataset was received from GDPH in a partially de-identified format for 5,315 active TB patients in Georgia. The dataset included TB disease patients from 2004 to 2016. Table 6 summarizes demographic

information for the study population. Males comprised 64% (3,403) of the data, individuals who identified as black comprised 50.2% (2,667) of the data, and individuals who identified as white comprised 14.3% (762) of the data. Birth country data was used to create 5 locations: the Americas without U.S. cases, Asia, Africa, Europe, and the U.S.

There were 860 (38.4%) TB cases from the Americas (which include South America and Canada) without U.S. cases, Asia followed with 857 (38.3%), Africa with 479 (21.4%), and Europe with 44 (1.9%) among the immigrants. There were 3,063 (57.6%) cases from the U.S. The percentage of unemployed individuals was 41.3% (2,193) and overall, most of the patients were in the 20 to 59 age group.

In the entire dataset, 42.2% (2,240) were immigrants to the U.S. Among the immigrants, 62.1% (1,390) were identified as male compared to 65.5% (2,005) in non-immigrants. Regarding race and ethnicity, 35.9% (803) identified as Asians, 36.2% (810) as Hispanics, and 23.1% (517) as Blacks among immigrants compared to 1.8% Asians, 5.1% Hispanics, and 70.2% among non-immigrants. Regarding employment, 19.2% (429) were unemployed among immigrants compared to 22.1% among non-immigrants.

Table 7 summarizes the age distribution of immigrants at entry and at time of TB diagnosis for immigrants, as well as the age at diagnosis for non-immigrants. The median age of TB diagnosis was 42 overall. The median age of immigrants at time of entry in to the U.S. was 27, and the median age of

immigrants at the time of TB diagnosis was 36. The largest age group at diagnosis was the 20 to 39 old age group for immigrants compared to the 40 to 59 year old age group for non- immigrants. Regarding recurrent TB cases, this was slightly more common among immigrants than non-immigrants (5.4% vs 4.2%). Of all incident TB cases among immigrants during 2004 to 2016, 42.9% (962) occurred within five years of their entry in to the U.S.

Table 8 summarizes the known risk factors among overall, immigrant and non-immigrant TB cases in Georgia. Overall, the most common known risk factors for TB were HIV positive (11.5%), diabetes (5.9%), and excess alcohol use (14.4%). Among immigrant and non-immigrant TB cases, the most common known risk factors were HIV positive, 8.3%in immigrant TB cases vs. 13.9% in non-immigrants, diabetes were 6.6% in immigrant TB cases vs. 5.5% in non-immigrant TB cases, and excess alcohol use in immigrant TB cases were 5.5% vs. 20.9% in non-immigrant TB cases. Immigrant TB cases were less likely to be from long term care facilities than non-immigrants (0.5 % vs. 2.4%). Injection drug use was also less common among immigrants than non-immigrants (0.5% vs 2%) as was non-injection drug use (2.3 % vs 15.3%). Finally, 3.7 % of immigrant TB cases were homeless individuals vs. 13% among non-immigrants.

Table 9 summarizes TB diagnosis tests and case verification methods as per CDC guidelines. Overall, the most common reasons for testing were, TB symptoms (28.2%) and abnormal chest radiograph (13.6%). A positive

culture (74.7%) was used as a case verification method in most of the cases. Among immigrants, 31.3% were diagnosed with TB due to TB symptoms compared to 26.1% in non-immigrant TB cases. A positive culture was the primary case verification method used among 76.3% of the cases among immigrant TB cases compared to 73.6% in non-immigrant TB cases. Overall, skin test positive cases encompassed 52.9% and IGRA positive cases encompassed 8.3%. Among immigrants, a positive skin test comprised 54.8% of individuals compared to 10.8% of individuals with a positive IGRA test. Among non-immigrants, a positive skin test comprised 51.6%% of individuals compared to 6.5 % of individuals with a positive IGRA test.

Table 6: Demographics of overall TB Cases (n=5,315) by immigrant status for years 2004 to 2016 in Georgia.

Variables	Overall(n=5,315)		Immigrants (n=2,240, 42.2%)		Non-Immigrants (n=3,063, 57.6%)	
Sex	n	%	n	%	n	%
Male	3,403	64	1,390	62.1	2,005	65.5
Female	1,909	35.9	848	37.8	1,057	34.5
Missing	3	0.06	2	0.1	1	
Race/Ethnicity						
Asian, non-Hispanic	861	16.2	803	35.8	54	1.8
Black, non-Hispanic	2,667	50.2	517	23.0	2,149	70.2
Hispanic, all races	972	18.3	810	36.1	157	5.1
White, non-Hispanic	762	14.3	89	3.9	673	21.9
Others*	53	1	21	0.9	30	0.9
Region of Origin						
The Americas outside U.S	860	16.2	860	38.4		
Asia	857	16.1	857	38.2		
Africa	479	9	479	21.3		
Europe	44	0.8	44	1.9		
U.S.	3,063	57.6			3,063	100.0
Missing	12	0.2				
Primary Occupation						
Health Care worker	123	2.3	64	2.9	58	1.9
Migrant Worker	60	1.1	56	2.5	4	0.1
Unemployed	2193	41.3	429	19.1	676	22.1
Student	86	1.6	37	1.7	49	1.6
Retired	282	5.3	84	3.8	196	6.4
Others*	2,571	48.4	1,570	70.1	2,080	67.9

*Others include missing and data which are not included in the given categories.

Table 7: Age distribution at diagnosis of overall TB Cases (n=5,315), and age at U.S. entry of immigrant TB cases (n=2,240) and non-immigrant cases (n=3,063) for years from 2004 to 2016 in Georgia.

Variables	Overall(n=5,315)		Immigrants (n=2,240, 42.2%)		Non-Immigrants (n=3,063, 57.6%)	
Age group at diagnosis	n	%	n	%	n	%
0 to =< 9 years	315	5.9	41	1.8	273	8.9
10 – 19 years	244	4.6	126	5.6	117	3.8
20 – 29 years	900	16.9	583	26	315	10.3
30 – 39 years	925	17.4	567	25.3	357	11.7
40 – 49 years	987	18.6	368	16.4	615	20.1
50 – 59 years	872	16.4	245	10.9	626	20.4
60 – 69 years	556	10.5	178	7.9	376	12.3
70 -79 years	296	5.6	90	4	206	6.7
80 – 89 years	183	3.4	36	1.6	147	4.8
90 – 99 years	37	0.7	6	0.3	31	1
Immigrants Age group at US entry						
0 to =< 9 years			100	4.5		
10 – 19 years			319	14.2		
20 – 29 years			717	32		
30 – 39 years			369	16.5		
40 – 49 years			203	9.1		
50 – 59 years			111	4.9		
60 – 69 years			61	2.7		
70 -79 years			29	1.3		
80 – 89 years			6	0.3		
90 – 99 years			3	0.1		
Age at Diagnosis- Median	42		36		48	
Less than or equal to 42	2,660	50.05	1434	64	1,219	39.8
Above 42	2,655	49.95	806	35.9	1,844	60.2
Age at US entry for immigrants- Median			27			
Less than or equal to 27 years			1100	49.1		
Above 27 years of age			1037	46.3		
Diagnosed within 5 years of US entry						
Yes	994	18.70	962	42.9		
No	1,281	24.10	1185	52.9		
Missing	3,040	57.20	93	4.2		
Previous diagnosis of TB-recurrent						
Yes	248	4.67	120	5.4	128	4.2
No	5,037	94.77	2105	93.9	2,921	95.4
Missing	16	0.30	15	0.6	14	0.5

Table 8: Distribution of known risk factors for TB disease by immigrant status for years from 2004 to 2016 in Georgia.

Variables	Overall(n=5,315)		Immigrants (n=2,240, 42.2%)		Non-Immigrants (n=3,063, 57.6%)	
Risk Factors	n	%	n	%	n	%
Contact of Infectious TB	385	7.2	106	4.7	204	6.7
End Stage Renal Disease	36	0.7	7	0.3	29	0.9
Immunosuppression-non	59	1.1	28	1.3	31	1
Incomplete LTBI Therapy	72	1.4	18	0.8	60	1.9
None	1,535	28.9	830	37.1	706	23.1
Other	2,919	54.9	1,131	50.5	1,582	51.7
Long Term Care Facility						
Yes	80	1.5	10	0.5	73	2.4
Missing	5,235	98.5	2,230	99.6	2,993	97.7
Injecting Drug Use						
Yes	73	1.4	12	0.5	61	2
No	5,166	97.2	2,204	98.4	2,953	96.4
Missing	76	1.4	24	1.1	49	1.6
Non-Injecting Drug Use						
Yes	520	9.8	51	2.3	468	15.3
No	4,727	88.9	2,161	96.5	2,557	83.5
Missing	68	1.3	28	1.3	38	1.2
Homeless past one year						
Yes	283	5.3	82	3.7	399	13
No	5,024	94.5	2147	95.9	2659	86.8
Missing	8	0.2	11	0.5	5	0.2
Correctional Facility						
Yes	282	5.3	82	3.7	198	6.5
Missing	5,033	94.7	2,158	96.3	2,865	93.5
HIV Status						
Positive	611	11.5	186	8.3	425	13.9
Negative	4,152	78.1	1,875	83.7	2,269	74.1
Refused	128	2.4	51	2.3	75	2.5
Not offered	333	6.3	90	4	242	7.9
Other	91	1.7	38	1.7	52	1.7
Diabetes						
Yes	317	5.9	148	6.6	168	5.5
No	1,535	28.9	830	37.1	702	22.9
Missing	3,483	65.5	1,262	56.3	2.193	0.1
Excess Alcohol Use						
Yes	766	14.4	124	5.5	640	20.9
No	4,470	84.1	2,089	93.3	2,373	77.5
Missing	79	1.5	27	1.2	50	1.6

Table 9: Reason for testing, case verification, and TB diagnosis tests among TB cases by Immigrant Status for 2004 to 2016 in Georgia.

Variables	Overall(n=5,315)		Immigrants (n=2,240,		Non-Immigrants (n=3,063, 57.6%)	
	n	%	n	%	n	%
Primary reason for TB testing						
TB symptoms	1,503	28.3	702	31.3	800	26.1
Abnormal Chest X-ray	721	13.6	283	12.6	436	14.2
Incidental Lab result	231	4.4	114	5.1	117	3.8
Contact Investigation	165	3.1	37	1.7	128	4.2
Employment Testing	12	0.2	7	0.3	5	0.2
Health Care Worker	6	0.1	5	0.2	1	
Targeted Testing	91	1.7	34	1.5	57	1.9
Immigration Medical Exam	80	1.5	79	3.5		
Missing	2,506	47.2	979	43.7	1,519	49.6
Skin Test Result						
Positive	2811	52.9	1227	54.8	1,579	51.6
Negative	928	17.5	287	12.8	641	20.9
Not done	867	16.3	441	19.7	423	13.8
Not Read	21	0.4	10	0.5	11	0.4
Other	688	12.9	275	12.3	409	13.4
IGRA Result						
Positive	441	8.3	242	10.8	198	6.5
Negative	108	2	57	2.5	51	1.7
Indeterminate	39	0.7	10	0.5	29	0.9
Not done	947	17.8	433	19.3	512	16.7
Missing	3,780	71.1	1,498	66.9	2,273	74.2
Skin Test Induration						
Less than/equal 7.2	962	18.1	300	13.4	35	1.1
7.2 to 9.8	34	0.6	16	0.7	18	0.6
Above 9.8	2,507	47.2	1,107	49.4	1,396	45.6
Missing	1,812	34.1	817	36.5	1,614	52.7
Method used for TB Case Verification						
Clinical Case Definition	767	14.4	337	15	429	14
NAA Positive Case	50	0.9	19	0.9	31	1
Positive Culture	3,972	74.7	1,709	76.3	2,254	73.6
Positive Smear/Tissue	13	0.2	6	0.3	7	
Suspect Case	5	0.1	2	0.1	3	0.1
Verified By provider Diagnosis	508	9.6	167	7.5	33	1.1
TB Confirmed by tests	4,035	75.9	1,734	77.4	2,292	74.8
TB Not Confirmed by tests	1,280	24.1	506	22.6	771	25.2

Overall TB Incidence in Georgia

Census Bureau data shows that there were a total of 10,310,371 individuals in the Georgia population in the year 2016 including 1,038,312 immigrants. It is estimated that approximately 1 in 10 (10%) Georgia residents is a documented immigrant. Also, an estimated 400,000 undocumented immigrants lived in Georgia.

Table 10 summarizes the total number of TB cases, as well as immigrant and non-immigrant TB cases per year from 2004 to 2016 in Georgia. There were a total of 536 TB cases in 2004, decreasing to 301 in 2016. Immigrant TB cases from the total cases in Georgia vary from 33% to 52% for the years 2004 to 2016, in which 2004 had 33.6%, 2013 had a peak of 51.6%, and 2016 had 46.8%. Figure 8 is a graphic representation of the data.

Georgia's population in 2004 was 8,769,252 as per U.S. Census Bureau. The annual incidence of TB disease was 6.1(95%CI: 5.9 – 6.3) per 100,000 in 2004. There were 411 TB cases in 2010 and the Georgia total population was 9,687,653. The annual incidence of TB disease for 2010 was 4.2 (95%CI: 4.0 -4.4) per 100,000. In 2016, the number of total TB cases were 301 and the total population in Georgia was 10,379,084. The annual incidence of TB disease was 2.9 (95%CI: 2.3 – 3.5) per 100,000 in 2016. This shows a downward trend in TB incidence in Georgia from 2004 to 2016, from 6.1 to 2.9 per 100,000 persons per year. A trend analysis is presented later in this chapter.

Concentrated Areas of TB cases in Georgia

Table 11 summarizes the counties with the highest number of TB cases. Most of the documented immigrant TB cases resided in four counties within metro-Atlanta area: DeKalb (924), Cobb (310), Fulton (897), and Gwinnett (596). This is due to the large overall population and therefore the large number of immigrants living in these counties. In fact, more than half of the cases in Hall, Cobb, DeKalb, Gwinnett and Clayton Counties were among immigrants. The TB disease burden in immigrants in Georgia is disproportionate considering they comprise 10% of population, but make up 33% to 52% of TB disease cases among total TB cases depending on the year.

Table 10: Number of Total TB cases, immigrant and non-immigrant TB cases per year from 2004 to 2016.

Year of Diagnosis	Total Cases	Immigrant cases		Non-Immigrant cases	
		n	% of Total Cases	n	% of Total Cases
2004	536	180	33.6	356	66.4
2005	502	185	36.9	317	63.1
2006	507	204	40.2	303	59.8
2007	472	192	40.7	280	59.3
2008	476	195	40.9	281	59.0
2009	411	173	42.1	238	57.9
2010	411	182	44.3	229	55.7
2011	347	161	46.4	186	53.6
2012	359	154	42.9	205	57.1
2013	339	175	51.6	164	48.4
2014	334	149	44.6	185	55.4
2015	320	149	46.6	171	53.4
2016	301	141	46.8	160	53.2
Total	5,315	2,240	42.1	3,075	57.9

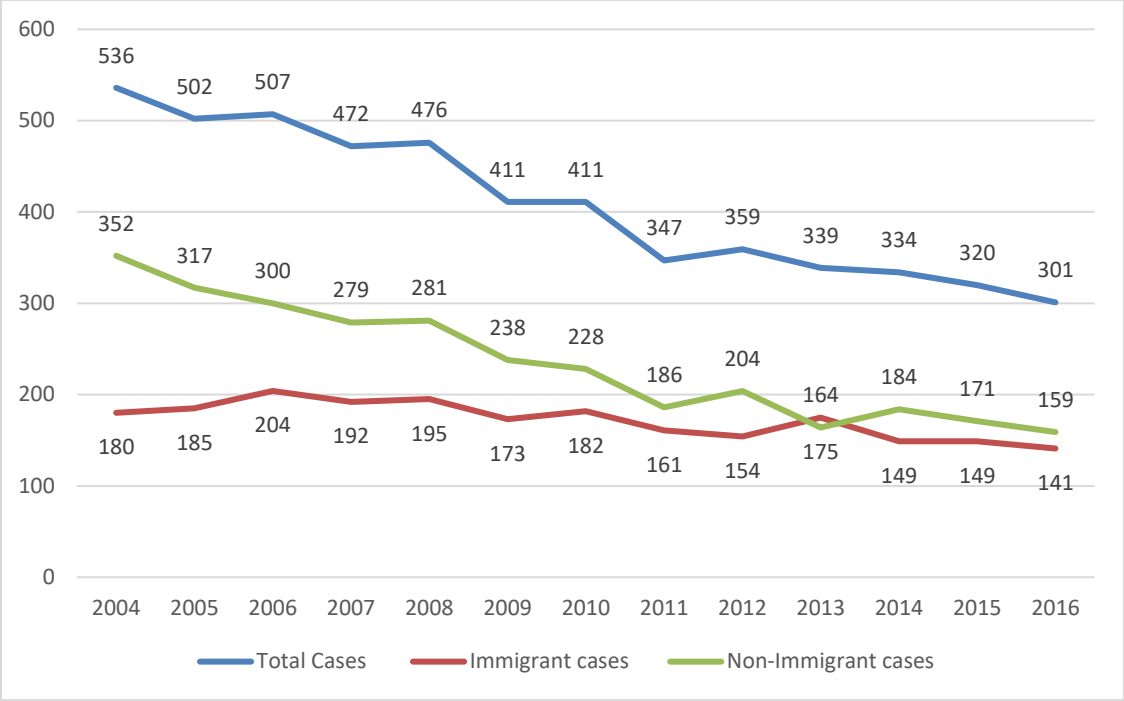

Figure 8: Number of TB cases and immigrant TB cases per year from 2004 to 2016 in Georgia

Table 11: Counties with most of the TB cases reported for years 2004 to 2016

County	Overall Cases	Immigrant Cases	Percentage
DEKALB	924	570	61.7
GWINNETT	596	468	78.5
FULTON	897	240	26.8
COBB	310	202	65.2
CLAYTON	150	79	52.7
HALL	82	42	51.2
CHATHAM	135	39	28.9
MUSCOGEE	132	30	22.7
COLUMBIA	146	25	17.1
RICHMOND	108	23	21.3
HOUSTON	78	21	26.9
BIBB	85	17	20
TROUP	53	3	5.7
Other Counties	1,619	481	29.7
Total	5,315	2,240	42.1

Cumulative Incidence of TB Disease for Year 2004 to 2016

The estimated annual incidence rate of TB disease among the Georgia population for overall, documented immigrants and non-immigrants was calculated by examining the total TB cases in the overall population, documented immigrants and non-immigrants population between 2004 and 2016 from the GDPH TB cases database to obtain the number of new cases of TB diagnosed annually per 100,000. The cumulative incidence rate per 100,000 per year was calculated from the average number of TB cases for 13 years including TB cases from 2004 to 2016. Years 2010 was chosen since the U.S. Census Bureau made available data regarding the total documented immigrant population in Georgia for that year and 2010 is the median year for years 2004 to 2016.

The overall Georgia population for 2010 was 9,688,680, the documented immigrant population was 920,381, and the non-immigrant population was 8,768,299. An average annual incidence of TB cases in Georgia (n=409) was calculated from 2004 to 2016 and applied to the 2010 population to find the overall annual incidence rate per 100,000 for the overall population. An average annual incidence of TB cases in documented immigrants (n=173; 42.3%) was calculated from 2004 to 2016 and applied to 2010 documented immigrant population to find the annual incidence rate per 100,000 for the documented immigrant population. An average annual incidence of TB cases in non-immigrants (n=237; 57.9%) was calculated from

2004 to 2016 and applied to 2010 non-immigrant population to find the incidence rate per 100,000 for the non-immigrant population.

The overall average annual TB disease incidence rate per 100,000 for the overall Georgia population was 4.2 (95%CI: 3.6 – 4.9) per 100,000 per year for the years 2004 to 2016, using the 2010 population as the denominator. The Georgia non-immigrant TB disease incidence rate per 100,000 was 2.7 (95%CI: 2.0 – 3.4), compared to 18.7 (95%CI: 18.6 – 18.8) for the Georgia immigrant population for the years 2004 to 2016, using the 2010 documented immigrant and non-immigrant population as the denominator.

The incidence rate ratio was 6.9 (95%CI: 6.8 - 6.9) for immigrants to be diagnosed with TB disease in Georgia for the years 2004 to 2016 compared with non-immigrants. It shows that immigrants had 6.9 times the rate of TB disease compared to non-immigrants in Georgia for the years 2004 to 2016. Since there were variations in incidence and population growth over the time period from 2004 to 2016 per year, this may be a better method to assess the burden of active TB disease incidence in the population per year.

Table 12 summarizes the TB incidence rates for overall, documented immigrants and non-immigrants per 100,000 for the year 2016 at the county level. There are 159 counties in Georgia. We found that there was at least one case reported in 58 counties. Of the 58 counties, there were 28 counties with only one reported TB incidence case, six counties with two cases only, six counties with three cases only, six counties with four cases only, and 12

counties with five or more TB cases reported. Counties with four or more cases, a total of 18 counties, were reported in Table 12 with annual rate per 100,000 for year 2016 and IRR with 95% CI for documented immigrants and non-immigrants. The six counties with the highest overall TB disease incidence had the highest annual TB rate per 100,000 among documented immigrants for the year 2016 with a range of 10 to 37 per 100,000 per year compared to 0.6 to 6.1 per 100,000 per year among non-immigrants.

Incident rate ratios (IRR) were calculated for these counties for the year 2016 and given in Table 12. DeKalb county had an IRR of 31.7 (95%CI: 31.5-31.8) between immigrant TB cases and non-immigrant cases. It shows that immigrants had 31.7 times the rate of TB disease compared to non-immigrants in that county. The highest IRR for immigrant vs non-immigrant TB cases were found in Fayette (IRR=27.0; 95%CI: 26.8- 27.1), Cobb (IRR=26.6; 95%CI: 26.4- 26.8), Lowndes (IRR=22.3; 95%CI: 22.0- 22.4), Gwinnet (IRR=16.8; 95%CI: 16.6- 16.9), and Barrow (IRR=12.7; 95%CI: 12.5 – 12.8) counties. There were seven more counties which showed a large IRR between immigrant TB cases vs. non-immigrant TB cases.

Rural County in Georgia is defined as counties with 35,000 or less population. According to that definition, among the counties reported in Table 12, Jefferson are Terrell were rural counties in 2016. In Jefferson County, there were five TB cases reported and all of them were from non-immigrant population. Immigrant population was very small in that county

for year 2016. In Terrell County, there were four TB cases reported and all of them were from non-immigrant population. There also, the immigrant population was very small in numbers. This shows that most of the immigrant TB cases were reported from urban counties and mostly from metro-Atlanta area were immigrants lived in large numbers.

Table 12: TB cases and rates of TB incidence in counties in Georgia (overall, immigrants and non-immigrants) for the year 2016

Counties	Overall TB Cases	Overall TB rate/100,000	Immigrant TB Cases	Immigrant TB rate/100,000	Non-Immigrant TB cases	Non-immigrant TB rate/100,000	IRR (95%CI) Immigrants vs. non-immigrants
Fulton	44	4.3	13	10.0	31	3.5	2.9(2.7-3.03)
DeKalb	43	5.8	37	30.7	6	1.0	31.7(31.5-31.8)
Gwinnett	33	3.6	28	12.3	5	0.7	16.8(16.6-16.9)
Cobb	24	3.2	20	16.9	4	0.6	26.6(26.4-26.8)
Clayton	12	4.3	7	18.8	5	2.1	9.1(8.9-9.2)
Bibb	11	7.2	2	37.4	9	6.1	6.1(5.9-6.2)
Muscogee	11	5.6	0		11	5.9	
Richmond	8	4.0	2	27.6	6	3.1	8.9(8.7-9.0)
Chatham	7	2.4	2	10.8	5	1.8	5.9(5.6-6.0)
Douglas	5	3.5	2	16.5	3	2.3	7.2(7.0-7.3)
Hall	5	2.5	2	6.2	3	1.8	3.4(3.2-3.5)
Jefferson	5	31.4	0		5	32.2	
Barrow	4	5.2	2	35.5	2	2.8	12.7(12.5-12.8)
Dougherty	4	4.4	0		4	4.6	
Fayette	4	3.6	3	26.9	1	1.0	27.0(26.8-27.2)
Lowndes	4	3.5	2	40.6	2	1.8	22.3(22.0-22.4)
Terrell	4	44.6	0		4	44.9	
Whitfield	4	3.8	0		4	4.7	
Missing county name	11		3		8		

Table 13 summarizes the annual TB incidence rates per 100,000 and 95% confidence interval and IRR with 95%CI for the overall population, for documented immigrants and for non-immigrants in Georgia for the years 2004 to 2016. The overall TB incidence rate was between 2.9 to 6.1 per 100,000 per year, and was lowest in 2016 and highest in 2004. Documented immigrant annual TB incidence rates per 100,000 were between 13.6 to 24.7 compared to 1.7 to 4.5 among non-immigrants between the years 2004 to 2016. Incident rate ratios for the years 2004 to 2016 shows an increasing trend except for year 2012. IRR was in the range of 4.6 in year 2004 to 9.6 in 2013 in documented immigrants vs non-immigrants. For years 2015 and 2016, IRR was somewhat stable.

A trend analysis using the Cochran-Armitage Trend Test was conducted for incident active TB disease among the overall population, immigrants, and non-immigrants for the period of 2004 to 2016. Overall data for active TB patients showed a statistically significant downward trend from year 2004 to 2016 (Gamma= -0.922; p=<.001; 95%CI: -1.000 - -0.832). The Pearson (r=-0.976; 95%CI: -1.000 - -0.952) and Spearman correlation (r=-0.982; 95%CI: -1.00 - -0.955) coefficients show evidence of a strong negative association between incidence rate and year Somers' D(R/C) = -0.910; 95% CI: -0.993 - -0.827 measures the association and because asymptotic 95% confidence limits do not contain zero, this indicates a strong negative association and implies a downward trend of incident TB disease

from year 2004 to 2016 among overall population in Georgia.

For documented immigrants, the incidence rate for active TB showed a statistically significant downward trend from year 2004 to 2016 (Gamma= -0.662; p=<.001; 95%CI: -0.935 - -0.390). The Pearson (r=-0.834; 95%CI: -0.967 - -0.706) and Spearman correlation (r=-0.828; 95%CI: -1.00 - -0.623) coefficients show evidence of a strong negative association between incidence rate and year. Somers' D(R/C) = -0.654; 95% CI: -0.912 - -0.396 measures the association and because asymptotic 95% confidence limits do not contain zero, this indicates a strong negative association and implies a downward trend of incident TB disease from year 2004 to 2016 among the immigrant population in Georgia.

For non-immigrants, the incidence of active TB disease show a statistically significant downward trend from year 2004 to 2016 (Gamma= -0.872; p=<.001; 95%CI: -998 -0.746). The Pearson (r=-0.968; 95%CI: -0.994 - -0.941) and Spearman correlation (r=-0.961; 95%CI: -1.00 - -0.905) coefficients show evidence of a strong negative association between incidence rate and year. Somers' D(R/C) = -0.872; 95% CI: -0.998 - -0.746 measures the association and because asymptotic 95% confidence limits do not contain zero, this indicates a strong negative association and implies a downward trend of incident TB disease from year 2004 to 2016 among the non-immigrant population in Georgia.

Table 13: Rates and 95% Confidence Interval of TB incidence in Georgia (overall, immigrants and non-immigrants) by year, 2004 to 2016

Year	Overall TB incidence/100000 (95% CI)	Immigrant TB incidence/100000(95 % CI)	Non-Immigrant TB incidence/100000(95 % CI)	IRR(95% CI) Immigrants vs. non-immigrants
2004	6.1 (5.4-6.8)	23.0(22.9 - 23.1)	4.5(3.8 - 5.2)	4.6(4.5 – 4.6)
2005	5.6(4.9-6.3)	23.0(22.9 - 23.1)	3.9(3.2 - 4.6)	5.3(5.2-5.3)
2006	5.6(4.9-6.3)	24.7(24.6 - 24.8)	3.7(3.0 - 4.4)	6.1(6.0-6.1)
2007	5.1(4.5-5.8)	22.7(24.6 - 24.8)	3.4(2.7 - 4.1)	6.2(6.1-6.2)
2008	5.1(4.5-5.8)	22.5(22.4 - 22.6)	3.3(2.6 -4.0)	6.2(6.1-6.2)
2009	4.3(3.7-5.0)	19.5(19.4 - 19.6)	2.8(2.1 - 3.5)	6.5(6.4-6.5)
2010	4.2(3.6-4.9)	19.8(19.7 - 19.9)	2.6(1.9 - 3.3)	7.6(7.5-7.6)
2011	3.6(3.0-4.3)	17.3(17.2 - 17.4)	2.1(1.4 - 2.8)	7.8(7.7-7.8)
2012	3.6(3.0-4.3)	16.1(16.0 - 16.2)	2.3(1.6 – 3.0)	6.8(6.7-6.8)
2013	3.4(2.8-4.1)	17.9(17.8 – 18.0)	1.8(1.1 -2.5)	9.6(9.5-9.6)
2014	3.3(2.7-3.9)	14.9(12.9 - 16.9)	2.0(1.4 - 2.5)	7.2(7.1-7.2)
2015	3.1(2.5-3.7)	14.6(12.6 - 16.6)	1.9(1.3 - 2.6)	7.8(7.7-7.8)
2016	2.9(2.3-3.5)	13.6(11.6 - 15.6)	1.7(1.1 - 2.4)	7.9(7.8-7.9)

Summary of Results for Aim One

Aim one results showed that the mean annual incidence rate for TB disease per 100,000 for the Georgia documented immigrant population was 18.7 (95%CI: 18.6 – 18.8), compared to 2.7 (95%CI: 2.01 – 3.39) for the Georgia non-immigrant population for the years 2004 to 2016, using the 2010 population as the denominator. The incidence rate ratio for the TB incidence in immigrants versus non-immigrants was 6.9 (95%CI: 6.8 - 6.9) in Georgia for the years 2004 to 2016. It shows that immigrants had 6.9 times the rate of TB disease compared to non-immigrants in Georgia for the years 2004 to 2016. This shows that the annual TB disease incidence per 100,000 among documented immigrant population was almost seven times higher than the incidence rate among the non-immigrant population for the years 2004 to 2016. The data for the overall population of active TB patients, for documented immigrants, and for non-immigrants all showed a statistically significant downward trend from year 2004 to 2016.

We looked at state wide and county level annual incidence TB rate per 100,000 and found that there was a difference between the annual TB incidence rate per 100,000 between documented immigrants and non-immigrants. Incident rate ratios (IRR) were calculated for the counties with four or more TB cases reported for the year 2016 between immigrant TB cases and non-immigrant cases. In two rural counties from where TB cases were reported in 2016, all of them were from non-immigrant population. Those counties had very small number of immigrant population in year 2016.

IRR were higher in urban counties, mostly in metro-Atlanta area, where large number of immigrants were living in 2016.

RESULTS FOR SPECIFIC AIM TWO

2. To describe the distribution of known risk factors for incident active TB disease among the immigrant population compared to non-immigrants in Georgia.

   H_0: The distribution of known risk factors does not differ between immigrants and non-immigrants with active TB disease in each group.

   H_1: The distribution of known risk factors does differ between immigrants and non-immigrants with active TB disease in each group.

Risk Factors for TB among Immigrants

Table 14 summarizes demographics of overall TB Cases (n=5,315), documented immigrant TB cases (n=2,240) and non-immigrant cases (n=3,063) for years from 2004 to 2016. It shows that immigrant TB cases were significantly more likely to be female and more likely to be Asian or Hispanic than non-immigrant cases. Among immigrants, the majority are from the Americas outside the U.S. and Asia. Non-immigrant TB cases were significantly more likely to be unemployed compared to immigrants TB cases.

Table 15 summarizes the age distribution of TB cases in Georgia for overall, documented immigrants and non-immigrants. It shows that immigrant cases were significantly more likely to be in the age group of 20 to 39 compared to 40 to 59 in non-immigrants. Median age of TB disease diagnosis for overall was 42 years, 36 years in immigrants compared to 48 years in non-immigrants which was a significant difference. Immigrants were

diagnosed with TB disease in their yearly ages compared to the later age of non-immigrants. There were 64% individuals in the immigrant group who were diagnosed prior to turning 42 years of age, which is higher compared to the 50% of individuals for overall cases. Also, almost half of the immigrants entered the U.S. when they were under the age of 27. Approximately 5% of the TB cases were recurrent disease and this was similar in both groups.

Table 16 summarizes the risk factors the overall population of TB cases in Georgia as well as immigrant and non-immigrant TB cases. It shows that contact with someone who has TB disease was more common with non-immigrants than documented immigrants (6.7% vs 4.7%). Immigrant TB cases were slightly but significantly more likely to have diabetes mellitus than non-immigrant TB cases (6.6% vs 5.5%). Non-immigrant TB cases were significantly more likely to be HIV positive (13.9% vs 8.3%), individuals who did not complete LTBI treatment (2% vs 0.8%), individuals with excess alcohol use (20.9% vs 5.5%), living in long term care facilities (2.4% vs 0.5%), users of injecting (2% vs 0.5%) and non-injecting drugs(15.3% vs 2.3%) , homeless in the past one year (13% vs 3.7%), and lived in correctional facilities (6.5% vs 3.7%) than documented immigrant TB cases in Georgia.

Table 17 summarizes the primary reasons for diagnosis of TB disease and the TB verification methods used at health departments. TB symptoms were significantly more likely to be the reason for TB diagnosis among immigrants compared to non-immigrants (31.3% vs 26.3%, p=0.001).

Significantly more TB cases were verified by physicians among immigrants than among non-immigrants (7.5% vs 1.1%, $p < 0.001$).

Table 14: Demographics of overall TB Cases (n=5,315), immigrant TB cases (n=2,240) and non-immigrant cases (n=3,063) for years from 2004 to 2016.

Variables	Overall(n=5,315)		Immigrants (n=2,240, 42.2 %)		Non-Immigrants (n=3,063, 57.6 %)		Immigrants vs. non-immigrants p-value*
Sex	n	%	n	%	n	%	0.012
Male	3,403	64	1,390	62.1	2,005	65.5	
Female	1,909	35.9	848	37.9	1,057	34.5	
Missing	3	0.1	2	0.1	1		
Race/Ethnicity							<.001
Black, non-Hispanic	2,667	50.2	517	23.1	2,149	70.2	
Hispanic, all races	972	18.3	810	36.2	157	5.1	
Asian, non-Hispanic	861	16.2	803	35.9	54	1.8	
White, non-Hispanic	762	14.3	89	4	673	22	
Others	53	1.0	21	0.9	30	1	
Country of Origin							
The Americas outside U.S.	860	16.2	860	38.4			
Asia	857	16.1	857	38.3			
Africa	479	9	479	21.4			
Europe	44	0.8	44	2			
US	3,063	57.6			3,063	100.0	
Missing	12	0.2					
Primary Occupation							<.001
Unemployed	2,193	41.3	429	19.2	676	22.1	
Retired	282	5.3	84	3.8	196	6.4	
Health Care worker	123	2.3	64	2.9	58	1.9	
Student	86	1.6	37	1.7	49	1.6	
Migrant Worker	60	1.1	56	2.5	4	0.1	
Other	2,571	48.4	1,570	70.1	2,080	67.9	
Immigrant Visa Status							
U.S Born	850	15.99	2	0.1			
Other	390	7.34	384	17.1			
Immigrant Visa	306	5.76	305	13.6			
Refugee	175	3.29	173	7.7			
Family/Fiancé Visa	77	1.5	76	3.4			
Employment Visa	39	0.7	38	1.7			
Tourist Visa	39	0.73	38	1.7			
Student Visa	37	0.7	37	1.7			
Missing	3,402	64.01	1187	53			

*Chi-Square test at the significant level of 0.05

Table 15: Age groups and diagnosis of overall TB Cases (n=5,315), age groups at US entry for immigrant TB cases (n=2,240) and non-immigrant cases (n=3,063) for years from 2004 to 2016.

Variables	Overall(n=5,315)		Immigrants (n=2,240, 42.2%)		Non-Immigrants (n=3,063, 57.6%)		p-value*
Age group at diagnosis	n	%	n	%	n	%	<.001
0 to equal to 9 years	31	5.9	41	1.8	273	8.9	
10 – 19 years	24	4.6	126	5.6	117	3.8	
20 – 29 years	90	16.9	583	26.0	315	10.3	
30 – 39 years	92	17.4	567	25.3	357	11.7	
40 – 49 years	98	18.6	368	16.4	615	20.1	
50 – 59 years	87	16.4	245	10.9	626	20.4	
60 – 69 years	55	10.5	178	8	376	12.3	
70 – 79 years	29	5.6	90	4	206	6.7	
80 – 89 years	18	3.4	36	1.6	147	4.8	
90 – 99 years	37	0.7	6	0.3	31	1	
Immigrants Age group at US entry							
0 to equal to 9 years			100	4.46			
10 – 19 years			319	14.24			
20 – 29 years			717	32.01			
30 – 39 years			369	16.47			
40 – 49 years			203	9.06			
50 – 59 years			111	4.96			
60 – 69 years			61	2.72			
70 -79 years			29	1.29			
80 – 89 years			6	0.27			
90 – 99 years			3	0.13			
Age at Diagnosis- Median	42		36		48		<.001
Less than or equal to 42	2,6	50.1	1434	64	1,219	39.8	
Above 42	2,6	49.9	806	36	1,844	60.2	
Age at US entry for immigrants							0.001
Less than or equal to 27			1100	49.1			
Above 27			1037	46.3			
Diagnosed within 5 year of US							<.001
Yes	99	18.7	962	43			
No	1,2	24.1	1185	52.9			
Missing	3,0	57.2	93	4.2			
Prior diagnosis of TB-recurrent							0.068
Yes	24	4.7	120	5.4	128	4.2	
No	5,0	94.7	2,105	94	2,921	95.4	
Missing	16	0.3	15	0.7	14	0.5	

*Chi-Square test at the significant level of 0.05

Table 16: Risk factors of overall TB Cases (n=5,315), immigrant TB cases (n=2,240) and non-immigrant cases (n=3,063) for years from 2004 to 2016.

Variables	Overall(n=5,315)		Immigrants (n=2,240, 42.2%)		Non-Immigrants (n=3,063, 57.6%)		p-value*
Risk Factors	n	%	n	%	n	%	
Contact of Infectious TB	385	7.2	106	4.7	204	6.7	<.001
End Stage Renal	36	0.7	7	0.3	29	1	
Immunosuppression-non HIV	59	1.1	28	1.3	31	1	0.309
Incomplete LTBI	72	1.4	18	0.8	60	2	<.001
None	1,535	28.9	830	37.1	706	23.1	
Other	2,919	54.9	1,131	50.5	1,582	51.7	
HIV Status							<.001
Positive	611	11.5	186	8.3	425	13.9	
Negative	4,152	78.1	1,875	83.7	2,269	74.1	
Refused	128	2.4	51	2.3	75	2.5	
Not offered	333	6.3	90	4	242	7.9	
Other	91	1.7	38	1.7	52	1.7	
Diabetes Mellitus							0.017
Yes	317	6	148	6.6	168	5.5	
No	1,535	28.9	830	37.1	702	22.9	
Missing	3,483	65.5	1,262	56.3	2.193	0.1	
Excess Alcohol Use							<.001
Yes	766	14.4	124	5.5	640	20.9	
No	4,470	84.1	2,089	93.3	2,373	77.5	
Missing	79	1.5	27	1.2	50	1.6	
Long Term Care Facility							<.001
Yes	80	1.5	10	0.5	73	2.4	
Missing	5,235	98.5	2,230	99.6	2,993	97.7	
Injecting Drug Use							<.001
Yes	73	1.4	12	0.5	61	2	
No	5,166	97.2	2,204	98.4	2,953	96.4	
Missing	76	1.4	24	1.1	49	1.6	
Non-Injecting Drug Use							<.001
Yes	520	9.8	51	2.3	468	15.3	
No	4,727	88.9	2,161	96.5	2,557	83.5	
Missing	68	1.3	28	1.3	38	1	
Homeless past one year							<.001
Yes	283	5.3	82	3.7	399	13	
No	5,024	94.5	2,147	95.9	2,659	86.8	
Missing	8	0.2	11	0.5	5	0.2	
Correctional Facility							<.001
Yes	282	5.3	82	3.7	198	6.5	
Missing	5,033	94.7	2,158	96.3	2,865	93.5	

*Chi-Square test at the significant level of 0.05

Table 17: Primary reason for diagnosis and case verification methods of by immigrant status for years from 2004 to 2016.

Variables	Overall(n=5,315)		Immigrants (n=2,240, 42.2%)		Non-Immigrants (n=3,063, 57.6%)		p-value*
Primary Reason for TB diagnosis	Number	%	Number	%	Number	%	<.001
TB symptoms	1,503	28.3	702	31.3	800	26.1	
Abnormal Chest X-ray	721	13.6	283	12.6	436	14.2	
Incidental Lab result	231	4.4	114	5.1	117	3.8	
Contact Investigation	165	3.1	37	1.7	128	4.2	
Employment Testing	12	0.2	7	0.3	5	0.2	
Health Care Worker	6	0.1	5	0.2	1		
Targeted Testing	91	1.7	34	1.5	57	1.9	
Immigration Medical	80	1.5	79	3.5			
Missing	2,506	47.2	979	43.7	1,519	49.6	
Case Verification method							0.001
Clinical Case Definition	767	14.4	337	15	429	14	
NAA Positive Case	50	0.9	19	0.9	31	1	
Positive Culture	3,972	74.7	1,709	76.3	2,254	73.6	
Positive Smear/Tissue	13	0.2	6	0.3	7	0.2	
Suspect Case	5	0.1	2	0.1	3	0.1	
Verified By provider	508	9.6	167	7.5	33	1.1	
TB Confirmed	4,035	75.9	1,734	77.4	2,292	74.8	
TB Not Confirmed	1,280	24.1	506	22.6	771	25.2	

*Chi-Square test at the significant level of 0.05

Table 18 summarizes the medical and diagnostic status of overall TB cases (n=5,315), immigrant TB cases (n=2,240), and non-immigrant TB cases (n=3,063) for years from 2004 to 2016. The PPD skin test was the most used test for diagnosis, but starting in 2009, clinicians began administering IGRA blood tests for diagnosis. For the 2,240 immigrant TB cases, the PPD skin test was positive in 54.8% compared with 51.6% in non-immigrants. The IGRA test was positive in 10.8% of immigrant TB cases compared to 6.5% in non-immigrants.

Table 19 summarizes the medical status of TB cases in Georgia at the time of TB diagnosis. Pulmonary TB was the most common site of disease (71.5%) followed by pleural TB (4.9%) and cervical (6.5%) among immigrant TB cases compared to 72.9%, 3.9%, 1.8% respectively among non-immigrants TB cases. It shows that the site of TB disease for immigrant TB cases was significantly more likely to be bone and joints (2.2% vs 0.8%), lymphatic cervical (6.5% vs 1.8%), and other lymphatic (1.9% vs 1.1%) compared to non-immigrants. Non-immigrant TB cases were slightly but significantly more likely to be with sputum smear positive (38.3% vs 36.0%) and with abnormal chest X-ray (82% vs 78%), and much more likely to have evidence of cavitary TB disease on chest present on chest x-ray than immigrant TB cases (55.7% vs 22%).

Table 20 summarizes information about drug therapy for TB cases in Georgia. The drugs isoniazid, rifampin, pyrazinamide, and ethambutol were

used to treat those TB cases. It shows that immigrant TB cases were slightly but significantly more likely to have drug resistance to rifampin (1.4% vs 0.7%), pyrazinamide (1.5% vs 0.3%) and rifabutin(0.4% vs 0.1%) than non-immigrant TB cases, although absolute differences are very small. This may not be clinically significant and may need further investigation to confirm those findings.

Table 18: Medical and diagnostic status of overall TB Cases (n=5,315), immigrant TB cases (n=2,240), and non-immigrant TB cases (n=3,063) for years from 2004 to 2016.

Variables	Overall(n=5,315)		Immigrants (n=2,240, 42.2%)		Non-Immigrants (n=3,063, 57.6%)		Immigrants vs Non-Immigrants P value*
Skin Test Result	n	%	n	%	n	%	<.001
Positive	2,811	52.9	1,227	54.8	1,579	51.6	
Negative	928	17.5	287	12.8	641	20.9	
Not done	867	16.3	441	19.7	423	13.8	
Not Read	21	0.4	10	0.5	11	0.4	
Other	688	12.9	275	12.3	409	13.4	
IGRA Result							0.001
Positive	441	8.3	242	10.8	198	6.5	
Negative	108	2	57	2.5	51	1.7	
Indeterminate	39	0.7	10	0.5	29	1	
Not done	947	17.8	433	19.3	512	16.7	
Missing	3,780	71.1	1498	66.9	2,273	74.2	
Skin Test Induration							0.806
Less than/equal 7.2	962	18.1	300	13.4	35	1.1	
7.2 to 9.8	34	0.6	16	0.7	18	0.6	
Above 9.8	2,507	47.2	1,107	49.4	1,396	45.6	
Missing	1,812	34.1	817	36.5	1,614	52.7	

*Chi-Square test at the significant level of 0.05

Table 19: Medical status of overall TB Cases (n=5,315), immigrant TB cases (n=2,240), and non-immigrant TB cases (n=3,063) for years from 2004 to 2016.

Variables	Overall(n=5,315)	Immigrants (n=2,240, 42.2%)		Non-Immigrants (n=3,063, 57.6%)		Immigrant vs non-immigrant p-value*
Site of Disease		n	%	n	%	<.001
Bone , joint	75	50	2.2	25	0.8	
Lymphatic, cervical	200	145	6.5	55	1.8	
Lymphatic, other	115	90	4.0	25	0.8	
Meningeal	76	43	1.9	33	1.1	
Pleural	227	109	4.9	118	3.9	
Pulmonary	3,834	1,601	71.5	2233	72.9	
Other	788	202	9.0	586	19.1	
Sputum Smear						<.001
Positive	1,979	806	36.0	1173	38.3	
Negative	2,531	1,195	53.3	1336	43.6	
Other	805	241	10.8	564	18.4	
Sputum Culture						<.001
Positive	2,986	1,276	57.0	1710	55.8	
Negative	1,462	694	31.0	768	25.1	
Other	867	270	12.1	597	19.5	
Culture of Tissue						0.001
Positive	1,690	705	31.5	985	32.2	
Negative	432	153	6.8	279	9.1	
Other	3,193	1,382	61.7	1811	59.1	
NAA Test						0.005
Positive	1,084	498	22.2	586	19.1	
Negative	266	136	6.1	130	4.2	
Other	3,965	634	28.3	3331	108.7	
Chest X-ray						<.001
Abnormal	4,261	1,748	78.0	2513	82.0	
Normal	742	373	16.7	369	12.0	
Other	312	119	5.3	193	6.3	
Chest X-ray cavity			0.0			0.107
Yes	2,198	492	22.0	1706	55.7	
No	1,212	1,015	45.3	197	6.4	
Other	1,905	733	32.7	1172	38.3	
Chest X-ray Miliary						0.490
Yes	64	31	1.4	33	1.1	
No	1,385	1,151	51.4	234	7.6	
Other	3,866	1,058	47.2	2808	91.7	

*Chi-Square test at the significant level of 0.05

Table 20: Drug interaction of overall TB Cases (n=5,315), immigrant TB cases (n=2,240), and non-immigrant TB cases (n=3,063) for years from 2004 to 2016.

Variables	Overall(n=5,315)	Immigrants (n=2,240, 42.2%)		Non-Immigrants (n=3,063, 57.6%)		Immigrant vs non-immigrant p-value*
Drug		n	%	n	%	
Isoniazid	3,033	1,385	61.8	1,648	53.8	
Rifampin	2,989	1,363	60.8	1,626	53.1	
Pyrazinamide	3,022	1,383	61.7	1,639	53.5	
Ethambutol	2,986	1,376	61.4	1,610	52.6	
Reason Therapy Stopped						
Completed	4,456	1,877	83.8	2,579	84.2	
Died	420	93	4.2	327	10.7	
Lost to follow-up	146	104	4.6	42	1.4	
Refused	35	17	0.8	18	0.6	
Other	258	149	6.7	109	3.6	
Isoniazid						0.319
Resistant	377	164	7.3	213	7.0	
Sensitive	3,536	1,519	67.8	2,017	65.9	
Other	1,402	557	24.9	845	27.6	
Rifampin						0.023
Resistant	52	32	1.4	20	0.7	
Sensitive	3,860	1,651	73.7	2,209	72.1	
Other	1,403	557	24.9	846	27.6	
Pyrazinamide						<.001
Resistant	44	34	1.5	10	0.3	
Sensitive	1,326	514	22.9	812	26.5	
Other	3,945	1,692	75.5	2,253	73.6	
Ethambutol						0.083
Resistant	19	13	0.6	6	0.2	
Sensitive	3,831	1,636	73.0	2,195	71.7	
Other	1,465	591	26.4	874	28.5	
Rifabutin						0.038
Resistant	12	8	0.4	4	0.1	
Sensitive	170	62	2.8	108	3.5	
Other	5,133	2,170	96.9	2,963	96.7	
Rifapentine						0.471
Resistant	0	0	0.0	0	0.0	
Sensitive	4	1	0.0	3	0.1	
Other	5,311	2,239	100.0	3,072	100.3	
Ethionamide						0.012
Resistant	25	7	0.3	18	0.6	
Sensitive	346	126	5.6	220	7.2	
Other	4,944	2,107	94.1	2,837	92.6	

*Chi-Square test at the significant level of 0.05

Overall Mean Values and Immigrants

Table 21 summarizes age at diagnosis and entry to the US. The mean age at entry to the U.S. for immigrants was 30 years, with a median age of 27 years. The mean age of diagnosis for immigrants was 39 years, with a median age of 36 years compared to mean age of 45 with a median age of 48. The mean number of years of TB diagnosis from the time immigrants entered in to the U.S. was 10 years, with a median number of years of 6.

Table 21: Overall Mean values of baseline variables (n=5,315)

Variables	**n**	**Mean**	**Range**	**Median**
Age at diagnosis- overall (years)	5,315	42.6±20.0	0.07 - 98	42
Age at diagnosis for immigrants (years)	2,240	39.0±16.9	0.07 - 98	36
Age at diagnosis for non-immigrants (years)	3063	45.3±21.7	0.08 - 96	48
Age at US entry for immigrants (years)	2,161	29.8±15.0	0.24 – 94.9	27
US entry to diagnosis – number of years for immigrants	2,147	9.5±10.4	0 – 66.2	6

Data File Preparation

Dataset variables were recoded to create the models in the statistical analysis. Sex, HIV status, diabetes, contact with infectious TB cases, age greater than 27 at entry in to the U.S. for immigrants, LTBI incomplete treatment, use immunosuppressant medication, and excess alcohol use were selected to add to the model. Frequencies and mean values of the variables were assessed. Association between the variables of interest were analysed with a chi-square test and results using categorical data analysis are provided in Table 22.

Table 22 summarizes the known risk factors for active TB disease. TB disease was confirmed with a diagnostic test (Nucleic Acid Amplification Test [NAAT], culture of tissue and other body fluids, smear/pathology/cytology of tissue and other body fluids, sputum culture, or sputum smear) in 2,292 persons (74.8%) in the non-immigrant population and 1,734 (77.4%) in the immigrants population. The remainder were confirmed by clinical case definition and verified by physicians in the dataset. We used the confirmed cases in our analysis, which resulted in 2,292 in the non-immigrant population and 1,734 cases in the immigrant population.

Association between Risk Factors and Immigration Status

Table 22 summarizes the association between known risk factors and immigration status in immigrants and non-immigrants with

confirmed TB disease. Pearson and Spearman correlation were conducted for the variables under consideration and no strong correlations were identified among variables. Odds ratios (OR) were calculated for the association between explanatory variables and immigration status. Results for these analyses are provided in Table 22. Immigrant cases of TB were less likely to be male than non-immigrant cases (OR=0.84; 95% CI=0.73 - 0.95). The likelihood that a patient with TB had diabetes did not differ significantly between immigrants and non-immigrants (OR= 0.78; 95% CI=0.6 - 1.02). Documented immigrant cases of TB were less likely to be HIV positive than non-immigrant cases(OR=0.56; 95% CI=0.45 - 0.69); immigrant cases of TB were less likely to have had prior contact of TB disease than non-immigrants (OR=0.32; 95% CI=0.22 - 0.46); immigrant cases of TB were less likely to be have not completed LTBI treatment than non-immigrants (OR=0.23; 95% CI=0.13 - 0.43); and immigrant cases of TB were less likely to have consumed excess alcohol compared to non-immigrants (OR=0.21; 95% CI=0.17 - 0.26). Limitations include small sample size or other unknown risk factors in this results.

Table 22: Comparison of the distribution of known risk factors between immigrants and non-immigrants TB cases in Georgia.

Variable	Immigrant (n=1,734) (%)	Non-Immigrant (n=2,301) (%)	Total	Odds Ratio	P-Value*
Male	1096 (63.3)	1542 (67.3)	2638		
Female	636 (36.7)	749 (32.7)	1385		
Total	1732	2291	4023	0.84 (0.73-0.95)	0.008
Diabetes	127 (17.3)	139 (21.1)	266		
Non-Diabetes	608 (82.7)	520 (78.9)	1128		
Total	735	659		0.78(0.6- 1.02)	0.070
HIV + ve	150 (9.4)	325 (15.5)	475		
Not HIV + ve	1448 (90.6)	1771(84.5)	3219		
Total	1598	2096	3694	0.56(0.45-0.69)	<.001
TB Contact	41 (6.3)	110 (17.5)	151		
No Tb Contact	608 (93.7)	520 (82.5)	1128		
Total	649	630	1279	0.32(0.22-0.46)	<.001
LTBI incomplete	14 (2.3)	51(8.9)	65		
Complete	608 (97.8)	520 (91.1)	1128		
	622	571	1193	0.23(0.13-0.43)	<.001
Immunosuppressant	22 (3.5)	27 (4.9)	49		
No Immunosupp	608 (96.5)	520 (95.1)	1128		
Total	630	547	1177	0.70(0.39-1.23)	0.310
Excess Alcohol	108 (6.3)	554 (24.6)	662		
Non- Alcohol	1601 (93.7)	1700 (75.4)	3301		
Total	1709	2254	3963	0.21(0.17-0.26)	<.001

*Chi square test with 0.05 significant level

Kaplan-Meier Estimate of time to diagnosis for immigrants

Figure 9 shows the median time in years for immigrants from date of entry in to the U.S. to TB disease diagnosis was 8.4 years (n=1,652; 95% CI: 7.7 - 9.2). This plot was fitted for immigrants only since the time variable is available for them and no comparison is made with non-immigrants.

Figure 10 shows a Kaplan Maier curve for the median years to diagnosis stratified by age at the time of entry in to the U.S. The median number of years to diagnosis was longer for individuals less than or equal to 27 years of age compared with individuals greater than 27 years of age (9.2 years, 95% CI: 8 - 10.1, vs 7.6 years, 95% CI 6.8 – 8.6, log rank p<0.001).

Figure 11 shows a Kaplan Maier curve for the median years to diagnosis stratified by sex. There is a significant difference with regards to median time from U.S entry to TB disease diagnosis between persons who were male vs female, and is longer for men than for women (9.2 years, 95% CI 8.2 – 10.2 vs 7.6 years, 95% CI 6.4-8.4; log rank p = p=0.039).

Figure 12 shows a Kaplan Maier curve for the median years to diagnosis stratified by HIV status positive or negative. There is a significant difference with regards to median time from U.S entry to TB disease diagnosis between persons who were HIV positive and those who are HIV negative, with a longer time to diagnosis for HIV negative individuals (8.4 years, 95% CI 7.7-9.3 vs 6.2 years, 95% CI 5.4 – 8.1 vs; log rank p = 0.006).

Figure 13 shows a Kaplan Maier curve for the median years to diagnosis stratified by diabetes. There is a significant difference with regards to median time from U.S entry to TB disease diagnosis between persons who were diabetic and those who are non-diabetic, with a longer time to diagnosis for individuals with diabetes (14.9 years, 95% CI 13.2-17.2 vs 9.2 years, 95% CI 8.1-10.2; log rank p = <.001).

Figure 14 shows a Kaplan Maier curve for the median years to diagnosis stratified by active TB contact. There is a significant difference with regards to median time from US entry to TB disease diagnosis between persons who were having active TB contact and those who are with no-active TB contact, with a longer time to diagnosis for individuals with active TB contact (11.8 years, 95% CI 9.8-19.2 vs 9.2 years, 95% CI 8.2-10.2; log rank p = 0.009).

Figure 15 shows a Kaplan Maier curve for the median years to diagnosis stratified by LTBI treatment complete vs LTBI incomplete treatment. There is no significant difference with regards to median time from US entry to TB disease diagnosis between persons who were with LTBI treatment complete vs LTBI incomplete treatment (9.2 years, 95% CI 8.2-10.2 vs 14.8 years, 95% CI 7.4- 20.9; log rank p = 0.343).

Figure 16 shows a Kaplan Maier curve for the median years to diagnosis stratified by immunosuppressant treatment vs who were not on immunosuppressant treatment. There is no significant difference with

regards to median time from US entry to TB disease diagnosis between persons who were under immunosuppressant treatment vs who were not on immunosuppressant treatment (15.6 years, 95% CI 5.8 - 20.6 vs 9.2 years, 95% CI 8.1 - 10.2; log rank p = 0.52).

Figure 17 shows a Kaplan Maier curve for the median years to diagnosis stratified by excess alcohol intake. There is a significant difference with regards to median time from U.S entry to TB disease diagnosis between persons who were taking excess alcohol and those where not taking excess alcohol, with a longer time to diagnosis for individuals who consume excess alcohol (15.4 years, 95% CI 12.3 – 18.8 vs 8.1 years, 95% CI 7.4 – 9.0; log rank p = 0.001).

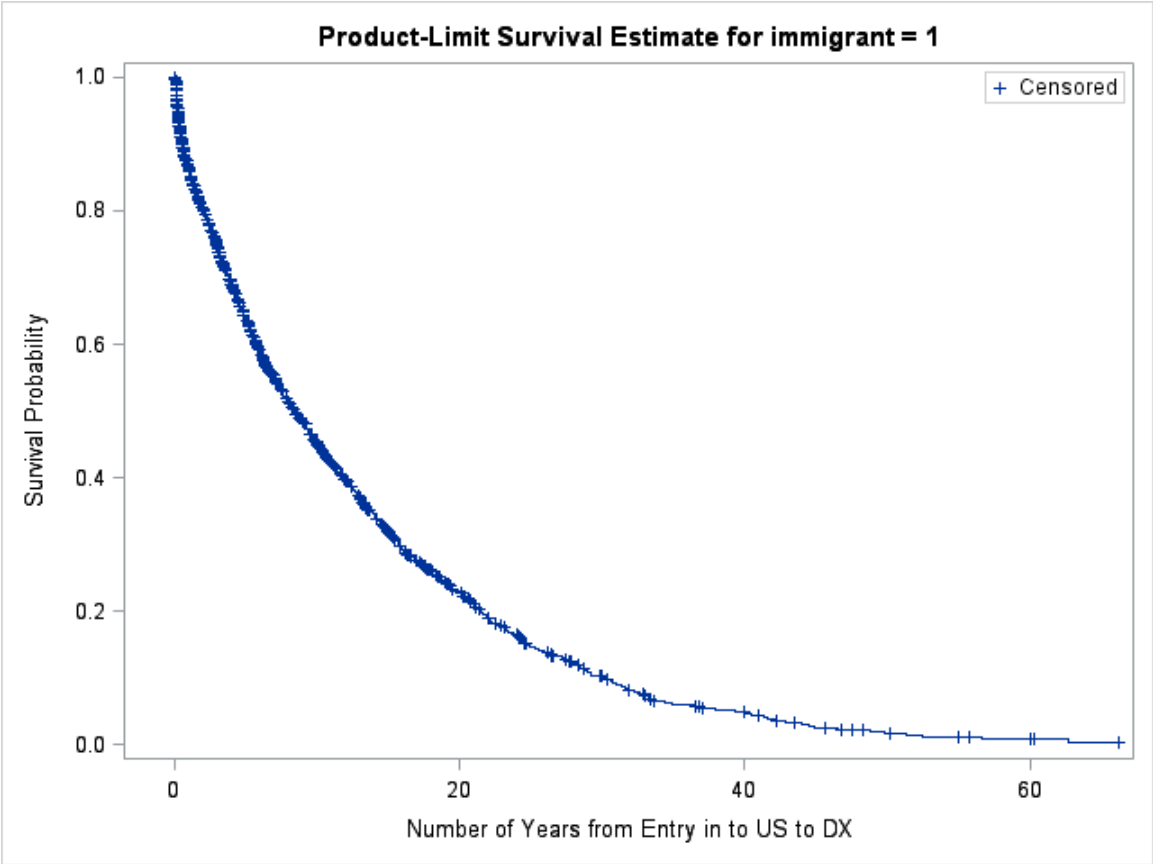

Figure 9: Median time from U.S entry to TB disease diagnosis for the immigrants (8.4 years, 95% CI: 7.7 - 9.2).

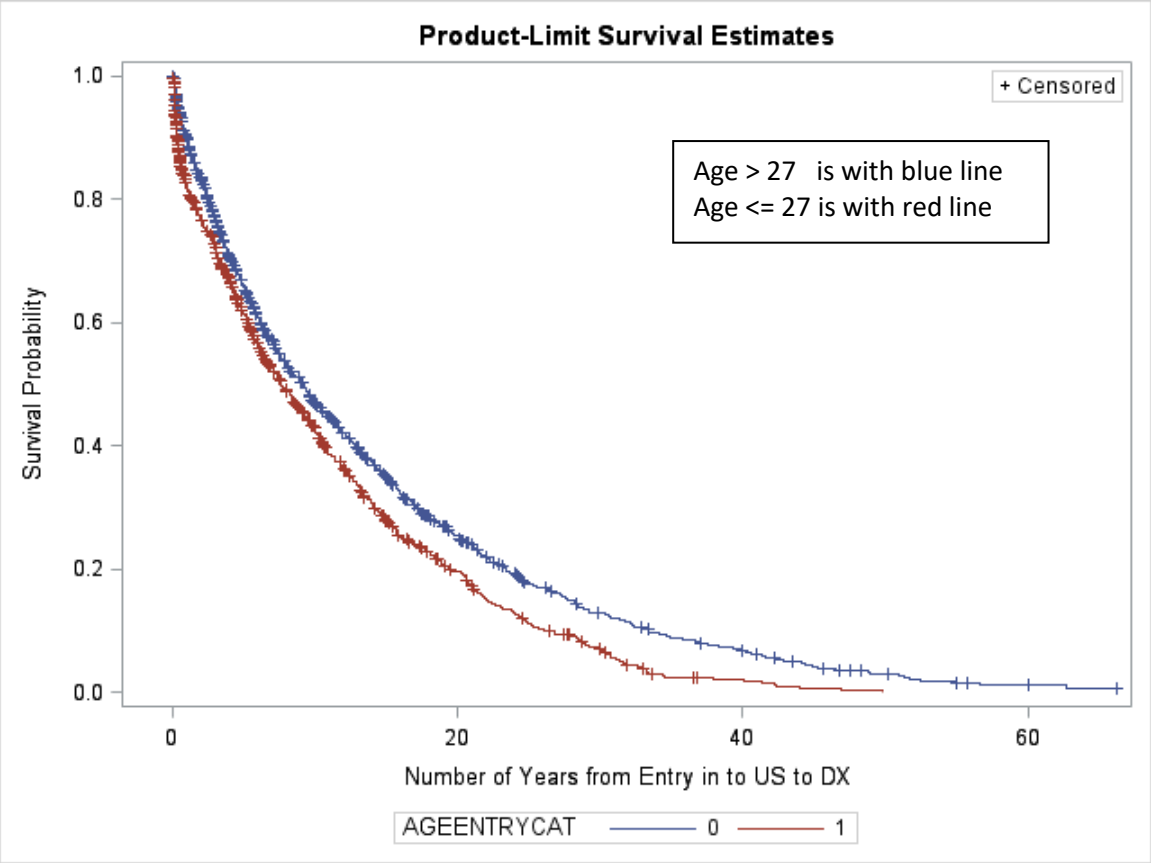

Figure 10: There is a significant difference with regards to median time from US entry to TB disease diagnosis between persons who were with Age >27 (blue line) or less than or equal to 27 years of age, red line (7.6 years, 95% CI 6.8 – 8.6; log rank p = <.001 vs 9.2 years, 95% CI 8 – 10.1).

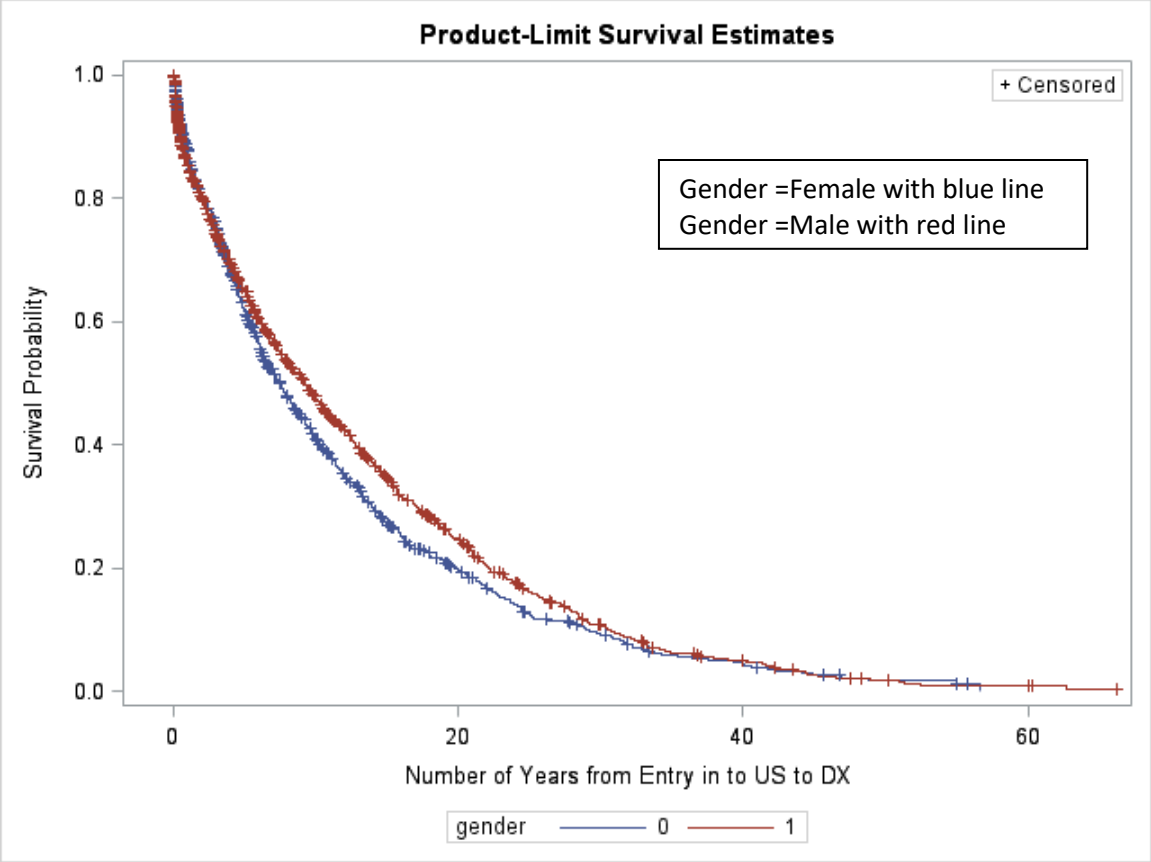

Figure 11: Median time from US entry to TB disease diagnosis for men (red line) vs women (blue line).

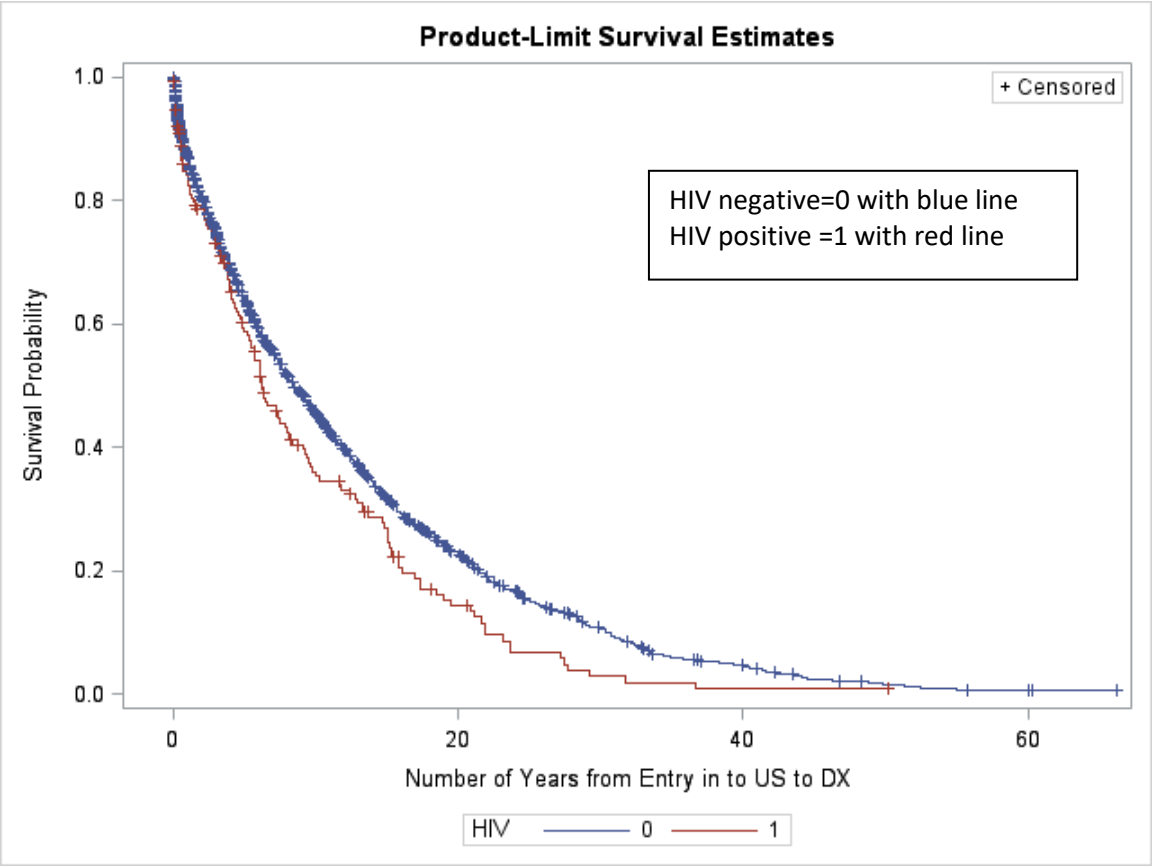

Figure 12: There is a significant difference with regards to median time from U.S entry to TB disease diagnosis between persons who were HIV positive (red line) and those who are HIV negative, blue line (6.2 years, 95% CI 5.4 – 8.1 vs 8.4 years, 95% CI 7.7-9.3; log rank p = 0.006).

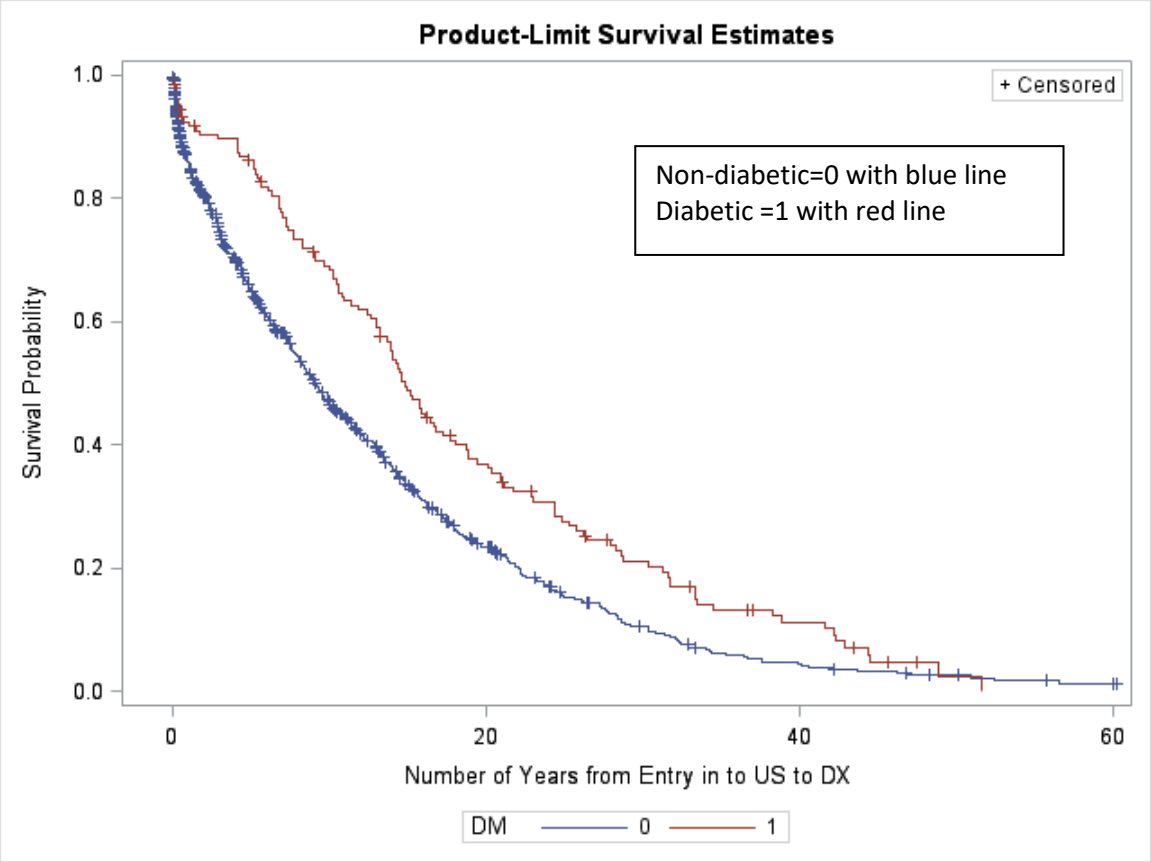

Figure 13: There is a significant difference with regards to median time from US entry to TB disease diagnosis between persons who were diabetic(red line) and those who are non-diabetic (blue line) (14.9 years, 95% CI 13.2-17.2 vs 9.2 years, 95% CI 8.1-10.2; log rank p = <.001).

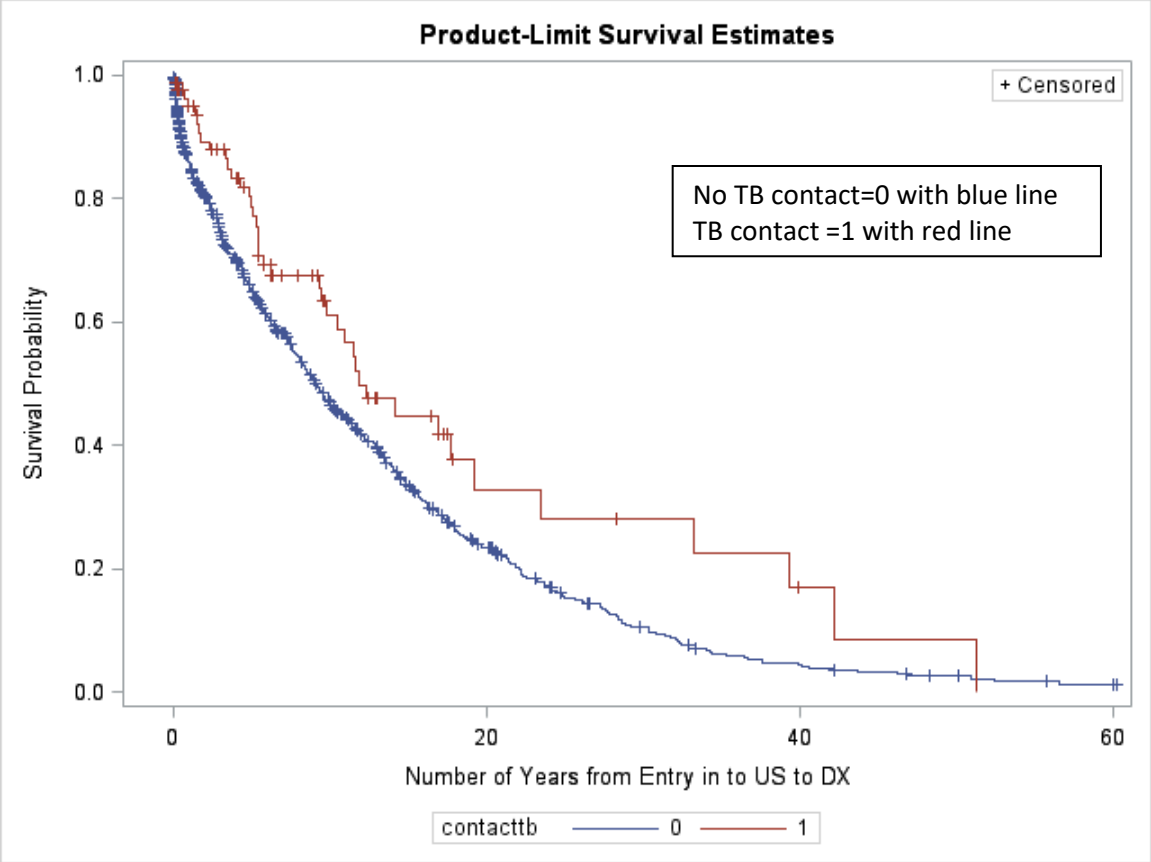

Figure 14: There is a significant difference with regards to median time from US entry to TB disease diagnosis between persons who were having active TB contact (red line) and those who are with no-active TB contact-blue line (11.8 years, 95% CI 9.8-19.2 vs 9.2 years, 95% CI 8.2-10.2; log rank p = 0.009).

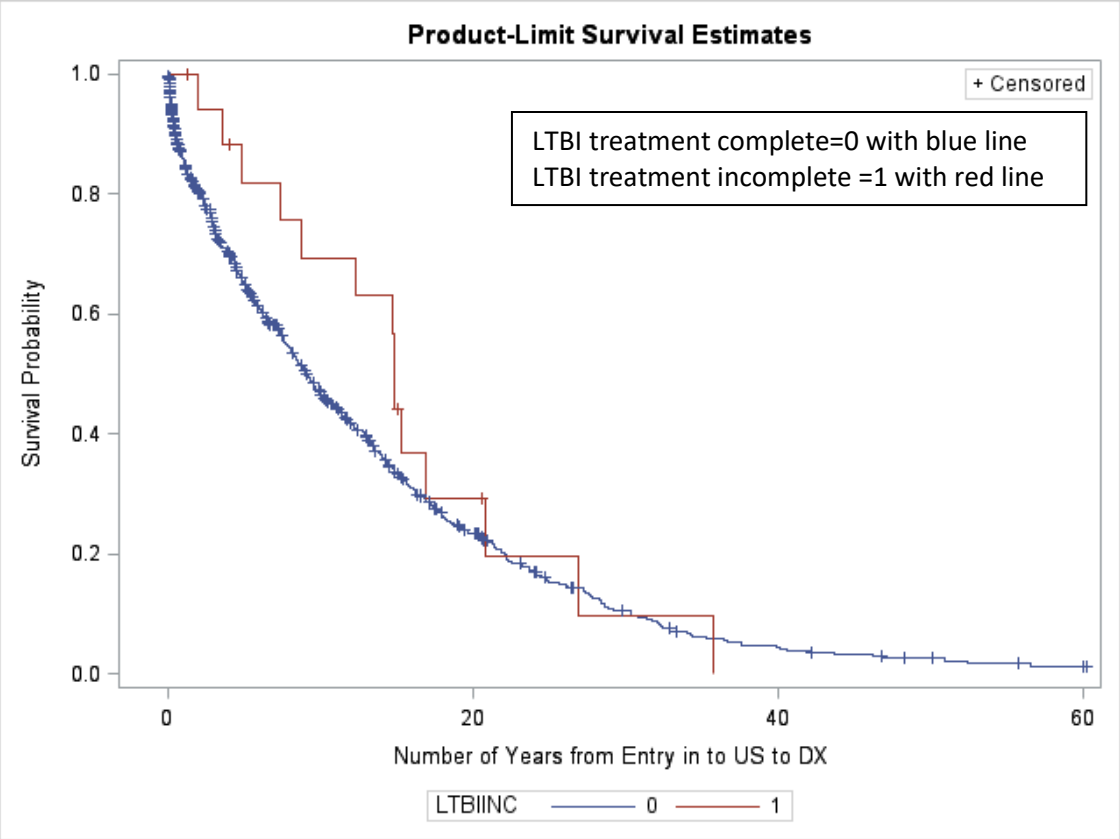

Figure 15: There is no significant difference with regards to median time from US entry to TB disease diagnosis between persons who were with LTBI treatment complete-blue line vs LTBI incomplete treatment-red line (9.2 years, 95% CI 8.2-10.2 vs 14.8 years, 95% CI 7.4- 20.9; log rank p = 0.343).

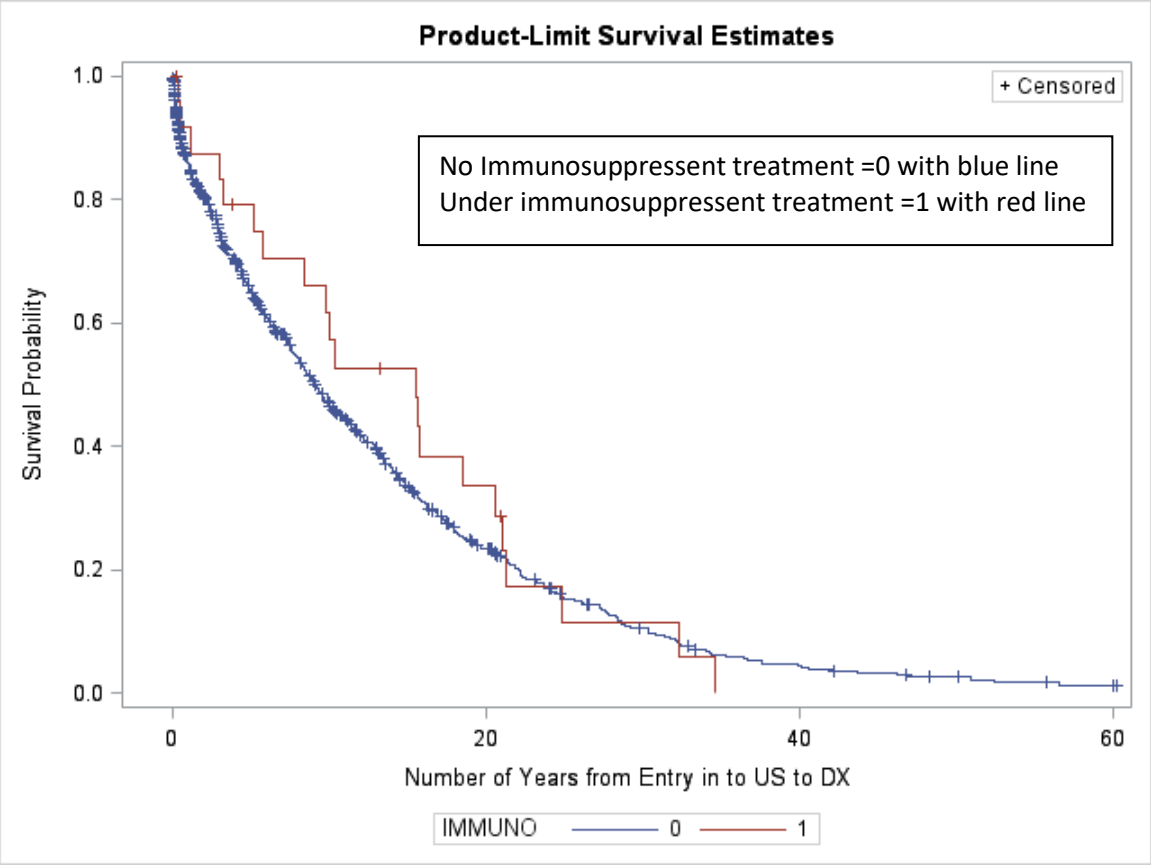

Figure 16: There is no significant difference with regards to median time from US entry to TB disease diagnosis between persons who were under immunosuppressant treatment-red line vs who were not on immunosuppressant treatment-blue line (15.6 years, 95% CI 5.8 - 20.6 vs 9.2 years, 95% CI 8.1 - 10.2; log rank p = 0.52).

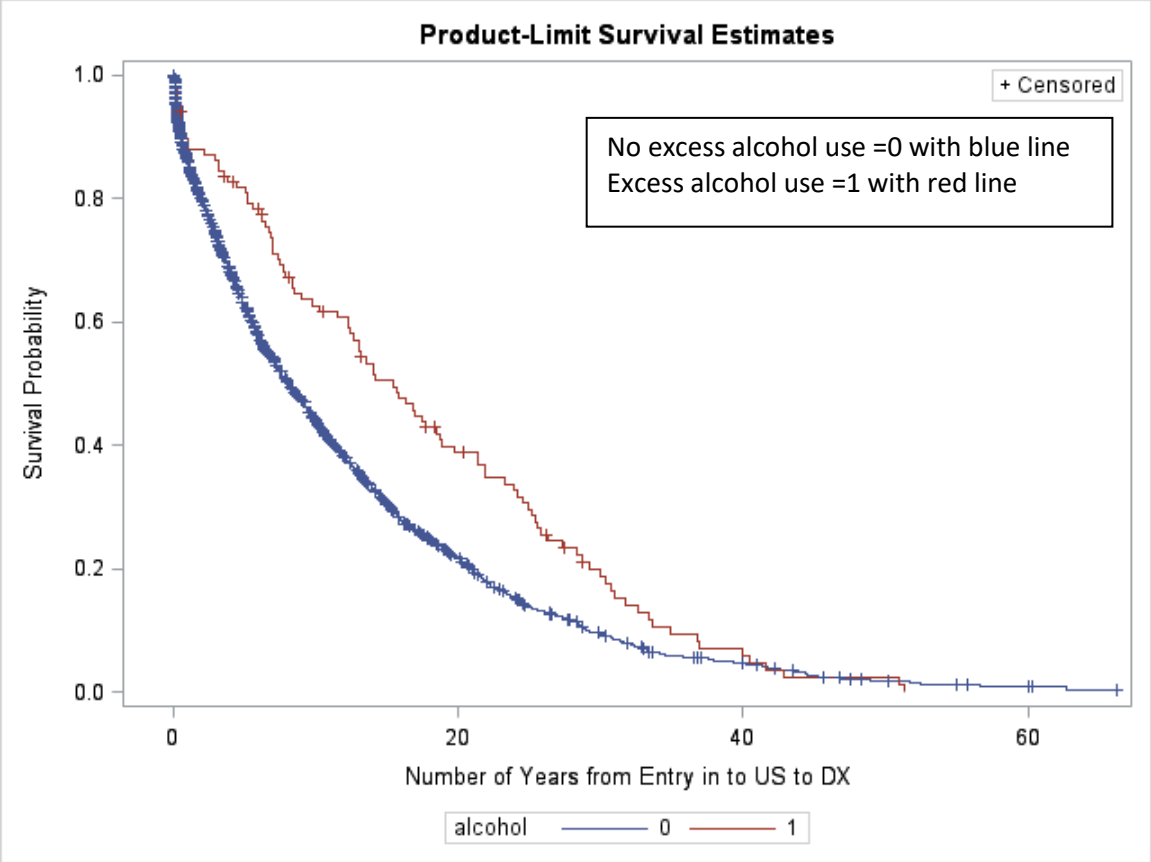

Figure 17: There is a significant difference with regards to median time from US entry to TB disease diagnosis between persons who were taking excess alcohol-red line and those where not taking excess alcohol - blue line (15.4 years, 95% CI 12.3 – 18.8 vs 8.1 years, 95% CI 7.4 – 9.0; log rank p = 0.001).

Limitations

This analysis was done using secondary data. Secondary data analysis have limitations since the data has already been collected by someone in the past. The dataset was not sufficient to analyze for confounding and interaction because of unknown confounders. Also, some subgroups include very small sample size. Another limitation was that undocumented immigrants were not included in the dataset.

Conclusion

Our study results show that the distribution of known risk factors does differ between immigrants and non-immigrants with active TB disease in each group. It shows that immigrants were diagnosed with TB disease at a younger median age of 36 years compared to 48 years for non-immigrants. Immigrant cases of TB were less likely to be male, to be HIV positive, to have prior contact with TB disease, and to have not completed LTBI treatment or used excess alcohol. Although these are all known risk factors, in the case of immigrants the distribution is different compared to non-immigrants. Those may need further studies to understand the underlying reasons.

The modifiable risk factors need aggressive attention in order to reduce TB disease incidence. There must be educational sessions on modifiable risk factors to assist immigrants with screening for TB disease on an annual basis from the time of their entry in to the U.S. Individuals living in the counties with higher TB incidence rates need to be educated on the known risk factors

like HIV disease, need of LTBI treatment and control of alcohol use. People who had contact with active TB disease patients need timely screening for active TB rule-out and if there is LTBI, need treatment. It is necessary to monitor patients who are on LTBI treatment to make sure they complete the treatment regimen. Also, individuals with known risk factors need to be screened according CDC guidelines.

It is necessary to have a detailed health policy to address the TB disease burden among immigrant and non-immigrant population including screening and education for people at risk for TB disease. There must be a collective effort from law makers, health care providers and public to address the spread of TB. Individuals with LTBI need to be treated early on and an awareness of risk factors among public need to be created through educational intervention and screening.

Summary of Results of Aim Two

Aim two results showed that the distribution of known risk factors does differ between immigrants and non-immigrants with active TB disease in each group. Further, our study shows that immigrants were diagnosed with TB disease at a younger median age of 36 years compared to 48 years for non-immigrants. Immigrant cases of TB were less likely to be male than non-immigrant cases. The likelihood that a patient with TB had diabetes did not differ significantly between immigrants and non-immigrants. Immigrant cases of TB were less likely to be HIV positive than

non-immigrant cases, immigrant cases of TB were less likely to be with prior contact of TB disease than non-immigrants, immigrant cases of TB were less likely to be who did not complete LTBI treatment than non-immigrants, and immigrant cases of TB were less likely to be who consumed excess alcohol compared to non-immigrants. Also, immigrant TB cases were less likely to be injecting or non-injecting drug users and lived in correctional facilities than non-immigrant TB cases. Immigrant cases were less likely to be homeless or from long term care facilities. Limitations include small sample size or other unknown risk factors in this results.

We looked into the documented immigrant TB cases to further understand the distribution of known risk factors using the Kaplan-Meier analysis. We found that the median time in years for immigrants from date of entry in to the U.S. to TB disease diagnosis was 8.4 years. Most of the immigrants come to the U.S. after testing for TB infection. But still a majority of them were diagnosed with TB disease in less than 9 years based on our study. Further studies in to the known risk factors and mobility of immigrants may needed to understand the cause of diagnosis with TB disease at a younger age among immigrants.

RESULTS FOR SPECIFIC AIM THREE

3. To assess latent tuberculosis infection (LTBI) in the U.S. population.

NHANES 1999-2000 Data Analysis

a). To determine whether bacille Calmette-Guerin (BCG) vaccination affects the results of the tuberculin skin test (TST) for LTBI in the U.S. population.

H_0: BCG vaccination is not associated with the results of TST for LTBI in the U.S. population.

H_1: BCG vaccination is associated with the results of TST for LTBI in the U.S. population.

Prevalence of LTBI

An analysis ready dataset for the years 1999-2000 was created by merging NHANES datasets across the following variables: demographics, TB TST results, blood pressure (mmHg units), body mass index in kg/m^2, HIV, and glycohemoglobin in mmol/mol. There were a lot of missing data in the dataset. Table 23 summarizes socio-demographics of all observations (n=9,965), persons with LTBI (n=410), and persons without LTBI (n=9,555) from NHANES Data 1999-2000. Of all observations, 49% were reported males, 34.05% were Mexican Americans, 24.9% married, and 49% were above the age of 19 years.

Persons with LTBI were significantly more likely to be men than those without LTBI (60.5% vs. 48.5%; p=<.001). Persons with LTBI were significantly more likely to be non-Hispanic whites than those without LTBI (52.9% vs. 33.6%; p=<.001). Persons with LTBI were significantly less likely to be a high school graduate than those without LTBI (14.4% vs. 34.5%; p=0.016). Persons with LTBI were significantly more likely to be a high school graduate or below in the age group of 20 years or above than those without LTBI (82.7% vs. 27.8%; p=<.001). Persons with LTBI were significantly more likely to be married than those without LTBI (45.1% vs. 24.1%; p=<.001). Persons with LTBI were significantly more likely lived in the U.S for less than five years than those without LTBI (11.5% vs. 4.3%; p=0.046). Persons with LTBI were significantly more likely to be in the income group of less than $24,999 per year than those without LTBI (39.8% vs. 33.1%; p=0.001). Persons with LTBI were significantly more likely to be above the age of 19 years than those without LTBI (82.7% vs. 47.5%; p=<.001). Crowding in households (defined as more than four people in the household) was not significantly different between persons with and without LTBI (35.1% vs. 36.9%; p=0.388).

Table 24 summarizes medical conditions of all observations (n=9,965), persons with LTBI (n=410), and persons without LTBI (n=9,555) from NHANES Data 1999-2000. Persons with LTBI were significantly more likely to be with hypertension than those without LTBI (44.4% vs. 18.4%; p=<.001).

In the LTBI group there were no persons was reported with HIV positive compared to 18 persons reported HIV positive in the non-LTBI group. Persons with LTBI were significantly more likely to be with diabetes than those without LTBI (7.6% VS. 3.9%; P=<.001)

The prevalence of LTBI from 1999-2000 was 4.1% (95% CI: 3.7 – 4.5) in the overall sample, and the U.S. population in 2000 was 282.2 million according to the U.S. census bureau. Applying the prevalence rate to the U.S. population gave the estimated number of persons with LTBI infection as 11,598,420 persons for the year 2000.

Table 23: Sociodemographic of observations (n=9,965), LTBI (n=410), and non-LTBI (n=9,555) from NHANES Data 1999-2000 (*Chi-Square test at the significant level of 0.05)

Variables	Overall (n=9,965)	LTBI (n=410, 4.1%)	Non-LTBI (n=9,555)	LTBI vs non-LTBI*
Sex	n (%)	n (%)	n (%)	p-value
Male	4883(49.0)	248(60.5)	4635(48.5)	<.001
Female	5082(51.0)	162(39.5)	4920(51.5)	
Race/Ethnicity				<.001
Non-Hispanic White	3423(34.4)	217(52.9)	3206(33.6)	
Non-Hispanic Black	2273(22.8)	30(7.3)	2243(23.5)	
Mexican American	3393(34.1)	48(11.7)	3345(35.0)	
Other – Including Multi- Racial	287(2.9)	96(23.4)	191(2.0)	
Other Hispanic	589(5.9)	19(4.6)	570(6.0)	
Education level age 6-19 years				0.016
High School Graduate, GED or below	3360(33.7)	59(14.4)	3301(34.5)	
Other/missing	6,605(66.3)	351(85.6)	6,254(65.5)	
Education level age 20 yrs and above				<.001
High School Graduate or below	2993(30.0)	339(82.7)	2654(27.8)	
College education	1863(18.7)	0	1863(19.5)	
Other/missing	6460(64.8)	71(17.3)	6389(66.9)	
Marital Status				<.001
Married	2485(24.9)	185(45.1)	2300(24.1)	
Widowed	475(4.8)	29(7.1)	446(4.7)	
Divorced	378(3.8)	32(7.8)	346(3.6)	
Separated	177(1.8)	21(5.1)	156(1.6)	
Never Married	2316(2.3)	67(16.3)	2249(2.4)	
Living with Partner	232(2.3)	14(3.4)	218(2.3)	
Other/missing	3902(39.2)	62(15.1)	3840(40.2)	
Time in US				0.046
Less than 5 years	457(4.6)	47(11.5)	410(4.3)	
5 or more years	1380(13.8)	194(47.3)	1186(12.4)	
Missing	8128(81.6)	169(41.2)	7959(83.3)	
Crowded				0.388
More than 4 people	3672(36.8)	144(35.1)	3528(36.9)	
4 or less	6293(63.2)	266(64.9)	6027(63.0)	
Income category				0.001
Up to 24,999	3334(33.5)	163(39.8)	3171(33.1)	
Above 24,999	5031(50.5)	173(42.2)	4858(50.8)	
Missing	1600(16.1)	74(18.0)	1526(16.0)	
Age Category				<.001
Above 19	4880(49.0)	339(82.7)	4541(47.5)	
Up to 19	4613(46.3)	71(17.3)	4542(47.5)	
Missing	472(4.7)		472(4.9)	

Table 24: Medical conditions of observations (n=9,965), LTBI (n=410), and non-LTBI (n=9,555) from NHANES Data 1999-2000

Variables	Overall (n=9,965)	Latent TB (n=410, 4.1%)	Non-LTBI (n=9,555)	LTBI vs non-LTBI comparison*
	n(%)	n(%)	n(%)	p-value
Hypertension				
Yes	2217(22.2)	182(44.4)	1760(18.4)	<.001
No	4998(50.2)	213(51.9)	4098(42.9)	
Missing	2750(27.6)	15(3.7)	1118(11.7)	
HIV Results				
Yes	18(0.2)	0	18(0.2)	
No	2707(27.2)	155(37.8)	2552(26.7)	0.275
Missing	7240(72.7)	255(62.2)	6985(73.1)	
Diabetes				
A1C >=6.5 Yes	407(4.1)	31(7.6)	376(3.9)	
No	5936(59.6)	343(83.7)	5593(58.5)	<.001
Missing	3622(36.3)	36(8.7)	3622(37.9)	

*Chi-Square test at the significant level of 0.05

BCG and the Immigrant Status

Table 25 summarizes immigration status and BCG vaccination status in the LTBI group and in the non-LTBI group. Persons with LTBI were significantly more likely to be an immigrant than those without LTBI (40.7% vs. 10.2%; p=<.001). Persons with LTBI were significantly more likely to have a BCG scar showing they received BCG vaccination than those without LTBI (19.3% vs. 5.7%; p=<.001). Immigrants were significantly at higher risk for being diagnosed with LTBI compared to non-immigrants (RR=6.60, 95%CI: 5.38-8.10). The relative risk of LTBI in individuals with BCG vaccination was significantly higher compared with those without BCG vaccination (RR=2.78, 95%CI: 2.21 – 3.50). This result showed that there was no significant or complete risk reduction with BCG vaccination. This may be due to number years passed after BCG vaccination or the quality of the vaccine itself. Data collected in 1999 and the participants were older population. This shows that BCG vaccination did not provide 100% protection from TB infection for longer period of time. Reaction to BCG vaccination cannot be ruled out in this interpretation. There was no data provided on false positives either. Almost 40% of the LTBI group were immigrants who mostly received BCG vaccination in their home country in their childhood. Still, this result proves that BCG vaccination affects the interpretation of latent TB infection in the U.S. population. We accept the alternative hypothesis that BCG vaccination is associated with the

results or interpretation of TST for LTBI in the U.S. population with the limitations in the data.

Table 26 summarizes a stratified analysis conducted to determine whether the association between immigrant status and LTBI differs by BCG status. A large difference was found among BCG groups when considering immigrant status. In BCG vaccinated group, the RR for LTBI was 2.87 (95%CI: 1.72 – 4.83) for those who were immigrants and later diagnosed with latent TB, compared to an RR of 7.05 (95%CI: 5.64 – 8.82) in non-immigrants without vaccination. There was a difference of 4.15 between the two relative risks which is more than 10% which means there was interaction with BCG vaccination status.

The overall distribution of PPD induration is provided in Figure 18.

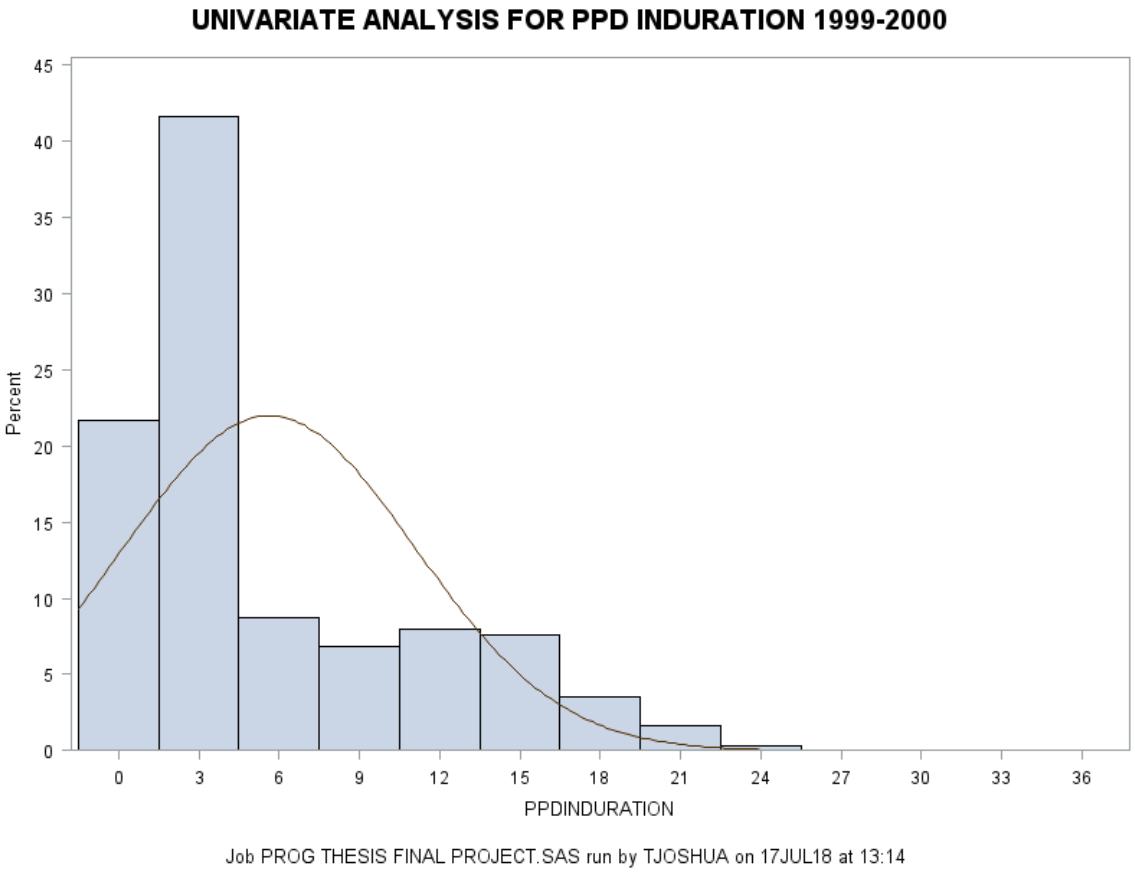

Figure 18: Distribution of TST measurements among overall participants

Table 25: Immigrant status and BCG scar data in the observations latent TB (n=410) and non-LTBI (9,555) from NHANES Data 1999-2000 and relative risk (RR)

Variables	LTBI (n=410) n (%)	Non-LTBI (n=9,555) n (%)	Total	RR (95% CI)	LTBI vs Non-LTBI p-value*
Immigrant Status				6.60(5.38-8.10)	<.001
Yes	167 (18.0)	760 (82.0)	927		
No	162 (2.7)	5773 (97.3)	5935		
Missing	81	3022	3103		
BCG Scar				2.78(2.21-3.50)	<.001
BCG Yes	79 (13.6)	504 (86.4)	583		
No BCG	331 (4.9)	6,470 (95.1)	6801		
Missing	0	2581	2581		

*Chi-Square test at the significant level of 0.05

Table 26: Stratified analysis by BCG status

	BCG received			BCG not received		
	LTBI	No LTBI	Total	LTBI	No LTBI	Total
Immigrants	29(20.6)	112	141	138 (17.6)	648	786
Non- Immigrants	22(7.1)	286	308	140 (2.5)	5485	5625
Total				278	6133	6411
		RR1=2.87(1.72-4.83)			RR2=7.05(5.64-8.82)	
		Diff	4.15			

Overall Mean Values

Table 27 summarizes overall mean values of physiologic variables at baseline for participants. The mean age with standard deviation (SD) in the overall group was 29.7 years ±24.8 years. Systolic blood pressure mean was 119.4 mmHg, diastolic blood pressure was 67.3 mm Hg, waist circumference was 84.6 cm, glycohemoglobin was 5.4%, and total cholesterol mean was 186.9 mg/dl. Detailed data is given in Table 27.

Table 28 and 29 summarizes the mean values for LTBI and non-LTBI groups. Mean age in the LTBI group was 46.4 compared to 30.6 in the non-LTBI group. Median age in the LTBI group was 48 compared to 20 in the non-LTBI group. Generally similar measurements were noted for blood pressure, cholesterol, waist circumference, and glycohemoglobin in both LTBI and non-LTBI groups.

Table 27: Overall mean values of baseline physiologic variables (n=9,965)

Variables	n	Mean (SD)	Range	Median
Age (years)	9,96	29.7±24.83	1 - 85	19.00
SBP (mmHg)	7,21	119.4±20.2	73 - 233	115.00
DBP (mmHg)	7,21	67.3±14.4	– 132	68.00
Waist Circumference(cm)	8,28	84.6±20.5	38.2 -173.4	84.70
Glycohemoglobin	6,36	5.4±1.0	2.5 – 15.1	5.2
Total Cholesterol (mmol/L)	7,42	186.9±42.9	72 - 575	182
HDL Cholesterol(mmol/L)	7,42	50.9±14.1	8 --38	49
LDL Cholesterol(mg/dl)	3,17	112.3±35.3	23 - 320	108
Triglyceride (mg/dl)	3,50	123.9±95.4	21 - 1538	98

Table 28: Overall mean values of baseline physiologic variables for Latent TB cases (n=410)

Variables	n	Mean(SD)	Range	Median
Age (years)	410	46.4±21.1	1 - 85	48.00
SBP (mmHg)	395	127.7±22.8	83 - 204	123.00
DBP (mmHg)	395	72.0±15.6	– 122	72.00
Waist Circumference(cm)	403	93.1±15.4	42 -152	94.40
Glycohemoglobin (mmol/mol)	386	5.7±1.2	3.7 – 14.7	5.2
Total Cholesterol (mmol/L)	383	198.2±42.8	91 - 346	196
HDL Cholesterol(mmol/L)	383	48.5±13.9	22 --97	45
LDL Cholesterol(mg/dl)	167	118.3±34.8	46 - 225	120
Triglyceride (mg/dl)	196	149.0±141.3	22 - 1330	119

Table 29: Overall mean values of baseline physiologic variables for non-Latent TB cases (n=6,976)

Variables	n	Mean(SD)	Range	Median
Age (years)	6,976	30.6±23.9	1 - 85	20.0
SBP (mmHg)	5,858	119.1±20.0	73 - 233	115.0
DBP (mmHg)	5,858	67.3±14.3	0– 122	68.0
Waist Circumference(cm)	6,652	85.0±20.4	42 -132	84.8
Glycohemoglobin (mmol/mol)	5,342	5.4±1.0	2.5 – 15.1	5.2
Total Cholesterol (mmol/L)	6,358	186.1±42.7	72 - 575	181
HDL Cholesterol(mmol/L)	6,353	51.1±14.1	8 -138	49
LDL Cholesterol(mg/dl)	2,703	111.8±35.3	23 - 320	107
Triglyceride (mg/dl)	2,959	122.1±93.5	24 - 1538	97

Associations between the Variables of Interest

Table 30 summarizes associations between the variables of interest using chi-square tests and the results, using categorical data analysis. Known risk factors for TB were analysed between LTBI and non-LTBI group. Male sex (p=<.001), BCG vaccinated (p=<.001), diabetes (p=<.001), immigrants (p=<.001), obesity (p=0.026), cholesterol (p=<.001), less than 5 years in the U.S. (p=0.046), income less than $25,000 (p=0.001), age greater than19 years (p=<.001), high blood pressure (p=<.001) were shown to have significant associations at the 0.05 significant level for the LTBI group compared to those without LTBI. No strong correlations were found between variables. Pearson and Spearman correlation analyses were conducted for the variables under consideration.

Relative Risk

Results are provided in Table 30. Males were significantly at higher risk compared to females to be diagnosed with LTBI (RR=1.56, 95%CI: 1.28 – 1.89), and individuals with age greater than 19 years were significantly at higher risk (RR= 4.40, 95%CI: 3.42 - 5.66. Patients with diabetes were significantly at higher risk to be diagnosed with LTBI (RR=1.88, 95%CI: 1.40-2.53), as were persons with high cholesterol (RR=1.58, 95%CI: 1.30- 1.92) and the obese (RR=1.28, 95%CI: 1.03 – 1.58). Immigrants were significantly at higher risk for being diagnosed with LTBI compared to non-immigrants (RR=6.60, 95%CI: 5.38-8.10), and

individuals with income less than $25,000 were significantly at higher risk (RR=1.41, 95%CI: 1.15 – 1.73). Crowding was not shown as a significant risk factor among LTBI group in this study, may be due to small sub group sample size.

Table 30: Relative risk (RR) and association for variables and LTBI vs. non-LTBI

Variable	Latent TB (%)	No Latent TB (%)	Total	RR (95% CI)	p-value*
Male	248 (6.8)	3413 (93.2)	3661		<.001
Female	162 (4.3)	3563 (95.7)	3725		
Total	410	6976	7386	1.56(1.28 – 1.89)	
Diabetes	43 (12.0)	315 (88.0)	358		<.001
Non-Diabetes	343 (6.4)	5027 (93.6)	5370		
Total	386	5342	5728	1.88(1.40-2.53)	
HIV +ve	0	17(100)	17		0.275
HIV -ve	155(6.5)	2212(93.5)	2367		
Total	155	2229	2384	0	
BCG Vaccination Yes	79 (13.6)	504 (86.4)	583		<.001
BCG Vaccination No	331(4.9)	6470 (95.1)	6801		
Total	410	6974	7384	2.78(2.21-3.50)	
Immigrant	167 (18.0)	760 (82.0)	927		<.001
No Immigrant	162 (2.7)	5773 (97.3)	5935		
Total	329	6533	6862	6.60(5.38-8.10)	
Cholesterol	173 (7.5)	2138 (92.5)	2311		<.001
No Cholesterol	210 (4.7)	4220 (95.3)	4430		
Total	383	6358	6741	1.58(1.30-1.92)	
Obesity	106 (6.8)	1451 (93.2)	1557		0.026
No Obesity	298 (5.3)	5289 (94.7)	5587		
Total	404	6740	7144	1.28(1.03-1.58)	
Crowded >4 people	144 (5.3)	2598 (94.7)	2742		0.388
=<4 people	266 (5.7)	4378 (94.3)	4644		
Total	410	6976	7386	0.92(0.75-1.12)	
Low income <25,000	163 (6.4)	2370 (93.6)	2533		0.001
>=25,000	173 (4.6)	3622 (95.4)	3795		
Total	336	5992	6328	1.41(1.15-1.73)	
Age >19(Median)	339 (8.8)	3504 (91.2)	3843		<.001
Age=<19	71 (2.0)	3472 (98.0)	3543		
Total	410	6976	7386	4.40(3.42–5.66)	

*Chi-Square test at the significant level of 0.05

Stratified Analysis

Tables 31 and 32 summarize a stratified analysis conducted to determine whether the association between BCG status and LTBI differs between immigrants and non-immigrants. Also, a stratified analysis was conducted to determine whether the association between BCG status and LTBI differs between the age groups of above and below or equal to 19 years of age. A large difference was found among immigrants and non-immigrants when considering BCG vaccination. In immigrants, the RR for LTBI was 1.17 (95%CI: 0.81 – 1.67) for those who were BCG vaccinated and later diagnosed with latent TB, compared to an RR of 2.86 (95%CI: 1.85 – 4.43) in non-immigrants. There was a difference of 1.69 between the two relative risks which is more than 10% which means there was interaction with immigration status.

BCG vaccination status and LTBI status is mixed up with immigration status in this analysis hence immigration status is a confounder variable. Confounding is a distortion in the estimated measure of association that occurs when the primary exposure of the interest BCG vaccination status was mixed up with immigrant status that is associated with the outcome LTBI. Immigration status is associated with BCG status and LTBI and distributed unequally among the immigrant LTBI and non-immigrant LTBI groups when compared. A large difference in relative risk was

happened due to this factor. Confounding is a bias and it happened with immigration status.

The relative risk of LTBI in individuals who were less than or equal to 19 years of age (RR= 5.63; 95%CI: 2.37-13.34) compared with individuals who were greater than 19 years of age (RR=1.72; 95%CI: 1.35 – 2.19) was significantly higher. There was a difference of 3.91 in the relative risk between two groups which is more than 10%, showing there was interaction among age groups when considering BCG vaccination and LTBI diagnosis using TST results.

BCG vaccination status and LTBI status is mixed up with age group in this analysis hence age group is a confounder variable. Confounding is a distortion in the estimated measure of association that occurs when the primary exposure of the interest BCG vaccination status was mixed up with age group that is associated with the outcome LTBI. Age is associated with BCG status and LTBI and distributed unequally among the immigrant LTBI and non-immigrant LTBI groups when compared. A large difference in relative risk was happened due to this factor. Confounding is a bias and it happened with age.

Table 31: Stratified analysis among Immigrants and non-immigrants

	Immigrants			Non-Immigrants		
	Latent TB	No LTBI	Total	Latent TB	No LTBI	Total
Yes BCG	29	112	141	22	286	308
No BCG	138	648	786	140	5485	5625
Total	167	760	927	162	5771	5933
		RR1=1.17 (0.81-1.67)			RR2=2.86 (1.85-4.43)	
		Diff	1.69			

Table 32: Stratified analysis among age groups

	Age group > 19 years			Age group=<19 years		
	Latent TB	No LTBI	Total	Latent TB	No LTBI	Total
Yes BCG	74	462	536	5	42	47
No BCG	265	3041	3306	66	3429	3495
Total	339	3503	3842	71	3471	3542
		RR1=1.72(1.35-2.19)			RR2=5.63(2.37-13.34)	
		Diff	3.91			

Mixture Model Analysis

Additionally, a mixture model analysis was conducted to assess the mean and median of the latent TB measures using TST results among overall participants and its significance in the assessment of latent TB diagnosis. A univariate analysis was conducted to assess the distribution of TST results and to determine the number of k components. Zero values were removed from the values to get curves from values '1' onwards since a value of zero was not defined clearly in the dataset. A model with two component distributions was chosen and fitted since that will show the indeterminate space under two curves with TST measurements. We were interested in the group of people coming under the indeterminate area based on the TST measurements. Among the overall participants with TST reading greater than 0, the mean and median TST induration were 14.29mm (SD=3.4) and 14mm, respectively. The mean for the lower distribution was 2.16mm (SD= 1.23). The mean for the upper distribution was 11.2 (SD=4.96). The 95^{th} percentile was 17mm and the 5^{th} percentile was 1 mm. The optimal cutoff value for separating the lower and upper distributions was estimated to be 4.8 mm. Figure 19 provides the univariate analysis for TST induration to assess distribution. The mixture model analysis in Figure 20 was created with the 2 factor method and it shows the curve with a mean value 11.2±4.96. There is an area under the two curves in between the two curves, which is indeterminate.

This area contain TST measurements belongs to both curves. We need to be cautious when determining LTBI using TST measurement since an accurate TST measurement cut-off value may be not help in diagnosing LTBI.

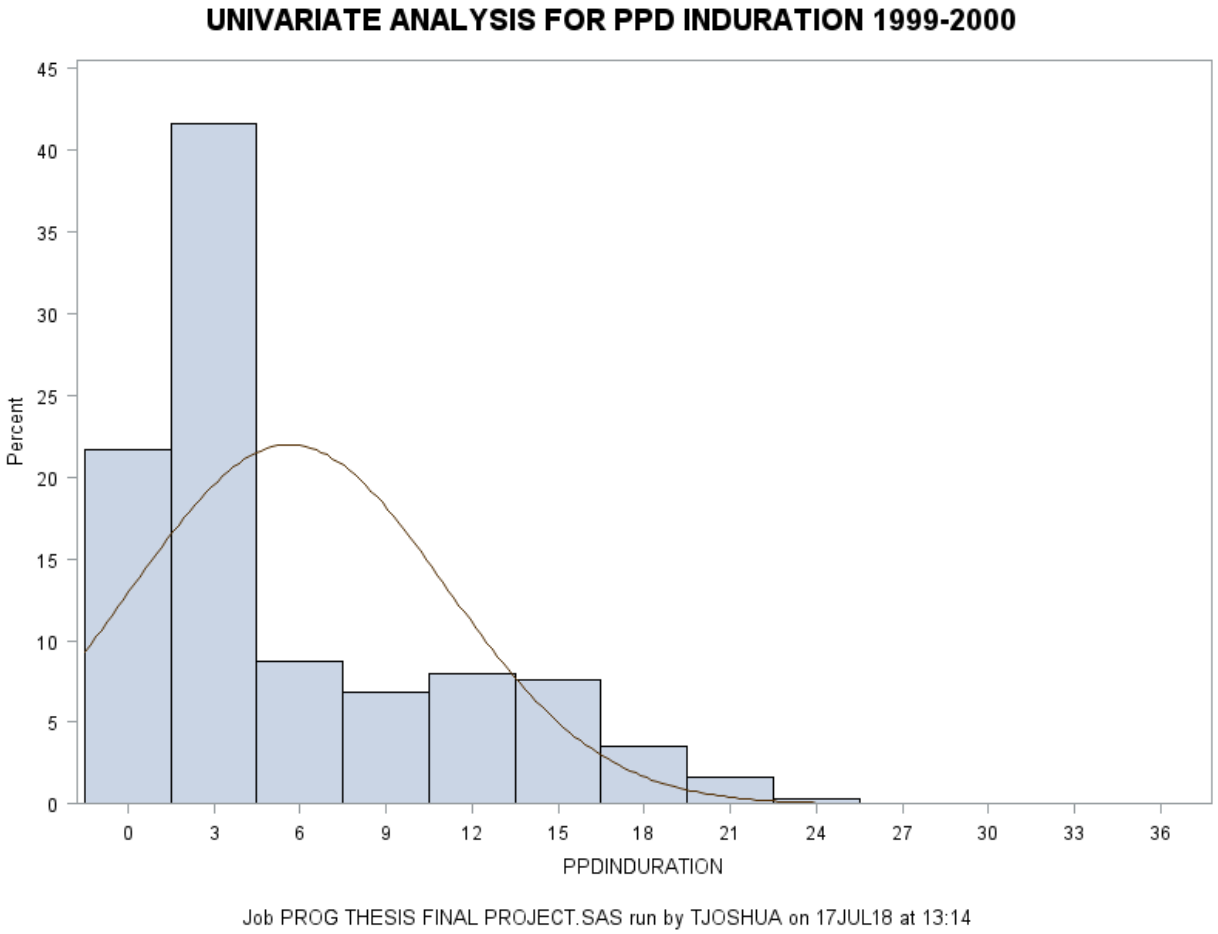

Figure 19: Distribution of TST measurements among overall participants

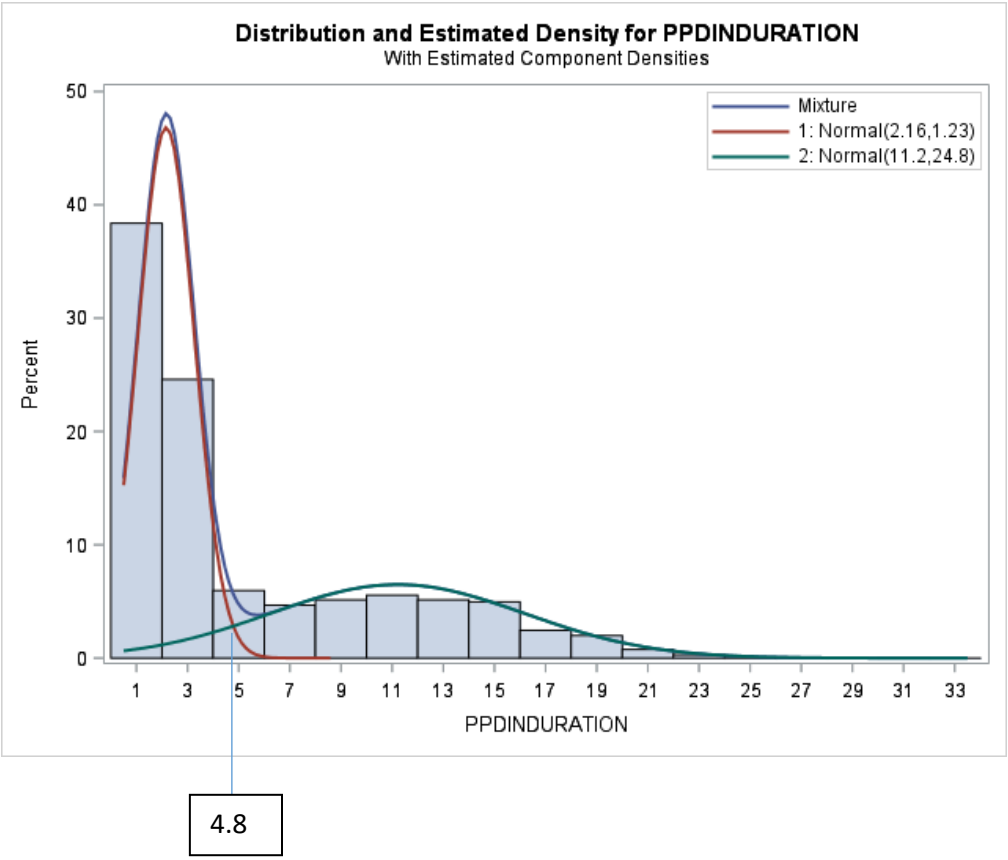

Figure 20: Mixture model analysis for overall TST measurement with 2 factors

NHANES 2011-2012 DATA ANALYSIS

b). To compare TST and Quantiferon diagnostic measurements for LTBI in the U.S. population

H_0: There is no difference between TST and Quantiferon diagnostic accuracy in assessing LTBI in the U.S. population.

H_1: There is a difference between TST and Quantiferon diagnostic accuracy in assessing the LTBI in the U.S. population.

Data File Preparation

An analysis ready dataset for the years 2011-2012 was created by merging NHANES datasets for the variables: demographics, TB TST results, TB Quantiferon test results, blood pressure, body mass index, exhaled nitric oxide concentration, HIV, vitamin D, and glycohaemoglobin. Table 33 summarizes the socio-demographic characteristics of the study population. A total of 9,756 observations were in the dataset. Overall, 49.8% of the data consisted of males and 30.5% were Mexican Americans compared to 13.9% non-Hispanic white individuals. There were 5.6% who reported military status, 31.3% reported a college level education, and the median age was 26. There were 4.5% diagnosed with LTBI in the overall population.

Persons with LTBI were not significantly more likely to be men than those without LTBI (54.3% vs. 49.6%; p=0.583). Persons with LTBI were significantly more likely to be Mexican American than those without LTBI (16.3% vs. 13.8%; p=<.001). Military status was not significant in diagnosing

with LTBI among LTBI and non-LTBI groups (6.1% vs. 5.6; p=0.052). Persons with LTBI were not significantly more likely to be with a high school graduate degree for the age group of 6 to 19 years than those without LTBI (6.3% vs. 26.3%; p=.004). Persons with LTBI were not significantly more likely to be with a high school graduate degree for the age group of 20 years and above than those without LTBI (51.1% vs. 24.4%; p=0.366). Persons with LTBI were not significantly differ based on income less than 24,999 than those without LTBI (41.6% vs. 42.4%; p=0.982). Persons with LTBI were significantly more likely to be above the age of 26 years than those without LTBI (86.2% vs. 48%; p=0.001).

Table 34 summarizes more sociodemographic characteristics of the data. Persons with LTBI were significantly more likely to be an immigrant than those without LTBI (72.6% vs. 18.9%; p=<.001). Persons with LTBI were significantly more likely to be married than those without LTBI (52.7% vs. 26.3%; p=0.017). Persons with LTBI were not significantly more likely to be spent less than 5 years in the U.S. than those without LTBI (11.3% vs. 3.1%; p=0.247). Persons with LTBI were not significantly more likely to be living in the crowded household than those without LTBI (31.9% vs. 32.3%); p=0.880).

Table 35 summarizes the health related data of the participants. Vitamin D deficiency was reported in 74.7% and diabetics were 6.2% in the overall data. Persons with LTBI were significantly more likely to be vitamin D3 deficient than those without LTBI (96.2% vs. 73.7%); p=0.036). Persons

with LTBI were significantly more likely to test positive with Quatiferon test than those without LTBI (49.1% vs. 3.5%); p=<.001). Persons with LTBI were not significantly more likely to be hypertensive than those without LTBI (1.8% vs. 1.1%); p=0.547). Persons with LTBI were significantly more likely to be diabetic than those without LTBI (15.2% vs. 5.9%); p=0.004).

Table 33: Socio-demographic data on overall (n=9,756), LTBI (n=442), and non-LTBI (n=9,314) from NHANES Data 2011-2012

Variables	Overall (n=9,756)	LTBI (n=442, 4.5%)	Non-LTBI (n=9,314, 95.5%)	LTBI vs non-LTBI comparison*
Sex			n (%)	p-value
Male	4856(49.8)	240(54.3)	4616(49.6)	0.583
Female	4900(50.2)	202(45.8)	4698(50.4)	
Race/Ethnicity				<.001
Mexican American	1355(13.9)	72(16.3)	1283(13.8)	
Other Hispanic	1076(11.0)	91(20.6)	985(10.6)	
Non-Hispanic White	2973(30.5)	25(5.7)	2948(31.7)	
Non-Hispanic Black	2683(27.5)	116(26.2)	2567(27.6)	
Other Race	1669(17.1)	138(3.1)	1531(16.4)	
Military Status				0.052
Yes	551(5.6)	27(6.1)	524(5.6)	
No	5456(5.6)	395(89.4))	5061(54.3)	
other	3749(38.4)	20(4.5)	3729(40)	
Education level age 6-19 years				0.004
High School Graduate, GED or below	2478(25.4)	28(6.3)	2450(26.3)	
Other	121(1.2)		121(3.1)	
Education level age 20 yrs and above				0.366
High School Graduate or	2501(25.6)	226(51.1)	2275(24.4)	
College education	3054(31.3)	183(41.4)	2871(30.8)	
Other	4201(43.0)	33(7.5)	4168(44.7)	
Income category				0.982
Up to 24,999	4130(42.3)	184(41.6)	3946(42.4)	
Above 24,999	5130(52.6)	236(53.4)	4894(52.5)	
Missing	496(5.1)	22(5.0	474(5.1)	
Age Category				0.001
Above 26	4848(49.7)	381(86.2)	4467(48)	
Up to 26	4516(46.3)	61(13.8)	4455(47.8)	
Missing	392(4.0)		392(4.2)	

*Chi-Square test at the significant level of 0.05

Table 34: Socio-demographic data on overall (n=9,756), LTBI (n=442), and non-LTBI (n=9,314) from NHANES Data 2011-2012

Variables	Overall (n=9,756)	Latent TB (n=442, 4.5%)	Non-LTBI (n=9,314, 95.5%)	LTBI vs non-LTBI comparison*
			n (%)	p-value
Immigrant Status				
Yes	2083(21.4)	321(72.6)	1762(18.9)	
No	7668(78.6)	121(27.4)	7547(81.0)	<.001
Missing	5(0.1)			
Marital Status				
Married	2683(27.5)	233(52.7)	2450(26.3)	
Widowed	467(4.8)	29(6.6)	438(4.7)	
Divorced	571(5.9)	41(9.3)	530(5.7)	
Separated	204(2.1)	30(6.8)	174(1.9)	
Never Married	1188(12.2)	51(11.5)	1137(12.2)	
Living with Partner	440(4.5)	25(5.7)	415(4.5)	0.017
Other	4203(43.1)	33(7.5)	4170(44.8)	
Time in US				
Less than 5 years	338(3.5)	50(11.3)	288(3.1)	
5 or more years	1663(17.0)	266(60.2)	1397(15.0)	0.247
Missing	7755(79.5)	126(28.5)	7629(81.9)	
Crowded				
More than 4 people	3149(32.3)	141(31.9)	3008(32.3)	0.880
4 or less	6607(67.7)	301(68.1)	6306(67.7)	

*Chi-Square test at the significant level of 0.05

Table 35: Health data on overall (n=9,756), LTBI (n=442), and non-LTBI (n=9,314) from NHANES Data 2011-2012

Variables	Overall(n=9,756)	Latent TB (n=442, 4.5%)	Non-LTBI (n=9,314, 95.5%)	LTBI vs non-LTBI comparison*
Vitamin D3			n (%)	p-value
Deficiency	7287(74.7)	425(96.2)	6862(73.7)	
Sufficient	455(4.7)	12(2.7)	443(4.8)	
Missing	2014(20.6)	5(1.1)	2009(21.6)	0.036
Hypertension				
Yes	107(1.1)	8(1.8)	99(1.1)	
No	161(1.7)	6(1.4)	155(1.7)	0.547
Missing	9474(97.1)	428(96.8)	9046(97.1)	
HIV Results				
Yes	19(0.2)		19(0.2)	
No	3587(36.8)	267(60.4)	3320(35.6)	
Missing	6150(63.0)		6150(66.0)	
Diabetes				
Yes	609(6.2)	67(15.2)	548(5.9)	0.004
No	9147(93.8)	375(84.8)	8772(94.2)	
TB Nil				
Yes	121(1.2)	13(2.9)	108(1.2)	0.237
No	9635(98.8)	429(97.1)	9206(98.8)	

*Chi-Square test at the significant level of 0.05

Prevalence of LTBI

Table 36 summarizes immigration status and Quantiferon test results for the overall population, for LTBI patients, and persons who are non-LTBI (n=9,756) from NHANES Data 2011-2012. A total of 442 (4.5%) individuals were diagnosed with LTBI based on TST measurements greater than or equal to 10 mm, as per CDC guidelines. Among those diagnosed with LTBI, 72.6% were immigrants. Quantiferon test results diagnosed in 49.1 of the LTBI group as positive. The prevalence of LTBI in the years 2011-12 was 4.5% (95% CI: 4.1 – 4.9) in the sample, and the U.S. population in 2012 was 313 million according to the U.S. Census Bureau. Applying the 2012 prevalence rate to the U.S. population gave the estimated number of persons with LTBI as 14,178,900.

Table 36: Immigration status and Quantiferon test of overall, LTBI, and non-LTBI Cases (n=9,756) from NHANES Data 2011-2012

Variables	Overall(n=9,756)	Latent TB (n=442, 4.5%)	Non-LTBI(n=9314, 96.5%)	LTBI vs Non-LTBI p- value*
Immigrant Status				<.001
Yes	2083(21.4)	321(72.6)	1762(18.9)	
No	7668(78.6)	121(27.4)	7547(81.0)	
Missing	5(0.1)		5(0.1)	
Quantiferon_In_Gold				<.001
Positive	543(5.6)	217(49.1)	326(3.5)	
Negative	6537(67.0)	219(49.5)	6318(67.8)	
Indeterminate	27(0.3)	3(0.7)	24(0.3)	
Missing	714(7.3)	3(0.7)	711(7.6)	

*Chi-Square test at the significant level of 0.05

Sample Population Mean Values

Table 37 summarizes mean values for the overall population. The mean age in the overall population was 31.4±24.5 and the median age was 26 among the overall population. Mean systolic blood pressure was 119.0, diastolic was 71.2, waist circumference was 86.2 cm, glycohemoglobin was 5.7, and total cholesterol was 183.2.

Tables 38 and 39 summarize the mean values for LTBI and non-LTBI participants. Laboratory based measurements were taken from a selected small sample from the overall population the NHANES data. Mean age was 48.8±17.7 among LTBI group compared to 39.9±22.2 in non-LTBI group. The median age was 51 in LTBI group compared to 40 in the non-LTBI group. All other mean values were generally similar between the LTBI and non-LTBI groups. Figure 21 shows the distribution of PPD Induration (TST measurements) among overall population for years 2011-2012.

Table 37: Overall mean values of baseline physiologic variables (n=9,756)

Variables	n	Mean	Range	Median
Age (years)	9756	31.4±24.5	0 - 80	26.00
SBP (mmHg)	355	119.0±21.7	79 - 220	116
DBP (mmHg)	355	71.2±14.7	0 --110	72
Waist Circumference(cm)	8204	86.2±22.3	38.7 - 176	86.96
Glycohemoglobin (mmol/mol)	6146	5.7±1.0	3.6 – 17.8	5.5
Total Cholesterol (mmol/L)	6988	183.2±41.4	59 -523	179
HDL Cholesterol(mmol/L)	6989	52.6±13.9	14 - 175	51
LDL Cholesterol(mg/dl)	2942	109.5±35.1	9 -331	106
Triglyceride (mg/dl)	2990	119.5±90.7	18 - 1562	96

Table 38: Mean values of baseline physiologic variables for latent TB cases (n=442)

Variables	n	Mean	Range	Median
Age (years)	441	48.8±17.7	6 - 80	51.00
SBP (mmHg)	355	119.0±21.7	79 - 220	116
DBP (mmHg)	355	71.2±14.7	0 --110	72
Waist Circumference(cm)	431	95.3±15.4	58 - 154	95
Glycohemoglobin (mmol/mol)	436	5.9±1.2	4 – 13.9	5.6
Total Cholesterol (mmol/L)	433	195.1±41.0	93 -338	193
HDL Cholesterol(mmol/L)	433	51.0±13.2	21 - 104	49
LDL Cholesterol(mg/dl)	210	114.7±32.1	36 - 214	112.5
Triglyceride (mg/dl)	211	126.5±71.3	34 - 610	108

Table 39: Mean values of baseline physiologic variables for non-latent TB cases (n=9,314)

Variables	n	Mean	Range	Median
Age (years)	981	39.9±22.2	6 - 80	40.00
SBP (mmHg)	52	125.0±23.7	82 - 193	119.5
DBP (mmHg)	52	69.2±13.1	43 --101	69
Waist Circumference(cm)	953	91.0±18.7	49.2 - 176	91
Glycohemoglobin (mmol/mol)	855	5.8±1.1	4.3 – 15.2	5.5
Total Cholesterol (mmol/L)	964	183.3±40.7	80 -413	179
HDL Cholesterol(mmol/L)	964	51.8±14.3	14 - 148	50
LDL Cholesterol(mg/dl)	409	109.9±34.3	35 - 286	107.0
Triglyceride (mg/dl)	420	120.2±113.9	21 - 1562	93.5

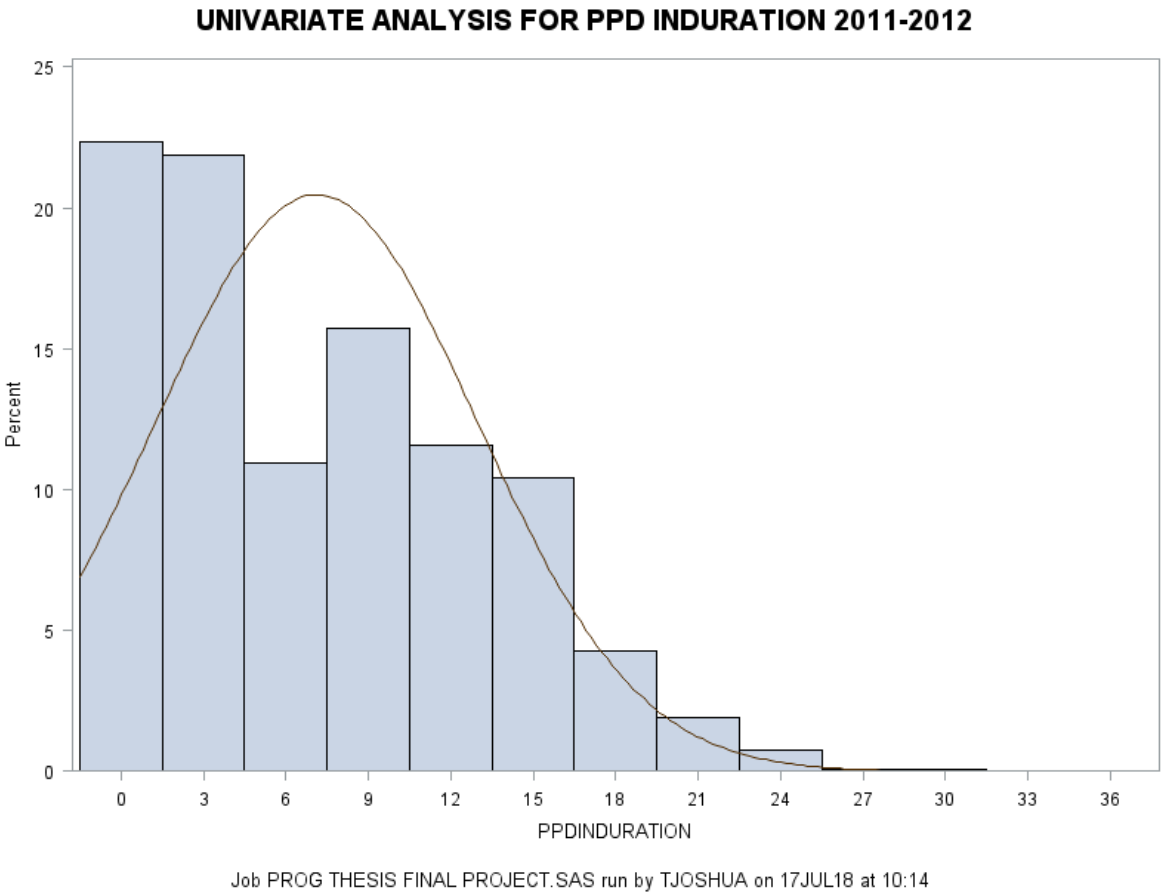

Figure 21: Distribution of PPD Induration among overall population for years 2011-2012

Association between the Variables of Interest

The associations between the variables of interest were analysed with chi-square test and the results, using categorical data analysis, are provided in Table 40. Male gender (p=0.583) and TB NIL(in vitro response of TB infection using negative control from Quantiferon Test results, the baseline interferon gamma level produced by the patient's lymphocytes) (p=0.237) were not significantly associated with LTBI at the 0.05 significant level, but diabetes (p=<.001), immigration status (p=<.001), obesity (p=0.069), cholesterol (p=<.001), age greater than 26 years (p=0.001), vitamin D3 deficiency (p=0.004), high triglyceride (p=0.002) were significantly association with LTBI at the 0.05 significant level.

Relative Risk between Risk Factors and Latent TB Infection Status

Table 40 summarizes the relative risks for the associations between the known risk factors and latent TB. Males were not significantly at higher risk compared to females to be diagnosed with LTBI (RR=0.96, 95%CI: 0.81 – 1.11), while individuals with age greater than 26 years were significantly at higher risk (RR= 2.36, 95%CI: 1.85 - 3.01. Patients with diabetes were significantly at higher risk to be diagnosed with LTBI (RR=1.37, 95%CI: 1.12-1.68), as were persons with high cholesterol (RR=1.36, 95%CI: 1.16- 1.58). The obese were not significantly at higher risk compared to non-obese to be diagnosed with

LTBI (RR=1.17, 95%CI: 0.99 – 1.37). Immigrants were at significantly higher risk for being diagnosed with LTBI compared to non-immigrants (RR=2.88, 95%CI: 2.40-3.45), while individuals with income less than $25,000 were not significantly at higher risk (RR=0.99, 95%CI: 0.85 – 1.17). Living in crowded homes, vitamin D deficiency, TB NIL high, and lived less than five years in the U.S were not shown as significant risk factors for being diagnosed with LTBI in this study, may be due to small sub group sample size.

Table 40: Relative Risk (RR) Ratio for variables and Latent TB status

Variable	Latent TB(%)	No Latent TB(%)	Total	RR (95% CI)	p-value*
Male	240 (30.5)	548(69.5)	788		
Female	202(31.8)	433(68.2)	635		
Total	442	981	1423	0.96 (0.81-1.11)	0.583
Diabetes	67(40.9)	97(59.1)	164		
Non-Diabetes	375(29.8)	884(70.2)	1259		
Total	442	981	1423	1.37 (1.12-1.68)	<.001
Vitamin D deficiency	425(31.5)	923(68.5)	1348		
No deficiency	12(19.0)	51(81.0)	63		
Total	437	974	1411	1.66 (0.99-2.77)	0.036
Immigrant	321(47.1)	360(52.9)	681		
No Immigrant	121(16.4)	619(83.6)	740		
Total	442	979	1421	2.88 (2.40-3.45)	<.001
Cholesterol	186(37.3)	313(62.7)	499		
No Cholesterol	247(27.5)	651(72.5)	898		
Total	433	964	1397	1.36(1.16-1.58)	<.001
Obesity	142(34.8)	266(65.2)	408		
No Obesity	300(29.9)	705(70.1)	1005		
Total	442	971	1413	1.17(0.99 -1.37)	0.069
Less than 5 years in US	50(53.2)	44(46.8)	94		
Equal or more than 5	266(46.7)	303(53.3)	569		
Total	316	347	663	1.14(0.92 -1.40)	0.247
Crowded >4 people	141(31.3)	309(68.7)	450		
=<4 people	301(30.9)	672(69.1)	973		
Total	442	981	1423	1.01(0.85-1.19)	0.880
Low income <25,000	184(30.9)	412(69.1)	596		
>=25,000	236(30.9)	527(69.1)	763		
Total	420	939	1359	0.99 (0.85 -1.17)	0.982
Age >26	381(36.9)	652(63.1)	1033		
Age=<26	61(15.6)	329(84.4)	390		
Total	442	981	1423	2.36 (1.85 -3.01)	0.001
TBNIL High	13(40.6)	19(59.4)	32		
Lower	429(30.8)	962(69.2)	1391		
Total	442	981	1423	1.32 (0.86-2.02)	0.237
Triglyceride high	122(38.6)	194(61.4)	316		
low	89(28.3)	226(71.7)	315		
Total	211	420	631	1.37(1.09-1.71)	0.006

*Chi-Square test at the significant level of 0.05

Association between Risk Factors and Latent TB Infection Status

Table 41 summarizes the association between known risk factors and latent TB status. Crude Odds ratios (OR) and adjusted ORs adjusted by age and immigrant status were calculated for the association between explanatory variables and LTBI status. LTBI cases did not differ significantly by gender compared to non-LTBI cases (OR=0.94; 95% CI=0.75 – 1.18). Adjusted OR was similar to the crude OR for gender (OR=0.95; 95% CI=0.74 – 1.21). Diabetic individuals were significantly more likely to be diagnosed with LTBI compared to non-LTBI individuals (OR=1.63; 95% CI=1.17 – 2.27). Adjusted OR was showing that diabetes status did not differ significantly among LTBI cases compared to non-LTBI individuals (OR=1.18; 95% CI=0.83 – 1.70). The likelihood that a patient with vitamin D deficiency to be diagnosed with LTBI differ significantly between LTBI and non-LTBI individuals (OR= 1.96; 95% CI=1.03 – 3.71). Adjusted OR was similar in with vitamin D deficiency between LTBI and non-LTBI groups (OR= 1.96; 95% CI=1.00 – 3.88). Documented immigrant cases were significantly more likely to be diagnosed with LTBI than non-LTBI individuals (OR=4.56; 95% CI=3.57 – 5.83). Adjusted OR by age was similar (OR=4.14; 95% CI=3.23 – 5.32). Individuals with high cholesterol were significantly more likely to be diagnosed with LTBI than non-LTBI individuals (OR=1.56; 95% CI=1.24 – 1.98). Adjusted OR by age and immigrant status show that cholesterol did not differ significantly between

LTBI and non-LTBI individuals (OR=1.02; 95% CI=0.79 – 1.33). Obesity did not differ between LTBI and non-LTBI individuals in the diagnosis of LTBI (OR=1.26; 95% CI=0.98 – 1.60) but when adjusted for age and immigration status, obese individuals were more likely to be diagnosed with LTBI than non-LTBI individuals (OR=1.31; 95% CI=1.00 – 1.72). Individuals who lived in the U.S for less than five years vs. equal or more than five years did not differ between LTBI and non-LTBI group(OR=1.30; 95% CI=0.84 – 2.01). Adjusted OR showed that individuals who lived in the U.S for less than five years were significantly more likely to be diagnosed with LTBI compared to non-LTBI individuals(OR=1.82; 95% CI=1.12 – 2.94). Individuals who lived in the crowded households were not likely to be diagnosed with LTBI compared to non-LTBI individuals in the same setting (OR=1.01; 95% CI=0.80 – 1.30). Adjusted OR showed the same results (OR=1.14; 95% CI=0.88 – 1.46). Income did not differ between LTBI and non-LTBI individuals in the diagnosis of LTBI (OR=0.99; 95% CI=0.79 – 1.26). Adjusted OR showed the same results (OR=1.14; 95% CI=0.88 – 1.46). Individuals younger than 26 years of age were significantly more likely to be diagnosed with LTBI compared to non-LTBI individuals (OR=3.15; 95% CI=2.33 – 4.26). Adjusted OR showed similar results (OR=2.59; 95% CI=1.89 – 3.55). Individuals with high triglycerides were significantly more likely to be diagnosed with LTBI compared to non-LTBI individuals (OR=1.6; 95% CI=1.14 – 2.23). Adjusted OR showed that triglycerides status did not differ

between LTBI and non-LTBI individuals (OR=1.24; 95% CI=0.88 – 1.80). Adjusted ORs were different for diabetes status, cholesterol, obesity, time in the U.S, and triglycerides. This showed that there was effect modification with immigrant status and age.

Table 41: Comparison of the distribution of known risk factors between LTBI and non-LTBI individuals in the U.S with crude and adjusted odds ratios

Variable	Latent TB	No Latent TB	Total	Crude OR (95% CI)	Adjusted OR by immigrant status and age p-value*
Male	240	548	788		
Female	202	433	635		
Total	442	981	1423	0.94 (0.75-1.18)	0.95 (0.74-1.21)
Diabetes	67	97	164		
Non-Diabetes	375	884	1259		
Total	442	981	1423	1.63 (1.17-2.27)	1.18 (0.83-1.70)
Vitamin D deficiency	425	923	1348		
No deficiency	12	51	63		
Total	437	974	1411	1.96 (1.03-3.71)	1.96 (1.00-3.83)
Immigrant	321	360	681		
No Immigrant	121	619	740		
Total	442	979	1421	4.56 (3.57-5.83)	4.14 (3.23-5.32)
Cholesterol	186	313	499		
No Cholesterol	247	651	898		
Total	433	964	1397	1.56(1.24-1.98)	1.02(0.79-1.33)
Obesity	142	266	408		
No Obesity	300	705	1005		
Total	442	971	1413	1.26(0.98 -1.60)	1.31(1.00 -1.72)
Less than 5 years in US	50	44	94		
Equal or more than 5	266	303	569		
Total	316	347	663	1.30(0.84 -2.01)	1.82(1.12 -2.94)
Crowded >4 people	141	309	450		
=<4 people	301	672	973		
Total	442	981	1423	1.01(0.80-1.30)	1.06(0.81-1.39)
Low income <25,000	184	412	596		
>=25,000	236	527	763		
Total	420	939	1359	0.99 (0.79 -1.26)	1.14 (0.88 -1.46)
Age >26	381	652	1033		
Age=<26	61	329	390		
Total	442	981	1423	3.15 (2.33 -4.26)	2.59 (1.89 -3.55)
Triglyceride high	122	194	316		
low	89	226	315		
Total	211	420	631	1.6(1.14-2.23)	1.24(0.88-1.80)

*Chi-Square test at the significant level of 0.05

Concordance among the TST Test and Quantiferon Test

Table 42 summarizes the kappa statistics analysis conducted to assess the concordance among the TST test and Quantiferon test. Out of 303 individuals who tested positive using the Quantiferon test, only 217 (71.6%) tested positive using the TST test. Out of 1,104 of individuals who tested negative using Quantiferon test, 219(19.8%) tested positive by TST measurement. There were 436 cases that were positive using TST measurement, and 303 that were positive from the Quantiferon test, indicating a difference of 133 cases. The kappa was 0.447 (0.395-0.498) indicating that there was a 44% overall agreement beyond that expected by chance alone between the Quantiferon test and TST, which is moderate. This may be due to many indeterminate results from Quantiferon test. Also, there may be false positive TST results. There is a difference between TST and Quantiferon in assessing the LTBI in the U.S. population.

Table 42: Kappa statistic for Quantiferon Test and TST (latent TB)

Quantiferon	TST ≥ 10	TST <10	Total
Positive	217	86	303
Negative	219	885	1104
Total	436	971	1407
	P=<.0001	Kappa=-0.447 (0.395-0.498)	

Mixture Model Analysis

Additionally, a mixture model analysis was conducted to assess the mean and median of the latent TB measures with TST results for overall population and its significance in the assessment of latent TB diagnosis among overall. A model with two component distributions were fitted since we were looking for the indeterminate cases in between the two curves. A univariate analysis was conducted to assess the distribution of TST results and to determine number of k components. Zero values were removed from the values to get curves from values '1' onwards. Among participants with TST reading greater than 0, the mean and median TST induration were 14.5mm (SD=3.4) and 14mm. The mean for the lower distribution was 1.39mm (SD= 0.66). The mean for the upper distribution was 10.1 (SD=5.07). 95^{th} percentile was 18 mm and 5^{th} percentile was 1 mm. The optimal cutoff value for separating the lower and upper distributions was estimated to be 2.8 mm. TST measurement was grouped in to less than or equal to 2.6 which means no infection, 2.6 to 8.9 means borderline and above 8.9 confirming latent TB. Figure 22 is a univariate analysis of TST induration frequency for overall. Figure 23 was created with 2 factor method and it shows the curve with mean value 11.3±4.96.

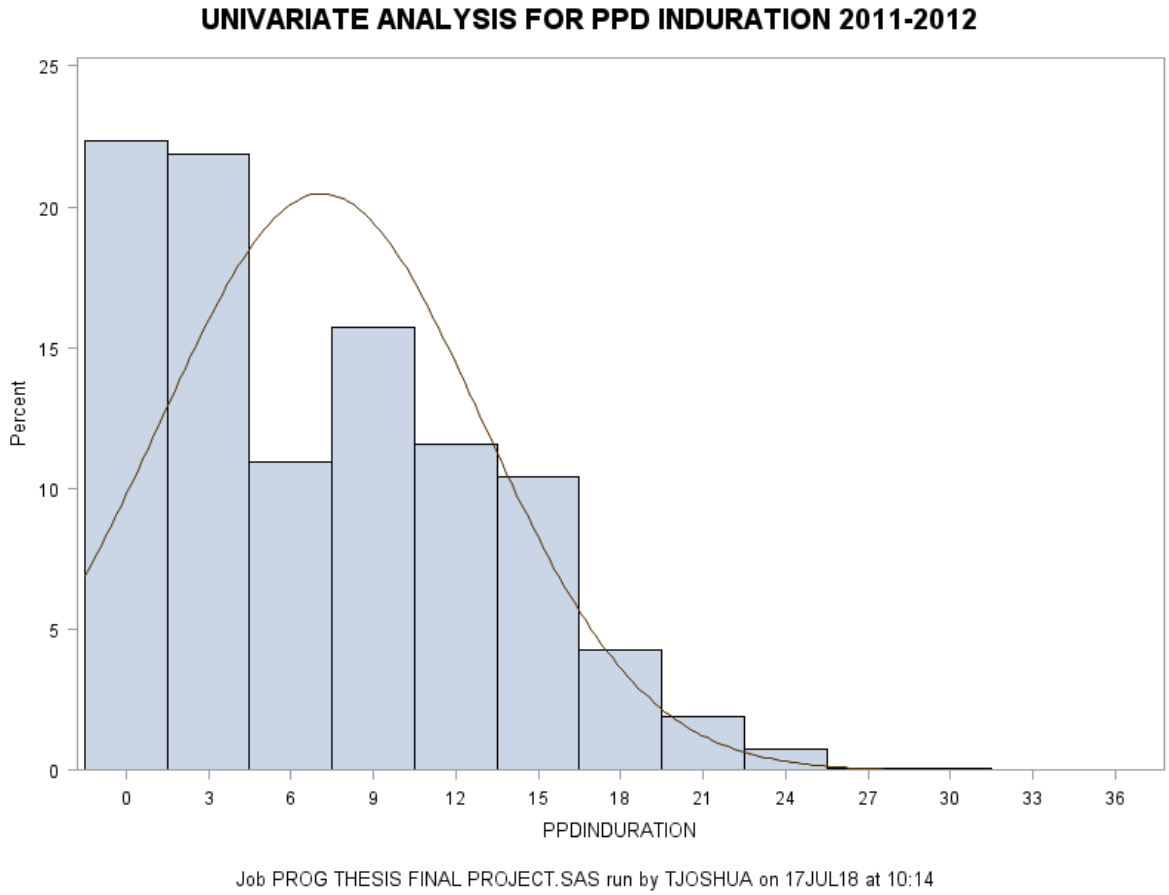

Figure 22: Distribution of TST results among overall population

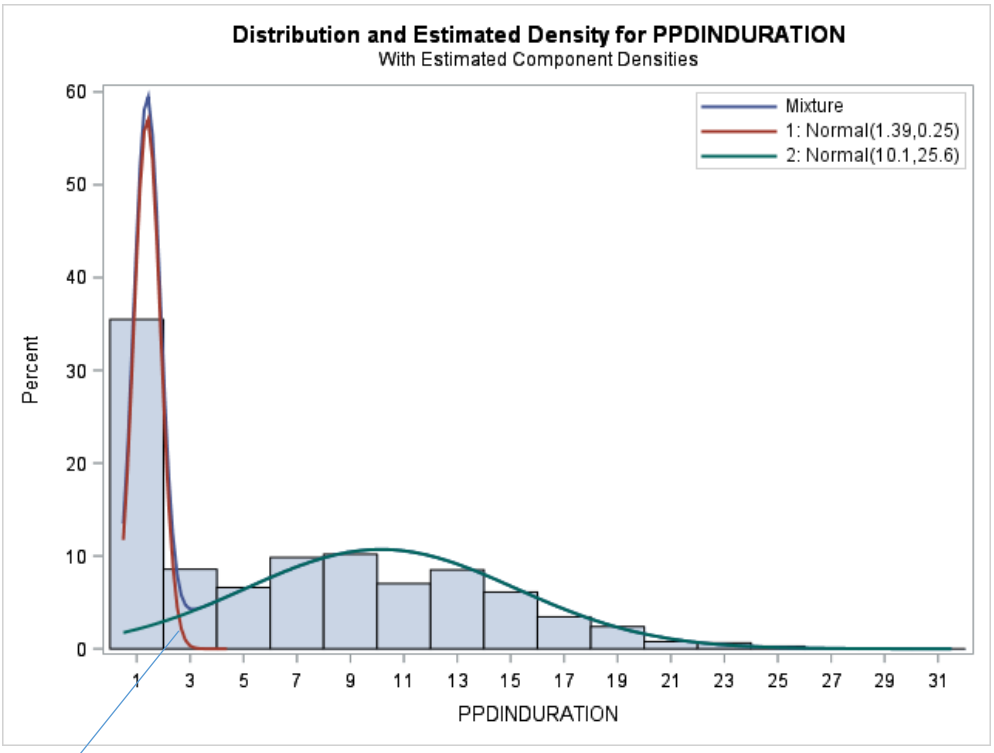

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Figure 23: Mixture model analysis for overall TST measurements with 2 factor

Summary of Results for Aim Three

Aim three part one results showed that persons with LTBI were significantly more likely to be men than those without LTBI, were more likely to be Mexican Americans than those without LTBI, were less likely to be a high school graduate in the age group of below 19 years than those without LTBI, were more likely to be a high school graduate or below in the age group of 20 years or above than those without LTBI, were more likely to be married than those without LTBI, were more likely lived in the U.S for less than five years than those without LTBI, were more likely to be in the income group of less than 24,999 per year than those without LTBI, were more likely to be above the age of 19 years than those without LTBI. Crowding in households (defined as more than four people in the household) was not significantly different between persons with and without LTBI. Immigrants were significantly at higher risk for being diagnosed with LTBI compared to non-immigrants (RR=6.60, 95%CI: 5.38-8.10).

The prevalence of LTBI from 1999-2000 was 4.1% in the sample, and the U.S. population in 2000 was 282.2 million according to the U.S. census bureau. Applying the prevalence rate to the U.S. population gave the estimated number of persons with LTBI infection as 11,598,420 persons for the year 2000. Our study shows that persons with LTBI were significantly more likely to be an immigrant than those without LTBI. Persons with LTBI were significantly more likely to be with a BCG scar

which confirm they received BCG vaccination than those without LTBI.

The relative risk of LTBI in individuals with BCG vaccination was significantly higher compared with those without BCG vaccination (RR=2.78, 95%CI: 2.21 – 3.50). Further with stratified analysis, we found that BCG vaccination was an effect modifier. This result showed that there was no significant or complete risk reduction with BCG vaccination. This may be due to number years passed after BCG vaccination or the quality of the vaccine itself which resulted in fading away the effectiveness of the vaccine. Data were collected in the year 1999 and the participants were older population at the time of diagnosis of LTBI. This shows that BCG vaccination did not provide 100% protection from TB infection for longer period of time.

Reaction to BCG vaccination cannot be ruled out in this interpretation. There was no data provided on TST false positives either. Almost 40% of the LTBI group were immigrants who mostly received BCG vaccination in their home county in their childhood. Still, this result proves that BCG vaccination affects the interpretation of latent TB infection in the U.S. population. We accept the alternative hypothesis that BCG vaccination is associated with the results or interpretation of TST for LTBI in the U.S. population with the limitations in the data.

A stratified analysis conducted to determine whether the association between BCG status and LTBI differs between immigrants

and non-immigrants and between the age groups of above and below or equal to 19 years of age. BCG vaccination status and LTBI status is mixed up with immigration status in this analysis hence immigration status is a confounder variable. Immigration status is associated with BCG status and LTBI and distributed unequally among the immigrant LTBI and non-immigrant LTBI groups when compared. A large difference in relative risk was happened due to this factor. Also, BCG vaccination status and LTBI status is mixed up with age group in this analysis hence age is a confounder variable. Age is associated with BCG status and LTBI and distributed unequally among the immigrant LTBI and non-immigrant LTBI groups when compared.

Aim three part two results show that men were not significantly at higher risk compared to females to be diagnosed with LTBI, individuals with age greater than 26 years were significantly at higher risk. Patients with diabetes were significantly at higher risk to be diagnosed with LTBI, as were persons with high cholesterol. The obese were not significantly at higher risk compared to non-obese to be diagnosed with LTBI. Immigrants were significantly at higher risk for being diagnosed with LTBI compared to non-immigrants, and individuals with income less than $25,000 were not significantly at higher risk. Living in crowded homes, vitamin D deficiency, TB NIL high, and lived less than five years in the U.S were not shown as

significant risk factors for being diagnosed with LTBI in this study, may be due to small sub group sample size.

The prevalence of LTBI in the years 2011-12 was 4.5% in the sample, and the U.S. population in 2012 was 313 million according to the U.S. Census Bureau. Applying the 2012 prevalence rate to the U.S. population gave the estimated number of persons with LTBI as 14,178,900. The prevalence of LTBI in 1999-2000 was 4.1% in the sample, and the U.S. population in 2000 was 282.2 million according to the U.S. Census Bureau. Applying the prevalence rate to the U.S. population gave the estimated number of persons with LTBI infection as 11,598,420 persons.

The difference in LTBI infected persons was 2,580,480 from 2000 to 2012, which is an increase of 22.3%. Even though the percentages of prevalence of LTBI is almost identical at different time points, it may be important to note that the population is increasing at a steady rate, and that increases the number of persons with LTBI in the population. Therefore, there is higher chance of reactivation of disease using the replacement principle of tuberculosis.

A kappa statistics analysis showed the agreement beyond that expected by chance alone between Quantiferon positive test results and LTBI based on TST measurements. Out of 303 positive Quantiferon test cases, only 217 (71.6%) tested positive by the TST. Out of the 1,104

individuals who tested negative by the Quantiferon test, 219(19.8%) tested positive by TST measurement. There were 436 cases who were TST positive and 303 who were Quantiferon positive, showing a difference of 133 cases. There was a 15.4% agreement by both tests in LTBI infection and an 80.2% agreement in no TB infection. The kappa was 0.447 (0.395-0.498) showing that there was a 44% overall agreement beyond that expected by chance alone between the Quantiferon test and the TST, which is moderate Hence, we accept the alternative hypothesis that there is a difference between TST and Quantiferon diagnostic accuracy in assessing the LTBI in the U.S. population.

CHAPTER 5

DISCUSSION

World Health Organization (WHO) data shows that TB is one of the leading ten causes of death worldwide. With the latest data available for 2016, 10.4 million people fell ill with TB and an estimated 10% (1 million) were children [1]. India, Indonesia, China, Philippines, Pakistan, Nigeria, and South Africa are the countries accounted for 64% of the total TB cases worldwide. Also, worldwide 40% of HIV positive patients' deaths were due to TB in 2016. One of the major public health crises worldwide is multidrug resistant TB (MDR-TB). MDR-TB largely resistant to the most effective TB drug rifampicin. WHO data states that an estimated 53 million people survived due to early diagnosis of TB and treatment [1].

There is a 5% to 10% risk for people infected with TB bacteria to become ill with active TB disease in their lifetime. Mild symptoms like cough, fever, night sweats, and weight loss may remain for many months for people who develop TB disease. An active TB disease patient may infect an estimated 10 to 15 people through close contact over a time period of a year [1]. A major concern is that adults in their most productive years may get infected with TB disease and this affects quality of life of such individuals. This may decrease the number of quality

adjusted years in a TB infected person's life. Individuals who are HIV positive are at the highest risk of developing TB disease. It is known that TB is a common cause of morbidity and mortality worldwide [1].

TB affects every part of the world, rich or poor. With the global economy and speed of immigration, TB infection can spread from one part to the other within a short time. All active TB cases are not stopped at the border and early diagnosis may be difficult, too. Another risk factor for TB is tobacco use. TB disease and death increases greatly due to use of tobacco. The percentage of TB cases attributable to tobacco use worldwide is 8%. TB prevention and care requires the cooperation of the community to do early screening and detection of latent TB and TB disease [1].

The TB incidence rate among foreign born persons in the U.S. (15.1 cases per 100,000 per year) has remained approximately 13 times above the incidence rate among U.S. born persons (1.2 cases per 100,000 per year). Our study showed that the mean annual incidence rate for TB disease per 100,000 for the Georgia documented immigrant population was 18.7 (95%CI: 18.6 – 18.8), compared to 2.7 (95%CI: 2.01 – 3.39) for the Georgia non-immigrant population for the years 2004 to 2016, using the 2010 population as the denominator. The incidence rate ratio for the TB incidence in immigrants versus non-immigrants was 6.9 (95%CI: 6.8 - 6.9) in Georgia for the years 2004 to 2016. It shows that immigrants had 6.9 times the rate of TB disease compared to non-immigrants in Georgia for the years 2004 to

2016. The data for the overall population of active TB patients, for documented immigrants, and for non-immigrants all showed a statistically significant downward trend from year 2004 to 2016. Since there were variations in incidence over the time period per year, this may be a better method to assess the burden of disease in the population. This shows the need of urgent attention to screening of immigrants for LTBI and active TB disease using better screening methods. BCG vaccination in immigrants need to be considered when the screening methods are selected for immigrants.

CDC report for the year 2017 [2] says that the overall incident rate of TB disease which include the U.S. born and non-U.S born in the U.S. was 2.8/100,000 per year, slightly lower than 2016. Incident rate of TB disease for the U.S-born was 1/100,000 per year and for the non-U.S born was 14.4/100,000 per year for the year 2017. The IRR was 14.4 for immigrants vs. non-immigrants in the U.S. for year 2017 There were six states in the U.S with higher than the overall incidence rate of 2.8/100,000 per year in Georgia for year 2017. They were Texas (IRR=7.9), California (14.3), New Jersey (IRR=16.1), Maryland (IRR=24.6), Massachusetts (IRR=31.6), and Minnesota (IRR=50.8). The IRR for Georgia for the year 2016 was 7.9. Georgia was at the 44th place considering the severity of the TB incidence rate ratios between immigrants and non-immigrants among the 50 U.S. states [2,3].

The known risk factors for immigrants were male gender, diabetes, HIV positive, prior contact of TB disease, LTBI incomplete treatment, and

excess alcohol use. Those are modifiable risk factors and immigrants need to be educated on those factors. This study shows that the median time in years for immigrants from date of entry in to the U.S. to TB disease diagnosis was 8.39 years. It may be better if immigrants get TB screening within two years of their entry in to the U.S. This will help early diagnosis and treatment, if necessary. Also, this will help to reduce the spread of infection and the intensity of disease.

High risk factors for TB infections are HIV/AIDS, close contacts with TB, organ transplant recipients, chronic renal failure patients who require dialysis, TNF-alpha blockers users, and Silicosis. Moderate risk factors are fibro nodular disease on chest x-ray, immigrants from high TB prevalence countries, health care workers, prisoners, homeless persons, and illicit drug users. Low risk factors are diabetes mellitus, smoking, use of corticosteroids, and underweight. High risk factors contribute to TB reactivation rate significantly. Patients with high risk factors should undergo screening and treatment for LTBI even if they live in countries with a low TB disease prevalence. In our study, data was collected through self-reporting. There were not many cases of HIV positive among immigrant TB cases may be due to low prevalence of HIV disease among the immigrant TB cases. Contact with active TB disease cases was expected large in the immigrant TB cases but it was reported too low may be due to recollection issues or did not like to report due to current laws. Also, excess alcohol use was reported too low with

unknown reasons. There were not many immigrant TB cases from long term facilities or prisons. Immigrant TB cases were mostly young, somewhat educated came to the U.S. looking for job. This might have a reason for the risk factors were not showing up as expected with other studies. Mostly employed immigrants were having better access to food and living standards. Also, they got better income compared to non-immigrant population [4,5].

Our study showed that persons with LTBI were significantly more likely to be an immigrant than those without LTBI. Immigrants were significantly at higher risk for being diagnosed with LTBI compared to non-immigrants. Also, the relative risk of LTBI in individuals with BCG vaccination was significantly higher compared with those without BCG vaccination. This result showed that there was no significant or complete risk reduction with BCG vaccination. This may be due to number years passed after BCG vaccination or the quality of the vaccine itself which resulted in fading away the effectiveness of the vaccine. Data were collected in the year 1999 and the participants were older population at the time of diagnosis of LTBI. This shows that BCG vaccination did not provide 100% protection from TB infection for longer period of time. Reaction to BCG vaccination cannot be ruled out in this interpretation. There was no data provided on false positives either. Almost 40% of the LTBI group were immigrants who mostly received BCG vaccination in their home county in their childhood. Still, this result proves that BCG

vaccination affects the interpretation of latent TB infection in the U.S. population.

Also, our analysis on concordance among the TST test and Quantiferon test shows that there was a 44% overall agreement beyond that expected by chance alone between the Quantiferon test and TST, which is moderate. Many studies were conducted comparing the agreement between TST and IGRAs in diagnosing TB infection. A study conducted in Iran comparing the TST and Quantiferon test found an agreement with a kappa of 0.19 (95%CI: 0.04 to 0.34). Study stated that high risk population may have a higher k statistic [6]. BCG vaccination may affect the results of TST and it can influence the k statistic. A meta-analysis to estimate the agreement between TST and QFT among healthcare workers in the U.S. with 30 studies found an overall k-statistic of 0.27 (95% CI: 0.22-0.32) and an adjusted kappa statistic for prevalence and bias was 0.41 (95%CI: 0.32-0.50)[7]. A prospective cohort study conducted from 2014 to 2016 in Uganda to investigate diagnostic agreement of the Quantiferon and TST tests found an overall concordance with a k statistic of 0.48 (95% CI: 0.30-0.66) which was similar to our study [8]. Most of the studies found similar kappa statistic like our study and there may be many factors causing this poor agreement between two tests. Individuals who received BCG should be given TB blood tests for screening, preferably.

Another important factor we noticed on the active TB disease reported from the rural counties in Georgia. All the active Tb cases were reported from non-immigrant population. Rural counties in Georgia have very small immigrant population and to understand the chances of TB disease spreading may need further studies. Those non-immigrant TB cases might have happened from reactivation of disease from LTBI cases. Other chances for TB infection was that those cases might have travelled to other countries were high prevalence of TB exists. Military service outside the country was another chance or they travelled to the counties in Georgia where higher prevalence of TB disease exists.

Educating the public about early detection and treatment is important in prevention methods. TB is treatable and curable. Drug susceptible TB disease is a challenge to the medical community. Co-operation between patients and healthcare workers is very important in prevention methods. TB and HIV speed each other's progress and it can be deadly when an individual has both diseases. Most cases of both HIV and TB are in Africa and it is very urgent to treat these individuals with effective medications. WHO added two medications called bedquiline and delamanid to treat MDR-TB cases in 2016 [1].

People need to understand that TB infection and TB disease are different. A person exposed to someone with active TB disease may breathed in the TB bacteria. That person can become infected with TB,

which is called latent TB or LTBI. People with healthy immune systems can fight the infection at the early stages and not become ill with TB disease immediately. A person with a positive TB skin test and a normal X-ray is not sick with contagious TB disease and they do not spread the TB disease to others. TB medications can kill the bacteria at that stage and prevent the development of disease in those people in the future [9].

Individuals with recent close contact with persons known to have TB disease are at a higher risk for TB infection. Children under 4 years old, and a tuberculin induration increase of at least 10 mm on TST within a 2 year period are other risk factors. Foreign born persons from Asia, Africa and Latin America where the prevalence of TB is high, homeless persons, persons living or working at nursing home, prison, or healthcare facility are also at higher risk for TB infection. Other risk factors include persons with HIV, intravenous drug users, end stage renal disease, silicosis, diabetes mellitus, immunosuppressive therapy, haematological malignancy, impoverished living conditions or malnourished, and a gastrectomy or jejunoileal bypass [10].

The goal of testing for any disease is to identify high risk individuals with a particular disease and treat them for the disease in early stages. Targeted diagnosis and treatment of persons with TB disease will help in the disease prevention. The majority of new active TB cases are diagnosed from individuals with LTBI. Identifying and

threating latent TB cases are very important. This will prevent the spread of TB infection and reduce the incidence of TB disease [11].

There are many screening methods available now to identify LTBI and active TB cases. Interferon gamma release assays (IGRAs) are in-vitro diagnostic alternatives to the TST and C-TB. These tests are based on the highly immunogenic antigens ESAT-6 and CFP10, which are specific to *Mtb*, and overcome the issues of the interaction with BCG vaccine and infection by non-tuberculous mycobacteria seen with the TST. The interpretation of the results of IGRAs are more objective and simple compared to the TST and C-TB. IGRAs, TSTs or C-TBs have low positive predictive values for the development of active TB. IGRAs are used in adults, but assessment in young children is unclear [12].

For IGRAs, a single visit is required. There is no need of return visit for reading results in this method. IGRAs have high sensitivity and specificity and do not cross react with most non-tuberculosis mycobacteria. Most importantly, they provide objective test results [13, 14]. Degree of induration on skin testing is assessed differently in high-risk populations. People living with HIV, recent contacts of persons with infectious TB, people who have previously had TB disease, and individuals who use immunosuppressant are advised for latent TB treatment if the induration is 5mm or above. Foreign born immigrants, intravenous drug users, excess alcohol users, individuals residing or working in high risk areas, those

employed in a mycobacteriology laboratory, people with certain medical conditions, and children less than 4 years of age should get treatment for latent TB if the induration is 10mm or above. If an individual has unknown risk factors, treatment should be provided for an induration measurement of 15mm or above [12].

The CDC guidelines recommend the use of IGRAs in all situations in which the TST was historically used, with IGRAs being the preferred test for persons who have been BCG vaccinated or are unlikely to return for TST reading [15]. IGRA interpretations are based on the amount of IFN-g that is released or on the number of cells that release IFN-g. Both the standard qualitative test interpretation (positive, negative, or indeterminate) and the quantitative assay measurements (Nil, TB, and Mitogen concentrations or spot counts) should be reported as per CDC guidelines.

A diagnosis of LTBI requires that TB disease be excluded by medical evaluation. This should include checking for signs and symptoms suggestive of TB disease, a chest radiograph, and, when indicated, examination of sputum or other clinical samples for the presence of M. tuberculosis. Decisions about a diagnosis of *M. tuberculosis* infection should also include epidemiological and historical information [14].

Results of our study agreed with the findings of other studies completed with NHANES data. Even though the percentages of LTBI are almost the same at different time points, it may be important to note that the

population is increasing at a steady rate, which increases the number of persons with LTBI in the population. Additionally, there is higher chance of reactivation of disease using the replacement principle of tuberculosis [16].

The prevalence of LTBI in 1999-2000 was 4.1% (95% CI: 3.7 – 4.5) in the sample, and the U.S. population in 2000 was 282.2 million according to U.S. Census Bureau. Applying the prevalence rate to the U.S. population gives the estimated number of persons with LTBI infection as 11,598,420 (more than 11 million) persons. The prevalence of LTBI in 2011-12 was 4.5% (95% CI: 4.1 – 4.9) in the sample and the U.S. population in 2012 was 313 million according to U.S. Census Bureau. Applying the 2012 prevalence rate to the U.S. population gives the estimated number of persons with LTBI infection as 14,178,900 (more than 14 million) persons. Difference in LTBI infected persons was 2,580,480 (more than 2 million) from 2000 to 2012, which is an increase of 22.3% over the 12 year period. Other studies using NHANES data agree with our findings [17 – 19].

Another area of concern is the high risk population among those infected with HIV. HIV is the strongest risk factor for TB and TB is the leading cause of death among people living with HIV. The majority of those deaths happen in the African continent, where the HIV burden is very high. Diabetes mellitus, smoking, and alcohol abuse are other major risk factors contributing to the development of TB disease from latent TB.

The Millennium Declaration by the United Nations General Assembly in September 2000 was a historical resolution [20].Eight goals were identified in that resolution and three of them were dedicated to health issues. TB, HIV/AIDS, and malaria were the three world epidemics that were given priority. One area of concern is the missing cases in the data. There may be millions of cases missing in the international data due to care and transmission problems. Technical support may be missing in rural areas and remote places where TB incidence may be high. There must be better methods to capture all TB cases and their outcomes with treatment.

Documented immigrants are screened for TB infection at their home country before traveling to the U.S. and if they are found with TB infection they have to get the treatment. Our study found that majority of the immigrant TB cases were diagnosed with TB disease within an estimated 9 years of their arrival to the U.S. This may be due to false negative TB screening at their home country before travelling to the U.S. Also, since those immigrants travel back to their home country on vacations may contribute to get infected with TB bacteria within this time period. They may receive relatives and friends coming from those countries with high prevalence of TB disease and infected with TB disease, too.

Health care cost in the U.S. is not affordable for unemployed, homeless, uninsured, and low income Americans. Currently, high risk population for TB is not getting screening for TB free of cost. LTBI people in

the U.S. are not receiving free treatment like active TB cases. It is well known that majority of the TB cases are developed from LTBI cases. It is high time to provide free screening and treatment for high risk populations and provide preventive services without cost to the LTBI patient too. It is essential to provide appropriate training to health care providers in the U.S. since most of them did not treat TB cases due to low prevalence of LTBI and TB disease [21].

Limitations

There were many limitations to this study. Three secondary data bases were used in this study. GDPH data was collected using CDC guidelines from many GDPH health departments in Georgia. There could be reporting error with data and it might have caused information bias. TB disease diagnosis methods may not be similar in every place and error percentage in that area was not assessable. NHANES data sets for years 1999-2000 and 2011-2012 were collected by NHANES. 1999-2000 dataset contained BCG information and 2011-2012 data did not contain that information and an oversampling happened with Asians in the race category. Data was collected through survey and laboratory data on selected few was collected by NHANES personnel. There were a lot of missing values in the dataset. NHANES used a complex method to make the data representing the national population. Selection bias and information bias was not assessable in the data.

Conclusion

The social determinants of health in the TB infectious disease area are poverty and high-risk populations. Addressing those two areas through meaningful interventions can reduce and eliminate the worldwide TB epidemic. The largest burden of disease are among the poorest and socially excluded groups of people. It does not mean that those with high socioeconomic status are excluded from this epidemic. In developing countries, servants work inside and outside of the homes of affluent people. These servants are mostly coming from the slums and other poor living conditions. They may be cases of active TB disease and can spread the disease within the homes of high socioeconomic status individuals, unknowingly. Essentially, TB is not a disease of the poor anymore. When people become richer, they may recruit more people to work in their homes. In India, most middle-income families have servants or maids as part of their family. In India, the middle class means “not poor”. Most of the time, the servants are unemployed individuals who are illiterate. These conditions may be true for other developing countries. This setting contributes to the spread of infectious diseases like TB at rapid speeds.

The spread of multidrug-resistance TB is another challenging area in TB control methods. This area needs special attention and further research in finding newer methods in diagnostics, drugs, and vaccines. End TB strategy was started by WHO with seventeen sustainable development goals in the

year 2014. The goal is to achieve a 90% reduction in TB-related mortality and TB-incidence by 2030. Since it is a worldwide goal, many government agencies and non-government agencies should work together; however, there may be challenges in bringing all these agencies together.

Monitoring and evaluation is an important area in TB infectious disease control and elimination programs. A robust initiative from the government is essential in achieving this goal. A strong coalition must be formed within communities and civil societies. Ethics, specifically in protecting and promoting human rights, holds an important role in this process. County, state, country, and world collaboration is necessary in creating strategy and developing targets. Further research is crucial to finding effective and rapid diagnostic tools. Latent TB cases must be treated since most of the active cases are developed from that population. Research needs to be conducted in whole-genome sequencing to identify if there are any mutations happening, to identify drug-resistance. Precision therapeutic schemes need to be identified in each patient's case to address drug-resistance TB cases. Research to find a better vaccine must be continued. Current vaccine is ineffective in preventing infection and TB disease on a wider perspective. A larger collaboration between numerous government and non-government agencies can aid in controlling and eliminating TB in the next few decades. Collaboration is key in modifying the risk factors and addressing the challenges in diagnosing and treating TB.

MOTIVATION

The motivation for this study included a local news event in Augusta, Georgia regarding the TB infection in area schools, which led to school closings for one week. There may be many reasons for this occurrence since the school district has been providing free lunch to all schools in the district from 2012. There are a criteria for free lunches in the schools related to the poverty and low income of parents. I considered about doing research in this area to find the root cause, so that remedial measures can be suggested.

There are many known risk factors for TB infection. One case of active TB can create chaos and school closings for a longer period of time. Days of school are lost with added mental stress to students, teachers, and parents. These outcomes can lead to serious long term consequences. Control and eradication methods must be in place in the community so that such events do not occur or repeated. One area of interest may be addressing the people coming back in to the community after living in or visiting high-risk areas. Regular re-screening of such individuals should be considered to control such disease occurrence. This study lends some insight to achieve such goals.

PUBLIC HEALTH IMPLICATIONS

There are numerous implications of this study. This study will increase awareness about the high incidence of TB in the immigrant population. Incidence may be higher in places were immigrants are more highly concentrated. There is a tendency for immigrants to live in close proximity to one another, hence increasing the incidence of disease in small areas. This scenario will increase the chance of close contact with community members and lead to rapid spread of disease.

It is necessary to have a health policy to screen the high-risk immigrant population within 6 months of their entry in to the U.S. and annually thereafter for at least 5 years. This method may help to identify and treat latent TB and TB cases early on. Cases among immigrants are primarily clustered in a few mostly urban high population counties.

Our results describe the distribution of modifiable risk factors such as close-contact with active TB disease, excess alcohol use, low socioeconomic status, overcrowded living conditions, substance abuse, HIV infection, diabetes, renal disease, and homelessness in immigrants. There should be a comprehensive health-care plan to address those risk factors to improve the lifestyles of individuals in this high-risk group and reduce the disease burden. At present, the state does not treat individuals with latent TB even though most of the TB disease cases come from latent

TB cases. It is necessary to create and enforce a policy to treat LTBI cases and eradicate TB disease early on.

FUTURE DIRECTIONS

For screening purposes, it is necessary to identify high-risk groups and provide suitable diagnostic methods. It is necessary to treat people with LTBI and TB disease with same urgency. Further, it is necessary to educate people about modifiable risk factors and the importance of annual screening for TB. It would be useful to work with law makers to create a policy to screen immigrants for TB disease, in practical manner.

For research purposes, we need to understand the modifiable risk factors in different regions since cultures and living habits are different. Moving patterns of immigrants and their intervals may be another interesting area of research. Another potential area of focus that may help to eradicate TB is in understanding the methods of TB disease spread in different countries with high prevalence of TB.

ORIGINALITY AND PUBLIC HEALTH RELEVENCE OF STUDY

The scope of this study covers immigration status and diagnosis of TB disease or latent TB with other modifiable risk factors. This may be the first study using the Georgia Department of Health TB data to assess the hypothesis regarding immigrants with diagnoses of TB disease within a 5 year time period. The Median age of the immigrants at the time of diagnosis, and other risk factors, are important in reducing the burden of TB in the state of Georgia.

STATEMENT OF CONTRIBUTION

Thomas V. Joshua conceptualized this study in all its parts, as well as, acquired, analyzed, and interpreted the data, and wrote this dissertation. This report is original in its entirety, and no part of it is has been previously published elsewhere. The findings and conclusions in this report are those of Thomas V. Joshua and do not necessarily represent the official position of the University of Georgia, the Georgia Department of Health, or Augusta University.

REFERENCES

1. World Health Organization. Available at http://www.who.int/tb/en/. Accessed on April 4, 2018.
2. CDC Report; 2017 STATE AND CITY TUBERCULOSIS REPORT. https://www.cdc.gov/tb/statistics/StateCity-TBReport.htm. Accessed on November 9,2019
3. Stewart, R. J., Tsang, C. A., Pratt, R. H., Price, S. F., & Langer, A. J. (2018). Tuberculosis - United States, 2017. *MMWR. Morbidity and mortality weekly report*, *67*(11), 317–323. doi:10.15585/mmwr.mm6711a2
4. Narasimhan, P., Wood, J., Macintyre, C. R., & Mathai, D. (2013). Risk factors for tuberculosis. *Pulmonary medicine*, *2013*, 828939. doi:10.1155/2013/828939
5. Baussano I, Williams BG, Nunn P, Beggiato M, Fedeli U, et al. (2010) Tuberculosis Incidence in Prisons: A Systematic Review. PLOS Medicine 7(12): e1000381. https://doi.org/10.1371/journal.pmed.1000381
6. Mostafavi, E., Nasehi, M., Hashemi Shahraki, A., Esmaeili, S., Ghaderi, E., Sharafi, S., & Doosti-Irani, A. (2016). Comparison of the tuberculin skin test and the QuantiFERON-TB Gold test in detecting latent tuberculosis in health care workers in Iran. *Epidemiology and health*, *38*, e2016032. doi:10.4178/epih.e2016032

7. Doosti-Irani, E. Ayubi, E. Mostafavi, Tuberculin and QuantiFERON-TB-Gold tests for latent tuberculosis: a meta-analysis, *Occupational Medicine*, Volume 66, Issue 6, August 2016, Pages 437-445, https://doi.org/10.1093/occmed/kqw035
8. Castellanos, M. E., Kirimunda, S., Martinez, L., Quach, T., Woldu, H., Kakaire, R., … Whalen, C. C. (2018). Performance of the QuantiFERON®-TB Gold In-Tube assay in tuberculin skin test converters: a prospective cohort study. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*, *22*(9), 1000–1006. doi:10.5588/ijtld.18.0073
9. Burke D. Of postulates and peccadilloes: Robert Koch and vaccine (tuberculin) therapy for tuberculosis. Vaccine 1993; 11:795–804. 2.
10. Parish HJ. Koch and immunization against tuberculosis. In: A history of immunization. 1st ed. Edinburgh: E&S Livingstone, 1965:92–107.
11. Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. N Engl J Med. 2002; 347:1860–1866.
12. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America.

(IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med. 2000;161((4 Pt 2)):S221–S247.

13. T-SPOT.TB TEST. http://www.tspot.com. Accessed on April 4, 2018.
14. QuantiFERON-TB Gold (QFT). http://www.quantiferon.com/us/products/quantiferon-tb-gold. Accessed on April 4, 2018.
15. CDC.GOV. https://www.cdc.gov/tb/publications/factsheets/testing/igra.htm. Accessed on April 4, 2018.
16. Whalen CC. The Replacement Principle of Tuberculosis. Why Prevention Matters. Editorial in American Journal of Respiratory and Critical Care Medicine Volume 194 Number 4 | August 15 2016. Accessed on April 5. www.atsjournals.org.
17. Miramontes R, Hill AN, Yelk Woodruff RS, Lambert LA, Navin TR, Castro KG, LoBue PA. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011-2012. PLoS One 2015; 10:e0140881.
18. Mancuso JD, Diffenderfer JM, Ghassemieh BJ, Horne DJ, Kao T-C. The prevalence of latent tuberculosis infection in the United States. Am J Respir Crit Care Med 2016; 194: 501– 509.
19. Ghassemieh BJ, Attia EF, Koelle DM, Mancuso JD, Narita M, Horne DJ. Latent tuberculosis infection test agreement in the National Health and

Nutrition Examination Survey. Am J Respir Crit Care Med 2016; 194: 493–500.

20. United Nations General Assembly. United Nations Millennium Declaration, Resolution Adopted by the General Assembly, 2000, A/RES/55/2. Available from: http://www.refworld.org/docid/3b00f4ea3.html.
21. Balaban, V., Marks, S. M., Etkind, S. C., Katz, D. J., Higashi, J., Flood, J., … Chorba, T. (2015). Tuberculosis Elimination Efforts in the United States in the Era of Insurance Expansion and the Affordable Care Act. *Public health reports (Washington, D.C. : 1974)*, *130*(4), 349–354. doi:10.1177/003335491513000413

ABBREVIATIONS

ACS - American Community Survey

ADH - antidiuretic hormone

ART - antiretroviral therapy

BCG – Bacille Calmette Guerin

CFP-10 – culture filtrate protein-10

EM – expectation- maximization

ESAT-6 – early secretory antigen of *Mycobacterium tuberculosis*-6

FDA - Food and Drug Administration

GDPH - Georgia Department of Public Health

HIV – human immunodeficiency virus, type-1

IGRA – interferon-gamma release assay

IGRAs - interferon-gamma release assays

KM - Kaplan-Meier

LTBI - latent TB infection

MDR TB - Multidrug-Resistant Tuberculosis

Mtb - Mycobacterium tuberculosis

NHANES - National Health and Nutrition Examination Survey

PPD - Purified Protein Derivative

SD – standard deviation

TB – tuberculosis

TST – tuberculin skin test

U.S. - United States

WHO – World Health Organization

XDR TB - Extensively Drug-Resistant Tuberculosis