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Characteristics and Odds of Having LTBI among Risk Groups (NHANES, 2011-2012)

Mirwais Zhuben

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Mirwais Zhuben

Master of Public Health

Georgia State University
School of Public Health

Abstract

Tuberculosis (TB) is a public health challenge globally. In the US, TB is unevenly distributed based on country of birth. Since 1993, TB disproportionately has been decreasing among US and foreign born persons. In 1993, the proportion of TB among foreign born persons was 30% while in 2012, 65% of TB cases were foreign born persons. US is a country with an open immigration policy which can challenge TB control by entering more immigrants with latent TB infection (LTBI). Therefore, this study is aimed to indentify the characteristics of LTBI persons, estimate the odds having LTBI among risk groups, and compare risk factors of LTBI between foreign and US born persons. In this study, a two year sample (NHANES, 2011-2012) is considered and 6,185 observations are included in the analysis. Among all LTBI (526), 21%, 46%, 31%, 7%, and 65% were diabetic, smoker, age group≥65, TB contact, and foreign born respectively. Among all risk factors, diabetes (OR=1.45, 95% CI: 1.14-1.86), smoking (OR=1.63, 95% CI: 1.33-1.86), age group ≥65 (OR=1.97, 95% CI: 1.58-2.45), TB contacts (OR=2.54, 95% CI: 1.69-3.82), and foreign born (OR=5.70, 95% CI: 4.65-7.00) were significantly associated with LTBI. The association between LTBI and foreign born is approximately six times higher than the association between US born and LTBI, indicating that TB infection exposure is very high among foreign born persons. This fact is an obstacle toward achieving TB eradication goal in the US. Thus, proper interventions such as screening and treatment of foreign born persons coming from TB endemic countries, particularly those who are in high risk groups will take TB control program one step closer to the eradication of the disease in the US.

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1.0.0. Rational and Objectives

Health disparities based on race/ethnicity, socio-economical status, and gender are very prominent in the United States (CDC, 2013). Tuberculosis (TB) is one of the diseases that disproportionately distributed among foreign born in the US. Since 1993, TB rate is disproportionately decreasing among US born individuals; however, for foreign born persons this trend has not been significant and the change is miniscule. TB elimination in the US is an important public health objective but little is done for TB among foreign born persons. The US is a country with an open immigration policy which can challenge TB control by entering more individuals with latent TB infection. Therefore, it is decided to conduct a study to estimate the burden of LTBI among foreign born persons. For this purpose, it is important to determine the risk groups facilitating TB disease and TB infection. Furthermore, the odds of having LTBI among risk groups in general population as well as subpopulations of foreign and US born are estimated which is clarified in below questions.

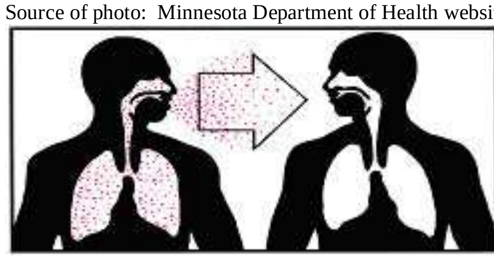
1. What are the characteristics of individuals with LTBI in the US, NHANES, 2011-2012?
2. What are the odds of having LTBI among risk groups in general population, NHANES, 2011-2012?
3. How the odds of having LTBI differ between foreign and US born subpopulations, NHANES, 2011-2012?

2.0.0. Literature Review

2.1.0. Introduction

One third of the world’s population is infected with TB infection. According to the Center for Disease Control and Prevention (CDC), in 2012, nearly nine million people developed an active form of TB disease, and also 1.4 million deaths due to TB occurred throughout the world (CDC, 2013; WHO, 2013). These statistics reveal the fatality rate and significance of the disease worldwide. TB, a chronic infectious disease, remains a serious public health challenge, particularly in developing countries. In mid 20th century, TB was controlled to some extent; however, after HIV emergence, particularly in Africa and increase in diabetes prevalence particularly in India and China, TB become a global concern (Wang et al., 2014). The primary cause of TB is Mycobacterium tuberculosis, a bacterial infection which commonly infects the lungs. It can, however, infect any organ, such as kidneys, brain, spine, bones, and skin. Since TB is an airborne disease, lungs are widely exposed to TB infection when a person gets close to a TB patient. When a TB patient coughs, sneezes, sings, or talks, TB infection spreads from the patient's lungs to the surrounding area. Droplets around five microns remain suspended in the air depending on penetration of sun light and ventilation of the space. Meanwhile, if another person breathes in the contaminated air or droplets, s/he might get infected, but development of active TB disease depends on the exposed individual's immunity status (American Lung Association, 2013).

Source of photo: Minnesota Department of Health website



When TB infection gets inside lungs or any other organ and does not develop active TB disease, this form of infection is called latent TB infection (LTBI). People with LTBI have a lifetime risk of developing active TB disease of 10%. Immunity is the main factor preventing the infection from activation, multiplication and keeps it in latent form. Thus, any condition that impairs or weakens the immunity in the body increases the risk of developing active TB disease above 10%. There are a multitude of different conditions that affect immunity and facilitate the activation and multiplication of the TB infection within the body, resulting in active TB disease. After activation, if the patient does not receive proper treatment, the consequences can be debilitating and could lead to death (Bates et al., 2004). Treatment is one of the most efficient and effective means of prevention among other TB control measures. After starting treatment, within two weeks TB patient stops spreading mycobacterium TB. Therefore, case finding in elimination of TB plays a paramount role. Besides its vital role, TB treatment has a dark side if it is not administered properly. Consequences of improper management of TB treatment can be disastrous and may result in drug resistant form of TB disease. Drug resistant TB is a manmade TB that does not respond against first line anti TB treatment. Drug resistant TB can be primary or secondary. When a person contracts drug resistant TB from another person, it is called primary drug resistant TB infection, whereas if a susceptible form of TB infection transforms to a drug resistant type owing to improper treatment management, it is known as secondary drug resistant TB infection (CDC, 2012; WHO, 2014).

2.2.0. HISTORY OF TB

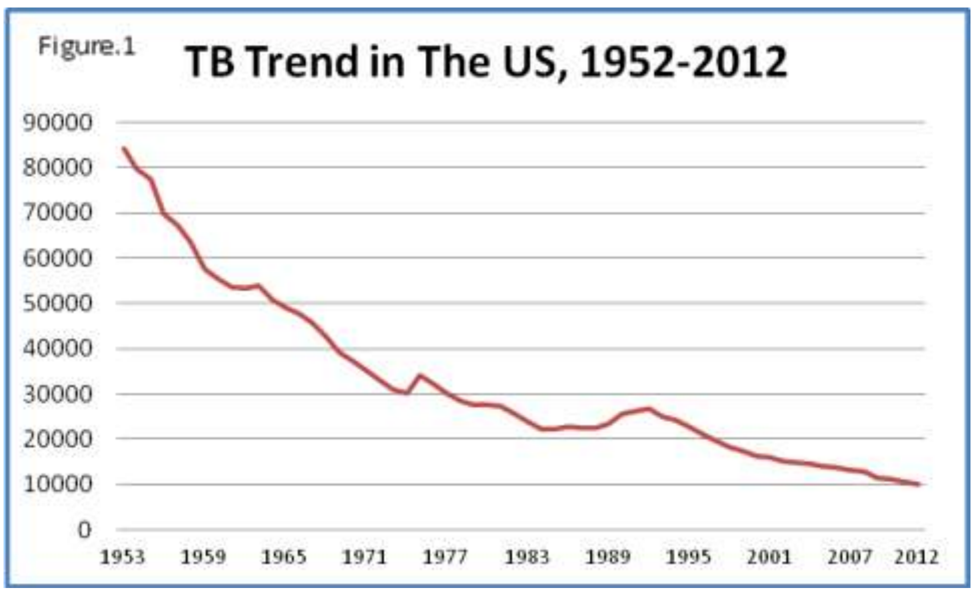
TB is an ancient disease; it has accompanied humans for very long time. Basing their views on genetic studies, some researchers, , believe that a progenitor of M. tuberculosis existed as early as three million years ago in East Africa and it is suggested that such progenitor might have infected primordial hominids (Gutierrez et al., 2005). Modern mycobacteria are believed to have emerged 20,000 years ago from a common ancestor (Sreevatsan et al., 1997). It is believed that M. tuberculosis evolved from M. bovis which is pathogenic for wide range of animals. However, the primary host is known to be cattle and after domestication of cattle Mycobacteria evolved and started to infect humans. Genetic studies demonstrated that the difference between M. tuberculosis and M. bovis is minuscule and they are genetically very similar (Daniel, 2000).

There are six major types of M. tuberculosis indentified worldwide and all six types exist in East Africa. Based on these findings, it is hypothesized that mycobacterium TB thrived along with its host in Eastern Africa but archeological evidence to confirm this assumption are lacking. However, TB was found in bones of the mummies from 2,400 BCE in Egypt. Furthermore, there are written texts that support the existence of TB 3,300 years ago in India and 2,300 years ago in China, substantiating TB's long history (Daniel, 2006). There is also abundant archeological evidence and extracting mycobacterium TB DNA from mummified humans in America which demonstrates the presence of TB 12,500 years ago in this region (Daniel, 2000). Daniel in his article concludes that TB might have reached America from Asia due to humans' immigration around 20,000 to 10,000 years ago (Daniel, 2000). TB has been known under different names: consumption, phthisis, or the white plague. Phthisis and consumption were the names that TB was known by in ancient Greece and its clinical manifestations were clearly described (Daniel, 2006). In the 1880s, people knew that TB was a disease that somehow is related to the air; they created sanatoria, therefore, to isolate TB patients, expose them to the fresh air and feed them with high calorie food (Harvard University Library, 2012). Before the discovery of Mycobacterium tuberculosis, people had believed that TB was hereditary rather than an infectious disease. Robert Koch first indentified Mycobacterium tuberculosis, the primary cause of TB, in 1882. This revolutionary discovery in TB history changed peoples' perception about TB, and motivated experts to work more intensively to find a cure for the disease. This event, later, had a great impact on the treatment of the disease because people started thinking over TB treatment in order to get this disease cured. Another very important event in the history of TB was the discovery of X-Rays as a diagnostic tool in the late 19th century. X-Ray is a method of imaging which facilitates the diagnosis of TB. X-Ray has been widely used in the diagnosis of

TB since the 19th century. A further important achievement against TB was obtained by Calmette and Guerin. They succeeded in decreasing the virulence (the ability to produce disease) of M. bovis and using it as a Bacille Calmette-Guerin (BCG) vaccine. This vaccine has saved millions of lives during 19th and 20th centuries. This vaccine still is in use saving children against severe form of TB disease in developing countries in Asia and Africa. Finally, during World War II, scientists succeeded in the discovery of a drug - streptomycin, an antibiotic against Mycobacterium tuberculosis (NJMS; Daniel, 2006; Daniel, 2000). After that, the series of anti TB-drugs advancement and discoveries in the eradication and treatment of TB have continued. These new drugs brought huge success against TB to humanity.

2.3.0. TB Trend in the US

In the United States, even though the DOT strategy was not in effect, TB incidence rate declined from 1953 to 1984. In the 1985, a sudden increase in number of TB cases was detected, particularly, in the densely populated cities and among minorities, posing a major challenge to public health. In addition to escalation in number of susceptible mycobacterium TB cases, an unfortunate increase in the number of drug resistant organisms was detected (Weis et al, 1994). This increase, in drug resistance in particular, might have been the result of irregular treatment indicating lack of universal DOT in the United States. After adoption of DOT in the United States, incidence and prevalence of TB annually have been decreasing since 1992 (CDC, 2012). According to the world health organization (WHO), TB prevalence decreased from 30 per 100,000 to less than 10 /100,000 population from 1990 to 2010 respectively. Likewise, the mortality rate among TB patients decreased from 8/100,000 to less than 2/100,000 population. Moreover, an incidence of 3.4/100,000 cases were reported in 2011 indicating a 6.4% drop in incidence rate comparing to the year 2010 (CDC, 2011). This evidence suggests that since DOT has been in place, a significant decline in TB cases rate has been observed. TB burden in the US is much lower comparing to other countries. In the year 2012, 9,951 cases were reported for an estimated incidence of 3.2 cases per 100,000 populations, and a decline of 6.1% from the previous year.   This was the first year since 1953 that fewer than 10,000 cases yearly were reported. However, TB incidence is disproportionately distributed among foreign born and minorities in the US. From 2010 to 2012, 44.2% of all the US counties did not report a new TB case which is a significant achievement in terms of TB control program. Even though TB trend (fig.1) looks a very successful practice in the US, a closer look at the data reveals that rate of TB has not changed much among foreign born persons, posing a challenge to current strategies against TB elimination in the US.



This figure (fig.1) is constructed based on the data from CDC. http://www.cdc.gov/tb/statistics/reports/2012/table1.htm

2.4.0 An Evaluation of Factors That Facilitate and Promote TB Disease

Based on literature, there is multitude of factors such as age, gender, race, poverty, genetic, diseases such as, HIV and diabetes as well as some unfavorable behaviors such as smoking, drinking and drug use that can promote TB infection and TB active disease.

2.4.1. TB, Immunity, and Age

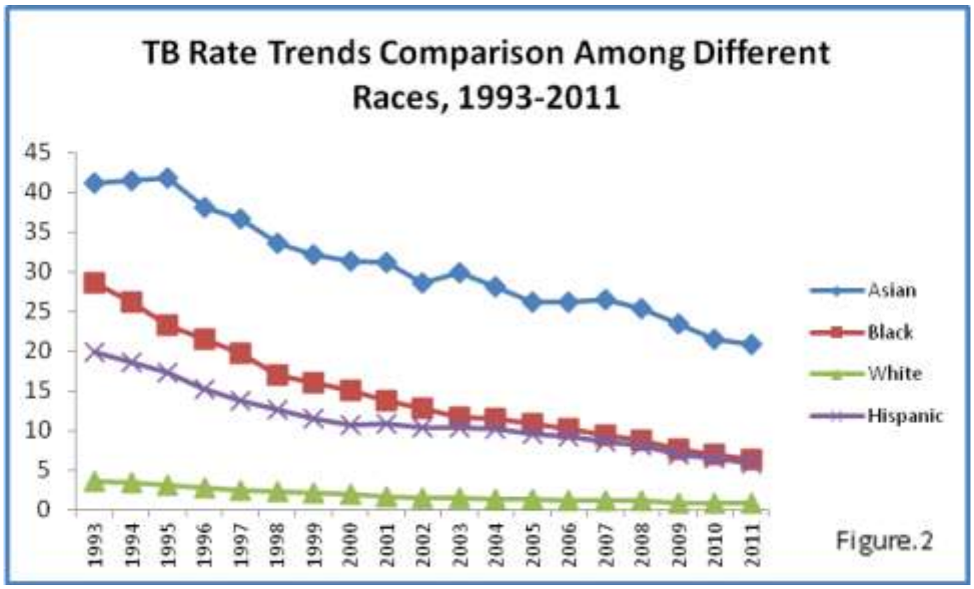
Among all preventive measures, immunity is the monumental factor in prevention against TB infection after exposure to this microorganism. Immunity is widely affected by age and identified as two interactive types, innate and acquired. Innate immunity is born with human and has cellular (macrophages, polymorphonuclear cells, natural killer cells, and dendritic cells) and non-cellular (C-reactive protein, serum amyloid protein, mnnose-binding protein, and the complement cascade) components. Acquired or adaptive immunity is a mix of cellular (cytotoxic) and humoral (antibody) responses antigen memory and the anamnestic response. Acquired immunity grows and thrives gradually when exposed to antigens as age increases toward adulthood. With aging, immune-competency declines, and immunity against infectious diseases such as TB diminishes (Castle, 2000). Even though strong initiatives are undertaken to lessen the rate of TB by WHO and TB control programs globally, high rate of TB among aging adults (≥65) remains a public health challenge. Since impaired immunity against TB in this population (≥65) is typical and since diabetes prevalence (18.9%) is higher among this population (≥65), TB remains undiagnosed and untreated for longer period of time and results in higher morbidity and mortality and probably higher transmission (Rajagopalan, 2001; CDC, 2011; CDC, 2012).

2.4.2. TB and Gender

TB is usually higher in male than female. The reason is not well understood; however, it is theorized that male might have higher exposure from young adulthood To TB infection (Nur et al., 2009, WHO, 2004).

2.4.3. TB and Race

Nothing is evenly distributed among humans globally. Likewise, socio and economical status unequally distributed throughout the world and is a fundamental factor intertwined with health outcomes. Since 1953, TB cases have been decreasing in the US; however, this decline is different among different races (fig.2). A number of investigators have attributed this disbalance in the distribution of TB among different races to socioeconomic status (SES) (Cantwell, 1998; Weis, 1988). Beside SES, physical characteristics associated with TB infection and TB disease susceptibility include body weight and chest size, blood type, and skin color and absorption of vitamin D (Cantwell, 1998; Stead, 1990).

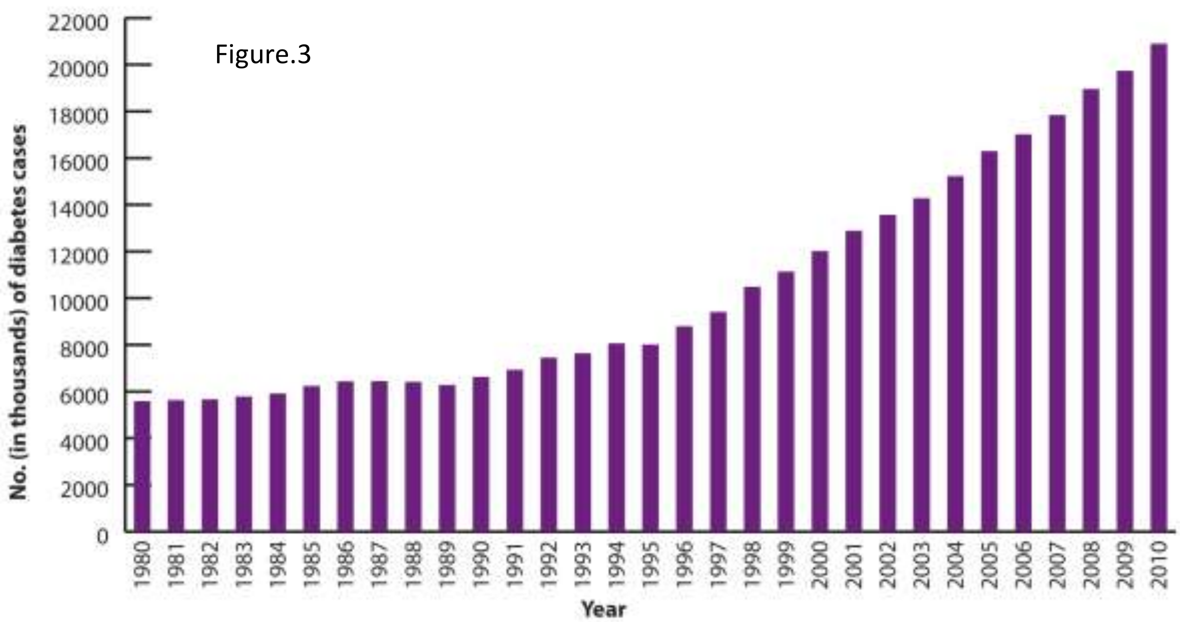


The data for this fig.2 is taken from CDC website. http://www.cdc.gov/tb/statistics/reports/2012/pdf/report2012.pdf

2.4.4. TB and Diabetes

Recurrent infection is higher among diabetic patients in comparison to non-diabetic individuals and also the course of infection among diabetic persons is far more serious and complicated than that of a non-diabetic. Keto-acidosis complicated by infections, for instance, is widely evident in 75% of total keto- acisdoisis incidences in diabetic patients. Furthermore, mortality among diabetic patients with infection is 43% signifying the interaction between diabetes and infection (Geerlings, 1999). That diabetes has an adverse effect on immunity against TB was indentified decades ago (Martinz & Kornfeld, 2014). However, investigations to understand this relationship have been renewed because the rate for diabetes and TB has been increasing in low and middle income countries. According to Martinz and Kornfeld, diabetes increases the risk of developing TB by three fold (2014). In a study in India, the investigator evaluated 827 TB patients. Among these TB cases, 25.3% were diabetic and 24.5% individuals were pre-diabetic (Viswanathan et al., 2012). Moreover, diabetes is a concern in the developed and high income countries since the proportion of obesity and of the older population—two important risk factors for diabetes have been increasing. In the US, according to CDC's 2012 diabetes report, incidence and prevalence of diagnosed diabetes annually has been increasing (fig.3). These facts signify the importance of determining the risk of developing TB among diabetic patients because in the year 2010, 8.3% of the US population was suffering from diabetes and based on presented statistics the rate appears to be increasing (CDC, 2012).

Figure 2. Annual Number of U.S. Adults Aged 18–79 Years with Diagnosed Diabetes, 1980–2010

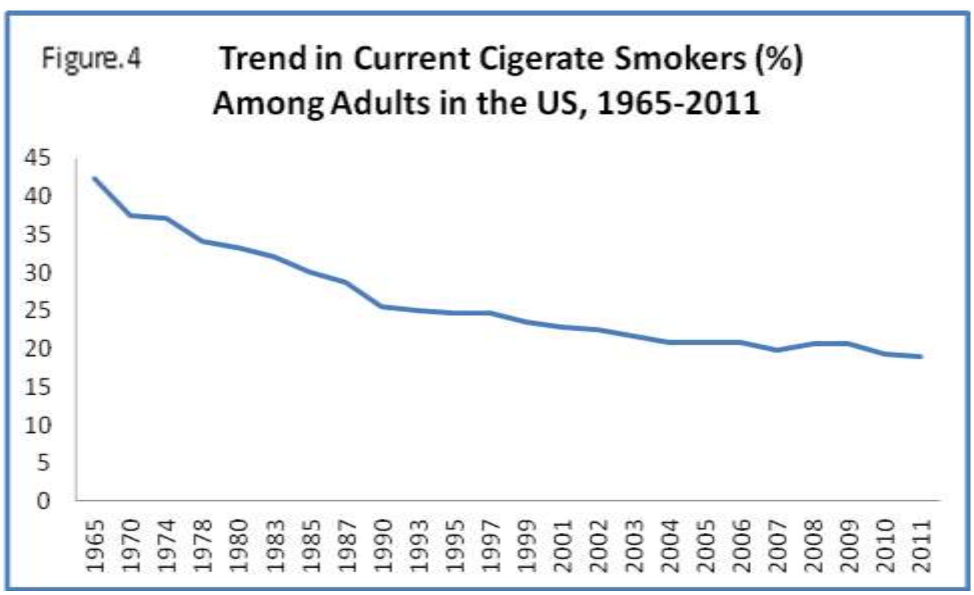


Source: National Diabetes Surveillance System, National Health Interview Survey data.

This figure (fig.3) is copied form CDC website. http://www.cdc.gov/diabetes/pubs/pdf/diabetesreportcard.pdf

2.4.5. TB and Smoking

TB and smoking tobacco are both significant challenges for public health (Bates, 2007). Smoking is considered a risky behavior for numerous adverse outcomes. Outcomes associated with smoking are preventable. Nationwide in the US, approximately 42.1 million adults (>18 years of age) are smokers resulting in preventable death annually. Based on statistics, 20% of entire deaths in the US annually are due to smoking and a further 16 million individuals suffering from diseases associated with smoking (CDC, 2014). In addition to other adverse outcomes associated with smoking, recently frequent studies found that smoking is a risk factor for developing TB as well. Smoking results in deposition of particles in lungs and airways affecting local immunity and cilia functions in respiratory system. Ciliary dysfunction impairing clearance of airways results in accumulation of particles that further damage local immunity in lungs and thus promote TB infection and severity of the diseases among smokers (Godoy et al, 2013; Singh et al, 2013). According to WHO, histo-pathological evidence revealed that a causal pathway exist between smoking and TB. A body of literature recently has accumulated confirming the higher prevalence of TB among smokers compared to non-smokers (Singh, 2013; Bates, 2007).



The data for this fig.4 is taken form CDC website. http://www.cdc.gov/diabetes/pubs/pdf/diabetesreportcard.pdf

2.4.6. TB and Foreign Born

In the US, even though TB is consistently declining, TB among foreign born persons is a significant public health problem. More than half of US TB cases develop among persons born out of the US. In the 2011, 62% of all TB cases were in foreign born individuals. Furthermore, in 2011 the rate among foreign born TB was approximately eleven times higher in comparison to US born TB cases (ALA, 2013). There is an obvious relationship in the changing proportion of TB cases among native-born and foreign-born (fig.5). In 1993, the proportion among the US born was approximately 70% whereas among foreign born was 30%. In 2012 almost this proportion reversed indicating approximately 35% of TB cases occurred among the US born persons while around 65% of TB cases developed among foreign born individuals.

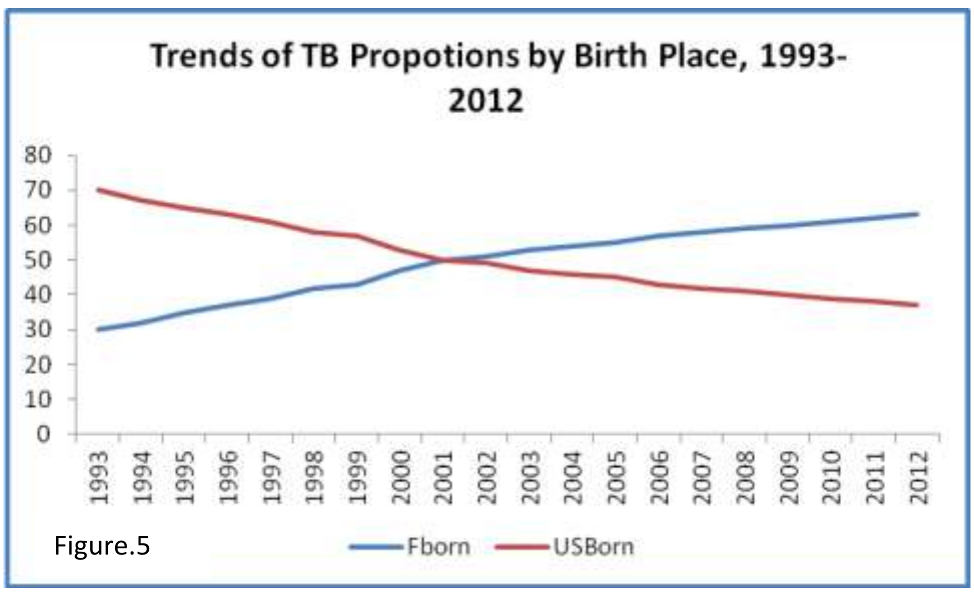
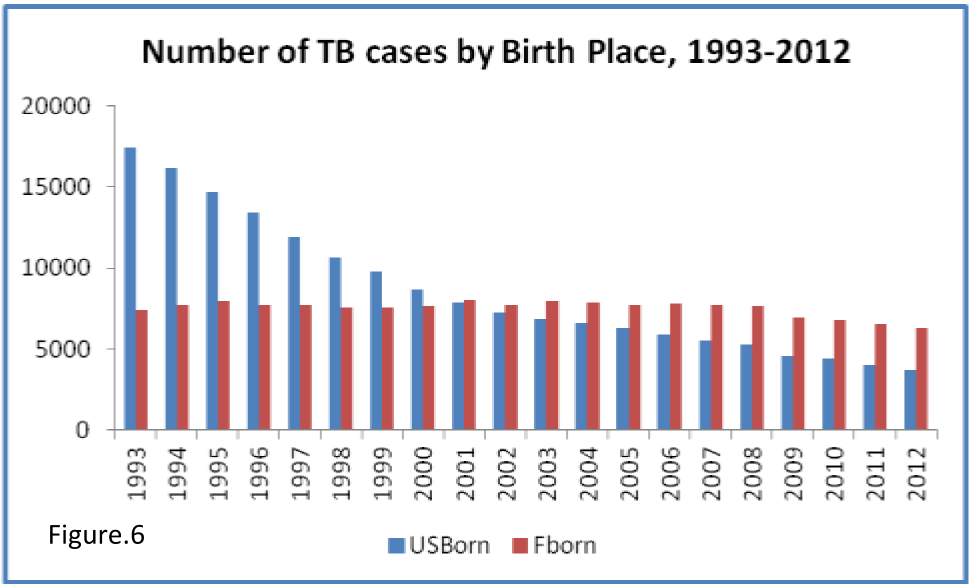


Figure.5

This graph is constructed based on 2012 data taken from CDC. http://www.cdc.gov/tb/statistics/reports/2012/table5.htm

Moreover, the number of TB cases among foreign born persons has not changed much. A close look at the data reveals that the decline in TB cases (15%) among foreign born between 1993 and 2012 was small. The decline among US born TB cases, in contrast, was 79% during the same period of time (fig.6).



This graph is constructed based on 2012 data taken from CDC. http://www.cdc.gov/tb/statistics/reports/2012/table5.htm

If such a trend continues, foreign born persons will eventually predominate more than they do now. The concern will arise that with current TB control strategies, eliminating TB from the US will be close to impossible because of continuing immigration from countries where TB is endemic (Cain & Kenzei, 2008; Cain et al., 2007).

2.4.7. TB and TB Contacts

Early diagnose and treatment for TB control programs is paramount. The most efficient and effective preventive strategy is to trace TB patients and start anti-TB treatment in order to break the chain of transmission. The top priority for TB control programs, therefore, is to find active TB disease individuals and their close contacts for starting treatment and screening for TB infection and active TB disease (MMWR, 1995). Late case detection in low TB prevalence setting like the US could be disastrous. For instance, a 23 years old TB index case caused an outbreak in Oklahoma State. Between 1996 and 2000, he was detained five times; he also shared housing with family and friends. He underwent antibiotic therapy for pneumonia. After he was diagnosed with pulmonary TB, his close contacts were estimated to be 294 individuals from which 251(85%) were within reach. All contacts underwent TB Skin Test (TST), among all tested contacts, 42% were positive, indicating recent exposure to M. tuberculosis. After further follow up, among 42% contacts TST tested positive, 19 of them developed active TB who were secondary TB cases (Andre et al., 2007). Untreated, those 19 cases could be responsible for considerable spread. Therefore, early case detection and contact investigation are backbone of the TB control programs. Another study considered 1,080 active TB cases; for all TB cases a total of 6,225 close contacts (an average of 4 contacts for each TB case) were identified. From all contacts, 2% detected with active TB and 28% found to be TST positive. This fact indicates that the risk of LTBI and active TB is higher among TB contacts in comparison to non-TB contacts (Marks et al., 2000).

2.4.8. TB and Poverty

Health is associated with socioeconomic status and is a topic of active research. A vast number of studies not only show association between variety of diseases and SES but also association between SES and severity of diseases (Schechter, 1997; Rabin, 2001; Steptoe, 2010; MacKinnon, 2007). TB, one of the adverse health outcomes, is more prevalent among poor societies (Spence, 1993). Therefore, TB prevalence is higher in developing and low income countries (Oren et al., 2013; PrayGod et al., 2013; Olson et al., 2012). A study by Olson and colleagues revealed that the risk of developing TB among low SES is higher compare to high SES. In this study, 170,590 verified TB cases from 1996 to 2005 were assessed to determine the relationship between TB and SES. Among all these cases, 52.2% included in analysis were foreign born TB cases. Investigators found that TB rate is higher among individuals living with low SES in comparison to those having high SES (Olson et al., 2012). Since the SES and TB relationship is historically well established, Spence decided to explore if this association still existed in UK. He conducted a study among TB cases in Liverpool, UK. After completing the study, he was able to show that a strong association between poverty and TB was still present (Spence, 1993).

3.0.0. Methodology

For achieving this study's objectives, the National Health and Nutrition Examination Survey (NHANES) for year 2011-2012 are used.

3.1.0. Data Source

NHANES, a national representative survey, is performed by CDC. Though periodic in its earlier years, it now uses a continuous rolling sample. The target population is non-institutionalized civilians who reside in the United States. Subjects are recruited through a complex, multi stage probability sampling from 50 states and District of Columbia. In this multi stage processes, the primary sampling unites (PSUs) are counties. Then segments are selected within the counties consisting of cluster of households. After selection of households, individuals are recruited to participate in the survey form those households. The number of subjects selected for the 2011-2012 NHANES were 13,431 individuals from which only 9,756 completed questionnaire and 9,338 subjects were examined for the survey purposes.

3.2.0. Data Obtaining Method

In order to achieve this study's objectives, variables related to demography, LTBI, diabetes, smoking status, TB blood test (the quantiFERON TB Gold IT test), occupation, ratio of family income to poverty, and body mass index were selected and downloaded from CDC website. Then all data files were merged based on individual subject's ID number (SEQN). After merging processes completed, the variables of interest were dichotomized for analysis purposes. After data cleaning process and data processing, 6,175 observations were included in the analysis.

3.3.0. Dichotomization process

The variables included in the analysis were: gender, age, race/ethnicity, marital status, served out of the US, country of birth, LTBI status, lived in a household with TB sick person, diabetes status, smoking status, body mass index, exposure to occupational dust, and ratio of family income to poverty. Variables such as LTBI, diabetes, and smoking originally do not exist in the NHANES 2011-2012. Therefore, these variables are created based on some criteria that are explained in coming paragraphs.

3.3.1. LTBI Status

LTBI status is not clearly defined in the NHANES 2011-2012. Each individual suspected for LTBI undergone to a blood test (the quantiFERON TB Gold IT test) to determine if s/he is confirmed TB case. Thus, LTBI confirmed individual in this paper is the person whose quantiFERON TB Gold IT test of blood came positive. LTBI status is dichotomous either positive (yes) or negative (no). Negative and indeterminate test result categorized as non LTBI status.

3.3.2. Diabetes Disease Status

Like TB, diabetes status is not defined; therefore based on some specific criteria, a new variable under diabetes is created. Diabetes is created as a dichotomous variable, either having the condition or not. Diabetes status is created from three different questions in data set. The first question asks, were you told that you have diabetes by a doctor? Are you currently taking insulin? Are you taking blood sugar lowering pills? If the answer for any of above questions is yes, then diabetes status is classified as yes and if the all three answers simultaneously are no, then the diabetes status is classified as no.

3.3.3. Smoking Status

Like diabetes and TB, smoking is not clearly defined in the database. Smoking variable was created by combining two questions. The first question asks that are you a current smoker? And the second question asks that have you ever smoked 100 cigarettes in your lifetime? If both or one of these two questions are answered yes, then the individual is classified as smoker. If the both questions are simultaneously answered no, then the individual is classified as non-smoker.

3.3.4. Age Group

Age is used as categorical dichotomous variable. Since old age (≥65) is associated with a higher rate of TB, age is categorized into two groups of less than 65 years and 65 and higher.

3.3.5. Exposed to Occupational Dust

Since dust and fumes can impair lungs function, they are included in the analysis. In this paper, persons considered to be exposed to occupational dust are individuals who were exposed to mineral dust, organic dust and exhaust fumes in their working environment in the past. All three variables are combined into one variable of occupational dust. All three variables in the database have five level answers of yes, no, refused, don’t know and missing. In dichotomization process, if for any of organic dust, mineral dust, and exhaust fumes exposure, the answer was yes, three variables is combined and classified as yes for a single variable of occupational dust exposure. If the answers for all three variable were, no, refused, don’t know, or missing, then it was classified as no for the new variable of dust exposure.

3.3.6. Body Mass Index (BMI)

Since low body mass is associated with TB, BMI is included in the analysis. In the database, BMI is given as range of values from 12.4 to 82.1. Since CDC classifies BMI less than 18.5 as underweight, in order to dichotomize this variable, BMI divided into tow portion of underweight (<18.5) and normal weight and above (≥18.5).

3.3.7. Lived in a household TB sick person (TB Contacts)

The question for TB contacts was: lived in household TB sick person? There were five answers of yes, no, refused, do not know, and missing. In order to dichotomize the answers for TB contacts, only yes is classified as person who was in contact of an active TB case (yes) and the rest of answers categorized as no.

3.3.8. Country of Birth

In the data base, under country of birth, there are five answers: US, others, refused, do not know, and missing. This variable is dichotomized as US born and foreign born. People who were born in the US classified as US born and all answers under other categorized as foreign born.

3.3.9. Ratio of family income to poverty (poverty)

In order to determine the level of poverty, the variable, ratio of family income to poverty is used. This variable in database contained range of values (0 to 5). This range of values is split into two portions and a new dichotomized variable of poverty is created. The values one and smaller than one categorized as yes response to poverty (poverty=yes). The values greater than one was classified as no response to poverty (poverty=no).

4.0.0. Data Analysis Strategy

SAS 9.2 software package was used to analyze the data. Proportions are used to determine the percentages of the risk groups among all LTBI persons. Furthermore, in order to determine the association between dependent and independent variables, univariate and multivariate modeling were used. Furthermore, the whole data was split into two portions of foreign and US born. The data was partitioned to compare the association between LTBI and independent variables in foreign, US born subpopulations and general population.

5.0.0. Results

A descriptive cross-sectional method used to describe the characteristics of the LTBI persons based on risk groups and the likelihood of contracting TB infection among risk groups within a sample of 6,175 subjects form NHANES 2011-2012 is calculated. Percentages and proportions are used to describe the characteristics of LTBI individuals among this population. Adjusted and unadjusted odds ratios were calculated to determine the association of risk groups with LTBI in general population, foreign and US born subpopulation.

5.1.0. Descriptive Results

5.1.1. Description of LTBI Persons Based on Risk Groups

A total sample size of N=6,175 was included in the analysis. Among study population, five hundred and twenty six (526) confirmed LTBI persons were detected. From all LTBI persons (526), 109 were diabetic, 243 had smoking habit, 178 had exposure to occupational dust, 162 were in age category ≥65 years, 35 were in contact to active TB cases, 340 were born out of the US, 26 served outside of the US, 199 were living below poverty line, 16 were in underweight category, and 319 were living either with their spouses or partners.

Diabetes rate was higher among males and age category <65 years. The race that had the highest diabetes rate was African American. Also smoking was not distributed evenly. Three times as many males as females were smoker; smoking distribution was approximately equal among both age groups. African American was with the highest smoking rate. More than third of all persons who had exposure to occupational dust were male and 71% of all persons exposed to occupational dust were in age group <65 years. Among all races, African Americans inclined the highest rate of exposure to occupational dust. Among all persons with LTBI, females and age group <65 were prominent. African Americans contained the highest proportion of all TB contacts. Foreign born persons was higher among males and age group <65. Again African American had the highest rate of foreign born persons. Ninety four percent of all persons served outside of the US were male and 81% of all persons served outside of the US were in age category of <65 and more than half of all persons served outside of the US were African Americans. Poverty proportion was higher among male, age group <65, and Asians. Being underweight was equally distributed among both age groups and was higher among males. The highest proportion of underweight persons was African Americans. Asians had the highest rate of living with spouse or partner.

Table (1) Characteristics of TB Cases by Risk Groups

		Sex (%)		Age (%)		Race/Ethnicity (%)					
Characters tics	**LTBI**	**Male**	**Female**	**<65Yrs**	**≥65Yrs**	**MA**	**OH**	**NHW**	**NHB**	**NHA**	**OR**
Total # of Cases	526	57	43	69.2	30.8	14.8	17.3	14.5	24	28.1	1.3
Diabetes	109	59.6	40.4	52.3	47.7	17.4	11.9	18.3	29.4	20.2	2.8
Smoking	243	73.7	26.3	60.5	39.5	16.9	17.3	19.8	26.3	18.9	0.8
Exposure to Dust	178	77.5	22.5	71.3	28.7	19.1	19,7	14	25.8	19.7	1.7
≥65 Yrs	162	60.5	39.5			9.3	20.4	21	27.2	20.2	1.9
TB Contact	35	45.7	54.3	65.7	34.3	8.6	14.3	20	37.1	20	0
Foreign Born	340	56.2	43.8	74.7	25.3	9.1	4.3	34.4	47.9	2.7	1.6
Served out of the US	26	96	4	80.8	19.2	0	3.9	30.8	61.5	3.8	0
Poverty	199	55.3	44.7	62.8	37.2	12.1	16.6	15.6	24	29.7	2

Underweight	16	62.5	37.5	50	50	6.3	0	25	37.5	31.3	0
Living with spouse or partner	319	64.9	35.1	73	27	16.6	16	12.2	17.2	36.7	1.3

MA: Mexican American
OH: Other Hispanic
NHW: non-Hispanic White
NHB: non-Hispanic Black
NHA: non-Hispanic Asian
OR: other races.

5.2.0. Analytic Results to Estimate Risk of contacting LTBI among Risk Groups

5.2.1. Univariate Analysis (Unadjusted Odds Ratios)

The unadjusted odds ratios were calculated for the risk groups to estimate the risk of contracting TB infection among those risk groups. Male gender indicates a significant higher association with LTBI in comparison to females (OR=1.4, CI: 1.17- 1.68). For diabetes, a determinant of TB disease, a statistically significant odds ratio (OR=1.75, CI: 1.4-2.19) was obtained indicating that diabetes is significantly associated with LTBI. For smokers an unadjusted odds ratio of 1.42 (CI: 1.19-1.7) is calculated which is statistically significant proving that smoking is associated with LTBI. After odds ratio calculation for age categories, it is found that the odds of contracting TB infection is higher among persons who are in age group ≥65 Yrs (OR=1.87, CI: 1.53- 2.27). The odds of contracting TB infection among persons who were in contact of an index TB case found to be quit high (OR=2.43, CI: 1.67-3.54) and statistically significant. Unadjusted odds ratio for foreign born was the highest among all risk groups. The odds of LTBI among foreign born person was approximately 5 times (OR=4.97, CI: 4.12-6) higher in comparison to the US born citizens. Living with spouse or partner turned out to be significantly associated with LTBI (OR=1.56, CI: 1.3- 1.88). However, the data failed to show a significant association between exposure to dust, served out of the US, poverty, being in underweight category and LTBI. The findings are summarized in table 2.

Table (2) Univariate Analysis

Variable	Odds Ratios	Confidence Limits	
Gender	1.4	1.17	1.68
Diabetes	1.75	1.4	2.19
Smoking	1.42	1.19	1.7
Exposure to Dust	0.86	0.71	1.04
≥65 Yrs	1.87	1.53	2.27
TB Contact	2.43	1.67	3.54
Foreign Born	4.97	4.12	6
Served out of the US	1.1	0.72	1.66
Poverty	1.07	0.89	1.28
Underweight	0.34	0.2	0.56
Living with spouse or partner	1.56	1.3	1.88

5.2.2. Multivariate Analysis for the entire sample (N=6175)

After controlling for potential confounders such as gender, race/ethnicity, served out of the US, exposure to dust, being underweight, and living with spouse or partner through logistic regression modeling, adjusted odds ratios for each variable of interest were obtained. Even though the odds ratios adjusted and controlled for potential confounders, odds ratios for predictors remained pretty much consistent with univariate analysis results. The adjusted odds ratios are exhibited in table 3.

Table (3) Multivariate Analysis (general population, N=6,175)

Variable	Odds Ratios	Confidence Limits	
Gender	1.259	1.023	1.55
Diabetes	1.453	1.137	1.858
Smoking	1.625	1.327	1.991
Exposure to Dust	0.863	0.697	1.069
≥65 Yrs	1.966	1.575	2.453
TB Contact	2.539	1.688	3.819
Foreign Born	5.702	4.646	6.999
Served out of the US	1.227	0.779	1.934
Poverty	1.078	0.889	1.309
Underweight	0.297	0.177	0.499
Living with spouse or partner	1.12	0.921	1.361
Race/Ethnicity	0.966	0.916	1.02

5.2.3. Multivariate Analysis in Subpopulations (Foreign Born and US Born)

When gender was considered within entire population (N=6,175) and logistic regression conducted, male gender was significantly associated with LTBI (OR=1.259, CI: 1.023-1.55). When logistic regression conducted in partitioned data for foreign born persons (table.4), the gender and LTBI association became statistically insignificant. However, gender for US born persons remained significant (table.5). When LTBI and diabetes association was considered in general model, it was significant (OR=1.53, CI: 1.137- 1.858). When this association was considered in subpopulations, it remained significant for US born persons. However, this association became insignificant for foreign born subpopulation. Evaluation of smoking revealed that its association with LTBI is significant across general population and both subpopulations but the association become stronger for the US born subpopulation. The association of old age (≥65 Yrs) remained consistent in both subpopulations as in general population. The association of living with TB active case and contracting TB infection was significant in general population. When the logistic regression conducted separately in two subpopulations, the association became insignificant for foreign born persons. However, this association became stronger for the US born persons (OR=4.192, CI: 2.482-7.081). Living with spouse was significantly associated with contracting TB infection in general population. When the association was estimated in subpopulations, this relationship became stronger for foreign born subpopulation, while it became insignificant for the US born subpopulation.

Table (4) Multivariate Analysis (Foreign Born), n=1,858

Variable	Odds Ratios	Confidence Limits	
Gender	1.22	0.934	1.595
Diabetes	1.186	0.847	1.662
Smoking	1.344	1.021	1.768
Exposure to Dust	0.937	0.705	1.245
≥65 Yrs	1.998	1.479	2.699
TB Contact	1.343	0.729	2.474
Served out of the US	0.189	0.024	1.471
Poverty	1.036	0.807	1.33
Underweight	0.223	0.107	0.462
Living with spouse or partner	1.557	1.195	2.028
Race/Ethnicity	0.96	0.905	1.019

Table (5) Multivariate Analysis (US Born), n=4,317

Variable	Odds Ratios	Confidence Limits	
Gender	1.431	1.018	2.01
Diabetes	1.722	1.201	2.469
Smoking	2.196	1.59	3.033
Exposure to Dust	0.81	0.582	1.128
≥65 Yrs	2.012	1.437	2.817
TB Contact	4.192	2.482	7.081
Served out of the US	1.377	0.836	2.266
Poverty	1.128	0.83	1.534
Underweight	0.407	0.196	0.847
Living with spouse or partner	0.709	0.519	0.969
Race/Ethnicity	1.017	0.889	1.164

6.0.0. Discussion

In this study, an uneven distribution of LTBI across gender is found. This finding indicates that the proportion of male is higher among LTBI persons than female. The proportion of TB was higher for male in both age categories. This finding is rather consistent with literature and previous studies. In a study conducted in Turkey, the rates for TB across sex were unequally distributed and the rates were higher among male (Nur, 2009). Furthermore, a report from WHO indicates that almost globally the distribution of TB is imbalanced between both genders and is higher among men in comparison to women (WHO, 2004). Same trend is confirmed through another study by Rao indicating that the male to female ratio in terms of TB was 2:1 portraying that male suffers more than female from TB globally (Rao, 2009).

Since TB is an infectious disease and also age has an influence on the immune system, age is one of the important determinants of TB disease. Within the sample analyzed in this paper, a higher odds of having LTBI among aging population (>64) found. In the multivariate analysis, approximately two fold increased association between LTBI and aging population is detected (OR=1.96, 95% CI: 1.5-2.44). Consistent with this finding, a study by Rajagopalan which conducted in 2001 confirms that TB is far prevalent in aging population in comparison to younger individuals. Moreover, a Meta analysis conducted in order to compare TB prevalence between younger and older age populations. The research team analyzed 12 observational studies and found that the prevalence of TB is higher among aging population (Guzman, 1999).

In the US, diseases including TB are disproportionately distributed among different races. In this paper 526 LTBI individuals were analyzed from which 32% was Hispanic, 28% was Asian, 24% was African American, and 15% was White. Even though the sample taken in NHANES was not population proportionate, this distribution approximate the proportion of TB cases distributed among different races in the US. A study by Cantwell aimed to estimate the risk of developing TB among different races in the US. In reference to White race, the investigator found that the risk of developing TB is higher among African American and followed by Asian, Hispanic, and Native American (Cantwell, 1998).

The association between diabetes and TB is well established in the literature (Bates, 2007). Even the mechanism is well explained, due to low immunity and increased concentration of glucose, mycobacterium gets activated and grown (Martinez, 2013). My findings in this paper are in line with numerous other studies in literature. Analysis after controlling for potential confounders suggest that the association between diabetes and LTBI is approximately 1.5 times (OR=1.48, 95% CI: 1.16-1.88) higher in comparison to the association between LTBI and non diabetic individuals. Findings in a meta-analysis considered 13 observational studies for evaluation of diabetes and TB relationship is comparable to this paper. Analysis of these 13 observational studies revealed a positive relationship between diabetes and TB. It was found that the probability of developing TB among diabetic patients were three folds higher in comparison to non diabetic individuals (Jeon, 2008). Another study conducted in India and evaluated a national wide survey in order to determine the risk of developing TB among diabetic patients. According to the author, in the year 2000, there were an estimated of 20.7 million diabetic cases and

900,000 incident TB cases in India. After analyzing and evaluation of data, the author found that diabetes was responsible for 14.8% (133,200) of all new incident cases in year 2000 (Stevenson, 2007). Furthermore, a study conducted in Mexico among 1,262 TB patients to determine the prevalence of diabetes among this population. The research team found that among 30% of those TB patients, diabetes was prevalent indicating the relationship between diabetes and TB (Corona, 2013). The investigators also found that the course and manifestation of TB in a diabetic patient is more severe, sputum conversion is delayed, and also the investigators confronted with higher probability of treatment failure and recurrent infection (Corona, 2013). A study in China found that the prevalence of TB among diabetic patients is 958 per 100,000 people which is 12 times higher than general population (Wang, 2014).

Smoking is well known risk factor facilitating TB disease and the mechanism is well described. Findings in this paper suggest that smoking is significantly associated with LTBI (OR=1.71, 95% CI: 1.41-2.08); these findings are comparable with recent conducted studies. A meta-analysis of 17 observational studies indicates that smoking increases risk for LTBI and TB disease by 1.7 and 2.3 to 2.7 times respectively (Bates, 2007). In another study in Cambodia, their findings suggest that there is a positive relationship between smoking and TB. The author argues that the findings add to other studies found the same relationship between smoking and TB in India, South Korea, Taiwan, Thailand, and Malaysia (Singh, 2013). A study by Shin in Mexico found a dose response relationship between cigarette smoking and TB infection. World Health Organization (WHO) and International Union Against Tuberculosis and Lung Disease (IUATLD) jointly reviewed all studies indicating causal relationship between smoking and TB. Based on their inclusion criteria, 50 studies were analyzed and evidences were found. Based on the findings and evidence, they concluded that there is a positive relationship between smoking and TB infection and TB disease (WHO, 2007).

TB among foreign born population is an issue almost among all advance countries, since foreign born citizens emigrate with LTBI from their countries of birth. Latter in some point of their life course, due to variety of reasons LTBI develops to active form of TB disease. Likewise, in the US, foreign born population is the main source of TB and they carry the highest burden of TB in the nation. In this paper a significant relationship between foreign born population and LTBI is found. Among all TB cases, approximately 65% were foreign born LTBI persons and after controlling for other predictors an OR=5.78, 95% CI: 4.75-7.05 is obtained. This relationship is relatively powerful than any other predictors and outcome relationship analyzed in this paper. CDC reports that the risk of developing TB among foreign born person is 12 times higher in comparison to individual born in the US (CDC, 2012). Based on American Lung Association, 2013 report, data from 2011 suggested that 62% of the entire TB cases in the US consisted of foreign born persons. Findings from this paper are slightly higher from American Lung Association, 2013 and indicate that 65% of total TB cases are foreign born persons in NAHNES survey 2011-2012.

Furthermore, the multivariate analysis separately conducted in foreign and US born subpopulations in order to evaluate and compare the association between LTBI and predictors in both subpopulations. This analysis revealed that the associated factors with LTBI significantly differ between both subpopulations (table.6).

Table (6) OR and 95% CI comparison between general population, foreign born and US born subpopulations

	GP			FBSP			USBSP		
Variables	**OR**	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**	
Gender	1.26	1.02	1.55	1.22	0.93	1.6	1.43	1.02	2.01

Diabetes	1.45	1.14	1.86	1.19	0.85	1.66	1.72	1.2	2.47
Smoking	1.63	1.33	1.99	1.34	1.02	1.77	2.2	1.59	3.03
Exposure to Dust	0.86	0.7	1.07	0.94	0.71	1.25	0.81	0.58	1.13
≥65 Yrs	1.97	1.58	2.45	2	1.48	2.7	2.01	1.44	2.82
TB Contact	2.54	1.69	3.82	1.34	0.73	2.47	4.19	2.48	7.08
Foreign Born	5.7	4.65	7						
Served out of the US	1.23	0.78	1.93	0.19	0.02	1.47	1.38	0.84	2.27
Poverty	1.08	0.89	1.31	1.04	0.81	1.33	1.13	0.83	1.53
Underweight	0.3	0.18	0.5	0.22	0.11	0.46	0.41	0.2	0.85
Living with spouse or partner	1.12	0.92	1.36	1.56	1.2	2.03	0.71	0.52	0.97
Race/Ethnicity	0.97	0.92	1.02	0.96	0.91	1.02	1.02	0.89	1.16

GP: general population
FBSP: foreign born subpopulation
USBSP: US born subpopulation

Based on odds ratios and 95% confidence intervals comparison in table (6), it is revealed that LTBI associated factors differs for foreign and US born subpopulations. In multivariate analysis for foreign born subpopulation almost all significant associations (except smoking) in the general population became insignificant. In contrast, when multivariate analysis conducted to quantify the associated factors and LTBI in US born subpopulation, the detected association, found in general population, increased in strength for US born subpopulation. This fact again emphasizes that risk factors for foreign born and US born subpopulations differ. High TB prevalence to some extent may explain this fact and may signify that foreign born persons were exposed to TB infection their early stage of life. In order to determine the risk factors for LTBI among foreign born persons may require further studies and analysis by region or even by country of birth. Individuals who are in close contact of active TB patient such as family member and coworkers are one of the highest populations at risk for TB infection and TB disease (Kifai, 2009). Therefore, early diagnosis and contact tracing are backbone in TB control programs. In this paper among all LTBI persons, only 7% were in close contact of active TB patients. It is also found that the odds LTBI among TB contacts is higher. My findings suggest that people who were in close contact of a TB patients were at approximately 2.5 times higher risk of contracting

TB infection (OR=2.43, CI: 1.62-3.63). A study investigated an outbreak in Oklahoma State found that a single TB index case caused the outbreak in only nine months. Among his contacts, 109 persons found to be positive for TB infection and 19 individual with active secondary TB were detected. This outbreak signifies the importance of contact investigation (Andre, 2007). Another very comprehensive study representing urban population of the US studied 4,793 close contacts of active TB patients. The investigator found that 36% of entire contacts were positive for TB infection (Marks, 2000).

7.0.0. Limitation

Like all studies, this paper has a number of limitations that should be considered while interpreting the findings. It is a cross-sectional study; thus, the temporality between outcome and predictor variables cannot be determined. Furthermore, the diabetes status in this paper is not based on glucose level in blood. Instead diabetes status is based on three questions form NHANES (Were you told that you have diabetes by a doctor? Are you currently taking insulin? Are you taking blood sugar lowering pills?). If the answers for all or at least one of these questions were yes, the subject was considered as a diabetic patient otherwise non diabetic.

8.0.0. Conclusion

Based on literature and findings in this paper, it is obvious that diabetic patients, smokers, foreign born persons, individuals who are in close contact of active TB patient, and aging population are vulnerable groups for contracting TB infection and disease. These factors are known globally and are strictly considered by all TB control programs around the world including developing and developed countries. In the US, TB incidence among foreign born persons is critical for TB elimination, however. Further placing policies, such as LTBI screening among those coming from TB endemic countries to specify LTBI and start treatment will be critical step toward TB elimination. However, screening all foreign born persons in the US would be impossible but approaching those with higher risk for screening and LTBI treatment will be a significant step toward TB elimination.

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