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An Examination of Known Tuberculosis Risk Factors and their Correlation across the United States

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ABSTRACT

David Young

An Examination of Known Tuberculosis Risk Factors and Their Correlation Across the United States

(Under the direction of Sheryl Strasser, PhD)

Background: Globally tuberculosis (TB) is one of the leading causes of mortality. There is scientific evidence of sociodemographic, behavioral and health risk factors associated with TB infection and TB disease. In the United States (US), there is a low endemicity of TB and a goal of TB elimination.

Objective: The primary objective of the study was to examine the correlation of TB risk factors at the state level in the US to obtain insights specific to the state of TB in the US. The risk factors examined were diabetes rates, smoking rates, alcohol abuse rates, AIDS rates, foreign-born vs. US-born, poverty as expressed by GINI and per capita income and race/ethnicity.

Methods: Secondary data from the Centers for Disease Control and Prevention (CDC) and US Census Bureau on line databases were used. Simple linear regression, bivariate correlation and multiple linear regression were carried out.

Results: Significant correlations were found at the state level between TB disease rates and being non-Hispanic White ($r=-0.856$, $p<0.001$), foreign-born ($r=0.649$, $p<0.001$), GINI ($r=0.588$, $p<0.001$) and AIDS diagnosis rates ($r=0.579$, $p<0.001$). No significant associations were found between TB disease rates and diabetes rates, smoking rates and alcohol abuse rates.

Conclusion: The focus of the fight against TB in the US should be on minority communities, those populated by the foreign-born and those with high rates of AIDS particularly where a large degree of income inequality is present.

CHAPTER I

INTRODUCTION

The United States (US) has made great strides in reducing the annual incidence rate of tuberculosis (TB) over the past century. In 1945 the rate was 73/100,000 and in 1993 it was 9.0/100,000 (Snider, 1997). In 2009 the rate of TB fell to 3.8/100,000 reaching an all-time low. However the goal of eliminating TB (defined as a case rate of 1/1,000,000) appears to be a distant target (CDC, 2010). One of the great challenges is the high level of global TB infection estimated to encompass nearly 1/3 of the world population or approximately 2 billion individuals (WHO, 2010). There are generally two broad approaches to fighting TB, 1) raising the standard of living whereby malnutrition and overcrowding are reduced and 2) chemotherapy both for those infected with TB as well as those with active TB disease. A substantial arsenal of drugs is available to fight TB, however the 6 month minimum length of the treatment protocol opens the door to incomplete treatment and provides the breeding ground for drug resistant strains of the disease.

Some of the risk factors which influence the incidence of TB include heavy alcohol use, smoking, drug use (injection and non-injection), homelessness, incarceration, residence in a long-term care facility, diabetes, HIV, foreign-born status in the US, and race/ethnicity in the US. All of these factors are currently tracked by the CDC in case reports. In the US, not all of these risk factors play the same role as they might on the world stage due to the relatively low level of TB endemicity in the US.

Study Objectives and Research Questions

The primary objective of this study was to examine the correlation of sociodemographic, behavioral, and health risks of TB at the state level in the US to seek insights regarding the globally known TB risk factors with regard specifically to the US. The variables examined were AIDS diagnosis rates, diabetes death rates, rates of smoking, rates of alcohol abuse, percentage of the population which is foreign-born versus US born, race/ethnicity (percentage which is non-Hispanic White) and poverty (as expressed by per capita income as well as GINI). The specific research questions were:

Is there a correlation between the frequency of known TB risk factors and TB rates in each state and the District of Columbia (DC)? (Subsequent references to the states or US imply inclusion of the 50 states plus DC unless otherwise stated.)

Can a significant predictive model be derived for TB rates for the individual states based on the state level risk factor data?

What intervention insights can be gleaned from an ecological study of TB rates versus TB risk factors at the state level that can be applied to the US population?

With a death rate in 2007 of 0.4/100,000, TB is a disease easily ignored by the wider population (United Nations Statistics Division, 2009). It is also a disease that is very opportunistic and capable of mutation. The late 1980's were a period when neglect of TB combined with the advent of HIV/AIDS and multi-drug resistant (MDR) TB demonstrated that the US was not immune to a resurgence of TB. The TB rate rose from 9.1/100,000 in 1988 to 10.5/100,000 in

1992 (CDC, 1990; CDC, 1998). That served as a warning and any additional insights that this research can provide regarding TB in the US can help to remind us of the need to pay continued attention to this disease and sharpen our focus on the issues most likely to continue the diminution of TB in the US.

CHAPTER II

LITERATURE REVIEW

BACKGROUND ON TB

TB results from infection by the Mycobaterium tuberculosis (M. TB). It typically manifests itself in the patient's lungs (pulmonary TB), however it may reside virtually anywhere in the body (extrapulmonary TB). The primary mode of transmission is airborne via infected droplet nuclei which are expelled when someone breathes, coughs, sings or otherwise exhales. Upon inhalation the immune system will attack the M. TB. The health of the individual combined with the virulence of the inhaled bacteria and the frequency of exposure contribute to whether or not the bacteria reach the lungs' alveoli and infect the individual. At this point the bacteria may travel to other parts of the body and/or will be attacked by the immune system forming a granuloma. 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 TB disease.

TB was the leading cause of death in early 19th century Europe and earned the name, *the white plague*. Economic development led to improved nutrition and easing of crowding, and TB rates began to fall. The first sanitorium for systematic open-air treatment of TB was opened in Görbersdorf, Silesia, Germany in 1854 by Hermann Brehmer. He advocated high altitude, abundant diet with some alcohol, and exercise in the open air under strict medical supervision. The results were regarded as highly successful surpassing any previous treatment. Others later emphasized rest, both physically and mentally (McCarthy, 2001). An additional benefit of the sanitoria was the removal of infectious patients from general society thereby breaking the chain

of infection. Despite these advances, mortality rates in the sanitoria ranged from 30% - 50% (Booneville Development Corporation, 2010; Modern Woodmen of America, 2010). On March 24, 1882, Robert Koch discovered M. TB, the bacterium which causes TB. This was a major breakthrough both in the understanding of how TB is transmitted as well as how it might be combated. But it would not be until the 1940's when the first antibiotic for TB would be discovered and introduced. Albert Schatz isolated streptomycin October 19, 1943 (Comroe, 1978). The antibiotic was used clinically in the late 1940's and was successful in curing TB. However, as a monotherapy, resistance developed to streptomycin. In the early 1950's isoniazid became available to treat TB. Isoniazid was inexpensive and better tolerated and could be used in conjunction with streptomycin to minimize resistance. The other leading drug against TB, rifampin or rifampicin, became available for clinical use in 1968 (Sensi, 1983). Together rifampin and isoniazid form the backbone of current TB treatment, and any resistance to this combination of drugs is especially dangerous. For this reason, a special category exists for strains of TB which have, at a minimum, this dual resistance and are labeled MDR TB. If an individual has a resistance to isoniazid, rifampin plus one of the quinalones and injectables, they have extensively-drug resistant (XDR) TB. This is highly dangerous with limited treatment options (Caminero, 2010; WHO, 2008).

TB rates declined in the US throughout the 20th century until the late 1980's when a combination of the advent of HIV/AIDS and a reduction in public health TB control activities led to a resurgence. A recognition of these problems led to actions which increased attention and intervention. The US returned to a path of declining TB rates from 1992 to the latest data available from 2009.

PREVENTION OF TB

VACCINES

The Bacille Calmette Guerin (BCG) vaccine was first used in 1921 and is still the only vaccine currently available. It is a live attenuated strain of Mycobaterium bovis. It has been most effective in protecting children against TB. Because of the variable effectiveness of the vaccine against adult pulmonary TB, and the vaccine's potential interference with tuberculin skin test reactivity, it is rarely used in the US (World Health Organization, 2010).

Both randomized placebo-controlled clinical trials and retrospective case-control and cohort studies have demonstrated a wide variation in vaccine efficacy, ranging from 80% to zero. The largest and most recent prospective randomized trial, the Chingleput study in southern India, failed to demonstrate any protection overall (CDC, 1998). This and other studies did indicate that the vaccine provided protection against common childhood forms of TB.

Currently there is a Product Development Partnership (PDP), Aeras Global TB Vaccine Foundation, charged with developing new, safe, effective and affordable vaccines against all strains of TB. They both develop vaccines as well as promote the testing of the most promising vaccines developed by other organizations. Currently they have six vaccines in various stages of the development process. Their ultimate goal is to develop, test, characterize, license, manufacture and distribute at least one new TB vaccine regimen for infants and another for adolescents and ensure their availability to all who need them (Aeras Global TB Vaccine Foundation, 2010).

ISONIAZID PREVENTIVE THERAPY

Patients without complicating factors who have LTBI have less than a 10% lifetime risk that the infection will convert into TB disease. For those co-infected with HIV the annual risk of conversion rises more than five-fold without highly active anti-retroviral (HAART) treatment (Badri, Wilson, & Wood, 2002). The WHO recommends that HIV patients with latent TB undergo a 6-9 month course of isoniazid preventive therapy (IPT). This protocol has been shown to reduce the probability of progression to active TB by approximately 90% (Comstock G. W., 1999). This treatment is also recommended for others with latent TB who can commit to completing the protocol. Concerns have been raised as to whether the treatment will lead to isoniazid resistance or complications such as liver damage. A meta-analysis showed a non-significant relative risk of 1.45 (95% CI 0.85-2.47) for developing isoniazid resistant TB. The authors concluded that any risk of a small increase in the incidence of isoniazid resistance attributable to wider use of IPT needs to be weighed against its benefit in reducing TB incidence. (Balcells, Thomas, Godfrey-Faussett, & Grant, 2006) A more recent study of South African miners who contracted TB following IPT concluded that the level of isoniazid resistance experienced by this group was comparable to those who had not undergone IPT. (van Halsema, et al., 2010) Alternative protocols including 4 months of Rifampin have shown promise as a substitute for IPT, but additional testing is required before new recommendations would be made (Lobue & Menzies, 2010). In the case of foreign-born individuals the CDC tracks the degree of isoniazid resistance by country of origin. This information could be used as a guide in the recommendation of IPT (Cain, Benoit, Winston, & MacKenzie, 2008).

A study was carried out addressing hepatotoxicity risk as a result of IPT. Only 0.15% of those completing IPT had hepatotoxic reactions to the IPT when patients 35 years of age and over were

excluded per guidelines. Cases representing extreme risk of progression to active TB were included regardless of age (Nolan, Goldberg, & Buskin, 1999).

NON-MEDICAL PREVENTIVE MEASURES

While chemotherapeutic approaches to combat TB justifiably have received substantial attention, we must remind ourselves that TB rates in the US were falling considerably before the first antibiotic to treat TB became available. TB death rates in the US were 194/100,000 in 1900. By 1940, prior to the introduction of antibiotic therapy, this had fallen to 46/100,000 (CDC, 1999). This was attributed to overall improvements in living standards such as less overcrowding and improved nutrition as well as private and public health programs aimed at reducing TB. Private and public health efforts included the pasteurization of milk and sanitoria which isolated infectious TB cases from their families and the public at large (Lönnroth, Jaramillo, Williams, Dye, & Raviglione, 2009). The introduction of antibiotics accelerated the rate at which TB declined in the US, however this does not preclude continued efforts to improve socioeconomic conditions as an additional strategy in the fight against TB both in the US as well as globally.

RISK FACTORS FOR TB

DIABETES

Diabetes mellitus (DM), generally referred to as diabetes, comes in 3 forms, Type 1, Type 2 and gestational diabetes. In type 1 diabetes, the body does not produce insulin. Insulin is a hormone that is needed to convert sugar, starches and other food into energy needed for daily life. Only 5-

10% of people with diabetes have this form of the disease (American Diabetes Association, 2010). Type 2 diabetes is the most common form of diabetes. Millions of U.S. residents have been diagnosed with type 2 diabetes, and many more are unaware that they are at high risk. Some groups have a higher risk for developing type 2 diabetes than others. Type 2 diabetes is more common in African Americans, Latinos, Native Americans, and Asian Americans, Native Hawaiians and other Pacific Islanders as well as the aged population. In type 2 diabetes, either the body does not produce enough insulin or the cells ignore the insulin (American Diabetes Association, 2010). Pregnant women who have never had diabetes before but who have high blood sugar (glucose) levels during pregnancy are said to have gestational diabetes. Gestational diabetes affects about 4% of all pregnant women - about 135,000 cases of gestational diabetes in the US each year (American Diabetes Association, 2010).

Biological Plausibility

Reports on the association between DM and TB are found as far back as 1000 A.D. when the Persian physician/philosopher, Avicenna, noted that 'phthisis', (a Greek term for TB), often complicated diabetes and that the presence of diabetes resulted in an increased risk of developing TB. Historically the incidence of TB in patients with diabetes has been high. The precise pathological relationship between TB and diabetes remains unclear. Diabetes is known to cause immune dysfunction and moderate suppression of the immune system. Specifically, diabetes has been shown to suppress cell mediated immunity. In particular, studies have found a decreased production of pro-inflammatory cytokines in conjunction with Type 1 diabetes as well as impaired functioning of macrophages. A reduced T-helper1 (Th1) cytokine response level is also seen amongst diabetic individuals. Th1 cytokines are vital in the control and inhibition of M. TB

bacilli. Several functions such as phagocytosis and chemotaxis are impaired in individuals with Type 1 and Type 2 diabetes (Young, Critchley, & Unwin, 2009).

Better regulation of diabetes has been found to provide improved cellular function. Some microorganisms have been shown to be more virulent in a high glucose environment. The response to TB infection could lead to an increase in insulin resistance or a decrease in insulin production, both plausible mechanisms highlighted in the literature through which TB infection could cause hyperglycemia. For example, aspects of the inflammatory immune response could result in an increase in blood glucose. Co-morbidity with TB and diabetes leads to a worsening of both conditions (Geerlings & Hoepelman, 1999; Young, Critchley, & Unwin, 2009).

Study Results

Several case–control studies have shown that the relative odds of developing TB in diabetic patients range from 2.44 to 8.33 compared with non-diabetic patients (Dooley & Chalsson, 2009). A 2008 meta-analysis found that the likelihood of developing TB among diabetics was three times more likely. Within this meta-analysis, the seven studies specific to the US and Canada found a substantially lower odds ratio of 1.46 (95% CI 1.25 to 1.70) (Jeon & Murray, 2008).

Prognosis - Double Burden of TB and Diabetes

The prevalence of diabetes is estimated to increase from 171 million people in 2000 to 366 million-440 million by 2030 (Dooley & Chalsson, 2009). The burden of communicable diseases is concentrated in low-income countries. Dooley and colleagues further point out that non-communicable diseases, which represented 47% of the disease burden in 1990 in low-income countries, have been predicted to rise to 69% by 2020. Higher rates of obesity and diabetes are

attributed to increasing industrialization and urbanization. Diabetes poses a large financial burden on developing countries. For example, in Africa, where mean per capita expenditures on health are US$30–800, the mean annual cost for diabetes care ranges between $2144 and $11,430 (direct costs $876–1220). In many countries, insulin is expensive or availability is poor: a 1-month supply of insulin can cost up to 20 days' wages. Thus, social and economic conditions heavily influence treatment options. Estimates specific to North America (Canada and the US) show an increase in the prevalence of diabetes from 11.6% to 13.6% of the population from 2010 to 2030 (Dooley & Chalsson, 2009).

SMOKING

History

For some time an association between tobacco smoking and TB has been suspected. However, TB is a social disease. Might the association just be the result of increased human interaction brought about by smoking in a cafe or bar? Or is it a result of confounding from its frequent combination with alcohol consumption? Or might it manifest itself amongst those in poorer economic circumstances who may live in overcrowded accommodations or be malnourished? The association between smoking and TB appears to be the least clear cut of the known risk factors and the most difficult to prove based on the myriad of potential confounders.

The necessary elements for TB are exposure to the tubercle bacillus and a host incapable of destroying the bacteria. All other risk factors play the role of exacerbating these fundamental risks. If smoking is a risk factor for TB, then it must either function chemobiologically to increase the susceptibility of the human host or physically to increase the probability of transmission by blowing of smoke or coughing by infectious individuals in the presence of others. If the association between smoking and TB is brought about by confounding, then

smoking may be a pointer to other risk factors. These include poverty which often manifests itself through overcrowding, poor nutrition, general ill health, poor access to health services and, increasingly, HIV infection with prostitution and intravenous drug use (Bothamley, 2005).

Biological Plausibility

The exact mechanism connecting tobacco smoking with TB is not completely understood, however there is accumulating evidence for the biological plausibility of this association. Normally the trachea, bronchi and bronchioles that form the airways that supply air to the lungs provide the first line of defense by preventing M. TB from reaching the alveoli. Smoking has been shown to inhibit the clearance of secretions on this route providing one path to infection.

Pulmonary alveolar macrophages (AMs) are both the target of M. TB infection as well as a primary defense mechanism against the bacteria. AMs from smokers have a reduced ability to phagocytize and/or kill bacteria. As reported with diabetes, smoking has been found to reduce the level of proinflammatory cytokines secreted. These cytokines are crucial for early responses to pathogens and the management of local host defenses (Lin HH, 2007; Sapori, 2002).

Epidemiological Evidence of an association

Three meta-analyses were conducted in 2007 examining whether tobacco smoking affected the rate of infection with TB, the rate of activation of TB and/or the mortality rate due to TB. The results are summarized in table 1. As the analyses were all conducted within 12 months of each other, the underlying sources had a large overlap and were only differentiated by varying exclusion criteria. Both Bates and Lin excluded studies whose populations were prone to high levels of TB (e.g. miners, silicotics, and HIV patients). Slama only included articles published in

English and did not include any articles published before 1967. Bates required all studies to provide adjustment for confounding by age and sex.

Table 1. Summary of recent meta-analyses on the association between tobacco smoking and TB

Meta-Analysis	TB Infection	TB Disease	TB Mortality
	Odds Ratios (Number of studies)		
Bates et al	1.7 (6)	2.3-2.7 (13)#	Non-homogeneous (5)
95% CI	1.46-2.04	1.97-2.75, 2.15-3.28	
Slama et al	1.8 (5)	2.3 (14)	2.2 (6)
95% CI	1.467-2.116	1.765-2.954	1.340-3.732
Lin et al	1.8-2.2 (6)*	1.62(8)-1.95 (12)**	2.0 (8)-2.3(3)***
95% CI	1.43-2.16, 1.65-2.93	1.15-2.29, 1.60-2.39	1.14-3.49, 1.43-3.77

The first value indicates ever smoked. The second value only includes current smokers.

Lin et al opted not to generate pooled OR's encompassing all results. Displayed are subgroups for adjusted for alcohol vs. not adjusted for alcohol (*), current smokers adjusted for alcohol vs. current smokers not adjusted for alcohol (**) and pulmonary TB vs. any TB (***).

A major issue in these analyses was a lack of homogeneity in the underlying study populations. This led Lin and colleagues to not calculate pooled odds ratios. Rather, they focused on publishing the results by subgroup. For similar reasons Bates and colleagues did not publish an odds ratio for TB mortality and concluded that additional studies would be needed regarding the association between tobacco smoking and TB mortality.

The underlying studies spanned a wide range in terms of variables adjusted for confounding. The studies which included a larger number of variables for adjustment demonstrated a somewhat mitigated association between smoking and TB but generally still presented a significant positive association. The authors of the analyses concluded that residual confounding was unlikely to account for the elevated risks found between smoking and TB.

All three analyses found a dose–response relationship had been demonstrated in most of the studies that had stratified on dose. They found evidence that the risk of TB increases with both daily dose of cigarettes and duration of smoking (Lin HH, 2007). All three studies concluded that the results indicated that a clinician could confidently advise TB patients to stop smoking and remain non-smokers or to avoid exposure to others' smoke in the context of good case management.

It has been noted in some countries that the differences in TB disease rates by sex begin to be seen in age cohorts when young men start smoking (Slama, et al., 2007). Another article presents evidence for the hypothesis that the differences in TB rates among men and women are influenced by the sex differences in tobacco use, in terms of prevalence of use, shorter duration of use or lower frequency of use. The analysis showed that 33% of the variance in the sex ratio of TB notifications could be explained by cigarette consumption (Watkins & Plant, 2006).

In the USA, there are a number of difficulties in assessing smoking as a risk factor for TB infection or TB disease. Among the most important are: (1) there is a low prevalence of TB infection in the general population; (2) as smoking rates have declined in the USA, smoking has become increasingly concentrated among subjects with low SES, leading to confounding with other risk factors for TB such as HIV infection, homelessness and alcoholism; and (3) stark

heterogeneity among TB risk groups. For example, the non-USA-born populations who currently constitute more than 50% patients of TB in the USA come from a diverse array of countries in various stages of the tobacco epidemic and their risk factors for TB are quite different than those represented by US-born TB cases (Davies, et al., 2006).

Prognosis

Given the association between tobacco smoking and TB, increasing rates of smoking in the developing world pose a severe risk to the health of this population (Mackay & Eriksen, 2002). At the same time knowledge of this threat allows individuals and organizations to take action and make decisions which could mitigate the threat.

In the US the association between smoking and TB must be viewed through the subpopulations where the TB threat is greatest. This means focusing on groups such as the foreign-born, prison populations, low income, HIV positive and the homeless. With regard to TB, smoking prevention and cessation should be a goal amongst all of these groups.

ALCOHOL

HISTORY

There has been a long-term school of thought which supports an association between alcohol abuse (defined as daily consumption of 40 grams or more of alcohol) and TB. Early studies from the 1950's to the 1980's have shown a risk ratio range varying from 55 to 9 (Lönnroth, Williams, Stadlin, Jaramillo, & Dye, 2008). These studies, however, did not allow for the confounding of various factors such as smoking, malnutrition and other aspects of poverty such as overcrowded conditions which are associated with TB. The challenge is two-fold: 1) to understand the risk ratio after all relevant confounders have been considered and 2) to understand to what degree the

risk ratio is a result of the physical effects of drinking such as damage to the immune system versus the effect of social interaction that is associated with drinking.

BIOLOGICAL PLAUSIBILITY

Possible biological pathways include a weakening of the immune system leading to higher risk of infection and break down from infection to TB disease. This may be through direct toxic effects of alcohol on the immune system, or indirectly through malnutrition, or other alcohol-related medical conditions. Studies have shown that intracellular survival of M. TB within the alveolar macrophage is enhanced by alcohol. Studies with mice have shown an association between alcohol consumption and defective lung granuloma formulation (Gamble, Mason, & Nelson, 2006).

In addition to biological pathways, the social interaction patterns of those who use alcohol have been associated with higher levels of TB infection. A case of multiple TB infections related to a pub in a small town in England was documented in 2007. Six cases were clearly identified as coming from the same TB strain and involved employees of the pub as well as clients. While the initial infections could partially be tied to social interaction at the pub, chronic alcohol abuse amongst at least five of the patients and difficulty in complying with treatment protocols may have also contributed to the infections. Ultimately one death was attributed to pulmonary TB as the primary cause (Bolam, Sarangi, Moul, Conlon, & Kammerling, 2007).

EPIDEMIOLOGICAL EVIDENCE

While there is considerable evidence of an association between alcohol and TB, the presence of a myriad of confounders complicates the relationship. The results from three meta-analyses that have been published since 2008 are shown and discussed in table 2.

Table 2. Summation of Meta-Analyses of an association between TB and excess alcohol consumption

Meta-Analysis	TB Disease
	Odds Ratios (Number of studies)
Lönnroth et al	2.94(8)
95% CI	1.89-4.59
Fok et al	1.4-2.6 (36)*
95% CI	1.1-1.9 2.1-3.3
Nava-Aguilera et al	2.27(16)
95% CI	1.69-3.06

Adapted from (Lönnroth et al., 2008; Fok, Numata, Schulzer, & FitzGerald, 2008; Nava-Aguilera, et al., 2009)

The Lönnroth analysis noted that control for confounding varied considerably across studies. There was virtually no control regarding the TB risk factors of malnutrition, diabetes and indoor air pollution. However they concluded that these factors would have to be of substantial magnitude to offset the fundamental finding of an association between excess alcohol use and TB (Lönnroth et al., 2008).

The Nava-Aguilera analysis looked at genotyping to try to determine what risk factors were associated with recent transmission of TB. It posited that unique genotypes were indicative of reactivation of TB while clustered genotypes were indicative of recent TB transmission. They concluded that alcohol posed a risk for recent transmission of TB. This finding did not exclude

alcohol from also playing a role in the reactivation of TB. The authors noted a high level of heterogeneity in the studies regarding TB and alcohol (Nava-Aguilera, et al., 2009). Another study found that patients who abuse substances were more contagious (e.g., smear positive) and remained contagious longer because treatment failure presumably extended periods of infectiousness. Increased transmission was consistent with the finding that patients who abuse substances were more likely to be involved in a localized genotype cluster, which can represent recent transmission (Oeltmann, Kammerer, Pevzner, & Moonan, 2009).

The Fok analysis looked at clustered cases (>=2) of TB and the risks associated with clustering of TB cases. It also separated its findings by areas of low incidence TB and high incidence TB. The higher association between alcohol use and TB was found in the low incidence TB areas (Fok, Numata, Schulzer, & FitzGerald, 2008).

Some work has been done with regard to the dose-response relationship showing a sharp diminishment in TB risk as alcohol consumption decreased. In the case of the Lönnroth analysis, alcohol consumption below 40 grams per day resulted in a risk ratio of 1.08 (95% CI 0.82-1.40). The results of a small but explicit study of the dose-response relationship are displayed in table 3.

Table 3: Dose-Response Relationship between alcohol intake and TB

Dose	Dose-Response relationship between alcohol intake and TB	
	Odds Ratios	Confidence Interval
10-25 ml/day	1.6	0.57-4.55
26-50 ml/day	2.38	0.89-6.44
51-75 ml/day	9.27	2.77-32.58
76-100 ml/day	8.5	1.93-40.54
>100 ml/day	35.55	6.41-260.70

Adapted from (Rehm, et al., 2009)

While there have been no documented studies regarding the effect of a reduction in alcohol consumption on TB incidence, there was the national campaign in Russia under Gorbachev from 1984-1987 (Rehm, et al., 2009). This campaign resulted in a decrease in per capita alcohol consumption from 14.2 ml/day to 10.7 ml/day (-24.6%) and a decrease in standardized TB mortality rates of 25% among men and 20% among women. While the data is ecological and other factors may have influenced the outcome, the results are striking.

Alcohol and Treatment of TB

Beyond the potential immunosuppressive effect of alcohol, changes in drug pharmacokinetics are another path which led to a worsened course of TB in heavy drinkers. Amongst heavy drinkers, significant decreases in the absorption of isoniazid and accelerated metabolism after oral administration were seen in studies of the pharmacokinetics of this drug in the treatment of TB co-morbid with alcohol dependence. The maximum concentration of the drug was effectively lowered and the half-life of the drug was shortened (Rehm, et al., 2010).

A recent Russian study showed that among patients with TB who interrupted the course of treatment, 47.7% were heavy drinkers. The odds ratio for an interruption of treatment was 3.8 for heavy drinkers compared to other patients. Other studies also indicated that heavy alcohol consumption disrupts seeking medical attention and adhering to the medication regimen to treat TB and leads to worse outcomes than abstinence. This supports the idea that a separate and presumably higher relative risk could be derived specific to the association between alcohol abuse and TB mortality (Rehm, et al., 2010).

PROGNOSIS

While global consumption of alcohol has been relatively flat in recent decades, regionally consumption has been declining in the developed countries of Western Europe and the US while it has been increasing in the less developed countries (WHO, 2004). This has potentially negative implications for TB globally as it is more highly endemic in the developing countries.

Alcohol consumption has been declining for decades in the US. The National Institute on Alcohol Abuse and Alcoholism reports that the per capita consumption of alcohol by Americans age 14 and older has dropped over time as shown in table 4.

Table 4. Trend in alcohol consumption in the US

Year	Yearly per capita consumption in gallons
2000	2.18
1990	2.43
1980	2.76

Adapted from (Hanson, 2009)

Alcohol consumption varies by race and ethnicity. Both current drinking (defined as consumption of 12 or more drinks in the past year) and heavy drinking are most prevalent among American Indians/Alaska Natives and Native Hawaiians and lowest among Asian Americans and Pacific Islanders.

Heterogeneity in drinking patterns is also found among different nationalities within specific ethnic groups. African-Americans whose ancestry is Caribbean consume less alcohol compared with African-Americans in general. Hispanic Americans of Central American, South American, or Caribbean ancestry consume less alcohol than Hispanics in general (including Hispanics of Mexican or Mexican American ancestries). Among Asians, Japanese Americans consume more alcohol than Asian Americans of other national origins. Heterogeneity in drinking patterns also varies by place of birth. For example, Asians and Pacific Islanders born in the US have lower alcohol abstention rates than those born elsewhere (Hanson, 2009).

Differences in alcohol consumption are also found among Native Americans. Those living on reservations drink less frequently than Native Americans living in off–reservation towns, but

reservation dwellers may engage in binge drinking (drinking five or more drinks per day) more frequently and consume more alcohol per occasion when they do drink.

Among adolescent minorities studied nationwide, African Americans show the lowest prevalence of lifetime, annual, monthly, daily, and heavy drinking, as well as the lowest frequency of being drunk. Hispanic adolescents have the highest annual prevalence of heavy drinking, followed by Whites. This subpopulation information can be used to target groups who are both at risk of alcohol abuse and TB.

Among all age and ethnic groups, men are more likely to drink than are women, and to consume large quantities in a single sitting. This is a pattern found throughout the world (Hanson, 2009).

HIV

Since 1990, TB infection rates have increased 4-fold in countries that are heavily affected by HIV, and TB is estimated to be the cause of death for as many as half of all persons with AIDS (CDC, 2008). As of 2005, the CDC estimated that 9% of all TB cases and nearly 16% of TB cases among persons aged 25 to 44 were occurring in HIV-infected persons. Because HIV infection so severely weakens the immune system, persons dually infected with HIV and TB, compared with persons not infected with HIV, are at very high risk for active TB disease, which may be contagious.

HIV first made its presence known in the US in the 1980's coinciding with a period of reduced attention and funding for TB control. These were two of the primary causes which led to an increase in the TB rate after decades of decline (CDC, 1999).

Biological Plausibility

TB and HIV are so closely related that they are referred to as co-epidemics or dual epidemics (Aliyu & Salihu, 2003). TB is an opportunistic infection which takes advantage of the weakened immune system generated by the progress of HIV. The patient is exposed both to the risk of a new TB infection as well as the reactivation of TB when infected with HIV. An analysis based on 7 cohort studies showed that the risk of TB disease for those infected with HIV rapidly rose as the CD4 cell count fell but the risk could be substantially reduced with the implementation of HAART. The results of that study are displayed in table 5 (Havlir, Getahun, Sanne, & Nunn, 2008).

Table 5. Relationship between CD4 Cell Count and Relative Risk of TB for HIV infected versus HIV uninfected -- Adapted from (Havlir, Getahun, Sanne, & Nunn, 2008)

Years after HIV Seroconversion	CD4 Cell Count	Relative Risk of TB for HIV infected versus HIV uninfected
0	650	1.0
2	580	2.3
4	480	3.0
6	330	3.7
8	180	4.6
Start ART at 10 years after seroconversion		
10	90	6.3
12	300	5.1
14	350	2.3
16	370	2.0

EPIDEMIOLOGICAL EVIDENCE

In a worldwide study performed on the available data linking HIV with TB, a strong positive relationship was established. While the majority of the cases emanated from sub-Saharan Africa, data were also collected for the US and other industrialized nations. An incidence rate ratio (IRR, TB incidence rate in HIV+ persons/TB incidence rate in HIV- persons) of 5.9 (with group averages ranging from 3.5 to 8.0) was found in developing countries (Corbett, et al., 2003). In the US, the IRR was estimated to be 60 by Corbett and colleagues (2003). While these numbers are somewhat dated being based on data from 1998, they are supported by the latest IRR numbers published by the WHO. The estimated IRR for countries with a high prevalence of HIV was 20.4 (95% confidence interval 18.7–22.3) and 27.6 (95% CI: 26.2–29) in settings with a low prevalence of HIV (WHO, 2009).

PROGNOSIS

There has been progress in the battle against the syndemic of TB and HIV. Knowledge of the hazard has led to increased levels of testing for HIV in those with TB and vice versa. Early and aggressive treatment of HIV with HAART has shown success in preventing the reactivation of latent TB and lessening the likelihood of initial TB infection. Regardless, HIV has continued to spread in developing countries and with the current protocols has transformed itself into a chronic condition. Numerically the situation is mixed. HIV incidence rates are declining in many areas of the world. Since 2001, the number of new infections in sub-Saharan Africa is approximately 15% lower, which is about 400,000 fewer infections in 2008 (UNAIDS, 2009). In East Asia, HIV incidence has declined by nearly 25% and in South and South East Asia by 10% in the same time period. In Eastern Europe, after a dramatic increase in new infections among injecting drug users, the epidemic has leveled off considerably. Data also show that at

approximately 33.4 million, there are more people living with HIV than ever before due to population growth and because people are living longer due to the beneficial effects of HAART (UNAIDS, 2009). With regard to TB, vigilance will be required to minimize the opportunities that it takes of this large and growing pool of HIV+ persons.

FOREIGN-BORN VERSUS US BORN

In 2009, 60.2% of the reported TB cases of known origin in the US were attributed to foreign-born residents (CDC, 2010). This percentage has steadily increased through the years from 29.8% in 1993. However, as shown in figure 1 the number of foreign-born TB cases has remained relatively constant throughout this time period despite large increases in the foreign-born population. Therefore the actual rate of TB/100,000 foreign-born persons has decreased from 34.0 in 1993 to 18.6 in 2009. This compares to a US-born TB rate of 1.7 in 2009.

The most recent decreases in the TB rate for the foreign-born population may be due in part to reductions in the rate of immigration in recent years and the possible return of migrants particularly to Mexico. As well, new technical instructions issued in 2007 regarding TB screening prior to immigration may have contributed to the decline. The instructions require culture of respiratory specimens in immigrants and refugees suspected of having pulmonary TB based on chest x-rays. Previously only smear microscopy, which is less sensitive, was required (CDC, 2010).

The rate difference between the US-born and foreign-born is largely attributable to the much higher rates of TB in the countries of origin. A study found that the US foreign-born population had lower rates of substance abuse (defined as any illicit drug use or alcohol abuse) and homelessness than the US-born population (Oeltmann, Kammerer, Pevzner, & Moonan, 2009).

Conventional contact tracing has been shown to be less effective amongst the foreign-born population.

In 2004, rates of TB disease among foreign-born persons residing in the US for more than 5 yr were over 30/100,000 among those from the Philippines, Vietnam, South Korea, and Ethiopia. These rates were higher than those in persons from Mexico and China who had been in the US for 1–5 yr (22.0/100,000 and 26.5/100,000, respectively) and 11–18 times higher than TB rates among U.S.-born persons (2.7/100,000). The authors suggested that targeted testing and LTBI treatment be carried out amongst foreign-born persons residing for more than five years in the US if the goal of TB elimination is to be achieved (Cain, et al., 2007).

Molecular epidemiology studies suggest that the majority of TB cases among foreign-born persons are due to activation of latent infection. In a study of the foreign-born population covering 2001-2006, the TB case rate was documented based on the individual's country of origin. The annual TB case rate/100,000 persons for foreign-born individuals who had been in the country less than 2 years was 75 while for those who had been in the country more than 2 years the rate was 16. The authors suggested that individuals from Vietnam and the Philippines be targeted for IPT to combat the disproportionately high case rates experienced by these groups (Cain, Benoit, Winston, & MacKenzie, 2008). In 2009, four countries accounted for approximately half (50.1%) of foreign-born TB cases: Mexico (1,574), the Philippines (799), India (523), and Vietnam (514) (CDC, 2010).

There are three broad approaches which are available to combat the high level of TB in foreign-born individuals in the US (Cain, Benoit, Winston, & MacKenzie, 2008). One is to provide IPT to the foreign-born found to have LTBI. This typically involves a nine month regimen of

isoniazid and regular doctor check-ups to ensure no injurious side effects such as liver damage are occurring. A second approach is to expand and strengthen the screening requirements of individuals coming to the US. This could involve broadening the pool of individuals, currently limited to immigrants and refugees, who must undergo screening and/or requiring individuals with LTBI to complete IPT as an entry condition. The third approach would be to assist in reducing TB at the source, working with countries that are the source of a high percentage of those who end up with active TB in the US to lower the prevalence of TB in their home countries. Cain and colleagues examined these 3 options and concluded that targeted implementation of all these options would be advisable to provide the greatest impact and more data to potentially justify broadening these interventions (2008).

A study in New York City of US citizens as well as documented and undocumented immigrants with TB found that the undocumented immigrants had a longer duration of symptoms prior to seeking medical care (8 vs. 4 weeks, $p = 0.023$) and presented with a significantly greater frequency of cough ($p= 0.02$) and hemoptysis ($p=0.012$) (Achkar, Sherpa, Cohen, & Holzman, 2008). The authors concluded that reducing barriers to health services for undocumented foreign-born persons to enhance TB control deserved additional study.

Figure one presents national TB surveillance data from the CDC which shows that while the rate of TB cases fell for foreign-born persons by 45.3% from 1993 to 2009 the descent was much steeper for the US-born population with a 77% drop over the same time period. This is largely explained by the continuing inflow of immigrants over this time period who hails from countries with substantially higher TB rates.

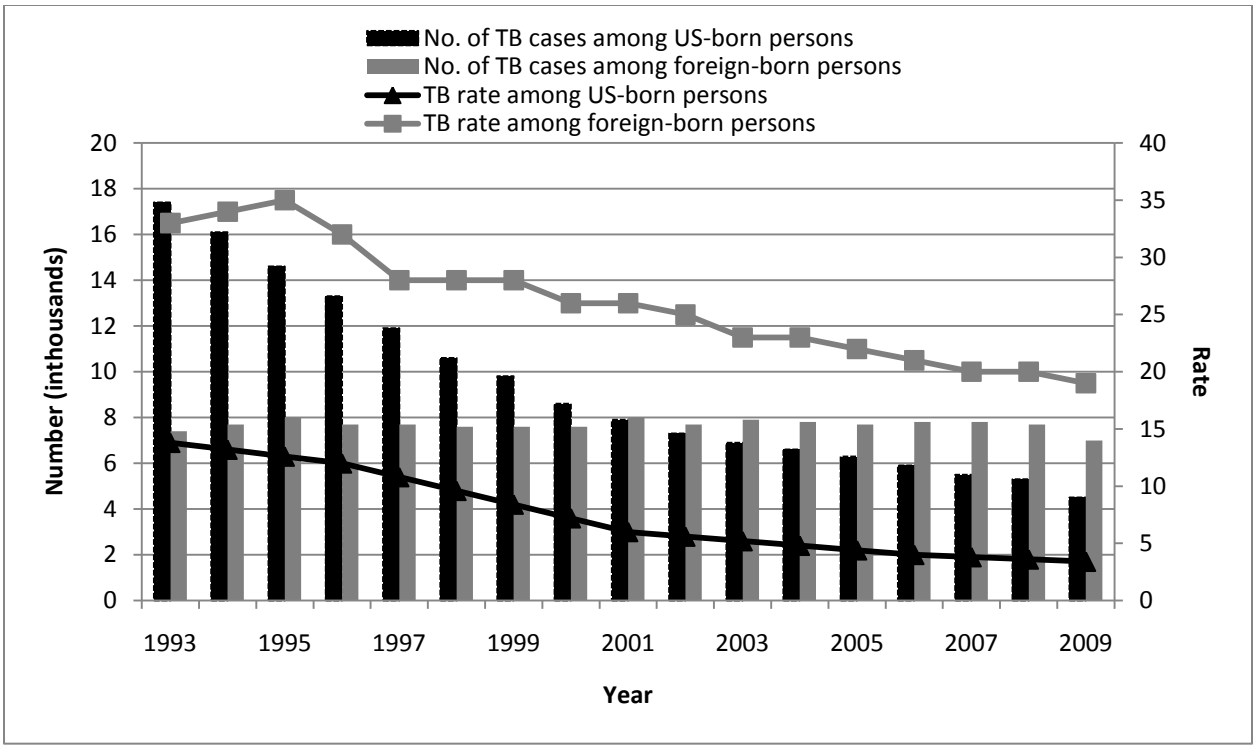

Figure 1. Number in thousands and rate/100,000 of TB cases in US-born versus foreign-born in the US from 1993 to 2009 Adapted from (CDC, 2010; CDC, 2010)

POVERTY

In the US, poverty can manifest itself in several ways related to TB. Overcrowded housing conditions create the environment in which TB can be more easily transmitted between individuals. Malnutrition can impair the ability of the immune system to defend against M. TB bacillus. Homelessness is an aspect of poverty that can aid TB transmission through overcrowded homeless shelters and/or a compromised immune system due to exposure to the elements. Incarceration is a condition disproportionately associated with the poor. Prisons have typically been a fertile environment for the spread of TB.

Epidemiological Evidence of an association

In a study published in 2008 comparisons of TB rates between the lower income quartiles (measured by the percent below the poverty line) by zip code versus the upper income quartiles were made in Chicago, Illinois, Fulton County, Georgia and the state of South Carolina (Lopez de Fede, Stewart, Harris, & Mayfield-Smith, 2008). The results presented in Table 6 show a strong association between poverty and TB.

Geographic Location	Rate of TB, Low Income Zip Code Areas	Rate of TB, High Income Zip Code Areas
Chicago, Illinois	22.2	4.7
Fulton County, Georgia	42.7	1.8
State of South Carolina	12.9	2.9

Table 6. TB rates per 100,000 population by low income and high income zip codes in selected regions Adapted from (Lopez de Fede et al., 2008)

The study looked separately at Whites and African-Americans as well as at all races. While the majority of those with TB were African-American males, the strong association between TB and poverty also held for Whites alone.

While Appalachia represents one of the poorer regions of the US, the TB rate for persons living in Appalachian counties was 2.4 per 100,000 in 2005 compared to 4.9 per 100,000 in non-Appalachian counties. This result may reflect that Appalachia is populated primarily by US born non-Hispanic Whites (88%) (Wallace, Armstrong, Pratt, Kammerer, & Iademarco, 2008). The historical difference in poverty rates between Appalachia and the rest of the country had narrowed from 4.1% in 1969 to 1.3% in 1999. As well Appalachia represents a broad region and its extremes of poverty are concentrated in central Appalachia.

Homelessness generally shows a strong association with TB. In 2004 the TB rate found among residents of a NYC homeless shelter was 171/100,000 compared to 4.8/100,000 for the overall US population in the same year. While no TB cases were identified at this homeless shelter from January 2005 to June 2006, a 31% rate of LTBI indicated that the threat of TB remained high (McAdam, Bucher, Brickner, Vincent, & Lascher, 2008).

RACE AND ETHNICITY

A study was conducted in London evaluating 202 twins of patients with TB. A concordance for TB infection was found to be more than twice as high in monozygotic twins compared to dizygotic twins (Coberly & Chaisson, 2007). This data was later reviewed by Comstock using multiple regression to control for the effect of other variables with the conclusion that inherited susceptibility is a risk factor for TB (Comstock, 1978).

While it has been asserted that there is some genetic connection between race and TB, substantial evidence has also been presented that this is simply a confounding resulting from socioeconomic status differences (Cantwell, McKenna, McCray, & Onorato, 1998; Stead, Senner, Reddick, & Lofgren, 1990). Regardless of any genetic component, race and ethnicity are manifestations of TB as a social disease. It is a disease which is perpetuated in communities plagued by overcrowding and poor access to medical care. It reflects the endemicity of TB in the countries of origin of many of the foreign-born. Predominantly White Western Europe was once plagued by endemic TB. Stockholm, Sweden, in the early 18th century suffered from a TB death rate worse than sub-Saharan Africa today (Lönnroth, Jaramillo, Williams, Dye, & Raviglione, 2009; Kaiser Family Foundation, 2010). At the peak of the epidemic in Europe, TB death rates were close to 1% per year in some urban areas, several times higher than the current rates in countries

with high HIV prevalence. The death rates in Stockholm and London were estimated to have exceeded 600/100,000 persons/year from 1750-1800 and beyond. Natural selection does not appear to have played a substantial role in the dramatic decreases in TB rates following the widespread epidemics in Western Europe (Lipsitch & Sousa, 2002). Rather the general improvement in standards of living such as the lessening of overcrowding and poverty through economic growth and social reform were attributed with decreasing the TB rate (Lönnroth et al., 2009).

Epidemiological Evidence of an association

The latest annual report from the CDC showed the TB rates in the US among Hispanics and African-Americans were approximately eight times higher than among non-Hispanic Whites, and rates among Asians were nearly 26 times higher (CDC, 2010).

In a study comparing Asian/Pacific Islanders (API) to non-Hispanic Whites, it was noted that APIs have had the highest case rates in the US for more than a decade. Those born in the Philippines and Vietnam have a higher proportion of TB drug resistance than non-Hispanic Whites (CDC, 2010).

Table 7. Trends in TB case rates between Asian/Pacific Islanders and Non-Hispanic Whites, 1993-2006, adapted from (Manangan, et al., 2009)

Race of US residents	TB Case Rates/100,000		Percent Decline
	1993	2006	1993-2006
Asian/Pacific Islander	44.1	25.2	42.9%
NH White	3.6	1.2	66.6%
All races	9.7	4.6	52.6%

During the study period, 1993-2006, API TB cases consisted of 94.1% foreign-born individuals while 11.9% of non-Hispanic Whites TB cases were foreign-born (Manangan, et al., 2009).

A study in Houston, Texas of TB cases among US-born African-Americans versus US-born non-Hispanic Whites found a large degree of clustering, 82% and 77%, respectively. This indicated that the primary source of TB was ongoing transmission within the community. US-born African-Americans were more likely than US-born Whites to be younger, unmarried, and unemployed; have less education; reside in the inner city, earn less income; use public transportation; have renal and extrapulmonary disease; be HIV seropositive, M. TB culture–positive, and part of a cluster; and have drug-resistant M. TB. A 28% rate of HIV co-infection for US-born African-Americans and 20% for US-born Whites ($p<0.001$) was found. Rates of HIV co-infection were markedly lower for Hispanics and Asians (9.1% and 1.7%, respectively) (Serpa, Teeter, Musser, & Graviss, 2009).

Tuberculosis mortality in 1925 was 87/100,000 among the general population, 603/100,000 among Indians overall, and 1510/100,000 among Arizona Indians. Poverty, malnutrition and

overcrowded living conditions compounded by cultural issues such as alcohol abuse and smoking had led to this disparity (Jones, 2006). By 2008, the CDC had reported that the American Indian TB case rate had fallen to 6.0/100,000. This was 5.5 times the rate of non-Hispanic Whites (CDC, September 2009).

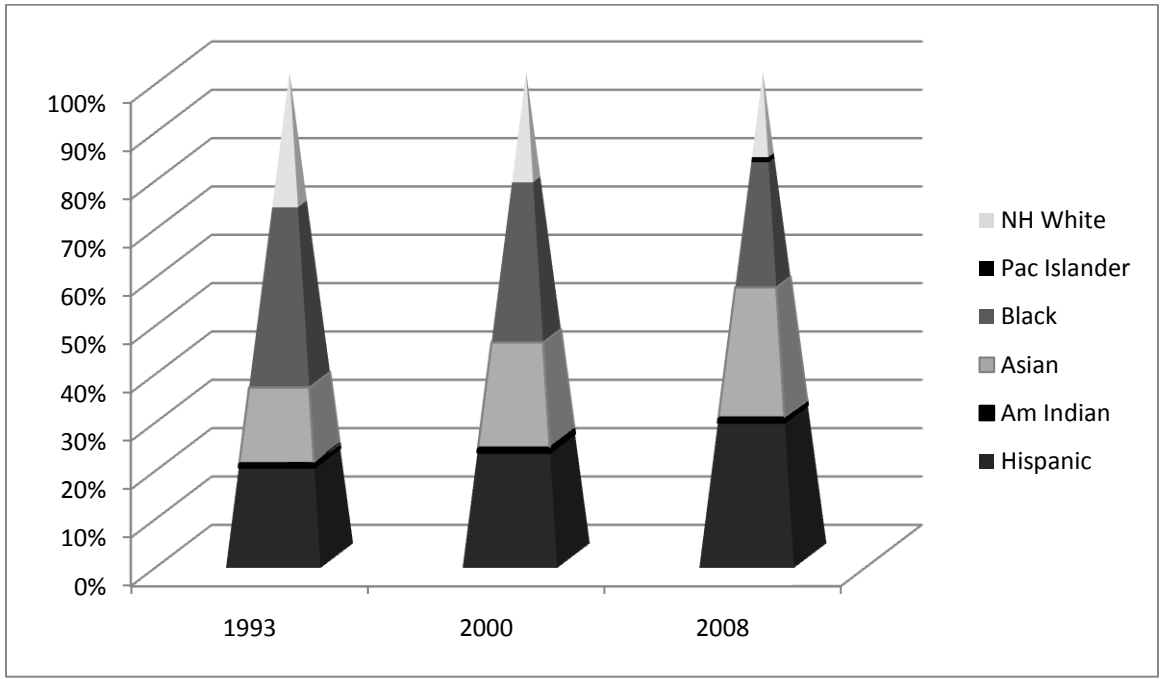

Figure 2. TB percentages by race/ethnicity, 1993-2008, adapted from (CDC, September 2009)

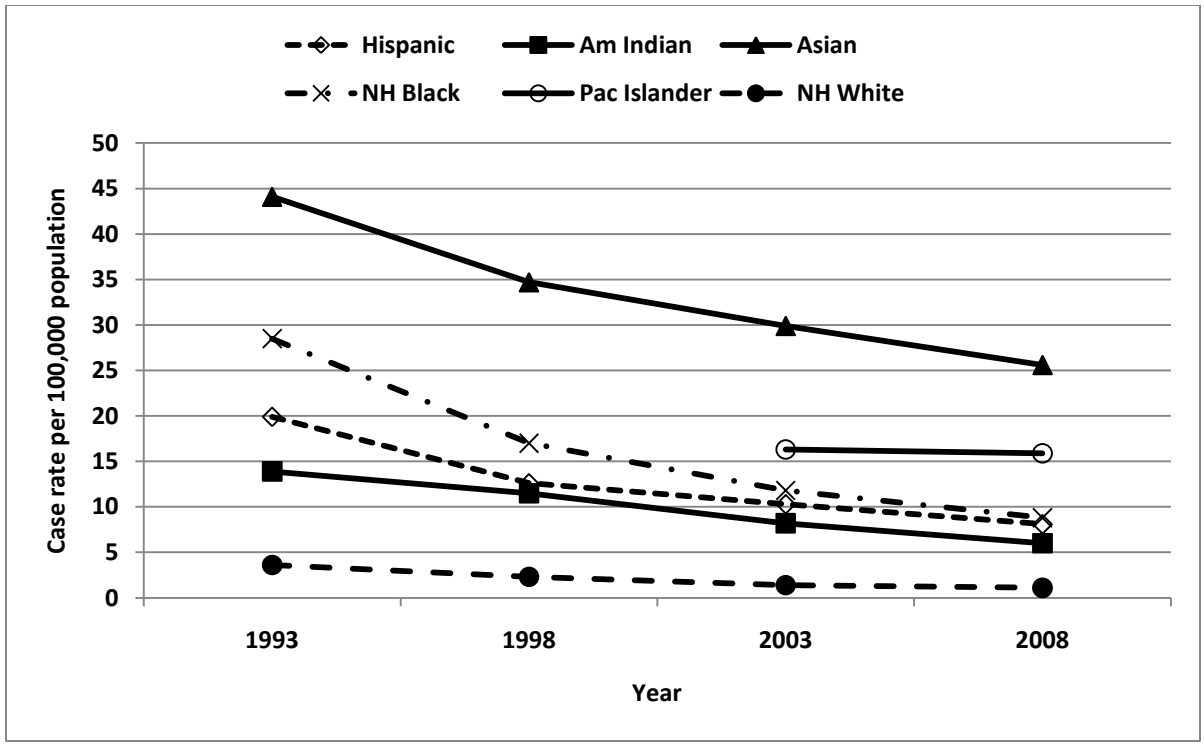

Figure 3. TB case rates per 100,000 by race/ethnicity, 1993-2008, adapted from (Surveillance Team, Division of Tuberculosis Elimination, CDC, 2009)

The racial and ethnic disparities with regard to TB represent a surrogate measure for the underlying risk factors for TB. While not viewed as an inherent cause of TB, this marker can be useful for programmatic purposes in the effort to eliminate TB.

CHAPTER III

METHODS

The primary objective of this study was to examine the correlation of sociodemographic, behavioral, and health risks of TB at the state level in the US to seek insights regarding the globally known TB risk factors with regard specifically to the US. The variables examined were AIDS diagnosis rates, diabetes death rates, rates of smoking, rates of alcohol abuse, percentage of the population which is foreign-born versus US born, race/ethnicity (percentage which is non-Hispanic White) and poverty (as expressed by per capita income as well as GINI). The specific research questions were:

Is there a correlation between the frequency of known TB risk factors and TB rates in each state and DC?

Can a significant predictive model be derived for TB rates for the individual states based on the risk factor data by state?

What intervention insights can be gleaned from an ecological study of TB rates versus TB risk factors at the state level that are unique to the US population?

DATA SOURCES

TB data (case reports by age groups, race / ethnicity, sex, vital status, year reported, state, metropolitan area, several patient risk factors, directly observed therapy, disease verification criteria and multi-drug resistant TB) were publicly available from the CDC's Online Tuberculosis Information System (OTIS) for 1993-2008. Behavioral and health data were obtained from the National Center of Health Statistics (NCHS)—Behavioral Risk Factor

Surveillance System (BRFSS). Demographic and socioeconomic data were retrieved from the US Census Bureau. The analysis examined 2008 data from all sources when available.

OTIS contains information on verified TB cases reported to the CDC by state health departments, the District of Columbia and Puerto Rico from 1993 through 2008. These data were extracted from the CDC national TB surveillance system. The CDC updates this database annually and includes data for 25 variables which users can access to produce cross-tabulations with multi-level stratification. Data are available at three levels of geographic detail: national, state and Metropolitan Statistical Areas (MSAs). This system was utilized to extract TB rates by state in 2008 (CDC, 2010).

The NCHS BRFSS is a state-based system of health surveys that collects information on health risk behaviors, preventive health practices, and health care access primarily related to chronic disease and injury. The BRFSS is an important source of timely, accurate data on health-related behaviors.

BRFSS was established in 1984 by the CDC; currently data are collected monthly in all 50 states, DC, Puerto Rico, the U.S. Virgin Islands, and Guam. The BRFSS utilizes the largest telephone health survey in the world to interview more than 350,000 adults each year. This database serves a critical role at the state level providing data to support health-related legislative efforts. The states also use BRFSS data to identify emerging health problems, establish and track health objectives, and develop and evaluate public health policies and programs (CDC, 2008).

The US Census Bureau conducts the American Community Survey (ACS) every year to collect data on social and economic issues. More than $400 billion in federal and state funds are distributed each year in part based on the information generated from this survey.

The topics addressed by the survey include:

- Age
- Income and benefits
- Disabilities
- Sex
- Health insurance
- Where you work and how you get there
- Race
- Education
- Where you live and how much you pay for some essentials
- Family and relationships
- Veteran status

The information collected is combined into statistics that are used to help justify expenditures on a broad range of initiatives from school lunch programs to new hospitals (US Census Bureau, 2010).

Table 8. List of variables with respective sources

Variable (All by State)	**Year**	**Source**
TB rate	2008	OTIS
AIDS diagnoses rates	2008	HIV Surveillance Report
Diabetes death rate	2008	BRFSS
Adult Smoking Rate	2008	BRFSS
Heavy Alcohol Use Rate	2008	BRFSS
Percentage Foreign-Born	2008	US Census Bureau/ACS
Per Capita Income	2008	US Census Bureau/ACS
GINI	2006	US Census Bureau/ACS
Percentage Non-Hispanic White	2008	US Census Bureau/ACS
Population	2008	US Census Bureau/ACS

Heavy drinkers are defined as adult men having more than two drinks per day and adult women having more than one drink per day.

The HIV Surveillance Report is located at:

http://www.cdc.gov/hiv/surveillance/resources/reports/2008report/table20.htm

GINI by state in 2006 comes from the American Community Survey (Webster & Bishaw, 2007).

STUDY POPULATION

The study population was the US population including the 50 states and DC. All ages, genders, and race/ethnicities were included.

STATISTICAL ANALYSES

Data were retrieved from CDC OTIS, CDC BRFSS, CDC HIV Surveillance Report and the US Census Bureau. The data was entered and merged in Microsoft Excel, and SPSS (version 18) was used for analysis. Data analyses were conducted in the following categories:

1) Scatterplots of individual TB risk factors versus TB rates for the 50 states and DC with simple linear regression. R^2 values were generated to determine the strength of the correlation. DC represents a unique environment as it is 100% urban and experiencing extremes of many of the risk factors. In the AIDS diagnosis rate scatterplot, the results were displayed with and without DC in order to more clearly display the results of the 50 states.
2) An analysis of the bivariate correlation between each risk factor and the TB rate by state was measured using Pearson's correlation and reported with p values as well as variable means and standard deviations.
3) Multiple linear regression to determine which predictor values were significant in a model of TB rates by state in the US. Variables were examined using backward elimination and forward selection approaches. The probability of F for entry was 0.05 and for removal was 0.10. The values were examined for collinearity using VIF measures.

CHAPTER IV

RESULTS

The principal purpose of this study was to examine known TB risk factors individually to see what correlation, if any, existed with TB disease rates across the US. Additionally multiple regression of the seven risk factors chosen for study were to be used as the basis for a predictive model for TB disease rates across the US.

SIMPLE REGRESSION OF RISK FACTORS

Below are the results of the single regression analyses for the following risk factors versus TB disease rates:

1) AIDS Diagnosis Rates (without and with DC)
2) Diabetes Death Rates
3) Percent of Adults who smoke
4) Percent of heavy drinkers
5) Percent of the population which is foreign-born
6) Poverty – Per capita income
7) Poverty – GINI
8) Percent of the population which is Non-Hispanic White

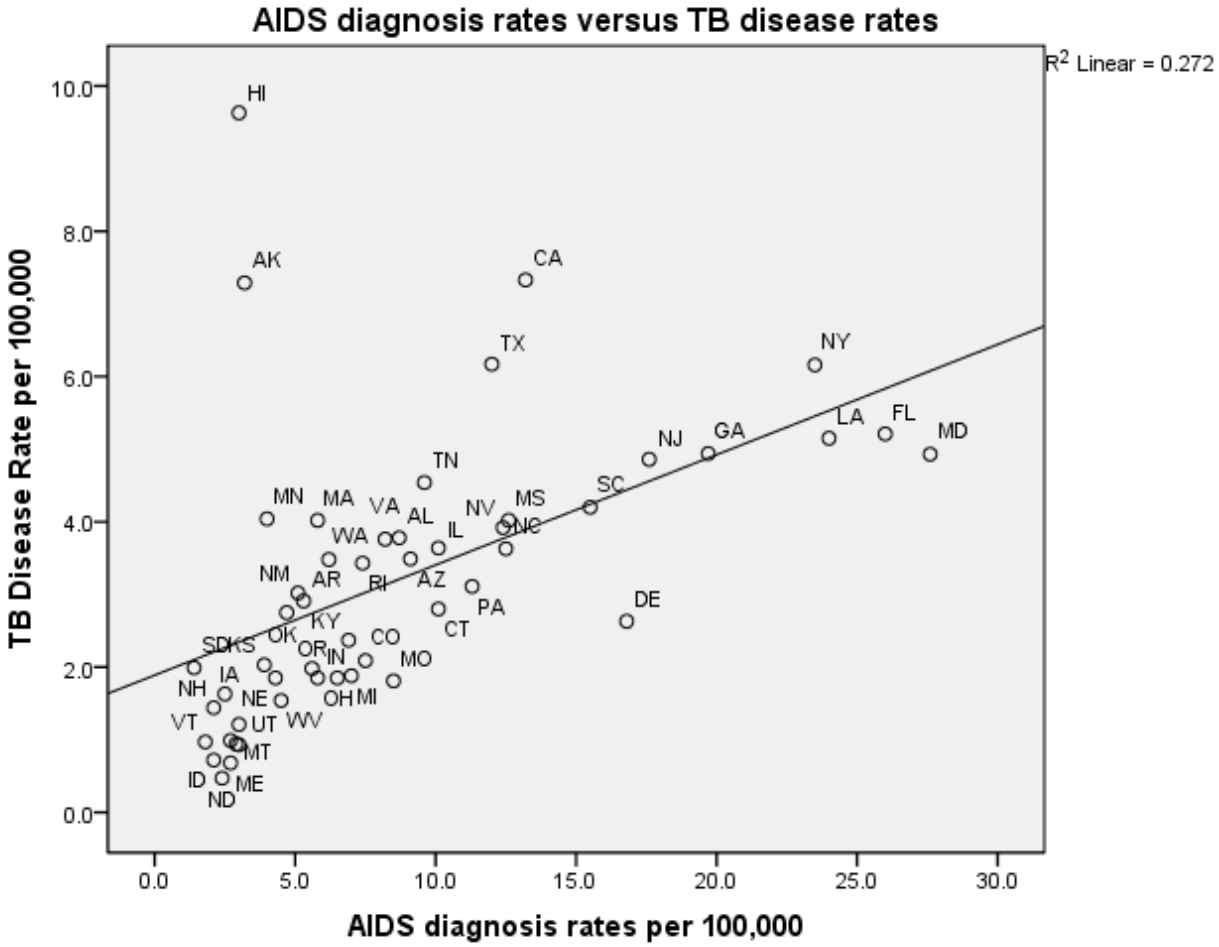

Figure 4. Simple regression of AIDS diagnosis rates per 100,000 versus TB disease rates per 100,000 by state – DC not included

This scatterplot show the AIDS diagnosis rates/100,000 versus TB disease rates/100,000 without the inclusion of DC in order to more clearly show the relationship among the 50 states. An analysis using Pearson's correlation coefficient indicated that there is a significant relationship between the AIDS diagnosis rate by state and the TB rate by state, $r(48) = 0.521$, $p<0.001$. For these data, the mean (SD) for AIDS diagnosis rate was 8.65 (6.67) and for TB rate was 3.20 (1.94).

The same analysis is repeated below with DC included.

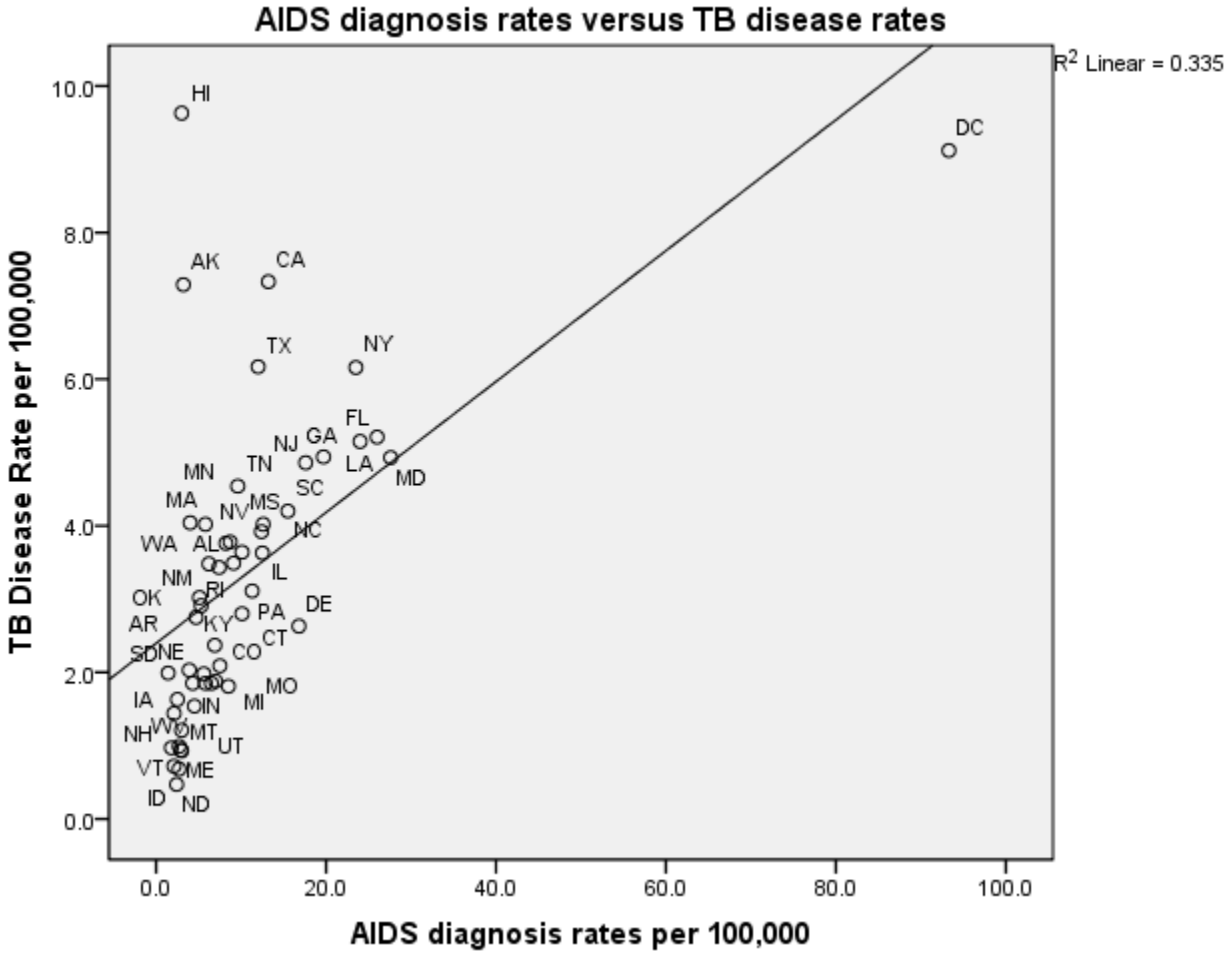

Figure 5. Simple regression of AIDS diagnosis rates per 100,000 versus TB disease rates per 100,000 by state

The scatterplot shows a positive relationship between the AIDS diagnosis rate by state and the TB disease rate by state. An analysis using Pearson's correlation coefficient indicated that there is a significant relationship between the AIDS diagnosis rate by state and the TB rate by state, $r(49) = 0.579$, $p<0.001$. For these data, the mean (SD) for AIDS diagnosis rate was 10.31 (13.57) and for TB rate was 3.32 (2.09).

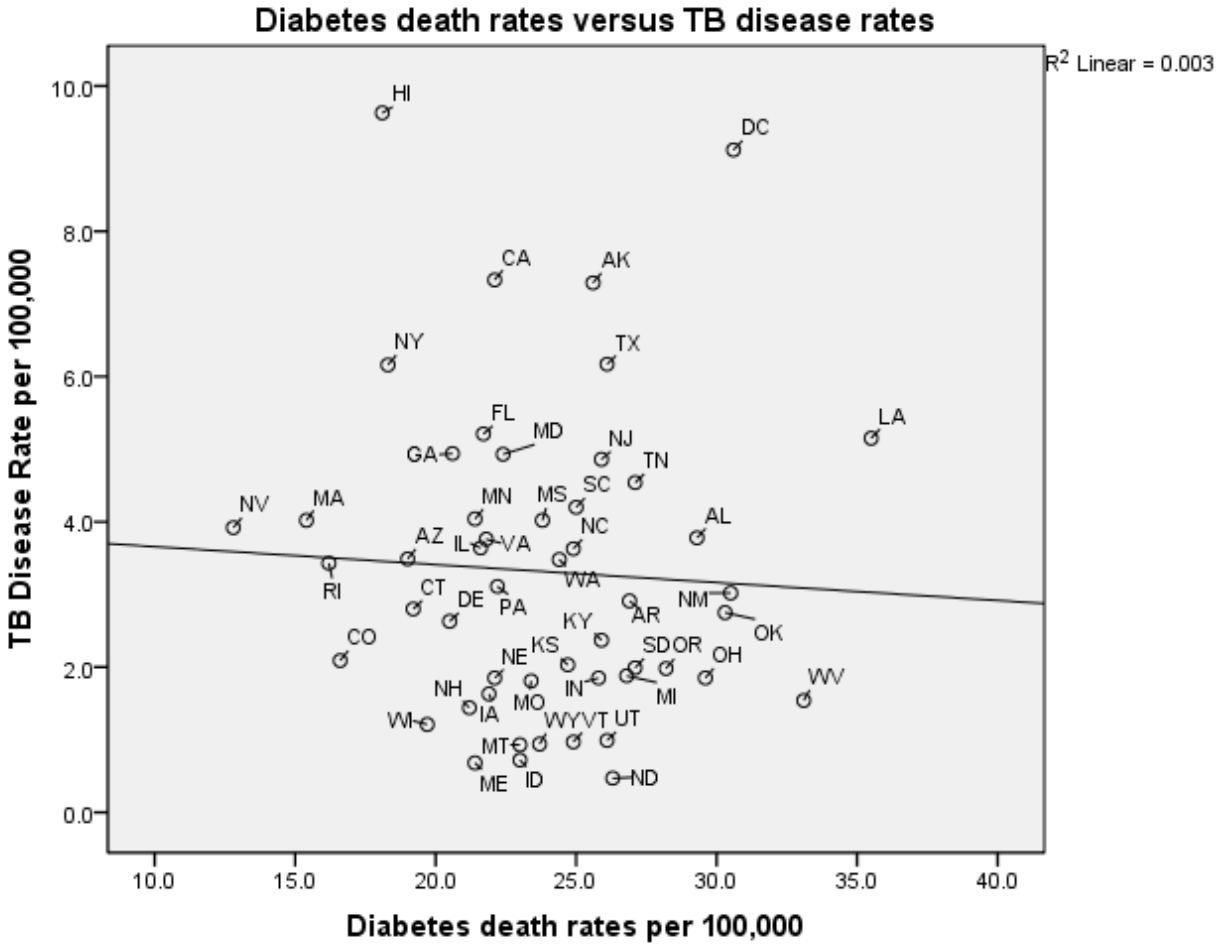

Figure 6. Simple regression of diabetes death rates per 100,000 versus TB disease rates per 100,000 by state

This scatterplot indicates that there is virtually no correlation between the number of diabetes deaths per 100,000 population and the TB rate. An analysis using Pearson's correlation coefficient indicated that there is not a significant relationship between the diabetes death rate by state and the TB rate by state, $r(49) = -0.053$, $p=0.71$. For these data, the mean (SD) for diabetes death rate was 23.80 (4.50) and for TB rate was 3.32 (2.09).

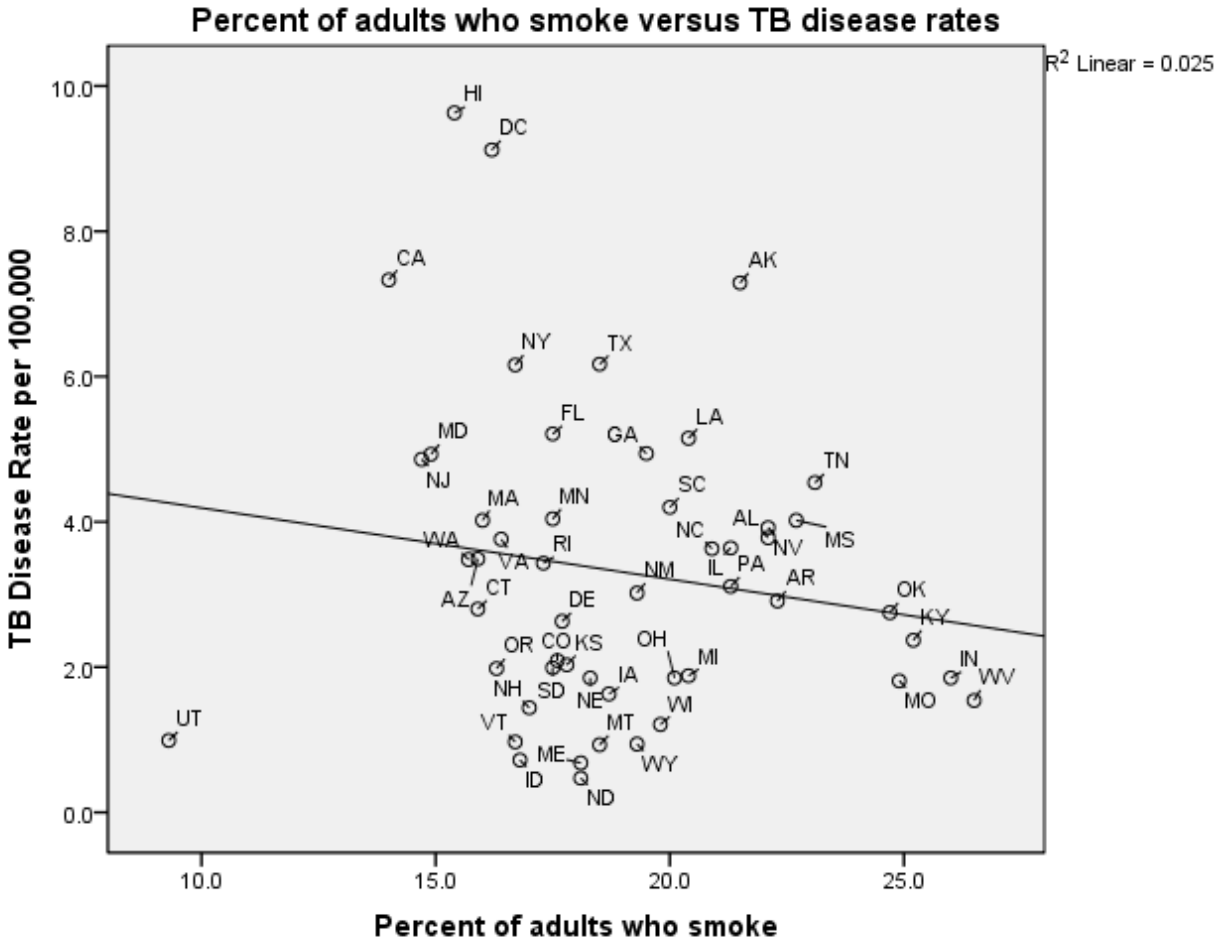

Figure 7. Simple regression of percent of adults who smoke versus TB disease rates per 100,000 by state

The scatterplot shows virtually no correlation between the rate of smoking in a given state and its TB rate. Smoking rates are highest in states with below average TB rates. An analysis using Pearson's correlation coefficient indicated that there is not a significant relationship between the percent of adults who smoke by state and the TB rate by state, $r(49) = -0.157$, $p=0.27$. For these data, the mean (SD) for percent of adults who smoke was 18.91 (3.36) and for TB rate was 3.32 (2.09).

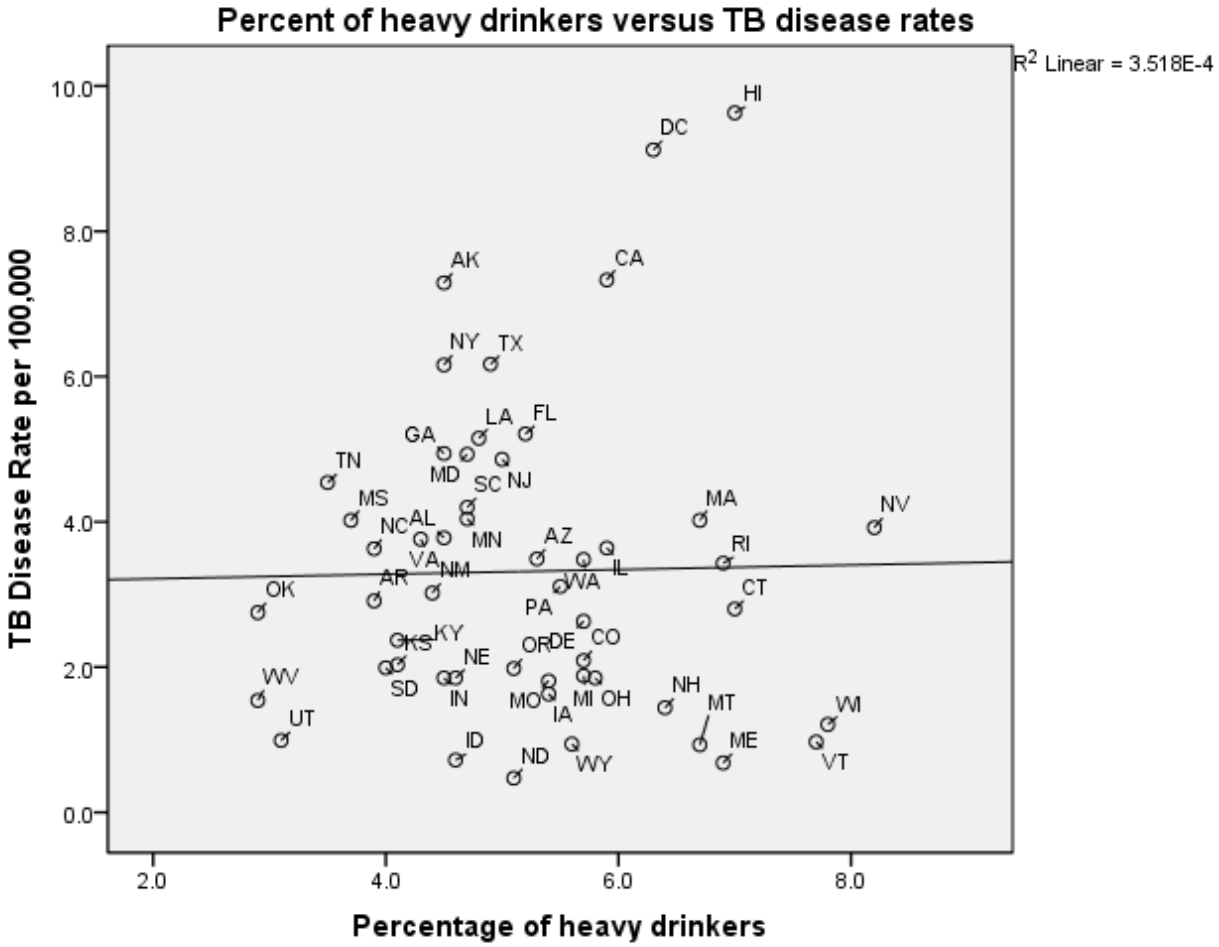

Figure 8. Simple regression of percentage of heavy drinkers versus TB disease rates per 100,000 by state

There is zero correlation exhibited between the rate of excess alcohol consumption by state and the TB rate by state. An analysis using Pearson's correlation coefficient indicated that there is not a significant relationship between the percent of heavy drinkers by state and the TB rate by state, $r(49) = 0.019$, $p=0.90$. For these data, the mean (SD) for percent of heavy drinkers was 7.27 (5.47) and for TB rate was 3.32 (2.09).

Heavy drinking rates appear disproportionately in the northernmost states which have low rates of immigration, high rates of Non-Hispanic White populations and low TB rates. Nevada with its unique gaming and entertainment culture has the highest percentage of heavy drinkers.

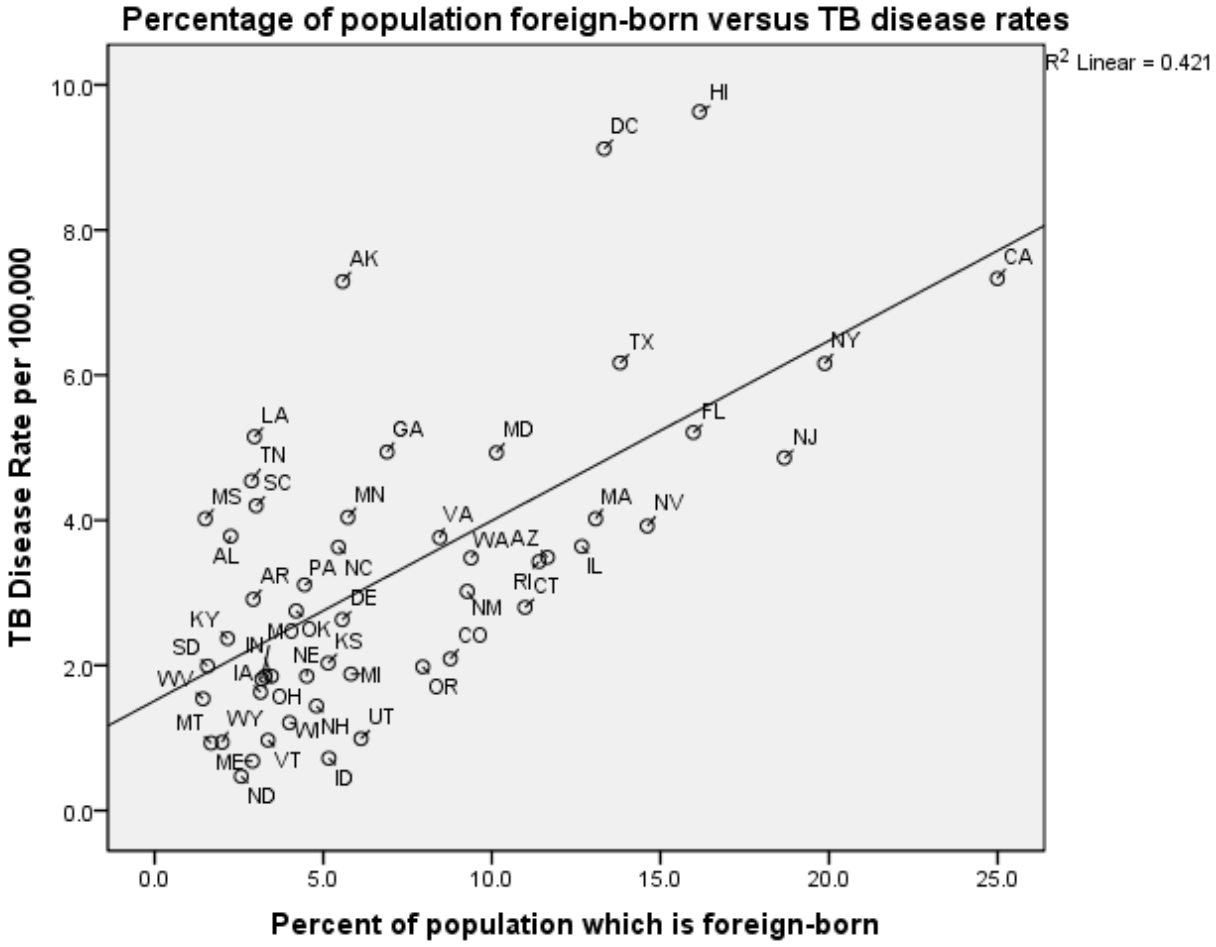

Figure 9. Simple regression of percentage of the population which is foreign-born versus TB disease rates per 100,000 by state

The scatterplot shows substantial correlation between the percentage of a state's population which is foreign-born versus the TB rate for the state. The greatest outliers are Hawaii, DC and Alaska, all of which exhibit TB rates higher than expected based solely on the percentage of their foreign-born population. The southeastern states with the exception of Florida are clustered

above the correlation line. States along the Canadian border with the exception of Minnesota fall below the correlation line.

An analysis using Pearson's correlation coefficient indicated that there is a significant relationship between the percent of the population which is foreign-born by state and the TB rate by state, $r(49) = 0.649$, $p<0.001$. For these data, the mean (SD) for percent of the population that was foreign-born was 5.21 (1.24) and for TB rate was 3.32 (2.09).

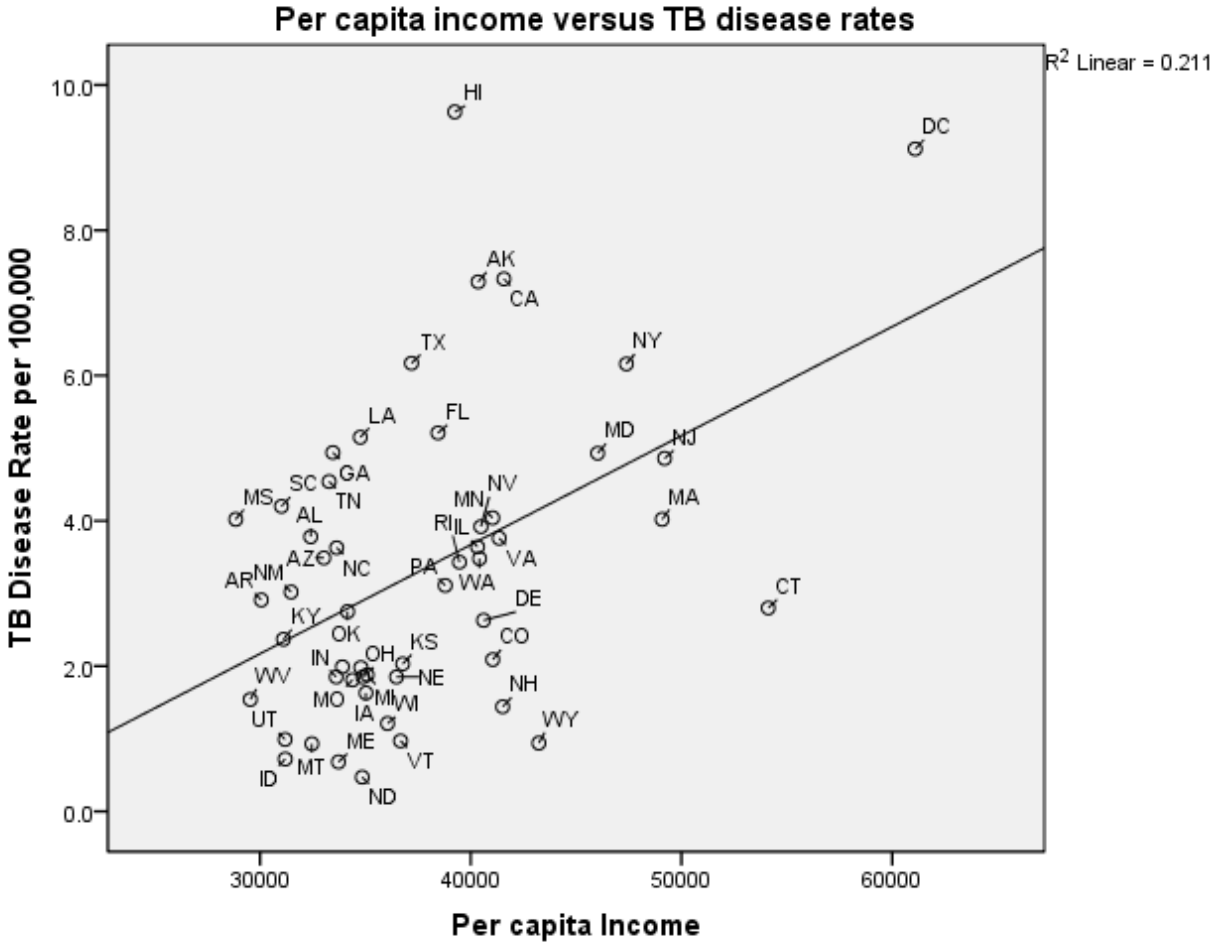

Figure 10. Simple regression of average per capita income versus TB disease rates per 100,000 by state

The scatter plot shows a positive relationship between per capita income and TB disease rates. An analysis using Pearson's correlation coefficient indicated that there is a significant relationship between per capita income by state and the TB rate by state, r(49) = 0.46, p=0.001. For these data, the mean (SD) for per capita income was $37,642 ($6406) and for TB rate was 3.32 (2.09).

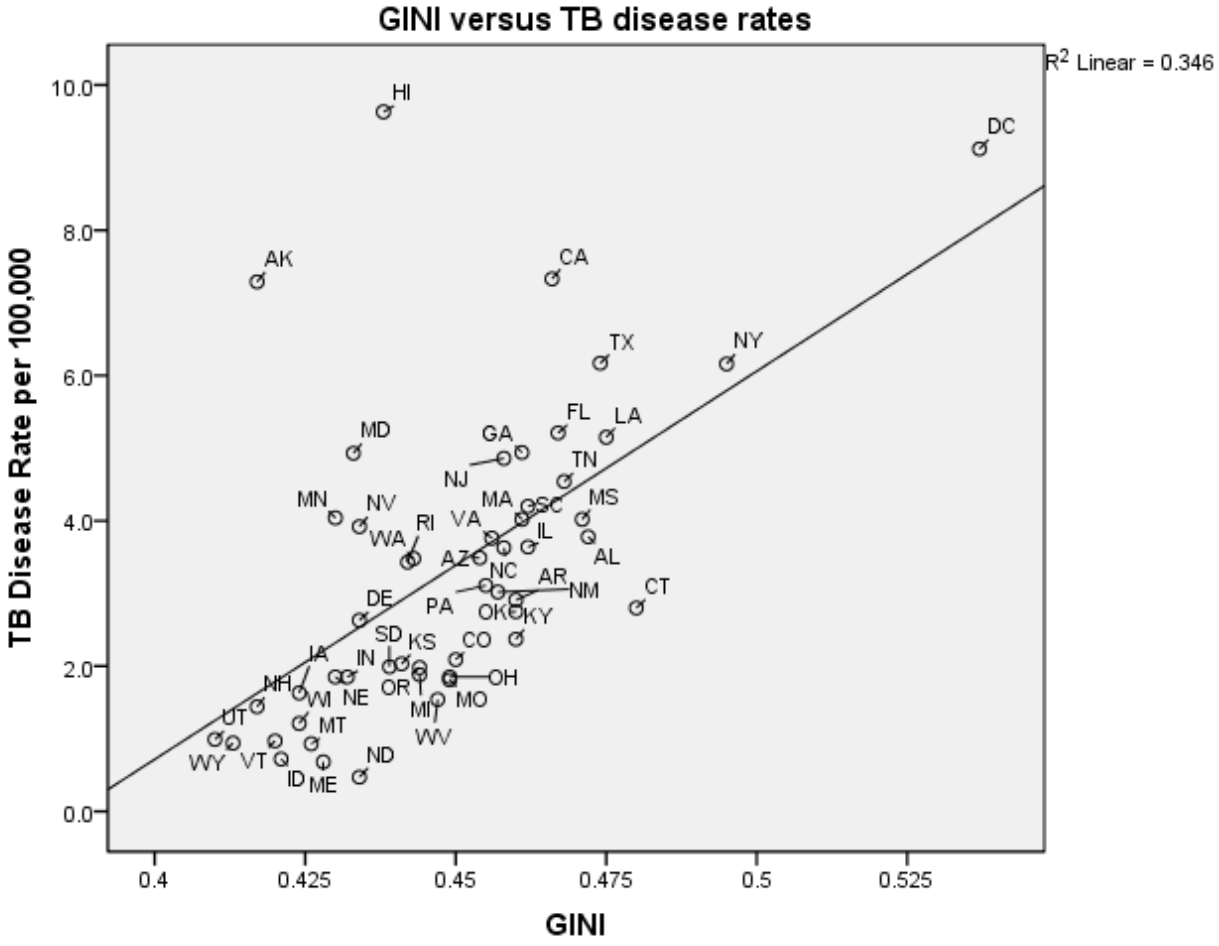

Figure 11. Simple regression of GINI versus TB disease rates per 100,000 by state

The scatterplot shows a positive relationship between GINI and TB disease rates. An analysis using Pearson's correlation coefficient indicated that there is a significant relationship between the GINI by state and the TB rate by state, $r(49) = 0.588$, $p<0.001$. For these data, the mean (SD) for the GINI was 0.449 (0.023) and for TB rate was 3.32 (2.09).

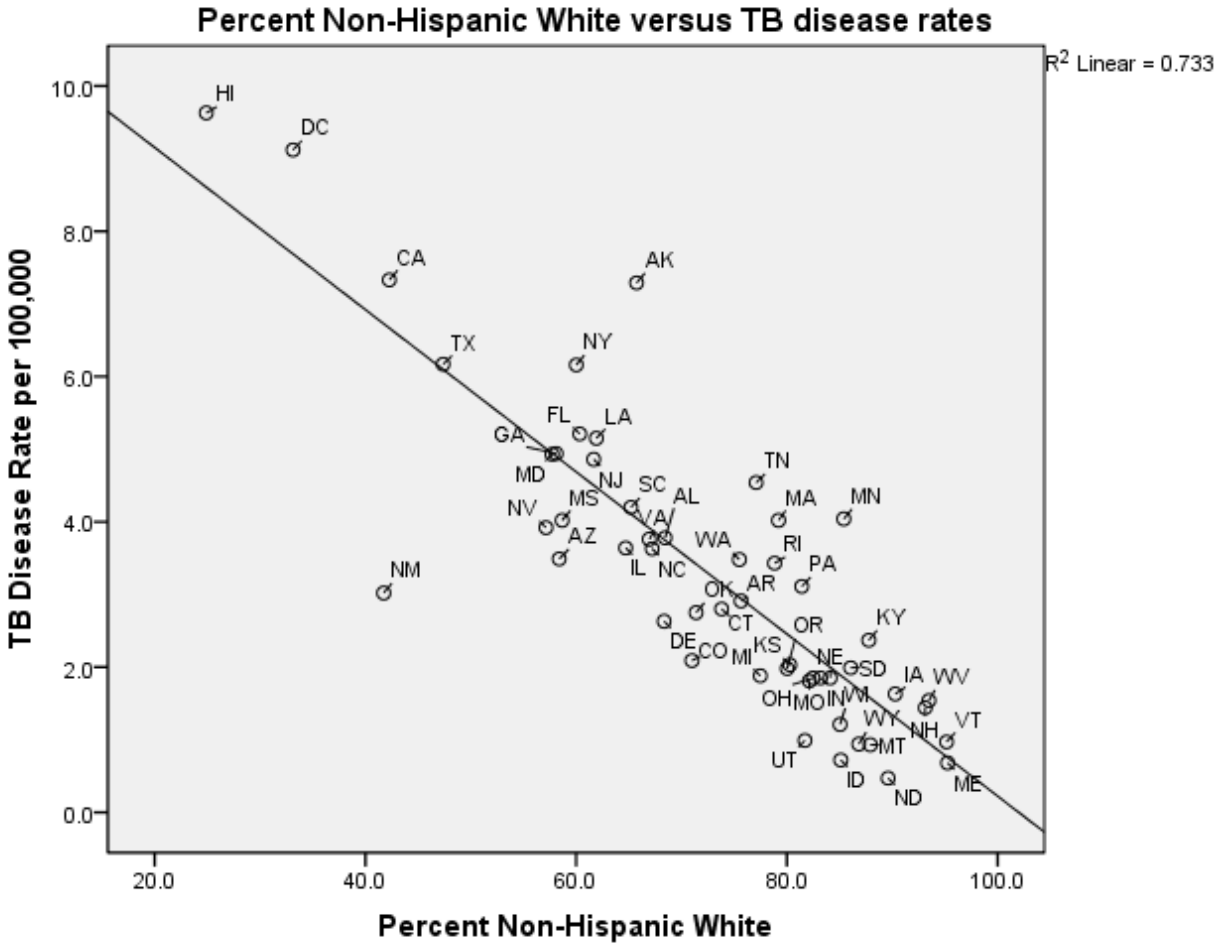

Figure 12. Simple regression of percent of the population which is non-Hispanic White versus TB disease rates per 100,000 by state

The scatterplot shows a very strong inverse relationship between the percentage of the population which was non-Hispanic White versus TB disease rates.

An analysis using Pearson's correlation coefficient indicated that there is a significant relationship between the percentage Non-Hispanic White by state and the TB rate by state, $r(49) = -0.856$ $p<0.001$. For these data, the mean (SD) for the percentage Non-Hispanic White was 72.3 (16.0) and for TB rate was 3.32 (2.09).

Alaska and New Mexico are the outliers.

MODEL FOR TB AS A FUNCTION OF RISK FACTORS

The dominating variable in forecasting the TB rate by state was the percent of the population which was Non-Hispanic White. The forward selection process chose this as the sole variable ($p<0.001$) to include in the model using the criteria of $p<0.05$ for the t-test. The backward elimination process which had a criteria of $p<0.10$ for the t-test additionally included the AIDS diagnosis rate/100,000 ($p=.067$). The percent of the population which is foreign-born ($p=0.154$) was included in the model because this group is disproportionately represented in the TB rate.

These variables provided the following model:

State TB rate/100,000 = 9.012 - 0.088 %NHW + 0.025 AIDS Diagnosis Rate/100,000 + 0.053 %Foreign-Born

The calculation of residuals showed one outlier, Alaska, greater than 3 standard deviations from the model. Another outlier, New Mexico, was just under 3 standard deviations from the mean.

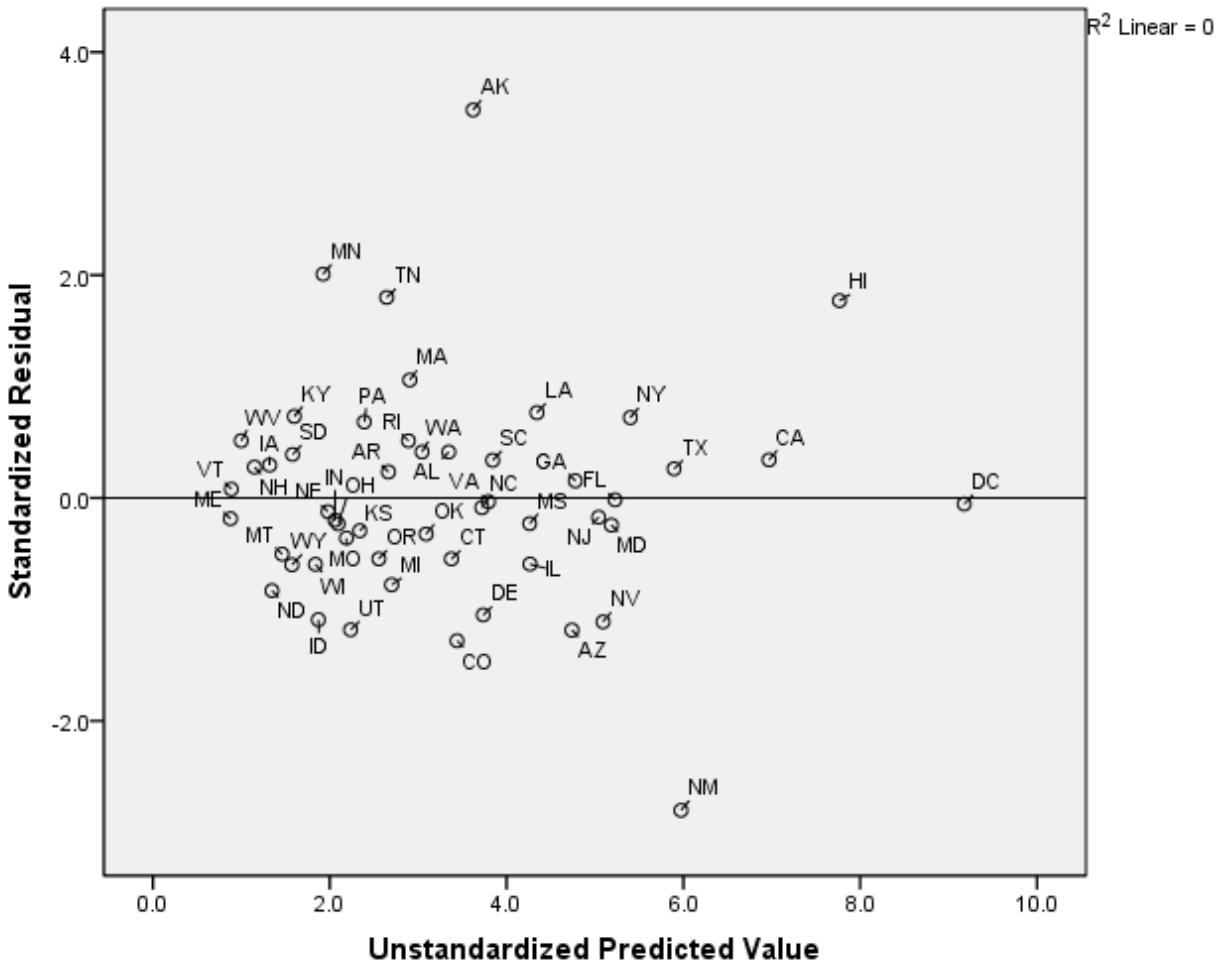

Figure 13. Unstandardized residuals versus predicted values for the proposed model

CHAPTER V

DISCUSSION

The primary objectives of this study were to examine sociodemographic, behavioral, and health risks of TB and their associations at the state level in the US. The variables examined were AIDS diagnosis rates, diabetes death rates, smoking rates, alcohol abuse rates, foreign-born versus US born, race/ethnicity and poverty. The specific research questions were:

Is there a correlation between the frequency of known risk factors and TB rates by state?

Can a significant predictive model be derived for TB rates for the individual states based on the individual state risk factors?

What intervention insights can be gleaned from an ecological study of TB rates versus TB risk factors at the state level?

All the variables examined have been documented as risk factors at the global level where TB is highly endemic. The US represents an area of low TB endemicity. Whereas 1 person in 3 is estimated to be infected with TB at the global level, only 1 person in 25 is estimated to be infected in the US (Khan, Wang, Hu, Bierman, Li, & Gardam, 2008). This changes the way in which we view the risk factors.

The risk factors can be categorized in 3 ways. First, there are risk factors which are primarily associated with exposure to the tubercle bacillus. These are labeled primary TB risk factors. They are the most important because if one is never exposed to the bacillus, the remaining risk factors are largely irrelevant. Secondary risk factors are those which reduce one's immunity and

may enhance the risk of infection as well as act to convert LTBI to active TB. The third category is hybrid risk factors. These risk factors may play an important indirect role in the exposure to the TB bacillus as well as contraction of the infection and progression to the active disease.

The associations found between the risk factors and TB disease are examined and discussed within the 3 categories that are outlined.

PRIMARY (EXPOSURE) RISK FACTORS

Foreign-Born

Being foreign-born generated the second highest correlation coefficient of the risk factors examined. It is a very strong predictor variable of the rate of TB disease within a state. Hawaii, Alaska and DC are the greatest outliers and have distinct populations which account for their deviation. Hawaii has a large established Asian-American population which has shown a high rate of TB but is not foreign-born. As well Alaska has a large Native American population which historically has had a high rate of TB. DC is a purely urban entity that includes substantial enclaves that are economically disadvantaged. Tuberculosis rates are generally higher in urban areas and amongst groups that are economically disadvantaged. The southeastern states form a cluster of states which exhibit higher rates of TB than projected by the percentage of their population which is foreign-born. They have seen a substantial influx of foreign-born persons in recent years comprising 8 of the top 10 states with the greatest percentage increase in the percentage of their population which is foreign-born (Migration Policy Institute, 2010). Since TB rates among the foreign-born are almost five times higher in the first two years after entry into the US, this could partially account for these states having disproportionately high TB rates in relation to their foreign-born population (Cain, Benoit,

Winston, & MacKenzie, 2008). Additionally these states have substantial US-born African-American populations that are economically disadvantaged contributing to their TB rates.

The annual case rates of TB in countries which are the largest sources of immigrants are well above the level in the US. In a sense the large gradient between the TB infection rate globally and that in the US has an effect similar to osmosis. The likelihood of infection prior to arrival in the US is substantially greater than for the native US population. The US currently requires all applicants for permanent residence (immigrants and refugees) to undergo a medical examination which includes testing for TB. For those 15 and older this includes a chest X-ray in addition to a medical exam for symptoms. If evidence is found for a positive TB diagnosis, treatment using directly observed therapy must be completed (unless a waiver is granted) before the individual may travel to the US. In a study published in the New England Journal of Medicine this was found to be a cost-effective measure to combat TB (Yecai Liu, 2009). This examination is not required by the approximately 30% of all foreign-born persons who fall into the categories of students, workers, visitors and undocumented migrants. 61% of colleges and universities require screening for TB (Taylor, Nolan, & Blumberg, 2005). There could be gains to be had if all or at least more universities required TB screening of entrants from high risk countries.

Many immigrants are driven to migrate by poverty. This compounds the situation by potentially adding overcrowding and/or malnutrition which could lead to spread or activation of the disease.

Race/Ethnicity

In the analysis the strongest correlation found was a strong inverse relationship between being non-Hispanic White and rates of TB disease. This risk factor serves as a marker for a number of

factors closer to the root causes of TB. Given current immigration patterns, this risk factor largely encompasses the foreign-born population which was discussed in the previous section while excluding White immigrants from Western Europe who are less likely to be infected with TB. By 2007 over 80% of the foreign-born population originated from Latin America or Asia. Other US groups not part of the Non-Hispanic White category such as African-Americans, American Indians and Native Alaskans, Asian-Pacific Islanders and Hispanics have historically had high TB rates (Cantwell, McKenna, McCray, & Onorato, 1998). As a social disease TB tends to be self-propagating within communities, however that is not sufficient to explain the ongoing disparities experienced by these groups. Their situation is exacerbated by elevated levels of poverty characterized by overcrowding, malnutrition and lack of access to healthcare services. There are also behavioral aspects which are disproportionately exhibited by certain subgroups. Alcohol abuse is an ongoing problem in the American Indian/Native Alaskan community. Smoking is disproportionately found in the American Indian/Native Alaskan and African-American communities. HIV disproportionately affects the African-American community and to a lesser degree the Hispanic community.

The two greatest outliers in this category, New Mexico and Alaska, pose interesting questions. Why has one state, New Mexico, managed to achieve a much lower TB rate than that projected by their racial/ethnic composition while Alaska has a much higher TB rate than projected? Alaska has a larger percentage American Indian/Alaskan Native population (15.2%) compared to New Mexico (9.7%). Alaska also proportionately has a larger Asian population (5.0%) than New Mexico (1.5%) (US Census Bureau, 2010). Additionally the largest minority in New Mexico, Hispanics (45.6%), forms a plurality of the population and has substantial political power holding the governor, speaker of the house and senate majority posts (Jennings, 2010).

Alaskan Natives and American Indians on the other hand while of political importance in their state do not have the numerical strength to control the government. Further research into how political power and ownership of health issues contributes to the health of a community is warranted.

Given the nature of TB to sustain itself within a given community it will be necessary to continue to focus on all groups which have historically had a high rate of TB disease and explore methods of empowering these groups to help themselves.

SECONDARY (IMMUNOLOGIC) RISK FACTORS

Diabetes rates and smoking rates showed no association with TB disease rates across the states. To some degree this reflects the secondary role of these risk factors. Diabetes has no social role that it plays with regard to TB. As such, the focus regarding diabetes is primarily on those already infected with TB. Given the tremendous growth in diabetes forecast, it is recommended that those at risk of developing diabetes be encouraged to take steps both to preclude diabetes as well as undertake IPT.

The potential social role that smoking could play in leading to increased exposure to TB is diminishing as smoking is prohibited in increasing numbers of public places. However, anyone who is in a high risk group to be infected or is already infected with TB should take steps toward cessation of smoking and in the case of LTBI subscribe to a protocol of IPT.

HYBRID RISK FACTORS

Alcohol usage involves both a social factor as well as an immunological issue. For some drinking involves going to a particular bar or congregating with a particular group. While human

contact is the primary mode of disease transmission, the actions taken in consuming alcohol are not very different from many other repetitive social actions taken by millions and subsequently pose no inherent increased risk. Alcohol abuse does have an association with homelessness which can lead to issues of malnutrition and exposure to TB via nosocomial institutions. Still the primary risk of alcohol abuse is the effect on the immune system and the subsequent risk for TB infection and progression of LTBI to active TB disease.

Poverty is a risk factor for TB disease although a positive relationship was found between per capita income by state and TB rates by state. This seeming contradiction points out both the hazards of an ecological study and the need to measure poverty in a more meaningful way at the state level. TB typically flourishes in areas with overcrowding, malnutrition and poor access to healthcare, all of which are indicative of poverty. A positive relationship was found between poverty and GINI by state suggesting that income inequality has a negative effect on TB health outcomes. However this effect was largely captured by the other risk factors under study and was not included in the final model of TB rates.

AIDS diagnoses rates showed a significant association with TB disease rates. There is nothing inherent about HIV/AIDS which should lead to exposure to TB. However the degree to which HIV is concentrated in specific communities such as the African-American, Hispanic and Gay communities, particularly those of lower income, may contribute to a social environment that sustains the spread of TB. Oddly, two states, South Carolina and Alabama, specifically segregate HIV positive inmates (Human Rights Watch, 2010). This dangerous practice has on at least one occasion led to a documented outbreak of TB. In 1999, a South Carolina inmate co-infected with HIV and TB was the source of 30 cases of TB in other prisoners plus one

healthcare worker within 6 months of the TB diagnosis of the source case (McLaughlin, Spradling, Drociuk, Ridzon, Pozsik, & Onorato, 2003). Additionally 96 people converted to infected status as a result of this outbreak. Someone already infected with TB is much more likely to progress to the active TB disease stage if they contract HIV. Vigilance and aggressive medical treatment for either TB infection and/or HIV is imperative to preclude the often deadly combination of these two infections. Nosocomial environments provide an avenue of potentially high TB infection risk. As the TB rate in the US falls, it is important that measures to protect everyone, especially HIV patients, from TB infection are maintained.

LIMITATIONS

This is an ecological study which carries inherent limitations regarding the conclusions one may draw. There were several major TB risk factors such as homelessness, incarceration and drug use which were not addressed. The study was limited by the use of secondary data in terms of extensibility and reliability.

CONCLUSIONS AND RECOMMENDATIONS

This study reviewed seven known risk factors associated with TB and provided evidence that the primary focus of the fight against TB in the US should be on minority communities, those populated by the foreign-born and those with high rates of AIDS particularly in conjunction with disadvantaged communities in areas of income inequality. This is consistent with the assertion by Coberly and Chaisson that the risk of TB infection is a function of exposure (2007). In a low endemicity environment, such as the US, the issues of exposure and infection predominate in an ecological study at the state level.

The US currently has resources deployed at the local, state, federal and global levels for surveillance, prevention and treatment of TB. Based on the findings of this analysis policy makers in the US may wish to consider the following recommendations to enhance prevention and treatment of TB in the US.

The use of IPT should be expanded among newly arrived infected immigrants and refugees who meet the age and health requirements for this therapy. The first two years after arrival are a period of a high rate of conversion to active TB disease. By attacking the infection first, we can both reduce the overall case rate and the spread of the infection. This would be the most cost-effective method of expanding the use of IPT. We could pilot this by focusing on countries with the highest known rates of TB infection that do not have a high rate of isoniazid resistance.

Communications should be improved with immigrant communities to ensure that they are aware of the diagnosis and treatment options available for TB as well as other communicable diseases. Special efforts are needed to overcome language barriers, fear and hostility that may be experienced by the foreign-born especially those who are undocumented. An updating of the immigration laws to reduce the number of residents who are undocumented would assist in this process.

Empower communities with high endemic rates of TB to create tailored solutions which they will implement and own. The US encompasses a broad range of cultures each of which has its own unique characteristics which affects their exposure to TB infection and disease. This information could be shared among the communities so that those efforts with the greatest success could be emulated as appropriate.

There should be an increase in the population of immigrants who are required to undergo testing prior to entry in the US. Anyone entering the US for an extended stay (>90 days) should be required to show proof that they have been tested and do not have active TB disease.

Achieving the elimination of TB from the US will have to involve some combination of reducing the rates of TB globally, aggressively treating the infected locally, especially new arrivals to the US, with IPT and empowering US communities of relatively high TB endemicity to create custom solutions to minimize the spread of the disease. For this goal to happen in the shorter term some breakthroughs in vaccine technology and treatment of LTBI will likely be necessary. However one should not dismiss the good while searching for the great. Sight should not be lost of efforts to improve living standards globally. Tremendous improvements in TB rates were achieved in Western Europe and the US before the introduction of chemotherapy and the same could be achieved globally. The US has made consistent and substantial strives in reducing the threat of TB from its society through aggressive efforts at the local, state, federal and global levels. These efforts must be continued and enhanced to ensure that TB rates maintain a downward trajectory.

APPENDIX

Table 9. Summary of simple regression results

Risk Factor	Correlation with TB disease rates at the state level	
	R	p value
AIDS diagnosis rates/100K	.579	<0.001
Diabetes deaths per 100K	-0.053	0.71
Percent of adults who smoke	-0.157	0.27
Percent of adults who drink heavily	0.019	0.9
Pecentage of population foreign-born	0.649	<0.001
Per capita income	0.46	0.001
GINI	0.588	<0.001
Percent of population non-Hispanic White	-0.856	<0.001

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