CHANGING THE PARADIGM: USING AN INTEGRATIVE APPROACH TO IMPROVE UNDERSTANDING OF TUBERCULOSIS CONTROL IN MICHIGAN

by

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ABBREVIATIONS

ACA: Affordable Care Act

ACS: American Community Survey

AI/PI: Asian and Pacific Islanders

CMI: Cell-mediated immunity

CDC: Centers for Disease Control and Prevention

DOT: Directly observed therapy

EBV: Epstein-Barr Virus

EPTB: Extra-pulmonary TB

FPL: Federal poverty level

GEE: Generalized estimating equations

HSV: Herpes Simplex Virus

IGRA: Interferon-gamma release assay

LTBI: Latent TB Infection

MDR-TB: Multi-drug resistant tuberculosis

MIRU: mycobacterial interspersed repetitive units

MTB: *Mycobacterium tuberculosis*

NIH: National Institutes of Health

PCR: polymerase chain reaction

RVCT: Report of a Verified Case of TB

RFLP: Restriction fragment length polymorphism

SES: Socioeconomic status

TST: Tuberculin skin test

TB: Tuberculosis

SES: Socioeconomic status

WHO: World Health Organization

ABSTRACT

Background. In the U.S., tuberculosis (TB) continues to disproportionately affect the poor, racial/ethnic minorities, and urban dwellers, yet traditional methods of TB control focus primarily on biomedical predictors for treatment and less on social factors that could direct prevention. Although characteristics of the social and physical environment increase vulnerability to TB, declining concern over those with disease and diminished resources have stunted understanding of risk and reduced the ability to respond.

Methods. Using TB case surveillance data combined with genotypic testing of samples from the Michigan Department of Health and Human Service and a novel socio-demographic survey, this dissertation takes an integrative approach to understanding the patterns of TB incidence and transmission. Research has involved: 1. Analyzing risk factors for TB incidence in Michigan; 2. Evaluating which risk factors both at the individual- and neighborhood levels were associated with pathogen genotypic and temporal clustering; and 3. Analyzing social characteristics of TB cases diagnosed in Metro Detroit to better understand how social vulnerability and behavioral contacts augment risk.

Results. From 2004 through 2012, the incidence of TB throughout Michigan declined by an average of 8% per year. However, significant disparities in the average incidence rate were observed by race and nativity. Overall, 22% of the foreign-born cases of TB were estimated to be resulting from recent transmission of TB compared to 52% of the U.S.-born cases. For the U.S.-born, recent transmission was predicted more by individual-level and neighborhood-level socio-

demographic factors than by clinical risk factors. Preliminary results from the socio-demographic survey suggest that while individuals with TB in Metro Detroit may be employed and have access to stable housing, they still experience significant financial strain.

Conclusions: The results of this dissertation highlight some of the ways in which TB incidence is socially patterned. Interventions aimed at reducing the incidence of TB in the foreign-born population should focus on reducing reactivation of latent TB infections. However, reducing the incidence of TB among the U.S.-born will require strategies that can reduce transmission of TB among socially disadvantaged groups, both at the individual- and neighborhood-level. In addition, continued analysis of the socio-demographic survey will help us further understand the social dynamics underlying the persistent disparities observed in TB incidence and transmission.

CHAPTER 1. BACKGROUND

1.1

1.2 Global Public Health Significance of Tuberculosis

"The microbe is nothing…the terrain is everything." These words spoken by Louis Pasteur some time ago remain true today given the current challenges in tuberculosis (TB) control—challenges in understanding how and why TB operates differentially among subgroups of human populations, challenges in explaining and reducing persistent disparities. The terrain in which TB operates is complex, and therefore successful control of TB will require approaches that are multi-faceted encompassing not only the biomedical context of individuals but also the social, environmental, and economic context.

TB has been around for hundreds of years and yet it still claims over a million lives annualy.[1] While TB has gone by myriad names: wasting disease, phthisis, and consumption to name a few, the etiology and natural history of the disease is unchanged. Given the long-standing threat to public health that TB has posed, it is critical that we continue seeking a better understanding of the disease and particularly how the disease operates differently within diverse populations. Additionally, as drug-resistant TB poses a growing threat to global health, it is even more critical to understand the contemporary social and environmental context in which TB lives and spreads so as to prevent the spread of drug-resistant TB the future.

In 2014, there were an estimated 9.6 million new cases of TB and 1.5 million deaths from TB.[2] Moreover, TB now parallels HIV as the leading cause of death worldwide; 12% of the new

TB cases in 2014 were among HIV-positive persons.[2] In addition, multi drug-resistant (MDR) TB continues to pose a serious threat to global TB control. It is estimated that if all existing TB patients were tested, 300, 000 additional cases of MDR-TB would be detected.[3] This is in addition to the estimated 480,000 previously diagnosed cases of MDR-TB.[3]

Although TB control measures have successfully reduced TB mortality by 47% since 1990,[2] TB continues to pose special challenges among subgroups of the population—including those with HIV, racial/ethnic minorities, immigrant and refugee populations, and other vulnerable populations in the global society. While the burden of TB is far less in developed countries, the challenge of TB in vulnerable populations remains a salient issue developed countries must continue to address.

1.3 Natural history of *Mycobacterium tuberculosis* infection

TB is caused by infection with *Mycobacterium tuberculosis* (MTB), an acid-fast bacillus that is most commonly identified in the lung tissue but can also cause disease in a number of non-lung tissues.[4] MTB is transmitted via droplets, most often through coughing, singing, or sneezing.[5] Exposure to MTB results in infection in a limited number of cases; only about 20-30% of those exposed to MTB through contact with an active case become infected with the bacterium.[5]

There are several factors that determine the probability of transmission of MTB from an infectious to a susceptive individual. One, the infectiousness of the individual with TB disease determines how many tubercle bacilli are released in the air during a transmission event—a greater number of tubercle bacilli released will increase the likelihood of exposure for a suceptible.[6] Two, environmental factors can affect the concentration of the MTB pathogen in any given space/time. These environmental factors include such things as the density of

infectious/susceptibles in a space, ventilation, and air pressure.[6] Third and finally, the proximity, frequency, and duration of exposure also determines the probability of transmission of MTB.[6] The closer in proximity a susceptible is to an infectious case, the higher frequency of exposure, and greater duration of exposure time can all increase the likelihood of infection.

MTB can enter the body via a number of entry points, the most common being the airway.[5] Infections via other entry points can produce localized infections at the entry site or disseminated infection throughout other organs and tissues via the lymphatic or blood system.[5] Infections that colonize tissue outside of the lungs are considered extra-pulmonary TB (EPTB).[5]

Once the MTB pathogen enters the body, TB disease can only arise via one of two possible pathways, a process highly regulated by the individual host immune response.[5] When MTB enters the body it lands on the alveolar surface, activating the initial immune response. The alveolar macrophages ingest the microbe triggering the release of cytokines, additional macrophages, and T-cells to control the infection.[5] This stage of infection is characterized by significant growth of the bacterial populations in the body as well as a sustained inflammatory response.[7] If the inflammatory process continues, individuals develop active TB disease and the individual is able to transmit TB to others; this occurs in 5-10% of people infected with MTB.[5] Additionally, it is the induction and the sustained activation of the inflammatory process that causes the characteristic tissue damage in the lungs, often resulting in the development of cavitary lesions in the lung tissue.[7]

In most cases, however, the body is able to control the initial infection by forming granulomas. The granuloma is a tissue nodule created to contain the infection.[5,8] The granuloma contains the MTB infection and prevents the bacteria from spreading to other sites. Individuals whose MTB is contained in granulomas are considered to have latent TB infection (LTBI).[8] 90-

95% of individuals who are infected with TB have immune systems that are able to control the TB infection, maintaining a state of LTBI.[5] However, individuals with LTBI are at risk for progression to TB disease. Progression to TB disease occurs when granulomas break open and MTB is again able to disseminate throughout the body. Of those individuals with LTBI, 5-10% will reactivate and develop TB disease sometime during their lifetime; most within the first 2 years.[5,8] The reactivation of LTBI is extremely context dependent—the most noted risk factors for reactivation of LTBI are older age, malnutrition, immunosuppression (especially infection with HIV), stress, and other factors affecting cell-mediated immunity.[5,8]

Only those with active TB disease are at risk for transmission of the pathogen to susceptible individuals.[5] The infectiousness of an active TB case is dependent on the number of tuberculosis bacilli that are released in the air in a given exposure event.[6] Within active cases, several factors have been shown to indicate a high degree of infectivity including: presence of a cough, lung cavitation, acid-fast bacilli present on the sputum-smear, TB disease of the lungs, airway, or larynx, not receiving adequate drug therapy, and positive sputum cultures.[6]

1.4 Diagnosis of MTB Infection and Disease

The clinical signs and symptoms of active TB disease are mostly non-specific and could apply to a number of disorders. Thus, diagnosis of TB is usually not made solely on the basis of clinical symptomology. The clinical manifestations of active TB disease are mainly resultant of the replication of a large numbers of TB bacilli in the body in addition to the prolonged inflammatory response.[5] The most common symptoms are fever, sweats (particularly night sweats), and sustained weight loss.[5] For pulmonary TB, the addition of a prolonged cough is a hallmark syptom.[5] The symptoms of EPTB often include fever, sweats, and weight loss as well as other symptoms that are specific to the site of disease.

Diagnosis of TB disease differs according to whether the infection is latent or active, pulmonary or extra-pulmonary. Primary diagnosis of TB is made through either a tuberculin skin test (TST) or a blood test.[9] The TST is administered by injecting a small amount of tuberculin purified protein derivative under the skin of the forearm.[9] Diagnosis of TB through the TST is based on the degree of localized immune response and is measured by the millimeters of induration at the injection site.[9] The TST can be administered and read outside of the laboratory. The TB blood test is a laboratory-based test and measures the immune system's reactivity to the bacterium; the blood test used in the U.S. is an interferon-gamma release assay (IGRA).[9] A positive result for either the TST or an IGRA test only indicates that a person has been previously infected with MTB. These tests cannot discriminate between active TB disease or LTBI.

Further tests are needed in order to discriminate between active TB disease and LTBI. Once infection with MTB is diagnosed, a sputum sample is routinely taken. This sputum sample is analyzed by microscopy and is used to grow the MTB in culture. The presence of acid-fast bacilli in the sputum-smear can confirm active TB disease in the individual.[9] The number of acid-fast bacilli in the sputum-smear is also counted and used to grade the degree of infectiousness of the patient—the greater the number of bacilli, the more infectious the patient.[6] The gold standard of laboratory confirmation of active TB disease is sputum-culture of MTB.[6] Sputum-culture is routinely performed for nearly all suspected active TB cases in the U.S. The ability for a sample to grow MTB in culture is also confirmatory of active TB disease.[9] Culture results are used to both increase the sensitivity of the TB diagnosis as well as provide the specimen for drug susceptibility testing and molecular strain typing of isolates.

In cases of LTBI, neither the sputum-smear nor the sputum culture will show

confirmatory results of TB disease. Thus, while the TST or blood test show the presence of infection with MTB, the sputum-smear and sputum culture are needed to confirm whether or not the individual is an active case of TB disease.

Distinction between pulmonary and EPTB often depends on the clinical signs and symptoms the individual displays. For those suspected of pulmonary TB disease, chest radiography is often done both to aid the diagnosis of TB as well as survey the extent of tissue damage occurring as a result of disease.[9] However, chest radiography does not confirm pulmonary disease in all patients. For instance, HIV positive persons with active, pulmonary TB disease may not show the typical pattern of cavitation or lesions in the lung tissue.[6] Thus, chest radiography results must be viewed with caution.

Symptoms of EPTB are often dependent on the specific tissue or body site in which TB disease is occurring. When possible a tissue sample from the suspected site will be taken and grown in culture. The tissue culture will be the definitive confirmation of active EPTB.

1.5 Treatment of LTBI and Active TB

TB is a notifiable disease in the United States and the responsibility of successful treatment of a TB case falls on the local public health department operating in the area in which the case is identified. [10] Private physicians who were involved in the diagnosis of the patient, or who serve as primary care providers, may also be involved with the treatment process. However, responsibility for completion of appropriate treatment ultimately lies with the local public health department. The Centers for Disease Control and Prevention (CDC) has published guidelines for treating TB based on the type of disease (pulmonary or EPTB), drug susceptibility, and additional patient characteristics.[10] Standard treatment for drug-susceptible pulmonary TB starts with an 8-week initial phase of therapy consisting of a 4-drug cocktail including: isoniazid,

rifampin, pyrazinamide, and ethambutol.[10] The continuation phase lasts 18 weeks and consists of isoniazid and rifampin.[10] Treatment continuation is determined based on monthly sputum cultures; 2 consecutive negative sputum cultures would be basis to end treatment after the initial 6 months.[10] In addition, the CDC strongly recommends the use of directly observed therapy (DOT) by the local public health agencies as means to enhance adherence to and successful completion of drug therapy.[10]

As evidenced above, TB treatment is extensive and often poses many challenges for the TB patient to complete a full course of treatment. As such, treatment non-adherence and treatment failure are critical issues TB control practitioners must address as they have serious implications for the burden of TB in a given area.

Treatment non-adherence encompasses any event in which the patient has an inability or refuses to take their TB medications as prescribed.[6] The reasons for non-adherence can range from individual beliefs and behaviors regarding the drug therapy to adverse reactions to medications to lack of access to proper health care. The responsibility for ensuring patients finish treatment falls all the local health department administering DOT.[6]

Treatment failure is defined as remaining sputum culture-positive while on regular treatment for TB.[11] The most common reason for treatment failure is non-adherence. However, other reasons for treatment failure may include: extensive lung cavitation, drug resistance, issues with malabsorption of drugs, and/or laboratory error.[10]

The consequence of both treatment non-adherence and treatment failure is the possibility for development of drug-resistant forms of TB. At an individual-level, the development of drug resistance leads to poor outcomes for the patient, including persistent TB disease. At a

population-level, the new drug-resistant strain of TB can be transmitted to other individuals causing drug-resistance to be circulated within a population.

1.6 Molecular Epidemiology of Tuberculosis

The use of molecular biology has become an integral part of epidemiology. The application of molecular biology to epidemiology enables the characterization of nucleic acid- or amino acid-based strain typing in the service of the goals of epidemiology—that is, the study of the distribution and determinants of disease in a given population.[12] In infectious disease surveillance, the tools of molecular epidemiology can be particularly useful as they allow for more sensitive and specific characterization of the pathogen strain and can also aid in identifying transmission patterns among cases.[12]

The use of molecular epidemiologic tools has led to enormous advances in TB control including increased sensitivity of TB diagnoses, discrimination of TB strain types, and identification of genotypic clusters of cases. In addition, previous point of care diagnostic services, namely TST and sputum-smear microscopy were subject to a certain degree of laboratory and/or clinical error. The use of molecular tools are much less vulnerable to such error in the diagnosis of TB, greatly improving the sensitivity of diagnostic services.[13]

MTB has been classified into 6 major lineages, each with multiple classes.[14] The strains in a given class and lineage differ according to several properties, with some strains being more virulent, for example, while others may be resistant to certain drugs.[13] The use of molecular epidemiologic tools has expanded our ability to analyze the phylogeny of each strain and subsequently tailor control strategies based on associated common traits. In addition, the ability to differentiate among strains of TB enables us to distinguish whether an individual is infected with multiple strains and/or whether the infection is the same strain as previous infections.[13]

There are three major types of genotyping technology used in TB control, each being based on analysis of different components of the MTB genome: restriction fragment length polymorphism (RFLP), polymerase chain reaction (PCR)-based spacer oligonucleotide (spoligo) yyping, and analysis of mycobacterial interspersed repetitive units (MIRU).[5]

When molecular typing first became prominent in TB research, RFLP techniques were primarily used. RFLP in MTB isolates is based on the IS6110 marker and is a simple and inexpensive method to distinguish strains of MTB at the subspecies and genotype family levels.[13] RFLP gained prominence in TB research when it was used to identify large clusters of genetically similar cases in two outbreak investigations in Los Angeles (1991-1992) and New York City (1992).[15,16] Since the mutation rate of MTB is low, it is assumed that genotypically clustered cases are most likely due to recent transmission of MTB.[17] Thus, the excess cases occurring in Los Angeles and New York were most likely epidemics of TB transmission stemming from only a few index cases.[18] This finding challenged the previous held hypothesis that TB in the developed world was primarily the result of reactivation of LTBI.[13] The outbreaks in Los Angeles and New York City were clear evidence that TB transmission was happening in the U.S. and elimination would not achieved without greater attention to this issue.

RFLP analysis is based on the pattern of IS6110 insertions in the TB genome.[19] IS6110 is an insertion sequence whose distribution differs depending on the strain.[19] Strains stemming from a common index case would theoretically have similar patterns of IS6110 distributions.[19] Because the transmission event happened in the past, giving the TB genome time to mutate, cases of TB resulting from reactivation of LTBI should have dissimilar IS6110 distributions.[19] Thus, the strength of RFLP method lies in the ability to establish genotypic similarity between cases. The weakness of RFLP, however, is that it requires a sample of culture which may take

several weeks to obtain.[19]

Spoligotyping, or spacer oligonucleotide typing is based on the distribution of spaces between a 36-base pair direct repeat sequence.[19] The presence or absence of the spacer differs between strains of MTB.[19] Spoligotyping technology uses PCR amplification and gel electrophoresis to determine the pattern of spacers and compare that to other MTB isolates to determine genetic similarity.[19] While spoligotyping does not offer equivalent discriminatory power compared to RFLP methods, it can be performed using smaller amounts of cultured bacterium, allowing for a quicker analysis of specimens.[19]

A more recently developed genotyping method uses mycobacterial interspersed repeat units (MIRUs) contained within the MTB genome to examine the number and size of each of 12 MIRUs.[19,20] A variable number of alleles exists at each of the 12 MIRU loci, allowing for many possible allelic combinations.[19] MIRU-typing is able to discriminate among strains of MTB nearly as well as IS6110-based typing, but can be done with less culture using a fully automated process that allows for the typing of large quantities of isolates.[19] Moreover, further discriminatory power can be achieved by including additional loci in the type process.[20]

Although molecular tools may enhance our knowledge and subsequent control of TB, there are limitations to the current standards of genotypic investigation. Reliance upon current genotyping methods as the sole basis for establishing transmission is predicated on the assumption that two genotypically identical isolates must have arisen from a single source case, and represent a transmission event. However, MTB has a low mutation rate, and genotypically similar isolates may reflect reactivation events from prior exposure, rather than recent transmission.[21] For this reason, CDC advocates for the use of a combination of molecular typing methods. Improved discrimination between cases can be achieved by combining spoligotyping

with MIRU, and/or by expanding the number of MIRU loci analyzed.[22] Additionally, the use of MIRU is advantageous as it can discriminate between strains nearly as well as RFLP methods with less culture time.[21,23]

Despite the enhanced discriminatory power of MIRU, whole genome sequencing provides even better resolution in characterizing TB cases.[21,24] Whole genome sequencing of MTB could provide valuable insights for TB control particularly in terms of differentiation between cases resultant from recent transmission from those resultant from reactivation of LTBI. Whole genome sequencing can detect microevolution within MTB lineages—changes that were previously undetectable.[25] By analyzing the pattern of accumulated mutations within isolates, it is even possible to infer the direction of transmission.[25] Previously TB control has relied on epidemiologic data to confirm suspected transmission events. Whole genome sequencing not only can highlight transmission events but may also point to individuals who are high transmitters. This can be especially helpful in situations where epidemiologic data may be difficult to collect. However, even whole genome sequencing poses challenges. Given the novelty of the application of this method to TB control, there is still much work to be done in the standardization of the methods by which whole genome sequencing is done.[26] Further, while the cost of whole genome sequencing has been steadily declining, the low resource setting in which many TB control programs operate may prove a barrier to the adoption of routine whole genome sequencing. Finally, despite the finer resolution of whole genome sequencing, many researchers believe that even whole genome sequencing can be confounded by the low mutation rate of MTB.[21,26]

Ultimately, the value of these different molecular methods lies in improved characterization of epidemiologic patterns of TB. In particular, epidemiologic studies of contact

patterns and other risk factors should be combined with molecular classification of strains to improve the quality and accuracy of inferences regarding transmission links.

1.7 Epidemiology of Tuberculosis in the United States

1.7.1 The History of TB in the U.S.

In order to understand the current climate of TB in the U.S., it is both helpful and necessary to understand the historical context in the U.S. in which TB flourished. In the 1800 census there were 5.3 million people living in the U.S.[27] 100 years later the population had grown to nearly 76.3 million.[27] The population went from 6.1% living in an urban area in 1800 to 39.6% in 1900.[27] Further, from 1820-1967 there were an estimated 44 million new, legal immigrants to the U.S.[28] TB had been a recurrent health issue in the U.S. prior to this period; however, the speed of population growth, the influx of immigrant populations, and the migration of populations to cities created conditions under which TB could reach near ubiquity in certain populations.

Cities, in particular, represented a novel population shift in how people lived and worked. And while for many cities symbolized new opportunities for economic growth, they were also havens for the spread of infectious diseases. Agrarian populations certainly were exposed to infectious diseases before this point. However, the physical space between individuals and communities would usually contain the disease before large-scale endemicity could be reached. The increasing migration of populations to cities where individuals often lived and worked in spaces that were crowded and degraded created the perfect conditions for sustained, large-scale outbreaks to occur.

New York City was one such focal point of urban migration and accordingly saw one of the largest, sustained TB outbreaks document in the U.S. The strategies developed to control TB

in New York City are representative of many of the public health approaches of the time. In 1875 there were 1 million people living in New York City—by 1900 there were 3.5 million people of which 1.3 were new immigrants.[27] The New York City Health Department was founded in 1870 to address increasing issues of sanitation and infectious disease in the city.[29] At the time, TB was the leading cause of death among New Yorkers and would continue to be so for decades.[30] Public health officials instituted robust control measures aimed at both reducing transmission and treating active cases. However, even then public health officials recognized the utility of improving the social and economic conditions of the population as a way to control the spread of TB. As a result of the robust public health measures put in place by the New York City Health Department, the city cut the death rate from TB in half between 1910 and 1920.[29]

Despite the ubiquity of TB exposure during the 19th and early-20th centuries, TB disproportionately burdened certain subpopulations. And treatments, including admission to the increasing numbers of sanatoriums were patterned along lines of social advantage. Sanatorium admission was reserved for primarily White, U.S.-born individuals.[31] By the early 20th century TB control was seeing great successes in reducing both the number of TB cases and deaths resultant from TB. Again, however, these successes were concentrated in certain groups. Foreign-born persons in the U.S. were still twice as likely to die of TB compared to their U.S.-born counterparts and African-Americans were nearly three to four times more likely to die of TB.[31]

1.7.2 Modern-day TB in the U.S.

Since 1953, the U.S. government has been routinely collecting surveillance data on TB across all states.[32] In 1985, the CDC created the Report of Verified Case of TB (RVCT) form, the first national tool able to capture patient-level data on demographics, clinical, and laboratory

characteristics for each TB case.[32,33] The RVCT form is still in use nationally and is augmented by the use of MTB genotyping data routinely collected for each case.

From 1953-1985, TB incidence rates in the U.S. declined by nearly 82%, corresponding to a drop in the annual cases from 53.0 per 100,000 population in 1953 to 9.3 per 100,000 in 1985.[32] However, there was a resurgence of TB from 1986-1992, primarily due to the rising HIV/AIDS epidemic and an increase in the number of foreign-born persons in the U.S.[32] This resurgence of TB resulted in an estimated 52,100 excess cases, with incidence peaking at 10.5 cases per 100,000 persons in 1992.[32] In 1993, U.S. TB incidence began to decline again, and is now at its lowest rate since 1953: 3.0 cases per 100,000 population in 2014.[32,34] However, in recent years the decline has slowed; the average percent decline in TB rates from 1992-2002 was 6.9% compared to a decline of 4.2% from 2012-2013.[32,35]

While TB has been declining overall within the U.S., TB rates in certain population subgroups and geographic areas have not exhibited the same rate of decline. Asian and Pacific Islanders (AI/PI) have the highest rates of TB and the incidence rate among this group is not showing a decline that will close the gap with other race/ethnicities in the coming years.[36] Whites have the lowest incidence rate since 1993, a trend that has remained unchanged currently.[36] The decline in the incidence rate, however, has recently stagnated,[32,35] in both urban and rural populations[37,38] and among foreign-born persons.[35]

1.7.3 Social and Environmental Determinants of Tuberculosis

The data above are indications of the stark social disparities that still exist in the incidence of TB infection and disease in the U.S. Overall, 64.5% of the cases in 2013 occurred in foreign-born persons, representing an incidence rate nearly 13 times that of U.S.-born persons.[35] Among the U.S.-born, blacks had an incidence rate 6.2 times that of whites in 2013.[35] In the

U.S., TB disproportionately affects the poor, racial/ethnic minorities, and those living in urban environments.[35,39,40] Moreover, TB differentially targets vulnerable populations such as those with HIV, the homeless, and the incarcerated.[35,39,40]

Much of the U.S. research concerning the social determinants of TB has been at the national level, characterizing trends across states using the National Tuberculosis Surveillance System (NTSS). Using the NTSS, Bloss et al. found that incidence among American Indian/Alaskan Native populations during 2003-2008 was more than five times greater than that of non-Hispanic whites.[41] Moreover, case rates for Native Hawaiians/Pacific Islanders were more than 13 times that of non-Hispanic whites.[41] In a 2011 study characterizing urban TB using NTSS data from 2000-2007, Oren et al. found the 48 cities selected for the study accounted for 36% of the total cases of TB in the U.S., and only 15% of the population of the U.S.[37] In addition, 29 of the 48 cities under investigation showed no significant change in TB incidence rates over the course of the study demonstrating the importance of understanding transmission in the urban context.[37] Olson et al. also used NTSS data from 1996-2005 to compare the rates of TB in U.S.-born populations versus foreign-born populations as well as the distribution of socio-demographic variables in these two groups.[42] They found that for both U.S.-born and foreign-born populations there was a higher incidence rate of disease in areas of lower socioeconomic status (SES).[42] This SES gradient was notably steeper for U.S.-born cases than for foreign-born cases.[42]

Several studies have begun to investigate TB disease dynamics in more specific contexts, namely Washington State, San Francisco, CA, and Baltimore, MD.[43–47] A series of studies in Washington State have been instrumental in beginning to explicate the pathway between neighborhood disadvantage and both TB incidence and disease progression.[44–46] In all of these

Washington studies, the exposure of interest was a marker of neighborhood-level disadvantage based on U.S. census data. The first study found that neighborhood-level disadvantage was associated with increased TB incidence even after controlling for individual level age and sex.[44] In the next study, higher neighborhood-level disadvantage was not associated with more severe pulmonary TB disease indicating that the neighborhood may be more important for disease transmission than disease progression or severity.[45] The third study used genotypic clustering as a proxy for recent transmission. Genotypic clustering was associated with neighborhood-level disadvantage; patients living in areas of higher disadvantage were at higher risk for clustering, particularly U.S.-born patients.[46]

There is clear evidence that social factors matter in terms of what puts an individual at risk for exposure to MTB as well as what puts an individual at risk for progress to disease once infection has occurred. Furthermore, recent studies have suggested that the social environment both at the individual- and neighborhood-level plays a critical role in determining risk and patterning disparities.

1.8 Summary & Specific Aims

In summary, there is a lack of research aimed at understanding TB incidence patterns in terms of both recent transmission and reactivation of latent TB infection in the modern-U.S. context, particularly in Michigan. Moreover, while we know there are enduring disparities in the incidence of TB in terms of socio-demographic factors, there are few studies that seek to understand the drivers of these disparities and the mechanisms by which they continue to persist despite organized TB control efforts. The dissertation research proposed below is designed to address many of the unanswered questions and troubling patterns described above. In particular, the goal is to improve our understanding of TB by first addressing the TB trends specific to the

state of Michigan, a topic for which there is little published literature. Second, we will use molecular epidemiology and spatial analysis tools to build upon what is currently known about clustering of TB cases by genotype, space, and time within the Michigan TB patients. Finally, we will use a subset of the TB population in Metro Detroit to begin to explore in detail the social profile of TB patients in hopes to better understand the factors that affect an individual's vulnerability to contracting TB, as well as the factors that affect an individual's progression to TB disease.

CHAPTER 2. WHY WE SHOULD STILL WORRY ABOUT TUBERCULOSIS IN THE U.S.: EVIDENCE OF HEALTH DISPARITIES IN TUBERCULOSIS INCIDENCE IN MICHIGAN, 2004-2012.

2.1 Abstract

Objectives. We examined nine-year trends in tuberculosis (TB) incidence patterns for the entire population of Michigan, and within demographic subgroups.

Methods. Using a cross-sectional study of TB surveillance data, we analyzed 1,254 TB cases reported in Michigan during 2004-2012. We used multivariable Poisson regression models to study trends in the TB incidence rate for the entire population and by race, nativity, sex, and age.

Results. Overall, the incidence rate of TB declined by average of 8% per year—10% among recently transmitted cases, and 8% among reactivation cases. For recently transmitted disease, Blacks had an average incidence rate 19 times greater than Whites, after controlling for nativity, sex, and age. For disease resulting from latent TB infection, foreign-born persons had an average incidence rate 19 times greater than U.S.-born after controlling for race, sex, and age.

Conclusions. Disparities in incidence persist despite ongoing TB control efforts. Greater disparities were observed by race and nativity demonstrating some of the ways that TB incidence

is socially patterned. Reducing these disparities will require a multi-faceted approach encompassing the social and environmental contexts of high-risk populations.

2.2 Introduction

The social underpinnings of tuberculosis (TB) disease have long been documented both in historical narratives and scientific literature. Yet, disparities in the incidence of TB related to nativity, race, and socio-economic status (SES) continue to persist despite organized TB control efforts. Applying a social determinants of health framework to infectious etiologies, specifically TB, could shed light on more distal social and environmental factors that may be inhibiting our ability to reduce enduring disparities in TB.[48] Such an approach may be able to shift our understanding from delineation of risk factors to a more comprehensive understanding of the processes producing such risk factors.[49]

Despite a resurgence of TB in the U.S. from 1986 to1992, incidence is now at its lowest (3.2 per 100,000 in 2012) since routine reporting began in 1953.[32,33] That decline, however, has recently stagnated,[32,35] in both urban and rural populations[37,38] and among foreign-born persons.[35] In addition, incidence of TB in the U.S. is much higher among racial/ethnic minorities, people of lower SES, those with HIV, the homeless, and the incarcerated.[35,39,40,50,51]Consistent with various studies that have examined the effects of SES on health,[52] TB incidence shows an SES gradient, whereby people with lower SES experience greater risk of TB—a gradient much steeper among U.S.-born cases.[50,53,54]

Many studies have reported disparities in TB incidence in the U.S., particularly racial disparities.[55–59] However, few studies have contextualized these disparities in the larger framework of social and environmental determinants of health, or offered a thorough examination of the mechanisms underlying these disparities. In the late 1980s and early 1990s, a

few studies examined the social and geographic context of TB cases as ways to understand the increase in TB incidence following the HIV epidemic.[54,60,61] More recently, studies in Washington State examined the relationship between neighborhood socioeconomic disadvantage and TB incidence and disease progression.[44–46] Findings suggest that residence in an area with greater neighborhood disadvantage is associated with increased TB incidence, accelerated progression of disease, and genotypic clustering, particularly among U.S.-born cases. Several recent studies posit that SES and/or an unequal burden of TB risk factors may be confounding the disparities in TB disease incidence and LTBI between blacks and whites in the U.S.[55,56] The persistent disparities documented in TB infection and disease raise the question as to if these patterns are context dependent. It may be that investigations of the social and geographic context of individuals may hold clues for understanding the drivers of TB disparities in different contexts, and for designing context-specific interventions to ameliorate them.

In the state of Michigan, successes in TB control have resulted in an incidence rate that is consistently lower than the national average.[36] Yet TB remains a notable public health issue. At present, about 75% of TB cases occur in the Detroit Metro Area while only 39% of the Michigan population resides there.[36,62] Moreover, about half of Michigan TB cases are U.S.-born, compared to 37% of the national TB cases.[33] In 2010, less than 8 % of the Michigan population was foreign-born, compared to 13% of the U.S. population.[63] Understanding the differential impacts of social factors on TB infection and disease, and specifically how such factors differ for recently transmitted versus cases resulting from reactivation of latent TB infection (LTBI), will help reduce risk and improve treatment.

Using Michigan surveillance data from 2004 to 2012, we examined TB incidence patterns for the entire population of Michigan, and within population subgroups. We used both

genotypic and temporal data to investigate trends separately for cases due to recent transmission and those due to reactivation of LTBI. We specifically sought to document disparities in TB incidence by race, nativity, sex, and age in Michigan with the aim of laying the foundation for future studies that can explore the mechanisms underlying such disparities.

2.3 Methods

2.3.1 Study population and data collection

A total of 1,800 TB cases were reported to the Michigan Department of Health and Human Services during January 1, 2004 - December 31, 2012 (**Figure 2.8-1**). The gold standard of TB diagnosis is whether TB culture grows from inoculation with a TB sputum and/or tissue sample in a laboratory setting. The resulting cultures allow for genotyping of TB isolates giving the ability to infer genotypic clusters via two genotypic measures: spoligotyping and 12-locus-MIRU-VNTR. Therefore, we limited our analyses to only those cases confirmed with a positive culture. Of the 1,800 total cases, 1,390 (77%) cases were culture-confirmed; 410 (23%) cases were clinical cases that were culture-negative. The clinical cases were composed of those cases that were culture-negative or did not have culture done. The distribution of race, age, sex, nativity, geographic area, and site of disease differed significantly comparing the culture positive, culture negative, and culture-not done cases (**Table 2.8-2**).

As with previous studies, a genotypic TB cluster was defined as two or more cases with identical spoligotype and 12-locus MIRU genotyping patterns in addition to a diagnostic date within a one year time period of one another.[38,64] Such clusters are not necessarily spatial clusters, and could occur over more than one year if the cases were connected by another case with an identical genotypic pattern within the one-year time frame.[38] If a case did not meet this definition, it was classified as a non-clustered case.[38] With this time-restricted genotypic cluster

definition, clustered cases were considered as a proxy for cases resultant from recent transmission; non-clustered cases to be a proxy for cases resultant from reactivation of LTBI. The inclusion of a time requirement allows for greater specificity in the classification of a genotypic cluster as a case resultant from recent transmission. Therefore, cases were excluded if they did not have both a spoligotype and a 12-locus-MIRU-VNTR result. Of the 1,390 culture-confirmed cases, 1,316 (95%) had both genotypic measures.

Demographic and clinical characteristics of the sample were drawn from de-identified TB surveillance data collected by the Michigan Department of Health and Human Services using the "Report of a Verified Case of TB" form.[65] Classifications of race, nativity, sex, and age were based on demographic data collected from the above form. We only included participants who self-identified as Black, Asian, or White in our racial classification. We focused only on race rather than race/ethnicity because the data did not capture multiple ethnic categories. Further, only 10% of the sample identified as Hispanic ethnicity. In order to ensure comparability with previous studies, age was defined as 18-64 or ≥65years old.[38,64] Cases under 18 years of age were excluded due to the difficulty in accurately ascertaining pediatric cases.[66] Sex and nativity were dichotomized as male or female and U.S.-born or foreign-born, respectively. The study sample represents 70% of the total number of reported TB cases in Michigan during the study period.

The study was approved by the Health Sciences and Behavioral Sciences Institutional Review Board at the University of Michigan.

2.3.2 Statistical Analyses

Using a cross-sectional study of TB surveillance data, we analyzed 1,254 TB cases reported in Michigan during 2004-2012. Incidence rates for the study time period were calculated overall for the study population, clustered and non-clustered cases separately, and then

by race, age, sex and nativity. Geographic variation was not considered because 94% of cases were identified in a metropolitan or micropolitan region. To generate the denominators for the total population and subgroup incidence rate calculations, population-level characteristics for Michigan were obtained from the American Community Survey through the U.S. Census Bureau.[67] Enumerating the population by nativity, race, sex, and age is considered identifiable data according to the U.S. Census. Thus, in order to obtain these subgroup population estimates, we took the available population numbers (for example, the number of persons who are foreign-born, white, and male) and applied the age proportions reported in the American Community Survey.

We first visually examined the trends in incidence both overall and among subgroups of race, nativity, sex, and age. We plotted the incidence rates over time and calculated the confidence intervals based on the Poisson distribution following the method developed by Buchanan[68] in Microsoft Excel (2011).

Poisson regression models were then developed to examine temporal changes in incidence overall and among clustered and non-clustered cases, and by subgroups of race, nativity, sex, and age. We first modeled the effect of each demographic factor by time (year) separately. To determine if the incidence rate trend in clustered cases was statistically different from that of non-clustered cases, we used a multinomial logistic regression model comparing the average percent decline in clustered and non-clustered cases.[69] Multinomial regression models allow for the direct comparison between the temporal trends for the two types of cases, a limitation of Poisson regression models.

As a final step we used a multivariable Poisson regression with a log link to model the average incidence rate ratio by subgroups of the population including all demographic factors.

All analyses were conducted in SAS V9.4 and statistical significance was assessed with a two-tailed alpha level of 0.05.

2.4 Results

Of the 1,254 cases in the sample, 473 (38%) fit our criteria for a clustered case, while 781 (62%) were considered non-clustered cases. The 473 clustered cases belonged to 95 unique clusters with the size ranging from 2 to 51 cases.

2.4.1 Characteristics of the study population

Of the 1,254 cases analyzed in this study 45% were foreign-born and 55% U.S.-born. The sample was 33% White, 42% Black, and 25% Asian. Cases ranged from 18 years of age to 104 years of age with a median of 49 years of age. 60% of the cases were male, 40% female. Finally, 70% of the cases had pulmonary TB, 22% extrapulmonary TB, and 8% had both pulmonary and extrapulmonary TB (**Table 2.8-1**).

2.4.2 State-wide incidence rate trends

From 2004 through 2012, the overall incidence rate of TB declined from 2.69 cases per 100,000 persons in 2004 to 1.28 cases per 100,0000 in 2012. The average annual percent decline was 8%, a statistically significant decline ($P < 0.001$) (**Figure 2.8-2**).

The incidence rate for both clustered and non-clustered TB declined over the time period. The decline in the incidence rate was the largest among clustered TB cases falling from 1.01 per 100,000 in 2004 to 0.36 per 100,000 in 2012. This corresponds to a statistically significant average annual decline of 10% ($P<0.001$). The incidence rate of non-clustered TB was 1.68 per

100,000 persons in 2004 and 0.92 per 100,000 persons in 2012, corresponding to a statistically significant average annual decline of 8% (P<0.001). The observed difference between the decline rate of clustered TB and non-clustered TB was statically significant according to the multinomial logistic regression model (P < 0.01).

Over the nine-year study period, the proportion of cases classified as clustered in the study sample decreased while the proportion of non-clustered cases increased. In 2004, clustered cases accounted for 38% of the study sample versus 28% in 2012. In 2004, non-clustered cases accounted for 62% of all cases versus 72% in 2012.

2.4.3 Subpopulation incidence rate trends

No significant differences were found in the rate of decline in the incidence comparing Blacks and Asians to Whites (**Figure 2.8-2**). Overall, Blacks had an average annual decline in the incidence rate of 11%, Asians 7% and Whites 8% (P=0.21 and P=0.67 for Blacks and Asians compared to Whites, respectively). Among the clustered cases, Blacks had an average annual decline in the incidence rate of 11%, Asians 4% and Whites 11% (P=0.97 and P=0.24 for Blacks and Asians compared to Whites, respectively) (**Figure 2.8-2**). Among non-clustered cases, Blacks had an average annual decline in the incidence rate of 11%, Asians 7%, and Whites 7% (P=0.20, P=0.86 for Blacks and Asians compared to Whites, respectively) (**Figure 2.8-2**).

There was a significant difference in the decline rate overall by nativity. However, this difference was attenuated when clustered and non-clustered cases were examined separately (**Figure 2.8-2**). Overall, the U.S.-born had an average annual decline of 8% and foreign-born 6% (U.S.-born vs. foreign-born: P=0.03). Among clustered cases, the U.S.-born had an average annual decline in the incidence rate of 11% and foreign-born 4% (U.S.-born vs. foreign-born: P=0.06). Among non-clustered cases, the U.S.-born had an average annual decline in the

incidence rate of 10% and foreign-born 7% (U.S.-born vs. foreign-born: *P*=0.25).

There were no differences in the rate of decline in the incidence by sex (**Figure 2.8-2**). Overall, males had an average annual decline in the incidence rate of 7% and females 10% (male vs. female: *P*=0.17). Among clustered cases, males had average annual decline of 9% and females 11% (male vs. female: *P*=0.68). For non-clustered cases, males had an average annual decline in the incidence rate of 6% and females 10% (male vs. female: *P*=0.13). Likewise, the two age groups did not differ in the rate of decline in the incidence (**Figure 2.8-2**). Overall, the 18-64 year age group had an average annual decline in the incidence rate of 9% and the 65+ age group 7% (65+ vs. 18-64: *P*=0.29). Among clustered cases, the 18-64 year age group had an average annual decline in the incidence rate of 9% per year and the 65+ age group 12% (65+ vs. 18-64: *P*=0.57). This trend was reversed among the non-clustered cases, the 18-64 age group had an average annual decline in the incidence rate of 9% compared to the 65+age group of 5% (65+ vs. 18-64: *P*=0.16).

2.4.4 Comparison of average incidence rate among subpopulations

We next evaluated whether there were significant differences in the average incidence rate ratio across subgroups for both clustered and non-clustered TB cases. Given no significant differences in the decline rate were found among subgroups when the demographic factors were examined one at a time, interactions between time and demographic factors were not included in the multivariable analysis. The greatest disparities in the average incidence rate, for both clustered and non-clustered cases, were observed by race and nativity (**Table 2.8-2**). However, the magnitude of the disparity differed between clustered and non-clustered cases.

Among clustered TB cases, Blacks had an average incidence rate 19 times greater than Whites, with Asians at nearly 8 times greater incidence than Whites, after controlling for

nativity, sex, and age (**Table 2.8-2**).In the same model, the foreign-born had an average incidence rate 5 times greater than the U.S.-born after controlling for race, sex, and age (**Table 2.8-2**).

Disparities were also observed in the non-clustered model, particularly by nativity. In the non-clustered model, the foreign-born had an average incidence rate 19 times greater than that of the U.S.-born when controlling for race, sex, and age (**Table 2.8-2**). Racial disparities were also observed: Blacks had an average incidence rate 6.5 times greater than that of Whites, Asians 4 times greater than that of Whites, when controlling for nativity, sex, and age (**Table 2.8-2**).

2.5 Discussion

This study analyzed temporal changes in TB incidence patterns in Michigan during 2004-2012, with particular attention to subgroups by race, nativity, sex, and age. We found the incidence rate of TB to be declining overall in Michigan. This decline was similar for recently transmitted cases and reactivated cases. Our results suggest both ongoing transmission and reactivation of LTBI are contributing to the burden of TB disease in Michigan. There were significant subgroup disparities in the average incidence rate, particularly by race and nativity.

On the whole, TB incidence is declining in the U.S. We observed an average yearly percentage decline of 8% in the incidence, greater than the average percentage decline (5%) reported for the U.S. as a whole in this time period.[33,70–77] The greater decline in Michigan might be partly explained by a population composition that differs from many of the more populous states contributing to the national TB burden such as California, Texas, New York, and Florida who accounted for nearly half of all TB cases in 2014.[34] The higher TB incidence rate in these states may be driven by their proximity to countries with an elevated TB burden, as well as a larger proportion of foreign-born persons as compared with Michigan.[78]

Our findings showed that both ongoing transmission and reactivation of LTBI are contributing to TB incidence in Michigan. Shea et al. reported 80% of U.S. TB cases during 2006-2008 resulted from reactivation of LTBI.[79] Similarly, the highest proportion of Michigan cases also resulted from reactivation of LTBI. Studies in Arkansas have reported similar findings, though with smaller proportions of cases attributable to reactivation.[38,64] Based on our analysis, TB control efforts need to implement measures that can both reduce *Mycobacterium tuberculosis* transmission and reduce reactivation of LTBI.

In general, we did not find significant differences in the TB decline rate in our subgroup analyses. However, there was evidence of disparities in the average incidence rate. Among recently transmitted cases, the greatest disparities were observed by race with Blacks being the highest risk group. The evidence is mixed regarding the racial distribution of TB. While some studies have also reported the greatest racial disparity in TB incidence between Blacks and Whites,[80] the national surveillance data suggests the greatest racial disparities exist between Asians and Whites.[34] Our multivariable models allowed us to explore these disparities while accounting for the effects of nativity. We saw the disparity between Asians and Whites reduced by nearly 40% when accounting for nativity. Conversely, the disparity between Blacks and Whites increased when we accounted for nativity. These findings suggest that nativity is suppressing the relationship between race and TB. Thus, accounting for nativity is critical to understanding the relationship between race and TB incidence.

Among cases resulting from reactivation of LTBI, the greatest disparities were observed by nativity. Immigrants may be infected in their country of origin and may reactivate sometime later when in the U.S. [81–83] However, the disparity observed between foreign-born and U.S.-born persons among the recently transmitted cases suggests they are also at risk for acquiring TB

infection while in the U.S. This may be resultant from increased exposure to active TB cases among other recent immigrants or it could it be a reflection of their social and environmental circumstances once in the U.S.

Our study is one of only a few to use a multivariable approach to disentangle the differential impact of socio-demographic factors on disparities in TB incidence in the U.S. Bivariate analyses of the socio-demographic patterning of TB risk miss important relationships that are only uncovered when controlling for other factors. Other studies that have used a multivariable approach have also found that social vulnerability based on minority race/ethnicity, nativity, and income was a better predictor of TB incidence than traditional TB risk factors.[84]

During the 19th and early 20th centuries TB was thought to be endemic in the U.S., particularly among those living in poor, crowded housing without access to basic resources: clean water, sanitation, ample food.[85,86] Yet, in recent decades the focus in infectious disease control in the U.S. has shifted to individual-level predictors of risk and disease, often ignoring the social and environmental context of individuals that may be more a salient predictor of risk. Our findings that disparities are not only present in TB incidence, but persistent despite organized TB control efforts, suggest that TB controls needs to begin again to address the social and environmental context in which TB cases are arising. It is not sufficient to simply describe the patterns of TB incidence without regard to how these factors are working together to augment risk in certain populations.

Additionally, despite our knowledge of the highly social nature of TB, control efforts in the U.S. rarely emphasize the social and environmental context as means for intervention. Recently, the World Health Organization has begun to recognize the inextricable links between social and economic determinants of TB incidence globally.[85,87] Globally, the burden of TB often

disproportionately falls on the most vulnerable populations. Hargreaves et al. suggests that global TB control needs to develop interventions that simultaneously incorporate the traditional biomedical approaches as well as approaches that address the social determinants of health.[87] These efforts have mainly been targeted to high-burden TB countries in order to reduce the global incidence of TB. However, we advocate for an extension of this expansive view of TB control to low burden TB settings as TB disparities often remain persistent in these settings. While many studies show social factors ranging from neighborhoods to social cohesion to be meaningful predictors of TB risk, we now need to move to incorporating these findings into TB control in the U.S.

2.6 Limitations

There were several limitations to our study regarding the exclusion criteria we applied to the selection of the study sample. Since our analyses were contingent upon the availability of genotypic data, we excluded 410 clinical cases (23% of the 1,800 cases reported in Michigan during this time). These cases were significantly different than culture-positive cases on a number of key covariates (Table 2.8-2). However, we believe the final study sample is representative of the total TB population and therefore, our findings are not significantly biased due to this exclusion (Table 2.8-1). Additionally, we excluded those cases less than 18 years of age (6.88% of the total 1,800 cases reported in Michigan during this time). Several studies have posited that pediatric cases are more likely to be recently transmitted TB thus excluding them could lead to an underestimation of the true trends in recent transmission.[88]

One critical limitation to our study was the availability of more detailed socio-demographic data. While our findings suggest significant social patterning of TB incidence, our ability to infer what may be driving the observed disparities is limited based on the data

available. Future studies would benefit from the collection of more detailed socio-demographic data. Additionally, our incidence rate calculations were based on extrapolations of census data. Updated population denominators were not available for all years, possibly reducing accuracy of some population-level data. However, the resulting bias is likely non-differential, biasing the observed estimates towards the null.

We used genotypic clustering as a proxy for recent transmission. While we believe that the addition of a time restriction in our genotypic cluster definition increased the specificity of the designation, some misclassification may still have occurred, particularly for those cases diagnosed in 2004. To be classified as clustered, a case had to share a genotype and a diagnostic date within one year of another case. Thus, there may have been some 2004 cases that were misclassified as non-clustered since we could not link them to cases diagnosed in 2003 because of non-comparable genotyping data for the 2003 cases. However, we do not believe this substantially biased our findings. Additionally, some studies have shown that the use spoligotyping and 12-locus-MIRU-VNTR as a marker as the basis for genotypic clustering may not be as effective depending on the strain of *Mycobacterium tuberculosis.*[89] Thus, future analyses should consider the prevalent MTB strain when deciding on the classification scheme for genotypic clusters.

2.7 Conclusions

This is the first study offering a more in-depth analysis of the trends in TB incidence in Michigan. Our findings suggest that both ongoing transmission and reactivation of LTBI are contributing to the incidence of TB in Michigan. Disparities in incidence persist despite ongoing TB control efforts, suggesting more targeted TB control is needed to reduce incidence in high-risk groups. The greater disparities by race and nativity demonstrate some of the ways that TB

incidence is socially patterned. Reducing these disparities will require a multi-faceted approach encompassing the social and environmental contexts of high-risk populations.

2.8 Tables & Figures

Table 2.8-1 Comparison of the Distribution of Selected Demographic and Clinical Characteristics Among all Culture-Confirmed Cases and the Study Sample.

	All culture-confirmed cases (n=1,390)		Study Sample (n= 1,254)	
Risk Factor	**No.**	**%**	**No.**	**%**
Race				
White	460	33.09	419	33.41
Black/African American	577	41.51	525	41.87
Asian	328	23.60	310	24.72
American Indian/Alaskan Native	5	0.36		
Native Hawaiian or Other	10	0.72		
Unknown	10	0.72		
Missing				
Age				
<18	40	2.87		
18-64	1004	72.24	939	74.88
65+	346	24.89	315	25.12
Sex				
Male	842	60.62	750	59.81
Female	547	39.38	504	40.19
Missing	1			
Nativity				
Foreign-born	609	43.91	557	44.52
US-born	778	55.09	694	55.48
Missing	3		3	
Geographic Area				
Metro	1300	93.53	1176	93.78
Micro	42	3.02	39	3.11
Rural	6	0.43	5	0.40
Unknown	42	3.02	34	2.71
Missing				
Site of Disease				
Pulmonary	972	70.03	880	70.29
Extrapulmonary	303	21.83	275	21.96
Both	113	8.14	97	7.75
Missing	2		2	

Table 2.8-2 Comparison of the Distribution of Selected Covariates Among all Reported TB Cases, Culture Positive, Culture Negative, and Culture-Not Done Cases.

	All reported TB cases (n=1,800)		**Culture Pos (n=1,390)**		**Culture Neg (n=259)**		**Culture-ND (n=151)**	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Race								
White	**618**	**34.39**	460	33.09	107	41.31	51	33.77
Black/African American	**721**	**40.12**	577	41.51	79	30.5	65	43.05
Asian	**428**	**23.82**	328	23.6	71	27.41	29	19.21
American Indian/Alaskan Native	**5**	**0.28**	5	0.36	0	0	0	0
Native Hawaiian	**3**	**0.17**	2	0.14	0	0	1	0.66
Other	**11**	**0.61**	8	0.58	2	0.77	1	0.66
Unknown	**11**	**0.61**	10	0.72	0	0	1	0.66
Missing	**3**	**0.17**	0	0	0	0	3	1.99
Age (years)								
<18	**124**	**6.88**	40	2.88	24	9.27	60	39.74
18-64	**1263**	**70.16**	1004	72.23	184	71.04	75	49.67
65+	**413**	**22.94**	346	24.89	51	19.69	16	10.6
Sex								
Male	**1047**	**58.2**	842	60.58	143	55.21	62	41.06
Female	**752**	**41.8**	547	39.35	116	44.79	89	58.94
Missing	**1**		1	0.07	0	0	0	0
Nativity								
Foreign-born	**798**	**44.48**	609	43.81	132	50.97	57	37.75
US-born	**996**	**55.52**	778	55.97	127	49.03	91	60.26
Missing	**6**		3	0.22	0	0	3	1.99
Geographic area								
Metro	**1690**	**94.05**	1300	93.53	247	95.37	143	94.7
Micro	**49**	**2.73**	42	3.02	5	1.93	2	1.32
Rural	**9**	**0.5**	6	0.43	2	0.77	1	0.66
Unknown	**49**	**2.73**	42	3.02	5	1.93	2	1.32
Missing	**3**	**0.17**	0	0	0	0	3	1.99
Site of Disease								
Pulmonary	**1188**	**66.22**	972	69.93	145	55.98	71	47.02
Extrapulmonary	**463**	**25.81**	303	21.8	91	35.14	69	45.7
Both	**143**	**7.97**	113	8.13	22	8.49	8	5.3
Missing	**6**		2	0.14	1	0.39	3	1.99

Culture-Pos = Culture status positive; Culture-Neg = Culture status negative; Culture-ND = Culture not done which includes those with an unknown culture status.

*Chi square tests were permed comparing the distribution of each covariate between culture-positive, culture-negative, and culture-not done TB cases. The distribution of each covariate was statistically different comparing each TB case type ($P < 0.001$).

Table 2.8-3. Incidence Rate Ratio of TB According to Selected Socio-Demographic Characteristics in Michigan, 2004-2012.

Variable	Clustered Cases IRR (95% CI)	Non-Clustered Cases IRR (95% CI)
Race		
White	Ref.	Ref.
Black	19.01 (17.64, 20.48)	6.54 (6.17, 6.93)
Asian	7.79 (6.89, 8.79)	4.00 (3.75, 4.27)
Origin		
U.S.-born	Ref.	Ref.
Foreign-born	4.91 (4.45, 5.40)	19.19 (18.12, 20.33)
Sex		
Male	Ref.	Ref.
Female	0.49 (0.46, 0.52)	0.74 (0.71, 0.78)
Age		
18-64 Years	Ref.	Ref.
65+ Years	1.01 (0.93,1.11)	3.05 (2.90, 3.20)

Models based on multivariate Poisson regression
IRR = incidence rate ratio
Ref. = reference group

Figure 2.8-1 Flowchart Illustrating the Selection of the Study Sample from the 1,800 Total TB Cases Reported in Michigan, 2004 - 2012.

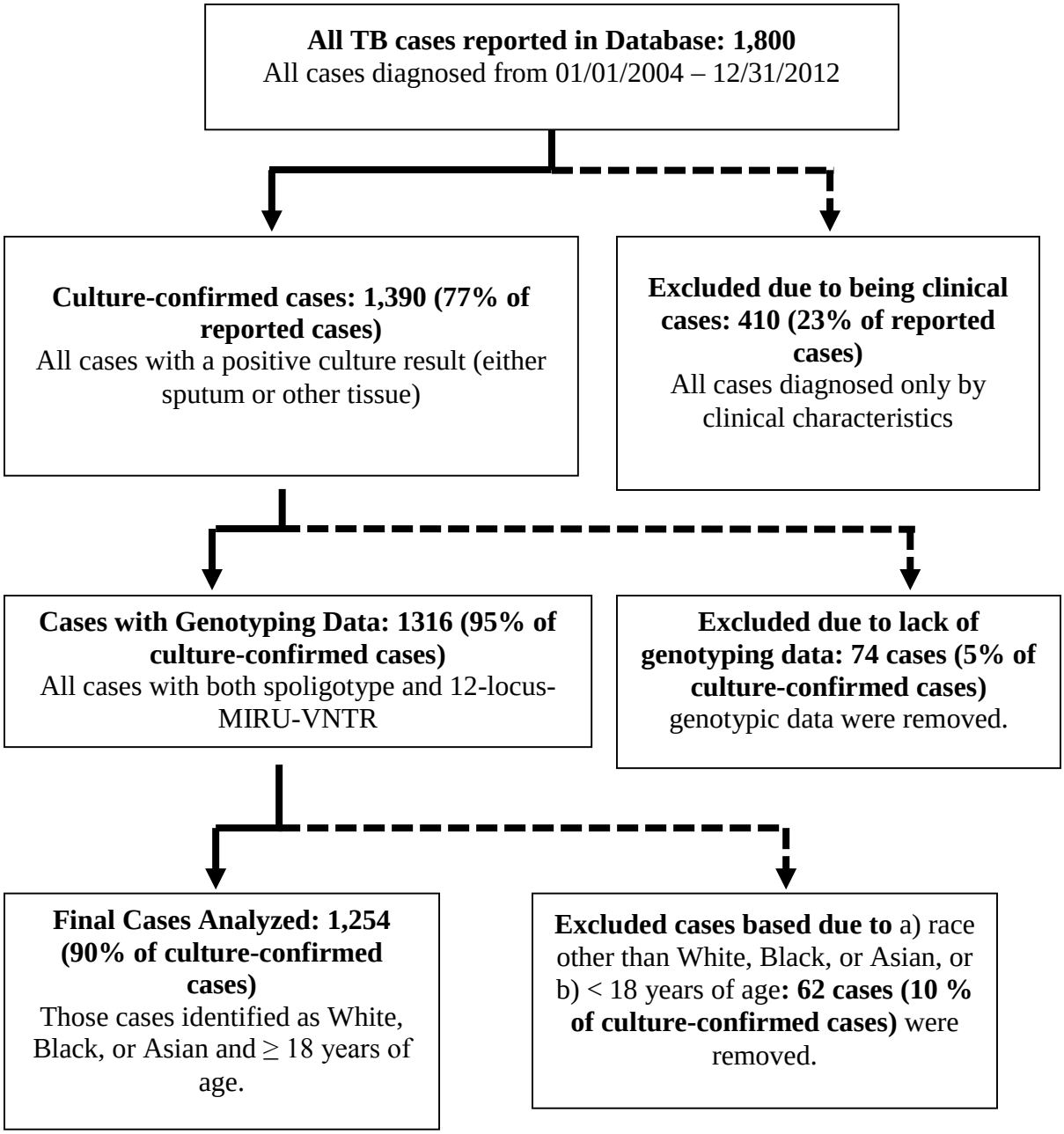


Figure 2.8-2 The Incidence Rate of Clustered and Non-Clustered TB Cases by Race, Nativity, Sex, and Age in Michigan, 2004-2012. For all figures, the error bars correspond to the 95% confidence interval.

Figure 1-2 a. Compasisons by race

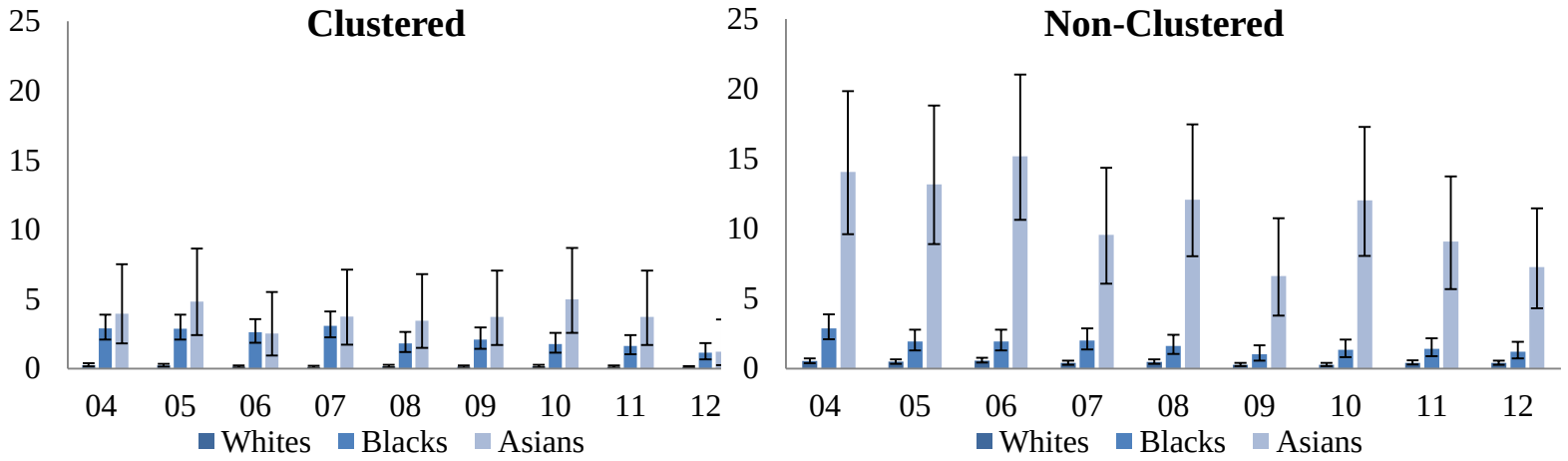


Figure 1-2 b. Comparisons by nativity

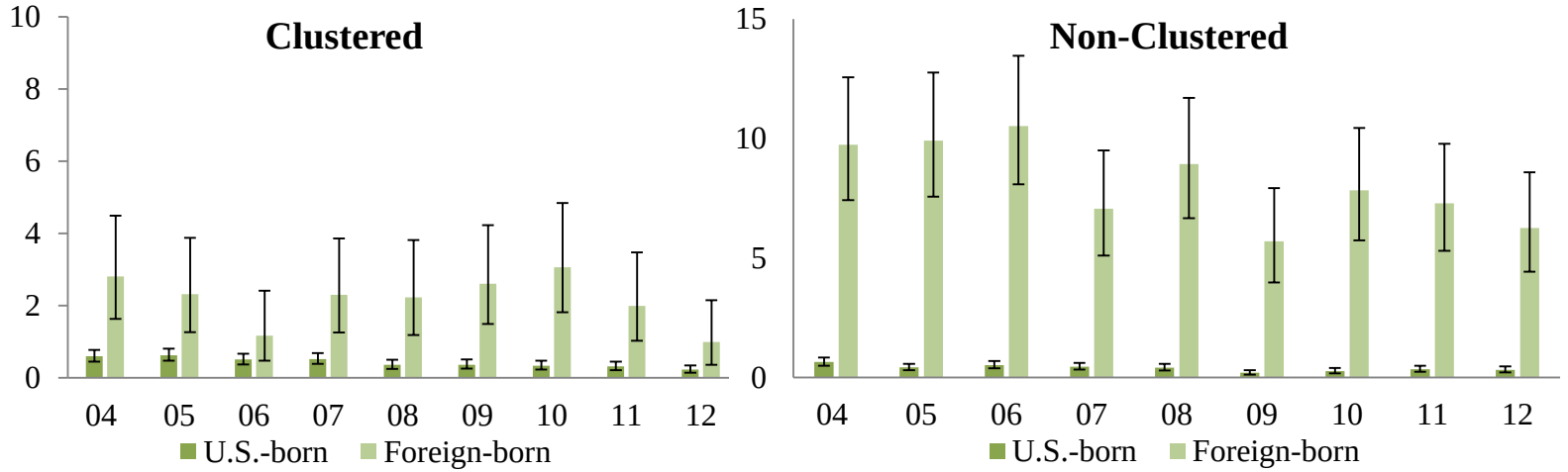


Figure 1-2 c. Comparisons by sex

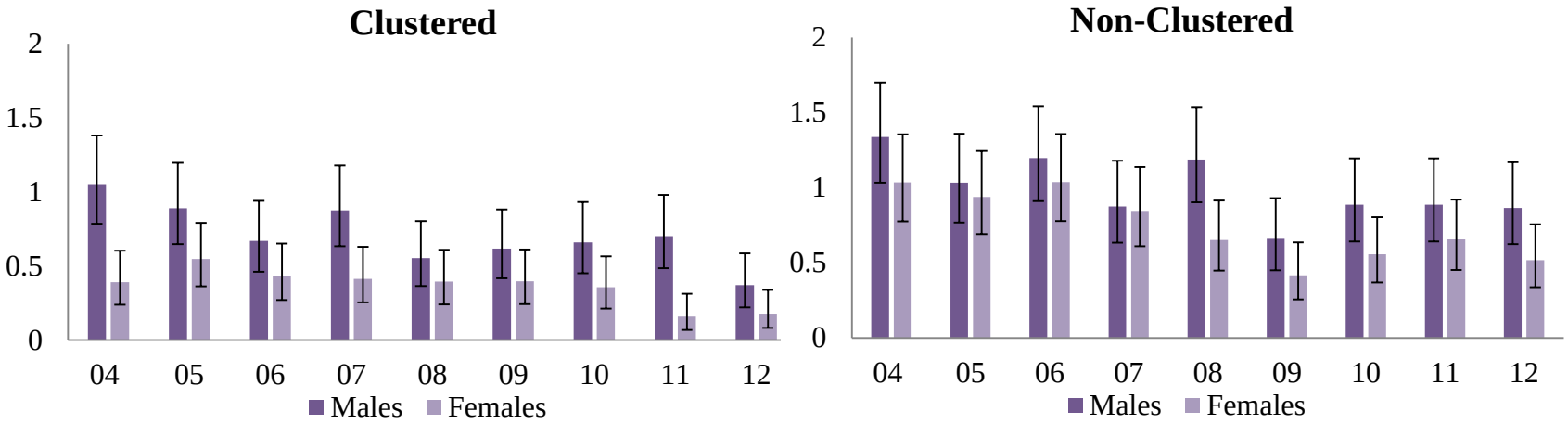
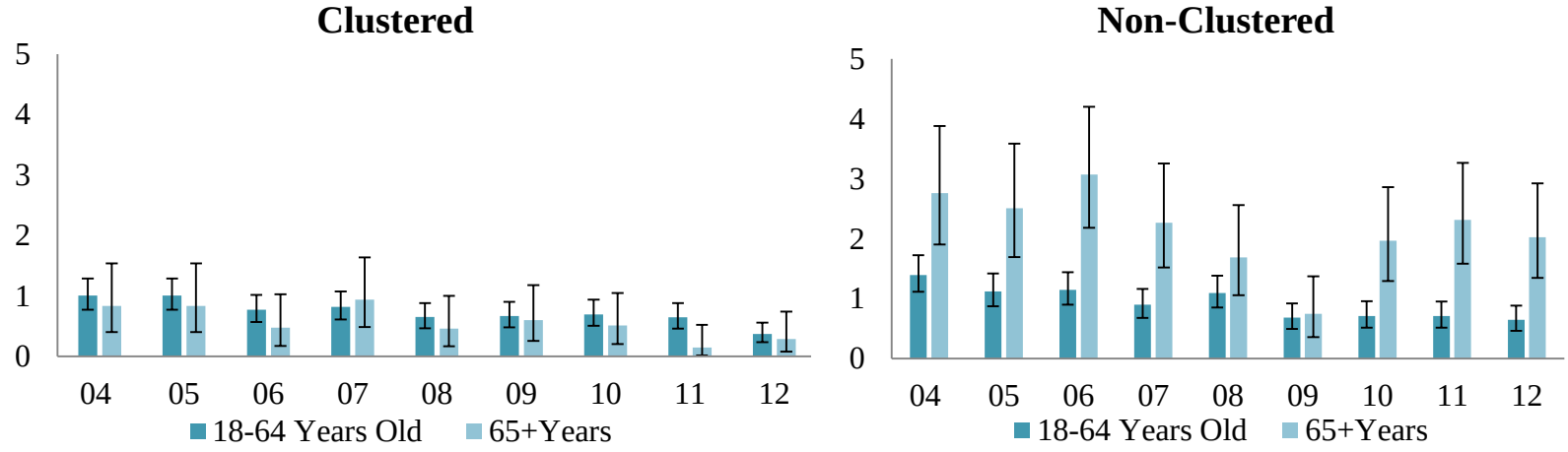


Figure 1-2 d. Comparisons by age



2.8-4 Supplemental Table. Comparison of the distribution of selected demographic and clinical characteristics among all reported cases in Michigan and the study sample.

	All reported TB cases (n=1,800)		Study Sample (n= 1,254)	
Risk Factor	**No.**	**%**	**No.**	**%**
Race				
White	618	34.39	419	33.41
Black/African American	721	40.12	525	41.87
Asian	428	23.82	310	24.72
American Indian/Alaskan Native	5	0.28		
Native Hawaiian or Other	3	0.17		
Unknown	22	1.22		
Missing	3			
Age groups (years)				
<18	124	6.88		
18-64	1263	70.16	939	74.88
65+	413	22.94	315	25.12
Sex				
Male	1047	58.20	750	59.81
Female	752	41.80	504	40.19
Missing	1			
Place of birth				
Foreign-born	798	44.48	557	44.52
US-born	996	55.52	694	55.48
Missing	6		3	
Geographic area				
Metro	1690	94.05	1176	93.78
Micro	49	2.73	39	3.11
Rural	9	0.50	5	0.40
Unknown	49	2.73	34	2.71
Missing				
Site of disease				
Pulmonary	1188	66.22	880	70.29
Extrapulmonary	463	25.81	275	21.96
Both	143	7.97	97	7.75
Missing	6		2	

CHAPTER 3. DRIVERS OF *MYCOBACTERIUM TUBERCULOSIS* TRANSMISSION IN THE U.S. CONTEXT

3.1 Abstract

Objectives: Using TB surveillance data and molecular genetic tests of *Mycobacterium tuberculosis*, we evaluated risk factors for TB clustering at both the individual and neighborhood levels among U.S.-born and foreign-born populations. We used genotypic clustering as a proxy for recent transmission.

***Methods*:** Using TB surveillance data, we analyzed 1,236 TB cases reported in Michigan during 2004-2012. We used univariate and multivariable, modified Poisson regression models to examine risk factors for TB genotypic clustering cross-sectionally for U.S.-born and foreign-born populations separately. Genotypic clusters were defined on the basis of spoligotype and 12-locus-MIRU-VNTR typing results. We examined four classes of variables: demographic factors, known TB risk factors, clinical factors, and neighborhood-level factors.

Results: Overall, 22% of the foreign-born cases of TB were clustered. Among the foreign-born, only race and being a contact of a known case of active TB were significant predictors of clustering. 52% of the U.S.-born cases of TB were clustered. For the U.S.-born, clustering was predicted more by individual-level and neighborhood-level socio-demographic factors than by clinical risk factors.

Conclusions: Interventions aimed at reducing the incidence of TB in the foreign-born population should focus on reducing reactivation of LTBI. However, reducing the incidence of TB among the U.S.-born will require strategies that can reduce transmission of TB among socially disadvantaged groups, both at the individual- and neighborhood-level.

3.2 Introduction

Although the overall incidence of tuberculosis (TB) has been declining in the U.S., stark disparities persist in the distribution of disease, particularly by race and nativity. Asian and Pacific Islanders (AI/PI) continue to have the highest rates of TB with no evidence of closing the gap with Whites.[36,41] Moreover, in recent years the rate of decline in TB incidence has begun to stagnate particularly among foreign-born populations,[35] and in both urban and rural populations.[37,38] A study using cases from the National Health and Nutrition Examination Survey (NHANES), 1999-2000, also found evidence of disparities in latent TB infection (LTBI) among African Americans and Hispanics born in the U.S., the foreign-born, and those in poverty.[90]

Previous studies have examined both individual-level and neighborhood-level factors linked to transmission. Individual-level risk factors for recent transmission include demographic characteristics such as younger age,[91–93]minority race/ethnicity status,[91,94] male sex,[92,93] and being native-born.[47,91,94,95] Additionally, several of the traditionally recognized TB risk factors published by the Center for Disease Control and Prevention (CDC) [65] such as homelessness,[47,91,92] incarceration,[91] and drug use[47] have also been linked with increased risk of recent TB transmission. Further, neighborhood-level studies have indicated that area-based measures of disadvantage are associate with increased rates of TB transmission, a finding particularly pronounced for U.S.-born populations.[46]

Rodwell et al. found that while many of the aforementioned risk factors appeared to be

statistically significant in univariate analyses, few retained their significance in multivariable models.[92] Moreover, the most significant factors in multivariable factors were not clinical, but rather indicators of social disadvantage. However, there are few studies that use multivariable models to investigate risk factors for TB transmission. Furthermore, several investigations have suggested the risk factors for transmission are different for foreign-born and U.S.-born populations.[96] Studies that do not separate these two populations may produce incorrect inferences regarding the drivers of transmission. This reinforces the need for research that accounts for population-specific risk factors for TB transmission using multivariable techniques that can disentangle the independent risk associations.

In 2012, Michigan had an annual incidence rate of 1.28 TB cases per 100,000[97]—notably lower than the national incidence rate of 3.2 per 100,000.[35] Despite being a low-incidence state, there is evidence of persistent disparities in TB incidence, particularly by race and nativity. In studies examining only recently transmitted cases, Blacks had an incidence rate nearly 19 times greater than Whites.[97] This is in contrast to the incidence of reactivation of LTBI in foreign-born people that is 19 times greater than the U.S-born.[97] These studies not only suggest that the drivers of transmission may differ from those of the reactivation of LTBI, but also these relationships may be fundamentally different between U.S.-born and foreign-born populations. Using TB surveillance data collected by the Michigan Department of Health and Human Services, we evaluated risk factors for TB transmission at both the individual- and neighborhood-level among U.S.-born and foreign-born populations separately. Despite Michigan having a relatively low number of TB cases, transmission is still occurring, and perhaps disproportionately more so among the most vulnerable.

3.3 Methods

3.3.1 Study population and data collection

A total of 1,800 cases of TB were reported in Michigan from January 1, 2004 to December 31, 2012. Of those, 1,390 (77%) were culture-confirmed and 410 (23%) were culture-negative clinical cases. Of the 1,390 culture-confirmed cases, 1,316 (95%) had complete genotype data available, including spoligotype and 12-locus-MIRU-VNTR results.

Our study sample was drawn from the 1,316 cases with complete genotype data and address information. Cases were excluded if they did not have both spoligotype and 12-locus-MIRU-VNTR results. Cases were also excluded if they did not have complete address information. The final study sample consisted of 1,236 cases, representing 69% of the 1,800 total cases reported during this time period.

Demographic and clinical characteristics of cases were drawn from TB surveillance data collected by MDHHS using the "Report of a Verified Case of TB" (RVCT) form developed by the Centers for Disease Control and Prevention (CDC).[65] Additionally, we included variables defined on the RVCT form as "known TB risk factors." Individuals were linked to their particular census block group by the address reported on the RVCT form. Such addresses were geocoded and subsequently linked with block group-level census data. Additionally, 104 cases (6% of the total 1,800 cases reported in Michigan) were missing address information and were therefore excluded from the analysis **(Table 3.8-6**). The 104 cases missing address information included those missing addresses altogether, those coded as homeless, and those with addresses listed as a hospital or laboratory. These cases were significantly different than those with address information by race, nativity, geographic area, and site of disease.

Block group characteristics were derived from the American Community Survey (ACS),

5-year estimates for 2012.[98] We used the block group as the unit of analysis for neighborhood effects because we believe that features of the block group can be a proxy for both household-level features such as degraded housing and vacancy and as well as access to neighborhood resources. We believe both dimensions could affect TB transmission. We defined block group-level disadvantage by developing a mean index created by summing the values for the following variables and taking the mean of the sum: percent Black, percent Hispanic, percent with less than a high school education, percent unemployed, percent utilizing public assistance, percent of vacant properties, and percent with a poverty to income ratio below 2. The U.S. Census defines having an income-to-poverty ratio below 2 as being "poor or struggling"; thus we used 2.0 as our cut-point for the income-to-poverty ratio in the summary index. A factor analysis was used to confirm the construction of the summary variable. The factor analysis showed that six of the seven variables loaded on to the same factor; percent Hispanic had a low loading value for the factor. Based on the factor analysis we then excluded percent Hispanic from the final summary index. We were also interested in exploring the proportion of the block group that is foreign-born. However, the ACS does not report these data for block groups.

This study was approved by the University of Michigan Institutional Review Board for Social and Behavioral Sciences and by the Michigan Department of Health and Human Services (MDHHS) Institutional Review Board.

3.3.2 Genetic Cluster Definition

To classify cases as resulting from recent transmission, we followed previous methods that used both spoligotype and 12-locus-MIRU-VNTR results, as well as diagnostic dates[38,64] to define genetically clustered TB cases. Clustered cases were those that shared an identical spoligotype and 12-locus-MIRU-VNTR result with at least one other case in the sample, and also

had a diagnostic data within one year of such a case. The addition of a time restriction into this definition allows for greater specificity in the classification of genetically clustered cases. Unique cases, or non-clustered cases, were those that either did not share an identical spoligotype and 12-locus-MIRU-VNTR result or did not have a diagnostic date within the one year time period.

Genetically clustered cases do not necessarily occur in spatial clusters. In addition, genetically clustered cases could become apparent after more than one year if they were connected by another case with an identical genotypic pattern with the one-year time frame. Genetically clustered cases were considered a proxy for those cases resultant from recent transmission; non-clustered were considered a proxy for those cases resultant from reactivation of LTBI.

3.3.3 Statistical Analysis

To determine which individual- and neighborhood-level factors were significant predictors of TB clustering, we analyzed the prevalence of recently transmitted cases in relation to four classes of variables: demographic factors, known TB risk factors, clinical factors, and neighborhood characteristics of the block group. Demographic factors included: nativity, race, age, and sex. Known TB risk factors included: HIV status, alcohol use, diabetes, injecting drug use, non-injecting drug use, long-term care facility stay, and homelessness. Clinical risk factors included: immunosuppression, sputum-smear status, sputum-culture status, site of TB disease, and initial chest radiography results. Block-group characteristics included: population density, proportion of the population over 64 years of age, and a summary index of neighborhood disadvantage.

Univariate, modified Poisson regression models were used to examine the prevalence of

recent transmission with each of the risk factors individually. For data reduction, we then used stepwise regression models to determine which variables, when considered together, were the most significant predictors of transmission. Lastly, we constructed a final set of multivariable modified Poisson models that included the variables determined to be significant based on the step-wise regression model as well as based on *a priori* knowledge.

Our final multivariable regression models were modified Poisson models[99] using generalized estimating equations (GEE) to account for nesting of cases within block groups. Such models allow for accurate parameter estimation and robust variance estimates by accounting for the correlated errors existing between cases in the same block group. The prevalence ratio and corresponding 95% confidence intervals were calculated using a Poisson regression model with a log link function.

Previous literature has suggested that the factors driving transmission are different for U.S.-born and foreign-born populations.[46,92,100] Accordingly, we also stratified our models by nativity and reported the statistical models for U.S.-born and foreign-born persons separately.

For all analyses, we used an alpha level of 0.05 to signify significance. For the stepwise regression, we used an alpha level of 0.2 in order for a variable to be selected into the model and an alpha level of 0.05 for retention in the final step-wise regression model.

3.4 Results

3.4.1 Characteristics of the study sample

1,236 individuals were included in our final study sample (**Table 3.8-1**). The sample was 23% Non-Hispanic White, 40% Non-Hispanic Black/African American, 25% Non-Hispanic Asian, 2% Non-Hispanic Other category, and 10% Hispanic. 72% of the sample was between the ages of 18-64 years. The sample was 60% male, 40% female. 45% of the sample was foreign-

born; 55% U.S.-born. 94% of the sample was reported in a metropolitan county. 69% of the sample had primarily pulmonary TB, 22% primarily extra-pulmonary TB (EPTB), and 8% both pulmonary and EPTB.

477 (39%) of the 1,236 individuals were classified as a genetically clustered case while 759 (61%) were classified as non-clustered. The 477 clustered cases belonged to 100 unique genetic clusters ranging in size from 2 to 49 cases. Another 6 individuals who were identified as part of clustered cases were singleton clusters because their counterparts were excluded from this study sample due to missing information on key covariates.

The proportion of clustering was significantly different comparing foreign-born and U.S.-born individuals (P-value < 0.0001) (**Table 3.8-2**). 52% of the U.S.-born individuals were clustered compared to 22% of the foreign-born individuals.

3.4.2 Regression analysis results

We investigated four classes of risk factors for being a clustered case of TB: demographic characteristics, known TB risk factors, clinical characteristics, and neighborhood characteristics. In the univariate models for the full sample there were 15 variables, across all four classes that were significant predictors of clustering. In particular, nativity was a significant risk factor for clustering in univariate models. The U.S.-born had a significantly higher prevalence of clustering compared to the foreign-born (P=<0.001) (**Table 3.8-2**). Based on these results and the methodology of previous studies, we decided to stratify our results on nativity, in addition to reporting results for the full sample.

For the foreign-born population, only two factors were significant predictors of clustering in univariate models: individual-level race and being a known contact of an infectious case of TB

(**Table 3.8-4**). These two factors retained their significant in the step-wise regression models and were the only two significant predictors in the final multivariable models. For the U.S.-born population, a wide range of factors were significant predictors of clustering in univariate models (**Table 3.8-4**).The step-wise regression model reduced the number of significant variables to age, sex, homelessness, known contact of an infectious case of TB, neighborhood density, and neighborhood disadvantage (results not shown).

Our final regression models included the variables identified in the step-wise regression models as well as race, sputum-smear status, and proportion of the neighborhood over 64 years of age. However, while we included the same variables in the final models for both the U.S.-born and foreign-born, the associations between each the factor and the prevalence of clustering was notably different for the two groups (**Table 3.8-5**).

In the final multivariable model for the U.S.-born, several factors were significant predictors of clustering: age, sex, known contact of an infectious case of TB, homelessness, density of the neighborhood, and neighborhood disadvantage after controlling for all other covariates in the model (**Table 3.8-5**). Those 65+ years had a 53% reduced prevalence of clustering compared to those 18-64 years ($P < 0.0001$). Males had a prevalence of clustering 1.19 times greater than females ($P < 0.05$). The prevalence of clustering among those who were a known contact of an infectious case of TB was 1.27 times greater than those without such a contact ($P < 0.05$). Further, the prevalence of clustering among those who reported a history of homelessness in the past 12 months was 1.25 times greater than those who did not ($P < 0.05$).

For the U.S.-born, both neighborhood density and neighborhood disadvantage were significant predictors of clustering after controlling for all other covariates in the model. The prevalence of clustering for individuals living in the highest density neighborhoods was 1.31

times greater than for those living in the lowest density neighborhoods (Q4 vs Q1; P< 0.0001) (**Table 3.8-5**). The prevalence of clustering for individuals living in the most disadvantaged neighborhoods was 1.83 times greater than for those living in the least disadvantaged neighborhoods (Q4 vs Q1; P < 0.05). There also seemed to be a dose-response relationship in terms of neighborhood disadvantage—there was an increased prevalence of clustering for each quartile increase in neighborhood disadvantage.

In the final multivariable model for the foreign-born, non-Hispanic Asians had a prevalence of clustering 1.41 times greater than non-Hispanic Whites; Hispanics had a prevalence of clustering 2.03 times greater than non-Hispanic Whites (P < 0.05) (**Table 3.8-5**). Those that were a known contact of an infectious case of TB had a prevalence of clustering 1.8 times greater than those without such a contact (P < 0.05).

Among the foreign-born we did not see an effect of the neighborhood environment on the prevalence of clustering. Differences in these observed effects between foreign-born and U.S.-born were tested in the full sample using statistical interactions between nativity and neighborhood density and neighborhood disadvantage, as well as between nativity and race. In the multivariable model for the full sample, there was a significant interaction between nativity and neighborhood disadvantage (P< 0.001), but only marginally significant interaction between nativity and neighborhood density (P=0.10) and nativity and race (p=0.08).

3.5 Discussion

This analysis identified factors that were significant predictors of clustering among TB cases identified by routine surveillance in the state of Michigan, 2004-2012. We used genotypic clustering as a proxy for cases resulting from recent transmission. We found that the factors predicting recent transmission for the foreign-born were notably different than those for the U.S.-

born, with the exception of being a known contact of an infectious case of TB. For the U.S.-born, recent transmission was influenced more by individual-level and neighborhood-level socio-demographic factors than by clinical risk factors. While clinical factors and traditional TB risk factors were associated with TB transmission in univariate models, few retained significance in multivariable models. Our findings point to the importance of the social and physical context of people in influencing TB transmission in a high-disparity environment, particularly among U.S.-born populations.

Our findings further shed light on the difference between foreign-born and U.S.-born populations and their risk of TB. 52% of the U.S.-born cases of TB resulted from recent transmission, compared to 22% of foreign-born cases. Thus, among the foreign-born, perhaps the greatest concern in TB control should be reducing the rate of reactivation of LTBI. For the foreign-born populations, the risk of TB is likely related to the prevalence of TB in their country of origin—those emigrating from high-burden TB settings may be infected in their country of origin and reactivate once in the U.S.[81–83] While there is mandatory screening for foreigners applying for immigration status for active TB and LTBI, this screening only applies to those applying for permanent visas in the U.S., missing the large proportion of legal immigrants applying for temporary visas.[101] TB control strategies for this population should be targeted at diagnosing cases of LTBI before reactivation has occurred—this would also reduce transmission in these populations.

In the foreign-born analysis we saw that Asians had an increased prevalence of recent transmission compared to Whites. This is after controlling for measures of the neighborhood environment and other social risk factors. More work is needed to understand how the Asian population as a whole differs from other foreign-born populations. It may be that Asian

immigrants are more likely to live in closer proximity to one another or in multi-family housing. Future studies should seek to better understand what is driving this disparity. Additionally, future studies would benefit from disaggregating the Asian racial group into the ethnically diverse groups that compose it. This may also facilitate a better understanding of what is driving recent transmission in this population.

The observed differences in the effects of race and neighborhood density between the foreign-born and U.S.-born were not statistically different, precluding any firm conclusions about different patterns in incidence by nativity. However, the differences in the effect of neighborhood socioeconomic disadvantage by nativity were statistically supported, suggesting there are notable effects of the residential environment on TB transmission even after adjusting for individual risk factors for the U.S.-born. Several studies have found evidence of higher TB rates in socially disadvantaged neighborhoods.[54,102,103] However, few studies have reported such stark differences in the effects of the neighborhood environment by nativity. In her 2000 paper on residential segregation and TB, Acevedo-Garcia posits there are both direct and indirect pathways by which the neighborhood environment may influence TB risk.[104] Directly, the neighborhood environment can pattern a) the spatial distribution of susceptible and infectious cases, b) the contact patterns between these groups, and c) the density of the susceptible pool.[104] The likelihood of transmission of TB is a function of the size of the susceptible pool and how densely such susceptibles are distributed in a given space.[105–107] In our study, we were able to examine neighborhood density specifically and found that it was a significant predictor of transmission among the U.S.-born—even after controlling for neighborhood disadvantage. This finding makes sense given that the U.S.-born population had a higher prevalence of transmission of TB. Thus, an active case of TB in a high-density neighborhood will result in a greater number

of secondary cases than if the case were in a low-density neighborhood.

We also found evidence of the indirect influence of the neighborhood on TB transmission among the U.S-born. We observed a neighborhood-level disadvantage gradient in the prevalence of recently transmitted TB whereby those living in more disadvantaged neighborhoods had an increased prevalence of recent transmission. Previous studies have found a similar gradient both in incidence of TB overall,[44,103] as well as specifically for transmission.[46] Notably, our finding of the SES gradient in TB transmission only held true among the U.S.-born which is consistent with a study that reported that neighborhood-level gradients in disadvantage were steeper for the U.S-born.[100]

In univariate models among the U.S.-born, both Blacks and Hispanics were at higher risk for TB transmission compared to Non-Hispanic Whites. This disparity was attenuated in multivariable models. Such models showed that neighborhood-level disadvantage was a more meaningful predictor of recent transmission than individual-level race in this population. This lends support to the fact that race is only a meaningful predictor of recent TB transmission insomuch as it is evidence of a much larger social pattern. In the case of TB, individual-level race is likely a proxy for disadvantage, and more specifically in our study, neighborhood-level disadvantage.

Other studies have also reported that the effects of the neighborhood environment depend on the race and ethnicity of the individual.[46,92,100,108] It may be that the neighborhood environment has different meanings, and confers different risks, depending on an individual's racial and ethnic identity. In the U.S., the neighborhood in which a person resides is not only indicative of the physical environment to which one is exposed but it also reflects a much deeper social history tied very closely to one's social identity. Thus, the neighborhood environment can

indirectly pattern the distribution of TB through such mechanisms as poverty, housing conditions, social disorganization, access to health care,[104] and political disinvestment. Moreover, Acevedo-Garcia argues that the quality of the social and physical environment are a result of larger structural influences such as structural racism and residential segregation, influences inextricably tied to individual-level race/ethnicity.[61] Structural influences such as residential segregation have been at work since early in the 20th century—systematically putting minority populations at risk.[109] Urban renewal and development efforts of the 1900s systematically benefited Whites while displacing minority populations resulting in minority communities with greater proportions of low quality housing, dilapidation, and material resource deprivation.[104] However, in addition to the lack of material resources, it is also the enduring stress of living in such an environment where one is continually exposed to structural disadvantage that can produce worse health outcomes for these populations[110–112] Such conditions have created silent epidemics whereby rates of diseases, such as TB are permitted to continue in isolated communities because those who are politically and socially advantaged are shielded from the enduring effects of the disease. Based on our findings, and consistent with other U.S.-based studies, transmission of TB is happening in insular communities defined by their socio-demographic make-up and hidden from their more advantaged counterparts.[92]

This framework also helps explain why we do not observe these same patterns in the foreign-born population. Only 28% of the foreign-born population lived in a disadvantaged neighborhood (above the median level of disadvantage); this is compared to 67% of the U.S.-born population. While some immigrant populations are likely to live in poor areas and be subject to extreme poverty, in our population seem to be of a higher SES class than the U.S.-born population. Further, even for those the foreign-born persons who may be living in disadvantaged

environments, these environments do not hold the same risk as they do for U.S.-born populations.

For both groups, being a known contact of an infectious case of TB was a significant risk factor for transmission of TB. This finding points to the success of current policies and procedures implemented at state and local health departments on active TB case findings. When an infectious case of TB is found, often the local health department will initiate a screening of all known contacts of the individual. The finding that those who are a known contact of an infectious case of TB are at greater risk for transmission is further proof that such a strategy is critical to identifying those at risk for transmission.

3.6 Limitations

There are several limitations to our study that should be considered in the interpretation of our study findings. First, inferences regarding individual-level risk based on group-level factors are vulnerable to the ecological fallacy. However, we are not assuming a causal relationship between neighborhood level factors and one's individual risk of TB transmission. Rather, we are making assumptions about the spaces and environments that might make one more or less susceptible to disease.

There were also limitations due to the exclusion criteria applied to derive the final study sample. Our analyses were contingent upon the availability of genotypic data and thus we excluded cases that were diagnosed based on clinical criteria, without culture confirmation. This could bias our results and could lead to underestimation of the association between each variable and prevalence of clustering if the clinical cases are significantly different than the culture-positive cases included in the analysis.

We only examined predictors of transmission within a sample of TB cases. Thus, it is plausible there are important predictors of TB transmission that are missed without comparisons to the larger TB-free population. A 2008 study used the 1999-2000 NHANES to estimate the national prevalence of LTBI. They estimated the prevalence of LTBI in the U.S. to be 4.8% (11, 213, 000).[90] Of those with LTBI, 5-10% will develop active disease sometime in their lifetime.[5,8] Our findings, therefore, may be generally applicable to the subset of those with LTBI who may reactivate and then subsequently be at risk to transmit the pathogen to susceptible individuals.

Additionally, while we believe that the addition of a time-restriction component adds greater specificity to our classification of recent transmission, there is a still the possibility of misclassification. However, we believe such misclassification would be non-differential and would bias any observed results towards the null.

Finally, the address information extracted from the RVCT form may not accurately capture the address for all individuals. Moreover, we excluded those without address information. This systematically leaves out the homeless population. However, the proportion of the study population without an address was less than 10% of the entire TB population and therefore, we do not believe such an exclusion significantly biased our findings. It is likely that any bias that would occur from such an exclusion is a bias towards the null, underestimating the true prevalence of clustering.

3.7 Conclusions

Our findings point to the need to consider the socio-economic context of individuals in designing interventions aimed at reducing transmission of TB. While a focus on individual-level factors, whether in our research studies or TB control strategies, may have been sufficient to reduce the incidence of TB in the U.S. overall in the last decades, such a focus is insufficient to

addressing enduring disparities in TB incidence, largely patterned along lines of social disadvantage. Reducing disparities in TB incidence, and particularly in TB transmission, will require strategies that can target high-risk groups and allocate resources effectively. Additionally, it may be that high-risk needs to be defined based on ecologic factors such as neighborhood poverty,[61] rather than on individual-level factors. Only then will TB elimination in the U.S. be possible in the foreseeable future.

3.8 Tables

Table 3.8-1 Comparison of the distribution of selected demographic and clinical characteristics among all TB cases (n=1,800) and the study sample (n=1,236) in Michigan, 2004-2012.

	Total TB Cases (n=1,800)		Study Sample (n=1,236)	
	No.	**%**	**No.**	**%**
Race				
Non-Hispanic White	439	24.39	285	23.06
Non-Hispanic Black/African American	706	39.22	497	40.21
Non-Hispanic Asian	423	23.5	304	24.6
Non-Hispanic Other	38	2.11	28	2.27
Hispanic	194	10.78	122	9.87
Age (years)				
<18	124	6.88	35	2.83
18-64	1263	70.16	891	72.09
65+	413	22.94	310	25.08
Sex				
Male	1047	58.2	735	59.51
Female	752	41.8	500	40.49
Missing	1		1	
Nativity				
Foreign-born	798	44.48	553	44.81
U.S.-born	996	55.52	681	55.19
Missing	6		2	
Geographic area				
Metro	1690	94.05	1158	93.69
Micro	49	2.73	39	3.16
Rural	9	0.5	5	0.4
Unknown	49	2.73	34	2.75
Missing				
Site of disease				
Pulmonary	1188	66.22	855	69.29
Extrapulmonary	463	25.81	277	22.45
Both	143	7.97	102	8.27
Missing	6		2	

Table 3.8-2 2x2 table comparing the proportion of clustering among foreign-born and U.S.-born populations.

	Clustered # (%)	**Non-Clustered # (%)**	**Total**
Foreign-born	121 (22)	432 (78)	553
U.S.-born	354 (52)	327 (48)	681
Total	475	759	1234

P-value < 0.0001 based on the Chi-Square test.
**2 individuals were missing data on nativity*

Table 3.8-3 Comparison of the distribution of selected covariates between clustered and non-clustered TB cases.

	Clustered Cases		Non-Clustered Cases		P-Value
	N	%	N	%	
Total	477	38.59	759	61.41	
Demographic Factors					
Nativity					
U.S.-born	354	74.21	327	43.08	<0.0001
Foreign-born	121	25.37	432	56.92	
Missing	2	0.42	0	0	
Race					
Non-Hispanic White	74	15.51	211	27.8	<0.0001
Non-Hispanic Black	277	58.07	220	28.99	
Asian	78	16.35	226	29.78	
Other	11	2.31	17	2.24	
Hispanic	37	7.76	85	11.2	
Age (years)					
<18	18	3.77	17	2.24	<0.0001
18-64	391	81.97	500	65.88	
65+	68	14.26	242	31.88	
Sex					
Male	308	64.57	427	56.26	0.0059
Female	168	35.22	332	43.74	
Missing	1	0.21	0	0	
Geographic Location					
Metro	459	96.23	699	92.09	0.0224
Micro	10	2.1	29	3.82	
Rural	2	0.42	3	0.4	
Unknown	6	1.26	28	3.69	
Known TB Risk Factors					
Diabetes					
Diabetes	23	4.82	46	6.06	0.3558
No Diabetes	454	95.18	713	93.94	
HIV					
HIV Test Positive	40	8.39	29	3.82	0.0024
HIV Test Negative	313	65.62	477	62.85	
HIV Test Not Done	71	14.88	144	18.97	
HIV Test Refused	39	8.18	82	10.8	
HIV Test Unknown	14	2.94	27	3.56	
Alcohol Use					
Alcohol Use	86	18.03	66	8.7	<0.0001
No Alcohol Use	365	76.52	670	88.27	
Missing	26	5.45	23	3.03	
Injecting Drug Use (IDU)					
IDU Use	27	5.66	12	1.58	<0.0001
No IDU Use	428	89.73	732	96.44	
Missing	22	4.61	15	1.98	
Non-Injecting Drug Use (IDU)					
Non-IDU Drug Use	68	14.26	33	4.35	<0.0001
No Non-IDU Drug Use	381	79.87	707	93.15	

Missing	28	5.87	19	2.5	
Stay in a Long-Term Care (LTC) Facility					
LTC Stay	20	4.19	27	3.56	0.8093
No LTC Stay	454	95.18	726	95.65	
Missing	3	0.63	6	0.79	
Homelessness					
Homeless	47	9.85	23	3.03	<0.0001
Not Homeless	420	88.05	729	96.05	
Missing	10	2.1	7	0.92	
Incarceration in last 12 months					
Incarcerated	11	2.31	9	1.19	0.2736
Not Incarcerated	464	97.27	745	98.16	
Missing	2	0.42	5	0.66	
Directly Observed Therapy Time					
< 18 weeks	81	16.98	134	17.65	0.1537
19-25 weeks	67	14.05	129	17	
26-31 weeks	90	18.87	169	22.27	
> 31 weeks	99	20.75	129	17	
DOT Missing	140	29.35	198	26.09	
Known Contact of an Infectious TB Case					
Infectious contact	53	11.11	35	4.61	<0.0001
No Infectious Contact	424	88.89	724	95.39	
Incomplete Latent TB Infection (LTBI) Treatment					
Incomplete LTBI	6	1.26	12	1.58	0.6443
No Incomplete LTBI	471	98.74	747	98.42	
Clinical Risk Factors					
End Stage Renal Disease					
ESRD	2	0.42	4	0.53	0.7908
No ESRD	475	99.58	755	99.47	
Organ Transplant or TNF-a Antagonist Therapy					
Transplant/Therapy	11	2.31	11	1.45	0.2674
No Transplant/Therapy	466	97.69	748	98.55	
Immunosuppression					
Immunosuppression	14	2.94	21	2.77	0.8622
No Immunosuppression	463	97.06	738	97.23	
Sputum-Smear (SS) Status					
SS Positive	251	52.62	305	40.18	<0.0001
SS Negative	122	25.58	212	27.93	
SS Not Done	102	21.38	241	31.75	
SS Unknown	2	0.42	0	0	
SS Missing	0	0	1	0.13	
Sputum-Culture (SC) Status					
SC Positive	339	71.07	441	58.1	<0.0001
SC Negative	32	6.71	60	7.91	
SC Not Done	106	22.22	252	33.2	
SC Unknown	0	0	5	0.66	
SC Missing	0	0	1	0.13	
Site of TB Disease					
Pulmonary TB (PTB) Only	359	75.26	496	65.35	0.0012
Extra-Pulmonary TB (EBTB) Only	81	16.98	196	25.82	
Both PTB and EPTB	37	7.76	65	8.56	
Missing	0	0	2	0.26	

Initial Chest Radiography (X-Ray)					
Normal Chest X-Ray	51	10.69	127	16.73	0.0101
Abnormal Chest X-Ray	407	85.32	591	77.87	
Chest X-Ray Not Done	16	3.35	37	4.87	
Chest X-Ray Unknown	3	0.63	2	0.26	
Missing	0	0	2	0.26	
Block Group Characteristics					
Density					
Q1	96	20.13	213	28.06	<0.0001
Q2	113	23.69	196	25.82	
Q3	116	24.32	193	25.43	
Q4	152	31.87	157	20.69	
Proportion of Population Over 64 Years					
Q1	118	24.74	191	25.16	0.5887
Q2	117	24.53	192	25.30	
Q3	113	23.69	196	25.82	
Q4	129	27.04	180	23.72	
Index of Neighborhood Disadvantage					
Q1	70	14.68	239	31.49	<0.0001
Q2	79	16.56	230	30.3	
Q3	135	28.3	175	23.06	
Q4	193	40.46	115	15.15	

Q = Quartile
Results based on chi-square test comparing the distribution of covariates among clustered and non-clustered TB cases.

Table 3.8-4 Results of univariate Poisson regression models estimating the prevalence of clustered cases for each single factor for the sample overall and U.S.-born and foreign-born separately.

	Overall Prevalence Ratio (95% CI)	U.S.-Born Prevalence Ratio (95% CI)	Foreign-Born Prevalence Ratio (95% CI)
Demographic Factors			
Nativity			
U.S.-born vs FB	2.38 (2.00, 2.83)**		
Race			
NH-Asian vs. NH-White	1.51 (0.92, 2.50)**	0.79 (0.23, 2.66)**	2.54 (1.28, 5.03)*
NH-Black vs NH-White	2.15 (1.74, 2.66)	1.96 (1.58, 2.43)	1.35 (0.55, 3.29)
NH-Other vs NH-White	1.51 (0.92, 2.50)	1.58 (0.95, 2.61)	1.98 (0.49, 8.03)
Hispanic vs NH-White	1.17 (0.84, 1.63)	1.73 (1.11, 2.71)	2.52 (1.21, 5.25)
Age (in years)			
<18 vs 18-64	1.17 (0.84, 1.63)**	1.05 (0.76, 1.47)**	1.57 (0.81, 3.06)
65+ vs 18-64	0.50 (0.40, 0.62)	0.39 (0.30, 0.50)	0.79 (0.51, 1.22)
Sex			
Male vs Female	1.25 (1.07,1.45)*	1.29 (1.10, 1.52)*	0.93 (0.68, 1.28)
Known TB Risk Factors			
Diabetes			
Diabetes vs No Diabetes	0.86 (0.61, 1.20)	0.78 (0.52, 1.18)	1.08 (0.58, 2.02)
HIV			
HIV+ vs HIV -	1.46 (1.17, 1.82)*	1.22 (1.0, 1.50)**	1.30 (0.60, 2.80)
HIV Not Done vs HIV -	*0.83 (0.68, 1.03)*	0.74 (0.59, 0.92)	0.87 (0.53, 1.42)
HIV Unknown vs HIV -	0.86 (0.56, 1.33)	0.67 (0.40, 1.13)	1.17 (0.49, 2.79)
HIV Refused vs HIV -	0.81 (0.62, 1.07)	0.69 (0.49, 0.96)	1.24 (0.79, 1.95)
Alcohol Use			
Alcohol Use vs None	1.60 (1.36, 1.89)**	1.26 (1.08, 1.48)*	0.94 (0.38, 2.29)
Injecting Drug Use (IDU)			
IDU vs None	1.88 (1.50, 2.34)**	1.37 (1.09, 1.73)*	3.16 (1.40, 7.15)*
Non-Injecting Drug Use (Non-IDU)			
Non-IDU Use vs None	1.92 (1.64, 2.25)**	1.45 (1.24, 1.70)**	1.36 (0.42, 4.43)
Long-Term Care Facility			
LTC vs No LTC	1.11 (0.79, 1.55)	0.81 (0.57, 1.16)	1.84 (0.62, 5.44)
Homelessness			
Homeless vs Not	1.84 (1.53, 2.20)**	1.62 (1.38, 1.89)**	0.91 (0.33, 2.53)
Incarceration			
Incarcerated vs Not	1.43 (0.96, 2.14)	1.11 (0.75, 1.64)	NA
DOT Therapy Time			
< 18 wks vs > 31 wks	0.87 (0.69, 1.09)	0.77 (0.60, 0.98)	1.22 (0.73, 2.01)
26-31 wks vs > 31 wks	0.80 (0.64, 1.00)	0.90 (0.72, 1.13)	0.89 (0.54, 1.47)
19-25 wks vs > 31 wks	*0.79 (0.62, 1.01)*	0.82 (0.63, 1.07)	1.08 (0.66, 1.78)
DOT missing vs > 31 wks	0.96 (0.79, 1.16)	0.90 (0.75, 1.09)	0.82 (0.48,1.42)

Infectious Contact			
Infectious contact vs Not	1.63 (1.35, 1.96)**	1.34 (1.11, 1.63)*	2.18 (1.40, 3.37)**
Incomplete LTBI Treatment			
Incomplete LTBI vs Not	*0.86 (0.45, 1.66)*	1.07 (0.59, 1.92)	0.50 (0.08, 3.22)
Clinical Risk Factors			
End Stage Renal Disease (ESRD)			
ESRD vs Not	0.86 (0.28, 2.68)	0.64 (0.13, 3.17)	1.53 (0.31, 7.63)
Organ Transplant or TNF-a Antagonist Therapy			
Transplant/Therapy vs Not	1.30 (0.85, 1.99)	1.12 (0.69, 1.82)	1.54 (0.60, 3.92)
Immunosuppression			
Immuno-suppressed vs Not	1.04 (0.69, 1.57)	0.75 (0.45, 1.25)	1.94 (0.98, 3.87)
Sputum-Smear Status			
SSP vs SSN	1.24 (1.04, 1.46)**	1.15 (0.96, 1.37)*	1.00 (0.70, 1.44)
SSND vs SSN	*0.82 (0.66, 1.01)*	0.80 (0.63, 1.02)	0.78 (0.52, 1.19)
SS Unknown vs SSN	2.74 (2.38, 3.15)	1.98 (1.69, 2.30)	NA
Site of TB Disease			
PTB vs EPTB	*1.43 (1.17, 1.75)***	1.13 (0.92, 1.40)	1.44 (0.98, 2.12)
Both PTB/EPTB vs EPTB Only	1.24 (0.90, 1.70)	1.32 (0.97, 1.79)	1.00 (0.52, 1.92)
Initial Chest Radiography			
Abnormal vs Normal	1.42 (1.12, 1.82)*	1.04 (0.81, 1.33)	1.64 (1.01, 2.66)
Not Done vs Normal	1.05 (0.66, 1.69)	0.87 (0.53, 1.43)	1.01 (0.37, 2.77)
Unknown vs Normal	*2.09 (0.99, 4.44)*	0.56 (0.57, 3.02)	3.41 (0.79, 14.64)
Block Group Characteristics			
Density			
Q2 vs Q1	1.11 (0.87, 1.42)**	1.19 (0.90, 1.57)**	1.05 (0.68, 1.62)
Q3 vs Q1	*1.24 (0.98, 1.56)*	1.38 (1.06, 1.79)	0.92 (0.59, 1.43)
Q4 vs Q1	1.65 (1.33, 2.04)	1.85 (1.47, 2.34)	0.95 (0.60, 1.49)
Proportion Over 64 Years			
Q2 vs Q1	0.97 (0.79, 1.20)	0.90 (0.73, 1.11)	0.82 (0.55, 1.22)
Q3 vs Q1	0.93 (0.75, 1.15)	0.80 (0.64, 0.99)	0.76 (0.47, 1.25)
Q4 vs Q1	1.03 (0.83, 1.27)	0.83 (0.67, 1.03)	1.14 (0.77, 1.69)
Index of Neighborhood Disadvantage			
Q2 vs Q1	1.13 (0.85, 1.50)**	1.58 (1.02, 2.44)**	0.86 (0.59, 1.26)
Q3 vs Q1	1.92 (1.52, 2.44)	2.72 (1.86, 3.98)	0.83 (0.54, 1.27)
Q4 vs Q1	2.76 (2.21, 3.44)	2.85 (1.96 (4.14)	1.42 (0.89, 2.27)

Results are based on univariate Poisson regression models

All models are adjusted for all other covariates

* indicates a P-value ≤ 0.05 based on type 3 effects

** indicates a P-value ≤ 0.001 based on type 3 effects

SSP = Sputum-Smear Positive; SSN= Sputum-Smear Negative; SSND = Sputum-Smear Not Done

PTB = pulmonary TB; EPTB = Extra-pulmonary TB

NA = not application due to a lack of cases within levels of the variables

Q = quartile

Table 3.8-5 Results of final multivariable Poisson regression models estimating the prevalence of clustering for the sample overall and U.S.-born and foreign-born separately.

	Overall (N=1,336)	**U.S.-Born (N=681)**	**Foreign-Born (N=553)**
	Prevalence Ratio (95% CI)	**Prevalence Ratio (95% CI)**	**Prevalence Ratio (95% CI)**
Demographic Factors			
Nativity			
U.S.-born vs. Foreign-born	2.61 (2.01, 3.40)**		
Race			
Non-Hispanic Asian vs. Non-Hispanic White	2.0 (1.42, 2.80)*	0.59 (0.18, 1.90)	2.41 (1.22, 4.75)*
Non-Hispanic Black vs Non-Hispanic White	1.32 (1.05, 1.65)	1.20 (0.95, 1.53)	1.22 (0.48, 3.06)
Other vs Non-Hispanic White	1.36 (0.77, 2.43)	1.22 (0.63, 2.36)	1.87 (0.46, 7.58)
Hispanic vs Non-Hispanic White	1.54 (1.11, 2.14)	1.33 (0.90, 1.97)	2.03 (0.95, 4.35)
Age (in years)			
<18 vs 18-64	1.04 (0.75, 1.45)**	1.09 (0.81, 1.46)**	1.52 (0.74, 3.13)
65 + vs 18-64	0.55 (0.44, 0.69)	0.47 (0.36, 0.61)	0.83 (0.52, 1.33)
Sex			
Male vs Female	1.12 (0.97, 1.30)	1.19 (1.02, 1.39)*	0.89 (0.64, 1.23)
Clinical Characteristics			
Sputum-Smear			
SSP vs SSN	1.06 (0.91, 1.24)	1.07 (0.91, 1.26)	1.02 (0.71, 1.47)
SSND vs SSN	0.90 (0.73, 1.10)	0.98 (0.799, 1.22)	0.77 (0.51, 1.18)
Known TB Risk Factors			
Infectious Contact			
Infectious contact vs Not	1.36 (1.13, 1.65)*	1.27 (1.04, 1.54)*	1.80 (1.83, 2.74)*
Homeless			
Homeless vs Not	1.24 (1.06, 1.44)*	1.25 (1.08, 1.45)*	0.78 (0.27, 2.24)
Block Group Characteristics			
Density			
Q2 vs Q1	0.94 (0.77,1.15)*	0.90 (0.72, 1.14)**	0.99 (0.64, 1.52)
Q3 vs Q1	1.0 (0.82, 1.22)	1.03 (0.83, 1.29)	0.93 (0.59, 1.46)
Q4 vs Q1	1.22 (1.00, 1.48)	1.31 (1.06, 1.62)	0.85 (0.52, 1.41)
Proportion of Population over 64 Years			
Q2 vs Q1	0.97 (0.82,1.17)*	1.06 (0.87, 1.29)	0.88 (0.59, 1.31)
Q3 vs Q1	0.95 (0.78, 1.15)	1.01 (0.83, 1.24)	0.78 (0.47, 1.29)
Q4 vs Q1	1.19 (0.99, 1.42)	1.16 (0.96, 1.41)	1.22 (0.79, 1.88)
Index of Neighborhood Disadvantage			
Q2 vs Q1	1.02 (0.78, 1.35)*	1.37 (0.89, 2.10)*	0.93 (0.64, 1.36)
Q3 vs Q1	1.28 (0.99, 1.66)	1.75 (1.15, 2.67)	0.93 (0.59, 1.48)
Q4 vs Q1	1.47 (1.12, 1.92)	1.83 (1.21, 2.76)	1.56 (0.89, 2.74)

Results are based on multivariable Poisson regression models

All models are adjusted for all other covariates

* indicates a P-value ≤ 0.05 based on type 3 effects

** indicates a P-value ≤ 0.001 based on type 3 effects

SSP = Sputum-Smear Positive; SSN= Sputum-Smear Negative; SSND = Sputum-Smear Not Done

Q = quartile

Table 3.8-6 Supplementary table comparing the distribution of key covariates among cases with address information and those without address information.

	Cases with Address Information		Cases Missing Address Information		P-Value
	#	%	#	%	
Total Cases = 1,800	1,696	94.22	104	5.78	
Race					
White	579	34.14	39	37.5	<0.0001
Black/African American	677	39.92	44	42.31	
Asian	410	24.17	18	17.31	
American Indian/Alaskan Native	5	0.29	0	0	
Native Hawaiian	3	0.18	0	0	
Other	11	0.65	0	0	
Unknown	11	0.65	0	0	
Missing	0	0	3	2.88	
Age (years)					
<18	117	6.9	7	6.73	0.7782
18-64	1187	69.99	76	73.08	
65+	392	23.11	21	20.19	
Sex					
Male	976	57.55	71	68.27	0.0971
Female	719	42.39	33	31.73	
Missing	1	0.06	0	0	
Nativity					
Foreign-born	759	44.75	39	37.5	<0.0001
US-born	935	55.13	61	58.65	
Missing	2	0.12	4	3.85	
Geographic area					
Metro	1596	94.10	94	90.38	<0.0001
Micro	46	2.71	3	2.88	
Rural	8	0.47	1	0.96	
Unknown	46	2.71	3	2.88	
Missing	0	0.00	3	2.88	
Site of disease					
Pulmonary TB (PTB) Only	1116	65.80	72	69.23	<0.0001
Extrapulmonary TB (EPTB) Only	441	26.00	22	21.15	
Both PTB and EPTB	137	8.08	6	5.77	
Missing	2	0.12	4	3.85	

Results based on chi-square test comparing the distribution of covariates among cases with address information and those without address information.

CHAPTER 4. THE SOCIO-DEMOGRAPHIC CHARACTERISTICS OF TUBERCULOSIS CASES IN METRO DETROIT

4.1 Background & Rationale

There is a long history of stark disparities in TB along lines of social disadvantage in the U.S. Despite the ubiquity of TB exposure during the 19th and early-20th centuries, TB disproportionately burdened certain subpopulations, namely racial/ethnic minorities and immigrants. The disparities in TB existed not only in terms of who was exposed to and developed TB but also in terms of who received treatment. Sanatoriums—popular in the early 1900s –were reserved almost exclusively for White, U.S.-born individuals.[31] Moreover, the subsequent declines in TB incidence throughout the 20th century were disproportionately concentrated in the most advantaged groups.

The disparities in TB incidence have persisted into current time—nationally, TB still disproportionately affects the foreign-born, racial/ethnic minorities, the poor, those living in urban environments, the homeless, and the incarcerated.[35,39,40] Our findings in Michigan further shed light on persistent and pervasive disparities, particularly along lines of race and nativity. From 2004-2012, Blacks had an average incidence 19 times greater than Whites among cases of recently transmitted tuberculosis (TB) (Aim 1)—this is compared to 6 times greater incidence in Blacks versus Whites nationally.[35] The foreign-born had an average incidence 19 times greater than the U.S.-born among cases of reactivation of latent TB infection (LTBI) (Aim 1). In our

analysis of risk factors for recently transmitted TB, markers of social vulnerability such as foreign-born nativity, minority race status, homelessness, drug use, stay in a long-term care facility were consistently the most significant predictors of TB transmission compared to clinical characteristics (Aim 2).

Despite evidence of significant disparities, data on the trends and distribution of TB are mainly focused on reporting of surveillance trends, and mostly at a national level. While there is an acknowledgement of the disparities in TB incidence among certain subgroups (i.e. minorities and socio-economically disadvantaged), there is a lack of work that aims to understand these trends and the mechanisms underlying them. Such a focus on national trends without careful attention to the systems creating and allowing disparities to exist may inadvertently give those involved in TB control a false sense of hope. While the absolute burden of disease has decreased in recent decades, disparities in incidence have increased. In the 1989 Strategic Plan for the Elimination of Tuberculosis in the United States, the CDC put forth a hypothesis that TB could be eliminated in the U.S. by 2010 because it was concentrated in "geographically and demographically defined pockets."[104,113] While this assertion by the CDC that TB has moved from being a disease common in the population to concentrated in disadvantaged populations is accurate, assertions such as this neglect the rising disparities that continue to persist in TB distribution among disadvantaged populations, particularly minority and foreign-born populations. In her paper on the links between residential segregation and infectious disease, Acevedo-Garcia argues that as public health professionals it is unacceptable for rising disparities to be tolerated even if the overall burden of disease is declining.[104] Further, she argues that residential segregation shields more advantaged groups from recognizing the continuing impact of TB, reducing incentives to address the disease.[104] Regardless of the national trends in TB

incidence, the concentration of TB in geographically and demographically confined groups creates conditions for disparities in TB to persist.

In addition to the focus on national aggregate trends, current TB studies tend to report single-factor descriptions rather than multivariable analyses that can account for complex relationships between variables. Few studies have offered a more thorough explanation of how social factors such as race, nativity, sex, and age may be working together to augment risk. For example, our findings in Aim 1 of this dissertation demonstrated a significant suppression effect of race by nativity. In a single regression model with only race, the disparity between Asian and Whites was greater than the disparity between Blacks and Whites. When nativity was included in the regression model, the disparity between Asians and Whites reduced by nearly 40%, while the disparity between Blacks and Whites increased making Blacks the highest risk racial group (Aim 1). In her study of residential segregation and TB, Acevedo-Garcia suggests that delineation of single risk factors without attention to the systems and mechanisms in which they operate actually precludes TB researchers from understanding the true epidemiology of TB.[104,114] Single-factor analyses likely miss important relationships that exist between social variables.

Both historical and contemporary evidence highlight the social patterning of TB, yet there is a scarcity of research explicitly aimed at understanding the pathways by which the social determinants of health are associated with TB. This is driven, in part by, a lack of detailed socio-demographic data on TB patients. Much of what we know about the social experience of TB patients in the U.S. is derived from evidence (both formal and anecdotal) decades old. To date, very few studies have been able to ascertain detailed socio-demographic data on TB patients. Researchers in Houston, TX sought to gather more in-depth data on TB patients by administering a survey in a population-based study of actively enrolled cases in order to assess the association

of ethnicity and the risk of being a recently transmitted cases of TB in this population.[115] Interestingly, they found that markers of socio-economic status such as education, employment, and income, and not ethnicity and nativity, were more significant predictors of being a recently transmitted case of TB.[115] Their study was focused on risk factors for transmission rather than documenting disparities in general TB disease, and was limited in the scope of variables considered. However, their findings point to the feasibility and need for studies that can gather more in-depth information on the social characteristics of TB cases.

Employing a social determinants of health framework is necessary to not only understand the patterns of incidence and disparities in TB, but also to design interventions that can focus resources on the most at-risk groups. Current socio-demographic data is limited to what is available on the patient chart and "Report of a Verified Case of TB" (RVCT)[65] form produced by the CDC. These data are often based on clinician observations and are mainly focused on collecting data on known TB risk factors. To address the lack of extensive socio-demographic data, we designed a survey instrument aimed to ascertain detailed multi-dimensional information on the social experience of those with TB. Our hope is that the data generated from this study will yield important insights into the modern TB epidemic and facilitate resources being efficiently and effectively allocated to those most at risk.

4.2 Study Design

This study is a cross-sectional analysis of current TB patients in Metro Detroit, Michigan. The study uses three health departments in the Detroit area: Oakland County Health Department, Wayne County Health Department, and Detroit City Health Department.

4.2.1 Study Site Recruitment

Much of the substantive work of this aim has been in the development of collaborations with the state and local health departments and design of a survey instrument to address the needs outlined above.

We decided to only focus on TB cases occurring in the Detroit Metro given that nearly 75% of the TB cases occur there.[36] In addition, we were particularly interested in understanding the social profile of both U.S.-born and foreign-born TB cases. Since many of the U.S.-born TB case are identified in the Metro Detroit area this seemed the appropriate geographic area to focus on.

We recruited three health departments to collaborate with us: Oakland County Health Department, Wayne County Health Department, and Detroit City Health Department. Within each health department we specifically partnered with the TB control unit. The survey is administered by the healthcare workers who routinely oversee directly observed therapy (DOT) to identified TB patients in their respective catchment areas. Information on the survey logistics for each site is listed in **Table 4.8-1**.

Our formal collaboration with each health department also included joint IRB approvals between the Michigan Department of Health and Human Services (MDHHS), the University of Michigan and each individual health department. To do this, we received a sign letter of support from each health department.

4.2.2 Survey Development

The process of developing a survey instrument to fit the needs of this specific patient population was an iterative process spanning months, and involving many different parties. The survey needed to accomplish three main objectives: one) collect detailed socio-demographics

variables relevant to the lives of persons with TB in a standardized format; two) collect these data in a manner feasible for the patients, study team, and the health department staff to carry-out; and three) create buy-in from both the state and local health departments to carry out the study.

In designing the survey instrument, we collated months of information that had been gathered from meetings with state and local TB control staff. We also examined the RVCT form to identify either components missing from the form, or questions that were based on clinician observation, rather than patient self-report. We used this information to identify the key question themes that should be addressed with the survey instrument.

We used previously validated surveys from major cohort studies to begin compiling potential question. These studies included: Jackson Heart Study,[116] Detroit Neighbor Health,[117] Multi-Ethnic Study of Atherosclerosis,[118] Health and Retirement Study,[119] and the Americans' Changing Lives Study.[120] However, there were also several major themes for which we could not find an adequate question in one of the aforementioned studies. In this case, we designed our own questions.

The survey instrument was designed to understand the current social profile of TB patients in terms of their basic demographics, social status, and economic status. We also wanted to gather on evidence on what their social profile was before they were diagnosed with TB. We did this explicitly with questions asking them to recall back to before their diagnosis. However, we also assumed that current life circumstances can be used as a proxy measure for their social experiences before TB. We hypothesized that social factors may have a role in patterning not only one's risk of getting active TB disease, but also the probability that one is exposed to Mycobacterium tuberculosis (MTB), the pathogen causing TB disease, as well as the likelihood

of transmission of MTB when active TB disease is present. Thus, two main questions guided the development of the survey: First, did this population show signs of being in poor health, including engaging in poor health behaviors before diagnosis of TB? Second, did individuals in this population spend time in locations throughout the community that could have increased their likelihood of exposure to and transmission of MTB? The locations individuals frequent as well as the quality of their housing or how many people live in a particular house can help us make inferences as to where individuals may be exposed to MTB as well as where they may be transmitting MTB. In addition, it is plausible that generally being sicker and having worse health behaviors could increase the likelihood of progression to active TB once infected with MTB.

The final survey was split into three main parts, each containing it's own battery of questions (**Table 4.8-1**). The final survey included 30-questions and takes approximately 20-25 minutes to administer. We piloted tested the survey for several months before survey launch. Pilot testing was done among several different populations including: healthcare workers and individuals representative of a range of income brackets. Further, before survey launch each health department read through the survey, gave feedback, and were presented with the final survey instrument before formal launch of the study. There were several changes made during the pilot testing process. The original survey instrument was much longer than the final version, taking more than 30 minutes to administer. However, based on feedback we shortened the survey so that it could be delivered in 20 minutes or less. Additionally, there were several sets of questions that seemed to be confusing to certain populations. To address this, we changed the language on some questions and pilot tested new language in order to ensure clarity in every question.

The survey is given at one time point in the course of the approximately 6-9 month drug

therapy period of each patient. When planning for survey administration it was decided, in collaboration with the health departments, that surveys should be administered once rapport has been built between patient and health care professional—at a minimum of four weeks into therapy.

4.2.3 Grant Support

We received funding support from the Rackham Graduate School Research Grant. This funding support covered the following items:

- Printing of 100 surveys to be administered to study participants;
- A $20 incentive for study participants to improve participation rates. The $20 incentive will be in the form of a gift card to a local grocery store such as Meijer;
- Travel expenses to and from study sites in the Detroit area;
- Funding in order to cover 3 lunches for each of the study sites in order to provide minimal compensation for the healthcare workers administering the survey;
- Funding to cover the purchase of an external hard drive to ensure secure storage of the survey data for subsequent analyses.

4.3 Study Protocols

4.3.1 Survey Participant Recruitment

Healthcare professionals administering DOT invite each patient to participate in the study. The healthcare professional explains the purpose of the study as well as any risks associated with participation in the study. They then give them the consent form. If the patient wishes to participate, they sign 2 copies of the written consent form: one to be left with the patient, one to be returned to the health department. In addition, there is a separate HIPPA authorization form that allows the healthcare worker to extract information from the patient chart.

The surveys include a cover page with the patient name and the survey ID #. This page is

removed by a representative from the health department. The study team only receives the survey with the ID #. The surveys are completely de-identified at the time of receipt by the study team. The health department is the only entity having the linking information; this information is not shared with the study team.

4.3.2 Inclusion/Exclusion Criteria

The inclusion criteria for this study are as follows: study participants must be patients identified at one of 3 Metro Detroit county health departments: Wayne County, Oakland County, and Detroit City Health Department. Any patient currently in treatment or who has completed treatment in the last year at one of the participating health departments is eligible to participate in study.

Additionally, we only invited those patients that can speak and understand English to participate in the survey. Those patients unable to speak and understand English were excluded from the study.

Patients who are under the age of 18 are excluded from the study.

4.3.3 Informed Consent

The healthcare professionals administering DOT present the study, describe its purpose and aims, outline risks and benefits associated with participation in the study as well as the length of the survey, and invite potential participants to sign the consent forms. Participants are invited to sign 2 consent forms: one that covers participation in the survey component of the study and one that covers the extraction of patient health information.

4.3.4 Confidentiality and Security

The study was approved by the Health Sciences and Behavioral Sciences Institutional Review Board at the University of Michigan, the Institutional Review Board at the Michigan Department of Health and Human Services, and each health department institutional review board. Since the Detroit City Health Department is associated with Wayne State University, the IRB approval for Detroit City Health Department came through the Wayne State University, Institutional Review Board.

The cover page of the survey includes the patient name and survey ID#. Only the survey ID# is visible on subsequent pages of the survey. The top page of the survey is removed by a representative of the health department prior to receipt of the survey by the study team.

Individuals are free to withdraw from the survey at any point. If an individual requests to have their consent and data revoked, it is allowed. Any data collected will be used in the analyses. We will not use any data for individuals who have declined to share their data with us.

4.4 Results

Our primary study objective was to better understand TB patients in Metro Detroit, specifically in terms of their social profile. To that end, much of our analyses were focused on a thorough description of our study population. We described baseline socio-demographic characteristics of the entire population. In addition, we also examined within sample differences in key characteristics by nativity. Results will be forthcoming until late 2016. Currently, the survey is launched in two health departments and a total of 23 surveys have been administered.

The results presented below are preliminary results based on a sample size of 23 with 65% of the surveys coming from the Wayne County Health Department specifically. We will continue to analyze the surveys until the end of the study period in March 2017.

4.4.1 Characteristics of the study population

Of the 23 individuals included in the analysis, 43% of the sample is U.S-born, 39% foreign-born and 18% are missing data on nativity (**Table 4.8-2**).The sample is 30% Black/African American, 26% White, 22% Asian Indian, and 22% some other race. Additionally, 26% of the sample identifies as Middle Eastern / North African descent. 65% of the sample is female and the mean age is 42.4 years.

4.4.2 Measures of socioeconomic status

In order to ascertain socioeconomic status (SES) we asked questions on the traditional measures of education and income as well as other questions regarding sources of income, ability to make one's monthly payments, and health insurance (**Table 4.8-2**). 17% of the sample had some high school education, 30% of the sample reported having a high school (or equivalent) education, and 53% reported having some college or above. 48% of the sample reported working currently for pay. However, 52% of the sample either refused to answer the income question or did not know their income. 17% of the sample reported having an income less than $15,000 per year. Further, 43% of the sample reported that making monthly bill payments was somewhat difficult, very difficult, or extremely difficult. 96% of the sample had some kind of health insurance: 13% of the sample had health insurance through Medicare, 57% through Medicaid, and the remaining through some other source such as their employer.

In order to augment the data derived from the SES-related questions, we also asked a series of questions on housing security, homelessness, and housing quality (**Table 4.8-3**). 96% of the participants reported having a permanent address, 4% of participants did not respond to the question. None of the participants reported being homeless in the last 12 months. 91% of participants reported sleeping in the sample place every night. 4% of the sample reported living

in a public housing project. The average household size for participants was 5.1 persons.

Using the income and Medicaid data together, we created an aggregate indicator of SES. We used the federal poverty level (FPL) as a baseline measure for incomes that are indicative of poverty. The average household size in our study sample was 5.1 (ranging from 2-12 persons). The FPL for a family of 5 is $28,410. We used these data to create cut-points for low SES. If an individual reported an income < $30,000 a year or they reported being on Medicaid, they were classified as low SES. If they reported an income between $30,000- $75,000 and were not on Medicaid, they were classified as mid-SES. Finally, if they reported an income $75,000 or greater they were classified as high SES. If respondents were missing data on both income and Medicaid, they were classified as SES unknown. Based on this variable, 87% of the sample was low SES, 9% mid-SES, and 4% SES unknown.

Food security questions were included in order to ascertain individual's access to healthy food as well as their economic ability to address basic food needs. 26% of the sample reported making food last until there was money to buy more was somewhat difficult. 70% of the sample reported being able to eat fresh fruits and vegetables every day. 9% of the sample reported having cut down on the number or size of meals because of money.

4.4.3 Measures of health-seeking behaviors

We also asked a series of questions aimed at understanding health-seeking behavior (**Table 4.8-3**). These questions encompassed both a person's willingness to seek out care and their ability to access healthcare. 87% of patients reported they were either very likely or somewhat likely to seek out medical attention for a persistent health symptom. The reasons they would not seek out healthcare included: prohibitive cost, inconvenience in terms of both time and distance, and inability to take off work.

4.4.4 Measures of subjective social status and social support

Participants were asked to report on their view of their social ranking among several groups of people as well as their ability to access certain types of social support (**Table 4.8-3**). All but one participant reported feeling about the same rank or above compared to their peers, neighbors, and other people in the U.S.

We asked a series of four social support questions addressing items related both to instrumental support and emotional support.[121] The mean level of social support ranged from 3.2 for the item related to having access to someone who can loan you $100 or less to 3.7 for the item related to someone to take you to the doctor. We also aggregated the four social support variables to create a social support summary variable with values ranging from 4-16.

While there are many bivariate relationships we would like to explore as we continue to collect survey data, we began with examining differences in SES and social support by nativity. 100% of U.S.-born persons were classified as low SES; foreign-born persons were 67% low SES, 22% mid-SES and 4% SES unknown (P=0.4977). Additionally, the U.S.-born reported lower levels of social support compared to the foreign-born (P-value = 0.3524). The mean level of social support for the foreign-born was 14.00 compared to 12.80 for the U.S.-born.

4.5 Discussion

Both the process of carrying out the study as well as the results offer important insights to understanding the socio-demographic profile of TB patients in Metro Detroit. Ultimately, we hope the process of ascertaining detailed socio-demographic information on TB patients will be replicated in other health departments both in Michigan, and nationally. In addition, we hope our findings will be used to guide TB control efforts, particularly in Metro Detroit where limited resources need to be allocated efficiently and effectively.

4.5.1 Discussion of Study Findings

Despite the methodological challenges we faced, we were still able to collect valuable information on the social experience of individuals with TB. Our original study hypothesis was that those with TB in Metro Detroit would be among the most vulnerable in society: low SES, high levels of instability in housing and food, and low social standing. Our findings, however, are much more nuanced than we anticipated. We found evidence of a working class population that is socially stable but with signs of low SES and financial strain. While these data are preliminary findings, we believe it is useful and necessary to begin to contextualize these findings in what is known in the broader social epidemiologic and TB literature. However, we recognize that the profile of TB in Metro Detroit is likely to evolve as we continue data collection.

17% of our study sample reported having less than a high school education slightly higher than the 13.7% of U.S. adults over the age of 25 years and the 10.7% of similar Michigan adults.[122] Further, 48% of the study sample reported currently working for pay, 13% were retired, 13% unemployed, and 26% had some other type of employment. The rate of employment in our sample was lower that what is reported for both the U.S. and Michigan, 63.9% and 61.5% respectively.[122] While compared to Michigan and the U.S., these data indicate that the study sample did have lower rates of employment and education, a large portion of this population was, nevertheless, working and fairly educated. This was contrary to our previous expectation of this population being mostly composed of the poorest of the poor.

52% of the sample refused to answer the income question; thus, we had to use other variables to infer the socio-economic status of individuals. 17% of the sample reported having an income less than $15,000 per year. 57% of the sample reported being on Medicaid. We used the

U.S. federal poverty level (FPL) to then contextualize both the income and Medicaid findings. The FPL is currently set at $11,770 for a household size of 1 and $24,250 for a household size of 4.[123] Based on the respondents that did report their income it is likely that at least 7 households are below the FPL (given the average household size of 5.1 in this sample). Further, to be eligible for Medicaid in Michigan, an individual has to have an income 133% of the FPL. Therefore, based on the Medicaid responses at least 57% of the sample is at or below 133% of the FPL.

To compare these data to Wayne County as a whole, we used the American Community Survey.[67] According to the ACS, the median income for Wayne County is $41,421. While the ACS does not report the proportions of the population below the FPL, they do report the income to poverty level ratio.[67] Based on those figures, 25% of the Wayne County population has an income to poverty ratio less than 1 –meaning their income is less than the FPL. Comparatively then, our population is likely on the lower end of the income spectrum in Wayne County.

The inferences regarding the SES of the study population were further supported by the responses to the questions regarding making monthly bill payments. 43% of the study population reported that making monthly bill payments was somewhat, very difficult, or extremely difficult. While neither the U.S. Census nor the U.S. Federal Reserve ask directly about one's ability to make monthly bill payments, the Federal Reserve does have indicators of financial hardship that are nationally representative. Approximately 33% of the U.S. population reported experiencing some level of financial strain with 10% reporting finding it "difficult to get by" in 2014.[124] Thus, it seems compared to the national standards, our study population was experiencing greater financial strain than the average American.

This financial strain was also evidenced in the data on food insecurity. 26% of the study

sample reported that is somewhat difficult to make food last until there is money to buy more. Further, 9% of the study sample reported having to cut down the number and/or size of meals because of monetary concerns. While both of these measures signal financial strain, having to cut down on the number and/or size of meals due because of monetary concerns also relates to food insecurity. In 2014, 14% of U.S. households were food insecure at some point in the preceding 12 months[125] – meaning that at some point in the last 12 months food intakes were reduced or eating patterns changed due to financial concerns. Therefore, despite being employed this population has significant signs of financial strain as evidenced by both their ability to make monthly bill payments and regularly access food.

The questions regarding subjective social status and social support lend further detail to the social profile of this study population. All but one study participant reported feeling the same or above their peers, neighbors, and other people in the U.S. These data suggest a sense of equality—contrary to the sense of isolation we anticipated finding. However, while the social support questions taken together indicate a high level of access to social support resources, the social support indicator with the lowest mean value was whether you had access to someone to loan you $100 or less. 74% of the sample reported having access to this sort of support all the time or most of the time. However, 26% of the sample reported having access to this support either some of the time or none of the time. This question is indicative of both emotional support as well as the perceived ability to draw on one's social network for tangible aid.[126,127] Taken together with the aforementioned data on income and financial strain, the variability on this question could indicate that this study population feels less able to access a financial safety net (or simply does not have a safety net). The reasons underlying this could be a lack of trust that anyone in your social network would loan you the $100 if they had it or it could be that there is

no one in your social network that has a disposable $100 to loan you. Regardless of the reason, these data add further detail to the financial strain experienced by this population.

Based on our findings, TB cases in Metro Detroit do not appear to be isolated and marginalized. We did, however, find evidence of low SES and financial strain despite this population being a seemingly socially stable, working class population**.** Moreover, both low SES and financial strain could affect several dimensions of TB risk, namely likelihood of progressing to active disease once infected with MTB, and to a lesser degree likelihood of exposure to MTB.

Low SES could put an individual at risk for TB through several pathways (**Figure 4.8-1**). It could be that being of low SES increases the likelihood of exposure to the MTB pathogen, mediated by the neighborhood environment. In their study outlining the pathways by which neighborhoods can influence health, Diez Roux and Mair put forward the notion that lower individual-level SES is often associated with living in a neighborhood of lower SES.[128] Lower SES neighborhoods often have lower quality housing, greater exposures to environmental risks, and less access to food and health resources.[128] From a transmission standpoint, lower housing quality evidenced through conditions of over-crowding or lack of ventilation, may increase physical contact between a susceptible individual and an infected individual who is actively expelling MTB.[104] Therefore, the opportunities for transmission to occur are arguably increased in neighborhoods of lower SES.

We also found evidence of significant financial strain, likely driven by being of a low SES. There were three dimensions to financial strain that became evident in these data: not being able to make monthly bill payments, not being able to make food last due to financial concerns, and not having access to financial safety nets. The combination of these factors could be seen as the cumulative effect of financial strain. These factors could affect an individual's likelihood of

progression to active TB disease once exposed to the MTB pathogen. As depicted in Pathway B, this pathway could operate through the activation of the stress response and resulting diminished immune function.

There is a substantial literature on the deleterious effects of stress on many aspects of health, including immune function. While short-term stressors such as those resulting from examinations or acute pain can have immediate effects on immune regulation, prolonged stress can have both acute and chronic effects on immune function.[129] Several studies have explored financial hardship as a marker of both acute and chronic psychosocial stress. Steptoe and Marmot used an aggregate measure of financial strain comprising difficulty paying bills, being able to replace items when needed, and being able to provide the basic needs of the family.[130] They found financial strain was significantly associated with a heightened stress response.[130] A prolonged stress response results in chronic inflammation leading to a weakened immune state. While this may not make an individual more at risk for exposure to TB, it certainly would increase the probability of infection once exposed to the MTB pathogen. Related, stress could reduce immune function such that the immune system is not able to contain latent TB infections.

Studies have documented associations with chronic stress and susceptibility to viral and bacterial infections such as cold, influenza, and toxoplasma, and salmonella as well as decreased responsiveness to vaccinations.[131–134] Cohen et al. reported that those experiencing stressors, such as under- or unemployment, lasting more than 1 month had a 2-3 times increased risk of contracting rhino-virus induced colds, independent of demographic characteristics or health behaviors.[135] Aiello et al. found evidence that both ecological stressors such as residential segregation and poverty can both influence reactivation of Herpes Simplex Virus, Type 2 (HSV-2) and Epstein-Barr Virus (EBV) as well as increase risk for acquisition of HIV and progression

of HIV to AIDS.[133]

The connection between stress and infectious disease, particularly TB has long been studied. The seminal work establishing this link was put forth in 1919 by Ishigami. He was one of the first to hypothesis that the association between stress and risk of TB disease was mediated by immune function.[131,136] In 1953, Wittkower even went so far as to say that a tuberculosis patient could better be diagnosed by their psychological characteristics than by chest radiography—in particularly indicting stress.[131,137] Based on this vast literature, Biondi and Zannino posit that experiences of stress are associated with alterations in the host's immunocompetence, particularly cell-mediated immunity (CMI) and therefore should themselves be considered causal risk factors of TB disease.[131]

Additionally, experiences of food insecurity likely increase the probability of progression to active TB disease once exposed to the MTB pathogen through diminished immune function resulting from either the stress pathway or through nutritional deficiencies. If food insecurity indicates some level of nutritional deficiency experienced by the individuals as is depicted in Pathway C (**Figure 4.8-1**), then it is plausible that this impacts individual's immune function.

Nutrition, particularly malnutrition is a long and widely known risk factor for TB.[138] In their famous thesis on the drivers of declines in mortality in England and Wales during the 1800s, McKeown and Record attributed the rapid decline in TB incidence of this period to improvements in the standard of living, especially improvements in nutritional status.[139] While many have since refuted their claims, there is yet substantial evidence of the relationship between nutrition and TB. It is likely that, similarly to that of stress, the association between nutrition and TB is mediated through compromises in immune function. Presumably, this is driven by compromises in CMI.[138,140,141] CMI can keep latent infections in check as well as

prevent new infections from occurring upon exposure to MTB.[5] Alternatively, the weight loss often resulting from MTB infection[138,141] can similarly weaken the CMI response increasing the likelihood of progression to active TB disease.

Moreover, it is also likely that immune function acts as an effect modifier on the pathway between exposure to the MTB pathogen and TB disease whereby the probability of transitioning from MTB infection to active TB disease is greater for those with a diminished immune function. This is presumably driven by changes in CMI in which T-cells are either no longer able to keep a latent MTB infection in check or they are not able to mount an adequate response to inhibit a primary infection from becoming active disease. As is depicted in **Figure 4.8-1**, changes in the immune function are central to understanding how social factors and one's social profile may augment several dimensions of TB risk.

4.5.2 Discussion of Survey Administration

Throughout survey administration we faced several methodological challenges, namely unit and item non-response. We examined reasons for both occurrences in order to mitigate the resulting bias as well as to understand how the survey should be modified in future iterations. Nationally, unit nonresponse, or unwillingness to participate in the survey, is increasing.[142] This increase is most notable in cross-sectional surveys in which researchers do not have the benefit of offering consistent financial incentives over time.[142] Further, unit nonresponse is more likely to occur among the disadvantaged: minorities, males, urban residents, singe persons, the poor, and those with fewer social ties and attachments[143]—precisely the population we were most interested in studying.

Massey and Tourangeau give three primary reasons for non-participation: noncontact—interviewers being unable to make contact with potential participants; refusals—contact is made

but participants decline to participate; and a residual category encompassing such reasons as too busy, sick, participant/interviewer differences.[142] Refusals consistently account for the largest proportion of unit nonresponse—typically 60-65%.[144] In our study, noncontact was less of an issue given that potential participants were patients enrolled in TB treatment. Refusals were, however, the primary reason for nonresponse. Since the interviewer has an established rapport with participants prior to the administration of the survey, we were able to gather anecdotal evidence for the reasons for nonresponse. Most of our refusals noted were among foreign-born persons who expressed fear of their data being transmitted to the U.S. government. The healthcare workers noted that the rate of nonresponse from foreign-born persons seemed to increase in times when contemporary immigration fears and policies were amplified in the public. They also noted this seemed more of an issue with newly arrived immigrants as opposed to those with established residency in the U.S. Thus, despite the one-time financial incentive we offered survey participants, the risks and threats to confidentiality outweighed the financial incentive for this particular population.

Item nonresponse, or refusing to answer specific questions, was also a methodological challenge we faced. Nationally, rates of item nonresponse are also increasing,[145] particularly for sensitive questions such as those dealing with income and receipt of government benefits.[145] Meyer, Wallace, and Sullivan hypothesize three reasons for item nonresponse: refusal to answer, inability to answer, or failure of the interviewer to accurately record the participant response.[145] Item nonresponse was notable in our study in terms of the income question. Over 64% of participants refused to answer this question at all. All three of the above factors certainly influenced participants' willingness to answer the income question in our study. Some participants simply refused to answer the question while others cited a fear of disclosure of

private information to the U.S. government. Others were simply unable to answer the question either because of language difficulties or being a member of a family unit in which he or she is not privy to such information.

The third explanation for item nonresponse, that of the failure of the interviewer to accurately record a response, applies both to the income-related questions in our survey as well as to a number of other sensitive questions. In some instances, the response given to a certain question was too obscure and time-consuming for the healthcare worker to disentangle and indicate on the survey. In these cases, the healthcare workers reported they would skip recording a response to the question. We also saw a related issue in our survey—failure of the interviewer to ask the question. In our survey training, we gave our interviewers the autonomy to decide whether or not to ask a question based on verbal and nonverbal cues from the participant. The healthcare workers indicated that questions of a sensitive nature such as income, housing, and social standing sometimes visibly upset the participant. On such occasions, the healthcare worker would simply not continue with the question or its related questions. One step we would like to implement in future iterations of the survey is the addition of an item on each question indicating if the interviewer skipped asking the question altogether. This may help us disentangle refusal to answer a question, inability to record a response, and failure to ask a question from one another. Regardless, we were often missing data on critical questions such as income. However, we still may be able to gain insights on SES based on other related questions.

One of the key lessons we learned throughout this process was that it mattered who, when, and where the survey was administered. This was particularly true given that we intended to survey those who may be vulnerable and/or marginalized in a population. Foreign-born persons would routinely report they believed U.S. government officials, such as immigration

workers, would receive the information, and there would be subsequent repercussions. Often the willingness of U.S.-born participants to answer questions honestly and to complete the survey in its entirety was associated with the level of rapport built between healthcare worker and patient. Healthcare workers consistently reported more incomplete surveys and greater general discomfort among their patients who were less open and willing to participate in care.

4.5.3 Strengths & Limitations

There are several major strengths to this study that can offer direction to future studies. In regards to the study design, ours is one of the first modern studies to utilize a survey instrument to collect detailed socio-demographic information on TB patients giving us a more detailed understanding of the social profile of those with TB. It is our hope that the data from our survey can provide insights into why the TB epidemic has continued in the U.S., and moreover why disparities in TB incidence are persistent. Hopefully, studies such as this can call attention to the need for tailored TB control strategies that account for the social and economic context in which cases arise.

Another key strength of our study is that it allows participants to self-report their socio-demographic characteristics as opposed to the previous reliance on health care worker observation on the RVCT form. This is crucial to understanding patterns by race, ethnicity, and gender where how an individual identifies him or herself can be much more indicative of their social experience than how a healthcare worker may identify them. Further, allowing self-report also opens up the opportunity for patients to share more of their story with the healthcare worker. This can be key to understanding such issues as housing stability and food insecurity where the data gathered on the survey are often indicative of a much larger social trend in the life of the individual.

Our study has also developed a framework for collaborations between state/local health departments and academia around issues of TB control. Such collaborations are mutually beneficial and can result in data that can better inform both TB control and TB research. For example, the data collected for the purposes of this study are also being used by each local health department to facilitate a better understanding of their patient population. Health departments have expressed an interested in being able to tailor their approaches to TB control based on the specific needs of their patient population. The data generated from this study, as well future use of this survey by the health departments, will allow them to achieve this goal.

There are also several limitations to our study. While there are many benefits to the survey being administered by healthcare workers (i.e. rapport, trust), some participants were still fearful of changes in availability and/or quality of care based on their participation or responses. Despite reassurances from the healthcare worker that the survey was in no way linked to their care, there were still instances of unit and item nonresponse owing to the survey being delivered by healthcare workers.

The healthcare workers consistently reported that how questions were interpreted and responses given varied based on nativity. For example, several reported questions as to how the foreign-born should report their education (i.e. should they report years of education in the U.S. vs in their country of origin). Given the high proportion of foreign-born persons in this population, it could be beneficial to tailor certain questions to better fit the needs of the foreign-born population. This may give more accurate responses to such questions.

Additionally, utilizing healthcare workers also presented difficulties in survey administration. While some healthcare workers were very thorough in their survey administration—asking all questions, recording all responses, ensuring the patients charts were

filled out, others were less thorough. In the future, we would like to employ a more extensive survey training and follow-up visits, including having each healthcare worker pilot the survey and receive feedback individually. We did address these issues in subsequent meetings with the health department staff, however, this would be better addressed during survey training.

Surveys are notoriously vulnerable to recall bias and our survey was no different. This was particularly concerning for the series of questions in which participants were told to recall the time before they had TB. For some participants, this may have been up to one year ago. Moreover, we suspect that participants may have remembered their time before TB as better than it was in comparison to their current status. Thus, questions such as self-rated health before TB are likely not a true representation of the individuals' status before TB.

Finally, since this was a descriptive study, we did not have a control group without TB. We could not compare our study results with a TB-free population, which would have allowed us to quantify the degree to which certain variables put those with TB at increased risk. However, we believe having the baseline socio-demographic characteristics of this population will make such studies possible in the future.

4.6 Next Steps

Data collection will continue until August 2016. We expect to have approximately 70 participants total from all three health departments. Our original study aim was to describe the social profile of the Metro Detroit TB population. However, we found that even within this population there was significant heterogeneity between health departments. Future analyses will focus on describing the study results separately for each health department.

Moreover, the participating health departments have expressed the need for this type of survey instrument in other TB control units as well as other infectious disease units. Eventually,

we aim to publish the study methodology and survey instrument in the hopes that it can be used on a national scale.

From an epidemiologic perspective, this study sets the stage for additional studies of the social experience of TB patients. The data from this study can highlight which variables are most relevant to understanding the social profile of the population with TB, helping to inform how future studies are constructed. For example, a follow-up study could employ a population-based case-control design in which TB cases in a particular area are matched with controls selected from the TB-free base population. By doing so, we could better understand how the population with TB compares to the TB-free base population.

4.7 Conclusions

Our study is one of the first to gather detailed data on the modern-day social profile of individuals with TB. Our findings suggest that despite evidence of stability on several social markers, the modern-day social profile of those with TB is one of low SES and significant experiences of financial strain. Perhaps what is most striking about our findings is that despite this being an employed population and not of significantly lower education, there is still evidence of this population not being able to meet basic financial needs. This implies that at-risk populations for TB should not simply be defined by traditional TB risk factors (i.e. homelessness, drug-use, stay in a correctional facility). Rather, our study findings suggest that at-risk populations need to include those for whom financial insecurity and strain are persistent issues. Tailoring TB control strategies to include such populations may be able to both decrease TB incidence overall and decrease persistent disparities.

4.8 Tables & Figures

Table 4.8-1 Study Sites

Health Department	Survey Start Date	Survey End Date	Current # of Surveys
Oakland County	9.8.15		5
Wayne County	7.23.15		15
Detroit City	3.1.16		3

Table 4.8-1 Major components of the survey instrument.

Survey Section	Specific Variables
Part 1: Demographics	Race
	Gender
	Martial Status
	Education
Part 2: Life Before TB	Self-rated health
	Alcohol usage, past and current smoking behavior, physical activity
	Healthcare-seeking behaviors, barriers to seeking healthcare
	Locations frequented throughout the community
Part 3: Current Status	Housing (history of homelessness, transience in housing, crowded housing condition)
	Neighborhood condition
	Health insurance, barriers to having health insurance
	Employment
	Income (including ability to make monthly bill payments
	Subjective social status
	Access to social support
	Food security

Table 4.8-2 Demographic characteristics of the study sample

N = 23								
Mean Age (years)	42.4							
	#	**%**		**#**	**%**		**#**	**%**
Origin			**Self-Rated Health Before TB**			**Education**		
U.S.-born	10	43	Excellent	10	43	Some high school	4	17
Foreign-born	9	39	Good	11	48	High school / GED	7	30
Missing	*4*	*18*	Fair	2	9	Some college	5	22
						Bachelor/Associate's Degree	5	22
Race/Ethnicity			**Alcohol Use Before TB**			Advanced Degree	1	4
Black/African American	7	30	Yes	8	34	Other professional degree	1	4
White	6	26	No	15	65			
Asian Indian	5	22						
Other	5	22	**Smoking Before TB**					
			Yes	7	30			
Middle Eastern/North African	6	26	No	15	65			
			Missing	*1*	*4*			
Gender			**Ever Smokers**					
Male	8	35	Yes	5	22			
Female	15	65	No	13	57			
			Missing	*5*	*22*			
Marital Status								
Married	10	43	**Physical Activity**					
Separated	1	4	Never	5	22			
Divorced	2	9	< 1 x per week	2	9			
Widowed	3	13	Once a week	7	30			
Living with a partner	2	9	Multiple times per week	3	13			
Single	5	22	Almost every day	6	26			

Table 4.8-3 Participant response to selected questions

	#	%
Total Surveys	23	100
Health-Seeking Behaviors		
Suppose you had a health symptom that had been bugging you for a couple of weeks, how likely would you be to seek out medical attention?		
Very Likely (1)	15	65
Somewhat Likely (2)	5	22
Somewhat Unlikely (3)	2	9
Unlikely (4)	1	4
What are the biggest reasons you wouldn't seek out medical attention?		
Cost	1	4
Too Far Away	1	4
Can't Take Off Work	1	4
Time/Inconvenience	2	9
Lack of health insurance	4	17
Other	11	48
Refused/Didn't Ask	3	13
Health Insurance		
Some kind of health insurance	22	96
Medicaid	13	57
Medicare	3	13

Table 4.8-3 Continued.

Income	**#**	**%**
Source of Income		
Working now for pay	11	48
Unemployed/Looking for work	2	9
Retired	3	13
Homemaker	3	13
Not working	1	4
Unpaid Family Worker	1	4
Student	2	8
How difficulty is it to make monthly payments?		
Not difficult at all	11	48
Somewhat difficult	8	35
Very difficult	1	4
Extremely difficult	1	4
Missing	*2*	*8*
Total Yearly Income ($)		
< 15,000	4	17
15,000 – 30,000	3	13
30,000 - 75,000	3	13
> 75,000	1	4
Do not know	4	17
Refused	8	35

Table 4.8-3 Continued.

Social Ranking

Thinking about your life, how would you say you rank among the following groups of people:

	Below # (%)	Same # (%)	Above # (%)	Missing # (%)
Your peers	1 (4)	19 (83)	1 (4)	2 (8)
Your neighbors	1 (4)	16 (70)	3 (13)	3 (12)
Other people in the U.S.	1 (4)	19 (83)	1 (4)	2 (8)

*Below (1); Same (2); Above (3)

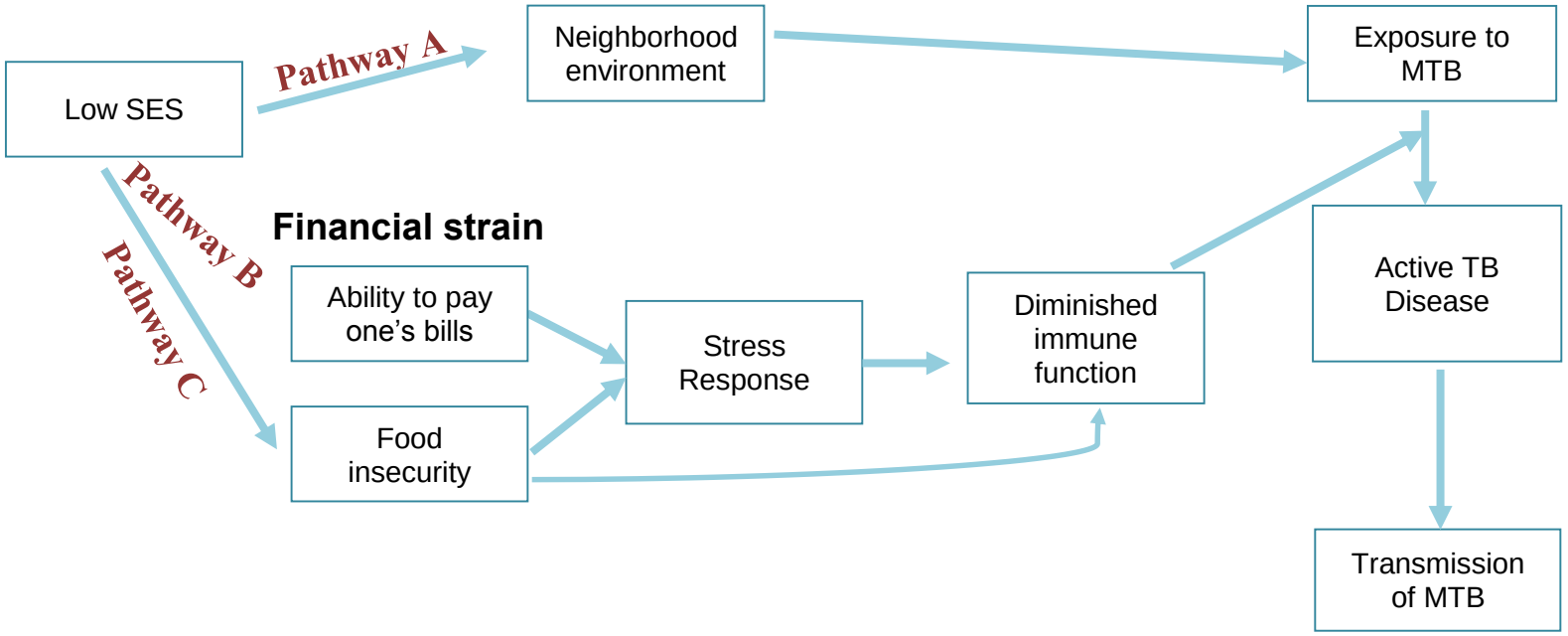
Types of Social Support	Means (SD)
Someone to confide in / talk to about your problems	3.33 (0.86)
Someone to take you to the doctor	3.43 (0.84)
Someone to help with daily chores if you were sick	3.65 (0.57)
Someone to loan you $100 or less	3.22 (1.04)

*All the time (4); Most of the time (3); Some of the time (2); None of the time (1); Don't know (1)

Table 4.8-3 Continued.

Food Security	**#**	**%**
How difficult is it for you to make your food last until you have money to buy more?		
Not difficult at all	17	74
Somewhat difficult	6	26
Very difficult	0	0
Extremely difficult	0	0
How often are you able to eat fresh fruits and vegetables?		
Everyday	16	70
A few times per week	5	22
Less than once per week	2	9
Never		
Have you had to cut down the number or size of meals because of money?		
Yes	2	9
No	21	91
How often have you had to do this?		
A few times per week	1	4
Less than once per week	1	4
Never or NA	3	13
Missing	*18*	*78*

Figure 4.8-1 Conceptual framework depicting how low SES and financial strain may affect TB risk.



CHAPTER 5. CONCLUSIONS

5.1 Review of major findings

This dissertation sought to use to use an innovative approach, integrating traditional molecular epidemiologic methods with spatial data and a novel socio-demographic survey to understand patterns of TB incidence in Michigan, and the drivers of persistent disparities in TB incidence. My goal is that the results of this dissertation will have direct implications for statewide and national TB control. In particular, I hope that the results of this dissertation will help us better understand the social patterning of infectious disease in the U.S. so that we might design interventions that can both reduce disparities and prevent disparities in infectious diseases from developing in the future.

This dissertation was composed of three studies. The first study analyzed trends in TB incidence for the state of Michigan from 2004 through 2012. The results of this study demonstrated that while the incidence of TB resulting from both recent transmission and reactivation latent TB infection (LTBI) is decreasing in Michigan, significant disparities are evident, particularly along lines of race and nativity (Chapter 2). The second study looked within the population of TB cases for predictors of recent TB transmission, using genotypic clustering as a proxy for cases resulting from recent transmission. The findings of this study suggest that the predictors of recent transmission are critically different for U.S.-born and foreign-born populations. For U.S.-born populations, the composition of the neighborhood environment, including density and neighborhood-level disadvantage, is a better predictor of recent transmission compared to traditional TB risk factors and/or clinical factors (Chapter 3). The third

and final study used the data collected from the preceding two studies, as well as anecdotal evidence collected from local public health departments, to pilot test a novel survey instrument aimed at ascertaining detailed data on the social profile of TB patients in Metro Detroit. This study found that while traditional markers of social vulnerability such as extreme poverty and homelessness may not be as evident in this population, there is evidence of persistent financial hardship and strain likely resulting in an increased risk for primary infection with *Mycobacterium tuberculosis* (MTB) as well as increased risk for progression from infection to active disease (Chapter 4).

5.1.1 Trends in TB Incidence in Michigan, 2004-2012 (Chapter 2)

In the first study of this dissertation, we examined trends in TB incidence both overall for the state of Michigan as well as among subgroups by race, nativity, sex, and age and did so separately for those cases resulting from recent transmission and reactivation of LTBI. TB incidence overall showed a decline from 2004-2012, declining from 2.69 cases per 100,000 persons in 2004 to 1.28 cases per 100,000 in 2012. We then examined whether these decline rates were significantly different for subgroups of race, nativity, sex, and age. Upon finding evidence that the decline rates were not different, we then proceeded to use multivariable models to compare the average incidence rate for each subgroup of the population. We found that among those cases resulting from recent transmission, the greatest disparities were observed by race—Blacks had an incidence rate 19 times greater than that of Whites when controlling for age, sex, and nativity. Among the cases resulting from reactivation of LTBI, the greatest disparities were observed by nativity—the foreign-born had an incidence rate 19 times greater than the U.S.-born when controlling for race, sex, and age.

Disparities in TB incidence in the U.S., particularly by race and nativity, are not a new

finding in TB research and control. For decades we have known that the foreign-born have a higher incidence rate of TB than the U.S.-born and that Blacks, Asians, and Hispanics have much higher rates of TB than Whites.[34] However, what this study offers is a more nuanced understanding of these disparities. Rather than reporting these disparities in a univariate model, as has often been done in the past, we used multivariable models to understand how the effects of each variable differ when examined together. Multivariable approaches are not often used, however, the few studies that do employ multivariable approaches also report that the inferences of their findings change substantially between univariate and multivariable approaches.[84] Both the magnitude of the disparities we found, as well as the degree of the suppression effect of nativity on race, are significant findings our study offers to the wider TB literature.

One of the ancillary goals of this study was to be able to begin to understand how social factors, such as race and nativity, may be driving disparities in TB incidence in Michigan. While we were constrained by the available data we could utilize in the study, it is a first step in understanding the pattern of TB incidence in Michigan. Follow-up work should seek to understand what race and nativity are proxies for in this population. Is it simply that the TB incidence in the foreign-born is driven by the baseline prevalence of TB in their country of origin? Or is there something particular about the social experience of foreign-born individuals once in the U.S. that puts them at greater risk for TB incidence? Moreover, what is race a proxy for in this population? Why do we see a greater incidence rate of transmitted TB among Blacks? These sorts of questions need to be examined from a social epidemiologic framework in order to move such studies from simply delineation of disparities to understanding mechanisms driving disparities so that we may intervene in the future.

5.1.2 Drivers of TB Transmission in Michigan (Chapter 3)

In the second study, we compiled the population of TB cases collected in Michigan from 2004-2012 and looked within the sample to understand drivers of recent transmission. As has been shown in previous studies, the drivers of transmission are notably different for U.S.-born and foreign-born populations[46,92,100] such that a stratified analysis is necessary to accurately understand the risk factors in each population. For the foreign-born population, there were only two significant predictors of recent transmission: race and being a known contact of an infectious case of TB. Among the foreign-born, Asians had an increased prevalence of recent transmission compared to Whites, after controlling for measures of the neighborhood environment, and other social risk factors. That being said, more work is needed to understand how the Asian population as a whole differs from other foreign-born populations. It may be that Asian immigrants are more likely to live in closer proximity to one another, or in multi-family households. Future studies could ask questions related to housing and crowding to better understand the origins of this disparity. Additionally, future studies would benefit from disaggregating the Asian racial group into the ethnically diverse groups that compose it. This may facilitate a better understanding of what is driving recent transmission in this population.

Among the U.S.-born, the most significant predictors of recent transmission were observed at the neighborhood-level. Both neighborhood-level density and neighborhood-level disadvantage were associated with a significantly higher prevalence of transmission, even after controlling for individual-level covariates such as race, sex, and age. Building on the previous study, these results help us begin to understand the racial disparities in TB incidence, particularly among the U.S.-born. Among U.S.-born populations, race is likely a proxy for neighborhood-level disadvantage such that when neighborhood-level factors are included in a model with

individual-level race, individual-level race is no longer a significant predictor of transmission.

Both the fields of social epidemiology and infectious disease epidemiology acknowledge the importance of place in determining risk of disease. For infectious disease, the importance of place is usually due to the creation of spaces for individuals to interact with a particular pathogen—be it the transmission of, or exposure to the pathogen.[107,146] For social epidemiology, the neighborhood can represent aspects of the structural barriers influencing individuals' ability to have and maintain health.[128,147] In this study, we found evidence that both aspects of the neighborhood environment matter for differentiating recent transmission from reactivation of LTBI. There are many within the field of TB research, particularly in low burden countries such as the U.S that have called for targeted TB resource allocation for high risk groups. Our findings suggest that the definition of high risk may need to incorporate markers of the neighborhood environment rather than only individual-level factors.

5.1.3 TB in Metro Detroit (Chapter 4)

In many ways, the third study is a natural response to the findings of the first two. The first two studies point to the ways in which TB incidence and transmission may be socially patterned. However, in both of those studies our ability to make inferences regarding the mechanisms underlying the social drivers was impeded by the data available. The third study of this dissertation attempted to address this gap by pilot testing a survey instrument that could collect much more detailed socio-demographic data on TB cases—specifically those identified in the Detroit Metro area.

We expected to find evidence that this population of individuals was of extremely low socioeconomic status (SES), socially marginalized, and vulnerable such that they would not have consistent income, housing, and food. However, the picture that is becoming clear as the surveys

continue to be analyzed is much more nuanced than we anticipated. We did not find evidence of extremely low SES; in fact, many of the participants had greater than a high school education, and nearly all of them were currently working. Despite this, however, a large proportion of this population was on Medicaid, had difficulty making their monthly bill payments, with some even showing signs of food insecurity. The persistent financial hardship and strain experienced by these individuals can cause significant stress, resulting in immune dysfunction and making individuals more likely to progress to active TB disease once infected with the MTB pathogen. Additionally, in light of the findings from the previous study (chapter 3) regarding the neighborhood environment, it may be that the evidence we found regarding the financial strain of individuals may also be indicative of a lack of upward mobility in terms of their social standing, and their ability to move from their neighborhoods. Thus, their financial strain may also be an indicator of residing in neighborhoods where one is more likely to be exposed to the MTB pathogen, and lacking the resources to move from such an environment. Future iterations of this survey instrument should collect patient address information so that neighborhood level factors could be linked with each survey response.

5.1.4 Working with local public health agencies

Developing collaborations with local health departments has proved a most fruitful and beneficial endeavor. In fact, much of the learning for this aim came from the relationships developed with each health department. During meetings with the health departments, TB control staff shared stories and observations from their patient populations, as well as what they perceived to be the biggest needs of these populations. Many of the TB control staff had been administering directly observed therapy (DOT) to TB patients for many years, and had seen how the TB epidemic had changed and evolved over time. The TB control staff takes time to learn

about each of their patients—adapting the location and timing of the drug therapy to be the most unobtrusive to each patient, thereby ensuring a high probability of treatment completion. It became clear the TB control staff knew much more detail about the patient's life than is collected or accounted for in the TB surveillance data. When we approached each of the health departments with the idea of a collaborative study, we did so from the perspective that the information we would collect on the survey was simply a standardized way to capture the wealth of anecdotal evidence they were already gathering on their own.

It is our hope that the survey instrument will continue to be used in the health departments as a tool to better understand patient populations and tailor resources accordingly. We also hope that this tool can be tailored for use by other infectious disease control teams. While the U.S. has done substantial work in reducing the burden of infectious diseases nationally, disparities across a range of diseases continue to persist and in many cases widen.[59] Better understanding how the social environment may pattern such disparities can give us tools to address these disparities currently, but may also give us the knowledge to prevent such disparities from developing in the future. As new infectious diseases continue to emerge, and current infectious disease continue to evolve, the U.S. will have to adapt the strategies by which we address such diseases, both to prevent outbreaks as well as prevent disparities in infectious disease incidence from becoming entrenched. We our hope our survey instrument will be one such strategy for U.S. infectious disease control.

5.2 Bringing it all together

The three studies of this dissertation are best understood as building upon one another. As I reflect on this dissertation, and the inferences and conclusions that can be drawn from it, several themes emerge: one, the importance of incorporating historical evidence into our work,

two, critically thinking about how we study race in epidemiology, and three moving towards a consequential epidemiology.

5.2.1 Incorporating History

Much of what I found in this dissertation is aligned with what we have known for decades about TB: that it targets society's most vulnerable, and is patterned along lines of social disadvantage.[86] My dissertation, in many ways, is then a remembrance of history and an incorporation of that into our current understanding of TB and the methodologies by which we address TB in the U.S. context.

Routine reporting of TB began around 1953 and from 1953-1985 the incidence of TB declined by nearly 82%.[32] Much of this decline is credited to the development of drug therapies, such as Streptomycin in 1944, that could target TB specifically and effectively.[148] Even after the resurgence of TB in the 1980s and 1990s, the advent of routine genotyping allowed those in TB control to use individual-level factors to halt population-level spread of the disease. These technologies have been enormously successful in reducing the incidence of TB in the U.S. However, one unintended consequence of these advances has been the failure to remember the historical knowledge of the ways in which TB responds to population-level changes.

The advances in TB control have been successful in reducing the incidence of TB, but these reductions are not experienced uniformly across the population. The successes in control of TB have been felt more by advantaged populations, creating a situation in which disparities in TB incidence can and do persist. Similar to what was reported in the 19th and early-20th centuries, TB remains disproportionately burdened among racial/ethnic minorities and immigrants.[31] History tells us that these disadvantaged populations are often created in the wake of population-level shifts: influx of immigrants, movements into and out of urban areas, re-

organizations of social structures. Thus, in conjunction with individual-level factors, our contemporary methods for TB control need to account for current and future population-level shifts that will likely result in new high-risk groups, or the perpetuation of the current stratification of the population.

5.2.2 Incorporating race into infectious disease epidemiology

We continue to see racial disparities in TB in the U.S.,[55,59] which has led some in the field to imply that these disparities can be attributed to the biological differences due to race. Much of this argument relies on flawed research[104] indicating that Blacks have a genetic susceptibility both to acquiring TB infection[80,149] and to developing active TB disease.[150] Given the decades of research showing there is greater heterogeneity within a particular racial group than across racial groups,[151] it is unlikely that genetic differences are able to account for the disparities observed in the susceptibility, acquisition, and progression of TB.[152] More likely, group level differences in susceptibility to TB infection or disease are linked to an individual's geographic origins.[104,152]

Although it is well accepted that race is a social construct, [153] difficulties arise in how best to operationally incorporate this knowledge into research. While many public health researchers regularly incorporate race into their statistical models and document racial patterns in their findings, this is often where the discussion ends. However, a larger issues remains: If race is a social construct, then only describing racial patterns in health, without any hypothesis or framework explaining what race is a proxy for in a given context, may serve to perpetuate the biologizing of race.

While social epidemiology has been leading the charge in incorporating a critical understanding of race into epidemiologic investigations, research focusing on structural determinants and "fundamental causes"[154] may leave many of those outside the field of social

epidemiology feeling paralyzed by the implications of such notions. That is, short of structural change, there is not likely to be reductions in the persistent disparities many of us are documenting. However, authors such as Acevedo-Garcia, argue that there are likely to be intermediaries in the long chain of events from structural influences to health—intermediaries that may be critical points for intervention.[155] Despite the complex pathways linking structural determinants to individual health outcomes, social epidemiology can lead the field by examining race in a way that illuminates the meditators on the pathway between social constructions of race and health with the goal of reducing racial disparities. For example, in chapter 3 of this dissertation we found that among the U.S.-born population, the association between race and recent transmission was null when neighborhood disadvantage was included in the statistical model. Rather than simply reporting racial disparities in recent transmission, this finding helps illuminate what may be driving the racial disparity in this context—the neighborhood environment. This gives those in TB control, at the state and local level, the necessary data to better tailor resources to high-risk neighborhoods.

5.2.3 Towards a consequential epidemiology

One question continually comes up as I bring together all three studies: how do the findings of this dissertation move us closer to the goal of eliminating TB in the U.S.? In 2013, Galea proposed a new approach to epidemiology known as "consequential epidemiology".[156] In making the case for this new approach he argues that, "academic epidemiology now spends most of its time concerned with identifying the causes and distributions of disease in human populations and far less of its time and imagination asking how we might improve population health."[156] He uses the foundational definition of epidemiology as part of a two-pronged mission that is aimed at understanding the distribution of disease and its determinants so that we may

intervene to improve population health[157] as the base for his charge.

In my dissertation, the first two studies are focused explicitly on understanding the distribution of TB, and specifically its social determinants. However, the third study is my attempt to bridge the gap between the academic study of TB and the public health practice of TB control (and perhaps other diseases). The first two studies are needed to understand and quantify contemporary disparities in TB and their drivers. While they have utility in their own right, they also provide the foundation for the third study. Designing a survey instrument using the tools of social epidemiology and survey research can certainly improve our understanding of the social characteristics of TB. Practically, however, it is my hope that the survey instrument will be used to inform TB control practices at the state- and local-levels. Such a tool can incorporate the knowledge we have of persistent disparities in TB into a mechanism to address and ameliorate these disparities.

5.3 Moving Forward

5.3.1 U.S. TB control

In 2014, there were 9.6 million new cases of TB and1.5 million deaths due to TB globally.[2] The World Health Organization (WHO) recently released their new goals to accelerate global progress towards ending TB.[2] Explicit in these goals is a framework for helping low incidence countries achieve TB elimination. The WHO classifies low incidence countries as those having less than 100 TB cases per one million population.[158] The goal is that low incidence countries achieve pre-elimination status (defined as < 10 TB cases per one million) by 2035 and elimination (defined as < 1 TB case per one million population) by 2050.[158] To that end, the WHO has outlined 8 priority actions that low-incidence countries should take in order to reach pre-elimination status:

- Ensure political commitment, funding, and stewardship for planning and essential services of high quality;
- Address the most vulnerable and hard-to-reach groups;
- Address special needs of migrants and cross-border issues;
- Undertake screening for active TB and latent TB infection in TB contacts and selected high-risk groups, and provide appropriate treatment;
- Optimize the prevention and care of drug-resistant TB;
- Ensure continued surveillance, program monitoring and evaluation, and case-based data management;
- Invest in research and new tools;
- Support global TB prevention, care, and control.[158,159]

The U.S. is among the 30 low-incidence countries targeted by the WHO for achievable elimination of TB in the near future. With the goal of eliminating TB in mind, the challenge for U.S. TB control is to consider how to implement the action items set forth by the WHO that will put us on a trajectory for elimination.

With declining incidence and obvious successes in TB control over the last century, it seems that TB elimination is, in fact, an achievable goal. However, elimination of TB in the U.S. faces two key obstacles: one) diminished funding at the federal, state, and local levels, and two) the existence of silent epidemics in geographically and demographically defined groups.[104]

In 2008 the Comprehensive Tuberculosis Elimination Act of 2008 was passed by Congress explicitly outlining funding to be allocated towards both TB research and TB control programs with an increased focus on high-risk groups, including the foreign-born.[160] The result of the legislation was increased funding to the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) to carry out the aims of the legislation. However, in the years following the passage of the law, the federal budget to both agencies was severely cut, limiting their ability to address the aims of the law.[161] In 2014, the legislation was re-introduced and is currently held up in sub-committee hearings in Congress. This legislation prioritizes funding to state governments, proposing to focus on high-risk groups such as the

foreign-born, uninsured, and homeless.[162] Importantly, it also has provisions to award special funding to state and local governments as well as to federally qualified health centers.[162]

This new legislation could address both challenges outlined above for TB elimination in the U.S. as it would renew political will and subsequent funding for TB activities. Not only does this give those in TB control the resources to carry out their activities, but it also incentivizes new initiatives to address high-risk populations. In addition, the special provision in the proposed legislation to include federally qualified health centers in funding awards is a particularly critical component of addressing persistent disparities in TB incidence, particularly among the U.S.-born. Federally qualified health centers were one of the community-based interventions provided for under the Affordable Care Act (ACA) to increase access to healthcare in disadvantaged communities—particularly minority communities and communities of low SES.[163,164] These disadvantaged communities are oftentimes politically and socially marginalized and thus, the weight of TB, among other diseases, often goes unnoticed and therefore, unaddressed in these populations. Implementing active TB case finding, and subsequent treatment, using the existing infrastructure of the federally qualified health centers may be a practical way to target TB control in a resource constrained environment.

5.4 Future research

This dissertation has set the stage for follow-up action in the fields of TB research and public health practice. One action that could benefit a range of infectious diseases is the collection of more comprehensive surveillance data. There are a number of infectious diseases in the U.S that are classified as notifiable diseases of which reporting is mandatory. Using this existing infrastructure as a mechanism to collect more detailed socio-demographic information, may facilitate a better understanding of high-risk groups for particular diseases. This could also

lead to a better understanding of enduring disparities in TB research. Future TB studies should aim to understand the mechanisms driving disparities in TB incidence and how those drivers may be different for U.S.-born and foreign-born populations. This dissertation is a necessary first step in documenting these disparities and highlighting potential mechanisms. Follow-up studies should employ more detailed socio-demographic data to understand the underlying systems, particularly structural influences, giving rise to such disparities.

Infectious disease research may also benefit from research that encompassing more than one infectious disease. This could be beneficial from both the social and biological viewpoints, as there is likely substantial overlap between high-risk groups among multiple infectious diseases. Understanding the social conditions that puts one at risk for multiple infectious disease could lead to more efficient and effective allocation of resources. In chapter 3 of this dissertation we found that for U.S.-born individuals, the neighborhood environment played a significant role in predicting whether an individual was a recently transmitted case of TB. However, the role the neighborhood environment plays in augmenting risk of MTB infection and TB disease is likely not limited to TB. These findings could be applied to a range of infectious diseases. Thus, in increasingly resource-constrained environments for research and public health practice, we, as a field, could benefit from studies that examine more than one outcome.

The shift to examining more than one infectious disease in a given study could also be beneficial for understanding the biological processes at work throughout the tenure of an infection/disease. Borrowing from the multimorbidity model[165] as well as the increasing number of studies examining pathogen burden,[166] we could also begin to examine the consequences of multiple co-occurring infectious diseases. There is a substantial literature developing investigating the effects of multiple infections on the pre-mature aging of the immune system.[167–

[169] While these studies mostly focus on sub-clinical infections that reactivate over the life course, it is reasonable to assume that the burden of multiple infectious diseases with clinical endpoints, such as TB, measles, pertussis, etc. may also have consequences for the aging of the immune system over the life course. The shift to examining more than one infectious disease in a given study could also be beneficial for understanding the biological processes at work throughout the tenure of an infection/disease. Borrowing from the multimorbidity model[165] as well as the increasing number of studies examining pathogen burden,[166] we could also begin to examine the consequences of multiple co-occurring infectious diseases. There is a substantial literature developing investigating the effects of multiple infections on the pre-mature aging of the immune system.[167–169] While these studies mostly focus on sub-clinical infections that reactivate over the life course, it is reasonable to assume that the burden of multiple infectious diseases with clinical endpoints, such as TB, measles, pertussis, etc. may also have consequences for the aging of the immune system over the life course.

Finally, the pilot study we carried out in Metro Detroit provides an excellent foundation for future studies both in TB and other related infectious diseases. It is proof of concept that such a study can be carried out, and that valuable data can be derived from it. Follow-up studies should focus on developing a control group for comparison. Our study was a pilot study and therefore did not have a population with which to make comparisons. Future studies that are able to quantify the differences that exist between the TB population and the TB-free population will provide better evidence for how TB control teams can more effectively address the needs of their patient populations.

5.5 Conclusion

Despite enormous successes in TB control over the course of the 20th century, TB continues to disproportionately affect the poor, racial/ethnic minorities, and urban dwellers. This dissertation has shown that significant disparities in TB incidence are persistent despite organized TB control efforts. Moreover, this dissertation has consistently demonstrated that the social and economic context of individuals is a critical factor in determining risk of TB as well as perpetuating disparities in TB. The social survey we piloted in Metro Detroit will lead to invaluable insights into the contemporary social profile of individuals with TB. Results from this dissertation research should have direct implications for statewide and national TB interventions.

APPENDIX A Social Survey

Tuberculosis in Michigan: Survey on socio-demographic factors among TB patients

The following information needs to be filled out by a representative of the health department:

Patient Name	
Date of Birth:	
Survey ID #:	
Survey administrator:	
Treatment start date	

INSTRUCTIONS:

Only those 18 years of age and older who can speak and understand English should be invited to participate. Do not offer the survey to persons not fitting those criteria.

The survey administrator should fill out the top portion of this page which will be used only by the health department. The patient name that corresponds to a given survey ID # will NOT be seen or used by the University of Michigan. The survey ID # is a 4 digit number located in the top right corner of every page.

Upon completion of this survey, the top page will be torn off and retained by the health department.

Once the above information has been filled in please proceed to the following page and read the introduction inviting the patient to participate in the survey. At the end of the survey there are questions to be filled out based on the patient chart. This information need not be obtained from the respondent. If a respondent chooses not to participate in the survey, this information should NOT be filled in.

At any point once the survey has started, a respondent may opt out of finishing the survey and receive full compensation for their time. If this happens, please thank them for their time and give them the incentive.

If at any point during the survey a participant seems upset by the questions, the interviewer may stop the survey. In this case, the participant would receive full compensation.

If the survey needs to be done on 2 separate occasions, please note down the date/time for the start and finish time of the survey.

Unless otherwise noted, all answer choices should be read aloud to the survey participants. Several questions indicate that you should allow the survey respondent to volunteer information. In this instance, the answer choices do not need to be read aloud.

SAY: *To help us better understand how tuberculosis spreads in Michigan, we are asking you to take part in a short survey administered through the University of Michigan. The survey will take about 20 minutes and your participation is completely optional. Information obtained in the survey will be used to inform the care given to future TB patients by the public health department. All information will be kept confidential and will not be traceable to you except through the health department. The information used by the University of Michigan will not include any identifying information that can be linked back to you. We are offering a $20 gift card for participation. At any point in the survey you may refuse to answer a question or stop the survey altogether and you will still receive the gift card.*

Are you willing to participate in the survey?

☐ **No→Thank subject for their time and stop interview.**

☐ **Yes→ Give respondent the consent form and HIPPA release form and ask them to read it. If the respondent has questions, you should answer them. If they agree to participate, they need to sign 2 copies of each of these forms. One copy of the consent form and HIPPA release form should be retained for their records; the other should be submitted to the health department.**

Continue with the survey on the following page.

	Date	Time
Start of survey administration		
Finish of survey administration		

SAY: ***To begin, I am going to ask you a series of basic questions about you currently.***

1. I know this may seem like an obvious question, but what race(s) do you consider yourself to be? [LET RESPONDENTS VOLUNTEER INFORMATION. CHECK ALL THAT APPLY]

☐ African American / Black / Negro [01] ☐ Caucasian / White [02] ☐ Asian Indian [03]

☐ American Indian or Alaska Native [04] ☐ Japanese [05] ☐ Chinese [06] ☐ Korean [07]

☐ Native Hawaiian [08] ☐ Filipino [09] ☐ Other Pacific Islander [10]

☐ Some other race [11]

_____

☐ *Refused [999]*

2. What is your ancestry or ethnic origin? [LET RESPONDENTS VOLUNTEER INFORMATION.]

FILL IN RESPONSE:

_____

☐ Do not know [10]

☐ *Refused [999]*

3a. Are you Spanish/Hispanic/Latino? [LET RESPONDENTS VOLUNTEER INFORMATION.]

☐ No, not Spanish/Hispanic/Latino [01] ☐ Yes, Mexican, Mexican American, Chicano [02]

☐ Yes, Puerto Rican [03] ☐ Yes, Cuban [04]

☐ Yes, other Spanish/Hispanic/Latino—*Print group* [05]

_____

☐ *Refused [999]*

3b. Are you of Middle Eastern or North African descent?

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

4. What gender do you consider yourself to be? [LET RESPONDENTS VOLUNTEER INFORMATION]

☐ Male [01] ☐ Female [02] ☐ Both male and female [03] ☐ Neither male nor female [04]

☐ Other [05] _____

☐ *Refused [999]*

5. Are you currently married, separated, divorced, widowed, living with a partner, or single? [LET RESPONDENTS VOLUNTEER INFORMATION]

☐ Married [01] ☐ Separated [02] ☐ Divorced [03] ☐ Widowed [04]

☐ Living with a partner [05] ☐ Single [06]

☐ Other [07] _____

☐ *Refused [999]*

6. What is the highest grade or level of school you have completed or the highest degree you have received?

☐ Some high school [01] ☐ High school or GED [02] ☐ Some college [03]

☐ Bachelor or Associate's Degree [04] ☐ Advanced graduate degree [05]

☐ Other professional degree [06]

☐ *Refused [999]*

SAY: For the next series of questions, I want you to think back to before you were diagnosed with TB. Answer the questions as you would have before you had TB.

7. Before you had TB, would you say that your health was excellent, good, fair, or poor compared to other people your age?

☐ Excellent [01] ☐ Good [02] ☐ Fair [03] ☐ Poor [04]

☐ *Refused [999]*

SAY: ***Now I am going to ask you about your personal behaviors before you were diagnosed with TB.***

8a. Did you ever drink beer, wine or liquor?

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

IF YES → CONTINUE TO #8B
IF NO → CONTINUE TO #8D

8b. In a typical month, about how many days did you drink beer, wine, or liquor?

Days: _____

8c. On days that you drank, about how many drinks did you have? By drink we mean a can or bottle of beer, glass of wine, shot of liquor, or a mixed drink.

Drinks: _____

IF RESPONDENTS ANSWERED #8B OR #8C, CONTINUE TO #9A.

8d. Have you always abstained from drinking alcohol?

☐ Yes [01] ☐ No [02] ☐ *Refused [999]*

9a. Did you smoke cigarettes before you had TB?

☐ Yes [01] ☐ No [02] ☐ *Refused [999]*

IF YES → CONTINUE TO #9B.
IF NO → CONTINUE TO #9C.

9b. In an average day, how many cigarettes did you usually smoke?

_____Cigarettes or _____Packs

IF RESPONDENT ANSWERS #9B, CONTINUE TO #10.

9c. Have you ever smoked?

☐ Yes [01] ☐ No [02] ☐ *Refused [999]*

10. Before your diagnosis of TB, how often did you engage in active sports or exercise?

☐ Never [01] ☐ Less than once a week [02] ☐ Once a week [03] ☐ Multiple times per week [04]

☐ Almost every day [05]

☐ *Refused [999]*

SAY: ***Now I am going to ask you a series of questions about health care. Remember, you are still answering these like you would have before you were diagnosed with TB.***

11a. Suppose you had a health symptom that had been bugging you for a couple of weeks (something like a shooting pain in your back, persistent flu-like symptoms, headache that wouldn't go away), how likely would you be to seek out medical attention?

☐ Very likely [01] ☐ Somewhat likely [02] ☐ Somewhat unlikely [03] ☐ Unlikely [04]

☐ *Refused [999]*

11b. What are the biggest reasons you wouldn't seek out medical attention? ([LET RESPONDENTS VOLUNTEER INFORMATION.ONLY READ ANSWER CHOICES IF RESPONDENT NEEDS PROMPTING)

☐ Cost [01] ☐ Too far away [02] ☐ Can't take off work [03] ☐ Lack of health insurance [04]

☐ Time/Inconvenience [05] ☐ Fear of doctors or medical treatments [06] ☐ Quality of care [07]

☐ Unpleasant interactions with healthcare professionals [08] ☐ No transportation [09]

☐ Embarrassed to see a doctor [10]

☐ Other (PLEASE SPECIFY) [11] _____

☐ *Refused [999]*

12. Now I'm going to list a series of locations in the community. On average, how often did you spend time in these locations before you were diagnosed with TB?

Location	Daily [01]	Weekly [02]	Monthly [03]	Never [06]	*Refused [999]*
a. Workplace: _____					
b. Place of worship (church, synagogue, mosque, temple)					
c. Schools (grade schools or universities)					
d. Corner stores/convenient stores					
e. Bar (club, nightclub, etc.)					
f. Liquor store					
g. Family member's house					
h. Friend(s) or neighbor's house					
i. Social or athletic clubs					
j. Homeless Shelter					
k. Jail or correctional facility					
l. On public transportation (bus, train)					
m. Long-term care, assisted living facilities, or group homes					
n. Healthcare facilities (doctors' offices, clinics, hospitals)					
o. Other place (define): 1) _____ 2) _____					

SAY: ***For the remainder of the survey I want you to answer the questions currently—what I mean is that your responses to the questions should reflect your current status.***

The next questions are going to ask you about your residence and the area surrounding it.

13. Do you have a permanent address?

☐ Yes [01] ☐ No [02] ☐ *Refused [999]*

IF YES → CONTINUE TO #14A
IF NO → CONTINUE TO #14B

14a. In the past 12 months are there times when you have been without a permanent address or homeless?

☐ Yes [01] ☐ No [02] ☐ *Refused [999]*

IF YES → CONTINUE TO #14B
IF NO → CONTINUE TO #15.

14b. How many weeks in the past 12 months have you been without a permanent address or homeless?

_____weeks

15. Altogether, how many people have you lived with in the past 12 months either temporarily or permanently (excluding yourself)?

_____people

16. Do you stay in the same place every night?

☐ All of the time [01] ☐ Most of the time [02] ☐ Some of the time [03] ☐ Rarely [04]

☐ Never [05]

☐ *Refused [999]*

17. Where do you stay most nights? (LET RESPONDENTS VOLUNTEER INFORMATION. DO NOT READ ANSWER CHOICES UNLESS NEEDED.)

☐ Their own home [01] ☐ Intimate partner's house [02] ☐ Family member's house [03]

☐ Shelter [04]

☐ Friend's house [05] ☐ On the street or in an abandoned building [06]

☐ Other [07] _____

☐ *Refused [999]*

18. How many times have you moved in the last 12 months?

☐ 0 times [01] ☐ 1-2 times [02] ☐ 3-4 times [03] ☐ More than 5 times [04]

☐ *Refused [999]*

19**.** Do you live in public assistance or section 8 housing?

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

20. How would you rate the condition of where you live?

☐ Excellent [01] ☐ Good [02] ☐ Fair [03] ☐ Poor [04]

☐ *Refused [999]*

21. How would you rate the quality of your neighborhood, that is the area within 2-3 blocks of where you live?

☐ Excellent [01] ☐ Good [02] ☐ Fair [03] ☐ Poor [04]

☐ *Refused [999]*

22. How would you rate the quality of your neighborhood compared to other neighborhoods in your city?

☐ Worse [01] ☐ About the same [02] ☐ Better [3]

☐ *Refused [999]*

23. Next I am going to read you some statements about your neighborhood. For these statements, please indicate if you strongly agree, agree, are neutral, disagree, or strongly disagree with the statement.

Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
a. I feel safe walking in my neighborhood, day or night.					
b. In my neighborhood the buildings and homes are well-maintained.					
c. I live in a close-knit neighborhood.					
d. People in my neighborhood are willing to help each other.					
e. There are many vacant houses or deserted houses or storefronts in my neighborhood.					
f. Vandalism is a big problem in my neighborhood.					

SAY: For the next set of questions I am going to ask you to compare yourself to the people around you. Remember, you are answering these questions according to how you currently feel.

NOTE TO THE INTERVIEWER: The following questions may be uncomfortable for participants to answer. Remind respondents they are welcome to skip any questions they are uncomfortable with.

Thinking about your life, where would you place yourself among the following groups of people:

24a. Your peers, by this I mean people that you spend time with that are around your age.

☐ Below your peers [01] ☐ Same as your peers [02] ☐ Above your peers [3]

☐ *Refused [999]*

24b. Your neighbors or people in your community

☐ Below your neighbors [01] ☐ Same as your neighbors [02] ☐ Above your neighbors [3]

☐ *Refused [999]*

24c. Other people in the U.S.

☐ Below other people in the U.S. [01] ☐ Same as other people in the U.S. [02]

☐ Above other people in the U.S. [3] ☐ *Refused [999]*

SAY: ***The following questions ask about health insurance, your income and the kind of work you do. Please answer them according to your current status.***

Please indicate which, if any, of the following kinds of health insurance you have?

25a. Medicare

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

25b. Medicaid

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

25c. VA or any other military health care plan

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

25d. Health insurance through your employer (or spouse's/partner's employer)

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

25e. Another type of health insurance (FILL IN BELOW)

_____

25f. No health insurance

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

IF THERE IS ANY TYPE OF HEALTH INSURANCE, MOVE TO #27A.
IF THERE IS NO INDICATION OF ANY HEALTH INSURANCE, MOVE TO #26.

26. What is the **main** reason that you do not have any health insurance right now? [LET RESPONDENTS VOLUNTEER INFORMATION]

☐ Cannot afford it/too expensive [01]

☐ Just changed jobs [02]

☐ Do not want it [03]

☐ Just moved [04]

☐ Do not need it [05]

☐ Unemployed [06]

☐ My job doesn't provide it [07]

☐ I'm not full-time [08]

☐ Temporary visitor or refugee status [09]

☐ Student without insurance [10]

☐ Insurance is outside of the U.S. [11]

☐ I'm too ill to get it [12]

☐ Don't know what to get [13]

☐ Other reason [14]

_____

☐ *Refused [999]*

27a. Now I'd like to ask you a few questions about the kind of work you do. First, are you working now for pay, looking for work, retired, a homemaker, a student, or something else? ([LET RESPONDENTS VOLUNTEER INFORMATION—CHECK ALL THAT APPLY)

☐ Working for pay [01] ☐ Unemployed / Looking for work [02] ☐ Retired [03]

☐ Homemaker [04] ☐ Student [05] ☐ Not working [06]

☐ Temporarily laid off, sick or maternity leave [07]

☐ Unpaid family worker [08]

☐ Other (Specify) [09] _____

☐ *Refused [999]*

IF ANSWER # 2, 3 → CONTINUE TO #27B.
ALL OTHER → CONTINUE TO #28.

27b. When did you last work for pay?

[record month/year] _____

28. How difficult is it for you to make your monthly bill payments?

☐ Not difficult at all [01] ☐ Somewhat difficult [02] ☐ Very difficult [3]

☐ Extremely difficult [4]

☐ *Refused [999]*

SAY: ***In order to get an accurate picture of your income, it helps to know the different sources of income you may have had in the past 12 months. We do not need detailed amounts, just whether you had income from the sources I will mention (this could be either you or your spouse/partner's income).***

29a. Income from wages or salary

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

29b. Unemployment compensations, disability or workers' compensation

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

29c. Social security payments, including payments for children

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

29d. Retirement pay, such as pensions or 401 (K) accounts

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

29e. Public assistance payments such as food stamps or welfare

☐ Yes [01] ☐ No [02]

☐ *Refused [999]*

29f. Any other sources of income (please list)

30. What is your total household yearly income from all sources (including your income from your job, government aid, and your spouse's income)? Is it less than $15,000 per year, between $15,000—$30, 000 per year, between $30,000—$75,000 per year, or is it more than $75,000 a year?

☐ < $15,0000 [01] ☐ $15,000 – $30,000 [02] ☐ $30,000 – $75,000 [03]

☐ > $75,000 [04] ☐ Do not know [05]

☐ *Refused [999]*

SAY: ***Now I am going to ask you a series of questions about your social life. Remember, you are answering them according to how you currently feel.***

People sometimes turn to others for companionship, assistance, or other types of support. How often are the following types of support available to you if need them?

31. Someone to confide in or talk to about yourself or your problems.

☐ All of the time [01] ☐ Most of the time [02] ☐ Some of the time [03]

☐ None of the time [04] ☐ Don't Know/Not sure [05]

☐ *Refused [999]*

32. Someone to take you to the doctor if you had to go.

☐ All of the time [01] ☐ Most of the time [02] ☐ Some of the time [03]

☐ None of the time [04] ☐ Don't Know/Not sure [05]

☐ *Refused [999]*

33. Someone to help you with your daily chores if you were sick.

☐ All of the time [01] ☐ Most of the time [02] ☐ Some of the time [03]

☐ None of the time [04] ☐ Don't Know/Not sure [05]

☐ *Refused [999]*

34. Someone to loan you $100 or less, if you needed it?

☐ All of the time [01] ☐ Most of the time [02] ☐ Some of the time [03]

☐ None of the time [04] ☐ Don't Know/Not sure [05]

☐ *Refused [999]*

SAY: ***Lastly, I am going to ask you a couple of questions about your food status. Please answer them according to how you currently feel.***

35. How difficult is it for you to make your food last until you have money to buy more?

☐ Not difficult at all [01] ☐ Somewhat difficult [02] ☐ Very difficult [3]

☐ Extremely difficult [4]

☐ *Refused [999]*

36. How often are you able to eat fresh fruits and vegetables?

☐ Everyday [01] ☐ A few times per week [02] ☐ Less than once per week [3]

☐ Never [4]

☐ *Refused [999]*

37a. Have you had to cut down the number or size of your meals because of money?

☐ Yes [01] ☐ No [02] ☐ *Refused [999]*

IF ANSWER YES → CONTINUE TO #37B

37b. How often have you had to do this?

☐ Everyday [01] ☐ A few times per week [02] ☐ Less than once per week [3]

☐ Never [4]

☐ *Refused [999]*

SAY: ***That concludes the survey. Thank you very much for your time. (Hand participant the gift card)***

THESE QUESTIONS ARE NOT GOING TO BE ASKED DURING THE SURVEY BUT SHOULD BE EXTRACTED FROM THE PATIENT CHART.

Information to be extracted from RVCT form	
1.County of residence	
2. Age (in years)	
3. Primary Reason Evaluated for TB	☐ TB symptoms [01] ☐ Abnormal chest radiograph [02] ☐ Contact investigation [03] ☐ Immigration medical exam [04] ☐ Targeted testing [05] ☐ Health care worker [06] ☐ Employment/administrative testing [07] ☐ Incidental lab report [08] ☐ Other [09]
4. Site of TB disease	☐ Pulmonary [01] ☐ Extra-pulmonary [02]☐ Unknown [03]
5. Symptoms at time of diagnosis	☐ Chronic cough [01] ☐ Weight loss [02] ☐ Night sweats [03] ☐ Other (please specify below) [04]
6. HIV Status	☐ Negative [01] ☐ Positive [02] ☐ Indeterminate [03] ☐ Refused [04] ☐ Not offered [05] ☐ Test done, results unknown [06] ☐ Unknown [07]
7. Country of Origin	☐ U.S. born [01] ☐ Foreign Born [02]
8. Immigration Status	☐ Not applicable/U.S.-born [01] ☐ Immigrant Visa [02] ☐ Asylee/parolee/refugee [03] ☐ Student Visa [04] ☐ Tourist Visa [05] ☐ Other Immigration Status [06]

	☐ Unknown [07]			
9. Homeless within past year	☐ No [01] ☐ Yes [02] ☐ Unknown [03]			
10. Resident of correctional facility at time of diagnosis	☐ No [01] ☐ Yes [02] ☐ Unknown [03]			
Previous Medical Diagnoses	**Currently**	**Before TB diagnosis**	**No**	**Unknown**
11a.High blood sugar or diabetes				
11b. Chronic lung condition (i.e. bronchitis, emphysema, or COPD				
11c. Asthma				
11d. High blood pressure or hypertension				
11e. Cancer				
11f. Arthritis				

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