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Latent Tuberculosis Infection Treatment Completion and Predictors of Noncompletion among Visa Holders in the Rural Setting

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Walden University
2018

Abstract

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MPH, Saint George's University School of Medicine, 2013

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Latent tuberculosis infection (LTBI), a product of exposure to *Mycobacterium tuberculosis* (*Mtb*), can lead to tuberculosis (TB) and further cause death if untreated. Fortunately, TB can be prevented with LTBI treatment. Targeting newly arrived visa holders for LTBI screening and treatment is an effective strategy for decreasing future TB burden. However, LTBI treatment completion rates are low, and researches had primarily focused on the nonrural U.S. setting. This study, using a retrospective cohort design under the epidemiological disease triangle framework evaluated (a) the treatment completion rates for 2 cohorts of visa holders (i.e., immigrants, $N = 31$ and refugees, $N = 109$) with LTBI residing in the rural setting using Pearson's chi-square analysis, (b) mean times on LTBI treatment using Kaplan-Meier survival analysis, and (c) predictors of time on treatment using Cox proportional hazard regression. Study findings revealed immigrants had higher treatment noncompletion rates over refugees (25.6% and 19.3%). The potential risk factors for noncompletion were being older than 24 years of age ($HR = 0.18$, $p = 0.01$). There were also significant interactions for the time on treatment between (a) being < 25 years old and visa type ($HR = 0.23$, $p = 0.04$), (b) being < 25 years and traveling longer (miles) to treatment facility ($HR = 0.25$, $p = 0.03$), or (c) being < 25 years and *Mtb* blood-test positive ($HR = 0.35$, $p = 0.05$). These findings suggest interventions targeting visa holders older than 24 years may increase the rate of treatment completion and decrease the future TB cases. Therefore, the study promotes social change by providing actionable, rural-population-specific information for the prioritization of visa holders at increased risk of experiencing LTBI treatment noncompletion.

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Dedication

This work is dedicated to my supportive, patient, caring family and friends. These individuals inspired me to stay the course, helped me look toward the future, listened to me “think out loud”, question findings, read and reread content audibly, and reaffirmed my aspirations and the benefits of this pursuit during times of challenge. I am incredibly honored to have each of these abovementioned parties cheering me on and look forward to the time I can repay them for their allegiance, kindness, and backing.

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Chapter 1: Introduction to the Study

Introduction

Tuberculosis (TB), an infectious disease caused by the bacteria *Mycobacterium tuberculosis* (*Mtb*), is most commonly associated with the lungs but can be found in other parts of the body causing long term sequellae such as airway constriction, neural deficits, infertility, or death (Shah & Reed, 2014). Hypothesized to have killed more persons than any other microbe by causing tuberculosis, *Mtb* has long been a burden to humanity (Daniel, 2006; Hartman-Adams, Clark, & Juckett, 2014; World Health Organization [WHO], 2016a). Although infection with *Mtb* exists on a spectrum of noninfectious latency to active disease, TB remains a leading global source of morbidity and mortality, joining the human immunodeficiency virus (HIV) in 2014 as the top cause of death despite its curableness (Nahid et al., 2016; Shah & Reed, 2014; WHO, 2015).

It is estimated that nearly one quarter to one third of the global population is asymptomatically infected with *Mtb* with an additional 1% newly infected each year (Campbell, Chen et al., 2015; Cardona, 2010; Houben & Dodd, 2016; Hartman-Adams et al., 2014; Moghaddam, Moghadam, Khademi, Bahreini, & Saeidi, 2016; Subedi et al., 2015; WHO, 2016a). Active, transmissible TB disease develops in 2% to 10% of persons infected with *Mtb* who fail to receive and complete preventive treatment, while others remain latently infected or naturally clear the infection (Campbell, Chen et al., 2015; Cardona, 2010; Houben & Dodd, 2016; Kahwati, Feltner, & Halpern, 2016; Lewinsohn et al., 2016; Raviglione & Sulis, 2016; Subedi et al., 2015; WHO, 2016a). In 2015, over 10 million incident cases of active TB were identified, with India, Indonesia, China,

Nigeria, Pakistan, and South Africa representing 60% of the global burden (WHO, 2016a). Annually, more than one million TB related deaths are recorded globally resulting in a mortality rate of 19 per 100,000 persons (Subedi et al., 2015). An estimated three million persons annually with infectious TB are never reported to officials and thus contribute significantly, yet silently, to the global spread of disease (Kamal, Suleman, Raza, Abassi, & Ayub, 2016; Raviglione & Sulis, 2016;).

Latent tuberculosis infection (LTBI), as a noncommunicable form of TB, is readily cured with up to 9 months of treatment but can reactivate to overcome the host immune system at an unpredictable point in time when left untreated. This reactivation can cause individual harm and spread disease to others (Hartman-Adams et al., 2014; Kahwati et al., 2016; Lewinsohn et al., 2016; Moghaddam et al., 2016). In the United States, foreign-born new migratory arrivals from TB endemic regions are at increased risk of being infected with *Mtb* and account for a high proportion of persons with active disease annually, which is thought to be the product of reactivation from exposure before migration (Dara, Gushulak, Posey, Zellweger, & Migliori, 2013). Often, these migrants at greatest risk of having LTBI hale from countries with poor sanitation, from congregate housing settings, from having poor housing in general, or possibly from temporary, overcrowded relocation camps that increase the likelihood of spread (Lim, Jarand, Field, & Fisher, 2016; Yun et al., 2015). If these persons migrate while infected with the *Mtb* pathogen, reactivation and spread years later may sustain the cycle of disease transmission. Research from the high-incidence and urban TB setting reveal that treating LTBI before reactivation can be a successful control strategy, can be the most cost-

effective strategy for preventing active TB disease, and for potentially reducing future TB rates (Association of State and Territorial Health Official, 2015; Centers for Disease Control and Prevention [CDC], 2013; Nuzzo, Golub, Chaulk, & Shah, 2015). Ensuring high rates of LTBI treatment completion is now regarded as a critical component to preventing future cases of TB disease and decreasing global morbidity and mortality.

A more comprehensive understanding of the epidemiology of treatment completion for foreign-born persons diagnosed with LTBI as well as the factors associated with treatment completion or noncompletion may assist TB control programs to more appropriately deploy resources to improve treatment completion rates and subsequently improve population health. Many of the identified predictors of treatment completion from studies in the international, high-incidence, and urban TB setting have been inconsistent, suggesting that geography and other regionally specific characteristics may play a role in influencing completion rates (Johnson et al., 2016; Malangu & Yamutamba, 2016). These inconsistencies further highlight the need for research across all settings with particular emphasis on the rural setting where TB resources may be scarce, as this setting is significantly underrepresented in published literature. Treatment completion research in the rural setting may better position public health institutions to organize interventions to improve completion rates in the most appropriate population and in the most effective manner, leading to a reduction in future disease burden and improving morbidity and mortality.

The contents of the following chapter outline the retrospective cohort study that aimed to determine LTBI treatment completion rates in the rural Idaho-based visa-

holding population as well as the potential predicting variables of completion or noncompletion. This chapter includes a brief description of TB and LTBI treatment, the known epidemiology of TB and LTBI in Idaho, the significance of this work for the rural setting, the assumptions, and the limitations of this study. Information submitted to the Idaho state TB Program from postmigration health evaluations on refugees, immigrants, and other visa holders completing LTBI therapy between 2011 and 2016 were analyzed to determine completion rates. This data was also used to determine at what point after initiating treatment visa holders were likely to fail and what factors were predictive of completion or noncompletion. The results of this study have the potential to influence public health practice in the rural environment by documenting LTBI treatment completion rates in the population most influenced by TB in the United States. Also, this research highlighted variables that could become targets of interventions to improve overall LTBI treatment completion rates in the rural foreign-born population.

Background of Tuberculosis and its Management

Mycobacterium tuberculosis is thought to have coevolved with humans prior to migration from the African continent and is now found globally (Esmail, Barry, Young, & Wilkinson, 2014). Historians suspect *Mtb* evolved from a low-pathogenic form with prolonged latency to the more pathogenic form currently challenging public health (Esmail et al., 2014). Persons at elevated risk of having LTBI include recent migrants from high-incident TB settings, persons currently or formally homeless, persons who live or work in congregate settings, and health care workers (Bibbins-Domingo et al., 2016; Fox, Dobler, Marais, & Denholm, 2016; Oren et al., 2016; Raviglione & Sulis, 2016;

Severi, Maguire, Ihekweazu, Bickler, & Abubakar, 2016). If undetected and untreated, persons with LTBI are at risk of developing active TB disease (Pareek, Greenaway, Noori, Munoz, & Zennet, 2016). The progression from latency to active TB has the potential to cause individual death, requires a significant amount of health care and public-sector resources to prevent transmission and ensure disease is cured, and can also leave long term lung tissue damage or other more severe consequences. Reducing the risk of reactivation by treating LTBI can prevent death, saves health care and public resources, and ensures those infected suffer minimal to no lifelong penalties from disease.

Assuming up to 10% of those infected with *Mtb* develop active disease, the current untreated LTBI reservoir in the United States could produce an additional 1.3 million cases of active TB in the future (CDC, 2013; Diel, Loddenkemper, & Nienhaus, 2016; Houben & Dodd, 2016; LoBue & Mermin, 2017). Additionally, and on average, three persons could be infected per each reported active case annually, adding to the 11 to 13 million estimated to already be latently infected and establishing a cycle of disease transmission that could be disrupted using preventive LTBI therapy (CDC, 2013; Houben & Dodd, 2016; Diel et al., 2016). With recent migrants being at high risk for exposure to *Mtb* and for having reactivation within 2 to 5 years after relocating, the consistent flow of new foreign-born arrivals (Migration Policy Institute, 2015) further supports the need to rapidly ensure the complete treatment of the infected at high rates (Pareek et al., 2016).

Treatment Regimens

Tuberculosis disease. The prompt recognition of signs and symptoms consistent with TB disease minimizes transmission and leads to more rapid cure of the individual

via treatment (Nahid et al., 2016). The combination of rifampin (RIF), isoniazid (INH), pyrazinamide, and ethambutol, collectively referred to as RIPE, are recommended for administration in one of four different regimens and over two distinct phases for at least 6 months in persons with active TB (CDC, 2013b; Nahid et al., 2016). For patients with newly diagnosed pulmonary tuberculosis, the preferred regimen consists of daily RIPE for a duration of 8 weeks or 56 doses (intensive phase) followed by RIF and INH for an additional 18 weeks or 126 doses (continuation phase) (Nahid et al., 2016). In most parts of the world, including Idaho, this regimen is delivered under directly observed therapy (DOT), or under the supervision of the managing provider or public health official to improve compliance and ensure no adverse events take place. Under most circumstances, treatment of active TB spans 6 months; however, complicated disease or drug resistance can extend the treatment time drastically (Nahid et al., 2016).

Latent tuberculosis infection. The treatment of LTBI has generally spanned 9 consecutive months; however, shorter regimens have more recently been developed (CDC, 2013a). Presently, 6 to 9 months of daily or twice weekly INH is the preferred treatment regimen as clinical trials have demonstrated this regimen to be the most efficacious (CDC, 2013a). Due to low adherence rates, the use of 4 months of daily RIF has also become popular (CDC, 2013a). This regimen is also appropriate for persons exposed to INH-resistant TB but cannot be used with HIV-positive persons. The most recent treatment advancement involves an intermittent combination dose of weekly INH and rifapentine (RPT) spanning 12 weeks. Shown to be noninferior to 6 or 9 months of INH, the INH and RPT combination is the shortest available regimen and may contribute

to improved overall treatment completion rates once widely used (CDC, 2013a; Stagg et al., 2014). Most frequently used to treat recently arrived visa holders in the United States with LTBI, recent known contacts to someone with TB disease infected with *Mtb*, and persons in congregate settings with LTBI, the more standardized, targeted use of LTBI treatment is expanding in the United States as a strategy to prevent future cases of active TB (Bibbins-Domingo et al., 2016).

Idaho Epidemiology

Tuberculosis. In Idaho, reflecting national trends, rates of TB disease have been on a steady decline. With an incidence rate of 1.1 per 100,000 persons in 2016, rates of TB in Idaho are consistently below the national rate of 3.0 per 100,000 persons (Idaho Department of Health and Welfare [IDHW], 2016). Those less than 5 years of age diagnosed with TB in Idaho have a 5-year average incidence rate for the period 2012 to 2016 of 1.44 per 100,000 persons, which is higher than adults at 0.75 per 100,000 persons (CDC, 2017a). Comparable to national trends, men in Idaho are diagnosed with TB disease twice as often as their female counterparts. The foreign-born are disproportionately impacted by TB in Idaho with a 5-year average (2012 to 2016) incidence rate of 9.5 per 100,000 persons, far exceeding that of the U.S.-born 5-year average (2012 to 2016) rate at 0.26 per 100,000 persons (IDHW, 2016). Of these foreign-born persons with TB, from 2012-2016, one quarter were refugees, over one tenth were immigrants, and nearly two tenths were other visa holders with the total foreign-born representing 73% of Idaho's TB burden (CDC, 2017a; IDHW, 2016).

Latent tuberculosis infection. Although a precursor to TB disease and a marker for future burden, rates of LTBI in both the U.S.-born and foreign-born in Idaho are not known, although estimates can be drawn. Using the prevalence of LTBI estimated from tuberculin-skin-test (TST) and interferon gamma release assay (IGRA) positivity reported by Miramontes et al. (2015) in the analysis of the 2011-2012 National Health and Nutrition Examination Survey, over 16,400 foreign-born persons in Idaho may be infected with *Mtb*. Although the foreign-born represent a small fraction of the overall Idaho population, infection is likely concentrated in this high-risk group, with many being a current or former visa holder. Although not directly reported on for the foreign-born in Idaho, visa holders are likely at heightened risk of being infected with LTBI if they have migrated from a region with high TB burden, have resided in a high-risk congregate setting such as a shelter or correctional facility, or have had known recent exposure to TB (Bibbins-Domingo et al., 2016; Lewinsohn et al., 2016). Additionally, with the foreign-born being at higher risk of progression from infection to disease within 2 to 5 years after arrival, targeting visa holders in Idaho for prophylactic LTBI treatment upon arrival may reduce future active TB burden (Lewinsohn et al., 2016).

Patient management. Persons suspected of having or diagnosed with active TB should promptly be placed on four-drug therapy. Generally, once identified, persons suspected of having or diagnosed with TB are assigned a TB case manager, often from the public sector. These case managers are responsible for ensuring transmission is controlled, contact investigations are carried out, treatment is adhered to, and the patient is free from adverse medication events. From 2012 to 2016, persons with TB reported to

Idaho public health officials initiated treatment within 7 days of being suspected of having disease or being diagnosed with disease 93.2% of the time (CDC, 2017a). This remains very close to the national target of 95% (CDC, 2017b). Furthermore, of persons initiating TB treatment during this time, 91% complete treatment within 12 months (CDC, 2017b). These high rates of treatment initiation and completion for active TB are critical to preventing transmission and protecting the population's health.

Contact tracing. Identifying persons exposed to *Mtb* is a core TB control function. This activity assists in the identification of persons potentially infected after exposure and can assist with the promotion of preventive treatment initiation. In Idaho, only persons with infectious TB disease (e.g., pulmonary or laryngeal disease, acid-fast bacilli positive lab results) receive contact investigations. Children under the age of 5 also receive a type of contact investigation, termed a source case investigation, to identify their source of exposure. Contact investigations initially focus on the immediate household and expand until all potential contacts have been identified, notified, and offered testing. Identified contacts are prioritized for follow-up by proximity to the index during exposure, age (with emphasis being given to those less than 5 years), and the presence of underlying medical conditions (Taylor, 2005). These contacts are offered testing and, if infected, LTBI treatment at no cost. In Idaho, from 2012 to 2016, 100% of TB cases reported to public health officials had contacts elicited.

LTBI treatment completion in contacts. Known contacts to infectious TB are given special attention in United States as these persons were likely infected within U.S. borders. Aiming to minimize transmission within the United States, information about

contacts to persons with infectious TB is gathered by local public health officials and aggregate treatment completion data are reported to the CDC. When a contact to an infectious TB case is identified and is diagnosed with LTBI, preventive treatment is recommended to ensure the contact does not develop future transmissible disease (Taylor, 2005). From 2012 to 2016, 441 contacts to persons with infectious TB were identified by public health officials in Idaho (CDC, 2017a). Of those, 10% were found to have LTBI with less than 48% successfully completing treatment (CDC, 2017a). This low rate of treatment completion in identified contacts indicates that a select number of infected persons known to public health officials may be at continued risk of developing active disease. In the resource limited setting, the small number of persons not completing LTBI treatment completion after being involved in a contact investigation may be deprioritized to the much larger pool of foreign-born persons entering jurisdictions as these individuals are more likely to accept treatment. During this same 2012-2016 time period, 5,030 visa holders arrived in Idaho representing a much higher potential pool of preventive LTBI treatment candidates. Additionally, with community transmission from a U.S.-born case being rare in Idaho, many of the contacts identified are members of the foreign-born population, further highlighting the need to prioritize treatment completion in this group.

Treatment Completion

Completion rates for persons diagnosed with active TB disease globally and in the United States are generally higher than those of persons diagnosed with LTBI (CDC, 2016a; WHO, 2016a). Worldwide in 2014, 83% of persons prescribed RIPE for active TB disease completed therapy (WHO, 2016a) compared to nearly 90% in the United

States (CDC, 2016a). The developed TB infrastructure in the United States promotes treatment completion as a priority strategy for reducing exposures and moving the country toward TB elimination. Additionally, the labor-intensive DOT strategies deployed by jurisdictions in the United States contribute significantly to the overall treatment completion success rate. In 2015, 92.1% of persons in the United States diagnosed with TB completed therapy under DOT (CDC, 2016a).

Successful completion of LTBI treatment, under most circumstances, cures the infected individual and prevents the development of active disease, can prevent future active TB complications and hospitalizations, and can improve long term tuberculosis morbidity and mortality (Denholm & McBryde, 2010; Nuzzo et al., 2015; Sandgren et al., 2016). However, LTBI treatment completion rates in the urban, high-incidence, or resource-rich setting in the United States reportedly range from 24% to over 90% (Cook, Maldonado, Yarnell, & Holbert, 2006; Spyridis et al., 2007; Young, Wessolossky, Ellis, Kaminski, & Daly, 2009). In specific populations, like those recently exposed to *Mtb*, the homeless, and IV drug users, completion rates vary but are frequently low. There are no published data on the treatment completion rates in rural, low-incidence settings with large immigrant populations, such as in Idaho. Treatment completion rates must remain consistently high in all groups and improve annually to move the United States toward elimination of TB risk, a task that requires a more comprehensive analysis of completion and noncompletion trends (Masini et al., 2016) from settings beyond the urban and high-incidence locales.

The U.S. foreign-born person typically achieves LTBI treatment completion rates less than the national elimination target of 85% (Sandgren et al., 2016). Presently, some research outlining factors associated with LTBI treatment noncompletion in U.S. foreign-born persons exists; however, study settings are limited to the urban, high-incidence, often TB resource-robust settings, leaving rural TB control programs to extrapolate findings to their settings (Cegolon et al., 2010; Codecasa et al., 2013; Coly & Morisky, 2004; Jiménez-Fuentes, de Souza-Galvao, Mila Augé, Solsona, Peiró, & Altet-Gómez, 2013; Li, Munsiff, Taratino, & Dorsinville, 2009; Stennis, Burzynski, Herbert, Nilsen, & Macaraig, 2016). This extrapolation may be a dangerous practice leading to assumptions that influence the distribution of scarce resources to an inaccurate target. With the prevention of reactivated TB through the treatment of LTBI becoming a highly favorable TB control strategy, a better understanding of the epidemiology of LTBI in every setting is needed. In the rural setting, where refugees, immigrants, and other visa holders may relocate and in whom LTBI and TB disease may be concentrated, the scarcity of TB resources likely indicates that recommendations from urban, high-incidence settings may be only tangentially relatable. By studying the LTBI treatment completion rates in the rural low-incidence setting, appropriately tailored recommendations for ensuring completion can be made.

Problem Statement

Since 1992, rates of TB in the United States have been on a steady decline. However, recent year-to-year decreases have begun to slow (CDC, 2015a; Miramontes et al., 2015; Salinas et al., 2016). Although well below the over 26,000 cases reported in

1992 at the height of the TB resurgence in the United States, the 9,557 cases reported in 2015 represent a 1.6% increase from the previous reporting year (CDC, 2016a). There must be strong efforts to understand the epidemiology of LTBI and preventive treatment completion trends in high-risk populations as these individuals act as a future reservoir for transmissible disease and contribute to the slowing of progress toward TB elimination (Salinas et al., 2016). Preventive treatment is the most cost-effective control strategy for low-incidence countries for averting future TB disease with some jurisdictions estimating that nearly 40% of cases of active TB are preventable (Blount et al., 2016; Campbell, Marra, Cook, & Johnston, 2014; CDC, 2013; Varkey, Jerath, Bagniewski, & Lesnick, 2007;). Hirsch-Moverman, Daftary, Franks, and Colson (2008) estimated that the 291,000 to 433,000 persons treated for LTBI in 2002 prevented 4,000 to 11,000 future cases of TB. High rates of completion of preventive therapy have the potential to reduce overall health care costs associated with TB control, improve immediate and future individual health outcomes, and dampen the potential future spread of drug-resistant strains of *Mtb* (Hirsch-Moverman et al., 2008).

Review of U.S. immigration surveillance data consistently indicates that a clear majority of the reported TB cases in the United States stem from reactivation in foreign-born persons. This reactivation frequently occurs within 2 to 5 years of entering the country after overseas exposure (Menzies, Winston, Holtz, Cain, & Mac Kenzie, 2010; Campbell, Chen et al., 2015; CDC, 2016a; Houben & Dodd, 2016). The increasingly important role foreign-born persons play in influencing TB trends in the United States indicates that this group should be a target of interventions that aim to increase LTBI

detection, treatment, and completion (CDC, 2013; CDC, 2016a). Although national TB control targets aim for 85% LTBI preventive treatment completion rates for foreign-born persons to reduce future rates of reactivation, this threshold is inconsistently met (Hirsch-Moverman et al., 2008). With LTBI treatment initiation rates below 70% for refugees and immigrants and completion rates below 55% nationally (CDC, 2016b), a significant pool of potential future reactivated cases of TB exists. In Idaho, a state that resettles more refugees per year than the 26 per 100,000 national average, foreign-born persons account for more than 65% of the reported TB cases (CDC, 2016b; Radford & Connor, 2016). Annually, a variable number of Idaho-arriving refugees, immigrants, and other permanent visa holders are diagnosed with LTBI, but it is unknown of those initiating therapy how many will complete prescribed regimens (CDC, 2016b). The undescribed LTBI treatment completion rates in Idaho may indicate there exists a large pool of persons at risk of experiencing reactivated TB who could spread disease to others and require costly health care interventions to address future advanced disease. It is unknown what factors may contribute to rates of completion or noncompletion in this rural setting.

Some published literature from the international, urban, and high-incidence TB settings inconsistently indicate a variety of host, environmental, and agent factors influence treatment completion rates for persons with LTBI (Campbell, Chen et al., 2015; Hirsch-Moverman et al., 2008; Johnson et al., 2016; Parsyan, Saukkonen, Barry, Sharnprapai, & Horsburgh, 2007; Sandgren et al., 2016;). What remains to be studied are the trends in treatment completion in the rural setting and what potential interactive host, agent, and environmental factors may be associated with treatment completion or

noncompletion. These invariable research findings highlight the importance that geographical setting may have on visa holder LTBI treatment completion rates, but the limited settings in which the epidemiology of LTBI completion rates has been studied do not ensure generalization. In Idaho, where geography can pose a significant barrier to accessing the limited TB resources, TB control program metrics aim for a LTBI treatment completion rate at or above the national 2020 target of 85% for persons initiating LTBI therapy (CDC, 2015b; CDC, 2016b), but the mean duration Idaho visa holders actually remain on therapy is unknown and may be critical to recommending when to intervene to improve completion. Understanding LTBI treatment completion rates in Idaho may also assist with identifying when visa holders are at greatest risk for not completing therapy (Vozoris & Batt, 2016). This gap in knowledge potentially prevents reductions to future TB-related morbidity and mortality in the rural setting (Li et al., 2009).

Studies are needed in the low-incidence rural setting to allow TB control programs serving high-risk populations in this landscape to identify the factors associated with treatment completion or noncompletion. Findings from such studies may promote the more appropriate use of interventions, considering the limited resources available. The Idaho State Tuberculosis Program is the entity responsible for coordinating and reporting on the medical evaluations of new foreign-born arrivals, so using data gathered and submitted to the program on refugees, immigrants, and other permanent visa holders requiring follow-up for medical conditions including TB and LTBI, the epidemiology of treatment completion for LTBI in this population can be better understood and a response appropriately tailored (IDHW, 2016; Lönnroth et al., 2015).

Purpose of the Study

If high LTBI treatment completion rates have the potential to reduce future disease burden and improve health, current research from the high-incidence and urban setting may not be adequate to guide the development of programs to improve completion rate interventions in the rural setting. The purpose of this study was to examine in depth the LTBI treatment completion and noncompletion rates in Idaho visa holders diagnosed with LTBI and to determine what factors were associated with treatment completion or noncompletion using time-to-event-based analytic techniques. A retrospective cohort was used to address the current gap in what is known about LTBI treatment completion and noncompletion in the rural U.S. setting. Event-based analysis was essential in determining how many months Idaho visa holders with LTBI remained on therapy, the probability that visa holders experienced the event (e.g., treatment noncompletion), as well as in determining which covariates were potentially associated with the outcome of interest. This analysis was particularly useful for identifying those potential covariates that may be host-, environment-, or agent-specific. Published research findings from the urban, high-incidence TB setting inconsistently indicate host factors such as age, gender, and country of origin, and environmental factors such as area of resettlement, influence treatment completion rates for persons with LTBI (Hirsch-Moverman et al., 2008; Sandgren et al., 2016). This research was essential for exploring whether these covariates consistently influence treatment completion in the rural setting, which is a phenomenon currently rarely explored in the United States and never explored in Idaho.

Research Questions and Hypotheses

The main research questions of this study were designed to explore the LTBI treatment completion rate in Idaho refugees, immigrants, and other visa holders and what host (i.e., gender, age, country of origin, smoking status, race/ethnicity), environment (i.e., distance to the health department/TB clinic and area of resettlement in Idaho [urban vs. rural]), and agent (i.e., TST or IGRA positivity) factors may be predictive of time on treatment until completion or noncompletion. The specific research questions for this study are outlined below.

RQ1: Is visa type (refugee, immigrant, parolee, asylee, or fiancé) associated with LTBI treatment completion among permanent visa holders initiating LTBI treatment in Idaho?

$H_0$1: There is no association between visa type and LTBI treatment completion among permanent visa holders initiating LTBI treatment in Idaho.

H_a1: There is an association between visa type and LTBI treatment completion among permanent visa holders initiating LTBI treatment in Idaho.

RQ2: Is the mean time distribution to last treatment for LTBI between permanent visa holders initiating LTBI treatment in Idaho significantly different?

$H_0$2: The mean time distribution to last treatment for LTBI between permanent visa holders initiating treatment in Idaho is not statistically difference.

H_a2: The mean time distribution to last treatment for LTBI between permanent visa holders initiating treatment in Idaho is statistically different.

RQ3: Is time on LTBI treatment in permanent visa holders initiating treatment in Idaho affected by sex, age, country of origin, visa type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity?

$H_0$3: Time on LTBI treatment in permanent visa holders initiating treatment in Idaho is not affected by sex, age, country of origin, visa-type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity.

H_a3: Time on LTBI treatment in permanent visa holders initiating treatment in Idaho is affected by sex, age, country of origin, visa-type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity.

Theoretical Framework for the Study

At the foundation of this current research lies the epidemiologic triangle, a model traditionally employed for disease causation, which outlines how agent-, host-, and environment-related factors influence the development of disease (Gordon, 1953). The epidemiologic triangle has been further applied to non-communicable disease and prevention research where the outcome of interest may be a behavior or health condition however, extremely complex relationships may not be appropriately described by this framework (Egger, Swinburn, & Rossner, 2003; Nganwa et al., 2010; Swinburn & Egger,

2002; Uzoigwe, Khaitsa, & Gibbs, 2007). Latent tuberculosis infection, although a noncommunicable state of disease, requires exposure to and the implantation of the microorganism *Mycobacterium tuberculosis.* The reactivation to active, transmissible disease is a product of a complex interaction between multiple factors. Successful LTBI treatment completion to prevent reactivation may be influenced by an interaction between factors making the epidemiologic triangle the main framework in which this research is constructed. In this context and for this research, although the epidemiologic triangle is most known for exploring disease causation, it is suspected that the host-, environment-, and agent-related factors discussed in detail in chapter 3 may play a critical role in influencing LTBI treatment completion. In this sense, the epidemiological triangle continues to be relevant framework for understanding what host, environment, and agent factors may influence preventive treatment outcomes as a potential precursor to exploring more behavior related factors in the future.

Epidemiologic Triangle Constructs

In the epidemiologic triangle, the bidirectional relationship and the intersection between the host, the agent, and the environment can result in the spread of infectious disease (Egger, Swinburn, & Rossner, 2003). Targeting and manipulating each of the points has historically led to the control of epidemics. The constructs of the model consist of the host, or the individual at risk of disease, whom interacts with the agent, or the necessary and disease causing component, but also with the environment in such a way that all three determine the timing, severity, and characteristics of disease (Haddon,

1980). By disrupting the agent, destabilizing the transmission promoting environment, and protecting or altering the host, disease eradication can be achieved.

This research employed these tenets in the context that high rates of LTBI preventive therapy completion disrupts progression to reactivated disease and that factors within each of the constructs of the epidemiologic triangle play a vital role in influencing completion. Additionally, the constructs were critical to interpreting the findings of this research to help explain what factors may be important to treatment noncompletion. Visa holders in Idaho infected with *Mtb* (the agent) and diagnosed with LTBI, may not complete LTBI preventive therapy due to the interaction or imbalance between personal (host) factors such as gender, age, and country of origin and their area of Idaho resettlement (the environment) in terms of urban versus rural or distance from their treating facility. By investigating host, agent, and environmental factors related to treatment completion and noncompletion, the epidemiologic triangle can be utilized to support the notion that a high rate of treatment completion is critical to preventing future disease by disrupting noncompletion through public health intervention.

This study expanded upon the epidemiologic triangle by analyzing host, environment, and agent data as independent study variables to better understand the relationship to the treatment completion outcome. Although more behavior oriented frameworks exist and could too be useful for exploring LTBI treatment noncompletion, the epidemiologic triangle was more appropriate for this research due to the extremely limited information available surrounding this phenomenon. As a starting point, it is expected that this framework will be essential to exploring the basic components of LTBI

treatment noncompletion in the rural setting. However, this research, constructed using the epidemiologic triangle, highlighted relationships potentially requiring additional exploration through a more behavior-oriented lens, such as the ecological perspective. This research employing the tenets of the epidemiologic triangle may be the first step in describing LTBI treatment completion and noncompletion influencing factors in the rural setting.

Nature of the Study

This was a retrospective epidemiological study using a secondary database to determine LTBI treatment completion rates and what factors influenced the likelihood visa holders fail treatment. Such a design is consistent with research grounded by Koch's germ theory of disease (1882) and the epidemiologic model (Gordon, 1953) as LTBI and TB treatment completion has been well documented as a disease of social context influenced by host, environment, and agent-related factors (Hirsch-Moverman, Bethel, Colson, Franks, & El-Sador, 2010; Raviglione & Sulis, 2016; Venkatraman, Morris, & Wiselka, 2013). The main dependent variable in this retrospective cohort research was treatment noncompletion while independent variables included demographic factors, smoking status, TST or IGRA positivity, distance to health department/TB clinic, time between arrival and medical evaluation, and area of resettlement in Idaho (urban versus rural). Any subsequently developed intervention should be based on altering the bidirectional interaction between these factors to improve LTBI treatment completion. To determine the mean survival time as well as the characteristics related to treatment failure, a retrospective cohort of Idaho refugees, immigrants, and other visa holders

attending Idaho TB clinics was used spanning five years. Treatment start and stop times for Idaho visa holders initiating LTBI therapy were converted to months on therapy to standardize these times for event analysis. This quantitative analysis should help in determining if survival time, again, in terms of treatment failure, are different in the rural-state setting when compared to the literature available for the urban setting, and if specific factors influence rates of completion.

Definitions

The definitions outlined below are referenced consistently throughout this research or may be unique to this research. The terms and phrases defined below were derived from Merriam-Webster's Online Dictionary and Medical Dictionary (2017) or *A Dictionary of Epidemiology* (Porta, 2014).

Definitions of Variables Used in the Study to Describe Participants

Birth country: The country in which a migrant (visa-holder) was born.

Immigrant: (I) An individual seeking permanent residence in a country. Includes "Immigrant" visa designation in the dataset. Does not include persons with temporary visas such as international students, temporary visitors, or persons working in the United States under a temporary work visa.

Other visa-holder: (OVH) Non-immigrant and non-refugee visas issued to U.S. migrants. Includes "Parolee" (P), "Fiancé" (K1, V1), and "Asylee" (A) visa designations in the dataset.

Refugee: (R) A person who has fled another country or power to the United States to escape danger or persecution. Includes "Refugee" visa designations in the dataset.

Definition of Key Terms Used in the Study

"A" classification: Inadmissible health condition found during predeparture medical examination including: 1) a communicable disease of public health significance; 2) a physical or mental disorder and behavior associated with violence; 3) a drug abuser or addict.

Active tuberculosis: A diseased state in which Mtb has overcome the host immune response generally causing: unexplained weight loss, anorexia, night sweats, fever, fatigue, and chills. If disease occurs in the lungs, persons with cough may transmit the pathogen to susceptible hosts.

Agent: A component of the Epidemiologic Triangle Model and factor (e.g. microorganism) essential for the establishment of disease.

"B" TB classification: Subset of B Classifications including: 1) B1 tuberculosis, pulmonary; 2) B2 tuberculosis, extrapulmonary; and 3) B3 tuberculosis, latent tuberculosis infection evaluation.

Case: A person having a disease or condition; in this research, TB or LTBI.

Censor: An observation of an unknown value likely the cause of a participant being lost to follow-up or not experiencing the event prior to study completion or event completion.

Elimination: WHO goal of <1 case of TB per one million population.

Environment: Physical, biological, social, cultural and other dimensional factors that interact to influence the health status of the individual.

Event/failure: Not completing LTBI treatment due to self-withdrawal or at the advice of a health care provider but having a documented date in which treatment was last taken after initiation.

Host: An individual affording lodgment to the infectious Mycobacterium tuberculosis agent after exposure.

Infectious tuberculosis: A clinical diagnosis made due to the presence of Mtb in respiratory specimens, signs and symptoms consistent with TB disease, and radiographic evidence of disease.

Interferon gamma release assay (IGRA): Whole-blood tests used to assist in diagnosing infection with Mtb. In the United States, refers to only two licensed products: 1) QuantiFERON®-TB Gold In-Tube or QuantiFERON® Plus; and 2) T-SPOT®.TB test.

Latent tuberculosis infection: The presence of Mtb in the body in a noninfectious state without the clinical signs and symptoms of disease.

Public health district (PHD): Primary outlets for public health services in Idaho (IDHW, 2017) with seven PHDs serving all 44 Idaho counties: Panhandle Health District, North Central Health District, Southwest District Health, Central District Health, South Central District Health, Southeastern Idaho Public Health, and Eastern Idaho Public Health.

Reservoir: A potential habitat of an infectious agent.

Rural residence: A census tract classification area that is not urban (see Urban residence definition). Includes 32 of Idaho's 44 counties classified by the U.S. Office of Management and Budget.

Survival/success: Completion of ≥90% of prescribed dosages of LTBI treatment.

Survival time: Length of time on LTBI treatment until completion or censoring recorded in months.

Treatment completion: Documented completion of ≥90% of prescribed LTBI treatment.

Treatment noncompletion: Documented completion of <90% of prescribed LTBI treatment, being censored as LTFU, or experiencing an adverse event that leads to the discontinuation of LTBI treatment.

TB control program: A public health entity charged with preventing the transmission of TB, ensuring the rapid detection of those with disease, and the appropriate treatment of those with disease and their contacts.

Tuberculin skin test (TST): An intradermal injection of tuberculin purified protein derivative that is useful in determining if an individual is infected with Mtb.

Urban residence: A census tract classification area that has 50,000 or more population. Refers to 12 metropolitan counties of Idaho's 44 total counties: Boise-Nampa-Caldwell (five counties); Idaho Falls (three counties); Pocatello (two counties); Coeur d'Alene (one county), and Lewiston (one county).

Assumptions

Consistent with survival analyses, it was assumed that for this research, censoring was independent of survival time. Additionally, no underlying probability distribution was used as a basis for the analysis however it was assumed that the hazard remained constant over time, which is also a standard assumption of survival analysis (Bewick, Cheek, & Ball, 2004). It was also assumed that all prearrival B TB classifications were accurate and that any post-arrival diagnoses were appropriate. The administration and interpretation of TST post-arrival, as well as the interpretation of IGRA results, was assumed to be accurate and consistent throughout the study timeframe. Lastly, it was assumed that the recommendation to initiate LTBI treatment regardless of PHD of residence was consistent and that ability to pay was not a contributing factor to not completing treatment since state-supplied free medications were available and frequently used.

Scope and Delimitations

This quantitative retrospective cohort study aimed to determine what the LTBI treatment completion rate was in Idaho refugees, immigrants, and other visa holders as well as what variables may have been predictive of noncompletion in this rural-based population. Annually and consistently, Idaho refugees, immigrants, and other visa holders account for a majority of the state's confirmed TB cases and thus, the completion of preventive therapy upon arrival may be critical to decreasing future rates of TB disease in the state and improving community health by preventing the risk of future transmission. Present research on this phenomenon has focused on the high-incidence, urban setting, leaving rural-based TB Control Programs to generalize findings to situations that may not

be relatable. This research and the subsequent focus on rural populations may help ensure TB Control Program interventions aimed at improving LTBI treatment completion rates are developed from conducting research in the appropriate setting but may also provide insight into the urban versus rural dichotomy of TB control.

The sample included in this study was limited to refugees, immigrants, and other permanent visa holders identified as possibly having LTBI during predeparture medical screening and categorized as a "Class B2 TB" or "Class B3 TB" migrant in the CDC's Electronic Disease Notification (EDN) system before relocation to Idaho. These visa holders had initiated LTBI treatment after being diagnosed in the United States. All migrants with the appropriate Class B TB notifications used in this research had initiated therapy after January 1, 2012 and completed LTBI treatment in Idaho before December 31, 2016. Non-permanent visa holders (*e.g.* student visas) were excluded from this cohort as these visas do not require extensive predeparture or post-arrival medical follow-up prior to entering the United States. The CDC's EDN system is the most robust source of both predeparture and post-arrival migrant medical screening information for Idaho. Those entities responsible for visa-holder evaluation have a contractual obligation to submit follow-up evaluation forms to the Idaho state TB Program to be reimbursed for performing these medical screenings. All contractor submitted data are entered into EDN. Additionally, this population is likely representative of much of the burden of disease in Idaho, which is a low-incidence TB state that rarely experiences verified TB transmission. Even in the most populated metropolitan centers where disease is concentrated, transmission rarely occurs. However, cases of TB disease have been

reported in domestic-born Idahoans indicating that LTBI may exist in a low level in this group as well, potentially limiting the broad generalization of this research. Independent variables used in this research were frequently deployed in other LTBI treatment research however, never in Idaho, rarely in the rural setting, and few consistent associations had been found. The results of this study may be applicable to rural, low-TB incidence jurisdictions with similar public health and health care structures as well as TB and LTBI epidemiology.

Limitations

This study may be limited by inconsistencies in predeparture medical practices, although overseas panel physicians should be abiding by the same CDC Technical Instructions (Dara et al., 2013; Lee et al., 2013). Also, post-arrival medical evaluation provider interpretation of diagnostic results may contribute to misclassification bias. These differences in practice may produce varying rates of data completeness but may also influence the overall rate in which migrants are recommended preventive LTBI therapy. In Idaho, the medical evaluation of migrants with Class B TB notifications suggestive of LTBI is often carried out by one of seven agencies that are different in terms of structure, resource, and mission which results in different degrees of care and could lead to differences in whether provider recommendations to treat are made. Additionally, some migrants arriving in Idaho do not come directly to the state; most arrive in urban U.S. areas with international airports designated to receive them and as such, may be at risk of TB exposure during any prolonged periods of time spent in these metropolitan areas prior to leaving for Idaho. This risk blurs whether exposure happened

overseas or domestically, however, as a low-incidence TB country, the United States rarely experiences widespread community transmission so the impact of this limitation should be relatively small.

An additional concern of this research involves the potential to underestimate the true rates of treatment completion due to migrants being lost to follow-up (LTFU) but also due to the interval in which medication adherence and completion is measured in Idaho. Visa holders may move out of state and complete therapy in the new jurisdiction or, since many are sent home with an entire month's worth of medication, may actually finish all required doses but not present back to the health department or TB clinic managing their care resulting in records indicating LTFU or noncompletion when preventive therapy may have actually been completed. Furthermore, government personnel responsible for dispensing LTBI treatment medications may only know if a patient does not complete treatment if they do not show up for monthly clinic visits or fill monthly prescriptions, limiting the level of data analysis that can be performed and the conclusions that can be drawn related to the number of days from initiation to failure. A more accurate and detailed log of actual dates medication is observed being ingested would be ideal however, would be logistically taxing in Idaho. Lastly, it is possible that some migrants seek care in the private sector and thus, could be excluded in this research if the provider does not submit follow-up TB data to the state.

Significance

Quantifying the completion rate and understanding the associated risk factors for treatment noncompletion in the rural U.S. setting will help bring the importance of the

low completion rate problem to the attention of public officials and the population in this setting. Additionally, this research may produce social change by providing a foundation for the deployment of more appropriate public health interventions in the rural setting. Early interventions may improve LTBI treatment completion rates in Idaho and lessen the future burden of TB disease in the state thus improving the community's overall health and reducing the strain on already limited TB resources in the state. These potential improvements in health may also be long term since the risk of re-exposure to *Mtb* in the low-incidence setting is small.

The results of this study may provide the Idaho state TB Control Program and the health care community with greater insight into LTBI treatment completion and noncompletion rates as well as into which visa holders have the greatest risk for not completing therapy. This study may also show which specific host, or environment, or agent factors influence treatment noncompletion and if made the target of an intervention, could improve completion rates. The findings of this research may also benefit similar communities facing treatment completion issues. Understanding of this phenomenon is paramount to eliminating the risk of reactivated and transmissible TB disease in Idaho visa holders and to potentially decreasing morbidity and improving mortality, and thus health, in all Idahoans. National TB stakeholders are increasingly calling for improvements in LTBI treatment completion rates and at the conclusion of this study critical information will be available to better understand how the Idaho TB Control Program may successfully reduce that state's future burden of TB disease by curing a majority of the current pool of those infected with *Mtb*.

Summary

The focus of Tuberculosis Control Programs in the United States is changing from narrowly concentrating on minimizing transmission to preventing active TB likely because of the recent year-to-year slowing in moving the country toward elimination. Although greater emphasis is being placed on preventing the large pool of persons in the United States with LTBI, most of whom are foreign-born, from developing active TB through prophylaxis, LTBI treatment completion rates remain low. Additionally, the research surrounding what factors may be associated with treatment completion or noncompletion is inconclusive and factors may be geographically unique. Increasingly, the foreign-born are being targeted upon entry to the United States for preventive therapy if infected with *Mtb*, but the rural setting is often overlooked in the treatment completion research and may be reliant upon implementing interventions that derived from non-generalizable research findings from the urban, high-incidence, TB resource-rich setting. The limited amount of rural-based LTBI treatment completion research may delay programs that serve this setting in reaching elimination, may lead to the misguided use of already strained resources, and may lead to sustained population TB morbidity and mortality.

In Idaho, a rural-state that frequently resettles more refugees per capita than the nation's 26 refugees per 100,000 residents average, accurate LTBI treatment completion rates for the foreign-born refugee, immigrant, and other visa-holding population are unknown as are the potential factors that may contribute to completion or noncompletion. This gap in knowledge if not filled could potentially indicate a sustained reservoir for

future disease transmission, sustained or increased morbidity and mortality, and a decreased ability to eliminate TB in the state. Interventions in the non-rural setting that aim to improve migrant LTBI treatment completion rates have successfully demonstrated a reduction in future TB disease trends. These findings emphasize the need for all jurisdictions serving a high volume of foreigners to ensure LTBI treatment completion does not fall below national standards. Idaho's high rate of migrant resettlement implies a greater risk for future TB disease transmission. This heightened risk calls for research into LTBI treatment completion and the potential predictors of noncompletion to guide treatment completion improving public health intervention development and deployment.

Chapter 2: Literature Review

Introduction

In the low-incidence tuberculosis setting such as the United States, the large LTBI reserve is the most immediate obstacle for achieving elimination of tuberculosis. To prevent future transmission if reactivation occurs, persons with LTBI may benefit from the 60% to 90% efficacy of eradicating *Mtb* by completing preventive treatment (Dobler & Marks, 2012; Getahun et al., 2015; Menzies, Jahdali, & Otaibi, 2011). With the foreign-born in the United States more likely to be infected with *Mtb*, targeting this high-risk group for preventive treatment could decrease the current pool of persons at risk of developing active TB (Blount et al., 2016; Pareek et al., 2016). Unfortunately, poor adherence to the LTBI regimen reduces effectiveness. Research from urban-based and high-incidence TB settings indicate that elimination in the United States will not be achieved until LTBI treatment completion rates are improved (Cook et al., 2006; Dobler & Marks, 2012; Sandgren et al., 2016). However, there is little published research about the epidemiology of LTBI treatment completion in foreign-born persons residing in the rural U.S. setting, which often has limited resources. A study of this type may help potentially reduce disease burden by preventing future transmission through interventions that improve LTBI treatment completion.

Predicting the risk of LTBI treatment noncompletion can be a successful approach to improving poor completion rates in high-risk populations (Shieh et al., 2006). Studies surrounding this phenomenon in various urban, high-incidence TB settings have produced inconsistencies in identifying the variables associated with preventive treatment

completion and noncompletion (Hirsch-Moverman et al., 2008; Johnson et al., 2016; Lin & Melendez-Torres, 2016). This gap highlights the potential role that geography and TB resource availability may play in ensuring high completion rates (Hirsch-Moverman et al., 2008; Johnson et al., 2016; Lin & Melendez-Torres, 2016). It has been determined that host, agent, and environmental factors associated with treatment completion may interact and influence treatment outcomes, making these factors appropriate targets for study (Coly & Morisky, 2004; Hirsch-Moverman, et al., 2008; Malangu & Yamutamba, 2016; Parsyan et al., 2007).

In Idaho, a frontier state in the top 10 for resettling persons of foreign-birth per capita (Radford & Connor, 2016), the future threat of LTBI reactivation will remain constant unless treatment completion rates can be better achieved. Identifying potential host, agent, and environmental predictors of failure for visa holders in Idaho will also assist with intervention development aiming to improve completion rates. The sporadic TB resources, limited availability of those with clinical expertise, and the vast geography of Idaho can pose significant barriers to high treatment completion rates. Early identification of noncompletion predisposing factors may help better target interventions, improve completion rates and community health, and have a positive social impact on the Idaho populace.

This chapter functions as a review of literature surrounding the known history of TB and LTBI, screening practices in the United States for TB and LTBI, the known epidemiology of TB and LTBI in the United States, the impact of and risk factors associated with having LTBI, and the documented predictors of LTBI treatment

completion in certain nonrural populations. The literature search and review focused on publications related to LTBI treatment completion and the specific associations ascertained between participants and completion rates in various, although infrequently rural, U.S. and international settings.

Literature Search Strategy

For this research, I identified the literature reviewed by querying electronic databases using Boolean searches including the phrases *LTBI* or *latent tuberculosis infection* and *treatment* or *treatment completion* or *treatment completion rates* or *preventive therapy* or *completion predictors* and *foreign-born* or *migrants* or *immigrants*. I carried out alternative searches, also using electronic databases, using *LTBI* or *latent tuberculosis infection* and *treatment adherence* or *predictors of adherence*. I utilized Google Scholar in early searching to gain more familiarity with the terminology of similar research. I relied heavily on MEDLINE, CINAHL, ProQuest Nursing and Allied Health Source, ProQuest Health and Medical Collection, PubMed, ScienceDirect, and EBSCO electronic databases to identify the peer reviewed studies informing this dissertation research. I also employed a Thoreau Multi-Database search to ensure any previously unsearched databases were identified. Initial broad searches were critical to the process of better defining future search terminology and strategies, but also in identifying authors and publications likely influential to LTBI treatment completion research.

The longstanding history of TB research indicated some prioritization of published works was necessary for this literature review. Seminal publications on the

history of *Mycobacterium tuberculosis* and tuberculosis as a disease are frequently referenced throughout this research; however, most peer-reviewed works critical to forming an understanding of LTBI, LTBI treatment initiation, LTBI treatment completion, and predictors of completion or noncompletion were limited to publication within the most recent 6 years (2012-2017). Summaries and critiques of the identified, applicable, peer-reviewed literature are found throughout this chapter. Additionally, references cited in the reviewed literature were also essential to identifying more potentially related publications. Lastly, I queried the ProQuest Dissertation database using the aforementioned search phrases in order to assist in identifying publications cited in dissertation research and sources possibly previously missed.

Methods Used in Latent Tuberculosis Infection Treatment Completion Research

I performed a literature review of 181 LTBI treatment completion or related published studies to determine what was known about predicting LTBI treatment completion or noncompletion in the United States, internationally, and in the rural setting. Most identified studies used the cohort design, but I also identified cross-sectional studies, systematic literature reviews, and randomized control trials. Few case control studies were deployed that aimed to compare treatment completion rates for different regimens assigned to different groups. Thirty-eight studies using cohort samples included an analysis of LTBI treatment completion and predicting variables compared to 11 observational studies, one randomized control trial, and nine systematic literature reviews. Of these, 22 were performed in low-incidence countries including the United States, Canada, United Kingdom, and Australia, 23 were from urban United States, nine

were from urban international settings, four were from rural international settings with a high-incidence of TB, and one covered urban and rural international high-incidence settings. Few identified studies included samples drawn from the rural U.S. setting.

Brief History of Tuberculosis and Latent Tuberculosis Infection

A significant cause of mortality globally, tuberculosis has long been a scourge to civilization. Advancements in science and technology have led to the discovery of *Mtb* at pre-Neolithic sites, but TB disease was also well documented in Greek and Biblical writing (Daniel, 2006; Herzog, 1998). Specifically, bony processes from 8,000 BCE have been found to be suggestive of Pott's Disease, or TB disease of the spine, while a bone unearthed from 5,000 BCE shows the changes that are consistent with tuberculosis disease (Daniel, 2006; Herzog, 1998). Acid-fast bacilli have also been isolated from a psoas abscess discovered in an Incan child well-preserved in a mummified state (Herzog, 1998). Together, these archaic discoveries demonstrate that TB has a long history.

Both Hippocrates and Aristotle described TB and its varying presentation in animals in 460 BCE and 384 BCE, respectively (Herzog, 1998). Efforts to describe the pathogenesis of *Mtb* emerged more consistently in the early 19th century in documented work by Théophile Laennec. The tubercle bacillus was identified as the cause of tuberculosis in 1882 by Heinrich and Koch, establishing a turning point in TB control and microbial science. During this time, consumption, the term used to describe persons with tuberculosis, was influencing multiple realms of life from science to fashion. The pale, gaunt, rose-colored cheeks of consumption sufferers brought into popularity the use of the corset as society responded to the high rates of TB by romanticizing the diseased state

(Daniel, 2006). In 1909, shortly after the infective nature of TB became the predominant theory regarding transmission, Clemens Freiherr von Piquet introduced the term “latent tuberculosis” from findings of a study in children involving Koch’s 1907 discovery of the TST. It was at this time that the notion that TB existed on a spectrum of latency to transmissibility became widely accepted.

In 1943, the advent of streptomycin, the only effective medication against TB at the time, brought TB control into the modern era (Daniel, 2006; Herzog, 1998). Shortly thereafter, the discovery of streptomycin-resistant strains prompted development of new drugs such as INH, pyrazinamide, ethambutol, and RIF in 1952, 1954, 1962, and 1963, respectively. These four drugs are still critical to treating TB disease today (Herzog, 1998; Nahid et al., 2016).

Characteristics of Mycobacterium Tuberculosis

Latent tuberculosis infection and tuberculosis disease are caused by *Mtb*. Although TB disease and LTBI are different manifestations of infection with *Mtb*, the organismal characteristics are critical to understanding the progression from infection to disease. The control of TB in the low-incidence setting has focused on identifying persons with active TB but has recently transitioned to targeting *Mtb* in its latent state.

Cell Biology

Described as a facultative intracellular parasite, the tubercle bacillus has evolved alongside its host to heighten immune system evading techniques (Daffé & Etienne, 1999; Vergne, Chua, Singh, & Deretic, 2004). The construction of *Mtb* likely contributes significantly to this success (Daffé & Etienne, 1999). The outermost structure, the

capsule, consists of a complicated mixture of polypeptides that ultimately aid in ensuring the biogenesis of any *Mtb* engulfing phagocyte is disrupted. This disruption prevents the human host immune cell from eliminating the tubercle bacilli and allows *Mtb* to quietly spread and suppress immunological detection (Daffé & Etienne, 1999; Vergne et al., 2004).

Reservoir

Humans are the only known reservoir of *M. tuberculosis* (Heymann, 2015). TB disease in humans is known to be caused by *M. tuberculosis, M. bovis, M. africanum, M. canetti*, and *M. microti*, collectively referred to as *Mtb* complex, with various animals acting as reservoirs for these other non-*Mtb* pathogens in the complex (Heymann, 2015). Particularly, *M. bovis* is known to be endemic in many cattle populations outside of the United States but can also be found in other animals such as deer, caribou, elk, or moose (Heymann, 2015). Transmission of *Mtb* between human and nonhuman hosts is possible.

Transmission

The primary means of transmission of the tubercle bacillus are the coughing, singing, or sneezing of an individual with infectious pulmonary disease. Transmissibility is assumed as long as the viable organism is present in sputum. Infection after mucous membrane exposure or exposure through broken skin is possible but rare. Consumption of *M. bovis* through unpasteurized milk can also cause TB disease in humans (Heymann, 2015).

Pathogenesis of Latent Tuberculosis Infection and Tuberculosis

Latent tuberculosis infection occurs in persons exposed to *Mtb* but in whom clinical signs and symptoms of active TB are absent. A susceptible host can become infected after inhalation of a single droplet nucleus expelled from an infectious contact with active pulmonary TB (Cardona, 2010; Getahun et al., 2015). An estimated 30 to 50% of those exposed to *Mtb* will become infected. The size of the inhaled droplet nuclei influences the site of implantation in the respiratory tract but once detected by the host immune system, alveolar macrophages engulf the *Mtb* bacilli allowing the pathogen to evade the immune defense systems and multiply (Cardona, 2010; Esmail et al., 2014; Ling Lin & Flynn, 2010). The immunologic response may produce a granuloma at the site of infection in which the bacteria may continue to multiply while evading a more pronounced host immune response. At this point, the host remains infected however *Mtb* dissemination is held off by the body's natural immune system. For some, bacterial eradication may never be achieved (Ling Lin & Flynn, 2010). In healthy individuals, the granulomas that may develop after inoculation with *Mtb* are thought to be the body's attempt to contain the infection. This containment prompts the latency stage in the cycle of the tubercle bacillus in its efforts to establish active TB (Ling Lin & Flynn, 2010).

Two to 10 weeks after inoculation diagnostic tools can be used to detect immunologic sensitization to *Mtb* (Ling Lin & Flynn, 2010). These tools have limitations in their usability and result interpretation due to varied sensitivity and specificity (Esmail et al., 2014; Leung, Lange, & Zhang, 2013; Ling Lin & Flynn, 2010). Clinicians and other health care providers use these diagnostic tools, the interpretation of a chest x-ray,

and an exposure risk profile to help support a diagnosis of LTBI as there is no technique to detect *Mtb* in the latent stage (Leung, Lange, & Zhang, 2013).

In settings where transmission of *Mtb* is limited, the lifetime risk of LTBI becoming active disease is estimated at 12% and most develop active disease within the first year after exposure (Esmail et al., 2014; Oren et al., 2016). For those whose reactivation does not occur within the first year, reactivation at longer time intervals is possible, but difficult to predict due to the limited number of studies on this phenomenon. TB activation may be the result of a weakened host immune system that allows *Mtb* to rupture the macrophages that were initially responsible for consuming the invader and either spreading *Mtb* to other body sites via lymphatic system or develop cavities in the lungs (Esmail et al., 2014). Under these circumstances the host is no longer considered to have LTBI, but instead active TB and respiratory tract expulsion could transmit *Mtb* to others. Active disease may progress rapidly and can be accompanied with fever, night sweats, weight loss, cough lasting greater than two weeks, and hemoptysis.

Tuberculosis Screening in the United States

The United States has a comprehensive system for evaluating migratory persons for medical conditions of public health concern. Since the late 1800's, the U.S. Public Health Service has been responsible for providing recommendations for the overseas medical examination of persons intending to relocate to the United States, including the requirement to test for LTBI and treat active TB, if identified during predeparture screening. These efforts are an attempt to reduce the incidence of imported disease (Lee et al., 2013; Liu, Posey, Cetron, & Painter, 2015). Panel physicians, U.S. Embassy

appointed health care providers, following strict CDC Technical Instructions, classify medically evaluated individuals into health categories after evaluation. Those identified as having Class A conditions, which include communicable diseases of public health significance, a lack of vaccine documentation (or associated waiver), a physical or mental illness associated with harmful action, and drug abuse, are permitted to enter the United States only under rare circumstances. Those with Class B conditions, which include sexually transmitted diseases, mental illness, and noninfectious TB, are allowed to enter but may require extensive medical follow-up once in the United States.

Evaluated individuals identified as having active, infectious TB are not permitted to enter the United States and are given a Class A condition categorization. Those with abnormal chest x-rays but negative sputum analyses, those with extrapulmonary TB, those suspected of having LTBI, and those with documented recent contact to an active case of TB receive a Class B TB designation and are permitted to enter the United States without treatment documentation (Lee et al., 2013; Liu, Posey, Cetron, & Painter, 2015). The results of these prearrival medical screenings are electronically submitted to state public health agencies prior to the migrant's arrival in the new host-country (Lee et al., 2013).

Annually, about 450,000 immigrants enter the United States along with an additional 75,000 refugees (Lee et al., 2013). Each entrant is subject to the screening of admissible and inadmissible diseases or conditions prior to entry (Blount et al., 2016; Lee et al., 2013; Liu, Posey, Cetron, & Painter, 2015; Varkey et al., 2007; Wingate et al., 2015). In 2009, a total of 104,954 refugees, immigrants, and other visa holders entered

the United States after clearing overseas medical examinations and receiving a medical condition classification. Of these arrivals with medical classifications, 99% were for non-inadmissible medical conditions, including non-infectious TB. All 50 states received refugees, immigrants, or other visa holders with a Class B TB however California, Texas, and New York consistently receive nearly 50% of these new arrivals. Nearly 57% of those arriving with a TB classification were thought to have non-infectious TB or LTBI (Lee et al., 2013). This persistently high rate of LTBI positivity in new arrivals emphasizes the sustained health threat to high-income countries, like the United States, will endure if LTBI is not addressed in this vulnerable population (Lönnroth et al., 2015).

Epidemiology of Tuberculosis and Latent Tuberculosis Infection

Risk Factors for Tuberculosis and Latent Tuberculosis Infection

Various persons are at increased risk of becoming infected with *Mtb*. In the low-incidence setting, persons at greatest risk of having LTBI include children under the age of five that have known contact to someone with infectious TB, people living with HIV and other immunocompromising conditions, persons starting anti-tumor necrosis factor therapy, health care workers, the homeless, persons residing or working in congregate settings, and those migrating from an intermediate- or high-incidence TB setting (WHO, 2016a). Persons at highest risk for progressing from LTBI to TB disease include people living with HIV, residents of correctional facilities, and children under five years of age. Comorbidities such as diabetes mellitus, smoking and the overuse of alcohol also place persons with LTBI at greater risk of progressing from latency to active disease (Raviglione & Sulis, 2016). Regardless which of the aforementioned risk categories are

concerned, LTBI treatment may be an effective control strategy for preventing disease in these persons (Lee et al., 2014; Martinez-Aguilar et al., 2015; Mirtskhulava et al., 2008; WHO, 2016a).

Incidence, Prevalence, and Mortality in the Pretreatment Era

With limited historical record keeping, geographical spread of tuberculosis overtime is not fully understood. Molecular analysis of identified ancestral stains of TB suggests that humans began spreading *Mtb* as the migration out of Africa to Europe and Asia took place (Gagneux, 2012; Levy, 2012; Pruitt, 2013). Additional limited historic documentation further supports that *Mtb* was introduced to the European and Asian populations through Indo-European cattle herders whilst nomadic from the ancestral lands in the Indian and Africa regions (Niemi, 2014). As the concentration of humans increased and villages were established, the proximity to cattle decreased, spread was sustained. In Northern America, tuberculosis swept through Indian communities after introduction from French-Canadian fur traders in the late 19th century. By this time, TB was well known in sub-Saharan Africa, India, and China. As global populations began to surge and travel across oceans was feasible, *Mtb* found its way to every country (Levy, 2012).

Although skeletal remains, depictions in art, and historical relics illustrate TB as a scourge on humanity for millennia, accurate counts of disease burden are not available until the early 17th century when the London Bills of Mortality were used to record the causes of death in the city. During this time, tuberculosis, or phthisis, was among the most common listed causes of death however, with no diagnostic tools available at that

time, misclassification was likely (Davies, 1994). A successful treatment for TB was unknown at this time.

In the early 20th century but still before the advent of treatment, improved housing standards dismantled slums and dispersed what were historically crowded centers for TB transmission. In developing countries, TB mortality began to decline roughly 1.7% per year in the pre-treatment era as sanitation improved (Davies, 1994) although *Mtb* continued to spread globally through colonization and the industrial revolution (Bates & Stead, 1993). For many centuries, TB was likely the cause of up to half of all human mortality events in Europe and North America (Gagneux, 2012). In many countries, the TB mortality decline lasted only until the 1980's before increases continued globally with over 10 million incident cases recorded in 2014 by the WHO (Chaisson, 2007). In the United States, consistent and accurate nationwide tracking of TB and TB mortality began in 1786 where 300 persons out of every 100,000 persons would die from tuberculosis (Wegner, 2013).

Incidence, Prevalence, and Mortality in the Posttreatment Era

Post-advent of successful treatment for TB around 1945, TB-related mortality rates in developed countries fell. From a high of 1,600 deaths per 100,000 people in 1800, the United States has seen a drastic decrease in TB mortality to less than 500 persons in 2015 (Centers for Disease Control and Prevention [CDC], 2016; Wegner, 2013). Although a significant improvement, these lower mortality rates are still not enough to rid the country of this disease (Al-Tawfiq & Memish, 2014). From 1985 to 1992, the average age of a TB sufferer in developed countries dropped from 49 years to

43 with much of TB disease burden in persons 25 to 44 years. Infants and children less than four years old experienced increasing incidence rates during this time. Disease was and continues to be concentrated in urban, minority populations (Chadha, 1997). In developing countries, the available data suggests a much slower decline in TB mortality.

In 2015, an estimated 10.4 million persons had TB disease with an additional three to four million thought to not have been reported contributing to sustained transmission (Kamal et al., 2016; Raviglione & Sulis, 2016; WHO, 2016a). Although accurately quantifying the incidence of TB globally has been a focus of public health for decades, the epidemic is larger than previously estimated (WHO, 2016a). In 1993, the WHO declared tuberculosis a global public health emergency, prompting the development of the global TB Elimination Strategy, after decades of soaring morbidity and mortality (WHO, 2014; WHO, 2016a). Twenty nine out of every 100,000 people died of tuberculosis in 2015 (WHO, 2016b). On the global scale, nearly two thirds of TB sufferers in 2015 were male, 90% were adult, and India, Indonesia, China, Nigeria, Pakistan, and South Africa consumed 60% of the burden (WHO, 2016a). As a disease of poverty, regression analysis has been used to estimate that more than seven million new cases occur annually in the under-developed and developing world (CDC, 1990).

Latent tuberculosis infection. TB infection is a global problem with an unequal distribution of burden. The WHO estimates 2 to 3 billion people are infected with *Mtb* with most residing in developing or under-developed nations (2016a). Similar to trends of TB disease, the foreign-born residing in the United States are more likely to be infected with *Mtb*, with an estimated 85% of TB disease cases being the product of longstanding

untreated LTBI (CDC, 2016; Miramontes et al., 2015). Approximations of LTBI prevalence in the United States are based off population screening research. In lieu of general population screening, populations at high risk of having LTBI may act as a proxy for establishing baseline estimates of burden. Using survey methodology, researchers with the 2011-2012 National Health and Nutrition Examination Survey (NHANES) identified participants eligible and willing to be tested for LTBI (Miramontes et al., 2015). The researchers determined that 4.7% of the U.S. population is likely latently infected with *Mtb* (Miramontes et al., 2015). This percentage escalates to over 20% for foreign-born residents in the United States (Kahwati et al., 2016). Based off this study, the 13,276,000 persons estimated to be infected are likely to be a majority male, aged 45 to 64 years, non-Hispanic Asian, and foreign-born (Miramontes et al., 2015). These persons remain at risk of reactivation without preventive treatment.

TB and LTBI trends. Globally, since 1997, the average change in incidence rate of TB in high-income countries was -2.2% compared to +1.8% in sub-Saharan Africa and other low-income countries (Dye, Lönnroth, Jaramillo, Williams, & Raviglione, 2009). In the era prior to treatment, TB incidence did decrease in most developed and developing countries by as much as 58% (Chadha, 1997). TB incidence is highly correlated with higher human development indexed countries, with lower child mortality, and with countries where access to improved sanitation is broad (Dye, Lönnroth, Jaramillo, Williams, & Raviglione, 2009). Although globally TB mortality has declined 22% from 2000 to 2015, significant reductions of TB and LTBI rates in high-income countries alone will not shift the global population toward TB elimination (WHO, 2016a).

Of the 10.4 million cases of TB in 2015, 6.3% were under the age of 15 years old. Persons living HIV accounted for 1.2 million of the total reported TB burden and the WHO reports that most persons living with HIV who subsequently develop TB reside in Africa, with more than 50% coming from Southern Africa (2016a).

Like global trends, 60% of the incident cases reported in the United States were men in 2015 and 66% were foreign-born (CDC, 2016). In 2015, nearly two thirds of TB cases reported occurred in those aged 15 years to 64 years. Those greater than 65 years accounted for 24% of the TB disease burden, while those aged zero to 15 represented only a fraction of reports. Asians have consistently had the highest rate of TB in the United States but have recently been joined by Native Hawaiians/Other Pacific Islanders. Of the foreign-born TB cases residing in the U.S. in 2015, Mexico, the Philippines, and India were reported to be the top three countries of origin. Less than 500 deaths were attributed to TB in the United States, representing a decrease of 71% when compared to the 1992 resurgence peak in the country (CDC, 2016). The overrepresentation of certain age groups, race/ethnicities, and persons from selected high-incidence countries demonstrates how TB becomes concentrated in specific populations in the low-incidence setting and how targeted LTBI treatment interventions may prove beneficial.

Latent tuberculosis infection trends are less well documented. In 1993, the first significant attempt to estimate the global burden of LTBI was performed resulting in a total of 1.86 billion (32%) of the world's population thought to be infected (Dye, Scheele, Dolin, Pathania, & Raviglione, 1999). Statistical analysis of these estimates indicated that the Africa, Eastern Mediterranean, and the Southeast Asian WHO regions had the highest

prevalence rate with over 995,000 persons thought to be infected (Dye, Scheele, Dolin, Pathania, & Raviglione, 1999). Currently, it is believed that 1.7 billion persons, or nearly a quarter of the global population, have LTBI. Six percent of those infected are thought to be less than fifteen years old, with 13% of those hailing from Africa. It is estimated that 56 million persons of the 1.7 billion infected had been inoculated within the two most recent years (Houben & Dodd, 2014).

Screening for and the administration of preventive LTBI therapy can act as a safeguard against eventual TB transmission with new emphasis being placed on decreasing the LTBI reservoir in the United States as a technique for moving the nation toward elimination and improving the year-to-year case reporting decreases (Houben & Dodd, 2016; Kahwati et al., 2016; Raviglione et al., 2016; Salinas et al., 2016). The elevated risk and rate of reactivation TB in U.S. foreign-born residents underscores the need to comprehensively understand the role various factors may play in preventive LTBI treatment completion since successful completion has a 90% efficacy rate in bacillary removal (Lin & Melendez-Torres, 2016; Malangu & Yamutamba, 2016).

Latent Tuberculosis Infection Treatment

For LTBI, provider-based decisions to initiate treatment are supported by diagnostic results, radiographic studies, clinical history, and the potential risk of exposure (Nahid et al., 2016). In some instances, empiric treatment for LTBI is warranted if suspicion of infection is high, yet diagnostic evidence is limited (Nahid et al., 2016). Tuberculosis Control Programs collaborate with the health care sector to identify persons suspected of being infected with *Mtb* to initiate curative treatment and prevent potential

future transmission (Nahid et al., 2016); a strategy that amplifies individual and community-level benefits (Menzies et al., 2004; Nahid et al., 2016). Latent tuberculosis infection is commonly treated with six, nine, or 12 months of INH with the latter duration of treatment having an efficacy of over 90% in killing *Mtb* (Dobler & Marks, 2012; Menzies et al., 2011; Nahid et al., 2016).

In response to low treatment completion rates with the six, nine and 12 month regimens, shorter courses of INH containing regimens are being deployed to treat LTBI with high efficacy rates consistently over 80% in the United States (Menzies et al., 2011; Nahid et al., 2016). Alternative regimens are still needed with the aim to reduce duration and improve treatment completion (Getahun et al., 2015). Innovative uses of three months of INH and RPT weekly are being utilized in various parts of the United States to treat LTBI and improve completion, as is four months daily of RIF (Denholm & McBryde, 2010; Menzies et al., 2004; Menzies et al., 2011; Page et al., 2006; Spyridis et al., 2007; Stennis, Burzynsk, Herbert, Nilsen, & Macaraig, 2016). Typically, successful completion of LTBI therapy cures the individual and barring no future exposures, may be protective for 19 years (Getahun et al., 2015).

Impact on Public's Health

Tuberculosis

Although some persons cured of active TB disease may have minimal negative health impacts, others not receiving treatment may develop chronic obstructive pulmonary disease, fibrotic scarring, fistulas, or tracheal stenosis. Each of these can be prevented with early detection and treatment of latent disease and without, can be life

threatening (Chakaya, Kirenga, & Getahun, 2016; Larson, 2000). The effects of untreated extrapulmonary tuberculosis may include permanent spinal pain, irreversible joint damage, meningitis, hepatic and renal insufficiencies, or heart disorders (Shah & Reed, 2014). As the single largest infectious disease killer of young persons and adults globally, untreated tuberculosis has health care, community, and economic impacts (Larson, 2000). With many of those suffering from TB making up a large portion of the global workforce, if diagnosed with TB, three to four months of productivity could be lost due to the requirements for isolation, frequent medical checkups, and the need to take medication often in front of a health care provider. On average, this temporary gap in employment caused by having TB may result in earnings losses of 20 to 30%. Persons diagnosed with TB may also experience social rejection, discrimination, or other psychological consequences (Larson, 2000). Combined, these factors emphasize the need to identify persons infected with TB before symptoms develop to reduce the likelihood of transmission, long term sequellae, and negative societal impacts.

Treatment. Effective tuberculosis treatment was announced in 1944 with the discovery of Streptomycin. Acquired resistance developed rapidly which promoted the development of INH as well as the concept of dual-therapy (Davies, 1994; TB Alert, n.d.). Over the next two decades, RIF and ethambutol were added to the recommended regimen (Davies, 1994). The estimated cost to treat TB disease ranges from $17,000 per U.S. patient with drug-susceptible TB to $430,000 per U.S. patient with extreme drug-resistant TB (Fitzpatrick & Floyd, 2012; Laurence, Griffiths, & Vassall, 2015; Marks et al., 2014). These costs include diagnostic procedures, hospitalizations, prescriptions, and

the personnel costs associated with providing medications via DOT (Laurence, Griffiths, & Vassall, 2015; Marks et al., 2014). Most often, these costs are extreme making the treatment of TB, a significant burden on people and communities.

Latent Tuberculosis Infection

With 90% of TB cases in the foreign-born population in the United States being attributed to reactivation, the impact LTBI has on the health of the public if not treated is significant. Notably, since global TB mortality has surpassed that of HIV and Malaria any attempt to reduce the number of persons infected with *Mycobacterium tuberculosis* could result in a decrease in mortality (Petersen et al., 2017; Schmit, Wansaula, Pratt, Price, & Langer, 2017; Semu, Fenta, Medhin, & Assefa, 2017). Community-wide LTBI preventive therapy studies have demonstrated a long-term reduction in TB incidence in Alaska, Greenland, and Tunisia. Latent tuberculosis infection preventive therapy has been used to successfully avert future cases of TB disease potentially eliminating the risk of death from active disease (Ragonnet, Trauer, McBryde, Houben, & Denholm, 2017; Semu et al., 2017).

Treatment. The publics' health benefits from the treatment of LTBI in high-risk groups (Dobler, Martin, & Marks, 2015; Larson, 2000). Because early detection and treatment of LTBI prevents reactivated transmissible disease, the entire populace' health is protected. Although most of the costs to treat LTBI fall onto the public sector, the marginal $495.21 average cost per patient receiving LTBI preventive therapy has the potential to not only improve population health, but decrease overall health care costs when compared to the $17,000 price tag to treat TB disease (Holland, Sanders, Hamilton,

& Stout, 2009; Horsburgh, 2017; Marks et al., 2014). Ultimately, by preventing future transmission as well as the potential lifelong negative impacts of TB, treating a high percentage of persons infected with *Mtb* could minimize the global impact this pathogen has on morbidity and mortality.

Latent Tuberculosis Infection Treatment Completion

The increasing emphasis being placed on ensuring successful completion of LTBI therapy has encouraged a transition away from solely researching the factors associated with treatment completion for active disease (CDC, 2016; Salinas et al., 2016). A growing number of studies are available exploring those factors associated with the noncompletion of all LTBI regimens so completion rate improving interventions can be developed (Cook et al., 2006; Page et al., 2006; Spyridis et al., 2007; Young, Wessolossky, Ellis, Kaminski, & Daly, 2009). Although often conducted in the international, urban, and high-incidence TB settings, research has begun to demonstrate setting-specific patterns in LTBI treatment noncompletion. Unfortunately, no two TB environments are the same in the United States so a single nationally developed approach to improving completion rates will likely not prove fruitful (Hirsch-Moverman et al., 2008). This suggests that TB Programs must each investigate LTBI treatment completion trends in their own jurisdictions.

Researchers in the United States have documented completion rates range from 30 to 62% for LTBI, much below the 85% national benchmark (Cook et al., 2006; Getahun et al., 2015; Li et al., 2009; Sandgren et al., 2016). Researchers have also concluded that the new shorter LTBI regimens promote higher completion rates however,

some of these regimens may not reduce the risks of adverse events and may come with an upfront increase in cost (Dobler & Marks, 2012; Goswami et al., 2012; Li et al., 2009; Lines, Hunter, & Bleything, 2015; Menzies et al., 2004; Shepardson et al., 2013). The documented low rate of treatment completion for LTBI highlights the need for broad research surrounding this trend from a variety of settings. Continuing to have completion rates below the national targets indicate the large reservoir of infected persons will persist for many years limiting the ability of TB Control Programs to achieve elimination.

Predictors of Latent Tuberculosis Infection Treatment Completion

Describing the potential independent variables predictive of LTBI treatment completion and noncompletion has been used to develop targeted interventions that aim to improve completion rates. With geography potentially playing a key role in the availability to LTBI treatment resources, exploring this localized phenomenon in all settings is essential (Campbell, Chen et al., 2015; Getahun et al., 2015; Spyridis et al., 2007; Varkey et al., 2007). The rural low-incidence setting has been excluded from much of the LTBI treatment completion research in the United States. This shortfall has left TB controllers limited in resources, challenged by geography, and bound by funding shortfalls, to deprioritize the assessment of LTBI treatment noncompletion rates in high-risk groups, such as foreign-born migrants. As a product of this prioritization, these setting may experience higher rates of noncompletion or may have a vague understanding of what host, environment, and agent factors could be modified to improve completion to reduce future morbidity.

Host. In the epidemiologic triangle, host-related factors refer to those that make an individual at risk for being exposed to or developing disease (Haddon, 1980). A significant amount of research on urban-based populations in the United States, as well as on populations from the international high-incidence TB setting has attempted to determine whether host factors such as sex, age, birth country, and smoking history, influence LTBI treatment completion. Findings of these research attempts have been mixed. Some research has examined these factors for active TB disease, which may have limited application to similar LTBI research since the treatment of disease involves multiple medications, improves severe symptoms which may incentivize adherence and involves taking prescribed treatment in front of a medical provider. Additional research is essential to understanding how host related factors may influence LTBI treatment outcomes particularly in the rural setting.

Sex. In the published research, no clear trend has emerged demonstrating whether males or females complete LTBI treatment at higher rates. Eight identified studies showed that females completed LTBI treatment at higher rates compared to men, four demonstrated the opposite finding. An additional eleven studies found no significant difference between the rates in which either sex completes LTBI treatment. However, understanding the role sex may play in LTBI treatment completion could be of importance in determining if disparities exist in a specific setting as these disparities are known to exist in terms of TB disease burden (American Lung Association, 2013; CDC, 2016; Larson, 2000). The retrospective cohort design has been the most frequently deployed method used to study the relationship between sex and LTBI treatment

completion, followed by the prospective cohort, and the cross-sectional design. Infrequently, randomized control trials were used to explore this phenomenon. As the body of treatment completion research grows, systematic literature reviews are also being conducted. Many of these studies utilized specific sample populations from specific geographic regions, decreasing their generalizability.

Multiple retrospective cohort studies similar in design to this current research have included sex as an independent variable for assessment against a LTBI treatment completion outcome. Many demonstrated females were more likely to complete treatment compared to males. LoBue and Moser (2003) and Lines et al. (2015) each explored sex in relation to LTBI treatment completion. LoBue and Moser (2003) noted sex as a predictor of treatment completion. In this retrospective cohort review of San Diego county's LTBI treatment completion database including 3,788 unique participant records for treatment initiators between 1999 and 2002, LoBue and Moser calculated an overall 64% treatment completion rate. Females (65%) were slightly more likely than males (62%) to complete treatment (95% C.I. 1.0, 1.4; $p < 0.01$). Lines et al. (2015) when using the retrospective cohort design to explore adherence among community health center TB clinic attendees ($n = 100$), female sex appeared to be associated with higher rates of adherence when compared to male sex (80.8% versus 73.7%, respectively;95% C. I. 1.22, 6.18; $p = 0.01$). Li et al. (2009) also determined that sex was predictive of treatment completion with a 15,000-participant sample from New York City providing more power than the smaller study noted previously. Treatment completion was still

suboptimal in both sexes. This study revealed a negative association between female sex and LTBI treatment completion.

Prospective cohort studies have also been conducted to explore the relationship between sex and LTBI treatment completion. Lavigne et al. (2006), in a prospective cohort sample drawn from Montreal, Canada residents, determined that females were more likely to adhere to LTBI treatment (*OR* = 1.9; 95% C.I. 1.1, 3.3) after controlling for age and smoking status. Although 87% of participants were foreign-born and just over half (56%) were male, this convenience-based sampling study does provide additional evidence that sex may be correlated with adherence in some settings (Lavigne et al., 2006). In the public health clinic in Tennessee, Priest, Vossel, Sherfy, Hoy and Haley (2004) drew a similar conclusion but found that female sex was more likely to be predictive of completion using multivariate analysis (*RR* = 1.70; 95% C.I.1.06, 2.75; *p* = 0.03) in 352 treatment completing patients. The sample was drawn from a single employer with a recent significant TB exposure event where administrative encouragement to complete treatment was present, potentially limiting generalization. Nonetheless, these findings demonstrate how social support can influence LTBI treatment completion covariates as well as how sex can act as a predictor of treatment completion (Priest, Vossel, Shefy, Hoy, & Haley, 2004). In 2004, Tulsky et al. published the findings of a prospective cohort including 119 homeless adults from San Francisco, California. The study showed sex as a potential predictor of treatment completion with males being more likely to complete (88.1%; 95% C.I. 1.36, 23.40; *p* = 0.02) when compared to females (72.2%). The study was limited by a smaller sample size and also

utilized cash incentives to demonstrate the impact on completion potentially skewing the results. It is important to note, however, that incentives are frequently deployed in TB control to improve completion (Tulsky et al., 2004).

Non-cohort based studies have also demonstrated a positive association between sex as a predictor of LTBI treatment completion. A cross-sectional review of 11,963 people prescribed LTBI treatment in Italy conducted by Codecasa et al. (2013) supported previous findings that sex could predict LTBI treatment completion. Codecasa et al. (2013) found that female sex had a protective effect (*OR* = 0.81; 95% C.I. 0.73, 0.89) against experiencing adverse treatment events. These findings suggested that females had improved completion when looking specifically at the use of INH as preventive therapy (Codecasa et al., 2013). From the county jail and homeless shelter setting, two populations likely not representative of the broader population but at high risk for having LTBI, LoBato et al. (2005), using a sample of 1,211 participants, built further upon the notion that sex may be predictive of treatment completion. In this observational study, the researchers found similar rates of completion in the two populations, with females being more likely to not complete treatment (73.9%; *OR* = 0.35; 95% C.I. 0.23, 0.54; $p < 0.001$) (LoBato et al., 2005). Conversely, the cross-sectional study conducted by Cegolon et al. (2010) found male sex to be more predictive of treatment failure (*OR* = 1.53; 95% C.I. 1.37, 1.71; $p < 0.001$), albeit the sample not limited to the incarcerated or homeless. This more robust sample of 12,929 participants was used to calculate a successful treatment completion rate near 88%, but demonstrates how in a given geographical setting, sex may be predictive of treatment completion. Lastly, in the only identified prospective,

randomized clinical trial Pettit et al. (2013) concluded that sex was a negative predictor of LTBI treatment completion, with females (49.9%) being less likely to complete treatment (*RR* = 1.67; 95% C.I. 1.32, 2.10; $p < 0.001$) on account of a greater risk of experiencing adverse medication events. Lastly, the systematic review including 62 articles that focused on the determinants of LTBI treatment initiation and completion performed by Stuurman et al. (2016) also identified that females had a higher rate of LTBI treatment completion although it was noted that studies focusing on specific populations (i.e. visa holders, racial/ethnic minorities) were scarce making rates inconsistent across all groups.

Despite a number of studies demonstrating sex as a predictor of LTBI treatment completion, some researchers have failed to draw this conclusion. Levesque, Dongier, Brassard, and Allard (2004) sampled 229 refugees in Canada and found no association between sex and treatment adherence (*OR* = 1.0). The study findings are limited due to the relatively small sample size of TST positive individuals (*n* = 49) but the even smaller (*n* = 24) number of persons whom initiated treatment with which data could be analyzed. The systematic reviews surrounding LTBI treatment adherence, conducted by Hirsh-Moverman, Daftary, Franks, and Colson (2008), Zuñiga (2012), and Lin and Melendez-Torres (2016) yielded mixed findings. Hirsch-Moverman et al. (2008) identified sex was poorly associated with treatment adherence in a review of 78 quantitative studies that analyzed adherence to LTBI treatment, as did Lin and Melendez-Torres (2016) in a more recent review including 20 articles identifying risk factors associated with LTBI treatment noncompletion. Zuniga (2016) reported sex as somewhat correlated when

qualitative methods were used to explore the relationship beyond quantitative means; the only systematic review drawing this conclusion. Of the two descriptive studies identified, which focused on Latino immigrants in the United States using random medical record chart abstraction from the urban public health clinic setting, sex failed to predict adherence (t = -0.302; p = 0.76; and $p > 0.05$, respectively) (Ailinger, Black, Nguyen, & Lasus, 2007; Ailinger, Moore, Nguyen, & Lasus, 2006).

Sex has been shown to play an inconsistent role in LTBI treatment completion with 10 study findings identifying sex as a predictor of treatment completion and 11 indicating no association. Although frequently included as an independent variable in LTBI treatment completion research, sex as a host factor has not been consistently associated with adherence or completion in either a positive or negative direction. These findings, stemming mostly from urban samples, highlight the need for rural-based samples to be included in the published research. Inclusion of samples drawn from various settings will provide a more comprehensive understanding of sex as a potential predictor of LTBI treatment completion and may provide more robust evidence that this potential host factor could be critical to understanding treatment completion.

Age. Multiple studies have demonstrated associations between age and LTBI treatment completion but consistencies between the direction and the age groups most commonly associated with completion or noncompletion have varied. In specific settings, the age of the individual initiating LTBI preventive therapy may influence the likelihood of completion in a negative way. Age was included as an independent variable of interest nearly as frequently as sex. Of the studies identified where researchers explored the

relationship between age and LTBI treatment completion, the cohort design is used most frequently. As is the case when exploring the independent variable “sex”, cross-sectional studies, systematic literature reviews, and randomized control trials are performed less frequently. Similar to the aforementioned research on sex and LTBI treatment completion, research surrounding age involved documenting treatment completion or adherence, the risk of progressing from LTBI to TB disease, but also using age as a predictor of treatment completion. In some instances where an association was found, young adults 18 to 30 years of age were more likely to complete LTBI treatment compared to others outside that age range however, regionally specific differences were observed. In general, completion rates decreased with increasing age.

In 1999, Bock, Metzger, Tapia, and Blumberg conducted a prospective cohort study exploring age as a potential predictor of LTBI treatment completion. Using a sample of 409 persons living in inner-city Atlanta, Georgia, the study did not show age as a consistent predictor of treatment completion across each stratified age group. Only those 65 years old or greater could be used to predict treatment completion in this study where participants ≥65 years old were ten times more likely to complete treatment compared to those less than 65 years old (OR = 10.11; 95% C.I. 3.45, 29.66; $p < 0.001$). Unfortunately, a low rate of LTBI diagnosis in the 409 participants as well as a low rate of completion (20%) limits the interpretation of these findings. Hovell et al. (2003) studied 268 adolescents from San Diego County and showed that age was again a predictor of negative adherence in that the rate of treatment completion decreased with increasing age ($p < 0.0001$). Additional research conducted by LoBue and Moser (2003)

supported that age may predict negative LTBI treatment completion using the retrospective cohort design of 3,788 patients initiating INH LTBI preventive therapy in San Diego between 1999 and 2002 (Age 0 to 14 years: *OR* = 4.1; 95% C.I. 2.2, 7.8; $p < 0.01$; Age 15 to 34 years: *OR* = 2.1; 95% C.I. 1.1, 3.9; $p = 0.02$). However, the retrospective nature of this study required researchers to use documented prescription refill records in order to determine adherence and eventual compliance (LoBue & Moser, 2003). The 64% completion rate may have been underestimated since participants may have obtained refill medications outside of a pharmacy reporting records (LoBue & Moser, 2003).

A 2004 prospective study that primarily aimed to explore the rates of hepatoxicity and treatment completion for LTBI using a newly recommended regimen, further demonstrated that older age was associated with noncompletion (*OR* = 1.08 per year; $p = 0.001$) (Priest, Vossel, Sherfy, Hoy, & Haley, 2004). The study recruited 598 participants from a single workplace that was experiencing an outbreak of active TB. Overall the treatment completion rate of 83% was promising and the documentation of age as an influencer of completion contributes to the field of knowledge since those ≥35 years were at increased risk of treatment failure compared to those less than 35 (Priest, Vossel, Sherfy, Hoy, & Haley, 2004). The overall application of age as a predictor of LTBI treatment completion is limited from this research since a majority of those discontinuing treatment did so due to severe hepatoxic events (Priest, Vossel, Sherfy, Hoy, & Haley, 2004). Instead of fully supporting the notion that age may be a negative predictor of

treatment completion, these researchers demonstrated that older age may be a risk factor of hepatoxicity and may contribute to the overall negative trend in completion.

Additional cohort research has been conducted by Rennie, Bothamley, Engova, and Bates (2007), Bieberly and Ali (2008), Morano, Walton, Zelenev, Bruce, and Altice (2013), Spicer, Perkins, DeJesus, Wang, and Powell (2013), and Rennert-May et al. (2016) which all demonstrated age as a potential predictor of treatment completion. Rennie, Bothamley, Engova, and Bates (2007) prospectively followed 675 London TB clinic attendees and estimated that a one year increase in age translated into a 1.04 greater risk of failing to complete treatment. This study also found that providing patients with a number of treatment regimen options of differing duration could improve completion. This was especially true for those falling in the workforce age groups that may not comply with preventive treatment due to pressures from other obligations (Rennie, Bothamley, Engova, & Bates, 2007).

When looking at very specific populations, Bieberly and Ali (2008) and Spicer et al. (2013) each concluded that age may be an important factor when hypothesizing who may or may not complete treatment. In the retrospective study involving 380 LTBI patients in the New Orleans area post-Katrina, those aged 19 to 34 had the highest rate of nonadherence, while children were more likely to complete (Bieberly & Ali, 2008). The eventual completion rate calculated at 19% further supports that those persons receiving LTBI treatment the typically fall into the workforce age range (15 to 64 in the United States) may be at increased risk of nonadherence or noncompletion. This research demonstrates that those in the working age range may be an important group to target

when recommending treatment. Opposite the working population are children, whom Spicer et al. (2013) also concluded became at greater risk of noncompletion with aging ($p = 0.02$). The 1,516 children participating in the study produced a high rate of treatment completion, nearly 90%, in the retrospective study that aimed to explore the demographic variables that may influence treatment completion. In this study population those not completing treatment differed significantly by age from those that did complete (Spicer et al., 2013) indicating that age may be useful in predicting completion.

Last of the identified cohort-based research studies that included the exploration of age as a predictor of treatment completion, Morano, Walton, Zelenev, Bruce, and Altice (2013) and Rennert-May et al. (2016) drew different conclusions although each did find an association. In the prospective cohort of 357 urban city U.S. residents, Morano, Walton, Zelenve, Bruce, and Altice (2013) determined that those in younger age groups tended to complete treatment at higher rates ($OR = 1.03$; $p = 0.039$) which is counter to the findings reported by Rennert-May et al. (2016) where younger age was associated with nonadherence in a retrospective cohort of Canadian refugees ($p < 0.05$). Although the studies drew somewhat different conclusions, the varying settings and sampled populations may have contributed to these findings.

In 2016, a study conducted by Asres, Jerene, and Deressa including 790 Ethiopians being treated for active TB did demonstrate an association between age and treatment completion ($OR = 1.02$; 95% C.I. 1.001, 1.022; $p = 0.5$). These findings may not be relatable to LTBI treatment completion due to the often severe symptoms of active TB which may encourage treatment completion for active disease. In 2010, Hirsch-

Moverman, Bethel, Colson, Franks, and El-Sadr used a more robust and less homogenous inner-city population, did find a slight correlation between age and LTBI treatment completion ($p = 0.053$) along with being married, being homeless, and ever using alcohol.

Years after research demonstrating age as a factor associated with treatment completion became consistently published, Levesque, Dongier, Brassard, and Allard (2004), using a prospective cohort, failed to conclude that age, when stratified for analysis, was associated with completion in the international setting. The limited sample size of 229 recruited and the even smaller sample of 24 that initiated and completed preventive therapy may have influenced these findings, but the researchers did note that age was a significant predictor of TST positivity and thus, having a diagnosis of LTBI (Levesque, Dongier, Brassard, & Allard, 2004). Although this research did not support age as a predictor of treatment completion, it does support the notion that older individuals with LTBI may require greater clinical attention to ensure prompt diagnosis and treatment of LTBI. In a prospective sample of 320 Canadians, Lavigne, Rocher, Steensma, and Brassard (2006) aimed to test the previously identified connection between smoking and LTBI treatment adherence, but to also test the potential influence demographics may have. Lavigne, Rocher, Steensma, and Brassard (2006) reported that age, region of birth, and nicotine dependence were not associated with adherence ($p = 0.4$, $p = 0.8$, $p = 0.6$, respectively) albeit the convenience sampling method as well as the self-reported nature of many of the study variables may have influenced this outcome. Also in the international setting, van Zyl et al. (2006) found no association between age

and treatment completion in 335 South African children known to be contacts to persons with active TB. The researchers hypothesize this may be attributed to the education parents were provided about the potentially severe outcomes associated with childhood TB, thus parental involvement led to greater adherence regardless of the child's age (van Zyl et al., 2006).

Overall, age as a host factor has been inconsistently associated with LTBI treatment completion but multiple populations and settings have been excluded from the published research with most studies focusing on very specific samples in very specific locales. The rural setting often differs significantly from the urban setting highlighting the need for age-related research in this setting to better assist rural TB Control programs in developing targeted interventions.

Birth country. In the United States, where most active TB occurs in the foreign born, renewed interest on preventing the progression from LTBI to infectious disease has led to increased emphasis on examining the role birth country may play in various aspects of TB control. Birth country, a potential host factor in the epidemiologic triangle that may influence treatment completion, has been less extensively explored in the LTBI treatment completion research, but trends have emerged from those studies examining this independent variable. Of the 14 identified studies where birth country was a key variable explored by researchers, half included findings suggesting birth country was positively associated with treatment completion. Most of these studies suggest the underdeveloped setting such as sub-Saharan Africa suffers from high rates of LTBI treatment noncompletion.

Research has been published on the impact birth country may have on LTBI treatment completion using retrospective methods. Parsyan et al. (2007), Spicer et al. (2013), and Rennert-May et al. (2016) all determined that birth country was positively correlated with LTBI treatment noncompletion. In 2007, Parsyan et al. drew this conclusion after analyzing completion data on 1,572 TB clinic attendees from Boston. The researchers identified a treatment completion rate below 40% with a majority of those failing treatment being from China, Vietnam, Haiti, and the Dominican Republic ($RR = 0.74$, $p < 0.0001$; $RR = 0.68$, $p = 0.0001$; $RR = 1.33$, $p < 0.0001$; and $RR = 1.10$, $p = 0.01$, respectively). The researchers argued that interventions seeking to improve completion should at a minimum, target these identified high-risk country-specific groups (Parsyan et al., 2007). In Columbus, Ohio, Spicer et al. (2013) assessed medical record data from 1,516 visits to Nationwide Children's Hospital and determined that sex, history of TB exposure, size of TST reaction, nor having LTBI learning material available in multiple languages improved treatment completion rates in children but region of birth did appear to be the most significant predictor of treatment completion success ($p < 0.001$). Similarly, Rennert-May et al. (2016) conducted analysis on a dataset from a Canadian refugee health screening center where 265 refugees started LTBI preventive therapy and concluded that not only was birth country predictive of treatment noncompletion, but that sub-Saharan countries of origin were highly associated with noncompletion ($p < 0.05$).

In 1999, while evaluating an inner-city tuberculin screening and INH preventive therapy program in Atlanta, Georgia, Bock et al. concluded that only 20% of those

intending to complete preventive treatment actually completed in a prospectively recruited sample of 409 treatment eligible participants. An early study exploring factors associated with LTBI treatment completion in a community-based intervention setting, Bock et al. (1999) concluded that foreign-birth was a predictor of participant treatment completion (*OR* = 2.11; 95% C.I. 1.12, 3.94; *p* = 0.0009). Using a sample of 496 persons recruited from a TB Clinic in Raleigh, North Carolina, Goswami et al. (2012) determined that birth country did have an impact on treatment completion. In this research, non- U.S. born participants tended to complete treatment at higher rates (*p* = 0.04) (Goswami et al., 2012). Fiske et al. (2014) corroborated this finding in a multi-center U.S. and Canada study of 1,371 persons recommended for preventive therapy however, when analyzing specific countries included in the dataset in relation to completion, no associations were identified (*p* = 0.87).

A single randomized control trial was identified, conducted by Hirsch-Moverman et al. (2010), that focused on predicting the factors associated with LTBI treatment completion in the United States using a sample of 314 individuals drawn from inner-city Harlem. The researchers concluded that foreign-birth was a predictor of noncompletion (*p* = 0.04), however, the study did not collect information on exact birth country making country-specific level of analysis impossible. Assuming foreign-birth to be a proxy to specific birth country variables, the researcher's findings may provide evidence to support the development of completion rate improving interventions that target the foreign-born, albeit one with a birth country level of specificity would be more ideal.

A single systematic literature review performed by Hirsch-Moverman et al. (2008) was identified that included a birth country assessment on treatment completion. Birth country was reported to not be a predictor of treatment completion however, at least five additional studies have been published since this systematic literature review where an association was identified. The somewhat dated nature of this review may limit its applicability to the current time, especially as the body of research surrounding the predictors of LTBI treatment completion grows.

Overall, although birth country has been studied somewhat regularly in relation to LTBI treatment completion, as an independent variable it has been considered a statistically significant predictor of completion in some studies, but a growing body of evidence to the contrary is also present. As with many of the other variables explored thus far, the urban, high-incidence setting is overrepresented in the research and thus, exploring this phenomenon in the rural setting is still needed.

Visa type. The role the visa held by migrants arriving in the United States may have on LTBI preventive treatment completion postarrival has been minimally studied. The visa held could be a contributing factor to completion or noncompletion as an indirect product of the requirements to change a visa holders' status. Refugees are thought to have a slightly greater likelihood of being exposed to *Mtb* and thus having LTBI due to the poor living conditions experienced in camps prior to migration (Lim et al., 2016) however, immigrants and other visa holders from TB endemic regions are also at risk. Consistently, all visa-types have been associated with poor LTBI treatment completion (Sandgren et al., 2016).

In 2004, Coly and Morisky sought to identify the predicting variables of LTBI treatment completion in foreign-born adolescents residing in Los Angeles. The authors identified that not addressing barriers to treatment completion would prevent the region from successfully combating future TB disease. In a prospective cohort involving nearly 38,000 LTBI clinic attendees from the United States and Canada, Sterling et al. (2006) attempted to estimate the number of persons initiating treatment and to describe the types of clinics and providers medically managing persons with LTBI. Sterling et al. sought to accomplish this to develop interventions that improve treatment completion (2006). With successful LTBI treatment completion decreasing future TB burden, Sterling et al. found that in these settings, over 80% of LTBI initiators were foreign-born and the public sector is mostly responsible for the management of these individuals. Although Sterling et al. did not seek to quantify completion rates by visa-type, the researchers did demonstrate that immigrant and refugee clinics, facilities serving different visa-types, accounted for more than 92% of the providers managing LTBI patients. These facilities may be an appropriate target for treatment completion improving interventions (Sterling et al., 2006).

In a retrospective cohort, Lim et al. (2016) found that refugees were at greater risk compared to immigrants for having LTBI and that treatment completion rates reached a low of 76% in the foreign-born arriving in Alberta, Canada. In this study, LTBI was more common in migrants 30 years of age and older, and most treatment defaulters stopped within the first month after initiating treatment. Although not a study directly measuring the impact visa-type may have on LTBI treatment completion, the findings of this

research have important implications. With refugees being at greater risk of LTBI, potentially targeting this visa-type for completion rate improving interventions may prove advantageous. Despite the limited generalizability of this study directly related to the small sample size of participants with LTBI (n = 49), this study demonstrated that Tibetans tended to be a greater risk of default. Special attention to this population that often enters industrialized countries under refugee-visas may improve treatment completion rates in this group in other settings (Lim et al., 2016).

No systematic reviews were identified that focused solely on the literature published surrounding the relationship between visa-type and LTBI treatment completion. This is likely due to the limited number of studies available where visa-type was an independent variable but some reviews did include a component of visa-type research. In 2015, Getahun et al. published guidelines surrounding the management of LTBI in the low-incidence TB setting. Getahun et al. drew attention to the fact that legal-status significantly impacted LTBI treatment initiation, adherence, and completion. Getahun et al. also noted that in general, LTBI treatment completion rates tend to be lower than the general population in visa-holding populations, with undocumented migrants or migrants staying past expired visas at even greater risk of failure (2015). This research helps highlight the gaps that exist in managing the care of migrants and persons on visas especially in settings where this population contributes significantly to the agricultural workforce, as is the case in Idaho. In a separate systematic literature review, Stuurman et al. (2016) sought to summarize the research surrounding LTBI treatment completion improving interventions, with visa-type being a variable covered in a limited

context. Stuurman et al. concluded that domestic-born persons with LTBI tended to complete treatment at higher rates and that cultural differences in immigrants likely influenced LTBI completion (2016). These researchers also concluded that some of the most important factors consistently associated with LTBI treatment completion are patient-related, such as the visa-type they arrive with after migration to a new country.

Although studied infrequently, visa-type has been shown in some capacity to have a potential impact on the outcome of LTBI treatment completion. With most studies indirectly referencing or measuring visa-type more work must be done to determine if this variable is truly predictive of treatment completion especially in the rural setting.

Smoking. Only a single study was identified that considered the impact smoking has on LTBI treatment completion. In a 2006 prospective cohort consisting of 320 convenience-sample recruited LTBI clinic attendees in Montreal, Canada, Lavigne, Rocher, Steensma, and Brassard determined that smokers involved in the study were less likely to complete LTBI treatment and had difficulty being compliant for the time on treatment prior to discontinuation ($p = 0.04$). In further univariate analysis, the researchers concluded that male smokers were at greater risk of noncompletion compared to their female smoking counterparts (Lavigne, Rocher, Steensma, & Brassard, 2006). The convenience-based sampling method may limit generalizability as those opting to participate in the study may differ significantly from other smokers choosing to be excluded. Additionally, the use of self-reported smoking status may bias results due to under- or over-reporting. The limited number of studies available exploring this phenomenon indicates interpreting these findings broadly should be done with caution.

Environment. In the epidemiologic triangle, environment-related factors refer to the structure surrounding the individual that interacts with characteristics of both the host and the agent to promote pathology but also the severity and duration of disease (Haddon, 1980). As with the host variables described previously, most published research exploring the role environmental factors may play in promoting or demoting LTBI preventive therapy has included only those from the urban and high-incidence TB setting, creating a gap in the understanding of this potential relationship in the rural setting. Although it has been noted that environmental factors play a key role in promoting treatment completion across a variety of diseases and conditions, these factors have been less frequently studied in relation to LTBI. Some studies have focused on the distance from the treating LTBI clinic and the patient's home and the role this may play on completing treatment. In the rural setting, understanding environmental factors may be critical to promoting higher rates of treatment completion as barriers to completing may be many and resources dedicated to improving completion limited.

Distance. The distance an individual has to travel to seek health care has been shown to negatively influence the uptake of public health services if considered great (Jacobs, Ir, Bigdeli, Annear, & Van Damme, 2012). Failure to complete LTBI preventive therapy can leave individuals at risk of developing reactivated disease in the future, promoting transmission to others. Few studies have been designed around distance-related variables and their association with LTBI preventive therapy completion despite guidelines recommending interventions aim to reduce distance-related barriers to achieve high rates of completion (Getahun et al., 2015). Of the independent variables included in

the exploration of predictors of LTBI treatment completion, distance has produced the least heterogeneous findings.

A retrospective cohort conducted by Spicer et al. in 2013 concluded that the pediatric patient's location in reference to the LTBI treatment dispensing facility was highly inversely associated with LTBI evaluation and treatment completion ($p < 0.001$). Those being more remote were at greater risk of not completing treatment (Spicer et al., 2013). Although the study had a robust sample of 1,516 participants drawn from an urban U.S. city, the patient's transportation options were often subject to that of their parents, potentially biasing these findings. No in-depth analysis was done on the number of miles a patient must travel before becoming at greater risk of treatment noncompletion. In a prospective cohort of 1,078 children residing in Rio de Janeiro, Silva et al. (2016) determined that the greater the distance to the health department, the more likely the participant would fail. In this study, the distance independent variable was measured in 30 minute increments as well as in cost, with persons 30 minutes and more away from the health department and paying greater cost being at greater risk of noncompletion ($p = 0.03$). In a cross-sectional study by Mindachew, Deribew, Tessema, and Sibhatu (2011) that focused on identifying the predictors of treatment completion in the HIV-positive population living in Ethiopia, the researchers concluded that persons living farther from the health department had a higher number of missed LTBI treatment doses and a higher rate of noncompletion. Although the study involved a very specific sample ($n = 319$ HIV-positive persons), subsequent interventions that aimed to improve adherence through education and incentives did prove successful (Mindachew, Deribew, Tessema, &

Sibhatu, 2011). These findings demonstrate how distance may be too difficult a barrier to overcome without assistance (Mindachew, Deribew, Tessema, & Sibhatu, 2011). Although few studies actually quantified the number of miles traveled before LTBI treatment noncompletion became likely, the findings of these studies suggest that in the rural setting, where travel to the nearest health department may be lengthy, distance may serve as a predictor of noncompletion for those living far from the nearest treatment dispensary.

Area of resettlement. Refugees and immigrants arriving in the United States are typically encouraged to resettle in areas where others from their native country may already be established (United Nations High Commissioner for Refugees [UNHCR], 2015). Many of these areas are urban localities (UNHCR, 2015). In recent years, four of the top 10 states with the highest per capita rates of resettlement were in rural America (Radford & Connor, 2016). This trend may influence LTBI treatment completion rates and the eventual elimination of TB in the United States if the rural setting suffers from low rates of completion. Although no identified studies explored the difference between resettling in the urban region compared to the rural region and its potential impact on LTBI treatment completion, some studies did explore how the urban setting may influence these rates. Although not necessarily generalizable to the rural setting, understanding LTBI treatment completion rates in the urban setting may assist in describing the overall trend and may support the need for more thorough research in a variety of settings.

Ailinger, Moore, Nguyen, and Lasus (2006), and Fluegge (2015) used the cross-sectional study design to each explore urban resettlement and LTBI treatment completion. Examining data gathered from 53 Latino immigrants relocating to the urban U.S. setting, Ailinger, Moore, Nguyen, and Lasus (2006) determined that adherence issues are complex. Additionally, the researchers concluded that in the sampled participants, adherence appeared especially difficult since the preventive nature of LTBI treatment was deemed a lower priority to adjustment to their new country. As such, completion rates tended to suffer. With the data from 552 urban TB clinic attendees, Fluegge (2015) found that as an area's disease burden increased, adherence dwindled requiring more creative approaches to improve completion. Specifically, Fluegge (2015) found that in the urban setting, persons with more frequent interactions with their Public Health Nurse providing their preventive therapy, the likelihood of treatment completion improved.

Dobler and Marks (2012), Morano, Walton, Zelenev, Bruce, and Altice (2013), Wingate et al. (2015), and Juarez-Reyes, Gallivan, Chyorny, O'Keeffe, and Shah (2015) each studied foreign-born cohorts in the urban setting to describe LTBI preventive treatment completion. In an Australian metropolitan area, 75% of the originally recruited 216 participants in a study conducted by Dobler and Marks (2012) assigned to a six-month regimen of INH for treatment of LTBI dropped out during the second half of the six-month period. This finding speaks to the negative impact the lengthy duration of treatment can have on individuals. The following year, Morano, Walton, Zelenev, Bruce, and Altice (2013) conducted a prospective cohort study involving 357 foreign-born

persons residing in inner city Connecticut that also suffered from lower rates of treatment completion albeit a mobile clinic dispatched to help improve these rates demonstrated some success. In the rural setting, such an intervention may be feasible however, could require the mobile clinic to travel much larger distances and thus, be more resource intensive. Potentially addressing this issue, Wingate et al. (2015) proposed that all international urban centers with a high incidence of TB could contribute to U.S. TB control cost-savings if overseas TB screening was more rigorous prior to United States entry since only 75% of those entering actually follow up for further medical evaluation. Lastly, Juarez-Reyes et al. (2015) deployed a short course, 12-week regimen of INH and rifapentine(3HP) to improve LTBI treatment completion rates in a prospective cohort drawn from an urban county jail, of which foreign-born participants were numerous. Unfortunately, the institutionalized nature of the sample may not allow for much generalization to the non-incarcerated population, but the drastic increase in successful LTBI treatment completion, from 18% before 3HP to 85% after, could produce some rural-setting successes.

Although lacking findings on urban versus rural resettlement on the rate of LTBI treatment completion, it is important to note that in the urban setting, completion issues in the foreign-born are complex. Overall, environmental factors have been more consistently associated with LTBI treatment completion compared to the host factors explored however the research settings and sampled populations included are not representative of persons outside of the urban or high-incidence setting. Additional

research is needed in the rural setting to determine whether environmental factors play a significant role in LTBI treatment completion rates.

Agent. The final component of the epidemiologic triangle that may be important to determining the predictors of LTBI preventive treatment completion are those related to the organism itself, or the agent, that may be necessary to produce the disease in question. In the case of LTBI, where no diagnostic tool exists that detects the presence of *Mtb* in a latent state, measuring immunologic response is used as a proxy for assuming infection, barring exclusion of active disease. The TST and the IGRA measure the host's immunologic response to *Mtb* antigens which if positive, suggest past infection and not necessarily current microbial presence (Collins, Geadas, & Ellner, 2016; Ling & Flynn, 2010). Unfortunately, the TST has limited sensitivity and specificity and may produce false-positive results as a product of BCG vaccination or infection with other nontuberculous mycobacteria found in the environment (Chee, Sester, Zhang, & Lange, 2013). The IGRA has improved sensitivity and specificity when compared to the TST in BCG vaccinated persons. An individual's positive response to a TST or an IGRA may make them eligible for preventive LTBI therapy and potentially cured of the risk of reactivation barring no future exposure (Chee, Sester, Zhang, & Lange, 2013). It is unknown if the extent of TST positivity, in millimeters, or IGRA positivity are related to LTBI treatment completion in the rural setting although some studies from the urban setting have demonstrated an association.

Studies examining TST positivity and IGRA positivity as well as the relationship with LTBI treatment completion are few. A limited number of studies have been

developed to look at general positivity and the relationship to LTBI treatment completion while many studies simply describe overall positivity trends often comparing TSTs to IGRAs. IGRA positivity in relation to LTBI treatment completion has been even less well studied compared to TSTs. Although specific studies examining the relationship between TST or IGRA positivity and LTBI treatment completion are lacking, reviewing the trends established in TST and IGRA positivity-related research is a critical step prior to deploying further in-depth research.

TST or IGRA positivity. As described by Campbell, Krot et al. (2015), men tend to be TST positive more frequently than women, immigrants tend to have higher rates of positivity by TST than by IGRA, and older age groups are also more likely to be TST positive compared to younger age groups. Levesque, Dongier, Brassard, and Allard (2004) also determined that age was a predictor of TST positivity, with older adults more likely to screen positive and the lifetime risk of reactivation estimated at 20% in TST positives (Horsburgh, 2004). This study did not include a LTBI treatment completion component so no conclusions can be drawn pertaining to a potential association. Lastly, from the only nationally representative sample known to have TSTs placed on the general populace, Miramontes et al. (2015) concluded that overtime, the rate of TST positivity in the United States has not changed significantly from 1999-2000 and 2011-2012 potentially indicating that the number of persons infected with *Mtb* is not growing**.**

The measure of TST positivity, for those studies including interval levels of measurement, was inconsistently associated with LTBI treatment completion. Two cross-sectional studies have been conducted surrounding TST positivity and LTBI treatment

completion status, with the researchers concluding that recent TST converters, persons who went from negative to positive within two years, were more likely to complete treatment compared to non-recent converters (Bieberly & Ali, 2008; Reichler et al., 2002). In 2002, Reichler et al. reviewed health department records from five urban U.S. sites for 447 individuals, 89% of whom completed treatment. Reichler et al. (2002) also concluded that recent converters were more likely to be offered treatment compared to their counterparts not known to recently convert potentially impacting the study findings due to these inconsistencies in provider practice. Bieberly and Ali (2008) also reported that recent converters had higher rates of treatment completion in their analysis of records from 380 patients residing in New Orleans. Unfortunately, 85% of those aged 19 to 34 included in the study were lost to follow-up, limiting the analysis for this group, but these findings are likely supported by the work reported by Reichler et al. (2002).

In a retrospective study, Çakar, Demir, Karnak, and Özkara (2014) concluded that TST positive persons residing in Ankara, Turkey were more likely to complete treatment however exact induration size was not available for analysis so it is difficult to conclude a specific reaction size-association may be present or absent. The higher rate of treatment completion, at 89% for Çakar, Demir, Karnak, and Özkara (2014) could demonstrate that certain TST positive persons may perceive their infected status as more severe, for example those with a larger induration, and might be more likely to complete treatment. Overall, TST positive-related factors have been somewhat consistently associated with LTBI treatment completion although these studies are only a minority of the number of studies strictly looking at what kinds of people tend to be TST positive. Similarly, a

prospective cohort designed and carried out by Fiske et al. (2014) demonstrated that those with indurations measuring 10 to 19 millimeters were likely to not complete the full course of LTBI treatment ($p = 0.04$; $OR = 0.51$; 95% C.I. 0.27, 0.97), characterizing this size of positive reaction as a predictor of treatment noncompletion.

In a study stratifying analysis by size of TST reaction, the retrospective cohort performed by Spicer et al. (2013) involving 1,516 children from urban Connecticut, failed to reveal consistencies between TST reaction size and LTBI treatment completion. This study was limited by the inability to verify actual treatment completion and was reliant upon pharmaceutical records for determining whether medications were picked up by those included in the study. This may have resulted in an underestimation of completion if persons filled their prescriptions from different pharmacies during the study period (Spicer et al., 2013). Interested in looking specifically at the risk of failing to complete treatment, Chang, Eitzman, Nahid, and Finelli (2014) performed a retrospective cohort involving 1,872 participants recruited from two different California county sites. With an overall completion rate of 78%, Chang et al. (2014) concluded that being aged 15 to 18 years, non-Hispanic race, development of hepatitis, and symptoms of adverse events were associated with noncompletion however, TST size of positivity was not.

No studies were identified that evaluated the relationship between IGRA positivity and LTBI treatment completion. As only one of two diagnostic tools available for supporting a diagnosis of LTBI, IGRA positivity is often studied in a comparative manner to TST. To date, no gold standard exists for diagnosing LTBI prompting researchers to continuously evaluate the sensitivity and specificity of the TST and IGRA

to provide evidence for the recommendation of the use of one diagnostic tool over the other. Current research indicates IGRAs are more sensitive than the TST in BCG vaccinated persons (LoBue & Castro, 2012) however the two tools currently remain interchangeable under most circumstances (LoBue & Castro, 2012).

Of the studies published exploring the impact the use of IGRAs have on LTBI treatment completion, none directly compared IGRAs to TSTs. A single retrospective study conducted by Shah et al. (2012) compared treatment initiation and completion rates pre-IGRA implementation and post-IGRA implementation including 607 participants and 750 in Baltimore, respectively. Shah et al. (2012) concluded that there was no difference between the rate of treatment initiation or treatment completion after the implementation of IGRAs in the Baltimore City Health Department. However, claiming IGRA positivity as a predictor of treatment initiation or completion was not possible due to the study's design which lacked the parallel arm that studied these trends with TSTs. Dewan et al. (2006) in a prospective cohort involving 4,143 persons evaluated for LTBI at six San Francisco clinics, attempted to evaluated the feasibility, acceptability, and cost of TB testing by IGRA. Again, the study design prevented the researchers from determining if IGRA positivity could predict LTBI treatment completion, but the researchers did identify that more patients completed the LTBI medical evaluation when tested by IGRA compared to TST. These results may indicate patients tested for LTBI via IGRA have greater perceived risk and are more likely to complete medical evaluation and possibly LTBI treatment; although this remains to be studied.

Despite the limited number of diagnostic tools available for the diagnosing LTBI, the restricted amount of research surrounding whether TST positive persons or IGRA positive persons complete treatment at different rates may further contribute to the fact that no gold standard exists, although agent factors such as this are likely critical. By exploring which of the two positive groups complete treatment at higher rates, TB Control Programs may be better equipped to implement interventions that promote efficiency and may contribute to reducing future rates of TB disease.

The Gap

This literature review has demonstrated that the rural setting remains underrepresented in study design, sampling, and in the overall number of publications documenting LTBI treatment completion trends. The number of resources available to control TB in the urban U.S. setting may differ dramatically compared to the rural setting, greatly limiting the applicability of published urban-setting research to the rural setting and drawing attention to this significant gap. Data on the host, environment, and agent-related predictors of LTBI treatment completion are growing however continue to disproportionately represent non-rural settings creating an impetus for rural setting research. Understanding LTBI treatment trends in the foreign-born residing in all U.S. settings will broaden the depth of understanding surrounding these persons whom are at greater risk of being infected with *Mtb* and may better assist all U.S.-based TB Control Programs move toward elimination.

The analysis of the LTBI treatment completion research is also somewhat homogenous identifying another gap that this research intends to assist in addressing. A

majority of the articles reviewed analyzed data using regression techniques however, this approach does not account for censoring and ignores the element of time which may be critical to the LTBI treatment completion trends described previously. Using survival analysis to explore host, environment, and agent-related independent variables and the relationship to LTBI treatment completion will help close these gaps as survival analysis accounts for censoring as well as the time to event.

The inconsistencies identified in the host, environment, and agent variables reviewed and their ability to predict LTBI treatment completion produces a strong call for greater research to explore these factors across a broader setting. Additionally, these inconsistencies may indicate that LTBI treatment completion is a localized phenomenon likely influenced by the individuals receiving treatment (host), their area of residence (environment), as well as their perceived severity of being infected and the risk of developing transmissible disease along with disease-related sequellae (agent). Studying, the factors associated with LTBI treatment completion in the rural setting could assist in closing this gap in knowledge but may also help better target specific, necessary treatment completion improving interventions in the rural setting.

Summary

This present literature review was conducted to determine what was currently known about LTBI treatment completion trends in the rural U.S. setting as TB Control Programs are increasingly pressured to address the pool of latently infected persons. To move the United States toward elimination in the face of declining rates of active disease, characterizing LTBI treatment completion trends in a variety of settings using a variety of

samples will likely achieve a more thorough understanding of the gaps that exist in practice that may prolong the move toward elimination. This literature search revealed the rural setting is wholly underrepresented in current research leaving TB Control Programs serving this setting reliant upon implementing treatment completion improving interventions that have been extrapolated from research done in the urban, resource rich setting. This dissertation research will add to the evidence currently available on the predictors of LTBI completion from the urban setting by characterizing the rural-based LTBI treatment completion trend.

Many host-related LTBI treatment completion factors have been explored. Multiple studies have noted inconsistencies in using sex as predictors of LTBI treatment completion research. Unlike sex, researchers tend to find age-related associations with LTBI treatment completion often however, the valid research published showing no association cannot be ignored. Birth country, also a thoroughly studied independent variable, is frequently supported as a predictor of LTBI treatment completion. Smoking status is understudied but too is thought to be a predictor of LTBI treatment completion. Exploring these factors in the rural setting, as is proposed by this dissertation research, will assist in filling the gap that currently exists surrounding this demographic.

Environment-related LTBI treatment completion factors are less well studied however, consistent trends have emerged. Persons traveling greater distances or spending more to travel to LTBI treatment facilities are consistently reported to be at greater risk of delaying LTBI medical evaluation or not completing LTBI treatment compared to their counterparts. Likely with greater distances to travel in the rural setting it is unfortunate

that virtually no studies have been published examining this phenomenon but instead, have focused solely on urbanites. Agent-related factors are equally less studied in relation to LTBI treatment completion although some studies are available that describe who tends to be TST or IGRA positive as well as compare the sensitivity and specificity of the TST and IGRA.

A retrospective study using survival analysis to identify potential predictors of LTBI treatment completion in the rural setting is a novel approach to addressing the gap that currently exists in the literature. Additionally, intending to describe LTBI treatment completion trends in the rural-based foreign-born population too is a unique approach that has thus so far failed to be adequately covered in the literature. The rural setting differs significantly in structure and resource availability from the urban setting and thus, studying LTBI treatment completion trends in this context will not only add to the body of knowledge but may also be critical to shaping appropriate public health interventions in this setting. The methodology for addressing this gap in knowledge is detailed in Chapter 3 where the rational for the study design, the data sources, the variables of interest, and the planned analysis used to quantify treatment completion and identify predictors of completion and noncompletion are described.

Chapter 3: Research Method

Introduction

This main purpose of this research was to describe the epidemiology of LTBI treatment completion in refugees, immigrants, and other visa holders resettling in the rural state of Idaho. Consistently, foreign-born persons account of over 60% of the active TB disease burden in Idaho, which is likely due to reactivation from prior overseas exposure (IDHW, 2016; Schmit et al., 2017). Preventive LTBI therapy initiated at the time of arrival in Idaho can reduce this risk of reactivation and may improve active TB disease rates over time in the state (Blount et al., 2016; Pareek et al., 2016). This research aimed to determine what independent variables predicted noncompletion for visa holders initiating LTBI treatment. Similar research had shown LTBI treatment completion could be influenced by host, environment, and agent factors (Coly & Morisky, 2004; Hirsch-Moverman et al., 2008; Malangu & Yamutamba, 2016; Parsyan et al., 2007). Identification of completion influencing variables could promote the development of targeted interventions in the resource-limited setting like Idaho. Unfortunately, little research had focused on the identification of these potential predictors in the rural-U.S. setting. This retrospective cohort study was consistent in research design and had a similar overarching goal with that of comparable work conducted in the high-incidence or international TB setting; however, I made modifications to account for the level of data available for testing the hypotheses in question, for making interpretations, and for drawing conclusions (Johnson et al., 2016; Malejczyk et al., 2014; Parsyan et al., 2007).

In this chapter I describe the study design to address the research questions, the sample size, the source of the data, the relevant variables, data cleaning and management, and the analytical methods. The chapter also covers any ethical concerns related to this research.

Research Design and Rationale

This was a retrospective cohort study using a secondary dataset. When attempting to describe the epidemiology of LTBI treatment completion and determine if certain host, environment, and agent factors are predictive of LTBI treatment completion, the retrospective cohort study had been demonstrated to be appropriate. Several researches had been conducted using this method (Chang et al., 2014; Li et al., 2009; Lines et al., 2015; Malejczyk et al., 2014; Parsyan et al., 2007; Spicer et al.; 2013). Collectively, these studies demonstrated the value of the cohort method to investigating LTBI treatment completion associated factors.

This retrospective cohort study identified two cohorts of LTBI subjects based on their visa status at the time of entering the United States. The study followed the subjects from receiving medical evaluations shortly after resettlement in Idaho to the expected time of completing LTBI treatment, if diagnosed with LTBI, during the study period. The primary dependent variable was LTBI treatment completion status among categories of visa holders. Independent variables included demographic characteristics (i.e., age, sex), visa type, smoking status, country of origin, distance from residence to LTBI treatment facility, urban or rural resettlement, TST or IGRA positivity, and the time measured in days between date of arrival and initial medical follow-up. The reason for selecting these

factors was that many had been shown to influence LTBI treatment completion from research conducted in the high-incidence TB setting, the international setting, and in the urban U.S. setting. These independent variables were assessed individually and collectively for their impacts on LTBI treatment completion or total time on LTBI therapy.

Since global migratory patterns change annually, this retrospective study was limited to a sample population completing LTBI treatment between January 1, 2012 and December 31, 2016. In Idaho, the number of visa holders arriving fluctuates, but since 2012, arrivals from Iraq, Democratic Republic of Congo, Myanmar, Somalia, and Bhutan have continuously represented the top five countries of origin for resettlers in the state (CDC, 2017). The retrospective cohort design fit this research due to the limited change in year-to-year arrivals by country in Idaho and should be useful for application to future visa-holder arrival trends. Additionally, since TB resources are scarce in Idaho, the retrospective nature of this study did not impose extra burden compared to other study designs as the data for analysis had already been collected.

Data Sources

Electronic Disease Notification System

Data for this research was derived from a single surveillance system, detailed in Figure 1. The CDC's EDN system is the only nationwide secure platform housing medical information for migrants arriving to the United States with notifiable conditions (CDC, 2011). The EDN houses the electronic versions of the Department of State forms required for migration including the results of overseas medical examinations, treatments,

and immunizations (CDC, 2011). This information is accessible to approved public health officials in the United States. The system allows for these state and local health departments to enter the results of postarrival tuberculosis follow-up examinations using a standardized TB Follow-up Worksheet for persons arriving with a TB Notification (CDC, 2011).

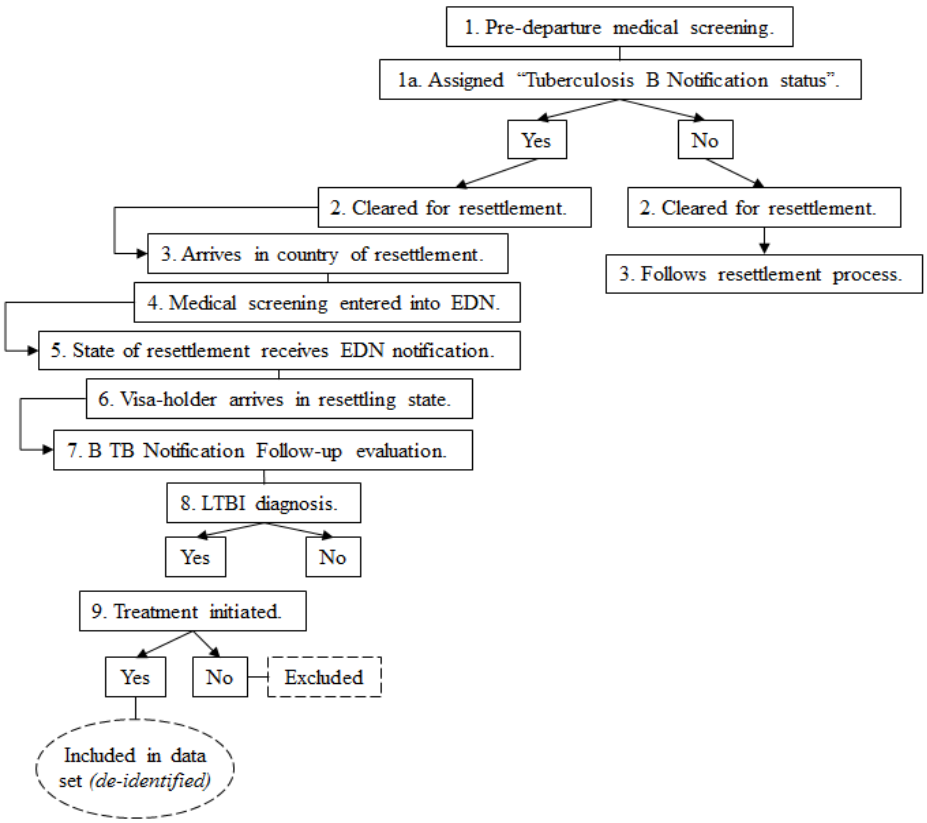

Figure 1. EDN data entry process and research data set methods.

EDN sources of data. The EDN system is populated daily with the Department of State forms collected by the U.S. Customs and Border Protection agents stationed at airports designated to receive migrants with admissible notifiable health conditions (CDC, 2011). These forms are sent to the CDC's quarantine stations for upload into EDN

shortly after new migrant arrival. The EDN program receives the collected forms from all 20 quarantine stations located at the U.S. ports of entry (CDC, 2011). Persons' records indicating follow-up for TB or LTBI from prearrival medical evaluations are marked with a "TB Notification" (CDC, 2011). Persons thought to be infected with *Mtb* but not infectious (e.g., latent tuberculosis) are designated with a B2 or B3 TB classification (CDC, 2011; Lee et al., 2013). These classifications were the focus of this research. The EDN forms are converted to electronic content and securely stored for future access by the visa-holder receiving jurisdiction. Although EDN houses multiple aspects of new migratory arrivals health status, the standardized TB Follow-up Worksheets currently contained most of the necessary data elements for this dissertation research. Access to any other EDN dataset was limited to Department of State forms 2053, 3026, and the TB Follow-up Worksheet (CDC, 2011).

Idaho EDN sources of data. Representatives of the Idaho State TB Program are notified via e-mail of all visa holders arriving in the state that require medical evaluation for LTBI or TB disease. Seven agencies in Idaho are responsible for coordinating the follow-up of these visa holders or performing these evaluations. Preliminary and final medical follow-up records on all newly arrived visa holders requiring follow-up for TB are submitted to the Idaho State TB Program, and I used data from records submitted between January 1, 2012 and December 31, 2016 for this research. In Idaho, at least one public health official or representative from each of the seven public health districts covering Idaho's 44 counties has record management access to EDN. This permission setting allows end users to receive electronic notifications for new migratory arrivals

requiring TB or LTBI follow-up, print the necessary overseas medical records, and generate a migrant-specific TB Follow-up Worksheet. Medical TB evaluations generally take place within 90 days postarrival. Initial findings are recorded, diagnoses made, and when necessary, treatment recommended. All TB Follow-up Worksheets are then submitted to the Idaho State TB Program per contractual arrangements. Submission of these follow-up forms makes the evaluating agency eligible for reimbursement for some of costs of these visa-holder medical evaluations from the State TB Program. Upon receipt, staff with the Idaho State TB Program enters the TB Follow-up Worksheet findings for electronic submission to the CDC. Visa holders recommended for TB or LTBI therapy had an initial TB Follow-up Worksheet submitted to the state and a final submitted at the time of treatment completion or disposition.

Access to Idaho data. The Idaho State TB Program manager and the Idaho state TB controller, along with local-level epidemiologists and health care providers associated with each of Idaho's PHDs can access EDN data through a CDC portal requiring validated credentials for log-in. Idaho EDN users can electronically download all predeparture, postarrival, and TB follow-up records for any visa holder arriving in the state with any classification. I accessed only B TB classifications for the purposes of this research. Data downloaded included all necessary variables for this research; however, matching of records was required as the data existed in three separate report exports. I used unique "alien numbers" assigned to every arriving visa holder to match records as this number was consistent across all EDN report exports. All matched records were combined into a single dataset for analysis.

To access the EDN data, I submitted an e-mail detailing the data request to the Idaho State TB Program for forwarding on to the Idaho Division of Public Health Institutional Review Board (IRB). This occurred before the Walden University IRB approval process to conduct this dissertation research so as to obtain a data use agreement (DUA) and letter of cooperation signed by an Idaho Division of Public Health representative. Requested data was de-identified and in Excel spreadsheet format with a single row representing the unique EDN record for a visa holder in Idaho for the specified timeframe and each column representing a demographic factor or a research variable. The EDN dataset included the following variables for this research, among others: sex, date of birth, country of origin, visa type, date of arrival, date of medical evaluation in the United States, smoking status, HIV status, address of resettlement, TST results, IGRA results, disposition code, treatment start date, and treatment stop date. Only a subset of the variables recorded in EDN were used in this dissertation research; they are described later in this chapter. The dataset was obtained from the Division after Walden IRB approval.

Instrumentation

Since this was a secondary database research, it did not have its own study instrument for data collection. EDN data are collected using standardized, nationally developed formal instruments (CDC, 2011). The Idaho state TB Program uses these EDN standard forms to collect TB and LTBI medical evaluation information on visa holders and these were used to produce the dataset for this research. The EDN TB Follow-up Worksheet is available only through the secure CDC application but includes

predeparture medical evaluation results, post-arrival medical evaluation findings, TB and LTBI treatment initiation data, and treatment completion data. The EDN TB Follow-up Worksheet has been and currently still is used nationally to ensure consistency in the reporting of TB medical evaluation findings after the foreign-born arrive in the United States. For this dissertation research, this instrument was not tested or further validated as the Idaho state TB Program has been relying on this form for data collection related to this research for over a decade. The version of the EDN TB Follow-up Worksheet used for this research can be found in Appendix A at the end of this dissertation.

The data analyzed for this study were submitted from six different public health departments and a single Federally Qualified Health Center (FQHC) specializing in the diagnosis and treatment of LTBI and TB disease. All seven entities utilized the standardized, nationally developed TB Follow-up Worksheet to record predeparture medical findings, post-arrival screening results, treatment decision, and final disposition. Dispositions include “no exposure, not infected”, “TB exposure, no evidence of infection”, “TB infection, no disease”, “TB, TB disease”, and “TB, inactive disease”. Tuberculosis Follow-up Forms from all seven entities were submitted to the Idaho state TB Program for data entry. The dataset used for this research was derived from EDN standard reports and exports for data entered for the “Idaho” jurisdiction.

Research Questions and Hypotheses

This study described LTBI treatment completion trends in the foreign-born residing in the rural state of Idaho and explored potential predictors of treatment

completion using host, environment, or agent-related factors that could influence the outcome. The specific research questions for this research are outlined below.

RQ1: Is visa type (refugee, immigrant, parolees, asylees, or fiancés) associated with LTBI treatment completion among permanent visa holders initiating LTBI treatment in Idaho?

$H_0$1: There is no association between visa type and LTBI treatment completion among permanent visa holders initiating LTBI treatment in Idaho.

H_a1: There is an association between visa type and LTBI treatment completion among permanent visa holders initiating LTBI treatment in Idaho.

RQ2: Is the mean time distribution to last treatment for LTBI between permanent visa holders initiating LTBI treatment in Idaho significantly different?

$H_0$2: The mean time distribution to last treatment for LTBI between permanent visa holders initiating treatment in Idaho is not statistically difference.

H_a2: The mean time distribution to last treatment for LTBI between permanent visa holders initiating treatment in Idaho is statistically different.

RQ3: Is time on LTBI treatment in permanent visa holders initiating treatment in Idaho affected by sex, age, country of origin, visa type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity?

$H_0$3: Time on LTBI treatment in permanent visa holders initiating treatment in Idaho is not affected by sex, age, country of origin, visa type, smoking status,

distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity

H_a3: Time on LTBI treatment in permanent visa holders initiating treatment in Idaho is affected by sex, age, country of origin, visa type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity.

Additional Research Questions

Although not directly related to above research hypotheses, this study also explored the potential association of the prescribed LTBI treatment regimen and treatment completion status. In Idaho, at least one TB Clinic is known to be consistently using the expedited 12 week LTBI treatment regimen while other clinics are known to rely on standard LTBI treatment spanning four, six, or nine months. This research attempted to determine if the regimen prescribed influences the likelihood of completion as some studies have shown shorter regimens equate to higher completion rates. The role LTBI treatment prescribing provider in Idaho may also be important to treatment completion and was thus, a secondary research result. Research participants were grouped by the prescribed treatment regimen during analysis of the first additional research goal and by the prescribing provider for the second additional research goal.

Population

This study included only visa holders in Idaho diagnosed with LTBI either by panel physicians overseas (*e.g.* predeparture) or by a health care provider representing one of Idaho's seven PHDs after arrival and whom have met the study eligibility criteria listed below. These visa holders arrived in Idaho through traditional United States immigration channels and had predeparture medical records designated as Class B TB, requiring medical follow-up upon arrival to the host jurisdiction, and had not initiated treatment overseas. Typically, U.S. migrants do not initiate LTBI treatment prior to arrival however, persons with active TB disease must complete treatment prior to departure. Visa holders with non-Class B TB notification but found to have LTBI after evaluation in Idaho were also included.

Sampling and Sampling Procedures

All visa holders that started LTBI therapy post-arrival to Idaho and whom were eligible for inclusion were included in this study. Sampling techniques were not used to select the study subjects. To be included in this study, the following criteria were met:

- Visa-holder diagnosed with LTBI.
- Clinical or laboratory findings consistent with active TB absent.
- Initiation of preventive therapy in Idaho.
- Preventive therapy start date on or after January 1, 2012.
- Preventive therapy completion date on or before December 31, 2016, for those completing treatment.

- Resided in Idaho at time of treatment initiation and completion, for those completing.
- If evaluated multiple times during the study timeframe, only the instance in which preventive treatment is initiated was included.

A visa-holder was considered to reside in Idaho if predeparture and post-arrival demographic EDN records indicated that individual's physical address was associated with an Idaho zip code. This determination was made by the Idaho state TB Program staff at the time of research dataset creation as the Idaho state TB Program is made aware of residence status changes and is responsible for transferring records between jurisdictions. The criteria for study exclusion was:

- Visa-holder diagnosed with LTBI not initiating preventive therapy.
- Visa-holder found to have active TB disease at the time of resettlement.
- Preventive treatment initiation outside of the timeframe specified above.
- Preventive treatment initiation in a jurisdiction other than Idaho.
- Visa holders initiating preventive therapy in Idaho but moving out of the state prior to completion.

Sample Size Calculations

The sample for this research was drawn from secondary data collection using nonprobability sampling procedure. All eligible visa holders in Idaho initiating LTBI preventive therapy were included in the research thus randomization was not involved. Since the rate of LTBI treatment completion in the Idaho visa-holding population was unknown, purposive sampling was best to ensure all eligible participants during the five-

year study period were intentionally included in the study. This sample may not be representative of similar groups at the national level, however, likely represent the visa-holding population in Idaho well.

A G*Power analysis (Faul, 2014) was used to estimate the minimum sample size required for evaluating the first research question involving the treatment completion rate among three study groups. The formula to calculate the degrees of freedom, a component of the sample size calculation, was (*rows* -1) x (*columns* - 1) where treatment completion status (yes, no) represented the rows and visa-type (refugee, immigrant, other) represented the columns. To detect a 10% of difference among groups using chi-square test and two degrees of freedom at an alpha level of 0.05 and a power of 0.80, assuming the LTBI treatment completion rate is 28.5%, this study would need 841 subjects divided across each group. To detect a 20% difference among groups using the same aforementioned parameters and a treatment completion rate of 24.5%, this study would need at least 229 subjects. To assess the impact of various treatment completion rates, Table 1 shows the samples size needed for different rates.

Table 1

Minimum Sample Size: χ^2 tests - Goodness-of-fit tests: Contingency tables

Treatment completion rate in each group	Alpha	Power	Detectable difference among three study groups	Sample size
10%	0.05	80%	77%	16
	0.05	90%	77%	21
20%	0.05	80%	33%	87
	0.05	90%	33%	114
30%	0.05	80%	7%	1,821
	0.05	90%	7%	2,392
24.5%	0.05	80%	20%	229
	0.05	90%	20%	300
28.5%	0.05	80%	10%	841
	0.05	90%	10%	300
40%	0.05	80%	14%	521
	0.05	90%	14%	684
50%	0.05	80%	33%	114
	0.05	90%	33%	87

This study used all eligible subjects without limiting to the minimum sample size. However, it was assumed that even if the database could only provide 76 subjects, it would have 80% power using survival analyses to detect the 20% difference at 0.05 significance level and a hazard ratio not equal to one indicating that survival was better in one or two of the groups.

Acquisition of the Database

A de-identified line list of the Idaho EDN data was obtained from the state TB Program through formal electronic request. The use of the EDN data for research purposes mandates the submission of an electronic request for the data. The data request was submitted to the Bureau of Communicable Disease Prevention (BCDP) prior to Walden IRB approval to establish a DUA, letter of cooperation, and the Division of Public Health “Research Determination” process, so appropriate documentation could be provided at the time of Walden IRB submission. At the time of this request, the IDHW

Division of Public Heaths' IRB process would have been initiated if the research determination team indicated the request was for research related data. However, the research determination team indicated the requested dataset was for public health practice, so the Division of Public Health's IRB was not needed to be consulted. The de-identified EDN database was requested in Excel spreadsheet format.

After Research Determination Committee approval was received from the IDHW Division of Public Health and Walden University IRB approval, creation of the secondary data file occurred. The Idaho TB Program removed all visa-holder names from the dataset. The EDN data reports available for download were merged into a single dataset using the unique alien number, which was removed prior to dissemination of the final dataset since alien numbers could be used to identify individuals. Physical addresses of resettlement were geocoded and miles between nearest public health department calculated. After calculation by TB Program staff, residence numbers and street names were deleted but zip codes retained to determine urban and rural residency. Visa-holder dates of birth were also removed from the line list after age was calculated by the Program staff. At the time of data analysis, ages were grouped and assigned a numerical value (Table 3). Since the data file created by the TB Program did not include Protected Health Information its use did not require informed consent.

Dataset Quality

The primary data entered into the EDN system for the Idaho jurisdiction is subject to routine quality assurance. Quarterly, TB Program staff query the EDN application to detect missing reports, arrivals transferring to out of state jurisdictions, and percentage of

TB Follow-up Worksheet variable completion. Arrivals missing TB Follow-up Worksheets are brought to the attention of local public health officials and an evaluation status determined. If the visa-holder was determined to have relocated to a non-Idaho jurisdiction, EDN records are electronically transferred and removed from the Idaho dataset. Missing variables associated with the TB Follow-up Worksheets are also brought to the attention of local public health officials and if made available, entered to improve data completion. Records are also reviewed for quality and identified fields with erroneous or questionable data are followed-up on and corrected when necessary.

Due to the recurring data quality assurance practices of the Idaho TB Program staff, it was hypothesized that the secondary dataset requested for this research was of high quality. The request for the secondary dataset called for the inclusion of incomplete records, however, none were identified by the Program and none required removal from the dataset prior to analysis for this research. This approach assisted in determining the percentage of data completion and thus, the potential quality of the data used in this research. Additionally, the routine review of the primary dataset likely reduced data entry errors, improving the quality of the secondary dataset. Missing data would have potentially only influenced the assessment of research question one and although the survival analysis involved in research questions two and three can handle missing data, the covariate analysis could have been negatively impacted if missing data was high, albeit was not. TB Program staff created variables could have introduced data entry errors, however, data reviews conducted prior to analysis for this research promoted improved data integrity.

Addressing data integrity issues. Prior to data analysis, the secondary dataset received from the Idaho state TB Program was assessed for data completion. Many of the variables for this dissertation research were derived from EDN required data entry fields however, not all variables, if left incomplete, would have prevented data entry staff from submitting the EDN content. Incomplete variables were possible but it was assumed that data would have been missing completely at random due to data quality assurance practices in place at the program level. Prior to receiving the dataset, it was planned that records with missing data would require deletions since the de-identified nature of the dataset would not allow for the TB Program to collect additional information. As such, listwise deletion had the potential to reduce the external validity of this research. Contractual obligations that assist in ensuring a high percentage of data completion for Idaho public health officials or health care providers evaluating newly arriving visa holders led to the assumption that data would be missing completely at random, but many data missing at random could have decreased the overall power of this study (Kang, 2013). This was not an issue, however. Encountering a small sample size at the start of data analysis may have indicated pairwise deletion should have been used to maintain the sample size, sustain power, and promote stable external validity (Kang, 2013). Again, however, missing data was not an issue with this dissertation research so no deletion methods were deployed.

Study Variables and Data Set Components

This research compared the treatment completion rates in categories of migrants and explored the potential risk factors as covariates on the completion rates. For this

research, LTBI treatment completion, or the primary endpoint, was defined as completing 90% or more of the doses originally prescribed at the time of visa-holder LTBI diagnosis within the prescribed regimen duration. Research participants on the expedited 12-week regimen should have completed 90% or more of doses by the twelfth week, those on four months of RIF must have completed 90% or more of doses by the end of month four, while those on six or nine months of INH should have completed 90% or more of doses by the end of month six or nine. The minimum number of doses for successful treatment completion is included in Table 2. This definition is consistent with real-world practice as persons prescribed LTBI treatment who complete at least 90% of their doses are considered successfully treated. This is also a standard of practice in Idaho.

Table 2

Minimum Number of Doses (≥90% of prescribed) for Completion

Age group	Regimen	Prescribed duration	Standard doses	Minimum doses***
Adult	INH+RPT	12 weeks	12	11
	RIF**	4 months	120	108
	INH**	6 months	180	162
	INH**	9 months	270	243
Children	INH+RPT*	12 weeks	12	11
	RIF**	4 months	Not Recommended	n/a
	INH**	6 months	Not Recommended	n/a
	INH**	9 months	270	243

Note. INH=Isoniazid, RPT=Rifapentine, RIF=Rifampin
*Children 12 and older
**Based off daily regimen
***Must be completed by end of "Prescribed Duration"

The study variables included completion status (yes or no) and subject demographics shown in Table 3. These demographic factors are also considered host-related factors in this dissertation research.

Table 3

Demographic Variables, Descriptions, and EDN Source Form

			Variable data source	
Variable	Variable description	Value	Form DS-2053	Form DS-3026
Sex	Nominal	1=Male 2=Female	X	
Age group	Nominal/Calculated	0=24 years 1=25-44 years 2=45+ years	X	
Country of origin (collapsed into WHO region)	Nominal	1=Americas 2=European or Eastern Mediterranean 3=African 4=South-East Asia 5=Western Pacific Region	X	
Visa type	Nominal	1= refugee 2=immigrant	X	
Smoking status	Nominal	0=Nonsmoker 1=Current smoker 2=Ex-smoker		X

Environment (Table 4) and agent-related (Table 5) independent variables were included in the dataset and were also used to determine what impact they may have on LTBI treatment completion.

Table 4

Environment-related Variables, Descriptions, and EDN Source Form

			Variable data source	
Variable	Variable description	Value	Form DS-2053	Form DS-3026
Distance between residence and treatment facility	Ordinal/Calculated	Number of miles	X	
Area of Resettlement	Nominal/Calculated	1=Urban 2=Rural	X	
Time between arrival and initial medical evaluation	Ordinal/Calculated	Number of days	X	

Table 5

Agent-related Variables, Descriptions, and EDN Source Form

		Variable data source			
Variable	Variable description	Value	Form DS-2053	Form DS-3026	Form Follow-up Worksheet
TST positivity	Nominal	0=Negative 1=Positive 2=Unknown			X
IGRA positivity	Nominal/Binary	0=Negative 1=Positive 2=Indeterminate 3=Invalid 4=Unknown			X

The EDN system has established a definition for each variable included in the system as well as acceptable values for data entry. This EDN data dictionary was critical to understanding the contents of report exports and all independent variables extracted from EDN included in this research are detailed below.

Sex. In the EDN, "sex" is a binary variable. Currently, only categorical entries are allowed with "M" representing male sex and "F" representing female sex. This variable is

also a mandatory element for data entry. Upon export of EDN data, sex is represented as "M" or "F". For data analysis, Male=1 and Female=2.

Age. Age is not a variable included in the EDN dataset that is available for export. Department of State variables such as date of birth are included in the EDN. Upon export, age was calculated by the Idaho TB Program staff to the nearest year from the listed date of birth and the date of arrival. Date of birth in EDN is reported in MM/DD/YYYY format and are values that were excluded from the final dataset, after age as calculated, due to the sensitive nature of this information. For the purposes of data analysis, age categories were established (Table 3).

Birth country. Information about birth country and country of residence prior to departure for the United States is gathered on all on visa holders in EDN. In most instances, birth country is populated in EDN however, may be unknown for some refugees. When unknown, prior country of residence was used as a proxy for birth country as both variables are included in the EDN export reports that produced the dataset for this research. Both variables in the EDN export report included a unique two-character code tied to the full country's name in the system supplied data dictionary for cross-referencing. The unique two-character country code was expanded in the dataset to include the respective country's full name. To further improve participant protection, the country of origin was assigned a numerical value associated with a WHO world region. The world regions included: Americas, European or Eastern Mediterranean, African, South-East Asian, and Western Pacific.

Visa type. The EDN system only stores information for permanent U.S. visa statuses. Immigrants are represented with an “I”, Parolee with a “P”, Fiancé with a “K1” or “V1”, Refugee with a “R”, and Asylee with an “A”. All visa holders are only granted one status so a combination of characters is not possible in the dataset. For the purposes of this research, refugee visas were assigned a numerical value of one in the dataset, immigrant visas a two, and parolee, fiancé, and asylee visas assigned a three. The refugee and immigrant visa types are the most common in Idaho. Due to their small numbers compared to the refugee and immigrant visa types, parolee, asylee, and fiancé visas were combined into a single group, designated by three in the dataset.

Smoking status. Current or former use of tobacco is recorded on Department of State form 3026 in EDN. As a nominal level of measurement, a yes response, coded as a one, prompts a skip pattern requesting information on current for former status. Current smokers receive a one while former smokers receive a two in the EDN export dataset. Lifetime non-smokers receive a zero when responding to current or former tobacco use and do not initiate the skip pattern functionality.

Distance. Each visa-holder must submit a physical U.S. address prior to resettlement. For the purposes of this research, submitted physical addresses in Idaho was used to calculate the “Distance” variable by the Idaho TB Program staff. Using geocoding software, the distance in miles between the visa-holder’s listed United States address and the Idaho Public Health District (or respective health agency) where evaluation for TB and LTBI takes place was determined. The calculated distance in miles

was retained in the final research dataset and physical house number and street name were excluded by the Idaho TB Program staff to assist with reducing identifiability.

Area of resettlement. Each visa-holder is assigned an Idaho public health agency responsible for their TB and LTBI medical evaluation upon arrival based off their physical address. Using the zip code variable in EDN, rural or urban resettlement was determined for use in the final dataset and was coded numerically with one representing urban resettlement and two representing rural resettlement.

Rural. In 2016, the population living in Idaho was estimated to be 1,683,140 by the United States Census Bureau. To determine rural or urban residency the Rural-Urban Commuting Area Code (RUCA) classification was used as developed by Morrill, Cromartie, and Hart (2011). Zip codes associated with visa-holder's physical Idaho addresses were used to determine rural status. Each Idaho zip code has been assigned a RUCA code by Morrill, Cromartie, and Hart with those codes greater or equal to five being classified as rural for this dissertation research. Values on the RUCA scale from one to four were classified as urban. Each record included in the research dataset was assigned a RUCA code after receiving the datafile from the state TB Program. This approach was consistent with urban-versus-rural classifications used in Idaho in other research.

Arrival and medical evaluation time. The Idaho state TB Program aims to have all newly arrived visa holders medically evaluated within 30, 60, or 90 days. In EDN, the date of arrival is recorded by Customs and Border Protection agents and the date of medical evaluation is recorded by Idaho public health officials using the EDN TB

Follow-up Worksheet. Both fields are recorded in MM/DD/YYYY format and are included in the DS-2053 export or the TB Follow-up Worksheet export. Time between arrival and initial medical evaluation was calculated by the Idaho state TB Program prior to release of the research dataset and the number of days populated the "Arrival and Medical Evaluation Time" variable.

TST or IGRA positivity. After arrival and during medical evaluations, visa holders recently migrated to the United States are tested for tuberculosis. In EDN, TB Follow-up Worksheets record the results for TST and/or IGRAs as well as the interpretation of the results. A TST or IGRA recording in the EDN export of zero was indicative of a positive result and would support the diagnosis populated on the Follow-up Worksheet. Values of one indicated positivity but for IGRAs, values of two represented indeterminacy, three represented an invalid IGRA result, and four represented an unknown IGRA result.

Dataset Cleaning and Management

The creation of the dataset for this research involved preliminary cleaning by TB Program staff to ensure participants could not be identified. After receipt of the secondary dataset, the proportion of missing values for the study variables described above was determined. A low proportion of missing variables would have led to listwise deletion if the sample size is large enough, while a high proportion of missing data for the study variables would have to pairwise deletion, however, neither was necessary.

After assessing data completion, data accuracy was reviewed for each study variable. This included a review of the accuracy of coded elements (i.e. Male=1,

Female=2) but also a review to ensure inappropriate coded values were excluded. Additionally, during this review, some variables were coded per the values in Tables 3, 4, and 5. This primarily involved the categorization of age group, country of origin regionalization, and area of resettlement determination (e.g. rural versus urban). Formatting of date specific variables (i.e. date of arrival, date of medical evaluation, date of treatment initiation, date of treatment completion) was reviewed as incorrect formatting could impact variables calculated off these values.

The secondary dataset was also reviewed to ensure participant records included meet the inclusion criteria for this research. This included reviewing disposition codes and removing records where visa holders were diagnosed with active disease, and reviewing treatment status variables to ensure treatment was initiated in Idaho.

The management of this dataset involved versioning. The original dataset received from the Idaho TB Program was preserved as the master datafile and as incomplete data was assessed, coded values reviewed, and accuracy of the participant records evaluated, changes to the dataset prompted the file to be saved with the appropriate versioning nomenclature (e.g. v1). Preservation of the original master file ensured any data cleaning errors could be corrected and the overall integrity of the secondary dataset for this research maintained.

Data Analysis Plan

The data supporting this dissertation research were analyzed using International Business Machines Corp (IBM) SPSS Statistics version 21 (IBM, 2012). All analysis code and output were saved for archival purposes but also to promote study duplicability.

A data dictionary was developed to ensure variables names, types, and manipulation of the dataset was recorded although many variables were already defined by the EDN. The originally planned statistical analysis for this research has been summarized in Table 6.

Table 6

Planned Statistical Analysis Tests and Measures

Research question	Independent variable	Dependent variable	Statistical analysis or measure
Is visa type (refugee, immigrant, parolee, asylee, or fiancé) associated with LTBI treatment completion among permanent visa holders initiating LTBI treatment in Idaho?	Visa-type (categorical, three levels)	LTBI treatment completion status (binary)	Pearson's chi-square and post hoc pairwise comparison with Bonferroni corrections
Is the median time distribution to last treatment for LTBI significantly different in permanent visa holders initiating LTBI treatment in Idaho?	Visa-type (categorical, three levels)	Time in months on LTBI treatment (interval; censored variable = noncompletion)	Kaplan-Meier estimator
Is time on LTBI treatment in permanent visa holders initiating treatment in Idaho affected by sex, age, country of origin, visa-type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, tuberculin skin test (TST) positivity, or interferon gamma release (IGRA) positivity?	Sex; Age; Country of Origin; Visa-type; Smoking-status. Distance from residence to treatment facility; Are of resettlement; Time between arrival and medical evaluation. TST positivity; IGRA positivity.	Time in months on LTBI treatment (interval; censored variable = noncompletion)	Cox proportional hazards regression model

Descriptive Analysis

Initial statistical analyses included a descriptive analysis of sample-specific data for each of the visa status groups, where continuous variable (such as age) were described with mean, median, range and categorical variables (such as sex, birth country, smoking status, and area of resettlement) were described with *n* and percent of the total. The results were planned to be presented in a similar tabular format as shown in Table 7, as

appropriate. Important identified participant characteristics are presented in tables in Chapter 4.

Table 7

Sample Descriptive Analysis Results

Variable	Refugee (*n* =)	Immigrant (*n* =)	Other (*n* =)	Total (*n* =)
Age in years				
Age groups				
<1				
1-4				
5-9				
…….				
Gender				
Female				
Male				
Smoking status				
Never				
Former				
Current				
…..				

Research Question Data Analysis

The first dissertation research question that aimed to explore the potential association between visa-type and treatment completion was addressed using bivariate analysis. Latent tuberculosis infection treatment completion was the dependent variable and visa-type was the independent variable. Treatment completion rates for visa holders were tested using pairwise comparisons so the impact visa-type may have could be assessed. Normality of the research population was initially assessed using histogram distribution and analyzing skewness and kurtosis. The Shapiro-Wilk Test of Normality was used as the numerical means to assess normality as this statistical test can handle small sample sizes or sample sizes up to 2,000 (Field, 2013). Additionally, this was an appropriate technique for the Chi-square analysis associated with research question one

since non-parametric (e.g. Kaplan-Meier) and semi-parametric (e.g. Cox Proportional Hazard) statistical techniques do not make assumptions regarding normality (Mills, 2011). Calculated Shapiro-Wilk values greater than 0.05 were indicative of normality in this research (Field, 2013). Assuming normal distribution of the samples by visa-type, Chi-square test were used to assess relationship between the categorical treatment completion variable and each level of visa-type. A calculated *p*-value was used to interpret the Chi-square test result against the first hypothesis. Post hoc chi-square pairwise comparison with Bonferroni corrections was planned for statistical differences to identify which groups differed specifically (McDonald, 2015). Since performing three pairwise comparisons would mean there would be a 14% chance of making a type I error ($1-(0.95)^3$), adjusted standardized residuals were planned to produce *z*-scores (McDonald, 2015). The produced *z*-scores were to be converted to chi-square test statistics and then to *p*-values if statistically significant findings were identified. For this research question, the number of chi-square analyses performed was equal to three, resulting in a Bonferroni of 0.0167. Values less than 0.0167 were to be deemed significant. If the distribution was not normal or if a Chi-square cell is less than five, Fisher's exact test was an alternative approach used (McDonald, 2015).

Nonparametric methods. Research question two, which aimed to determine if visa type was associated with time on treatment, was assessed using the non-parametric Kaplan-Meier (KM) statistical approach. This approach was identified a priori to be the best technique for determining the probability research participants will not experience the event (e.g. treatment noncompletion) at time *t*. This technique demonstrated if

specific visa-types experienced greater LTBI treatment survivorship (Mills, 2011). This approach allowed censoring to be considered, unlike other statistical techniques (e.g. regression) (Mills, 2011).

Kaplan-Meier. In the EDN dataset, the number of months on treatment was calculated for each eligible participant using treatment initiation indicators and treatment completion/disposition indicators. Treatment completion was the censoring variable of concern and the *x*-axis for the KM plot, representing the observation period, spanned nine months. Additionally, the KM technique was appropriate for handling a sample that was small (Mills, 2011). The KM analysis allowed for the counting of visa holders in Idaho that remain at risk of treatment noncompletion prior to a specified time (e.g. an acceptable end of treatment) (Mills, 2011). This allowed the survival probability, in terms for treatment completion for this dissertation research, to be estimated (Mills, 2011). This analysis was also critical to determining the mean time LTBI treatment initiators remain on therapy.

The KM analysis was performed to compare the visa categories described previously simultaneously after assessing all KM assumptions were met. The KM method requires six assumptions be met for results to be valid: 1) the event status should include two mutually exclusive and exhaustive states, 2) time to event should be clearly defined, 3) left censoring should be minimized, 4) independence should exist between the event and censoring, 5) there should be no secular changes, and 6) a similar amount of censorship should occur in each group (Mills, 2011). Additionally, since multiple treatment regimens are appropriate for LTBI and no single regimen is preferred or

superior, visa holders were grouped by prescribed treatment regimen for separate KM analyses. Four regimens were consistently prescribed in Idaho: six months of INH, nine months of INH, four months of RIF, or 12 weeks for INH/RPT. The KM plots were used to visualize the survival distribution and demonstrated a difference in survivorship (treatment noncompletion) in the analyzed groups when one function ran below another (Mills, 2011). The calculated KM estimator was used to estimate the survival probability, or the likelihood of not experiencing the event at time *t*, for each visa-type group (Mills, 2011). The median survival time was also produced when calculating the KM estimator and was compared for the visa-type groups to assess central tendency (Mills, 2011). Lastly, the log-rank test was used to determine whether there was a statistically significant difference between the three survival curves. The log-rank statistic, sampling variances, and covariances were used to produce the chi-square statistic with a *p*-value less than 0.05 representing a difference in survival (Mills, 2011).

Cox Proportional Hazards Regression. This research hypothesized covariates influence the rate of LTBI treatment completion in Idaho visa holders making Cox Proportional Hazards (CPH) appropriate as a mechanism of statistical analysis to assess this hypothesis. Additionally, since many of the covariates in this research remained fixed over time the use of CPH for time-fixed variables was further supported (Mills, 2011). Cox proportional hazard is also useful when the baseline hazard for a phenomenon is unknown (Mills, 2011) as was the case in the rural setting for this LTBI treatment completion research. Since extrapolating a baseline hazard from research conducted on samples drawn from the high-incidence or urban setting may be flawed, the CPH analysis

planned was appropriate. Additionally, CPH generally fits data well which is advantageous when the shape of the probability distribution is unknown (Mills, 2011), as was the case in this dissertation research.

For this research, LTBI treatment initiation were defined as picking up the first months' supply of medication from the managing clinic while completion was defined as having documented pickup for at least 90% of refills as appropriate for the prescribed regimen. In Idaho, these dates are recorded on the EDN TB Follow-up Worksheet as "Treatment start date" and "Treatment end date", respectively. In the event a visa-holder is lost to follow-up during treatment, discharge diagnoses reflect this and the last known date of medication adherence was recorded as "Treatment end date". A participant was determined to not have completed LTBI treatment completion if treatment was terminated earlier than acceptable for their prescribed regimen. In some instances, receiving at least 90% of the prescribed doses constitutes treatment completion. These scenarios were apparent when examining discharge diagnoses for persons that had shorter durations of treatment than planned during their initial regimen documentation.

For this survival analysis, treatment completion status was the censor indicator and month on treatment was the time variable. Prior to conducting CPH analysis, meeting the assumption of proportional hazards was assessed using graphical methods (Mills, 2011). Since none of the covariates were time-dependent, no statistical analysis, such as scaled Schoenfeld residuals, were performed to assess the assumption of proportional hazards was met (Mills, 2011). Graphically, parallelism of the curves was assessed for fit of the proportional hazards assumption (Mills, 2011).

Since this research hypothesizes that host, agent, or environment-related factors influence LTBI treatment completion, multiple covariates were incorporated into the CPH analysis. This includes sex, age group, country of origin, visa-type, smoking status, distance between residence and treating facility, area of resettlement, time between arriving in Idaho and the time of initial clinical evaluation for LTBI, and TST positivity or IGRA positivity. The CPH formula for fixed covariates used in this research was $h_i(t) = h_0(t)\{exp(\beta_1 x_{il} + \ldots + \beta_k x_{ik})\}$ with x representing a covariate (Mills, 2011). Each covariate was added into the model for analysis against the event. To be included in the model, covariates needed to pass the proportionality of hazards assumption (Mills, 2011).

The results of the CPH models included hazard ratios (HRs), the 95% confidence interval, and the Wald test p-values (Mills, 2011). The hazard ratio is often reported in statistical output as the exponential coefficient and if greater than one, indicated the analyzed covariate was associated with an increased hazard of experiencing the event of interest (Mills, 2011). The likelihood-ratio test was used to determine significance at $p<0.05$.

Additional Exploratory Analysis

An additional goal of this research was to determine if the prescribed LTBI treatment regimen also influenced completion by visa-type. Since it was suspected that the independent variables, in this case six or nine months of INH, or four months of RIF, or 12 weeks of INH and RPT, effect the treatment completion dependent variable, Cox Proportional Hazard Regression was used to suggest which of the independent variables had a major effect on time until LTBI treatment completion. To explore this additional

phenomenon, it was assumed that each observation was independent (Field, 2013). The produced *p*-value was used to determine significance at $p < 0.05$. Cox Proportional Hazard Regression was also used to assess whether prescribing provider influenced LTBI treatment completion. For this additional analysis, LTBI treatment completion remained the dependent variable, while prescribing provider became the independent variable. Again, it was assumed that each observation was independent and significance was determined if $p < 0.05$.

Threats to Validity

Threats to External Validity

The dataset used for this dissertation research was dependent upon health care provider interpretation of diagnostic, radiologic, and risk-factor evaluations on visa holders intending to migrate to the United States. Since tools used to diagnose latent tuberculosis infection only detect the presence of an immune response to *Mycobacterium tuberculosis* (Ling Lin & Flynn, 2010), differences in diagnosis patterns may exist. In the EDN system, this is potentially mitigated by post-arrival health care medical evaluations following review of visa-holder's predeparture medical evaluation as prearrival LTBI diagnoses may be validated. An additional threat to external validity was related to the relatively new application of IGRAs. Historically, the TST was the only tool available to help determine *Mtb* exposure however false positives are common among those vaccinated with bacille Calmette-Guerin (BCG) (Chee, Sester, Zhang, & Lange, 2013). As such, visa holders evaluated toward the beginning of the study period with a TST only may have been misdiagnosed.

Threats to Internal Validity

The conclusions drawn in this research may be threatened by inconsistencies in the implementation of LTBI treatment recommendations across jurisdictions in Idaho. Additionally, although completing at least 90% of prescribed doses of LTBI treatment may be deemed successful completion, health care provider discretion may also be used to determine treatment completion potentially impacting this research by producing variance in discharge diagnoses. Other unmeasured factors may also influence treatment completion in the study population and will likely not be captured directly by this research. For example, persons with known direct contact to someone with tuberculosis may be more likely to accept and complete treatment due to their experiences (Priest, Vossel, Shefy, Hoy, & Haley, 2004). Also, persons under the age of 18, the legal age in Idaho to make independent medical decisions, may be forced to complete treatment by their parents or guardians which may mask true effects of age on completion. Lastly, familial support and other household factors may too influence LTBI treatment completion as persons with greater support have been shown to complete treatment at higher rates (Priest, Vossel, Shefy, Hoy, & Haley, 2004) however, these potential data points are not collected in the EDN system.

The internal validity of this research may also be influenced by the secondary nature of the data being analyzed. The data in this study was collected for a different purpose and only the previously collected data will be available for analysis. Although the Idaho state TB Program does perform data quality checks at the time of data entry, for

the purposes of this research, the data cannot be validated nor can additional follow-up information be collected.

To detect a true effect and avoid low statistical power, using a large enough sample for this research was essential (Ellis, 2015). The sample size estimates discussed previously are the smallest possible recommended for analysis which, if larger, the sample should have produced sufficient effects and avoided problems with low statistical power.

Since no gold standard exists for the diagnosis and treatment of LTBI (LoBue & Castro, 2012), variations in who got tested, who got diagnosed, and who was recommended for treatment may have influenced this research. It was assumed that those visa holders initiating LTBI treatment in Idaho were truly infected with *Mtb* and were receiving treatment appropriately. Routine dataset cleanup may help ensure this was accurate. Overseas medical screening results were influential in the determination of whether a visa-holder was assigned a B TB Notification (Lee et al., 2013). Occasionally, foreign-born persons with LTBI enter Idaho without a B TB Notification but EDN allows for these records to be included in data export. To ensure persons without B TB Notifications but who are identified as having LTBI after arrival in Idaho, the EDN discharge diagnosis variable was reviewed for all visa holders that entered Idaho during the timeframe of interest. This approach helped ensure that visa holders arriving with a B TB Notification but determined to not be infected upon arrival in Idaho were excluded from the dataset. This would have left only those visa holders appropriately recommended LTBI treatment in the dataset.

Missing data and selection bias was addressed in the data cleanup process. Visa-holder records missing any of the identified necessary variables for analysis were to be excluded from this research however, this was not necessary due to high variable percent completion. True infection status was verified by reviewing EDN records and post-arrival TB Follow-up Worksheets for each visa-holder included in the study sample to ensure each was appropriate for inclusion.

Retrospective cohort studies inherently have threats to internal validity. This study design lacks a comparison or control group, includes subjects that may mature overtime influencing analyzed variables and participant outcomes, and may suffer from high rates of attrition (Gordis, 2008). Although no control group was used in this research, comparisons were made between visa-types, prescribed LTBI treatment regimens, and area of residence potentially assisting in overcoming this limitation. Maturation was also likely not an issue in this research due to the relatively small window of time each person had to experience the event. With the longest available LTBI treatment duration spanning nine months, it was anticipated that participant characteristics did not change greatly during this time in such a way that influenced the outcome. Lastly, high rates of attrition may have occurred in this research however, would help demonstrate why this research was necessary. High rates of LTBI treatment noncompletion may indicate that a large reserve of persons latently infected with *Mtb* remain at risk of developing active TB and possibly transmitting disease to others. A large number of visa holders initiating treatment with a subsequently large number

dropping out may assist in demonstrating that greater attention needs to be paid to ensuring these individuals complete treatment.

Ethical Considerations

Information and data related to this research was not requested until after Walden University IRB and IDHW Division of Public Health approval was sought and obtained. Despite the requested dataset being de-identified, its original proximity to health information protected under the Health Information Portability and Accountability Act (HIPAA) heightened measures to protect the data. Although the EDN database in which the research dataset was derived contained Protected Health Information, Idaho state TB Program staff were asked to remove potentially identifiable information from the research dataset. This approach ensured research participants were not identifiable from the research data file. All data collected for this research were stored in an electronic manner that required security-only access such as a password to the storage device and data file.

Beyond the small possibility of a data breach, participation in this research came with no known risk. A data breach would likely only take place if the de-identified dataset associated with this research was linked back to the original EDN data source from which dataset producing reports were run. Although the EDN platform is accessed through secure networks and this dataset was stored on a separate encrypted, backed-up secure laptop, in the event of a data breach, all participants included in the dataset were to be notified and contact procedures carried out to the full extent possible as defined by the policies and procedures of Walden University and the IDHW. No breaches were

identified, however. To add greater security, the research dataset was only accessible to the dissertation research principal investigator and the dissertation research committee, if needed, and passwords to the laptop and the Excel file were not shared with others nor were the passwords the same to access the laptop or file.

Summary

This dissertation study made the same assumptions of those consistent with performing time to event analysis. It was also assumed that the foreign-born arriving in Idaho under permanent visas were representative of the true population infected with *Mtb* since surveillance data suggests that more than 60% of the TB cases in Idaho are foreign-born (IDHW, 2016). This study was limited in terms of design and data specificity. The retrospective nature of this study involved no control group for comparison. Data related to treatment initiation and completion were recorded in month, day, and year format however, persons initiating LTBI treatment in this sample were likely only monitored for treatment adherence monthly. This approach limited the time to event analysis units of measurement to months instead of the more ideal unit in days or weeks. Regardless, findings from this study may inform Idaho public health officials of the potential LTBI treatment noncompletion predictors which may promote intervention development to improve rates and decrease future active disease burden.

The aim of this study, the design, and data analysis was to describe the epidemiology of LTBI treatment completion in the visa-holding population residing in Idaho. By determining if low treatment completion rates can be improved in selected persons through public health intervention, the Idaho TB Program may more

appropriately deploy limited resources that promote the greatest impact. Identifying the factors associated with LTBI treatment noncompletion may better position the program to respond to the threat of untreated LTBI in the face of further declining TB resources, ultimately improving the population's health and prompting social change. The results of this research, the management of the database received from the Idaho state TB Program, and the analysis are presented in Chapter 4 and discussed in further detail in Chapter 5.

Chapter 4: Results

Introduction

In this chapter I discuss the results of the analysis of this retrospective cohort exploring LTBI treatment completion rates in permanent visa holders residing in Idaho as well as the potential factors that may contribute to mean time on treatment. I obtained the data used in the analysis from the Idaho State Tuberculosis Program. Data downloaded from the Idaho jurisdiction on the CDC's EDN platform consisted of a combination of overseas medical evaluation data, postarrival TB evaluation medical data, and demographic information reported to the Idaho State TB Program by permanent visa-holder evaluating agencies voluntarily or through contractual obligation. Six of the seven agencies providing data were located in the public sector while the seventh agency, a Federally qualified health center, functioned on behalf of a public agency previously responsible for collecting some of the data used in this analysis.

This study received Walden IRB approval under approval number 01-09-18-0538791. The IDHW's Division of Public Health IRB waived their requirement for IRB submission after proof of Walden's IRB approval was submitted to the agency's Research Determination Committee. Software used for analysis was SPSS version 24 (IBM, 2016). Differences in observed treatment completion rate by visa type were evaluated using Pearson's chi-square test to determine if a variance occurred by chance. I assessed the association between the mean time on treatment and independent variables using Kaplan-Meier and Cox Proportional Hazard Regression. I selected independent variables based off availability of data but also from a previously conducted literature

review that highlighted relationships in the nonrural setting. This chapter includes the results of detailed statistical analysis that addresses LTBI treatment completion trends and possible contributing factors to noncompletion in permanent visa holders arriving in the rural State of Idaho from 2012 through 2016 using univariate and multivariate statistical techniques.

Research Questions and Hypotheses

Research questions under study focused on the association between visa type and LTBI treatment outcome as well as the potential contributing factors to LTBI treatment noncompletion. Via the analyses determined during study design I aimed to explore LTBI treatment completion rates in permanent visa holders, typical duration on treatment, and variables important to LTBI treatment noncompletion. Throughout this chapter, the results of data analysis for each specific research question are discussed.

RQ1: Is visa type (refugee, immigrant, parolee, asylee, or fiancé) associated with LTBI treatment completion among permanent visa holders initiating treatment in Idaho?

$H_0$1: There is no association between visa type and LTBI treatment completion among permanent visa holders initiating LTBI treatment in Idaho.

H_a1: There is an association between visa type and LTBI treatment completion among permanent visa holders initiating LTBI treatment in Idaho.

RQ2: Is the mean time distribution to last treatment for LTBI between permanent visa holders initiating LTBI treatment in Idaho significantly different?

$H_0$2: The mean time distribution to last treatment for LTBI between permanent visa holders initiating treatment in Idaho is not statistically difference.

H_a2: The mean time distribution to last treatment for LTBI between permanent visa holders initiating treatment in Idaho is statistically different.

RQ3: Is time on LTBI treatment in permanent visa holders initiating treatment in Idaho affected by sex, age, country of origin, visa type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity?

$H_0$3: Time on LTBI treatment in permanent visa holders initiating treatment in Idaho is not affected by sex, age, country of origin, visa type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity.

H_a3: Time on LTBI treatment in permanent visa holders initiating treatment in Idaho is affected by sex, age, country of origin, visa type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity.

Data Cleaning

The dataset required minimal cleaning as routine data quality checks performed by the Idaho TB Program ensured accuracy and a high percentage of variable completion.

Coding of variables was required for text fields including visa type, birth country, and treatment regimen as described in Chapter 3. I collapsed age into three categories and calculated time between medical evaluation and original date of arrival using Excel formulas to quantify the number of days between these aforementioned points in time. I created and populated area of resettlement using Idaho zip codes, also as outlined in Chapter 3. I kept all other variables either in their original EDN coding form or TB Program coding form. I ran frequencies for missing values for all study variables yielding 100% completion for all data elements.

Study Sample

Between January 1, 2012 and December 31, 2016, 5,042 permanent visa holders arrived in Idaho. Only a subset of 455 (9%) arrivals required evaluation for tuberculosis after reaching Idaho. Over 81% (370) of those requiring postarrival medical evaluation completed a full evaluation, whilst nine (2%) initiated but failed to complete, and 76 (17%) did not initiate evaluation. Of those fully medically evaluated, 163 (44%) were recommended treatment, with six being excluded after receiving a diagnosis of active TB disease. Of the remaining 157 recommended for LTBI treatment, 140 (89%) initiated treatment and were included in this study (Figure 2).

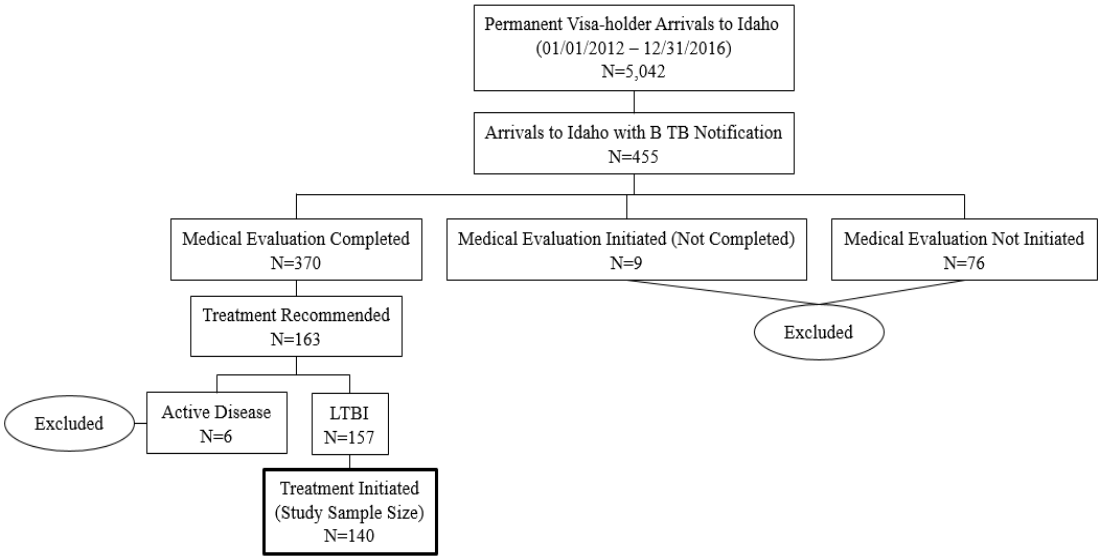

Figure 2. Count of permanent visa-holder arrivals, medical evaluation, and treatment statuses.

The final dataset obtained from the Idaho State TB Program included no missing values due to existing data quality practices at the time of medical evaluation record submission. For records submitted on arrivals relocating to Idaho from 2012 through 2016, none were removed due to incomplete variables. Annually and on average, the State of Idaho resettles 1,008 permanent visa holders, with 91 each year requiring medical evaluation for tuberculosis. The 9% of arrivals from 2012-2016 included in this study was consistent with the rate of arrivals requiring TB evaluation annually and thus, this study population was likely representative of the Idaho permanent visa-holding population.

Permanent visa holders included in this study held only refugee and immigrant visas. Although persons holding asylee, parolee, and fiancé visas arrived in Idaho during the study, none met the study inclusion criteria and were excluded. No arrivals resettling in North Central Health District were eligible for inclusion, thus this jurisdiction is not

represented in the study. All remaining six Idaho public health jurisdictions were represented, however. The excluded jurisdiction receives very few foreign-born arrivals annually under normal circumstances.

Power Analysis

Prior to conducting the analysis necessary to explore the study research questions, I performed a power analysis using G*Power (Faul, 2014). The lack of asylee, fiancé, and parolee visas in this analysis changed previously calculated degrees of freedom from two to one. After making this adjustment and conducting post-hoc power analysis, the analyzed data from the unique 140 participants had 80% power to detect a 23.6% difference in treatment completion between the groups at 0.05 significance. Although a more robust sample would have improved power, considering the makeup of Idaho's foreign-born population, the study sample should have been representative of the broader, foreign-born, EDN TB notification audience and should have detected important differences.

Descriptive Epidemiology

Among 140 participants, 109 were refugees and 31 were immigrants. As shown in Figure 3, 88 (80.7%) refugees and 23 (74.2%) immigrants completed LTBI treatment.

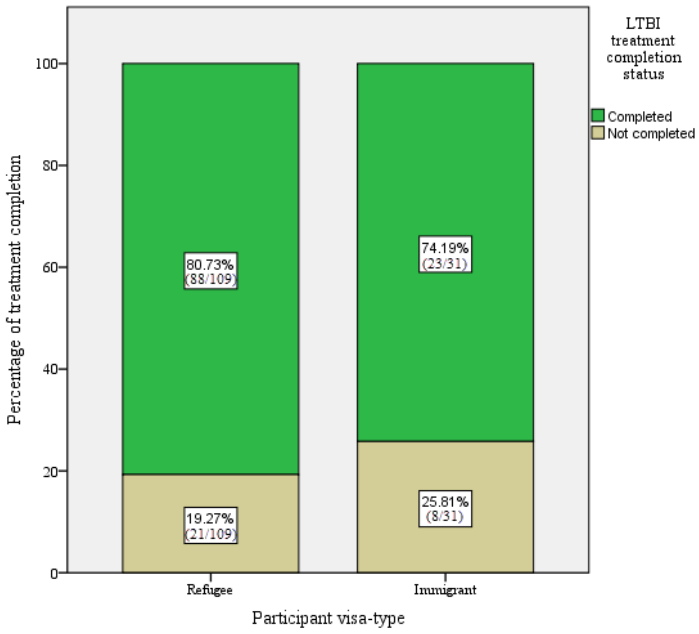

Figure 3. Study participants by visa-type and treatment completion status.

Demographics and characteristics of study subjects are presented in Table 8. I performed a chi-square test for independence to evaluate if the variables included were related or whether their distributions differed. I found no observed distributions to be statistically significant suggesting the variables were not highly related. However, I found notable differences between the participant visa types included in the study. Sixty one percent (61%) of refugee study participants were male compared to only 41% of immigrants. The study included more refugees in the 45 years of age and older (45+) group compared to the other age categories, while more immigrants were found to be in the zero to 24 years age group. The median age for refugee treatment completers was just slightly older than immigrants at 27.5 years of age and 28.0 years of age, respectively. For noncompleters, a wider age difference was noted between the two visa-types with the median age of refugee noncompleters being 38.0 years and immigrant noncompleters 26.0 years. More of the refugees included in the study originated from Southeast Asia

(41%) compared to other WHO regions, while 45% of immigrants originated in the Americas WHO Region. Denying current or former tobacco use was consistent across both visa types and LTBI treatment completion statuses.

Table 8.

Demographic and characteristics of study subjects

	Refugee					Immigrant				
	Complete N=88		Incomplete N=21			Complete N=23		Incomplete N=8		
Covariate	*n*	%	*n*	%	*p*[a]	*n*	%	*n*	%	*p*[a]
Sex					0.72					0.77
M	54	61.36	12	57.14		10	43.48	3	37.50	
F	34	38.64	9	42.86		13	56.52	5	62.50	
Age (median in years)	27.5		38.0		0.10	28.0		26.0		0.05
0-24	29	32.95	2	9.52		16	69.57	4	50.00	
25-44	22	25.00	7	33.33		1	4.35	3	37.50	
45+	37	42.05	12	57.14		6	26.09	1	12.50	
Birth Country					0.88					0.42
Americas	0	0.00	0	0.00		10	43.48	4	50.00	
Europe or EM*	20	22.73	4	19.05		0	0.00	1	12.50	
Africa	30	34.09	8	38.10		2	8.70	1	12.50	
SEA	36	40.91	9	42.86		1	4.35	0	0.00	
WP	2	2.27	0	0.00		10	43.48	2	25.00	
Tobacco use					0.11					0.28
Never	75	85.23	16	76.19		20	86.96	8	100.0 0	
C or F	13	14.77	5	23.81		3	13.04	0	0.00	
Distance to treatment facility (median in miles)	3.1		3.1		0.62	5.9		3.1		0.82
0-10.9	18	20.45	2	9.52		0	0.00	0	0.00	
11-20.9	69	78.41	19	90.48		13	56.52	5	62.50	
21+	1	1.14	0	0.00		10	43.48	3	37.50	
Resettlement Area		100.0		100.0	--					0.94
Urban	88	0	21	0		14	60.87	5	62.50	
Rural	0	0.00	0	0.00		9	39.13	3	37.50	
Time between arrival and evaluation (median in days)	20.5		21.0		0.56	21.0		22.0		0.77
<30	69	78.41	18	85.71		7	30.43	3	37.50	
30-59	15	17.05	3	14.29		9	39.13	2	25.00	
60+	4	4.55	0	0.00		7	30.43	3	37.50	
TST result					0.25					0.23
Positive	36	40.91	12	57.14		13	56.52	4	50.00	
Negative	6	6.82	0	0.00		0	0.00	1	12.50	
Not done	46	52.27	9	42.86		10	43.48	3	37.50	

(*table continues*)

	Refugee					Immigrant				
	Complete N=88		Incomplete N=21			Complete N=23		Incomplete N=8		
Covariate	*n*	%	*n*	%	*p*[a]	*n*	%	*n*	%	*p*[a]
IGRA result					0.76					0.95
Positive	16	18.18	5	23.81		6	26.09	2	25.00	
Negative	1	1.14	0	0.00		0	0.00	0	0.00	
Not done	71	80.68	16	76.19		17	73.91	6	75.00	

Note. [a]chi-square test of independence (χ^2);.*Abbreviations: EM=Eastern Mediterranean, SEA=South-East Asia, WP=Western Pacific; C=Current smoker, F=Former smoker.

Study participants with a refugee visa had a lesser distance between their residence and LTBI treatment facility compared to immigrants. For refugee treatment completers and non-completers, the mean distance to travel in miles was 3.1 whilst immigrant treatment completers traveled 5.9 miles to their treatment facility. The time between arrival and medical evaluation was also different across visa-type and treatment completion status. Over three quarters of refugees completing treatment received medical evaluation within 30 days after arrival, while only just over a third of immigrant treatment completers did. For treatment non-completers, 85.7% of those holding refugee visas were still evaluated within 30 days after arrival but nearly two thirds of immigrants were evaluated more than 30 days after arrival. The median days between arrival and medical evaluation for refugee treatment completers and non-completers, and immigrant treatment completers and non-completers varied minimally at 20.5 days, 21.0 days, 21.0 days, and 22.0 days, respectively.

Tuberculosis medical evaluation. All 140 study participants received evaluation for LTBI and TB both prior to departure and after arrival. Due to potential variations in the overseas screening process, postarrival medical TB screening findings are described. Administration of TST or IGRA varied with 72 (51.4%) study participants and 30 (21.4%) study participants having a TST placed or an IGRA drawn, respectively (Table

8). For refugees and immigrants where a TST was placed and treatment was not completed, the rate of positivity was higher in refugees and immigrants (57.1%, 50.0%). For IGRAs in participants not completing treatment, immigrants had a higher rate of positivity at 25.0% compared to the refugee positivity rate of 23.8%. A large number of study participants did not have a TST or IGRA performed.

LTBI treatment regimen trends and completion. Four LTBI regimens were prescribed throughout the study period to treat infection with *Mycobacterium tuberculosis* (Table 9). Due to the small number of participants prescribed 3HP and 4RIF, these regimens were combined into one "Expedited" regimen category for chi-square analysis but remained as separate regimens for survival analysis. This approach was taken due to the difference in treatment duration between the two regimens which, if left combined, would not produce accurate survival analysis results. Overall, more than 66% of LTBI treatment initiators were prescribed nine months of INH. It is important to note that 3HP became a recommend treatment for LTBI near the beginning of the study period potentially impacting the early lower rate of use observed. Visa-type-based differences in the LTBI regimen used were also observed in this study. No immigrants included in this study were prescribed 3HP and only one was prescribed four months of RIF. Typically, immigrants were prescribed INH regimens. Over 90% of immigrants were prescribed nine months of INH, compared to 59% of refugees.

Table 9.

LTBI Treatment Regimen Trends by Visa-type and Completion Status

		Refugee					Immigrant				
		Complete N=88		Incomplete N=21			Complete N=23		Incomplete N=8		
		n	%	*n*	%	*p*[a]	*n*	%	*n*	%	*p*[a]
Prescribed						0.23					0.56
LTBI	Expedited	32	36.36%	4	19.05%		1	4.35%	0	0.00%	
treatment	6INH	7	7.95%	1	4.76%		2	8.70%	0	0.00%	
regimen	9INH	49	55.68%	16	76.19%		20	86.96%	8	100.00%	

Note. [a]Fisher's exact test; Expedited: 12 weeks of Rifapentine/Isoniazid (3HP) or 4 months of rifampin (RIF); 6INH: 6 months of isoniazid; INH: 9 months of isoniazid.

Null Hypothesis 1: Visa Type Is Not Associated with Latent Tuberculosis Infection Treatment Completion

Chi-Square Assumptions

The purpose of this hypothesis was to answer the research question whether LTBI treatment completion status was influenced by visa-type of study participant. Given both the dependent variable of treatment completion status and independent variable of visa-type were categorical, the Pearson's chi-square test was used to test this hypothesis. Overall, 79.3% of LTBI treatment initiators completed therapy. Refugees completed LTBI treatment at a slightly higher rate than their immigrant counterparts, 80.7% versus 74.2% respectively. However their difference is not statistically significant ($\chi^2 = 0.63$, $p = 0.43$) (Table 10).

Table 10.

Pearson Chi-square Analysis of Visa-type and LTBI Treatment Completion Status

			Treatment completion			
			Yes	No	χ^2	p^a
					0.63	0.43
Visa	Refugee	*n*	88	21		
		% within Visa	80.7%	19.3%		
	Immigrant	*n*	23	8		
		% within Visa	74.2%	25.8%		

Note. [a]chi-square test.

The categorical variables visa-type and treatment completion status included cell frequencies greater than five and the two variables were independent of one another, making the use of chi-square valid. Additionally, no extreme values were identified, there were no overlaps in variables, data discrimination was not an issue, data were not analyzed after sorting, and the data were not structured in a manner that allowed for many processes to approach the natural limit (Buthman, 2018).

Null Hypothesis 2: Mean Time Distribution to Last Treatment Is Not Different by Visa Type

The purpose of this hypothesis was to determine if the mean time distribution to last LTBI treatment was different by visa-type. Kaplan-Meier (KM) survival analysis was used to assess this relationship. All six KM assumptions described in chapter 3 were satisfied supporting the use of KM survival analysis.

As shown in Table 11, the mean time that refugees remained on LTBI treatment during the study was 7.85 months compared to the mean time of 7.51 months for immigrants. However, the difference in mean treatment duration is not statistically significant (*p*-value from Log Rank was 0.74). The null hypothesis that no difference in

mean time on LTBI treatment between two types of visa holders was not rejected suggesting the mean times on treatment were similar.

Table 11.

Kaplan-Meier Time on Treatment by Visa-type

Visa	Mean time on treatment (months)	Std. Error	95% Confidence interval		*p*[a]
			Lower bound	Upper bound	0.74
Refugee	7.85	0.24	7.39	8.31	
Immigrant	7.51	0.49	6.56	8.46	

Note. [a]Log Rank (Mantel-Cox).

However, the survival curves show some separation between the two groups early in the months on treatment, particularly around months 2 through 4 (Figure 4). The rate of cumulative survival for immigrants dropped earlier compared to refugees. This suggests that non-completers in immigrants would stop the treatment sooner than their refugee counterparts. This is reflected in the survival tables (data not shown) for the cumulative probability of survival at time *t* with immigrants having a cumulative survival at month six of 0.74 and refugees, 0.82. As more time passed during the study, the difference between the probabilities of cumulative survival of the two visa groups began to narrow suggesting the number of treatment non-completion events were similar at this stage. The final cumulative survival probabilities for refugees was 0.75 and 0.74 for immigrants.

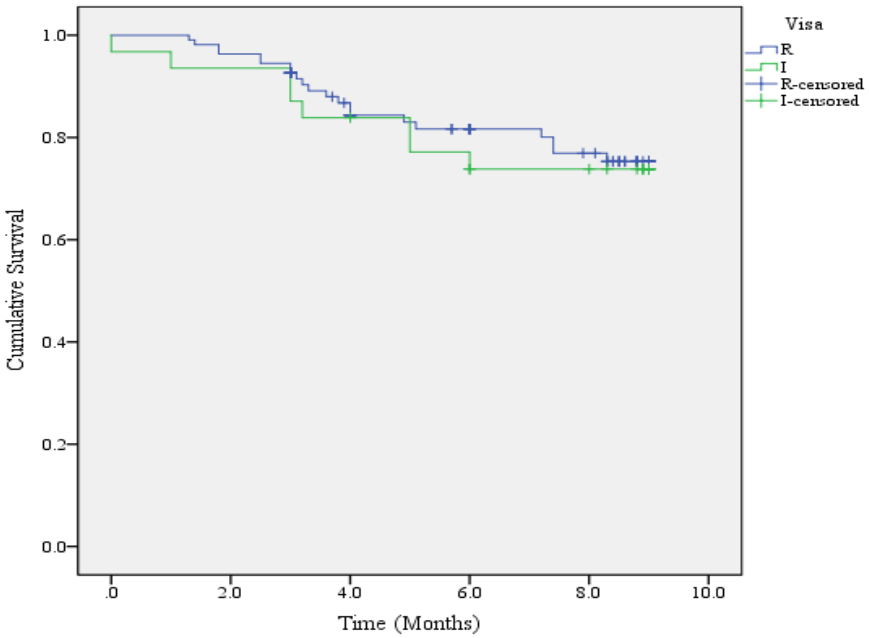

Figure 4. Cumulative Survival Curve for Refugee and Immigrant Study Participants.

Null Hypotheses 3: Time on Latent Tuberculosis Infection Treatment Is Not Affected by Covariates

Cox Proportional Hazard Regression Assumptions

The purpose of this hypothesis was to address whether potential covariates influenced the mean time on LTBI treatment until noncompletion of visa holders in the rural Idaho setting. To evaluate this question, Cox Proportional Hazard Regression was used to compare the estimated mean time on treatment in study participants after adjusting for sex, age, birth country, visa-type, history of tobacco use, distance between residence and LTBI treatment facility, area of resettlement, time between arrival and medical evaluation for LTBI or TB, TST positivity, or IGRA positivity. Subjects who had completed LTBI treatment were censored at the last dose date as determined by Idaho public health nurses. Cox Proportional Hazard Regression (CPHR) assumption of

independent observations was satisfied using goodness-of-fit test performed on each covariate explored as a potential predictor of mean time on treatment and thus influencer of treatment completion (Table 12).

Table 12.

Test of Proportional Hazard Assumption for Covariates

Variable	chi2	df	*p*-value
Sex	0.33	1	0.57
Age (years)	4.55	2	0.16
Birth Country	5.02	5	0.42
Visa-type	0.69	1	0.43
History of tobacco use	0.61	2	0.67
Distance to treatment facility (miles)	0.31	2	0.89
Area of resettlement[a]	0.70	1	0.70
Time between arrival and evaluation	0.27	2	0.73
TST result	1.17	2	0.323
IGRA result	0.50	2	0.67

Note. [a]No refugees resettled in the rural setting so pooled analysis unavailable.

The assumption of a constant hazard over time was upheld by producing the log-log plots found in Appendix D. Time-dependent Cox regression was not performed for this analysis as no variables were time-dependent.

Normal CPHR was performed to test covariates against LTBI treatment completion status using 140 study participants. The CPHR analysis examined LTBI treatment completion status as the survival endpoint. Survival curves for categorical variables of more than two levels were generated for visual interpretation (Appendix E). Hazard ratios were calculated to assess if participants experienced LTBI treatment noncompletion over time while considering the included independent variables. *P*-values and 95% confidence intervals were also calculated and interpreted to determine statistical

significance of analysis. In situations where the categorical variable had greater than two levels, the reference group was set as the last strata of the categorical variable being assessed. The reference groups by categorical variable strata can be found in Appendix F.

Findings

The null hypothesis that covariates do not influence LTBI treatment completion was not rejected as the model overall was not statistically significant ($p = 0.64$). However, when examining covariate strata impact on time until treatment noncompletion, age subcategory for those zero to 24 years ($HR = 0.18$, $p = 0.01$) had a statistically significant relationship with LTBI treatment noncompletion status (Table 13). Study participants less than 25 years old experienced LTBI treatment noncompletion less frequently compared to the reference study participants who were 45 years of age and older. Under one fifth of study participants less than 25 years of age experienced LTBI treatment noncompletion compared to the older reference group. Alternatively stated, being less than 25 years reduced the risk of LTBI treatment noncompletion by 82% compared to study participants who were 45 years of age and older based on the observed survival hazard ratio of 0.18. This also suggests study participants in this age group had a greater mean time on LTBI treatment compared to other study participants.

Table 13.

Covariates Associated with Time until LTBI Treatment Noncompletion in Cox Model

Variable(s)	*HR*	*SE*	*p*-value	95% CI Lower	95% CI Upper
Sex)					
Male	0.99	0.42	0.99	0.44	2.27
Female (RG)	-	-	-	-	-
Age‡					
Age (1: 0-24 years)‡	0.18	0.69	0.01	0.05	0.68
Age (2: 25-44 years)	0.96	0.48	0.93	0.37	2.46
Age (3: 45+ years) (RG)	-	-	-	-	-
Birth Country					
Birth Country (1: Americas)	4.07	1.01	0.17	0.56	29.57
Birth Country (2: Europe or Eastern Mediterranean)	2.24	1.09	0.46	0.27	18.88
Birth Country (3: Africa)	2.85	1.11	0.35	0.32	25.18
Birth Country (4: South-East Asia)	1.30	1.15	0.82	0.14	12.53
Birth Country (5: Western Pacific) (RG)	-	-	-	-	-
Visa					
Refugee	0.50	0.78	0.38	0.11	2.32
Immigrant (RG)	-	-	-	-	-
Time to Evaluation					
Time to Evaluation (0: <30 days)	0.34	0.89	0.22	0.06	1.94
Time to Evaluation (2:30-59 days)	0.36	0.92	0.27	0.06	2.18
Time to Evaluation (3: 60+ Days) (RG)	-	-	-	-	-
Area of Resettle					
Urban (1)	0.00	137.21	0.95	0.00	5.32E+112
Rural (2) (RG)	-	-	-	-	-
Distance to Treatment Facility					
Distance to Treatment Facility (1:0-10.9 miles)	21,853.49	137.21	0.94	0.00	1.36E+121
Distance to Treatment Facility (2: 11-20.9 miles)	0.00	184.87	0.96	0.00	1.11E+153
Distance to Treatment Facility (3: 21+ miles) (RG)	-	-	-	-	-
History of Tobacco Use					
Yes (1: Current or former)	1.07	0.57	0.91	0.35	3.24
No (2: Never) (RG)	-	-	-	-	-
TST Result					
Positive (0)	2.03	0.53	0.19	0.71	5.78
Negative or Not Done (1) (RG)	-	-	-	-	-
IGRA Result					
Positive (0)	1.60	0.54	0.38	0.56	4.57
Negative or Not Done (1) (RG)	-	-	-	-	-

Note. Abbreviations: *HR* = Hazard Rate, *SE* = Standard Error; RG = reference group. ‡denotes statistically significant at $p<0.05$.

The hazard for treatment noncompletion in study participants 25 to 44 years was similar to those 45 years and older. For male study participants, the hazard of noncompletion was comparable to females but those study participants hailing from the

America WHO Region had an increased hazard of noncompletion versus those from the Western Pacific WHO Region. Refugee study participants as well as those being medically evaluated less than 30 and less than 60 days after arrival had decreased hazards compared to immigrants or those medically evaluated more than 60 days after arrival, respectively. Participants resettling in the urban setting had a decrease hazard of noncompletion compared to those resettling in the rural setting while those current or former tobacco users had a comparable hazard to non-users. Those needing to travel up to 10.9 miles from their residence to the nearest LTBI treatment facility had a higher hazard of noncompletion but those traveling no more than 20.9 miles, a lower hazard compared to those traveling more than 21 miles. Lastly, study participants with a TST positive result had a higher hazard but those with a positive IGRA had a comparable hazard for noncompletion compared to participants testing negative or not having a TST or IGRA performed.

Despite a lack of statistical significance across all covariates individually, important survival curve trends did emerge. Across all covariates, participants prescribed 9INH experienced the most events and had the lowest cumulative survival. This trend suggests poor overall mean time on treatment and poor completion on this regimen.

Final Model Interpretation

The third null hypothesis for this study was that mean time on LTBI treatment in permanent visa holders initiating treatment in Idaho was not affected by sex, age, country of origin, visa-type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity,

or IGRA positivity. The analyses performed on the effect covariates may have on time on LTBI treatment until noncompletion found age to be the only statistically significant potential influencer of time until noncompletion when compared to reference groups. This finding provides evidence that the age covariate was associated with time on treatment until noncompletion but the null hypothesis should not be rejected overall.

Ad Hoc Analyses

To further explore the potential factors on the time until LTBI treatment noncompletion, the following additional analyses were performed as ad hoc.

1. The interactive impact of sex, age, country of origin, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and medical evaluation, TST positivity, or IGRA positivity on time on LTBI treatment until noncompletion.
2. The impact of sex, age, country of origin, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity on time on LTBI treatment after stratifying by visa-type.
3. The impact of prescribed treatment regimen on time on LTBI treatment.
4. The impact of medical co-morbidities on time on LTBI treatment.
5. The impact of the prescribing medical provider on time on LTBI treatment.
6. The interactive impact of the prescribing provider and treatment regimen on mean time on LTBI treatment.

7. The interactive impact of distance and regimen on mean time on LTBI treatment.

The first ad-hoc analysis involved performing CPHR to test whether the interactive effect of study variables influenced mean time on treatment until noncompletion. The purpose of this ad hoc analysis was to explore if the interaction of any study variables influenced the participant time until noncompletion since published research indicates treatment completion can be impacted by many complicated, overlapping host, environment, and agent factors (Coly & Morisky, 2004; Hirsch-Moverman et al., 2008; Malangu & Yamutamba, 2016; Parsyan et al., 2007). The interactions performed can be viewed in Appendix G. All corresponding statistically significant interaction hazard ratios, *p*-values, and the 95% confidence interval bounds are summarized in Table 14.

Table 14.

Ad Hoc Analysis 1: Statistically Significant Covariate Interactions using Cox Proportional Hazard Regression

				95 % CI	
Variables	*HR*	*SE*	*p*	Lower	Upper
CPHR with levels of Age interacting with levels of Visa-type[a]					
Age (1: 0-24 years)	1.31	1.12	0.81	0.15	11.82
Age (2: 25-44 years)	8.27	1.16	0.07	0.85	80.50
Age (3: 45+ years)	-	-	-	-	-
Visa (Refugee)	2.26	1.05	0.44	0.29	17.51
Visa (Immigrant)	-	-	-	-	-
Age (1: 0-24 years) in Visa (1: Refugee)‡	0.23	0.74	0.04	0.05	0.97
Age (2: 25-44 years) in Visa (1: Refugee)	0.96	0.44	0.94	0.41	22.29
CPHR with levels of Age interacting with levels of Distance to LTBI Treatment Facility[b]					
Age (1: 0-24 years)	12,646.67	103.79	0.93	0.00	2.80E+92
Age (2: 25-44 years)	1.15	0.42	0.74	0.50	2.64
Age (3: 45+ years)	-	-	-	-	-
Distance to Treatment Facility (1: 0-10.9 miles)	13,553.08	103.79	0.93	0.00	2.99E+92
Distance to Treatment Facility (2: 11-20.9 miles)	0.00	179.77	0.96	0.00	8.2E+148
Distance to Treatment Facility (3: 21+ miles)	-	-	-	-	-
Age (1: 0-24 years) in Distance to Treatment Facility (1:0-10.9 miles)‡	0.25	0.63	0.03	0.07	0.86
Age (2: 25-44 years) in Distance to Treatment Facility (1:0-10.9 miles)	1.25	0.4	0.58	0.57	2.75
Age (1: 0-24 years) in Distance to Treatment Facility (2: 11-20.9 miles)	0.58	490.06	0.98	0	--
CPHR with levels of Age interacting with levels of IGRA positivity[c]					
Age (1: 0-24 years)	0.35	0.59	0.08	0.11	1.14
Age (2: 25-44 years)	1.45	0.48	0.45	0.57	3.70
Age (3: 45+ years)	-	-	-	-	-
IGRA Result (0: Positive)	1.46	0.67	0.57	0.39	5.37
IGRA Results (1: Negative or Not Done)	-	-	-	-	-
Age (1: 0-24 years) in IGRA (0: Positive) ‡	0.35	0.59	0.05	0.12	1.03
Age (2: 25-44 years) in IGRA (0: Positive)	1.24	0.74	0.77	0.29	5.32

Note. Abbreviations: *HR* = Hazard Rate; *SE* = Standard Error. [a]Reference Group = 45+ years, Immigrant. [b]Reference Group = 45+ years, 21+ miles from treatment facility. [c]Reference Group = 45+ years, IGRA negative or not done. ‡ Denotes statistically significant at $p<0.05$.

For the analysis of interactive predictors of mean time on LTBI treatment until noncompletion, the overall model significance of $p = 0.03$ suggests the null hypothesis should be rejected. Additionally, the Log-likelihood was reduced in the second block where interaction terms are included compared to the first block where main effects are assessed suggesting the accuracy of the model improves when interaction terms are included. The interactive effect of some study covariates appeared to influence the mean time until treatment noncompletion.

The age (zero to 24 years) and visa-type (refugee) interaction term suggested the effect of age on time until LTBI treatment noncompletion was different by visa-type (*HR* = 0.23, *p* = 0.04). The main effect of the age variable for those less than 25 years, if statistically significant, would have suggested the risk of LTBI treatment noncompletion was 31% higher than those 45 years of age and older in the reference group (*p* = 0.81). However, this would be exclusive of visa status as the visa-type term was held at zero. Likewise, the risk of noncompletion would have increased by a rate of 2.26 when age was held at zero in refugees compared to immigrants (*p* = 0.44) but again, only if this finding were statistically significant. In terms of interaction, the hazard of 0.23 indicates that for study participants zero to 24 years of age who held a refugee visa, the risk of noncompletion was 77% lower than the comparator group indicating a greater mean time on treatment.

When assessing the age (zero to 24 years) and distance from study participant residence and LTBI treatment facility (zero to 10.9 miles) interaction term, this study identified the effect of age on time until LTBI treatment noncompletion differed by distance (*HR* = 0.25, *p* = 0.03). The hazard associated with the interaction term indicates that those zero to 24 years of age living less than 11 miles away from their LTBI treatment facility experienced a rate of LTBI treatment noncompletion 75 times less than the comparator group. Furthermore, the somewhat wide confidence interval around this interaction term hazard ratio estimate did not cross one and suggests the true risk of LTBI treatment noncompletion in this group was 93% less than the comparator group.

The interaction between age (zero to 24 years old) and IGRA result (positive) also appeared to be a predictor of time on treatment until noncompletion (*HR* = 0.35, *p* = 0.05). The main effect for age (zero to 24 years) while all other variables were held constant, resulted in a decreased hazard of LTBI treatment noncompletion by 65% compared to the 45 years of age and older reference group (*p* = 0.08). The main effect for IGRA result (positive) however, resulted in a 46% increase in the risk of experiencing noncompletion compared to the reference group that tested IGRA negative or did not have an IGRA performed (*p* = 0.57). For this interaction term, being in the study participant group less than 25 years old who were IGRA positive reduced the likelihood of LTBI treatment noncompletion by 65% when compared to study participants 45 years of age and older and IGRA negative or who did not have an IGRA performed. Notably, the 95% confidence interval for this interaction crosses one, suggesting the true risk of noncompletion reported could be due in part by chance.

The second ad-hoc analysis involved stratifying the dataset by visa-type prior to analysis. CPHR analysis was performed to assess variable interaction terms by visa-type as study participants may differ according to visa. Statistically significant interactions can be found in Table 15 in Appendix H.

For refugees, the following interactive effects were identified:

- Age (zero to 24 years) and visa-type (Refugee) (*HR* = 0.21, *p* = 0.04).
- Age (zero to 24 years) and distance (less than 11.0 miles between residence and LTBI treatment facility) (*HR* = 0.21, *p* = 0.05).

- Age (zero to 24 years) and history of tobacco use (having a current or former history of tobacco use) (*HR* = 0.22, *p* = 0.05).
- Age (zero to 24 years) and area of resettlement (urban) (*HR* = 0.21, *p* = 0.04).

All interaction terms above were associated with experiencing less treatment noncompletion events at specific age categories and a longer duration on LTBI treatment when compared to the reference group. Ultimately, for this model, the null hypothesis that the mean time on LTBI treatment for study participants with a refugee or immigrant visa was not influenced by select covariates was not rejected (Refugee model *p* = 0.74, Immigrant model *p* = 0.22).

More specifically, the age (zero to 24 years) and visa-type (Refugee) interaction term in this analysis suggested these participants experienced LTBI treatment noncompletion 79% less often compared to refugees who were 45 years of age and older (*p* = 0.73). For the interaction between visa (refugee) and distance (<11 miles) only one fifth of those study participants experienced LTBI treatment noncompletion compared to the reference study participants. Additionally, for the interaction term in the same less than 25-year age category reporting current or former tobacco use, being in this grouping reduced the likelihood of LTBI treatment noncompletion by 78% compared to older (45+ years), non-smoking refugee study participants (*p* = 0.05). Finally, the interaction between belonging to the refugee group less than 25 years and resettling in the urban Idaho environment corresponded with a 79% reduction in the likelihood of experiencing LTBI treatment noncompletion when compared to study participants reference groups (*p*

= 0.04). At the conclusion of the study period, refugees less than 25 years of age frequently experienced a greater mean time on treatment.

For immigrants, two interaction terms that were found to be statistically significant influencers of mean time on LTBI treatment until noncompletion included: (a) age (25 to 44 years) and birth country (Africa WHO Region) (*HR* = 12.20, *p* = 0.05), and (b) age (25 to 44 years) and area of resettlement (urban) (*HR* = 4.42, *p* = 0.05). For the interaction of immigrant study participants aged 25 to 44 years hailing from the Africa WHO region, participants were at significantly elevated risk for experiencing treatment noncompletion compared to immigrant study participants 45 years of age and older and who were from the Western Pacific WHO Region. Specifically, these participants experienced LTBI treatment noncompletion at a rate 12.2 times higher than the aforementioned reference group indicating mean time on treatment was low. The very wide confidence interval around this estimate indicates the true risk of LTBI treatment noncompletion for this group compared to reference study participants was in excess of a rate 140 times higher.

For the interaction term of this same 25 to 44 years old age category and area of resettlement (urban), those resettling in the urban-Idaho setting were 4.4 times more likely to experience noncompletion compared to immigrant study reference group members who were 45+ years old resettling in the rural-Idaho setting signifying these participants had a decreased mean time on LTBI treatment. Interpretation of the 95% confidence interval, however, suggests chance may have been a contributing factor to this finding as one was included in the range.

The third ad-hoc analysis was performed because multiple treatment regimen options exist potentially influencing the time until treatment noncompletion (Dobler & Marks, 2012; Goswami et al., 2012; Li et al., 2009; Lines et al., 2015; Menzies et al., 2004; Shepardson et al., 2013). Data were analyzed by controlling for treatment regimen and no statistically meaningful relationship was identified between visa-type and mean time on LTBI treatment (Appendix H, Table 16). For this model, the null hypothesis that the mean time on LTBI treatment was not influenced by the regimen prescribed could not be rejected ($p = 0.89$).

Study participant medical co-morbidity influence on mean time on LTBI treatment was also assessed. The null hypothesis for ad-hoc analysis model four suggested the mean time on LTBI treatment was not influenced by the presence of a medical comorbidities and this hypothesis was not rejected (data not shown). Medical co-morbidities were assessed individually and for interaction. Finally, to improve the medical comorbidity sample size, a new "any comorbidity" variable was created for analysis that included all study participants with at least one medical comorbidity recorded in the dataset. The results of this analysis were statistically non-significant (Table 17, Appendix H) ($p = 0.84$). These findings suggest the medical co-morbidities recorded in the dataset did not influence mean time on LTBI treatment for the study participants.

The fifth and sixth ad-hoc analysis assessed the impact the prescribing provider may have had on mean time on LTBI treatment until completion. When the impact between provider and mean time on LTBI treatment was assessed (ad hoc analysis five),

the null hypothesis that health care provider did not influence mean time on LTBI treatment was not rejected (data not shown). The interactive effects assessed in ad-hoc analysis six suggest that an interaction between provider and prescribed treatment as an influencer of mean time on LTBI treatment until noncompletion also did not exist and the null was not rejected ($p = 0.59$) (Appendix H, Table 18). Provider specific patterns did emerge, however. As seen in Table 18 in Appendix H, Provider 18, when prescribing 4 months of RIF had study participants experience treatment noncompletion at a rate over 11 times more frequent compared to the study reference group receiving 9 months of INH as prescribed by provider 23 ($HR = 11.21$, $p = 0.02$). This finding suggests that the interactive effect of prescribing provider and prescribed regimen are not widespread but provider-specific predictors of mean time on treatment may exist.

Lastly, the interaction term of distance between study participant residence and LTBI treatment facility and the regimen was assessed. For this seventh ad-hoc model, the null hypothesis was that the interaction between distance to LTBI treatment facility and the prescribed regimen did not influence mean time on LTBI treatment. This hypothesis was not rejected ($p = 0.89$) and the analytic findings are reported in Table 19 found in Appendix H. Hazards for study participants prescribed 3HP, 4RIF, or 6INH having less than 20.9 miles between residence and LTBI treatment facility were comparable to those prescribed 9INH having more than 21 miles between residence and LTBI treatment facility.

Summary

The purpose of this retrospective cohort study was to document LTBI treatment completion and noncompletion rates in visa holders arriving in Idaho and initiating treatment. The study also aimed to determine whether an association existed between the type of permanent visa held and LTBI treatment completion for foreign-born individuals resettling in the rural U.S. Additionally, the study sought to determine if the mean time on LTBI treatment was influenced by selected factors in these permanent visa holders. A single dataset derived from the Idaho jurisdiction on the CDC EDN platform was used to test the following null hypotheses:

$H_0$1: There is no association between visa type and LTBI treatment completion among permanent visa holders initiating LTBI treatment in Idaho.

$H_0$2: The mean time distribution to last treatment for LTBI is not significantly different between permanent visa holders initiating LTBI treatment in Idaho.

$H_0$3: Time on LTBI treatment in permanent visa holders initiating treatment in Idaho is not affected by sex, age, country of origin, visa-type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity

The findings from this analysis suggests none of the null hypotheses should be rejected at a significance level of 0.05. Chi-square analysis conducted to answer research question one suggests an association between visa-type and LTBI treatment completion status does not exist and the alternative hypothesis should not be accepted. Kaplan-Meier survival analysis demonstrated the difference in mean treatment duration was not

statistically significant across visa-types and the null hypothesis that no difference in mean time on LTBI treatment between two types of visa holders was not rejected.

The impact of sex, birth country, visa-type, smoking status, distance from residence to LTBI treatment facility, area of resettlement, the time between arrival and medical evaluation, TST positivity, or IGRA positivity were not statistically significant however, age was statistically significant. Specifically, being aged less than 25 years was associated with a longer mean time on treatment and higher treatment completion rate. However, overall, the CPHR model assessing the impact covariates have on mean time until treatment noncompletion was not statistically significant.

Ad-hoc analysis examining the interactions between covariates did produce statistically significant findings, however. The mean time to last LTBI treatment for study participants was influenced by the (a) interactions of age (group one, zero to 24 years) and visa-type (refugee), (b) age (group one, zero to 24 years) and distance between residence and LTBI treatment facility being less than 11 miles, and (c) age (group one, zero to 24 years) and being IGRA positive in Idaho when compared to study reference groups.

Greater, in-depth interpretation of the findings outlined here will be provided in chapter 5. This will also be accompanied by the current limitations surrounding this research and recommendations for further research. The positive social change implications for this research will also be discussed in chapter 5 as the findings mentioned above highlight potentially important areas for public health practice change.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

Annual U.S. tuberculosis surveillance data for 2017 suggest more than 80% of the 9,093 cases of active TB reported were due to reactivation of untreated LTBI likely acquired outside of the United States (Stewart, Tsang, Pratt, Price, & Langer, 2018). Providing increased opportunities for appropriate, risk-based screening and preventive treatment for LTBI may have averted the progression from infection to active disease in many of these individuals, minimizing the risk of transmission and improving the health of those infected and the health of their contacts. Tuberculosis elimination experts continue to urge that U.S. TB control programs devote more resources to the prevention of disease through detecting and treating LTBI whilst continuing to reduce transmission through early detection of those with active disease (Stewart et al., 2018).

In the face of decreasing TB control-related resources, including funding, a skilled workforce, and research seeking out innovative preventive short-course regimens, the ability to increase LTBI screening and treatment efforts broadly in the public sector seems unlikely (Bayer & Castro, 2017). In the rural setting, which is already disproportionately negatively impacted by resource limitations, renewed emphasis on LTBI preventive strategies will likely have to take advantage of existing infrastructure to be successful. Placing greater emphasis on ensuring high rates of preventive treatment completion of those already being screened and initiating LTBI treatment in the rural setting may be one approach to moving closer to TB elimination. However, there exists a paucity of findings from LTBI interventions deployed in the rural U.S. setting. This gap

leaves TB control officials serving rural populations reliant upon the extrapolation of findings from potentially dissimilar research settings.

This retrospective cohort study was undertaken to quantify the LTBI treatment completion rate in rural Idaho for permanent visa holders, determine the mean time on treatment, and identify potential predicting variables of noncompletion. These efforts had the potential to promote more targeted treatment completion thus improving public health interventions. The epidemiologic triangle underpinned this research with multiple host, environment, and agent-related variables extracted from review of similar published research materializing in this study. De-identified pre- and postarrival medical evaluation records from the CDC EDN system were used to establish the dataset analyzed to address the study areas of inquiry. Study participant LTBI treatment completion estimates were produced, Kaplan-Meier survival curves generated and interpreted, and Cox Proportional Hazard Regression was used to calculate hazard ratios using sex, age, birth country, visa type, history of tobacco use, distance from residence to treatment facility, area of resettlement in Idaho, time to medical evaluation after resettlement, TST positivity, or IGRA positivity as study covariates.

In this chapter, the key study findings are summarized, an interpretation of these findings in the context of the epidemiologic triangle and existing body of knowledge are provided, and the limitations of this research study are acknowledged. This chapter will also provide recommendations for further research as well as the social change implications of the current research findings.

Interpretation of Major Findings

This study used three research questions to assess the impact of the immigration status of visa holders arriving in Idaho on the treatment completion status for LTBI:

RQ1: Is visa type (refugee, immigrant, parolee, asylee, or fiancé) associated with LTBI treatment completion among permanent visa holders initiating LTBI treatment in Idaho?

RQ2: Is the mean time distribution to last treatment for LTBI between permanent visa holders initiating LTBI treatment in Idaho significantly different?

RQ3: Is time on LTBI treatment in permanent visa holders initiating treatment in Idaho affected by sex, age, country of origin, visa type, smoking status, distance between residence and treatment facility, area of resettlement, time between arrival and initial medical evaluation, TST positivity, or IGRA positivity?

Visa Type and Latent Tuberculosis Infection Treatment Completion

This study showed that immigrants had a higher treatment noncompletion rate than refugees, 25.8% versus 19.3%, although, the difference was not statistically significant. However, the nonsignificant finding may be caused by a few sample-related factors. First, this study sample contained mostly refugees (n = 109) and fewer than 35 immigrants. Although the numbers of refugees included was somewhat robust, the number of immigrants included was small. This small number equated to a small number of recorded events which may have contributed to this finding. Second, immigrants were disproportionately prescribed longer regimens compared to refugees in this study. With longer treatment regimens having been shown to be associated with poorer completion in

the urban setting (Juarez-Reyes et al., 2015; McClintock et al., 2017; Shepardson et al., 2013; Wingate et al., 2015), immigrants in this study were not provided an equal opportunity to gain access to expedited regimens that may have influenced treatment completion status. Although their overall percent of noncompletion was just slightly less than refugees, having a more evenly distributed treatment prescribing pattern across all visa types in this study may have highlighted important differences.

A higher noncompletion rate in immigrants is different than that reported by Lim et al., (2016) which identified Tibetan refugees had a greater risk of noncompletion than immigrant visa holders in the urban Canadian setting. Such difference may be caused by the study setting and demographic characteristics of the study subjects. The study by Lim et al. (2016) included more refugees (n = 180) albeit from a single country of origin. All refugees in this study were privately sponsored by Canadian citizens, potentially making more resources available for medical evaluation and treatment completion compared to Canadian migrants not sponsored. Typically, in Idaho, refugees are sponsored by resettlement agencies and not private citizens.

Although visa type alone did not have a statistically significant impact on the completion rate, it is important to note that a quarter of immigrants failed to complete LTBI treatment compared to less than 20% of refugees. This difference may still be critical to public health practice. Though the results deviated from trends established using samples drawn from urban settings, it may show the trend of treatment completion in the rural setting with more refugees. Additionally, these findings bring attention to treatment completion rates for a rural population and support previous findings that no

two environments are the same. Completion rate improving interventions should be targeted after considering rural or urban-setting-specific characteristics (Hirsch-Moverman et al., 2008).

Mean Time Distribution to Last Latent Tuberculosis Infection Treatment by Visa

Refugees and immigrants may be inherently different, so assessing differences in mean time on LTBI treatment until noncompletion was necessary. This study showed that immigrants had an average time on LTBI treatment of 7.51 months compared to an average of 7.85 months for refugees, though the difference was not statistically significant. It is worth noting that for this research question analysis, average time was calculated without factoring the differing treatment regimen durations, which varied from 3 months to 9 months. Additional ad-hoc analysis was performed to address this with the mean time in months for 3HP, 4RIF, 6INH, and 9INH being 2.96 months, 3.83 months, 5.4 months, and 7.7 months, respectively. Although few studies have been published surrounding this phenomenon, a previous study by Parsyan et al. (2007) had identified similar population group-specific differences in mean time on LTBI treatment. Parsyan et al. (2007) reported that when Haitian (refugees) and the Dominican Republicans (immigrants) resettled in Boston, they experienced less time on treatment and a higher rate of noncompletion compared with U.S.-born Bostonians and Boston residents hailing from other foreign countries. Unlike this current research, though, when compared to each other, Parsyan et al. (2007) found Haitian refugees to have higher odds of noncompletion and thus a lesser mean time on LTBI treatment compared to Dominican Republic immigrants. Considering this published finding and the findings of this current

study, the visa type held by LTBI treatment initiators may be an important factor to consider when estimating mean time on treatment. However, more work in this area is needed to draw this conclusion.

Despite the relatively small number of noncompletion events in this study sample, notable trends potentially influential to public health practice emerged related to treatment noncompletion in participants. Immigrants experienced all events within the first 6 months of treatment initiation with no events being recorded in months 7, 8, or 9. This meant immigrants had a final estimated cumulative proportion of survival at month 6 and until the end of the study of 0.738. Considering this, treatment completion improving interventions for immigrants should target this 6-month window when the number of noncompletion events is greatest. Refugees, however, experienced a majority of events between months 3 and 6 but had the last recorded event just after the start of month 8. This difference between when noncompletion events are experienced by visa type may influence public health interventions, although additional studies drawing similar conclusions would help support this notion.

Reasons for the difference in mean time on LTBI treatment could not be determined from the data available; however, these findings represent a real actionable difference between the two groups in practice. Additionally, reasons for regimen-specific noncompletion events could not be determined. With immigrants failing to complete treatment shortly after initiation and refugees failing to complete later in the course, the two populations may benefit from separate completion improving interventions.

Predictors of Time on Latent Tuberculosis Infection Treatment

The two previous research questions only examined visa type as a sole factor influencing treatment completion and time on treatment. However, it is known that other factors can impact treatment completion status and time on treatment. Known risk factors impacting LTBI treatment completion status and overall time on treatment in the urban and international setting are age (Bieberly & Ali, 2003; Bock et al., 1999; Hovell et al., 2003; Lobue & Moser, 2003; Spicer et al., 2013), birth country (Fiske et al., 2014; Parsyan et al., 2007; Spicer et al., 2013), visa-type (Lim et al., 2016; Sandgren et al., 2016), and distance to health care facility (Getahun et al., 2015; Silva et al., 2016; Spicer et al., 2013). Cox proportional hazard regression used in this study showed that as a model overall, the covariates of age, sex, history of tobacco use, area of resettlement, birth country, distance to health care facility, time between arrival and medical evaluation, TST positivity, or IGRA positivity were not influencers of time on LTBI treatment until noncompletion.

Among all the covariates, age may be an important factor to consider when predicting risk for LTBI treatment noncompletion using Cox Proportional Hazard Regression, however. Participants zero to 24 years of age, regardless of visa-type, experienced the least number of treatment noncompletion events compared to study participants 25 years of age and older. This translated into a higher cumulative survival and an 82% reduced risk of experiencing noncompletion. Participants in this age group were thus expected to have a longer mean time on treatment and were less likely to experience LTBI treatment noncompletion. Although the exact reason why being less than 25 years old in this study was associated with a greater mean time on treatment and

higher completion is unknown, this finding supports those in published literature surrounding minority migrant populations in San Diego, migrant TB clinic attendees from San Diego County, post-Katrina survivors from urban New Orleans, and patients referred to a large metropolitan health care facility in Columbus, Ohio (Bieberly & Ali, 2003; Lobue & Moser, 2003; Hovell et al., 2003; Spicer et al., 2013). Possibilities are likely not due to confounding as tests for confounding were negative, however, could be due to parental or guardian involvement during younger ages (van Zyl et al., 2006). Alternatively, younger persons infected with *Mtb* and not successfully treated have more years of lifetime risk ahead of them possibly leading to greater provider education surrounding the benefit of treatment.

Birth country, visa-type, and distance to treatment facility were not predictors of mean time on treatment until noncompletion in this study as they were for other published work (Fiske et al., 2014; Getahun et al., 2015; Lim et al., 2016; Parsyan et al., 2007; Sandgren et al., 2016; Silva et al., 2016; Spicer et al., 2013). The assessment of birth country in this study may have been influenced by the use of WHO Regions instead of specific countries of origin. This use of the WHO Region was deployed to increase factor strata sample size for analysis however, may have masked country specific LTBI treatment noncompletion trends. The analysis of visa-type as a predictor may have been influenced by the relatively small number of immigrants included in this study compared to refugees. Additionally, differences in the prescribed regimen were present based on visa-type with no immigrants being prescribed the 3HP expedited regimen. This pattern produced a study participant pool where it was more likely that immigrants would be

prescribed longer treatment durations despite longer treatment durations having documented lower rates of completion in various urban-based populations (Juarez-Reyes et al., 2015; McClintock et al., 2017; Shepardson et al., 2013; Wingate et al., 2015). Lastly, with no refugees resettling in the rural Idaho setting, the mean distance to the nearest LTBI treatment facility was smaller than immigrants since refugees tended to resettle less than five miles from their treatment facility. This resettlement pattern excluded the analytic comparison of rural refugee resettlement and rural immigrant resettlement, possibly hiding a true phenomenon observed in urban U.S. city-based research that showed the greater the distance traveled, the less likely treatment completion would be achieved (Getahun et al., 2015; Spicer et al., 2013).

Interactive Terms, Comorbid Conditions, and Provider Impact

Ad-hoc Cox Proportional Hazard Regression analyses were conducted to identify the interactive covariate terms potentially influencing time on LTBI treatment. The interaction between (a) age and visa-type, (b) age and distance to LTBI treatment facility, and (c) age and IGRA positivity were found to be important influencers of the time on treatment until noncompletion.

The assessment of interaction between age and visa-type identified that LTBI noncompletion differed by visa-type. Refugees zero to 24 years of age had a 77% lower risk of experiencing noncompletion compared to immigrants 45 years and older. This finding suggests younger refugees experienced a longer time on treatment in contrast to their older immigrant counterparts. Supporting this finding are the results of a study from an inner-city Atlanta sample where Bock et al. (1999) identified older study participants,

defined as those 45 years of age and older, had a higher rate of noncompletion and thus, younger participants a lower. Similarly, in San Diego, Hovell et al. (2003) determined that as study participant age increased, LTBI treatment completion decreased. Although visa-type was not assessed by factors of age in either of these studies, it has been shown to be an important component in determining LTBI treatment completion.

The assessment of interaction between the host factor age and the environmental factor distance between residence and LTBI treatment facility revealed noncompletion also differed by distance. Visa holders 45 years and older living more than 21 miles away from their LTBI treatment facility had a risk of experiencing noncompletion 75 times higher than persons zero to 24 years of age living less than 11 miles from their treatment facility. This finding suggests that being younger than 25 years old and being treated for LTBI in combination with living closer to their treatment facility, equated to a higher mean time on treatment and a lower risk of noncompletion. This finding is corroborated by the research conducted in urban Brazil where younger study participants traveling further or taking longer to reach their treatment facility experienced higher rates of noncompletion (Silva et al., 2016). Spicer et al. (2013) also found age and distance to be inversely related to treatment completion but an increase in both factors resulted in a decrease in completion.

Finally, the assessment of interaction between the host factor age and the agent factor IGRA result indicates noncompletion differed by IGRA result. The risk of experiencing LTBI treatment noncompletion was reduced by 65% in IGRA positive, zero to 24-year-old persons. Utilizing IGRAs to diagnose LTBI are a helpful, yet nonessential

tool, however, studies suggest these blood tests increase perceived severity and improve the likelihood of treatment completion (Alsdurf, Hill, Matteelli, Getahun, & Menzies, 2016). Although this study could not validate this specific conclusion, being IGRA positive and of a younger age potentially could support these claims if investigated further. The assessment of age and IGRA positivity from this study may be the first amongst its kind with no similar studies being identified.

Visa-specific interactive term findings. Visa-type specific predictors of LTBI treatment noncompletion were also found. The interactive impact of age and visa-type highlighted that persons zero to 24 years of age holding a refugee visa were 79% less likely to experience LTBI treatment noncompletion; that refugees of the same less than 25 age group also living less than 11 miles from their treatment facility were 79% less likely to experience noncompletion; that persons less than 25 years old reporting current or former tobacco use were 78% less likely to experience noncompletion; and refugees less than 25 years old resettling in the urban setting were 78% less likely to experience noncompletion. Individually, most of these findings have been demonstrated in similar research from urban-setting drawn samples however, these studies did not address interaction (Parsyan et al., 2007; Rogo et al., 2017).

For immigrants, the interactive impacts of age and birth country, and age and area of resettlement resulted in a greater risk of noncompletion. Immigrants aged 25 to 44 years hailing from the Africa WHO Region, experienced noncompletion at a rate 12 times higher than the 45 year old and older reference group hailing from the Western Pacific. Additionally, immigrants of this same 25 to 44-year age group resettling in the

urban environment experienced noncompletion four times more often compared to persons 45 years and older from the rural setting. These findings suggest immigrants aged 25 to 44 years may be at heightened risk of experiencing noncompletion and in the resource limited setting, may benefit from targeted interventions. Each of these findings are similar to those demonstrated in research from urban-setting drawn samples however these similar studies did not address the interactive impact as this study on the rural population did (Ailinger, Black, Nguyen, & Lasus, 2007; Hirsch-Moverman et al., 2010; Shieh et al., 2006).

Study Limitations

Given this was a study based on a secondary database, there were some limitations related to:

- The intent of the original data collection;
- Data availability and the inability to collect additional data;
- Results not being generalizable to the urban setting or areas with a different makeup of visa holders; and
- The sampling methods used, the small sample size, and the subsequent small number of events that may have impacted statistical power.

Original Intent of Data

Components of chapter 1 highlighted the purpose of the CDC's EDN system from which the data for this study were derived suggesting that data were not originally collected to address the current research questions. This may have provided opportunity for important variables related to LTBI treatment completion and this current research to

be excluded since they were not collected in the first place. Furthermore, the CDC EDN system only houses data for U.S. permanent visa-holding migrants so this study was unable to include similar data from the general, non-migrant U.S. population potentially making these findings less generalizable to a broad population. Additionally, the reason for LTBI treatment noncompletion was not well documented and was thus, excluded from the study dataset. Reasons for noncompletion may be due to other variables not included in this research so these study findings should likely not be considered the only important factors when assessing noncompletion risk. Lastly, treatment completion has been shown to be a complicated phenomenon with this study including no social support variables which have been documented to influence adherence.

Data Availability, Collection of Additional Data, and Generalizability

This study did not include visa holders seeking care in the private market making data on this group unavailable for comparison. This limits the extent to which these study findings can be applied to this private-care seeking population. Additionally, one Idaho jurisdiction did not have visa holders represented in this study possibly limiting the generalizability of these findings to that jurisdiction. Power analyses performed suggest this study obtained a sufficient sample size to be representative, however, the exclusion of a jurisdiction is unfortunate. Furthermore, unlike treatment for active disease, treatment for LTBI is not mandated in Idaho law potentially influencing patient perception of disease severity and influencing treatment initiation however this could not be validated due to a lack of data. Lastly, the de-identified dataset did not allow for

additional information to be collected on study participants that may have been useful variables to include in this research to justify noncompletion events.

Sampling and Sample Size

This study did not deploy formal sampling techniques to select participants as to include the highest number of eligible visa holders. However, nearly 20% of visa-holding arrivals with a B TB notification possibly suggestive of LTBI were automatically excluded due to a lack of medical follow-up information. It is unknown if these individuals had LTBI, but if that were the case, their contributions to the overall sample size may have improved statistical power and decreased further the likelihood that some of the major findings were less likely to have occurred due to chance. Additionally, the lack of medical information collected on these individuals reduced study generalizability.

Given the considerable number of B TB Notifications received by Idaho public health officials, the sample size for this study, representing only 9% of those arrivals, is relatively small. The small sample likely lead to the small number of events recorded and may have influenced the ability to perform multivariate analysis since some of the variable strata approached or became zero. Additionally, the study population is likely not representative of entire Idaho population infected with *Mtb*, limiting extrapolation of these findings only to newly arriving refugee and immigrant visa holders and not U.S.-born Idahoans.

The sample size issues described provide opportunity for improvement. This study had very strict inclusion criteria that decreased B TB notification evaluation result data availability from visa-holding arrivals to Idaho. By excluding visa holders diagnosed

with LTBI who were recommended treatment but failed to initiate treatment within the first month, by excluding visa holders on LTBI treatment moving from non-Idaho jurisdictions, and by excluding visa holders who may have been evaluated and accepted LTBI treatment in subsequent years after arrival but still during the study timeframe, the number of visa holders included in this study was decreased and the visa-type diversity restricted to refugees and immigrants. This reflection highlighted it may be advantageous in the future to include these abovementioned visa holders to increase the sample, diversify the types of visas held by participants, and to improve overall study power and generalizability to a broader visa-holding population.

Recommendations for Further Research and Public Health Practice

This current study was the first of its kind for the rural Idaho-setting, but does present additional opportunities for further research. With the rural-setting in general being underrepresented in the published literature, there is a need to further explore the factors that contribute to the urban versus rural differences identified between this work and the published work from the urban setting. Additionally, increasing the sample size for research focused on the rural setting would also be beneficial as this study suffered from a relatively small sample. The proactive collection of more socioeconomic and familial support factors in the rural setting could also contribute to explaining the differences noted between urban and rural jurisdictions.

In this study, data were not available for why a participant did not complete LTBI treatment, likely related to the retrospective nature of this study design. This highlights an important area for future prospective rural-setting research. Persons who fail to complete

LTBI treatment for medical reasons may differ from those failing to complete by choice and these potential differences need to be explored. Since some medical reasons for stopping LTBI treatment may be unavoidable, future prospective research in this arena could take this into account. Furthermore, potential spurious correlations possibly the product of unassessed factors could be taking place in this retrospectively designed study. Public health interventions developed for the rural setting may have greater success in improving LTBI treatment completion when targeting non-medically related modifiable noncompletion risk factors.

Due to the complex nature of treatment completion, additional research into the interaction between factors is needed especially in the rural setting. Although costlier and labor intensive, a prospective cohort, as discussed above, involving visa holders diagnosed with LTBI in Idaho would allow for data to be collected on additional variables of interest, would potentially allow for documentation of reasons for non-completion, and may allow for a greater number of participants to be enrolled for sample size improvement. Alternatively, an additional retrospective study with less restrictive inclusion criteria or possibly spanning a timeframe greater than five years may also contribute to the body of knowledge surrounding this phenomenon and may support the findings of this research.

This study consistently demonstrated that refugees under the age of 25 experienced higher rates of treatment completion when acting interactively with visa-type, distance to treatment facility, history of tobacco use, and area of resettlement however, some of these findings have not yet been described in published works.

Additionally, the interactive relationship between holding an immigrant visa and birth country as well as being an immigrant and resettling in the urban setting needs further exploration as this study included a very small number of immigrants.

Lastly, no immigrant study participant was prescribed the expedited LTBI treatment regimen lasting the shortest duration of 12 weeks. Although a number of refugees were prescribed the expedited regimen, this study may have been improved if comparison between visa-types on the expedited regimen could have been performed. As the use of the expedited regimen expands, future research should focus on the differences between treatment completion status by visa-type when a broader variety of visa-types are available for analysis.

Recommendations for improving public health practice may be derived from this study. As demonstrated by the regimen-specific time on treatment analysis, nine months of INH likely should not be as heavily relied on in the rural setting as completion rates were inferior to shorter regimens. The use of expedited regimens, when appropriate, for treating LTBI should be improved. Also, providing all visa-types greater access to non-9INH regimens should be a focus of public health practitioners as this study demonstrated mostly refugees were prescribed expedited regimens. Furthermore, although more resource intensive for the rural setting, visa holders at higher-risk of noncompletion in Idaho may benefit from more frequent interactions with public health practitioners. This may help ensure adherence and continuously promote LTBI treatment completion. Additionally, more frequent interactions may be beneficial in the early stages of treatment for immigrants or the mid- to later-stages of treatment for refugees as these

areas were where the largest number of noncompletion events took place. Finally, a more thorough assessment of clinic-based completion rates may inform LTBI treatment prescribing practitioners which regimens are garnishing the highest completion rates in their clinics. The outcome of such a clinic-based assessment may provide evidence for the utilization of the most appropriate LTBI regimen for the clinic patient population.

Social Change Implications

The results of this study can fundamentally be used to assist the TB control workforce serving geographically large, rural states understand LTBI treatment completion in likely the population at greatest risk of being infected with *Mtb*. In the rural setting, public health resources for TB control are scarce and information potentially driving public health intervention development may stem from research findings using samples drawn from the urban setting where TB disease is more abundant. This research identified some rural-jurisdiction specific LTBI treatment noncompletion trends and predictors but also correlated with some findings from the urban setting suggesting geographic variation was present. This research may promote social change in the rural setting by providing actionable, rural-population specific information for the prioritization of visa holders at increased risk of experiencing LTBI treatment noncompletion. Furthermore, with visa holders being a focus of this research, findings may help scope state-based Refugee Health Screening Program priorities.

Ensuring high rates of LTBI treatment completion can prevent future cases of active disease reducing health care costs and hospitalizations, improving individual quality of life, preventing transmission, and improving community health. In the clinical

context, this study has reaffirmed other work that longer courses of LTBI treatment have lower rates of completion indicating a shift in TB control narrative is needed to promote broader use of expedited regimens. As this study, and others have demonstrated, host, environment, and agent factors are important considerations in the development of successful public health interventions. This study has highlighted that age, visa, birth country, and history of tobacco use are important interactive host factors, distance to treatment facility and area of resettlement important interactive environment factors, and IGRA positivity interactive agent factors to consider when assessing risk of LTBI noncompletion. Lastly, this study adds to the incredibly limited body of knowledge surrounding LTBI treatment completion in the rural setting potentially making these findings available to other rural jurisdictions with limited TB control resources.

Conclusion

This research attempted to address the identified gap surrounding the quantification of LTBI treatment completion rates in the non-urban setting, the mean time on treatment in the rural setting, and the predictors of noncompletion. The study found noncompletion in immigrants approached 26% whilst noncompletion remained below 20% in refugees. Though the difference was not statistically significant, the rates of noncompletion in both groups remains of concern.

The refugee study participants had a mean LTBI treatment time of 7.85 months compared to 7.51 months for immigrants. Across both visa-types, study participants prescribed nine months of INH had the lowest mean time on treatment compared against the recommended duration. This finding suggests other shorter regimens should be

considered before nine months of INH, when clinically appropriate, for this rural population.

Age had a significant impact on the probability of time on treatment until noncompletion in this study. Specifically, being aged less than 25 years of age equated to an 82% less likelihood of experiencing LTBI treatment noncompletion. When age interacting with visa (refugee), or distance to LTBI treatment facility (<11 miles), or being IGRA positive, study participants zero to 24 years of age had a 77%, 75% and 65% less likely chance of experiencing noncompletion, respectively. A finding of this nature suggests public health interventions that target refugees and immigrants older than 25 years may result in an increased rate of completion, although more work is needed to draw this conclusion.

Although this research has important implications for the rural Idaho TB-control setting, further research, potentially with a more robust sample size drawn from the rural setting, would assist in validating these findings. The inclusion of more diverse visa-types may promote broader finding applicability as this research only included refugees and immigrants. Additionally, more effort to explore the interaction terms described in this study is needed as these factors are rarely described in the published literature in an interactive sense. Regardless, the findings presented add to the body of literature on LTBI treatment completion and potentially arm TB controllers in the rural, resource limited setting with evidence for setting and visa-type specific treatment completion improving interventions.

For Idaho, the results of this study provide TB control leadership with the first documented estimates of LTBI treatment completion for this vulnerable population. Additionally, this study provides potential risk factor-related information for the development of actionable interventions targeting those at increased risk of LTBI noncompletion. Lastly, the dissemination of these results to Idaho public health and TB control officials will help those entities prioritize communication to partners, scope recommendations, and place greater emphasis on the observed differences between refugee and immigrant LTBI treatment completion rates without solely relying on findings from urban setting research.

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Appendix A: Electronic Disease Notification Tuberculosis Follow-up Worksheet

EDN TB Follow-Up Worksheet

A. Demographic Last reviewed: 6/21/2013

A1. Name (Last, First, Middle):	A2. Alien #:	A3. Visa type:	A4. Initial U.S. entry date:

A5. Age:	A6. Gender:	A7. DOB: ___/___/_____	A8. TB Class:

A9.Country of examination: | A10.Country of birth:

A11a. Address:
A11b. Phone:
A11c. Other:

A12. a. Sponsor agency name:
b. Phone(s):
c. Address:

B. Jurisdictional Information

B1. Arrival jurisdiction: | B2. Current jurisdiction:

C. U.S. Evaluation

C1. Date of Initial U.S. medical evaluation: ___/___/_____

Mantoux Tuberculin Skin Test (TST)

C2a. Was a TST administered? ☐ Yes ☐ No ☐ Unknown
If YES, C2b. TST placement date: ___/___/_____
☐ Placement date unknown
C2c. TST mm: _____ ☐ Unknown
C2d. TST interpretation: ☐ Positive ☐ Negative ☐ Unknown
C2e. History of Previous Positive TST ☐

Interferon-Gamma Release Assay (IGRA)

C3a. Was IGRA administered? ☐ Yes ☐ No ☐ Unknown
If YES, C3b. Date collected: ___/___/_____ ☐ Date unknown
C3c. IGRA brand: ☐ QuantiFERON® ☐ T-SPOT ☐ Other (specify):
C3d. Result: ☐ Positive ☐ Negative ☐ Indeterminate ☐ Invalid ☐ Unknown
C3e. History of previous positive IGRA ☐

U.S Review of Pre-Immigration CXR

C4. Pre-immigration CXR available?
☐ Yes ☐ No ☐ Not Verifiable

C5. U.S. interpretation of pre-immigration CXR:
☐ Normal
☐ Abnormal (must select one below):
☐ Not consistent with active TB
☐ Non-cavitary, consistent with TB
☐ Cavitary, consistent with TB
☐ Poor Quality
☐ Unknown

C6. Other pre-immigration CXR abnormalities:
☐ Volume loss ☐ Infiltrate ☐ Granuloma(ta)
☐ Adenopathy ☐ Other (specify)

U.S. Domestic CXR

C7. U.S. domestic CXR done?
☐ Yes ☐ No ☐ Unknown
If YES, C8. Date of U.S. CXR: ___/___/_____

C9. Interpretation of U.S. CXR:
☐ Normal
☐ Abnormal (must select one below):
☐ Not consistent with active TB
☐ Non-cavitary, consistent with TB
☐ Cavitary, consistent with TB
☐ Unknown

C10. U.S. domestic CXR abnormalities:
☐ Volume loss ☐ Infiltrate ☐ Granuloma(ta)
☐ Adenopathy ☐ Other (specify)

Comparison

C11. U.S. domestic CXR comparison to pre-immigration CXR:
☐ Stable
☐ Worsening
☐ Improving
☐ Unknown

U.S. Review of Pre-Immigration Treatment

C12a. Completed treatment pre-immigration? ☐ Yes ☐ No
If YES, ☐ Treated for TB disease ☐ Treated for LTBI
C12b. Treatment start date: ___/___/____ ☐ Start date unknown
C12c. Treatment end date: ___/___/____ ☐ End date unknown
C12d. Treatment reported by:
☐ Treatment documented on DS forms
☐ Patient reported treatment completion **at** or **before** panel physician examination
☐ Both-documented on DS forms & patient reported
☐ Unknown
C12e. Standard TB treatment regimen was administered?
☐ Yes ☐ No ☐ Unable to verify

C13. Arrived on treatment?
☐ Yes ☐ No ☐ Unknown
If YES, ☐ TB disease ☐ LTBI
C13a. Start date: ___/___/____ ☐ Start date unknown

C14: Pre-Immigration treatment concerns?
☐ Yes ☐ No
If YES,
☐ Treatment duration too short
☐ Incorrect treatment regimen
☐ Other, please specify:

Alien # | **EDN TB Follow-Up Worksheet (Cont)** | Last reviewed: 6/21/2013

C15. U.S. Microscopy/Bacteriology* Sputa collected in U.S.? ☐ Yes ☐ No *Covers all results regardless of sputa collection method.

#	Date Collected	AFB Smear	Sputum Culture	Drug Susceptibility Testing
1	___/___/_____	☐ Positive ☐ Negative ☐ Not Done ☐ Unknown	☐ NTM ☐ MTB Complex ☐ Contaminated ☐ Negative ☐ Not Done ☐ Unknown	☐ MDR-TB ☐ Mono-RIF ☐ Mono-INH ☐ Other DR ☐ No DR ☐ Not Done
2	___/___/_____	☐ Positive ☐ Negative ☐ Not Done ☐ Unknown	☐ NTM ☐ MTB Complex ☐ Contaminated ☐ Negative ☐ Not Done ☐ Unknown	☐ MDR-TB ☐ Mono-RIF ☐ Mono-INH ☐ Other DR ☐ No DR ☐ Not Done
3	___/___/_____	☐ Positive ☐ Negative ☐ Not Done ☐ Unknown	☐ NTM ☐ MTB Complex ☐ Contaminated ☐ Negative ☐ Not Done ☐ Unknown	☐ MDR-TB ☐ Mono-RIF ☐ Mono-INH ☐ Other DR ☐ No DR ☐ Not Done

D. Evaluation Disposition

D1. Evaluation disposition date: ___/____/_____

D2. Evaluation disposition:

☐ Completed evaluation
- *If evaluation was completed, was treatment recommended?*
  - ☐ Yes
    - ☐ LTBI
    - ☐ Active TB
  - ☐ No

☐ Initiated Evaluation / Not completed

☐ Did not initate evaluation

If evaluation was NOT completed, why not?
- ☐ Not Located
- ☐ Lost to Follow-Up
- ☐ Refused Evaluation
- ☐ Unknown
- ☐ Moved within U.S., transferred to:
- ☐ Moved outside U.S.
- ☐ Died
- ☐ Other, specify

D3. Diagnosis
- ☐ Class 0 - No TB exposure, not infected
- ☐ Class 1 - TB exposure, no evidence of infection
- ☐ Class 2 - TB infection, no disease
- ☐ Class 3 - TB, TB disease
  - ☐ Pulmonary ☐ Extra-pulmonary ☐ Both sites
- ☐ Class 4 - TB, inactive disease

D4. *If diagnosed with TB disease,* ☐ RVCT Reported D5. RVCT #: ☐ RVCT # unknown

E. U.S. Treatment

E1. U.S. treatment initiated: ☐ Yes ☐ No ☐ Unknown

If NO, specify the reason:
- ☐ Patient declined against medical advice
- ☐ Lost to follow-up
- ☐ Moved within U.S, tranferred to:
- ☐ Died
- ☐ Moved outside the U.S.
- ☐ Other (specify)
- ☐ Unknown

If YES: ☐ TB disease ☐ LTBI

E2. Treatment start date: ___/____/_____

E3. U.S. treatment completed: ☐ Yes ☐ No ☐ Unknown

If NO, specify the reason:
- ☐ Patient stopped against medical advice
- ☐ Lost to follow-up
- ☐ Adverse effect
- ☐ Provider decision
- ☐ Moved outside the U.S.
- ☐ Moved within U.S, tranferred to:
- ☐ Died
- ☐ Unknown
- ☐ Other (specify)

If treatment was completed, E4. Treatment completion date: ___/____/_____

If treatment was iniated but NOT completed, E5. Treatment end date: ___/____/_____

F. Comments

G. Screen Site Information

Provider's Name:

Clinic Name:

Telephone Number:

Appendix B: Department of State Form 2053

Photo

U. S. Department of State

MEDICAL EXAMINATION FOR IMMIGRANT OR REFUGEE APPLICANT

OMB No. 1405-0113
EXPIRATION DATE: 09/30/2010
ESTIMATED BURDEN: 10 minutes
(See Page 2 - Back of Form)

Name *(Last, First, MI.)* , , ,
Birth Date *(mm-dd-yyyy)* **Sex:** ☐ M ☐ F
Birthplace *(City/Country)* /
Present Country of Residence **Prior Country**
U.S. Consul *(City/Country)* /
Passport Number **Alien** *(Case)* **Number**
Date *(mm-dd-yyyy)* **of Medical Exam** **Date** *(mm-dd-yyyy)* **of Prior Exam, if any**
Date Exam Expires *(6 months from examination date, if Class A or TB condition exists, otherwise 12 months) (mm-dd-yyyy)*
Exam Place *(City/Country)* / **Panel Physician**
Radiology Services **Screening Site** *(name)*
Lab *(name for HIV/syphilis/TB)* / /

(1) Classification *(check all boxes that apply):*

☐ **No apparent defect, disease, or disability** *(see Worksheets DS-3024, DS-3025 and DS-3026)*

☐ **Class A Conditions** *(From Past Medical History and Physical Examination Worksheets)*

- ☐ TB, active, infectious *(Class A, from Chest X-Ray Worksheet)*
- ☐ Syphilis, untreated
- ☐ Chancroid, untreated
- ☐ Gonorrhea, untreated
- ☐ Granuloma inguinale, untreated
- ☐ Lymphogranuloma venereum, untreated
- ☐ Human immunodeficiency virus (HIV)
- ☐ Hansen's disease, lepromatous or multibacillary
- ☐ Addiction or abuse of specific* substance without harmful behavior
- ☐ Any physical or mental disorder (including other substance-related disorder) with harmful behavior or history of such behavior likely to recur

*amphetamines, cannabis, cocaine, hallucinogens, inhalants, opioids, phencyclidines, sedative-hypnotics, and anxiolytics

☐ **Class B Conditions** *(From Past Medical History and Physical Examination Worksheets)*

- ☐ TB, active, noninfectious *(Class B1, from Chest X-Ray Worksheet)*
  Treatment: ☐ None ☐ Partial ☐ Completed
- ☐ TB, inactive *(Class B2, from Chest X-Ray Worksheet)*
  Treatment: ☐ None ☐ Partial ☐ Completed
  See Section 4 on page 2 for TB treatment details
- ☐ Syphilis *(with residual deficit)*, treated within the last year
- ☐ Other sexually transmitted infections, treated within last year
- ☐ Current pregnancy, number of weeks pregnant
- ☐ Other *(specify or give details on checked conditions from worksheets)*
- ☐ Hansen's disease, prior treatment
- ☐ Hansen's disease, tuberculoid, borderline, or paucibacillary
- ☐ Sustained, full remission of addiction or abuse of specific* substances
- ☐ Any physical or mental disorder (excluding addiction or abuse of specific* substance but including other substance-related disorder) without harmful behavior or history of such behavior unlikely to recur

*amphetamines, cannabis, cocaine, hallucinogens, inhalants, opioids, phencyclidines, sedative-hypnotics, and anxiolytics

(2) Laboratory Findings *(check all boxes that apply):*

Syphilis: ☐ Not done

	Test name	Date(s) run *(mm-dd-yyyy)*	Negative	Positive	Titer 1	Notes
Screening			☐	☐		
Confirmatory			☐	☐		

Treated ☐ Yes ☐ No
If treated, therapy: ☐ Benzathine penicillin, 2.4 MU IM ☐ Other *(therapy, dose)*:E
Date(s) treatment given *(3 doses for penicillin)*

HIV: ☐ Not done

	Test name	Date(s) run *(mm-dd-yyyy)*	Negative	Positive	Indeterminate	Notes
Screening			☐	☐	☐	
Secondary			☐	☐	☐	
Confirmatory			☐	☐	☐	

DS-2053
09-2007 *(Formerly OF-157)*

(3) Immunizations *(See Vaccination Form, check all boxes that apply)* **Not required for refugee applicants.**

☐ Vaccine history complete

☐ Vaccine history incomplete, requesting waiver *(indicate type below)*

☐ Incomplete vaccine history, no waiver requested

☐ Blanket waiver ☐ Individual waiver

I certify that I understand the purpose of the medical examination and I authorize the required tests to be completed.

Applicant Signature | Panel Physician Signature | Date *(mm-dd-yyyy)*

(4) Tuberculosis Treatment Regimen

(Fill out if applicant has taken in the past, or is now taking TB medication. If drug doses or dates not known or not available, mark "unknown".)

☐ Check if therapy currently prescribed *(if current, don't mark "End Date")*

Medication	Dose/Interval *(i.e., mg/day)*	Start Date *(mm-dd-yyyy)*	End Date *(mm-dd-yyyy)*
☐ Isonaizid (INH)			
☐ Rifampin			
☐ Pyrazinamide			
☐ Ethambutol			
☐ Streptomycin			
☐ Other, specify			

Applicant's weight (kg)

Remarks

PAPERWORK REDUCTION ACT AND PRIVACY ACT NOTICES

Public reporting burden for this collection of information is estimated to average 10 minutes per response, including time required for searching existing data sources, gathering the necessary data, providing the information required, and reviewing the final collection. Persons are not required to provide this information in the absence of a valid OMB approval number. Send comments on the accuracy of this estimate of the burden and recommendations for reducing it to: U.S. Department of State (A/RPS/DIR) Washington, DC 20520.

We ask for information on this form, in the case of applicants for immigrant visas, to determine medical eligibility under INA Sections 212(a) and 221(d), and, in the case of refugees, as required under INA Section 412(b)(4) and (5). If an immigrant visa is issued or refugee status granted, you will convey this form to U.S. Department of Homeland Security (DHS) for disclosure to the Centers for Disease Control and Prevention and to the U.S. Public Health Service. Failure to provide this information may delay or prevent the processing of your case. If an immigrant visa is not issued or refugee status is not granted, this form will be treated as confidential under INA Section 222(f).

Appendix C: Department of State Form 3026

U.S. Department of State

MEDICAL HISTORY AND PHYSICAL EXAMINATION WORKSHEET

For use with DS-2053

OMB No. 1405-0113
EXPIRATION DATE: 09/30/2010
ESTIMATED BURDEN: 35 minutes
(See Page 2 - Back of Form)

Name *(Last, First, MI)* | Exam Date *(mm-dd-yyyy)*

Birth Date *(mm-dd-yyyy)* | Passport Number | Alien *(Case)* Number

1. Past Medical History *(indicate conditions requiring medication or other treatment after resettlement and give details in Remarks)*
NOTE: The following history has been reported, has not been verified by a physician, and should not be deemed medically definitive.

No Yes

General
- Illness or injury requiring hospitalization *(including psychiatric)*

Cardiology
- Angina pectoris
- Hypertension *(high blood pressure)*
- Cardiac arrhythmia
- Congenital heart disease

Pulmonology
- History of tobacco use
  - Current use Yes No
- Asthma
- Chronic obstructive pulmonary disease *(emphysema)*
- History of tuberculosis *(TB)* disease
  - Treated Yes No
  - Current TB symptoms Yes No

Neurology and Psychiatry
- History of stroke, with current impairment
- Seizure disorder
- Major impairement in learning, intelligence, self care, memory, or communication
- Major mental disorder *(including major depression, bipolar disorder, schizophrenia, mental retardation)*
- Use of drugs other than those required for medical reasons
- Addiction or abuse of specific* substance *(drug)*
  *amphetamines, cannabis, cocaine, hallucinogens, inhalants, opioids, phencyclidines, sedative-hypnotics, and anxiolytics
- Other substance-related disorders *(including alcohol addiciton or abuse)*
- Ever taken action to end your life

No Yes

- Ever caused SERIOUS injury to others, caused MAJOR property damage or had trouble with the law because of medical condition, mental disorder, or influence of alcohol or drugs

Obstetrics and Sexually Transmitted Diseases
- Pregnancy Fundal height ____ cm
  Last menstrual period Date *(mm-dd-yyyy)* ____
- Sexually transmitted diseases, specify ____

Endocrinology and Hematology
- Diabetes mellitus
- Thyroid disease
- History of malaria

Other
- Malignancy, specify ____
- Chronic renal disease
- Chronic hepatitis or other chronic liver disease
- Hansen's Disease
  - Tuberculoid Borderline Lepromatous
  - *OR* Paucibacillary Multibacillary
  - Treated Yes No
- Visible disabilities *(including loss of arms or legs)*, specify ____
- Other requiring treatment, specify ____

2. Physical Examination *(indicate findings and give details in Remarks)*

No Yes Applicant appears to be providing unreliable or false information, specify ____

Height ____ cm Weight ____ kg Visual Acuity at 20 feet: Uncorrected L 20/ ____ R 20/ ____

BP ____ / ____ *(mmHg)* Heart rate ____ /min Respiratory rate ____ /min Corrected L 20/ ____ R 20/ ____

***N, normal; A, abnormal; ND, not done**

N*	A*	ND*		N*	A*	ND*	
☐	☐	☐	General appearance and nutritional status	☐	☐	☐	Inguinal region *(including adenopathy)*
☐	☐	☐	Hearing and ears	☐	☐	☐	Extremities *(including pulses, edema)*
☐	☐	☐	Eyes	☐	☐	☐	Musculoskeletal system *(including gait)*
☐	☐	☐	Nose, mouth, and throat *(include dental)*	☐	☐	☐	Skin *(including hypopigmentation, anesthesia, findings consistent with self-inflicted injury or injections)*
☐	☐	☐	Heart *(S1, S2, murmur, rub)*	☐	☐	☐	Lymph nodes
☐	☐	☐	Breast	☐	☐	☐	Nervous system *(including nerve enlargement)*
☐	☐	☐	Lungs	☐	☐	☐	Mental status *(including mood, intelligence, perception, thought processes, and behavior during examination)*
☐	☐	☐	Abdomen *(including liver, spleen)*				
☐	☐	☐	Genitalia *(including circumcision, infection(s))*				

DS-3026
09-2007

3. Additional Testing Needed Prior to Approving Medical Clearance

No	Yes	
☐	☐	Physical examination or laboratory results contradict medical history
☐	☐	Referral prior to departure If yes, provide results
☐	☐	Referral prior to departure If yes, provide results

4. Follow-up Needed After Arrival

☐ No ☐ Yes, within 1 week ☐ Yes, within 1 month ☐ Yes, within 6 months

☐ For continuing medication, list type, dose, and frequency

☐ For continuing other treatment, specify

5. Remarks *(describe any abnormal history, abnormal findings, and resulting interventions)*

PAPERWORK REDUCTION ACT AND PRIVACY ACT NOTICES

Public reporting burden for this collection of information is estimated to average 35 minutes per response, including time required for searching existing data sources, gathering the necessary data, providing the information required, and reviewing the final collection. Persons are not required to provide this information in the absence of a valid OMB approval number. Send comments on the accuracy of this estimate of the burden and recommendations for reducing it to: the U.S. Department of State (A/ISS/DIR) Washington, DC 20520.

AUTHORITIES The information is sought pursuant to Sections 212(a), 221(d), 101, and 412(b)(4) and (5) of the Immigration and Nationality Act.

PURPOSE The primary purpose for soliciting medical information is to determine whether an applicant is eligible to obtain a visa and alien registration. This form is designed to record the result of the medical examination required by INA 221(d), which determines whether an applicant has a medical condition that renders the applicant ineligible under INA Section 212(a).

ROUTINE USES The information solicited on this form may be made available to the U.S. Department of Homeland Security for disclosure to the Centers for Disease Control and Prevention and to the U.S. Public Health Service. The information provided also may be released to federal agencies for law enforcement, counter-terrorism and homeland security purposes; to Congress and courts within their sphere of jurisdiction; and to other federal agencies for certain personnel and records management matters.
Although furnishing this information is voluntary, failure to provide this information may delay or prevent the processing of your case.

Appendix D: Log-Log Functions for Covariates

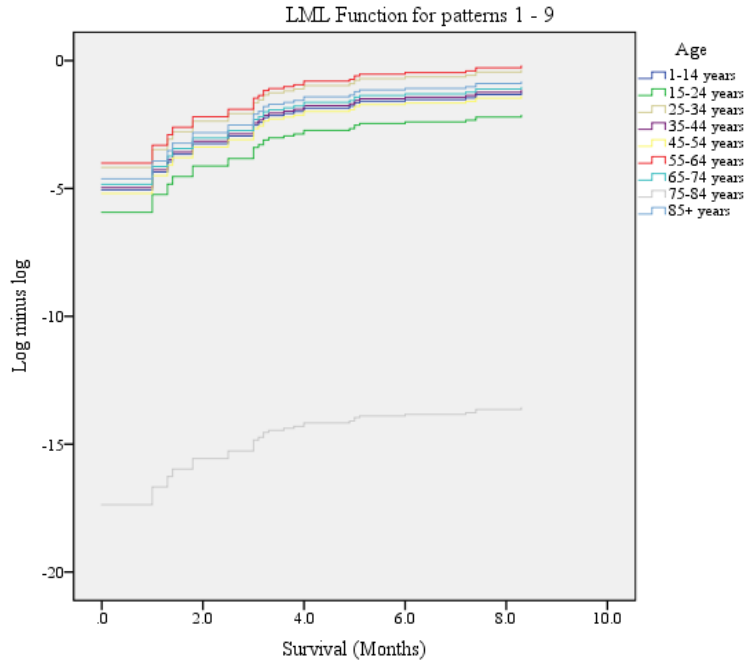

Figure D1. Log-log curve for age.

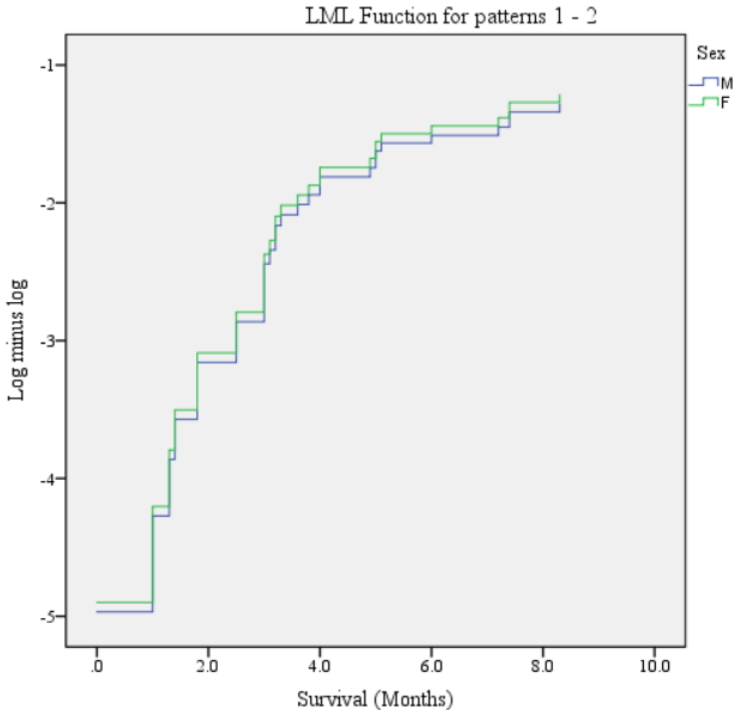

Figure D2. Log-log curve for sex.

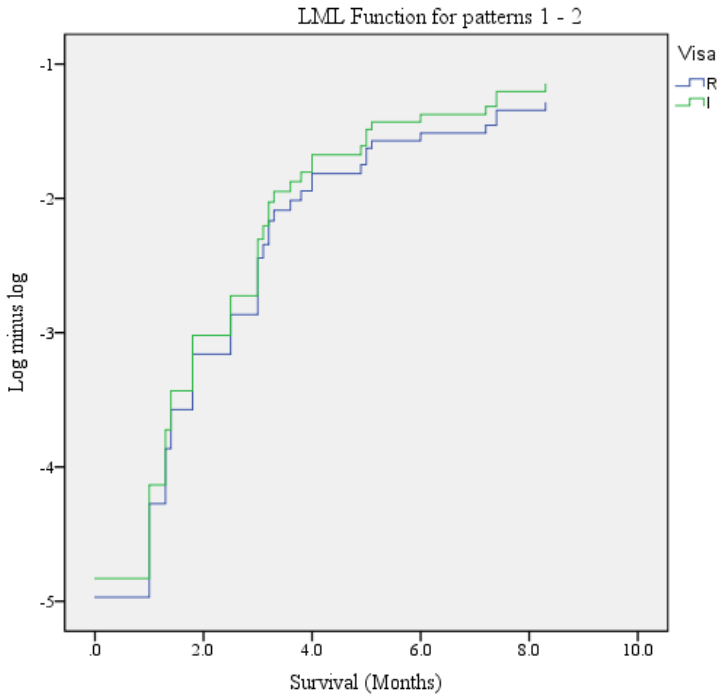

Figure D3. Log-log curve for visa-type.

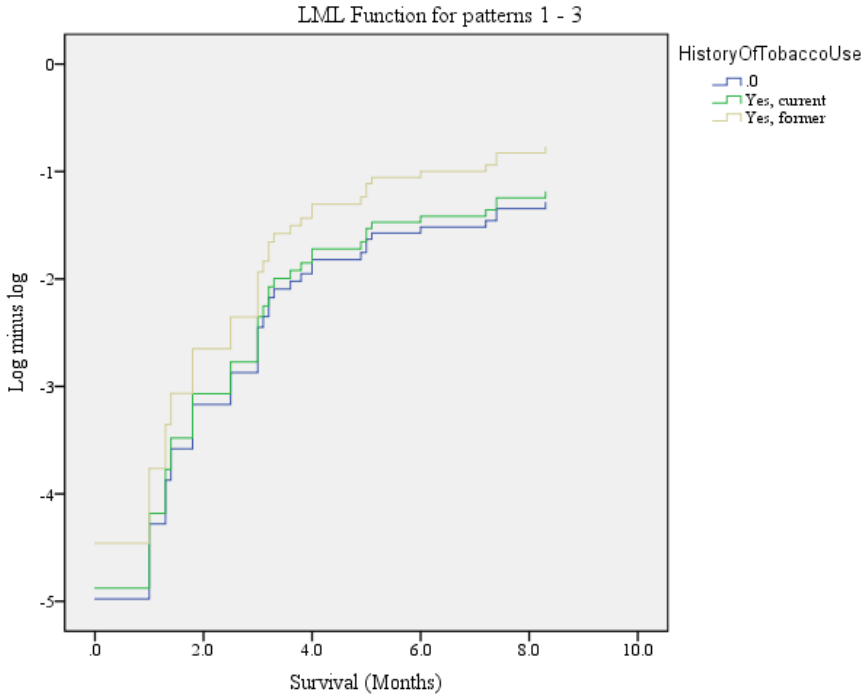

Figure D4. Log-log curve for history of tobacco use.

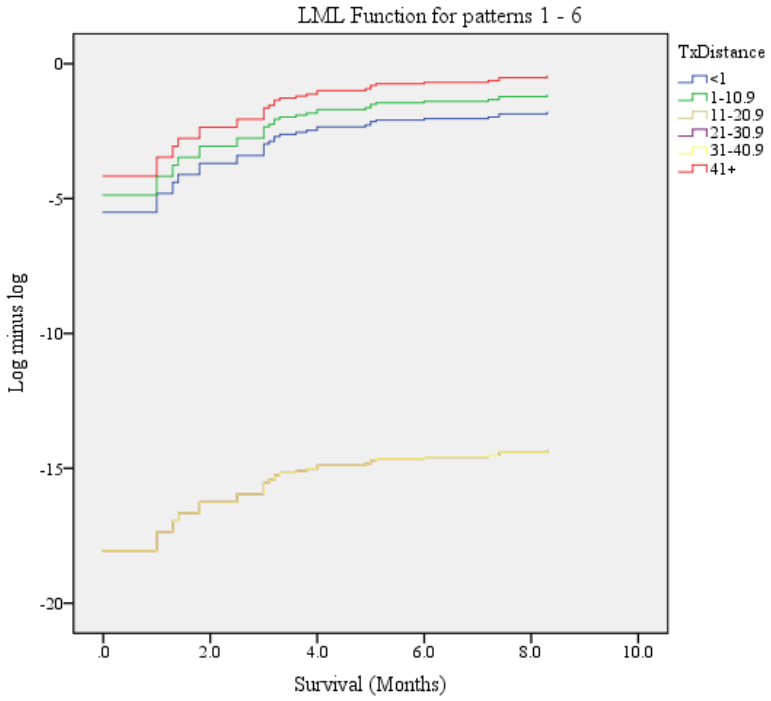

Figure D5. Log-log curve for distance between residence and treatment facility.

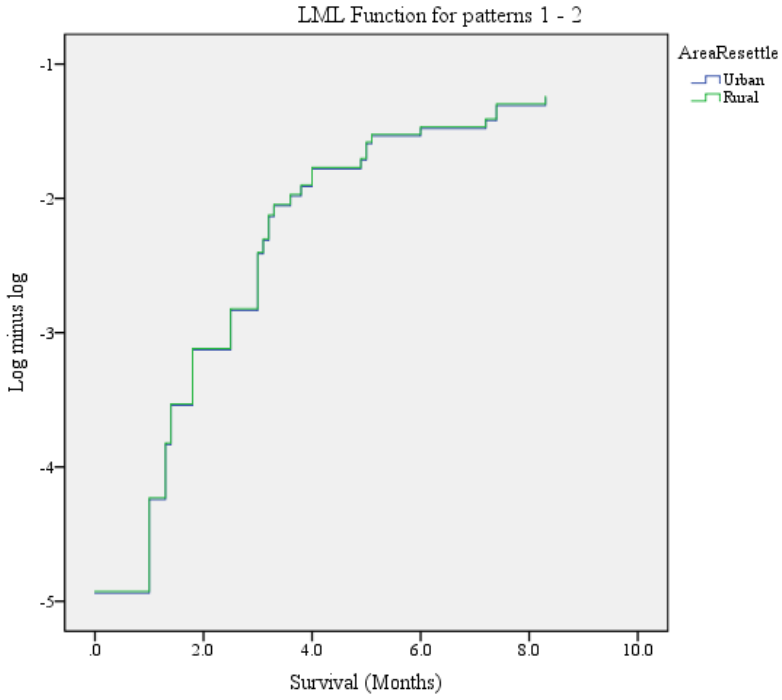

Figure D6. Log-Log Curve for Area of Resettlement.

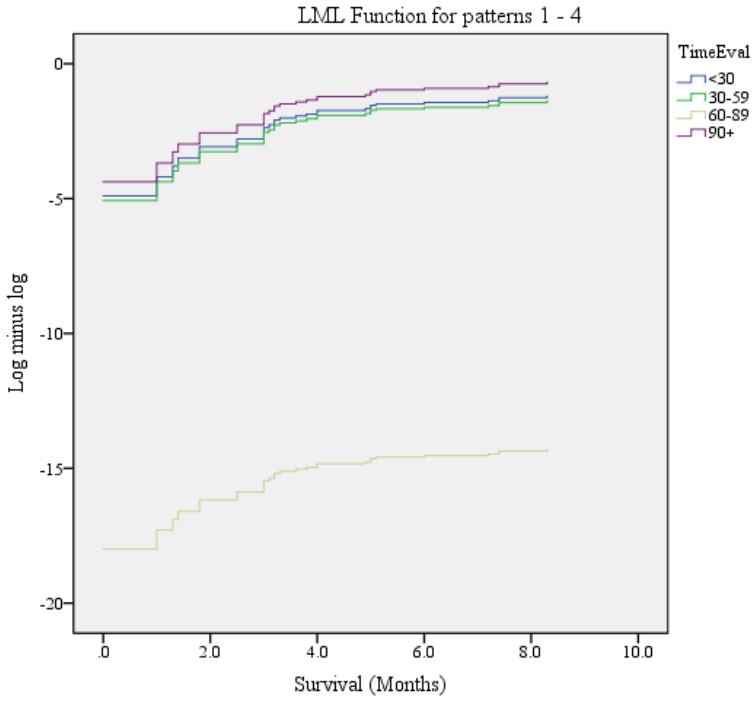

Figure D7. Log-log curve for time between arrival and Medical Evaluation.

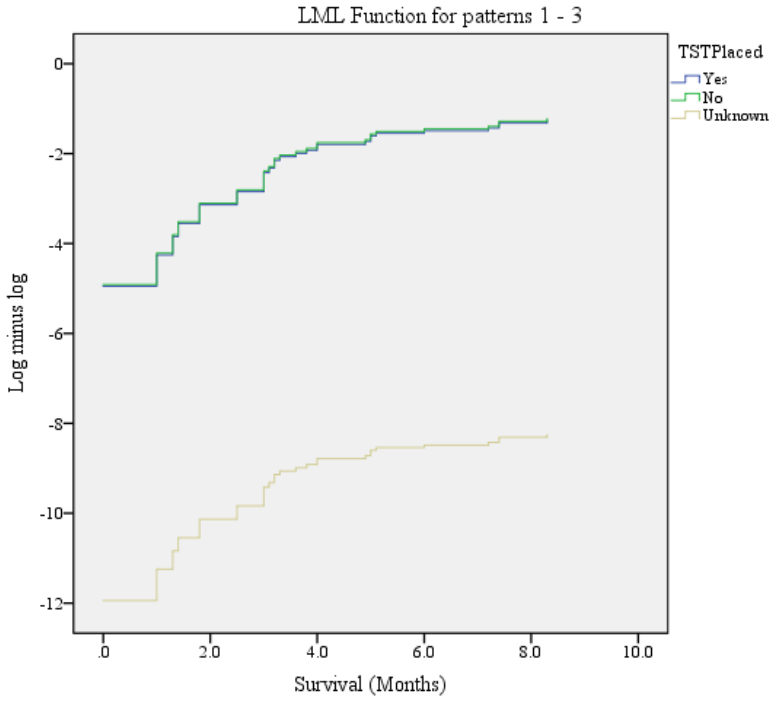

Figure D8. Log-log curve for TST.

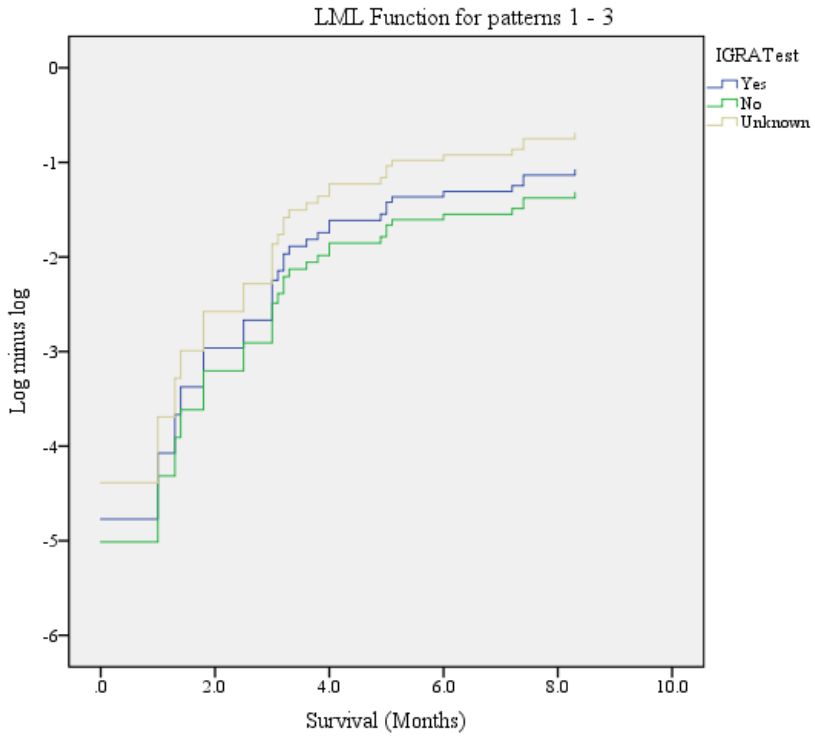

Figure D9. Log-log curve for IGRA.

Appendix E: Cox Proportional Hazard Regression Survival Curves

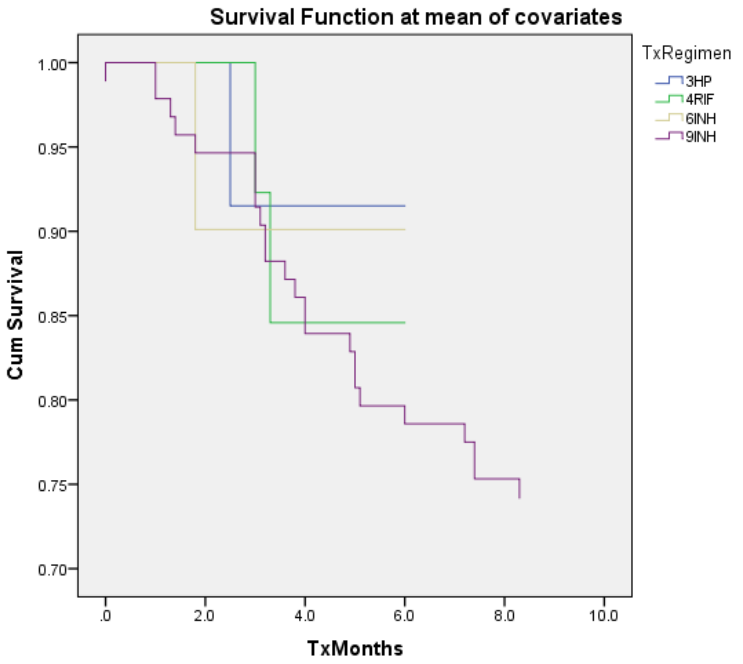

Figure E30. Survival function for male participants.

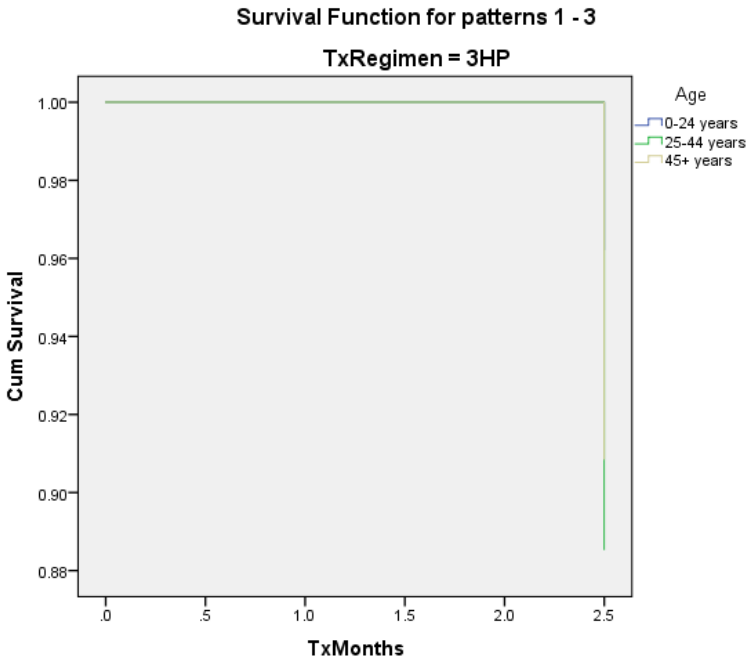

Figure E31. Survival function for participants on 3HP by age group.

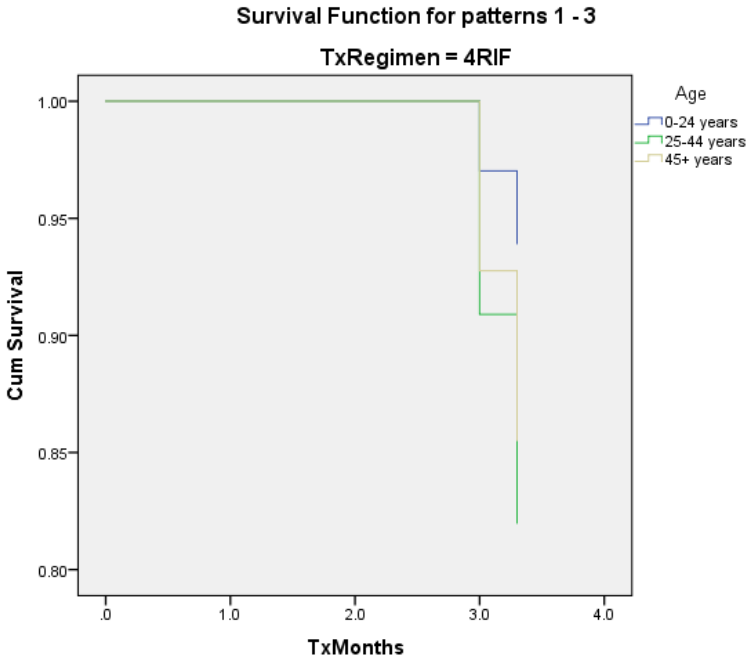

Figure E32. Survival function for participants on 4RIF by age group.

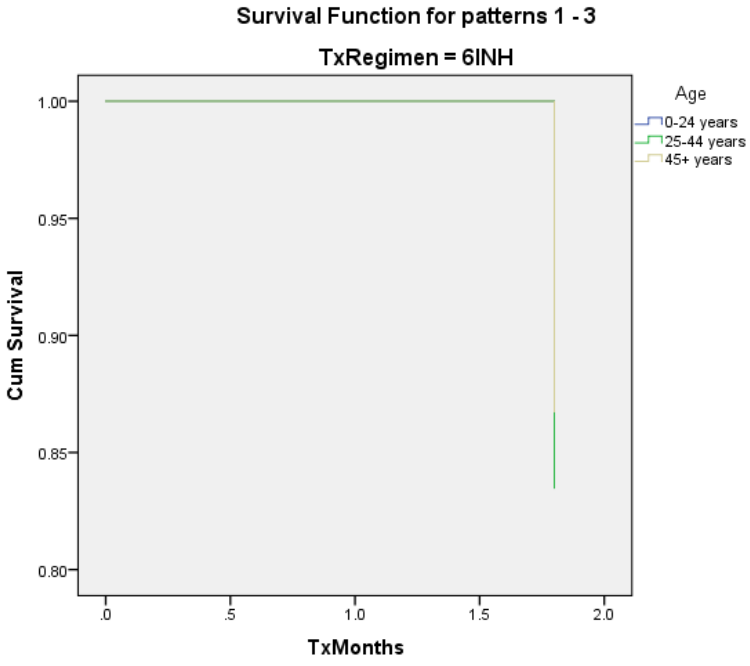

Figure E33. Survival function for participants on 6INH by age group.

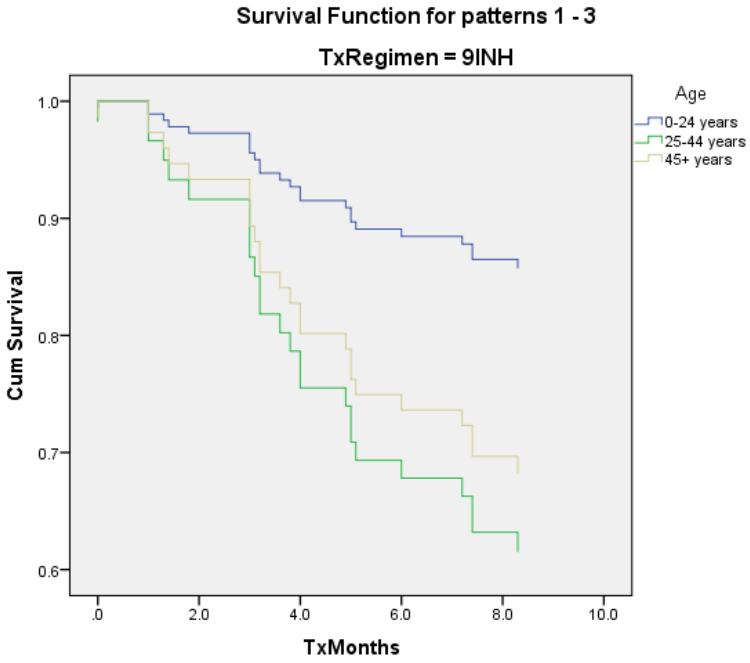

Figure E34. Survival function for participants on 9INH by age group.

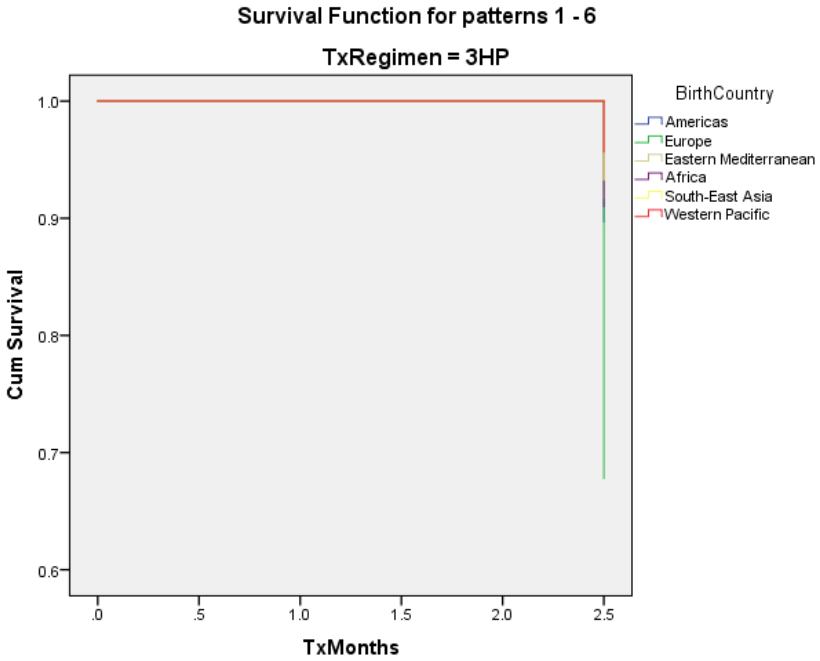

Figure E35. Survival function for participants on 3HP by birth country

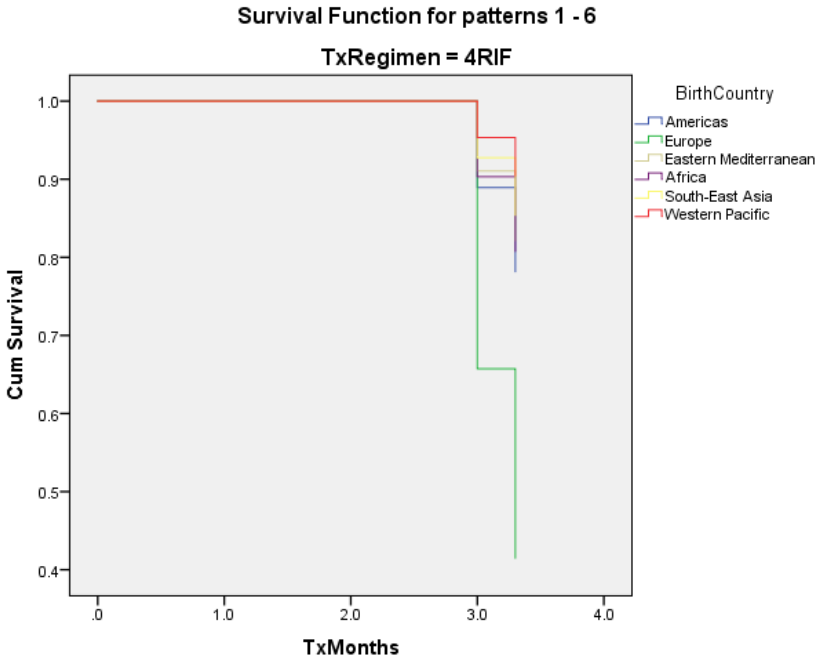

Figure E36. Survival function for participants on 4RIF by birth country.

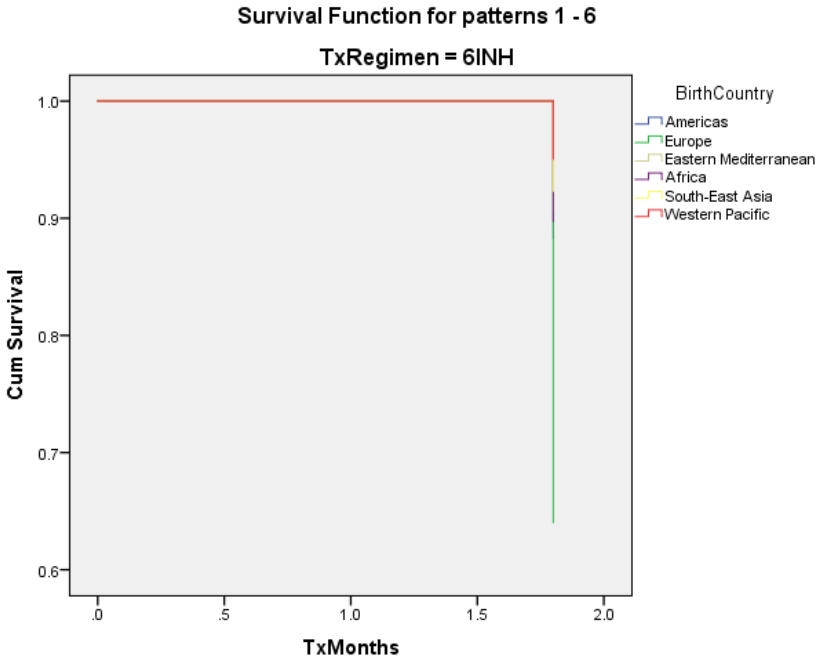

Figure E37. Survival function for participants on 6INH by birth country.

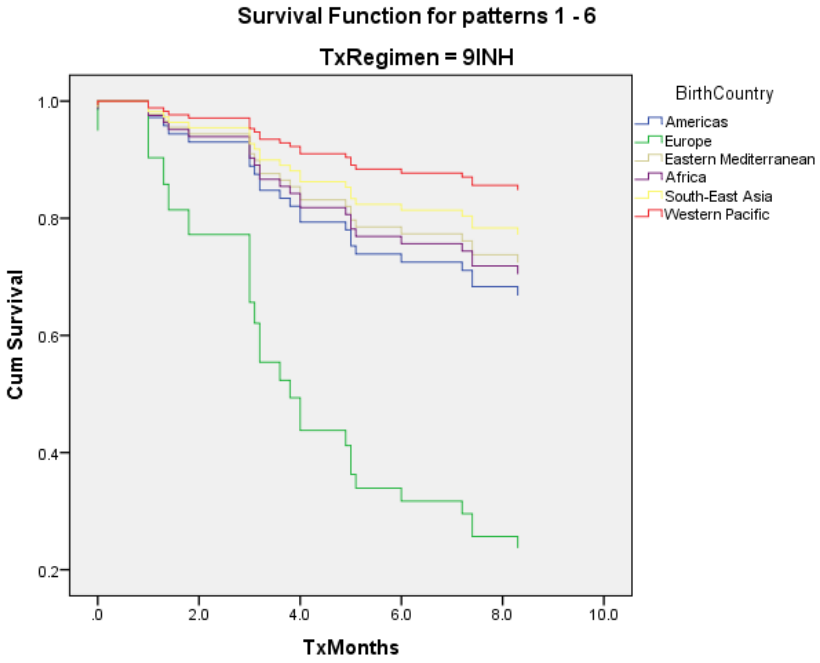

Figure E38. Survival function for participants on 9INH by birth country.

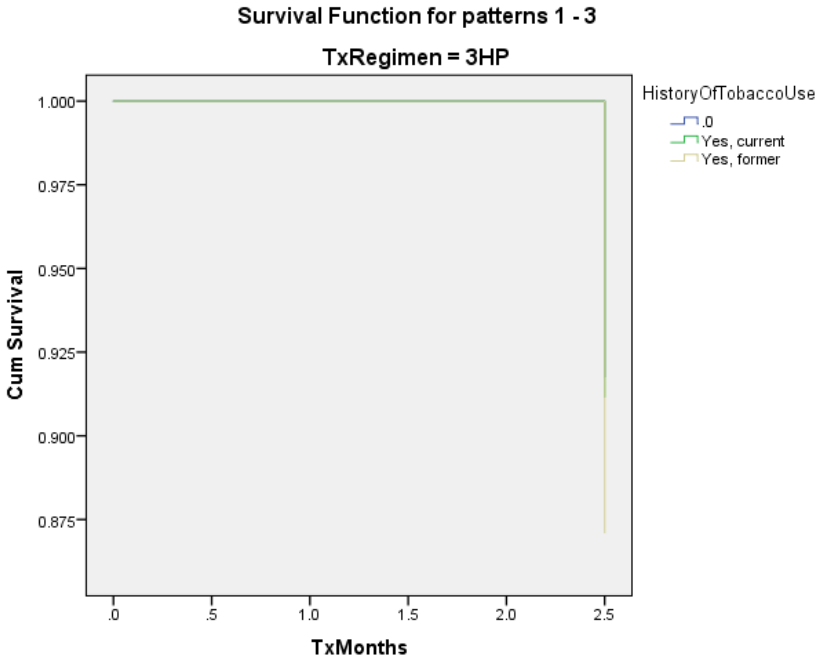

Figure E39. Survival function for participants on 3HP by smoking status.

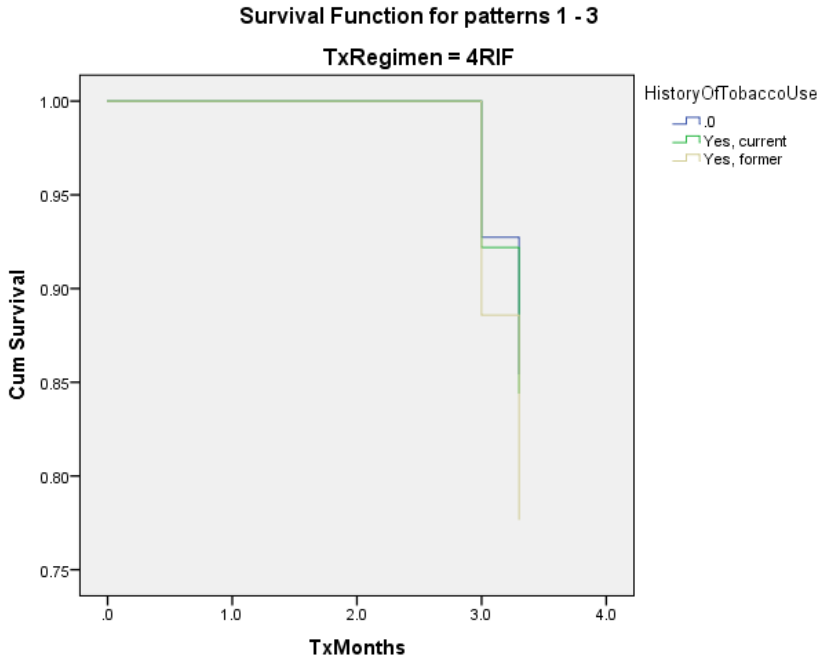

Figure E40. Survival function for participants on 4RIF by smoking status.

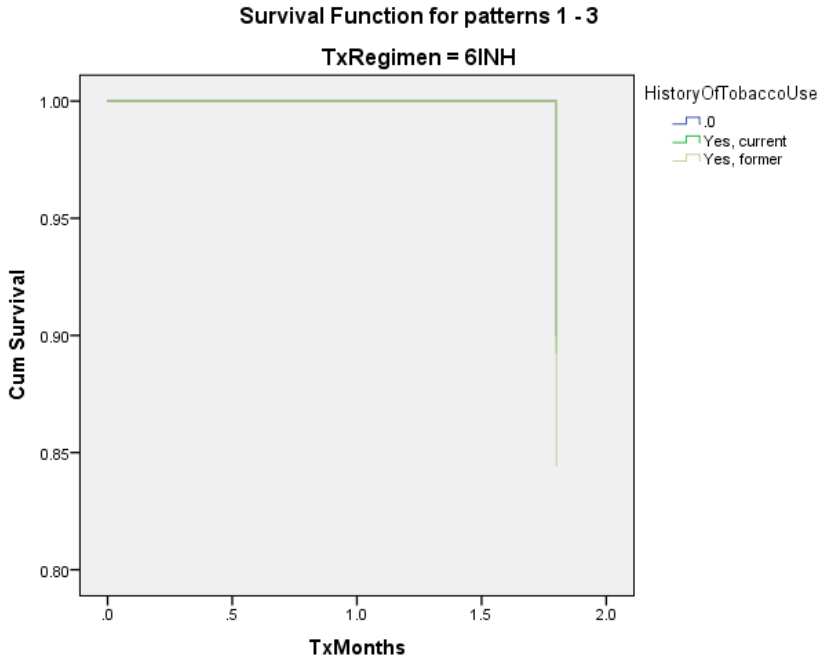

Figure E41.Survival function for participants on 6INH by smoking status.

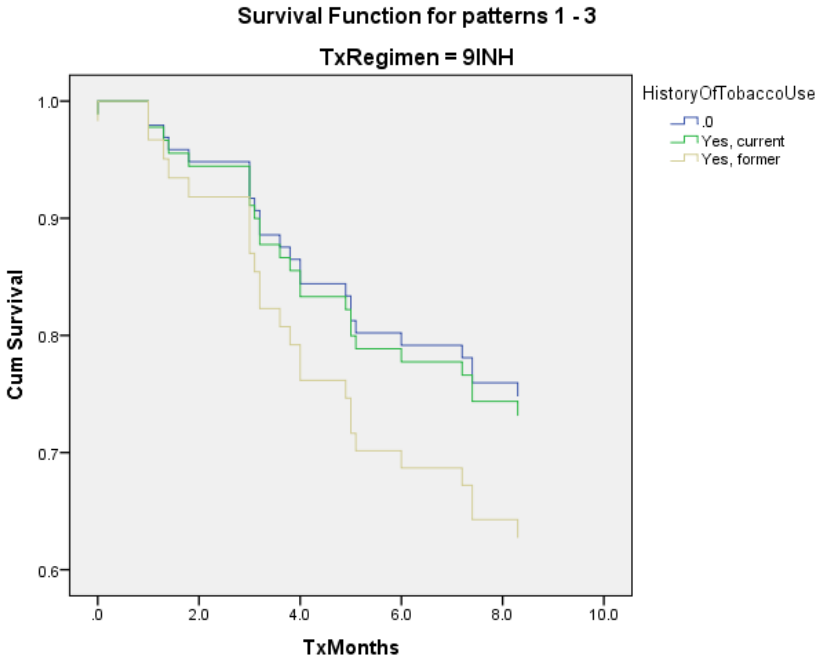

Figure E42. Survival function for participants on 9INH by smoking status.

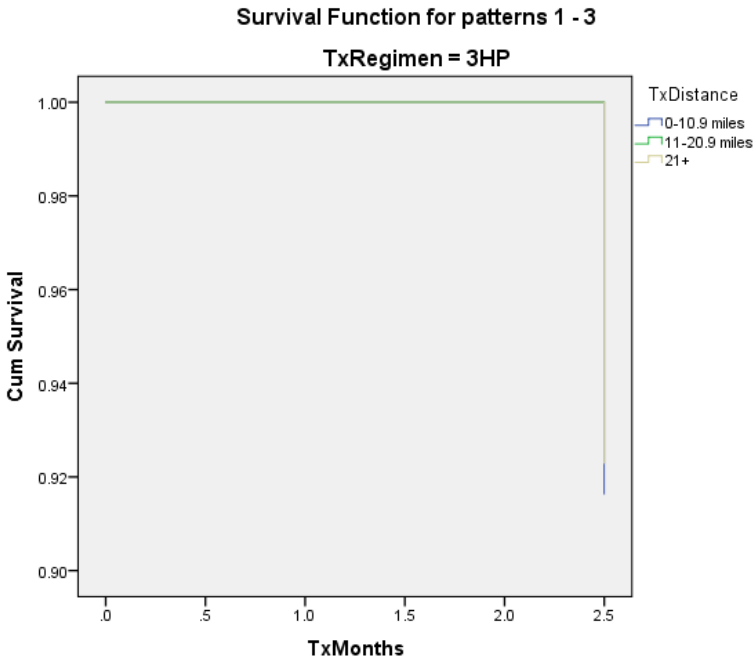

Figure E43. Survival function for participants on 3HP by treatment facility distance.

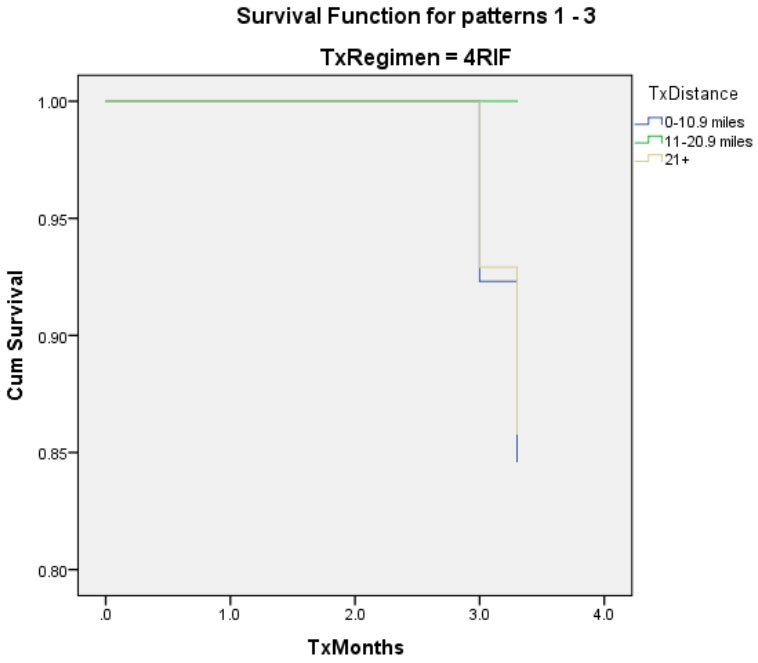

Figure E44. Survival function for participants on 4RIF by treatment facility distance.

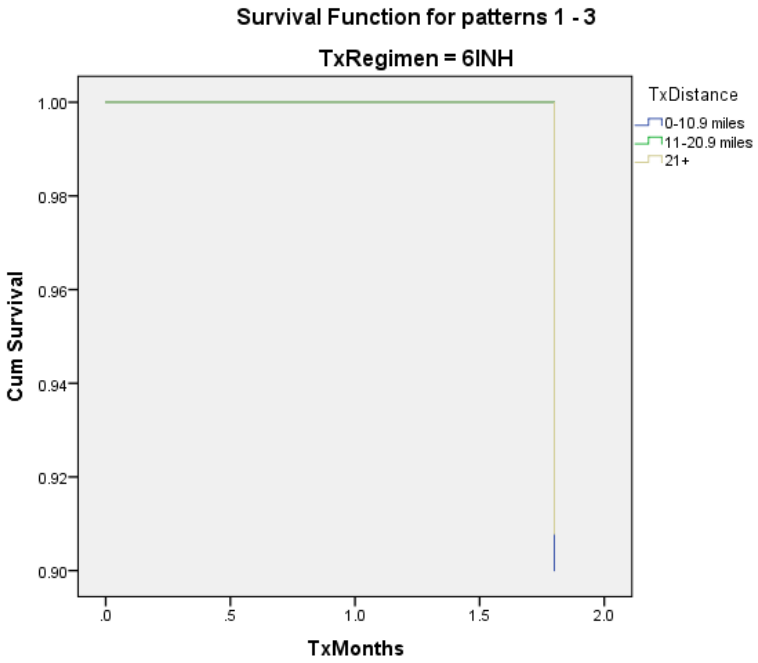

Figure E45. Survival function for participants on 6INH by treatment facility distance.

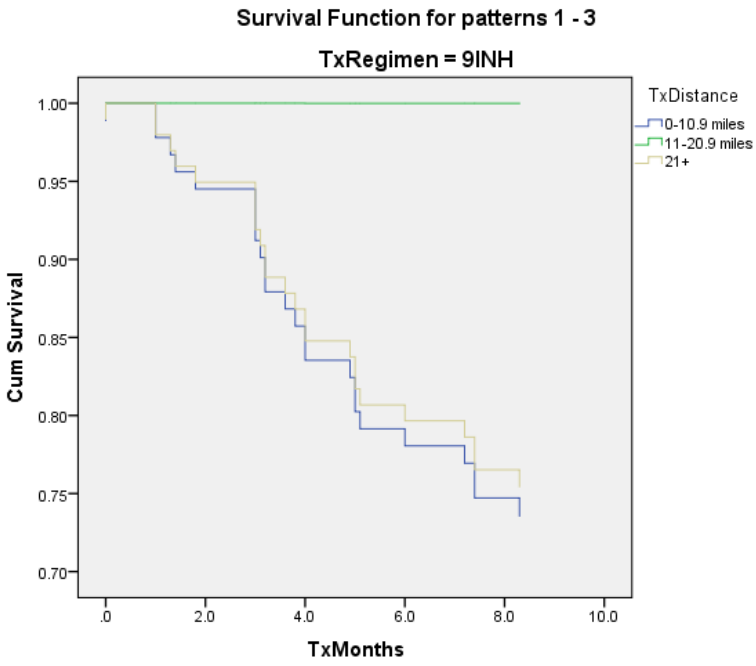

Figure E46. Survival function for participants on 9INH by treatment facility distance.

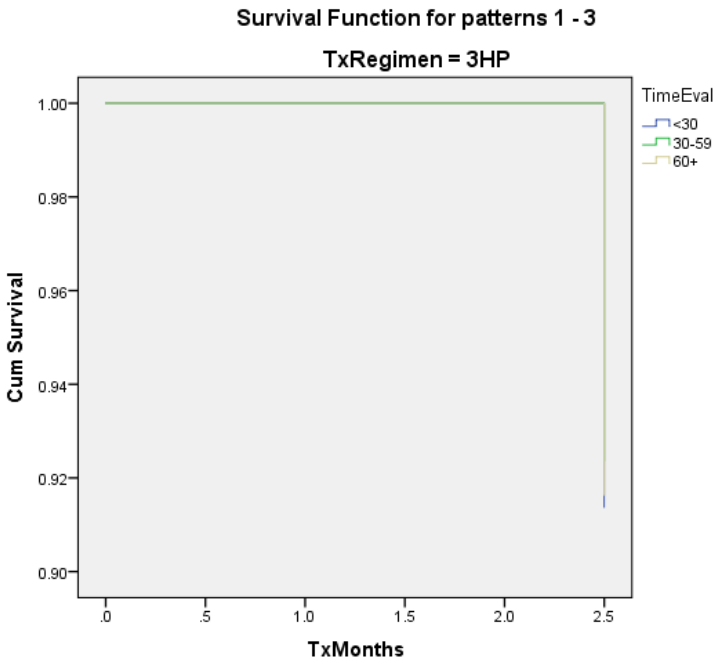

Figure E47. Survival function for participants on 3HP by time between evaluation.

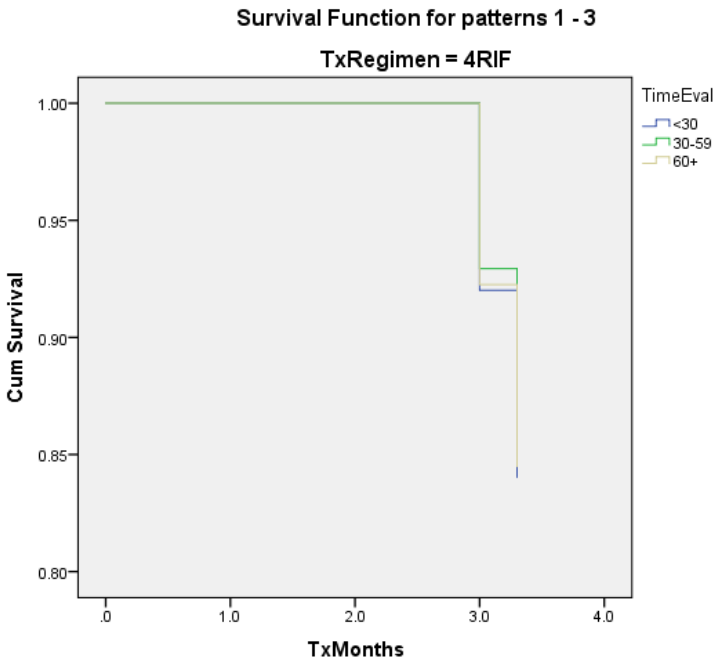

Figure E48. Survival function for participants on 4RIF by time between evaluation.

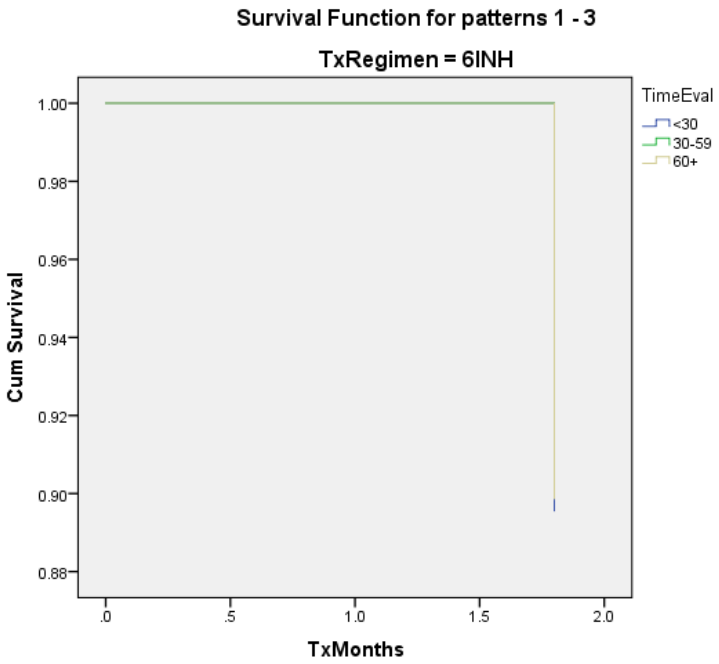

Figure E49. Survival function for participants on 6INH by time between evaluation.

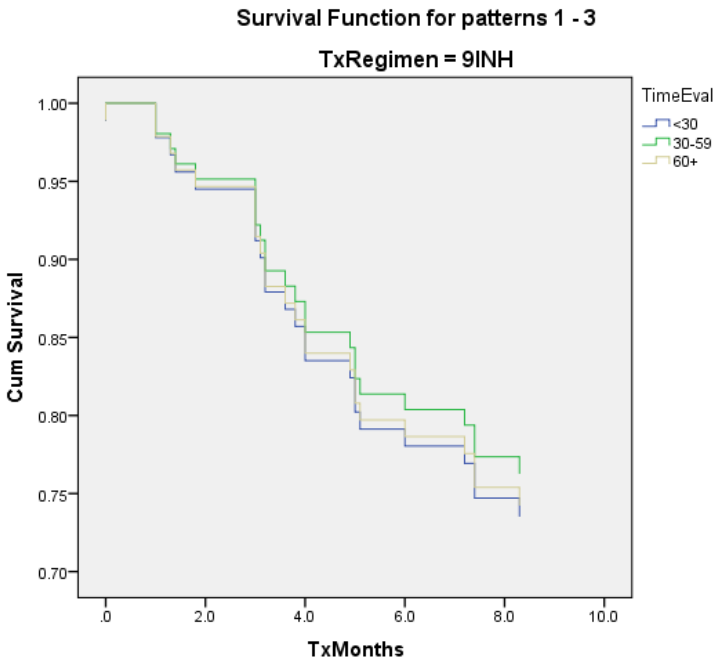

Figure E50. Survival function for participants on 9INH by time between evaluation.

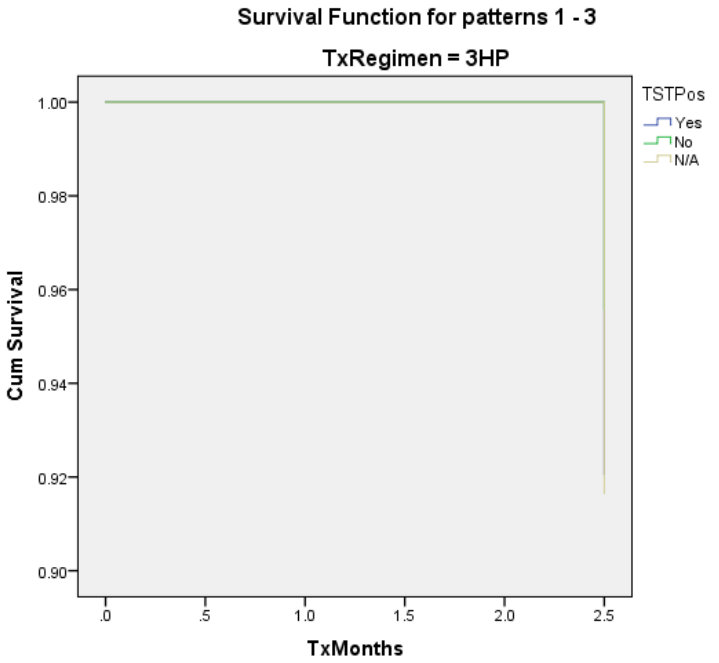

Figure E51. Survival function for participants on 3HP by TST positivity.

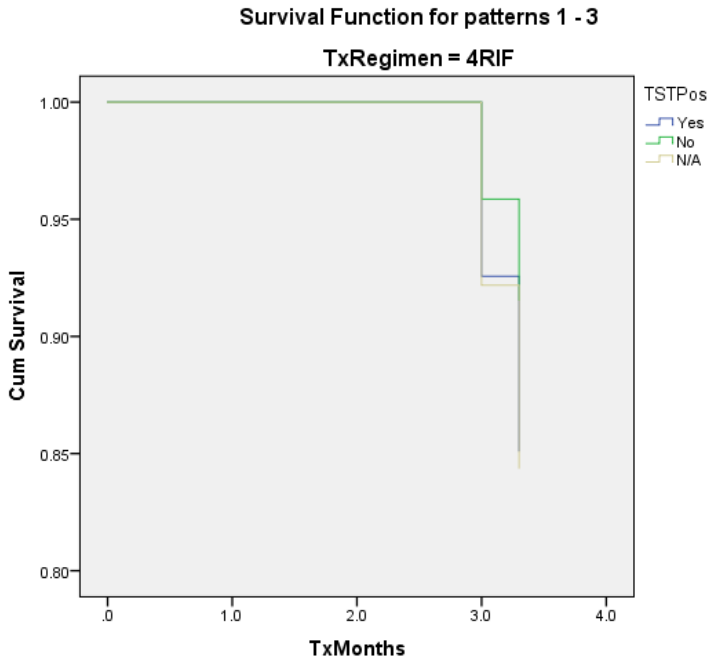

Figure E52. Survival function for participants on 4RIF by TST positivity.

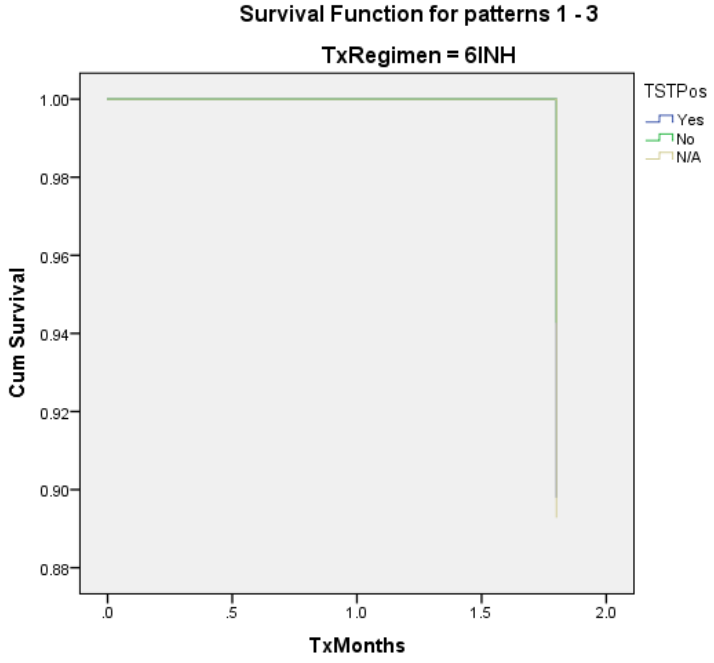

Figure E53. Survival function for participants on 6INH by TST positivity.

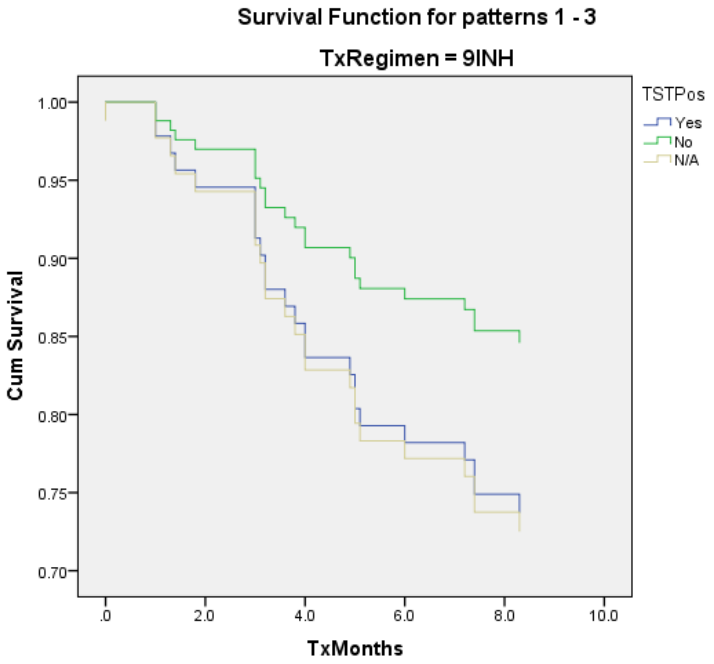

Figure E54. Survival function for participants on 9INH by TST positivity.

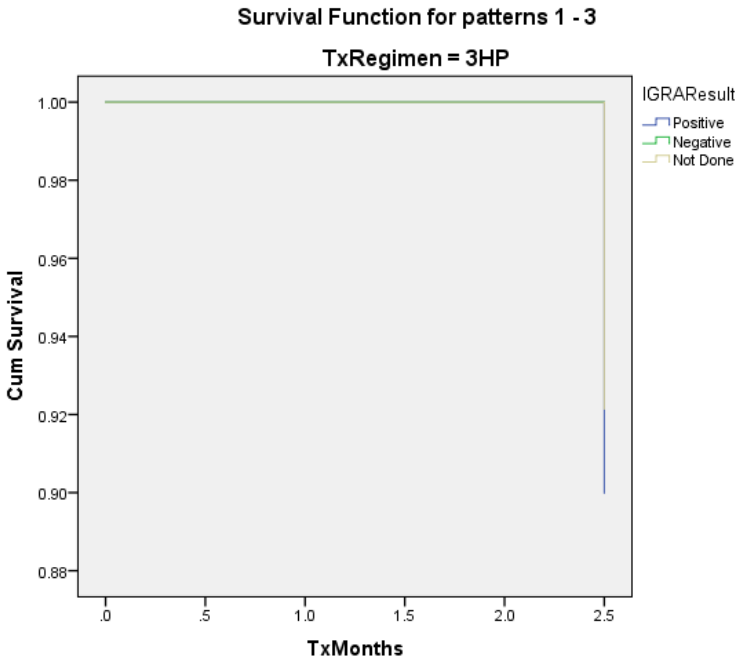

Figure E55. Survival functions for participants on 3HP by IGRA positivity.

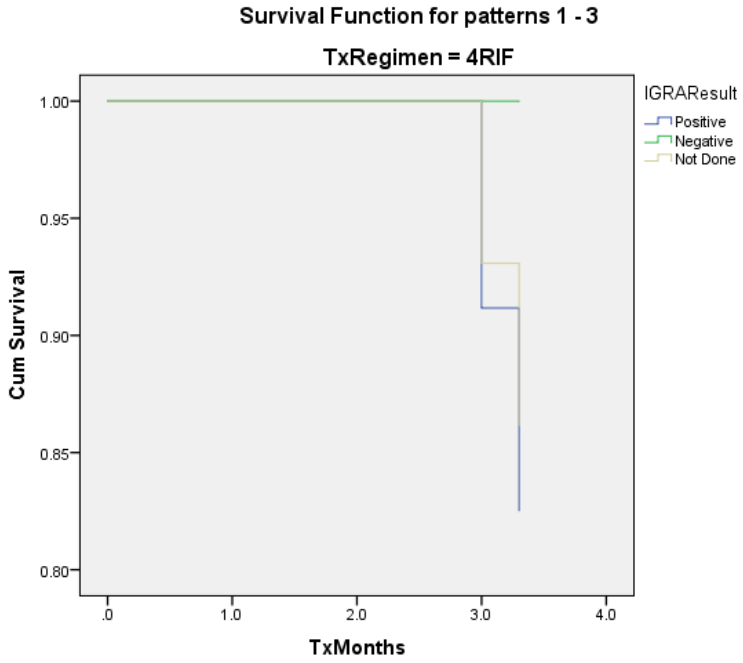

Figure E56. Survival functions for participants on 4RIF by IGRA positivity.

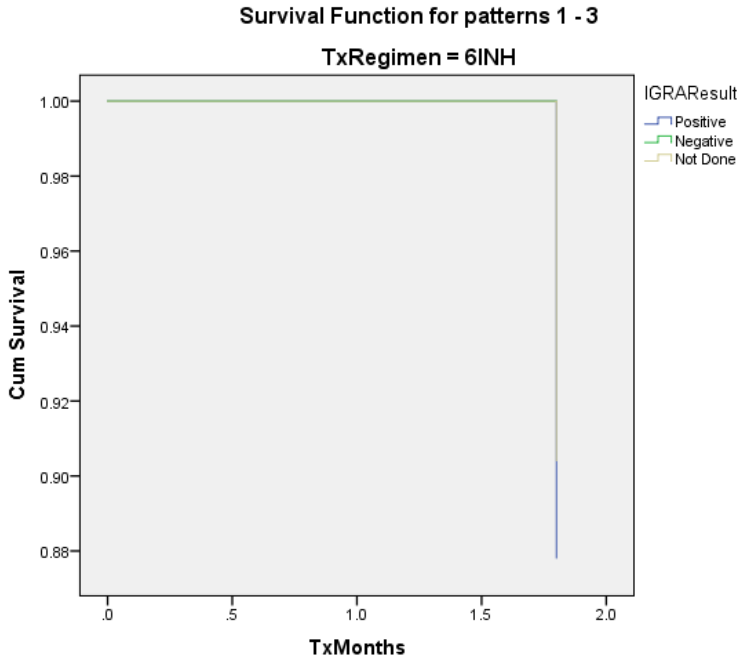

Figure E57. Survival functions for participants on 6INH by IGRA positivity.

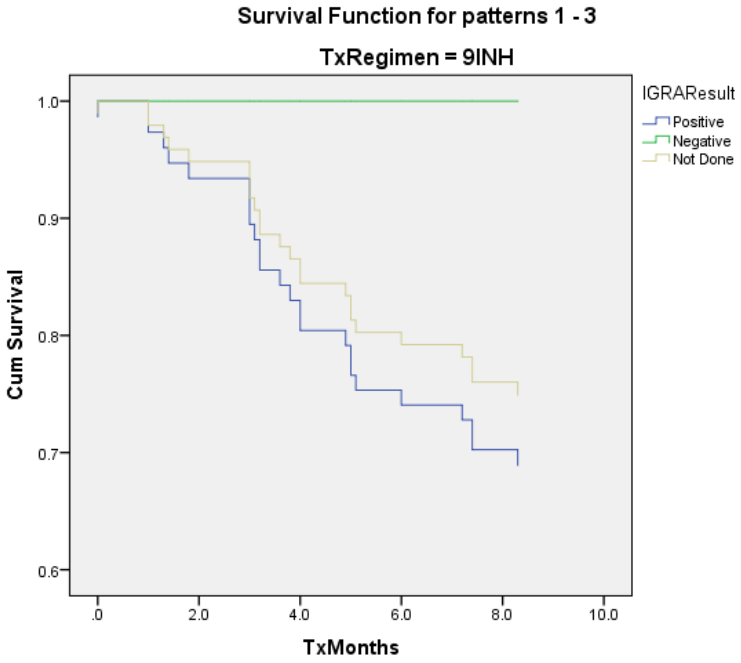

Figure E58. Survival functions for participants on 9INH by IGRA positivity.

Appendix F: Cox Proportional Hazard Reference Groups

Cox Proportional Hazard Analysis Reference Groups Without Visa-stratification

Variable(s)*	Number in Stratum (*N = 140)*
TxRegimen	
TxRegimen (1: 3HP)	24
TxRegimen (2: 4RIF)	13
TxRegimen (3: 6INH)	10
TxRegimen (4: 9INH)	**93**
Sex	
Male (1)	79
Female (2)	**61**
Age	
Age (1: 0-24 years)	51
Age (2: 25-44 years)	33
Age (3: 45+ years)	**56**
BirthCountry	
BirthCountry (1: Americas)	14
BirthCountry (2: Europe or E. Mediterranean)	25
BirthCountry (3: Africa)	41
BirthCountry (4: South-East Asia)	46
BirthCountry (5: Western Pacific)	**14**
Visa	
Refugee (1)	109
Immigrant (2)	**31**
TimeEval	
TimeEval (1: <30 days)	97
TimeEval (2: 30-59 days)	29
TimeEval (3: 60+ days)	**14**
AreaResettle	
Urban (1)	129
Rural (2)	**12**
TxDistance	
TxDistance (1: 0-10.9 miles)	126
TxDistance (2: 11-20.9 miles)	1
TxDistance (3: 21+ miles)	**13**
HistoryOfTobaccoUse	
No (1)	119
Yes, current or former (2)	**21**
TSTPos	
Positive (1)	65
Negative or not done (2)	**75**
IGRAResult	
Positive (1)	29
Negative or not done (2)	**111**

*Note. *Bold font signifies Reference Group.*

Cox Proportional Hazard Analysis Reference Groups: Count by Visa-type

Variable(s)*	Refugee (*N=109)*	Immigrant (*N*=31)
TxRegimen		
TxRegimen (1: 3HP)	24	0
TxRegimen (2: 4RIF)	12	1
TxRegimen (3: 6INH)	8	2
TxRegimen (4: 9INH)	**65**	**28**
Sex		
Male (1)	66	13
Female (2)	**43**	**18**
Age		
Age (1: 0-24 years)	31	20
Age (2: 25-44 years)	29	4
Age (3: 45+ years)	**49**	**7**
BirthCountry		
BirthCountry (1: Americas)	0	14
BirthCountry (2: Europe or E. Mediterranean)	24	1
BirthCountry (3: Africa)	38	3
BirthCountry (4: South-East Asia)	45	1
BirthCountry (5: Western Pacific)	**2**	**12**
TimeEval		
TimeEval (1: <30 days)	87	10
TimeEval (2: 30-59 days)	18	11
TimeEval (3: 60+ days)	**4**	**10**
AreaResettle		
Urban (1)	109	19
Rural (2)	**0**	**12**
TxDistance		
TxDistance (1: 0-10.9 miles)	108	18
TxDistance (2: 11-20.9 miles)	0	1
TxDistance (3: 21+ miles)	**1**	**12**
HistoryOfTobaccoUse		
No (1)	91	28
Yes, current or former (2)	**18**	**3**
TSTPos		
Positive (1)	48	17
Negative or not done (2)	**61**	**14**
IGRAResult		
Positive (1)	21	8
Negative or not done (2)	**88**	**23**

*Note. *Bold font signifies Reference Group.*

Appendix G: Cox Proportional Hazard Regression Models

Model	Variable(s)
1	TxRegimen
	TxRegimen (3HP)
	TxRegimen (4RIF)
	TxRegimen (6INH)
2	Sex
	Sex*Age
	Sex*BirthCountry
	Sex*Visa
	Sex*HistoryOfTobaccoUse
	Sex*TxDistance
	Sex*AreaResettle
	Sex*TimeEval
	Sex*TSTPos
	Sex*IGRAResult
3	Age
	Age*BirthCountry
	Age*Visa
	Age*HistoryOfTobaccoUse
	Age*TxDistance
	Age*AreaResettle
	Age*TimeEval
	Age*TSTPos
	Age*IGRAResult
4	BirthCountry
	BirthCountry*Visa
	BirthCountry*HistoryOfTobaccoUse
	BirthCountry*TxDistance
	BirthCountry*AreaResettle
	BirthCountry*TimeEval
	BirthCountry*TSTPos
	BirthCountry*IGRAResult
5	Visa
	Visa*HistoryOfTobaccoUse
	Visa*TxDistance
	Visa*AreaResettle

(*table continues*)

Model	Variable(s)
5, continued	Visa*TimeEval
	Visa*TSTPos
	Visa*IGRAResult
6	HistoryOfTobaccoUse
	HistoryOfTobaccoUse*TxDistance
	HistoryOfTobaccoUse*AreaResettle
	HistoryOfTobaccoUse*TimeEval
	HistoryOfTobaccoUse*TSTPos
	HistoryOfTobaccoUse*IGRAResult
7	TxDistance
	TxDistance*AreaResettle
	TxDistance*TimeEval
	TxDistance*TSTPos
	TxDistance*IGRAResult
8	AreaResettle
	AreaResettle*TimeEval
	AreaResettle*TSTPos
	AreaResettle*IGRAResult
9	TimeEval
	TimeEval*TSTPos
	TimeEval*IGRAResult
	TSTPos
	TSTPos*IGRAResult
10	IGRAResult
11	Sex*Age*BirthCountry*Visa*HistoryOfTobaccoUse*TxDistance*AreaResettle*TimeEval*TSTPos*IGRAResult

Appendix H: Ad Hoc Analyses Result Tables

Table H1

Ad Hoc Analysis 2: CPHR with Visa-type Stratification and Covariate Interactions

Visa	Variables	*HR*	*SE*	p-value	95 % CI Lower	95 % CI Upper
Refugee	CPHR with levels of Age interacting with levels of Visa-type[a]					
	Age (1: 0-24 years)	0.67	1.14	0.73	0.73	6.22
	Age (2: 25-44 years)	0.33	1.44	0.44	0.02	5.57
	Age (3: 45+ years)	-	-	-	-	-
	Visa (Refugee)	-	-	-	-	-
	Visa (Immigrant)	-	-	-	-	-
	Age (1: 0-24 years) in Visa ‡	0.21	0.77	0.04	0.05	0.96
	Age (2: 25-44 years) in Visa	0.90	0.48	0.83	0.35	2.31
	CPHR with levels of Age interacting with levels of Distance to LTBI Treatment Facility[b]					
	Age (1: 0-24 years)	0.67	1.14	0.73	0.73	6.22
	Age (2: 25-44 years)	0.33	1.44	0.44	0.02	5.57
	Age (3: 45+ years)	-	-	-	-	-
	Distance to Treatment Facility (1: 0-10.9 miles)	0.73	373.48	0.99	0.00	-
	Distance to Treatment Facility (3: 21+ miles)	-	-	-	-	-
	Age (1: 0-24 years) in Distance to Treatment Facility (1:0-10.9 miles) ‡	0.21	0.77	0.05	0.05	0.98
	Age (2: 25-44 years) in Distance to Treatment Facility (1:0-10.9 miles)	4.11	0.77	0.07	0.91	18.61
	Age (1: 0-24 years) in Distance to Treatment Facility (2: 11-20.9 miles)	0.00	1,242.96	0.99	0.00	--
	CPHR with levels of Age interacting with levels of History of Tobacco Use[c]					
	Age (1: 0-24 years)	0.67	1.14	0.73	0.73	6.22
	Age (2: 25-44 years)	0.33	1.44	0.44	0.02	5.57
	Age (3: 45+ years)	-	-	-	-	-
	History of Tobacco Use (1: Yes)	0.53	0.65	0.33	0.15	1.89
	History of Tobacco Use (2: Never)	-	-	-	-	-
	Age (1: 0-24 years) in History of Tobacco Use (1: Yes) ‡	0.22	0.77	0.05	0.05	0.99
	Age (2: 25-44 years) in History of Tobacco Use (1: Yes)	1.00	0.49	0.99	0.38	2.65
	CPHR with levels of Age interacting with levels of Area of Resettlement[d]					
	Age (1: 0-24 years)	0.67	1.14	0.73	0.73	6.22
	Age (2: 25-44 years)	0.33	1.44	0.44	0.02	5.57
	Age (3: 45+ years)	-	-	-	-	-
	Area of Resettlement (1: Urban)	-	-	-	-	-
	Area of Resettlement (2: Rural)	-	-	-	-	-
	Age (1: 0-24 years) in Area of Resettlement (1: Urban) ‡	0.21	0.77	0.04	0.05	0.96
	Age (2: 25-44 years) in Area of Resettlement (1: Urban)	0.90	0.48	0.83	0.35	2.31
Immigrant	*CPHR with levels of Age interacting with levels of Birth Country[e]					
	Age (1: 0-24 years)	0.67	1.14	0.73	0.73	6.22
	Age (2: 25-44 years)	0.33	1.44	0.44	0.02	5.57
	Age (3: 45+ years)	-	-	-	-	-
	Birth Country (1: Americas)	6,189.81	137.51	0.95	0.00	6.9E+120
	Birth Country (2: Europe or Eastern Mediterranean)	12,694.36	137.51	0.95	0.00	1.4E+121
	Birth Country (3: Africa)	15,379.85	137.51	0.94	0.00	1.7E+121
	Birth Country (5: Western Pacific)	-	-	-	-	-
	Age (1: 0-24 years) in Birth Country (1: Americas)	1.96	0.82	0.41	0.39	9.77
	Age (1: 0-24 years) in Birth Country (3: Africa)	0.00	1,208.45	0.99	0.00	--

(*table continues*)

Visa	Variables	HR	SE	p-value	95 % CI Lower	95 % CI Upper
	Age (2: 25-44 years) in Birth Country (2: Europe or Eastern Mediterranean)	5.70	1.17	0.14	0.58	56.54
	Age (2: 25-44 years) in Birth Country (3: Africa) ‡	12.20	1.25	0.05	1.06	140.36
	CPHR with levels of Age interacting with levels of Area of Resettlement[f]					
	Age (1: 0-24 years)	0.67	1.14	0.73	0.73	6.22
	Age (2: 25-44 years)	0.33	1.44	0.44	0.02	5.57
	Age (3: 45+ years)	-	-	-	-	-
	Area of Resettlement (1: Urban)	0.00	146.14	0.96	0.00	3.4E+21
	Area of Resettlement (2: Rural)	-	-	-	-	-
	Age (1: 0-24 years) in Area of Resettlement (1: Urban)	0.42	1.12	0.44	0.05	3.77
	Age (2: 25-44 years) in Area of Resettlement (1: Urban) ‡	4.42	0.77	0.05	0.98	20.05

Note. Abbreviations: *HR* = Hazard Rate; *SE* = Standard Error. [a]Reference Group = 45+ years, Immigrant. [b]Reference Group = 45+ years, 21+ miles from treatment facility. [c]Reference Group = 45+ years, No history of tobacco use. dReference Group: 45+ years, Rural. eReference Group: 45+ years, Western Pacific. fReference Group: 45+ years, Rural. ‡ Denotes statistically significant at p<0.05. *Analysis excluded when sample = 0 in categorical variable subgroup.

Table H2

Ad Hoc Analysis 3: Treatment Regimen and Mean Time on LTBI Treatment

Visa	Variable	*HR*	*SE*	*p*-value	95% CI Lower	95% CI Upper
Refugee	Regimen					
	Regimen (3HP)	1.16	0.83	0.86	0.23	5.88
	Regimen (4RIF)	1.11	0.77	0.89	0.25	5.07
	Regimen (6INH)	0.69	1.04	0.72	0.09	5.31
Immigrant	Regimen					
	Regimen (4RIF)	0.04	11.17	0.78	0.00	1.35E+08
	Regimen (6INH)	0.04	6.01	0.60	0.00	5603.88

Note. Abbreviations: *HR* = Hazard Rate; *SE* = Standard Error; HP = Isonaizid/Rifapentine; RIF = Rifampin; INH = Isoniazid.

Table H3

Ad Hoc Analysis Model 4: Medical Co-Morbidities by Visa-Type

Variable		Visa R 109 *n*	R %	Visa I 31 *n*	I %	*p*-value
Angina Pectoris	No	108	99.08%	31	100.00%	0.79[a]
	Yes	1	0.92%	0	0.00%	
Hypertension	No	103	94.50%	27	87.10%	0.43[a]
	Yes	6	5.50%	4	12.90%	
Chronic Obstructive Pulmonary Disorder	No	108	99.08%	30	96.77%	0.63[a]
	Yes	1	0.92%	1	3.23%	

(*table continues*)

Variable		Visa R 109		Visa I 31		
		n	%	*n*	%	*p*-value
History of TB	No	105	96.33%	29	93.55%	0.64[a]
	Yes	4	3.67%	2	6.45%	
History of Stroke	No	107	98.17%	31	100.00%	0.63[a]
	Yes	2	1.83%	0	0.00%	
Seizure Disorder	No	107	98.17%	31	100.00%	0.63[a]
	Yes	2	1.83%	0	0.00%	
Sexually Transmitted Disease	No	108	99.08%	31	100.00%	0.79[a]
	Yes	1	0.92%	0	0.00%	
Diabetes Mellitus	No	108	99.08%	30	96.77%	0.79[a]
	Yes	1	0.92%	1	3.23%	
Any Comorbidity	No	94	86.24%	26	83.87%	0.93[b]
	Yes	15	13.76%	5	16.13%	

Note. [a]Fischer's Exact; [b]Chi-square

Table H4

Ad Hoc Analysis 6: Interaction Between Provider and LTBI Treatment Regimen

				95 % CI	
Variables	*HR*	*SE*	*p*-value	Lower	Upper
*CPHR with levels of LTBI Treatment Regimen interacting with levels of Prescribing Provider[a]					
Treatment Regimen (1: 3HP)	1.00	2.19	1.00	0.01	73.11
Treatment Regimen (2: 4RIF)	1.00	3.51	1.00	0.00	967.07
Treatment Regimen (3: 6INH)	1.00	2.13	1.00	0.02	64.42
Treatment Regimen (4: 9INH)	-	-	-	-	-
Provider(1)		2.30			
Provider(2)	1.00	2.66	1.00	0.01	90.82
Provider(3)	1.00	2.10	1.00	0.01	182.44
Provider(4)	1.00	1.94	1.00	0.02	61.32
Provider(5)	1.00	2.66	1.00	0.02	45.01
Provider(6)	1.00	4.67	1.00	0.01	182.44
Provider(7)	1.00	2.66	1.00	0.00	9406.45
Provider(8)	1.00	2.66	1.00	0.01	182.44
Provider(9)	1.00	2.82	1.00	0.01	182.44
Provider(10)	1.00	1.90	1.00	0.00	252.18
Provider(11)	1.00	3.53	1.00	0.02	41.54
Provider(12)	1.00	2.92	1.00	0.00	1009.73
Provider(13)	1.00	2.60	1.00	0.00	302.95
Provider(14)	1.00	2.66	1.00	0.01	161.65
Provider(15)	1.00	2.06	1.00	0.01	182.44
Provider(16)	1.00	2.66	1.00	0.02	56.44
Provider(17)	1.00	3.57	1.00	0.01	182.44

(*table continues*)

Variables	*HR*	*SE*	*p*-value	95 % CI Lower	95 % CI Upper
Provider(18)	1.00	2.12	1.00	0.00	1084.58
Provider(19)	1.00	3.86	1.00	0.02	63.95
Provider(20)	1.00	2.66	1.00	0.00	1913.83
Provider(21)	1.00	3.53	1.00	0.01	182.44
Provider(22)	-	-	-	-	-
Provider(1)*Treatment Regimen(1: 3HP)	1.68	1.06	0.62	0.21	13.39
Provider(3)*Treatment Regimen(1: 3HP)	0.00	1,387.84	0.99	0.00	--
Provider(4)*Treatment Regimen(1: 3HP)	1.46	1.06	0.72	0.18	11.64
Provider(13)*Treatment Regimen(1: 3HP)	0.00	1,962.70	1.00	0.00	--
Provider(18)*Treatment Regimen(1: 3HP)	0.00	1,602.54	0.99	0.00	--
Provider(3)*Treatment Regimen(2: 4RIF)	0.00	1,980.31	1.00	0.00	--
Provider(4)*Treatment Regimen(2: 4RIF)	0.00	897.17	0.99	0.00	--
Provider(6)*Treatment Regimen(2: 4RIF)	0.00	1,980.31	1.00	0.00	--
Provider(10)*Treatment Regimen(2: 4RIF)	1.59	1.03	0.66	0.21	12.03
Provider(17)*Treatment Regimen(2: 4RIF)	0.00	1,980.31	1.00	0.00	--
Provider(18)*Treatment Regimen(2: 4RIF)‡	11.21	1.06	0.02	1.41	89.08
Provider(1)*Treatment Regimen(3: 6INH)	0.00	1,208.87	0.99	0.00	--
Provider(3)*Treatment Regimen(3: 6INH)	0.00	1,191.13	0.99	0.00	--
Provider(4)*Treatment Regimen(3: 6INH)	3.53	1.03	0.22	0.47	26.36
Provider(10)*Treatment Regimen(3: 6INH)	0.00	1,684.52	0.99	0.00	--
Provider(11)*Treatment Regimen(3: 6INH)	0.00	1,684.52	0.99	0.00	--
Provider(17)*Treatment Regimen(3: 6INH)	0.00	1,735.83	0.99	0.00	--
Provider(21)*Treatment Regimen(3: 6INH)	0.00	1,684.52	0.99	0.00	--

Note. Abbreviations: *HR* = Hazard Rate; *SE* = Standard Error; HP = Isonaizid/Rifapentine; RIF = Rifampin; INH = Isoniazid. *Analyses excluded when Provider did not prescribe Regimen subgroup. [a]Reference Group: Provider 24, 9INH. ‡Denotes statistically significant at $p<0.05$.

Table H5

Ad Hoc Analysis 7: Interaction Between Distance and Prescribed Regimen

Variables	*HR*	*SE*	*p*-value	95 % CI Lower	95 % CI Upper
*CPHR with levels of LTBI Treatment Regimen interacting with levels of Distance Between Residence and LTBI Treatment Facility[a]					
Treatment Regimen (1: 3HP)	0.00	184.94	0.97	0.00	8.5E+153
Treatment Regimen (2: 4RIF)	0.92	0.76	0.92	0.21	4.06
Treatment Regimen (3: 6INH)	0.45	1.03	0.44	0.06	3.34
Treatment Regimen (4: 9INH)	-	-	-	-	-
Distance to Treatment Facility (1: 0-10.9 miles)	1.06	0.62	0.93	0.32	3.55
Distance to Treatment Facility (2: 11.0-20.9 miles)	0.00	103.44	0.94	0.00	3.64E+84
Distance to Treatment Facility (3: 21+ miles)	-	-	-	-	-
Regimen (1: 3HP)*Distance (1: 0-10.9 miles)	0.96	0.78	0.96	0.21	4.43
Regimen (2: 4RIF)*Distance (2: 11.0-20.9 miles)	0.95	0.75	0.94	0.22	4.13
Regimen (3: 6INH)*Distance (1: 0-10.9 miles)	0.46	1.03	0.45	0.06	3.44

(*table continues*)

Note. Abbreviations: *HR* = Hazard Rate; *SE* = Standard Error; HP = Isoniazid/Rifapentine; RIF = Rifampin; INH = Isoniazid. *Analyses excluded when Regimen not prescribed for study participant in Distance subgroup = 0. [a]Reference Group: Regimen 9INH, Distance 21+ miles; Denotes statistically significant at $p<0.05$.