Clinical, Laboratory and Treatment Outcome Characteristics of Foreign-Born Pulmonary Tuberculosis Patients in Alberta by Immigration Status, 2004-2013

by

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Abstract

Canada is a low TB incidence country, with a rate of 4.4 per 100,000 in 2014. Despite this low incidence rate, TB affects certain groups disproportionately, most notably foreign-born persons from high incidence countries and Indigenous peoples. This study compares clinical, laboratory, and treatment outcome characteristics of two groups of foreign-born pulmonary (PTB) patients in Alberta: Canadian citizens/permanent residents and temporary residents/refugees. A retrospective cohort analysis was conducted on culture-positive PTB patients classified as foreign-born and diagnosed in Alberta between 2004 and 2013. Univariate and multiple logistic regression analyses were performed to determine whether there are predictors of advanced disease and poor treatment outcomes based on clinical and laboratory characteristics and immigration status. Results showed some differences between Canadian citizens/permanent residents and temporary residents/refugees. Of the 1200 foreign-born TB cases, 80.0% were Canadian citizens/permanent residents and 20.0% were temporary residents/refugees. More temporary residents/refugees (38.0%) were identified through an Immigration, Refugees and Citizenship Canada (IRCC) referral than Canadian citizens/permanent residents (8.7%). Patients who were identified through an IRCC referral were less likely to have advanced disease (OR 0.04, $p<0.001$). Older age, positive HIV status, and advanced disease were associated with unsatisfactory treatment outcomes. Current IRCC screening and surveillance practices are missing a significant number of individuals who later go on to develop active TB. Review of these screening practices, with more attention given to preventative therapy, must be considered in low-incidence immigrant-receiving countries such as Canada.

Dedication

This thesis is dedicated to my family who have supported me throughout this journey and encouraged me to never give up.

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List of Abbreviations

AFB	acid-fast bacilli
CDC	Centers for Disease Control and Prevention
CTBRS	Canadian Tuberculosis Reporting System
DOT	directly observed treatment
DST	drug susceptibility testing
EMB	ethambutol
EPTB	extrapulmonary tuberculosis
IME	immigration medical exam
INH	isoniazid
iPHIS	integrated Public Health Information System
IRCC	Immigration, Refugees and Citizenship Canada
LTBI	latent tuberculosis infection
MDR-TB	multi-drug resistance tuberculosis
NAAT	nucleic acid amplification test
PHAC	Public Health Agency of Canada
PERU	Program Evaluation and Research Unit
PTB	pulmonary tuberculosis
PZA	pyrazinamide
RMP	rifampin
TB	tuberculosis
US	United States
WHO	World Health Organization

Chapter One: Introduction to Problem and Background

Introductory Statement

Tuberculosis (TB) is a communicable disease caused by the bacillus *Mycobacterium tuberculosis*. Despite ongoing efforts by the global health community to decrease the burden of disease, TB continues to be a major source of morbidity and mortality in many countries around the world. In 2014, the number of new or relapsed cases of TB globally was estimated to be 9.6 million (World Health Organization, 2015). This is equivalent to an approximate incidence rate of 133 cases per 100,000 population. Accounting for approximately 83% of the incident cases of TB globally, 22 high burden countries are prioritized by the majority of TB initiatives and programs. In Canada, the incidence rate of TB has slowly declined over the last two decades, resulting in a rate of 4.4 per 100,000 in 2014 (Public Health Agency of Canada, 2016). Despite this low incidence rate, TB is found to affect certain population groups disproportionately, most notably foreign-born persons from high incidence countries and Indigenous peoples. In 2014, the incidence rate in these two groups was found to be 13.7 per 100,000 and 20.4 per 100,000, respectively (Public Health Agency of Canada, 2016). In comparison, the incidence rate among Canadian-born non-Indigenous peoples was found to be 0.6 per 100,000.

A high TB incidence rate among the foreign-born population is not a new or emerging issue unique to Canada. In fact, many other high income, low incidence immigrant-receiving countries, such as the United States and Australia, also encounter similar trends. In 2015, 66.4% of all the reported TB cases in the United States (US) were diagnosed among foreign-born persons (Centers for Disease Control and Prevention, 2016b). The incidence rate among this group was almost 13 times higher than US-born persons, at 15.1 per 100,000 vs. 1.2 per 100,000 (Centers for Disease Control and Prevention, 2016b). Similarly, the incidence rate of TB among foreign-born persons was over 19 times the rate among Australian-born persons in 2013 (Toms, Stapledon, Waring, Douglas, & The National Tuberculosis Advisory Committee, 2015). One contributor to this pattern may be the steady increase in international migration, particularly from high TB incidence countries to low TB incidence countries. Previous studies have found that many cases of TB diagnosed in foreign-born persons are due to the reactivation of latent TB infection that was acquired in the person's country of birth prior to immigration (Jensen et al., 2012; Kunimoto et al., 2004). With Canada receiving an average of approximately 250,000 new immigrants and refugees every year (Public Health

Agency of Canada, 2014a), screening and surveillance becomes an important public health measure during the immigration process. However, an increase in immigration rates is not the only factor that contributes to this trend. Other factors such as age, migration status, barriers to accessing primary care, and insufficient screening and surveillance after immigration may also contribute to the high rates of TB in the foreign-born population (Reitmanova & Gustafson, 2012). For example, only immigrants found with a past history of TB or evidence of old healed TB on a chest radiograph during pre-immigration screening are put under medical surveillance in Canada (IRCC, 2014). Individuals with latent TB infection are not put under surveillance and if they happen to develop active TB later on, this will contribute to the rates of TB in the foreign-born. Barriers to accessing primary care may also contribute to the incidence of TB if those with active disease are unable to access timely treatment and spread the bacterium to close contacts, such as family members.

In addition to the high incidence rate of TB in the foreign-born population, there are also concerns regarding the treatment outcomes in this group. More specifically, delays in access to TB treatment can cause the disease to progress and worsen, in addition to increasing the chance of transmission (Gershon, Wobeser, & Tu, 2008), and therefore result in worse treatment outcomes. In a study conducted in Spain, it was found that total compliance to TB treatment was slightly lower in immigrants compared to native-born Spaniards (Ballesteros et al., 2014). There was also a higher dropout rate in the immigrant group (Ballesteros et al., 2014). These factors could potentially result in worse treatment outcomes in the foreign-born population.

Research on the epidemiology of tuberculosis in foreign-born persons has been conducted in a number of countries and jurisdictions, including the United States, Australia, Finland, Spain, Switzerland, and Hong Kong. While Canada may bear similarities to some of these nations, there nonetheless are important differences in the immigration processes and healthcare systems. Furthermore, exploration into the demographic, clinical, and laboratory characteristics among foreign-born persons with different immigration statuses has not been conducted in Canada. This information may provide insight into the experience of TB among different groups of foreign-born persons in major immigrant-receiving countries, as well as the challenges these groups face in accessing TB services. It may also provide suggestions to improving current TB screening and surveillance practices in Canada. This study aims to

characterize the demographic, clinical, laboratory, and treatment outcome characteristics among two groups of foreign-born pulmonary tuberculosis (PTB) patients in Alberta: Canadian citizens/permanent residents and temporary residents/refugees.

Background of the Problem

Overview of Tuberculosis

Tuberculosis is a communicable disease caused by infection with *Mycobacterium tuberculosis*. Not all of those infected will develop active disease – approximately 5% of those infected will develop active TB within a year or two of their infection (Public Health Agency of Canada, 2014a). Another 5% go on to develop disease later in life. Thus, 90% of infected individuals never progress to active TB. Progression from latent TB infection (LTBI) to active TB is highly dependent on host factors such as the individual's immune response, age and sex (Public Health Agency of Canada, 2014a).

Active TB disease usually affects the lungs (pulmonary TB), but it can also spread to and affect other parts of the body (extrapulmonary TB). Common symptoms of pulmonary TB disease include persistent coughing (for a duration of at least 2-3 weeks), chest pain, coughing of blood or sputum, fatigue, weight loss, fever, and night sweats (Centers for Disease Control and Prevention, 2016a). Symptoms and signs of extrapulmonary TB depend on the area of the body that is affected. Examples of signs include lymphadenopathy, pleural effusion and abdominal or bone and joint involvement (Public Health Agency of Canada, 2014a). TB is an airborne disease (Centers for Disease Control and Prevention, 2016a). Transmission can occur if an individual with active TB coughs, sneezes, or speaks, expelling TB-infected droplets into the air, which then evaporate down into very small particles. If other individuals nearby breathe in these particles, there is a chance they may become infected. However, transmission is dependent on air circulation and ventilation, proximity to the source case, as well as the duration of exposure to the source case (Public Health Agency of Canada, 2014a). The transmission of TB is generally due to cases of active pulmonary TB, as extrapulmonary TB disease is rarely infectious (Centers for Disease Control and Prevention, 2016a).

The Public Health Agency of Canada recommends that all individuals who have signs or symptoms of active TB undergo testing (Public Health Agency of Canada, 2014a). The

standard testing algorithm in Canada includes: chest radiography, sputum smear microscopy, nucleic acid amplification tests (NAATs), mycobacterial culture and phenotypic drug susceptibility testing (DST). Chest radiography involves obtaining posterior-anterior and lateral views of the patient's lungs in order to detect abnormalities, which are more likely if the patient presents with symptoms (Public Health Agency of Canada, 2014a). Typical chest radiographic features are upper lung zone disease, cavitation, volume loss and poorly defined nodules. Chest radiography can also provide information about the extent of disease. Although chest radiography is a common first step when investigating a potential case of pulmonary TB, it is often not enough to provide a conclusive diagnosis. Sputum smear microscopy, a more definitive diagnostic test for TB disease, especially if accompanied or followed by a NAAT, is a method where samples of the patient's sputum are spread onto a glass slide, treated with a stain, and observed under a microscope to detect the presence of mycobacteria. The gold standard diagnostic test for active TB continues to be mycobacterial culture, in which the bacterium is grown on solid and/or liquid medium. Although cultures can take between 2-7 weeks to grow, they are more sensitive than smears. Phenotypic DST involves the use of culture to determine the presence of drug resistance. This is an important step to determine the most effective antibiotics to treat the disease. Newer NAATs also include genotypic drug susceptibility testing, allowing for earlier detection of drug resistance.

The current recommended treatment regimen in Canada for drug-susceptible TB consists of four anti-TB drugs: isoniazid (INH), rifampin (RMP), ethambutol (EMB), and pyrazinamide (PZA). Specific treatment regimens vary by individual and should be based on drug susceptibility test results. The usual course of treatment ranges from 6 to 9 months, but can also be extended if there is a risk of relapse of disease. Adherence to the entire course of TB treatment is important to effectively eliminate the TB bacteria and prevent drug resistance from developing. One method to ensure adherence to treatment is through directly observed treatment (DOT), in which a healthcare provider supervises the administration of treatment to ensure that the patient takes all of the prescribed doses of medication. Non-adherence to treatment can cause the TB bacteria to become resistant to one or more of the anti-TB drugs; if a patient is diagnosed with drug-resistant TB, the infection becomes much more difficult to treat, and the treatment regimen becomes less well tolerated and longer in duration (Public Health Agency of Canada, 2014a).

Increase in International Migration

An increasingly globalized world has rapidly increased the rate of international migration over the past decade, with 244 million immigrants reported in 2015 (Menozzi & Hovy, 2016). Migration is an important issue for both developing and developed countries. It often occurs as a result of social, economic, political, academic, or environmental pressures (Gushulak & MacPherson, 2004). It is also an important contributor to the sustainable growth and development of communities in both the home and host countries (Menozzi & Hovy, 2016). However, migration can also have a large impact on the epidemiology and spread of infectious diseases (Gushulak & MacPherson, 2004). Migrants are some of the most vulnerable groups in society, particularly those who are forced to leave their homes due to conflict, poverty, or inequality (Menozzi & Hovy, 2016). Their health is highly dependent on the environment of their country of origin, the environment in which they pass through in their transition, and the environment of their host country (Gushulak & MacPherson, 2004). This has important public health implications, particularly in countries that receive large numbers of migrants. Countries must be proactive in taking extra steps to ensure that any potential infectious diseases that pose a risk to the health of the public are managed and contained.

In 2015, Canada hosted the seventh largest number of international migrants (Menozzi & Hovy, 2016). Although Western and Central Europe were once a major source of migrants, they are now predominantly from Latin America, Asia, and Africa (Gushulak, Pottie, Hatcher Roberts, Torres, & DesMeules, 2011). With approximately 86% of all global TB cases occurring in Asia and Africa (World Health Organization, 2015), this has an important implication for the control of TB disease within the foreign-born population in Canada. TB diagnosed in the foreign-born population is generally the result of reactivation of latent TB that was acquired in the individual's home country, rather than a newly acquired infection in Canada. Thus, with the majority of new immigrants arriving from Asia and Africa, there is a risk that this population has been exposed to or is carrying TB. Canada, like many other countries, currently has policies in place to screen for communicable diseases such as TB during the immigration process. This is an important step to ensure the timely treatment of any known cases and the prevention of its spread in Canada.

Canada's Immigration Medical Exam (IME)

According to the National Household Survey, Canada had a foreign-born population of approximately 6,775,765 people in 2011 (Statistics Canada, 2015a). This population represented 20.6% of the total population of Canada, with the majority (94.8%) living in four provinces – Ontario, Quebec, Alberta, and British Columbia.

Immigration, Refugees and Citizenship Canada (IRCC) mandates that permanent resident applicants, temporary residents, and refugees undergo an immigration medical examination (IME) prior to coming to Canada, unless otherwise specified (IRCC, 2017). More specifically, those who apply as a visitor, student or worker (temporary residents) and plan to stay for less than 6 months generally do not require a medical exam, while temporary residents who plan to stay for more than 6 months and meet certain criteria do (as listed on the IRCC website – Appendix A). In general, IME results are valid for a period of 12 months. Individuals who undergo a medical exam and are found to have a medical condition of public health significance are required to report to their provincial or territorial public health authorities for surveillance upon arrival in Canada. Currently only inactive tuberculosis, which is defined as a past history of TB or evidence of old healed TB on a chest radiograph, is a medical condition for which medical surveillance is required (IRCC, 2014). If active TB is diagnosed at an overseas IME, then the individual is required to complete a satisfactory course of treatment in order to obtain permission to enter Canada.

Canada's Foreign-Born Health/Healthcare

Newly arrived foreign-born individuals who willingly choose to relocate have typically been found to be healthier than the general Canadian-born population due to a phenomenon called the 'healthy immigrant effect' (Gushulak et al., 2011; McDonald & Kennedy, 2004). This comes from the observation that many immigrants are usually those that are physically and mentally healthy enough in order to relocate to a different country. Since they also must undergo health screening through immigration authorities, immigrants that are able to migrate successfully are generally in good health (McDonald & Kennedy, 2004). However, it has also been well documented that many immigrants' health status generally declines over time (Gushulak et al., 2011). While age plays an important role, this observation can also be attributed to a variety of other factors. The stressors associated with moving to a different country, including economic hardships, employment instability,

language barriers, and poverty, can further exacerbate any existing health conditions or trigger illness in this population.

Previous studies have found a disparity in access to healthcare between Canadian-born and foreign-born individuals. A scoping review conducted by Kalich et al. in 2015 found that language barriers was the most cited barrier to accessing healthcare (Kalich, Heinemann, & Ghahari, 2015). Other obstacles listed include lack of information on how to access the healthcare system, long wait times, and cultural differences (Kalich et al., 2015). Language barriers and cultural differences are important factors to consider when exploring immigrant access to healthcare. Many newly arrived immigrants do not speak English or French, which can make it difficult to communicate with healthcare providers about their previous and current health conditions as well as any diagnosis and treatment options. This is an example of a barrier that could potentially deter immigrants from seeking health care altogether, and one that could be addressed given the proper resources and support.

Access to healthcare is an important factor to take into consideration when exploring the experience of TB within the foreign-born population. During the IME, individuals who are found to have active TB are required to undergo a satisfactory course of treatment in their home country prior to coming to Canada (Public Health Agency of Canada, 2014a). However, individuals found to have, or are suspected to have, latent TB are generally accepted into Canada. Those who are found to have an abnormal chest radiograph are required to report to provincial or territorial public health authorities in Canada. It is essential that these individuals be provided adequate and timely access to healthcare services in order to ensure that they do not progress to active TB. This would also ensure that any developing signs of active TB are caught early on and treated accordingly.

Latent TB infection is defined as 'the presence of immune responses to *Mycobacterium tuberculosis* antigens without clinical evidence of active TB' (World Health Organization, 2015). According to evidence-based guidelines from the WHO, systematic testing and treatment of LTBI of immigrants from high TB burden countries is conditionally recommended based on local TB epidemiology and resource availability (World Health Organization, 2015). One of the main determinants of whether to systematically target LTBI is whether the benefits of treatment outweigh the potential drug-related side effects or

adverse events. In ideal circumstances, targeting LTBI in specific high-risk groups, such as the foreign-born population, especially those from countries with high incidence of TB, may be economically beneficial for the healthcare system. Although it is not the only strategy required for TB elimination, the management of LTBI as a public health intervention has the potential to contribute to the elimination of TB in low incidence countries such as Canada.

Knowledge Gaps

Previous research on TB in foreign-born persons in Canada has focused primarily on the immigrant population as a whole (Cowie & Sharpe, 1998; Kunimoto et al., 2004; Long, Sutherland, Kunimoto, Cowie, & Manfreda, 2002; Varughese, Langlois-Klassen, Long, & Li, 2014; Yip et al., 2007). While a few select studies have looked into the potential effects of factors such as documentation status, there exists a gap in the literature with regards to specific sub-groups of the foreign-born and their experience with TB. It is expected that compared to permanent residents, temporary residents and refugees will have different and unique characteristics as a result of their immigration status that could affect their experience with TB disease. For example, foreign-born individuals who have become permanent residents in Canada are generally those who have been living in the country longer than temporary residents and refugees. This demographic characteristic could potentially impact the way that TB is diagnosed, how it progresses, and how it is treated. For this reason, exploration into the experience of TB in specific sub-groups of the foreign-born in Canada could provide major insight into the way TB is managed in this population. This could potentially help improve the management of TB within the foreign-born population, in addition to informing policies regarding the surveillance of those with latent TB infection.

Study Objectives

Hypothesis

Compared to foreign-born Canadian citizens/permanent residents, temporary residents and refugees in Alberta, Canada with culture-positive pulmonary tuberculosis have more advanced disease and worse treatment outcomes.

This study was mainly exploratory and descriptive, aiming to address the following three objectives:

Objective 1: To compare the demographic and immigration characteristics of foreign-born pulmonary tuberculosis patients by immigration status (Alberta, 2004 - 2013).

Objective 2: To compare the clinical and laboratory characteristics of foreign-born pulmonary tuberculosis patients by immigration status (Alberta, 2004 - 2013).

Objective 3: To compare the treatment outcomes of foreign-born pulmonary tuberculosis patients by immigration status (Alberta, 2004 - 2013).

Study Setting

This study was conducted in Edmonton, Alberta, Canada using patient data from across the province. Alberta is an appropriate study setting to address the knowledge gaps in the literature for many reasons. It is one of four major immigrant-receiving provinces in Canada, which provides a sufficiently large number of patients to make meaningful comparisons. Immigrants to Alberta are a highly diverse group of foreign-born individuals coming from various countries and backgrounds, closely reflecting the Canadian immigrant population as a whole.

Assumptions, Limitations, and Scope

This study was focused on the experience with TB disease of foreign-born patients specifically in Alberta. Although results can be applicable to other immigrant-receiving provinces in Canada, there are likely differences in the provincial public health systems that should be taken into consideration. These systematic differences could potentially affect the way TB patients are diagnosed and managed in each province. This study was also limited by the sample size, specifically within the temporary resident and refugee groups. It is acknowledged that there are important differences between temporary residents, who are generally those that have planned to stay in Canada for a temporary period of time, and refugees, who are generally those that have been forced to flee their home country, which could affect their experience with TB. However, since the sample size in both groups was relatively low, it was decided that the characteristics of temporary residents and refugees were similar enough to combine them into one group in order to make comparisons with foreign-born Canadian citizens/permanent residents. The scope of this study was limited to looking at culture-positive pulmonary TB patients older than 14 years of age. Since there are clinical differences between adult and pediatric cases, study results are only applicable to adult tuberculosis cases and should not be generalized to pediatric tuberculosis.

Chapter Two: Review of Related Literature and Studies

A search of published literature was conducted using PubMed, Ovid MEDLINER, Global Health and CINAHL using combinations of the following keywords: “tuberculosis”, “TB”, “PTB”, “immigrant”, “foreign-born”, “temporary resident”, “refugee”, “characteristic”, “symptom”, and “presentation”. Seventeen relevant articles spanning the years 1998 to 2015 were found to provide a general overview of the current research that has been conducted on TB in foreign-born persons. Seven of the studies were conducted in the United States, two in Canada, and one each in Australia, Switzerland, Finland, Denmark, Spain, Hong Kong, and Taiwan. This includes the epidemiology of TB in foreign-born persons in various countries and jurisdictions, as well as the clinical and social factors surrounding the experience of TB disease. This literature review aims to highlight the gaps within the literature, particularly in Canada and the province of Alberta, and how the proposed research objectives will address the unanswered questions.

Introduction

TB is a major public health concern, being identified as the leading cause of death from an infectious disease, alongside the human immunodeficiency virus (HIV) (World Health Organization, 2015). According to the 2015 Global Tuberculosis Report, there were approximately 9.6 million new cases of TB worldwide in 2014. This translates to an incident rate of approximately 133 per 100,000 population. However, the majority of cases were found in Asia and the African Region, making up around 86% of the cases globally. Countries such as Canada, the United States, and Australia, among others, are identified as low-incidence countries (Lönnroth et al., 2015). A low-incidence country is defined as one that has <100 TB cases per million population. Countries in this category are most often high-income countries and usually have different priorities than those with a greater burden of TB because there is the potential for TB elimination (Lönnroth et al., 2015). In high income, low-incidence countries the emphasis is placed on improving TB services and healthcare access for the most vulnerable groups.

In Canada, the most vulnerable groups primarily include the foreign-born population and Indigenous peoples (Public Health Agency of Canada, 2014a). With an incidence rate that is almost 25 times the Canadian-born non-Indigenous population, foreign-born persons bear a high burden of TB disease. A relatively high incidence of TB in the foreign-born

population is a trend that is found in many low-incidence countries. Studies conducted in the United States highlight the epidemiology of TB among the foreign-born population across the country and in various states. Davidow et al. found that among the 4,295 TB patients diagnosed in New Jersey between 1994 and 1999, 47% were foreign-born (Davidow, Mangura, Napolitano, & Reichman, 2003). This high proportion of foreign-born TB cases is also consistent with the results of a study in southern Florida, where 49% of the 629 TB cases were foreign-born (Granich et al., 1998), as well as New York City, where 69% of the 194 cases were foreign-born (Asghar, Pratt, Kammerer, & Navin, 2008). This trend is not surprising and aligns with the findings published by the US Centre for Disease Control, with 66.4% of all the reported TB cases in the US diagnosed among foreign-born persons in 2015 (Centers for Disease Control and Prevention, 2016b).

Studies have also been conducted on TB in different ethnic groups in the US, including Africans, South Asians, Filipinos, and Mexicans (Abraham, Winston, Magee, & Miramontes, 2013; Asghar et al., 2008; Joseph, Waldman, Rawls, Wilce, & Shrestha-Kuwahara, 2008; Manangan et al., 2011). Abraham et al. reported that the 2009 incidence rate of TB among those who originated from Africa was 27 times as high as among those who were born in the US (Abraham et al., 2013). It is likely that the trends in other foreign-born ethnic groups are similar, highlighting the increasing disparities in TB rates between foreign-born and US-born individuals. Studies in other low-incidence countries have reported similar findings, with specific ethnic groups having a greater risk of TB diagnosis. A common theme found in many of the articles is the diagnosis of TB in emigrants from Asian and African countries. In a study conducted in Australia by McBryde and Denholm, it was found that the highest risk of TB incidence was found in emigrants from South Asia and sub-Saharan Africa (McBryde & Denholm, 2012). Studies in the US, Denmark, Hong Kong, Taiwan, and Alberta, Canada have identified emigrants from Asian countries as having the highest rates of TB (Achkar, Sherpa, Cohen, & Holzman, 2008; Bai et al., 2008; Cowie & Sharpe, 1998; Leung et al., 2015; Leutscher et al., 2012; Long et al., 2002), with emigrants from Vietnam, the Philippines, China, Hong Kong, and India having some of the highest rates of TB diagnosis in Alberta (Long et al., 2002).

Common factors surrounding TB disease that were investigated in the articles include age and HIV status (Abraham et al., 2013; Asghar et al., 2008; Ballesteros et al., 2014;

Garcia-Garcia et al., 2011; Kherad, Herrmann, Zellweger, Rochat, & Janssens, 2009; Räisänen et al., 2016). Many studies, including those conducted in the US, Finland, Switzerland, and Spain found that immigrants diagnosed with TB were on average significantly younger than TB patients in the native populations (Abraham et al., 2013; Asghar et al., 2008; Ballesteros et al., 2014; Garcia-Garcia et al., 2011; Kherad et al., 2009; Räisänen et al., 2016). It was also found that HIV status of foreign-born TB patients was dependent on their country of origin. For example, Abraham et al. found that TB patients originating from Africa had the highest percentage of positive HIV test results, while Asghar et al. and Manangan et al. respectively found that South Asian and Filipino TB patients were more likely to be HIV negative (Abraham et al., 2013; Asghar et al., 2008; Manangan et al., 2011).

The study conducted by Achkar et al. explored the experience of TB in documented and undocumented foreign-born persons compared to the US-born population using a cross-sectional study of medical records (Achkar et al., 2008). They found that undocumented foreign-born persons diagnosed with TB had significantly higher frequencies of cough and hemoptysis, as well as longer median duration of symptoms compared with US-born persons. Although Canada has a different healthcare system than the US, there is the potential that immigration status could play a role in the experience of TB in foreign-born persons. More specifically, temporary residents or refugees may have different experiences with TB than permanent residents. This has not been explored in Canada and thus more research is needed to understand the impact of immigration status on TB experience in the foreign-born population.

As more countries begin to fall into the low-incidence category, more research is needed to develop strategies to improve access to TB services for foreign-born persons. In order to do this, further exploration into the experience of TB in the foreign-born population should be conducted.

Table 2.1: Tuberculosis in foreign-born populations in high-income countries, 1998-2015

Article Title	Authors/ Year	Location	Source of Data	Key Points
Differences in clinical presentation among persons with pulmonary tuberculosis: a comparison of documented and undocumented foreign-born versus US-born persons	JM Achkar, T Sherpa, HW Cohen, and RS Holzman. 2008.	New York City, United States	Medical records from a New York City public hospital	● Undocumented foreign-born persons presented with significantly higher frequencies of cough and hemoptysis and had significantly longer median duration of symptoms, compared with US-born persons ● Positive association found between undocumented foreign-born status and prolonged symptom duration
Tuberculosis among Africans living in the United States, 2000-2009	BK Abraham, CA Winston, E Magee, and R Miramonte. 2012.	United States	US National Tuberculosis Surveillance System	● In 2009, TB incidence rate among Africans was 48.1/100,000, 3 times as high as among other foreign-born, 27 times as high as among US-born patients ● Africans had the highest percentage of TB cases with a positive HIV test result ● Africans had higher odds of having extrapulmonary TB disease and low odds of having MDR-TB
Tuberculosis in South Asians living in the United States, 1993-2004	RJ Asghar, RH Pratt, JS Kammerer, and TR Navin. 2008.	United States	US National Tuberculosis Surveillance System	● 50.5% of South Asian TB patients between 1993 to 2004 were between 25 and 44 years of age ● South Asian TB patients were more likely to have extrapulmonary disease, be uninfected with HIV, and not to be offered HIV testing or not to accept an HIV test if offered than other foreign-born TB patients
Tuberculosis among persons born in the Philippines and living in the United States, 2000-2007	LP Manangan, CJ Salibay, RM Wallace, S Kammerer, R Pratt, L McAllister, and V	United States	US National Tuberculosis Surveillance System	● Filipinos were more likely than other groups to be employed as health care workers and to have used private health care providers ● Filipinos were less likely to be HIV positive and to be offered HIV testing ● Culturally appropriate public

	Robison. 2011.			health efforts such as education and case management are important in addressing TB among Filipinos
TB perspectives among a sample of Mexicans in the United States: results from an ethnographic study	HA Joseph, K Waldman, C Rawls, M Wilce, and R Shrestha-Kuwahara. 2008.	Atlanta, United States and Georgia, United States	Interviews with respondents from TB clinics	● Presence of widespread misperceptions about TB transmission and low perceptions of risk ● Reported barriers to care included lack of transportation, limited clinic hours, costs of services, inconvenient clinic location, and communication problems with staff
Rethinking the socioeconomics and geography of tuberculosis among foreign-born residents of New Jersey, 1994-1999	AL Davidow, BT Mangua, EC Napolitano, and LB Reichman. 2003.	New Jersey, United States	New Jersey Department of Health and Senior Services Case Report	● 4, 295 TB patients, 2005 (47%) were foreign-born ● They resided in more affluent, more educated, and less crowded areas than US-born patients ● They were more likely to have been employed during the 2 years before diagnosis
Tuberculosis among foreign-born residents of southern Florida, 1995	RM Granich, PLF Zuber, M McMillan, JD Cobb, J Burr, ED Sfakianaki, M Fussell, and NJ Minkin. 1998.	Southern Florida, United States	State TB Registry	● 49% of 629 TB cases in three counties (Broward, Dade, Palm Beach) were in foreign-born ● 26% were infected with HIV ● Only three cases identified by overseas immigrant screening ● 68% had been in the US five or more years at time of diagnosis
TB in a low-incidence country: differences between new immigrants, foreign-born residents and native residents	G Laifer, AF Widmer, M Simcock, S Bassetti, A Trampuz, R Frei, M Tamm, M Battegay, and U Fluckiger. 2007.	Basel, Switzerland	The University Hospital Basel Patient Records	● Screened 42, 601 new immigrants – 112 had chest radiographs suspicious for TB ● New immigrants with TB detected in a screening program are often asymptomatic and have a low yield of rapid diagnostic tests, at a higher risk for resistant MTB strains
Examining the impact of patient characteristics	PW Colson, GL Couzens, RA Royce,	United States and Canada	Standardized in-person interviews, national TB	● Significant predictors of correct TB knowledge included region of origin, education, income, age, visa

and symptomatology on knowledge, attitudes, and beliefs among foreign-born tuberculosis cases in the US and Canada	T Kline, T Chavez-Lindell, S Welbel, J Pang, A Davidow, and Y Hirsch-Moverman. 2014.		surveillance data, and federal immigration databases	status, place of diagnosis, BCG vaccination, and TB symptoms ● Significant predictors of higher perceived risk/stigma scores included region of origin, age, place of diagnosis, English fluency, time in the US/Canada, TB symptoms, and house-hold rooms ● Findings call for improved health education, along with efforts to reduce stigma and enhance realistic risk assessments
Risk of active tuberculosis in immigrants: effects of age, region of origin and time since arrival in a low-exposure setting	ES McBryde and JT Denholm. 2012.	Victoria, Australia	Australian Bureau of Statistics and the Victorian Department of Health TB Database	● Incidence of active TB following immigration to Australia was highly dependent on region of origin, with the highest risks being in immigrants from South Asia and sub-Saharan Africa ● Substantial risk of TB in Victorian immigrants persists well beyond the first 2-3 years following arrival
Tuberculosis in immigrants in Finland, 1995-2013	PE Raisanen, H Soini, T Vasankari, PW Smit, JP Nuorti, J Ollgren, P Ruutu, and O Lyytikainen. 2015.	Finland	Statistics Finland and National Infectious Disease Register	● Proportion of immigrant cases increased from 5.8% in 1995 to 32.1% in 2013 ● TB cases in immigrants were significantly younger, more often female, and had extrapulmonary TB more often than native-born cases
Clinical presentation, demographics and outcome of tuberculosis (TB) in a low incidence area: a 4-year study in Geneva, Switzerland	O Kherad, FR Herrmann, JP Zellweger, T Rochat, and JP Janssens. 2009.	Geneva, Switzerland	Computerized database and medical records of TB patients at the Division of Pulmonary Diseases, Geneva University Hospital	● 252 patients (84% foreign-born, 25% asylum seekers) ● 11% of foreign-born TB patients co-infected with HIV ● Time to diagnosis remains long ● Foreign-born patients were on average younger than indigenous patients
Demographic and clinical characteristics in relation to patient and health system delays in a	P Leutscher, G Madsen, M Erlandsen, J Veirum, K	Denmark	Patient medical records from Aarhus University Hospital	● Study confirmed a typical delay of months in duration in the diagnosis and treatment of TB ● Increased TB awareness is needed, in particular in communities with immigrants

tuberculosis low-incidence country	Ladefoged, V Thomsen, C Wejse, and O Hilberg. 2012.			originating from high-endemic areas ● PTB most prevalent among Danish patients, EPTB most prevalent among immigrants from the Middle East, Asia, and Africa
Social, clinical and microbiological differential characteristics of tuberculosis among immigrants in Spain	JM Garcia-Garcia, R Blanquer, T Rodrigo, JA Cayla, JA Caminero, R Vidal, M Casal, J Ruiz-Manzano, and the Working Group on Completion of Tuberculosis Treatment in Spain. 2011.	Spain	Electronic case reports	● 1,490 patients included, 1,048 natives and 442 (29.7%) immigrants ● Variables significantly associated with immigrant TB cases: younger age, living in group situation, unemployment
Clinical characteristics of tuberculosis in immigrants and autochthonous populations, in 2 hospitals of Catalonia	AL Ballesteros, J Oriol, I Francisco, S Fernandez, FG Bradgado, and A Vinyes. 2014.	Catalonia, Spain	Dr. Josep Trueta University Hospital and the Badalona Healthcare Services databases	● Immigrants were younger, 70.8% had lived in Spain for less than 5 years ● PTB was most common clinical presentation, similar frequencies in immigrants and natives
Immigrants and tuberculosis in Hong Kong	CC Leung, CK Chan, KC Chang, WS Law, SN Lee, LB Tai, Eric CC Leung, and CM Tam. 2015.	Hong Kong	TB notification registry of Hong Kong	● Moderately higher sex- and age- standardized incidence ratios were observed among various immigrant groups ● Older age, birth in particular Asian countries, non-permanent residents, previous history of treatment, and resistance to isoniazid and/or rifampicin were independently associated with poor treatment outcome

Tuberculosis among foreign-born persons in Taiwan, 2002-2005	KJ Bai, CY Chiang, CN Lee, JW Chang, LC Wu, and MC Yu. 2008.	Taiwan	Official publications of the Ministry of the Interior and the Taiwan CDC National TB Registry	● Significant differences in age, sex and regional distribution between foreign-born and Taiwan-born TB cases ● Majority came from Mainland China and Vietnam (73%), followed by Philippines, Thailand and Indonesia ● Risk of developing TB disease is highest in the first 5 years of arrival and declines gradually thereafter
Socio-cultural factors influencing prevention and treatment of tuberculosis in immigrant and Aboriginal communities in Canada	N Gibson, A Cave, D Doering, L Ortiz, P Harms. 2005.	Alberta, Canada	Qualitative interview data	● Although patients with active disease learn about TB from health professionals, people in high-risk populations need to learn more about TB transmission and prevention prior to contact ● Low level of TB knowledge in the communities and individuals before diagnosis
Tuberculosis among immigrants: interval from arrival in Canada to diagnosis. A 5-year study in southern Alberta.	RL Cowie and JW Sharpe. 1998.	Alberta, Canada	Alberta's provincial TB database and immigration documents	● Immigrants accounted for 248 (70.6%) of 351 cases of TB in southern Alberta during 5 year period ● Majority of immigrants (73.4%) were of Asian origin ● Mean period between immigration and diagnosis was 11.2 years
The epidemiology of tuberculosis among foreign-born persons in Alberta, Canada, 1989-1998: identification of high-risk groups.	R Long, K Sutherland, D Kunimoto, R Cowle and J Manfreda. 2002.	Alberta, Canada	Alberta Health and Wellness computerized registry of TB cases and Canadian population census	● Highest rates of TB were in immigrants from Asia, particularly Vietnam, the Philippines, China, Hong Kong and India ● Most (90%) TB patients from these countries had not been identified as requiring medical surveillance in Canada after arrival ● Efforts aimed at reducing transmission in this group must focus on upgrading the standards and quality of TB control programs in their country of origin

Chapter Three: Methodology of the Study

Study Design

A retrospective cohort analysis was conducted on foreign-born active TB cases notified between January 1st, 2004 and December 31st, 2013 (study period). Data was collected using the "Alberta Health Services: Active Tuberculosis Case Report Form – New and Relapsed Cases" at time of diagnosis. The Active Tuberculosis Case Report Form is a notification form that is filled out when a patient is diagnosed with active TB in Alberta. This form includes information on the patient's demographic and clinical characteristics, as well as their country of birth and year of arrival in Canada. Members of the University of Alberta Tuberculosis Program Evaluation and Research Unit (PERU) had previously entered this information into an Excel spreadsheet. Any missing data was supplemented with information collected from the integrated Public Health Information System (iPHIS). iPHIS is a public health database containing information on cases of reportable diseases and is used to inform provincial health authorities and the Public Health Agency of Canada (PHAC). All patient identifiers were removed and study participants remained anonymous during the conduct of this study. Data was inputted into a STATA file for analysis.

Study Area

This study was conducted in Alberta, Canada, which has an estimated population of 4.2 million, with Calgary, Edmonton, and Lethbridge being the three most populous cities (Statistics Canada, 2016). Tuberculosis cases are diagnosed and managed in three public health clinics – the Calgary TB Clinic, the Edmonton TB Clinic, and the Provincial TB Clinic. The Provincial TB Clinic is a virtual clinic that services rural Alberta, including First Nations communities, through local community and public health centres. All cases of tuberculosis diagnosed in the province are legally reportable, with public health authorities submitting data on active TB cases to the Canadian Tuberculosis Reporting System (CTBRS) for national-level surveillance.

Study Population

Patients included in the study were culture-positive pulmonary tuberculosis patients (age $\geq$15), who were classified as foreign-born and diagnosed in Alberta between January 1st, 2004 and December 31st, 2013. Culture-positive pulmonary TB was a requirement due to the fact that cultures are the current gold standard for TB diagnosis and thus ensure a consistent

comparison between patients. The study population also excluded those who were less than 15 years of age (pediatric tuberculosis) because there are differences in the presentation of disease between adult and pediatric cases of TB. Culture-positive pulmonary TB patients over the age of 15 years constitute the greatest public health risk of TB transmission. Patients who were given the following ICD-9 codes indicative of pulmonary and extrapulmonary TB were included in the analysis: 011.0-011.9 (pulmonary tuberculosis), 012.1 (tuberculosis of intrathoracic lymph nodes), 012.2 (isolated tracheal or bronchial tuberculosis, 018.0 (acute miliary tuberculosis, unspecified), 018.8 (other specified miliary tuberculosis), and 018.9 (unspecified miliary tuberculosis). Pulmonary TB primarily affects the lungs, while extrapulmonary TB refers to TB diagnosed in organs other than the lungs. Approval for human research was obtained from the University of Alberta Health Research Ethics Board – Health Panel.

Study Numbers

Between January 1st, 2004 and December 31st, 2013, there were a total of 1524 patients diagnosed with active tuberculosis across Alberta. Of these 1524 patients, 1200 were foreign-born and 324 were either classified as Canadian born non-Indigenous or Indigenous. After removing those who did not meet the age, population group and culture-positive criteria, a total of 647 patients remained. One patient was missing their year of arrival and immigration status and was subsequently removed from the analysis, bringing the total number of cases included in the study to 646 patients (Appendix B).

Objective 1: To compare the demographic information and immigration status of foreign-born pulmonary tuberculosis patients by immigration status (Alberta, 2004 - 2013).

Measurements

Demographic information collected at the time of diagnosis included: age (15-34, 35-64, >64 years), sex (female, male), country of birth, time since arrival in Canada, and whether the case was an Immigration, Refugees and Citizenship Canada (IRCC) referral (no, yes, unknown). IRCC referral indicates whether or not the patient was diagnosed while under immigration medical surveillance. Country of birth was categorized into six groups: the top five countries where the most cases emigrated from (The Philippines, India, China, Vietnam,

and Ethiopia) and all other countries grouped as “other”. Time since arrival was determined by calculating the number of years between the July 1st of the year of arrival in Canada and the date of TB diagnosis, which in Alberta is the start date of treatment.

Analysis

Statistical analysis was performed using Stata Statistical Software: Release 2013. Study participants were initially categorized into three groups – Canadian citizens/permanent residents, temporary residents, and refugees. However, due to the small sample size obtained for temporary residents and refugees, the two groups were combined for all analyses. Canadian citizens/permanent residents and temporary residents/refugees were compared using age, sex, country of birth, time since arrival in Canada, and IRCC referral.

Objective 2: To compare the clinical and laboratory characteristics of foreign-born pulmonary tuberculosis patients by immigration status (Alberta, 2004 - 2013).

Measurements

Clinical and laboratory characteristics collected at the time of diagnosis include: disease type (new active, relapse/retreatment), smear status (negative, positive), cavitation (no, yes), combined pulmonary and extrapulmonary (no, yes), drug resistance (no, yes), and HIV status (negative, positive, unknown). Disease type was determined by whether the case was a first episode of TB disease (new active) or whether there was a previous diagnosis of TB (relapse/retreatment). Smear status was determined by a positive or negative airway secretion smear, obtained from any of the following: sputum, bronchial wash, or gastric aspirate. Combined pulmonary and extrapulmonary was determined by an ICD-9 code indicative of pulmonary tuberculosis and at least one other code indicative of extrapulmonary tuberculosis. Drug resistance was determined by the presence of resistance to any one of the following four first-line drugs: isoniazid, ethambutol, rifampin, or pyrazinamide. In this study, advanced disease was defined as the presence of any one or combination of the following: a positive smear and presence of lung cavitation; combined pulmonary and extrapulmonary TB; or disseminated TB.

Analysis

Statistical analysis was performed using Stata Statistical Software: Release 2013. Canadian citizens/permanent residents and temporary residents/refugees were compared for disease type, smear status, cavitation, combined pulmonary and extrapulmonary, drug resistance, and HIV status. Chi-squared tests were used to determine statistical significant differences between study groups for study variables with a p-value < 0.05 indicating statistical significance.

Univariate logistic regression was performed to explore the associations of demographic, clinical, and laboratory characteristics with the presence of advanced disease. Unadjusted odds ratios (OR) were calculated for: age, sex, country of birth, time since arrival, IRCC referral, immigration status, disease type, drug resistance and HIV infection. Based on these results, a multiple logistic regression was then performed to determine adjusted ORs. Any characteristics that were found to have a p-value ≤ 0.2 in the univariate logistic regression were initially included in the multivariable model. Age and sex were deemed to be biologically important variables, and time since arrival and immigration status as clinically important. Thus, these four characteristics were included in the final multivariable model regardless of their p-value. A multivariable logistic regression model was fitted with all these variables. The final multivariable logistic regression model was developed by removing one variable, at each step, with the highest p-value which was not significant at $p=0.05$ (excluding the biologically and clinically important variables). This was repeated until all the remaining variables in the final model had a p-value ≤ 0.05. Any potential confounding effect of the removed variable was assessed at each step of the model development by determining whether the addition of the removed variable changed the odds ratios for those variables remained in the model by greater than 20%. Potential interactions were assessed by adding each interaction term to the main effects model individually. If the interaction was significantly associated with the outcome ($p \leq 0.05$), it was included in the model. Finally, all significant interaction terms were added to the model at the same time and the term with the highest p-value (>0.05) was removed. This was repeated until statistically significant interaction terms remained in the final model. The fit of the model was assessed through the Hosmer-Lemeshow test.

Objective 3: To compare the treatment outcomes of foreign-born pulmonary tuberculosis patients by immigration status (Alberta, 2004 - 2013).

Measurements

Treatment outcome was separated into three different categories: satisfactory, unsatisfactory, and other. Patients were classified as having a satisfactory treatment outcome if their outcome was labeled as "treatment completed" or "cure"; an unsatisfactory treatment outcome if their outcome was labeled as "fatal", "non-compliant", "absconded", or "treatment ongoing"; and other if their outcome was labeled as "unknown", "transferred to another province", or "transferred outside of Canada".

Analysis

Statistical analysis was performed using Stata Statistical Software: Release 2013. Univariate logistic regression was performed to explore the associations of demographic, clinical, and laboratory characteristics with the treatment outcome. Unadjusted odds ratios (OR) were calculated for: age, sex, country of birth, time since arrival, IRCC referral, immigration status, disease type, drug resistance and HIV infection. Based on these results, a multiple logistic regression was then performed to determine the adjusted ORs. Any characteristics that were found to have a p-value ≤ 0.2 in the univariate logistic regression were initially included in the multivariable model. Age and sex were deemed to be biologically important variables, and time since arrival, IRCC referral and immigration status as clinically important. Thus, these five characteristics were included in the final multivariable model regardless of their p-value. A multivariable logistic regression model was fitted with all these variables. The final multivariable logistic regression model was developed by removing one variable, at each step, with the highest p-value which was not significant at $p=0.05$ (excluding the biologically and clinically important variables). This was repeated until all the remaining variables in the final model had a p-value ≤ 0.05. Any potential confounding effect of the removed variable was assessed at each step of the model development by determining whether the addition of the removed variable changed the odds ratios for those variables remained in the model by greater than 20%. Removing advanced disease changed the odds ratios by greater than 20%, and thus was included in the model. Potential interactions were assessed by adding each interaction term to the main effects model individually. If the interaction was significantly associated with the outcome ($p \leq 0.05$), it was included in the model. Finally, all significant interaction terms were added to the model at the same time and the term with the highest p-value (>0.05) was removed. This was

repeated until statistically significant interaction terms remained in the final model. The fit of the model was assessed through the Hosmer-Lemeshow test.

Chapter Four: Results

Objective 1: To compare the demographic information and immigration status of foreign-born pulmonary tuberculosis patients by immigration status (Alberta, 2004 - 2013).

Table 4.1: Demographic characteristics and immigration status of adult foreign-born culture-positive pulmonary tuberculosis patients in Alberta, 2004 - 2013

Demographic Characteristics	Total No. (%)	Immigration Status		*p-value
		Canadian Citizen/ Permanent Resident No. (%)	Temporary Resident or Refugee No. (%)	
No. Assessed	646	517 (80.0)	129 (20.0)	-
Age				<0.001
15-34	222 (34.4)	156 (30.2)	66 (51.2)	
35-64	246 (38.1)	197 (38.1)	49 (38.0)	
>64	178 (27.5)	164 (31.7)	14 (10.8)	
Sex				0.983
Female	291 (45.1)	233 (45.1)	58 (45.0)	
Male	355 (54.9)	284 (54.9)	71 (55.0)	
Country of Birth				<0.001
The Philippines	131 (20.3)	83 (16.0)	48 (37.2)	
India	108 (16.7)	99 (19.2)	9 (7.0)	
China	66 (10.2)	59 (11.4)	7 (5.4)	
Vietnam	45 (7.0)	44 (8.5)	1 (0.8)	
Ethiopia	43 (6.7)	37 (7.2)	6 (4.7)	
Other	253 (39.1)	195 (37.7)	58 (45.0)	
Time Since Arrival				<0.001
≤2 Years	236 (36.5)	136 (26.3)	100 (77.5)	
> 2 Years	410 (63.5)	381 (73.7)	29 (22.5)	
IRCC Referral				<0.001
No	552 (84.4)	472 (91.3)	80 (62.0)	
Yes	94 (14.6)	45 (8.7)	49 (38.0)	

*p-values calculated using chi-squared test

Sociodemographic Characteristics

Over the study period, there were a total of 646 foreign-born tuberculosis patients diagnosed in Alberta with culture-positive TB: 517 (80.0%) Canadian citizens/permanent residents and 129 (20.0%) temporary residents/refugees (99 temporary residents and 30 refugees) (Table 4.1). There was a statistically significant difference in the distribution of age between the two groups. The greatest numbers of Canadian citizens/permanent residents were between 35-64 years of age (38.1%), while the greatest numbers of temporary residents/refugees were between 15-34 years of age (51.2%) ($p<0.001$). There was no significant difference in the proportion of females and males between the two groups ($p=0.983$). In the Canadian citizens/permanent residents group, 45.1% of the patients were female, while in the temporary residents/refugees group, 45.0% of the patients were female.

There was a significant difference ($p<0.001$) in the countries of origin in the two groups. While the greatest numbers of Canadian citizens/permanent residents were in the 'Other' category at 37.7%, which was comprised of all other countries other than the top five, the second greatest number of patients was from India at 19.2%, followed by the Philippines, China, Vietnam, and Ethiopia at 16.0%, 11.4%, 8.5%, and 7.2%, respectively. Similarly, the greatest numbers of temporary residents/refugees were in the 'Other' category at 45.0%. However, the second greatest number of patients was found to be from the Philippines at 37.2%. This was followed by India, China, Ethiopia and Vietnam at 7.0%, 5.4%, 4.7%, and 0.8%, respectively.

In the Canadian citizen/permanent residents group, 73.7% of patients had lived in Canada for greater than two years, while in the temporary residents/refugees group, only 22.5% had lived in Canada for greater than two years ($p<0.001$). Only a small number of Canadian citizens/permanent residents were diagnosed through an IRCC referral at 8.7%, with 91.3% of individuals being identified through other means. In comparison, 38.0% of temporary residents/refugees were diagnosed through an IRCC referral, with 62.0% of patients not being identified through this process ($p<0.001$).

Objective 2: To compare the clinical and laboratory characteristics of foreign-born pulmonary tuberculosis patients by immigration status (Alberta, 2004 - 2013).

Table 4.2: Clinical and laboratory characteristics of adult foreign-born culture-positive pulmonary tuberculosis patients by immigration status in Alberta, 2004 - 2013

Clinical and Laboratory Characteristic	Total No. (%)	Immigration Status		p-value
		Canadian Citizen/ Permanent Resident No. (%)	Temporary Resident or Refugee No. (%)	
No. Assessed	646	517 (80.0)	129 (20.0)	-
Disease Type				0.946
New Active	595 (92.1)	476 (92.1)	119 (92.3)	
Relapse/Retreatment	51 (7.9)	41 (7.9)	10 (7.7)	
Smear Status				0.035
Negative	322 (49.8)	247 (47.8)	75 (58.1)	
Positive	324 (50.2)	270 (52.2)	54 (41.9)	
Cavitation				0.972
No	490 (75.9)	392 (75.8)	98 (76.0)	
Yes	156 (24.1)	125 (24.2)	31 (24.0)	
Combined Pulmonary and Extrapulmonary				0.019
No	501 (77.5)	391 (75.6)	110 (85.3)	
Yes	145 (22.5)	126 (24.4)	19 (14.7)	
Drug Resistance				0.017
No	566 (87.6)	461 (89.2)	105 (81.4)	
Yes	80 (12.4)	56 (10.8)	24 (18.6)	
HIV Status*				0.152
Negative	569 (93.3)	449 (92.6)	120 (96.0)	
Positive	41 (6.7)	36 (7.4)	5 (4.0)	
Unknown	36 (5.6)	32 (6.2)	4 (3.1)	
Advanced/Complicated Disease†				0.043
No	380 (58.8)	294 (56.9)	86 (66.7)	
Yes	266 (41.2)	223 (43.1)	43 (33.3)	

* Only assessed HIV status of those who were tested (n=610); total of unknown = 36, CC/PR=32, TR/R=4
†Advanced or complicated disease is defined as: a positive smear and presence of lung cavitation; combined pulmonary and extrapulmonary TB; or disseminated TB

Clinical and Laboratory Characteristics

A large majority of patients in both the Canadian citizens/permanent residents and temporary residents/refugees group were diagnosed with new active TB, at 92.1% and 92.3%, respectively (p=0.946), with only a small number diagnosed with relapse/retreatment of TB (Table 4.2). The proportion of those with a negative or positive smear status was different between the two groups. In the Canadian citizens/permanent residents group, 52.2% were smear positive, while in the temporary residents/refugees group, 41.9% were smear positive (p=0.035). In terms of lung cavitation, it was found that 24.2% of Canadian citizens/permanent residents presented with cavitation, while 24.0% of temporary residents/refugees did. This result was not statistically significant (p=0.972). There was a significant difference between the two groups in the proportion of those diagnosed with only pulmonary TB versus those diagnosed with a combination of pulmonary and extrapulmonary TB (p=0.019). 24.4% of Canadian citizens/permanent residents and 14.7% of temporary residents/refugees presented with combined pulmonary and extrapulmonary TB.

Drug resistance, to any one or more anti-TB drugs, was not common in Canadian citizens/permanent residents group at 10.8%. The proportion was slightly higher in temporary residents/refugees at 18.6%, with the difference being statistically significantly (p=0.017). HIV status was similar across both groups, with 92.6% of Canadian citizens/permanent residents and 96.0% temporary residents/refugees presenting as HIV negative. This result was not statistically significant (p=0.152). Finally, 43.1% of Canadian citizens/permanent residents were found to have advanced/complicated disease, compared to 33.3% of temporary residents/refugees (p=0.043).

Table 4.3: Predictors of advanced or complicated* disease in adult foreign-born culture-positive pulmonary tuberculosis patients in Alberta, 2004 - 2013

	Advanced Disease			
Demographic, Clinical, and Laboratory Characteristic	**Univariate Analysis**		**Multivariable Analysis**	
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age				
15-34	1.00 (reference)			
35-64	1.22 (0.85-1.76)	0.280	1.59 (0.80-3.14)	0.183
>64	0.42 (0.27-0.65)	<0.001	1.37 (0.44-4.24)	0.586
Sex				
Female	1.00 (reference)			
Male	1.47 (1.07-2.02)	0.017	1.45 (1.02-2.07)	0.038
Country of Birth				
The Philippines	1.00 (reference)			
India	1.17 (0.70-1.96)	0.550		
China	0.61 (0.32-1.16)	0.134		
Vietnam	1.11 (0.56-2.21)	0.766		
Ethiopia	1.75 (0.87-3.50)	0.115		
Other	1.10 (0.71-1.68)	0.678		
Time Since Arrival				
≤2 Years	1.00 (reference)			
>2 Years	1.57 (1.13-2.19)	0.007	1.71 (0.94-3.10)	0.079
IRCC Referral				
No	1.00 (reference)			
Yes	0.05 (0.02-0.14)	<0.001	0.04 (0.01-0.12)	<0.001
Immigration Status				
Canadian Citizen/ Permanent Resident	1.00 (reference)			
Temporary Resident or Refugee	0.66 (0.44-0.99)	0.044	0.87 (0.52-1.45)	0.592
Disease Type				
New Active	1.00 (reference)			
Relapse	0.69 (0.38-1.27)	0.238		
Drug Resistance				
No	1.00 (reference)			
Yes	1.27 (0.79-2.03)	0.325		
HIV Status				
Negative	1.00 (reference)			
Positive	2.61 (1.35-5.04)	0.004		
Age * Time Since Arrival				
35-64 Years * >2 Years			0.47 (0.20-1.11)	0.087
>64 Years * > 2 Years			0.16 (0.04-0.56)	0.004

* Advanced or complicated disease is defined as: a positive smear and presence of lung cavitation; combined pulmonary and extrapulmonary TB; or disseminated TB

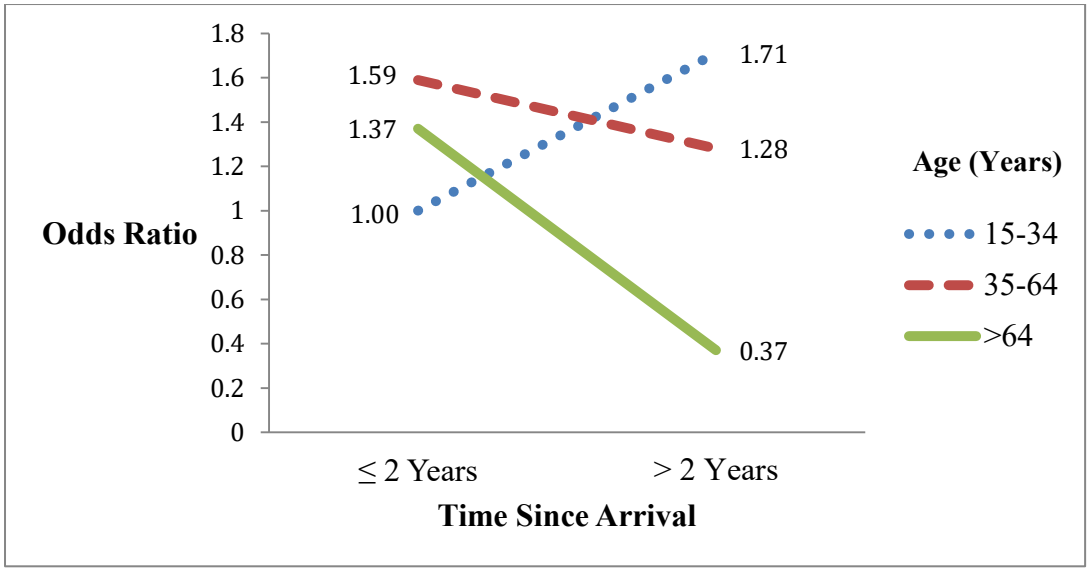

Figure 4.1: Odds ratios of the interaction between age and time since arrival

Predictors of Advanced or Complicated Disease

In the univariate analysis (Table 4.3), it was found that age, sex, country of birth, time since arrival, IRCC referral, immigration status, and HIV status met the criteria for inclusion in the multivariable model ($p \leq 0.2$). Age and sex were also included on the basis that they likely have a biologically significant effect on advanced disease, and time since arrival and immigration status likely having a clinically significant effect. Country of birth and HIV status were not found to be statistically significant in the final model and were subsequently dropped.

In the final multivariable model (Table 4.3), it was found that sex and IRCC referral were significantly associated with advanced disease ($p<0.05$). Males were more likely to have been diagnosed with advanced disease compared to females (OR 1.45, $p=0.038$). Patients who were diagnosed through an IRCC referral were significantly less likely to have advanced disease compared to those who were not (OR 0.04, $p<0.001$).

The interaction between age and time since arrival was statistically significant. Among 15-34 year old patients, those who have lived in Canada for less than or equal to two years were less likely to have advanced disease compared to those who have lived in Canada for more than two years. However, the reverse is true among older patients aged >64 years. Those who have lived in Canada for less than or equal to two years were more likely to have

advanced disease compared to those who have lived in Canada for more than two years (Figure 4.1).

The fit of the model was assessed through the Hosmer-Lemeshow test. The results of this test produced a p-value of 0.95 and thus, it can be concluded that the model fits reasonably well.

Objective 3: To compare the treatment outcomes of foreign-born pulmonary tuberculosis patients by immigration status (Alberta, 2004 - 2013).

Table 4.4: Treatment outcome of adult foreign-born culture-positive pulmonary tuberculosis patients by immigration status in Alberta, 2004 - 2013

		Immigration Status		
	Total No. (%)	**Canadian Citizen/ Permanent Resident No. (%)**	**Temporary Resident or Refugee No. (%)**	***p-value**
No. Assessed	646	517 (80.0)	129 (20.0)	-
***Treatment Outcome**				<0.001
Satisfactory	564 (87.3)	457 (88.4)	107 (83.0)	
Unsatisfactory	55 (8.5)	51 (9.9)	4 (3.1)	
Other	27 (4.2)	9 (1.7)	18 (13.9)	

*Treatment outcome category of 'satisfactory' is defined as: treatment completed and/or cured; 'unsatisfactory' is defined as: fatal, non-compliant, absconded, or treatment ongoing; and 'other' is defined as transferred outside of Canada or unknown

Treatment Outcome

Treatment outcome was divided into three categories: satisfactory, unsatisfactory, and other. Satisfactory is defined as treatment completed and/or cured; unsatisfactory is defined as fatal, non-compliant, absconded, or treatment ongoing; and other is defined as transferred outside of Canada or unknown. The majority of Canadian citizens/permanent residents (88.4%) and temporary residents/refugees (83.0%) had a satisfactory treatment outcome (Table 4.4). More temporary residents/refugees had treatment outcomes in the 'other' category than Canadian citizens/permanent residents (13.9% compared to 1.7%). These differences were statistically significant ($p<0.001$).

Table 4.5: Predictors of treatment outcome* in adult foreign-born culture-positive pulmonary tuberculosis patients in Alberta, 2004 - 2013

Demographic, Clinical, and Laboratory Characteristic	Treatment Outcome			
	Univariate Analysis		Multivariable Analysis	
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age				
15-34	1.00 (reference)			
35-64	1.87 (0.74-4.73)	0.184	1.09 (0.37-3.26)	0.877
>64	7.54 (3.25-17.5)	<0.001	6.90 (2.39-19.9)	<0.001
Sex				
Female	1.00 (reference)			
Male	1.16 (0.66-2.04)	0.594	1.22 (0.60-2.49)	0.578
Country of Birth				
The Philippines	1.00 (reference)			
India	4.44 (1.40-14.1)	0.011		
China	7.10 (2.19-23.0)	0.001		
Vietnam	3.24 (0.77-13.6)	0.108		
Ethiopia	2.30 (0.49-10.7)	0.287		
Other	2.64 (0.88-7.95)	0.083		
Time Since Arrival				
≤2 Years	1.00 (reference)			
> 2 Years	3.43 (1.59-7.41)	0.002	2.06 (0.68-6.27)	0.201
IRCC Referral				
No	1.00 (reference)			
Yes	0.22 (0.05-0.93)	0.039	0.92 (0.17-5.17)	0.929
Immigration Status				
Canadian Citizen/ Permanent Resident	1.00 (reference)			
Temporary Resident or Refugee	0.33 (0.12-0.95)	0.039	1.02 (0.26-4.10)	0.973
Disease Type				
New Active	1.00 (reference)			
Relapse	0.95 (0.33-2.75)	0.925		
Drug Resistance				
No	1.00 (reference)			
Yes	0.72 (0.28-1.86)	0.495		
HIV Status				
Negative	1.00 (reference)			
Positive	3.41 (1.40-8.32)	0.007	6.24 (2.16-18.0)	0.001
Advanced/Complicated Disease				
No	1.00 (reference)			
Yes	1.63 (0.94-2.84)	0.084	2.13 (1.01-4.50)	0.047

*Only assessed those with known HIV status and treatment outcomes (n=587)

Predictors of Treatment Outcome

In the univariate analysis (Table 4.5), it was found that age, country of birth, time since arrival, IRCC referral, immigration status, HIV status, and advanced disease met the criteria for inclusion in the multivariable model ($p \leq 0.2$). Sex was included on the basis that it likely has a biologically significant effect on treatment outcome. Time since arrival, IRCC referral and immigration status were included due to the likelihood of their having a clinically significant effect. Country of birth was found to be statistically insignificant in the final model and was subsequently dropped.

In the final multivariable model (Table 4.5), it was found that age, HIV status, and the presence of advanced disease were significantly associated with unsatisfactory treatment outcome ($p<0.05$). Patients who were greater than 64 years of age were more likely to have unsatisfactory treatment outcomes compared to patients who were between 15-34 years of age (OR 6.90, $p<0.001$). Patients who were HIV positive were significantly more likely to have unsatisfactory treatment outcomes compared to those who were HIV negative (OR 6.24, $p=0.001$). The presence of advanced disease also increased the odds of having an unsatisfactory treatment outcome (OR 2.13, $p=0.047$).

The fit of the model was assessed through the Hosmer-Lemeshow test. The results of this test produced a p-value of 0.81 and thus, it can be concluded that the model fits reasonably well.

Chapter Five: Discussion and Conclusion

Summary of Results

Comparison of Canadian Citizens/Permanent Residents and Temporary Residents/Refugees

The first and second objectives of this study were to compare the demographic, clinical and laboratory characteristics of foreign-born pulmonary tuberculosis patients in Alberta by immigration status. These results contribute to the current literature on the experience of TB in the foreign-born population in Canada, as well as the effectiveness of current screening and surveillance practices.

Sociodemographic Characteristics

In this study, it was found that between January 2004 and December 2013, a total of 1524 patients were diagnosed with active TB in Alberta. Of this total, 1200 (78.7%) patients were foreign-born and 324 (21.3%) were Canadian born (non-Indigenous or Indigenous). Compared to the national figures reported in 2010 in which the proportion of active TB cases among the foreign-born was approximately 67.0% (Public Health Agency of Canada, 2014a), the proportion in Alberta was slightly higher between 2004 and 2013. Of the 1200 foreign-born patients, a total of 647 patients met the inclusion criteria to be included in the study, with one patient excluded due to missing data. Of the 646 patients, 517 (80.0%) were Canadian citizens/permanent residents and 129 (20.0%) were temporary residents/refugees.

The distribution of age was significantly different between the two groups. Patients between 35-64 years of age accounted for the highest proportion of Canadian citizens/permanent residents at 38.1%, while those between 15-34 years of age were the largest group of temporary residents/refugees at 51.2% ($p<0.001$). This difference may be due to the temporary residents/refugees group consisting of individuals such as students (whom are likely pursuing post-secondary education) and temporary workers (whom are likely young and healthy enough to pursue work in a different country). Both groups had similar distributions of males and females, with 54.9% of Canadian citizens/permanent residents and 55.0% of temporary residents/refugees being male. This result is similar to national trends, where the incidence rate of TB is higher among males than females (Public Health Agency of Canada, 2014a), as well as globally, where the male to female ratio is 1.7 (World Health Organization, 2015).

The 646 foreign-born patients originated from 77 different countries around the world, with the top five countries being the Philippines (131), India (108), China (66), Vietnam (45), and Ethiopia (43). This is not surprising as the majority of global TB cases occur in Asia (58%) and Africa (28%) (World Health Organization, 2015), and previous research has shown that many cases of TB in the foreign-born are due to reactivation of latent TB infection that was acquired in their home country (Jensen et al., 2012; Kunimoto et al., 2004). This result is also consistent with previous research conducted in Alberta which found that the top five countries of birth of foreign-born patients between 1989 and 1998 was Vietnam, China, the Philippines, India, and Hong Kong (Long et al., 2002). Similarly, in a study conducted on tuberculosis among foreign-born persons in Taiwan, the top five countries of birth were Mainland China, Vietnam, the Philippines, Thailand, and Indonesia (Bai et al., 2008). These results continue to highlight the burden of TB in Asian countries as well as low TB incidence immigrant-receiving countries such as Canada. With the knowledge that the majority of foreign-born TB cases in Canada occur in individuals from specific high-burden countries, targeted screening and preventive therapy in this group would likely reduce the number of TB cases.

The greatest proportion of Canadian citizens/permanent residents were in the 'Other' category (37.7%), followed by India (19.2%), the Philippines (16.0%), China (11.4%), Vietnam (8.5%), and Ethiopia (7.2%). In comparison, the most temporary residents/refugees were in the 'Other' category (45.0%), followed by the Philippines (37.2%), India (7.0%), China (5.4%), Ethiopia (4.7%), and Vietnam (0.8%). These results were significantly different ($p<0.001$). The Philippines makes up the greatest proportion of temporary residents/refugees. This may be attributed to the fact that the Philippines has consistently been one of the top countries of citizenship of individuals in Canada's Temporary Foreign Worker Program (Government of Canada, 2016), contributing to the high number of Filipino temporary residents. In a study conducted on TB in the Filipino population living in the United States, it was found that compared with other Asian/Pacific Islander patients, Filipino TB patients were more likely to be employed as health care workers or as migrant workers and less likely to be unemployed (Manangan et al., 2011). Currently IRCC mandates that individuals who plan to work in certain occupations, such as clinical laboratory workers or patient attendants, must undergo an immigration medical exam (Appendix A). This is an important strategy to identify those who could potentially be a public health risk, particularly

those working in jobs that require close contact with people, especially young or immune-compromised people. Combined with the knowledge that a large number of temporary workers in Canada are from the Philippines, targeted screening for LTBI in this group, and those from other high TB-burden countries, would help to identify those at risk of developing active TB.

A majority of Canadian citizens/permanent residents (73.7%) have lived in Canada for greater than two years. In comparison, only 22.5% of temporary residents/refugees have lived in Canada for greater than two years. This difference was statistically significant ($p<0.001$). One possible explanation for this difference may be the inherent nature of individuals in both status groups. Temporary residents/refugees are generally made up of temporary workers and students, as well as those who have recently fled their home country, and therefore will have shorter residency than those who have been in the country long enough to become Canadian citizens/permanent residents.

In the Canadian citizen/permanent residents group, 91.3% of patients were identified through passive case detection, with only 8.7% of patients being identified through an IRCC referral. In temporary residents/refugees, 62.0% of patients were not identified through this process, while 38.0% were identified through an IRCC referral. This difference was statistically significant ($p<0.001$). It is concerning that a majority of TB patients in both groups were not identified through an IRCC referral as this indicates that the current system is missing the opportunity to identify these individuals before they develop active TB disease. In a similar study conducted in Alberta in 2002, it was found that only 8.0% of foreign-born cases between 1989 and 1998 were identified through an IRCC referral (Long et al., 2002). While IRCC mandates that permanent resident applicants, temporary residents, and refugees undergo an immigration medical examination prior to coming to Canada, this system does not systematically screen for LTBI (IRCC, 2014). Only those with inactive pulmonary TB (a past history of TB or evidence of old healed TB on a chest radiograph) are referred for medical surveillance.

As reported by Kunimoto et al., foreign-born TB cases are not likely to transmit to others; thus incident TB in the foreign-born is judged to most likely be due to reactivation of LTBI acquired overseas (Kunimoto et al., 2004). With a majority of foreign-born TB patients

currently being diagnosed through passive case-finding rather than medical surveillance, scaled up screening of LTBI within subgroups of the foreign-born and subsequent provision of preventive therapy would likely decrease the number of reactivated TB cases. Although there is no set formula to determine who should undergo LTBI screening, results from this study and previous literature suggests that certain characteristics may be associated with an increased risk of reactivated TB. Groups identified as having increased risk of TB exposure and latent TB infection are highlighted in the Canadian Tuberculosis Standards – 7th Edition (Appendix E) (Public Health Agency of Canada, 2014a). Two groups particularly relevant to the foreign-born population include immigrants from countries with high TB incidence and travellers to countries with high TB incidence. Based on the results of this study, immigrants from India, China, the Philippines, Vietnam and Ethiopia should continue to be considered for targeted LTBI screening in Canada.

Although not explored in this study, previous research has found that a number of foreign-born active TB cases are due to recent travel to their countries of origin (Kik et al., 2011; Ormerod, Green, & Gray, 2001). In particular, foreign-born individuals who travel to visit friends and relatives in their country of origin are particularly at risk due to factors such as longer stays, spending time in high-risk areas, and not seeking pre-travel advice due to the perception of less personal risk from travel-related disease (Angell & Cetron, 2005; Bacaner, Stauffer, Boulware, Walker, & Keystone, 2004). This group is difficult to target for LTBI screening because a significant number do not seek pre-travel advice, and upon returning to Canada, they are not required to undergo any specific medical examinations. One strategy to target this group would be improving cultural competency in health care providers and addressing language barriers in order to increase the number of foreign-born individuals seeking pre-travel advice (Angell & Cetron, 2005).

In order to scale up the screening of LTBI within subgroups of the foreign-born and increase provision of preventive therapy in Canada, various challenges and barriers must be taken into consideration. According to the WHO, it is estimated that between 2-3 billion people worldwide have latent TB infection, which is equal to approximately one third of the world's population (World Health Organization, 2015). With such a large pool of individuals with LTBI, most of whom will not develop TB, the challenge is to identify and screen those at the greatest risk of reactivation based on the available evidence. As previously mentioned,

this would include foreign-born individuals coming from high-risk countries, and specifically in Alberta, those from India, China, the Philippines, Vietnam, and Ethiopia. In addition, results from this study and evidence from previous literature suggests that those between 15-34 years of age and who have recently arrived (< 2 years) may also be good targets for screening (Langlois-Klassen et al., 2011). Another barrier to effective LTBI screening and treatment implementation is the poor adherence to LTBI treatment regimens (Page et al., 2006). The current recommended treatment regimen for LTBI is daily isoniazid taken for 9 months (Public Health Agency of Canada, 2014a). Other alternatives include daily isoniazid taken for 6 months and daily isoniazid and rifampin taken for 3-4 months (Public Health Agency of Canada, 2014a). A study conducted by Page et al. found that the adherence rate to the 9-month isoniazid regimen in a US public health clinic was approximately 52.6% (Page et al., 2006). Emerging treatment regimens, such as 4 months of rifampin, with shorter durations and lower rates of hepatoxicity, could help to increase treatment adherence (Ziakas & Mylonakis, 2009).

Implementing strategies to scale up screening of LTBI within subgroups of the foreign-born and subsequent provision of preventive therapy would likely improve on Canada's current IRCC referral process. More individuals at risk of developing active TB would be identified earlier and preventive therapy would decrease the number of TB cases found through passive case finding.

Clinical and Laboratory Characteristics

Smear status was statistically different between the Canadian citizens/permanent residents and temporary residents/refugees (p=0.035). In Canadian citizens/permanent residents, 52.2% had a positive smear, while in temporary residents/refugees, 41.9% had a positive smear. This finding has significant public health implications because based on previous research, it has been found that smear positive individuals are more likely to transmit than those who are smear negative (Behr et al., 1999). With slightly more Canadian citizens/permanent residents having a positive smear, it is possible that they may be more infectious than temporary residents/refugees. This should be taken into consideration when a diagnosis is made.

There was also a significant difference between the two groups in the proportion of patients diagnosed with only pulmonary TB and patients diagnosed with a combination of pulmonary and extrapulmonary TB (p=0.019). In Canadian citizens/permanent residents, 24.4% were diagnosed with combined pulmonary and extrapulmonary TB. In temporary residents/refugees, 14.7% presented with both pulmonary and extrapulmonary TB. Previous research has not specifically explored the association between immigration status and extrapulmonary TB. It is difficult to determine why more Canadian citizens/permanent residents presented with combined pulmonary and extrapulmonary TB. Since more of the temporary residents/refugees are being actively screened for pulmonary TB upon arrival, this may be why we are more likely to find this type of disease in this group compared to Canadian citizens/permanent residents. Because the Canadian citizen/permanent resident patients are mainly found through symptoms, their disease may be more advanced and involve more than one site. In a study conducted by Abraham et al. on tuberculosis among Africans living the US, it was found that Africans are more likely to have extrapulmonary TB (Abraham et al., 2013), while Asghar et al. also found that South Asian TB patients more commonly develop extrapulmonary TB than other foreign-born patients (Asghar et al., 2008). Extrapulmonary TB was also found to be more prevalent among immigrants from the Middle East, Asia, and Africa in a study conducted in Denmark (Leutscher et al., 2012).While country of birth seems to be correlated with an increased risk of extrapulmonary TB, this may not be applicable to these results as both groups had similar top five countries of origin. Other risk factors for extrapulmonary TB identified in a study in San Francisco include younger age, female sex, and HIV infection (Ong et al., 2004).

In terms of drug resistance, 10.8% of Canadian citizens/permanent residents were resistant to one or more anti-TB drugs. In temporary residents/refugees, this proportion was higher at 18.6%. This result was statistically significant (p=0.017). Previous research has found that resistance to any one of the four first-line drugs (isoniazid, ethambutol, rifampin, or pyrazinamide) is more common in foreign-born cases (Long & Langlois-Klassen, 2013). According to the Public Health Agency of Canada, between 2006 and 2010, foreign-born individuals were 1.9 times more likely to have isoniazid-resistance/rifampin-resistance and 13 times more likely to have multidrug-resistance TB (MDR-TB) (Public Health Agency of Canada, 2014a). When exploring the effects of immigration status, the results of this study found that drug resistant TB was more common in temporary residents/refugees than in

Canadian citizens/permanent residents. Temporary residents/refugees are more likely to be recent arrivals, and since drug resistance is growing globally, they are more likely to be harbouring resistant bacilli. In a previous study of multidrug-resistant TB in Alberta between 1982 and 2011, it was found that younger individuals (age <65 years) were associated with MDR-TB (Long & Langlois-Klassen, 2013). Since temporary residents/refugees have been found to be younger than Canadian citizens/permanent residents, it is not surprising that a higher proportion of temporary residents/refugees presented with drug resistance.

Advanced/Complicated Disease

Univariate analysis was conducted to explore the relationship between age, sex, country of birth, time since arrival, IRCC referral, immigration status, disease type, drug resistance, and HIV status with advanced disease. A multivariable model was subsequently developed to determine whether any of these variables were independently associated with advanced TB disease.

In the final adjusted multivariable model, sex and IRCC referral were found to have a significant association with advanced disease ($p<0.05$). Males were found to be more likely to have advanced disease (OR 1.45, $p=0.038$) compared to females. One possible cause for this finding is the different health care-seeking behaviours between males and females. Men generally do not seek out health care as often as women, perhaps because socially it is seen as less masculine to do so (Courtenay, 2000). As a result, any signs and symptoms that would indicate TB disease might not be picked up in the early stages, further delaying their diagnosis and potentially increasing their chances of progressing to advanced disease. Concerns about potential job loss may also contribute to the delays in TB diagnosis in males. In a study conducted by Onazi et al. in Nigeria, more male TB patients experienced loss of jobs compared to female TB patients (Onazi et al., 2015). This may be due to differing expectations between males and females. In addition, Statistics Canada reports that employment rates were higher among males compared to females, in both the Canadian-born and foreign-born groups in 2006 (Statistics Canada, 2015b). As a result, if a male patient is one of the main sources of income for a household, they may be less likely to seek out care for TB symptoms in the early stages of disease. Patients who were identified through an IRCC referral were less likely to have advanced disease compared to those who were identified through passive case finding (OR 0.04, $p<0.001$). This observation may be due to

the earlier detection of TB disease in patients identified through the IRCC program and the provision of treatment before they progressed to advanced disease. Patients identified through other means may not have been recognized as having TB until they were into the advanced stages of disease. This result highlights the importance and effectiveness of the IRCC medical surveillance program. If improvements are made to the program in order to increase the number of TB patients identified through an IRCC referral, it is possible that fewer patients will progress to advanced disease.

In the final adjusted multivariable model the interaction between age and time since arrival was found to be statistically significant. Patients between 15-34 years of age who have lived in Canada for less than or equal to two years were less likely to have advanced disease compared to those who have lived in Canada for more than two years. In comparison, patients >64 years of age who have lived in Canada for less than or equal to two years were more likely to have advanced disease compared to those who have lived in Canada for more than two years. The reason for this reversed trend is unclear and more research is needed to explore the interaction between age and time since arrival and advanced disease.

Treatment Outcome

In order to assess treatment outcome, patients were divided into three categories, including satisfactory, unsatisfactory, and other. In total, 564 patients (87.3%) had a satisfactory treatment outcome (treatment completed or cure), 55 patients (8.5%) had an unsatisfactory treatment outcome (fatal, non-compliant, absconded, or treatment ongoing), and 27 patients (4.2%) were in the 'other' category (unknown, transferred to another province, or transferred outside of Canada). This result is consistent with previous research conducted in Alberta between 1996 and 2012, where 87.0% of foreign-born patients reached treatment completion or cure (Gao et al., 2015). This study also reported that Canadian-born Indigenous individuals were more likely to die than Canadian-born non-Indigenous or foreign-born individuals. With foreign-born TB patients having relatively better outcomes, increased emphasis and support for Canadian-born Indigenous TB patients should be a priority.

Univariate analysis was conducted to explore the relationship between age, sex, country of birth, time since arrival, IRCC referral, immigration status, disease type, drug

resistance, HIV status and advanced/complicated disease with treatment outcome. A multivariable model was subsequently developed to determine whether any of these variables were independently associated with poor treatment outcome.

In the final adjusted multivariable model, age, HIV status, and advanced disease were significantly associated with unsatisfactory treatment outcome ($p<0.05$). Patients who were greater than 64 years of age were more likely to have an unsatisfactory treatment outcome compared to patients between 15-34 years of age (OR 6.90, $p<0.001$). In other words, patients greater than 64 years of age were more likely to have passed away, been non-compliant, absconded, or to be engaged in ongoing treatment. This result is not surprising because it is well documented that older age is associated with an increase in comorbidities (van den Akker, Buntinx, Metsemakers, Roos, & Knottnerus, 1998) and this may affect the diagnosis and treatment of health conditions in older patients (Karlamangla et al., 2007). It is also consistent with previous studies conducted in the United States and Australia, which found that fatality was associated with older age (Nguyen, Hamilton, Xia, & Stout, 2011; Walpola, Siskind, Patel, Konstantinos, & Derhy, 2003). According to the 2012 Canadian Community Health Survey, 85% of seniors aged 65 to 79 and 90% of those aged over 80 years old reported having at least one chronic condition (Public Health Agency of Canada, 2014b). The subsequent diagnosis of TB in these older patients is an additional complication that can drastically affect treatment outcome and extra support should be provided to improve prognosis.

Patients who were co-morbid with HIV were more likely to have an unsatisfactory treatment outcome compared to those who were HIV negative (OR 6.24, $p<0.001$). A link between TB and HIV co-infection is well established (Corbett et al., 2013; Long & Boffa, 2010). According to the World Health Organization, of the 9.6 million people who developed TB in 2014, approximately 1.2 million were HIV-positive (World Health Organization, 2015). Furthermore, HIV was responsible for 25% of all TB deaths in the same year (World Health Organization, 2015). The results of this study further confirm the association between HIV infection and negative TB outcome, and highlight the need to know the HIV status of the patient. In Alberta, near universal HIV testing of TB patients, was achieved through the "opt-out" approach (Long et al., 2014). Through this approach, TB patients are routinely tested for HIV unless they actively inform their provider of their decision not to be tested.

Knowing the HIV status of a patient is an important step when deciding how to manage a TB case, and the "opt-out" approach is an effective way to achieve this.

Those who had advanced disease were more likely to have unsatisfactory treatment outcomes (OR 2.13, p=0.047). In this study, advanced disease is defined as: a positive smear and presence of lung cavitation; combined pulmonary and extrapulmonary TB; or disseminated TB. It is reasonable that patients who are identified prior to reaching the advanced stages of disease have better prognoses and increased chances of satisfactory treatment outcomes. This result emphasizes the importance of earlier detection of TB in order to prevent progression to advanced disease, and subsequently an unsatisfactory treatment outcome.

Study Strengths

The comparison of different immigration statuses (Canadian citizens/permanent residents compared to temporary residents/refugees) of foreign-born individuals was a strength of this study. There have been many studies on TB in the foreign-born population in Canada and other low TB incidence countries. However, few have explored the impact of immigration status on the experience and progression of TB. Based on the results of this study, immigration status is an additional factor that should be considered in order to improve the management of TB in the foreign-born population.

The use of a retrospective cohort analysis allowed for the opportunity to capture the experience of a diverse group of foreign-born individuals in Alberta over a period of 10 years. In addition, because Alberta represents one of four major immigrant-receiving provinces in Canada, study results are relevant at the national level. As a high income, low-incidence immigrant-receiving country, it is anticipated that results can also be generalizable to other countries with similar immigration patterns.

Study Weaknesses

The sample size used in the analysis was obtained through the inclusion of all foreign-born TB cases in Alberta who met the criteria outlined in the study. Since this was a retrospective study, this number was dependent on the actual number of active TB cases that occurred during the study period. Due to low sample sizes in both the temporary resident and

refugee groups, they were combined into a single group for analysis purposes. It is acknowledged that there are important differences between temporary residents and refugees that may have affected the interpretation of the results.

Active Tuberculosis Case Report Forms and iPHIS were the main source of data for this study. Some of the data obtained from these sources, such as HIV status and treatment outcome, included the option of 'unknown'. For HIV status, this meant that the patient's status is unknown, the patient refused testing, or testing was not offered. For treatment outcome, this meant that the patient's outcome was unknown, they were transferred to another province, or they were transferred outside of Canada. Because this study was interested in the impact of a positive/negative HIV status and satisfactory/unsatisfactory treatment outcome, this unknown information made it difficult to assess the full impact of these variables on the outcome of the results.

Conclusions

To date, few studies have explored the potential effects of immigration status on the experience of TB in foreign-born patients in Canada. This study aimed to characterize the demographic, clinical, laboratory, and treatment outcome characteristics among foreign-born PTB patients in Alberta, specifically exploring the impact of immigration status.

Overall, the results of this study were consistent with previous findings. Between 2004 and 2013, the majority of active TB cases in Alberta were diagnosed in the foreign-born population, which is similar to national trends. Approximately 80.0% of these patients had either Canadian citizen or permanent resident status, and 20.0% had temporary resident or refugee status. There were a few significant differences between Canadian citizens/permanent residents and temporary residents/refugees. Compared to Canadian citizens/permanent residents, temporary residents/refugees were generally younger, with the top country of origin being the Philippines (compared to India for the Canadian citizen/permanent resident group). Most temporary residents/refugees have lived in Canada for less than two years, with more patients having been identified through an IRCC referral than Canadian citizens/permanent residents. More temporary residents/refugees presented with a negative smear and drug resistance. Finally less temporary residents/refugees presented with both

pulmonary and extrapulmonary TB, and advanced/complicated disease than Canadian citizens/permanent residents.

Contrary to the original hypothesis, it was found that temporary resident/refugee status was not associated with more advanced disease or worse treatment outcomes. In fact, data showed that temporary residents/refugees were less likely to have advanced disease compared to Canadian citizens/permanent residents, although this was not statistically significant. This may have been due to the fact that more temporary residents/refugees were identified through an IRCC referral, and as a result, were likely caught in the earlier stages of TB disease and provided the appropriate treatment prior to progressing to advanced disease. The earlier detection of TB would likely mean the earlier provision of treatment and increased chances of satisfactory treatment outcome. These results emphasize the importance of the IRCC referral process and the role that it plays not only in identifying individuals with TB, but also in ensuring their timely access to treatment and care.

Factors that were found to be associated with advanced disease include the male sex and patients who were not identified through IRCC referral. In terms of treatment outcomes, older patients, positive HIV status, and advanced disease were associated with unsatisfactory treatment outcome, while temporary resident/refugee status was not.

Recommendations for Further Research

A cohort study exploring additional characteristics of patients such as duration of TB symptoms prior to seeking care, combined with qualitative interviews would provide valuable information on the experience of TB within different sub-groups of the foreign-born population. This information would also provide insight into any differences in the knowledge, attitudes, and beliefs of patients based on their immigration status. Additionally, an increased sample size of temporary residents and refugees may allow for the analysis of each group separately to explore any potential differences between those immigration statuses.

Recommendations for Practice

An important focus surrounding new immigrants should be placed on conditions surrounding their resettlement such as obtaining housing, accessing community resources,

and accessing healthcare. These factors are critical to ensuring that the risk of reactivation of LTBI is lowered. More specific recommendations include revisions to the IRCC screening and surveillance program and increased LTBI screening and treatment in high-risk groups. Current IRCC screening and surveillance practices are missing a significant number of individuals who later go on to develop active TB, suggesting that LTBI is an important factor that must be considered in low-incidence countries such as Canada.

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Appendices

Appendix A:

Medical exam requirements for temporary residents (visitors, students and workers)

If you plan to visit for six months or less:
You generally do not require a medical exam, unless you plan to work in certain occupations (see below).

If you plan to visit for more than six months:
You will need a medical exam if you:

- have lived temporarily for six or more consecutive months
  - in one or more of these **countries or territories**
  - in the one year immediately before the date you want to enter Canada. (**This applies even if you are a citizen of a country that does not need a visa to enter Canada.**) or
- will come to Canada to work in an occupation in which public health must be protected. See below for jobs for which you need a medical exam.
- apply for a Parent and Grandparent Super Visa.

If you do need a medical exam, the visa office will tell you how to proceed.

▾ Jobs for which you need a medical exam

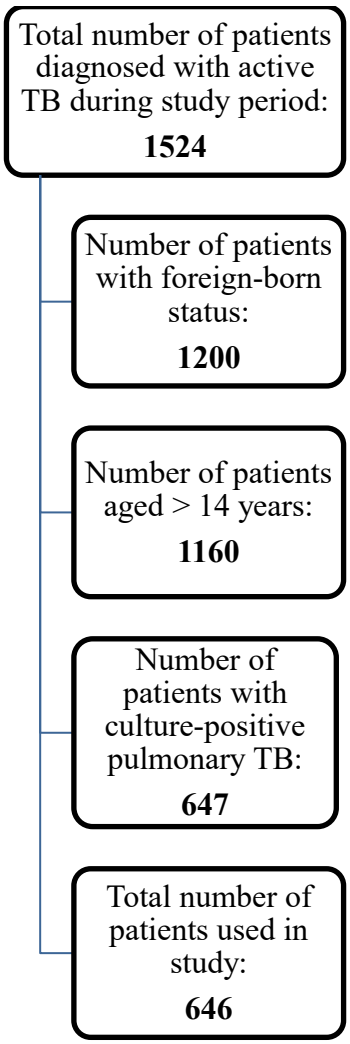
You may have to get a medical exam because of the type of job you want to do in Canada. Examples of such jobs are:

1. Jobs that bring you into close contact with people, such as:
   - workers in the health sciences field
   - clinical laboratory workers
   - patient attendants in nursing and geriatric homes
   - medical students admitted to Canada to attend university
   - medical electives and physicians on short-term locums
   - teachers of primary or secondary schools, or other teachers of small children
   - domestics
   - workers who give in-home care to children, the elderly and the disabled
   - day nursery employees and
   - other similar jobs
2. Agricultural workers who have visited or lived in one of these countries for more than six months during the past year.

Immigration, Refugees, and Citizenship Canada. (2017, March 30). Medical exam requirements for temporary residents (visitors, students and workers). Retrieved from http://www.cic.gc.ca/english/information/medical/medexams-temp.asp

Appendix B:

Study Numbers



*One patient was missing their year of arrival and immigration status and was removed from the study

Appendix C:

```
. logistic advanced_disease i.sex i.CIC_referral i.immigration_status_y i.age_at_dx_x#i.years_in_canada_y

Logistic regression                             Number of obs   =        646
                                                LR chi2(8)      =     125.35
                                                Prob > chi2     =     0.0000
Log likelihood = -374.98644                     Pseudo R2       =     0.1432
```

advanced_disease	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
1.sex	1.4535	.262647	2.07	0.038	1.020007	2.071224
1.CIC_referral	.0397841	.0217172	-5.91	0.000	.0136477	.1159737
5.immigration_status_y	.8690399	.2277731	-0.54	0.592	.5199266	1.452571
age_at_dx_x#years_in_canada_y						
1 6	1.707414	.5200792	1.76	0.079	.9398584	3.101811
2 5	1.588976	.5528289	1.33	0.183	.8034733	3.142413
2 6	1.280662	.3530476	0.90	0.370	.7460684	2.198316
3 5	1.369148	.7900259	0.54	0.586	.4418651	4.242392
3 6	.3674648	.1095834	-3.36	0.001	.2048212	.6592598
_cons	.7747479	.1868937	-1.06	0.290	.4828627	1.243075

Appendix D:

Table 1. Groups with increased risk of TB exposure and latent TB infection[4]

Groups at risk	Prevalence of positive TST	Setting or group usually responsible for screening
Close contacts of an active case of pulmonary TB	Variable, higher than source population	Public health, primary care
Immigrants from countries with high TB incidence		Public health, primary care
Children	15%-23%	
Adult (lived >20 years in country with high TB incidence)	53%-61%	
Injection drug user		Primary care, treatment facilities
(TST ≥10 mm)	66%	
(TST ≥5 mm)	31%	
Homeless	18%-51%	Primary care, shelters, public health
Aboriginal communities*		Public health, primary care
Adults	14%-30%	
Children	5%-29%	
Health care workers*	11%-46%	Occupational health, public health
Residents of long-term care facilities*	6%-25%	Primary care, facility director of care, public health
Residents of correctional facilities*	12%-72%	Inmate health services, public health
Travellers to countries with high TB incidence	Variable	Travel medicine, primary care
Reference		
Canadian-born non-Aboriginal children	1-3%	Targeted screening not recommended
Canadian-born non-Aboriginal adults, not BCG vaccinated	7%	
Canadian-born non-Aboriginal adults, BCG vaccinated	65%	
Canadian-born non-Aboriginal adults, BCG vaccination nonspecified	13%	

*BCG status not specified

Public Health Agency of Canada. (2014). *Canadian Tuberculosis Standards 7th Edition*.