COMPARATIVE INCIDENCE OF TUBERCULOSIS IN CANADA: THE PAST, PRESENT AND FUTURE

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By

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Abstract

Canada and the United States (US) are both high income, low tuberculosis (TB) incidence countries with similar TB control programs, yet an explicit comparison of TB incidence over time is lacking.

Objective one explored the impact of TB and other disease case definition change, and methods to control for the change via a general literature search. Underreporting/increases in reported cases and differences in sensitivity and specificity measures were among others noted to arise from changes in case definition. For appropriate comparisons within and between populations, consistent ascertainment criteria of cases should be adopted.

Objective 2 explored and compared TB incidence rates in Canada and the US from 1953-2015. TB rate from 1953-2015 was retrieved for both countries. Joinpoint and direct standardization were performed. Canada's TB rates/100,000 were higher from 1953-1974. Canada's average annual percent change in rate from 1975-2015 was -2.9% compared to the US -4.1%. Case definition change, HIV+/TB co-infection, and Foreign-born (FB) TB were the main contributors to the differences.

Objective three compared the rate of TB decline in subpopulations. TB cases and population by ethnicity from 2001-2011, and the percent of HIV+/TB co-infection cases from 1997-2012 were retrieved for Canada and the US. Segmented and decomposition analysis was performed. FB and Indigenous TB rate declined by -3.7% and -6.3% in the US and by -1.7% and -4.5% in Canada. Changes in age-specific rates declined overall rates in Canada by 80.1% and the

US at 66.7%. Overall, the percentage of HIV+/TB cases declined more rapidly in the US than in Canada. After adjusting for age, FB and Indigenous populations, rates decline more in the US than in Canada.

Objective four forecasted and then compared year-over-year TB rates between Canada and US from 2017-2035. TB rate from 1975-2016 and rates by ethnicity from 1993-2016 were retrieved for both countries. Autoregressive integrated moving average and multivariate vector autoregression models were performed. The forecasted models showed a gradually decreasing trend from 2017-2035, reaching a rate of 2.2 for Canada and 1.3 for the US by 2035. The prediction suggests that achieving 2035 WHO set target could be a challenge for both countries.

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Dedication

I dedicate my thesis work to my beloved parents, Rev. Daniel Kojo Essien and Augustina Afia Bentum Essien whose constant prayers, advice, words of encouragement and countless support inspired and sustained me throughout the course of my PhD program.

I also dedicate this thesis work to my beloved brothers whose continual and selfless help sustained me in pursuit of this degree.

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List of Abbreviations

AAPC – Average Annual Percent Change

ACF – Autocorrelation Function

AIC – Akaike Information Criterion

APC – Annual Percent Change

ARIMA – Autoregressive Integrated Moving Average

CDC – Centers for Disease Control

CI – Confidence Interval

FB – Foreign Born

FNHA – First Nations Health Authority

HIV - Human Immunodeficiency Virus

IGRAs -Interferon Gamma Release Assays

IND – Indigenous

INH – Isoniazid

LM – Lagrange Multiplier

LTBI – Latent Tuberculosis Infection

NAA – Nucleic Acid Amplification

NIND – Non-Indigenous

NITHA – Northern Inter Tribal Health Authority

PACF – Partial Autocorrelation Function

PHAC – Public Health Agency of Canada

RMP – Rifampin

TB – Tuberculosis

TST- Tuberculin Skin Test

VAR – Vector Autoregression

WHO – World Health Organization

Chapter 1. Introduction/Literature review

Tuberculosis (TB) is an ancient infection (Dutt, 2011) that affects quality of life (Hansel et al., 2004), and has a high mortality rate (Dye, 2006). Measured in disability-adjusted years of life lost, over 80% of the burden of TB is attributed to premature death rather than illness (Dye, 2006). In 2014, an estimated 1.5 million deaths due to tuberculosis were recorded in the global population (WHO, 2015), and in 2016, that increased to 1.7 million worldwide (CDC, 2018). Although both developed and resource-limited countries are faced with TB-related deaths, most occur in resource-limited countries (Mohajan, 2015). Factors that may potentially contribute to increasing the rate of tuberculosis among individuals living in resource-limited countries include poor management (Gondil et al., 2018), while others, such as overcrowding (Kompala et al., 2013) and HIV infections (Dye et al., 1999), are considered potential risk factors for the onset of TB.

Despite control measures in developed countries designed to eliminate TB, factors continue to hinder TB elimination. For instance, Clark et al. found that overcrowded housing in First Nations communities increased an individual's risks of TB infection (Clark et al., 2002). Wolleswinkel-van den Bosch et al. reported that a high proportion of new tuberculosis cases observed in the Dutch population might be attributed in part to infections from migrant populations (Wolleswinkel-Van den Bosch et al., 2002). Also, McBryde and Denholm found an elevated incidence of TB among immigrants in Australia especially individuals emigrated from South Asia and sub-Saharan Africa (McBryde & Denholm, 2012).

Over the years, the United States and Canada have implemented prevention and intervention based programs to reduce the incidence of TB. Examples of existing TB programs include: the national TB program (CDC, 2015) and Minnesota Department of Health TB prevention and control program (Minnesota Department of Health, 2018) in the United States; and TB Service for First Nations communities in BC (First Nations Authority, 2018) and TB Prevention and Control Saskatchewan (Saskatchewan Health Authority, 2017) in Canada.

Although both Canada and the United States have had some success in TB control, the rate of TB decline began to differ between the countries after experiencing the same incidence rate in 2004 (Gallant et al., 2012; CDC, 2017).

This chapter will focus on a brief description of TB risks worldwide, including specific details on the United States and Canada, the global, local and country-specific economic burden of TB, clinical/laboratory diagnostics, transmission and pathogenesis of TB, as well as highlight risk factors for TB.

1.1 Epidemiology of Tuberculosis

1.1.1 Tuberculosis Pathogenesis and Transmission

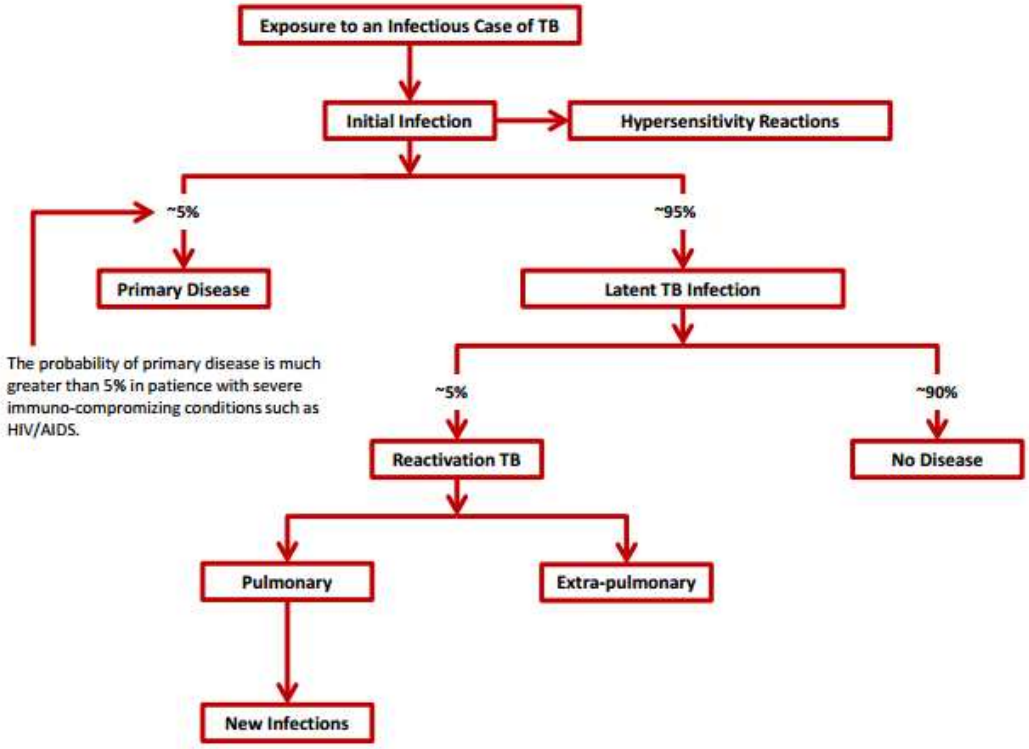
Human TB is known to be caused by *Mycobacterium tuberculosis* (Glickman et al., 2001). Virtually any human body organ can be infected by the bacteria (Dutt, 2011); however, the most frequently used portal of infection is the lungs (Dutt, 2011). Although other modes of transmission are rare (Glazious et al., 2014), the most common route is between an infectious pulmonary TB patient and a susceptible individual by droplet nuclei (Dutt, 2011; Glazious et al., 2014), aerosolized by means such as talking, sneezing, coughing and singing (Dutt, 2011). Other

identified factors that may facilitate the transmission of tuberculosis especially in a resource-limited environment include overcrowding and poor ventilation (Kompala et al., 2013); both are mechanisms that increase transmission of an aerosolized pathogen.

TB pathogenesis encompasses many phases or stages which include: exposure, primary infection and clinical disease (Long et al., 2014). Previously naive individuals infected with *Mycobacterium* TB will develop primary infection about 5% of the time (Long et al., 2014). Without prophylaxis, of the 95% that do not develop active disease (or primary TB) within two years of infection, about 5% will develop reactivation TB later in life if they are otherwise healthy (Long et al., 2014). However, the remaining 90% with LTBI never progresses to develop TB disease (Long et al., 2014). Among individuals with latent TB infection, the development of active TB can be made possible by factors classed as bacterial, host and/or environmental conditions (Getahun et al., 2015). Additionally, other immune suppressors such as Human Immunodeficiency Virus (HIV) infection (Selweyn et al., 1989), and end-stage renal disease (Yousef et al., 2014) among others, have been identified as important factors for the development of active TB.

The pathogenesis of post-primary TB or reinfection continues to be a controversial issue. While some studies support the argument of exogenous reinfection (Van Rie et al., 1999; Shen et al., 2006), others do not (Stead, 1967; Arend & Van Dissel, 2002). For example, William Stead noted that exogenous reinfection should not be considered as an important factor but rather use observed evidence showing that "*chronic pulmonary tuberculosis develops from reactivation of dormant foci implanted during primary infection*" (Stead, 1967).

Figure 1-1 describes the various



stages in the pathogenesis of tuberculosis.

Figure 1-1: Phases of Tuberculosis Pathogenesis. Source: Canadian TB Standards Edition 7 with permission from Public Health Agency of Canada

1.1.2. *Clinical/Laboratory Diagnostics*

Diagnosis of TB is usually performed using standard algorithms or procedures which in most cases start with the ascertainment of medical history (e.g., HIV status, TB exposure, and other health conditions) and physical examination including pulmonary examination and lymph node examination for TB suspects (Jacobson, 2017; CDC, 2013). A test for Mycobacterium tuberculosis infection detection may be followed using either Mantoux tuberculin skin test

(TST) or Interferon-gamma release assays (IGRAs) (CDC, 2013). Despite its wide usage and soaring popularity, the TST requires highly skilled persons to administer and read test results to avoid false readings (Nayak & Acharjya, 2012). The IGRAs besides being more specific than the TST (Pai & Menzies, 2007), they are preferred choice for testing TB infection in individuals previously exposed to Bacillus Calmette-Guérin vaccination (Jacobson, 2017; Pai & Menzies, 2007). However, when it comes to the cost and simplicity of test procedure, the TST is preferable (WHO, 2011). Although the three components earlier highlighted cannot be underestimated in TB diagnostics, more rigorous testing algorithms are subsequently applied to test for active TB (Pai et al., 2014). These include chest radiography, smear microscopy, Mycobacterial culture and drug-susceptibility testing, and nucleic acid amplification test (NAATs) (CDC, 2013; Pai et al., 2014). Chest radiography is one algorithm widely recognized as a useful test for TB screening (Melendez et al., 2016) coupled with its highly appreciable sensitivity seen as a major advantage to its use, chest radiography specificity has been found to be poor (WHO, 2016). The smear microscopy and Mycobacterial culture are both prominent microbiological methods of diagnosis of TB, however, Mycobacterial culture is regarded as the gold standard for active TB disease detection (Pai et al., 2014). On the other hand, although, diagnosis and detection of TB and drug resistance may be carried out using the molecular method of NAATs, for definitive diagnosis Mycobacterial culture is still required (Pai et al., 2014).

1.1.3. *Economic Burden*

Besides high mortality and incidence rates (WHO, 2018), exposure to TB poses a high economic burden on countries around the world. Annually, about 12 billion dollars (US) is spent on TB

worldwide (WHO, 2017); specifically, an estimated $3 billion yearly in India (John et al. 2009), $8-29 million yearly in Philippines (Peabody et al., 2005) and approximately 2 billion dollars from 2011 and beyond in Indonesia (Collins et al., 2017). Across the European Union, a cost totaling nearly 6 billion euros was spent on TB in 2012 (Diel et al., 2014). Diel et al. reported that in Germany, on average, the costs of TB treatment for both inpatients and outpatients in 2009 was about 7,368 euros per adult case and 7,300 euros per child case (Diel et al., 2012). Similar to the south and east Asian countries, a high economic burden has been observed in South, Central and North America. In 2013, an estimated 246 million dollars spent on tuberculosis control among 15 selected countries in South, Central and North America (Pan American Health Organization, 2013).

The United States and Canada are not exceptions in terms of the economic burden of tuberculosis experienced by other countries in the world. Within the time interval 2010 to 2014, the government of the United States contributed over $2.8 billion dollars towards the eradication of global TB (U.S. Government, 2014). In 2006, the direct cost of TB amounted to $752 million dollars in the United States (Holmquist, 2008). In Canada, overall TB-related direct and indirect costs amounted to $74 million Canadian dollars in 2004 (Menzies, 2008) with about $47,000 Canadian dollars spent to treat a single case of active TB (Menzies, 2008). The 2004 cost per case of active TB in Canada included research, hospitalization for active TB, screening of health care workers, clinical care, TB drugs and laboratory test (Menzies, 2008). Evidence provided suggests that achieving a reduction or total elimination of TB is a crucial means of saving lives and reducing TB-related spending.

1.1.4. *Incidence of Tuberculosis*

According to the World Health Organization, globally, about 10 million new active TB cases were recorded in 2017 (WHO, 2018). Among all the WHO regions most new cases of TB were reported in South-East Asia (44.9%), with Africa ranking second (24.9%) (Table 1-1) (WHO TB Control, 2018).

In the Americas, of the 268,400 TB incident cases that were found in 2011, 67% originated from South America (Pan American Health Organization, 2013). Although an elevated incidence of TB has been observed in impoverished countries (Castañeda-Hernández et al., 2013), TB cases in developed countries cannot be overlooked.

TB continues to be reported in the United States (2.9 cases per 100,000 persons in 2016) CDC, 2017), Canada (5 cases per 100,000 in 2016), Australia (6 cases per 100,000 in 2016) and the United Kingdom (10 cases per 100,000 in 2016) (Public Health England, 2018).

Table 1-1: Estimated TB Incidence, 2016

	Incidence		
WHO Region/Some large countries within each region	No. in thousands	% of global total	Rate/100,000 population
Africa • *Nigeria, Ethiopia, DR Congo*	2590	24.9	253.9
The Americas • *US, Canada, Mexico*	274	2.6	27.5
East Mediterranean • *Afghanistan, Bahrain, Djibouti*	766	7.4	114.5
Europe • *Germany, France, UK*	290	2.9	31.7
South-East Asia • *India, DPR Korea, Indonesia*	4670	44.9	239.5
Western Pacific • *China, Philippines, Viet Nam*	1800	17.3	95.2

Global Total	10400	100	139.8

Source: Global Tuberculosis Report, 2017 (Table 3.2, page 29) (WHO, 2017) with permission from WHO.

2.1. Tuberculosis in Canada and the United States

The TB epidemic in Canada dates back several centuries with its root traced back to the earlier European settlers (Grzybowski & Allen, 1999). TB was reported to be the biggest single cause of death in Canada in 1867 (Canadian Public Health Association, 2018), with TB-associated mortality reported in 1880 (nearly 200 per 100,000), 1901 (180 per 100,000), and 1908 (165 per 100,000) (Saskatchewan Lung Association, 2018). The rate decreased to 84 per 100,000 prior to the emergence of the "*first reliable national statistics for Canada*" in 1926 (Saskatchewan Lung Association, 2018). The mortality rate of TB is an important epidemiologic measure imperative to public health practitioners as it can "*give an indication of the extent of TB in a population, and of the size of the task faced by a national TB control programme*" (United Nations, 2008). The TB incidence rate in Canada has also been documented annually since 1924 (Gallant et al., 2012), ranging from 43.6 per 100, 000 in 1924 (Gallant et al., 2012) to 4.8 per 100, 000 in 2016 (Vachon et al., 2018). Despite a dramatic improvement achieved in TB incidence rates in Canada after the 1980s (Gallant et al., 2012), the three decades since then have seen only moderate declines (Gallant et al., 2012).

The United States, like Canada, has a long history of TB. In the nineteenth and the onset of the twentieth centuries, TB was the single greatest cause of death in the United States (American Lung Association, 2007). The available annual incidence rate of TB in the United States ranged

from 52.5 per 100,000 in 1953 to 2.9 per 100,000 in 2016 (CDC, 2017). However, with changes in the surveillance case definition, incidence rate prior to 1975 are not comparable to those in 1975 or later (Armstrong & Miramontes, 2014). In the decade 1993 to 2003, a decrease of 44% was observed in the United States TB incidence (American Thoracic Society, 2005). This decline was attributed to a well-planned national strategy and infusion of sufficient resources after the first TB re-emergence in the United States (American Thoracic Society, 2005). Additionally, in the last two decades, that rate has continued to decline to its lowest rate of 2.9 per 100,000 in 2014 and 2016 (CDC, 2017).

1.2.1. *Risk Factors of Tuberculosis*

Although active TB begins with exposure to the MTB bacillus (Chisholm et al., 2016), other identified potential triggers or risk factors may facilitate the progression of disease (Narasimhan et al., 2013). Human immunodeficiency virus (HIV) has been found to be a strong driver of both initial infection and progression of TB disease (Corbett et al., 2003). In addition, higher rates of tuberculosis have been found in individuals with chronic kidney disease (Shen et al., 2015). Organ transplantation has been reported as a potential factor as evidenced by an increased tuberculosis incidence among organ recipients (Torre-Cisneros et al., 2009). Other previous studies have also identified silicosis/silica exposure as a potential risk factor for tuberculosis (Yarahmadi et al., 2013; Farazi et al., 2015).

Other factors such as socio-economic status (e.g. unemployment) (Sarvi et al., 2014), age, sex (Zhang et al., 2011), smoking (Den Boom et al., 2005), alcohol consumption (Kuznetsov et al., 2013) and overcrowding (Kompala et al., 2013) have been found to contribute to increases in

TB incidence. The importance of adjusting for all these factors in TB-related research cannot be underestimated. Zhang et al. noted that "*the occurrence of specific types of extrapulmonary TB significantly varied among different age groups or origins*" (Zhang et al., 2011). Controlling for factors such as age which is known to frequently experience a shift in distribution/compositional difference within populations over time, through standardization can provide a way to 'remove' the effect of differences in age distribution (Ong et al., 2006).

1.3. Tuberculosis: Foreign-born and Indigenous Population

Ethnic differences continue to impede the decline of TB incidence (Noppert et al., 2017; Bakhshi et al., 1997). For instance, Bakhshi et al. found higher rates of tuberculosis in African Caribbean individuals as compared to Caucasians (Bakhshi et al., 1997). Among TB-related ethnic groups, Indigenous and Foreign-born populations continue to disproportionately experience an elevated risk of TB (Halverson et al., 2014). For instance, in 2016, Foreign-born individuals accounted for 70% of the reported TB cases in Canada, and Canadian born Indigenous people had the highest rate of 23.5 per 100, 000 population (Vachon et al., 2018). Among Indigenous people in Canada, First Nations individuals accounted for 63% of TB cases, followed by the Inuit at 34% and Métis at 3% (Vachon et al., 2018). Similarly, 68% of cases reported in the US in 2016 were among Foreign- born and the highest rates occurred in US-born Native Hawaiian/Pacific Islanders (9.2 per 100, 000 population) and American Indian/Alaska Natives (5.0 per 100,000 population) (Schmit et al., 2017). These trends are not only limited to Canada and the US but have also been observed in other countries (Public Health England, 2017; Chang et al., 2011) with 74% of TB cases in the United Kingdom reported among Foreign-born individuals (Public

Health England, 2017). Also, Taiwanese Aboriginals reported a rate of 176 per 100,000 compared to 65 per 100,000 in Taiwanese Non-Aboriginals (Chang et al., 2011). Due to the differences observed in the different ethnic groups, controlling for these differences in TB-related research is imperative (Ong et al., 2006). For instance, in a comparative study of TB-related risk factors including ethnicity among 13 Malaysian states and territories, Ong et al. applied direct standardization to control for the effect of ethnic differences (Ong et al., 2006).

1.4. Examples of Tuberculosis Elimination Programs in Canada and the United States

There are several tuberculosis elimination programs that have been initiated in Canada and the United States. Some TB elimination programs available in Canada include: STOP TB Canada (STOP TB Canada, 2017); the Northern-Inter Tribal Health Authority TB program (NITHA) (NITHA, 2011); and First Nations Health Authority Tuberculosis Program in BC (FNHA, 2018). The STOP TB Canada program is a partner of the global STOP TB program which collaborates with other governmental and non-governmental organizations including "*provincial and territorial TB programs and the International Union against TB and Lung Disease"* (STOP TB Canada, 2017). The STOP TB Canada program's main focus is geared towards eliminating TB in Canada by communicating TB-related control issues to the international, national and local communities and as well providing easy access to educational materials and other resources to enhance the fight against TB (STOP TB Canada, 2017). The NITHA TB program is another TB program implemented in Saskatchewan that aims to provide TB-related services including *"orientating nurses and training community workers to administer Directly Observed Therapy (DOT) to clients, performing contact tracing and managing TB outbreaks"* in First Nation

communities (NITHA, 2011). The FNHA TB service also provides TB control interventional programs/services for Canadian First Nation communities to *"close the gap disparities of TB incidence in First Nations people"* (FNHA, 2018). Activities carried out by the FNHA program include but not limited to "*assurance to timely and culturally safe diagnosis, treatment and follow-up care for those exposed to and diagnosed with TB"* (FNHA, 2018). The services are run on a collaborative basis among First Nations communities, provincial governments, federal public health agencies and other health professionals (FNHA, 2018).

In the United States some examples of tuberculosis elimination programs include: the US national TB program primarily aims to "*promote health and quality of life by preventing, controlling and eventually eliminating TB from the United States*" (CDC, 2015) by conducting routine surveillance, resourcing laboratories and provide logistics, funding and other TB-related program support (CDC, 2015). The STOP TB USA, a joint effort TB program in the United States focused on "*eliminate TB as a public health threat in the United States*" by embarking on scientific and educational activities as well collaborate with communities to enhance TB prevention, care and control (STOP TB US, 2017). The Harris County Public Health (HCPH) TB Elimination Program focused on "TB prevention and control" (Harries County Public Health, 2017) is another TB prevention and control program in the United States. This program provides a special interventional method through the "*use of video Directly Observed Therapy (VDOT) in which health care workers observed patients taking their TB medications remotely via a mobile device*" (Harries County Public Health, 2017).

1.5. Purpose of the Thesis Work

No single country in the world has achieved 100% elimination of TB. Despite efforts made by most countries, some of whom have declining trends like Canada and the United States, TB remains a global health problem (Zaman, 2010).

Although both Canada and the United States have not relented in their efforts towards the total elimination of tuberculosis, the differing rise and fall of tuberculosis rates (Gallant et al., 2012; CDC, 2017) warrant further investigation into contributing factors and country-specific approaches in handling the disease. For instance, since 1980 the rate of decline in annual TB rate slowed in Canada and for two decades within this period annual TB rates in Canada plateaued (Gallant et al., 2012). Although the annual decline in TB rate did not stall in the United States (CDC, 2017) as it did in Canada during the same time interval, the United States did experience a decade of a plateau (CDC, 2017).

In spite of the same annual rate of tuberculosis observed in Canada (5.0 per 100,000) (Gallant et al., 2012) and the United States (5.0 per 100,000) in 2004 (CDC, 2017), over the decade between 2004 and 2014, the annual rate decreased in the United States (2.9 per 100,000) (CDC, 2017) whereas Canada did not experience much of a decrease at all (4.5 per 100,000) (Gallant et al., 2012). Investigating factors at an ecological level that contribute to the difference in annual tuberculosis rate between Canada and the United States will: (1) broadly deepen our understanding of the tuberculosis epidemic in both countries and (2) help inform appropriate prevention and interventional strategies which will further reduce the disease in both countries.

Therefore, this dissertation will explore what led to the slowed decrease of TB in Canada and provide some probable projections of TB pre-elimination rates for both Canada and the US.

The chapters of the thesis will take the form of four manuscript-style chapters. Chapter 2 will focus on an overview of the importance of assessing surveillance case definition, identifying differences in TB and other disease case definition, as well uncover potential methodologies available to control differences in case definition. Chapter 3 will explore TB incidence rates in Canada and the United States over time and compare the national trends. Chapter 4 will compare the rates of TB decline in FB and IND TB cases, and examine the impact of shifts in FB and IND population by age and age-specific rates, as well the influence of HIV/TB co-infections over time between Canada and the United States. Finally, Chapter 5 will forecast and then compare year-over-year TB rates between Canada and the United States from 2017-2035.

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Chapter 2. Surveillance Case Definition: An overview

2.1. INTRODUCTION

Epidemiologically, defining what is a 'case' is a crucial means to classify individuals as having a particular disease status, syndrome or other health condition (Gregg, 2008). Standardized classification criteria tend to enhance the specificity of disease reporting (CDC, 1997), assist in accurate monitoring of disease burden over time or location (WHO, 2010) and enable consistent reporting of diseases or notifiable conditions among geographical regions (Washington State Department of Health, 2015). There are different purposes in which a case definition may be used (Chan&Donovan, 2005). These include outbreak detection (Gregg, 2008), service provision and improvement, surveillance, research and clinical care/diagnosis (Chan&Donovan, 2005).

However, different purposes may require different elements to be included in a case definition. For instance, while clinical and/or laboratory features characterize surveillance case definitions, restrictions on time, place and person are added to an outbreak case definition to better characterize the circumstances within an outbreak (Gregg, 2008; Stein et al. 2011). Notably, to determine the standard of clinical care or confirm clinical diagnoses, the use of a standardized case definition as a sole criterion is usually inadequate and often inappropriate (CDC, 1997). Thus, case ascertainment based on a single case definition especially in situations where multiple categories of the disease exist may not be adequate to capture all the relevant cases (National Institutes of Health, 1994). For example, a multi-faceted case definition is required to capture all "*three dimensions of chronic fatigue syndrome (CFS): fatigue, functional impairment,*

and eight accompanying symptoms (post-exertional malaise, impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, new headaches, unrefreshing sleep)" (Unger et al., 2016; Fukuda et al., 1994).

Irrespective of the possibility of ongoing use of a surveillance case definition for a particular disease, in some instances, definitions are either revised, modified or changed (Selik et al. 1990; State of Alaska Epidemiology Bulletin, 1993; WHO, 2014) as new scientific information/evidence emerges (Nelson and Sifakis, 2007). Changing a case definition may not only result in reporting delays (Tabnak et al., 2000), over/under-estimation of disease prevalence (Mckeown et al., 2015) but it also inhibits the comparison of disease reporting between regions or between time periods (CDC, 1997). For instance, a 1993 case definition change in acquired immune deficiency syndrome (AIDs) in the United States (Selik et al., 1990; State of Alaska Epidemiology Bulletin, 1993) paved the way for all HIV-infected individuals who had CD4+ < 200/µL or a CD4+ percentage < 14 and individuals with invasive cervical cancer, pulmonary TB or recurrent pneumonia to be included (CDC, 1992). However, the change increased the number of cases in 1993 by 111% over the reported cases in 1992 (CDC, 1994).

Arguably, when comparing particular disease occurrence either within or between countries, a consistent case definition is imperative (CDC, 1990) to avoid any bias that might arise simply from differences, changes, or modifications in the definition (Selik et al., 1990; State of Alaska Epidemiology Bulletin, 1993; CDC, 1994).

Biases may be inevitable in every standard case definitions (Sergeant and Perkins, 2015). Hence, this paper seeks to epidemiologically explore how a change in case definition can impact

our understanding of disease by taking into account specific real-world examples, primarily focusing on Tuberculosis, but using examples from other diseases as required. In addition, it will address potential methodologies available to control for such case definition derived changes in the analysis of disease trend.

2.2. METHODS

The search for published studies for this paper encompasses both general literature search for non-specific disease case definition and TB specific case definition. Databases in which the search was conducted includes MEDLINE, PubMed and PMC. Besides these sources, other authoritative books addressing disease case definition and published national disease reports were also searched. The search primarily focused on the following terms: case definition (for TB and other diseases) with both clinical and/or laboratory features, impact of case definition change and case definition change adjustment methods.

Based on the information retrieved from the search, a random selection of other disease and TB specific examples were chosen and compared based on similarities within or between their geographical regions (e.g., national versus local or two different countries within the same WHO regions). Similarities considered for selection and comparison of the retrieved information include belonging to the same WHO region (WHO, 2018), same income-level classification (e.g., high, low, lower middle and upper middle) (World Bank 2016), having similar WHO TB surveillance program (Mor et al., 2008) and low TB incidence countries (Lönnroth et al. 2015). The comparison aimed at ascertaining any differences in case definition that might have

contributed to difference in disease incidence or rate especially as it relates to TB either within or between geographical regions.

2.3. The case definition: why is it important to define?

The impact of the changes or differences in disease case definitions has been documented in the published literature. For example, these impacts may manifest as differences in disease counts reported within or between different geographical regions (e.g., country). A local example of this is what counts as a case of West Nile Virus (WNV) in Saskatchewan (Saskatchewan Ministry of Health, 2014) versus the rest of Canada (Public Health Agency of Canada, 2009). Since 2009, Saskatchewan has only reported cases of West Nile Virus Neurological Syndrome (WNNS) while the rest of Canada includes both WNNS and West Nile fever (febrile cases) in their surveillance numbers (Saskatchewan Ministry of Health, 2014; Public Health Agency of Canada, 2009). This is in the face of substantial differences in the rate of reporting and diagnosis of West Nile fever as compared to WNNS diagnosis and reporting.

Differences in the WNNS case definitions from Saskatchewan and the rest of Canada are outlined in Table 2-1.

Table 2-1: Saskatchewan and Public Health Agency of Canada Case Definitions

Saskatchewan Case Definition	Public Health Agency of Canada Case Definition
Clinical Criteria • History of exposure in an area where West Nile Virus (WNV) activity is occurring **OR** • History of exposure to an alternative mode of transmission **AND**	Clinical Criteria • History of exposure in an area where West Nile Virus (WNV) activity is occurring **OR** • History of exposure to an alternative mode of transmission **AND**

• Meningitis, encephalitis, acute flaccid paralysis, or other acute signs of central or peripheral neurologic dysfunction, as documented by a physician **AND** • Absence of a more likely clinical explanation	• Onset of fever **AND** Recent onset of at least one of the following: • Encephalitis (acute signs of central or peripheral neurologic dysfunction) **OR** • Viral meningitis (pleocytosis and signs of infection, e.g. headache, nuchal rigidity) **OR** • Acute flaccid paralysis (e.g. poliomyelitislike syndrome or Guillain-Barré-like syndrome) OR • Movement disorders (e.g. tremor, myoclonus) OR • Parkinsonism or Parkinsonian-like conditions (e.g. cogwheel rigidity, bradoykinesia, postural instability) OR • Other neurological syndromes
Confirmed Case Clinical criteria **AND** at least one of the following laboratory criteria: • Four-fold or greater change in virus-specific quantitative antibody titers in paired sera **OR** • Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid, **OR** • Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen **OR** • Virus specific IgM antibodies in serum with confirmatory avidity test in the same or later specimen **OR** • Virus-specific IgM antibodies in CSF and a negative result for other IgM antibodies in CSF for arboviruses endemic to the region where exposure occurred	Confirmed Case Clinical criteria **AND** at least one of the confirmed case diagnostic test criteria: • A significant (e.g. fourfold or greater) change in WN virus neutralizing antibody titres (using a PRN or other kind of neutralization assay) in paired acute and convalescent sera, or CSF **OR** • Isolation of WN virus form, or demonstration of WN virus-specific genomic sequences in, tissue, blood, CSF or other body fluids **OR** • Demonstration of WN virus antigen in tissue **OR** • Demonstration of flavivirus antibodies in a single serum or CFS sample using a WN virus IgM EIA, confirmed by the detection of WN virus specific antibodies using a PRN (acute or convalescent specimen) **OR** • A significant (e.g. fourfold or greater) change in flavivirus haemagglutination inhibition (HI) titres in paired acute and convalescent sera or demonstration of a seroconversion using a WN virus

	IGM EIA AND the detection of WN specific antibodies using a PRN (acute or convalescent serum sample)

Sources: Saskatchewan Ministry of Health, 2014 and Public Health Agency of Canada, 2009

2.4. Case definition: a special case of tuberculosis

Tuberculosis like other disease research may be affected by the way the 'cases' are defined. As a result, the adaption of a standard case definition in TB research enhances the identification of TB case and assists in the selection of suitable standard treatment regimens (WHO, 2010). The following details the case definitions for tuberculosis by the WHO (WHO, 2013), USA (CDC, 2009) and Canada (Menzies, 2014) (Table 2-2).

Table 2-2: Comparison of Tuberculosis Surveillance Case Definition

WHO	United States	Canada
1. Bacteriologically confirmed case: • Someone for which a biological specimen is positive by smear microscopy, culture or WRD (such as Xpert MTB/RIF). • All such cases should be notified, regardless of whether TB treatment has started.	1.Laboratory criteria: • Isolation of M. tuberculosis from a clinical specimen, OR • Demonstration of M. tuberculosis complex from a clinical specimen by nucleic acid amplification test, OR • Demonstration of acid-fast bacilli in a clinical specimen when a culture has not been or cannot be obtained or is falsely negative or contaminated.	1.Laboratory confirmed case: • Cases with Mycobacterium tuberculosis complex demonstrated on culture, specifically M. tuberculosis, M. africanum, M. canetti, M. microti, M. pinniprdii or M. bovis (excluding M. bovis Bacillus Calmette Guérin (BCG) strain).

2. Clinical confirmed case: • Not bacteriologically confirmed but diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. • This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary case without laboratory confirmation. • Clinically diagnosed case subsequently found to be bacteriologically positive (before, or after starting treatment) should be reclassified as bacteriologically confirmed.	**2.** Clinical criteria: ***Must meet all the following criteria*** • Positive TB skin test result or positive interferon gamma release assay for M. tuberculosis • Other signs and symptoms compatible with TB (e.g., abnormal chest radiography, abnormal chest computerized topography scan, or other chest imaging study, or clinical evidence of current disease) • Treatment with two or more anti-TB medications • A completed diagnostic evaluation	2.Clinically confirmed case: Cases ascertained in the absence of culture proof, cases clinically compatible with active tuberculosis that have, for example: • chest x-ray changes compatible with active tuberculosis • active non-respiratory tuberculosis (meningeal, bone, kidney, peripheral lymph nodes, etc) • pathologic or post-mortem evidence of active tuberculosis • favourable response to therapeutic trial of anti-tuberculosis drugs

Sources: WHO, 2013; CDC, 2009; and Menzies, 2014.

2.4.1. *TB case definition (s) in Canada*

The confirmation of tuberculosis cases in Canada may be carried out through laboratory approaches and/or clinical examination (Pai, 2014). In Canada, ***the laboratory-confirmed cases*** are "*cases with Mycobacterium tuberculosis complex demonstrated on culture, specifically M. tuberculosis, M. africanum, M. canetti, M. caprae, M. microti, M. pinnipedii or M. bovis (excluding M. bovis (BCG) strain)*" whereas ***clinically confirmed cases*** are cases ascertained "*in the absence of culture proof, cases clinically compatible with active tuberculosis that have, for example: (1) chest x-ray changes compatible with active tuberculosis; (2) active non-respiratory tuberculosis(meningeal, bone, kidney, peripheral lymph nodes, etc); (3) pathologic or post-mortem evidence of active tuberculosis; (4) favourable response to therapeutic trial of antituberculosis drugs*" (Menzies, 2014). Although from 1990 to date the definition of ***new cases of TB*** in Canada has remained constant (i.e., "*no documented evidence or history of previously active TB*") (Long et al., 1999). However, previously treated cases earlier referred to as ***relapse cases*** which included "*documented evidence or history of previously active TB that became in-active*" (Long et al., 1999) were changed to ***re-treatment cases*** from 2008 onwards (Menzies, 2014). Currently, ***re-treatment tuberculosis*** cases in Canada can be ascertained using either of the following criteria:

A.

(i) "documented evidence or adequate history of previously active tuberculosis that was declared cured or treatment completed by current standards, and

*(ii) at least a 6-month interval since the last day of previous treatment and diagnosis of a subsequent episode of TB that meets the **active TB case definition**"* (Menzies, 2014) ***OR***

B.

(i) "documented evidence or adequate history of previously active TB that cannot be declared cured or treatment completed by current standards; and

(ii) inactive disease for 6 months or longer after the last day of previous treatment;

*(iii) diagnosis of a subsequent episode of TB that meets the **active TB case definition**"* (Menzies, 2014).

Additionally, TB cases may be defined based on diagnostic sites which are broadly categorized as ***respiratory*** or ***non-respiratory*** (Fisher, 2014). While ***respiratory*** TB comprises "*pulmonary TB, plus TB of the pleura, the intrathoracic or mediastinal lymph nodes, nasopharynx, nose or sinuses*", ***non-respiratory*** rather refers to TB in all other body sites that are not within the purview of the disease sites of respiratory TB (Fisher, 2014). Cases included under both respiratory and non-respiratory may then be further subdivided; for example, ***respiratory TB*** in Canada is considered under the following subdivisions: primary, pulmonary and other respiratory (Public Health Agency of Canada, 2015) while ***non-respiratory*** includes miliary, lymph, central nervous system (CNS) and other sites (Fisher, 2014).

2.4.2. *TB case definition (s) in the United States*

The tuberculosis case definition in the United States has experienced substantial changes between 1953 and 1975 onwards. According to work published by Armstrong et al. (2014) the first TB case definition in 1953 encompasses individuals depicting either category A or B criteria:

A.

Cases with "bacteriological proof of TB or, in those without laboratory evidence, had other significant evidence of disease (e.g., characteristics chest radiograph or clinically active extra pulmonary TB)" (Armstrong and Miramontes, 2014) **OR**

B.

"Included previously unreported TB cases such as those with a history of active disease or previous treatment within the past 5 years" (Armstrong and Miramontes, 2014).

However, "*cases reported as (category B) one year were not precluded from being reported as (category A) cases in subsequent years*" (Armstrong and Miramontes, 2014). This definition identified 84,304 per 100,000 TB cases in 1953 in the United States. Presently, the United States like Canada, confirms TB cases either through laboratory or clinical criteria (Armstrong and Miramontes, 2014). The detailed criteria for ascertaining TB cases in the United States are outlined in Table 2-3.

Table 2-3: TB case definition in the United States

Hierarchy	Criteria	Definition
1.	Laboratory confirmation-culture confirmed	Isolation of *M. tuberculous* complex from a clinical specimen
2.	Laboratory confirmation-nucleic acid amplification test (NAAT)	Demonstration of Tuberculous complex from a clinical specimen by NAAT
3.	Laboratory confirmation-positive smear for acid-fast bacilli (AFB)	Demonstration of AFB in a clinical specimen when a culture has not been or cannot be obtained or is falsely negative or contaminated
4.		***Must meet all the following criteria***

	Clinical confirmation	• Positive TB skin test result or positive interferon gamma release assay for M. tuberculosis • Other signs and symptoms compatible with TB (e.g., abnormal chest radiography, abnormal chest computerized topography scan, or other chest imaging study, or clinical evidence of current disease) • Treatment with two or more anti-TB drugs • A completed diagnostic evaluation
5.	Provider diagnosis	The patient does not meet any of the above criteria but the provider believes the patient has a TB diagnosis

Sources: Armstrong, L.R. and Miramontes, R (2014) & Reported TB in the US 2016 (CDC, 2017).

2.4.3. *Similarities and differences in surveillance case definition in Canada and the US over time*

From 1953-2015 national TB rates in Canada included **new** ("*no documented evidence or adequate history of previously active TB*") (Public Health Agency of Canada, 2015) and ***previously reported cases*** (Gallant et al., 2014) whereas in the US from 1953-1974 (Armstrong and Miramontes, 2014) it included ***new active cases*** only and from 1975-2015 new ***and previously reported cases*** (Figure 2-1) (Armstrong and Miramontes, 2014). The case definition used in the US in 1953 was changed in 1975 onwards where "*cases formerly classified as reactivation TB were included in morbidity data*" (Armstrong and Miramontes, 2014). The 1975 increase in US

case rates (increased by 12.8%) resulted from the US change in surveillance case definition that now included ***previously reported cases*** (Armstrong and Miramontes, 2014; CDC, 2017).

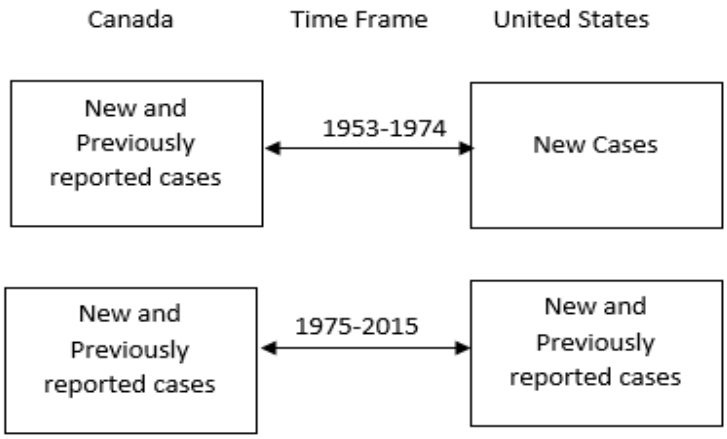

Figure 2-1: Case definition similarities and differences between Canada and US from 1953-2015

Depending on which definition, whether clinical or bacteriological, is used, reported cases may vary. Insight into the impact of changes in case definition can be attained by considering the different criteria used to define TB surveillance cases.

2.5. The impact of case definition change: a special case of tuberculosis

Table 2-4 summarizes some scenarios that could have occurred concerning a number of cases reported in Canada if different case definitions were used. From 2010 to 2012 if TB cases in Canada were ascertained based on a case definition that utilizes only culture positive as diagnostic criteria, then at least 80% would have been confirmed as cases for treatment. On the other hand, the use of smear positivity as the only diagnostic criteria would have identified 35-

40% as confirmed cases for treatment. Also, the use of smear positive, smear negative and culture positive as diagnostic criteria would have resulted in case ascertainment or confirmation of 71-76%. Comparing all three scenarios revealed that the number of cases reported might vary greatly depending on the case definition used. This comparison was based on only laboratory context. The identification of the majority of cases through the use of culture as a major diagnostic criteria was not surprising because compared to culture, smear microscopy has been found to have lower sensitivity (Ondimu et al., 2017) and specificity (Nour et al., 2011).

Table 2-4: Case Definition Impact on Number of Cases Reported in Canada, 2010-2012

Year	Total Cases[a]	Culture Positive[b] N (%)	Smear Positive[c] N (%)	Smear Positive, Culture Positive, and Smear Negative, Culture Positive N (%)**
2010	1587	1268 (79.9)	553 (34.9)	1132 (71.3)
2011	1618	1334 (82.5)	643 (39.7)	1243 (76.8)
2012	1685	1367 (81.1)	633 (37.6)	1251 (74.2)

[a] New and previously reported cases
[b c] Cases which were laboratory-confirmed based on culture-positive or microscopy smear positive
** Not including cases with unknown smear status.
Source: Tuberculosis in Canada 2012 (Public Health Agency of Canada, 2015)

Table 2-5 shows a comparison of TB cases based on four different case definitions. From 2007 to 2016 in Saskatchewan, a case definition that captured all cases (new and previously reported cases) yielded a rate of 8.1 per 100,000 population compared to 7.4 per 100,000 population if only new cases were ascertained. While all cases assessed based on culture positivity resulted

in a rate of 6.1 per 100,000 population, those based on only smear positivity yielded a rate of 3.0 per 100,000 population.

Table 2-5: Number of Tuberculosis cases in Saskatchewan, 2007-2016

Year	All Cases[a]	New Cases[b]	All Culture Positive Cases[c]	All Smear[d]
2007	105	96	61	40
2008	97	93	77	36
2009	90	81	70	41
2010	82	74	53	32
2011	83	75	63	34
2012	88	85	71	25
2013	87	78	71	30
2014	88	78	70	30
2015	70	66	57	22
2016	91	82	76	35
Total	**881**	**808**	**669**	**325**
Ave	**88.1**	**80.8**	**66.9**	**32.5**
Rate[e]	**8.1**	**7.4**	**6.1**	**3.0**

[a] New and previously reported cases
[b] "*No documented evidence or adequate history of previously active TB*" (Public Health Agency of Canada, 2015)
[c d] Cases which were laboratory-confirmed based on culture-positive or microscopy smear positive (Pai, 2014)
[e] Rate per 100,000 population

Source: TB Prevention and Control Saskatchewan (TB Prev & Control, 2017).

Similar to Canada, the case definition based on culture diagnostic criteria used in the US from 2010 to 2012 identified more cases compared to the definition based on only smear microscopy (Table 2-6). Another difference was observed between laboratory confirmed cases and cases identified based on clinical criteria. From 2010-2012, a case definition based on laboratory

criteria identified 76-78% whereas clinical case definition in the same time period was able to identify 16-17% of all cases. On the contrary, the clinical case definition identified more cases compared to 5-6% provider's diagnosis (the patient does not meet any of the above criteria but the provider believes the patient has a TB diagnosis). The higher proportion of TB cases identified in both Canada and the US via the use of a culture positive case definition further suggests that cases of TB ascertained in most high-burden resource-limited countries which predominantly rely on smear microscopy may be underreported compared to those in well-resourced settings (Parsons et al., 2011).

Table 2-6: Case Definition Impact on Number of Cases Reported in the United States, 2010-2012

Year	Total Cases	Culture Positive N (%)	Smear Positive N (%)	Positive NAA N (%)	Clinical Case Definition N (%)	Provider Diagnosis N (%)
2010	11,157	8,457 (76)	69 (1)	105 (1)	1878 (17)	648 (6)
2011	10,509	8,087 (77)	61 (1)	121 (1)	1678 (16)	562 (5)
2012	9,940	7,628 (77)	38 (0)	119 (1)	1640 (16)	515 (5)
NAA-Nucleic Acid Amplification Source: Reported Tuberculosis in the United States, 2016 (CDC, 2017)[35]						

The consequences associated with a case definition change or differences which include altering disease reporting, in addition to making the data incomparable overtime, have been observed and reported in other published studies (CDC, 1997; Goldstein et al., 2016; Peel Public Health, 2004).

2.6. The assessment of the impact of changes in case definition: a special case for tuberculosis

Not only do case definition changes affect the number of cases reported but also often result in changes in the definition's sensitivity and specificity (Teutsch et al., 2010). Ascertaining the performance of a diagnostic test depends on measures such as the sensitivity and specificity (Giesecke, 2017), which can be applied to case definitions as well. Depending on whether a surveillance or outbreak detection case definition was applied, the sensitivity and the specificity may vary (Stein et al. 2011). For instance, there is evidence that surveillance case definitions tend to have high sensitivity (Stein et al. 2011) whereas outbreak case definitions tend to be more specific especially in the later stage of an outbreak investigation when a stricter case definition is often applied (Stein et al. 2011). Differences between surveillance case definitions may also be observed by assessing sensitivity and specificity measures. While a larger proportion of true cases are identified using a more sensitive surveillance case definition (Giesecke, 2017), it is more likely to include a large number of cases not having the disease (false positives that arise because of the trade off with specificity) (Stein et al. 2011).

In contrast, a more specific case definition captures individuals who truly have the disease under study but tend to miss some true cases (false negatives because of the trade-off with sensitivity) (Stein et al. 2011; Giesecke, 2017). For example, Kohl et al (2005) attributed partially the difference between West Nile cases reported in Colorado, Nebraska and Kansas to "*higher specificity and lower sensitivity of the Kansas definition*" (Kohl et al., 2005). Thus, a change in case definition to an expanded definition may lead to low specificity and high sensitivity whereas a change that leads to exclusivity in the definition may result in high specificity and low

sensitivity. The use of a strict case definition including situations where cases have been confirmed through clinical and laboratory means tends to "*increase specificity and reduce misclassification of disease status*" (Reingold, 1998). Since there is no clear cut decision as to how to apply the sensitivity and specificity to a case definition (Stein et al. 2011), balancing both on a case by case basis has been recommended (Teutsch et al., 2010).

2.7. Methodologies for addressing the impacts of case definition change analytically

Although there is the likelihood that misclassification might occur if studies span two time periods with different case definitions applied to a particular disease (Goldstein et al., 2016), an analysis focusing on or restricted to periods where the same case definition could be used. Analysis can then be accomplished with joinpoint/segmented regression to further break down this time span with similar case definitions. Alternatively, Bayesian approaches (Pourhoseingholi et al., 2012) could be used to adjust counts of disease cases for periods prior to the change in definition to periods after the definition change (e.g., TB counts from 1953-1974 to the post 1974 counts). The latter approach was not considered for use in this thesis.

Joinpoint also known as segmented regression (Kim et al., 2000) *"describes changes in data trends by connecting several different line segments on a log scale"* (Xie et al., 2014). This method provides the opportunity for statistical significant change-point in the trend to be identified (Kim et al., 2000). This approach may be inappropriate if only a limited number of data points are available. For instance, it is recommended that a minimum of seven data points should be available for a joinpoint regression to be considered (Kim et al., 2000).

Suppose (x_1, y_1), …… (x_N, y_N) are the observations for the response variable y_z (e.g. TB rate) and independent variable x_z (e.g. calendar year) where $z = 1, 2, \ldots\ldots, N$ (Kim et al., 2000). Then according to Kim et al. and Xie et al., the joinpoint regression model can be expressed as (Kim et al., 2000; Xie et al., 2014):

$$\mathrm{E(y/x)} = \beta_0 + \beta_1 \mathrm{x_z} + \alpha_1(\mathrm{x_z} - \tau_1)^+ \ldots\ldots\ldots\ldots + \alpha_\mathrm{p}(\mathrm{x_z} - \tau_\mathrm{p})^+ \quad \textit{Equation 2-1}$$

The regression coefficients are $\beta_0, \beta_1, \alpha_1, \ldots\ldots\ldots, \alpha_\mathrm{p}$ with the unknown break points represented by $\tau_\mathrm{p}'s$ and $(x_z - \tau_\mathrm{Y})^+ = (x_z - \tau_\mathrm{Y})$ for $(x_z - \tau_\mathrm{Y}) > 0$ and 0, otherwise.

The response variable y_z or its transformed form can assume the following underlying distributions (Xie et al., 2014):

$\mathrm{y_z} \sim \mathrm{N}(\mu_\mathrm{Z}, \sigma^2)$ when $\mathrm{y_z}$ or its transformed values are homoscedastic.
$\mathrm{y_z} \sim \mathrm{N}(\mu_\mathrm{Z}, \sigma_\mathrm{z}^2)$ when $\mathrm{y_z}$ or its transformed values are heteroscedastic.

For this thesis, in order to fit a joinpoint to periods (1975-2015) where the same TB case definition were used in both countries, and the following steps were considered. The file containing the response variable (TB rates) and the independent variable (calendar year) was first uploaded in the joinpoint programming software (NIH, 2019A). This programming software was built by the National Institute of Health (NIH, 2019A) and has successfully been used to analyze 1971-2007 TB mortality trends in Spain (Llorca et al., 2012).

In this software, there were several decisions to be considered in order to identify the best models and the optimal number of breakpoints. This included (a) the selection of equation

type: linear or non-linear; (b) selection of least square method: grid search method or Hudson's method; (c) selection of maximum number of breakpoints; and (d) the method for selecting the optimal number of break points: permutation tests or Bayesian information criterion (BIC) (Jiang et al., 2010; NIH, 2018). Since normality assumption was not achievable using the raw TB rate data, the option of the log-linear approach was considered. While the log-linear approach enhances the data to achieve normality or at least be approximately normal, it also eases the interpretation of the trend (Kafle, 2014). Also, in terms of the least square approach, the grid search method was chosen over the Hudson's method. The grid search method allows *"finite number of discrete locations that are tested to find the best model fit"* (NIH, 2018). Computational intensiveness has been identified as major difference observed between the two methods (Jiang et al., 2010). Jiang et al. found the Hudson's method to be *"10 times slower than the grid search method"* (Jiang et al., 2010). The selection of the maximum number of breakpoints for the study data was guided by the recommended algorithmic default setting of the joinpoint program (NIH, 2019B). Thus, *"the default value for the maximum number of joinpoint depends on the number of data points"* (NIH, 2019B). From the grid search method, a maximum of nine break points can be considered (NIH, 2019B). Hence based on the recommended criteria and the allowable maximum number of breakpoints by the grid search method, a maximum number of 6 breakpoints were selected (NIH, 2019B). The optimal number of joinpoints was selected via the permutation tests which "*ensure that the approximate probability of the overall Type I error is less than the specified significance level (e.g., default = 0.05)"* (NIH, 2018). The Bayesian information criterion has been found to be less parsimonious when compared to the permutation test (Jiang et al., 2010). The permutation test works by

testing the null hypothesis H_0: the number of breakpoints =Υ_a against alternative hypothesis H_b: the number of breakpoints = Υ_b. The algorithms start with $\Upsilon_a = MIN$ and $\Upsilon_b = MAX$ where Υ_b deceases by 1 whenever the null hypothesis was accepted and Υ_a increases by 1 whenever the null hypothesis was rejected. The algorithm continues in the same manner until Υ_a equals Υ_b. This occurs when the final breakpoint is selected (NIH, 2018).

The slope estimates obtained from each model was used to compute the metric (annual percent change-APC) for the quantification of the change in the trend (Kim et al., 2017). For a break point with a slope β_i, the APC can be calculated from the formula

$$\mathrm{APC} = \{\exp(\beta_i) - 1\} * 100$$ (Kim et al., 2017) *Equation 2-2*

To quantify the change in trend for the entire study period (e.g. 1975-2015), the average annual percent change was applied (Kim et al., 2017). This metric incorporates the trend transitions in it calculation (Clegg et al., 2009).

2.8. The case definition: In Conclusion

Changes in case definitions, as evidence by exploring several diseases, highlights that for appropriate comparisons within and between populations, consistent ascertainment criteria of cases should be adopted or at minimum be openly reported. This confirms a statement by Luepker et al. (2003) that case definitions of diseases such as coronary heart disease (CHD) that are consistent and universal accepted allows for the "*determination of rates and comparisons within and between populations*" (Luepker et al., 2003). Detection of false negative cases, increases in reported cases of disease, underreporting of disease cases and reporting delays of cases of disease were the main consequences noted to arise from a case definition change.

Additionally, case definition change may also result in differences in sensitivity and specificity measures which may make data directly incomparable.

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Chapter 2 provided an overview of the importance of assessing the case definition used for data collection before estimates from such data are compared. These are especially important when comparing the estimate of diseases between or within geographical regions. The investigation carried out in this chapter led to the important recognition of the differences in TB case definition used in the past between Canada and the United States. This information was essential especially to ***Chapter 3*** of the thesis which sought to specifically embark on an in-depth comparison of both past and present TB incidence in Canada and the United States. Furthermore, this chapter also provided options as to methods currently available in the literature which could be used to adjust or handle differences arising from revision/change in case definition in ***Chapter 3***. The background information emerged from this chapter shed light on some difficulties that may arise from Canada-US TB rate comparison in ***Chapter 3*** and possible methods to be applied to mitigate such difficulties.

The ***Chapter 3*** has been submitted for consideration for publication in the Canadian Journal of Public Health (Submission ID-CJPH-D-18-00285). In ***Chapter 2 and 3*** I conducted literature review, cleaned the data, performed the statistical analysis, interpretation of results and wrote up the Chapters.

Chapter 3. Tuberculosis in Canada and the United States: A Review of Trends from 1953-2015

3.1. INTRODUCTION

Tuberculosis (TB) is a preventable and treatable disease (WHO 2018), that has not been eliminated in most parts of the world (Chiang et al. 2013) including Canada and the United States (Lönnroth et al. 2015). TB in North America date back to the 18th and 19th centuries (Grzybowski and Allen 1999; Grigg 1958), for which national incidence reporting in Canada and the United States only commenced in 1924 and 1953 respectively (Gallant et al. 2014; Woodruff et al. 2015). There are TB related similarities between these countries: high income (World Bank 2016), low TB incidence (Lönnroth et al. 2015), similar surveillance programs (Mor et al. 2008), isoniazid (INH) and rifampin (RMP) implemented for treatment at the same time (Menzies and Elwood 2014), treatment of Latent TB Infection (LTBI) implemented within a year (Mount and Ferebee 1961), and the majority of cases occurring in the Foreign-born (FB) population (Public Health Agency of Canada 2015; Centers for Disease Control and Prevention 2017). There are some differences however: the United States in 1993 (Centers for Disease Control and Prevention 2017) was several years ahead of Canada in 1997 (Tuberculosis Prevention and Control Canada 2000) for first reporting TB with HIV/AIDS nationally, Canada ranks 6th and the United States 14th for highest proportion of Foreign-born population (OECD 2018) and 18th and 29th for the highest net positive immigration respectively (Index Mundi 2018). From 1953 to 1974 the United States surveillance case definition included only new cases compared to Canada with new and previously reported cases (Gallant et al. 2014; Armstrong and Miramontes 2014). In 1975, the United States changed its surveillance case

definition resulting in an increase in annual surveillance numbers (Armstrong and Miramontes 2014). Considering this background, it was an unexpected observation over the last decade that TB rates in the United States declined more rapidly than in Canada (Public Health Agency of Canada 2015; Centers for Disease Control and Prevention 2017).

Epidemiologically, time-trend analysis is a graphical procedure used to assess changes in disease patterns over time (Kim et al. 2000). Ely likened the analysis of trends which involve time as a major component to a screening tool needed to "*decide whether a more intensive investigation into underlying causes is justified*" (Ely et al. 1997). This highlights the need for exploring incidence trends as the first step in carrying out in-depth investigations of disease drivers to guide national and global goals in TB control. Explicit comparison of TB incidence rates over time between Canada and the United States has not been published. To better understand some of the differences we proposed to explore TB incidence rates in Canada and the United States over time and compare the national trends.

3.2. METHODS

3.2.1 *Incidence data*

This study used retrospective national annual TB incidence rate data from 1953-2015 retrieved from the Public Health Agency of Canada (PHAC) and the Centers for Disease Control (CDC), United States (Gallant et al. 2014; Centers for Disease Control and Prevention 2017; Gallant et al. 2017). Population data were obtained from Canada quinquennial and the United States decennial census data (Statistics Canada 2011; Grieco et al. 2012).

The TB rate in Canada from 1953-2015 included new and previously reported cases. In the United States from 1953-1974 it included new active cases only and from 1975-2015 new and previously reported cases (Gallant et al. 2014; Armstrong and Miramontes 2014). Data on implementation of treatment drugs and treatment of LTBI, TB program funding cuts, case definition change, first reports of HIV, percent of HIV/TB co-infection, percent Foreign-born population and percent Indigenous population were obtained as listed in Table 3-1. Ethics approval was obtained from University of Saskatchewan ethics review board (U of S BIO#16-329).

Table 3-1: Sources of data list by reference number

Metric	Country	Year & %	Source
Implementation date INH	Canada and United States	1952	Menzies & Elwood (2014)
Implementation TLTBI	Canada and United States	1961	Mount & Ferebee (1961)
Implementation date RMP	Canada and United States	1968	Menzies & Elwood (2014)
TB program funding cuts	United States	1970	United States Congress (1993)
Surveillance case definition change	United States	1975	Armstrong et al. (2014)
First national reported TB/HIV	Canada	1997	Public Health Agency Canada (2000)
	United States	1993	Centers for Disease Control (2017)
%foreign-born population	United States	2010 &12.9%	Grieco et al. (2012)
	Canada	2011 &20.6%	Statistics Canada (2011)
%Indigenous (IND) population	United States	2010 &1.7%	Norris et al. (2012)
	Canada	2011 & 4.2%	Statistics Canada (2011)
% cases with HIV/TB co-infection	United States	2012 & 7.2%	Centers for Disease Control (2017)
	Canada	2012 & 8.0%	Public Health Agency Canada (2015)

3.2.2. *Data analysis*

A time-trend analysis comparing TB incidence rates between Canada and the United States from 1953-2015 was performed using Microsoft Excel 2016. The United States TB rate in 2010 was directly standardized to the 2011 Canadian FB, IND and Non-Indigenous (NIND) population distribution. Thus, the crude United States FB, IND and NIND rate in 2010 was multiplied by the 2011 standard Canadian proportion of FB, IND and NIND population to obtain the FB, IND, NIND adjusted rate. The TB rate share which is the proportion of the annual rate contributed by each country's FB, IND and NIND was calculated by multiplying the crude FB, IND and NIND TB rate by the percent total population. In addition, joinpoint/segmented regression model was applied to identify points (years) with a statistically significant log-linear trend in TB case rates from 1975-2015. This method is more robust than single summary trend statistics (Kim et al. 2000; Qiu et al. 2009). The Grid search method was used to test the locations for the best model (NIH, 2018) and a maximum number of six joinpoints was used. Additionally, inferential permutation test was applied to select the appropriate optimal number of change points (NIH, 2018). The joinpoint method has been applied in several fields of research including TB and cancers (Kim et al. 2000; Baker et al. 2016). The annual percent change (APC) with 95% confidence intervals (CIs) were estimated from the models and p-values < 0.05 were considered a statistically significant joinpoint.

3.3. RESULTS

3.3.1. *Trend of Tuberculosis Incidence Rates from 1953-2015*

Fig 3-1 shows a comparison of TB incidence rates from 1953-2015. It shows that from 1953-1974 rates in Canada were higher compared to the United States. From 1975-1985, rates were similar for both countries. From 1974 to 1975 the United States rate increased by 12.8% (case definition change), equalling the Canadian rate. During 1986-2000, rates in Canada continued to decline while an increase was observed in the United States. Between 2001 and 2004, rates were again similar. From 2004-2015 rates in Canada appeared to plateau whereas in the United States they decreased. Important events which were expected to influence rates are highlighted in Fig 3-1 and listed in Table 3-1. Fig 3-2, an expanded view of rates from 1997 to 2015, showed that the Canadian rate declined throughout this period but at a significantly slower pace than the United States.

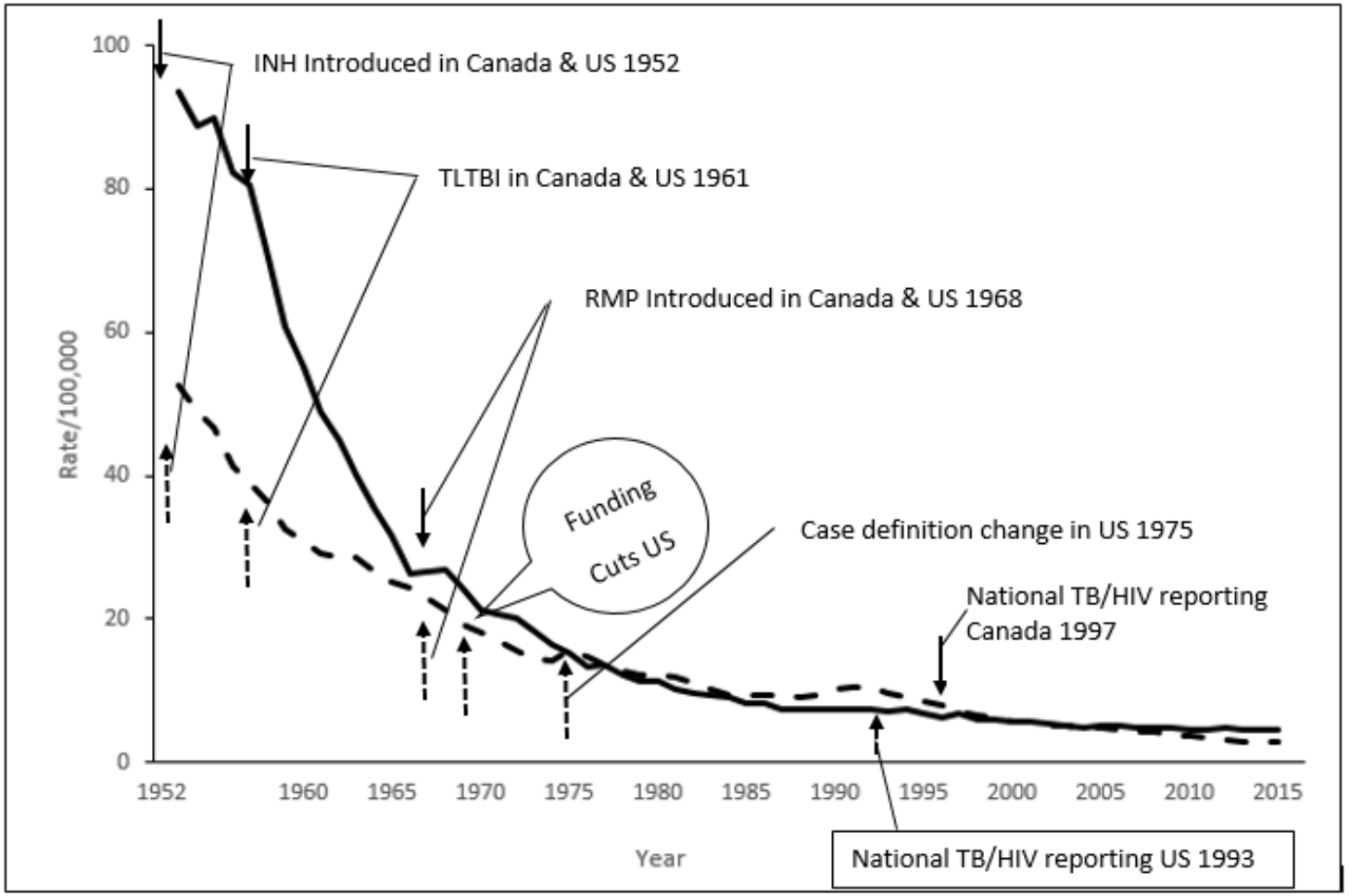

Figure 3-1: Tuberculosis incidence rates/100,000 in Canada and the United States from 1953-2015. Canada, solid black line; the United States interrupted black line

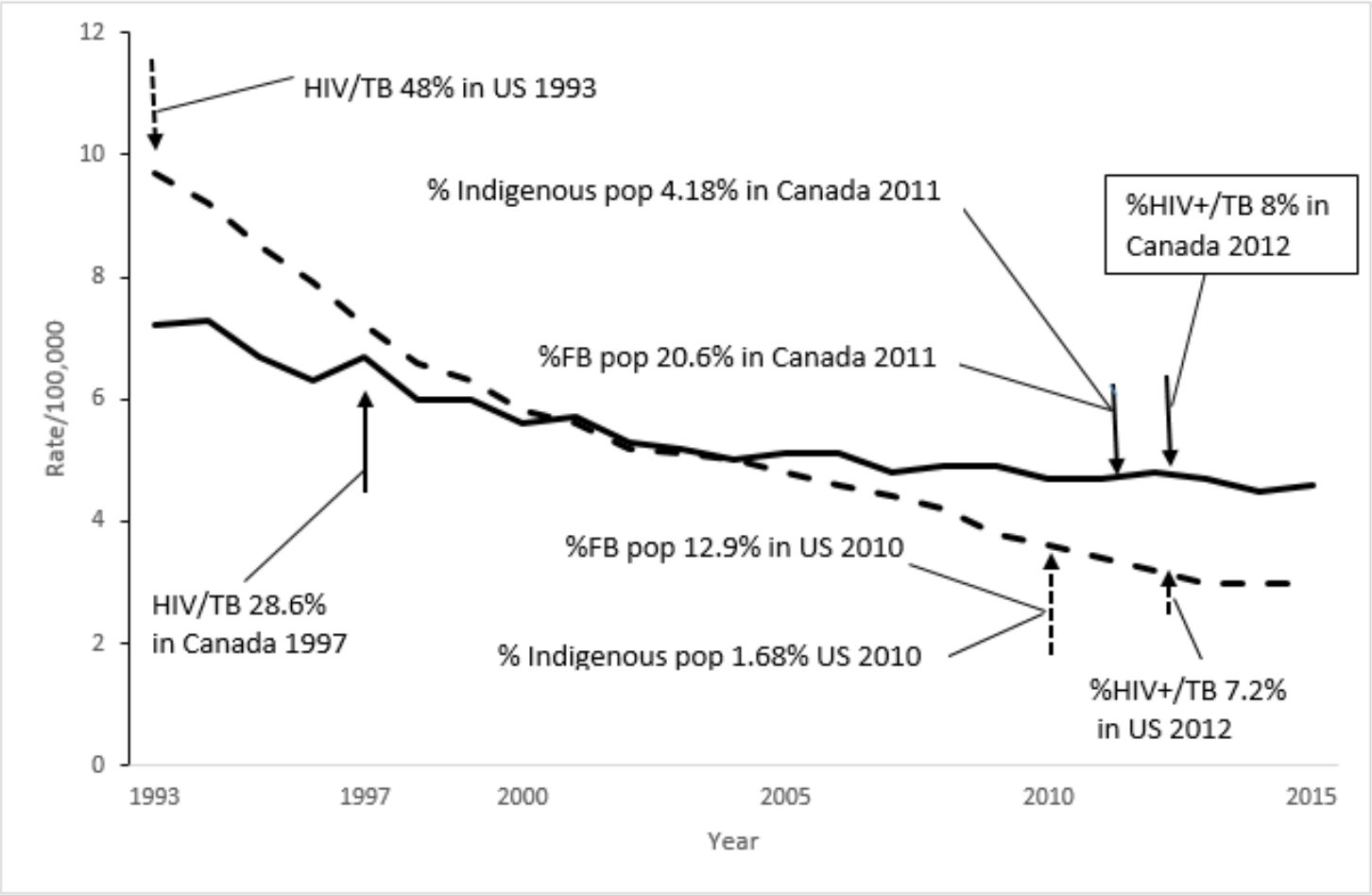

Figure 3-2: Tuberculosis incidence rate/100,000 in Canada and the United States from 1993-2015. The period of interest is 2004-2015.

Canada, solid black line; United, interrupted black line

3.3.2. *Comparing Tuberculosis Incidence Rate 2010 and 2011*

Table 3-2 lists the population, percent total population and rate of TB by ethnicity for both countries. The total crude rate for Canada was 4.7 as compared to 3.6 for the United States. The Canadian rate share shows the Indigenous crude TB rate of 21.6 contributed 0.9% to the total annual rate; in the United States the crude rate was 2.9 and contributed 0.05% to the annual rate. Table 3-3 shows that the United States rate adjusted to the Canadian ethnic composition was 4.8 compared to the Canadian rate of 4.7.

3.3.3. *Joinpoint Trend in Tuberculosis Incidence Rate, 1975-2015*

The models of TB incidence rates were broken into six segments in the United States (1975, 1985, 1992, 2000, 2007, 2011) and four segments in Canada (1987, 1993, 2003 and 2015), corresponding to where changes in the trend line occurred (Table 3-4). A decrease in APC was identified in all four segments in Canada whereas in the United States an increase of 1.9% was observed in 1985-1992. In Canada, the 1987-1993 segment decrease was not significant (APC=-0.4%, CI -2.1 to 1.3); whereas, in the United States, for all six segments, the APCs were significant. The average APC in rate from 1975-2015 for Canada was significantly lower -2.9% compared to the United States -4.1%.

Table 3-2: Population and TB rates by FB, IND and NIND Canada and the United States, 2010 & 2011

Population	Canada 2011				United States 2010			
	Population	Population % Total	Rate	Rate Share	Population	Population % Total	Rate	Rate Share
Foreign-born	6,775,800	20.2	16.3	3.3	39,900,000	12.9	17.1	2.2
Canadian-born Indigenous	1,400,685	4.2	21.6	0.9	5,200,000	1.7	2.9	0.05
Canadian born Non-Indigenous	25,200,203	75.6	0.7	0.5	263,600,000	85.4	1.6	1.4
Total	33,476,688	100	4.7	4.7	308,700,000	100	3.6	3.6

Table 3-3: Adjusted US TB rates using Canada percent population by FB, IND and NIND, 2010 & 2011

Population	Canada % Population	Crude United States Rate	Adjusted United States Rate
Foreign-born	20.2	17.1	3.5
Canadian-born Indigenous	4.2	2.9	0.1
Canadian born Non-Indigenous	75.6	1.6	1.2
Total	100	3.6	4.8

Table 3-4: Annual percent change in TB case rates/100,000, Canada and US, 1975-2015

United States						Canada					
Segment	Breakpoint		Incidence Rate			Segment	Breakpoint		Incidence Rate		
	Lower end point	Upper end point	APC	95% CI Lower CI	Upper CI		Lower end point	Upper end point	APC	95% CI Lower CI	Upper CI
1	1975	1985	-5.1^	-5.7	-4.6	1	1975	1987	-5.5^	-5.9	-5.0
2	1985	1992	1.9^	0.7	3.3	2	1987	1993	-0.4	-2.1	1.3
3	1992	2000	-7.1^	-8.1	-6.2	3	1993	2003	-3.4^	-4.1	-2.7
4	2000	2007	-3.7^	-5.0	-2.5	4	2003	2015	-1.0^	-1.5	-0.6
5	2007	2011	-6.9^	-10.3	-3.3						
6	2011	2015	-3.5^	-5.8	-1.2						
			AAP	95% Cl					AAPC	95%Cl	
Full Range	1975	2015	-4.1	-4.7	-3.6	Full Range	1975	2015	-2.9	-3.2	-2.5

Abbreviations: APC, Annual Percent Change; AAPC, Average Annual Percent Change; CI, confidence interval
^ Significantly different from zero alpha=0.05

3.4. DISCUSSION

This study is the first extended comparison of TB incidence rate trends between two North American low-incidence countries with similar national TB surveillance programs, Canada and the United States. Our prior expectations, possibly biased, were that rates and trends would be similar. The data showed that there were differences over six decades. The joinpoint intervals assigned by the regression model presented unequal intervals. All but the 1985-92 United States breakpoints showed a significant increase. All but the 1987-1993 Canada breakpoints showed a significant decline. These intervals quantified the line graph result. The United States average annual percent decline was significantly greater than the Canadian decline over the 41-year interval, 4.1% compared to 2.9%. This compares to the United States designated 2015-20 target of 53% (3 to 1.4/100,000) reduction over the 5 years or 10% per year and compares to the Canadian designated 1990-2015 target of 50% reduction (7.0 to 3.6/100,000) over 25 years or 2% per year (Public Health Agency of Canada 2014; Centers for Disease Control 2015). The Canadian and the United States targets compare to the WHO designated 2015-2025 target of 50% reduction or 5% per year (WHO 2014).

One of the advantages of using joinpoint was identifying intervals for which the change point was significant. It also quantified and compared the trends transitions for a more precise comparison, as well is more robust than single summary trend statistics (Qiu et al. 2009).

The overall trend for the 63 year-interval (1953-2015) showed that the Canadian rates were higher between 1953 and 1974. Part of this difference, 10-15%, was due to Canada including new and previously reported cases compared to the United States reporting new cases only

(Gallant et al. 2014; Armstrong and Miramontes 2014). This was based on the US percent increase in 1975 due to previously reported cases. Further explanation is speculative since age, ethnicity, origin of birth, and gender were not available before 1970 (Personal communication Adam Langer CDC Feb 13, 2017 with permission).

Rates were similar beginning in 1975 when the United States case definition changed and was similar to the Canadian definition. The United States rates rose in the mid-1980s coincident with a sizable proportion of cases resulting from HIV+/TB coinfection. The effect of TB program funding cuts beginning in 1970 also contributed (United States Congress 1993). Canadian rates declined more slowly during this interval probably related to HIV+/TB coinfection (Table 3-4) but with a lower proportion compared to the United States and less impact.

The TB rate in the United States declined more rapidly thereafter such that by 2005 they were lower than the rate in Canada. This trend continued to the end of the observation period. Much of the difference related to the proportion of the FB population of 20.6% in Canada (2011 census year) and 12.9% in the United States (2010 census year) (Statistics Canada 2011; Grieco et al. 2012). The majority of cases in both countries were FB, with comparable rates (Public Health Agency of Canada 2015; Centers for Disease Control and Prevention 2017). The United States rate when standardized to Canadian ethnic distribution was similar to the rate in Canada. A similar rate was the hypothesized outcome for two high-income low-incidence countries with similar surveillance programs.

The proportion of FB population with the accompanying TB cases mostly explains the lower United States rate in the last decade since the difference in HIV+ TB cases narrowed. The rate

share confirmed that it was the major contributor to the total rate. Canada's Indigenous rate was 38 times the Non-Indigenous Canadian born rate in 2010 but contributed only 19% to the annual rate (Public Health Agency of Canada 2015). The Non-Indigenous Canadian born contribution was 11% (Public Health Agency of Canada 2015).

Different TB risk for different population groups is another possible cause of divergent trends in TB case rates between Canada and the United States. This and age-specific rates require more detailed investigations to quantify the effects of all the factors.

Strengths and limitations

The strength of the data was based on a six-decade interval of annual reports by Canada and the United States. From 1975 onward the case definition for both countries was the same. In a national context, Canada and the United States are comparable countries for high income and low TB incidence with similar epidemiological influences.

Weaknesses of the data include the fact that Non-Indigenous Canadian and the United States born populations are not homogeneous. Canadian cases were not stratified beyond Non-Indigenous Canadian-born as they were in the United States as Canada does not break down Non-Indigenous ethnicity in Canadian born cases. In the United States, the 2010 TB cases and incidence rates for Asian-American, African-American, and Hispanic-American were significant in proportion to total United States cases and rates.

Divergent rates resulting from program performance could not be excluded. The comparison in this study was WHO surveillance reports by country. Comparison of program outcomes was beyond the scope of this study. Such a comparison would include percent of TB treatment

completion, the extent of drug resistance, and relapse, screening and uptake of treatment of LTBI.

For comparative purposes the United States cases were standardized to Canadian ethnic categories in 2011. Since the proportions of ethnic categories change over time, the results of standardizing TB incidence rates would vary over time.

3.5. CONCLUSIONS

Canada and the United States TB incidence rates have been different for longer intervals over the last six decades than they have been the same. This was unexpected since both are low incidence and high-income countries, with identical TB surveillance programs. Surveillance case definition, TB program funding, HIV/TB co-infection, and TB in FB persons were the main contributors to the differences. Higher TB rates in the Canadian Indigenous population was a smaller contribution to the annual rate since the Indigenous proportion of the total population was small. From 2004-2015 the lower United States rates were mainly due to a larger proportion of FB persons in Canada. Incidence rates decreased in both countries from 1997 but significantly more rapidly in the United States. Further exploration of contributing factors such as adjusting for age-specific rates and age composition in both populations is needed.

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After accounting for case definition differences identified and also incorporating an adjustment method in ***Chapter 2*** to ***Chapter 3***, probable factors such as HIV/TB co-infection, ethnicity and shifts in demographic compositional factors (e.g., age) were identified as possibly responsible for incidence rate differences between the two countries. This background provided the basis for ***Chapter 4's*** rationale to embark on an in-depth investigation into these factors. Following up ***Chapter 3*** with ***Chapter 4*** was vital to better elucidate rate differences especially in the last decade between the two countries. In ***Chapter 4*** I conducted literature review, cleaned the data, performed the statistical analysis, interpretation of results and wrote up the Chapter.

Chapter 4. Comparing Tuberculosis in Canada and the United States: the impact of Foreign born and Indigenous populations and HIV/TB Co-infection

4.1. INTRODUCTION

Despite both Canada and the United States (US) having a well-resourced health care system (Martin et al., 2018; Ridic et al., 2012) coupled with huge financial commitments towards the reduction/elimination of TB (47,000 dollars in Canada and US$ 17, 000 to 482 000 per TB case respectively) (Menzies et al., 2008; Castro et al., 2016) as well similar TB surveillance programs (Mor et al., 2008), TB incidence rates are statistically significantly different between the two countries especially in the last decade (Essien et al., 2018). Among several other factors including age (Zhang et al., 2011) that may contribute to rate difference between these two populations, there is evidence that ethnicity and HIV strongly drive tuberculosis rates (Salinas et al., 2016; Houben et al., 2010).

Between 2001 and 2011, Foreign-born (FB) and Indigenous (IND) populations in Canada have increased by 25.5% (Stat Can Ethnocultural Portrait, 2003; Stat Can Immigration and Ethnocultural Diversity, 2013) and 7.8% (Stat Can Aboriginal Peoples in Canada, 2003; Stat Canada, 2013); FB and IND increased by 28.5% (Malone et al., 2003; Grieco et al., 2012) and 16% (Ogunwole, 2002; Norris et al., 2012) in the US between 2000 and 2010. These increases might have resulted in a shift in age and age-specific TB rate distribution in both countries. However, the extent to which the shift in age distribution might have affected the national TB rates has not yet been explored.

Furthermore, while both Canada (8.1%) and the US (8.0%) had almost the same proportions of reported HIV positivity among TB cases with known HIV status in 2010 (PHAC TB in Can 2012, 2015; CDC, 2017), in 2012 the percent in HIV/TB was rather higher in Canada (8.0%) (PHAC TB in Can 2012) than in the US (7.2%) (CDC, 2017). Considering this background, an explicit comparison elucidating the contribution of FB, IND, and HIV/TB coinfection to differences in TB rates between the two countries is needed but yet lacking.

As both migrant numbers (Stat Can Ethnocultural Portrait, 2003; Stat Can Immigration and Ethnocultural Diversity, 2013; Malone et al., 2003; Grieco et al., 2012) and IND population (Stat Can Aboriginal Peoples in Canada, 2003; Stat Canada, 2013; Ogunwole, 2002; Norris et al., 2012) continued to increase in the two countries, coupled with challenges associated with HIV transmission rates (Hall et al., 2009). A better understanding of the pattern of influence of these factors would essentially help to inform tailored interventions (White et al., 2017; Unnikrishnan et al., 2015). Hence, we compared the rates of TB decline in FB and IND TB cases, and examined the impact of shifts in FB and IND population by age and age-specific rates, as well the influence of HIV/TB co-infection patterns over time between the two countries.

4.2. METHODS

4.2.1. *Data*

Annual national retrospective Foreign-born age-stratified TB incidence case counts data in 2001, 2006 and 2011 and Indigenous population in 2006 and 2011 were retrieved from Public Health Agency of Canada reports (Health Canada, 2003; PHAC TB in Can 2006, 2008; PHAC TB in Can 2012, 2015) and Centre of Disease Control (CDC) WONDER in the United States (CDC OTIS,

2018). In addition, population data were obtained from Canadian census (Stat Can 2001 Census of pop, 2001; Stat Can 2011, 2011; Stat Can 2006 Census of pop, 2006; Stat Can Aboriginal People in Can, 2006) and census data in the US (US Census Bureau, 2016; Pew Research Center, 2014, US Census Bureau, 2017). Although Information on annual immigration numbers stratified by age distribution in Canada were available for four census years (2001, 2006, 2011 and 2016) (Stat Can 2001 Census of pop, 2001; Stat Can 2011, 2011; Stat Can 2006 Census of pop, 2006; Stat Can 2016 Census of pop, 2016), Foreign-born TB incidence cases by age distribution were only available for three years (2001, 2006 and 2011). Despite the availability of immigration and age-stratified TB incidence case counts data in the United States from 1993-2016 (CDC OTIS, 2018), all analyses were restricted to three years (2001, 2006 and 2011) due to data limitations in Canada.

To better understand the trends, data on the percentage of cases with HIV+/TB co-infection were retrieved from annual TB reports in Canada (PHAC TB in Can 2008, 2015; Health Canada, 2000; PHAC TB in Can 2008, 2012; PHAC TB in Can 2009, 2013) and in the US (CDC, 2017); as well, the list of WHO regions with Foreign-born TB that immigrate into both countries were identified (PHAC TB in Can 2012, 2015; CDC, 2012).

4.2.2. *Data Analysis*

The immigration numbers and TB incidence cases were retrieved for the age groups: less than 15 years, 15-24 years, 25-44 years and 45-64 years and 65+ years, and the age-specific rates were estimated as cases of TB per 100,000 population. Using the 2011 immigration population as a standard population, Foreign-born TB incidence case counts in 2001, 2006 and 2011 were

directly standardized by multiplying the age-specific crude rate and age-specific distribution of the standard population to obtain the age-adjusted rates. The age-adjusted case rates obtained were further analyzed using a segmented regression model to assess years in which the TB incidence in the Foreign-born population significantly changed in the two countries. Segmented regression methods robustly subdivide models that are nonlinear in nature to linear with the aim of enhancing the efficiency of identifying change points (Kazemnejad et al., 2014). Inferential permutations tests were applied to detect and select the number of optimal change points (Kim et al., 2000) and the log-linear annual percent change and the associated 95% confidence intervals were estimated for each distinct segment. In a subsequent analysis, decomposition method/analyses were performed to assess to what extent the difference between Foreign-born crude TB incidence rates in Canada and US was attributable to changes in age group specific rate and age composition/structure. The decomposition approach explicitly described by Preston (Preston et al., 2001, p.28) was used and has successfully been used to compare California's Foreign-born population TB rates in 2000 and 2010 (Oh, 2014). The decomposition of the differences in TB incidence rate in Canada from 2001 and 2006 was carried out by letting R^{2001} and R^{2006} represent the crude TB incident rates for the year 2001 and 2006 immigrant populations in Canada and letting R_Z^{2001} and R_Z^{2006} represent the age group specific TB rate for 2001 and 2006 respectively. In addition, the age distributions of 2001 and 2006 immigrant populations were represented as C_Z^{2001} and C_z^{2006}, where z denotes the age grouping of the population (under 15 years, 15-24 years, 25-44 years and 45-64 years and 65+ years). All the decomposition analyses were performed in Microsoft Excel 2016.

The contribution due to differences in age composition/structure was computed from the following equations:

Equation 4-1

$$\sum_{Z}(C_Z^{2001} - C_Z^{2006}) * \left[\frac{R_Z^{2001} + R_Z^{2006}}{2}\right]$$

Likewise, the contribution due to differences in age specific TB rate was calculated from

Equation 4-2

$$\sum_{Z}(\mathrm{R}_Z^{2001} - \mathrm{R}_Z^{2006}) * \left[\frac{\mathrm{C}_Z^{2001} + \mathrm{C}_Z^{2006}}{2}\right]$$

The total contribution of both age composition/structure and age specific TB rate differences was computed using

Equation 4-3

$$\sum_{Z}(C_Z^{2001} - C_Z^{2006}) * \left[\frac{R_Z^{2001} + R_Z^{2006}}{2}\right] + \sum_{Z}(R_Z^{2001} - R_Z^{2006}) * \left[\frac{C_Z^{2001} + C_Z^{2006}}{2}\right]$$

In order to obtain the proportion of differences that was attributable to age composition/structure and age-specific TB rate, formulas in (4.4) and (4.5) were used.

Proportion of difference due to changes in age composition/structure was computed using

Equation 4-4

$$\frac{A}{A+B} * 100 \quad OR \qquad \frac{A}{C} * 100$$

Proportion of difference due to changes in age specific TB rate was computed using

Equation 4-5

$$\frac{B}{A+B} * 100 \quad OR \quad \frac{B}{C} * 100$$

All the remaining comparisons (2006-2011 and 2001-2011) including Indigenous population were performed in a similar manner for both countries.

4.3. RESULTS

4.3.1. *Age-adjusted rates and segmented regression model*

Table 4-1 and Figure 4-1 summarize both the age-adjusted rates and a segmented regression model of Foreign-born TB incidence between Canada and the United States. In 2001, the age-adjusted TB incidence rate observed in the United States immigrant population was higher (25.3 per 100,000 population) compared to that observed in Canada (19.9 per 100 000 population). However, over a five-year period (2001-2006), the United States Foreign-born TB incidence rate experienced a more rapid decline of -3.7% compared to Canada which declined by -2.5%. From 2006-2011, Canada experienced a decline of -0.9% whereas US rates decreased by -3.6%. Overall, over the ten-year interval (2001-2011), the Foreign-born TB incidence rate in the United States declined more (AAPC=-3.7%; -4.1 to -3.2) compared to Canada (AAPC=-1.7; -7.3 to 4.1).

Table 4-1: Foreign-born TB incidence rate comparison between Canada and the US

Years	Canada Foreign-born TB Incidence Rates				United States Foreign-born TB Incidence Rates			
	Age-adjusted Rates per 100,000 population	Unadjusted Rate per 100,000 population	APC	95% CI	Age-adjusted Rates per 100,000 population	Unadjusted Rate per 100,000 Population	APC	95% CI
2001 2006 2011	19.89 17.53 16.72	18.8 14.8 13.5			25.27 20.90 17.39	26.6 21.9 17.3		
Break points	**Segmented Regression Results**							
2001-2006 2006-2011 2001-2011			-2.5% -0.9% **AAPC*** -1.7%	-7.3 to 4.1			-3.7% -3.6% **AAPC*** -3.7^%	-4.1 to -3.2

(^) – Significantly different from zero at alpha=0.05
APC -Annual percentage change
AAPC** - Average annual percentage change
CI – Confidence interval

An examination of the pattern of migration based on WHO regions in both countries (Table 4-2) shows that besides controlling for age, region of birth of new migrants in part contributed to the differences in the TB rate decline between the two countries. Thus, while in Canada, the highest number of Foreign-born TB cases (40.6%) were reported in persons born in the Western Pacific, in the US, the highest was reported in persons born in the Americas (38.7%) with Mexico alone contributing 57.7% of the total Americas cases.

Table 4-2: Proportion of Foreign-born TB by WHO region in Canada and the US, 2011

Canada			United States		
WHO Regions	N	%	Country	N	%
Wester Pacific	444	40.6	Americas**	2483	38.7
Southeast Asia	273	24.9	**Western Pacific**	2048	31.9
African	136	12.4	**Southeast Asia**	882	13.8
European	108	9.9	**African**	500	7.8
Americas	67	6.1	Eastern Mediterranean	280	4.4
Eastern Mediterranean	67	6.1	European	221	3.4

** Out of 2483 cases in the Americas, 1432 cases were from individuals born in Mexico (57.7%).
TB report in Canada and the United States, 2011 (PHAC TB in Can 2012, 2015; CDC, 2012).

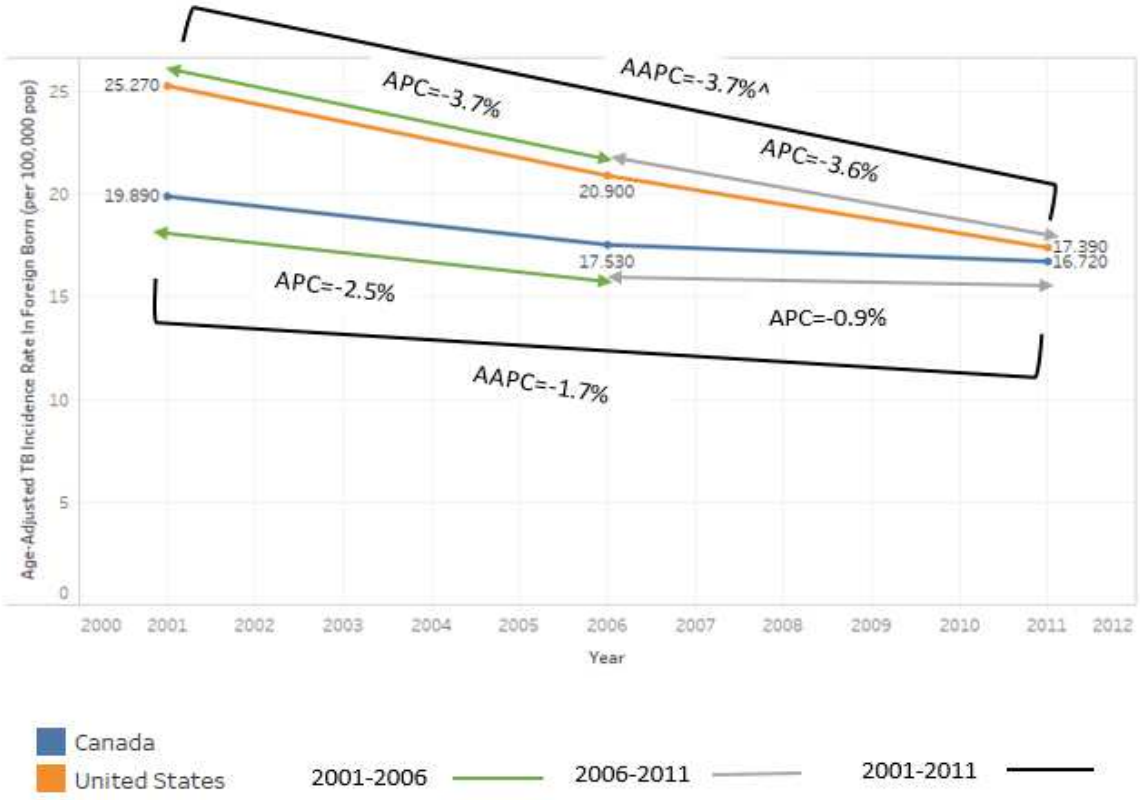

Figure 4-1: A plot comparing foreign born average annual percent change (AAPC), annual percent change (APC) and age-adjusted rate between Canada and the United States from 2001-2011

Table 4-3 summarizes and compares the age-adjusted rates and annual percent change of TB incidence, specific to the Indigenous population, between Canada and the United States. In both 2006 and 2011, the age-adjusted TB incidence rates observed in Canada's Indigenous population was higher compared to that observed in the United States. Results further revealed that from 2006-2011, the United States Indigenous population TB incidence rate declined more rapidly by -6.3% than in Canada which declined by -4.5%.

Table 4-3: Indigenous Population TB incidence rate comparison between Canada and the US, 2006-2011

	Canada	United States
Years/Break Points	Age-adjusted Rates per 100,000 population	Age-adjusted Rates per 100,000 population
2006 2011	28.4 22.5	6.96 5.03
Segmented Regression Results		
Break Points 2006-2011	**APC*** -4.5%	**APC*** -6.3%

*APC -Annual percentage change

4.3.2. *Tuberculosis in Canada and the United States: the impact of shifts in migrant's population by age and age-specific rates from 2001-2006*

The 1062 and 1042 cases of Foreign-born TB observed in Canada in 2001 and 2006 resulted in estimated crude incidence rates of 19.4 per 100,000 population and 16.8 per 100,000 population respectively, which yielded a decrease of 2.6 per 100,000 population (Table 4-4). Of the absolute decrease in rate (2.6 per 100,000 population) observed in Canada between 2001 and 2006, differences in the age group specific rate accounted for 101.1% of the decline and -1.1% to compositional changes in age. Estimates higher than 100% mean if there were no compositional changes, there would have been a much higher decrease in TB incidence than what the study observed. In contrast, the negative estimate was an indication that compositional factors of age-specific TB rate were opposed by age group compositional factors.

Although a similar pattern of contribution was observed in the United States for the same time interval, age composition/distribution increased Foreign-born TB rates more in the United States than in Canada. Thus, the 8033 and 7,844 cases of Foreign-born TB observed in the United States in 2001 and 2006 with estimated crude rates of 25.3 per 100,000 and 20.9 per 100,000 respectively, resulted in an absolute decline of 4.4 per 100,000 population. The differences in age-group specific rate contributed 104.4% to the decline in the crude rate and -4.4% to compositional changes in age from 2001-2006.

The decomposition results from 2006-2011 revealed an absolute decrease of 0.5 per 100,000 population and 3.5 per 100,000 population in Canada and the United States respectively (Table 4-5). While both differences in age-group specific rate and changes in age composition/distribution contributed to the decline in Foreign-born TB incidence rate in the

two countries, the majority of the decline observed in Canada (80.1%) and the United States (66.7%) was attributed to differences in age-group specific rates. However, in comparing the contribution of changes in age composition/structure to the overall decline in rate between the two countries, the United States had a higher (33.3%) decline attributed to changes in age distribution/structure when compared to Canada (19.9%).

As a whole, the pattern for a 10-year period (2001-2011) showed that the decline in Foreign-born TB incidence rate in Canada was largely due to changes/difference in age-group specific rate whereas in the United States, both changes in age composition/structure and age-group specific rate contributed more to the decline of Foreign-born TB rates (Table 4-6).

4.3.3. *Tuberculosis in Canada and the United States: the impact of shifts in Indigenous population by age and age-specific rates from 2006-2011*

The 320 and 303 cases of TB in Indigenous populations TB observed in Canada in 2006 and 2011 resulted in estimated crude incidence rates of 27.3 per 100,000 population and 21.6 per 100,000 population respectively, which equates a decrease of 5.7 per 100,000 population (Table 4-7). Of this absolute decrease in rate observed between 2006 and 2011, a difference in age- group specific rate accounted for 105.7% of the decline and -5.7% to compositional changes in age. The pattern of contribution observed in the United States was consistent with that observed in Canada. Thus, the decomposition results from 2006-2011 revealed an absolute decrease of 1.7 per 100,000 population in the United States. Of this, a difference in age-group specific rate contributed 104.3% to the decline in the crude rate and -4.3% to compositional changes in age.

4.3.4. *Combined Percent of Contribution of Foreign Born and Indigenous Population Additive Components, 2006-2011*

The total sum of contributions of changes in age composition and age specific TB rate from 2006 and 2011 FB and IND populations were used to estimate the additive components in Table 4-8. Results of the decomposition analysis from 2006-2011 (Table 4-8) demonstrate that in the United States, 66% of the decline in the overall crude rate of TB was due to changes in Foreign-born (age-specific TB rate distribution and age composition together) and 34% of the decline was attributable to changes in Indigenous populations (age-specific TB rate distribution and age distribution). In contrast, in Canada during the same interval, only 9.5% of the decline in the crude rate of TB was attributable to changes in Foreign-born (age-specific TB rate distribution and age distribution) whereas 90.5% of the decline was due to changes in Indigenous populations (age-specific TB rate distribution and age-distribution).

Table 4-4: Decomposition of an overall contribution of TB incidence rate in Foreign-born populations in Canada and the United States due to changes in age composition/structure and age group specific rate, 2001-2006

Canada

	2001			2006			Contribution	
Age/years	Cases	Population Estimate[d]	Rate[a]	Cases	Population Estimate[d]	Rate[a]	Age Composition Difference	Specific Rate Difference
Under 15	20	316825	6.3	23	345705	6.7	0.015	-0.022
15-24	115	470335	24.5	163	549255	29.7	-0.067	-0.455
25-44	411	1812050	22.7	377	1975895	19.1	0.276	1.173
45-64	221	1820995	12.1	215	2100805	10.2	-0.059	0.640
65+	295	1028280	28.7	264	1215285	21.7	-0.194	1.348
Total	1062	5448485	19.4	1042	6186945	16.8	[b]**-0.029(-1.1%)**	[c]**2.684 (101.1%)**

United States

	2001			2006			Contribution	
Age/years	Cases	Population Estimates[f]	Rate[a]	Cases	Population Estimates[f]	Rate[a]	Age Composition Difference	Specific Rate Difference
Under 15	273	2152000	12.7	203	2151586	9.4	0.113	0.206
15-24	1180	4506000	26.2	1107	4459490	24.8	0.577	0.183
25-44	3402	14195000	24.0	3266	16374741	19.9	0.202	1.811
45-64	1880	7701000	24.4	1968	10182185	19.3	-0.648	1.310
65+	1298	3257000	39.9	1300	4301395	30.2	-0.435	1.053
Total	8033	31811000	25.3	7844	37469397	20.9	[b] **-0.191 (-4.4%)**	[c] **4.563(104.4%)**

a-Estimated Foreign-born TB case rate per 100, 000 population

b-Negative value/proportion indicates an increased in the contribution to TB rate

c-Positive value/proportion indicates a decline to the contribution of TB rates

d- Denominators for estimating rates were obtained from Statistics Canada

f- Denominators for estimating rates were obtained from United States Census Bureau and American Community Survey

Table 4-5: Decomposition of an overall contribution of TB incidence rate in Foreign-born populations in Canada and the United States due to changes in age composition/structure and age group specific rate, 2006-2011

Canada	2006			2011			Contribution	
Age/years	Cases	Population Estimate[d]	Rate[a]	Cases	Population Estimate[d]	Rate[a]	Age Composition Difference	Specific Rate Difference
Under 15	23	345705	6.7	21	376915	5.6	0.002	0.061
15-24	163	549255	29.7	141	568215	24.8	0.133	0.422
25-44	377	1975895	19.1	418	2103250	19.9	0.174	-0.003
45-64	215	2100805	10.2	254	2368000	10.7	-0.103	0.002
65+	264	1215285	21.7	271	359385	19.9	-0.087	-0.003
Total	1042	6186945	16.8	1105	5775765	16.3	**[b] 0.119 (19.9%)**	**[c]0.479 (80.1%)**

United States	2006			2011			Contribution	
Age/years	Cases	Population Estimates[f]	Rate[a]	Cases	Population Estimates[f]	Rate[a]	Age Composition Difference	Specific Rate Difference
Under 15	203	2151586	9.4	122	1780881	6.9	0.083	0.131
15-24	1107	4459490	24.8	717	4211197	17.0	0.152	0.900
25-44	3266	16374741	19.9	2524	16690753	15.1	-0.104	2.111
45-64	1968	10182185	19.3	1829	12492484	14.6	-1.013	1.418
65+	1300	4301395	30.2	1371	2506259	54.7	2.049	-2.221
Total	7844	37469397	20.9	6563	37681574	17.4	**[b]1.167 (33.3%)**	**[c] 2.339 (66.7%)**

a-Estimated Foreign-born TB case rate per 100, 000 population

b, c-Positive value/proportion indicates a decline to the contribution of TB rates

d- Denominators for estimating rates were obtained from Statistics Canada

f- Denominators for estimating rates were obtained from United States Census Bureau and American Community Survey

Table 4-6: Decomposition of an overall contribution of TB incidence rate in Foreign-born populations in Canada and the United States due to changes in age composition/structure and age group specific rate, 2001-2011

Canada	2001			2011			Contribution	
Age/years	Cases	Population Estimate[d]	Rate[a]	Cases	Population Estimate[d]	Rate[a]	Age Composition Difference	Specific Rate Difference
Under 15	20	316825	6.3	21	376915	5.6	0.015	0.039
15-24	115	470335	24.5	141	568215	24.8	0.060	-0.025
25-44	411	1812050	22.7	418	2103250	19.9	0.472	0.900
45-64	221	1820995	12.1	254	2368000	10.7	-0.173	0.479
65+	295	1028280	28.7	271	359385	19.9	-0.289	1.713
Total	1062	5448485	19.4	1105	5775765	16.3	[b] **0.085 (2.7%)**	[c] **3.106 (97.3%)**

United States	2001			2011			Contribution	
Age/years	Cases	Population Estimates[f]	Rate[a]	Cases	Population Estimates[f]	Rate[a]	Age Composition Difference	Specific Rate Difference
Under 15	273	2152000	12.7	122	1780881	6.9	0.199	0.333
15-24	1180	4506000	26.2	717	4211197	17.0	0.646	1.166
25-44	3402	14195000	24.0	2524	16690753	15.1	0.064	3.956
45-64	1880	7701000	24.4	1829	12492484	14.6	-1.744	2.810
65+	1298	3257000	39.9	1371	2506259	54.7	1.697	-1.249
Total	8033	31811000	25.3	6563	37681574	17.4	[b] **0.862 (10.9%)**	[c] **7.016 (89.1%)**

a-Estimated Foreign-born TB case rate per 100, 000 population

b, c-Positive value/proportion indicates a decline to the contribution of TB rates

d- Denominators for estimating rates were obtained from Statistics Canada

f- Denominators for estimating rates were obtained from United States Census Bureau and American Community Survey

Table 4-7: Decomposition of an overall contribution of TB incidence rate in Indigenous populations in Canada and the United States due to changes in age composition/structure and age group specific rate, 2006-2011

Canada	2006			2011			Contribution	
Age/years	Cases	Population Estimate[d]	Rate[a]	Cases	Population Estimate[d]	Rate[a]	Age Composition Difference	Specific Rate Difference
Under 15	62	348900	17.8	38	392105	9.7	0.241	2.339
15-24	71	212010	33.5	59	254515	23.2	-0.026	1.867
25-44	103	331035	31.1	97	367145	26.4	0.579	1.279
45-64	57	224380	25.4	82	304235	26.9	-0.677	-0.306
65+	27	56460	47.8	27	82685	32.7	-0.438	0.809
Total	320	1172785	27.3	303	1400685	21.6	[b] **-0.321(-5.7%)**	[c] **5.988(105.7%)**

United States	2006			2011			Contribution	
Age/years	Cases	Population Estimates[f]	Rate[a]	Cases	Population Estimates[f]	Rate[a]	Age Composition Difference	Specific Rate Difference
Under 15	9	548994	1.6	12	605084	1.9	-0.010	-0.070
15-24	11	417483	2.6	8	439927	1.8	0.008	0.139
25-44	54	684393	7.9	26	694446	3.7	0.094	1.179
45-64	63	544997	11.6	54	609383	8.8	-0.095	0.634
65+	28	173564	16.1	32	198166	16.1	-0.073	0.000
Total	165	2369431	6.9	132	2547006	5.2	[b]**-0.076(-4.3%)**	[c] **1.882(104.3%)**

a-Estimated Indigenous TB case rate per 100, 000 population

b, c-Positive value/proportion indicates a decline to the contribution of TB rates

d- Denominators for estimating rates were obtained from Statistics Canada

f- Denominators for estimating rates were obtained from United States Census Bureau and American Community Survey

Table 4-8: Combined Percent Contribution of Decline in TB Rates by Foreign-born and Indigenous Populations, 2006-2011

	Contribution	
Population	Canada	United States
Foreign-born	0.598 (9.5%)	3.506 (66%)
Indigenous	5.6665 (90.5%)	1.805 (34%)
Total	6.2645 (100%)	5.311 (100%)

4.3.5. Trends in HIV/TB Coinfection from 1997-2012

The numbers show that the highest percentage of cases with HIV+/TB coinfection recorded between 1997 and 2012 occurred in 1997 with 29% and 23% of cases reported in Canada and the US respectively (Figure 4-2). While the percentage of cases with HIV+/TB coinfection declined rapidly in Canada from 29% in 1997 to 11% in 1999, within the same time interval, cases with HIV+/TB coinfection in the US only declined by 3%.

Unexpectedly, HIV+/TB coinfection cases in Canada sharply increased to 22% in 2002 after a rapid decline of 11% experienced in 1999. However, within the same time interval, the US continued to experience a steady downward trend in HIV+/TB coinfection case percent. In 2004, the percentage of cases with HIV+/TB coinfection in Canada finally dropped to 11% and exhibited a continuously increasing and decreasing trend for the remaining eight years. In the US on the other hand, the percentage of cases with HIV+/TB coinfection have continuously declined since 2002. As a whole, over the fifteen years (1997-2012) investigated, descriptively there appear to be a more rapid decline in percentage of cases with HIV+/TB coinfection in the US than in Canada. However, a firm/explicit conclusion as to the extent to which HIV+/TB contributed to differences in rates between the two countries cannot be made by this thesis.

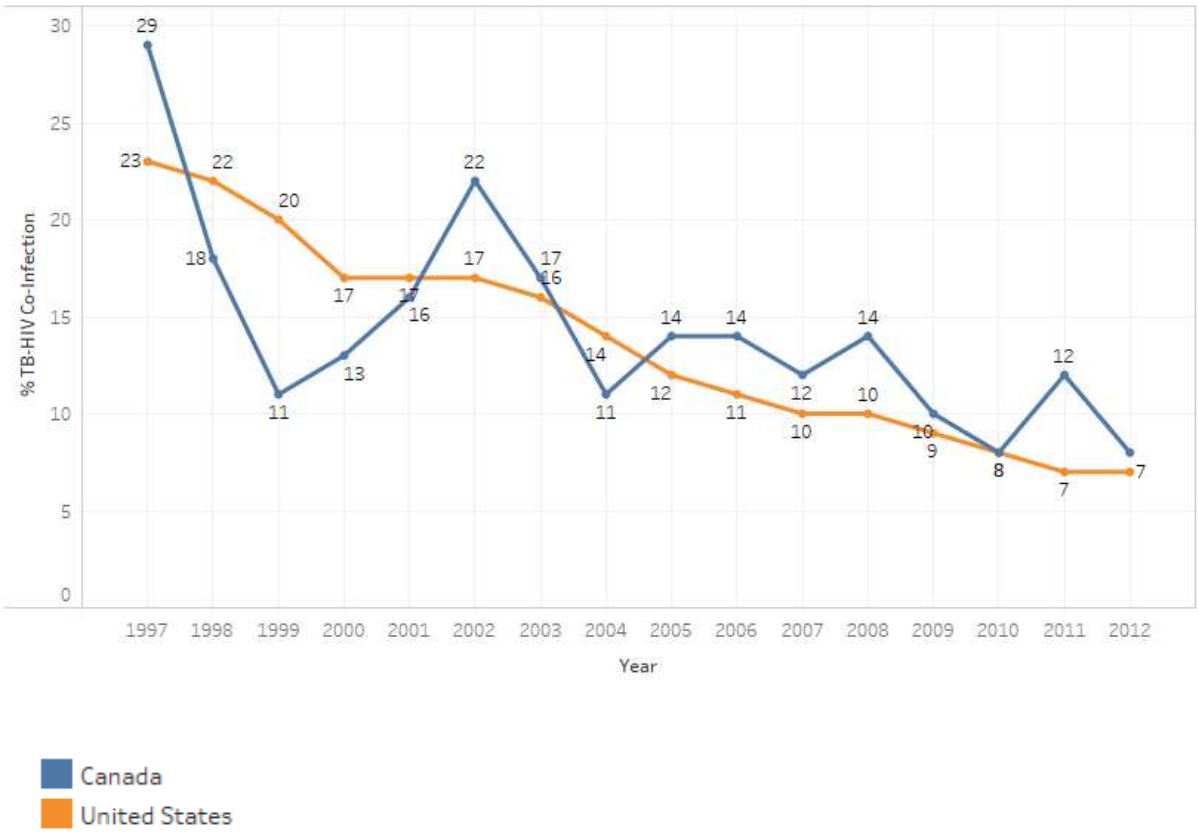

Figure 4-2: A plot of proportion of HIV+/TB co-Infection between Canada and US, 1997-2012

4.4. DISCUSSION

The overall assessment of immigration patterns on TB incidence rates on both countries shows that over the ten (2001-2011) and five (2006-2011) years investigated, both Foreign-born and Indigenous TB incidence rates declined more rapidly in the US than in Canada with the major driver of the decline attributed to changes in Foreign-born and Indigenous population age-specific TB rates. As a whole, between 2006 and 2011, both changes in Foreign-born and Indigenous population contributed much to the decline in TB crude rates in the US whereas in Canada only changes in Indigenous population largely contributed to the decline in TB crude rates. In addition, over the same interval, the percentage of cases with HIV+/TB coinfection experienced an abrupt decline in the US compared Canada.

The difference observed in Foreign-born TB rates between US and Canada may be due to the differing proportion in the number of Foreign-born individuals, especially those high incidence countries, who enter both countries (Saraiya & Binkin, 2000; Greenwood & Warriner, 2011). For instance, a study of fifty Metropolitan areas in the US found that a "*10% increase in the number of high-incidence immigrants results in a 2.87% increase in TB among the Foreign-born population*" (Greenwood & Warriner, 2011). In addition, as the Foreign-born population in the US increased from 601,708 in 1986 (Arnold, 1989) to 19.8 million in 1990 (Center for Immigration Studies, 1994), TB cases in Foreign-born individuals between 1986-1993 also increased from 21.6 percent (4925 cases) in 1986 to 29.6 percent (7346 cases) in 1993 (McKenna et al., 1995). This has also been evident in Canada as an increase in the number of immigrants has shown a corresponding increase in the proportion of TB cases (Roth et al.,

2012). For instance, while the migrant population in Canada increased by 2% between 1981-1986, from 1986-1991 the population of Foreign-born only grew by 11% (Badets & Chui, 2004). This increase in Foreign-born populations probably led to an increase in the Foreign-born TB incidence during that period. Saraiya et al. found that between 1985-1995, Canada's Foreign-born TB cases grew from 859 cases (40%) in 1985 to 1116 cases representing 58% in 1995 (Saraiya & Binkin, 2000).

The pattern of immigration is considered as another source of population change (Edmonston, 2016). Gushulak et al. noted that traditional countries in Western and Central Europe predominantly known to supply immigrants to Canada and the US has changed since 1960 (Gushulak & Macpherson, 2004). Reports show that countries supplying immigrants (Europe/Canada: 84%) (Radford & Budiman, 2018) that migrated most to the US in 1960 shifted from 1965-2015 to Latin America (51%) and Asia (25%) (Pew Research Center, 2015) whereas immigrants known to predominately migrate to Canada in the early years shifted to Asia (including the Middle East) (Stat Can 150 years of Immigration in Can, 2016). Data available in US from 2010-2014 shows that individuals born in Mexico accounted for the highest Foreign-born TB cases (CDC, 2015) whereas in Canada data from 1990-1998 and 2012-2014 revealed that immigrants from China, the Philippines and Vietnam recorded the highest Foreign-born TB cases (PHAC TB in Can 2012, Njoo & Long, 2000; PHAC TB in Can 2013, 2017; PHAC TB in Can 2014, 2016). In comparing country of origin TB rates between Mexico and Asian countries including China, Philippines and Vietnam, Cash-Goldwasser et al. noted that TB rates in Mexico were lower than those observed in Asia, Africa and Eastern Europe (Brunette, 2018), suggesting

that the differences in Foreign-born TB rate between Canada and US reflect the differences in rates observed in the respective country of origin.

Furthermore, differences in Foreign-born TB rate between the two countries could be in part attributed to a shift in immigrant population age structure and age-specific rate. The present time period (2001-2011) investigated in this study revealed that out of the absolute decrease in rate of 3.1 per 100, 000 population observed in Canada between 2001 and 2011, differences in age-specific rate accounted for 97.3% of the decline in Foreign-born TB rate and 2.7% attributed to changes in age structure. Conversely, in the same time period (2001-2011) investigated in the US, of the absolute decrease of 7.9 per 100,000 population observed, differences in age-specific rate accounted 89.1% of the decline in rate and 10.9% to changes in age composition. Despite the significant contribution of differences in age-specific rate to Foreign-born TB rates in both countries, changes in age structure contributed more to the decline in the US than in Canada.

The present study suggests that changes in age-specific rates are a strong driver for rate difference between the two populations, which is consistent with a previously published study (Oh, 2014). Oh's study on two Foreign-born populations in 2000 and 2010 in California found that differences in age-specific rate contributed 126.8% of the decline in the Foreign-born TB rate whereas age decomposition accounted for -26.8% (Oh, 2014). That study and other evidence from the literature support the concept that to achieve further declines in Foreign-born TB incidence, special attention should be given to age-specific TB interventions (Edelman et al., 2014).

Despite 16% growth in Indigenous populations observed in the US (Ogunwole, 2002; Norris et al., 2012) compared to 7.8% in Canada (Stat Can Aboriginal Peoples in Canada, 2003; Stat Canada, 2013), TB rates declined more rapidly in the US Indigenous population (-6.3%) compared to that in Canada (-4.5%). The difference observed in both could not be explained by changes in age composition and age-specific TB rates as both experienced a similar effect. The results found in this work for Indigenous populations in both countries is consistent with other published studies (Patel et al., 2017; Bloss et al., 2011). Between 2003 and 2008, the greatest decline of -27.4% was observed in Indigenous populations compared to other racial/ethnic groups in the US (Bloss et al., 2011). In contrast, between 2007 and 2008, the Indigenous population contributed to the slow decline in TB cases in the Canadian prairie provinces (Patel et al., 2017).

As well, differing proportions of HIV/TB coinfection may have contributed to the differences in rates between the two countries. Although this thesis cannot make a firm/explicit conclusion as to the extent to which HIV+/TB contributed to differences in rates between the two countries due to data limitations (CDC, 2017; PHAC TB in Can 2008, 2012). The data on HIV/TB coinfection and national TB incidence rates from the US report (CDC, 2017) appear to show that since 2003 the pattern of TB rate of decline in the US was consistent with the proportion of decline in HIV/TB coinfection. Whereas in Canada (Gallant et al., 2014), the pattern appears to show that the TB rate of decline was only consistent with the proportion of decline in HIV/TB coinfection between 2003 and 2008. This confirms the statement by Luetkemeyer that "*the decline in HIV-related TB in the United States and other industrialized countries has paralleled an overall decline in TB cases*" (Luetkemeyer, 2013).

However, the divergence in the trend between TB rate and proportion of HIV/TB coinfection in Canada from 2009 onwards suggests that differences in rates between the two countries may not be solely dependent on HIV/TB coinfection but on multiple other factors as well. Thus, since the total number of TB and HIV co-epidemic cases in a setting highly depends on the extent of overlap existing between persons living with HIV and TB infected individuals (Raviglione et al., 1996), and "*narrow overlap between TB infected and HIV-infected population segments*" exists in well-resourced settings/countries (Baussano et al., 2006), HIV infection has been found to predominantly offer a moderate contribution to the total TB cases in these settings (Baussano et al., 2006; Rose et al., 2002). For instance, Raviglione et al. noted that while rates of both HIV and TB infections are high among young adults in resourced limited countries, a corresponding elevated risk of TB and HIV co-epidemics occurs (Raviglione et al., 1996). However, in well-resourced countries, the adults/elderly accounts for a large number of TB-infected cases, hence their risk of infection as it relates to HIV is lower (Raviglione et al., 1996).

Strength and Limitation

The present study used a decomposition method which robustly allowed for the difference in rates to be separated into two additive components (Preston et al., 2001; Oh, 2014). In addition, the direct standardization method used enabled the study to adjust for confounding by age on the rate difference. Despite the earlier highlighted strengths, the study also had some limitations. Thus, due to limited data available in Canada, with the exception of 2001, 2006 and 2011, the present study could not compare Foreign-born and Indigenous TB rates in the two countries for other years. Also, a further challenge was encountered as the present study could not explicitly compare and elucidate the impact of HIV/TB coinfection on the national TB rate

due to data limitations in both countries. Despite several efforts put in place including national HIV/AIDS and TB surveillance systems to have comprehensive national data on HIV/TB coinfection in Canada, underreporting still poses "*serious limitations on the interpretation of HIV/TB coinfection in Canada*"(Halverson et al., 2014) . Phypers noted that data "*reported to the Canadian TB Reporting System (CTBRS) are inadequate to measure the HIV positivity among TB cases*" (Phypers, 2007). Additionally, there is evidence that reporting of HIV status of individuals diagnosed with active TB in 2008 "*varied across the provinces and territories ranging from 0% to 96%*" (PHAC TB in Can 2008, 2012). Additionally, end users of US HIV/TB co-infection data have been encouraged to interpret their findings with caution as data on reported HIV/TB in the US national reports "*are not representative of all TB patients with HIV infection*" (CDC, 2017). Also, data reporting differences hindered the present study from comparing the top 5 or 10 countries of FB TB cases in Canada and the US. Thus, national TB reports in Canada captures FB TB cases only by STOP-TB partnership TB epidemiological regions which is similar to the WHO regions except for the division of Africa and Europe WHO regions into two separate groups (PHAC, 2015), whereas US reports capture both WHO regions and the top 30 countries (CDC, 2017). Hence the study comparison focused on only WHO regions.

4.5. CONCLUSIONS

As a whole, after adjusting for the effect of age, Foreign-born and Indigenous TB over the period investigated declined more in the US than in Canada. From this analysis, within Foreign-born and Indigenous population, age is a strong driver for TB rates overall as evidenced by age-specific rates differences. In addition, the pattern of decline of the proportion of cases with

HIV/TB co-infection in both countries corresponded to the pattern of decline in Foreign-born TB rate in the two countries. Ultimately, to achieve further declines in Foreign-born and Indigenous TB incidence which will consequently lead to a reduction in TB burden in both countries, special attention should be given to age-specific TB interventions.

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The past and present assessment of TB incidence trends in both countries from ***Chapter 2*** through to ***Chapter 4***, necessitated a follow up ***Chapter 5*** to look ahead to the next nineteen years in terms of the TB rate in the two countries. This follow up chapter is to add to the ***Chapter 4*** to project how further changes in the two populations especially due to immigration could impact TB rates in the two countries and whether meeting the WHO TB pre-elimination phase is possible. ***In Chapter 5*** I conducted literature review, cleaned the data, performed the statistical analysis, interpretation of results and wrote up the Chapter.

Chapter 5. **Forecast Analysis of Tuberculosis (TB) rates in Canada and the United States from 2017-2035**

5.1. INTRODUCTION

Despite similar TB surveillance programs (Mor et al., 2008) in Canada and the US, TB rates over the past four decades have declined more rapidly in the US compared to Canada (Essien et al., 2018). Although both countries have not achieved the proposed targets set for the reduction of TB incidence (Phypers et al., 2007; CDC, 1989), some progress has been made. In Canada, from 2006-2015, a targeted TB rate of 3.6 cases per 100,000 population by 2015 was set (Phypers et al., 2007); however, the 2015 rate was 4.6 cases per 100, 000 population (Gallant et al., 2017). Likewise, in 1987, the US targeted a 38% reduction in TB rate from 9.3 per 100,000 in 1987 to 3.5 per 100,000 in 2000 (CDC, 1989); however, the reported rate in 2000 was 5.8 per 100,000 (CDC, 2017). Despite these unmet targets, WHO has proposed a pre-elimination target of < 1 TB case per 100,000 population in low-incidence countries, including Canada and the United States, by 2035 (WHO, 2014). However, no forecast analysis has been performed to monitor whether Canada and the United States will be able to achieve this WHO pre-elimination.

The percent of Foreign-born, Indigenous and Non-Indigenous populations are changing in both countries (Norris et al., 2012; Grieco et al., 2012; Malone et al., 2003; Ogunwole, 2002; US Census, 2001; US Census, 2010; Stat Can, 2013; Stat Can, 2007; Stat Can, 2017) and the TB incidence, especially in Canada, continues to experience moderate yearly increase/decrease from 2006 to 2015 (Vachon et al., 2018; Public Health Agency of Canada, 2008) compared to a US decline of nearly 30.5% (CDC, 2017). Therefore, establishing accurate and useful prediction

models which take into account the complexities and the time lags with this disease could be helpful to best target prevention and management programs, as well monitor the set targets. This study aimed to forecast and then compare year-over-year TB rates between Canada and US from 2017-2035.

5.2 METHODS

5.2.1. *Incidence data*

The national TB incidence rate data in Canada and the US for 1975 to 2016 were obtained from the Public Health Agency of Canada (PHAC) (Gallant et al., 2017; Vachon et al., 2018; Gallant et al., 2014) and the Centers of Disease Control (CDC) US reports (CDC, 2017). Additionally, all available data on the rates of TB for Foreign-born (FB), Indigenous (IND) and Non-Indigenous (NIND) persons (1993-2016) were also obtained for both countries (CDC, 2017; Public Health Agency of Canada, 2015; Public Health Agency of Canada, 2013; Public Health Agency of Canada, 2007). Both the TB rates in Canada and the US from 1975-2016 were estimated from new and previously reported cases (Gallant et al., 2017; Vachon et al., 2018; Gallant et al., 2014; Armstrong & Miramontes, 2014) and expressed as a rate per 100,000 population.

5.2.2. *Modeling Approach*

An autoregressive integrated moving average (ARIMA) model (Newbold, 1983) was applied to forecast TB incidence rates in both Canada and the US from 2017-2035. ARIMA models are widely used (Wang et al., 2016) and have been reported to out-perform other statistical models for forecasting (Wang et al., 2018). The Box-Jenkins method (Oppenheim, 1978) was adopted to fit the ARIMA model for this study by following four steps which take into account the

stationarity of the data (mean, variance and covariance of the time series are constant over time) (Gupta & Udrea, 2013; Stadnytska, 2010), model selection, parameter estimation and model diagnostics (Jere & Moyo, 2016).

In the first step for building the ARIMA model, a graph of the raw annual TB incidence rate was plotted against respective years to determine conditions that typically characterize non-stationarity (time series do not have constant mean, variance and covariance) (Pfaff, 2008) including deterministic trends (i.e. increasing or decreasing trend) of the raw rate and whether the variation changes with the level of the time series (Xie et al., 2015). Once any of these were established, a log transformation (log 10) (Lütkepohl & Xu, 2012) and one stage differencing (d) were applied to stabilize the variance, detrend the data (Kugiumtzis & Tsimpiris, 2010) and create stationarity (Moosazadeh et al., 2014). Additionally, the Augmented Dickey-Fuller test for unit root (Stadnytska, 2010) was performed to inferentially evaluate the stationarity of the data. Thus, if the series had no unit root (alternative hypothesis) it was considered stationary; otherwise, it was considered non-stationary (Libanio, 2005). No unit roots "*implies that the series has a finite variance which does not depend on time*" (Libanio, 2005). To determine the possible lag values for autoregressive (p) and the moving average (q), the graphs of the autocorrelation function (ACF) and partial autocorrelation function (PACF) were depicted and examined for possible values of p and q. For model selection and estimation, several manually built models were considered based on several guess values of p and q. The model with the smallest Akaike's Information Criterion (AIC) was selected as the best model for the study forecast. The goodness of the model fit was assessed through the residual correlation and the normality diagnostic plots. All analyses were performed in SAS 9.4.

To assess how the independent effect of changes in FB, FBP, IND and NIND TB may have on the national forecasted TB in both countries, a vector autoregression (VAR) model was applied (Zivot & Wang, 2006; Lütkepohl, 1999). The VAR model is described as a "*natural extension of the univariate autoregressive model to dynamic multivariate time series*" (Zivot & Wang, 2006). VAR models simply incorporate "*each variable as a linear function of its own past values, the past values of all other variables being considered, and a serially uncorrelated error term*" (Stock & Watson, 2001).

The VAR model has been applied to several diseases including dengue hemorrhagic fever (Mahdiana et al., 2017) and pertussis (Zhang et al., 2016). Both estimated proportions of FB populations in both countries and national TB rates (NTBR), FBR, INDR and NIND TB rates from 1993-2016 were used. The national TB rate was the response variable of interest in this thesis. Thus, to estimate and understand how FBR, INDR and NIND rates together project national TB rates from 2017 to 2035 in both countries. To begin the VAR process, the Johansen co-integration test was applied to test for co-integration among all variables (NTBR, FB, IND and NIND TB rates) (Aljandali and Tatahi, 2018). Co-integration is defined as the *"existence of a stationary linear combination of nonstationary time series"* (Jones and Nesmith, 2007). Once its established that these variables were not co-integrated (Johansen test $p>0.05$), the unrestricted VAR model was used (Aljandali and Tatahi, 2018). Since stationarity is critical assumption to be met before the VAR model can proceed, the Augmented Dickey Fuller (ADF) test was applied to the first differenced log10 -transformed NTBR, FB, IND and NIND TB rates to test for stationarity (Aljandali and Tatahi, 2018). Once the stationarity is satisfied, the selection of the appropriate lag length for the model was carried out. For optimal lag length selection, the AIC criteria was

used where the lag length with the smallest AIC was considered optimal for used in the model (Liew, 2004). Once the optimal lag length is selected, the unrestricted VAR model was then fitted to the data. The Lagrange Multiplier (LM) test for residual autocorrelation (Bose et al., 2017) and the Jarque-Bera test for normality were performed to assess the goodness of the VAR models (Caceres, 2006). A p-value greater than 0.05 for both tests was an indication that the models were good enough for the study forecast. Analysis on FB population proportions was carried out in a similar manner for both countries.

To further understand the extent to which different possible percent decrease or increase scenarios in FB, IND and NIND during the forecasted period might have on the overall TB rates, a *"conditional forecast or scenario analysis"* of the VAR was performed in Eviews software (Eviews, 2014). Eviews allows for scenario to be specified for VAR conditional forecast (Eviews, 2014). These scenarios were based on computed average annual percent change (AAPC) of actual TB rates from 2010-2016 in both countries (Table 5-1). The Joinpoint approach discussed in chapter 2, section 2.7 of the thesis was used to compute the AAPC.

Table 5-1: Summary of proportions actual TB rate used for the "conditional forecast"

	United States **AAPC 2010-2016**	Canada **AAPC 2010-2016**
FBR	-4.0%	-4.8%
INDR	-3.1%	3.0%
NINDR	-6.2%	-3.0%

The AAPC provides the opportunity for the "*average annual percent changes over a period of multiple years*" to be described by a single number (NIH, 2018). In addition, the Canadian 2011-2016 FB population increase of 5% (Stat Can, 2016) was set as the highest percent change for all

FB population change scenarios. All VAR model results were depicted graphically for both countries.

5.3. RESULTS

Figure 5-1 depicts an initial plot of the raw TB incidence rates in Canada and in the US for the years 1975-2016. The overall plot showed a decreasing trend during the time period but with an increasing peak in the US between 1985 and 1992. The time plot also showed variation in the trends indicating lack of stationarity in the data. Stationarity was achieved through the application of log transformation, single difference for both the Canadian and the US data (Figure 5-2). Stationarity was supported by the Dickey Fuller unit root test which yielded p-values of $p<0.001$ for Canada and $p=0.037$ for the US.

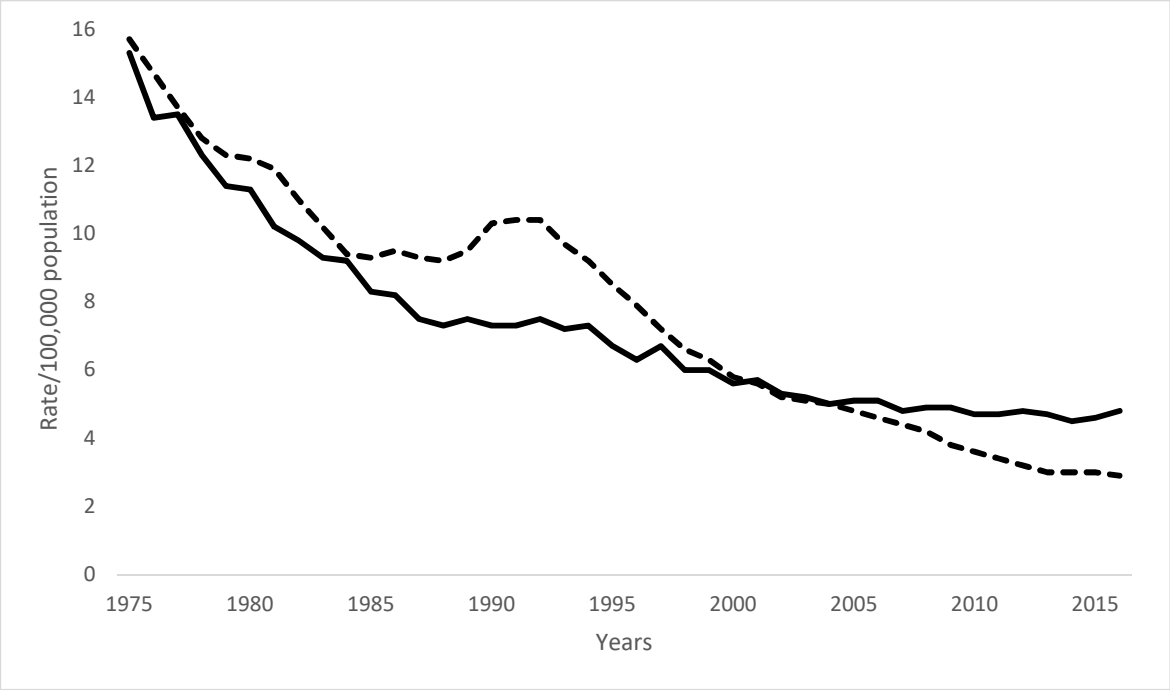

Figure 5-1: Tuberculosis incidence rates/100,000 in Canada and the United States from 1975-2016. Canada, solid black line; the United States interrupted black line

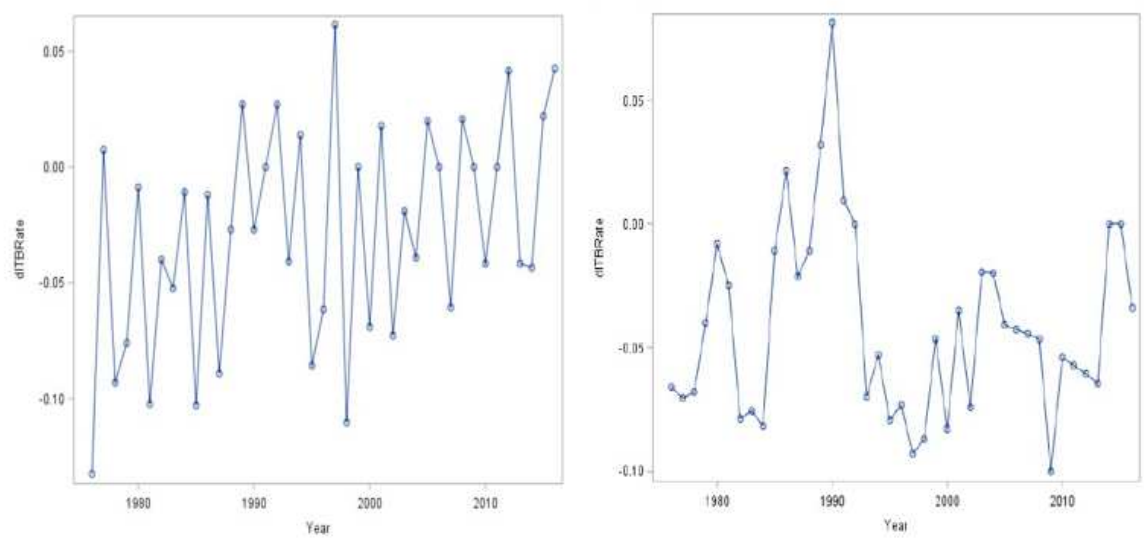

Figure 5-2: Difference of the log transformed data

5.3.1. *Autoregressive integrated moving average (ARIMA) model*

Although both plot showed no obvious trend, the first difference for Canada's log rate showed more short term fluctuations compared to the US differenced log rates. To determine the best ARIMA model for the study forecast, a preliminary analysis of the stationary data was performed. The auto correlation (ACF) and partial auto correlation (PACF) plots produced by the initial analysis were examined for the appropriateness of potential models to be considered. From Figure 5-3 and 5-4, possible lag choices for both ACF and PACF including q=0, 1 and 2 and p=0, 1, 2, and 3 were selected to fit several different ARIMA models.

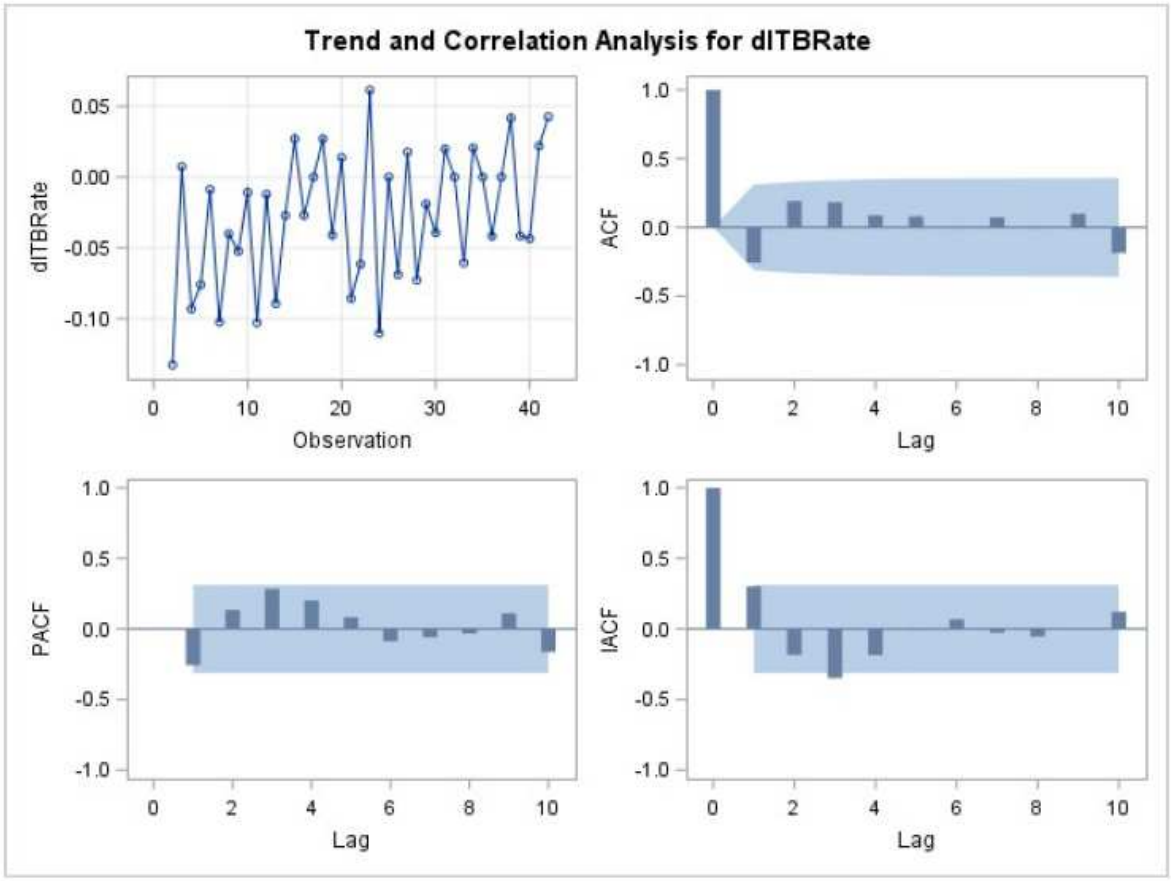

Figure 5-3: Auto Correlation and Partial Auto Correlation plots for Canada

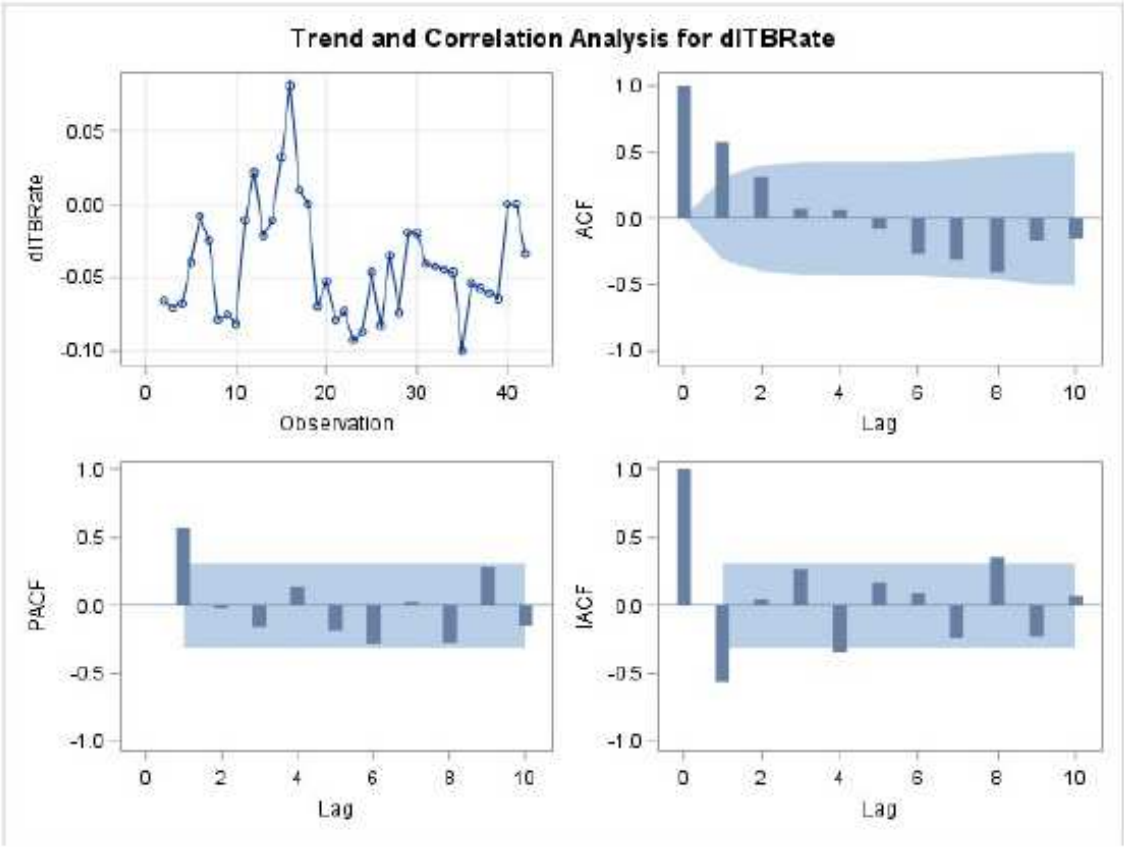

Figure 5-4: Auto Correlation and Partial Auto Correlation plots for United States

Based on the smallest AIC's, -134.0 and -164.7, the Autoregressive Integrated Moving Average ARIMA model of (3, 1, 0) for Canada where 3 is the order of the autoregressive part, 1 is the degree of first differencing and 0 is the order of the moving-average and ARIMA (1, 1, 0) for the US were selected as the best prediction model for the study forecast (Table 5-2). The white noise probability plots (Figures 5-5 and 5-6) show that the model residuals supported the white noise process.

Table 5-2: Model Selection and Parameter Estimate

	Canada				
Models	**Coefficients**		**SE**	**SE**	**AIC**
	AR	MA	AR	MA	
ARIMA (1, 1, 0)	AR (1) -0.272		0.159		-133.1
ARIMA (0,1, 1)		MA (1) 0.187		0.165	-132.2
ARIMA (1, 1, 1)	AR (1) -0.423	MA (1) -0.159	0.540	0.596	-131.3
ARIMA (2, 1, 1)	AR (1) -1.217 AR (2) -0.271	MA (1) -1.000	0.233 0.164	0.197	-131.1
ARIMA (2, 1, 0)	AR (1) -0.230 AR (2) 0.135		0.169 0.172		-131.8
ARIMA (3, 1, 0)	AR (1) -0.273 AR (2) 0.225 AR (3) 0.331		0.164 0.172 0.167		-134.0
	United States				
ARIMA (1, 1, 0)	AR (1) 0.578		0.131		-164.7
ARIMA (0,1, 1)		MA (1) -0.433		0.145	-159.7
ARIMA (1, 1, 1)	AR (1) 0.564	MA (1) -0.021	0.236	0.286	-162.7
ARIMA (2, 1, 1)	AR (1) -0.032 AR (2) 0.398	MA (1) -0.575	1.341 0.729	1.389	-160.9
ARIMA (2, 1, 0)	AR (1) 0.588		0.163		-162.7

	AR (2) -0.019		0.165		
ARIMA (3, 1, 0)	AR (1) 0.586 AR (2) 0.071 AR (3) -0.160		0.163 0.190 0.166		-161.7

SE-Standard Error

In addition, the PACF plots (Figure 5-5 and 5-6) show that, with exception of lag 8 of the US plot, the remaining partial autocorrelation lie within the standard error bends. The histogram plots (Figures 5-7 and 5-8) also show that the distribution of the residuals is centered on zero with the bell shape clearly depicted; an indication of a normally distributed residual. The quantile-quantile (Q-Q) plot also shows that quite a number of points pass through the straight. This suggests that the theoretical quantiles are almost identical to the actual quantiles of the residuals. Hence, the normality assumption of the residuals was met (Figures 5-7 and 5-8). Therefore, the chosen models do not violate any of the model's assumptions and were deemed good enough for the study forecast.

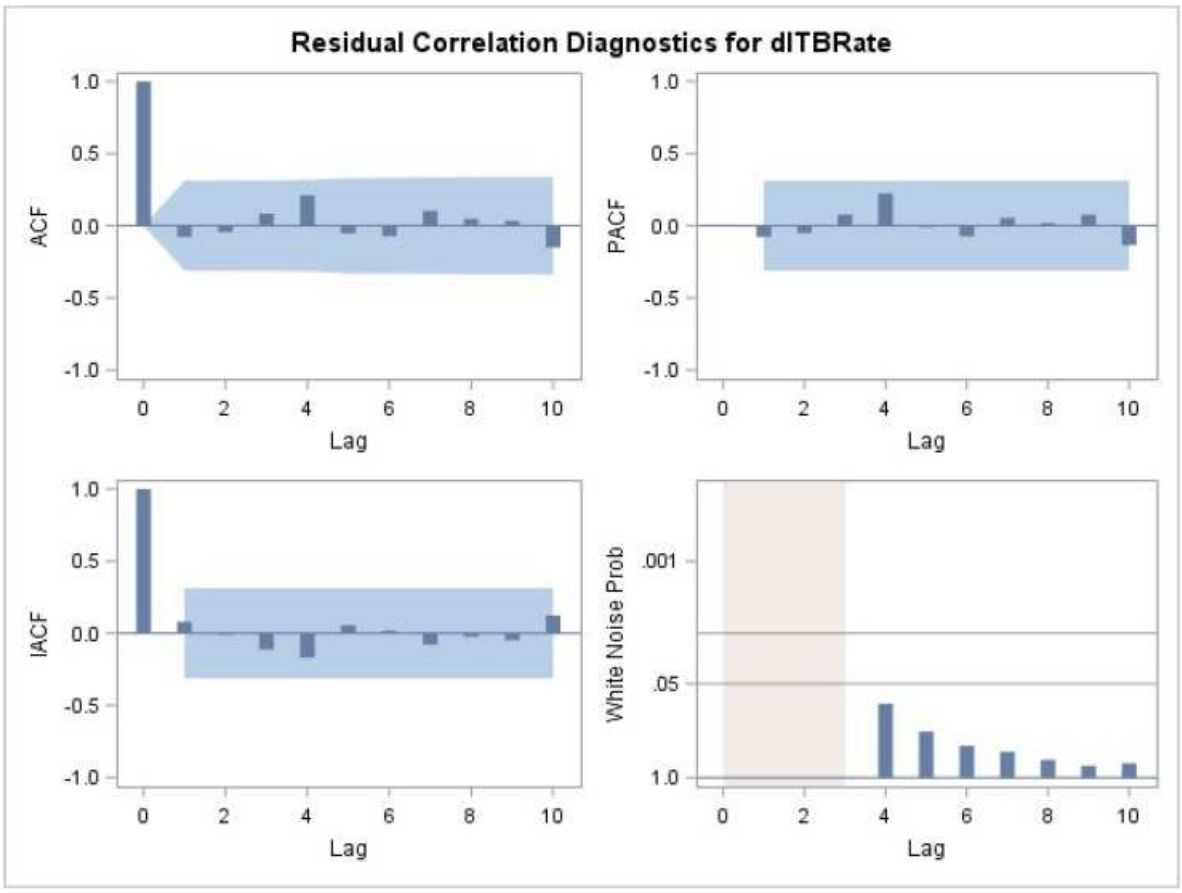

Figure 5-5: Plots of model residuals of annual TB rates recorded in Canada from 1975-2016

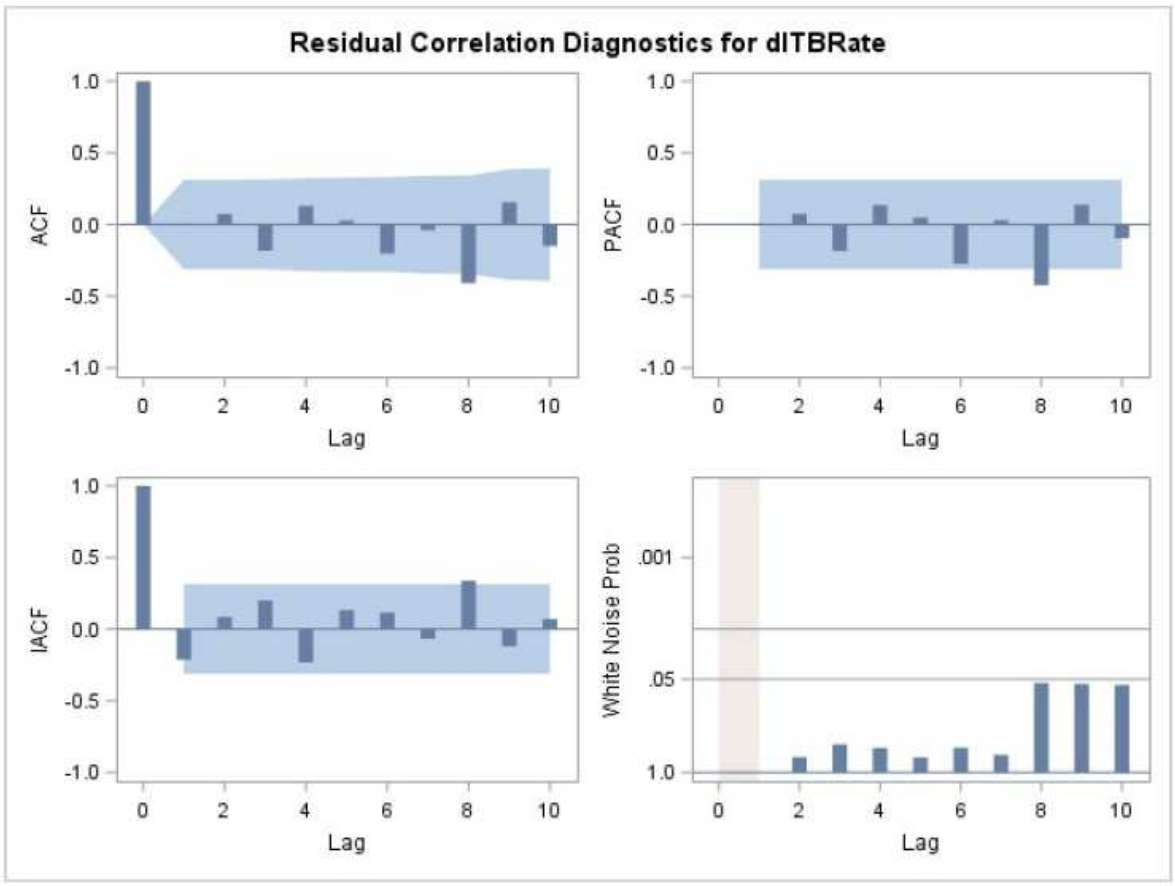

Figure 5-6: Plots of model residuals of annual TB rates recorded in the United States from 1975-2016

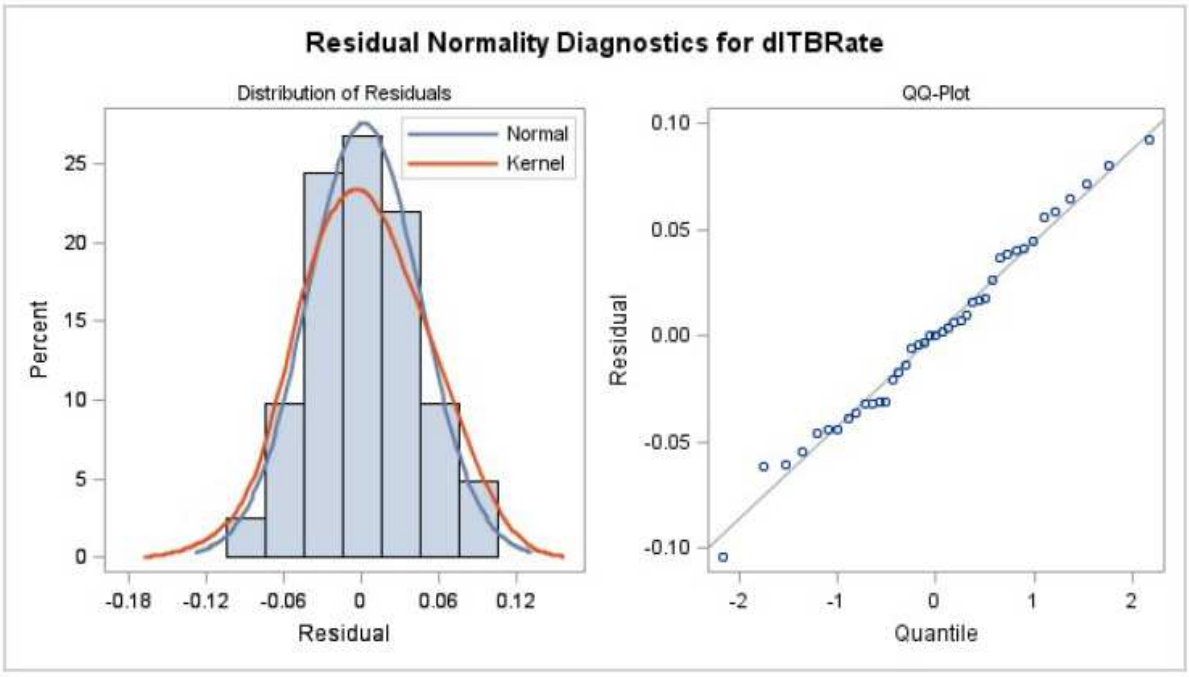

Figure 5-7: Plots for normality test for model residuals for Canada TB model

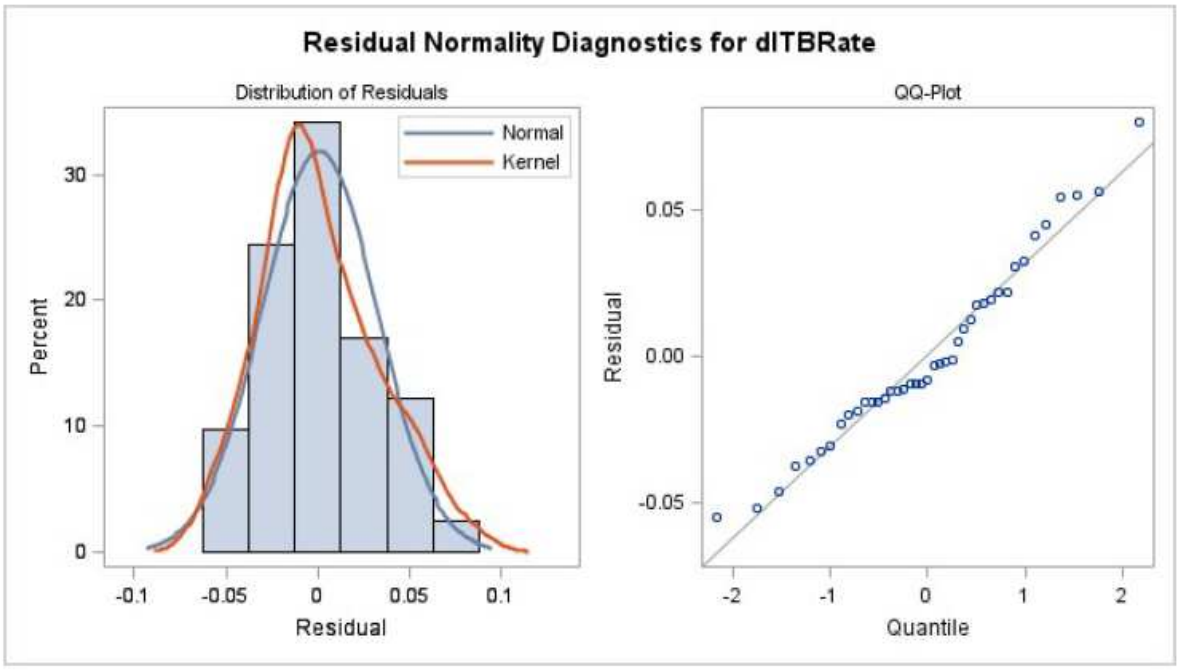

Figure 5-8: Plots for normality test for model residuals for the United State TB model

Table 5-3 summarizes the 2017 to 2035 forecast rate and 95% prediction intervals for TB incidence in Canada and the US. Based on predictions from our ARIMA models, the forecasted TB incidence rate for 2017 were approximately 4.6 and 2.8 per 100,000 population in Canada and the US respectively. These rates are expected to decline to approximately 2.2 and 1.3 per 100,000 population by 2035.

Table 5-3: ARIMA model forecasts for Canada and the United States, 2017-2035

	Canada			United States		
Year	Point Forecast	Lo 95	Hi 95	Point Forecast	Lo 95	Hi 95
2017	4.76	4.69	4.82	2.86	2.80	2.92
2018	4.72	4.57	4.85	2.78	2.69	2.96
2019	4.67	4.45	4.88	2.67	2.57	2.99
2020	4.60	4.33	4.91	2.53	2.46	3.02
2021	4.51	4.09	4.98	2.46	2.35	3.01
2022	4.39	4.01	5.02	2.42	2.12	2.87
2023	4.25	3.92	4.99	2.37	2.08	2.91
2024	4.07	3.86	4.75	2.34	1.96	3.03
2025	4.87	4.01	5.03	2.29	1.84	3.07
2026	3.64	3.57	4.91	2.25	1.72	3.11
2027	3.38	3.21	5.07	2.21	1.60	2.98
2028	3.09	3.04	4.98	2.17	1.48	3.02
2029	2.97	2.68	5.06	2.12	1.44	2.90
2030	2.93	2.43	5.10	1.87	1.40	2.93
2031	2.75	2.18	5.12	1.70	1.36	2.81
2032	2.61	2.06	5.17	1.65	1.24	2.85
2033	2.39	2.01	5.31	1.57	1.12	2.89
2034	2.30	1.89	5.07	1.48	0.96	2.92
2035	2.22	1.77	5.11	1.27	0.84	2.69

Prediction interval is the interval in which the future TB rates are expected to lie
Lo 95-lower limit of the 95% prediction interval

Hi 95-Upper limit of the 95% prediction interval

5.4. Vector Autoregression (VAR)

5.4.1 Results for changes in FB, IND and NIND TB rates

No co-integration was found among FB, IND, NIND and NTBR (p=0.1654) in Canada. The Augmented Dickey-Fuller test revealed that the differenced log transformed TB rates of all three groups (FB: p=0.001; IND and NIND: p<0.001) in Canada met the stationarity assumption. Similarly, there was an absence of co-integration in the US variables (p=0.6774). The differenced log transformed United States FB, IND and NIND TB rates also passed the stability test with respective p-values of p=0.03, p=0.01 and p<0.001. The optimal lag length was found at lag 2 based on the smallest AIC values.

Of the four-dimensional outcomes, the differenced log transformed national TB rate outcome for Canada conditional on the past realization values of NTBR, FBR, INDR and NINDR was found to be

$$\widehat{NTBRate_t} = 1.56 + 8.18 * FBR_{t-1} - 0.06 * NTBR_{t-1} - 3.07 * INDR_{t-1} + 0.29 * NINDR_{t-1} - 1.11 * FBR_{t-2} + 0.65 * NTBR_{t-2} - 3.99 * INDR_{t-2} + 0.12 * NINDR_{t-2}.$$

Equation 5-1 ……(Model 1)

Where t=time (in years), FBR= Foreign-born TB rate, INDR=Indigenous TB rate, NINDR = Non-Indigenous TB rate, NTBRate=national TB rate and t-1, t-2 = represent the past values/observations. The LM test for the VAR model 1 revealed p-values of p=0.22 at lag 1 and p=0.24 at lag 2. Since the null hypothesis of the LM test which states that there is no serial correlation at lags agrees with the obtained p-values, the model's assumption of no serial

correlation was met. The p-value of 0.85 obtained from the Jarque-Bera multivariate normality test also supported the assumption of normally distributed residuals.

The forecast result from the VAR model (Figure 5-9) which accounted for FB, IND and NIND TB rates shows that the 2016 rate (4.8 per 100, 000 pop) in Canada was expected to decline to 3.38 per 100,000 population by 2035. The “what if” analysis generated from the model revealed that a 4.8% decrease in FB rate each year from 2017 reduced the overall TB rate more in Canada when compared to the same percent decrease in IND rate. Similarly, a 3% increase in FB rate for each forecasted year increased the overall Canadian TB rate compared to same increase in IND TB rate (Figure 5-9). As a whole, the increase or decrease in FB rate contributes significantly to the overall decrease/increase in Canadian TB rate compared to the contribution of both IND and NIND rates (Figure 5-10).

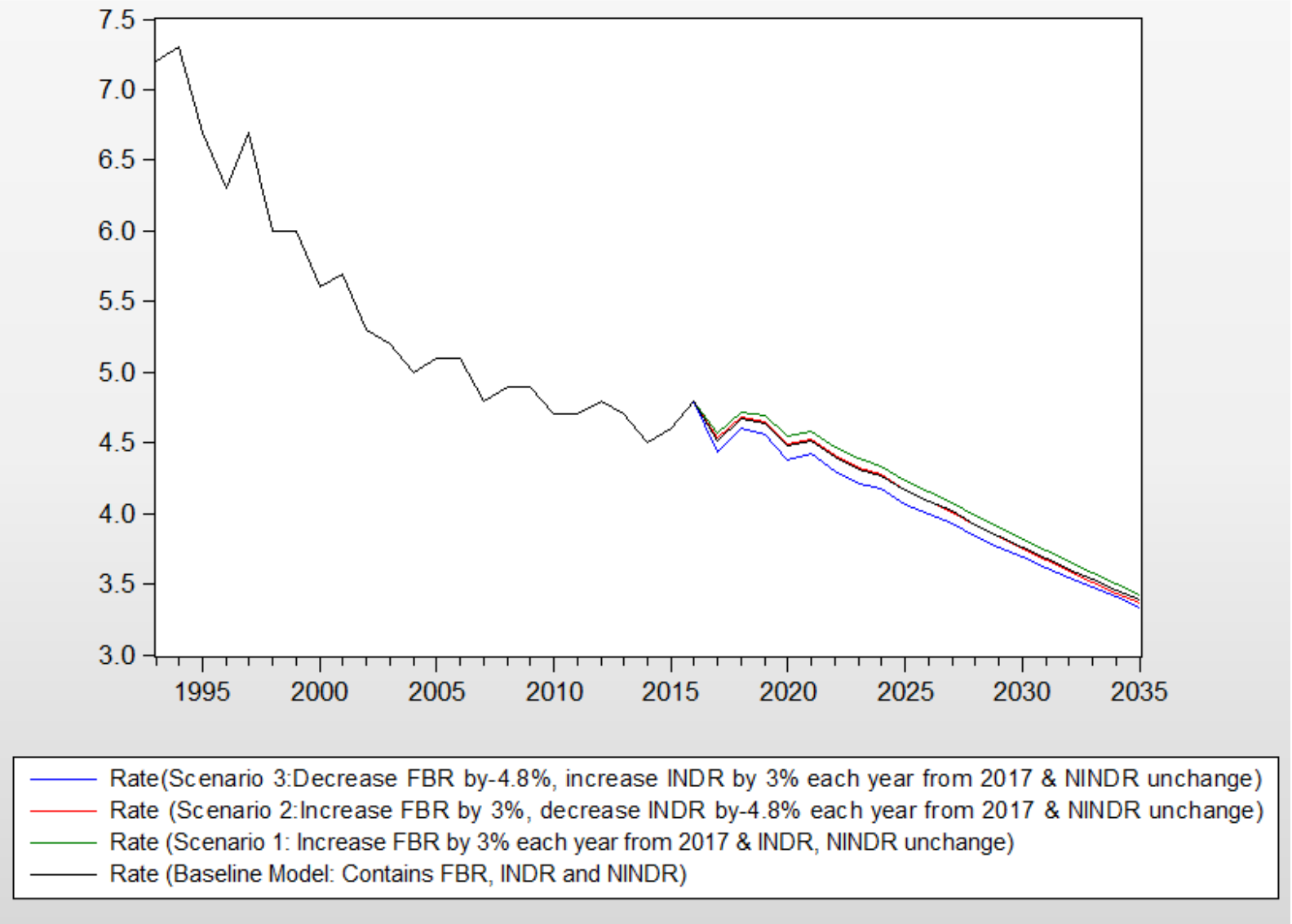

Figure 5-9: Conditional forecast for possible future TB rates in Canada

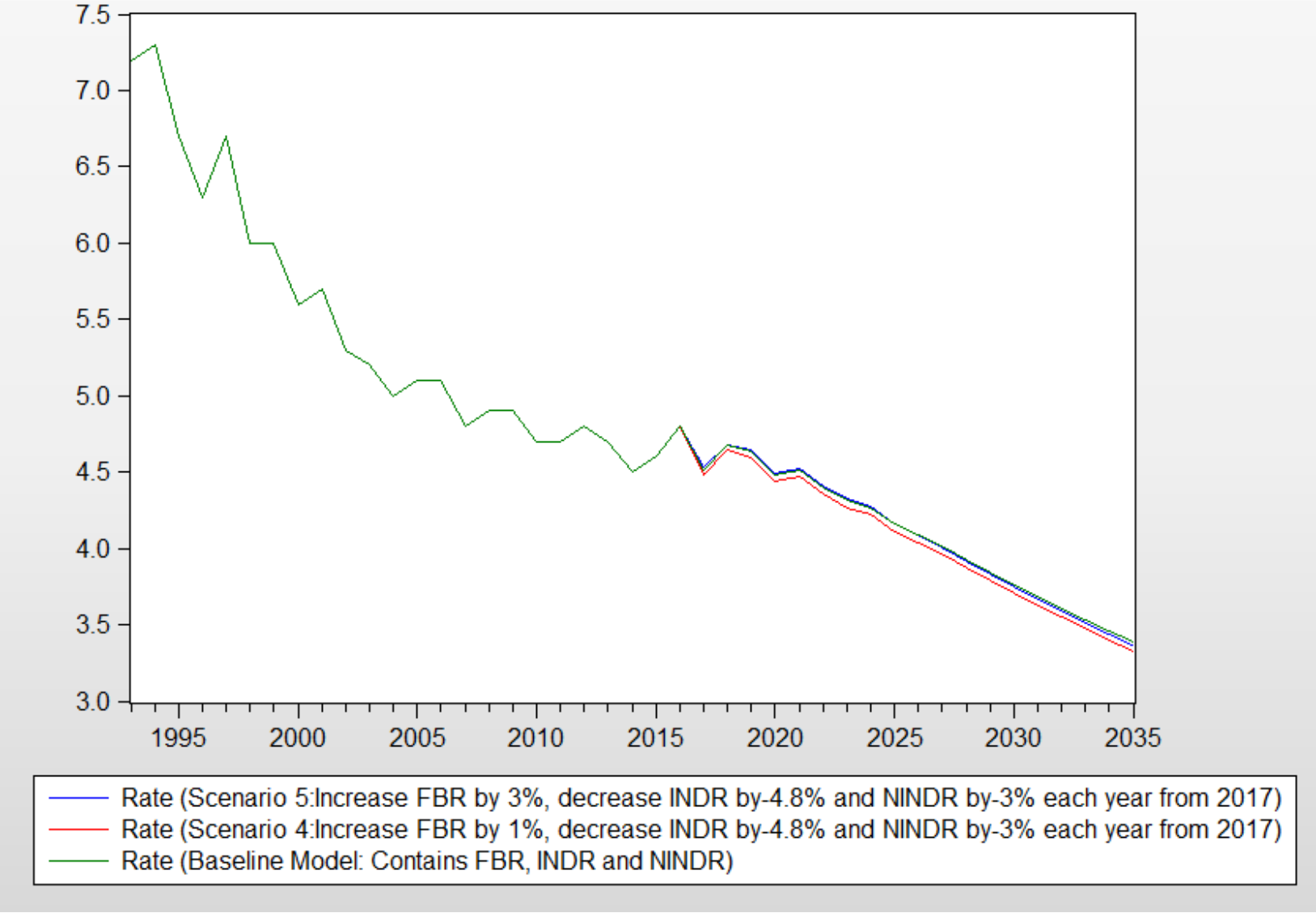

Figure 5-10: Conditional forecast for possible future TB rates in Canada

Of the four-dimensional outcomes, the differenced log transformed national TB rate outcome for US conditional on the past values of NTBR, FBR, INDR and NINDR was

$$\widehat{NTBRate_t} = -2.45 + 0.74 * FBR_{t-1} + 0.95 * NTBR_{t-1} - 0.01 * INDR_{t-1} + 0.35 * NINDR_{t-1} + 0.22 * FBR_{t-2} - 0.10 * NTBR_{t-2} + 0.14 * INDR_{t-2} - 0.05 * NINDR_{t-2}.$$

Equation 5-2 …… (Model 2)

The model diagnostics based on the LM test showed that at both lag 1 and lag 2 with p-values p=0.61 and p=0.70 satisfied the no serial correlation assumption. Also the normality of residuals assumption was met as the Jarque-Bera revealed a p-value of 0.93.

After accounting for FB, IND and NIND rates, the VAR model showed that by 2035 the US national rate was expected to decline to 1.31 per 100,000 population (Figure 5-11).

The conditional forecast also revealed no difference between the baseline rate and the scenario where the forecasted FB rate was decreased by -3.1% and IND by -4.0%. In contrast, a difference concerning a decline in the overall TB rate in the US was observed between the baseline and the scenario where the forecasted FB rate was rather decreased by -4.0% and IND by -3.1%. Also, there was no differences in the overall rate in scenarios where either IND or NIND rates decrease by -4.0% and FB rate decrease by -3.1% (Figure 5-11). Figure 5-12 also revealed that wherever there was a higher percent decrease or increase in FB rate, a significant difference concerning a decrease or an increase in the overall TB rate was observed in the US. For instance, a decrease in FB rate by -6.2% each year starting 2017 decreased the overall TB rate in the United States compared to same decrease in NIND rate. As a whole, decreasing FB

rate by -6.2%, IND by -3.1% and NIND by -4.0% resulted in the lowest rate of 1.19 per 100,000 population by 2035.

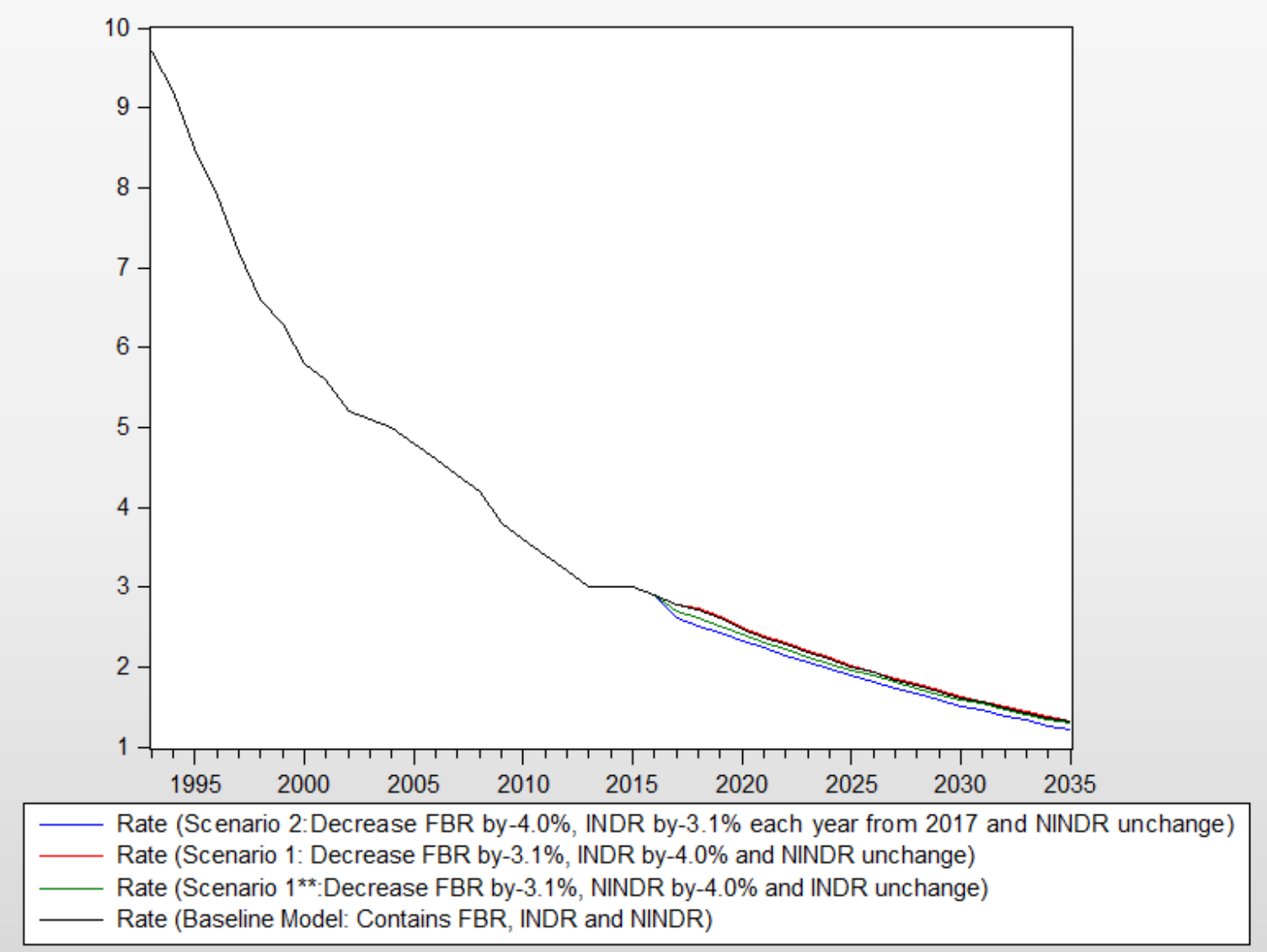

Figure 5-11: Conditional forecast for possible future TB rates in the United States

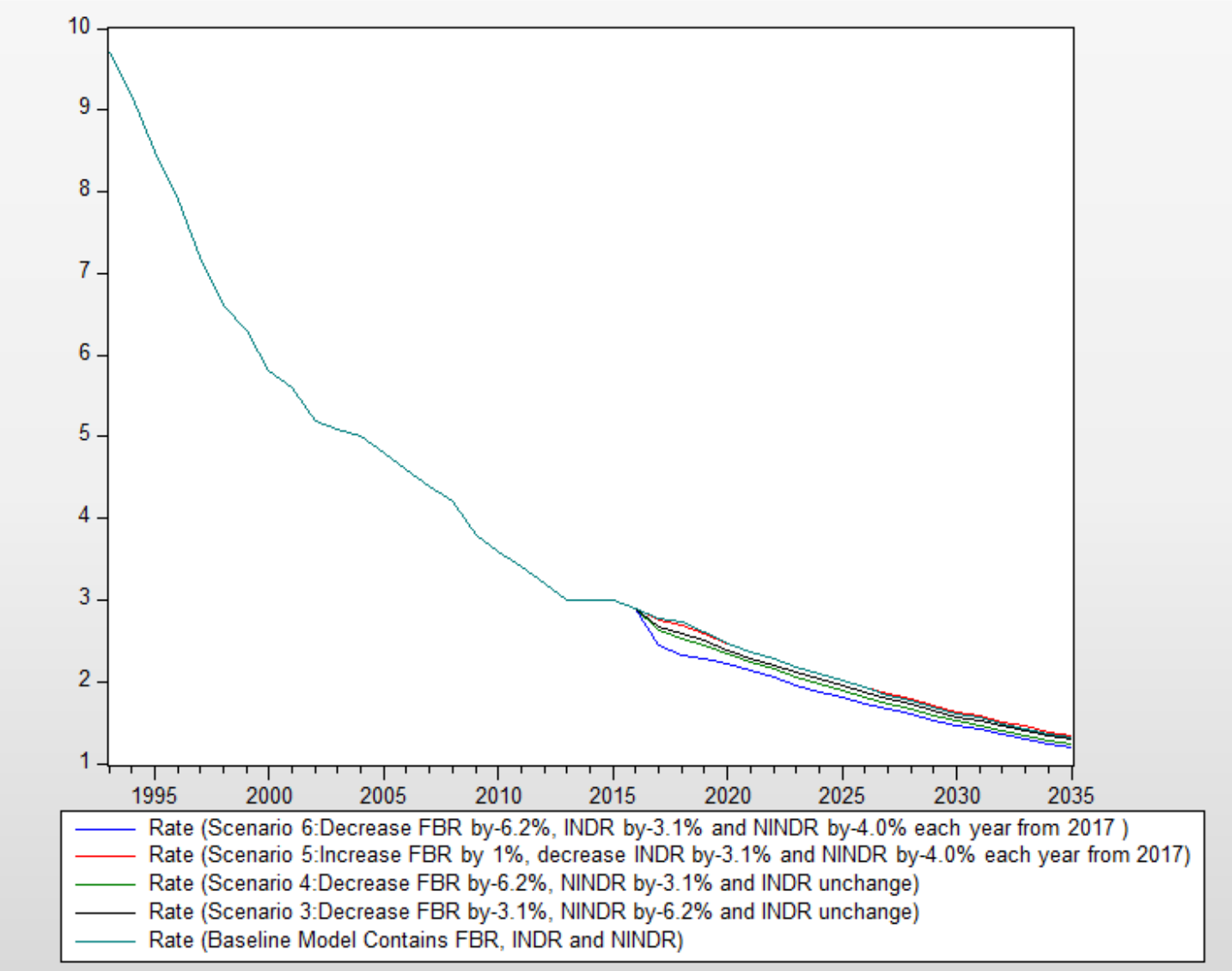

Figure 5-12: Conditional forecast for possible future TB rates in the United States

5.4.2. Results for changes in FB population proportions

In assessing the effect of changes in FB populations in both Canada and the US, the Johansen's test found no co integration in the study variables (FBP, FBR, INDR and NINDR) with p=0.3928 and 0.4476 respectively. The ADF test revealed that the differenced log transformed variables in Canada satisfied the stationarity assumption (FBP: p=0.0298; FBR: p=0.0087; NID and NIND: P<0.001). Of the five-dimensional outcomes, the differenced log transformed national TB rate outcome for Canada conditional on the past realization values of NTBR, FBP, FBR, INDR and NINDR was found to be

$$\widehat{NTBRate}_t = -0.029 - 0.052 * FBP_{t-1} + 0.089 * FBR_{t-1} + 0.093 * NTBR_{t-1} - 0.042 * IND_{t-1} - 0.003 * NIND_{t-1} + 0.069 * FBP_{t-2} - 0.191 * FBR_{t-2} + 0.042 * NTBR_{t-2} + 0.048 * IND_{t-2} + 1.320 * NINDR_{t-2}$$

Equation 5-3 ……(Model 3)

Where FBP is the FB proportion in Canada. The assumption of no serial correlation was met as p-value for the LM test for VAR model at lag 1 was 0.28 and 0.35 at lag 2. In addition, the model's residual was found to be normally distributed based on the Jarque-Bera test (p-value =0.95). The results from the unrestricted VAR plot shows that an increase in FB population by either 3% or 5% for each forecasted year increased the overall TB rate in Canada whereas a -3% decrease in FB population resulted in overall rate decreased (Figure 5-13).

The US TB and FB population variables investigated showed no violation in the stationarity assumption as evidenced by the ADF test (PFB: p=0.0266; FBR: p=0.0113, INDR: p=0.0207 and NINDR: p=0.0229). Out of the five-dimensional outcomes, the differenced log transformed

national TB rate outcome for US conditional on the past realization values of NTBR, FBP, FBR, INDR and NINDR was

$$\widehat{NTBRate_t} = 0.176 - 10.943 * FBP_{t-1} + 0.211 * FBR_{t-1} + 0.541 * NTBR_{t-1} + 0.973 * IND_{t-1} - 0.274 * NIND_{t-1} + 10.867 FBP_{t-2} + 0.014 * FBR_{t-2} + 0.234 * NTBR_{t-2} - 0.010 * IND_{t-2} + 0.256 * NINDR_{t-2}$$

Equation 5-4 ……(Model 4)

Both the LM test at lag 1 and lag 2 satisfied the no serial correlation with p=0.49 and 0.63. Additionally, the Jarque-Bera test (p-value =0.07) for the model residuals met the normality assumption. Scenario's considered in Figure 5-14 showed that an increase or decrease in FB population in the US for each forecasted year resulted in an increase or decrease in overall US TB rate. Due to data limitations, impact of IND and NIND population changes were not considered in the analysis.

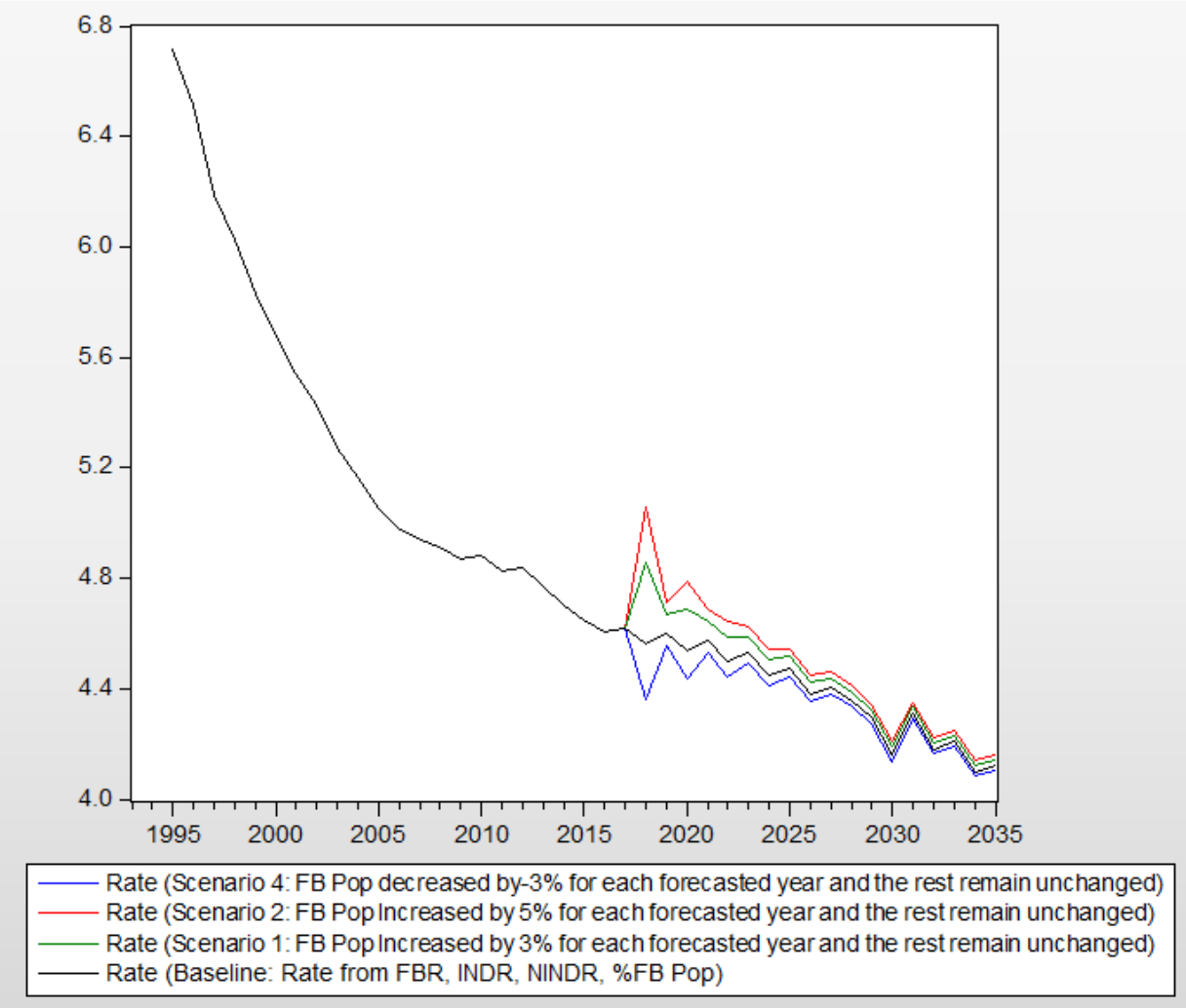

Figure 5-13: Conditional forecast of the Influence of changes of FB population in Canada

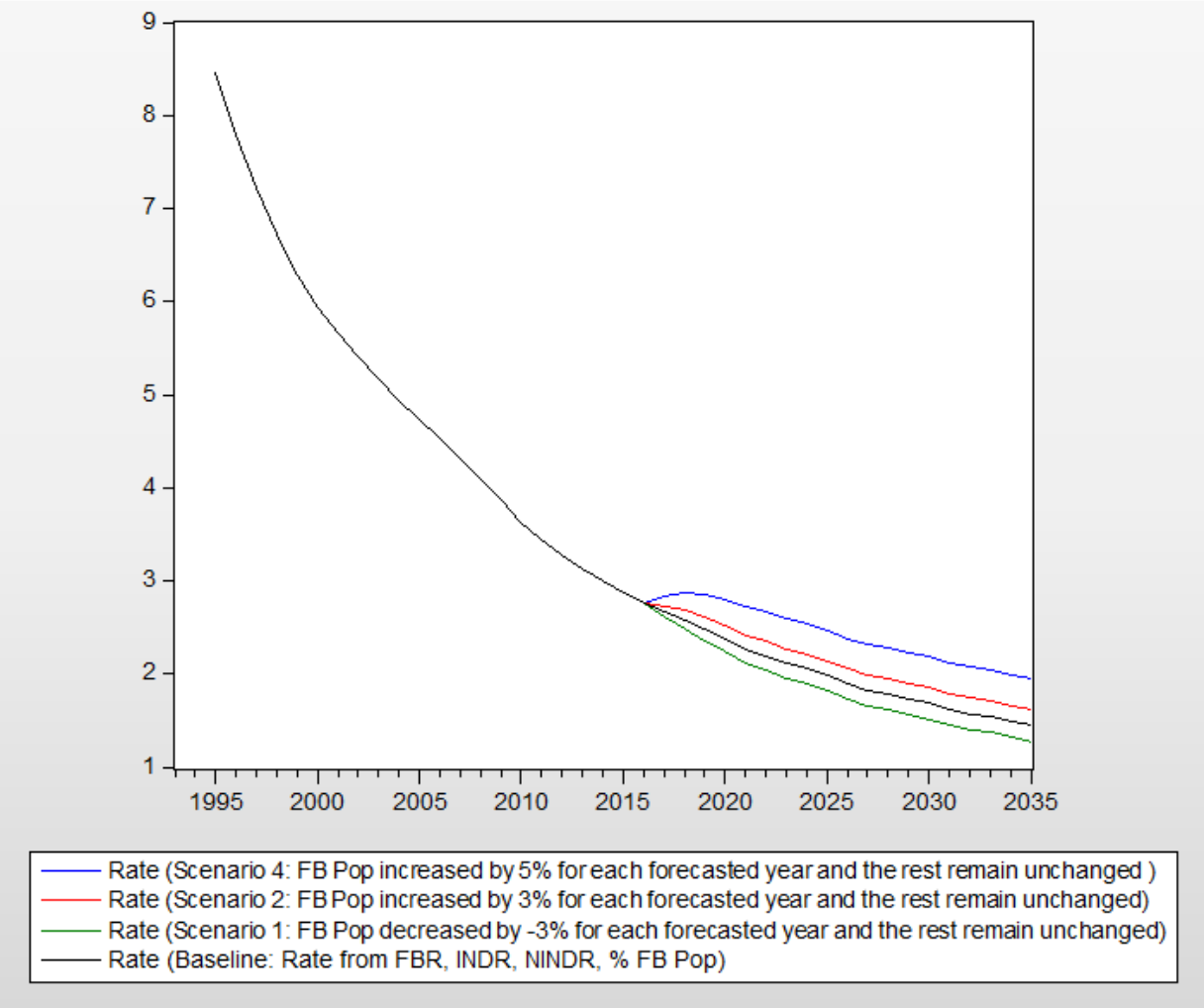

Figure 5-14: Conditional forecast of the Influence of changes of FB population in the United States

5.5. DISCUSSION

Overall, the univariate forecasted TB rate using ARIMA models showed a gradually decreasing trend from 2017 to 2035, reaching a rate of 2.2 for Canada and 1.3 for the US by 2035. The current study found the attainment of the best prediction with ARIMA (3, 1, 0) for Canada and ARIMA (1, 1, 0) for the US. After accounting for FB, IND and NIND rates via the VAR model from 1993-2016, the declining pattern of the forecasted rate from 2017 to 2035 in both countries remained unchanged. The narrow prediction interval observed in the ARIMA forecast in the present study also supported the prediction reliability of the models. From 2016 to 2035 the TB rate in Canada via the ARIMA model was predicted to be reduced by 54.1% whereas in the US rates were expected to be reduced by 56.2%. Although the WHO has projected a pre-elimination (< 1 per 100,000 population) in low TB incidence countries by 2035 (WHO, 2014), our study predictions based on the two statistical approaches revealed that achievement of that set target might be difficult in both countries. The US forecast rates in 2035 were closer to the WHO set target compared to Canada. According to WHO, a decline of -17% and -16% in rate is required annually in Canada and the US to achieve the 2035 set target.

The difference observed in the forecasted rates between the two countries could be largely attributed to FB in the US and FB and IND in Canada. All the scenarios considered in both countries revealed that the more the FB rate decreases or increases, the more the overall TB rate decreases or increases. A 3% increase in the Canadian FB rate each year from 2017 which would have resulted in a rate higher than the baseline rate was stabilized by a -4.8% decrease in IND rate for each forecasted year. This resulted in the stabilized rate being the same as the

baseline forecasted rate. A further -3% decrease in the Canadian NIND rate for each forecasted year did not change the rate stabilized by the -4.8% IND rate decrease. No significant difference was observed in the US overall rate in scenarios where either IND or NIND rate decreased by -4% and FB by -3.1%.

The declining trend of the forecasted TB rate in Canada is in line with a Canadian provincial forecast of TB incidence which projected a decline of 42% by 2030 (Klotz et al., 2013). A declining trend in TB incidence has also been forecast in New York in the US where a decline of 2- 4.4% per year from 2015 to 2025 is projected (Fojo et al., 2017). Nationally, rates in the US have also been forecasted to decline from 2010 to 2020 with rates in US-born projected to decline by 47% and 6% among Foreign-born (Woodruff et al., 2013).

The declining or increasing pattern of TB rate observed in both countries also reflect the pattern of population changes in the two countries. As FB populations increased in Canada and the US for each forecasted year, the overall TB rates in both countries also increased. Likewise, a decrease in the FB population also resulted in a decrease in overall TB rates in the two countries. Furthermore, in Canada FB TB cases increased by 3.1% from 2001-2011 (Public Health Agency of Canada, 2015; Health Canada, 2003). This in part could be due to a 5.9% increase in Canada's net immigration during this same period (Edmonston, 2016). The effect of changes in population has also been observed in other low TB incidence countries (Hanway et al., 2016; Cain et al., 2007). Hanway et al. noted that for two European countries, Norway and Sweden, 0.54% and 0.37% increases in FB populations each year from 2000 to 2013 increased each country's average annual TB notification rates by 3.85% and 2.64% respectively (Hanway et al., 2016).

Differences in rate as it relates to changes in population especially in FB populations in Canada and the US may be linked to immigration policies in the two countries (Borjas, 1993; Kaushal & Lu, 2015). After the major changes in immigration policies in 1962 and 1967 in Canada and 1965 in the US (Boyd, 1976), the Canadian policy focus changed to target immigrants with "*observable socioeconomic characteristics*" where the US change focused on "*applicant's family ties with U.S. residents or citizens*" (Borjas, 1993). Kaushal and Lu noted that as of 2006 "*Canada surpassed the US in drawing highly-educated immigrants while continuing to attract fewer low-educated immigrants*" (Kaushal & Lu, 2015). This clearly shows that the immigration policies in both countries are different and have a differential impact on the pattern of immigrants and TB incidence in both countries.

Although ARIMA models may have the limitation of being more effective for short-term forecasts (Levenbach, 2017, p.226), none of the model assumptions in the present study were violated. Moreover, the univariate ARIMA model showed consistent results as did the multivariate VAR model. In addition, the narrow prediction intervals supported the predicted reliability of rates in both countries. Several methods including dynamic models (Klotz et al., 2013; Fojo et al., 2017), Bayesian approach (Fojo et al., 2017) and segmented linear regression models (Woodruff et al., 2013) have been carried out to forecast TB rates in both Canada and the US, all pointing to a decreasing trend in rates in the two countries. This clearly shows consistency in findings among the various methods used. As a limitation, the present study could not further assess the effect of seasonal variation on the predicted rates since national monthly/quarterly data were not available. Fares, after systematically reviewing published studies and synthesizing the evidence, found seasonality to be a probable factor that might

impact TB transmission dynamics (Fares, 2011). Due to data limitations, only data on ethnicity from 1993-2016 were considered for the VAR model.

5.6. CONCLUSIONS

Based on predictions from our ARIMA and VAR models for the two low TB incidence countries Canada and the US, the results show a decreasing trend in the total TB rate in both countries from 2017-2035. The prediction suggests that achieving the 2035 target set by the WHO could be a challenge for both countries. The “conditional forecast” analysis also revealed that to achieve further rapid declines in overall TB rates in both countries, more targeted interventions especially geared towards reduction of TB incidence in Foreign-born individuals are needed. Despite the study prediction only approximating actual rates, these findings can be utilized to further optimize current TB prevention and control programs.

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Chapter 6. General Discussion and Conclusions

This thesis primarily compared the TB incidence rate in Canada and the US by assessing where differences exist in the national TB incidence trend, sought possible explanations for differences in the trends and forecasted and compared TB incidence rates between the two countries. The investigation was carried out with four objectives in four manuscript-style chapters. A summary regarding the flow of the thesis, methodological considerations and insight into the impact of changes in population and immigration pattern, and differences in immigration policies and seasonality on TB are discussed in this chapter.

6.1. The flow of the thesis

Chapter 2 is an investigation into TB incidence in Canada by revealing some negative impacts that could be encountered if different case definitions were used for a particular disease (e.g., TB) that span two time periods. In addition, this ***chapter*** also provided insight into the use of joinpoint regression to analyze periods where the same TB case definition was used in both countries. Based on the evidence presented in ***Chapter 2***, this necessitated a full-scale review into the national TB incidence trend from 1975-2015 in both countries, as presented in ***Chapter 3***. The time interval (1975-2015) was considered based on findings in ***Chapter 2*** which shows that TB incidence data before and after 1975 in the United States were not comparable. Also through findings presented in ***Chapter 2***, joinpoint regression was chosen for use in ***Chapter 3*** to analyze periods with comparable TB case definition. ***Chapter 4*** which was born out of ***Chapter 3*** carried out an in-depth investigation into probable factors identified in ***Chapter 3*** as possibly responsible for TB incidence rate differences between the two countries. These factors

were HIV+/TB co-infection, ethnicity and demographic factors such as age. After assessing both past and present data on TB incidence trends in both countries, ***Chapter 5*** was carried out to forecast and compare possible future TB incidence rates from 2017-2035 in both countries taking into account changes in the population structure over time.

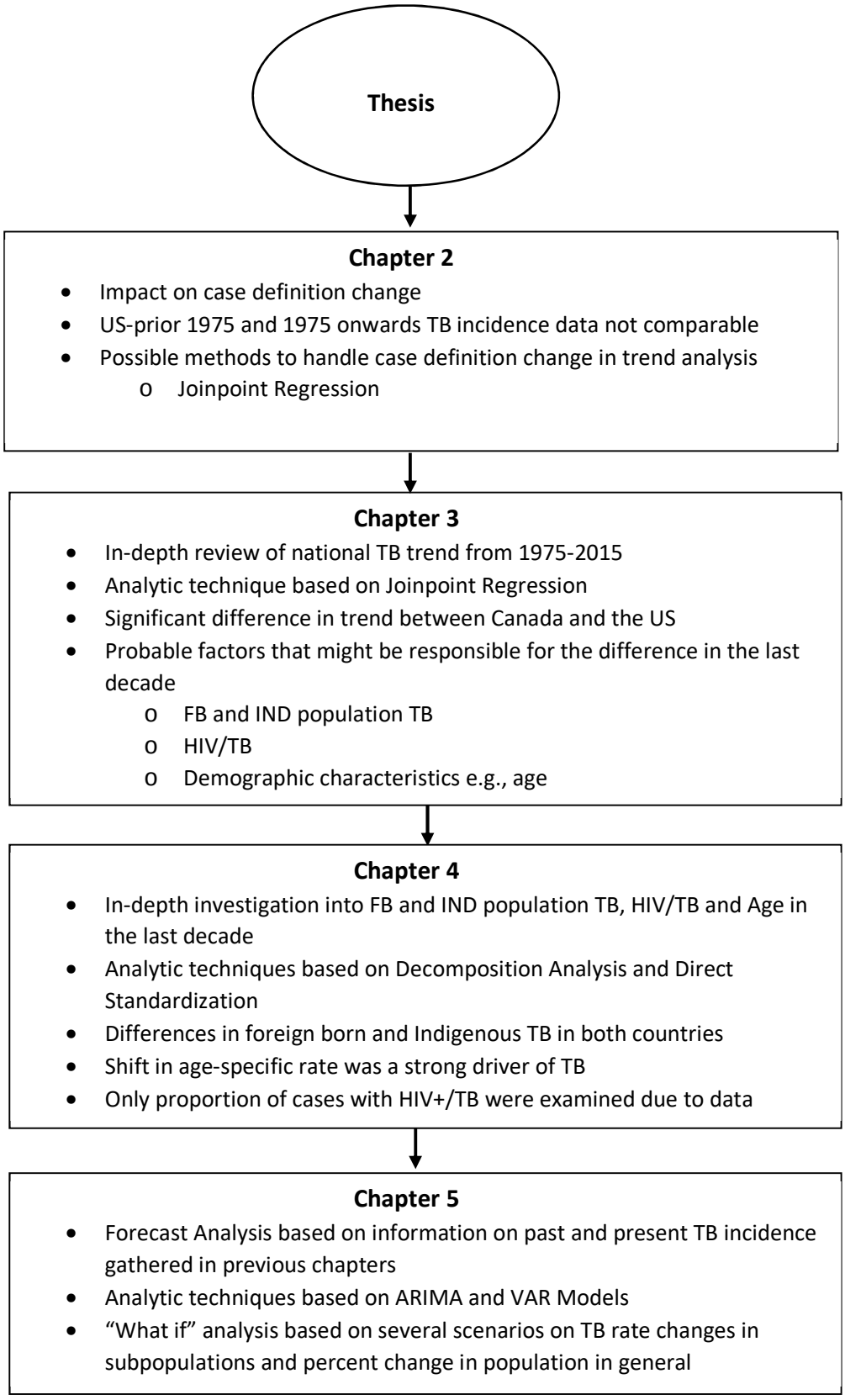

Figure 6-1: Thesis flowchart

6.2. CONCLUSIONS

Changes in case definitions, as evidenced by exploring several diseases, highlights that for appropriate comparisons within and between populations, consistent ascertainment criteria of cases should be adopted or at minimum be openly reported. Also, change in a case definition may either result in exclusivity or expansion. The narrower the definition becomes, the higher the specificity and the lower the sensitivity; whereas, the broader the definition becomes, the higher the sensitivity and the lower the specificity. Detection of false negative cases, increases in reported cases of the disease, underreporting of disease cases and reporting delays of cases of the disease were other consequences noted to arise from a case definition change.

Chapter 3 results show that Canada and the United States TB incidence rates have been different for longer intervals over the last six decades than they have been the same. Case definition change and HIV co-infection contributed to the 1980s US rate increase. TB rates decreased in both countries from 1997 but more rapidly in the US. Canada's proportion of total population of Foreign-born and the Indigenous population was higher. Chapter 4 results also revealed that after adjusting for the effect of age, Foreign-born and Indigenous, TB over the period investigated declined more in the US than in Canada. From this analysis, within the Foreign-born and Indigenous populations, age is a strong driver for TB rates overall as evidenced by age-specific rate differences. In addition, the pattern of decline of the proportion of cases with HIV+/TB co-infection in both countries corresponded to the pattern of decline in Foreign-born TB rate in the two countries.

Finally, Chapter 5 results suggest a gradually decreasing trend in total TB rates in both countries from 2017-2035. The prediction suggests that achieving the 2035 TB reduction target set by the WHO could be a challenge for both countries. The "what if" analysis also revealed that to achieve a further rapid decline in overall TB rates in both countries, more targeted interventions especially geared towards reduction of TB incidence in Foreign-born populations are needed.

6.3. METHODOLOGICAL CONSIDERATIONS

6.3.1. *Data availability, accessibility and reliability*

Data from national population census, national TB incidence and HIV+/TB percent were used for all analyses presented in the thesis. The national population census, national TB incidence and HIV+/TB data in Canada were obtained from Statistics Canada (Stat Can, 2001; Stat Can, 2011; Stat Can, 2006; Stat Can, 2016) and Public Health Agency of Canada (Health Canada, 2003; Public Health Agency of Canada, 2008; Public Health Agency of Canada, 2015; Health Canada, 2000; Public Health Agency of Canada, 2013). Similarly, the US national population census data were obtained from the Census Bureau (US Census Bureau, 2001; Pew Research Center, 2014; US Census Bureau, 2016; US Census Bureau, 2017), and national TB rate and HIV+/TB from the Centre for Disease Control (CDC, 2018; CDC, 2017). Due to data availability and accessibility constraints, analyses were mainly focused on data that spanned the following time intervals: national TB incidence rate 1953-2016 (CDC, 2017; Gallant et al. 2014); national population census 2001, 2006 and 2011 (Stat Can, 2001; Stat Can, 2011; US Census Bureau, 2001; Pew Research Center, 2014; US Census Bureau, 2016; US Census Bureau, 2017; Stat Can,

2006) and HIV+/TB 1997-2012 (Public Health Agency of Canada, 2015; Health Canada, 2000; Public Health Agency of Canada, 2012; Public Health Agency of Canada, 2013).

Additionally, differences in data reporting between the two countries (i.e. the top 5 or 10 countries where TB cases originated from) constrained explicit comparisons. In the national TB reports in Canada, Foreign-born TB cases were grouped into STOP-TB partnership TB epidemiological region which is similar to the WHO regions, except for the division of Africa and Europe WHO regions into two separate groups, making a total of eight regions. The regions were: Established Market Economies (EME) and Central Europe (CEUR); Africa, high HIV prevalence (AFR-High); Africa, Low-HIV prevalence (AFR-Low); American Region-Latin American Countries (AMR); Eastern European Region (EUR); Eastern Mediterranean Region (EMR); South-East Asian Region (SEAR); and Western Pacific Region (WPR) (Public Health Agency of Canada, 2015). However, data on the top 5 or 10 FB TB countries in Canada were not available at the national level (Public Health Agency of Canada, 2015). The United States nationally reports both Foreign-born TB by WHO regions and by top 30 countries of birth (CDC, 2017). Hence all studies looking at immigration patterns in both countries were then constrained to WHO regions only.

Other constraints encountered include different dates of the first national report on TB or HIV/TB cases and differences in reporting Foreign-born TB in both countries. For example, in Canada, the first national TB/HIV co-infected case was reported in 1997 (Health Canada, 2000); whereas in the US, the first case reported in 1993 (CDC, 2017).

Despite data on HIV+/TB co-infection being available from 1997 to 2012 in both countries, due to underreporting-related issues across jurisdictions in both countries (CDC, 2017; Halverson et

al., 2014), a firm/explicit conclusion as to the extent to which HIV+/TB contributed to differences in rates between the two countries cannot be made. The Centre for Disease Control in their 2016 TB report in the US urges end users of HIV+/TB co-infection data to interpret their findings with cautions as data on reported HIV+/TB in the US national reports "*are not representative of all TB patients with HIV infection*" (CDC, 2017).

6.3.2. *Statistical methods for analysis*

Despite several advantages that might necessitate the use of ecologic or aggregate data, including "*comparison of groups rather than individuals*", easy access to data at low cost and simplicity as it relates to analysis and presentation (Morgenstern, 1995), not much "*attention was given to statistical methods or inference*" (Morgenstern, 1995). The reason for little attention being paid to statistical methodology advancement/development for ecologic studies could be due to the earlier soaring popularity of descriptive analyses (Morgenstern, 1995). Morgenstern noted that prior to the 1980s "*ecologic studies were usually presented in the first part of epidemiology textbooks as simple descriptive analyses*" (Morgenstern, 1995). However, after 1980, some techniques have emerged to advance the analytic approaches in an aggregate study (Morgenstern, 1995; Young, 2004).

This thesis used five of the prominent analytic techniques in analyzing aggregated data. The methods used were direct standardization (Naing, 2000), joinpoint/segmented regression (Kim et al., 2000), decomposition analysis (Preston et al., 2001), autoregressive integrated moving average (ARIMA) model (Shumway and Stoffer, 2000) and vector auto regression (VAR) model (Zivot & Wang, 2006; Lütkepohl, 1999). These methods are not new to TB related research and

have gained some popularity in the field of TB as reported elsewhere (Oh, 2014; Moosazadeh et al., 2014; Baker et al., 2016; Gorbach, 2016). In order to ensure that none of the model specific (e.g., ARIMA) assumptions were violated, several tests were employed including the Augmented Dickey-Fuller test for unit root (Stadnytska, 2010), Lagrange Multiplier (LM) test for residual autocorrelation (Bose et al., 2017) and the Jarque-Bera test for normality (Caceres, 2006).

6.4. Factors investigated in the thesis: effect of changes in population and immigration pattern on TB incidence

Changes in the population, such as demographic characteristics (e.g., age distribution), make increases or decreases in population size inevitable (UN, 2015). Not only do these changes impact the economic situation of a country (Thuku et al., 2013) but disease incidence including TB (CDC, 2013). For instance, when the Foreign-born populations in Norway and Sweden increased by 0.54% and 0.37% annually for a period of fourteen years (2000-2013), this resulted in an increase in average annual TB notification rates of 3.85% in Norway and 2.64% in Sweden (Hanway et al., 2016). Also, in 1993, the US age-specific TB rate among individuals in the age group 0-4 years was found to be 5.2 per 100,000 population whereas among the age group 15-24 years was 5.0 per 100,000 population. However, for a period of eight years (1993-2000), the age-specific TB rate among persons aged 0-4 years declined to 2.8 per 100,000 population compared to 4.1 per 100, 000 population in individuals aged 15-24 years (CDC, 2017). This clearly depicts that as the US population increased by 9.2% from 1993 to 2000 (Byerly & Deardorff, 1995; US Census Bureau, 2002), a shift in the age-specific TB rate was observed (CDC, 2017). In addition, from 1993 to 2000, the population in the 0-4 year age group

decreased by 2.6% whereas persons aged 15-24 increased by 8.8% (Byerly & Deardorff, 1995; US Census Bureau, 2002).

The pattern of immigration is considered as another source of population change (Edmonston, 2016). These changes can have variable impact on the incidence of TB, especially due to immigrants from high TB incidence countries moving to low TB incidence countries (Lillebaek et al., 2002; Aldridge et al., 2016). In 2012, the percent of Foreign-born TB cases in Canada was 65% (Public Health Agency of Canada, 2015). Out of this, 42% of the cases came from individuals who were born in the Philippines, China and Vietnam (Public Health Agency of Canada, 2015). In the same year in the US, the percent of Foreign-born TB cases was found to be 63% with individuals born in Mexico accounting for 20.9% of the cases and 25.1% from the Philippines, China and Vietnam (CDC, 2013). The source country TB rates for 2012 were 265 per 100,000 population in the Philippines, 147 per 100, 000 population in Vietnam, 73 per 100, 000 population in China (WHO, 2013) and 23 per 100, 000 population in Mexico (Delgado-Sanchez et al., 2015). This suggesting that differences, as it relates to TB incidence in both countries, could in part attributed to differences in source country TB incidence.

6.5. Differences in immigration policies between Canada and the United States

Prior to 1962 in Canada and 1965 in the United States immigration to both countries was based on a nationality quota system (Lo, 2011; Boyd, 1976). After the major changes in immigration policies in 1962 and 1967 in Canada and 1965 in the US (Boyd, 1976), the Canadian policy focus changed to target immigrants with "*observable socioeconomic characteristics*" where the US change focused on "*applicant's family ties with U.S. residents or citizens*" (Borjas, 1993).

Kaushal and Lu noted that as at 2006 "*Canada surpassed the US in drawing highly-educated immigrants while continuing to attract fewer low-educated immigrants*" (Kaushal & Lu, 2015). This was further highlighted in a 2015 published report on Canada-US immigration policies comparisons (Canada Immigration, 2015; Orrenius & Zavodny, 2014). The report revealed that while more than 60% of newly admitted permanent residents in Canada came via an economic immigration program, in the US, new green card holders admitted via economic immigration categories accounted for only 16 percent (Canada Immigration, 2015; Orrenius & Zavodny, 2014). This clearly shows that the immigration policies in both countries are different and have a differential impact on the pattern of immigrants and TB incidence in both countries. Moreover, as varying patterns of migration were attributed to different declining levels of TB rates in the majority of European countries (Gilbert et al., 2009), this could as well be linked to differences in country-specific immigration policies.

6.6. Factors not investigated in the thesis: effect of seasonality on TB transmission

Besides the facilitation of TB transmission by several factors including overcrowding (Kirenga et al., 2015) and HIV infection (Corbett et al., 2003), seasonality has also been suggested by most authors (Willis et al., 2012; Yang et al., 2016) as a probable factor that might have an impact on TB transmission dynamics and hence has to be considered in TB-related research (Wubuli et al., 2017). However, according to Willis et al, the mechanism of the influence of seasonality on TB transmission remains unknown (Willis et al., 2012). In an attempt to explain this mechanism, Fares outlined some factors which are seasonally dependent and might play a role in the transmission of TB (Fares, 2011). These factors include "*serum vitamin D level variability, indoor*

activities and seasonal changes in immune function" (Fares, 2011). While some studies show that TB peaks in March and troughs in December (Bras et al., 2014; Yang et al., 2014), others showed that TB rather peaks between April-September and troughs between October-March (Douglas et al., 1996; Kelsey et al., 1999). Although evidence in published studies from different countries support the impact of seasonality on TB transmission (Bras, et al., 2014; Yang et al., 2014; Douglas et al., 1996; Kelsey et al., 1999), the periods (months) as to when TB peaks or troughs is still not clear. Seasonality was not assessed in this study because national monthly/quarterly TB data were not available.

Major Strengths and Limitations

This thesis used varied and robust methods which allowed for the effect of potential confounding factors including age and ethnicity to be controlled and differences in rate to be separated into two additive components. Another strength was that a significant amount of the analytical work of this thesis was performed using data with long time lags which provided the opportunity for differences in TB incidence that existed in the past and present between the two countries to be explored. With regards to limitations, this thesis could not explicitly compare and elucidate the impact of HIV/TB co-infection on the national TB rate due to data limitation in both countries. Also, this thesis could not further assess the effect of seasonal variation on the predicted rates since national monthly/quarterly TB data were not available. Divergent rates resulting from program performance could not be excluded. The comparison in this thesis especially Chapter 3 was WHO surveillance reports by country. Comparison of program outcomes was beyond the scope of this thesis. Such a comparison would include

percent of TB treatment completion, the extent of drug resistance, relapse, screening and uptake of treatment of LTBI.

6.7. Practical Significance

The findings reported in this thesis have broadly deepened our understanding of the TB epidemiology in both Canada and the United States by shedding light upon some events in the past that affected TB incidence, factors that presently might be responsible for the differences in TB incidence and how shifts in population could impact the future incidence of TB in both countries. Secondly, findings in this thesis will be helpful to people managing tuberculosis interventions. Finally, this thesis has uncovered some challenges associated with the use of national HIV/TB co-infection data in both countries and encouraged all jurisdictional agencies in charge of HIV/TB to collect and report all HIV/TB-related data to national TB programs or public health agencies.

6.8. Direction for future research

This thesis has uncovered some gaps which would be essential to address in future research. This includes research involving comprehensive data on HIV/TB co-infection to elucidate the impact of HIV/TB co-infection on the national TB trend in both countries. As monthly or quarterly TB data becomes available at the national level, future research would be needed to investigate the effect of seasonal variation on TB incidence in both countries.

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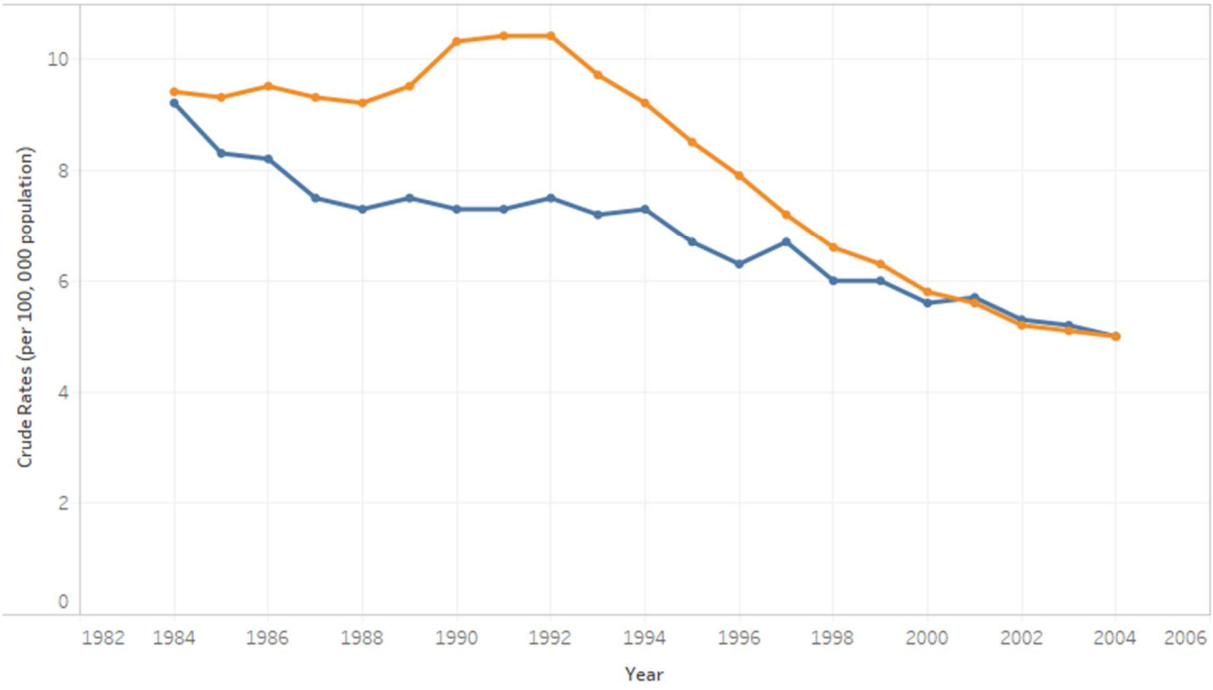
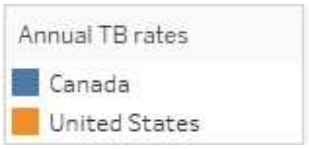
Appendix A. 1: Graphical Display of Research Rationale

Annual TB rates between Canada and US 1984-2004

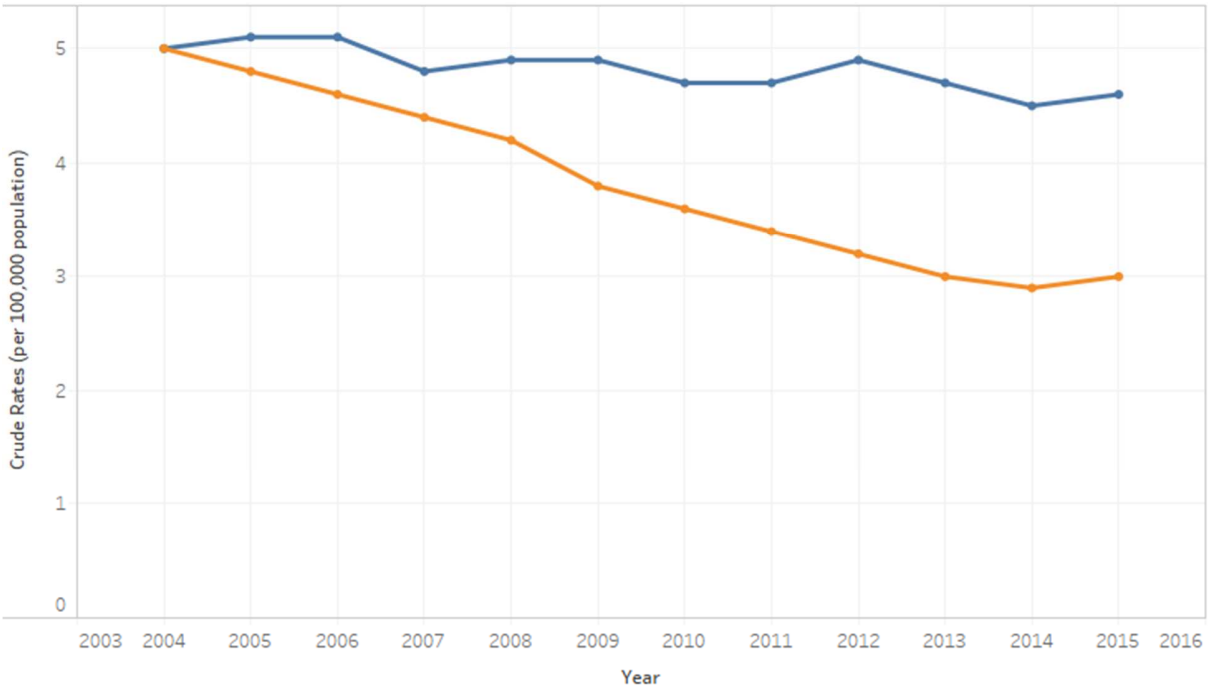


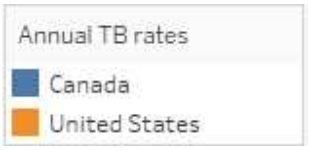


Canada AAPC=-3.0^ 95%CI -3.8, -2.1

US AAPC=-3.2^ 95%CI -3.8, -2.5

Annual TB rates between Canada and US 2004-2015

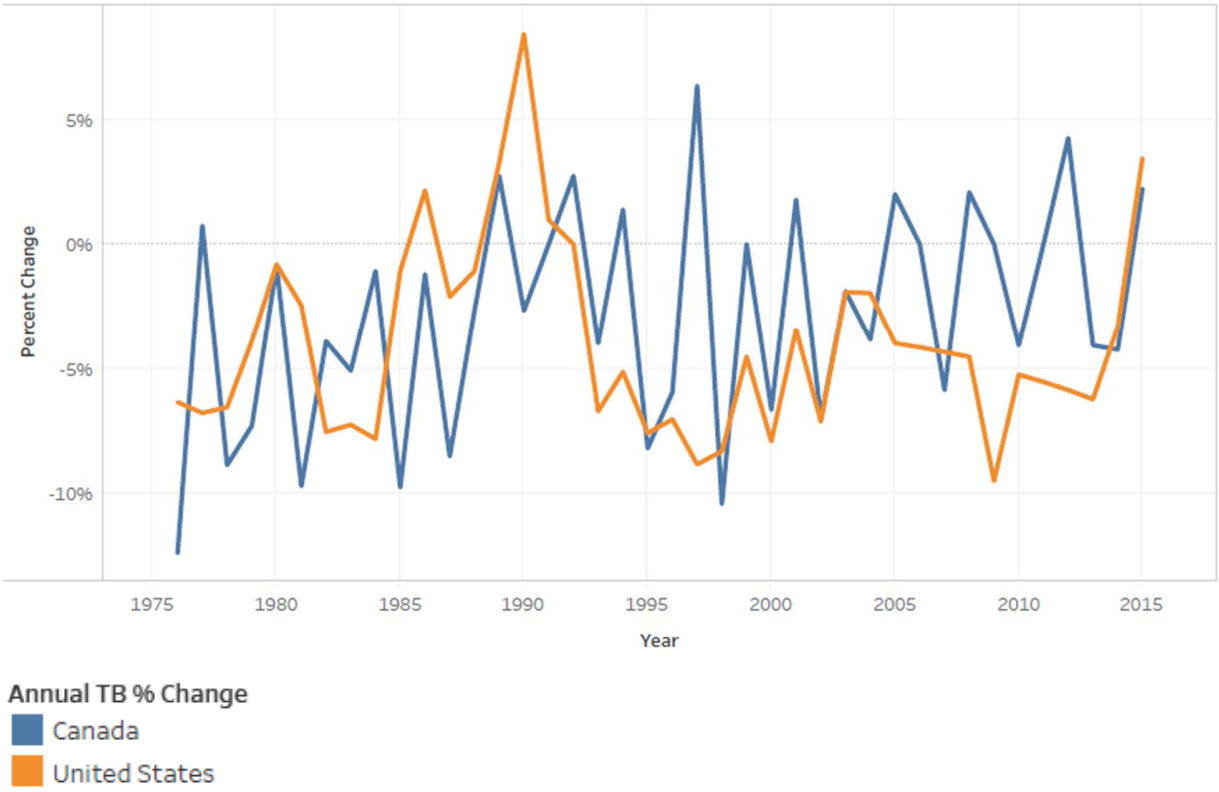




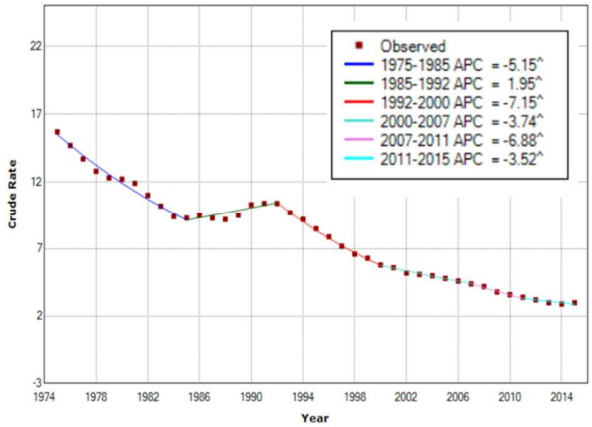
Canada AAPC=-0.9^ 95%CI -1.3, -0.5

US AAPC=-4.6^ 95%CI -5.5, -3.7

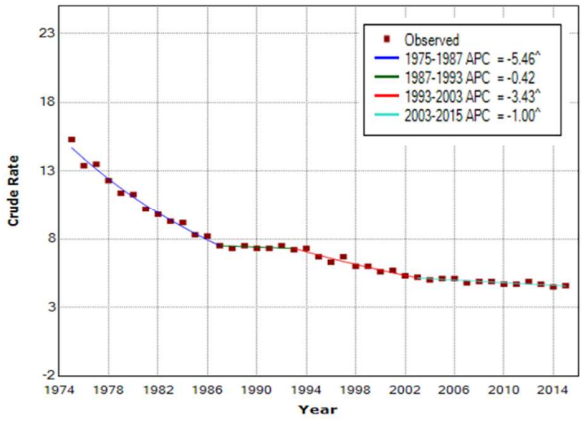
Appendix A. 2: Graphical Representation of APC in TB Rate in Canada and the US from 1975-2015



Appendix A. 3: Graph Showing Joinpoint Models of TB Incidence Rate in Canada and the US from 1975-2015



United States



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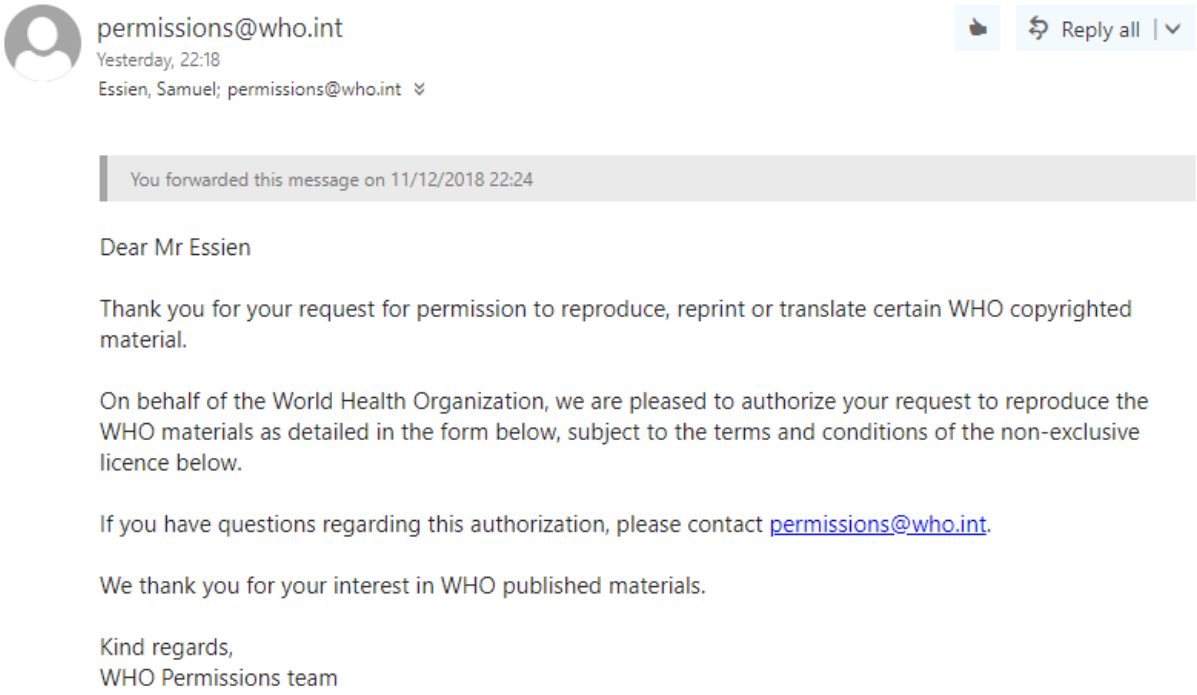

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