The Effectiveness of Tuberculosis Control Strategies that Target Social Determinants of Health in Three First Nations and Métis Communities: A Mathematical Modeling Approach

by

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Abstract

BACKGROUND: Despite the overall decline in tuberculosis (TB) incidence in Canada, rates among Indigenous peoples have not decreased since the late 1990s. On-going transmission associated with the time from the onset of symptoms to treatment have been identified as major contributor to the persistence of TB in Canadian Indigenous communities. The social determinants of health associated with time to treatment represent additional challenges faced by Indigenous communities. OBJECTIVES: a) describe TB transmission across the Prairie Provinces of Canada (Alberta, Saskatchewan, and Manitoba), b) determine a baseline estimate for time to treatment (analogous to transmission period or total delay in diagnosis) and to identify its associated risk factors, c) construct a TB transmission agent based model (ABM) that integrates multivariate relationships between the time to treatment and associated risk factors that includes the social determinants of health in three First Nations and Métis communities in Alberta and Saskatchewan (TB-ABM), and d) to simulate three TB control strategies and assess their impact on TB cases (latent and active) and transmission. These control strategies include reductions in comorbidities, improved healthcare access, and an LTBI screening and treatment strategy. METHODS: Data management and statistical analysis (descriptive and multivariable logistic regression) was conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA) and Microsoft Excel 2011. The TB-ABM was constructed, validated, and simulated using MATLAB 2015a (The MathWorks, Inc.). RESULTS: Evidence of on-going transmission was highest among First Nations living in northern reserves. The median estimated time to treatment was 30 days and durations that exceeded this cut-off

value were defined as a “delayed time to treatment”. Factors that increase the odds of delayed time to treatment (>30 days) in the multivariate model included having a regular family doctor and not having a working x-ray machine and technician in a community. Simulations using the TB-ABM indicated that decreasing latent TB infection (LTBI) in high burden communities could have significant impacts on incidence overall. Reductions in LTBI among those infected within 5 years ranged between 40% and 71% based on screening 50% of people every six months (assuming a compliance of 60%). Healthcare access in the TB-ABM was defined as the location people first sought care for TB symptoms (either within or outside the community). Simulations from the TB-ABM estimated a 10% to 16% decrease in transmission events based on a 75% reduction of people accessing services outside the community. CONCLUSION: Interventions that directly interrupt on-going transmission in Indigenous communities through improving the social determinants of health such as healthcare access is important to help decrease TB burden. The overall use of mathematical modeling can provide insight and numerical evidence of the impact that risk factors including the social determinants of health can have on TB transmission and case-rates among First Nations and Métis peoples across the Prairies.

Preface

This thesis is an original work of Marie Betsy Varughese. The data used in this research project, of which this thesis is a part, received ethics approval from the University of Alberta Research Ethics Board, The Determinants of Tuberculosis Transmission in the Canadian-born Population of the Prairie Provinces, No. MS8_Pro00003492, July 20, 2012. Other approvals were obtained from Health Canada, and other universities from the Prairie Provinces of Canada (Alberta, Saskatchewan, and Manitoba).

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List of Abbreviations

AB	Alberta
ABM	Agent based model
AIC	Akaike's Information Criterion
AI/AN	American Indian/ Alaskan Native
AOR	Adjusted odds ratio
CIHR	Canadian Institutes of Health Research
DOH	Determinants of health
DTT	Determinants of Tuberculosis Transmission in the adult, Canadian-born population of the Prairie Provinces
FN	First Nations
HIV	Human immunodeficiency virus
IBM	Individual based models
INH	Isoniazid
LRT	Likelihood Ratio Test
LTBI	Latent TB infection
MB	Manitoba
MDR	Multidrug resistant TB (resistance to isoniazid and rifampicin)
MIRU	Mycobacterial Interspersed Repetitive Units
MTBC	*Mycobacterium* tuberculosis complex
NH/PI	Hawaiian/Pacific Islander
NML	National Microbiology Laboratory

OCAP	Ownership, control, access, and possession
ODE	Ordinary differential equation
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PNC	Provincial Network Committees
PTB	Pulmonary tuberculosis
ROC	Receiving operating curve
SDOH	Social determinants of health
SI	Status First Nations
SIR	Susceptible-Infected-Recovered
SK	Saskatchewan
TB	Tuberculosis
TB-ABM	Tuberculosis Agent Based Model
VNTR	Variable number tandem repeats

Chapter 1: Introduction

Tuberculosis (TB) incidence in Canadian Indigenous peoples (First Nations, Métis, and Inuit) is 20 to 50 times higher than that of Canadian-born non-Indigenous peoples. This is especially true in the Prairie Provinces of Canada (Alberta, Saskatchewan, and Manitoba) where TB rates among First Nations (FN) peoples are also disproportionately higher than non-Indigenous peoples both in urban centers and rural communities. TB across the Prairies in FN and/or Métis communities is highly focal with only a few communities experiencing a considerable burden of TB. The occurrence and transmission dynamics of TB in FN and/or Métis communities are complex due to the social and economic determinants of health such as overcrowding, food insecurity, increased stress, lack of access to healthcare, and generally poorer socioeconomic conditions. The duration between the onset of symptoms and treatment is an underlying factor that potentiates on-going TB transmission, which is a challenge, faced by some FN and/or Métis communities.

Existing literature does support the belief that TB is both a medical and social disease. This means that intervening on social determinants of health (SDOH) may reduce transmission and would be an important consideration in Indigenous communities that experience on-going transmission. An estimation of the impact of any intervention related to the SDOH on TB cases and overall incidence is not possible without using mathematical modeling. Thus, the knowledge and insights gained from mathematical modeling can provide evidence to help TB policy makers and clinicians make informed decisions about TB control strategies that will be most effective.

1.1 Research Objectives

The primary data source of data is the seven-year, Canadian Institutes of Health Research (CIHR) and Health Canada co-funded '*Determinants of Tuberculosis (TB) Transmission in the adult, Canadian-born population of the Prairie Provinces*' (DTT) Project (2006-2013). The Prairie Provinces include Alberta, Saskatchewan, and Manitoba. The DTT project gathered quantitative (demographic data, geography, contact history, and method of diagnosis), and the molecular epidemiological information on all adult (>14 years old) Canadian-born, culture-positive, pulmonary TB (PTB) patients, hereafter defined as "potential TB transmitters", diagnosed between January 1st 2007 and December 31st 2008 in Alberta, Saskatchewan, and Manitoba. For each potential TB transmitter, the DNA fingerprint (24-loci MIRU-Mycobacterial Interspersed Repetitive Units) of the initial isolate of *Mycobacterium tuberculosis* was obtained and compared to DNA fingerprints of all other TB case isolates within a 2.5 year transmission window (six months prior and two years after the date of diagnosis of the potential transmitter) to identify secondary cases.

The main research objectives for this dissertation are outlined in three interrelated projects.

In Project 1 (Chapter 4), the primary objective is to determine whether cross-jurisdictional collaboration of provincial TB programs and increased surveillance would be beneficial to reduce potential TB transmission across the Prairies. Tuberculosis transmission is described across the Prairies and clustering is analyzed by population group, latitude, and geographical location. The fingerprinting data (2006-2010) is used for this analysis.

In Project 2 (Chapter 5), the primary objective is to determine a baseline estimate for time to treatment of pulmonary TB among First Nations (FN) and Métis peoples across the Prairie Provinces. Time to treatment in this project is defined as the onset of cough (a symptom that is associated with TB transmission) to the date of diagnosis (defined as the start date of treatment in the DTT project). The secondary objective is to identify risk factors associated with time to treatment. The risk factor information for each TB case diagnosed between 2007 and 2008 was obtained primarily from the quantitative questionnaires administered in the DTT project, which included demographics, health and social determinants such as age, sex, income, education level, recreational tobacco use, housing density, substance abuse, health-care access, mobility, and co-morbidities (HIV, diabetes, and/or renal disease). Information not available in the quantitative questionnaires was augmented with other secondary data sources such as the TB registry.

In Project 3 (Chapter 6: Part 1), the first objective is to construct an agent based TB transmission model (TB-ABM) of three high burden FN and Métis communities in northern Alberta and Saskatchewan. The TB-ABM includes heterogeneous contact structures (close household, close non-household, and casual), an individual's age and gender, household structure, contact investigations, time to treatment, and individual attributes associated with time to treatment (e.g. housing density and comorbidities). The time to treatment parameter in the TB-ABM is predicted using the risk factors identified in Project 2. The time to treatment model parameter acts as a link between the TB-ABM and potential risk factors. The secondary objective is to assess the model by (i)

comparing baseline outputs to existing data (DTT project and other secondary sources) and conducting (ii) sensitivity analysis, and (iii) uncertainty analysis.

In Project 3 (Chapter 6: Part 2), the main objective is to investigate the impacts to TB cases by investigating three main control strategies. These include: i) reduction in comorbidities, ii) improvement of access to healthcare, and iii) a preventative latent TB screening and treating strategy. Five-year predictions are assessed for each control strategy. Outcomes measured in the TB-ABM include TB cases, latent TB cases, and total transmission events.

1.2 Organization of the Dissertation

This dissertation includes seven chapters including the introduction. Chapter 2 is a literature review and provides background information about Indigenous populations in Canada, TB, risk factors associated with TB, and mathematical modeling. Chapter 3 is a systematic review to examine the body of literature about delay in diagnosis studies of TB conducted among Indigenous populations worldwide.

Chapter 4, Chapter 5, and Chapter 6 are written as independent chapters that include a summary, introduction, methods, results, discussion, and conclusion. Each of these chapters used different methods and is thus presented independently. The analysis in Chapters 4 and 5 provides justification, context, and insight towards the construction of the TB-ABM presented in Chapter 6 (Part 1). In Chapter 6 (Part 2), simulations of control strategies are presented using the TB-ABM. In Chapter 7, overall conclusions and future directions are provided based on the results from the preceding chapters.

Chapter 2: Literature Review- Indigenous Peoples in Canada, Indigenous Health, Tuberculosis and Mathematical Modeling

2.0 Introduction

One of the overarching purposes of this dissertation is to quantitatively estimate the impact of intervening on risk factors (including social determinants (SDOH)) associated with tuberculosis (TB) transmission with a particular focus on high burden Indigenous communities across the Prairies. The term "Indigenous" or "Aboriginal" in Canada includes status and non-status First Nations (FN), Métis, and Inuit peoples. The term status refers to FN peoples (often referred to as status Indian) who are registered with Aboriginal Affairs and Northern Development Canada according to the *Indian Act* of Canada [1]. This review aims to examine and summarize literature about TB, its risk factors, and mathematical modeling with a primary focus on Indigenous peoples. This review includes both primary and secondary literature sources. An overview of Indigenous peoples in Canada and across the Prairies, Indigenous health, TB including its risk factors, and mathematical modeling is provided.

2.1 Indigenous Peoples in Canada

The relationship between Indigenous peoples and the Canadian government is complex in terms of both history and governance. The colonization of Indigenous peoples negatively impacted social, cultural, and political structures and initiated a relationship of economic dependence [2]. These effects of colonization have resulted in current challenges facing Indigenous peoples in Canada such as food insecurity, poor housing quality, limitations on income, and barriers to healthcare access.

The main governing documents for FN people include the numbered treaties, the *Indian Act* (1876), and *Bill C-31* (1985). A treaty is defined as an international agreement between nations and the numbered treaties were negotiated between 1871 and 1930 [3]. These treaties include terms such as the agreement for land called reserves, hunting and fishing practices, and monetary payments. Reserves are defined as "parcels of land held by Canada on behalf of the FN" people [3]. With respect to FN identity, the *Indian Act* and the 1985 *Bill C-31* to amend the *Indian Act* are two pieces of legislation that determined access to government programs and services to those who were defined legally as "Indian" or "status Indian" [3]. Prior to *Bill C-31*, changes to the definition of "Indian" affected people who may have lost their "status" for various reasons that include voting in a federal election, having a university degree, and to females marrying non-First Nations men and any descendants of that union [2, 4]. Bill C-31 was necessary to address gender discrimination in the *Indian Act* that was contrary to the *Canadian Charter of Rights and Freedoms* (1982) [2]. Additional differentiations in terms of band membership resulted after *Bill C-31* where First Nations could have: 1) status with band membership, 2) status without band membership, 3) non-status with band membership, and 4) non-status with no band membership [2]. There are approximately 130 000 non-status Indians in Canada who have been unable to reclaim their status after *Bill C-31* [4].

Shortly after the recognition of Métis people as Indigenous persons under section 35 of the *Canadian Constitution Act* in 1982, four laws were passed in 1990 that related to Métis governance, land, and resources [5, 6]. These laws included the *Constitution of Alberta Amendment Act*, *Métis Settlements Act*, *Métis Settlements Land Protection Act*, and *Métis Settlements Accord Implementation Act* [6]. In the same year, eight settlement

titles of land were transferred to the Métis people in Alberta [2, 7]. The eight settlements include East Prairie, Elizabeth, Fishing Lake, Kikino, Buffalo Lake, Gift Lake, Paddle Prairie, and Peavine [2, 7]. The formal recognition of Métis peoples as Indigenous in the constitution have not afforded them the same rights as FN nor Inuit peoples living in Canada at this time. At the time of writing, only the Northwest Territories provide non-insured health benefits to Métis peoples [8]. Formal registration of Métis status under the *Métis Settlement Act* allows Métis peoples authority over preserving land rights, self-governance, and culture that is separate from other Indigenous groups in Canada [6]. The Métis registry had a negative impact on those persons who identified as both Métis and FN, since they were unable be included in the registry without simultaneously relinquishing their "Indian status" [2]. The recognition by the Supreme Court of Canada (April 2016) that Métis (and "non-status Indians") peoples fall under the purview of Federal responsibility may potentially help those who are currently pursuing land claims and/or additional government services [6].

In the context of this dissertation, definitions of FN pertain to those with status unless noted otherwise. Tables that use Statistics Canada as a source may include non-status FN when summarizing Indigenous identity and enumerations of on-reserve FN peoples. Additional limitations with using Statistics Canada Census data are that communities with less than 250 inhabitants were not included, some reserves and settlements may have incomplete enumerations or there may be some communities who declined to participate altogether [9-11]. In the 2006 and 2011 census, approximately 22 and 32 reserves, respectively were incompletely enumerated or declined to participate accounting for approximately 40,000 people [10, 11]. The response rate for the National

Household Survey in 2011 was 77%, which suggested that non-response bias for this survey was minimized [12].

2.2 Indigenous Communities in Alberta, Saskatchewan and Manitoba

Table 2.1 describes the Indigenous population in Canada stratified across the Prairie Provinces using Statistics Canada census results in 2006 and 2011, which included the study period of the Determinants of Tuberculosis Transmission (DTT) Project (2006-2013). The proportion of Indigenous peoples in Canada made up 4% of the total Canadian population in 2006 (1.2 million of 31 million people) and 2011 (1.4 million of 33 million people) (see Table 1) [13, 14]. In 2011, the Indigenous population in the Prairies was 0.6 million representing 41% of the total Indigenous population in Canada [13]. First Nations and Métis peoples represented over 97% of the overall Indigenous population in the Prairie Provinces in 2006 and 2011 [13, 14]. Approximately 40% and 50% of all Canadian FN and Métis peoples respectively lived in Alberta, Saskatchewan, and Manitoba (see Table 2.1).

The median age of Indigenous peoples across the Prairies was 13 years younger and their overall life expectancy was lower compared to the general population [13, 15-18]. Table 2.2 compares demographic characteristics of reserve and Métis settlements in Alberta with overall provincial estimates from 2006 to 2011. First Nations and Métis peoples on-reserve/settlements generally have higher proportions of houses requiring major repair, more over-crowding, increased unemployment rate, lower household income, and reduced high-school completion rates compared to the general population in Alberta, Saskatchewan, and Manitoba (see Table 2.2). The proportion of houses on-reserve requiring major repairs slightly increased in Alberta and decreased in

Saskatchewan between 2006 and 2011, while Manitoba remained the same (see Table 2.2). Métis settlements in Alberta showed a 3% reduction in homes requiring major repairs and a 2% reduction in overcrowding (see Table 2). Overcrowding on-reserve increased by 3% to 4% across the prairies. Overall, high school completion rates and median household incomes increased between 2006 and 2011. In Manitoba, median household incomes on-reserve did not show any appreciable increase between 2006 and 2011 (see Table 2).

The Aboriginal Peoples Survey (APS) is a national survey for social and economic conditions among FN people (off-reserve), Métis, and Inuit (>5 years old) conducted every five years [19]. The response rate for the 2012 APS was 76% [19]. First Nations (off-reserve) peoples (>14 years old) have a higher proportion of households requiring major repairs, overcrowding, and unemployment rates and lower median after-tax household income and completion of high school rates compared to non-Indigenous peoples [15, 20-23]. These differences in socioeconomic factors and social determinants of health (SDOH) highlight additional challenges that impact the overall health of FN (on- and off-reserve) and Métis peoples across the prairies.

2.3 Social Determinants of Health

The overall health of an individual is dependent on their determinants of health (DOH), which include the interactions of social, physical, environmental, and economic factors [24]. Under the term DOH, the SDOH describes underlying factors and conditions people experience from birth that can shape their daily life and overall well-being; examples include education, trauma, housing, income inequality, food insecurity, health

care access, and race [25, 26]. The SDOH are important factors that have direct impacts to the overall health of an individual.

The cyclic affect these factors can have can add challenges to a person's ability to have an improved health status. For example, Indigenous peoples who have low incomes and live in rural and/or remote areas may not have access to transportation. This may impact access to food (i.e. grocery stores) and healthcare. Grocery stores in rural areas may not be stocked regularly, which can increase prices for high quality foods. Poor nutrition increases the susceptibility to infection and access to healthcare may be delayed due to financial stress and lack of transportation.

2.4 Indigenous Health in Canada

From a historical context, the intergenerational trauma experienced at residential schools, which ran in Canada from 1840 to 1996, included isolation from family, abuse, poor education, inadequate housing, over-crowding, inadequate or non-existent medical facilities, nutritional deprivation, increased rates of communicable diseases, injury, and mortality were compounded by losses of language and culture, which have had and are continuing to have a negative impact on the health and wellness of Indigenous peoples [27-31].

The current health status of Indigenous peoples is generally poorer than the general Canadian population. The DOH and SDOH where disparities between Indigenous and non-Indigenous peoples are much greater include income, education, physical environment (e.g. water quality and housing conditions), access to health services, homelessness, experiences of racism, and food insecurity. [4, 20, 32-42].

The influence of these, and other health determinants on infectious and chronic illnesses is well recognized in the medical and scientific literature [20, 43]. The incidence of some infectious and chronic diseases is disproportionately higher for Indigenous compared to non-Indigenous peoples. Infectious diseases such as TB, human immunodeficiency virus (HIV), and hepatitis C occur at higher rates than the non-Indigenous population [44-50].

Approximately 63% of FN (on- and off-reserve) and 60% of Métis peoples have at least one chronic disease compared to 49% of the total Canadian population [20, 21, 39]. The prevalence of diabetes (5% to 11% higher), hypertension (4% higher), and arthritis (8% higher) in FN (on- and off-reserve) peoples is greater compared to the total Canadian population [20, 39, 51]. Among Métis peoples, the prevalence of diabetes (2% higher), hypertension (16% higher), and arthritis (21% higher) is greater compared to the total Canadian population [52].

2.5 Health delivery: Indigenous Peoples in Canada

Indigenous healthcare delivery is fraught with jurisdictional challenges in Canada since, in general, healthcare is a provincial responsibility while Indigenous peoples themselves fall under federal jurisdiction [17]. With the exception of Métis peoples in the Northwest Territories, the delivery of non-insured health benefits (NIHB) are eligible only to registered (by the Indian Act) FN peoples or an Inuk recognized by an Inuit land claim organization; these claims fall under federal jurisdiction [8, 17, 53]. Currently, the First Nations and Inuit Health Branch (FNIHB) manages the NIHB program and generally covers medical expenses such as dental care, drugs, mental health counseling, and vision care [53]. The NIHB program is analogous to health insurance where

providers can directly bill NIHB or clients pay up front and are subsequently reimbursed for out of pocket expenses.

Legislative authority for TB prevention and control is under provincial and territorial jurisdiction in Canada [54, 55]. The territorial governments are solely responsible for TB prevention and control for the entire population [54, 55]. In the provinces, the responsibility of TB prevention and care for FN and Inuit peoples is shared and varies by region based on their level of collaboration with Health Canada's FNIHB regional offices, provincial governments, and FN or Inuit organizations or communities [54, 55]. TB control and prevention is provided by the provincial government to Inuit communities located within provincial boundaries such as Nunavik in Northern Québec. The Newfoundland and Labrador government provides TB prevention and care for Nunatsiavut and the Nunatsiavut Government receives funding from FNIHB to add to existing provincial services [54, 55].

2.6 Tuberculosis: Disease

The *Mycobacterium tuberculosis* complex is comprised of various strains of acid-fast bacteria that cause TB. The vast majority of TB cases are caused by *Mycobacterium tuberculosis* [56, 57]. Rarely, other members of the *Mycobacterium tuberculosis* complex cause TB, for example *M. bovine* and *M. africanum*. Latent TB infection (LTBI) and active TB disease are two stages that differ by symptomology and infectivity. Persons with LTBI are asymptomatic with no possibility for transmission unless their condition changes. Symptoms of active pulmonary TB disease include coughing for three weeks and longer, fever, night sweats, weight loss, and enlarged lymph nodes [58].

Transmission occurs through the mechanism of expelling sputum and aerosolizing the bacteria through actions such as coughing and sneezing [59]. TB disease may further be differentiated into two states, smear-positive and smear-negative status, which differ by the likelihood of transmission (smear positive > smear negative).

Smear-positive tuberculosis (>5000 organism/ml) is approximately five times more likely to transmit infection than smear-negative culture-positive samples [59-61]. The duration of exposure required for a transmission event can take minutes, days, months, or years depending on the concentration of viable bacteria in the air and the direct or indirect distance of the source case to susceptible contacts [59]. Other factors included tubercle bacilli per volume, air circulation and ventilation, presence of UV light, and the immunological status of the contact [57, 59, 62]. DOH such as substance abuse and malnutrition are thought to down-regulate the immune response to infections such as TB, and are conditions that make contacts more susceptible to infection post-inhalation of the bacterium [63-65].

The lifetime risk for progression of latent to active TB in immunocompetent individuals is approximately 5% to 10%, and 50% of these events occur within the first two years of infection [66]. This risk of progression from new infection to active TB (within 5 years of infection) increases with younger age and for individuals who have compromised immune systems [66-69]. The tuberculin skin test and interferon-γ release assays (IGRAs) are immunological tests that help diagnose LTBI [70]. Optimal treatment for LTBI is isoniazid (INH) daily for nine months [67]. Shorter LTBI treatments such as four months daily rifampicin have improved adherence and cure [67, 71-73].

Most cases of active TB involve the respiratory tract (pulmonary TB), however, 25% of immunocompetent individuals and 70% of patients with advanced HIV have extrapulmonary TB, those with HIV infection often have both [58, 74-76]. Peripheral lymph nodes, the pleura, the bones and joints, the genitourinary system, peritoneum, gastrointestinal tract, and the central nervous system are common sites for extrapulmonary TB [58, 75, 76] where transmission does not occur unless TB is also concurrently present in the lungs [54].

Smear examination and culture of sputum in the case of pulmonary TB are diagnostic tools for active TB disease [58]. Diagnosis of extrapulmonary TB involves a smear and culture result of a biopsy from the infected organ. First and second line drugs that can be used for the treatment of active TB are described in Table 2.3. Treatment of active TB disease does not guarantee complete recovery and recurrent TB due to the same strain is possible (relapse). Successfully treated individuals who recovered from active TB could be susceptible to new strains (re-infection). In low burden countries, most recurrent cases of TB are due to relapse versus re-infection [77, 78]. Directly observed therapy (DOT) can help improve adherence to TB treatment [67]. Increased adherence and completion of TB treatment prevents risks of relapse and acquired drug resistance.

The TB drug resistance surveillance conducted by the Public Health Agency of Canada (PHAC) in 2014 reported that 9.5% (131/1376) of *M. tuberculosis* isolates were resistant to at least one of the first-line drugs: INH, rifampicin, pyrazinamide, and ethambutol [79]. Six percent (84/1376) of isolates were resistant to INH [79]. Nine extensively drug resistant TB cases were identified in Canada between 1998 and 2014

[79, 80]. Extensively drug resistant TB is defined as resistance to at least INH and rifampicin (MDR-TB), second-line drugs including any fluroquinolone, and to at least one injectable second line drugs such as amikacin, capreomycin, and kanamycin [79, 81, 82].

2.7 Tuberculosis Incidence rates over the past 50 years

In Canada, 1568 new active and re-treatment TB cases were reported to the Canadian Tuberculosis Reporting System in 2014 [46]. Historical trends showed a sharp decline of TB cases prior to 1986 and gradual reductions thereafter averaging 1627 cases per year between 2004 and 2014 [46, 83-85]. The national incidence of TB in Canada also declined from its peak around 1945 of approximately 127 cases per 100 000 population to 4.4 cases per 100 000 population in 2014 [46, 83]. Since 1980, Canadians 75 years and older had the highest age-specific rates of TB [46, 83, 86]. Rates of TB incidence were also higher among males than females [46, 86]. The introduction of sanatorium treatment, initial advances in antimicrobial therapy for TB treatment, the Bacillus-Calmette-Guérin (BCG) vaccine, natural selection, acquired immunity, in addition to overall improvement of nutrition, housing, sanitation, and education were major factors that contributed to the decline of TB cases, incidence, and related deaths observed since 1945 [86, 87] .

The decline of TB incidence and cases over the past 50 years is evident, however the total number of TB cases per year between 2004 and 2014 has remained relatively constant. Despite the overall decline, rates continue to be different by population groups. As such, much of the decline was in the Canadian-born non-Indigenous population whose contribution to Canadian cases dropped from 68% to 10% between 1970 and 2014

(incidence of 0.6 per 100,000 population) [46, 86]. TB cases in Canada are disproportionately higher among the foreign-born (69% of the total cases) and in Indigenous peoples (20% of the total cases) who make up approximately 21% and 4% of the total population, respectively [13, 14, 46].

Rates of TB among the foreign-born changed over the past 50 years in part due to shifts in immigration source countries around 1960 from primarily low TB incidence (<15 smear positive cases per 100 000 population) to high TB incidence (≥15 smear positive cases per 100 000 population) countries [88-90]. TB cases among the foreign-born accounted for 18% of the total in 1970 and increased to 65% in 2000 [91, 92]. The foreign-born caseload remained relatively constant thereafter and the observed reductions in foreign-born TB incidence were due to increases in the denominator [1, 91, 93]. TB in the foreign-born population occurs mostly from the reactivation of latent TB acquired in their country of origin and transmission is relatively infrequent [90, 94-96].

A focus on Indigenous Peoples

Indigenous peoples contributed over 50% of Canadian-born TB cases despite the fact that they represent only 4% of the total population [13, 14, 46]. TB incidence in the Indigenous population continues to be the highest when compared to the two other major population groups: the foreign-born and Canadian-born non-Indigenous [54, 97]. TB incidence rates among status First Nations and Inuit in 1970s ranged between 150 cases to 590 cases per 100 000 population [84]. These rates substantially declined between the 1980s and 1990s, but have fluctuated between 20 and 30 cases per 100 000 population

after 1998 [93]. Since 1970, the proportion of the total TB cases for Indigenous people has persisted between 15% and 20% [46, 84, 91, 98].

Incidence rates in the Inuit population are the highest compared to the other Indigenous groups (status FNs and Métis). Across Canada, in 2014, the TB rate in the Inuit population was 198 cases per 100 000 population compared to 20 cases per 100 000 population for on-reserve status FN, 15 cases per 100 000 for off-reserve status FN, and 3.2 cases per 100,000 population for Métis people [46]. The distribution of Indigenous TB cases was different across the Prairie Provinces. Incidence rates and cases were higher in Manitoba (n=84 cases; 38 cases/100 000 population) and Saskatchewan (n=64 cases; 36 cases/100 000 population) while in Alberta, the TB incidence was 6.3 per 100 000 population (16 cases) in 2014 [46]. Pulmonary TB cases among Indigenous peoples have been generally localized to a handful of northern reserve communities and Métis settlements/communities (above the 53rd parallel) across the Prairie Provinces (Alberta, Saskatchewan, and Manitoba) thereby focalizing the risk [99].

2.8 Pathogenesis of TB

The overall pathogenesis of TB is described in Figure 1. The main difference between the foreign-born persons and Indigenous peoples is the way TB is acquired. Immigrants who arrived from countries with a high TB burden also tend to experience higher rates of poverty, resulting in challenges in meeting TB control standards similar to low burden countries, difficulty affording medicine, and adequate access to health facilities [100-102]. In Canada, foreign-born persons mainly have acquired a TB infection (latent TB) in their country of origin and their cases are a result of the reactivation to active TB.

In contrast, the Indigenous population experiences both on-going transmission and the reactivation of TB. The high incidence of TB among Indigenous children ≤4 years old (19 cases per 100 000 population in 2010) suggests that on-going transmission occurs in some Indigenous communities [54]. Molecular results of the clustering of TB cases in Indigenous populations are supported evidence of on-going transmission [94, 103, 104]. In 2012, the proportion of primary TB disease cases that were Indigenous peoples was high (42/63; 67%) compared to the foreign-born (9/63; 14%)[105]. Those who do not progress to TB disease within five years have a lifetime risk of 5% for the reactivation of TB if they remain immunocompetent [97].

2.9 Risk Factors of Tuberculosis: Overview

The disparity of TB in Indigenous peoples is a reminder of the social and medical characteristics of the disease. Identifying risk factors for TB infection, disease, and transmission requires a biological, social, environmental, and economic perspective. Upstream, midstream, and downstream factors are terms used in literature to explain current disease burdens using the interactions between policy, the DOH, and TB pathogenesis [54, 106-109]. Upstream factors include inequality through economic, social, and environmental policy [106]. Midstream factors include poor healthcare access, prolonged time to seeking healthcare, socioeconomic status, and health behaviors. Midstream factors impact downstream factors, which include diabetes, smoking, alcohol consumption, food insecurity, overcrowding, and poor ventilation [106]. Downstream factors are associated with increased transmission resulting in TB infection or an impaired immune response increasing the chance for reactivation [106].

Upstream factors are represented through Indigenous peoples' history of colonialism, racism, social exclusion, and lack of self-determination, which has contributed to their overall health status [110]. Historically, the negative experiences with TB treatment, removal of TB patients from communities into sanatoriums, high rates of TB morbidity and mortality and TB deaths that occurred in residential schools have impacted and shaped current Indigenous TB patients perspectives on illness, healthcare, and decisions to seeking care [29, 111-114]. These experiences also highlight that in the past, Indigenous peoples have not been included in deciding TB policy and directing their own care as described in the patients' charter of rights and responsibilities [115].

Indigenous peoples live with higher rates of poverty, crowded housing, poor ventilation, lower socioeconomic status, challenges in accessing healthcare, substance use, and have higher rates of comorbidities such as diabetes [116-119]. These midstream and downstream factors can increase the risk of infection and disease and represent areas of focus for interventions and strategic responses towards reducing TB in Indigenous communities [106]. Community involvement and policies improving the economic and social inequities among Indigenous peoples are important to help achieve reductions in TB [1, 101].

2.10 Tuberculosis Risk Factors: A focus on Indigenous Peoples

Delay in Diagnosis

Delay in diagnosis is an important factor that if intervened upon with can reduce the period of transmission [120]. Delay in diagnosis can be stratified further into overlapping definitions such as patient, health systems', and treatment delay [121]. Patient delay is defined as the duration between the onset of symptoms and first seeking a

medical provider. Health systems' delay is defined as the duration between first seeing a medical provider and the date of treatment. Treatment delay is defined as the duration between diagnosis date and treatment date (if treatment occurred after diagnosis date). Total delay is defined as a combined duration of patient and health systems' delay.

In literature, there has been some confusion about the term "delay in diagnosis" due to the many different definitions in literature [122, 123]. For example, some studies define "delay in diagnosis" as the duration between the onset of symptoms and the diagnosis date [123-129]. Other frequently used definitions such as: 1) the duration between the onset of symptoms and treatment date (also called total delay) [130-134] and 2) the duration between visiting a health provider (or medical exam) and the date of diagnosis [135]. Some studies included patients with pulmonary TB [125, 128, 129, 131], while others have looked at both pulmonary and extra pulmonary TB [126, 130, 133, 136]. The "diagnosis date" definition itself could imply the date when sputum samples were collected, positive result of a culture, and/or a smear positive result [128]. Treatment could be provided prior to or after a formal diagnosis date (culture-positive result) depending on factors such as clinical presentation and sputum smear positivity.

To complicate matters further, there is variability in terms of the duration that constitutes a delay. Generally in the literature, delay in diagnosis is based on a pre-determined cut-off value e.g. four weeks or a median duration based on empirical data [122, 123, 137]. A "delayed" event could also be arbitrary and vary by region based on how they define what duration constitutes a "delayed diagnosis" of TB. The variability in definitions, inclusion/exclusion criteria, ambiguity of "diagnosis date", and cut-off values

used to define a delayed event highlight the challenges that exist with comparing studies across regions, population groups, and/or countries.

For the purposes of this thesis, the term "delay in diagnosis" defined as the duration between the onset of symptoms and diagnosis or treatment will be retained when referring to literature that uses this term. However, for new analysis conducted in this dissertation, the term "time to treatment" will be used and is defined as the duration between the onset of cough and the start date of treatment (defined as the date of diagnosis in the DTT project). This term is analogous to total delay in literature or the transmission period. This term does not incorporate the term "delay", but applies this definition to a pre-determined cut-off range based on the data. For example, a transmission period of greater than 30 days would be defined as "delayed time to treatment". A transmission period of within 30 days would be defined as "timely treatment".

Delay in diagnosis can increase the risk of infectiousness, advanced disease, and mortality [128, 138-141]. Systematic reviews by Sreeramareddy et al. and Storla et al. examining literature from both low and high income countries estimated a delay in diagnosis of 25 to 185 days (mean or median) and 60 to 90 days, respectively [122, 123]. The few studies conducted in Canada have estimated delay in diagnosis of TB ranging between 12 and 105 days [128, 142-145]. These studies did not directly estimate diagnosis delay among Indigenous peoples.

In various studies conducted in low and high income countries, risk factors associated with "delayed diagnosis" (i.e. greater than a predetermined cut-off value) included gender, age, poverty, extra pulmonary TB, alcohol/substance use, low education

level, low awareness of TB, self-treatment, stigmatization, not HIV infected, location (i.e. rural versus urban), and having asymptomatic smear negative TB disease [122, 128, 143, 146].

Recreational Tobacco Use and Alcohol Consumption

The prevalence of smoking among FN (on-reserve) (43%), FN (off-reserve) (27%), and Métis (26%) peoples is greater than the non-Indigenous population (15%) [21, 39, 40]. The prevalence of smoking among Indigenous youth (14-17 years old) living off-reserve is at least twice as high compared to non-Indigenous youth [147]. A systematic review by Bates et al. reported that the risk of TB infection with tobacco smoking was 1.73 (95% CI, 1.46-2.04) times greater than non-smoking [148]. Other systematic reviews and studies have reported on associations between direct and indirect (second-hand) smoking with TB [54, 148-152], indicating that tobacco use is a risk factor for TB infection and progression to disease.

The prevalence of consuming alcohol in a 12-month period was 65%, 69%, and 62% among on-reserve FN, off-reserve FN, and Inuit peoples and is lower compared to the non-Indigenous population (76%) and Métis people (75%) [21, 39]. However, heavy alcohol consumption defined as more than four drinks on one occasion at least once a month was higher among Indigenous peoples who consumed alcohol (on-reserve FN: 41%; off-reserve FN: 35%; Métis: 30%; Inuit: 39%) compared to the non-Indigenous population (23%) [21, 39]. A systematic review estimated a relative risk of 2.94 (95% CI: 1.89-4.59) for active TB with heavy alcohol consumption (>40 g/day) [54, 153, 154]. Increased alcohol consumption has been identified in several studies as a risk factor also

associated with acquiring LTBI [54, 152-155]. Heavy alcohol use potentially impairs the immune system and is often paired with nutritional deficiency, which may increase susceptibility to TB infection [153, 154]. Social mixing patterns associated with alcohol use may increase the exposure risk to people with active TB [154].

Housing quality and Crowding

Measures of housing quality include the proportion of houses requiring major repairs. In Canada, 43%, 15%, 13%, and 36% of houses required major repairs among FN (on-reserve), FN (off-reserve), Métis, and Inuit, respectively compared to 7% in the non-Indigenous population [21]. Crowding is defined as the proportion of houses that have rooms occupied by more than one person. Estimates of crowding among FN (on-reserve) and Inuit peoples are seven to ten times higher compared to the non-Indigenous population [21]. Across the prairies, the proportion of houses on-reserve that require major repairs is five times higher compared to provincial estimates (See Table 2.2). In Alberta, Saskatchewan, and Manitoba, between 16% and 23% of FN (on-reserve) peoples lived in rooms occupied by more than one person, which is higher compared to the prairie provinces overall (between 1% and 3%) (See Table 2.2).

There is a higher risk of TB infection from overcrowding, poor air circulation, and ventilation [54, 156, 157]. A study estimated that an increase of 0.1 persons per room in a community was associated with a 40% increased risk of at least two TB cases within a three-year period (i.e. 1997 to 1999)[158]. Other literature have identified overcrowding as a risk factor for TB transmission [54, 156, 157, 159, 160]. In addition,

crowding, room volume, and air change are described as risk factors associated with new TB infections [159-161].

Socioeconomic Status

Tuberculosis is considered a social disease and its burden often align with rates of poverty [54, 101, 157]. Low socioeconomic status, household income, and low education completion rates represents upstream determinants of health that impact proximate risk factors such as poor household quality, overcrowded environments, comorbidities, and food insecurity [54, 101]. The disparity between Indigenous and non-Indigenous peoples in terms of these socioeconomic indicators are critical to understanding why TB persists among Indigenous peoples. Indigenous peoples generally experience higher unemployment rates, household crowding, and food insecurity, and lower education completion rates compared to non-Indigenous peoples [15, 20, 22, 23, 39]. These disparities were similar among on-reserve FN peoples across the Prairie Provinces (See Table 2.2). Achieving reductions in TB requires additional efforts towards improving these socioeconomic indicators that could help prevent latent infection and active TB disease [101].

Human Immunodeficiency Virus

HIV infection compromises the immune system and is the most powerful risk factor for the progression to active TB disease in those with latent infection [54, 162]. Generally, primary disease develops in 5% of people recently infected with TB (within the first two years), and there is a 5% lifetime risk thereafter [54]. However, TB

pathogenesis is impacted by HIV, and risk of disease is much greater for people with HIV infection [54]; approximately 50-110 fold higher compared to people with no other known risk factors [163].

Indigenous peoples have HIV rates three times higher than non-Indigenous peoples [47, 48]. The prevalence (diagnosed and undiagnosed) rate of HIV among Indigenous peoples was 544 per 100 000 population compared to total population (208 per 100 000 population) in 2011[47]. The proportion of HIV cases among Indigenous peoples was highest among females and youth between 15 and 29 years old accounted for 32% [47].

Although historic underreporting of HIV infection makes estimating TB-HIV co-infection challenging [54], in 2012 the Canadian HIV-TB co-infection rate ranged between 3% and 8% [105]. A study (2003-2012) was conducted in Alberta to measure HIV-TB co-infection after an "opt-out" approach was implemented where patients were routinely tested for HIV unless they indicated a wish not to be tested [163, 164]. In this study, HIV-TB co-infection in Alberta occurred in 10% of Indigenous peoples compared to 1% and 2% among Canadian-born non-Indigenous peoples and the foreign-born from other than sub-Saharan countries, respectively [165]. HIV-TB co-infection is an important consideration in Indigenous communities that have a high burden of HIV and TB because the two diseases tend to have a synergistic relationship that makes outcomes worse and treatment more difficult for both.

Diabetes Mellitus

Diabetes mellitus (DM) is a chronic illness that compromises the immune response to infections such as TB [166]. People with TB-DM have challenges with TB treatment and have higher risks for relapse and reinfection [54, 167]. The age standardized prevalence rate for diabetes among FN (on-reserve), FN (off-reserve), and Métis peoples, were 17%, 10%, 7%, respectively compared to 5% in the non-Indigenous population [51, 168, 169]. The prevalence of TB-DM was higher in areas with a high prevalence of DM and TB and the risk for TB infection and disease was 3-fold [167]. The increased prevalence of diabetes in Indigenous peoples may contribute to increased risks for TB infection and disease.

A systematic review by Stevenson et al. described the odds ratio of TB as 1.5 to 7.8 times more among persons with diabetes [170]. In another systematic review conducted by Jeon et al., there was an increased risk of TB among people with Diabetes (RR=3.11; 95% CI: 2.27-4.26) [166]. Two North American FN studies were included with a relative risk of 1.85 (95% CI: 0.34-10.19) [166]. One of these studies conducted in Saskatchewan estimated that rate ratios of TB between women with and without diabetes were only significant between 50 and 59 year olds with risk ratios of 2.7 (95% CI: 1.28-5.72) and 3.9 (95% CI: 1.58-9.67) for registered FN and other Saskatchewan people (including non-Indigenous, Metis, and non-registered FN people), respectively [118]. Screening patients with diabetes, especially in populations such as Indigenous communities where rates are higher may help direct TB control efforts.

2.10 Mathematical Modeling: Overview

The complexity of TB transmission dynamics at the population level includes individuals that could be susceptible, infected, infectious, or recovered. The contact tracing and treatment protocols that occur after a diagnosis of active TB are all important considerations to help understand the overall dynamical process of TB. A mathematical model is a useful tool for understanding these processes. It is a simplified representation of a complex dynamical system [171] that can otherwise be challenging to understand as a whole. The use of mathematical modeling is an integral part of this dissertation (see Chapter 1). Table 2.4 includes definitions of common mathematical modeling terminology.

A focus on epidemiological models and terminology

A plethora of different types of mathematical models exist in literature. Deterministic and stochastic models are two main types of mathematical modeling methods that are used to describe epidemiological processes. Deterministic models (also called compartmental models) describe a dynamical process that occurs on average using input parameters as risk/rates with no random variation and explicitly defined static contact structures [171, 172]. Stochastic models describe a dynamical process among individuals with random variability and contact structures (network) with input parameters that rely generally on probabilities [171].

Deterministic models use difference equations (discrete time) or differential equations (continuous time). Difference equations models use input parameters that are risk based. The relationship between risk and rate is:

$$Risk = 1 - e^{-rate}.$$

An early susceptible-infected-recovered (SIR) epidemiological model developed between 1926 and 1927 by Kermack and McKendrick used differential equations. Ordinary differential equations (ODEs) denoted by notations such as $\frac{dS}{dt}, \frac{dI}{dt}, and \frac{dR}{dt}$ (analogous to derivative) described the rate of change at any point in time [171-173]. The Mckendrick and Kermack SIR model is an integral foundation to mathematical epidemiology. The basic reproduction number, force of infection (based on the mass action principle), herd immunity threshold, and final size of an epidemic was estimated using the Mckendrick and Kermack model [171, 172]. An important assumption of deterministic models is that the population inside a compartment is identical and well mixed [171, 172]. The force of infection commonly denoted by $\beta I(t)$ is defined as the per capita rate for an effective contact per unit time [171, 172]. The transmission rate β can be further broken as the product of transmission probability and contact rate per unit time. Other types of popular compartmental models include susceptible-exposed-infected-recovered (SEIR) and susceptible-infected-susceptible (SIS) [171, 172]. Equations are constructed from transitions into (denoted by "+") and out (denoted by "-") from the compartments. The possibilities of adding compartments are endless and primarily depend on the type of disease and the data available. Ordinary differential equation models can also incorporate other complexities such as delay, mobility, and age structures [171, 172, 174]. In more recent models, epidemiological models using real data have benefited from the addition of different fitting methods (e.g. non-linear least squares and maximum likelihood methods) to estimate unknown input parameters [171].

Sensitivity analyses are also typically conducted to determine input parameters that are most influential in a model [171].

Some types of stochastic models used in epidemiology include discrete-time compartmental models, continuous time compartmental model, and individual based models [171]. These types of models have some randomness features and can incorporate contact, age structure, mobility, and differences in transmission probability [174]. In discrete-time compartmental models, individuals of one type are considered a single compartment e.g. susceptible individuals are counted within the susceptible compartment. Individuals can get infected, but totals at a point in time are based on the previous generation [171]. Similar to discrete-time compartmental models, continuous time compartment models considers individuals of one type within a single compartment, but time steps are based on when the next event will occur such as infection or recovery [171]. Individual based or agent based models (ABMs) follows every individual through disease state transitions. Similar to SIR, SEIR, and SIS disease dynamics in ODE modeling, disease transitions in ABMs occur at an individual level. In ABM modeling, each time step can be fixed or continuous and simulations are generally computationally demanding [171].

Stochastic models in epidemiology often have a contact network associated with a simulation. The choice of an appropriate contact structure can have significant impacts to model outcomes [175]. Standard contact structures exist in the literature. Random networks are individuals connected independent of spatial and social position. Lattice networks places individuals on a grid in space where individuals are connected to their neighbors. Small world contact structures are lattice networks with a few long-range

connections. Disease in small world contact structures is clustered with a lower probability of transmission to individuals further apart. Spatial networks place individuals in space and they are connected based on a probability proportional to their distance. Scale free networks connects individuals proportional to the current number of connections i.e. there many people have few contacts while a few people have many contacts. Scale free networks follow a power law distribution, highlighting the impact of transmission when a highly connected individual becomes infected. Individual based simulation networks have tailored contact structures of individuals and are often used to best understand the transmission dynamics of sexually transmitted infections. A visual representation of these network structures is described in Figure 2.2. [171, 176]

Mathematical models are excellent tools to help understand complex dynamics. However, the endless possibilities of compartments and parameters to describe all details in a dynamical process may lead to complex models that require many parameter values, increased computational time, and impact ease of knowledge translation. A mathematical model that focuses on important aspects of disease dynamics describes a healthy balance between overly simplistic models to highly (but not necessary) complex models. Both deterministic and stochastic modeling methods have been used for understanding TB transmission dynamics [177-179].

Deterministic TB modeling

There are many TB mathematical models in the literature with the landmark paper published in 1962. This paper describes the process of model construction and using a differential equation model (discrete in time) incorporating birth, death, susceptibility,

latent, and disease compartments [180]. Subsequent ODEs used to model TB transmission have incorporated various features such as a latent TB compartment, vaccination, age structures, treatment types, resistance, HIV, multiple cities, cost analysis, historical data, diagnosis delays, and time dependent parameters [181-195].

Results from deterministic TB models suggest that preventing and treating latent TB infection is one of the most important factors that can help to reduce TB morbidity [186, 189, 193, 196, 197]. The prevention of latent TB infection, analogous to interrupting TB transmission through active or early case finding, active screening, or contact tracing has also been shown to impact reductions in TB [186, 187, 196, 198-201]. The effectiveness of control strategies can be dependent on whether TB rates are driven by latent TB reactivation or primary TB disease from recent transmission. In geographical areas where TB rates are driven by latent TB reactivation, control efforts towards reducing transmission may not be effective [174, 202, 203].

Individual Based Modeling/Agent Based Modeling of TB

There are many examples where individual based models (IBMs) or agent based models (ABMs) have been used to simulate TB transmission dynamics [175-177, 179, 204-212]. These models have incorporated various contact structures i.e. close and casual contacts, age, gender, contact tracing, treatment, resistance, preferential mixing, and varying household size.

Similar to deterministic models, results from IBMs suggest that preventative therapy of latent TB infection can reduce TB cases [211]. Guzzetta et al. (2011) compared three models: 1) An ODE model with homogenous mixing, no age structure,

and constant population size, 2) age-structured stochastic individual based model with no household structure, a constant population size, and the incorporation of age dependent probability of developing TB, and 3) an individual based model with household, school, and workplace structure with less contacts between households when they are further apart. The findings of that paper suggest that a socio-demographic individual based model was a better approach to evaluate TB control strategies that require non-homogenous mixing such as strategies to improve contact investigations [177]. A study conducted in Saskatchewan found that in a hypothetical Indigenous community of 15,000, if the loss of follow-up in contact investigations improved from 35% (30% to 40%) to 10%, a 5.4% reduction of TB cases on average could be prevented [209]. Another study using an ABM conducted among Inuit communities found a significant reduction of TB incidence occurred from decreasing the duration between the onset of TB disease and treatment [204]. An interesting observation from Tuite et al. was that reducing housing density did not have a significant reduction in TB incidence [204]. The reduction in housing density was simulated by adding more houses, but improvement to ventilation was not considered [204]. Another study shared the importance of age and preferential mixing in TB transmission dynamics was determined to be an important factor where interventions such as screening and treatment could have the greatest impact [212]. Although individual based models are computationally demanding, the flexibility to examine interventions heterogeneously is one important advantage of using IBMs. The potential for examining other DOH such as housing density and factors affecting contact tracing could be implemented using IBMs.

The inclusion of social determinants of health with mathematical modeling

SDOH represent important risk factors associated with TB. These factors potentially impact the risk of TB transmission, infection, and progression [203, 213]. These factors can include healthcare access, low socioeconomic status, malnutrition, and low education level [203, 213]. Factors such as early case detection (time to diagnosis) are associated with other risk factors (including SDOH). Considering how the interaction of these risk factors affect TB transmission and disease is complex and methodologically challenging to implement in a mathematical model [213].

Few TB studies have investigated intervention strategies that modify these factors. A study by Ackley et al. deterministically modeled historical TB epidemics using data from FN peoples in Saskatchewan [188]. In this model, malnutrition was indirectly incorporated by a constant that described reductions on specific parameters such as progression to active TB, mortality rate, reinfection, and proportion of newly infected cases that progress to TB disease (fast progression) [188]. The effect of malnutrition on fast progression of TB was considered the top 5 most important parameters that impact TB transmission dynamics [188].

The impact of smoking on progression among FN people in Saskatchewan on TB cases was integrated using an ABM [209]. In a previously mentioned study conducted among Inuit communities, the impact of reducing housing density on TB incidence was examined using individual based modeling [204]. Modeling results from a South Korean study also found that education programs/campaigns about health and TB was among the top three factors that had the greatest impact for reducing TB transmission [199].

2.11 Conclusion

This chapter represents a review of literature examining the historical context of Canadian Indigenous peoples and health with a focus on FN and Métis communities in the Prairie Provinces, the etiology of TB, current trends of TB in Canada, risk factors of TB, and mathematical modeling of TB with an emphasis on Indigenous communities. There is a great disparity of TB in FN and Métis communities compared to non-Indigenous peoples. Understanding factors behind the high TB burden among Indigenous peoples is complex and involves the understanding of how comorbidities, excessive alcohol consumption, health seeking behaviour, and SDOH such as healthcare access, socioeconomic status, and housing conditions impact TB incidence. The heterogeneity of TB cases in Indigenous communities across the prairies where a few communities have a much higher burden than others indicates that a community-specific or tailored approach towards TB reduction strategies would work best. In communities where on-going transmission was identified as a major driver for TB incidence, examining the impact of early case finding may represent one approach. Time to treatment defined herein as the duration between the onset of cough to the start date of treatment, represents a measure that describes the transmission period. Factors associated with a delayed time to treatment (> pre-determined cut-off value) can be incorporated into a mathematical model as a parameter, which can provide quantitative evidence about their impact on TB cases and incidence. Agent based modeling will be used in this dissertation to integrate risk factors associated with time to treatment (transmission period) into a TB transmission model. The significance of this research will not only extend existing methodological approaches of integrating SDOH into an ABM, but also provide

quantitative understandings about how these risk factors impact TB cases and transmission. This will add to existing knowledge assisting TB policy makers and clinicians in making informed decisions.

Table 2. 1 Indigenous population in Canada, Alberta, Saskatchewan, and Manitoba in 2006

	Canada	Alberta	Saskatchewan	Manitoba
	2006[1]			
Total Population	31 241 030	3 256 355	953 850	1 133 515
Total Aboriginal Population[2]	1 172 785	188 365	141 890	175 395
First Nations	698 025	97 275	91 400	100 640
Métis	389 780	85 495	48 120	71 805
Inuit	50 480	1 610	215	565
	2011[3]			
Total Population	33 476 690	3,645,255	1 033 385	1 208 270
Total Aboriginal Population[2]	1 400 690	220 695	157 740	195 900
First Nations	851 560	116 670	103 210	114 225
Métis	451 795	96 870	52 450	78 835
Inuit	59 440	1 985	290	575

[1] [14]
[2] Indigenous Identity defined by Statistics Canada includes persons who reported being First Nations, Métis, or Inuit and/or Registered or Treaty Indian status, and multiple Indigenous responses
[3] [325]

Table 2. 2 Demographic characteristic of First Nations peoples on-reserve in Alberta, Saskatchewan, and Manitoba[1]

	Alberta[2]						Saskatchewan[3]				Manitoba[4]			
	On-reserve First Nations		Métis Settlement		Provincial		On-Reserve First Nations		Provincial		On-Reserve First Nations		Provincial	
Number of Reserves/ Settlements	140		8		--		143		--		104		--	
First Nations Language(s)	45 Blackfoot, Cree, Chipweyan, Dene, Sarcee, and Stoney		-- Michif		-- --		70 Cree, Dakota, Dene, Nakota, and Saulteaux		-- --		63 Cree, Ojibway, Dakota, Ojibway-Cree, and Dene		-- --	
	2006	2011	2006	2011	2006	2011	2006	2011	2006	2011	2006	2011	2006	2011
Median Population Size	1004	1297	500	585	--	--	757	952	--	--	1010	1199	--	--
Year Round Access to Roads	93%	93%	100%	100%	--	--	96%	96%	--	--	63%	63%	--	--
Percent of Houses Needing Major Repairs	49%	52%	36%	33%	7%	7%	51%	46%	11%	11%	52%	52%	10%	10%
Percent of People Who Live in Rooms Occupied by >1 person	16%	19%	9%	7%	1%	2%	18%	21%	1%	2%	19%	23%	2%	3%
Median Household Income	30,825	37,071	39,424	47,313	63,988	78,632	22,240	26,498	46,705	61,703	22,720	22,362	47,875	57,299
Unemployment Rate	27%	21%	22%	14%	4%	6%	29%	29%	6%	6%	28%	28%	6%	6%
Completion of at Least High School (>14 years old)	34%	37%	42%	48%	77%	81%	37%	40%	70%	75%	28%	30%	71%	74%

[1] Overall Sources: [316], [260], [9], [15]
[2] [326], [2]
[3] [327, 328]
[4] [329, 330]

Table 2. 3 Description of Canadian first line anti-TB drugs and their side effects

Drug Name	Treatment of Latent TB infection (LTBI) or Active TB Disease (ATBD)	Possible Adverse Side Effects
First-line drugs		
Isoniazid	LTBI & ATBD	- Liver dysfunction[1] - Hepatotoxicity increasing with age[2]
Rifampicin	LTBI[3] & ATBD	- Hepatotoxicity[4] - Renal toxicity[4] - Memory impairment[4] - Body fluids turning orange/red in colour[4] - Skin rash, fever, gastrointestinal symptoms, and thrombocytopenia[4]
Pyrazinamide	LTBI[7] & ATBD	- Hepatotoxicity[5] - Hyperuricemia[7]
Ethambutol	ATBD	- Decreased visual activity[6] - Decreased visual fields or color blindness[8]

[1] [331]
[2] [332]
[3] [71]
[4] [333]
[5] [67]
[6] [334]

Table 2. 4 A glossary of mathematical modeling terminology and definitions

Terminology	Definition[1]
Deterministic	A dynamical process that occurs on average using input parameters as rates with no random variation. Equations: difference or differential
Stochastic	A dynamical process among individuals with random variability and input parameters are generally probabilities
Discrete time	Time measurements using steps e.g. t=0, t=1, t=2,…
Continuous time	Time measurements where the steps are infinitely small
Static models	Models that do not explicitly include contact structures
Network models	Models that have contact structures
Basic reproduction number	The average number of cases that are generated by one infectious case in a fully susceptible population
Effective contact	A contact that leads to a successful transmission event occurring between a susceptible and infectious person
Force of infection	The per capita rate for an effective contact per unit time $\beta I(t)$
Herd immunity	Indirect protection of unvaccinated people among those who are vaccinated in a population
Final size of an epidemic	Total people infected during an outbreak
Nodes	Representations of agents, such as people or animals
Lattice network	Contact structure that places people on a grid where neighbors are connected
Random network	Contact structure that consist of connections independent of spatial and social position
Small world network	Contact structure similar to a lattice network with few long range connections
Spatial network	Contact structure dependent on spatial coordinates and connections are proportional to the distance between two nodes
Sensitivity Analysis	Methods that vary parameters using sampling procedures such as Latin Hypercube sampling, to assess which parameters are influential in a model
Degree distribution	A collection of total connections in a contact network
Proportional mixing	Contact patterns where connections are proportional to the total based on a stratified group such as age and gender

[1] Definitions from [171]

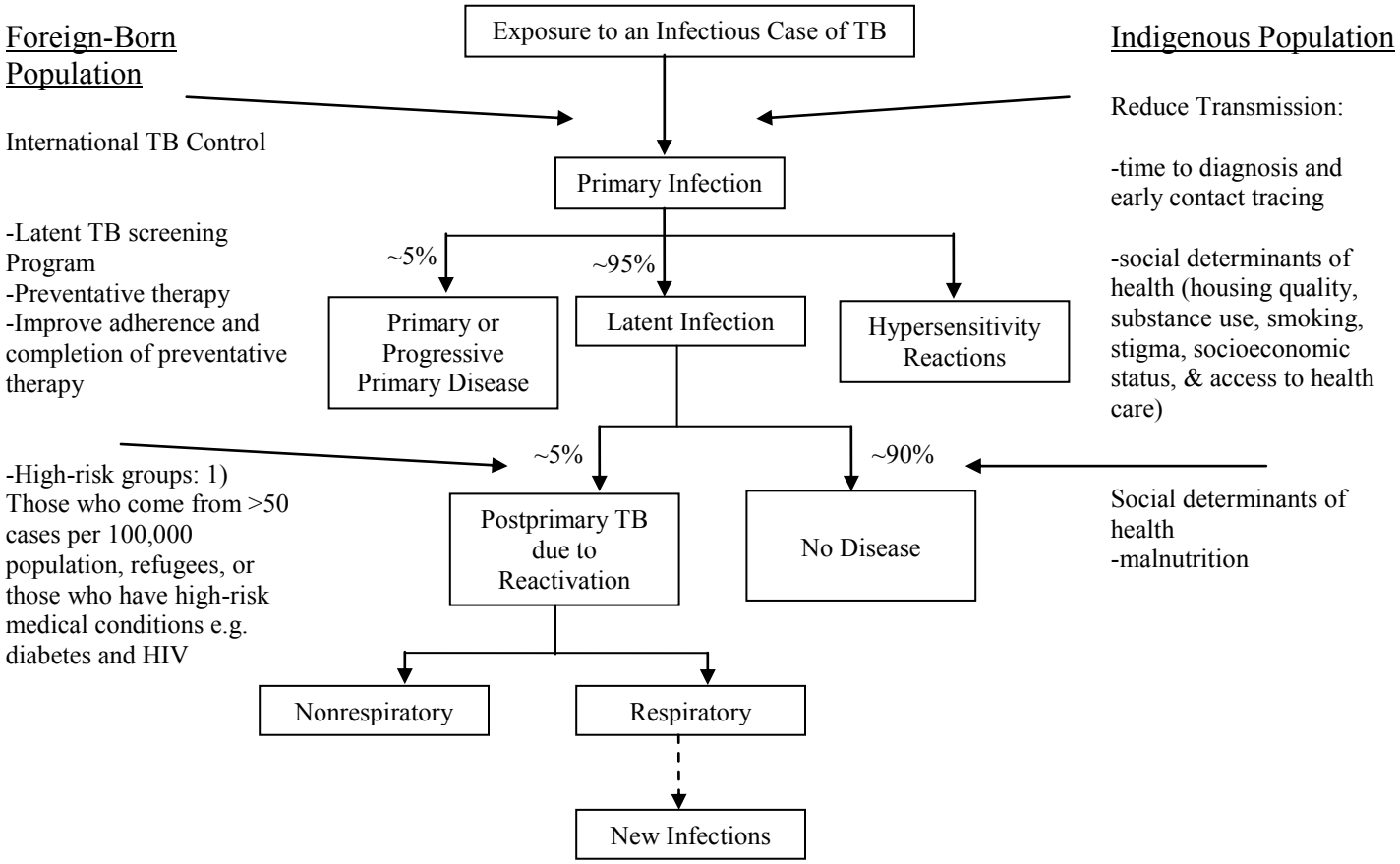

Figure 2. 1 The pathogenesis of TB and differences in strategic response for foreign-born and Indigenous populations. The main figure is taken directly from the Canadian TB standards[1]

[1] [97]

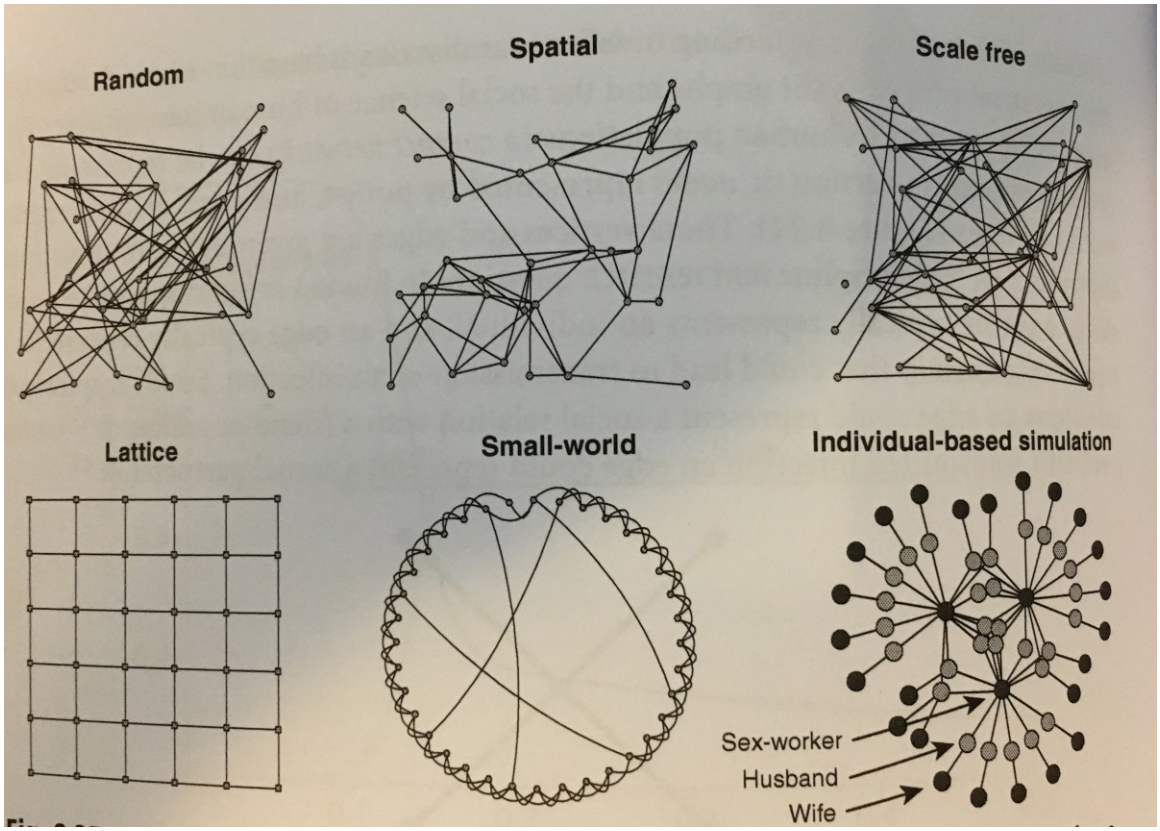

Figure 2. 2 Types of network structures in stochastic modeling[1]

[1] [171, 176]

Chapter 3: A Systematic Review of Literature about Delay in Diagnosis of Tuberculosis among Indigenous Peoples Worldwide

3.0 Summary

INTRODUCTION: In 2015, there were 10.4 million incident cases of tuberculosis (TB) and 1.8 million deaths from the disease. An important priority for TB control includes the improved interruption of transmission through a reduction in diagnosis delay. The risk of more advanced disease, and mortality can also be increased by diagnosis delays. Previous systematic reviews about diagnosis delay have not focused on Indigenous peoples whose rates of disease are generally higher than those of non-Indigenous peoples. OBJECTIVES: This systematic review aims to summarize and assess literature about time to diagnosis and treatment of TB among Indigenous peoples. It includes the scope of the literature itself, comparisons with non-Indigenous peoples, and risk factors unique to the Indigenous population group. METHODS: A literature search was conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) framework. Databases used included Ovid and PubMed databases. RESULTS: Eleven studies met the inclusion criteria for the systematic review. Diagnosis delay estimates was comparable or greater in Indigenous than non-Indigenous peoples. Variability in geographical location (i.e. remoteness), healthcare access, and regions with endemic TB influenced comparisons made between Indigenous and non-Indigenous peoples. Most risk factors significantly associated with delay in diagnosis were independent of Indigenous status except for language barriers. CONCLUSION: The availability of literature about diagnosis delay of TB focusing on Indigenous people is sparse

considering that Indigenous peoples total at least 370 million across 90 countries worldwide and generally have higher rates of TB disease. Increased research in this area is required to better support the results of this systematic review.

3.1 Introduction

Tuberculosis (TB) is one of the ten top causes of death worldwide with 1.8 million dying from the disease in 2015, 95% of these in low and middle income countries [214]. In 2015, incident TB cases totaled 10.4 million with an average rate of decline of 1.4% annually since 2000 [215]. The management of TB requires early detection of TB cases, reducing the reservoir of latently infected people, and ensuring high treatment completion rates [122, 130]. Strategies to achieve reductions in TB incidence are challenging and complex as they involve addressing biological, social, environmental, and economic perspectives [106]. Risk factors associated with TB transmission and progression include health inequalities, poor healthcare access, longer diagnosis delay, low socioeconomic status, chronic illnesses, overcrowding, and poor ventilation [106].

Diagnosis delay, defined in this systematic review as the duration between the onset of symptoms and diagnosis or treatment, has been identified as a major contributor to TB transmission [122, 216]. Early detection of pulmonary TB cases especially among those that exhibit symptoms associated with transmission represent important areas of intervention that could help reduce the reservoir of latent infection and prevent advanced disease and mortality [128, 138, 139]. The interruption of TB transmission through early diagnosis is complex given its many risk factors. Adding to its complexity, risk factors associated with delay in diagnosis include both patient and healthcare system level factors. Based on previously conducted systematic reviews, diagnosis delay estimates

averaged between 25 and 185 days and risk factors included poor access to healthcare, initial visits to traditional or private practitioners, poverty, substance use, extra pulmonary TB, smear-negative TB, HIV, self-treatment, stigma, and lacking knowledge of TB [122, 128, 137, 143, 146, 217].

Systematic reviews conducted to date have not focused on Indigenous peoples, whose rates of TB are generally higher than non-Indigenous peoples [218]. Further assessment of literature about diagnosis delay among Indigenous peoples could help identify potential knowledge gaps and possibly reduce this rate disparity. This systematic review aims to summarize and assess literature about delay in diagnosis of TB among Indigenous peoples worldwide using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) framework [218, 219]. The assessment highlights the scope of literature available, compares estimates of diagnosis delay among Indigenous peoples to non-Indigenous peoples, and identifies additional risk factors that are unique to the Indigenous population group. Pulmonary TB was the main focus in this systematic review since it is the disease site associated with highest transmission. Literature that did not include pulmonary TB was excluded.

3.2 Methods

A literature search was conducted and focused on studies that provided estimations of diagnosis delay and risk factors for that delay (when available). The term Indigenous peoples is defined as those who are self-identified as belonging to this population group [218, 220, 221]. In this systematic review, diagnosis delay was defined as the duration between the onset of symptoms and diagnosis or treatment. The duration

between the onset of symptoms and treatment is also referred to as total delay, which can be stratified into two main parts defined below:

Patient delay: the time from onset of symptoms to first visit with a medical professional.

Healthcare system delay: the time from the first visit with a medical professional to start of treatment.

A cut-off point for diagnosis delay, often defined as the median estimate within a study, represented a threshold value of delay. A "delayed" event was any duration greater than the cut-off value and a "timely diagnosis" was any duration less than the cut-off value.

Search Strategy

Ovid and PubMed databases were used to search for literature about estimation of and risk factors (when available) for diagnosis delay of TB among Indigenous peoples. A combination of text word, broad, and narrow search terminology about tuberculosis, Indigenous peoples, and diagnosis delay were used to search for literature. Table 3.1 describes the search terms used in the systematic review. Databases in Ovid include Embase (1974-2016), Global Health (1910-2016), Ovid Medline (1946-2016), Journals@Ovid Full Text, and all Evidence-based Medicine (EMB) Reviews (Cochrane Database of Systematic Reviews: 2005-2016; ACP Journal Club: 1991-2016; Database of Abstract of Reviews of Effects: 1st quarter 2015; Cochrane Central Register of Controlled Trials: 2016; Cochrane Methodology Register: 3rd quarter 2012; Health Technology Assessment: 3rd Quarter 2016; NHS Economic Evaluation Database: 1st Quarter 2015).

Duplicate records were removed prior to assessing literature. The search methodology was conducted in October 2016.

The narrow search terms for Indigenous peoples were obtained from a systematic review conducted by Tollefson et al. that quantified the burden of TB disease among Indigenous peoples [218]. This previously conducted systematic review obtained Indigenous group names from Bartlett et al. and organizations participating in the United Nations Permanent Forum on Indigenous Issues (UNPFII) [218, 221].

Selection of Studies

Studies were selected using a two-step process and two independent reviewers. Consensus between reviewers was reached when discrepancies arose about the inclusion and exclusion of literature. Figure 3.1 describes the selection of studies using the search strategy including both inclusion and exclusion criteria. The first screening excluded abstracts with no information about Indigenous peoples, tuberculosis, and diagnosis delay related terminology (see Table 3.1). Abstracts with no information about Indigenous peoples, but included tuberculosis and diagnosis delay related terminology conducted in countries with Indigenous groups were excluded if there was no disaggregate information (i.e. a study that presented results stratified by Indigenous and non-Indigenous groups) provided within the main text. The second screening involved reviewing the main text and excluding literature that did not include pulmonary tuberculosis and estimates for diagnosis delay. Literature was limited to those written in English and those with accessibility in full-text. There were no restrictions on sample size and publication dates to maximum the number studies included in the systematic review.

Analysis of Studies

Information extracted from studies included the year of study, country, total study size, Indigenous population group, type of data (single population or disaggregate), total sample size of Indigenous population group (if disaggregated information provided), definition(s) of diagnosis delay, estimate of diagnosis delay (mean, median and/or single estimate), and factors associated with diagnosis delay (if provided). Disaggregate information represented studies with samples that included both Indigenous and non-Indigenous peoples and data reported was stratified by population group. Studies often present delay in diagnosis as either a mean or median duration. However, percentiles were reported when the mean and median estimate for diagnosis delay was not available. Mean values for patient and health systems' delay were combined to estimate diagnosis delay (if reported separately). Literature that estimated diagnosis delay using pulmonary and extra pulmonary TB cases were included in the systematic review even though this estimate may be overestimated by including extra-pulmonary TB cases. In these articles, diagnosis delay estimates were reported for pulmonary TB alone when available. For studies that reported risk factors associated with diagnosis delay of TB, analytic methods and risk factors associated with diagnosis delay (p-value<0.05 when available) were reported. Risk factors associated with diagnosis delay that was reported, as major themes in qualitative studies were also included. The direction of the association is represented with ↑ and ↓ for 'delayed diagnosis' and 'timely diagnosis', respectively.

3.3 Results

The search conducted using keywords in Table 3.1 resulted in a total of 523 records using Ovid search databases (n=363) and PubMed (n=160). Figure 3.1 describes

the total studies obtained, screened, and selected for the systematic review. Removing duplicate records yielded a total of 496 records (Figure 3.1). A total of 24 records (23 full text journal articles, 1 conference abstract) assessed for eligibility resulted in the final selection of 11 records in the systematic review (Figure 1). Studies represented Indigenous peoples from North (n=2) and Latin (n=1) America, Australia (n=1), New Zealand (n=1), Asia (n=3), Africa (n=1), Vanuatu (n=1) and Solomon Islands (n=1). Table 3.2 provided a detailed summary of studies that met the inclusion criteria for the systematic review and included the year of study, country, Indigenous population group, type of data, definition of diagnosis delay, diagnosis delay estimate, factors associated with diagnosis delay (when applicable), and study reference.

North and Latin America

Three studies represented Indigenous peoples from North and Latin America. Indigenous groups in Canada include First Nations, Métis, and Inuit and represented 4.3% of the total Canadian population as of 2011 [13, 218, 221]. American Indian/Alaskan Native (AI/AN) and Native Hawaiian/Pacific Islander (NH/PI) are Indigenous groups in the United States and accounted for 0.9% of the total United States population based on 2008 population estimates [124, 218, 221]. Latin America (including Mexico and the Caribbean) has approximately 34 million Indigenous peoples (8% of the total population) from 450 ethno-linguistic groups [221]. The overall incidence of TB was generally highest in the Latin America Region followed by Indigenous groups in Canada and United States [218], however, in Latin America, some specific Indigenous

groups (e.g. Aguaruna, Nomastshiguenga, Shawi, and Shapra) may have a comparable or lower TB incidence than non-Indigenous peoples [218].

There were no dedicated studies focusing on diagnosis delay from Canada and the United States. Estimates of diagnosis delay were based on a TB outbreak investigation in Canada and an observational study in the United States. In both of these studies, diagnosis delay was defined as the time between onset of symptoms and diagnosis date. Smear-positive sputum was defined as the date of diagnosis in the Canadian study. In the United States study, the date of diagnosis definition was unknown and may be overestimated if the culture-positive date was used. The study from Canada estimated a diagnosis delay of 120 days from the source case of an outbreak investigation (Table 3.2) [222]. An observational study conducted in Arkansas, United States between 2000 and 2005 reported that 65% of symptomatic NH/PI TB patients (n=26/40) had a delay in diagnosis greater than 60 days from symptom onset. Factors associated with delayed diagnosis (>60 days) included language and transportation barriers, difficulty navigating the health system, and not seeking medical care (Table 3.2). [124, 125, 223] The analytical methodology and significance level used in the observational study were unknown [124, 125]. A study conducted in Lima, Peru estimated a median patient delay of 20 days and self-therapy was a significant risk factor [224]. Healthcare system delay was not measured in this study. The total number of Indigenous peoples (Andean and Amazonian) represented in the study was also unknown. The migration of Indigenous peoples to shantytowns around Lima suggested that this proportion might be much larger. A unique feature of this study was the inclusion of both confirmed (63% of total) and suspected (37% of total) TB patients. Suspected TB patients were selected if their

duration of cough was greater than 15 days, which may have inflated the median duration of delay in diagnosis. Confidence intervals were not provided for these estimates.

Australia and New Zealand

Two studies estimated diagnosis delay among Indigenous peoples from Australia and New Zealand, who made up 2.4% and 14% of the total population, respectively [221]. Overall, Indigenous groups in Australia are often also called "Aboriginal Australians", "Aborigines", "Natives", "Indigenous Australians", and "Torres Strait Islanders", however, there is a preference to using local names such as Wa's Nyoongar, Wongi, and Tamitji people [221]. Indigenous groups in New Zealand are the Maori and prefer to be called "Tangata Whenua" or "people of the land" [221]. Although, the incidence of TB among Indigenous peoples were lower in Australia and New Zealand compared to Indigenous groups of other countries [218], the burden of TB was still disproportionately higher among Indigenous than non-Indigenous populations in Australia and New Zealand [218].

In a study conducted in Queensland, Australia, the median patient and healthcare system delay were 30 and 11 days, respectively [132]. The study included and presented data from all notified TB (pulmonary and extra pulmonary) cases between 1985 and 1998 (n=782) in addition to, a secondary analysis with only pulmonary smear-positive cases (n=375). The Indigenous population was presented as disaggregate data by risk group type. The study summary in Table 3.2 presented estimations from only pulmonary smear-positive TB cases (n=375 cases; n=47 cases among Indigenous peoples). Risk factors associated with diagnosis delay were assessed by delay type (patient vs. healthcare

system) and stratified by risk group type (Indigenous, non-Indigenous, and migrants). A Cox proportional hazards model was used to identify risk factors associated with both patient and healthcare system delay. The analysis showed that Indigenous peoples were at a decreased risk of patient delay (RR<1) and had no significant association for healthcare system delay. A chart review conducted among all smear-positive pulmonary TB cases with diagnosis delays of more than 90 days showed that an uninvestigated cough and misdiagnosis of a chest x-ray was associated with longer patient delay. Obtaining confirmation of diagnosis and referrals for specialist treatment were associated with longer healthcare system delay. The chart review results were not stratified by Indigenous and non-Indigenous group and risk factors represent results for the study population as a whole.

A study conducted in Waikato Health District, New Zealand included all notified TB cases (1992-2001) and estimated a delay in diagnosis period of 28 days (15^{th} percentile) [136]. Approximately 47% of all notified TB cases were Indigenous (Maori and Pacific Islander). This study estimated diagnosis delay by TB type (pulmonary and extra-pulmonary) and ethnic group (Indigenous and non-Indigenous). An analysis of both Indigenous and non-Indigenous TB cases showed that the only factor associated with diagnosis delay (>28 days) was increasing age. Indigenous status was not a significant predictor. Approximately 38% of notified TB patients did not have information about diagnosis delay and their demographic information was not analyzed. The impact of the missing information on diagnosis delay estimates was unknown. The end point of the delay in diagnosis estimate was the case notification date and its potential underestimation could occur if the duration between diagnosis and treatment was not

included. Risk factor analysis for these studies (Australia and New Zealand) included both Indigenous and non-Indigenous cases and its unknown whether these results would differ if Indigenous cases were only considered.

Asia and Africa

Africa has more than 14.2 million Indigenous peoples who are grouped as hunter-gatherers, fisher people, or pastoralists [221] and only one study met the inclusion criteria for the systematic review (see Table 3.2). Indigenous people in Asia reside in countries such as Taiwan, Thailand, China, Philippines, Indonesia, Vietnam, and India [218, 221]. Indigenous people from Asia accounted for three studies that were conducted in Thailand, Taiwan, and India. There is no Thai word to describe Indigenous, but hill tribes and village people are other synonymous terms [221]. The population of hill tribe people was 9.2 million (14% of the total population) located across 20 provinces in the Northern and Northwestern parts of Thailand [225, 226]. The population for Indigenous groups living in the South and Northeast were unknown [225]. Approximately 400,000 Indigenous peoples (1.8% of the total population) representing 14 tribes (e.g. Saisiyat, Rukai, Puyuma, and Atayal) live in Taiwan [227, 228]. The Indigenous population in India (also knowns as Adivasi) is one of the largest worldwide with an estimated 84.3 million people (8.2% of the total population) across approximately 250 tribes [218, 221]. The TB incidence among Indigenous peoples in Asia (Thailand, Taiwan, and India) and Africa were generally higher than non-Indigenous peoples [218, 229].

A study conducted in the Afar Region of Ethiopia between 2009 and 2010 estimated a diagnosis delay of 70.5 days among pastoralists (44^{th} percentile) and non-

pastoralists (54th percentile) [130]. Semi-structured interviews conducted of patients (pastoralists: n=91; non-pastoralists: n=125) in two DOTS clinics included both pulmonary and extra pulmonary TB. Risk factors associated with patient delay (>20 days) included self-treatment, first visiting a non-formal health provider, and residing greater than 10 km away from a health facility. The proportion of pastoralists (60.4%) experiencing patient delay was greater than non-pastoralists (36%). Risk factors associated with diagnosis delay included having extra pulmonary TB, first visiting a health clinic compared to a hospital, and Indigenous status (i.e. pastoralist). TB cases diagnosed in other DOTS clinics were not included [130]. Risk factor analysis was not stratified by TB type (pulmonary and extra-pulmonary) and Indigenous status (pastoralists and non-pastoralists). A study conducted in Thailand (n=557) between 1998 and 2000 estimated a median patient and healthcare system delay of 21 and 7 days, respectively among smear-positive pulmonary TB cases. There were 74 Hill Tribe people included in the study. Overall patient delay (>21 days) was associated with Hill Tribe ethnicity, borrowing money to visit hospital, and no previous visit to a hospital. No multivariable analysis was conducted for healthcare system delay, but univariate analysis show that being female was significantly associated with longer healthcare system delay (>7 days). A study conducted in Taiwan estimated healthcare system delay among pulmonary TB patients between 2002 and 2006 [135]. Healthcare system delay was stratified as diagnostic delay (time from first medical exam to diagnosis) and treatment delay (time from diagnosis to treatment). The mean healthcare system delay was 18 days with a margin of error of 44 days among Indigenous peoples in Taiwan (n=2530). Risk factors associated with diagnostic delay (>9 days) included diagnosis at a medical center

and living with family. Risk factors associated with treatment delay (>2 days) included being Indigenous, living alone, and diagnosis at non-medical center. Risk factors associated with healthcare system delay (diagnostic and treatment delay) included increasing age, smear-negative result, culture-positive result, and a normal chest x-ray result. The analysis of risk factors in these studies from Ethiopia, Thailand, and Taiwan were conducted at an aggregate level, which included both Indigenous and non-Indigenous populations. Risk factors associated with delay in diagnosis that were specific to Indigenous peoples were unknown.

A study conducted in Odisha, India among Indigenous (Tribal) patients with smear-positive pulmonary TB estimated a median diagnosis delay of 24 days. Risk factors associated with patient delay (>21 days) included travelling at least 5 km to a health facility, lack of TB awareness, cost of treatment/transport, and illiteracy [131]. Risk factors associated with healthcare system delay (>7 days) included administrative verification to distribute medicine and visit to traditional or private practitioners after TB diagnosis [131]. The estimate of diagnosis delay might be underestimated since the study only included smear-positive pulmonary TB cases [122]. Although the study stated that all participants were Indigenous, 10% (n=28) were stated as "others" (without a clear definition) suggesting the possibility of a mixed study population.

Melanesia Region

The Melanesian region consists of six countries, Vanuatu, the Solomon Islands, Fiji, and Papua New Guinea in addition to islands affiliated with other countries such as New Caledonia (France) and Maluku Islands (Indonesia) [230]. A total of two studies

estimated diagnosis delay among Indigenous peoples from Vanuatu and the Solomon Islands. Vanuatu located in the South Pacific Ocean is an archipelago of 82 islands where approximately 98% of the total population (n=279,000) are Indigenous (Melanesian or Ni-Vanuatu) [126, 230]. The Solomon Islands located north of Vanuatu have approximately 674,000 (99% of the total population) Indigenous peoples (Melanesian, Polynesian, and Micronesian) [231]. The incidence of TB in Vanuatu and the Solomon Islands ranges between 50-100 cases per 100,000 population [232].

The two studies conducted in Vanuatu and the Solomon Islands had estimates for diagnosis delay that included both pulmonary and extra-pulmonary TB. Diagnosis delay estimates might be overestimated if pulmonary TB were only considered [122]. A study conducted in Vanuatu estimated a median delay in diagnosis of 49 days among Indigenous (Melanesian) TB patients between 2010 and 2012 [126]. Although the sample size was small (n=35), qualitative analysis showed that risk factors associated with diagnosis delay included a misunderstanding about TB, misdiagnosis, and first visiting a traditional practitioner for TB symptoms. A study conducted in the Solomon Islands (East Kwaio) between 2011 and 2012 estimated a diagnosis delay that ranged between two and three years among Indigenous patients (Kwaio people) [233]. Risk factors associated with delay in diagnosis determined from interviews (n=3) and a focus group (n=12) included preference for traditional practitioners, long distance to health services, cost of health services, cultural taboos, social isolation, and old age. In East Kwaio, many people live in extremely remote locations where there are no roads to the local hospital, community-based TB services, or DOTS [233]. These areas report lower TB detection

and treatment completion rates [233]. The exceptionally long diagnosis delay may be attributed to these challenges of accessing TB services [233].

Comparisons between Indigenous and non-Indigenous peoples

Comparisons of median/mean diagnosis delay estimates were made using results within studies if Indigenous status was considered a sub-population. Among studies focusing on Indigenous peoples, national literature (when available) was used as a comparative group. Table 3.3 describes diagnosis delay comparisons of studies included in the systematic review with other national studies. Comparisons for Vanuatu and the Solomon Islands were not made due to the unavailability of national literature.

In Canada, the delay in diagnosis of TB was comparable or slightly longer in Indigenous (First Nations) than non-Indigenous peoples (see Table 3.3). Although this comparison was based on one estimate in a study, later results (see Chapter 5) were consistent with the observation that delay in diagnosis was comparable in Indigenous and non-Indigenous peoples. There were no published studies that estimated diagnosis delay of TB among the Inuit and Métis and comparisons between these Indigenous groups were unknown. In the United States, diagnosis delay among Indigenous peoples was generally longer than non-Indigenous peoples (see Table 3.3).

New Zealand and Taiwan delay in diagnosis estimates were comparable between Indigenous and non-Indigenous peoples (see Table 3.3). Although diagnosis delay estimates for the New Zealand study were comparable, missing data among 38% of the cases may impact these comparisons [136]. The study reported that 85% of all TB cases had a delayed diagnosis of over four weeks, which was important given that most TB

cases in the study lived in rural areas and were further from secondary health services [136]. In this study, Indigenous peoples (Maori and Pacific Islander) disproportionately represented 50% of the total cases while making up only 25% of the total population [136, 234].

In Australia and India, studies showed that diagnosis delay in India and patient delay in Australia were lower in the Indigenous population group (see Table 3.3) [131, 132, 137]. The authors in the Australian study caution its interpretations since the age-adjusted case fatality rate is higher in the Indigenous population group and 30% of Indigenous cases who were smear-positive reported having no symptoms [132]. Recall bias could impact these results. The authors also noted that the improved healthcare delivery and advanced disease might be other factors leading to earlier diagnosis [132]. In Odisha, India, patient delay was longer in Indigenous peoples (see Table 3.3). Patient delay among Tribal patients were impacted by illiteracy (87%), poor knowledge of TB (99%), living at least 5 km from a health facility (42%), and first consulting traditional practitioner or private doctors for TB symptoms [131].

In Peru, comparisons of delay in diagnosis between Indigenous and non-Indigenous peoples were inconclusive. Table 3.3 shows that patient delay was shorter among Indigenous (Andean & Amazonian) than non-Indigenous population groups using one study as a comparison. The other two studies could not be used for making comparisons due to differing definitions of delay (1st study: diagnosis delay and 2nd study: healthcare system delay). The study conducted in Lima included patients from shantytowns (populated by the migration from Andean and Amazonian communities) [224]. In this study, the proportion of Indigenous peoples in the population was high,

however its exact ratio was unknown. The comparison study conducted in Iquitos, Loreto (in Peru) also included participants from shantytowns. The proportion of Indigenous peoples in the comparative study was also unknown and may not be representative of the population in Peru making comparisons inconclusive.

Comparisons of diagnosis delay between Indigenous and non-Indigenous peoples were inconsistent in studies published in Thailand and Ethiopia. In Thailand, within study comparisons showed that patient delay was longer for Indigenous (Hill Tribe) compared to non-Indigenous peoples [127]. However, two studies conducted in Southern Thailand reported non-Indigenous peoples had either comparable or longer patient and healthcare system delays compared to the Hill Tribe people in Northern Thailand [235, 236], which indicated some geographical variability. Similarly, for Ethiopia, within study comparisons showed that the Indigenous peoples (Pastoralists) had a longer delay in diagnosis than the non-Indigenous population [130]. Comparisons to another study conducted among the general population in the Amhara Region (in Ethiopia) reported diagnosis delay estimates that were comparable to Pastoralists [121].

Risk factors associated with Diagnosis delay

Table 3.4 summarizes the risk factor analysis conducted across all eleven studies. Among studies where Indigenous peoples were a sub-population group, being male and having Indigenous status were both associated with either delayed or timely diagnosis (see Table 3.4) [132, 135]. Across all studies (see Table 3.4), increasing age, diagnosis at a non-medical center, visits (or 1st visit) to traditional practitioners/non-formal health providers, misdiagnosis, self-treatment, greater distance to health facility, cost of

healthcare, and administrative challenges were associated with delayed diagnosis (including patient, healthcare system, and treatment delays). Language barriers, reduced TB knowledge, cultural taboos, and fear of social isolation were additional risk factors associated with delayed diagnosis among studies that solely focused on Indigenous peoples.

3.4 Discussion

Although there is an estimated total of at least 370 million Indigenous peoples across 90 countries worldwide [220], the search strategy resulted in only 11 studies that met the inclusion criteria for the systematic review (see Figure 1). Overall, delay in diagnosis studies in literature not specific to Indigenous peoples has also been limited with between 23 and 58 studies included in systematic reviews [122, 123, 137]. In addition, studies about TB burden among Indigenous peoples worldwide were low, with 91 studies included in a systematic review conducted by Tollefson et al. [218].

In this systematic review, the literature estimating diagnosis delay among Indigenous peoples was sparse and six of the eleven studies (55%) focused solely on Indigenous peoples [124, 124, 126, 131, 222, 224, 233]. The other five studies included diagnosis delay estimates stratified by Indigenous status [127, 130, 132, 135, 136] and Indigenous group was assessed as a risk factor for delay in diagnosis.

Studies conducted in one Indigenous group within a country or geographical area may not be generalizable to other Indigenous groups even within the same area due to cultural diversity. For example, cultural values, colonization history, the utilization of traditional medicine, and location (i.e. degree of remoteness) were some differences between Indigenous groups that may impact comparisons about delay in diagnosis of TB.

Among studies where Indigenous status was a sub-population group, within study comparisons were made to better control for population distributions and methodology. In addition, the few delay in diagnosis studies included in this systematic review made comparisons challenging and warrants caution in its interpretation.

Public Health Importance

Overall, all eleven studies except one [233] had an average (mean or median) diagnosis delay within 25 to 185 days, a similar range obtained from a systematic review conducted by Sreeramareddy et al. [123]. One study that fell outside this range was conducted in Malaita (Solomon Islands), a community that was extremely remote with barriers to healthcare access primarily due to the distance, cost, and cultural values (preference for traditional practices) [233]. The geographical variability in terms of healthcare access i.e. cost and distance, overall TB burden, and cultural values impacted delay in diagnosis estimates. Based on the 11 studies, delay in diagnosis estimates were either comparable or higher in Indigenous compared to non-Indigenous peoples.

Although there were some exceptions [131, 137, 236, 237], these studies highlight the importance of interrupting transmission through early diagnosis is a crucial factor to reducing TB cases. The benefits of improving risk factors associated with delay in diagnosis can help both Indigenous and non-Indigenous peoples worldwide.

Delay in diagnosis estimates reported from countries with a TB burden that was medium (50-100 cases per 100,000 population) and high (>100 cases per 100,000 population) were inconsistent between Indigenous and non-Indigenous peoples (see Table 3.3). In these countries, people independent of Indigenous status might face similar

circumstances of increased poverty, malnutrition, overcrowding, reduced access to healthcare, and poor social capital [238]. This suggested that risks for TB transmission might not be different between Indigenous and non-Indigenous peoples in these countries. Indigenous peoples in low TB incidence countries such as Canada, United States, Australia, and New Zealand generally report higher rates of poverty, poor housing conditions, chronic illnesses, and addictions [94, 136, 160, 239, 240] and are not immune to the risk factors most commonly associated with increased susceptibility to TB also found in medium and high incidence countries. The burden of TB was further compounded among Indigenous peoples who have experienced a colonial past that included depopulation, legal control, ideology, urbanization, and paternalism such as massacres, acts defining identity, land settlement agreements, residential schools, discrimination, and the inhumane treatment of TB [241-244].

In this review, there were risk factors which (see Table 3.4) were consistently associated with delayed diagnosis, similar to what has been reported in other systematic reviews on this topic [122, 137]. Risk factors identified for delayed diagnosis included reduced healthcare access, low education or knowledge about TB, and cultural taboos (see Table 3.4) [122, 137]. Long distances to a medical facility, diagnosis at a non-medical center or traditional practitioner, self-treatment, and cost of transportation were specific healthcare access risk factors that were associated with delayed diagnosis [125-127, 131, 233]. Although staff education and training of medical centres (public/private/formal/informal) and medical professionals could improve factors related to healthcare access, structural challenges such as poverty and food insecurity impact the feasibility and acceptance of public health interventions [245]. Recognizing the

relationship between these structural factors and public health interventions [245], specifically in countries or population groups that experience a higher rate of poverty is important to determine ways of overcoming barriers to healthcare access. In terms of healthcare costs, patients with TB experienced costs not only for diagnosis and treatment, but indirect costs related to reductions in household incomes from loss of wages and additional travel costs [246, 247]. For Indigenous peoples living in remote locations, these costs were further compounded and was shown to be a significant risk factor for delayed diagnosis [127, 233].

The use of self-treatment, non-medical centres/persons, traditional practitioners, and cultural taboos were areas where TB education could improve patient delays. Traditional medicine is an integral part of the culture in some Indigenous communities and encouraging the use of non-traditional medicines can be challenging. In addition, costs and distance to health facilities were reported to result in greater use of local traditional practitioners [126, 233]. Encouraging the use of western medicine located further away can pose additional challenges. Making healthcare more accessible is important to help shorten patient delays. Forming collaborative relationships with Indigenous communities including traditional practitioners could help encourage people with TB to seek additional care from western medicines.

Limitations

The literature that met the inclusion criteria after using the search methodology was sparse with only eleven studies. This limits the generalizability of the conclusions about delay in diagnosis comparisons between Indigenous and non-Indigenous

populations and its risk factors. This systematic review highlighted the need for more studies to better understand delay in diagnosis among Indigenous peoples since their overall TB burden is generally higher than non-Indigenous peoples [218]. The research methodologies within studies varied from population based studies to the use of secondary data sources, each having its own biases and limitations. The definitions of delay varied across studies, and is a limitation noted in other systematic reviews [122, 123, 137, 217].

Reporting on comparisons between studies was a challenge given the variation of diagnosis delay definitions used in literature. This systematic review reported diagnosis delay definitions by study in Table 3.2 and classified the estimates as diagnosis, patient, healthcare system, or total delay. Most studies used similar start and end points and where definitions were different, comparisons were not made (see Table 3.3). The definition of delayed and timely diagnosis was also variable across studies. The word "delay" can be misleading since this cut-off point based on pre-determined knowledge or estimated from data is arbitrary. In studies where the median or mean estimates did not exist, percentile estimates were provided instead (see Table 3.2) and represented an arbitrary cut-off value. Comparisons made (without meta-analysis) between studies using different cut-off values were a limitation in this systematic review.

The search methodology used in the systematic review included literature that focused on pulmonary TB. However, in four studies, both pulmonary and extra pulmonary TB were included in the estimation of diagnosis delay [126, 130, 136, 233]. Extra pulmonary TB, generally associated with longer diagnosis delay [122] was reported as a risk factor in one of the four studies [130] (see Table 3.2). Two studies that estimated

diagnosis delay only included smear-positive pulmonary TB cases [131, 236]. Smear-negative TB cases, generally associated with longer delays [122, 137] may have underestimated delay in diagnosis.

3.6 Conclusion

The World Health Organization's goal for the reduction of TB incidence by 50% (compared to 2015 estimates) by 2035 requires improved case finding, increased treatment completion rates, reducing risk factors associated with progression from latent infection to disease, and most importantly the prevention of new TB cases. Understanding factors that can potentially reduce the time between the onset of symptoms and treatment (diagnosis delay) is important for the interruption of on-going transmission. Especially in high burden settings, the prevention of new TB cases also reduces the reservoir of latent TB cases that allow TB to persist. The fact that the incidence rate of TB is generally higher among Indigenous peoples motivated this systematic review that aimed to compare estimates of and risk factors for delay in diagnosis with non-Indigenous peoples. While only eleven studies that met the inclusion criteria were included in this systematic review, delay in diagnosis estimates are overall comparable or greater in Indigenous compared to non-Indigenous peoples and risk factors are similar between both population groups. Due to the limited availability of literature about diagnosis delay among Indigenous peoples, future work is required to better support these observations. Overall, addressing risk factors associated with delay in diagnosis would have clear benefits to both Indigenous and non-Indigenous peoples, in the prevention of TB.

Table 3. 1 Keywords used for search strategy in the systematic review of delay in diagnosis studies among Indigenous peoples

Theme	Search Terms[1]
Tuberculosis	TB OR tuberculosis OR pulmonary TB OR pulmonary tuberculosis
Diagnosis Delay	diagnos* delay OR treatment delay OR treatment seek* OR time delay OR delay* in diagnos* OR delay* in treatment OR patient delay OR health system* delay OR health provider delay OR health seek* period OR doctor delay
Indigenous Peoples[2]	american native continental ancestry group OR indigenous OR "indigenous people*" OR "indigenous population*" OR north american indian, inuit* OR oceanic ancestry group OR first nation* OR metis OR aborigin* OR torres strait islander OR maori OR cook islander, OR Wa's Nyoongar OR Wongi OR Tamitji OR Koori OR Tangata Whenua, native american OR alaska natives OR roma OR bushmen OR herdsmen OR hill people OR tribe OR tribal OR eskimo* OR amazon* OR adivasi OR lahu OR akha OR mon OR lua OR mbri OR karen OR hmong OR miao OR hui AND (minority and china) OR (aka OR babenjelle OR babongo OR bacwa OR bagyeli OR baka OR bakola OR bakoya OR bambuti OR batwa OR pygmy OR aasax OR akie OR aweer OR barabaig OR dahalo OR datoga OR elmolo OR hadzabe OR hadza OR maasai OR ogiek OR sandawe OR sengwer OR waata OR yaaku OR amazigh OR imazighn OR berbers OR tuareg OR afar OR aka OR babendjelle OR boranna OR dinka OR fulani OR kanuri OR karamajong OR manjo OR nuer OR peul OR pygymy OR tuareg OR tubu OR wodaabe OR bassari OR bororo OR daza OR nemadi OR ogoni OR teda OR khoekhoe OR khoikhoi OR basarwa OR khwe OR nama OR san) AND africa OR tsumkwe OR aleut OR alutor OR chelkancy OR chukchi OR chulymcy OR chuvancy OR dolgan OR ency OR evenk OR itelmen OR kamchadal OR kereki OR kety OR khanty OR koryak OR kumandincy OR mansi OR nanaicy OR negidalcy OR nenets OR nganasan OR nivkhy OR orochi OR oroki OR saami OR sami OR selkup OR shorcy OR soioty OR tazy OR telengity OR teleuty OR tofolar OR tubolar OR tuvin-todjin OR udege OR ukagiry OR ulchi OR veps

[1] Search Terms for Tuberculosis AND Diagnosis delay AND Indigenous populations
[2] Narrow key word search terminology obtained from Tollefson et al. and Bartlett et al.[218, 221]

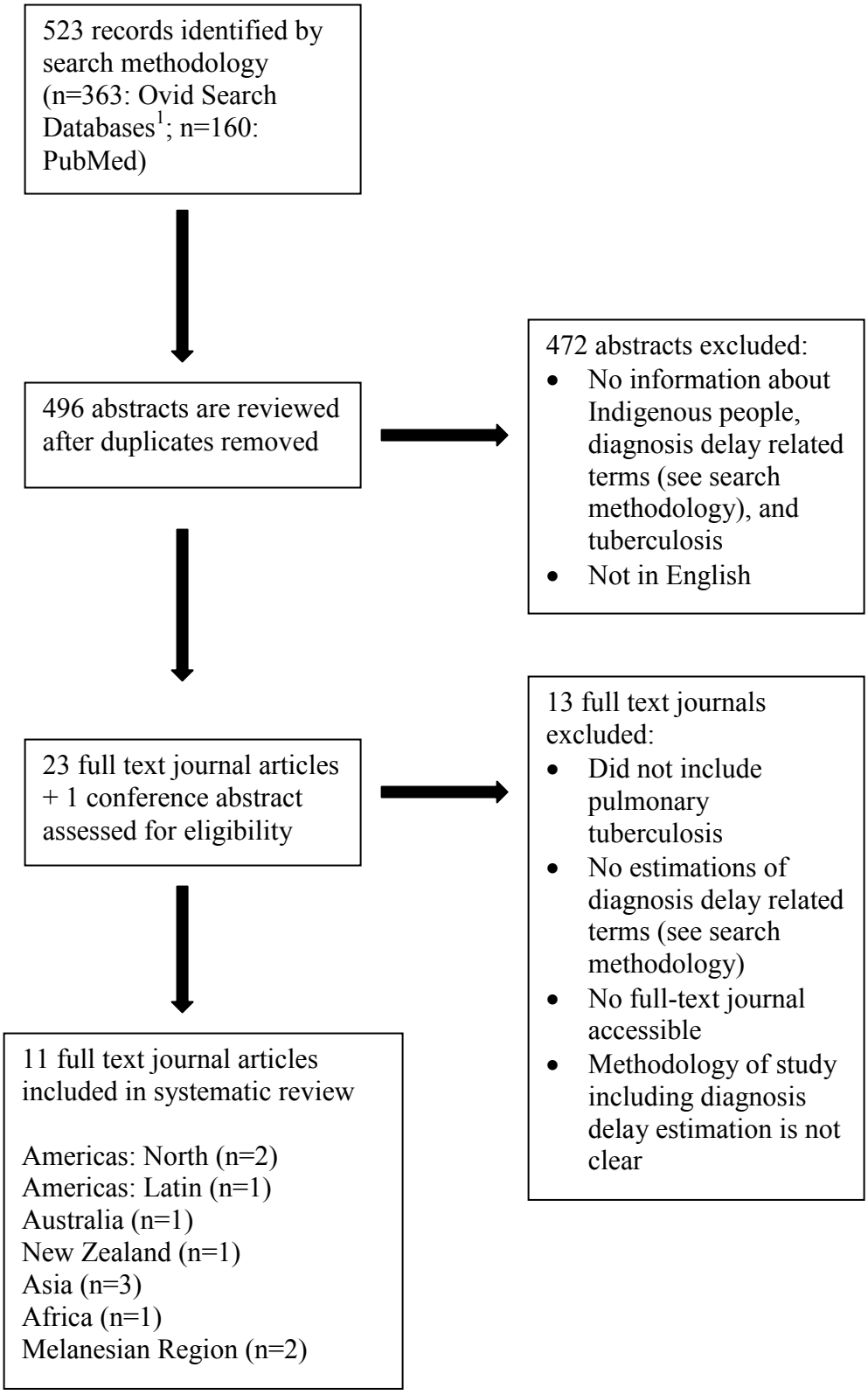

Figure 3. 1 Search methodology results and selection of studies for the systematic review using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) framework

Table 3. 2 Summary of delay in diagnosis (n=11) among Indigenous populations

Year of Study	Country (Total Study Size)	Indigenous Population Group (Total)	Type of Data (Disaggregate/ Single Population)	Diagnosis Delay (DD) (Delayed Diagnosis: ↑ ; Timely Diagnosis: ↓)				Study
				Definition of DD	Estimate, (Type): Comparison	Factors Associated with DD (Analytic Method other than Multiple Logistic Regression)		
1987	Canada (n=1)	First Nations (n=1)	Single population (estimate)	Duration of symptoms prior to diagnosis	120 days (Single)	N/A		[222]
2002-2006	Taiwan (n=78,118)	Aboriginal (n=2,530)	Disaggregate (estimate DD) / Single population (factors)	Time between first medical examination and treatment (Health systems' delay)	18 ± 44 days (Mean)[2]	Diagnostic delay[1] -inc. age (↑) -inc. reporting year (↑) -living with family (↑) - smear-negative (↑) -culture-positive (↑) -normal chest x-ray (↑) -diagnosis at medical center (↑)	Treatment delay[1] - male (↑) ; -inc. age (↑) -dec. reporting year (↑) -Aboriginal/abroad (↑) -living alone (↑) - smear-negative (↑) - culture-positive (↑) -normal chest x-ray (↑) -diagnosis at non-medical center (↑)	[135]
1992 - 2001	Waikato Health District, New Zealand (n=244)[§]	Maori (n=110) & Pacific Islanders (n=4)	Disaggregate (estimate) / Single population (factors)	Duration between the onset of symptoms and case notification	28 days (15th percentile)[2]	(Chi-square test) -inc. age (↑)		[136]
2009-2010	Afar Region, Ethiopia (n=216)[§]	Pastoralists (n=91)	Disaggregate (estimate) / Single population (factors)	Duration between the onset of symptoms and TB treatment (patient & health systems' delay)	70.5 days (44th percentile)	Patient delay -self-treatment (↑) -1st visit to non-formal health provider (↑) - >10 km to health facility (↑) (Mann-Whitney)	Health systems/Total delay -extra pulmonary TB (↑) -1st visit health clinic (↑) -Pastoralists (Mann-Whitney) (↑) (associated with total delay only)	[130]

[§]Include pulmonary and extra pulmonary TB [#]Include smear-positive pulmonary TB cases only

[1] Health systems delay: 1) Diagnostic delay: Time from first medical exam to diagnosis; 2) Treatment delay: Time from diagnosis to treatment
[2] DD reported across all ethnic groups, there is not significant association between DD and ethnic group (including Indigenous status)

Table 3.2. (Continued)*

Year of Study	Country (Total Study Size)	Indigenous Population Group (Total)	Type of Data (Disaggregate/ Single Population)	Diagnosis Delay (DD) (Delayed Diagnosis: ↑ ; Timely Diagnosis: ↓)				Study
				Definition of DD	Estimate (Type): Comparison	Factors Associated with DD (Analytic Method other than Multiple Logistic Regression)		
2007	Odisha, India (n=261)[#]	Tribal (n=261)	Single population (estimate & factors)	Duration between the onset of cough or other symptoms and TB treatment (patient and health systems' delay)	24 days (Median) / 37.5 days (Mean)	<u>Patient delay</u> (Bivariate analysis) -lack of TB awareness (↑) -long distance (>5km) to health facility (↑) -cost of treatment/ transport (↑) -illiteracy (↑)	<u>Health systems delay</u> (Bivariate analysis) -administrative verification for patient distribution of medicine (↑) -visit to traditional/private practitioner after TB diagnosis (↑)	[131]
1985-1998	Queensland, Austrailia (N=375)	Aboriginal & Torres Strait Islanders (n=47)	Disaggregate (estimate) / Single population (factors)	Duration between the onset of symptoms and TB treatment (patient and health system delay)	Patient: 30 days Health system: 10 days (Median)	<u>Patient delay</u> (Cox proportional hazards model) - High & Low risk migrants, & Indigenous peoples[1] (↓) -Uninvestigated cough & misdiagnosis of chest x-ray[2] (↑)	<u>Health systems delay</u> -high risk migrant (↓) -male (↓) -waiting for confirmation of diagnosis & referral for specialist treatment[3] (↑)	[132]
2000-2005	Arkansas, United States (n=861)	Native Hawaiians/ Pacific Islanders (n=40)	Single population (estimate & factors)	Duration between onset of symptoms and diagnosis	60 days (35th percentile)[3]	(analytical method unknown) -not seeking medical care (↑) -difficulty navigating health system (↑) -language barrier (↑) -transportation barrier (↑)		[124, 125]

[§]Include pulmonary and extra pulmonary TB [#]Include smear-positive pulmonary TB cases only

[1] Interpretation with caution of Indigenous population having significantly shorter delays: a) higher age-adjusted case fatality rate and b) recall bias
[2] Chart review of smear-positive TB cases (>90 days diagnostic delay & >7 treatment delay): summary of reasons for delay
[3] Estimate from Native Hawaiins/Pacific Islanders between 2000 and 2005 from referenced study Chideya et al. [223]

Table 3.2. (Continued)*

Year of Study	Country (Total Study Size)	Indigenous Population Group (Total)	Type of Data (Disaggregate/ Single Population)	Diagnosis Delay (DD) (Delayed Diagnosis: ↑ ; Timely Diagnosis: ↓)			Study
				Definition of DD	Estimate (Type): Comparison	Factors Associated with DD (Analytic Method other than Multiple Logistic Regression)	
2010-2012	Vanuatu (n=35)[§]	Melanesian (n=35)	Single population (estimate & factors)	Duration between onset of symptoms and diagnosis	49 days, IQR: 28 - 168 (Median)[1]	(Qualitative analysis) -misunderstand about TB (↑) -misdiagnosis (↑) -visit traditional practitioner first (↑)	[126]
2011-2012	Malaita, Solomon Islands (n=16)[§]	Kwaio people (n=4; 1 focus group n=12)	Single population (estimate & factors)	Duration between feeling unwell and presenting to hospital	2-3 years (range)	(Qualitative analysis) -visit traditional practitioner (↑) -long distance to health services (↑) -cost of health services (↑) -cultural taboos (↑) -social isolation (↑) -old age (↑)	[233]
2004	Lima, Peru (n=116)	Andean & Amazonian (unknown)	Single population (estimate & factors)	Duration from onset of symptoms to visit to the National TB Control Program	Patient: 20 days (Median)	(Wilcoxon rank sum test) Patient delay -self-therapy (↑)	[224]
1998-2000	Chiang Rai Province, Thailand (n=557)[#]	Hill Tribe (n=74)	Disaggregate (estimate) / Single population (factors)	Duration between the onset of cough or other symptoms (if cough not present) and TB diagnosis	Patient: 21 days Healthcare systems: 7 days (Approx[2]. Median)	Patient delay -Hill tribe ethnicity (↑) -Borrowed money to visit hospital (↑) -No previous visit to hospital (↑) -HIV-positive patients married or widowed (↓)	[127]

[§]Include pulmonary and extra pulmonary TB [#]Include smear-positive pulmonary TB cases only

[1] Calculated using data presented in the study

[2] Represents approximately 50% of respondents (51.4% and 47.3%) with long patient and provider delay, respectively. Patient delay is defined as the duration between the onset of cough or other symptoms (if cough not present) and the first visit with a doctor. Provider delay is defined as the duration between the first visit with a doctor and TB diagnosis.

Table 3. 3 Comparison of delay in diagnosis to other national studies

Country	Study Estimate (S)	Comparison Estimate (C)	Information about Comparison Estimate	National TB Rate[1] (95% CI)	Reference of Comparison Studies
Canada	120 days [222] (Single Estimate)	Quebec: 105.1 days (95% CI: 87.7 – 122.5)	- Comparable DD estimates		[128]
		Ontario: 62 days (IQR: 31-114 days)	- Higher DD in S than C - Included PTB & extra PTB	5.1 (4.3-5.8) per 100,000 population	[144]
		Ontario: 84 days (Mean)	- Higher DD in S than C		[142].
Taiwan	18 days (Mean) [135]	Within study: 17 days (Mean)[2]	- Comparable within study	68 per 100,000 population[3]	[135]
		Southern Taiwan: 44 days (median)[4]	- Unable to compare due to difference in DD definition		[248]
Waikato Health District, New Zealand	28 days (15th percentile) [136]	28 days (15th percentile)	-Comparable within study	7.4 (6.4-8.5) per 100,000 population	[136]
		Auckland: 120 days (Median)	- Unable to compare due DD estimate type		[249]
Afar Region, Ethiopia	70.5 days (44th percentile) [130]	70.5 days (64th percentile)	-Higher DD within study	192 (142-250) per 100,000 population	[130]
		Amhara Region: 80 days (IQR: 44.2 – 129.8)	-Comparable DD estimates		[121]
Odisha, India	24 days (Median) [131][5]	PD: 18.4 days (Median), Range 6-268 days; DD: 55.3 days (Median): Range: 32-118	- Systematic review results - Higher DD in C than S - Higher PD in S than C	217 (112-355) per 100,000 population	[137]
Queensland, Australia	PD: 30 days, HCS: 10 days (Median) [132]	PD: 51 days, HCS: 15 days (Median)	-Within study, higher PD in C than S -Comparable HCS between population groups	6 (5.2-6.9) per 100,000 population	[132]

DD: Diagnosis delay; PD: Patient delay; HCS: Healthcare system delay; PRD: Provider delay; PTB: Pulmonary tuberculosis

[1] 2015 Incidence Rate[232]
[2] Treatment delay
[3] Average TB incidence between 2004 and 2008 [335]
[4] Diagnosis delay
[5] PD: 24 days (Median) and HCS: 3 days (Median) = DD: 24 days (Median)

Table 3.3 (Continued)*

Country	Study Estimate (S)	Comparison Estimate (C)	Information about Comparison Estimate	National TB Rate[1] (95% CI)	Reference of Comparison Studies
United States	60 days (35th percentile) [124, 125]	Maryland: 89 days (Median) New York: 57 days (Median)	- Unable to compare due DD estimate type -Included PTB & extra PTB - Higher DD in S than C		[250] [251]
Solomon Islands	2-3 years (range) [233]	--	--	89 (69-112) per 100,000 population	--
Vanuatu	49 days (median) [126]	--	--	63 (52-74) per 100,000 population	--
Chiang Rai Province, Thailand	PD: 21 days, PRD: 7 days [127] (Approx. Median-See Table 2)	PD: 21 days (70th percentile), PRD: 7 days (median)	-Indigenous group higher PD than non-Indigenous group		[127]
		Southern Thailand: PD-26 days (PD) (median)	-Included PTB & extra PTB -Comparable PD estimate	172 (102-259) per 100,000 population	[235]
		Southern Thailand: PD-31 days, HCS-20 days	-Higher DD in C than S		[236]
Lima, Peru	PD: 20 days (median) [224]	Iquitos: PD: 61 days (IQR: 30-91 days)	- Higher PD in C than S		[237]
		Ventanilla, Lima: 60 days (IQR: 30-99 days)[2]	- Unable to compare due to difference in DD definition	119 (92-150) per 100,000 population	[252]
		South Lima: HCS- 26 days (median) [3]	- Unable to compare due to difference in DD definition		[253]

DD: Diagnosis delay; PD: Patient delay; HCS: Healthcare system delay; PRD: Provider delay;
PTB: Pulmonary tuberculosis

[1] [232]
[2] Diagnosis delay
[3] Median delay from symptom onset to seeking diagnostic testing

Table 3. 4 A summary of risk factors associated with delay in diagnosis among Indigenous peoples

Risk Factor	Delayed Diagnosis	Timely Diagnosis	Delayed Diagnosis (with Indigenous cases only)[1]
Increasing age/older age	#,*[135], [136]		[233]
Male	*[135]	†[132]	
Indigenous status	*[135], †[130], §[127]	§[132]	
Language barrier			[124]
Living with family	#[135]		
Living alone	*[135]		
Smear-negative	#,*[135]		
Culture-positive	#,*[135]		
Normal chest radiograph	#,*[135]		
Extra-pulmonary TB	†[130]		
Diagnosis at medical center/1st visit to health clinic	#[135], †[130]		
Diagnosis at non-medical center/1st visit to non-formal health provider/1st visit or general visit to traditional practitioner	*[135], §[130]		†[131], [126], [233]
No previous visit to hospital	§[127]		
Misdiagnosis	§[132]		[126]
Self-treatment/not seeking medical care	§[130]		[124], [224]
Greater distance to health facility	§[130]		§[131], [233]
Cost of treatment/cost of transport/transportation barrier	§[127]		§[131], [124], §[233]
Lack of TB awareness/illiteracy, misunderstanding about TB			§[131], [126]
Administrative delays i.e. verification for distribution of medicine, waiting for confirmation of diagnosis & referral for specialist, difficulty navigating health system	†[132]		†[131], [124]
Cultural taboos			[233]
Social isolation			[233]
HIV positive patients married or widowed		§[127]	

Diagnostic delay * Treatment delay § Patient delay † Health systems delay

[1] No risk factors negatively associated with diagnosis delay (with Indigenous cases only)

Chapter 4: Would Cross-Jurisdictional Collaboration of Provincial Tuberculosis Programs be Beneficial? An analysis of Tuberculosis Transmission in the Canadian-Born across the Prairies between 2006 and 2010

4.0 Summary

INTRODUCTION: Canada is a large country comprised of relatively few high density and many sparsely populated areas. Although healthcare services in Canada are designed to be equitable among all Canadians, geographical and jurisdictional challenges associated with delivery can create barriers to access. Tuberculosis (TB) disease underscores these challenges as cases are unequally distributed among population groups and community types in Canada. Some Indigenous communities experience a much greater burden of TB while others experience very little to none. Surveillance data can be used to assess the impact of jurisdictional challenges on communicable diseases such as TB, which is not bound by provincial or community borders. OBJECTIVE: The objective of this chapter is to use surveillance data for TB collected in connection with the *Determinants of TB transmission (DTT) project* to assess whether provincial TB programs across the prairies are appropriately managing TB transmission among the Canadian-born population. METHODS: The DTT project used a mixed-methods approach (qualitative interview, quantitative questionnaires, and molecular epidemiologic data) to understand the determinants of TB transmission across the Prairie Provinces. Descriptive analyses were conducted on data from the questionnaires (2007-2008) and molecular data (2006-2010). A 24-loci MIRU (Mycobacterial interspersed repetitive units) analysis of molecular data by population group, latitude, and community type was conducted. RESULTS: Clustering of TB was highest among First Nations and Métis people, cases diagnosed above the 53rd parallel, and

on-reserve/in Métis Settlements. Evidence of clustering and mobility patterns across the Prairies indicated that TB transmission extended beyond provincial and jurisdictional borders. Issues relating to healthcare access on-reserve may be a contributory factor to increased transmission since the travel associated with difficulty accessing healthcare services off-reserve may have increased the possibility of TB transmission. CONCLUSION: Increased cross-jurisdictional communication and surveillance may help reduce transmission between provinces.

4.1 Introduction

Canada is a large country comprised of a few high density and many sparsely populated areas. Although healthcare services in Canada are designed to be equitable among all Canadians, geographical and jurisdictional challenges associated with delivery can create barriers to access. Tuberculosis (TB) disease highlights these challenges due to cases being unequally distributed among population groups and community types in Canada. Of the total TB cases in 2014 (n=1,568), 12%, 20%, and 68% were contributed by Canadian-born non-Indigenous, Indigenous, and foreign-born population groups, respectively. These population groups represent approximately 75%, 4%, and 21% of the total Canadian population, respecitvely [13, 14, 46]. Across the Prairie Provinces (Alberta, Saskatchewan, and Manitoba), some Indigenous communities experience a great burden of TB and evidence of on-going transmission in these communities has been identified as a major contributor to the persistence of TB [54, 94, 99, 103, 104]. The use of surveillance data can help assess jurisdictional challenges that impact communicable diseases such as TB, which is not bound by provincial or community borders.

The *Determinants of TB transmission (DTT) project* was a seven-year (2006-2013) cohort study that aimed to understand the determinants of TB transmission across the Canadian Prairies using quantitative, qualitative, and molecular epidemiological information. TB rates estimated

from the data collected in connection with this project indicated localized pockets with a high incidence of disease in a few communities located above the 53rd parallel [99]. Understanding the determinants of TB transmission in population groups disproportionately affected highlights the social and medical characteristics of this disease. Poor healthcare access, prolonged time between onset of symptoms and diagnosis, low socioeconomic status, comorbidities, and overcrowding are some examples of risk factors that can potentially increase the risk of TB transmission, infection, and progression to disease [106].

The objective of this chapter is to use surveillance data for TB collected in connection with the DTT project to assess whether provincial TB programs across the prairies are effectively managing TB transmission among the Canadian-born population. The analyses presented herein use both the quantitative questionnaires and molecular data to highlight the jurisdictional challenges associated with TB control and elimination efforts. TB prevention and control programs are mandated provincially, but healthcare on-reserve is a federally provided service [254]. For people who travel on- and off-reserve, between communities and across provincial borders, complex jurisdictional factors result in insufficient and siloed care. The potential for clustering of *M. tuberculosis* strains and mobility data that indicates movement across the Prairies underscores the need for collaborative efforts to eliminate TB in Indigenous peoples on the Canadian Prairies.

4.2 Methods

Data

The Determinants of TB Transmission (DTT) project was a seven-year (2006-2013) study that gathered epidemiological information about active TB cases across the prairies [99]. This study followed the Canadian Institutes of Health Research (CIHR) Guidelines for Health

Research Involving Aboriginal People and the principles of OCAP (Ownership, Control, Access, and Possession) [255]. The DTT project included Indigenous researchers, Provincial Network Committees (PNC), and communications with First Nations governance to seek out and obtain approvals for collecting community and individual level TB surveillance data. These administrative and engaged scholarship activities have been previously described elsewhere [255].

The DTT project included a prospective cohort study conducted between 2007 and 2008 among culture-positive Canadian-born adults (>14 years old) with pulmonary TB defined as "potential TB transmitters". For the purpose of this study, Canadian-born adults include any person over 14 years of age who was born in Canada. The cohort of potential transmitters thus included people who identify as First Nations (Registered and non-Registered), Métis, Inuit, and Canadian-born 'others' [99]. In this prospective cohort study, quantitative and qualitative data along with genotyping of *M. Tuberculosis* isolates were used to understand the socio-cultural, historical, and health determinants of TB transmission [99, 255, 256]. The date of diagnosis for each potential transmitter was defined as the start date of treatment. The use of a 2.5-year transmission window (six months prior and two years after the date of diagnosis of each potential TB transmitter) was used to look evidence of any transmission events where the potential transmitter may be considered a putative source case. Transmission events were determined by investigating the contact lists and 'background' of all culture positive cases in the prairies to look for conversions, new positive TSTs and secondary cases. All "background TB cases" diagnosed between 2006 and 2010 were genotyped using 24-loci MIRU, and these genotyping methods allowed us to identify 'clusters' of cases (≥2 cases with an identical MIRU pattern).

Quantitative questionnaires were completed and semi-structured interviews were administered at the time of TB diagnosis. The questionnaires were used to gather additional

information over and above that which is routinely collected, for example, risk factors, mobility data, TB symptomology, healthcare access, and housing information. Provincial TB registries, a contact database, chest radiography/laboratory results, and community access forms (for Indigenous respondents living on-reserve at the time of diagnosis) were secondary sources of data used to supplement the quantitative questionnaires. Qualitative interviews were also conducted among smear-positive (highly infectious) potential transmitters (n=56) until saturation was achieved [257]. Most interviews in Alberta and Manitoba were conducted in hospitals and clinics while in Saskatchewan, many occurred in First Nations and Métis communities [255]. In Saskatchewan TB treatment more frequently occurs in the community where interviews were conducted in mobile clinics and patient's homes [255, 257].

All potential transmitters in the study had their culture sample fingerprinted using molecular genotyping methods. These fingerprints were compared against the fingerprints of all culture-positive TB cases diagnosed in the prairies between 2006 and 2010. Genotyping was conducted by the National Microbiology Laboratory (NML) using variable number tandem repeat (VNTR) methods. VNTR specific to *Mycobacterium* tuberculosis complex (MTBC) is called Mycobacterial interspersed repetitive units (MIRU). Variable number tandem repeat differentiates between strains of MTBC through a sequence of numbers obtained by assessing the expression of multiple loci using PCR (polymerase chain reaction) amplification [258, 259]. A 12-loci MIRU fingerprint patterns of *M*. tuberculosis strains for all cases diagnosed in the Prairies between 2006 and 2010 were obtained from NML. During the course of the DTT study, NML switched its routine genotyping methods from 12 to 24-loci MIRU analysis and most samples (78%) were analyzed using the latter, more discriminatory method. TB strains without 24-loci MIRU results did not have any matches with the 248 potential TB transmitters using 12-loci MIRU, were contaminated, or did not have enough DNA in the sample to conduct the test.

Study Design

The main objective of the study was to describe TB transmission among Canadian-born peoples across the prairies. The analyses include a descriptive statistical analysis of demographic, socioeconomic, and mobility information obtained from the quantitative questionnaires (2007-2008), and DNA fingerprinting data gathered from NML (2006-2010). The data presented here came from the DTT quantitative questionnaires, Provincial TB registries, and the DNA fingerprinting database of all culture positive TB cases across the prairies.

Data Management and Statistical Analysis

Microsoft Excel 2011 and SAS 9.3 (SAS Institute Inc., Cary, NC, USA) were used for data management and descriptive analyses. Multiple data sources obtained within the DTT project were used to supplement and improve the completeness of the quantitative questionnaires. Household size was categorized based on Statistics Canada Census results in 2006 and 2011 [16, 260]. Community type was defined as major metropolitan (Winnipeg, Saskatoon, Regina, Edmonton, and Calgary), non-major metropolitan area (≥ 500 people and not major metropolitan), Métis settlement (defined by the Métis settlements General Council), and reserve community [99]. Métis communities in Saskatchewan and Manitoba were defined as communities with at least 25% Métis residents using the Statistics Canada Census, which were not reserves, major metropolitan areas, but have otherwise been considered non-major metropolitan areas. [99].

The study defined Indigenous peoples in Canada to include First Nations (Registered and non-Registered), Métis, and Inuit peoples. Occupation or work type was categorized as industrial (labourer, maintenance, and mine/oil jobs), medical-social (child, medical, fire, and education services), and other (food/hunting, managerial, and airline employment). Substance use was

defined as injection, alcohol, or other drug use. Comorbidities included respondents with HIV, diabetes and/or renal disease, three major risk factors for the reactivation of LTBI. Location of TB diagnosis was stratified as on- and off-reserve. Health locations on-reserve included clinics, hospitals, and/or nursing stations within a First Nations or Métis reserve/settlements. Health locations off-reserve included clinics and hospitals outside of First Nations or Métis communities (this includes the Canadian-born other population group). The duration of time for possible transmission events was used as a proxy to define the time to treatment. Duration of cough prior to treatment was used to estimate the time to treatment. The time to treatment estimate includes only potential transmitters who responded with either "yes" or "no" for having a cough prior to diagnosis. Among those without a cough (a response of "no"), the duration was set to zero days. The genotyping data was verified and checked for completeness. MIRU patterns (12 and 24) with an unexpressed locus was consistently denoted by "x" in that locus and included in the analysis. Date of diagnosis, age, TB registry number, population group, postal code, and province were included in the dataset and allowed for the analysis to be stratified by province. Additional data management was conducted to determine the latitude (south or north of the 53rd parallel) and community type (Major Metropolitan, Non-Major Metropolitan, Reserve, and Métis Settlement). The Statistics Canada Postal Code Conversion File was used to determine latitude and community type [261].

Descriptive analysis included comparing groups using t-tests for continuous data and chi-square tests for categorical data. Fisher's exact test was used for comparisons of categorical data where the cell count was less than five. The quantitative questionnaires were based on self-reported data, which were not always complete and subtotals of responses are denoted by "n" in the tables. DNA fingerprinting data were analyzed for unique and common patterns using the 12 and 24-loci MIRU results and stratified by population group, latitude, and community type.

Although analysis conducted included 12- and 24-loci MIRU, only results for the more discriminatory analysis (24-loci MIRU) are presented in this chapter. Clustering was defined as at least two TB cases that had an identical fingerprinting pattern by 24-loci MIRU between 2006 and 2010. Clustering patterns by province are described by using acronyms where AB, SK, and MB denote Alberta, Saskatchewan, and Manitoba, respectively. For example, AB-SK is defined as a clustering pattern that occurred in both Alberta and Saskatchewan. Confidence intervals were constructed using the z-test calculation for proportions.

4.3 Results

Overview of the DTT data

There were a total of 248 culture-positive TB cases (also called 'potential transmitters' or respondents) between 2007 and 2008 from the DTT project. The overall response rate for the quantitative questionnaires was 74% (183/248). By province, the response rate for Alberta, Saskatchewan, and Manitoba were 86% (32/37), 84% (72/86), and 63% (79/125), respectively. Table 4.1 offers an overview of all Canadian-born adults (>14 years) with pulmonary, culture-positive TB that participated in the quantitative and qualitative interviews by smear status and population group (SI: Status Indian, NSI: non-Status Indian, M: Métis, I: Inuit, and CBO: Canadian-born Other). The proportion of all potential transmitters who were smear-positive was 58% (145/248) (see Table 4.1). Among Indigenous peoples, the overall response rate for the quantitative questionnaires was 75% (167/223) and represented all respondents who participated in the qualitative interviews (N=56; Alberta=14, Saskatchewan=24, and Manitoba=18). Most Indigenous respondents (98%; 55/56) who participated in the qualitative interview were smear-positive, while one other Alberta respondent was at first thought to be smear-positive and discovered later to be smear-negative.

Figure 4.1 describes the breakdown of the 1308 background TB cases (2006-2010) that was genotyped using 24-loci MIRU. Overall, 78% (1015/1308) of the TB cases were fingerprinted. A subset of these cases responded to the DTT quantitative questionnaires administered to culture positive Canadian-born TB cases (>14 years old) between 2007 and 2008. The completion rates for population group and community type were 99.6% and 98.3%, respectively (see Figure 4.1). Approximately 13% (174/1308) of the isolates without a 24-loci MIRU did not have a match by 12-loci MIRU to the 248 potential TB transmitters in the DTT project. The majority of these isolates were foreign-born (87%; 150/172), lived in major metropolitan centres (78%; 135/174), and resided south of the 53rd parallel (67%; 117/174). These isolates were approximately distributed equally across the three age groups: a) 0-34 years, b) 35-64 years, and c) >64 years old. Nine percent (119/1308) of the isolates did not have a result due to non-expression, contamination, and/or lack of DNA in the sample to conduct the test. The distribution of these isolates in terms of population group, community type, age, and latitude were comparable to the demographic data presented in this chapter.

Descriptive analysis of the quantitative questionnaires

The demographic information by province of the potential TB transmitters gathered from the DTT quantitative questionnaires is described in Table 4.2. Most respondents with culture positive pulmonary TB between 2007 and 2008 were Indigenous (90%; 223/248). By province, approximately 93% of Saskatchewan and Manitoba cases were Indigenous compared to 70% in Alberta. Status First Nations (SI) and Métis peoples comprised of 82% (182/223) and 17% (38/223) of Indigenous TB cases, respectively. There were two non-status First Nations TB cases, one each in Alberta and Manitoba and one Inuit case in Alberta (see Table 4.2). By Indigenous population group, 70% (129/184) and 61% (23/38) of First Nations and Métis peoples lived on-

reserves and settlements, respectively. Thirty percent (67/223) of all Indigenous TB cases lived in major and non-major metropolitan centres. Respondents who lived north of the 53rd parallel accounted for 67% (166/248) of the total TB cases. The main mother tongue languages of SI respondents were Algonquian (40%; 72/182), Athapaskan (30%; 54/182), and English (24%; 44/182). Most respondents had a mother tongue language of Algonquian (73%; 58/79) in Manitoba and Athapaskan (67%; 48/72) in Saskatchewan. In Table 4.2, education level, mother tongue (language), cavitation status, and household size had incomplete response rates. Response rates ranged from 57% to 100% for education level, language, cavitation status, and household size. Approximately 55% (136/248) of all respondents across the prairies were between 35 and 64 years old. Eighty-five percent (154/182) of respondents did not have a high school diploma and the proportion was highest in Saskatchewan (80%; 69/72). The proportion of respondents in Manitoba without a high school diploma ranged between 53% (66/125) and 85% (66/78) depending on whether missing values were included. Cavitation was observed in 43% (84/197) of all TB cases diagnosed between 2007 and 2008. Based on the household size cut-off value of 2.5 people, which was reported as the average for all of Canada in the 2006 and 2011 Census, 76% of respondents live in households with greater than 2.5 people. There were no statistical differences in the proportion of people living in households of greater than 2.5 by province.

Socioeconomic factors by province obtained from the DTT quantitative questionnaires are described in Table 4.3. The response rate ranged between 38% and 100% among factors reported in Table 4.3 which was denoted by 'n' with the response rate in parenthesis. Response rates were the lowest for individuals indicating social assistance (38%-44%) (see Table 4.3). However, of those who responded, 58% (62/107) were on social assistance. Social assistance was statistically different across the provinces ($p<0.05$) with Saskatchewan (58%; 22/38) and Manitoba (65%; 36/55) having higher proportions of people on social assistance than Alberta (29%; 4/14). The

proportion of all respondents who were employed was 38% (69/183) with no significant differences by province. Fifty-nine percent (37/63) of employed respondents were in industrial type jobs, which included labourer, maintenance, and mine/oil industries. In Saskatchewan, 63% (10/16) of respondents who worked in the industrial related employment also traveled compared to 57% (4/7) and 27% (3/11) for Alberta and Manitoba, respectively. Approximately 23% (41/182) of respondents were incarcerated in the period of time up to two years prior to the date of diagnosis of TB. Respondents with HIV, diabetes, and/or renal disease accounted for 27% (50/184) of the respondents; these proportions were higher in Alberta (32%; 12/37) and Manitoba (37%; 24/66) compared to Saskatchewan (17%; 14/81).

Table 4.4 describes factors related to seeking and access to healthcare among respondents from the DTT quantitative questionnaire. Overall, 57% (108/191) and 41% (78/191) of respondents first saw a doctor and nurse, respectively, after having symptoms related to TB. In Manitoba, a higher proportion of respondents first saw a nurse (58%; 45/78) for their TB symptoms compared to a doctor (40%; 31/78). Thirty-nine percent (46/118) of respondents who live on-reserve and/or in Métis settlements accessed off-reserve health services after experiencing symptoms (see Table 4.4). Health services accessed for initial TB symptoms among respondents living on-reserve and/or in a Métis community (response rate: 75%; 118/158) were distributed differently across the province ($p<0.001$). Health services off-reserve were accessed more frequently in Alberta (68%; 13/19). In Saskatchewan, respondents accessed health services on-reserve (42%; 19/45) and off-reserve (49%; 22/46) equally. In Manitoba, a higher proportion of respondents access health services on-reserve (76%; 41/54). Doctors visiting a health centre or nursing station among respondents living on-reserve and/or in a Métis community were mostly weekly/bi-weekly (44%; 38/87) followed by daily (21%; 18/87), never (21%; 18/87) and monthly (15%; 13/87) (see Table 4.4). Doctors were reported to visit monthly only in Manitoba (see Table

4.4). The mean and median duration of cough prior to treatment (a proxy for transmission period) was 65 days and 28 days, respectively (see Table 4.4).

Mobility information from the DTT quantitative questionnaires and genotyping data (12 and 24 MIRU DNA fingerprinting of *M.* Tuberculosis strains) are used to describe potential transmission across the prairies. Table 4.5 describes the mobility of respondents 12 weeks prior to the date of TB diagnosis obtained from the quantitative questionnaires. Overall, the response rates varied between 38% and 54% (see Table 4.5). The greatest proportion of respondents traveled to visit family and/or for work (62%; 95% CI: 61.7-62.3) and Manitoba had the greatest average duration of travel outside their community (35.2 days; 95% CI: 34.3-36.1) compared to Alberta and Saskatchewan (see Table 4.5). For family and work travel, Manitoba and Saskatchewan had longer average durations outside their community (see Table 4.5). The average duration for health related visits were greater in Saskatchewan (5.8 days; 95% CI: 5.6-6.0) and Manitoba (6.2 days; 95% CI: 6.0-6.4) compared to Alberta (2.2 days; 95% CI: 2.1-2.3). A greater proportion of respondents in Saskatchewan (48.8%; 95% CI: 48.3-49.3) and Manitoba (17.0%; 95% CI: 16.7-17.4) had travelled for leisure/shopping compared to Alberta (10%; 95% CI: 9.6-10.4). Travel generally remained within the province, however the average trips per person from Alberta to Saskatchewan and Saskatchewan to Alberta were 1.25 (95% CI: 1.21-1.29) and 0.44 (95% CI: 0.42-0.45), respectively (see Table 4.5). The average trips per person between Saskatchewan and Manitoba were the lowest across the Prairies (see Table 4.5).

Genotyping analysis of all TB cases (2006-2010) across the prairies

Table 4.6 describes the demographic analysis of the 1015 24-loci MIRU fingerprints between 2006 and 2010. Overall, 86% (875/1015) of TB cases were diagnosed among people (≤64 years old) ($p<0.01$). The proportion of TB cases among people (>64 years old) was highest

in Alberta (21%; 73/351). Most TB cases were diagnosed among the foreign-born (37.8%; 383/1015) and First Nations (46.1%; 447/1015) population group ($p<0.01$). Seventy-two percent (251/351) of total Alberta TB cases were among the foreign-born. In Saskatchewan (59.8%; 141/239) and Manitoba (64.2%; 273/425), TB cases were highest among First Nations peoples (see Table 4.6). Tuberculosis cases were distributed fairly evenly above and below the 53rd parallel in Alberta and Manitoba. In Saskatchewan, two times as many TB cases were diagnosed north of the 53rd parallel ($p<0.01$). By community type, TB cases were mostly diagnosed in major metropolitan (51.6%; 517/1015) and reserve (31.7%; 318/1015) locations (see Table 4.6).

Figure 4.2 describes the 24-loci MIRU DNA fingerprinting results of all TB cases across the prairies overall and by population group between 2006 and 2010. There were a total of 504 24-loci MIRU (1015 TB cases) patterns (see Figure 4.2). Approximately half of MIRU patterns were in Alberta exclusively (see Figure 4.2). There were two (<1%) 24-loci MIRU fingerprinting patterns representing 22 TB cases common across the prairies (see Figure 4.2). One pattern was only shared between Saskatchewan and Manitoba representing 115 TB cases, respectively (see Figure 4.2). There were 436 TB cases with unique patterns between 2006 and 2010. Tuberculosis cases with unique fingerprinting patterns that appeared once were highest for Alberta (68%; 238/351) followed by Manitoba (32%; 138/425) and Saskatchewan (25%; 60/239). The distribution of TB strains by population group for AB-MB patterns showed that 81% of these cases were among the foreign-born. There were no Canadian-born non-Indigenous TB cases that shared patterns common across the prairies (see Figure 4.2).

A stratified analysis of clustering by population group, latitude, and type of community was conducted and described in Table 4.7. Overall, clustering was highest among First Nations and Métis peoples, cases diagnosed above the 53rd parallel, and on-reserve/in Métis Settlements. Clustering was lowest among the foreign-born (22.7%). In Manitoba, clustering of Canadian-

born non-Indigenous TB cases (62.5%; 95% CI: 47.5-77.5) was comparable to Indigenous (79.5%; 95% CI: 74.7-84.3) TB cases (see Table 4.7)

4.4 Discussion

DNA fingerprinting methods have been used previously to understand transmission patterns in Canada [60, 94, 103, 262-268]. In this current study, among all TB cases diagnosed between 2006 and 2010, clustering by 24-loci MIRU was lowest in Alberta (32%). The distribution of cases in Alberta occurred mostly in the foreign-born (75.6%; 226/299). Increased clustering was observed in Saskatchewan (75% of total TB cases) and Manitoba (68% of total TB cases) between 2006 and 2010. Overall, clustering was highest among First Nations and Métis people, cases diagnosed above the 53rd parallel, and on-reserve/in Métis Settlements (see Table 4.7). Among the Canadian-born population, 74% of the total cases (n=629) were clustered. Other studies have described similar estimates for clustering of TB cases in Canada with greater clustering among the Indigenous population [94, 103, 263, 267]. The foreign-born population mainly acquire TB infection from their country of origin resulting in the reactivation of TB in Canada, which has been generally associated with low clustering of TB cases [94, 266, 269]. Higher rates of clustering associated with evidence of on-going transmission or increased delays in diagnosis and/or treatment have been observed in Canadian Indigenous populations [263-265, 267]. In 2008, 79% of the total TB cases in Alberta were in the foreign-born population while 78% and 67% of the total TB cases in Saskatchewan and Manitoba were among the Indigenous population [93], which was representative of the distribution of TB cases in the fingerprinting analysis (see Table 4.6).

Genotyping results appeared to reflect mobility patterns where interprovincial travel was lowest between Saskatchewan and Manitoba (see Table 4.5). For the one SK-MB strain, 98%

(113/115) of TB cases were in Manitoba. This pattern may be an emerging one in Saskatchewan. Interprovincial travel was highest between Alberta and Saskatchewan, which shared 12 identical strains by 24-loci MIRU, accounting for 161 TB cases. Types of travel among all Canadian-born TB cases diagnosed between 2007 and 2008 were stratified as health related, leisure/shopping, and family/work. Overall, 16% to 62% of TB cases travelled in the 12 weeks prior to their diagnosis. The greatest proportion of people with TB between 2007 and 2008 travelled for family visits or work with an average duration of 28 days. Except for Alberta, the average duration for family or work travel was greater for outside the community. The larger proportion of TB cases from Saskatchewan (17%; 41/248) and Manitoba (31%; 77/248) compared to Alberta (6%; 14/248) that resided in reserves compared to major and non-major metropolitan could explain durations of travel that were greater for outside versus within community travel. Approximately 27% of respondents that traveled for employment had TB strains that were in common with at least two provinces suggesting the potential for TB transmission across provincial boundaries. In addition, the distribution of TB cases with AB-MB patterns (see Figure 4.2) were clustered mostly in the foreign-born (81.1%; 30/37) may also be suggestive of work related travel to Alberta given its oil and gas industry.

Travel for leisure or shopping and health related visits was reported for 28% and 16% of the TB cases with an average duration of two and five days, respectively (see Table 4.5). These types of travel mainly occurred for outside community trips suggest potential challenges in accessing healthcare and other amenities such as grocery stores. Across the prairies, 39% of Indigenous people living on-reserve or in Métis settlements (46/118; response rate: 75%) first accessed health services outside the community for their TB symptoms. Physicians were primarily the first off-reserve point of care among Indigenous peoples living on-reserve and in Métis communities across the prairies. Among respondents accessing on-reserve health services,

physicians utilized for initial TB symptoms were 5% in Manitoba (2/41; response rate: 62%;), 21% in Saskatchewan (4/19; response rate: 96%;), and 50% in Alberta (2/4; response rate: 83%;) (see Table 4.4). Approximately 20% of respondents living on-reserve or in Métis communities across the prairies reported no physician visits to a health centres or nursing stations.

The increased utilization for health services off-reserve and decreased access to physicians on-reserve highlights challenges to healthcare access faced by some First Nations and Métis communities across the prairies. Canadian surveys focusing on Indigenous peoples have reported on reduced healthcare access through measures such as the availability of a healthcare professional, unmet healthcare needs (requiring healthcare without receiving it), cultural appropriateness of care, and economic barriers [20, 39, 270-272]. The stigmatization of TB [29, 54, 256] may play an added role with the underutilization of physicians in Indigenous communities where physician visits are on a daily to weekly basis. Analysis of qualitative interviews in the DTT project supported these quantitative findings where decisions about healthcare access was associated with socioeconomic deprivation such as fear of job loss and negative impacts of colonialism including ways TB treatment was implemented in the past [256]. There also may be additional challenges with guaranteeing anonymity in smaller communities. Access to physicians on a monthly basis was only reported in Manitoba with greater utilization of nurses instead. Manitoba has more communities defined as remote compared to Saskatchewan and Alberta [273]. Challenges with accessing healthcare providers were increased for isolated, remote, and small communities and accompanied with evidence of increased utilization of nurses compared to physicians [270, 271]. A proxy for time to treatment was measured in the DTT quantitative questionnaire. The median (mean) duration of time from the onset of cough to diagnosis was 28 days (65 days) across the prairies with the lowest estimate in Manitoba (Table 4.4). The increased utilization of health services on-reserve and from nurses in Manitoba may

suggest why the time to treatment was lower compared to Saskatchewan and Alberta. The skewness of the time to treatment data suggested that there were few people with much longer periods where transmission could occur.

In the DTT questionnaire, travel for shopping among respondents suggested possible challenges in accessing amenities such as grocery stores. Food insecurity continues to be disproportionately higher among Indigenous peoples relative to the total Canadian population [20, 39, 271]. The lack of affordable and nutritious foods in northern communities relate to the high costs associated with transporting those foods [39, 274]. Reduced availability of nutritious food in some northern communities [275] represent additional factors that may encourage those who can afford travel to seek reasonably priced and nutritious foods outside resident communities.

Approximately 23% of respondents were incarcerated within two years prior to the date of diagnosis (see Table 4.3). Correctional facilities have been reported to have higher TB rates and evidence of outbreaks, suggesting that these environments are conducive for TB transmission [265, 276-280]. Evidence of clustering observed in studies suggests the potential for transmission of strains from other provinces. In this study, clustering of strains shared with at least two provinces across the prairies occurred in 56% (23/41) of respondents who were incarcerated compared to 44% (62/141) of non-incarcerated respondents (p=0.09).

Policy Implication

By 24-loci MIRU analyses, a total of 22 TB cases representing two strains were shared across the three Prairie Provinces (see Figure 4.1). The distribution of these cases by population group was split approximately evenly among foreign-born and Indigenous (First Nations and Métis) peoples (see Figure 4.2). The population difference between the foreign-born and

Indigenous peoples indicates a disproportionately higher degree of clustering in First Nations and Métis peoples. The potential impact of TB transmission that occurs across provincial boundaries is an important consideration for current TB control guidelines aimed at preventing TB transmission among Indigenous groups. Approximately 41% of all Indigenous peoples in Canada live in Alberta, Saskatchewan, and Manitoba and therein they encompass nine treaty regions (see Figure 4.3) [13, 281]. Treaty areas in Canada signify historical relationships between Indigenous communities that are not bounded by current provincial boundaries.

In Canada, a national TB program does not exist, however TB prevention and control is primarily under provincial jurisdiction, with some responsibilities being shared with Health Canada (Federal government) who are mandated to ensure that services are accessible to First Nations on-reserve and Inuit peoples [17, 55, 282, 283]. The role Health Canada plays in TB prevention and control at a provincial level is heterogeneous across Canada and is dependent on provincial legislation such as provincial public health acts, as well as TB burden, geographical challenges, and the structures of local public health programs [55]. Addressing potential transmission of TB between provinces with current guidelines that do include the management of cross-jurisdictional contact investigations is important [284, 285]. Despite best efforts to follow these guidelines, some challenges with program delivery may include language barriers, stigma, resource challenges (i.e. adequate personnel for tracking contacts/follow-up assessments), sharing of contacts, and mobility between communities and across provinces [283, 286, 287].

In Alberta, delays in assessment and lower completion rates for assessment and preventative therapy were highlighted among Indigenous contacts living off-reserve between 2001 and 2010 [283]. Since identifiers for contacts involved with out-of-province investigations are not uniform across the Prairie Provinces, completion rates for assessments and preventative therapy are unknown. However, these completion rates may be even lower among out-of-

province contacts of Indigenous TB cases. Evidence of mobility within and between the Prairie Provinces and the high proportion of clustering shared with at least two provinces among Indigenous TB cases highlights a need for prairie-wide TB policies. The use of unique identifiers available to the Prairie Provinces can help estimate completion rates for assessment and preventative therapy among out-of-province contact investigations. Early contact assessment and improved completion rates for preventative therapy among out-of-province contacts can mitigate the potential spread of TB strains across provinces. Obtaining contact information can be challenging in some vulnerable populations where there is resistance to share contact names and recalling all contacts may not be possible especially among highly mobile individuals [287]. Program delivery that is culturally sensitive, involves community engagement, rapport building among healthcare workers, and training to improve contact interview skills are important [283, 287].

Limitation

There were various study limitations. The quantitative questionnaire was based on self-reported responses and is subject to recall bias. Non-response bias was observed in the DTT questionnaire and documented in the tables presented, and was generally higher in Manitoba. Information about social assistance, frequency of doctor's visits, and mobility had greater non-response bias and therefore results for these responses should be interpreted with caution. However, these responses did corroborate the literature and genotyping analysis. The proportion of people in Saskatchewan with comorbidities was relatively low compared to Alberta and Manitoba. Response rates for respondents with diabetes were poor for Saskatchewan and Manitoba and comorbidities may be underreported. Although only 78% (1015/1308) of TB cases between 2006 and 2010 were analyzed by 24-loci MIRU, results were based on using the more

discriminatory method. Analysis using 12-loci MIRU fingerprinting results was relatively consistent with the 24-loci MIRU analyses with a moderate increase in clustering and size of clusters. Clustering estimations did not discriminate between those that occurred due to recent transmission or historical transmission, only that there was a match by 24-loci MIRU analysis. A closer examination on whether background cases were due to a reactivation of a previous or recent transmission event would better help estimate clustering due to recent transmission.

4.5 Conclusion

Tuberculosis continues to affect Indigenous peoples disproportionately compared to the Canadian-born non-Indigenous population. Healthcare access issues were identified in some Indigenous communities by increased use of medical services off-reserve and decreased access to physicians on-reserve. Travel for medical services off-reserve may contribute to a lengthened time from the onset of symptoms to diagnosis where transmission of the organism is much more likely to occur. Molecular information was used to determine the potential for TB transmission to extend beyond provincial boundaries, especially among First Nations and Metis peoples on-reserve/in Metis Settlements living above the 53rd parallel. This evidence was supported by mobility patterns across and within the Prairie Provinces. Conducting TB investigations involving out-of-province contacts collaboratively across the prairies may mitigate TB transmission across provinces, while building enhanced surveillance and infrastructure to help evaluate efforts made in conducting these types of investigations.

Table 4. 1 An overview of all "potential transmitters" in the DTT project (2007-2008) that participated in the quantitative questionnaires and qualitative interviews by population group and smear status

	248 "Potential Transmitters" (SI=182; NSI=2; M=38; I=1; CBO=25)									
	Smear Positive (N=145)					Smear Negative (N=103)				
	SI (N=92)	NSI (N=2)	M (N=30)	I (N=1)	CBO (N=20)	SI (N=90)	NSI (N=0)	M (N=8)	I (N=0)	CBO (N=5)
Quantitative Questionnaire	70	1	29	1	11	60	0	6	0	5
Qualitative Interview	35	1	18	1	0	1	0	0	0	0
No Quantitative Questionnaire and Qualitative Interview	22	1	1	0	9	30	0	2	0	0

SI: Status Indian; NSI: Non-Status Indian; M: Métis: I:Inuit; CBO: Canadian-born Other;

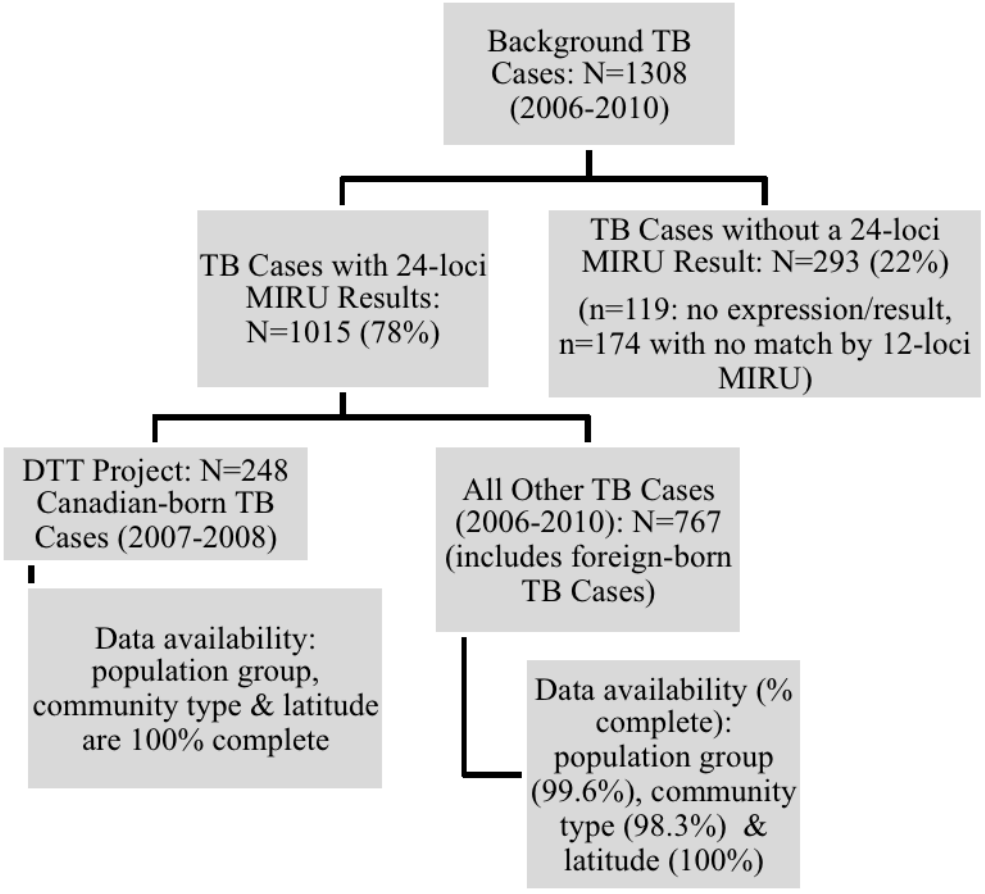

Figure 4. 1 Total TB strains with 24-loci MIRU between 2006 and 2010

Table 4. 2 Demographic factors from the quantitative questionnaire of all 248 'potential transmitters' in the DTT Project (2007-2008) by province

Demographic Variable	Prairie Provinces N=248 (%)	Alberta N=37 (%)	Saskatchewan N=86 (%)	Manitoba N=125 (%)	P-value*[1]
Gender	n=248 (100)	n=37 (100)	n=86 (100)	n=125 (100)	
Male	147 (59.3)	24 (9.7)	45 (18.2)	78 (31.5)	0.259*
Female	101 (40.7)	13 (5.2)	41 (16.5)	47 (19.0)	
Age	n=248 (100)	n=37 (100)	n=86 (100)	n=125 (100)	
15-34	92 (37.0)	9 (3.6)	39 (15.7)	44 (17.7)	
35-64	136 (55.0)	22 (8.9)	42 (16.9)	72 (29.0)	0.095*
>64	20 (8.0)	6 (2.4)	5 (2.0)	9 (3.6)	
Education	n=182 (73)	n=32 (86)	n=72 (84)	n=78 (62)	
No High School Diploma	154 (84.6)	19 (10.4)	69 (37.9)	66 (36.3)	
High School Diploma	16 (8.8)	7 (3.9)	2 (1.1)	7 (3.9)	<0.001*
University/College	12 (6.6)	6 (3.3)	1 (0.6)	5 (2.8)	
Indigenous	n=248 (100)	n=37(100)	n=86 (100)	n=125 (100)	
No	25 (10.0)	11 (4.4)	6 (2.4)	8 (3.2)	<0.001*
Yes	223 (90.0)	26 (10.5)	80 (32.3)	117 (47.2)	
Treaty/Non-Status	184 (74.2)	19 (8.5)[2]	54 (24.2)	111 (49.8)[2]	
Métis	38 (15.3)	6 (2.7)	26 (11.7)	6 (2.7)	<0.001*
Inuit	1 (0.4)	1 (0.5)	--	--	
Community Type	n=248 (100)	n=37(100)	n=86 (100)	n=125 (100)	
Major Metropolitan	65 (26.2)	14 (5.7)	13 (5.2)	38 (15.3)	
Non-Major Metropolitan	26 (10.5)	9 (3.6)	7 (2.8)	10 (4.0)	<0.001*
On-Reserve	132 (53.2)	14 (5.7)	41 (16.5)	77 (31.1)	
Métis Settlement	25 (10.1)	--	25 (10.1)	--	
North of 53rd Parallel	n=248 (100)	n=37(100)	n=86 (100)	n=125 (100)	
No	82 (33.1)	11 (4.4)	23 (9.3)	48 (19.4)	
Yes	166 (66.9)	26 (10.5)	63 (25.4)	77 (31.1)	0.188*
Language	n=182 (73)	n=31 (84)	n=72 (84)	n=79 (63)	
English	44 (24)	10 (5.5)	15 (8.2)	19 (10.4)	
Algonquian	14 (7.7)	6 (3.3)	8 (4.4)	58 (31.9)	
Athapaskan	54 (29.7)	6 (3.3)	48 (26.4)	--	
Siouan	2 (1.0)	4 (2.2)	--	--	<0.001*
Other[3]	8 (4.4)	5 (2.8)	1 (0.6)	2 (1.1)	
Smear Status	n=248 (100)	n=37(100)	n=86 (100)	n=125 (100)	
Negative	103 (41.5)	11 (4.4)	26 (10.5)	66 (26.6)	0.001*
Positive	145 (58.5)	26 (10.5)	60 (24.2)	59 (23.8)	
Cavitation	n=197 (79)	n=37(100)	n=79 (92)	n=81 (65)	
No	113 (57.4)	20 (10.2)	43 (21.8)	50 (25.4)	0.584*
Yes	84 (42.6)	17 (8.6)	36 (18.3)	31 (15.7)	
Household Size[4]	n=170 (69)	n=27 (73)	n=72 (84)	n=71 (57)	
>2.5 People	129 (75.9)	17 (10.0)	58 (34.1)	54 (31.8)	0.190*
≤2.5 People	41 (24.1)	10 (5.9)	14 (8.2)	17 (10.0)	

[1] Overall significant (p-value<0.05) independent of province denoted by *
[2] Includes one Indigenous person without status
[3] Other Includes: French, German, Acadian, Inuktitut, Somalian, Other, Chinese
[4] Cut-off value based on the 2006 and 2011 Census [13, 14]

Table 4. 3 Socioeconomic factors from the quantitative questionnaire of all 248 'potential transmitters' in the DTT Project (2007-2008) by province

Variable	Prairie Provinces N=248 (%)	Alberta N=37 (%)	Saskatchewan N=86 (%)	Manitoba N=125 (%)
Social Assistance	n=107 (43)	n=14 (38)	n=38 (44)	n=55 (44)
No	45 (42.1)	10 (9.4)	16 (15.0)	19 (17.8)
Yes	62 (57.9)	4 (3.7)	22 (20.6)	36 (33.6)
P-value[1]	0.100		0.044*	
Work Status	n=183 (74)	n=32 (86)	n=72 (84)	n=79 (63)
No	114 (62.3)	19 (10.4)	39 (21.3)	56 (30.6)
Yes	69 (37.7)	13 (7.1)	33 (18.0)	23 (12.6)
P-value[1]	<0.001*		0.099	
Work Type[2]	n=63 (91)	n=9 (69)	n=33 (100)	n=21 (91)
Industrial[3]	37 (58.7)	7 (11.1)	18 (28.6)	12 (19.1)
Medical-Social[4]	11(17.5)	1 (1.6)	4 (6.4)	6 (9.5)
Other[5]	15 (23.8)	1 (1.6)	11 (17.5)	3 (4.8)
P-value[1]	<0.001*		0.276	
Smoking	n=187 (75)	n=32 (86)	n=76 (88)	n=79 (63)
No	57 (30.5)	15 (8.0)	15 (8.0)	27 (14.4)
Yes	130 (69.5)	17 (9.1)	61 (32.6)	52 (27.8)
P-value[1]	<0.001*		0.013*	
Incarceration[6]	n=182 (73)	n=31 (84)	n=72 (84)	n=79 (63)
No	141 (77.5)	23 (12.6)	55 (30.2)	63 (34.6)
Yes	41 (22.5)	8 (4.4)	17 (9.3)	16 (8.8)
P-value[1]	<0.001*		0.789	
Substance Use[7]	n=194 (78)	n=36 (97)	n=78 (91)	n=80 (64)
No	90 (46.4)	15 (7.7)	33 (17.0)	42 (21.7)
Yes	104 (53.6)	21 (10.8)	45 (23.2)	38 (19.6)
P-value[1]	0.315		0.359	
Alcohol Dependency	n=154 (62)	n=35 (95)	n=56 (65)	n=63 (50)
No	75 (48.7)	23 (14.9)	24 (15.6)	28 (18.2)
Yes	79 (51.3)	12 (7.8)	32 (20.8)	35 (22.7)
P-value[1]	0.747		0.072	
Comorbidities[8]	n=184 (74)	n=37 (100)	n=81 (94)	n=66 (53)
No	134 (72.8)	25 (13.6)	67 (36.4)	42 (22.8)
Yes	50 (27.2)	12 (6.5)	14 (7.6)	24 (13.0)
P-value[1]	<0.001*		0.026*	

[1] Overall significant (p-value<0.05) independent of province denoted by *
[2] Response rates of total who responded "yes" to work status
[3] Includes labourer, maintenance, and mine/oil industries
[4] Includes child, medical, fire, and education services
[5] Includes food/hunting, managerial, and airline employment
[6] Incarcerated in the past 2 years
[7] Includes injection/other drug use
[8] HIV, diabetes and/or renal disease

Table 4. 4 Healthcare access information from the quantitative questionnaire of all 248 'potential transmitters' in the DTT Project (2007-2008) by province

Variable	Prairie Provinces N=248 (%)	Alberta N=37 (%)	Saskatchewan N=86 (%)	Manitoba N=125 (%)
Person: Seek Care First about TB symptoms	n=191 (77)	n=31 (84)	n=82 (95)	n=78 (62)
Nurse	78 (40.8)	5 (2.6)	28 (14.7)	45 (23.6)
Doctor	108 (56.5)	24 (12.6)	53 (27.8)	31 (16.2)
No one	1 (0.50)	0 (--)	0 (--)	1 (0.5)
Other	4 (2.1)	2 (1.1)	1 (0.5)	1 (0.5)
p-value	<0.001		<0.001	
Duration of Cough prior to diagnosis	n=185 (75)	n=32 (86)	n=78 (95)	n=75 (60)
Mean (days)	65.2	84.0	85.3	36.3
Median (days)	28.0	29.0	30	7
95% Confidence Interval	(47.0,83.4)	(11.4,156.6)	(56.2,114.5)	(22.8,49.8)
Interquartile range	(1,60)	(0,75)	(14,60)	(0,60)
Location: Seek Care First about TB symptoms[1]	n=118 (75)	n=19 (83)	n=45 (94)	n=54 (62)
Health On-reserve	64 (54.2)	4 (3.4)	19 (16.1)	41 (34.8)
Health Off-reserve	46 (39.0)	13 (11.0)	22 (18.6)	11 (9.3)
Other	2 (6.8)	2 (1.7)	4 (3.4)	2 (1.7)
p-value	<0.001		<0.001	
See traditional healer for TB symptoms	n=107 (43)	n=9 (24)	n=21 (24)	n=77 (62)
No	90 (84.1)	8 (7.5)	16 (15.0)	66 (61.7)
Yes	17 (15.9)	1 (0.9)	5 (4.7)	11 (10.3)
p-value	<0.001		0.554	
Have a regular family doctor	n=183 (74)	n=32 (86)	n=72 (84)	n=79 (63)
No	96 (52.5)	14 (7.7)	33 (18.0)	49 (26.8)
Yes	87 (47.5)	18 (9.8)	39 (21.3)	30 (16.4)
p-value	0.506		0.077	
Doctor Visit to Health Centre/ Nursing Station[1]	n=87 (55)	n=11 (48)	n=38 (79)	n=38 (44)
Never	18 (20.7)	7 (8.1)	10 (11.5)	1 (1.2)
Yes (Daily)	18 (20.7)	3 (3.5)	2 (2.3)	13 (14.9)
Yes (Weekly, bi-weekly)	38 (43.7)	1 (1.2)	26 (29.9)	11 (12.6)
Yes (Monthly)	13 (14.9)	0 (--)	0 (--)	13 (14.9)
p-value	<0.001		<0.001	
Antibiotics prescribed prior to diagnosis	n=182 (73)	n=30 (81)	n=73 (85)	n=79 (63)
No	97 (53.3)	14 (7.7)	39 (21.4)	44 (24.2)
Yes	85 (46.7)	16 (8.8)	34 (18.7)	35 (19.2)
p-value	0.374		0.700	
X Ray Machine[2]	n=118 (75)	n=11 (48)	n=37 (77)	n=70 (80)
No	52 (44.1)	8 (6.8)	34 (28.8)	10 (8.5)
Yes	66 (55.9)	3 (2.5)	3 (2.5)	60 (50.9)
p-value	0.198		<0.001	

[1] 123 out of 158 respondents (Alberta: 23; Saskatchewan: 48; Manitoba: 87) from on-reserve and Métis settlement communities have health centres or nursing stations. Response rate are among respondents from on-reserve and Métis settlement communities.

[2] Among respondents from on-reserve and Métis settlement communities (n=158)

Table 4. 5 Mobility information 12 weeks prior to TB diagnosis from the quantitative questionnaire of all 248 'potential transmitters' in the DTT Project (2007-2008) by province

Variable	Prairie Provinces N=248 (95% CI)	Alberta N=37 (95% CI)	Saskatchewan N=86 (95% CI)	Manitoba N=125 (95% CI)
	Mobility in the Past 12 Weeks			
Total Responses (Response rate)	n=108 (44)	n=20 (54)	n=41 (48)	n=47 (38)
	Health Related Visits			
Percentage of people	15.7 (15.5,16.0)	10.0 (9.6,10.4)	12.2 (11.9,12.5)	21.3 (20.9,21.7)
Average Duration (Days)	5.56 (5.45,5.68)	3.70 (3.51,3.98)	5.76 (5.55,5.96)	6.19 (6.01,6.37)
Duration In Community (Days)	0.28 (0.26,0.30)	1.50 (1.40,1.60)	0 (--)	0 (--)
Duration Outside Community (Days)	5.29 (5.18,5.40)	2.20 (2.10,2.30)	5.76 (5.55,5.96)	6.19 (6.01,6.37)
	Leisure and Shopping Travel			
Percentage of people	27.8 (27.5, 28.0)	10 (9.6,10.4)	48.8 (48.3,49.3)	17.0 (16.7,17.4)
Average Duration (Days)	2.00 (1.97,2.05)	2.70 (2.55,2.85)	2.85 (2.8,2.91)	0.98 (0.95,1.00)
Duration In Community (Days)	--	--	--	--
Duration Outside Community (Days)	2.00 (1.97,2.05)	2.70 (2.55,2.85)	2.85 (2.80,2.91)	0.98 (0.95,1.00)
	Family Visits and Work Travel			
Percentage of people	62.0 (61.7, 62.3)	75.0 (74.4, 75.6)	48.8 (48.3, 49.3)	68.1 (67.7, 68.5)
Average Duration (Days)	27.58 (27.02,28.15)	22.90 (22.51,23.29)	8.71 (8.53,8.89)	46.04 (44.78,47.30)
Duration In Community[1] (Days)	7.71 (7.53,7.90)	14.95 (14.60,15.30)	0.61 (0.58,0.64)	10.83 (10.44,11.22)
Duration Outside Community (Days)	19.87 (19.45,20.29)	7.95 (7.69,8.21)	8.10 (7.92,8.28)	35.21 (34.29,36.14)
Destination Province	**Province of TB Diagnosis (Average Trip(s) per Person)**			
Alberta	1.53 (1.50,1.56)	6.40 (6.26,6.54)	0.44 (0.42,0.45)	0.40 (0.38,0.42)
Saskatchewan	1.31 (1.29,1.32)	1.25 (1.21,1.29)	2.63 (2.60,2.67)	0.17 (0.16,0.18)
Manitoba	3.35 (3.29,3.41)	0 (--)	4.88×10^{-2} (4.66×10^{-2} ,5.09×10^{-2})	7.66 (7.54,7.78)

[1] Among those that responded – reported statistics on those people

Table 4. 6 Demographic variables of the culture positive TB strains with 24-loci MIRU fingerprinting data (N=1015) diagnosed between 2006 and 2010 (* denoted overall significance p-value < 0.05

Demographic variable	Prairie provinces N=1015 (%)	Alberta N=351 (%)	Saskatchewan N=239 (%)	Manitoba N=425 (%)	P-value
Age (years)					
0-34	418 (41.2)	132 (37.6)	121 (50.6)	165 (38.8)	
35-64	457 (45.0)	146 (41.6)	96 (40.2)	215 (50.6)	<0.01*
>64	140 (13.8)	73 (20.8)	22 (9.2)	45 (10.6)	
Population Group					
Canadian-Born Non-Indigenous	85 (8.4)	33 (9.4)	12 (5.1)	40 (9.4)	
Foreign-Born	383 (37.8)	251 (71.5)	28 (11.9)	104 (24.5)	
First Nations	467 (46.1)	53 (15.1)	141 (59.8)	273 (64.2)	<0.01*
Métis	76 (7.5)	13 (3.7)	55 (23.3)	8 (1.9)	
Inuit	1 (0.1)	1 (0.3)	--	--	
Latitude					
North (above 53rd parallel)	512 (50.4)	182 (51.9)	159 (66.5)	171 (40.2)	<0.01
South (below 53rd parallel)	503 (49.6)	169 (48.2)	80 (33.5)	254 (59.8)	
Community Type					
Major Metropolitan	517 (51.6)	260 (74.9)	55 (23.7)	202 (47.8)	
Non-Major Metropolitan	108 (10.8)	56 (16.1)	22 (9.5)	30 (7.1)	<0.01*
Reserve	318 (31.7)	31 (8.9)	96 (41.4)	191 (45.2)	
Métis Settlement	59 (5.9)	--	59 (25.4)	--	

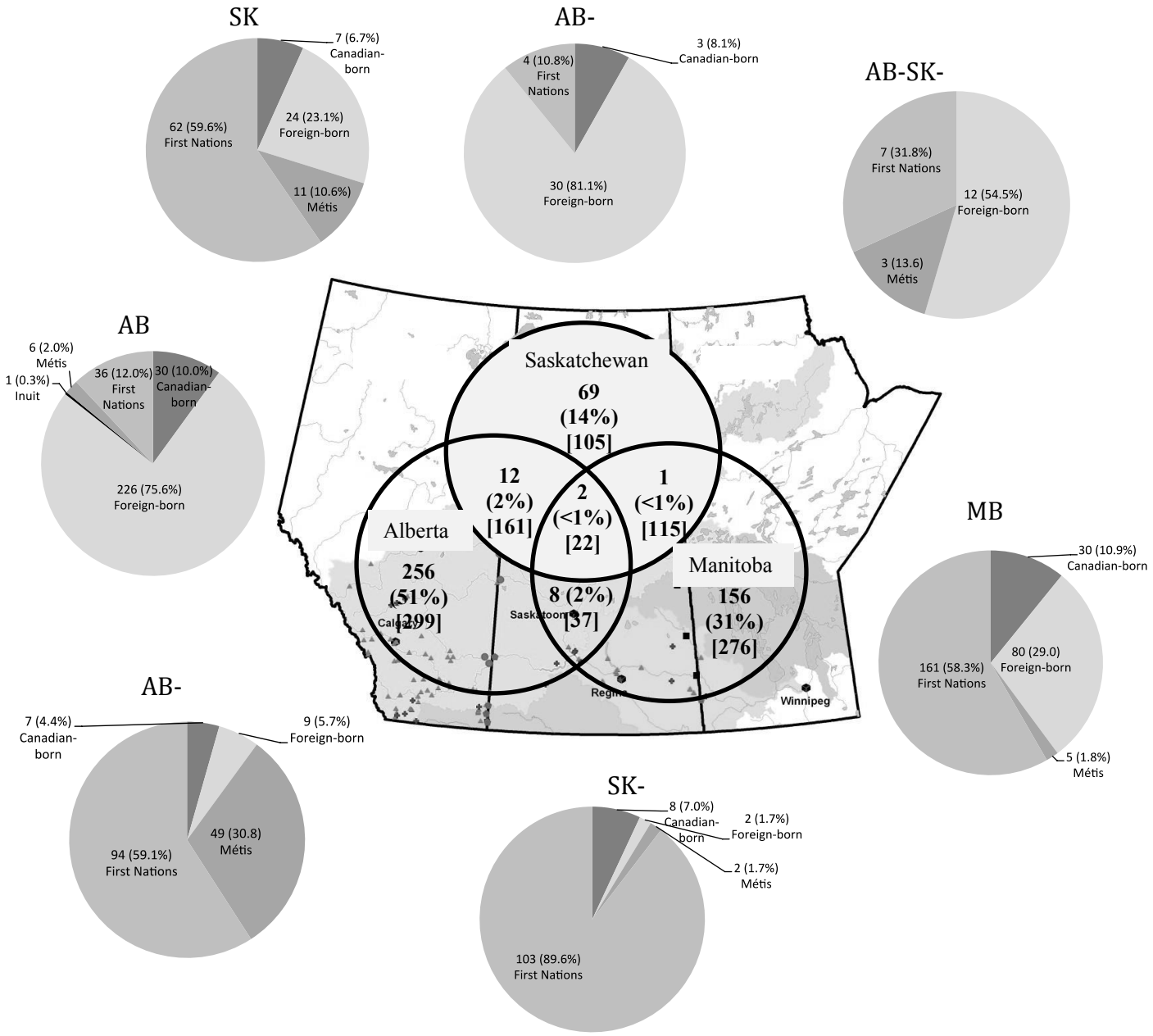

Figure 4. 2 DNA fingerprinting results of M. tuberculosis strains of all TB cases across the prairie provinces and population group between 2006 and 2010[1] for 24-loci MIRU (n=504) patterns (percentage of total patterns) [total isolates]

[1] http://aep.alberta.ca/water/programs-and-services/water-for-life/partnerships/albertas-transboundary-water-agreements/prairie-provinces/images/wfl-P-T-Prairie-Provinces-map.jpg

Table 4. 7 The percentage of clustering among all TB strains (95% confidence interval) with 24-loci MIRU fingerprinting pattern (N=1015) diagnosed between 2006 and 2010 stratified by population group, latitude, and city type

Demographic Variable	Percent (%) of TB strains that are Clustered (95% Confidence Interval)			
	Prairie Provinces N=1015 (%)	Alberta N=351 (%)	Saskatchewan N=239 (%)	Manitoba N=425 (%)
Population Group				
Canadian-Born Non-Indigenous	43.5 (33.0-54.1)	24.2 (9.6-38.9)	16.7 (0-37.8)	62.5 (47.5-77.5)
Foreign-Born	22.7 (18.5-26.9)	16.3 (11.8-20.9)	7.1 (0-16.7)	26.0 (17.5-34.4)
First Nations	79.2 (75.5-82.9)	64.2 (51.2-77.1)	82.3 (76.0-88.6)	79.5 (74.7-84.3)
Métis	78.9 (69.8-88.1)	15.4 (0-35.0)	83.6 (73.9-93.4)	50.0 (15.4-84.6)
Latitude				
North (above 53rd parallel)	66.2 (62.1-70.3)	34.6 (27.7-41.5)	84.3 (78.6-89.9)	80.1 (74.1-86.1)
South (below 53rd parallel)	44.5 (40.2-48.8)	17.8 (12.0-23.5)	46.3 (35.3-57.2)	55.9 (49.8-62.0)
Community Type				
Major Metropolitan	40.4 (36.2-44.7)	21.2 (16.2-26.1)	47.3 (34.1-60.5)	53.0 (46.1-59.9)
Non-Major Metropolitan	33.3 (24.4-42.2)	14.3 (5.1-23.5)	31.8 (12.4-51.3)	43.3 (25.6-61.1)
Reserve	78.9 (74.4-83.4)	67.7 (51.3-84.2)	79.2 (71.0-87.3)	80.1 (74.4-85.8)
Métis Settlement	89.8 (82.1-97.5)	--	89.8 (82.1-97.5)	--

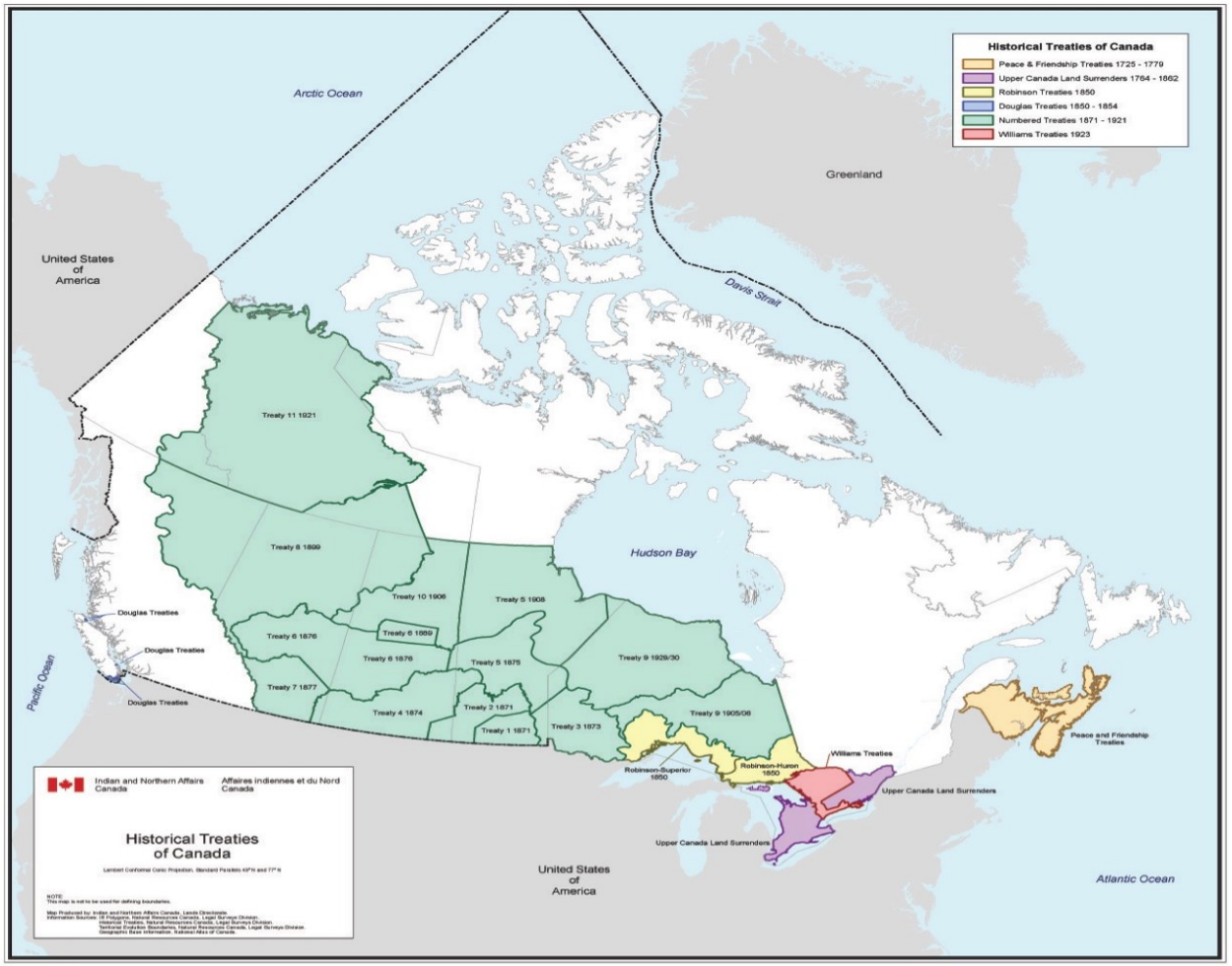

Figure 4. 3 Historical treaties of Canada (Image from : [288])

Chapter 5: Risk Factors Associated with Time to Treatment of Pulmonary Tuberculosis in Indigenous People on the Prairies

5.0 Summary

BACKGROUND: Incidence rates of tuberculosis (TB) among Indigenous peoples have not decreased since the late 1990s, despite an overall decline in TB incidence in Canada. On-going transmission associated with delayed time to diagnosis or treatment is a potential contributor to the persistence of TB in Indigenous communities. This study aims to estimate the time to treatment and to identify its risk factors among Indigenous peoples in the Canadian Prairie Provinces. METHODS: Data was obtained from the *Determinants of TB Transmission project*, a seven-year (2006-2013) cohort study that described the epidemiology of pulmonary TB Canadian-born cases in Alberta, Saskatchewan, and Manitoba. Time to treatment was defined as the time from the onset of cough to the date of TB diagnosis defined as the start date of treatment. Descriptive statistics and logistic regression were used to identify risk factors associated with the time to treatment. RESULTS: One-hundred and fifty cases diagnosed in 2007 and 2008 were examined. The median time to treatment was 30 days (IQR: 3.5-60). Risk factors independently associated with delayed time to treatment (>30 days) included not having a working x-ray machine and technician (AOR: 4.90; $p<0.01$) and having a family doctor (AOR: 4.1; $p=0.03$). Timely treatment (≤30 days) was associated with increased household size (AOR=0.86; $p=0.01$). CONCLUSION: Reducing the duration between the onset of symptoms and treatment can potentially help mitigate transmission from TB cases. This study represents one of few studies investigating risk factors associated with time to treatment among Indigenous peoples in Canada.

5.1 Introduction

Over the past two decades, tuberculosis (TB) incidence rates in Canada have gradually declined from 7 (in 1990) to 5 (in 2010) cases per 100,000 population [54]. Despite the overall decline in TB incidence, Indigenous peoples in Canada experience a disproportionate burden of TB where rates have not declined since the late 1990s [97]. In 2014, the overall TB incidence rate for Indigenous peoples was 20 cases per 100,000 population [46].

Across the Prairie Provinces (Alberta, Saskatchewan, and Manitoba) in high incidence Indigenous communities, evidence of on-going transmission includes high TB rates in children, a large number of secondary pulmonary TB cases from a source case, and clustering of strains using genetic analysis [54, 94, 99, 103, 289-291]. The interruption of on-going transmission in high incidence Indigenous communities is an important consideration for reducing TB burden. Early diagnosis and treatment reduces TB transmission, and the likelihood of advanced disease and mortality [128, 138, 139]. Delay in diagnosis as a term used in literature measures the potential period of transmission and is often defined as the duration between the onset of symptoms and diagnosis or treatment, analogous to total delay [122, 137].

Total delay includes patient, health provider (including health systems delay), diagnostic, and treatment delays [121, 217]. It has been studied by many countries worldwide [121, 122, 128, 137, 144]. The estimated duration of diagnosis delay reported from low and high income countries ranged between 25 and 185 days [122, 137]. In Indigenous communities, these estimates have ranged between 18 days to several months [124, 135, 222, 292].

Factors previously associated with delay in diagnosis have generally included low access to healthcare [121, 145, 293, 294], reduced knowledge of TB or low educational level [293, 294], initial visit to a private practitioner [121, 293], stigma [295], prior prescription of antibiotics or self-treatment [121, 145], alcohol and/or substance use [296, 297], and comorbidities [122, 293].

Among Indigenous peoples in Canada where TB rates are disproportionately higher than Canadian-born non-Indigenous people, factors associated with diagnosis delay have not been well-documented in the literature.

The objective of this chapter is to estimate the time to treatment and identify its risk factors among Indigenous peoples using the information gathered from the *Determinants of Tuberculosis Transmission (DTT) project.* Time to treatment is used in this chapter to describe the duration between the onset of cough, the primary symptom associated with the transmission of TB and the date of diagnosis defined as the start date of treatment. Although delay in diagnosis as a term is used in literature, time to treatment is a better description of the estimate in this study, which is analogous to total delay or transmission period.

5.2 Methods

Data

The DTT project is a seven-year (2006-2013) study aimed at understanding the dynamics of TB transmission among the Canadian-born on the Prairies [99]. As part of the DTT project, a prospective cohort study conducted between 2007 and 2008 of culture-positive Canadian-born adults (>14 years old) with pulmonary TB termed "potential TB transmitters" used mixed-methods (quantitative and qualitative) to explore and understand the socio-cultural, historical, and health determinants of TB transmission in Canadian-born persons [99, 255]. The quantitative questionnaire gathered demographic, risk factor, mobility, TB symptomology, the duration of symptoms prior to treatment, healthcare access, and housing information. Canadian-born adults are defined as any person who is born in Canada or in a foreign country to Canadian parents [99]. Canadian-born adults comprises of First Nations (Registered and non-Registered), Métis, Inuit, and Canadian-born 'others'.

Study Design

The study's main focus was to identify and describe risk factors associated with time to treatment among First Nations, Métis, and Inuit (Indigenous) peoples. The outcome of the analysis was time to treatment, which was defined as the duration of time from the onset of cough to the date of diagnosis defined as the start date of treatment or the date of death in the event the patient died before treatment could be started. Those without cough symptoms were given a value of 0 days of duration in the analysis. Using the median cut-off, a period longer than this value was defined as 'delayed time to treatment' for the logistic regression analysis. A period within the median value was defined as a 'timely treatment'. The primary data used for descriptive and univariate analysis, and multivariate logistic regression is obtained from the DTT quantitative questionnaires.

Data Management and Statistical Analysis

Microsoft Excel 2011 and SAS 9.3 (SAS Institute Inc., Cary, NC, USA) were used for data management, descriptive analysis, and logistic modeling. Missing data from the quantitative questionnaires was reconciled (when available) using the TB registry, chest radiography/ laboratory results, and community access forms (the latter relevant to Indigenous respondents living on-reserve at the time of diagnosis). In the analysis, Indigenous mother-tongue language included Algonquian, Athapaskan, and Siouan. English was defined as a non-Indigenous mother-tongue language. Household density was categorized using the median value in the quantitative questionnaire. Missing information was imputed using the contact investigation data by estimating the total close household contacts for each respondent and classifying them based on the median value. The categorization of age was arbitrary and three groups were constructed to

young, middle age and elderly people. Residence was categorized as major metropolitan area (includes Winnipeg, Saskatoon, Regina, Edmonton, and Calgary), non-major metropolitan area (≥ 500 people and not a major metropolitan area), Métis settlement, and reserve community [99]. Métis settlements in Alberta are designated land defined by the Métis settlements General Council [99]. In Saskatchewan and Manitoba, Métis settlements were defined as populations with at least 25% Métis residents (based on the Statistics Canada Census) [99]. The first location to seek care for TB symptoms was dichotomized as "Health on" and Health off". "Health on" included clinics, hospitals, and/or nursing stations within the community of residence. "Health off" included clinics and hospitals outside the community of residence.

Descriptive analysis included comparing median durations (with interquartile ranges) of time to treatment across risk factors reported in the DTT quantitative questionnaires. Any differences observed were tested using chi-square and t-tests. Fisher's exact tests were used for comparisons when the expected counts were less than five. For symptomology, mean and median durations of time to treatment with 95% confidence intervals and inter-quartile ranges were estimated.

A step-wise forward selection logistic regression was used to identify factors associated with time to treatment. Predictors significant at a 25% level in the univariate analysis were included for multivariate logistic regression. Predictors with p-values less than 0.25 during the univariate analysis were assessed for collinearity ($|\rho|>0.8$) and linearity. Predictors in the multivariable logistic regression were included if the p-value was within 0.1. Assumptions for logistic regression include a binary outcome, independent observations, and linear relationships between predictors and the log odds of the outcome [298]. The interpretation of this model provides associations in terms of an odds ratio between a risk factor and outcome.

Interaction terms were tested among predictors in the multivariable logistic regression model. Confounding was assessed by observing a change in coefficients in the log odds scale of greater than 20% with either adding or removing a confounder [298]. In addition, the likelihood ratio test (LRT) was used to determine whether adding predictors ("full model") has a better fit to the data than excluding it ("reduced model") [298]. Model selection was conducted using the Akaike's Information Criterion (AIC) (non-nested models)[298] and selection was based on models with the lowest AIC values.

Model assessment included evaluating the overall fit and predictive ability of the model [298, 299]. The overall fit was assessed using goodness of fit tests (Pearson and Deviance for categorical and Homser-Lemeshow for continuous variables). Accepting the null hypothesis implies that the fitted model has a better fit than the saturated model. The receiving operating curve (ROC) was used to assess the predictive ability of the model. Using various cut-off values of the outcome (between 0 and 1), the comparison between predicted and observed probabilities help estimate the sensitivity and specificity of the model's overall predictive ability. High sensitivity and specificity yield a higher ROC estimate, which indicates a stronger predictive model.

5.3 Results

In total, 222 out of 248 (90%) of culture positive Canadian-born adults diagnosed with pulmonary TB between 2007 and 2008 were determined to be "true" TB transmitters defined as TB cases that were not secondary cases of a potential transmitter in the DTT study [300]. Among the true TB transmitters, 90% (198/222) were Indigenous adults diagnosed during the DTT study period in Alberta (n=22), Saskatchewan (n=68), and Manitoba (n=108). Figure 5.1 describes the proportion of people with completed quantitative questionnaires from the DTT project. One

hundred and forty-eight people (75% of 198 Indigenous peoples) completed the quantitative questionnaires. Secondary information such as the TB registry was used to help reconcile some of the information about the 50 Indigenous respondents without completed quantitative questionnaires. Therefore it was possible that totals could exceed 148 responses for descriptive results.

Table 5.1 describes the demographics of Canadian Indigenous adults (n=198) diagnosed with pulmonary TB between 2007 and 2008 overall and by province. Of 198 pulmonary TB cases, 81% (n=160) and 19% (n=37) were First Nations and Métis, respectively. Ninety-three percent (184/198) of the cases were between 15 and 65 years old. Location of TB cases included reserve communities (112/198; 56%), major metropolitan areas (44/198; 22%), non-major metropolitan areas (19/198; 10%), and Métis settlements (23/198; 12%). The median household size was five people (IQR: 4).

There were a total of 109 (55%) male and 89 (45%) female pulmonary TB cases and approximately half were between 35 and 64 years old (See Table 5.1). Stratified by province, there were no significant differences ($p>0.05$) in age, gender, and household size (See Table 5.1). Indigenous population group, community type, and language spoken at birth were significantly different ($p < 0.05$) across provinces (See Table 5.1).

The duration of TB symptoms of 198 Indigenous peoples stratified by province is described in Table 5.2. The overall response rate for respondents reporting symptoms ranged between 39% (78/198) and 76% (151/198). Symptoms included cough (80.0%; n=150), fever (60.3%; n=151), night sweats (66.9%; n=151), weight loss (72.1%; n=147), fatigue (53.9%; n=78), and chest pain (31.6%; n=79) (See Table 5.2). The median duration of cough, fever, and night sweats was 30 days (IQR: 57), 14 days (IQR: 56), and 14 days (IQR: 60), respectively across the Prairie Provinces.

The study's estimated median and mean time to treatment was based on the duration of cough. The median and mean time to treatment was 30 days (IQR: 57 days) and 65.7 days (95% CI: 48.8 – 82.6), respectively. Most respondents (80%; 120/150) experienced cough as a symptom of pulmonary TB. The median value for time to treatment was robust and unaffected using a definition that considered the onset of any symptom. A time to treatment definition that considered any symptoms such as the duration of cough, fever, night sweats, weight loss, fatigue, and chest pain resulted in a median value of also 30 days. The median cut-off value of 30 days for time to treatment was used in the multivariable logistic regression. 'Delayed time to treatment' was any duration greater than 30 days, while a timely treatment was at most 30 days.

Table 5.3 describes the univariate analysis of risk factors (p-value < 0.25 only) associated with time to treatment of TB among Indigenous peoples across the Prairie Provinces. The response rate of risk factors in Table 5.3 was between 70% (138/198) and 76% (150/198). Univariate analysis indicated that risk factors associated with time to treatment ($p<0.05$) included having comorbidities (OR=2.36; 95% CI: 1.05-5.31). Comorbidities (diabetes, HIV, and renal disease) were reported among 28% (34/120) of respondents. Among respondents that reported having health problems (35%; 51/142), diabetes (47%; 24/51) and HIV (14%; 7/51) accounted for 61% of the total responses. These predictors were correlated with each other and were not simultaneously included in the multivariable logistic analysis. Healthcare access risk factors univariately associated with delayed time to treatment ($p<0.05$) included prior treatment of antibiotics (OR=2.21; 95% CI: 1.11-4.40), seeking a doctor first about TB symptoms (OR=2.05; 95% CI: 1.02-4.09), accessing a healthcare facility outside the community first for TB symptoms (OR=2.08; 95% CI: 1.02-4.25), and not having a working x-ray machine and technician in a community (OR=2.72; 95% CI: 1.33-5.56). Having a non-Indigenous mother tongue (OR: 2.51;

95% CI: 1.10-5.72) and a housing density of at most five people (OR: 2.21; 95% CI: 1.10-4.44) were additional risk factors univariately associated with delayed time to treatment ($p<0.05$).

In the study, 24% (36/150) of the respondents self-reported a time to treatment (duration of cough) of greater than 60 days and 22% (8/36) of these reported having a cough for at least one year. Table 5.4 compares the demographic and risk factors between a cohort with a time to treatment of greater than 60 days (n=36) and at most 60 days (n=162). Of the cohort of people with delayed time to treatment (>60 days), 61% (22/36) were male and 22% (8/36) and 47% (17/36) were diagnosed in Alberta and Saskatchewan, respectively. Although not statistically significant, 10% more respondents with delayed time to treatment (>60 days) had health problems or comorbidities compared to those with a time to treatment of at most 60 days. Seventy percent (23/33) of respondents with delayed time to treatment (>60 days) lived in households with less than six people compared to 45% (48/106) of respondents with a time to treatment of at most 60 days. For risk factors related to healthcare access, 66% (23/35) sought a physician first for TB symptoms, 71% (25/35) accessed health services outside the community, and 62% (21/34) were previously provided with antibiotics prior to TB diagnosis among people with delayed time to treatment (>60 days); this compared to 53% (58/109), 56% (58/103), and 47% (51/108) among respondents with a time to treatment of at most 60 days, respectively.

Table 5.5 represents the multivariable logistic model that describes the risk factors independently associated with time to treatment. Of the total respondents with an estimate for time to treatment (i.e. duration of cough), 85% (127/150) were included in the multivariable logistic regression analysis. Gender was not confounding in the multivariable analysis. Age was included in the logistic regression as it was a confounding variable to having health problems. The risk factors in the multivariable logistic model were all significant at a p-value of less than 0.05; however, the inclusion of age as a confounding variable increased the p-values to greater

than 0.05 for health problems and mother tongue language. Independent risk factors associated with delayed time to treatment included having health problems (AOR=1.53; p=0.39), a non-Indigenous mother tongue (AOR=2.64; p=0.07), no working x-ray machine and technician in a community (AOR=4.90; p<0.01), and a regular family doctor (AOR=2.45; p=0.05). Increased household size was associated with timely treatment (AOR: 0.86; p=0.01). The Hosmer-Lemeshow goodness of fit test (p=0.22) indicated that the multivariable logistic model had a good fit compared to the saturated model and its overall predictive ability was 81% (ROC value).

5.4 Discussion

This study provided an estimate of and identified risk factors for time to treatment among Indigenous peoples across the Prairie Provinces using the data gathered from the DTT project. The median time to treatment was 30 days (IQR: 57), while the average was 65.7 days (95%: 48.8-82.6). Risk factors associated with time to treatment in the multivariable logistic regression analysis included healthcare access predictors, having health problems (AOR: 1.53), and a non-Indigenous mother tongue language (AOR: 2.64). Healthcare access predictors included having a regular family doctor (AOR: 2.45) and no working x-ray machine and technician in a community (AOR: 4.90). Increased household size was associated with timely treatment of TB (AOR: 0.86). In the analysis of respondents with a time to treatment of greater than 60 days, qualitative differences in comorbidities, household density, and healthcare access risk factors were identified. These observations were supported by the multivariable logistic regression analysis.

In literature, diagnosis delay defined as the duration between the onset of symptoms and diagnosis or treatment ranged from 25 to 185 days among studies conducted in low and high income countries [123]. The median time to treatment estimated in this study was within the range reported by the systematic review conducted by Sreeramareddy et. al [123]. A Canadian

study conducted in 17 hospitals across four cities between 1992 and 1995 estimated a median delay (from admission to treatment) of 12.5 days (range: 0 – 250) [143]. A study conducted in Quebec between 1998 and 2007 reported a mean time to diagnosis or treatment of 105.1 days (95% CI: 87.7 – 122.5) among Canadian-born people [128]. Studies conducted in Ontario estimated a time to treatment of 62 (median: IQR - 31 to 114 days) and a time to diagnosis of 84 days (mean) [142, 144].

Studies conducted in Quebec and Ontario defined delay in diagnosis as the duration between any symptom and the date of diagnosis [128, 142] and treatment [128, 144]. In consideration of making comparisons with other Canadian literature, the duration from the onset of any symptom to the date of treatment was estimated using the DTT data. The average time to treatment was 92.2 days (95% CI: 72.3 – 112.1) comparable to other Canadian studies [128, 142, 144].

Time to diagnosis or treatment focusing on Indigenous populations was sparse and variable in literature (See Chapter 3) making comparisons to this study's estimate challenging. Studies conducted in Indigenous populations have included delay estimates of 18 days (mean: health systems delay; Taiwan), least 60 days (35^{th} percentile: time to diagnosis; United States), 53 days (median: time to treatment; Queensland) to several months (source case: outbreak study; Canada: time to diagnosis)[124, 132, 135, 222].

In this study, the mean time to treatment (66 days) was approximately twice as high as the median (30 days) estimate, which indicated that some patients experienced much longer periods where TB transmission could occur. Ad-hoc results of respondents with time to treatment durations of greater than 60 days (see Table 5.4) showed that 22% (8/36) had durations for at least one year. This was significant considering that 69% (25/36) of these respondents were smear positive. The relative transmission rate for smear positive status is between 4 and 5 times

higher than smear negative status [54]. The potential for on-going transmission would be much greater among these individuals (time to treatment >60 days) especially if they had high contact rates and were smear positive.

Systematic reviews of delay in diagnosis studies highlight its definition as variable across the medical literature [122, 123, 137]. Examples of the start point for delay in diagnosis included the onset of any symptom, a pulmonary related symptom, or cough [122]. The end period for delay in diagnosis had varied definitions such as the end of health system delay (e.g. date of diagnosis) or the start date of treatment [122]. The overall definition of total delay included many parts such as patient, health provider, health system, diagnostic facility, and treatment delay [121]. These sub-definitions can be variable across studies [122, 123].

As an alternative, a precise term analogous to total delay was used to describe the estimate obtained in this study. The use of "delay" imposes that all estimates are a delayed estimate and discussions about what a reasonable time to diagnosis or treatment is needed to help ease comparability between studies conducted in literature. Time to treatment in this study was defined as the duration of time between the onset of cough (or hemoptysis) and the start date of treatment or the date of death prior to treatment. The start date of treatment was used instead of the diagnosis date since the latter can be documented using different definitions. These included, the date sputum samples were collected, when the culture was positive, and/or a smear positive result. A positive culture result could take up to six to eight weeks while a smear result can be provided within 24 hours of receiving the sputum sample [54]. Treatment can also be provided prior to or after a formal diagnosis date depending on factors such as clinical presentation and smear positive result. An approach to standardize the endpoint of transmission in Alberta, Saskatchewan, and Manitoba was to use the start date of treatment. The start point of time to treatment was the onset of cough (or hemoptysis), however, it was possible that persons with TB

disease could be asymptomatic. The use of cough (or hemoptysis) helped to estimate the risk period for TB transmission since cough is the symptom most closely associated with transmission [54, 94, 99].

The use of the median estimate for time to treatment ensured that the analysis conducted was robust and unaffected by the use of different definitions such as the start point being defined as the onset of any symptom versus the onset of cough used in this study. The median time to treatment estimate using the start point as the onset of any symptom also resulted in a duration of 30 days. Univariate and multivariate results presented in this study were not affected using a time to treatment definition where the start point was of the onset of any symptom.

Factors associated with time to treatment in our study included having health problems (AOR=1.53; p=0.39) in the multivariable logistic regression (see Table 5.5). Of respondents having health problems, diabetes and HIV accounted for 61% (31/51) of the responses. Diabetes and HIV are both known to increase the risk of developing active TB and their rates continue to be disproportionately higher in Indigenous populations compared to non-Indigenous populations in Canada [51, 301, 302]. The association of diabetes and HIV with longer delays in diagnosis has previously been reported in literature [143, 303-305]. Respiratory tract infections in people with diabetes and HIV have symptoms that confound those with TB, which can explain in part the association of diabetes and HIV with longer delays in diagnosis [304, 306, 307]. Additionally, atypical radiographic results for TB and HIV-associated stigma were other potential explanations for longer delays in diagnosis in HIV infected TB cases [305, 308, 309]. For healthcare workers, TB education about its association with other comorbidities such as HIV and diabetes, stigma, and cultural awareness are important especially in high burden communities [256, 286]. The continued efforts for prevention of diabetes and HIV in Indigenous communities can therefore have additional benefits by potentially reducing TB transmission.

Delayed time to treatment associated with having a regular family doctor was a risk factor also reported in other TB studies from low and medium incidence countries [121, 146, 293, 310-312]. Most of these studies estimated a longer time to diagnosis or treatment among people who visited a health clinic [121, 146, 293, 312], while others also described this association with visiting private practitioners [310, 311]. Some reasons for this seemingly inverse relationship have been proposed to be an overall lack of TB diagnostic equipment, poor knowledge leading to TB diagnosis, and inadequate turn around time on test results. These challenges faced by clinics and medical practitioners in resource challenged countries can increase the time to diagnosis and treatment [121, 146, 310, 312].

Health delivery to Indigenous peoples in Canada is complex since health services are provided provincially and regulated federally through the non-insured health benefits program whose eligibility is based on First Nations people registered under the *Indian Act* and Inuk people recognized by the Inuit land claim organization (except Métis people and non-Status First Nations people)[53]. Among approximately 600 First Nations communities across Canada, there were a total of 76 nursing stations and at least 195 health centres where nurses were often the first point of care [313]. Although not significant in the univariate analysis, the median time to treatment among people who first saw a nurse for their TB symptoms were diagnosed one week earlier than physicians (see Table 5.3). In some communities, family doctors either are available daily, or travel on-site on a weekly, bi-weekly, and/or monthly basis. The availability of family doctors on-reserve can introduce challenges building rapport and trust through limited frequency and duration of patient visits, high turnover rates, continuity of care, understaffing, and lacking knowledge to recognize TB symptoms [54, 256], which was also supported by the results from the qualitative interviews conducted in the DTT project [256]. These additional challenges may contribute to delayed time to treatment.

The quality of care may not have been entirely captured with the question about having a regular family doctor. A secondary multivariable logistic regression model in Table 5.6 describes an equally predictive model (ROC=0.83), which is not as parsimonious to the multivariable model presented in Table 5.5. The predictors between these two multivariate models were similar with the exception of comorbidities, which was highly correlated with having health problems. The interaction between having a regular family doctor and comorbidities (p=0.07) highlighted that if an individual has a regular family doctor and comorbidities, the adjusted odds ratio of delayed time to treatment decreased to 1.35 (from AOR: 12.3). Therefore having comorbidities may have required regular appointments with a family doctor, which increased the opportunity to recognize TB symptoms earlier.

The stigma of TB faced by on-reserve and Métis settlement communities [29, 99, 111, 256, 257] may impact where people first seek care for TB symptoms. Approximately half of respondents in the DTT project living on-reserve that reported having a regular family doctor first sought care for TB symptoms outside their community. Although not significantly different, respondents from on-reserve communities whose first point of care was outside their community (Health-off) had a median time to treatment of 30 days (IQR: 78 days) compared to within (Health-on: 14 days; IQR: 52) (see Table 5.3). Seeking care outside the community can potentially be influenced by the availability of diagnostic and personnel resources, and guaranteeing anonymity due to the stigmatization of TB. In the multivariate analysis, not having a working x-ray machine and technician within the community was associated with delayed time to treatment (AOR: 4.90; p<0.01) (see Table 5.5) in this study.

Housing density was associated with timely treatment (AOR: 0.86; p=0.01). A plausible explanation was that people in larger households might encourage a family member with TB symptoms such as coughing to seek care from a medical professional earlier, which was

supported by the results from the qualitative interviews conducted in the DTT project [256]. Similar results that compare marital status (single/married) were observed in two studies where single people were associated with longer delays in diagnosis [314, 315].

This study had some limitations. The results were based on self-reported responses to the DTT questionnaire and subject to recall bias. The DTT questionnaire was administered using semi-structured interviews, which helped minimize the recall bias. The DTT quantitative questionnaires may not have included individuals that were not yet diagnosed between 2007 and 2008, whose start of treatment occurred after 2008 introducing some selection bias. Alcohol dependency and drug use were not significant predictors for time to treatment in the analysis unlike other studies identified by a systematic review conducted by Storla et al. [122]. Self-reporting of alcohol dependency and drug use was challenging to describe and interpret given the sensitivity of these questions. Although semi-structured interview were conducted, there may not have been enough time to build rapport and trust with respondents to better answer these sensitive questions thereby introducing some misclassification bias.

5.5 Conclusion

The estimated median duration for time to treatment in this study was 30 days (IQR: 57). The higher average time to treatment (65.7 days; 95% CI: 48.8 – 82.6) indicated that some individuals have much longer periods of where transmission could occur. Identifying risk factors associated with time to treatment offered insights to potential areas of intervention that could help reduce TB transmission. The results of this study indicated that increasing access to chest x-ray machines with a working technician might help promote earlier diagnosis and treatment. Continued efforts to improve the overall health of Indigenous peoples through the prevention of comorbidities such as diabetes and HIV may have secondary impacts that include reducing the

time to treatment. Further investigation is needed to understand reasons why having a family doctor was associated with delayed time to treatment. Future research investigating risk factors associated with patient and health system delay or total health encounters prior to TB diagnosis and treatment could provide additional insights related to healthcare access and seeking care for TB symptoms. Overall, the risk factors associated with time to treatment included household size, health-care access, having health problems, and Indigenous language. The interruption of ongoing transmission in communities with a high burden of TB through the reduction of time to treatment could have an impact to mitigate transmission from TB cases. This study represents one of few studies investigating risk factors for time to treatment among Indigenous peoples in Canada.

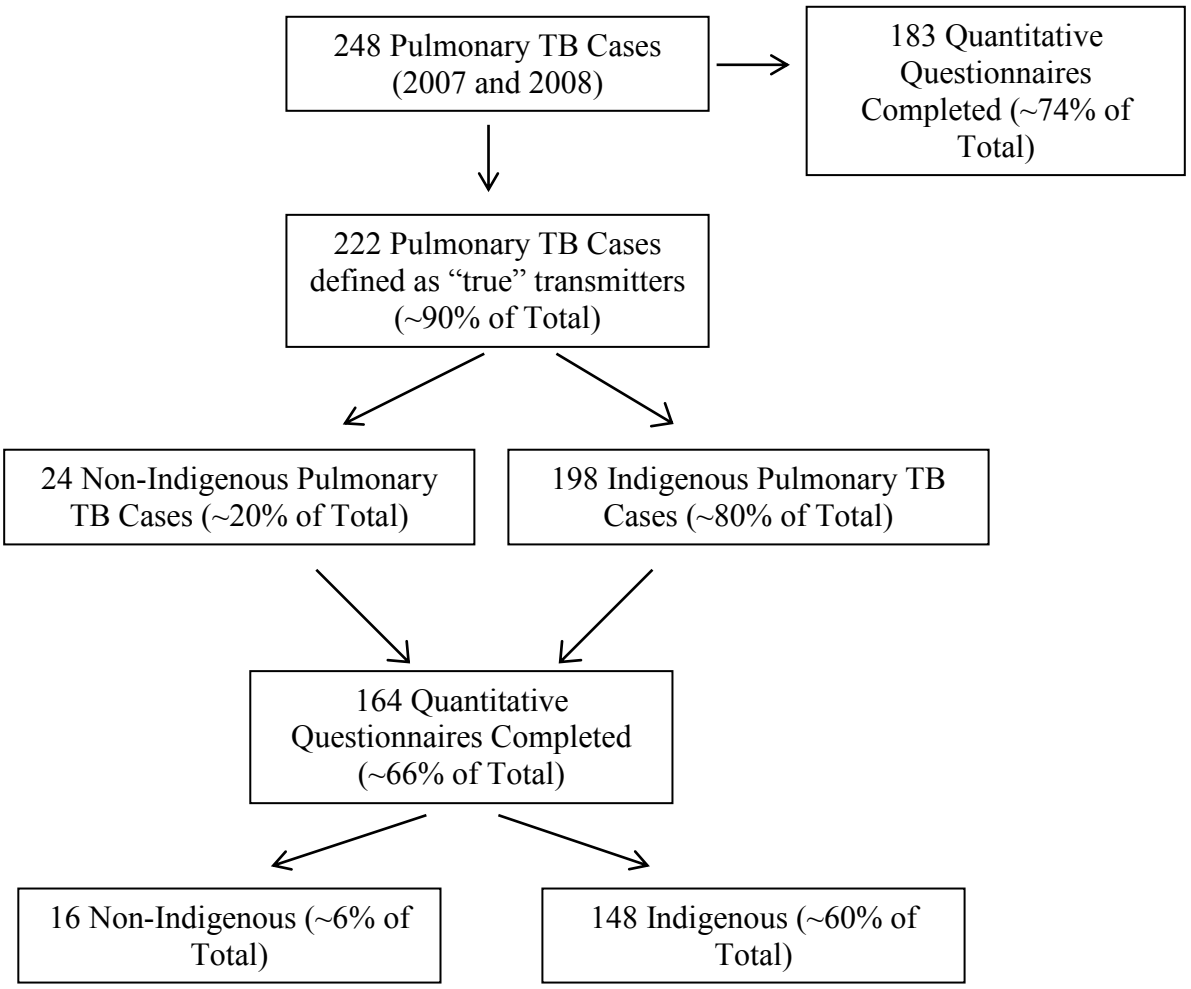

Figure 5. 1 An overview of the primary data from the Determinants of Tuberculosis Transmission Project conducted between 2007 and 2008

Table 5. 1 Demographic variables of Canadian Indigenous peoples (N=198) with pulmonary TB diagnosed between 2007 and 2008 by province, n(%)

Demographic Variable	Prairie Provinces N=198 (%)	Alberta N=22 (%)	Saskatchewan N=68 (%)	Manitoba N=108 (%)	P-value[1]
Gender	n=198 (100)	n=22 (100)	n=68 (100)	n=108 (100)	
Male	109 (55.1)	12 (54.6)	34 (50.0)	63 (58.3)	
Female	89 (44.9)	10 (45.5)	34 (50.0)	45 (41.7)	0.55
Age	n=198 (100)	n=22 (100)	n=68 (100)	n=108 (100)	
15-34	77 (38.9)	4 (18.2)	32 (47.1)	41 (38.0)	
35-64	107 (54.0)	15 (68.2)	32 (47.1)	60 (55.6)	
>64	14 (7.1)	3 (13.6)	4 (5.8)	7 (6.4)	0.16*
Indigenous Population[2]	n=198 (100)	n=22 (100)	n=68 (100)	n=108 (100)	
Treaty/non-Status	160 (80.8)	15 (68.2)	43 (63.2)	102 (94.4)	
Métis	37 (18.7)	6 (27.3)	25 (36.8)	6 (5.6)	
Inuit	1 (0.5)	1 (4.6)	0 (--)	0 (--)	< 0.01*
Community Type	n=198 (100)	n=22 (100)	n=68 (100)	n=108 (100)	
Major Metropolitan	44 (22.2)	7 (31.8)	8 (11.8)	29 (26.9)	
Non-Major Metropolitan	19 (9.6)	5 (22.7)	5 (7.3)	9 (8.3)	
Reserve Community	112 (56.6)	10 (45.5)	32 (47.1)	70 (64.8)	
Métis Settlement	23 (11.6)	0 (--)	23 (33.8)	0 (--)	< 0.01*
Language: Mother Tongue[3]	n=148 (75)	n=19 (86)	n=58 (85)	n=71 (66)	
English	30 (20.3)	4 (21.1)	11 (19.0)	15 (21.1)	
Algonquian	67 (45.3)	5 (26.3)	7 (12.1)	55 (77.5)	
Athapaskan	44 (29.7)	5 (26.3)	39 (67.2)	0 (--)	
Siouan	3 (2.0)	3 (15.8)	0 (--)	0 (--)	
Other[4]	4 (2.7)	2 (10.5)	1 (1.7)	1 (1.4)	< 0.01*
Household Size[3]	n=148 (75)	n=20 (91)	n=65 (96)	n=63 (58)	
>5 people	72 (48.7)	10 (50)	28 (43.1)	34 (54.0)	
≤5 people	76 (51.3)	10 (50)	37 (56.9)	29 (45.0)	0.46

[1] * Denotes overall significance level of 0.05
[2] one person each from Alberta and Manitoba were non-Status First Nations
[3] Non-response: (25%; 50/198)
[4] Other Includes: French, Acadian, and Inuktitut

Table 5. 2 Durations of symptoms among Canadian Indigenous pulmonary TB cases (N=198) between 2007 and 2008 by province, n(%)

Symptom	Prairie Provinces N=198 (%)	Alberta N=22 (%)	Saskatchewan N=68 (%)	Manitoba N=108 (%)
Cough	n=150 (76)	n=19 (86)	n=63 (93)	n=68 (63)
No	30 (20)	2 (11)	6 (10)	22 (32)
Yes	120 (80)	17 (89)	57 (90)	46 (68)
Median Duration (Days)	30	60	30	14
IQR	57	60	76	60
Mean Duration (Days)	65.7	81.4	89.3	39.5
95% C.I. of Mean	(48.8,82.6)	(36.4,126.5)	(55.1,123.5)	(24.8, 54.2)
Fever	n=151 (76)	n=20 (91)	n=62 (91)	n=69 (64)
No	60 (40)	9 (45)	20 (32)	31 (45)
Yes	91 (60)	11 (55)	42 (68)	38 (55)
Median Duration (Days)	14	5	21	4
IQR	56	30	60	32
Mean Duration (Days)	42.3	33.4	56.9	31.7
95% C.I. of Mean	(30.1,54.5)	(2.3,64.4)	(32.8,81.0)	(18.4,45.0)
Night Sweats	n=151 (76)	n=19 (86)	n=63 (93)	n=69 (64)
No	50 (33)	4 (21)	17 (27)	29 (42)
Yes	101 (67)	15 (79)	46 (73)	40 (58)
Median Duration (Days)	14	30	21	4
IQR	60	103	52	56
Mean Duration (Days)	49.3	44.2	68.4	33.2
95% C.I. of Mean	(33.8,64.7)	(19.4,68.9)	(35.1,101.7)	(19.9,46.6)
Weight Loss	n=147 (74)	n=19 (86)	n=60 (88)	n=68 (63)
No	41 (28)	5 (26)	10 (17)	26 (38)
Yes	106 (72)	14 (74)	50 (83)	42 (62)
Median Duration Days	16	42	30	8
IQR	60	90	56	30
Mean Duration (Days)	57.4	62.6	68.6	46.1
95% C.I. of Mean	(40.5,74.3)	(30.8,94.5)	(41.9,95.3)	(18.9,73.2)
Fatigue	n=78 (39)	n=17 (77)	n=20 (29)	n=41 (38)
No	36 (46)	13 (76)	9 (45)	14 (34)
Yes	42 (54)	4 (24)	11 (55)	27 (66)
Median Duration (Days)	4	0	3	14
IQR	52	0	30	60
Mean Duration (Days)	40.6	27.4	40.0	46.3
95% C.I. of Mean	(23.7,57.4)	(-2.5,57.3)	(-0.8,80.7)	(22.4,70.2)
Chest Pain	n=79 (40)	n=18 (82)	n=19 (28)	n=42 (39)
No	54 (68)	14 (78)	12 (63)	28 (67)
Yes	25 (32)	4 (22)	7 (37)	14 (33)
Median Duration (Days)	0	0	0	0
IQR	8	0	14	14
Mean Duration (Days)	26.6	38.8	16.4	20.4
95% C.I. of Mean	(10.4,42.9)	(-12.7,90.4)	(-4.0,36.7)	(4.7,47.4)

Table 5. 3 Univariate analysis of Canadian Indigenous pulmonary TB cases between 2007 and 2008 (unadjusted odds ratios)

		Time to Treatment (days)		Delayed Time to Treatment (time > 30 days)	
	N	**Median**	**IQR**	**OR**	**p-value**
Age	150				0.117
15-34	64	21	53	0.67	--
35-64	81	30	86	1.40	--
>64	5	30	45	Ref	--
Province	150				0.131
Alberta	19	60	60	2.49	--
Saskatchewan	63	30	76	1.79	--
Manitoba	68	14	60	Ref	--
Language (Mother Tongue)	138				0.029
Non-Indigenous	30	58	76	2.51	--
Indigenous	108	25	58	Ref	--
Smear Status	150				0.227
Positive	98	30	61	1.54	--
Negative	52	14	60	Ref	--
Household Size	139				0.027
≤5 people	71	30	106	2.21	--
>5 people	68	19	44	Ref	--
Health Problems	142				0.1288
Yes	51	30	119	1.72	
No	91	28	57	Ref	
Comorbidities	120				0.037
Yes	34	60	147	2.36	--
No	86	30	53	Ref	--
Have a Regular Family Doctor	142				0.094
Yes	70	30	83	1.79	--
No	72	21	53	Ref	--
Person: Seek First about TB Symptoms	144				0.043
Doctor	81	30	110	2.05	--
Nurse	63	21	60	Ref	--
Location: Seek First about TB Symptoms	138				0.045
Health-off[1]	83	30	78	2.08	--
Health-on[2]	55	14	52	Ref	--
A Working X-ray Machine and Technician in Community	148				0.006
No	46	56	92	2.72	--
Yes	102	21	57	Ref	--
Antibiotics Provided Prior to TB Diagnosis	142				0.024
Yes	72	30	92	2.21	--
No	70	14	60	Ref	--

[1] Health-off includes clinic and hospital outside community of residence
[2] Health-on includes clinic, hospital, and/or nursing station within community of residence

Table 5. 4 A descriptive analysis of demographic variables and risk factors for respondents with time to treatment of greater than 60 days in Canadian Indigenous pulmonary TB cases between 2007 and 2008

Demographic Variable/Risk Factors	N=36 (%) (>60 days)	N=162 (%) (≤60 days)
Gender		
Male	22 (61)	57 (50)
Female	14 (39)	57 (50)
Province		
Alberta	8 (22)	11 (10)
Saskatchewan	17 (47)	46 (40)
Manitoba	11 (31)	57 (50)
Age		
15-34	11 (31)	53 (46)
35-64	23 (64)	58 (51)
>64	2 (5)	3 (3)
Community Type		
Major Metropolitan	9 (25)	24 (21)
Non-Major Metropolitan	4 (11)	10 (9)
Reserve Community	20 (56)	61 (53)
Métis Settlement	3 (8)	19 (17)
Health Problems		
Yes	15 (44)	36 (33)
No	19 (56)	72 (67)
Comorbidities		
Yes	12 (36)	22 (25)
No	21 (64)	65 (75)
Household Size		
≤5 people	23 (70)	48 (45)
>5 people	10 (30)	58 (55)
Smear Positive		
Yes	25 (69)	73 (64)
No	11 (31)	41 (36)
Language (Mother Tongue)		
Indigenous	23 (70)	85 (81)
Non-Indigenous	10 (30)	20 (19)
Person: Seek First about TB Symptoms		
Doctor	23 (66)	58 (53)
Nurse	12 (34)	51 (47)
Location: Seek First about TB Symptoms		
Health-off[1]	25 (71)	58 (56)
Health-on[2]	10 (29)	45 (44)
A Working X-ray Machine and Technician in Community		
Yes	19 (53)	83 (74)
No	17 (47)	29 (26)
Antibiotics Provided Prior to TB Diagnosis		
Yes	21 (62)	51 (47)
No	13 (38)	57 (53)

[1] Health-off includes clinic and hospital outside community of residence
[2] Health-on includes clinic, hospital, and/or nursing station within community of residence

Table 5. 5 Multivariate logistic regression of risk factors associated with time to treatment in Canadian Indigenous pulmonary TB cases between 2007 and 2008

	Time to Treatment (days): N=127	
	AOR[1]	**p-value**
Age	0.10	<0.01
Language (Mother Tongue)		0.07
Non-Indigenous	2.64	--
Indigenous	Ref	--
Health Problems		0.39
Yes	1.53	--
No	Ref	--
Household Size	0.86	0.01
A Working X-ray Machine and Technician in Community		<0.01
No	4.90	--
Yes	Ref	--
Have a Regular Family Doctor		0.05
Yes	2.45	--
No	Ref	--

[1] AOR: Adjusted Odds Ratio

Table 5. 6 A secondary multivariate logistic regression model of risk factors associated with time to treatment among Canadian Indigenous pulmonary TB cases between 2007 and 2008

	Time to Treatment (days): N=104	
	AOR[1]	**p-value**
Age	0.98	0.67
Language (Mother Tongue)		0.04
Indigenous	0.02	--
Non-Indigenous	1	--
Comorbidities		0.01
Yes	12.26	--
No	1	--
Household Size	0.83	0.02
A Working X-ray Machine and Technician in Community		<0.01
Yes	0.15	--
No	1	--
Have a Regular Family Doctor		0.03
Yes	4.10	--
No	1	--
Comorbidities and Have a Regular Family Doctor		0.07
Yes	0.11	--
No	1	--
Language (Mother Tongue) and Age		0.07
Yes	1.09	--
No	1	--

[1] AOR: Adjusted Odds Ratio

Chapter 6-Part 1: AB-SK Agent-Based TB Transmission Model: Three First Nations and/or Métis Communities in Northern Alberta and Saskatchewan

6-1.0 Summary

INTRODUCTION: In Canada, tuberculosis (TB) rates are disproportionately higher among Indigenous peoples compared to the Canadian-born non-Indigenous populations. These rates have remained between 20 and 30 cases per 100,000 population. As on-going transmission is a significant challenge in Indigenous communities, time to treatment represented one key factor that could potentially increase TB transmission. OBJECTIVE: This chapter aims to describe the methodology used to integrate determinants of health (including social determinants) into an agent based model that simulated TB transmission (TB-ABM) in three high incidence First Nations and Métis communities in northern Alberta and Saskatchewan. METHODS: The seven-year CIHR and Health Canada co-funded *Determinants of TB transmission (DTT) project* (2007-2013) was instrumental in providing data used in the TB-ABM that was relevant to these communities. A multivariable linear regression model helped to provide a link between significant risk factors (including social determinants) and the time to treatment as a continuous parameter in the TB-ABM. The TB-ABM included different types of contact structures, TB transmission dynamics, contact tracing, birth, death, and variable time to treatment durations among TB cases based on an individual's attributes. Sensitivity and uncertainty analysis was conducted to assess the TB-ABM. RESULTS: The TB-ABM fit well with existing data (at baseline) from the DTT project and other secondary sources. The most sensitive parameter in the TB-ABM was the progression from latent to active TB. CONCLUSION: The use of the TB-ABM can provide numerical evidence and insights on how potential control strategies that impact social/health determinants influence active and latent TB in Indigenous communities.

6-1.1 Introduction

In Canada, tuberculosis (TB) rates are disproportionately higher among Indigenous peoples compared to the Canadian-born non-Indigenous population [46, 97]. Since 1998, the overall TB incidence rate for Indigenous peoples has fluctuated between 20 and 30 cases per 100,000 population [93]. Tuberculosis incidence rates were different across the Prairie Provinces and ranged between 6.3 cases per 100,000 population (in Alberta) and 38 cases per 100,000 population (in Manitoba) in 2014 [46]. A seven-year mixed-method Canadian prairie-wide study called the *Determinants of Tuberculosis Transmission (DTT) project* highlighted that the distribution of TB cases was very uneven with many more cases residing above the 53rd parallel [99]. The unequal distribution of TB cases among Indigenous communities across the Prairies requires a further understanding of why specific communities experience a greater burden of TB than others.

Molecular evidence of clustering and the high incidence of TB among children suggested that on-going transmission continues to be an important issue for TB control in some high incidence Indigenous communities [54, 94, 99, 103, 104] (Chapter 4). Preventing the transmission of TB is not only dependent on improving environmental factors such as housing density/quality and preventing the progression of latent TB, but includes efforts that can help reduce the time from symptom onset to treatment (time to treatment or total delay). This is especially important in situations where the potential for person-to-person contact via expelling sputum through actions such as coughing and sneezing is much greater. Time to diagnosis and treatment has been reported to increase the risk of transmission, advanced disease, and mortality [128, 138-141].

A systematic review of diagnosis delay studies conducted in high and low income countries has estimated a range for delay between 25 and 185 days [122, 123]. In Chapter 3, a

systematic review of delay in diagnosis studies conducted among Indigenous peoples only included 11 studies worldwide. There was only one Canadian study of an outbreak identified in this systematic review that estimated a delay in diagnosis of 120 days [222]. Other Canadian studies estimated delay in diagnosis for both pulmonary and/or extra pulmonary tuberculosis. Population groups (i.e. foreign-born, Indigenous, and Canadian-born non-Indigenous) in these studies were not clearly stratified [142, 144]. However, one study conducted in Quebec estimated an average delay in diagnosis of 105.1 days (95% CI: 87.7 – 122.5) among Canadian-born cases [128]. Although the proportion of TB cases among Indigenous peoples was unknown, this estimate suggests that the time to diagnosis and treatment may be an important consideration in Indigenous communities that have a high burden of TB.

The estimated median time to treatment estimated from TB cases among Indigenous peoples in the DTT project was 30 days (mean: 66 days) (see Chapter 5). The 30-day median estimate was within the range of time to diagnosis and treatment estimates (12 days to 105 days) obtained from a few Canadian studies [128, 142-145]. The average time to treatment was at least twice in magnitude as the median indicating that a few Indigenous peoples experienced much longer durations between the onset of cough and the start date of treatment. The multivariate logistic model in Chapter 5 determined that healthcare access and having concomitant health problems (such as: diabetes, hypertension, HIV, renal disease, arthritis, asthma, stomach problems, and mental health related diagnosis) were significant risk factors for time to treatment. Risk factors associated with time to treatment could offer insights to potential interventions for reducing the transmission period. Measuring the impact of improving these risk factors associated with time to treatment is complex and challenging due to other simultaneous dynamics such as latent TB reactivation, contact investigations, and mobility.

Mathematical modeling represents a tool that is a simplified representation of complex processes [171] that can be challenging to understand as a whole. In the context of TB, outcomes such as TB cases could be measured using mathematical modeling given multiple simultaneous dynamical processes such as reactivation of TB, contact tracing after TB diagnosis, treatment protocols (including preventative therapy), and mobility between communities. Although many types of models exist in the literature, the use of agent based models (ABMs) to describe TB transmission dynamics has many advantages such as including random individual variability and contact structures, simulating disease dynamics at the individual level, and flexibility to include individual-level traits that influence disease outcomes such as health problems [171]. The integration of social determinants (SDOH) into disease outcomes is particularly challenging [213]. The impact of loss to follow-up during contact investigations, preventative therapy, and reducing housing density and time to treatment on TB cases in Canadian Indigenous communities represent risk factors (social and environmental) that have been investigated using ABMs [204, 209].

In an Inuit study conducted by Tuite et al., results from an ABM that described TB transmission indicated that the duration between onset of TB disease and treatment had a significant impact to reducing TB incidence [204]. The inclusion of time to treatment and its risk factors would represent an extension of previous TB models that describe transmission dynamics among Indigenous peoples in Canada. The analysis conducted in Chapter 5 (time to treatment estimate and risk factors) will help provide insight for risk factors that would be included in the ABM.

The integration of SDOH into an ABM that describes the dynamics of TB transmission could offer a way of assessing impacts of potential interventions to the reduction of TB cases. This chapter aims to describe, construct, and calibrate a TB transmission agent based model (TB-

ABM) piloted in three high incidence First Nations and/or Métis communities in northern Alberta and Saskatchewan. These three communities share the same treaty area that span across two provinces. Determinants of health (DOH) including SDOH are assigned to individuals based on risk factors that are significantly associated with time to treatment identified in Chapter 5.

6-1.2 Methods

Community Descriptions

The ABM aimed to describe TB transmission in three First Nations and/or Métis communities sized between 300 and 2500. Table 6a.1 describes the community characteristics included in the ABM. These communities located in northern Alberta and Saskatchewan are located in one treaty area and generally experience high rates of TB as observed in the DTT project. These communities include two reserves and one village (or Métis Settlement). The Statistics Canada census for 2006 was used to obtain demographic information such as age, gender, housing density, and household structures [316]. Missing information was supplemented using the 2011 census community profiles [9]. These three communities were anonymously called “Community A”, “Community B”, and “Community C” throughout this chapter 6 (Part 1 and Part 2).

Model Description

The TB transmission agent based model (TB-ABM) consisted of two main parts, the contact structure and TB disease dynamic. The contact structure included three types of contacts: close household, close non-household, and casual contacts. Familial ties extending beyond household structures among Indigenous peoples on-reserve required a contact structure that included both close household and non-household contacts. Close household contacts consisted

of individuals sharing the same household with a TB case. Close non-household contacts included people that share breathing space with the TB case daily without necessarily sleeping in the same household on a regular basis [54], for example familial relations (aunt/uncle and grandparent/grandchild). Casual contacts consisted of other types of interactions not included as close household and non-household contacts and occur with less frequency and intensity [54]. Mobility was included into the contact structure by assigning "visitors" to an individual from another community. Those who were "visitors" were assumed to transiently share close household and non-household contacts with the individual that received them during the simulation. The TB-ABM simulations ran for approximately two years between 2007 and 2008 using weekly time units. Table 6a.2 describes the TB-ABM assumptions about the overall disease dynamics, network characteristic, and contact investigation.

The TB transmission dynamic described in Figure 6a.1 outline the overall state changes an individual can have throughout a simulation. An individual could either be susceptible (S), have latent TB infection (LTBI) for > 5 years (L_s), have LTBI for ≤ 5 years (L_f), have active TB (I), receive a TB diagnosis (D), and become recovered (R). The transmission rate (β) was defined as the product between the contact rate per week and the transmission probability (contact rate × transmission probability). Transmission rate by contact type (ch: close household; cnh: close non-household; ca: casual) were varied by a multiplicative factor (F) between 0 and 1 where $\beta_{ch} > \beta_{cnh} > \beta_{ca} = \beta_{ch} > F_{cnh} \times \beta_{ch} > F_{ca} \times \beta_{ch}$. Individuals who shared contacts with other communities (i.e. visitors) had transmission rates analogous to β_{ch} and β_{cnh}. The progression of TB was denoted by ε_s (LTBI for >5 years) and ε_f (LTBI ≤5 years). The probability of death (μ) and birth (b) were independent of disease status where death rates did not differ between susceptible people and active TB cases (see Table 6a.2). The minimum age of pregnancy was 15 years old [317] with an assumption of a maximum of five births occurring per week across all three communities (see

Table 6a.2). Time to treatment varied at the individual level using a relationship derived from a linear regression model (see Multivariable Linear Regression Analysis below). The proportion of successful treatment of active TB was denoted by α. Note: Although state "D" and "R" are separate, all persons diagnosed were recovered right away analogous to time to treatment estimated in Chapter 5.

The diagnosis of a TB case followed a process of contact investigation described in Figure 6a.2. In the ABM-TB model, contact investigations occurred within a week of TB diagnosis. A simulated individual in a community at the start of the simulation was defined as their "home community". The contact investigation was dependent on whether a potential TB case was diagnosed within or outside their home community. If a TB case was diagnosed in the home community, all close household and non-household contacts were assessed. Assumptions were made for the proportion of visitors (CoI_1) and casual (CoI_4) contacts assessed (see Table 6a.2). An assumed proportion of visitors were lost to follow-up if returning to their home community (L_f). Among people with active TB while visiting other communities, various assumptions were made using a uniformly distributed range of values: 1) probability that TB diagnosis and contact investigation occurred (CoI_2), 2) The proportion of contacts investigated (CoI_3), and 3) the proportion of visitor contacts in a contact investigation that were lost to follow-up from returning to their home community (L_f). Secondary TB cases identified were treated successfully (α) and no further contact investigation was conducted assuming that most contacts would have already been assessed (see Table 6a.2). All individuals that were part of the contact investigation will undergo a TST test using a range (drawn from a uniform distribution) based on its sensitivity (Se_{tst}) obtained from literature. There were some proportion of individuals who tested positive for LTBI (L_f) that would accept and complete preventative therapy (P_{cp}). The overall effectiveness (Ef) proportion was estimated from the product between an individual

testing positive for LTBI (Se_{tst}) and the proportion of people that accept and complete LTBI treatment (P_{cp}), assuming an efficacy for preventative therapy of 100%.

Data and Materials

Parameter values in the TB-ABM were either estimated directly from the *Determinants of TB Transmission (DTT) project* or from literature. The DTT project (2006-2013) was a seven-year study that gathered epidemiological information about active TB cases that occurred across the Prairie Provinces [99] (see Chapter 4). The DTT project included a prospective cohort study (2007-2008) among culture-positive Canadian-born adults (>14 years old) with pulmonary TB defined as "potential TB transmitters". This cohort included First Nations (status and non-status), Métis, Inuit, and Canadian-born 'others' [99]. The DTT project data pertinent to this chapter included the quantitative questionnaires (2007-2008), genotyping results (2006-2010), and the contact investigation abstraction of "potential TB transmitters". Quantitative questionnaires included demographic information, risk factors, mobility data, TB symptomology, healthcare access, and housing information (see Chapter 4). Genotyping results included background TB cases defined by a 2.5-year transmission window (six months prior and two years after the date of treatment of each "potential TB transmitter"). Additional information from contact investigations conducted during the study period of the DTT project included information such as contact type, BCG vaccination status, and TST results.

Microsoft Excel 2011, SAS 9.3 (SAS Institute Inc., Cary, NC, USA), and MATLAB 2015a (The MathWorks, Inc.) were used for parameter estimation and model assessment and simulation.

Parameter Estimation

Parameters in the TB-ABM were calculated using estimates obtained from the DTT project and literature. Parameter estimates unavailable in literature were assumed using the overall knowledge about TB (see Table 6a.2).

Network Characteristic and Mobility

Close household contact (C_{hc}) rates were calculated using housing density obtained from Statistics Canada community profiles as the mean in a Poisson distribution [15, 316]. Community specific information of contact investigations conducted among potential transmitters in the DTT project was used to estimate the mean close non-household (C_{nhc}) and casual contacts (C_{ca}) per week. The number of contacts assigned to an individual in the ABM followed a Poisson distribution using the estimated mean. Since community A had limited information and was similarly sized with community C, contact data (close non-household and casual) were averaged among these two communities. Ten percent (pr_{ca}) of casual contacts among individuals in the TB-ABM were assumed to change weekly (F_{ca}) during the simulation (see Table 6a.2).

Mobility included two quantities that were estimated using the information from the DTT project: 1) length of travel between Alberta and Saskatchewan and 2) the proportion of people that travel. The quantitative questionnaire included responses about travel, which were used to estimate mobility (see Chapter 4). The average length of travel was used to estimate the frequency that between community contacts would change (F_{bc}) during the simulation. The TB-ABM assumed a constant proportion of people that travelled (v) between communities. The proportion of people that travelled between provinces were assumed to be equal during the simulation where $V_{AB}=V_{AC}$, $V_{BA}=V_{CA}$, $V_{CB}=V_{BC}$ and these estimations excluded trips less than five days to better align to the time unit used in the TB-ABM (time unit=week).

TB Disease Dynamic

The per person-week slow progression probability from latent to active TB (ε_s), defined as an individual with TB infection for greater than five years was estimated using the annual rate per person and converting it to a weekly probability using $P = 1 - e^{-rt}$ [1], where r and t is the rate and time, respectively. The rate is first converted to a weekly quantity prior to using [1] [178, 318].

Multivariable Linear Regression Analysis

The TB-ABM used a proposed method of integrating risk factors (including SDOH) to predict TB disease. One model parameter where risk factors that include SDOH can have an impact on TB transmission and disease was time to treatment defined in Chapter 5 as the duration between the onset of cough and the start date of TB treatment. Chapter 5 used a logistic regression to assess various risk factors associated with time to treatment where the outcome was a probability.

Similar to the methodology in Chapter 5, a multivariable linear regression analysis was conducted to obtain an estimate that was continuous so that individuals that had active TB disease in the TB-ABM could be assigned a predicted time to treatment based on significant predictors identified in Chapter 5. Time to treatment as an outcome was highly variable and a log transformed outcome was used for the multivariable linear regression analysis. The quantitative questionnaires from the DTT project were used in this analysis. Refer to Chapter 5 for statistical modeling methods, which included univariate analysis, testing for collinearity, and confounding, and modeling using forward selection. The cohort for the multivariable linear regression analysis was similar to Chapter 5 except individuals with a time to treatment of zero days were excluded

in the multivariable linear regression analysis (20%; 30/150). This was implemented separately into the TB-ABM using community specific data. Approximately 8.3% of TB cases in Community A, B, and C were treated for TB within a week from the onset of symptoms. Otherwise, the linear regression model was used to predict the time to treatment at the individual level. Housing density and age were included as continuous predictors similar to Chapter 5. Significant predictors identified in Chapter 5 were also significant in the multivariable linear regression model.

Assigning Individual Attributes

Assigning each individual with attributes in the TB-ABM provided a 1) link of predicting the time to treatment if active TB develops and 2) a multiplicative factor for progression from latent to active TB disease that is triggered if an individual has comorbidities. Age and household size associated with individuals in the model were estimated directly from the TB-ABM. The community profiles from Statistics Canada provided information about the proportion whose mother tongue was Indigenous [260], which was randomly assigned to individuals in the TB-ABM. Comorbidity was defined as an individual with diabetes, HIV, and/or renal disease. Using the Alberta Healthcare Insurance Plan (AHCIP) physician claims data, population registry files, hospital discharge abstract files, and Alberta Health postal code translation file, age related rates for comorbidities among status First Nations peoples living in the North Zone was estimated. The stratification of Alberta by health zones is described using the
Alberta Health Services Continuum Zone map in Figure 6a.3 [319]. Rates per 100 were obtained for 5 age groups: 1) 0-14 years old, 2) 15-29 years old, 3) 30-49 years old, 4) 50-64 years old, and 5) >64 years old. Across all three communities, rates for comorbidities were randomly assigned by age group in the TB-ABM. Among individuals with comorbidities, the rate of

progression from latent to active TB was increased by a multiplicative factor of 1.9 [166]. The multiplicative factor was based on a relative risk obtained from two Indigenous studies among people with diabetes [166]. The DTT Project data provided community specific information about a working x-ray machine and technician, proportion having a regular family doctor, and the location where people first sought care for their TB symptoms.

TB-ABM: Initial Conditions

Initial conditions for active TB were estimated from the DTT project data, which included the quantitative questionnaires, genotyping results of TB cases between 2006 and 2010, and contact investigation abstraction of "potential transmitters". The model was initialized for eight weeks using the date of diagnosis (defined as the date of treatment) of TB cases that occurred in Community A, B, and C. The time between the onset of symptoms and TB treatment was either directly estimated from the DTT quantitative questionnaires or predicted using the multivariable linear regression model.

Parameter Calibration of the TB-ABM

Parameter calibration using least square methods was conducted in two stages: 1) calibrating birth and death per day probability independent of disease dynamics and 2) calibrating TB transmission (β), initial community LTBI proportions, progression of latent (within 5 years) to active TB (ε_f), and multiplicative factors for transmission for close non-household (F_{cnh}) and casual contacts (F_{ca}). Overall, the top five results selected primarily based on the lowest sum of squares was considered as plausible parameter sets that best described the data. Replications of between 15 and 30 were used per parameter set during the initial stage of parameter calibration. A total of 10,000 parameter sets were simulated to determine the best five. For stage two, the best

ranked parameter estimation for birth and death probability (stage one) was used in the TB-ABM. Pattern Oriented Modeling (POM) is an iterative method that considers epidemiological knowledge for parameter calibration [320]. POM was used to further examine the parameter space of the best five results in stage two using 100 replications per parameter set. TB-ABM parameter calibration was simulated using Jasper, a supercomputer grid provided by WestGrid (www.westgrid.ca) and Compute Canada (www.computecanada.ca).

Parameter Calibration Stage One

The outcome for birth and deaths were estimated based on First Nations specific birth and death rates of 22 births per 1000 population and 4.8 per 1000 population, respectively [317]. The total births and deaths for each community at the end of the year were estimated using the rates and community size (see [2] and [3]).

$$Total\ Births\ per\ community = \frac{22}{1000} \times Community\ \ Size \quad [2]$$

$$Total\ Deaths\ per\ community = \frac{4.8}{1000} \times Community\ \ Size \quad [3]$$

$$Sum\ of\ \ Squares = \sum_{i} (data - mean\ \ simulated\ \ outcome)^2 \quad [4],$$

$$where\ i = Community\ \ A,\ \ Community\ \ B,\ \ and\ Community\ \ C$$

The TB-ABM was simulated for one year using 15 to 30 replications. The sum of squares for fitting births (or deaths) (see [4]) was calculated by taking the squared difference between the mean births (or deaths) using each proposed parameter and the birth data (or death data) at the end of the year estimated from equations [2] (or [3]). The minimum age of birth was 15 years old, which was obtained from literature [317]. A range of up to five births per week total across

all three communities was included in the fitting (see Table 6a.2). Parameter fitting was first conducted by using a range between 0 and 1 for both birth and death probability. The range was narrowed to [0.30,0.70] and [0.25,0.35] to determine the best five parameter sets that best fit the existing data for birth and death probability, respectively. The best parameter set, defined as having a fit to the data that yielded the lowest sum of squares was used for parameter calibration in stage two and baseline simulations.

Parameter Calibration Stage Two

There were several unknown parameters in the TB-ABM that required the use of least square methods to determine the best fit to existing data. The unknown parameters included TB transmission rate (β), intial community LTBI proportions ($LTBI_A$, $LTBI_B$, and $LTBI_C$), progression of latent (within 5 years) to active TB (ε_f), and multiplicative factors for transmission for close non-household (F_{cnh}) and casual contacts (F_{ca}). Unknown parameters were fit simultaneously and assessed to determine which parameter set yielded the lowest sum of squares.

The sum of squares was estimated using the total active TB cases obtained from the genotyping data in the DTT project. Postal codes were used in the genotyping data to attribute TB cases to the three communities. The duration of the simulation during model calibration was approximately two years analogous with the DTT study period, 2007 to 2008. The sum of squares was calculated using five time points during the simulation: week 8, week 21, week 40, week 56, and week 89 (see Equation 5).

$$Sum\ of\ Squares = \sum_i \sum_j (Data_j - Mean\ Model\ Data_j)_i^2 = \quad [5],$$
$$= \sum_i \sum_j (Total\ TB\ Cases_j - Mean\ Total\ TB\ Cases_j)_i^2$$

$$where\ \ i = Community\ A, Community\ \ B, and\ \ Community\ \ C\ and\ j = 8, 21, 40, 56, 89$$

TB transmission rate, β included the transmission probability and contact rate that occurred per week. The contact rate may be different for Community B since it is approximately 3 to 6 times higher than Community A and C. For parameter calibration, the transmission rate for Community A and C (β_{AC}) was allowed to differ from Community B (β_B) assuming a constant transmission probability. Tuberculosis transmission was also greatest among close household contacts and was reduced by a factor (F) between 0 and 1 among close non-household (F_{cnh}) and casual contacts (F_{ca}) where $F_{cnh} > F_{ca}$. An assumption of $F_{cnh} > F_{ca}$ was used based on space and length of exposure being greater for close non-household than casual contacts (see Table 6a.2).

The initial LTBI proportion in TB-ABM stratified by community could not be estimated from the data. Although the contact abstraction data was available, the investigation of contacts (usually based on a concentric approach) was potentially biased against persons who could be TST negative. These estimates were used as a guide to construct plausible parameter ranges for least squares fitting during Stage two. By community, two initial LTBI proportions were required to be estimated: 1) "new" LTBI cases (L_f) and 2) "reactors" (L_s). Using the overall total prevalence of LTBI of 25% [321], the proportion of L_f by community was fitted using least squares and L_s by community was estimated indirectly using equation [6]:

$$\text{Pr}oportion\ of\ \text{Re}actors\ (L_s)_i = 0.25 - \text{Pr}oportion\ \ of\ \ new\ \ LTBI\ (L_f)_i \qquad [6]$$
$$where\ \ i = Community\ \ A,\ \ Community\ B,\ \ and\ \ Community\ C$$

Using least square methods, the top five ranked parameter sets that yielded the lowest sum of squares (see equation 5) from 30 replications, sampling across 10,000 samples were selected. Among the top 5 ranked parameter sets, POM was used to further examine the parameter space

by comparing model outputs to the ratio between a TB cases and the total number of transmission events. The total number of transmission events was defined as individuals during a contact investigation that were determined to be either new positives or converters. Replications of 100 were used during recalibration of each ranked parameter set to improve its overall fit to the data from the DTT Project.

Model Assessment

Model assessment of the TB-ABM included baseline, sensitivity, and uncertainty analysis of the fitted parameters significant to TB cases, transmission, and progression (Stage two). The outcomes measured for baseline, sensitivity, and uncertainty included the time to treatment duration, total TB transmission events, and total latent (L_f) (prevalence) and active TB cases (accumulated total).

Sensitivity Analysis

The parameters assessed for sensitivity included TB transmission rate (β), initial community LTBI proportions ($LTBI_A$, $LTBI_B$, and $LTBI_C$), progression of latent (within 5 years) to active TB (ε_f), and multiplicative factors for transmission for close non-household (F_{cnh}) and casual contacts (F_{ca}). Each parameter was altered by ± 0.1% one at a time and 500 replications were simulated. The change from baseline was estimated using equation 7 where p is the value of a specific parameter at baseline. $C_{Sensitivity}$ represents a coefficient that estimates the degree of sensitivity where high values indicate more sensitivity parameters that have the greatest impact to model outcomes.

$$C_{Sensitivity} = \log_{10}\left|\frac{(Outcome\ \ at\ \ 1.001p)-(Outcome\ \ at\ \ p)}{0.001p}\right|, for\ \ +0.1\%\ \ and \qquad [7]$$

$$C_{Sensitivity} = \log_{10}\left|\frac{(Outcome\ \ at\ \ 0.999p) - (Outcome\ \ at\ \ p)}{-0.001p}\right|, for\ \ -0.1\%$$

Model sensitivity was assessed for the TB-ABM among all five parameter sets determined previously. The same random seed was selected for each parameter when comparing between baseline outcomes and a change within 0.1%.

Uncertainty Analysis

The minimum and maximum among all five ranked models (stage two) were used to construct the parameter ranges for TB transmission rate (β), initial community LTBI proportions ($LTBI_A$, $LTBI_B$, and $LTBI_C$), progression of latent (within 5 years) to active TB (ε_f), and multiplicative factors for transmission for close non-household (F_{cnh}) and casual contacts (F_{ca}). Replications of 50 for 1000 parameter sets were simulated using the TB-ABM. The mean and variation in model outcomes were estimated.

6-1.3 Results

The TB-ABM network included three communities (two First Nations reserves and one Métis Settlement) located in northern Alberta and Saskatchewan and its population ranged between 360 and 2500 people (see Table 6a.1). The median age and household density ranged between 20 and 30 years old and three to five people per household, respectively.

Table 6a.3 and Table 6a.4 describe the estimated model parameters for the TB-ABM, which include disease dynamics, network characteristics, contact investigation, and mobility. Close non-household contact rates per week were highest in Community A and C compared to Community B. Casual non-household contact rates was highest in Community B. The proportion

of travel estimated from the DTT project was highest between Community B and Community C due to their close proximity in distance. Individuals in the TB-ABM who were diagnosed with TB were treated successfully (α=1) right away analogous to time to treatment.

Table 6a.5 describes the multivariable linear regression model used to relate risk factors to time to treatment, defined as the period between the onset of cough and the start date of TB treatment. Risk factors associated with time to treatment were similar to Chapter 5 (see Table 5.6). Unlike the logistic regression model in Chapter 5, records of individuals with a duration of "0" for estimates of time to treatment was not included. This accounted for 20% (30/150) of the data. Overall, having an Indigenous mother tongue (β = -1.79; $p < 0.05$), a working x-ray machine and technician in a community (β = -1.19; $p < 0.05$), and household size (β = -0.07; $p < 0.05$) was associated with reduced durations of time to treatment. Having comorbidities (β= 1.81; $p < 0.05$) and a regular family doctor (β= 0.83; $p < 0.05$) was associated with increased durations of time to treatment. The interaction between comorbidities and having a regular family doctor was associated with reduced time to treatment durations (β= -2.04; $p < 0.05$). The multivariable linear regression model was integrated into the TB-ABM to help assign an individual infected with active TB with a time to treatment based on their attributes during the simulation. Individual attributes based on the multivariable linear regression model are described in Table 6a.6. Based on Statistics Canada, the proportion of people who had an Indigenous mother tongue in Community A, B, and C was 0.53, 0.88, and 0.96, respectively (see Table 6a.6). Only Community A did not have a working x-ray machine and technician. The proportion of people that had a regular family doctor was highest in Community B (p=0.80). The proportion people with comorbidities were the same across all three communities independent of province. These proportions were based on Alberta statistics. The highest proportion of people with comorbidities were 50 years and older.

Initial conditions described in Table 6a.7 were estimated using the data from the DTT project (2007-2008). Week 1 and week 89 were analogous to roughly the beginning of 2007 and the end of 2008, respectively. The postal codes of the communities in the genotyping data (described in Chapter 4) were used to determine the initial active TB case events that were simulated in the TB-ABM. In total, Community A, B, and C had 1, 6, and 2 TB cases, respectively that were initiated during the first eight weeks of the simulation (see Table 6a.7). The duration of time to treatment data was obtained from the DTT project, however, when unavailable, the multivariable linear regression model was used to estimate this predicted value.

Table 6a.8 and Table 6a.9 describe the data used for parameter calibration of birth/death rates (stage 1) and parameters related to the TB disease dynamic such as TB transmission (β_{AC}, β_B), progression (ε_f), reduction factors on TB transmission by contact type (F_{cnh} and F_{ca}), and initial latent TB infection ($LTBI_A$ /$LTBI_B$/$LTBI_C$), respectively. In Table 6a.9, the TB cases stratified by community were an accumulated total. From the DTT project, the total active TB cases in Community A, B, and C at the end of 2008 (T=89 weeks) was 2, 28, and 7 cases, respectively (see Table 6a.9).

Table 6a.10 describes the parameter calibration results for the birth and death per week probability stratified by Community A, B, and C in the TB-ABM. The birth probability per week that yielded the lowest sum of squares (SS=0.25) was 0.589 based on a total of up to four births per week. The death probability per week that yielded the lowest sum of squares ($SS=8.00\times10^{-4}$) was 0.281 (see Table 6a.10).

Table 6a.11 describes the top five ranked parameter sets estimated from stage two calibration. The lowest sum of squares for stage two parameter calibration was 18.41. Figure 6a.4 shows the 95% confidence interval of the accumulated total of active (a) and the prevalence of

latent (b) TB cases by community and time (T=8, 21, 40, 56, and 89 weeks) across the top five ranked parameter sets after 500 replications. The simulated active TB cases across the three communities in all five ranked models were within the 95% confidence interval (see Figure 6a.4). The LTBI proportion ranged from 1% to 3%, 15% to 18%, and 7% to 11% for Community A, B, and C, respectively. The prevalence of LTBI was relatively constant in all three communities throughout the simulation (for 89 weeks) (see Figure 6a.4). The parameter estimation for LTBI progression was between 1.9×10^{-3} and 2.5×10^{-3}. The probability of TB transmission for Community A and C was between 0.027 and 0.038. For Community B, TB transmission was at most two times higher (0.048 to 0.055). The probability of TB transmission was lower for casual (reduction factor: 0.42-0.53) compared to close non-household (reduction factor: 0.73-0.76) contacts. The overall distribution of time to treatment after 500 replications is described in Figure 6a.5. The mean time to treatment ranged from 33.3 days (95% CI: 32.58-34.00) to 34.72 days (95% CI: 33.93-35.52) (see Table 6a.11). The overall simulated distribution of time to treatment was similar across all five ranked parameter sets (see Figure 6a.4).

Table 6a.12 describes the local sensitivity analysis conducted on all ranked TB-ABM parameter sets in the TB after 500 replications. The coefficients in Table 6a.12 represent the average $\log_{10}$ change across all ranked models using four outcomes: 1) active TB cases, 2) LTBI cases, 3) total transmission events, and 4) time to treatment. The sum of these coefficients was assessed to determine the overall sensitivity of parameters in the TB-ABM. The most sensitive parameter was the progression of latent to active TB and the initial proportion of LTBI in Community A (see Table 6a.12). The least sensitive parameters were the reduction factors on transmission for casual and close non-household contacts. The probability of TB transmission and the initial LTBI proportion for Community B and C were moderately sensitive.

Uncertainty analysis was conducted using the minimum and maximum values of parameters across all ranked parameters sets described in Table 6a.11. Figure 6a.6 and Figure 6a.7 describe the minimum, maximum, and mean of the total accumulative TB and prevalent LTBI cases within the simulation period (T=89 weeks) across all three communities after 1000 replications. In Figure 6a.6, the TB cases from the DTT data lied within the minimum and maximum ranges during the uncertainty analysis for Community B. For Community A and C, the DTT data at 21 and 40 weeks were either under- (Community C) or over- (Community A) estimated outside the minimum and maximum ranges (see Figure 6a.6). The distribution of the mean time to treatment was assessed during uncertainty analysis after 1000 replications (Figure 6a.8). The distribution is normally distributed peaking between 33 and 34 days.

6-1.4 Discussion

The quote by Sir William Osler that "tuberculosis is a social disease with a medical aspect" emphasizes the importance of considering the SDOH. Through the construction of the TB-ABM, this chapter aimed to propose a modeling methodology that can allow for SDOH to be included into a mathematical model through the use of statistical relationships of key factors that contribute to TB transmission and cases. One key factor associated with TB transmission was the duration between the onset of symptoms most associated with transmission (e.g. coughing) and the start date of treatment defined as time to treatment. In Chapter 5, a logistic regression analysis was conducted using the quantitative questionnaires (2007-2008) gathered from the DTT project. In the context of First Nations and Métis peoples, on-going transmission of TB has been supported through the use of genotyping evidence that showed higher rates of clustering compared to the foreign-born and/or Canadian-born non-Indigenous populations (see Chapter 4)

[54, 94, 99, 103, 104]. Few and localized First Nations and Métis communities across the prairies experience a much greater burden of TB, with rates similar to some Inuit populations [99].

To illustrate the use of this methodology, three closely situated high incidence First Nations and Métis communities (Total population~3500) in northern Alberta and Saskatchewan were chosen. The use of ABMs was beneficial in this approach as it considered non-homogenous mixing, allowed for randomness, and included individual heterogeneity into TB transmission dynamics [177, 209]. One drawback of using ABMs was its computation needs and great efforts were taken to simply and include the most essential aspects of the TB dynamic.

ABMs have been used in literature to simulate and understand TB transmission dynamics [175-177, 179, 204, 205, 207-211, 322]. These models included features such as contact structures (close and casual contacts), age, gender, preferential mixing, varying household size, contact tracing, and treatment. In some of the literature, determinants such as housing density and smoking (risks with TB reactivation) were included [204, 209]. The ABM constructed in this chapter included three types of contacts (close household, close non-household, and casual), birth, death, age, gender, varying household size, contact tracing, treatment, and mobility within the three communities. Other individual attributes were included based on predictors significantly associated with time to treatment, which was informed from the results in Chapter 5. These attributes included comorbidity status, having a regular family doctor, and speaking an Indigenous mother tongue. Attributes included in the TB-ABM were estimated using community specific data, if available, otherwise, provincial data was used. The structure and TB dynamics of the TB-ABM included some simplifications: 1) contact structures were randomly connected (no preferential mixing), 2) TB cases identified during a contact investigations were not furthered, 3) a TST offered during contact investigation occurred within a week of TB diagnosis (did not simulate a 2-step TST normally conducted), and 4) new births assumed contacts similar to the

mother and did not include possible casual contacts. Although these simplifications were made, the main goal was to capture the most integral parts of the TB transmission dynamic without adding additional complexity, which may add more assumptions and increase computational needs with little gains in overall insight.

The two-step calibration process to first estimate birth and death fit well to Statistics Canada First Nations specific rates (see Table 6a.8 and 6a.10) [317]. Although the best parameter estimate was used in the second step of the calibration process, the range for probabilities for birth (0.574-0.589) and death (0.264 – 0.326) across all five parameter sets were narrow (see Table 6a.10). The second step of the calibration process estimated TB transmission (β_{AC}, β_B), progression (ε_f), reduction factors on TB transmission by contact type (F_{cnh} and F_{ca}), and initial latent TB infection ($LTBI_A$ /$LTBI_B$/$LTBI_C$), which compared well to the data. The sum of squares ranged between 18.41 and 26.91 (see Table 6a.11).

Challenges of non-identifiability existed since eight parameters were estimated simultaneously using one dataset i.e. active TB cases obtained from the DTT project. Community specific data from the contact investigation data obtained from the DTT project provided some insight to overall transmission through the use of TST results, which helped to overcome some of these challenges. Although contact investigation data were not representative, since investigations were tailored to determine people most impacted from transmission, these results did offer some insights about community specific TB transmission and the prevalence of LTBI. Overall, the community specific prevalence of LTBI (≤5 years) from the contacts dataset was 3%, 7%, and 11% for Community A, B, and C. This compared well to Community A and C. The estimated LTBI proportion for Community B from parameter calibration ranged between 15% and 18%. The possibility of underestimation from the data was possible based on the overall size of Community B (3 to 6 times larger) compared to Community A and C, which may impact how

many people were involved in a contact investigation. On average, there were approximately 1.5 to 3 transmission events per TB case, which suggested that the prevalence of LTBI was not decreasing. The results from parameter calibration supported these findings in Figure 6a.4 where the overall prevalence of LTBI either remained the same or showed a slight increase over time during the TB-ABM simulation.

A multivariable linear regression model was used to determine a relationship between significant predictors identified in Chapter 5 and time to treatment as a continuous log transformed outcome. The analysis was restricted to non-zero durations. Approximately 8.3% of the TB cases in Community A, B, and C had time to treatment of zero days, which was incorporated separately into the TB-ABM. The multivariable linear regression model allowed for the TB-ABM simulation to assign an individual with active TB with a pre-determined duration of transmission (in weeks) based on specific attributes that were identified as statistically significant ($p<0.05$) (see Table 6a.5). In addition, the duration of time to treatment was further adjusted if a TB case was diagnosed during a contact investigation. The multivariable linear regression model had poor predictive ability ($R^2=0.45$). The equivalent multivariate logistic regression (see Table 5.6) had a predictive ability of 83% (ROC Value). The interpretation of this result is that the prediction of the exact duration may not be accurate, but individuals were correctly assigned durations for delayed time to treatment (>30 days) or timely treatment (≤30 days) accurately. The main goal of the TB-ABM was not to predict the exact durations for time to treatment, but to help assign individuals with an appropriate duration that represented timely and delayed time to treatment based on specific individual attributes. The multivariable linear model allowed for the outcome to remain continuous, which was an input in the TB-ABM (see Figure 6a.1).

The overall simulated mean time to treatment ranged between 33.3 and 34.7 days across all ranked parameter sets (Table 6a.11). The median and average time to treatment using the DTT

project community specific data (n=25) was 30 days (IQR: 50.0 days) and 57 days, respectively. The distribution of time to treatment of TB was highly variable and ranged between 0 and 365 days. Excluding the outlier time to treatment values, the median and mean was 30 days (IQR: 51.5 days) and 37 days. Using the Rank 1 parameter set, the overall simulated mean and median time to treatment was 34 days (95% CI: 33.03 – 34.58) and 21 days (IQR: 14 days) respectively and compared well to the DTT data. The median time to treatment was slightly underestimated, but the overall simulated distribution of the median time to treatment included 30 days. In the uncertainty analysis (see Figure 6a.5), the overall simulated distribution of the mean time to treatment also ranged from 18 to 70 days, which included the estimated time to treatment average from community specific DTT data (without the exclusion of outliers).

Local sensitivity analysis showed that the progression from latent to active TB (ε_f) could have the greatest impact on accumulated active TB cases, prevalent latent TB cases (L_f), and total transmission events after a small perturbation (see Table 6a.12). The estimate of ε_f estimated from parameter calibration had a relatively narrow range (1.9×10^{-3} to 2.5×10^{-3}) across all five ranked parameter sets in Table 6a.11. The total active TB cases simulated from the TB-ABM compared well to the DTT data across all three communities. The increased sensitivity of the initial proportion of LTBI in Community A could be impacted by the much lower counts of active, latent, and total transmission events compared to Community B and C i.e. an increase of 1 TB cases from a total of 3 cases will have a larger impact than an increase of 1 TB cases from a total of 10 cases.

Assigning attributes to the TB-ABM was primarily based on data from Statistics Canada and the DTT project (see Table 6a.6). The comorbidity rate in Alberta was applied to Saskatchewan and was equivalent across all three communities. Differences in rates between Alberta and Saskatchewan could impact interpretations of control strategies implemented in the

TB-ABM. The risk of progression among people with comorbidities was based on people with only diabetes [166]. The risk of progression among people with HIV infection could be up to 20-fold higher [323]. Approximately 7% (2/28) of the TB cases had HIV across all three communities. The underestimation in risk of progression would potentially have limited impact to the overall results.

Overall there were 22 assumptions (see Table 6a.2) for both the TB disease dynamic and contact investigation components of the TB-ABM. Most unknown probabilities that could impact model outcomes occurred during contact investigations. Minimal information about probabilities at various stages of the contact investigation were limited in literature from Alberta and Saskatchewan [283]. The benefit of ABMs is that these unknowns can be built in using probability ranges such that, parameter estimates represent relative differences that agree with epidemiological knowledge. For example, the probability of a TB case being diagnosed during a contact investigation within their community is greater than being away from their home community. Contact investigations were assumed to occur within a week; however, these could take up to a few weeks to complete. Contact investigation are complex and follow a concentric approach primarily starting from household contacts especially in children under five years old, HIV infected persons, or others at high risk of TB progression [54]. In the TB-ABM, contacts included in the contact investigation were selected at random without considering these factors. These simplifications highlight areas for extending and improving the TB-ABM for future studies.

Contract structures remained static for close and non-household contacts except for birth and death events in each simulation. Some dynamic changes were included for casual contacts and mobility between communities. Approximately 10% of casual contacts per individual were

assumed to change per week (see Table 6a.2). Mobility between communities was estimated from the DTT data and the overall median time for travel was two weeks (see Table 6a.3).

There were some limitations in the TB-ABM model and simulations. During contact tracing, a two-step TST usually implemented was not included in the TB-ABM. In a two-step TST, a second TST is conducted at least 8 weeks after the first test. In the TB-ABM, only one TST was conducted within a week of TB diagnosis. The TB-ABM only considered one strain and simplified the TB dynamic process by not including re-infection. Across these three communities, there were two strains that had the most clustering based on genotyping data gathered from the DTT project between 2006 and 2010. The high clustering observed from community specific data further supported that on-going transmission is an important challenge in Indigenous communities. Preferential mixing was not included in the contact structure of the TB-ABM. Extensions for the TB-ABM could incorporate these additional complexities. The transfer from L_f to L_s was not included since most new latent infection occurred within five years. This can be included in future work to extend TB-ABM simulations beyond five years.

6-1.5 Conclusion

This chapter aimed to describe the methodology used to integrate DOH (including SDOH) into a mathematical model that simulated TB transmission. As on-going transmission is a significant challenge in Indigenous communities, three high incidence First Nations and Métis communities in northern Alberta and Saskatchewan were used to pilot this modeling approach. The parameters estimated directly and indirectly (parameter calibration) fit well to existing community specific data. The mean distribution of time to treatment estimated using a multivariable linear regression model corroborated with the data from the DTT project. Sensitivity analysis highlighted that the most important parameter that had the greatest impact to

the model outcomes was the progression of latent to active TB. Although there were various model assumptions and limitations, the TB-ABM successfully simulated baseline TB dynamics across the piloted communities. The use of mathematical modeling to assess model outcomes based on various control strategies can provide numerical evidence to support existing hypothesis in literature. The TB-ABM included complexities such as contact structures, TB transmission dynamics, contact tracing methods, and time to treatment estimates predicted using individual attributes. Assessing control strategies given these multiple complexities would be costly to implement in real-life settings. However, conducting hypothetical simulation analysis using the TB-ABM can provide valuable insights on impacts that control strategies involving risk factors that include the SDOH can have on various model outcomes such as active and latent TB cases.

Table 6a. 1 Community characteristics included in the TB-ABM (2007-2008). Note: Although this model uses actual estimates, the characteristics presented in this table are rounded for anonymity purposes

Characteristic[1]	Community A (Male / Female)	Community B (Male / Female)	Community C (Male / Female)
Total People	360	2500	650
Median Age	30	20	20
Total Household	130	600	150
One Adult (≥ 25 years) Household	40	110	20
Two Adult (≥ 25 years) Household	20	40	10
Household Density	3	4.0	5

[1] [15, 316]

Table 6a. 2 The TB-ABM (2007-2008) assumptions for the overall TB disease dynamic, network characteristics, and contact investigation

Assumption #	Assumption Description
	TB Disease Dynamic/Network Characteristic
1	The overall model assumes a single strain transmission dynamic
2	Density dependent transmission rate (β) where $\beta_{Com\ B} \geq \beta_{Com\ A,C}$
3	TB transmission is greatest for close household followed by close non-household and casual contacts
4	Probability of death is independent from disease status i.e. death rates did not differ between susceptible people and active TB cases
5	The minimum age of pregnancy was 15 years old [317]
6	A maximum total of five births per week across all three communities
7	New births follow similar traits as the birth mother except for comorbidity status
8	Assume all new latent TB cases (L_f) at the start of the simulation occurred within two years.
9	Active TB treatment has an efficacy rate of 100%
10	Approximately 10% of casual contacts change every week
11	Individuals that travel between communities have a minimum age of 18
12	The proportion that travel between communities remain constant during the simulation
	Contact Investigation (CI)
13	CI occurs within a week of a diagnosed index active TB case
14	CI includes all close household and non-household contacts
15	If a TB case is found during a CI, no further investigation occurs in connection with this case with the assumption that most contacts would have been included in the initial CI
16	If a TB case is diagnosed in the "home[1]" community, the proportion that visitors investigated during a CI is uniformly distributed between 0.7 and 1.0
17	If a TB case is diagnosed in the "home" community, the proportion that casual contacts are investigated during a CI is uniformly distributed between 0 and 0.3
18	Among TB cases that occur outside the "home" community, the probability of TB diagnosis and contact investigation is uniformly distributed between 0.2 and 0.5
19	Proportion of contacts in a CI who are lost to follow-up when they return to their "home" community is uniformly distributed between 0.5 and 0.8
20	Among TB cases that are diagnosed outside their "home" community, the proportion of contacts investigated is uniformly distributed between 0.4 and 0.7
21	The efficacy for preventative therapy for latent TB was 100%
22	Preventative therapy was provided to only individuals with latent TB infections within 5 years (L_f)

[1] Home community: Individual place of residence

Table 6a. 3 The TB-ABM (2007-2008) non-fitted parameter description and estimation for Community A, B, and C

Parameter	Description	Community A	Community B	Community C	Reference
		Disease Dynamics			
ε_s	Progression from latent TB to active TB greater than 5 years from infection (per person/week)	6.00×10^{-5}	6.00×10^{-5}	6.00×10^{-5}	[178, 318]
α	Proportion of successful treatment of active TB	1	1	1	[178]
		Network Characteristics			
C_{hc}	Close household contacts (average household density)	2.9	4.0	4.6	[15, 316]
C_{nhc}	Close non-household contacts (average per week)	6	3	6	DTT Project Data - Community specific
C_{ca}	Casual contacts (average per week)	4	6	4	
F_{ca}	Frequency that casual contacts change	Every week	Every week	Every week	Assumption
pr_{ca}	Proportion of casual contacts that are changed	10%	10%	10%	
F_{bc}	Frequency that between community contacts change	Every 2 weeks	Every 2 weeks	Every 2 weeks	DTT Project Data
pr_{bc}	Proportion of between community contacts that are changed	50%	50%	50%	
	Contact Investigation[1] (Note: All range parameter estimates assume a uniform distribution)				
Se_{tst}	Pooled tuberculin skin test sensitivity	(0.59,0.97)	(0.59,0.97)	(0.59,0.97)	[324]
P_{cp}	Proportion that accepted and completed latent TB treatment[2]	(0.30,0.54)	(0.30,0.54)	(0.30,0.54)	[283]
CoI_1	Proportion of visitors investigated in a contact investigation of an index case	(0.7,1)	(0.7,1)	(0.7,1)	
CoI_2	Given TB case occurs outside home community: Probability TB case is diagnosed and a contact investigation would occur	(0.2,0.5)	(0.2,0.5)	(0.2,0.5)	
CoI_3	Proportion of contacts investigated given an index case is away from their home community	(0.4,0.7)	(0.4,0.7)	(0.4,0.7)	Assumption
CoI_4	Proportion of casual contacts investigated in a contact investigation of an index case	(0,0.3)	(0,0.3)	(0,0.3)	
L_f	Proportion lost to follow-up from outside community contacts	(0.5,0.8)	(0.5,0.8)	(0.5,0.8)	

[1] Proportion of in-community contacts (close household and non-household contact) investigated in a contact investigation of an index case was assumed to be 1.0

[2] Assume efficacy of latent TB treatment was 100%

Table 6a. 4 Parameter estimation of mobility parameters in the TB-ABM (2007-2008)

Parameter	Description	Estimate (weeks)	Reference
V_{AS}	Length of travel from Alberta to Saskatchewan (min, avg, max)	(0,1,2)	DTT Project Data
V_{SA}	Length of visits from Saskatchewan to Alberta (min, avg, max)	(0,1,4)	
V_{SS}	Length of visits within Saskatchewan (min, avg, max)	(0,2,12)	
V_{AB},V_{AC}	Proportion of people that travel from community A to B and C	0.10	
V_{BA},V_{CA}	Proportion of people that travel from community B and C to A	0.05	
$V_{CB,}V_{BC}$	Proportion of people that travel from community C and B	0.37	

Table 6a. 5 Multivariable linear regression model with the outcome of time from the onset of cough to treatment (days) Note: Cohort-all Indigenous TB cases in the Determinants of TB transmission project (2007-2008) that were defined as 'true transmitters'

	Time to Diagnosis (days): N=88	
	Log β	**p-value**
Intercept	4.797	<0.001
Age	-0.009	0.636
Language (Mother Tongue) (0=Non-Indigenous, 1=Indigenous)	-1.791	0.048
Comorbidity (0=No, 1=Yes)	1.807	<0.001
A Working X-ray Machine and Technician in Community (0=No, 1=Yes)	-1.190	<0.001
Household Size	-0.073	0.008
Have a Regular Family Doctor (0=No, 1=Yes)	0.828	0.005
Comorbidity and Have Regular Family doctor (0=No, 1=Yes)	-2.044	0.001
Language (Mother Tongue) and Age	0.044	0.050

Table 6a. 6 Individual attributes assigned in the TB-ABM (2007-2008) using multivariable linear regression model predictors

Parameter	Description	Community A	Community B	Community C	Reference
a	Age	Table 1	Table 1	Table 1	[15, 316]
La	Proportion whose language (mother tongue) was Indigenous	0.53	0.88	0.96	[260]
C_m	comorbidity€	[0.02 0.07 0.19 0.40 0.55]			Alberta Health
P_{dr}	Risk of progression (ε_r) of people with comorbidities	1.9	1.9	1.9	[166]
C_X	A working X-ray machine and technician in community [0=No, 1=Yes]	0	1	1	DTT Data
H_s	Household size	Table 1	Table 1	Table 1	[15, 316]
F_D	Proportion that have a regular family doctor	0.53	0.80	0.50	DTT Data
Sk_{Loc}	Location: proportion seek first about TB symptoms	017 - 0.50	0 – 0.24	0.24 – 0.29	DTT Data

€ Comorbidity [Diabetes, HIV, Renal Disease] by age: (i) 0-14 years old, (ii) 15-29 years old, (iii) 30-49 years old, (iv) 50-64 years old, and (v) >64 years old
Note: All range parameter estimates assume a uniform distribution)

Table 6a. 7 The TB-ABM initialization of active TB cases in Community A, B, and C using data from the Determinants of Tuberculosis Transmission Project (2007-2008)

Model Time (T in weeks)	Community A	Duration of delayed time to treatment (weeks)	Community B	Duration of delayed time to treatment (weeks)	Community C	Duration of delayed time to treatment (weeks)
			Active TB			
T=1	1	8	3	1 case: 8, 2 cases: Predicted from LLR€ model	1	Predicted from LLR€ model
T=3	0	--	1	4	1	6
T=6	0	--	1	3	0	--
T=8	0	--	1	0	0	--

€ Multivariable Linear Regression

Table 6a. 8 Data used in the TB-ABM (2007-2008) for fitting birth and death rates (stage 1)

Parameter Data	Rate per 1000 population-year	Community A (N=365)	Community B (N=2346)	Community C (N=659)	Reference
Total birth year	22	8	52	15	[317]
Total deaths per year	4.8	2	11	3	

Table 6a. 9 Data used in the TB-ABM (2007-2008) for fitting (stage 2) for initial LTBI proportion ($LTBI_A/LTBI_B/LTBI_C$), progression of LTBI (ε_f), TB transmission (β_{AC}, β_B), and multiplicative factors for TB transmission (F_{cnh} and F_{ca})

Total TB Cases (time in weeks)	T=8	T=21	T=40	T=56	T=89	Reference
Community A	1	2	2	2	2	DTT Data
Community B	6	9	13	21	28	
Community C	2	2	2	4	7	

Table 6a. 10 Top five fitting results (stage 1) for birth and death rates (up to four births per week) using the TB-ABM (2007-2008)

Parameter Fitting Results	Sum of Squares	Parameter Estimate (Fitted)	Community A (N=365)	Community B (N=2346)	Community C (N=659)
		Birth			
Birth Data	--	--	8	52	15
Rank 1	0.25	0.589	8.24	52.28	14.66
Rank 2	0.30	0.574	8.54	51.92	15.08
Rank 3	0.41	0.576	8.50	51.66	14.80
Rank 4	0.44	0.582	8.24	52.44	15.44
Rank 5	0.59	0.583	8.72	52.04	14.74
		Death			
Death Data	--	--	2	11	3
Rank 1	8.00×10^{-4}	0.281	2.02	10.98	3.00
Rank 2	3.60×10^{-3}	0.326	1.96	11.02	3.04
Rank 3	3.60×10^{-3}	0.302	2.06	11.00	3.00
Rank 4	3.60×10^{-3}	0.261	2.00	10.94	3.00
Rank 5	4.00×10^{-3}	0.264	2.00	11.02	3.06

Table 6a. 11 Top five fitting results (stage two) for initial LTBI proportion ($LTBI_A/LTBI_B/LTBI_C$), progression of LTBI (ε_f), TB transmission (B_{AC}, B_B), and multiplicative factors for TB transmission (F_{cnh} and F_{ca}) for the TB-ABM (2007-2008)

				TB Transmission		Multiplicative Factor for TB Transmission		Simulated		Total Simulated Active TB Cases (T=Weeks)				
Parameter Fitting Results	Sum of Squares	Initial $LTBI_A$ /$LTBI_B$/$LTBI_C$ Proportion	Progression of LTBI (ε_f)	TB Transmission in Community A and C (β_{AC})	TB Transmission in Community B (β_B)	Close Non-Household Contact (F_{cnh})	Casual Contact (F_{ca})	Mean Time to Treatment (95% CI)	Com	T=8	T=21	T=40	T=56	T=89
Rank 1	18.41	0.03/0.16/0.09	2.1×10^{-3}	0.027	0.055	0.75	0.42	33.80	A	0.94	1.10	1.37	1.61	2.23
								(33.03-	B	6.32	9.85	14.80	18.96	27.54
								34.58)	C	2.00	2.72	3.69	4.59	6.68
Rank 2	21.29	0.02/0.18/0.11	1.9×10^{-3}	0.036	0.054	0.73	0.35	33.29	A	0.90	1.04	1.23	1.42	1.93
								(32.58-	B	6.28	9.76	14.56	18.65	26.86
								34.00)	C	2.00	2.77	3.87	4.89	7.02
Rank 3	21.41	0.02/0.16/0.08	2.3×10^{-3}	0.038	0.052	0.76	0.43	33.74	A	0.92	1.08	1.29	1.54	2.19
								(33.03-	B	6.41	10.16	15.15	19.35	28.13
								34.45)	C	2.02	2.70	3.81	4.83	7.12
Rank 4	24.88	0.01/0.16/0.07	2.2×10^{-3}	0.036	0.049	0.73	0.51	34.72	A	0.92	1.07	1.27	1.48	2.05
								(33.93-	B	6.41	10.20	15.33	19.82	28.84
								35.52)	C	1.93	2.63	3.63	4.54	6.61
Rank 5	26.91	0.03/0.15/0.08	2.5×10^{-3}	0.027	0.048	0.75	0.53	34.53	A	0.93	1.09	1.39	1.68	2.38
								(33.79-	B	6.37	10.14	15.34	19.79	29.08
								35.27)	C	1.93	2.62	3.73	4.74	7.01
		Active TB Cases from Community (Com) Based Data												
Overall	--	--	--	--	--	--	--	30		9	13	17	27	37
Com A	--	--	--	--	--	--	--	--		1	2	2	2	2
Com B	--	--	--	--	--	--	--	--		6	9	13	21	28
Com C	--	--	--	--	--	--	--	--		2	2	2	4	7

Table 6a. 12 Sensitivity analysis after 500 replications of model parameters in the TB-ABM averaged over a ±0.1% change in parameter values across all five ranked models (see equation 7)

	$C_{Sensitivity}$ (Average)				
Parameter	Active TB Cases	Latent TB Cases (L_f)	Total Transmission Events	Delayed time to treatment	Overall Total
Multiplicative Factor for Transmission: Casual Contacts	2.92	3.19	3.23	1.84	11.17
Multiplicative Factor for Transmission: Close Non-Household Contacts	2.73	3.02	3.13	1.67	10.55
Progression of Latent to Active TB	**5.13**	**5.06**	**5.46**	**4.23**	**19.88**
TB Transmission: Community A and C	3.76	3.88	4.08	3.25	14.98
TB Transmission: Community B	3.65	4.01	4.05	3.01	14.72
Initial Proportion of Latent TB for Community A	4.29	4.58	4.43	3.43	16.73
Initial proportion of Latent TB for Community B	3.21	3.61	3.51	2.59	12.91
Initial Proportion of Latent TB for Community C	3.68	3.95	3.74	2.81	14.18

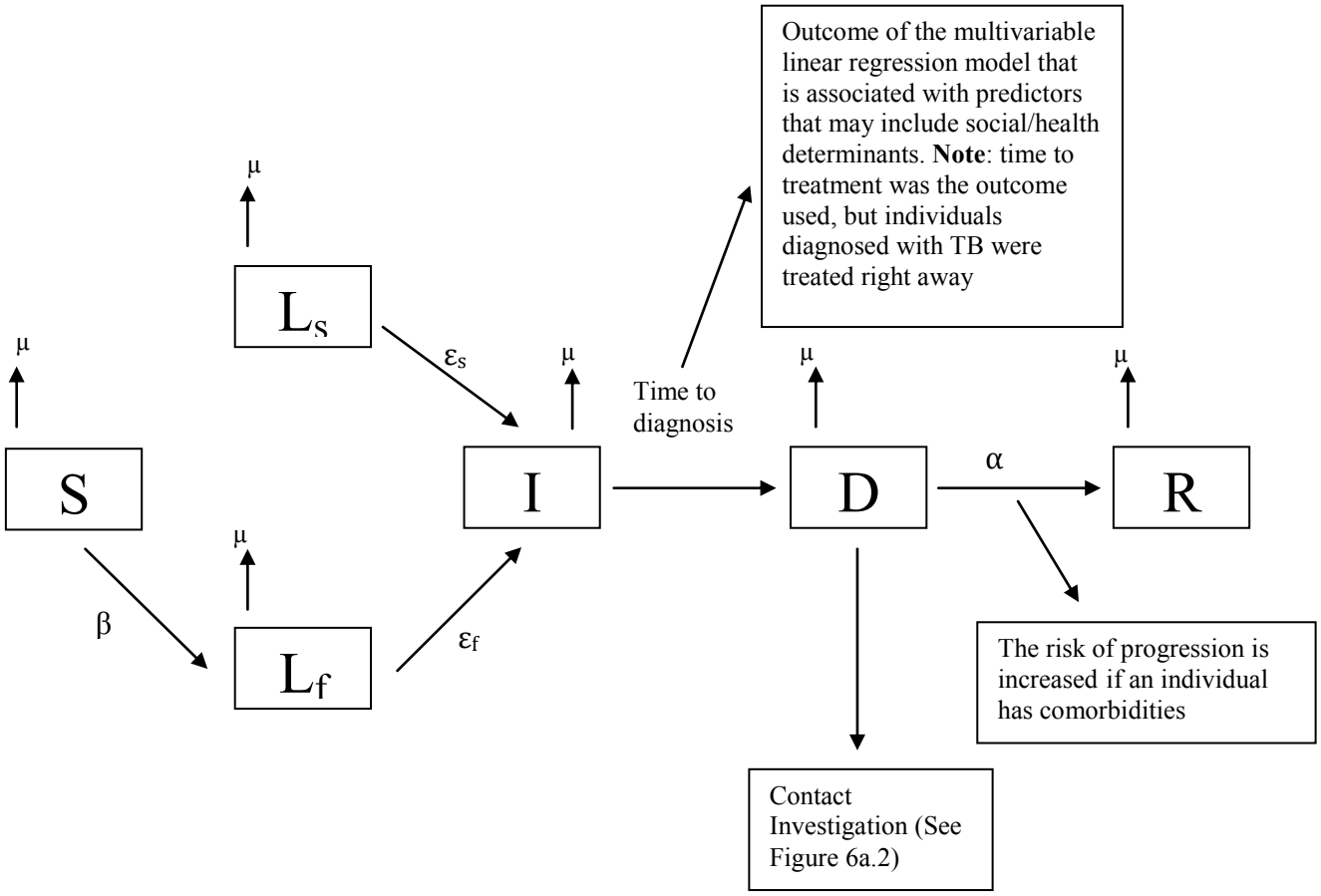

Figure 6a. 1 The agent based model describing TB transmission dynamics of all individual-level states: (1) S: susceptible, (2) L_s: reactors (or latent TB over 5 years), (3) L_f: Latent TB (≤ 5 years), (4) I: TB disease, (5) D: diagnosis of TB, and (6) R: recovered. Parameter descriptions: (i) μ: probability of death (calibrated), (ii) β: transmission rate between S and I, (iii) ε_s or ε_f : progression from latent to TB disease, and (iv) α: treatment completion probability. Note: births (b) occurred among all women ≥ 15 years old at a calibrated probability independent of disease status

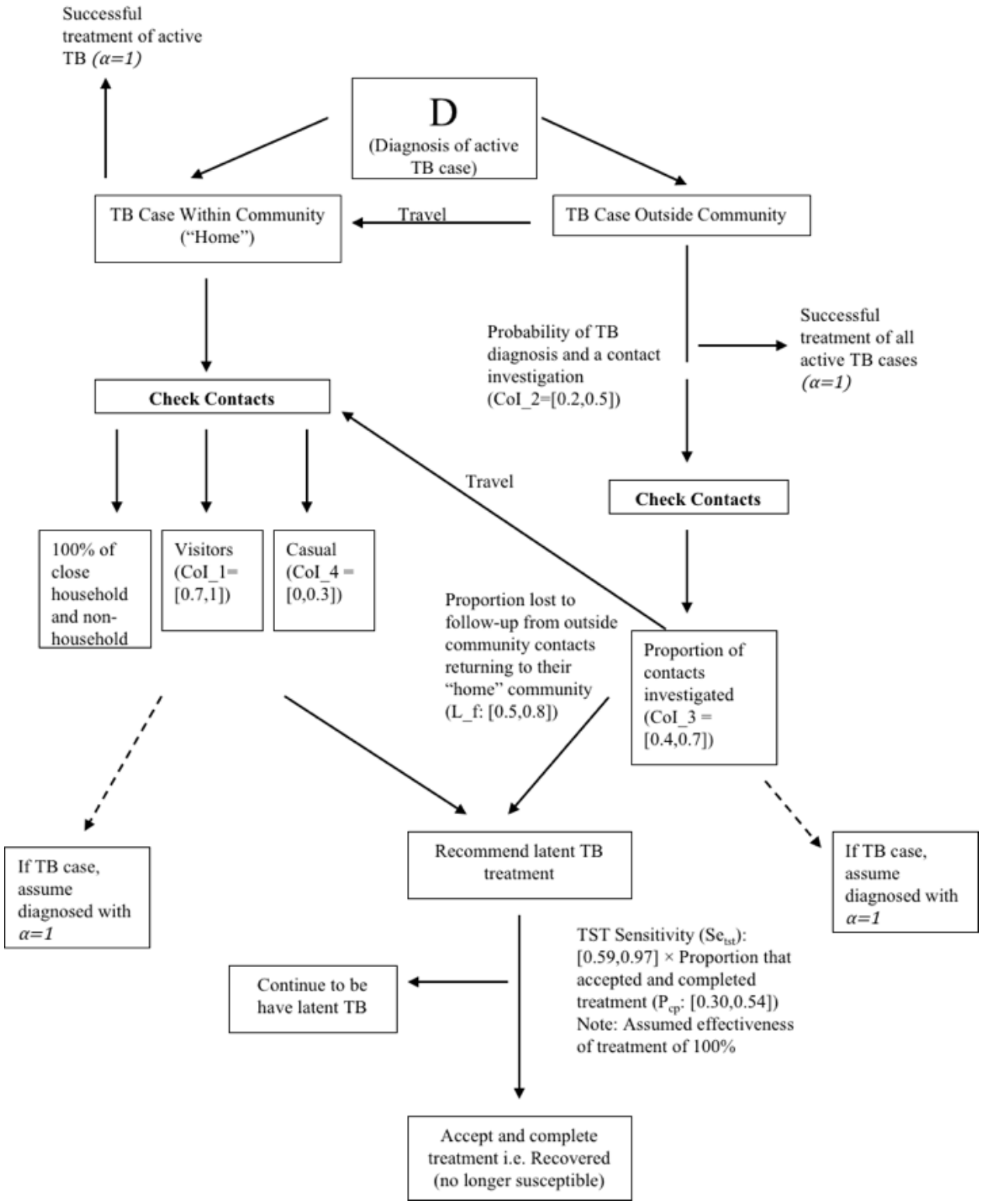

Figure 6a. 2 The contact investigation process in the TB-ABM model (see Figure 6a.1). Note: refer to Table 2 for parameter descriptions

Figure 6a. 3 The Alberta Health Services (AHS) continuum zone map [319]

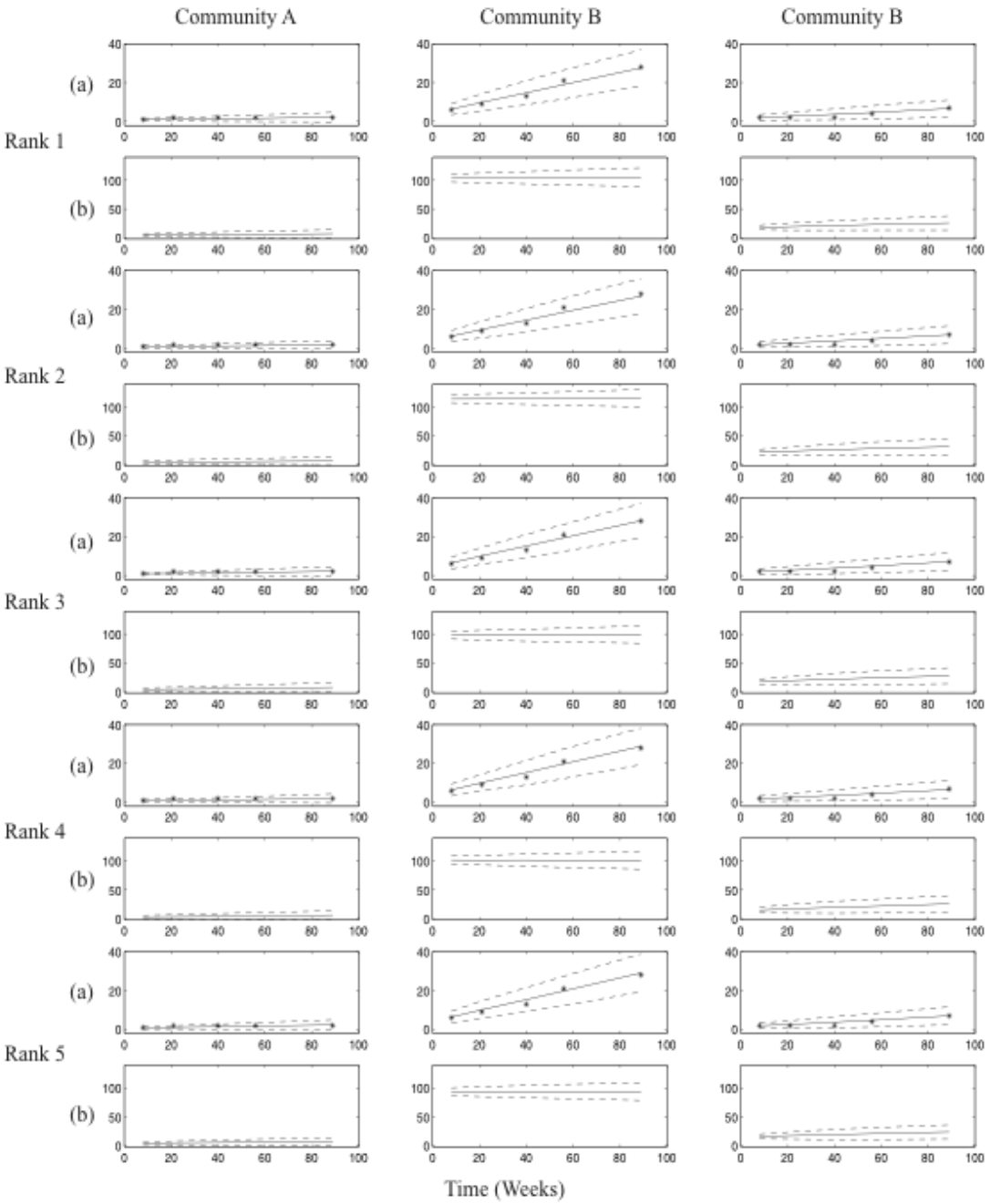

Figure 6a. 4 Baseline analysis using the TB-ABM simulation between 2007 and 2008 after n=500 replications across the top five ranked models and communities on outcome, which include (a) total TB (accumulated) and (b) total latent TB case (L_f) (prevalence). Dashed lines represent the 95% confidence interval, solid line represents the average, the dots represent the data obtained from the DTT project

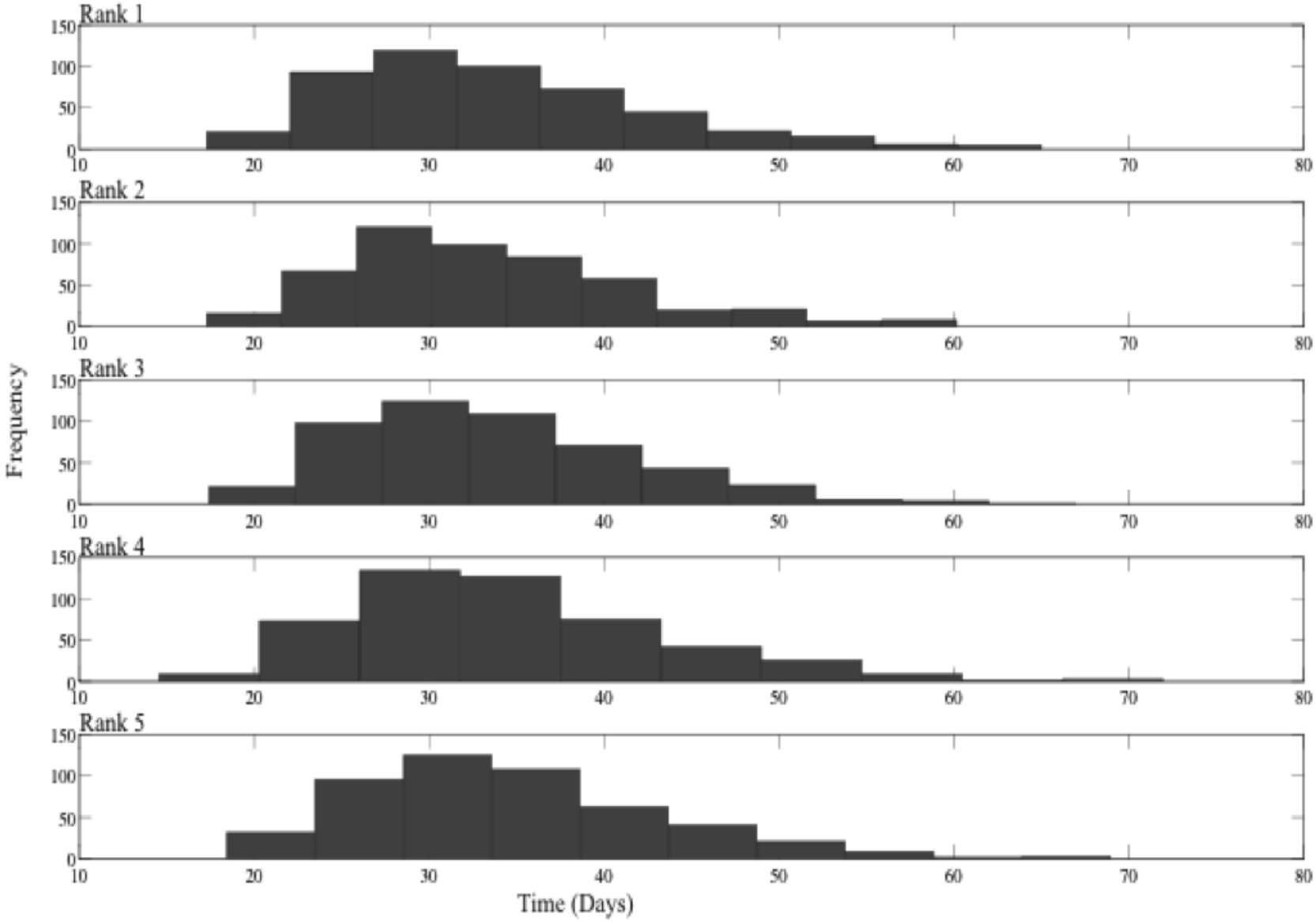

Figure 6a. 5 Baseline analysis using the TB-ABM simulated between 2007 and 2008 after n=500 replications across the top five ranked models on the mean distribution in time to treatment as the outcome

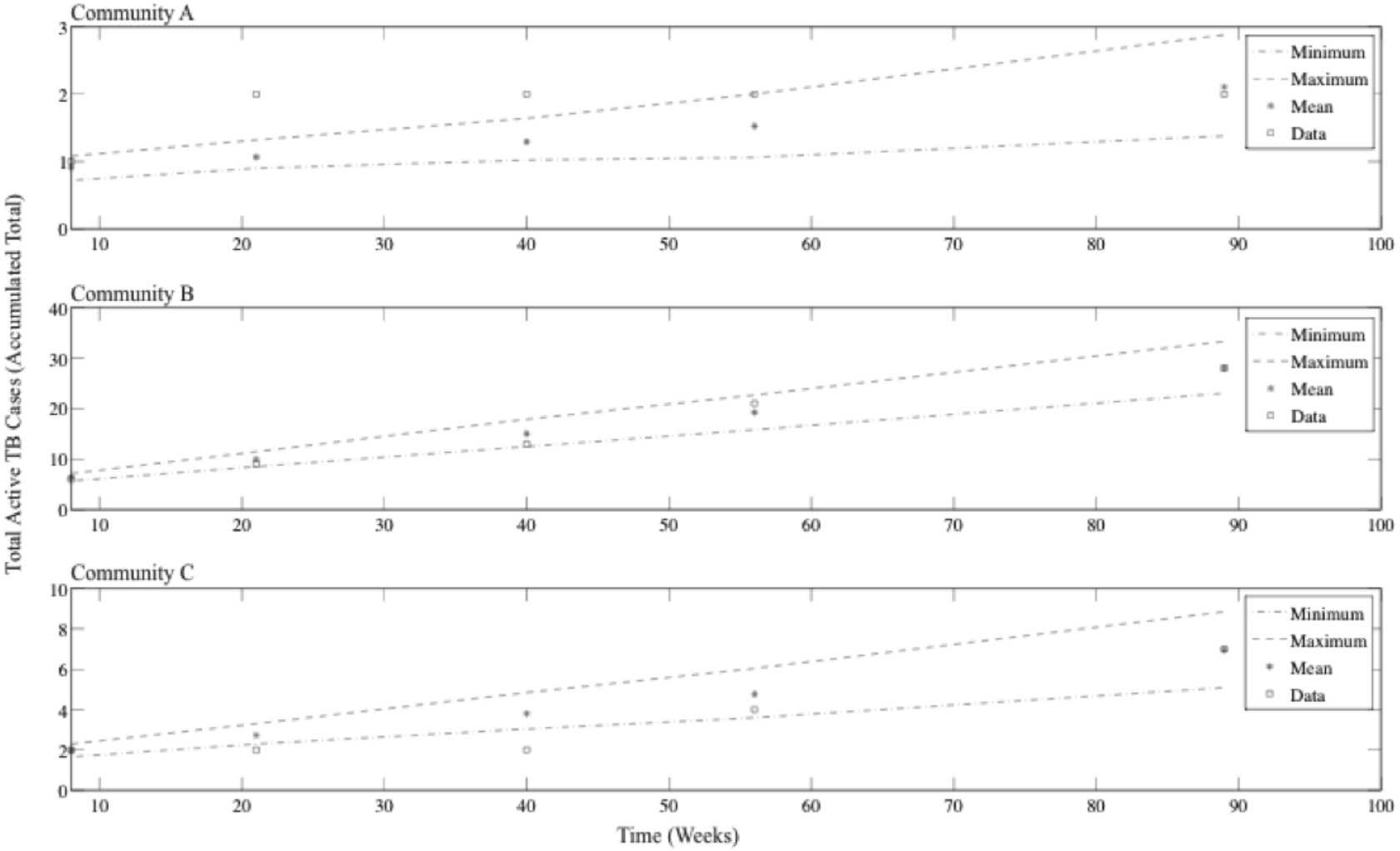

Figure 6a. 6 Uncertainty analysis on total active TB cases (accumulated) across Community A, B, and C using the TB-ABM simulated between 2007 and 2008 after n=1000 replications

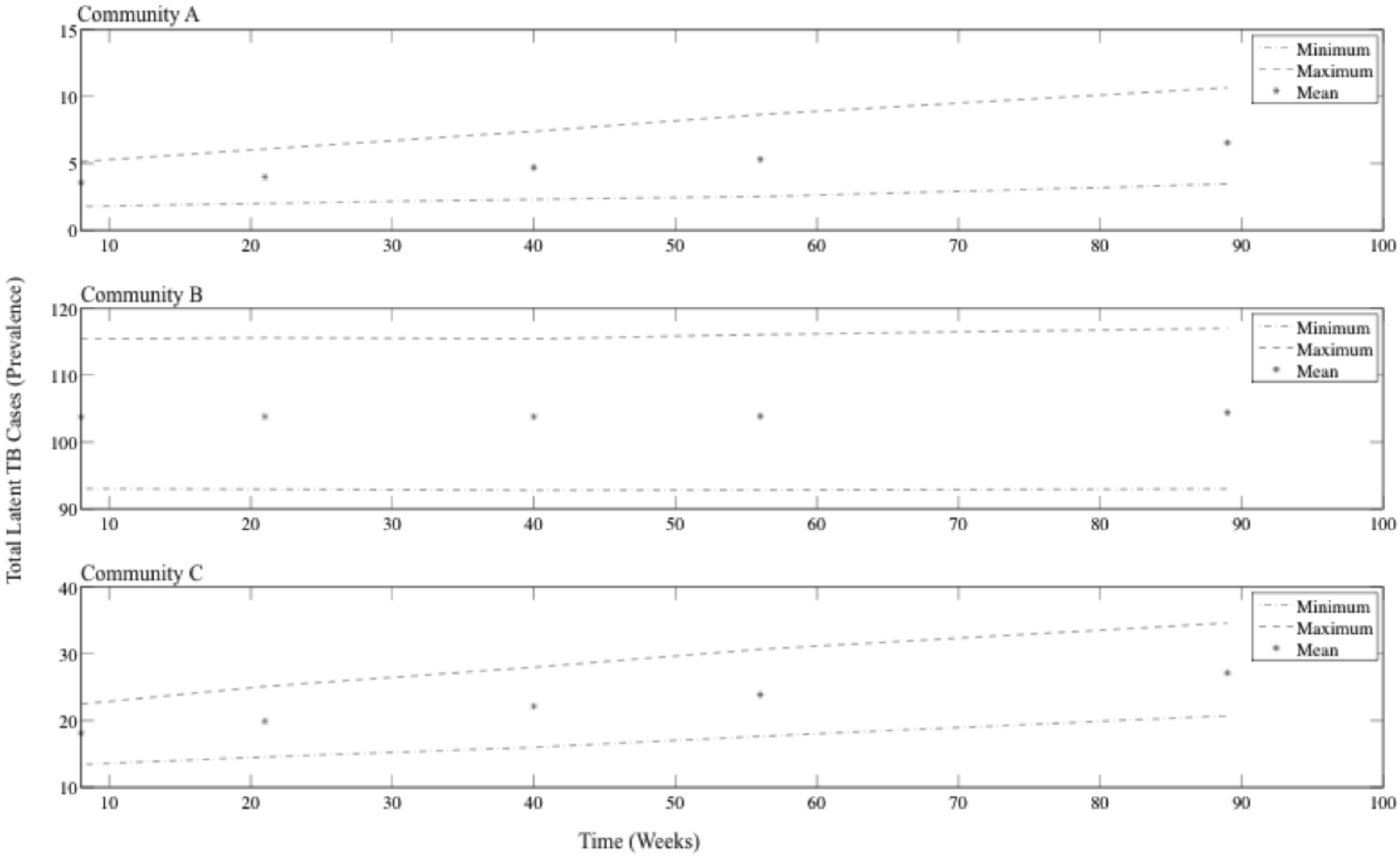

Figure 6a. 7 Uncertainty analysis on total latent TB cases (L_f) (prevalence) across Community A, B, and C using the TB-ABM simulated between 2007 and 2008 after n=1000 replications

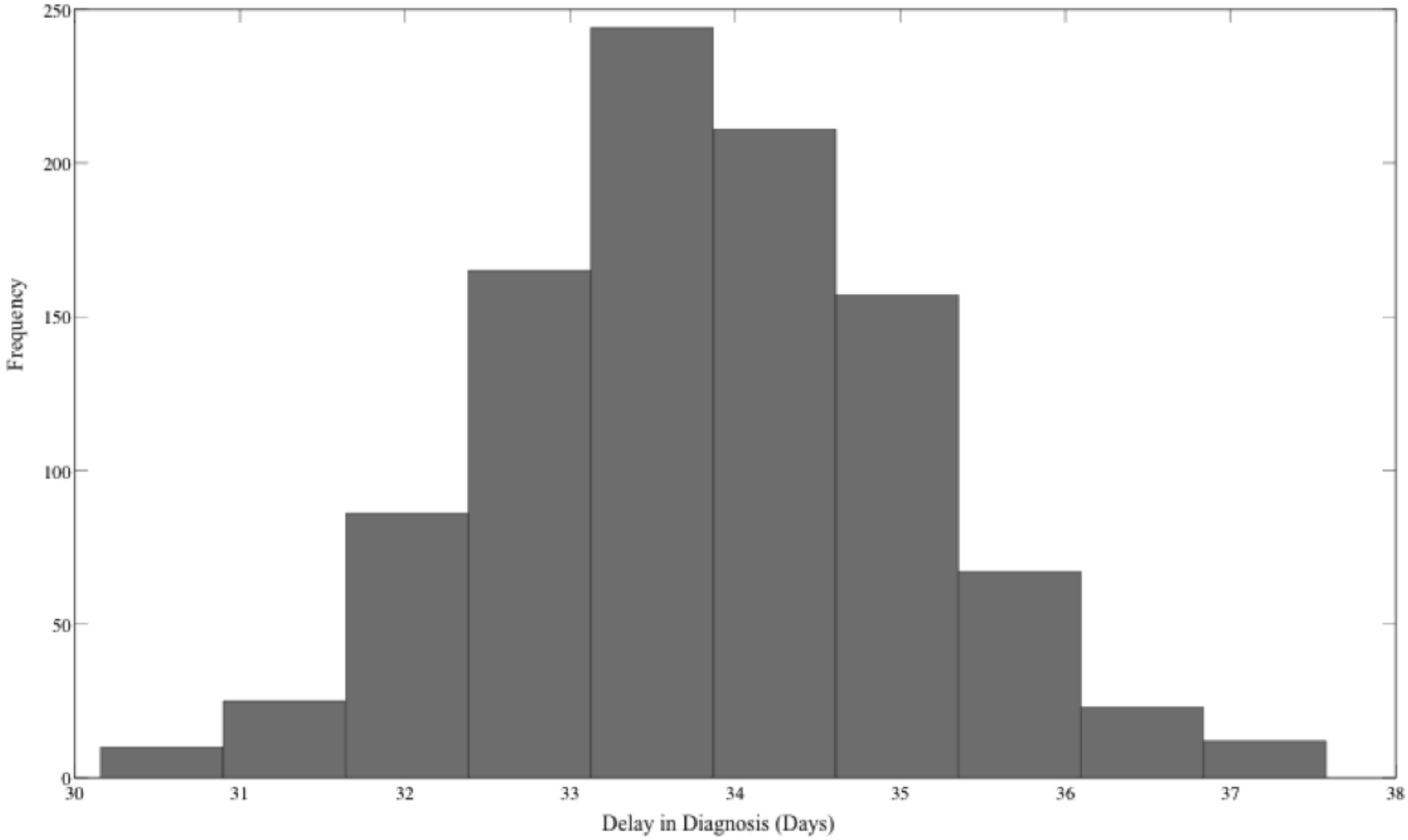

Figure 6a. 8 Uncertainty analysis on the mean duration of time to treatment of active TB using the TB-ABM between 2007 and 2008 after n=1000 replications

Chapter 6- Part 2: TB-ABM Simulation of TB Control Strategies: 1) Comorbidity Reduction, 2) Improvement of Healthcare Access, and 3) Screening and Preventative Therapy for Latent TB

6-2.0 Summary

INTRODUCTION: Deterministic and stochastic models have been used to describe tuberculosis (TB) transmission dynamics across Canada. In the Canadian context, TB cases are disproportionately distributed in the foreign-born and among Indigenous peoples. The added complexity of on-going transmission in high incidence Indigenous communities represents an additional challenge towards reducing the overall burden of TB. Quantifying the role social determinants of health (SDOH) play in TB transmission and progression would provide evidence to support existing knowledge. OBJECTIVE: The main objective of this chapter was to use the TB agent based model (TB-ABM) described in Chapter 6: Part 1 to investigate control strategies that impact the determinants of health (including SDOH) and the prevalence of LTBI. These strategies included reduction in comorbidities, improvement of healthcare access, and screening and treating of latent TB. METHODS: The TB-ABM utilized two statistical relationships associated with time to treatment to assess the impact to TB cases (latent and active) and transmission. The TB-ABM was simulated for a total of five years and predictions were validated using existing data. RESULTS: Simulated total active TB cases compared well to existing data. Latent TB screening every six months (based on a 60% compliance) was the most optimal strategy with reductions in LTBI (≤ 5 years) cases of between 40% and 71% in 5 years. Strategies that reduce comorbidities by 75% and increase access of within community health services for TB symptoms (healthcare access) had the greatest reductions in total TB transmission (7% to 18%) in 5 years. CONCLUSION: The reduction of TB in high incidence Indigenous

communities requires both decreasing latent TB infections in the short-term and interrupting on-going transmission through the improvement of risk factors that include the SDOH in the long-term.

6-2.1 Introduction

The use of agent based models (ABMs) have been used to simulated TB transmission dynamics [175-177, 179, 204, 205, 207-211]. The interactions between the determinants of health (DOH) (including social determinants (SDOH)) and TB transmission and progression can be challenging to implement in a mathematical model [213]. In literature, some of these risk factors include early case detection, alcohol use, smoking, healthcare access, low socioeconomic status, malnutrition, and low education level [203, 213].

Some Canadian TB transmission models constructed in the context of Indigenous peoples have incorporated DOH (including SDOH) despite its methodological challenges. Overall, factors such as malnutrition, improvements in the loss of follow-up, smoking reduction, housing density, and LTBI screening and preventative treatment have been incorporated into either deterministic [188] and/or ABMs that describe TB transmission in Indigenous populations in Canada[204, 209]. Interventions such as reduction in housing density were conducted by changing the network structure at the start or during an ABM simulation [204]. Malnutrition, smoking, loss to follow-up during contact investigations, and LTBI screening and treatment were directly implemented using constants applied at specific parts of the TB transmission dynamic [188, 204, 209]. Although, this approach was beneficial in offering insights into how specific risk factors (DOH/SDOH) impact active and latent TB cases, these constants were derived either from univariate associations or assumed based on epidemiological knowledge (from the literature). An extension of this approach was to consider multivariate associations of key parameters important

to TB transmission. One important parameter associated with transmission was the duration between the onset of symptoms and the start date of treatment, defined as time to treatment. Evidence of on-going transmission highest among First Nations and Métis peoples across the Prairies (Chapter 4) supported the investigation of risk factors associated with time to treatment. The use of a multivariate relationship between significant predictors and time to treatment among Indigenous TB cases across the prairies was investigated in Chapter 5.

In Chapter 6: Part 1, a TB transmission ABM (TB-ABM) was constructed and validated for three high incidence First Nations and Métis communities in northern Alberta and Saskatchewan. The aim for this chapter is to simulate and assess three TB control strategies using the TB-ABM that utilizes the multivariate relationship between significant risk factors (DOH/SDOH) and time to treatment. These two TB control strategies include the reduction in comorbidities (HIV, diabetes and/or renal disease) and improvement of healthcare access. Healthcare access is defined as location where people first sought care for their TB symptoms (i.e. within versus outside their community). The sensitivity results showed in Chapter 6: Part 1 that fluctuations in progression from latent to active TB would most affect model outcomes, the third control strategy includes LTBI screening and preventative treatment. The data used for constructing the multivariate model for time to treatment and TB-ABM parameter estimates was derived primarily from the seven-year *Determinants of Tuberculosis Transmission (DTT) Project* (2006-2013).

6-2.2 Methods

The TB-ABM in Chapter 6: Part 1 was used to simulate three TB control strategies that involved specific risk factors (DOH/SDOH) and reduction in LTBI prevalence significant to TB transmission and progression. These control strategies included reduction in comorbidities,

improvement of healthcare access, and screening and preventative therapy for LTBI. Comorbidities included HIV infection, diabetes, and/or renal disease. The improvement of healthcare access included increasing the proportion of people that would seek medical care within versus outside the community. Screening and treatment of LTBI only included people who were recently infected (i.e. within five years).

The TB-ABM was extended to simulate beyond 89 weeks (as described in Chapter 6: Part 1) to approximately five years (~250 weeks). Total TB cases in Community A, B, and C obtained from the DTT project was used to determine the overall fit to the simulated data. The statistical relationship presented in Chapter 6: Part 1 between significant risk factors and time to treatment was used in the TB-ABM. An additional statistical relationship restricting the DTT data to Indigenous cases in Alberta and Saskatchewan above the 53rd parallel was also used to predict time to treatment in the TB-ABM. The latter statistical relationship includes the healthcare access predictor based on the location where people first sought care (within/outside community). The TB control strategies using both statistical relationships in the TB-ABM were assessed for relative reductions (from baseline) in accumulated active and prevalent latent TB cases (L_f) and accumulated total transmission events. The best ranked parameter set (see Chapter 6: Part 1) was used for all simulations in this chapter. Simulations were conducted using Jasper, a supercomputer grid provided by WestGrid (www.westgrid.ca) and Compute Canada (www.computecanada.ca).

A 2nd Statistical Relationship of Risk factors Associated with Time to Treatment

The statistical model used in Chapter 6: Part 1 did include an indicator for healthcare access through the predictor, having a regular family doctor (see Chapter 5). However, it was not possible to simulate the improvement of healthcare access by using this predictor. A reduced

dataset of Indigenous TB cases in Alberta and Saskatchewan located above the 53rd parallel was used to determine an alternative model (defined as Statistical Model 2) located in the context of the three-piloted communities. A multivariable linear regression analysis was conducted similarly to Chapter 6: Part 1 (defined as Statistical Model 1) methods. This statistical model was integrated into the TB-ABM and assessed for its overall fit to the DTT data.

Projection of TB-ABM to 5 Years

Based on the best ranked parameter set using Statistical Model 1 and Statistical Model 2, the total TB cases simulated from the TB-ABM for 250 weeks (~ five years) and a 95% confidence interval was compared to the DTT data (4 years: 2007-2010). The DTT data included all background culture positive TB cases between 2006 and 2010. The predictive ability of the TB-ABM was assessed by using the total TB cases between 2009 and 2010 (two years beyond the calibration period) to assess whether the DTT data was within the 95% confidence interval constructed using simulated results (n=500 replications). Note: The 5th year for the prediction could not be compared with data from the DTT project since this exceeded the study period.

Tuberculosis Control Strategies

Three TB control strategies simulated using the TB-ABM involved 1) specific risk factors (DOH/SDOH) associated with TB transmission and progression and 2) screening and preventative therapy for LTBI to reduce its prevalence. A total of 500 replications were used per simulation to determine the average percentage reduction of accumulated active and prevalent latent TB cases (L_f), and accumulated total transmission events from baseline. Each control strategy included various sub-types that included changes in frequency and/or reduction to assess

its overall effectiveness. The random seed was held constant for each set of simulations (baseline and intervention sub-types).

TB Control Strategy 1: Reduction in Comorbidities

A person having comorbidities was defined as those with HIV infection, diabetes, and/or renal disease. The impact that comorbidities have on TB infection and progression has been established in literature [54, 162, 166, 167]. The association of comorbidities with time to treatment was identified as a significant predictor in the multivariable linear regression model (Chapter 6: Part 1). A relative risk was also applied on the progression from latent to active TB among individuals with comorbidities. Baseline comorbidity rates by age used to randomly assign individuals as having or not having comorbidities was reduced by factor of 50%, 75%, and 90%. These effects were simulated for five years using the TB-ABM and average percentage reductions was estimated on year five. Similarly, the second multivariable linear regression model was also used to assess for impacts associated with reductions in comorbidities.

TB Control Strategy 2: Improvement of Healthcare Access

The improvement of healthcare access was a significant predictor in the secondary model (Statistical Model 2) that restricted the analysis of the DTT data to Indigenous cases in Alberta and Saskatchewan above the 53rd parallel. Healthcare access was defined in this chapter as the location where people first sought care for their TB symptoms i.e. within or outside their community. The improvement of healthcare access translated to increasing the proportion of people that would seek care within their community i.e. with increased access to medical personnel within Indigenous communities. Increased healthcare access of 50%, 75%, and 90% was simulated using the TB-ABM. Baseline proportions of healthcare access were estimated

directly from the DTT data specific to the three piloted communities. These proportions were randomly assigned to individuals, and reductions on these proportions were simulated using the TB-ABM.

TB Control Strategy 3: Screening and Treating of LTBI

A control strategy that would screen for LTBI and treat those that have been infected within 5 years (L_f) using a single step TST and isoniazid for LTBI treatment was simulated across all three communities in the TB-ABM. Four factors for this control strategy were varied to assess for average percentage reductions in accumulated active and prevalent latent TB cases and accumulated total transmission events: 1) the proportion that accepted and completed preventative therapy (ranged from 60% to 100%), 2) frequency of screening (every four weeks, four months, six months, and 12 months), 3) proportion of people screened (ranged from 50% to 100%), and 4) probability of diagnosing active TB from a TST test (ranged from 50% to 100%). The probability of diagnosing active TB from a TST (used for diagnosing latent TB) can be challenging if a person is asymptomatic, therefore, this ambiguity was considered in the TB-ABM simulations. This screening and treating strategy was an additional dynamic to the baseline TB transmission dynamics, which included contract tracing methods. This control strategy was simulated for both statistical models.

6-2.3 Results

Three control strategies were simulated using the TB-ABM that provided insight to its impact on accumulated active and prevalent latent TB cases (L_f) and total transmission events. Control strategies that reduced comorbidities, improved healthcare access, and screened and treated for LTBI were simulated using the TB-ABM (n=500 replications). The average

percentage reduction in model outcomes was assessed using two statistical relationships associated with time to treatment (refer to Chapter 6: Part 1 for Statistical Model 1).

Table 6b.1 describes the multivariable linear regression model (Statistical Model 2) that restricted the DTT data to Indigenous peoples residing in Alberta and Saskatchewan above the 53rd parallel (N=49). Similarly to Statistical Model 1, age was a confounding variable and predictors included comorbidity (β=1.310; p=0.02), a working x-ray machine and technician in the community (β=-1.47; p<0.01), having a regular family doctor (β=0.34; p=0.28), and an interaction between comorbidity and having a regular family doctor (β=-1.675; p=0.01). Healthcare access was defined as the location where people first sought care about their TB symptoms (within community=0; outside community=1) (β=0.3933; p=0.25). Increased time to treatment durations were associated with healthcare access outside the community, having comorbidities, and having a regular family doctor, which agreed with associations in Statistical Model 1. Decreased time to treatment were associated with communities that had a working x-ray machine and technician and the interaction between having a regular family doctor and comorbidities. These statistical models generally agreed with results in Chapter 5, with the exception that Statistical Model 2 did not include housing density and having an indigenous mother tongue.

The use of Statistical Model 2 in the TB-ABM warranted an assessment of its overall fit with the best ranked parameter set found in Chapter 6: Part 1. The calibration conducted in the previous chapter used the DTT data between 2007 and 2008 (T=0 to T=89 weeks) to determine the best ranked parameter set that fit well to model outcomes. The accumulated active and prevalent latent TB cases (L_f), and total transmission events fit similarly to Statistical Model 1. There was no need for recalibration of unknown model parameters in the TB-ABM using Statistical Model 2.

TB control strategies were modeled using the TB-ABM for a total of five years (2007 to 2011 or T=0 to T=250 weeks). A total of 500 replications were simulated to obtain five-year projections using the TB-ABM. Comparisons made between the DTT data and model simulations were based on a four-year projection since no data was available for the fifth year. Figure 6b.1 and Figure 6b.2 describe the 95% confidence interval of accumulated total TB cases after 500 TB-ABM simulations using Statistical Model 1 (Figure 6b.1) and Statistical Model 2 (Figure 6b.2) at baseline predicting to T=200 weeks (~four years). Simulated totals were compared to the DTT data between 2007 and 2010 (~four years). A 95% confidence interval was provided in Figure 6a.1 and Figure 6b.2 based on the distribution of the 500 replications. The TB-ABM models outputs using both statistical models compared well with the DTT data between 89 and 200 weeks (post-calibration prediction). The DTT data was contained within the 95% confidence interval. At t=197 weeks (~four years), the total TB cases for Community A, B, and C was 6, 54, and 9 cases respectively using the DTT data. The total active TB cases using the TB-ABM (at t=197 weeks) using Statistical Model 1 were 4.8, 57.3, and 14.9 for Community A, B, and C, respectively. Similarly, the total active TB cases using the TB-ABM (at t=197 weeks) for Community A, B, and C using Statistical Model 2 were 4.5, 55.0, and 14.3 cases, respectively. The prediction for Community C at t=197 weeks was over-estimated by approximately five and six active TB cases.

The overall incidence of TB in 2010 across all three communities was estimated using the DTT data. The denominator for TB incidence rate in 2010 was estimated using 2011 population totals since data in 2010 was not available. The incidence of TB using the DTT data was 500 cases per 100,000 population (in Community A and B) and 130 cases per 100,000 population (in Community C). The simulated TB incidence rates using Statistical Model 1 and Statistical Model 2 in 2010 was 300 cases per 100,000 population (in Community A) and 400 cases per 100,000

population (in Community B and C). The discrepancy with the TB incidence rate in Community A was sensitive to small numbers and if the simulated total cases increased by one, these rates would compare well to the DTT data. Simulated TB incidence rates in Community C were over-estimated in the TB-ABM largely due to the overestimation of TB cases seen in Figure 6b.1 and Figure 6b.2 at t=197 weeks (2010).

The baseline five-year prediction (at t=250 weeks) for the total active TB cases was estimated for Community A (5.9-6.4 cases), Community B (70.0-71.9 cases), and Community C (18.7-19.1 cases) using both statistical models. The five-year prediction in Community C for total active TB cases is most likely over-estimated.

Control strategies were simulated separately using both statistical relationships except for improving healthcare access, which was not simulated in Statistical Model 1. Table 6b.2 describes the average percentage increase (reduction) in accumulated active and prevalent latent TB (L_f) cases and total TB transmission events for control strategies that would reduce comorbidities and improve healthcare access. Trends in percentage reductions were similar for both statistical models and the magnitude of reductions was marginally higher using Statistical Model 1 (see Table 6b.2). The difference in reduction of comorbidities between 50%, 75%, and 90% on all model outcomes were fairly uniform. The reduction in comorbidities and improvement of healthcare access had the greatest impact on decreasing total transmission events compared to reductions in latent TB (L_f) and active TB cases. Based on a 75% reduction in comorbidities, total transmission events decreased by 10% to 18% (see Table 6b.2) across all three communities. The reduction in active and latent TB (L_f) cases based on a 75% reduction in comorbidities ranged from 7% to 11% and 4% to 14%, respectively. Reductions in TB incidence ranged between 9% and 12% (based on 75% reduction). For healthcare access, a 75% improvement (i.e. with accessing services within the community) showed a reduction in total

transmission events that ranged from 10% to 16%. Reductions in active and latent TB (L_f) cases based on a 75% improvement in healthcare access ranged from 1% to 3% and 7% to 10%, respectively.

Table 6b.3 describes the reductions in accumulated active and prevalent latent TB (L_f) cases and total transmission events after a LTBI screening and treating strategy using the TB-ABM. A selected subset of simulations was presented in Table 6b.3 that varied by accepting (and completing) preventative therapy, frequency of screening, proportion screened, and the probability of diagnosing an active TB case from a positive TST. Significant reductions in latent (L_f) and active TB cases and transmission events were observed using both statistical models. Annual screening strategies would be most effective if among everyone that was screened, those who have recent latent TB infection (L_f) accepted and completed preventative therapy, and if all cases (including active TB) could be diagnosed from a positive TST. Reductions ranged from 30% to 55% for active TB cases, 54% to 86% for LTBI (L_f) cases, and 23% to 53% in total transmission events (See Table 6b.3: LTBI-1). Similar to LTBI-1, reductions were comparable and increased marginally by screening frequency (reduction in four weeks > four months > six months) (see Table 6b.3: LTBI-3, LTBI-4, and LTBI-7).

The proportion screened that accepted and completed LTBI treatment had the greatest impact to all model outcomes. In LTBI-8 and LTBI-9 (every six month screening and treating) showed 1.5 to 2 times greater reductions if acceptance and completion increased from 60% to 80% and everyone was screened (see Table 6b.3). Similar reductions in model outcomes were estimated with screening every four or six months (LTBI-4 and LTBI-7). Although an annual screening and treatment strategy given 100% acceptance and completion and proportion screened ("perfect" intervention) would yield significant reductions in active and latent TB cases and total TB transmission events, any deviations on screening/treating parameters would have a reduced

impact to model outcomes (LTBI-2). A six month screening and treating strategy would be optimal (LTBI-7 to LTBI-11). Reductions of active and latent TB (L_f) cases and total transmission events from a six month screening and treating strategy ranged from 20% to 60%, 19% to 94%, and 17% to 63%, respectively based on using both statistical models (see Table 6b.3). Simulated reductions of TB incidence using a six month screening and treating strategy ranged between 36% and 78% for Community A, B, and C.

6-2.4 Discussion

Disease dynamics of TB in Canada affect Indigenous peoples for different reasons compared to the foreign-born population. Among Indigenous peoples who live in high burden communities, evidence of on-going transmission (Chapter 4) [54, 94, 103, 104] is an important characteristic that contributes to latent TB cases. The risk of transmission, advanced disease, and mortality can be increased with delays in diagnosis and treatment [128, 138-141]. Risk factors (DOH and SDOH) associated with time to diagnosis or treatment and progression from latent to active TB have been established in literature [54, 106-109]. The DOH (including SDOH) such as poverty, crowded housing, food insecurity, low socioeconomic status, challenges in healthcare access, and comorbidities are often experienced by Indigenous peoples who live in communities with a high TB burden [116-119]. The quantitative impacts that DOH (including SDOH) has on the TB disease dynamic are difficult to understand without the use of mathematical modeling.

The use of mathematical models has offered insights into TB disease dynamics using both deterministic and stochastic methods [181, 182, 187, 188, 204, 209]. Conducting epidemiological studies to measure the quantitative role that DOH (including SDOH) has on TB cases and incidence has ethical implications, require long periods of time, and have much higher costs. The integration of SDOH using ABMs has been incorporated in three Canadian TB studies about

Indigenous communities [188, 204, 209]. Some examples included housing density, smoking, and malnutrition [188, 204, 209]. Largely these studies have integrated SDOH into models as a univariate constant derived from literature (or assumed) onto specific parameters within the TB dynamic. Simulations from these models helped to provide insight into potential reductions in TB cases and transmission [188, 204, 209]. This motivated this current work, which provided an extension of current modeling methods to determine ways of integrating SDOH into an ABM through parameters that have the greatest impact to disease dynamics. A multivariable relationship between significant predictors and time to treatment was constructed and integrated into the TB-ABM in Chapter 6: Part 1.

TB Control strategies included decreasing comorbidities, increasing healthcare access, and latent TB screening and treatment was investigated by assessing reductions in TB cases (active and latent (L_f)), transmission, and incidence. Similar to Tuite et al. [204], latent TB screening and treatment in this study had a significant impact on reducing TB burden in three high incidence communities in northern Alberta and Saskatchewan. The most optimal frequency of screening that provided reductions in TB cases and transmission was six months. The percentage reductions were sensitive to changes in the proportion screened and those that accepted and completed treatment. Considering LTBI-11 (see Table 6b.3), reductions of TB cases (active and latent (L_f)) and transmission ranged from 19% to 38%, 40% to 71%, and 11% to 32%, respectively in five years. Reductions in Community A should be interpreted with caution since total TB cases (active and latent (L_f)) and transmission events were small and high percentage reductions reported could occur with little absolute change in cases.

In high incidence Indigenous communities such as Community A, B, and C where on-going transmission continues to be an important issue, reducing time to treatment represented another part of the TB dynamic that has been shown to be significant at reducing new TB

infections [204]. The methodology in this dissertation allowed for an ABM to estimate reductions in TB cases and transmission from potential control strategies that target specific DOH (including SDOH). In this study, risk factors such as comorbidities and healthcare access associated with time to treatment was integrated into the TB-ABM. Comorbidities and health care access were indirectly associated with on-going transmission (time to treatment) while comorbidities were directly associated with the progression from latent to active TB (through a constant applied based on an individual's comorbidity status). Two control strategies that were simulated included reducing comorbidities and improving healthcare access. The TB-ABM simulations for reductions in comorbidities and improved healthcare access achieved the greatest reductions in total transmission compared to latent and active TB cases. Reductions in total TB transmission based on a 75% reduction in comorbidities and accessing health services outside communities (healthcare access) ranged from 10% to 18% and 10% to 16%, respectively.

From a TB policy perspective, mathematical models such one presented in this study (TB-ABM) can provide numerical evidence that align with existing knowledge. For instance, the role and importance of SDOH on TB transmission and progression have been well established in the literature [54, 101, 153, 157, 158, 166]. The two well established 'levers' that encourage TB to persist in high burden Indigenous communities include i) on-going transmission and ii) progression of TB. These levers were included as recommendations in Health Canada's Strategy Against Tuberculosis for First Nations On-Reserve; they are 1) prevention, diagnosis, and TB management (i.e. targeted screening, treatment compliance), 2) focusing on population that have the greatest risk of developing TB (comorbidities and healthcare access), and 3) develop and maintain partnerships [55].

A latent TB screening and treating strategy made significant impacts to reducing latent TB (L_f), while active TB cases were decreased indirectly. The TB-ABM simulations suggested

that in the short term, a latent TB screening and treating strategy would reduce total latent (L_f) TB cases, while indirectly decreasing active TB and total transmission. In the long-term, intervening on risk factors that directly affect on-going transmission such as comorbidities and healthcare access would help reduce the persistence of TB in Indigenous communities that experience a high burden. The underlying factors that relate to comorbidities and healthcare access such as socioeconomic status, education, stress, and food insecurity should be addressed, which would extend beyond benefits gained from TB reduction alone. Health inequities shaped by these SDOH can impact overall life expectancy, comorbidities (not including genetic predisposition), health behaviors, and overall health costs [26].

The overall prediction of the TB-ABM for an additional 2 years (~ post 89 weeks) compared well to the DTT data and was contained in the 95% confidence interval (see Figure 6b.1 and Figure 6b.2). The predictive ability of the TB-ABM allowed for not only relative comparisons of percentage reductions, but providing insight to the absolute reductions that could occur from the control strategies presented in this chapter. In Community C, the deviation of simulated active TB cases from the DTT data (at T=136 weeks) suggested the possibility of interventions that took place in response to a TB outbreak (or increased TB cases) such as intensified contact tracing and increasing the proportions of people completing preventative therapy. The TB-ABM during the five-year period was relatively static in its assumptions and did not include the possibility of interventions such as changes to TB screening (e.g. community wide or school screening) and more intensified contact tracing methods in response to observed increases in TB cases within a community setting. The overall mobility between Community B and C may have also been overestimated, which could contribute to the increased prediction of active TB cases in Community C. Therefore, the percentage reductions in model outcomes for

Community C may be overestimated based on these prediction results and should be interpreted with caution.

The TB-ABM integrated two statistical relationships that were associated with time to treatment. A subset analysis that focused on Indigenous TB cases in northern (above the 53rd parallel) Alberta and Saskatchewan included healthcare access as a significant predictor for time to treatment. Healthcare access was defined as the location people first sought care for their TB symptoms (within/outside their community). The complexity of improving healthcare access does not translate to increased infrastructure alone. Personnel support, good rapport building, cultural competency, and community involvement represent some areas that could help increase health seeking within communities [256, 286]. For example, having a regular family doctor in this dissertation was associated with increased odds of delayed time to treatment. A regular family doctor as a predictor did not capture their overall frequency of visits, rapport, or engagement with the community to encourage positive health seeking behaviors.

Although, the predictive ability of the Statistical Model 2 was poor (Adjusted R^2= 55%), this prevents the multivariate model from determining exact transmission periods by individual attributes. Despite the poor predictive ability of the multivariate model, the logistic regression in Chapter 5 generally afforded individuals well based on timely treatment (≤ 30 days) and delayed time to treatment (>30 days). The simulated mean time to treatment of 30 days was only under-estimated by 7 days based on the DTT data (mean=37 days). The TB-ABM also made adjustments to the time to diagnosis if TB cases were diagnosed earlier due to contact investigations. This dynamical feature of the TB-ABM also contributed to its overall predictive ability. The slow dynamics of TB [182] may have also reduce sensitivities to model outcomes even though the simulated time to treatment was underestimated using Statistical Model 2.

A control strategy about housing density was not presented in this study due to other housing characteristics that depend on TB transmission such as housing ventilation, quality, and area [116], which were not included in the TB-ABM. Housing density by increasing households in an ABM about TB in an Inuit community did not show a significant decrease. This non-significant decrease was associated with complexities mentioned earlier that were not included in the ABM [204]. Other considerations included whether contact investigations of household contacts would extend further to non-household contacts, if housing density were reduced.

The TB-ABM had several limitations. DOH (including SDOH) associated with the risk of TB progression such as food insecurity (malnutrition), smoking, alcohol consumption, and HIV [148, 152-154, 165] was not included in the TB-ABM. The risk of comorbidities on TB progression was only included as a univariate constant [166]. The inclusion of multivariate associations of risk factors associated with TB progression could better describe the overall cost-effectiveness of potential control strategies that target DOH (including SDOH). Contact investigations were simplified (occurred in one week) in the TB-ABM and did not extend further from initial contacts if an active TB case was diagnosed. Given the size of the three communities, contacts included initially in a contact investigation may have more overlap if a TB case was diagnosed. An integration of a two-step TST that could increase case finding of LTBI was not included in the TB-ABM. The increased computational resources used in ABMs required assessing the inclusion of dynamics that were most important. Although a two-step TST can be simulated, further assessment would be needed to determine its significance to the overall TB transmission dynamic. The DTT data provided information for total active TB cases, which were obtained by postal codes. The possibility of misclassification of TB cases in Community B and Community C was possible based on their close distance. The possibility of resistance to

preventative therapy such as isoniazid followed from non-compliance was not included in the TB-ABM and can be possible extensions for the TB-ABM.

6-2.5 Conclusion

The overall implication of this study was two-fold. The methodology of integrating a multivariate relationship associated with key variables in disease dynamics provided a novel way to assess how SDOH impact disease outcomes. The use of the TB-ABM suggested that if efforts were first placed with reducing latent TB in high incidence communities, the overall burden of TB would be significantly reduced. The long-term benefits of reducing comorbidities and increasing healthcare access have an impact on transmission directly and highlight that these latter risk factors (DOH and SDOH) are important for reducing TB in high burden Indigenous communities where TB persists due to on-going transmission. Increased and enhanced TB surveillance, much like the DTT project, can ensure mathematical models have the data to provide long-term projections (beyond five years) of impacts potential interventions that target DOH (including SDOH) could have on TB cases within communities. Evidence such as the results presented in this chapter can be beneficial to TB policy makers and clinicians to help make informed decisions towards reducing the burden of TB in Indigenous communities across Canada.

Table 6b. 1 Multivariable linear regression model of time to treatment among all Indigenous TB cases north of the 53rd parallel defined as 'true transmitters' in Alberta and Saskatchewan (Statistical Model 2)

	Time to Treatment (days): N=49	
	Log β	**p-value**
Intercept	2.228	<0.0001
Age	0.0502	0.0002
§Location: Seek First about TB symptoms (0=In community, 1=Outside community)	0.3933	0.2475
Comorbidity (0=No, 1=Yes)	1.310	0.0218
A Working X-ray Machine and Technician in Community (0=No, 1=Yes)	-1.472	<0.0001
Have a Regular Family Doctor (0=No, 1=Yes)	0.3397	0.2819
Comorbidity and Have Regular Family Doctor (0=No, 1=Yes)	-1.675	0.0137

§ Includes reserves, Métis, and non-major metropolitan communities

Table 6b. 2 Percentage increase (reduction) in accumulated active and prevalent latent TB (Lf) cases, and total TB transmission events from baseline after 500 replications of control strategies that reduce comorbidities (C) and improve healthcare access (HA) in five years using the TB-ABM

		Percentage increase (reduction) in active TB cases from baseline in 5 years			Percentage increase (reduction) in LTBI (L_f) cases from baseline in 5 years			Percentage increase (reduction) in total transmission events from baseline in 5 years		
Intervention	Reduction in comorbidities/ healthcare access (%)	Com A	Com B	Com C	Com A	Com B	Com C	Com A	Com B	Com C
Statistical Model 1 (From Chapter 6: Part 1)										
Baseline (at T=250 weeks)		**6.4**	**71.9**	**19.1**	**11.9**	**114.1**	**36.7**	**17.2**	**97.2**	**42.7**
C-1	50	(5.9)	(4.9)	(5.0)	(6.7)	(3.1)	(5.8)	(10.6)	(8.5)	(9.0)
C-2	75	(10.9)	(8.0)	(9.4)	(13.7)	(5.2)	(8.7)	(17.9)	(14.2)	(13.5)
C-3	90	(15.9)	(10.4)	(12.1)	(16.6)	(6.8)	(12.9)	(23.2)	(18.6)	(19.6)
Statistical Model 2 (From Table 6b.1)										
Baseline (at T=250 weeks)		**5.9**	**70.0**	**18.7**	**10.6**	**107.7**	**35.1**	**14.5**	**85.8**	**40.3**
C-1	50	(5.7)	(4.9)	(6.6)	(4.3)	(3.5)	(3.4)	(7.2)	(9.4)	(7.8)
C-2	75	(8.5)	(7.1)	(8.3)	(6.5)	(3.5)	(7.1)	(10.6)	(12.2)	(12.0)
C-3	90	(12.5)	(9.3)	(10.6)	(10.6)	(5.2)	(10.6)	(16.0)	(16.3)	(16.2)
Baseline (at T=250 weeks)		**5.9**	**70.0**	**18.7**	**10.6**	**107.6**	**35.0**	**14.5**	**85.6**	**40.3**
HA-1	50	~0	(2.1)	(2.7)	(2.4)	(6.4)	(5.9)	(2.5)	(12.8)	(7.6)
HA-2	75	(1.1)	(2.7)	(2.8)	(10.2)	(8.2)	(7.3)	(9.7)	(16.1)	(9.3)
HA-3	90	(4.7)	(2.9)	(4.2)	(11.7)	(10.6)	(9.7)	(14.2)	(20.2)	(12.1)

Table 6b. 3 Percentage increase (reduction) in accumulated active and prevalent latent TB (L_f) cases, and total TB transmission events from baseline after 500 replications of control strategies that screened and treated for LTBI in five years using the TB-ABM

Intervention	Accept and complete treatment (%)	Frequency of screening	Proportion screened	Probability of TB diagnosis from TST	Percentage increase (reduction) in TB cases in 5 years			Percentage increase (reduction) in LTBI (L_f) cases in 5 years			Percentage increase (reduction) in total transmission events		
					Com A	Com B	Com C	Com A	Com B	Com C	Com A	Com B	Com C
Model 1 (From Chapter 6: Part 1)													
Baseline					**6.4**	**71.9**	**19.1**	**11.9**	**114.1**	**36.7**	**17.1**	**97.1**	**42.7**
LTBI-1	100	Every year	1.00	1.00	(55.3)	(41.3)	(30.7)	(86.0)	(57.6)	(54.5)	(52.8)	(32.8)	(22.4)
LTBI-2	60	Every year	0.50	0.50	(27.6)	(18.7)	(13.3)	(49.8)	(32.4)	(28.2)	(24.8)	(13.3)	(10.2)
LTBI-3	100	Every 4 weeks	1.00	1.00	(65.0)	(51.7)	(43.5)	(97.7)	(69.9)	(69.3)	(74.1)	(52.0)	(35.7)
LTBI-4	100	Every 4 months	1.00	1.00	(63.6)	(48.0)	(39.9)	(95.0)	(66.4)	(65.7)	(64.7)	(39.7)	(27.7)
LTBI-5	80	Every 4 months	1.00	1.00	(61.0)	(46.4)	(38.0)	(94.1)	(65.2)	(64.4)	(62.6)	(37.7)	(25.8)
LTBI-6	60	Every 4 months	0.50	0.50	(46.8)	(33.8)	(25.9)	(83.0)	(55.6)	(51.5)	(43.6)	(24.4)	(14.5)
LTBI-7	100	Every 6 months	1.00	1.00	(60.0)	(46.1)	(36.7)	(93.5)	(64.5)	(63.1)	(60.3)	(37.5)	(24.1)
LTBI-8	80	Every 6 months	1.00	1.00	(57.8)	(43.3)	(35.1)	(91.6)	(62.5)	(61.6)	(56.2)	(35.3)	(24.8)
LTBI-9	60	Every 6 months	0.50	1.00	(40.6)	(27.6)	(20.7)	(72.7)	(47.8)	(42.8)	(38.1)	(20.5)	(12.6)
LTBI-10	80	Every 6 months	0.50	0.50	(46.4)	(32.1)	(23.6)	(80.0)	(53.0)	(48.5)	(40.8)	(22.4)	(14.3)
LTBI-11	60	Every 6 months	0.50	0.50	(37.7)	(28.5)	(19.3)	(70.9)	(47.3)	(43.4)	(31.7)	(19.1)	(12.6)
Model 2 (From Table 1)													
Baseline					**5.9**	**70.0**	**18.7**	**10.6**	**107.8**	**35.1**	**14.5**	**85.9**	**40.3**
LTBI-1	100	Every year	1.00	1.00	(53.0)	(40.4)	(28.9)	(84.8)	(56.4)	(52.7)	(49.1)	(29.8)	(19.8)
LTBI-2	60	Every year	0.50	0.50	(24.0)	(18.9)	(12.0)	(47.3)	(31.7)	(24.9)	(19.1)	(11.4)	(6.1)
LTBI-3	100	Every 4 weeks	1.00	1.00	(63.2)	(50.1)	(41.1)	(97.1)	(68.7)	(68.9)	(70.5)	(51.9)	(37.8)
LTBI-4	100	Every 4 months	1.00	1.00	(59.2)	(47.6)	(37.9)	(94.4)	(64.9)	(65.2)	(59.7)	(40.0)	(26.8)
LTBI-5	80	Every 4 months	1.00	1.00	(57.2)	(45.4)	(35.6)	(93.4)	(63.8)	(63.8)	(55.5)	(36.1)	(23.8)
LTBI-6	60	Every 4 months	0.50	0.50	(42.8)	(33.5)	(25.2)	(81.0)	(54.6)	(51.3)	(33.8)	(21.1)	(14.3)
LTBI-7	100	Every 6 months	1.00	1.00	(58.6)	(45.2)	(35.6)	(93.9)	(62.8)	(61.7)	(59.6)	(35.2)	(22.0)
LTBI-8	80	Every 6 months	1.00	1.00	(55.9)	(42.2)	(33.4)	(90.4)	(61.2)	(59.6)	(53.2)	(32.8)	(21.4)
LTBI-9	60	Every 6 months	0.50	1.00	(37.6)	(26.0)	(19.2)	(71.4)	(47.4)	(42.0)	(34.2)	(19.0)	(11.0)
LTBI-10	80	Every 6 months	0.50	0.50	(43.6)	(31.3)	(23.5)	(78.5)	(52.0)	(48.1)	(36.6)	(21.0)	(12.3)
LTBI-11	60	Every 6 months	0.50	0.50	(32.2)	(27.4)	(20.6)	(69.8)	(46.1)	(40.7)	(28.0)	(17.1)	(10.5)

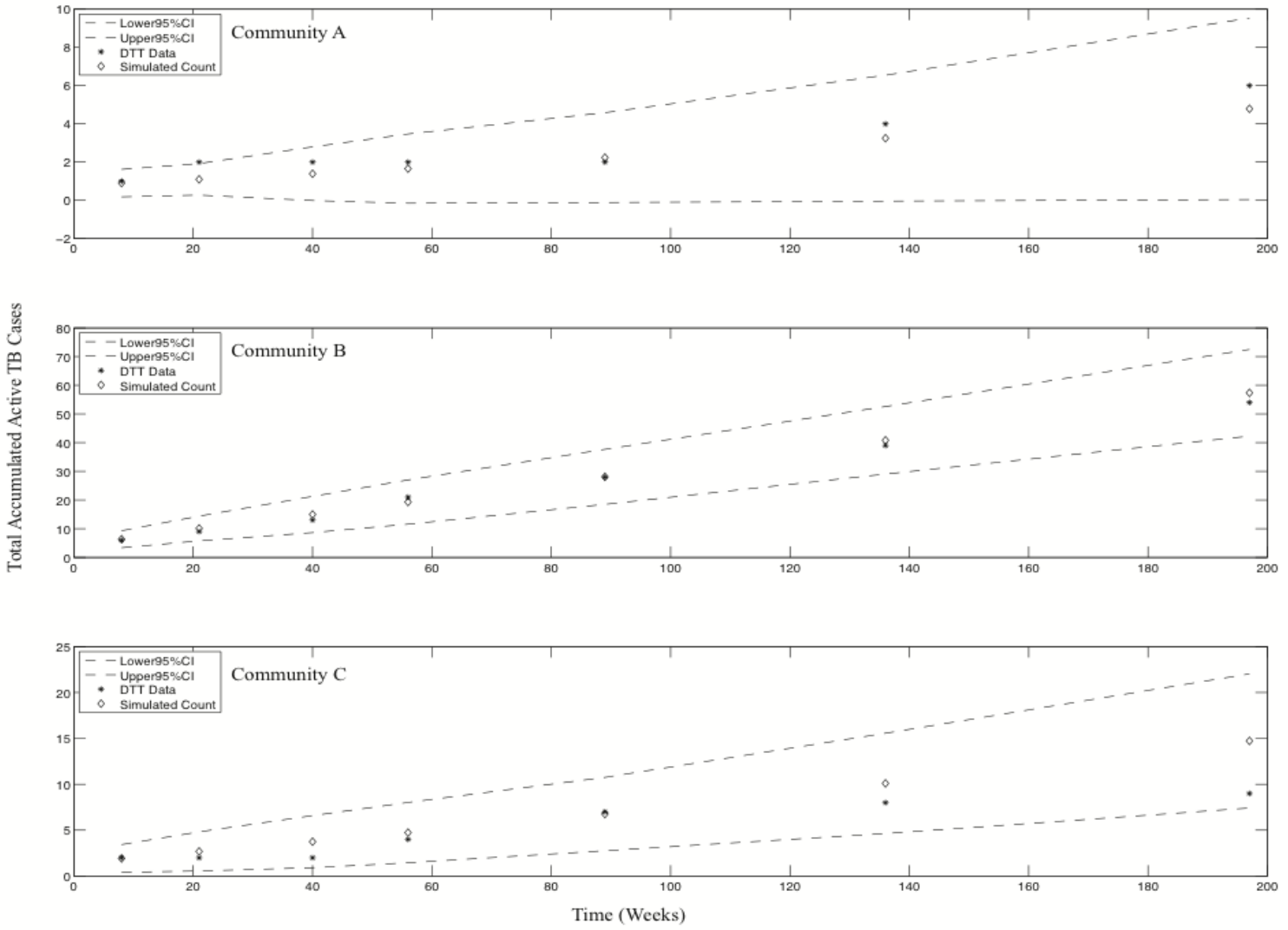

Figure 6b. 1 A 95% confidence interval of accumulated total active TB cases after 500 TB-ABM replications (Statistical Model 1) at baseline predicting to T=200 weeks (~years) between 2007 and 2010 (denoted by the diagonal marker). The background DTT data (2007-2008), denoted by filled circles was used to compare to simulated results

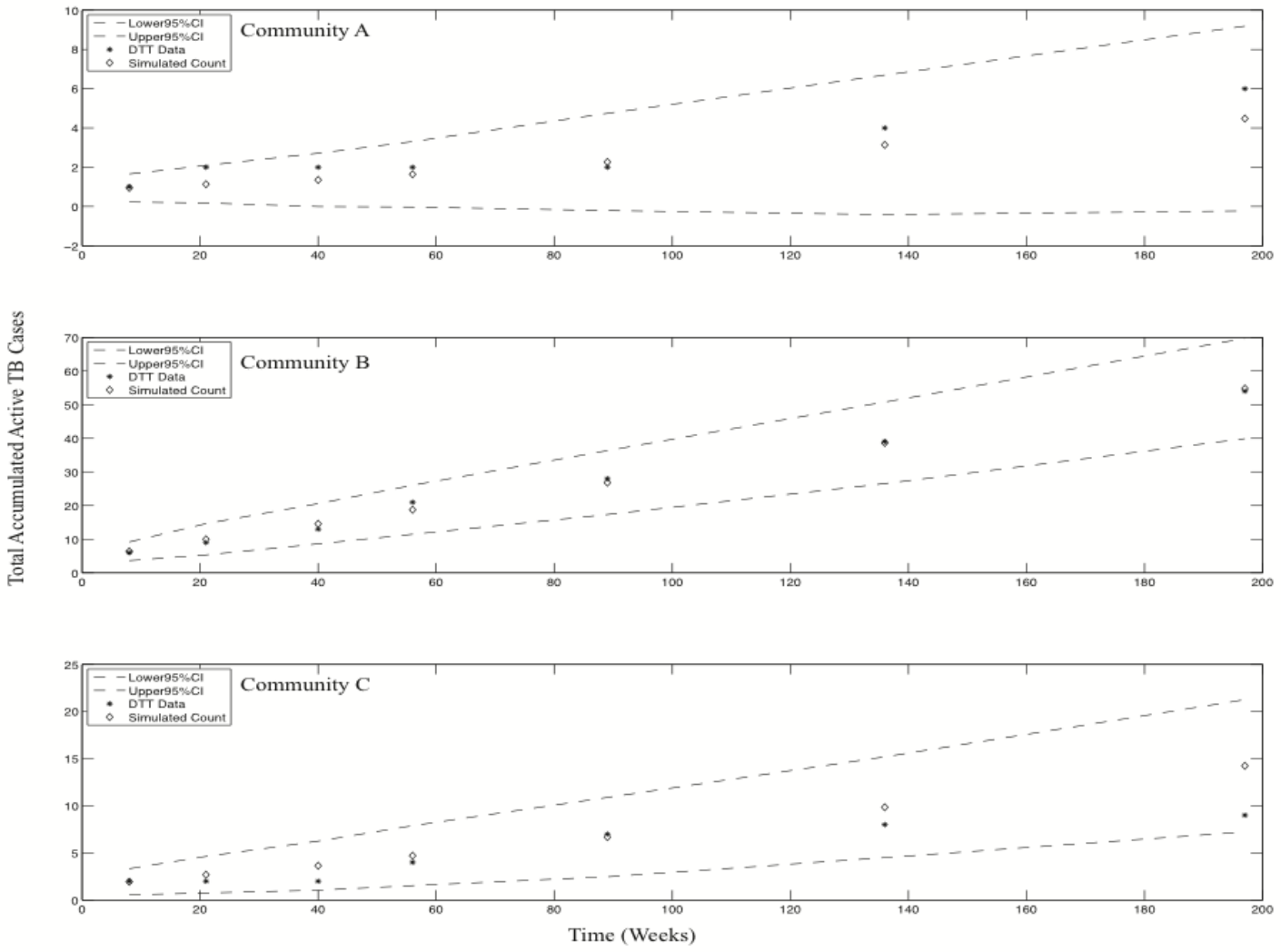

Figure 6b. 2 A 95% confidence interval of accumulated total active TB cases after 500 TB-ABM replications (Statistical Model 2) at baseline predicting to T=200 weeks (~4 years) between 2007 and 2010 (denoted by diagonal marker). The background DTT data (2007-2010), denoted by filled circles was used to compare to simulated results

Chapter 7: Conclusion

The distribution of tuberculosis (TB) cases in Canada is disproportionately higher in the foreign-born and among Indigenous peoples. Incidence rates of TB in the Indigenous population have decreased minimally since the 1990s. The added challenge of on-going transmission among Indigenous peoples in high incidence communities contributes to the persistence of TB. The social determinants of health (SDOH) represents underlying risk factors that make the goal of TB reduction and elimination in these communities challenging.

This dissertation utilized the data gathered from the seven-year, CIHR and Health Canada co-funded, *Determinants of Tuberculosis Transmission (DTT) Project,* which included quantitative questionnaires of all culture positive pulmonary TB cases in the Canadian-born (>14 years old) between 2007 and 2008 in Alberta, Saskatchewan, and Manitoba. In addition, background TB cases between 2006 and 2010 were genotyped using 24-loci MIRU (Mycobacterial Interspersed Repetitive Units). The data from these two sources were instrumental throughout this thesis.

The analysis conducted in Chapter 4 showed that clustering was highest among First Nations and Métis peoples, on-reserve communities, and living in the north (above the 53rd parallel). Evidence of clustering supports the idea that on-going transmission continues to be a major issue in these communities. Time to treatment, defined as the duration between the onset of symptoms and start date of treatment (analogous to total delay) was used as a measure of the transmission period. A systematic review whose results were described in Chapter 3 reports the results of delay in diagnosis studies conducted worldwide among Indigenous peoples. The analysis of 11 studies highlighted that delay in diagnosis estimates were highly variable, but were

generally comparable or higher in Indigenous compared to non-Indigenous peoples. Of these 11 studies, only one was conducted in Canada. This outbreak study was published as a result of a contact investigation and it estimated a time to diagnosis of 120 days.

Using the quantitative questionnaires from the DTT project, a logistic regression analysis was conducted in Chapter 5 to determine risk factors significantly associated with time to treatment. The definition of time to treatment in this analysis was further fine-tuned and defined as the duration between the onset of cough and the start date of treatment to better describe the period where transmission could occur. The outcome, time to treatment, was dichotomized based on the median value in the DTT data, which was 30 days. The analysis focused solely on Indigenous peoples who made up 90% of the total Canadian-born TB cases between 2007 and 2008. Risk factors associated with delayed time to treatment (>30 days) included having concomitant health problems, a regular family doctor, no working x-ray machine and technician in a community, and a non-Indigenous mother tongue. Risk factors associated with timely treatment (≤ 30 days) included increased household size. The increased odds of delayed time to treatment was associated with having a regular family doctor highlighted the challenges in describing healthcare access in Indigenous communities. The possibility of having a regular family physician that visited Indigenous communities infrequently such as weekly, biweekly, and monthly was suggestive of additional barriers to healthcare access. Overall, this chapter fills a gap in literature about time to treatment among Indigenous peoples across the Canadian Prairie Provinces.

The recognition that persistence of TB driven by on-going transmission associated with time to treatment whose risk factors included SDOH motivated the research objectives of this thesis. There have been many deterministic and stochastic models conducted in Canada about TB transmission dynamics, some also focused on Indigenous peoples. However, these studies used

univariate associations or assumed constants (based on epidemiological knowledge) that were applied to specific parameters in a mathematical model. Although these approaches provided insight into TB transmission dynamics, the interactions between multiple simultaneous risk factors (such as SDOH) significant to TB transmission (and progression) and TB cases are challenging to describe and quantify. In this thesis, an approach for integrating SDOH into a mathematical model was developed. Instead of using univariate relationships (described previously), a multivariable relationship was integrated into an agent based model (ABM). This represents an extension of previous methods that aimed to include SDOH into mathematical modeling.

The DTT data was a unique and extensive project that allowed for the possibility of constructing multivariate relationships and estimating model parameters that was used in the ABM of this dissertation. In Chapter 6: Part 1, the construction of an ABM about TB transmission (TB-ABM) in three high incidence First Nations and Métis communities in northern Alberta and Saskatchewan was described and validated using the DTT data. A unique feature of this TB-ABM was the use of a multivariate relationship between time to treatment and significant risk factors found in Chapter 5. A multivariable linear regression model was constructed to allow for a continuous outcome that could predict the time to treatment (in weeks) based on individual attributes. This prediction occurred among individuals who had active TB during a simulation. Parameter calibrations were used to estimate birth and death probability, the probability of TB transmission, progression, initial latent TB, and reduction factors for TB transmission based on contact types (close non-household/casual). The TB-ABM was shown to perform well to predict baseline scenarios for the two years between 2007 and 2008, which aligned within the study period of the DTT project.

In Chapter 6: Part 2, three control strategies were simulated using the TB-ABM that impacted the determinants of health (including SDOH) and LTBI prevalence. These included reduction in comorbidities, improvement of healthcare access, and a LTBI screening and treating strategy. A second multivariable linear regression model was constructed that focused on Indigenous peoples in northern (above the 53rd parallel) Alberta and Saskatchewan reflective of the geographical location of the TB-ABM. In this secondary multivariate model, healthcare access was a significant predictor. Healthcare access was defined as the location persons first sought care for their TB symptoms (within/outside the community). The impact of interventions on TB cases (active and latent (L_f)) and transmission was based on a five-year prediction. Overall conclusions were that in high incidence communities, the first step to TB reduction would be a LTBI screening and treating strategy. However, long-term strategies that improve the SDOH such as healthcare access can directly reduce transmission important for decreasing TB in high burden Indigenous communities.

The use of the DTT data in this dissertation showed that enhanced TB surveillance could be conducted successfully and the information gathered would be important for parameter estimations in mathematical models, which can provide insight into reductions in TB cases and incidence based on intervention analysis. In addition, the continued need for enhanced TB surveillance across the Prairies is important considering the evidence of on-going transmission and the potential mobility of strains across the Prairies Provinces (Chapter 4). Risk factors associated with time to treatment (Chapter 5) were integrated successfully into an ABM (Chapter 6: Part 1). Overall the use of mathematical modeling provided insights and numerical evidence of impacts risk factors (DOH and SDOH) can have on TB cases and transmission among First Nations and Métis peoples across the Prairies (Chapter 6: Part 2). The TB policy implication of using this methodology is providing evidence to decision makers on questions that generally have

limited numerical evidence. For example, providing estimates about reductions in TB cases and incidence to changes in SDOH (e.g. healthcare access). The applicability of this proposed method to other infectious diseases similar to TB is possible given the availability of data.

Most importantly, the three high TB incidence First Nations and Métis communities modeled in this dissertation totaled approximately 3500 people. The high burden of TB in these communities continues to be evident (at present). Reducing TB burden in these high incidence communities is possible (based on TB-ABM simulations), and especially when considering the small populations. Engagement of stakeholders involved with the DTT project would be included in future steps to determine if these potential interventions would be feasible. The next steps thereafter would involve determining if communities included in this dissertation would be interested in these proposed interventions.

Other future directions pertaining directly to this dissertation and the TB-ABM are listed below:

7.1 Future Directions

- Require routine reporting of time to treatment for individuals in TB programs
- Conduct a cost-effectiveness analysis on interventions that would increase healthcare access and screen and treat for latent TB infection
- Include preferential mixing into the TB-ABM to determine if differences in baseline results occurs
- Modify the TB compartment to split individuals that were recently infected with TB within two years and between three to five years to better reflect rates of progression from latent to active TB

- Modify the TB contact investigation process to determine if adding this complexity makes an overall difference in baseline results. The modification would include a more representative concentric approach i.e. one that targets children and persons at high risk for progression. In addition, the contact investigation would occur over a period of a few weeks.
- Investigate the impacts to TB cases (active and latent) and transmission from intervening on parameters that relate to contact investigations such as loss to follow-up
- Assessing different approaches to contact investigations to determine if plausible modifications could improve its overall effectiveness
- Investigate the effect on mobility on TB cases and transmission. Current estimations on mobility may be overestimated
- Investigate the impacts on TB cases and transmission with age dependent approaches to control strategies presented in this dissertation
- Introduce the possibility of resistance among those that accept and do not complete treatment. Investigate the long-term implications of drug resistance with conducting a LTBI screening and treating strategy
- Conduct a spatial-temporal analysis using the fingerprinting data from the DTT project to determine significant clusters over time across the Prairies

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