The Characteristics of Tuberculosis Transmission in the Indigenous people of the Canadian Prairies

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Abstract

Tuberculosis (TB) incidence in the Indigenous people of Canada continues to be disproportionately higher than that of the non-Indigenous and foreign-born people. For more than a decade, the rate of TB in the Indigenous people of Canada has remained relatively constant despite recent population growth. Most researchers have speculated that demographic and geographic risk factors along with the colonially and historically rooted poor social circumstances are associated with the ongoing transmission in the Indigenous people, thus raising concerns for TB control efforts.

This thesis combined conventional and molecular DNA fingerprinting of *Mycobacterium tuberculosis* isolates to *(1) identify and describe the demographic and geographic characteristics of all transmission events from Canadian-born pulmonary TB cases on the Prairie Provinces in 2007 and 2008;* and *(2) describe the predictors of new infection and secondary cases based on host, environmental, and behavioral characteristics of the transmitters*.

We found that transmission was most common from Registered First Nations potential transmitters who resided in reserve communities. Recent infection was slightly higher in contacts with reportedly lower exposure to the transmitter, but active disease was most notable in the infected close contacts. A significant proportion of transmission events suggested extensive geographic mobility between the residence of transmitters and their contacts, which poses a considerable challenge to jurisdictionally contain TB transmission. Upon further investigation, the likelihood of observing a transmission event was significantly greater in transmitters with advanced stages of pulmonary disease and in those that resided in households with poor ventilation.

In light of these findings, it is clear that provincial TB control programs must strive to prioritize the demographic, geographic, clinical, and social determinants in the Indigenous people of the Prairies. Collaborative effort of healthcare workers, educators, and community leaders is required to disrupt the chain of transmission in this population group, whilst acknowledging traditional Indigenous values.

Preface

Ethics Approval

This thesis is an original work completed by Smit Patel. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Determinants of Tuberculosis Transmission", Approval# Pro00003492, Date: September 2006. Approval of this study was also received from Saskatchewan (Behavioral Research Ethics Board), Manitoba (Health Research Ethics Board) and Health Canada. Additionally, informal approvals were received from First Nations and Inuit Health Branch (FNIHB) Headquarters and the Assembly of First Nations. TB Registry access agreements were established between the University of Alberta and Manitoba Health and Healthy Living (MHHL), and including various sub-contracts between the University of Alberta, University of Saskatchewan, and University of Manitoba. For the purpose of this thesis, the Indigenous peoples were defined according to the Constitution Act of 1982 as Registered (Status) and now Registered First Nations, Métis, and Inuit.

Collaborators

The research conducted for this thesis was in the context of Prairie-wide research collaboration, led by Dr. Richard Long (MD, FRCPC, FCCP) at the University of Alberta with Dr. Vern Hoeppner being the lead collaborator for Saskatchewan and Pam Orr and Martha Ainslie for Manitoba respectively. Other members of the scientific team included Dr. Dennis Kunimoto, Dr. Sylvia Abonyi, Dr. Maria Mayan, and Dr. Dick Menzies. The project was supported by grants from the Canadian Institutes of Health Research, the First Nations and Inuit Health Branch of Health Canada, and the University Hospital Foundation. I have designed the methodological and statistical tools referred in Chapters 3 and Chapter 4 and with the assistance and collaboration of Tuberculosis Program Evaluation & Research Unit (Principal Investigator: Dr. Richard Long and Project Manager: Courtney Heffernan) and the School of Public Health (Dr. L. Duncan Saunders and Dr. A. Senthilselvan. Chapter 3 and 4 are based on the manuscript jointly with Dr. Richard Long (MD, FRCPC, FCCP), Dr. L. Duncan Saunders (MBBCH, PhD), Dr. A Senthilselvan (PhD), and Courtney Heffernan (MA). Chapter 2 and 5 are my original work.

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List of Abbreviations

AFB	Acid-fast bacteria (bacilli)
AIDS	Acquired Immune deficiency Syndrome
BCG	Bacille Calmette-Guérin
CCI	Conventional contact investigation
CI	Confidence Interval
DNA	Deoxyribonucleic acid
DOTS	Directly observed therapy-short course
EMB	Ethambutol
GIS	Geographic Information System
HIV	Human Immunodeficiency virus
INH	Isoniazid
IS6110-RFLP	Insertion Sequence 6110-Restriction fragment length polymorphism
LTBI	Latent tuberculosis infection
MIRU-VNTR	Mycobacterium interspersed repetitive units-Variable number tandem repeats
MTB	*Mycobacterium tuberculosis*
MTBC	*Mycobacterium tuberculosis* complex
OR	Odds Ratio
PTB	Pulmonary tuberculosis

PZA	Pyrazinamide

List of Abbreviations (CONT'D)

RMP	Rifampin
SNA	Social Network Analysis
SNP	Single-nucleotide polymorphism
TB	Tuberculosis
TST	Tuberculin skin test
WHO	World Health Organization
WGS	Whole genome sequencing

CHAPTER 1. INTRODUCTION

1.1 Tuberculosis Disparity

Despite the overall decline in annual cases in Canada, the incidence of tuberculosis (TB) is approximately 25 times higher in the Indigenous population than that in the non-Indigenous people (1-5). The Indigenous peoples account for less than 5% of the total Canadian population yet represent well over 50% of all Canadian-born cases, thus pressuring TB control workers and community leaders to provide more effective interventions for interruption of transmission and prevention of disease in those already infected (3). It is known that low socio-economic status (e.g. overcrowding and malnutrition) and high-risk behaviors (e.g. substance abuse and tobacco smoking) are common many Indigenous communities, but the impact of these social and behavioral factors on transmission of TB has yet to be defined in light of new medical discoveries and social policies (6-10).

1.2 Demographic and Geographic Context

The Canadian Prairies include the provinces of Alberta, Saskatchewan, and Manitoba. Together these provinces report a disproportionate number of Canadian-born TB cases (5). Over the previous decade, these provinces have experienced rapid population growth, a result of significant economic progress and greater job opportunities. With a combined population of 5.3 million and a median age of 37 years, Canadian-born persons represented approximately 86% of the total population in the Prairies in 2006. The proportion of the total population that was First Nations, Métis, and Inuit was 6.3%, 4.4%, and <1%, respectively (11). For the purpose of the following analyses, the communities on the prairies were grouped into four major types characterized by the composition of the population group and density. These communities included the major metropolitan, non-major metropolitan, First Nations reserve communities, and Métis Settlements (northern villages).

1.3 Knowledge Gaps

While it is known that the burden of TB is disparate within the Canadian-born population, the characteristics of individuals involved in TB transmission events have not been

investigated in great detail. The use of both molecular and conventional epidemiologic tools is necessary to fully understand the complexity of TB transmission. The goal of this study is to investigate the role of demographic, geographic, clinical, and social characteristics in TB transmission activity on the Prairies.

1.4 Study Objectives

This study is undertaken in the context of a larger Canadian Institutes of Health Research (CIHR) and Health Canada funded research project, *The Determinants of Tuberculosis Transmission (DTT)* initiated in 2006 (8). The study describes the distribution and relationship between pulmonary TB cases in the Canadian-born population of the Prairies. Two sequential research objectives followed by related research questions have been developed to address gaps in TB control program and identify avenues for improvement. The first objective identifies and characterizes potential TB transmitters, their secondary cases, and infected contacts, in order to understand "to whom" and "from whom" transmission is occurring in the Prairies. The second objective compares the characteristics of potential transmitters who did or did not have transmission events. Together, these epidemiological studies are aimed at gaining greater evidence of the determinants of TB transmission on the Prairies.

Objective#1

To identify and describe the characteristics of Canadian-born potential TB transmitters diagnosed on the prairies in 2007 and 2008 and their transmission events

Research Question #1

What are the clinical characteristics of Canadian-born adult culture-positive pulmonary cases (potential TB transmitters) diagnosed in 2007 and 2008 on the Prairies?

Research Question #2

What is the distribution by age, sex, population group, and community of residence of the potential TB transmitters, their reported contacts, and their newly infected contacts?

Research Question #3

Is there an association between population group, community of residence, and distance of transmitter and infected contacts on the Prairies?

Objective #2

To identify risk factors for TB transmission among Indigenous potential transmitters in 2007 and 2008.

Research Question #1

Do host, environmental, and behavioral factors predict whether an adult Canadian-born Indigenous potential transmitter is responsible for transmission events?

1.5 Structure of Thesis

This thesis consists of a literature review followed by two studies describing the transmission characteristics of TB in the Indigenous peoples on the Prairies. The literature review (Chapter 2) will describe the current knowledge of tuberculosis epidemiology in Canada with emphasis on Indigenous peoples followed by a description of current methodologies that are commonly used to identify and measure transmission. A descriptive study aimed at quantifying and characterizing transmission events will follow the literature review (Chapter 3). Potential transmitters will be further investigated to describe the likelihood of transmission (Chapter 4). The significance, limitations, and recommendations gleaned from these studies will be addressed in a final discussion (Chapter 5).

Chapter 2: LITERATURE REVIEW

2.1 Epidemiology of Tuberculosis in Canada

Mycobacterium tuberculosis (MTB), the causative agent of tuberculosis (TB) disease is one of the oldest and most persistent pathogens in Canada. Its prevalence in the marginalized communities along with the growing foreign-born population can be attributed to its complex natural history and ability to exploit weakness in the socio-economic development of its host. Reports dating back to the early 20th century suggest that TB claimed 8% of all deaths in Canada, surpassing the number of deaths caused by cancer (1, 2). This significant morbidity and mortality in Canada and elsewhere spurred numerous scientific and technological advances to improve the standard of prevention, detection, and treatment of TB. All provinces and territories in Canada now report new active and re-treatment cases of TB to the Canadian Tuberculosis Reporting System (CTBRS), a national surveillance system managed by Public Health Agency of Canada (PHAC). The CTBRS includes demographic and clinical information on cases meeting the Canadian case definition regardless of population group (Canadian-born or Foreign-born) (1,3).

2.1.1 TB in the Foreign-born

According to the most recent report published by PHAC, foreign-born persons account for 66% of the Canadian TB burden and are most commonly reported in the immigrant-receiving provinces of British Columbia, Alberta, Ontario, and Quebec (1,3). The increasing proportion of TB cases in Canada that are foreign-born reflects the immigration from high-incidence countries over the past 50 to 60 years (4,5). Between 1970 and 2007, the proportion of the Canadian population that is foreign-born increased approximately 15% to 20% (5).

Like many immigrant-receiving countries, recent immigration from high-incidence regions has introduced multi-drug resistance TB (MDR-TB) into Canada with potentially serious clinical and public health implications (3,6-8). MDR-TB is defined as TB disease caused by MTB strains resistant to the most common first line drugs, isoniazid (INH) and rifampin (RMP). It requires the use of second line anti-tuberculosis drugs to be administered to the affected patient over a lengthy time period. The prompt diagnosis and effective treatment of MDR-TB is important to

prevent the spread of resistant strains (9-14). Despite a global increase in drug resistant TB and continued high immigration into Canada from high incidence countries, MDR-TB comprises les than 1% of reported cases in Canada and is currently not a major concern (3).

2.1.2 TB in Canadian-born Population

The burden and incidence of TB in the Canadian-born has decreased since the availability of effective antibiotic treatments and improvements in socio-economic conditions over the last century (8). Between 1970 and 2007, the number of TB cases in Canadian-born non-Indigenous people had decreased by 95% reaching near elimination status (0.7 non-Indigenous cases per 100,000) in 2007 (1,3). Unfortunately, progress in the Indigenous population has not kept pace with progress in the non-Indigenous population and TB still remains a major concern in the Canadian-born Indigenous peoples (Registered Indian, non-Registered Indian, Métis, and Inuit) and their communities. The incidence rate in this population remained constant despite overall improvements in living conditions and treatment in Canada (1, 15). In 2007, the incidence rate (26 cases per 100,000) in the Indigenous population was 37 times higher than the non-Indigenous and 2 times higher than the foreign-born population (1,3). Of the Indigenous people, the Inuit had the highest rate of disease in 2007 (84 cases per 100,000). Registered Indian persons represented the majority (1,3) of the Indigenous TB cases and the second highest rate of disease in 2007 (1,3)(Appendix A).

2.1.3 Geographic Distribution of TB

The geographic distribution of TB in Canada is related to the distribution of high-risk population groups. The majority of TB cases were reported in the foreign-born persons residing in major metropolitan areas of Western (British Columbia, Alberta, Saskatchewan, Manitoba) and Central (Ontario and Quebec) Canada (8-10). TB cases tend to be concentrated in selected Indigenous communities of Saskatchewan, Manitoba, Quebec and the Territory of Nunavut and the poorer areas of major metropolitan communities. Within the Indigenous population, there is significant disparity in the provincial distribution of TB. Although the Inuit people residing in Northern communities comprise only 15% of all Indigenous cases and less than 5% of the Indigenous population, their rate of disease in 2007 was remarkably 6 times higher than in the

Registered Indian population (1,3,16). The majority of the Indigenous TB cases in 2007 resided in Saskatchewan and Manitoba where their rate of disease was 50 times higher than in the non-Indigenous population. In Atlantic Canada, the burden of TB is substantially lower primarily due to smaller population size of the Indigenous and foreign-born people (1,3).

2.2 Tuberculosis Disease, Transmission and Risk Factors

2.2.1 Microbiology of TB

The discovery of MTB by the German physician, Robert Koch in 1882 was a major step in understanding this deadly disease (17). MTB is part of a larger family of tuberculosis-causing pathogens referred to as the Mycobacterium Tuberculosis Complex (MTBC) comprising of *Mycobacterium canetti*, *Mycobacterium bovis, Mycobacterium africanum, Mycobacterium caprae, Mycobacterium microti,* and *Mycobacterium pinnipedii* (1,18). Unlike most bacteria, Mycobacteria *spp.* has a unique cell wall structure consisting of waxy mycolic acid layer which is identified microscopically using Ziehl-Neelsen or auramine-based staining (19). MTB targets the lungs of its hosts due to higher concentration of oxygen required for growth. Pulmonary TB (PTB) is the most common disease site, accounting for approximately 80% of all Canadian-born cases (1,3). In pulmonary cases, MTB can be transmitted in aerosols created primarily by coughing or sneezing. Once aerosolized, MTB can remain suspended in indoor air currents for prolonged period increasing the risk of transmission to susceptible contacts by inhalation (20,21). Extra-pulmonary TB is less common and often occurs in those with immune compromising conditions. In such conditions, there may be clinical implications for diagnosis rather than public health urgency (22,23).

2.2.2 Natural History of TB

Some of the challenges in TB elimination relate to the natural history of MTB and its pathogenic mechanisms. TB is characterized by a non-infectious dormant period known as latent tuberculosis infection (LTBI) followed by an active disease stage. A new infection can occur if a susceptible individual is exposed to an infectious case, typically occurring after frequent and prolonged contact. Once the infectious droplets are inhaled, MTB is able to effectively replicate inside alveolar macrophages, stimulating the cell-mediated and delayed

type hypersensitivity response. In early stages of latent infection, the cell-mediated immunity assists the formation of granuloma consisting of immune cells that are designed to wall-off and prevent the spread of infection (24-27). In immunocompetent individuals, cell-mediate immunity is usually sufficient to contain further growth of MTB and prevent the progression to disease. Approximately 90% of newly infected contacts of an infectious case remain infected for a lifetime without ever developing active disease. The lifetime risk for overt disease is approximately 10% of which one-half of all cases are likely to develop within 18 to 24 months of infection. The establishment of disease during these months is commonly referred to as primary TB disease and disease that occurs thereafter is considered to be post-primary (1,28). Earlier progression to disease is known to occur frequently in those with weakened cell-mediated immunity (for example young children and the HIV co-infected) (29-35). The prolonged latency and slow progression to active disease is characteristic to tuberculosis and represent challenges to TB control and elimination efforts.

2.2.3 TB Transmission

Although infectiousness varies by case, the main determinants of infectiousness are AFB-Smear positive (>5000 bacteria cells/mL) status, cough, and cavitation on chest radiography. Advanced disease is usually associated with an increased likelihood of transmission due to the higher concentration of MTB in the respiratory secretions. Once aerosolized, infectious droplets evaporate down to microscopic droplet nuclei (1-5µm). Each aerosolized droplet contains an estimated 1-3 MTB organisms. Despite the well-understood association between smear positivity and infectiousness, new research has now provided evidence that the measurement of cough aerosols maybe a more discriminative approach for describing the probability of transmission than AFB-smear-positivity alone. A study conducted by Fennelly et *al* had reported considerable heterogeneity of infectiousness between smear positive PTB patients, a finding consistent with earlier animal studies. Patients that were capable of producing well-aerosolized droplets (≤ 5µm/droplet, falling rate of 0.5mm/sec) were most likely to transmit compared to those that did not produce an effective aerosol (36-40). The higher infectiousness associated with cavitations is possibly linked with the liquefaction

process (i.e. degradation of the granuloma) consequently increasing the growth and mobilization MTB into the bronchial airways prior to expulsion (36,37).

2.2.4 Determinants of TB Infection and Disease

The proximity of the infectious case and their contacts are thought to affect the likelihood of infection and disease. It is well understood that close contacts of an infectious smear-positive PTB case are at higher risk for infection due to more frequent exposure and duration compared to casual or community contacts (41,42). Observational studies indicate that transmission of MTB from smear-positive patients in close contacts was approximately 3 times more likely than in casual contacts (41). Within the first 18 to 24 months of the initial infection, each subsequent exposure carries an independent risk for disease (1,43).

Direct and indirect determinants of TB transmission and disease are mostly dependent upon host and environmental characteristics of the population at risk. Although the intrinsic characteristics of MTB were hypothesized to play a role in increased infectivity, majority of research has been focused on understanding host and environmental factors affecting transmission and disease. Typically those <5 years of age and immunocompramised contacts are at highest risk for disease. Although transmission from children is less likely, they are at high risk for severe disseminated disease after infection. In the Canadian-born population, PTB is most common in adults between 15-64 years of age with greatest risk of disease in males (1,3,44). The linkage between genetic risk factors and the risk of TB disease have also been studied to some extent. Vitamin D supplementation for otherwise healthy individuals is suggested to have a protective effect by enhancing cellular immunity against the infection (45). This evidence is supported by several human and animal molecular studies that identified that single nucleotide polymorphisms in the Vitamin D receptor gene expression pathway increases the risk for TB infection, symptoms, and severity (46-47).

The upstream determinants of TB such as low socio-economic status, insufficient education, and poor heath seeking behaviors suggests weaknesses in the current social, environmental, and economic policies. Some of these determinants play a role in increasing the frequency and duration of exposure while others promote risk for active disease (1,48-50). Contacts of an

infectious case residing in overcrowded and poorly ventilated households are of increased risk for inhalation of MTB droplets and subsequent infection. Remote communities, inner-city neighborhoods, and homeless shelters in Canada are known to be associated with outbreaks due to higher prevalence of PTB patients and inadequate ventilation (49, 51). Co-existing Immunosuppressive conditions such as HIV-AIDS, diabetes, malnutrition and behaviors such as substance abuse, and tobacco smoking diminish the immune system's ability to contain the primary infection, thus leading to much faster progression to active disease. Although transmission in these patients have not been reported to be significantly different than otherwise healthier patients, the potential consequences of TB disease are far more serious (48-54).

2.3 TB in the Indigenous population

2.3.1 Global Indigenous TB Burden

Global studies have documented that the incidence and prevalence of TB is disproportionately higher in the indigenous population, which comprise just fewer than 5% of the global population and 15% of the world's poorest. (55) The most recent systematic review has identified the occurrence of TB in countries with well-known indigenous groups based on a collection of epidemiological records. Of those that reported, the high-density communities of India and remote regions of Latin America were identified to have the highest incidence rate in 2008 (55). In high-income countries of Canada, United States, Australia, and New Zealand, the rate of TB was observed to be relatively lower. Thus far, TB remains most problematic and rampant in the Inuit people of Canada of which the incidence of disease was 150 times higher than their Canadian-born non-Indigenous counterparts followed by the First Nations (Status and Non-status Indian) people in 2009. Despite the marked differences between indigenous groups across the globe, most are affected by similar socio-economic circumstances, poor health outcomes, and increased risk for TB. Compared to the non-indigenous population, the indigenous people are less likely to have access to the adequate housing, education, and medical treatment and more likely associated with unemployment, poverty, overcrowding, and co-morbidity (56-58). These complex social and clinical determinants must be addressed at a national and regional level in order to decrease the current burden of TB in the indigenous.

2.3.2 Canadian-born Indigenous TB

TB in the Canadian-born Indigenous people is often depicted as a "tip of the ice-berg" issue with deeper historical, cultural, and socio-economic factors at play. TB disease by the Mycobacteria complex existed in the western world long before the arrival of the "Old World" European settlers. The earliest molecular evidence of TB in North America was discovered in ancient Peruvian remains dating from 900 AD (56). Despite the endemicity of TB, the Indigenous people in the North American continent represented a thriving population of some 20 million persons prior to the European contact. Remarkably, in the first few centuries of colonial expansion, the Indigenous population is understood by scholars to have plummeted by approximately 95% (56). Most scholars suspect that this sudden decrease was attributable to the introduction of new infectious diseases including TB in conjunction with the rapid socio-cultural and environmental changes attendant upon the arrival of the European settlers (1,56). Such changes would ultimately lead to the historic Canadian TB epidemic in the late 19th century (1,59,60).

Canadian-Indigenous people are identified as the First Nations, Métis, and the Inuit as defined in the Canadian Constitution. Approximately 81% of the First Nations populations are officially registered as Indian according the *Indian Act of 1876,* and referred to as the Registered Indian or Status Indian people (61,62). The active nomadic Indigenous life that once flourished prior to the European contact was quickly shifted into a sedentary lifestyle marked by discrimination and persecution by the colonial powers. The demand for cultural integration by means of residential schools and the movement into reserve communities had an enormously detrimental effect on the mental, physical, and socio-economic well being of the Indigenous people (1, 63-65).

Based on historical documentation and research, the social determinants of TB disease appeared to have been much more influential in the disparity of TB in the Indigenous population than biomedical factors alone (66). The First Nations and Inuit people are often plagued by poverty associated with substandard housing conditions, insufficient education, and high risk behaviors (ie. substance abuse, alcoholism). In reserve communities, the First Nations people have inconvenient access to regular medical treatment as a result of their geographic

isolation. Similarly, in off-reserve communities, the Registered Indian people are more likely to reside in communities linked to urban poverty compared to the non-Indigenous people. The access to better housing conditions has often been limited due to discrimination and coercion from urban landlords (67). The Inuit, who account for the minority of the Indigenous population in Canada, are further stricken by a higher prevalence of HIV-AIDS and diabetes mellitus thus increasing the risk for TB reactivation and subsequent transmission (66,69,70). These social and geographic barriers in addition to poor lifestyle choices and underlying disease establish a contextual framework for ongoing TB transmission.

Historically, close interaction between the First Nations people and European Settlers often resulted in intermarriage. The succeeding generations that were self-identified as mixed Indigenous-European ancestry and recognized as having a unique set of socio-cultural values were referred to as the Métis people (71). Although the burden of TB is significantly less in the Métis compared to the Registered Indian population, selected Métis communities have experienced an ongoing high incidence of TB associated with similar historically-seeded social factors such as institutional discrimination and geographical isolation from major-metropolitan areas (71).

2.4 Canadian TB control

The federal, provincial, and territorial governments are responsible for TB control and prevention in Canada (72). The responsibilities of the federal government include overseeing and reporting the trends and the general direction for TB control in the country and providing a framework for TB prevention and control. The First Nations and Inuit Health Branch of Health Canada has a more immediate responsibility for TB control in reserve communities. The actual delivery of TB services is managed provincially and territorially based on the availability of resources, funding, and the specific needs of the community. In all levels of government, the three major domains of TB control include TB prevention, diagnosis, and treatment (72). Strategies that advance these areas of control are an essential step towards the goal of Canada-wide TB elimination.

2.4.1 Prevention of TB

Although upstream social, environmental, and demographic determinants have a profound effect on transmission and disease, population group targeted vaccination has also played a substantial role in lessening the risk for TB. The Bacille Calmette-Guérin (BCG) vaccine is currently the only available vaccine against TB. BCG-vaccine consists of a live attenuated strain of *M. bovis* developed by the Pasteur Institute in Paris, France in 1921 (1). In Canada, BCG is not routinely implemented across all population groups but is instead administered selectively to Inuit and on-reserve First Nation children. Vaccination is most effective at infancy (age <1 year) to prevent the severe forms of primary TB (i.e. miliary TB and TB meningitis). BCG efficacy is reported to vary considerably, with some studies reporting 50 and 80% efficacy for preventing the risk of reactivated and disseminated disease respectively (73-75). Moreover, the protective effects of the vaccine is known to wane over time after administration at infancy, showing significantly less protection after 10 years of age (76).

Prior to the discovery of effective antibiotic treatments, individuals with TB disease were often relocated to sanatorium facilities across Canada. TB sanatoria were constructed in the late 19th century to segregate those with disease from those without and to provide rest, and nutrition. Despite this attempt limit TB transmission and provide support, sanatorium experiences had its negative aspects. Patients were separated from their families and communities for long periods of time resulting in emotional distress and disease exacerbation. Additionally, a significant proportion of these patients have undergone invasive surgical procedures, which may have contributed more to the patient's suffering than genuine cure (77). From the 1940s onward, an increasing proportion of the patients were of Indigenous ancestry. Similar to residence schools, the Registered Indian and Inuit people were forcibly institutionalized in sanatoria facing language barriers, new diets, and unfamiliar culture contributing to the feelings of distrust and fear of modern medicine in the future (78).

In the 1950s the first multidrug treatment regimen were made available. Those identified with latent infection with high risk for active disease due to underlying co-morbidities (ex. HIV co-infection, diabetes, kidney disease, and immunosuppressive medication), began to

be offered prophylactic treatment using isoniazid (INH) and or rifampin (RMP) (1). Although the acceptance of TB prophylaxis is not mandated in Canada, it is strongly recommended to prevent the disease reactivation and disrupt the chains of on-going transmission.

2.4.2 Detection and diagnosis of Pulmonary TB

Timely diagnosis of TB infection and disease is central to Canadian TB control and the Stop TB strategy recognized by the WHO (79). In order to prevent disease progression and disrupt transmission, TB must be diagnosed promptly. LTBI is most commonly diagnosed using an intradermal injection of a purified protein derivative (PPD) referred to as the Mantoux technique (alternatively known as the tuberculin skin test or TST). This screening procedure is the gold standard test routinely implemented in contact tracing investigations and across most demographics exposed to MTB (79). In most cases, a single positive reaction (≥5mm induration) in contacts is considered indicative of latent infection (1). Among the general population, the sensitivity and specificity of the Mantoux test is approximately 75% to 89% and 85% to 95% respectively (80). Compared to unvaccinated healthy patients, the specificity and sensitivity of BCG vaccinated and immunocompromised patients is low respectively. Furthermore, a false positive TST is common in young children within 10 years of BCG vaccination if vaccinated during infancy (< 1 year) and in older children and adults who are vaccinated after infancy (76). The Interferon Gamma Release Assay (IGRA) is an alternative screening method targeted to specific Canadian-born populations for which the specificity of the TST is low. IGRA indirectly identifies infection by detecting the cell-mediated immune response against MTB antigens with much higher specificity (>95%) independent of BCG-status (80). Although, the Mantoux and IGRA methods for latent TB infection provide excellent ability to detect MTB when used appropriately, as a general rule they should not be used to differentiate LTBI from active disease (80).

In routine contact investigations, a comprehensive clinical and microbiological evaluation is required to sufficiently diagnose active TB. The typical symptoms of active TB include unexplained weight-loss, nightsweats, fever, and cough with or without hemoptysis (ie. presence of blood in airway secretions) of at least 2 weeks (1). If such symptoms are present or

if a positive TST or IGRA is reported, a chest radiograph is performed. Typically, chest radiographs are able to show one or more features of pulmonary disease (for example volume loss, presence of cavitation, and the upper lobe distribution of inflammation) (1). Despite the importance of chest radiography in the TB diagnosis algorithm, its limitations, namely poor inter-rater reliability and relatively low sensitivity and specificity are apparent. Other mycobacteriologic tests are required to make a definitive diagnosis. (1).

AFB-smear microscopy is widely used in Canada to determine the level of infectiousness of suspected pulmonary TB case. Similar to the radiography procedure, smear microscopy methods yields variable sensitivity and generally high specificity. Depending on the type of smear staining procedure, patient population, and skill level of the microbiologist, the sensitivity of smear microscopy is known to vary from 20% to 80%(1). To boost the sensitivity, it is strongly recommended that at least 3 specimens be submitted for AFB smear and culture. A smear-positive result suggests that there are sufficient mycobacteria present per volume of sputum to indicate that the individual is infectious; however, culture is required for drug susceptibility assessment and molecular typing of the strain. Culture-dependent methods are the gold standard for confirming active TB diagnosis and more commonly in pulmonary disease. Each specimen sent for AFB-smear microscopy is also cultured in solid and liquid media. Compared to smear microscopy, the sensitivity and specificity of culture methods is considerably higher for microbiological confirmation of MTB disease.

Culture-independent techniques have made great strides in the last 15 years for improving the efficiency of active TB diagnosis. In Canada mycobacterial nucleic acid amplification tests (NAAT) are performed on smear positive specimen to rapidly confirm the presence of MTB complex, versus non –tuberculosis mycobacterium, and drug susceptibility status. Compared to conventional culture-dependent techniques, NAAT offers significantly faster diagnosis as results become available within hours instead of weeks. Faster results typically suggest earlier diagnosis, correct treatment regimen, and lower potential for transmission. NAAT relies mostly on the Polymerase Chain Reaction (PCR), a sensitive molecular strategy that is able to amplify minuscule traces of MTB DNA. With targeting genetic

amplification, NAAT can also be used to identify the resistance profile of the particular isolate such that the correct treatment can be initiated. Although several tests have been approved for use by the WHO and Health Canada, the Xpert MTB/RIF© test (Cepheid Inc,Sunnyvale, CA) has proven one of the most successful and cost-effective strategies for determination the diagnosis and treatment. The Xpert MTB/RIF test is a fully automated, real-time PCR test utilizing the former GeneXpert© platform. It has the capacity to detect MTBC and RMP resistance, a marker for MDR-TB all within 2 hours (1).

2.4.3 Treatment of TB

The treatment of active disease involves use of a minimum number of drugs depending on the resistance profile of the particular strain. The first line anti-tuberculosis drugs include INH, RMP, ethambutol (EMB), and pyrazinamide (PYZ) according to the Canadian Tuberculosis Standards. The initiation of the appropriate TB treatment regimen is essential to prevent further transmission of the infectious case and the induction of drug resistance. Clinical evidence has suggested that correct treatment is able to render the smear-positive patient non-infectious within weeks (1, 81) from the start date of treatment. Transmission is further reduced if cases are diagnosed much earlier in the infection stage rather than at symptomatic stages of advanced disease (82).

Although efforts at containing and preventing multi-drug resistant disease have been exceptionally good in Canada, immigration and the subsequent import of multi-drug resistant tuberculosis still remains a concern. Directly observed treatment (DOT) is recommended strategy by the World Health Organization (WHO) for adequate and effective case management. DOT prevents the development of multi-drug resistance by a comprehensive patient-centered approach ensuring that the patient completes the entirety of the required treatment regimen. As part of the WHO guideline of the STOP TB strategy, the 5 core components of DOTS include 1) government commitment for increased sustainable financing 2) case detection through quality-assured bacteriology using microscopy methods 3) standardized

treatment, with supervision and patient support 4) An effective drug supply and management system and 5) Monitoring and evaluation of each case (81,83).

2.5 Estimation of Transmission

2.5.1 Contact Tracing Investigation

In Canada, conventional contact tracing investigations (CCI) are routinely conducted on all TB patients with confirmed pulmonary disease. CCI offers an epidemiological approach to identify and assess the infection or disease status of all contacts that had recent contact with a PTB (ie. potential transmitter). CCI aims to prevent further transmission by promptly identifying and treating the source case, secondary cases, and infected contacts. Those contacts that are at high risk for disease are strongly recommended for preventive treatment, whereas confirmed secondary cases are administered mandatory antibiotic regimen. Typically, active disease is prevalent in approximately <2% of close contacts (household or non-household), and less prevalent in casual and community contacts (1).

Currently, the classical “concentric circle” approach is used in Canada to prioritize contacts following the diagnosis of an infectious TB case (1). This method suggests that those that are in close contact with the PTB case are most likely to be infected and have the greatest priority to be screened. The investigation may proceed in a stepwise fashion to contacts with lesser exposure if transmission seems likely. Despite, the expected higher probability of transmission to close contacts compared to casual contacts, the “concentric circle” approach does not consider the less exposed casual contacts that may present strong risk factors for developing early active disease (i.e. HIV- co-infection, diabetes, alcoholism, malnutrition, etc). Also it is difficult to identify and characterize those contacts that congregate frequently in complex public locations (ie. bars, schools, Indigenous ceremonies) (1). Even after proper investigation, CCI is limited to detect active disease and or infection status in reported contacts recalled by the PTB case. Errors in recalling all contacts or intentionally excluding certain contacts may underestimate the true extent of transmission. Such limitations may be overcome by newer, location-based and social network approaches that supplement contact investigations.

2.5.2 DNA fingerprinting Strategies

Isolate fingerprinting methods are currently used to confirm secondary cases and assist in delineating MTB strains responsible for outbreaks. The *IS6110*-Restriction Fragment Length Polymorphism (RFLP) has been widely implemented globally as the gold standard technique for distinguishing MTB strains and estimating transmission events between infectious index cases and their contacts. *IS6110*-RFLP is a culture-dependent fingerprinting technique that characterizes the *IS6110* insertion sequence in the MTBC chromosome (84). The number and position of the *IS6110* sequence is determined, quantified and visualized in a gel-electrophoretic approach and compared with other strains to examine its similarities. Identical strains will present an identical number and position of *IS6110* sequences upon visualization. However, RFLP is typically time consuming and labour intensive as it requires high-quality MTB DNA and cannot readily distinguish strains with fewer than 6 copies the of the insertion sequence (84). In such situations, a secondary culture-independent PCR-based genotyping techniques such as spoligotyping and Mycobacterium Interspersed Repetitive Units- Variable Number Tandem Repeats (MIRU-VNTR) may be used to improve the discriminatory power of RFLP. In the latter technique, the number of repetitive sequences between various direct sequence repeat loci are quantified without re-culturing and isolating the chromosomal DNA. Compared to RFLP, spoligotyping and 24-loci MIRU-VNTR provide faster detection of clusters (i.e. 2 or more identical isolates) in outbreak scenarios and within communities with ongoing transmission activity (85,86). Despite the rapid results and confirmation of transmission using these methodologies, molecular epidemiology cannot be used to identify the culture-negative TB cases and contacts with infection only. Researchers must therefore interpret molecular evidence of transmission with caution and if available, all conventional contact tracing and epidemiological evidence of transmission must be considered when estimating TB transmission in a population.

2.5.3 Emerging Methods

In addition to routine isolate fingerprinting and conventional epidemiological investigations, emerging methods allow one to more accurately describe the characteristics and key players in MTB transmission. The use of whole-genome sequencing (WGS) of MTB chromosome have led to promising results for determining the evolutionary rate, directionality of patient to patient transmission, and drug resistance profile on a real time basis (87-88). Compared to the routine MIRU-VNTR and RFLP techniques, WGS offers far greater discriminatory power in transmission in high-burden TB communities and lower cost per isolate sequenced (89-91). A recent study conducted in Vancouver, British Colombia successfully implemented WGS in culture-positive patients in an inner-city community undergoing a TB outbreak. From what was observed to be a single outbreak using the 24 loci-MIRU-VNTR approach, the researchers determined that 2 distinctive yet concurrent outbreaks were present with each outbreak originating from a different MTB lineage (92). The directionality of transmission was easily determined by the order of accumulated single nucleotide polymorphisms (SNPs) with higher number of SNPs associated with more recent exposure (92).

Location- based social network analysis (SNA), and geographical information system (GIS) approaches offer greater insight in determining geographical risk factors or "TB hot spots" across communities (93). SNA tools are now increasingly used to understand the commonality and social patterns of contacts of known infectious cases such that preventive treatment can be better prioritized to key persons and location with highest risk of infection or disease (92,94-96). Moreover, GIS is more commonly used to assess the geographic burden of disease across community, regions, and or time intervals. As surveillance tool, GIS may provide value in evaluating interventions that reduce transmission and disease burden over time (97-99).

2.6 Summary

Tuberculosis is often described as a social as well a medical disease. In Canada, the burden of TB is strongly linked to socio-economic circumstances. Although the burden of TB related morbidity and mortality has significantly decreased since the early 20th century due to remarkable social, medical, and public health improvements, TB elimination is still a long way

away. Current epidemiological data has now indicated that the burden of TB is highest in the foreign-born whereas incidence continuously remains higher in the Indigenous population. Although drug resistance is not a major issue in the Canadian-born, ongoing transmission still remains in the Registered Indian and Inuit communities burdened by poverty, poor living conditions, and multiple co-morbidities. To continue in a positive trend for TB control, research must maintain a focus on reducing the rate of TB in the Canadian-born Indigenous people by strengthening all aspects of TB control while improve the social determinants of health.

CHAPTER 3: CHARACTERISTICS OF TUBERCULOSIS TRANSMITTERS, INFECTED CONTACTS, AND SECONDARY CASES AMONG THE CANADIAN-BORN PEOPLE ON THE PRAIRIES

3.1 ABSTRACT

BACKGROUND: Indigenous people are disproportionately affected by tuberculosis (TB). This study aimed to identify and characterize the transmission events from culture-positive Registered Indian, Métis, and to a lesser extent, non-Indigenous pulmonary tuberculosis (PTB) patients diagnosed in the Prairie Provinces of Alberta, Saskatchewan, and Manitoba in 2007 and 2008.

METHODS: TB contact investigation data was used in conjunction with 24-loci DNA fingerprinting of *Mycobacterium tuberculosis* isolates to identify and describe all infected contacts and secondary cases on the prairies. Demographic and geographic characteristics of all cases and contacts were retrieved from provincial TB registries and contact investigations and analyzed in contingency tables.

RESULTS: Of the 248 potential PTB transmitters 221(89%) were identified as true source cases. These cases gave rise to 1189 transmission events. The proportion of the newly infected contacts that were secondary cases was highest in those <15 years of age, close contacts, and in Métis persons. Most transmission was within the same population group and community type as the transmitter. In Manitoba, approximately 23% of inter-postal code transmission events were >100 kilometers apart.

***CONCLUSION*:** Most transmission events on the prairies were observed to occur in the same postal code with the majority of secondary cases identified as close contacts. Prompt and thorough contact investigations should be focused in reserve communities and Métis persons.

3.2 BACKGROUND

Pulmonary tuberculosis (PTB) is responsible for ongoing transmission of TB in the Registered Indian and Métis people of Alberta, Saskatchewan, and Manitoba ('the prairies'). The diagnosis and treatment of PTB cases and their most vulnerable contacts is essential in order to disrupt the chains of transmission and continues to be a high priority of provincial TB control programs (1). Demographic and geographic markers of transmission have been described in vulnerable contacts globally; however, these factors have not been assessed comprehensively in the Indigenous people involved in transmission events on the prairies (2-4).

Evidence of TB transmission has been identified and described in the Canadian-born using molecular methods that aim to characterize *Mycobacterium tuberculosis* strains. Common molecular fingerprinting techniques include *IS6110* Restriction Fragment Length Polymorphism (RFLP) and Mycobacterium Interspersed Repetitive Units-Variable Number Tandem Repeats (MIRU-VNTR). Public health applications of these methods have identified genotypic TB clusters, to be associated with the community of residence of the index PTB case (5-9). Although these methods provide insight in the geospatial distribution of transmission, they do not identify the social and demographic characteristics of transmission. For accurate identification and description of transmission dynamics on the prairies, fingerprinting data must be interpreted in the context of conventional epidemiological and geographic data (10, 11).

This study was undertaken in the context of a larger Canadian Institutes of Health Research (CIHR) and Health Canada funded research project, titled the *Determinants of Tuberculosis Transmission or "DTT"* project. The objective of the study is to describe the distribution of TB cases in the Canadian-born population by characterizing the PTB transmitters, recently infected contacts, and secondary cases in order to understand "to whom" and "from whom" transmission of *M. tuberculosis* is occurring on the prairies. Specifically, this study will assist provincial TB control programs by: 1) critically assessing the cases and contacts involved in transmission based on the characteristics of newly infected contacts and secondary cases; and 2) identifying priorities and potential targets for TB elimination.

3.3 METHODS

Study Participants definition and identification

Pulmonary Tuberculosis (PTB) Potential Transmitters

The transmission events from culture-positive Canadian-born adults (age > 14 years) diagnosed with pulmonary tuberculosis in Alberta, Saskatchewan, and Manitoba in 2007 and 2008 ("study period") were investigated in this study. These PTB cases were referred to as *"potential transmitters"* due to their likelihood of transmitting *M. tuberculosis* by airway secretions. All potential transmitters diagnosed in the study period were prospectively identified and included the Registered Indian, Métis, and the Canadian-born Other (Inuit, Non-Registered Indian, and non-Indigenous Canadian-born). Of the 248 potential transmitters, 223 (90%) were identified as Indigenous persons.

Transmission Events

Transmission events in this study were defined as contacts with new infections and secondary cases that were or were not identified as a contact (see below). TB nurses in each province conducted contact tracing investigations on all transmitters. The National Microbiology Laboratory in Winnipeg, Manitoba assisted in identifying secondary cases by performing 24-loci MIRU-VNTR DNA fingerprinting on all initial isolates of culture-positive TB cases. A 30-month transmission window was examined for each potential transmitters diagnosed between 2007 and 2008 in order to capture all transmission events. This window began 6-months before and ended 24 months after the date of diagnosis of the potential transmitter, creating a 4.5 year timeframe (July 1, 2006 to December 31, 2010) for the study that included all identifiable transmission events from all potential transmitters (Appendix B). Based on the level of infectiousness and epidemiological evidence of transmission, a subgroup of the 248 potential transmitters was more appropriately labeled as secondary cases. These secondary cases were considered as transmission events of one or more of other "potential transmitters" and the remaining transmitters referred to as "source cases" were assessed comprehensively for transmission (Appendix C).

Contacts with new infection

In this study, TB nurses and Community Health Representatives were responsible for conventional contact investigations (CCI) (13). Infection was determined according to the results of tuberculin skin tests (TST) conducted by TB nurses. Contact data was stored in an electronic database format for each province and requested for analysis. Contacts were presumed recently infected by a transmitter if the following outcomes were conclusive:

i. *TST Converters:* According to the Canadian TB Standards, a true TST conversion is defined as an increase of TST of 10 mm induration or greater when an earlier test resulted in a reaction of <5 mm induration. If the earlier induration was observed between 5 mm and 9 mm, then an increase of 6 mm or more is also indicative of a conversion. This definition is a more sensitive criterion, which is suggested for those that are immune compromised or for an outbreak investigation (12, 13).
ii. *TST New Positives:* A contact was also considered to be positive for tuberculosis infection in this study if a TST test was not conducted prior to the diagnosis of the source. Additionally, the current induration size must be ≥ 5 mm after diagnosis (14)

Secondary TB Cases

This group of transmission events included all clinically confirmed secondary cases diagnosed in the 30-month transmission window of the "potential transmitter". Secondary cases were identified from provincial TB registries and epidemiological evidence. These cases included:

i. Type I Secondary cases: Culture-positive cases reported as contacts of a transmitter and having a near identical isolate (fingerprint match of at least 23 of 24 loci). These cases may include the subgroup (as previously described) of the 248 potential PTB transmitters that were judged to be more appropriately as secondary cases.
ii. Type II secondary cases: Culture-negative cases reported as contacts of a transmitter
iii. Type III secondary cases: Culture-positive cases that were not identified as contacts but were linked molecularly (share an identical 24 loci isolate with that of the potential transmitter) and spatially (reside in the same forward sortation area as determined by

the first three digits of their postal code of residence) to the transmitter (Appendix D & E).

Measurements

TB Case and Contact Characteristics

The age, sex, and population group of all TB-cases (transmitters and secondary cases) diagnosed between July 2006 and December 2010 in each province, were retrieved from provincial TB registries and stored in an electronic database for analysis. Clinical data on smear status, cough, and chest radiography was then added on to the transmitters. Contact investigators included data on age, sex, and exposure status (ie. close or casual/other contact) tuberculin skin test results, and community of residence of contacts in accordance with the Canadian TB Standards. The proximity of the contact and time spent with the probable source case was used to identify the "closeness" of the contact relative to the case. Individuals who were in regular and prolonged contact with the infectious case regardless of age and population group were classified as *close contacts* to the infectious case. Contacts that had generally infrequent or occasional contact with the transmitting case were identified as *causal/other* contacts (14).

Geographical Characteristics

The community of residence of all individuals identified as having been a transmission event was determined by the postal code of their place of residence. The first three digits referred to as the forward sortation area or FSA determined the community of residence using 2006 Statistics Canada data. Communities were grouped into four types: *reserve communities* (defined by First Nations and Inuit Health office in each province): *major metropolitan* (Edmonton, Calgary, Saskatoon, Regina, Saskatchewan and Winnipeg), *non-major metropolitan*, and *Métis Settlements* or, as they are referrred to in Saskatchewan, Northern Villages. In Alberta, the Métis Settlements were defined in accordance with the Métis Settlements General Council. For Saskatchewan and Manitoba, these communities were identified in the the Indigenous Canada Portal and consists of communities containing 25% or more Métis residents based on Statistics Canada census data**.** Non-major metropolitan communities consisted of

communities of 500 or more persons that were neither major metropolitan areas nor Métis Settlements (1).

Statistical Analysis:

Characterization of PTB transmitters

The true source cases were identified from the 248 PTB transmitters based on clinical and epidemiological criteria. Those confirmed to be the true source cases were categorized into cases responsible for ≥ 1 transmission event and cases that did not transmit (no transmission events). The transmitters were described according to demographic, geographic, and clinical characteristics. The association between the province of residence and the population and clinical characteristics was assessed using Pearson's chi-square test or Fisher's exact test if expected counts in 80% of the cells were less than 5. The difference in the median number of contacts per transmitter was assessed using the Mann-Whitney U test.

Characterization of Infected Contacts and Secondary cases

The contacts were identified and categorized into two groups: close and other (casual, community, and unknown contacts). Contact characteristics of age, sex, population group along with evidence of transmission (TST history and active disease status) was described according to level of exposure. Characteristics of contacts were organized into contingency tables and analyzed using a Pearson's chi-square test or Fisher's exact test to test the differences in the distributions.

Individuals who were determined to be a transmission event (new infection or secondary case) were described according to demographic, geographic, exposure status, and province. The frequency of inter-population group transmission was assessed using a contingency table, which included the population group of the transmitter and the infected contacts and secondary cases. The association between the transmission event characteristics and the province of residence was investigated using Pearson's chi-square test or the Fisher's Exact test.

The secondary attack rate (SAR) was estimated separately for each demographic and geographic characteristic. SAR was defined as a proportion of recently infected contacts that were diagnosed with active disease within the 30-month transmission window of the respective source case. The denominator included all recently infected contacts (TST new positive and converters) in addition to the contact confirmed secondary cases (Type I and II) that were presumably infected. A two-sample proportion test was used to compare the estimates of SAR between the categories of each characteristic.

$$\text{Secondary Attack Rate (SAR \%)} = \frac{\text{Number of contacts with active disease (Type I and II secondary cases)}}{\text{Total Number of TST new positives, converters, and secondary cases}} \times 100\,\%$$

Geographic Analysis of Transmission

Although *M. tuberculosis* infection and disease is known to occur primarily in those living in close contact and in the same community as the source, preliminarily molecular analysis has suggested the possibility of on-going inter-community transmission. This observation was based on a few large clusters of identical *M. tuberculosis* DNA fingerprinting patterns from culture-positive cases distributed throughout the province of Manitoba (15).

To further investigate the extent of inter-community transmission, ***i)*** *the association between the community of residence of the transmitter and infected contact/secondary case;* and ***ii)*** *the relationship of the geographic proximity between the transmitter and infected contacts/secondary cases* was described. In the first analysis, a geographic matrix was constructed to include the 4 community types in the Prairie Provinces (major metropolitan, non-major metropolitan, reserves, and Métis Settlements) representing the residence type of the source cases and their infected contact/secondary cases. The geographic distribution was analyzed by the Pearson's chi-square test of association. In the second analysis, the direct distance between the residence of the source case and their respective infected contacts/secondary case was determined on the basis of postal code. The postal codes were obtained from contact registries and the direct distance was determined using Juice Analytics

Excel Geocoding Tool (16). Distance of transmission events was categorized and visually described.

All variables of contact and transmitters cases were coded into databases and analyzed using STATA 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP).

Ethics Approval

This descriptive project was undertaken in the context of a larger mixed method study: *Determinants of Tuberculosis Transmission*, a CIHR and Health Canada funded project. Approval of this study was received from the University of Alberta (Health Research Ethics Board), Saskatoon, Regina, (Research Ethics Board), Manitoba (Health Research Ethics Board), and Health Canada. Additionally, informal approvals were received from Health Canada – First Nations and Inuit Health Branch (FNIHB) Headquarters and Assembly of First Nations. TB registry access agreements were established between the University of Alberta, Manitoba Health and Healthy Living (MHHL), and the Saskatoon Health Region.

3.4 Results

Characteristics of potential transmitters

Of the 248 culture-positive PTB cases ("potential transmitters") identified, 221(89%) were determined to be the true transmitters and 27(11%) were determined to be secondary cases on the basis of available clinical and epidemiological data (Appendix C). The potential transmitters included 158 (72%) Registered Indian people, 37 (17%) Métis, 24 (11%) non-Indigenous, and 2 (<1%) Inuit and non-Registered Indian (Appendix F).

The characteristics of the 221 potential transmitters were described according to whether or not they had or didn't have one or more transmission events (Table 3-1). The majority of transmitters were identified as being ≥35 years of age (62.4%), male (57.5%), residing in a reserve community (51.1%), residing in Manitoba (52%), and as having acid-fast bacilli (AFB) smear positive disease (62%). There were significant differences in the distribution

of community of residence ($p<0.02$), AFB-smear positivity ($p<0.002$), and chest radiography ($p<0.02$) between cases that did or did not transmit. As expected, the median number of contacts per transmitter was significantly greater in transmitters identified with ≥1 transmission events (median = 22 contacts, IQR=24) compared to those without transmission events (median = 6 contacts, IQR=14) (Table 3-1).

Characteristics of Reported Contacts by Contact Type

The characteristics of reported contacts of PTB transmitters based on contact type is shown in Table 3-2. The 221 potential transmitters were listed as having 5,871 contacts during contact investigations. There were significant differences in the distribution of age group, population group, province of residence, and active disease status between close and other contact type ($p<0.0001$). A majority of close contacts were identified as a Registered Indian person (2,464 contacts, 85%), age <64 years (2096 contacts, 72.3%), and resided in Manitoba (1,842 contacts, 53.5%). Less than 1% of all identified contacts were diagnosed with active disease (Table 3-2).

Characteristics of Infected Contacts and Secondary Cases by Province of Residence

Contacts were characterized by the province of residence of the PTB transmitter in Table 3-3. A total of 1,189 transmission events were identified in the study period by conventional and molecular epidemiological linkage. The type of transmission event observed was related to the province of origin ($p<0.0001$). Of all transmission events, 982 (82.6%) were identified as recently infected contacts and 207 (17.4%) were secondary cases. Compared to Alberta, Type III secondary cases (unreported contacts) were more common in Saskatchewan and Manitoba. These cases comprised only 10% of all transmission events and 59% of secondary cases (Table 3-3).

There were significant differences in the distribution of age group, community of residence, and the population group of the infected contacts and secondary cases according to their province of residence (Table 3-3). *M. tuberculosis* transmission was most likely to occur in adults between 15 to 64 years of age compared to the combined occurrence in children <15

years and the elderly >64 years. In Saskatchewan, children <15 years that were completely assessed for transmission had a relatively higher proportion of infection or disease compared to the other provinces (132 events, 37.4%). Transmission was most common in the Registered Indian people ($p<0.001$) and in reserve communities ($p<0.001$). According to inter-population group transmission analysis as shown in Table 3-4, most transmission events occurred in the same population group as the source case particularly in the Registered Indian people.

The secondary attack rates (SAR) in the infected contacts of the potential transmitters are shown in Table 3-5. Secondary cases were identified in approximately 8% of all newly infected contacts. The SAR varied significantly with age, population group, and contact type. SAR was observed to be highest in children <15 years (SAR=12.2%, 95% confidence interval (CI) 8.4% - 16%, $p<0.05$), Métis origin (SAR=17.2%, 95% CI 8.0 - 26.4%, $p=0.002$), and residence in Métis Settlements (SAR=20.5%, 95% CI 8.6% - 32.4%). Although 53% of identified transmission events occurred in "other" contacts, the SAR was highest in close contacts of the transmitter (11.1%, 95% CI 8.3 - 13.9%, $p <0.001$) (Table 3-5).

Geographic Analysis

The distribution of transmission events relative to the community of residence of the transmitters and their postal code are shown in Table 3-6 and Figure 3-1 respectively. Overall, transmission was recognized to occur mostly within the same community type as the transmitter with the greatest likelihood in the reserve communities (n=679 events, 83.2%) (Table 3-6). A total of 1161 of 1189 (97.7%) infected contacts and secondary cases were identified with a full postal code for distance analysis. Figure 3-1 and 3-2 describes the distribution of infected contacts and secondary cases by exposure (close or other) and distance from the potential transmitter respectively. Although the relative proportion of close contacts in each distance category did not vary significantly in each distance category (0 km: 41.2%; 0-9km: 47.7%; 10-100km: 39.6%; >100 km: 37%) ($p=0.25$) (Figure 3-1). The distance between source and their transmission events varied significantly by province. Transmission occurred mostly within the same postal code (0 km apart) of the potential transmitter in each province.

In Manitoba, a significantly higher proportion of infected contacts were identified to reside >100km from the potential transmitter (Figure 3-2).

3.5 DISCUSSION

This study has investigated the characteristics of the cases and contacts involved in *M. tuberculosis* transmission on the prairies. Potential transmitters with evidence of advanced disease (ie. smear positivity and cavitation) were responsible for most transmission events. Generally, transmission occurred within the same population group and community type as the source case or transmitter. Among the contacts of the Registered Indian source cases, approximately 83% contacts resided in reserve communities and 97% were identified as Indigenous (Registered Indian and non-Registered Indian). Although the population group and location of most transmitters was consistent with previous transmission studies of the Indigenous peoples (1,15), a significant proportion of transmission events involved cases and contacts residing in a geographically distinct communities than the transmitter. For example, In Manitoba, approximately 23% of inter-postal code transmission events were geographically distant suggesting considerable case-contact mobility. A molecular study conducted by the National Microbiology Lab identified transmission to be associated with a dominant strain in inner-city Winnipeg and remote northern communities of Manitoba (16). Mobility presents a significant challenge and also, an opportunity for TB control programs to devise strategies to prevent the spread of infection and disease in the Indigenous people. These novel strategies must take into account the mobile behaviors of the transmitters and contacts in order to effectively detect and disrupt the chains of transmission. This study also provided evidence that transmission into the “other contacts” (ie. casual and community contacts) was far more common than previously recognized. This observation may be associated with communal living and high-risk social behaviors (i.e. substance abuse) prevalent in many Indigenous communities (17-21). Approximately 2% of all identified close contacts had active disease, an observation consistent with CCI outcomes in a high-burden setting (22). These contacts are presumed to share the same air space as the transmitter more frequently over greater duration than casual contacts, thus; increasing the risk for re-infection provided that transmission is ongoing.

Secondly, many close contacts were identified to belong to the demographic vulnerable groups; the children <15 years and the elderly >65 years. The combination of prolonged exposure and relatively weaker immunity of these contacts increases the risk of progression to active disease (23-27)

This study determined probable transmission events on the prairies based upon clinical, conventional and molecular epidemiological evidence. The comprehensive and collaborative approach used in the study is a unique alternative to quantify and describe transmission. Thus far, current research has identified TB transmission to occur exclusively in the 24 months following the diagnosis of an infectious case (28). Such approach does not account for a period of exposure prior to diagnosis of the infectious case of which an immunologically susceptible contact (i.e. child) may have been infected or diagnosis first. Here, we have identified those potential transmitters most likely to be sources cases and have adopted a 6-month period prior to their diagnosis to capture index cases (typically culture-negative children <15 years). Additionally, molecular fingerprinting has identified culture-positive secondary cases that would have otherwise have not been identified by CCI. Of the 207 secondary cases, molecular fingerprinting identified the majority (59%) of these cases as unreported "community contacts".

Despite the methodological strengths, there were several limitations that should be addressed in future studies. Although the localization of transmission events was restricted to the province of residence of the transmitter, transmission across provincial borders on the Prairies is possible due to known mobility of the cases and contacts. Most reserve communities were associated with a single postal code covering an extensive area; therefore, the actual distance between the household residence of the transmitters and their infected contacts/secondary cases maybe largely underestimated in this study. At the time of the study, a protocol for contact tracing collaboration and data sharing did not exist but would have been useful to accurately determine the true geographic range of transmission. Secondly, transmission into close-household members compared to non-household close has been documented to occur frequently (29-31); however, the distinction between household and non-household close contacts is ambiguous in the Indigenous people and was not systematically

defined across the prairies. Lastly, the underlying clinical and social determinants of infection and disease were not interpreted beyond basic demographic and geographic characteristics in this particular study. The demographic and geographic based approach used in the study largely discounts the endogenous risk factors (i.e HIV-AIDS, diabetes) and the socio-behavioral lifestyle (i.e. housing quality, malnutrition, and substance abuse) associated with increased risk of infection and disease (31-35). The social context of the Indigenous people must be carefully considered for transmission to be interrupted in the Canadian-born population. Considering the limitations of the study, future studies must transcend basic CCI and incorporate higher resolution geographic and social network tools to identify key persons and locations pivotal to TB transmission (36-39).

Recent transmission of *M. tuberculosis* from adult PTB transmitters in the Prairie Provinces continues to be problematic in the Registered Indian population and in reserve communities. Here, this study has identified mobility to play a critical role in ongoing transmission and a challenge to containment and elimination efforts. Also, it was noted that casual contacts were of greater risk for infection in Saskatchewan and Manitoba but active disease was more likely to occur in close contacts overall. Provincial control programs must consider social and behavioral characteristics in addition to demographic and geographic risk factors of the transmitters and contacts in their contact investigation practice.

Table 3-1. Characteristics of pulmonary tuberculosis (PTB) transmitters by frequency of transmission

	Transmission Frequency			P-Value
	Total Assessed N(%)	≥ 1 Transmission Events N (%)	No Transmission N (%)	
Total No. Assessed	221 (100)	175 (100)	46 (100)	
Demographics				
Age				
15 to 34	83 (37.6)	69 (39.4)	14 (30.4)	0.26
≥ 35	138 (62.4)	106 (60.6)	32 (69.6)	
Sex				
Male	127 (57.5)	99 (56.6)	28 (60.9)	0.60
Female	94 (42.5)	76 (43.4)	18 (39.1)	
Population Group				
Non-Indigenous	24 (11.3)	18 (20.3)	6 (13)	
Registered Indian	158 (73.8)	130 (74.3)	28 (60.9)	0.17
Métis/ Other Indigenous[1]	39(14.9)	27 (15.4)	12 (26.1)	
Community of Residence				
Major metropolitan	59 (26.7)	43 (24.6)	16 (34.8)	0.03
Non-major metropolitan	26 (11.8)	22 (12.6)	4 (8.7)	
Reserve Community	113 (51.1)	96 (54.9)	17 (37)	
Métis Settlements	23 (10.4)	14 (8)	9 (19.6)	
Province				
Alberta	32 (14.5)	27 (15.4)	5 (10.9)	0.26
Saskatchewan	74 (33.5)	55 (31.4)	19 (41.3)	
Manitoba	115 (52)	93 (53.1)	22 (47.8)	
AFB Sputum Smear Positivity				
Negative	84 (38)	58 (33)	26 (57.8)	0.004
Positive	137 (62)	117 (67)	20 (42.2)	
Chest Radiography				
Normal to Non-Cavitary	101 (45.7)	75 (42.9)	26 (56.5)	0.02
Abnormal Cavitary	87 (39.4)	77 (44)	10 (21.7)	
Unknown	33 (14.9)	23 (13.1)	10 (21.7)	
Symptomology				
Presence of Cough	95 (43)	80 (45.7)	15 (32.6)	0.05
Absence of Cough	20 (9.1)	12 (6.9)	8 (17.4)	
Unknown	106 (48)	83 (47.4)	23 (50)	
Median no. of contacts per case (IQR)	19(38)	22(24)	6(14)	<0.0001*
Mean no. of contacts per case (95% CI)	27 (23- 30)	31 (27 - 36)	8.0 (5 -11)	<0.0001*

1. "Other Indigenous" include the Inuit (n=1, <1%), and non-Registered Indian persons n=24, 11%)

2. Includes close and casual contacts

* P-value corresponds to the Mann-Whitney U test

Table 3-2. Characteristics of the reported contacts of PTB transmitters (n=221)

	Total N (%)	Contact Type		P-value
		Close N (%)	Other[1] N (%)	
Total No. Identified	5871 (100)	2899 (100)	2972 (100)	
Demographics				
Age				
<15	1355(23.1)	767(26.5)	588(19.8)	<0.0001
15 to 34	2066 (35.2)	930(32.1)	1136 (38.2)	
35 to 64	2116 (36)	1012(34.9)	1104 (37.2)	
>64	249 (4.2)	154 (5.3)	95 (3.2)	
Unknown	85 (1.5)	36 (1.2)	49 (1.7)	
Sex				
Male	2825(48.1)	1423(49.1)	1402(47.2)	0.328
Female	2964(50.5)	1435 (49.5)	1529(51.5)	
Unknown	82(1.4)	41(1.4)	41(1.4)	
Population Group				
Registered Indian	4789(81.6)	2464(85)	2325(78.2)	<0.0001
Métis/Other Indigenous	359 (6.1)	145 (5)	214 (7.2)	
Non-Indigenous	500 (8.5)	184 (6.4)	316 (10.6)	
Foreign-born	223 (3.8)	106 (3.7)	117 (3.9)	
Province				
Alberta	1329 (22.6)	634(21.9)	695 (23.4)	<0.0001
Saskatchwan	1122 (19.1)	423 (14.6)	699 (23.5)	
Manitoba	3420 (58.3)	1842 (63.5)	1578 (53.1)	
Tuberculin skin test (TST)				
Completely assessed				
Negative	1207(20.6)	610(21.2)	597(19.9)	0.68
Previous positive	1529 (26)	742(25.8)	787 (26.3)	
Newly Infected[2]	1124(19.1)	545 (19)	579 (19.3)	
Incompletely assessed[3]	2011 (34.3)	977 (34)	1034 (34.5)	
Active Disease				
Culture-positive	50(0.9)	30 (1)	20 (0.7)	0.03
Culture-negative	34(0.6)	23 (0.8)	11 (0.4)	
Absence of disease	5787(98.6)	2846 (98.2)	2941(98.9)	

1. "Other Contacts" includes casual, community, and unknown contact types

2. TST indicating "New infection" include all TST new positives and converters with or without disease

3. "Incompletely Assessed" includes contacts identified with a single TST negative test <8 weeks after the date of diagnosis of the source case

Table 3-3. Characteristics of all identified infected contacts and secondary cases by province of residence

		Province			
	Prairie-wide N (%)	Alberta N (%)	Saskatchewan N (%)	Manitoba N (%)	P-value
Total No. assessed	1189 (100)	153 (100)	388 (100)	648 (100)	
Demographics[Ψ]					
Age					
<15	297 (25.7)	27 (17.7)	132 (37.4)	138 (21.3)	<0.0001
15 to 34	384 (33.4)	61 (39.9)	111 (31.7)	212 (32.7)	
35 to 64	425 (36.8)	56 (36.6)	98 (27.8)	271 (41.8)	
>64	47 (4.1)	9 (5.9)	11 (3.1)	27 (4.2)	
Sex					
Male	604 (52.3)	75 (49)	172 (48.7)	357 (55.1)	0.03*
Female	532 (46.2)	78 (51)	180 (51.3)	274 (42.3)	
Unknown	17 (1.5)	0 (0)	0 (0)	17 (2.6)	
Population Group					
Canadian-born					
Registered Indian	928 (80.4)	89 (58.2)	262 (74.2)	577 (89)	<0.0001*
Métis/Other Indigenous	58 (5)	6 (3.9)	52 (14.7)	0 (0)	
Non-Indigenous	118 (10.2)	32 (20.9)	30 (8.5)	56 (8.6)	
Foreign-born	44 (3.8)	26 (17)	3 (0.9)	15 (2.3)	
Unknown	5 (0.5)	0 (0)	5 (1.7)	0 (0)	
Community of Residence					
Major-metropolitan	178 (15)	33 (21.6)	43 (11.1)	102 (15.7)	<0.0001
Non-major metropolitan	162 (13.6)	47 (30.7)	57 (14.7)	58 (9)	
Reserves	761 (64)	56 (36.6)	230 (59.3)	475 (73.3)	
Métis Settlements	51 (4.3)	0 (0)	51 (13.1)	0 (0)	
Unknown	37 (3.1)	17 (11.1)	7 (1.8)	13 (2)	
Transmission Type					
TST converter	212 (17.8)	37 (24.2)	94 (24.2)	81 (12.5)	<0.0001*
New Positive TST	770 (64.8)	98 (64.1)	224 (57.7)	448 (69.1)	
Type 1 Secondary Case	50 (4.2)	9 (5.9)	21 (5.4)	20 (3.1)	
Type 2 Secondary Case	34 (2.9)	4 (2.6)	13 (3.4)	17 (2.6)	
Type 3 Secondary Case	122 (10.3)	4 (2.6)	36 (9.3)	82 (12.7)	
Unknown[1]	1 (0.1)	1 (0.7)	0 (0)	0 (0)	

1. "Unknown" case could not be traced conventionally nor molecularly to a known transmitter but was presumed to be a secondary case based on strong clinical evidence

* Chi-square test of assocation was calculated excluding the unknown proportions

Ψ Contains missing age, sex, population group data for n=36 Saskatchewan Type III cases (Data Pending)

Table 3-4. Distribution of transmission events by population group of the PTB transmitter and infected contacts or secondary cases

	Population group PTB transmitter			
Population group of infected contact and secondary case	Registered Indian N(%)	Métis N(%)	Other[1] N(%)	P-value*
Total Assessed	920 (100)	153 (100)	80(100)	
Registered Indian	848 (92.2)	60 (39.6)	19 (23.8)	<0.0001
Métis	10 (1.1)	47 (30.5)	1 (1.3)	
Other[1]	46 (5)	31 (20.1)	41 (51.3)	
Foreign Born	14 (1.5)	13 (8.4)	17 (21.3)	
Unknown	2 (0.2)	2 (1.3)	2 (2.5)	

*Analysis excludes n=36 Type III secondary cases residing in Saskatchewan (Data Pending)

1. "Other" includes Canadian-born non-Indigenous, Inuit, and non-Registered Indian individuals

Table 3-5. Demographic distribution of infected contacts, secondary cases, and the secondary attack rate (SAR)

	Total No. of infected contacts and secondary cases[2] N(%)	No. of contact-confirmed secondary cases[3] N(%)	Secondary Attack Rate (%, 95% CI)[4]	P-value[1]
Total Assessed	1066	84	7.9 (6.3 - 9.5)	
Age				
<15*	286(26.8)	35 (41.7)	12.2 (8.4 - 16)	
15 to 34	356 (33.4)	23 (27.4)	6.5 (3.9 - 9.1)	0.01
35 to 64	377 (35.4)	25 (29.8)	6.6 (4.1 - 9.1)	0.01
>64	47 (4.4)	1 (1.2)	2.1 (0 - 6.2)	0.04
Sex				
Male*	566 (53.1)	47 (56)	8.3 (6.0 - 10.6)	
Female	500 (46.9)	37 (44.1)	7.4 (5.1 - 9.7)	0.59
Population Group				
Canadian-born Other*	94 (8.8)	3 (3.6)	3.2 (0 - 6.8)	
Registered Indian	822 (77.1)	69 (82.1)	8.4(6.5 - 10.3)	0.07
Métis	64 (6)	11 (13.1)	17.2 (8.0 - 26.4)	0.002
Foreign-born	36 (3.4)	1 (1.2)	2.8 (0 - 8.2)	0.91
Unknown	50 (4.7)	0 (0)	0.0	
Community of Residence				
Major Metropolitan*	148 (13.9)	12 (14.3)	8.1 (3.8 - 12.5)	
Non-Major Metropolitan	157 (14.7)	9 (10.7)	5.7 (2.1 - 9.3)	0.41
Reserve Communities	680 (63.8)	54 (64.3)	7.9 (5.9 - 9.9)	0.94
Métis Settlements	44 (4.1)	9 (10.7)	20.5 (8.6 - 32.4)	0.02
Unknown	37 (3.5)	0 (0)	0.0	
Contact type				
Close*	495 (46.4)	55 (65.5)	11.1 (8.3 - 13.9)	
Other	571 (53.6)	29 (34.5)	5.1 (3.3 - 6.9)	0.0003

* Reference group

1. P-value is derived from the two-sample proportions test and is defined as the probability that the observed SAR is due to chance compared to the reference rate

2. Infected contacts include all TST New Positive, Converters in addition to contact confirmed secondary cases (Type I and II)

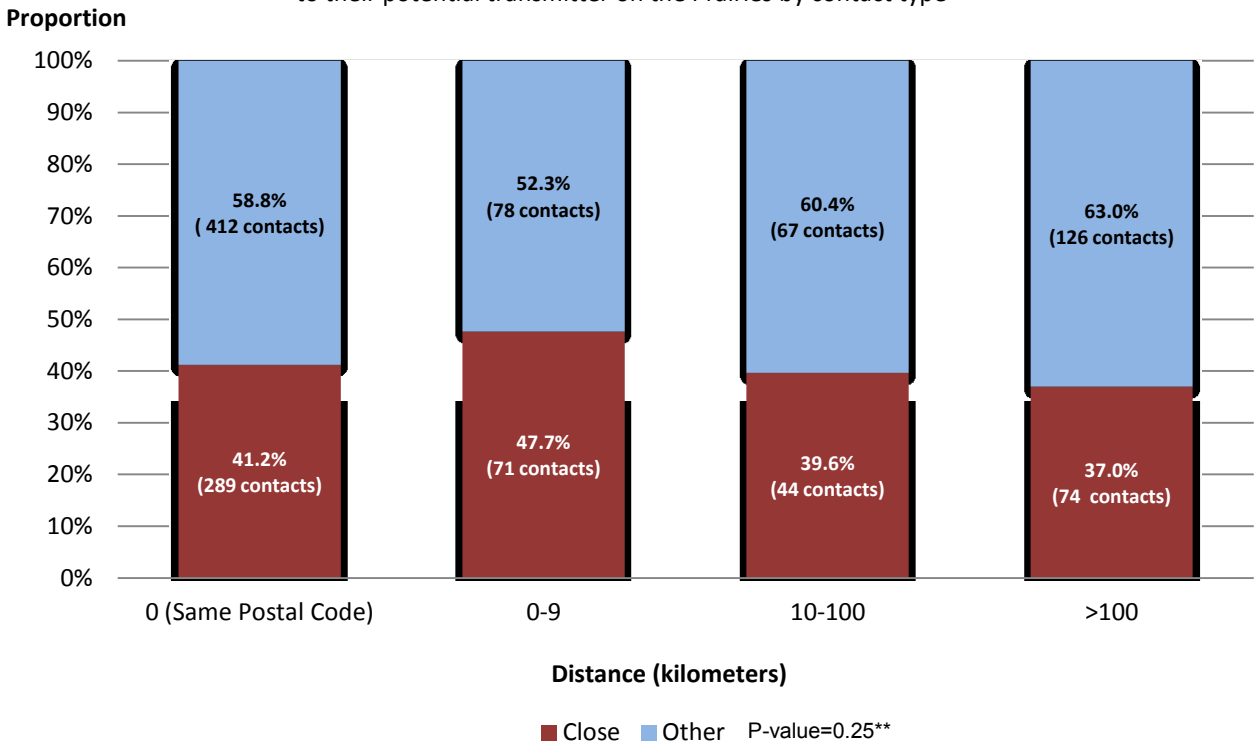
3. Secondary cases include Type I and II secondary cases

4. "Secondary Attack Rate" refers to the proportion of new infections (TST conversion or new positive) that were also diagnosed with active disease in the 30-month transmission window of their source. This proportion excludes the culture-positive secondary cases that could not be identified in contact tracing

Table 3-6 Distribution of transmission events by community type of PTB transmitters and infected contacts or secondary cases

	Residence of PTB transmitter				
"Residence" of infected contact or secondary case	Major Metropolitan N(%)	Non-Major Metropolitan N(%)	Reserve N(%)	Métis Settlements N(%)	P-value
Total Assessed	181 (100)	121(100)	816(100)	71 (100)	
Major Metropolitan	133(73.5)	5 (4.1)	39 (4.8)	1 (1.4)	<0.0001
Non-Major Metropolitan	9 (5)	74 (61.2)	72 (8.8)	7 (9.9)	
Reserves	31 (17.1)	33 (27.3)	679 (83.2)	18 (25.4)	
Métis Settlements	0 (0)	0 (0)	6 (0.7)	45 (63.4)	
Unknown	8 (4.4)	9 (7.4)	20 (2.5)	0 (0)	

Figure 3-1. Proportion of infected contacts and secondary cases residing in various distance to their potential transmitter on the Prairies by contact type*

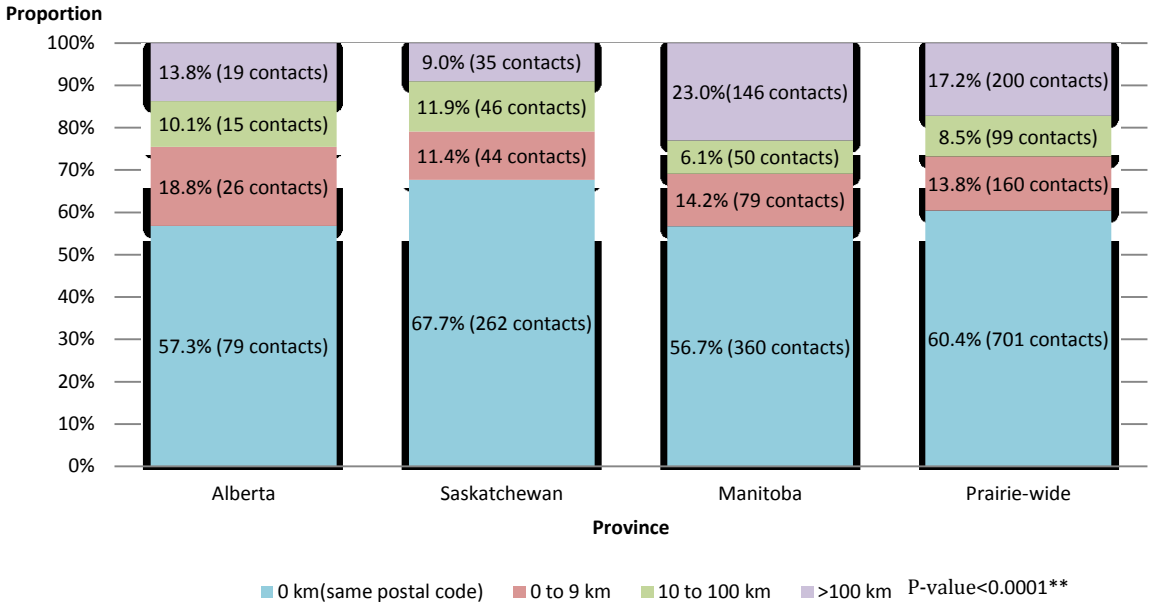


P-value analyzed by Pearson's chi-squared test

*Includes those infected contacts and secondary cases with complete postal code information available (n=1161 of 1189 transmission events)

** p-value from Pearson's chi-squared test

Figure 3-2.Proportion of infected contacts and secondary cases by distance from the potential transmitter and province of residence*



*Complete postal code data was available for 1161 of 1189 transmission events

**p-value analyzed from Pearson's chi-squared test

CHAPTER 4: THE PREDICTORS OF TUBERCULOSIS TRANSMISSION OUTCOME IN THE CANADIAN-BORN POPULATION OF THE PRAIRIES

4.1 ABSTRACT

BACKGROUND: The incidence of pulmonary tuberculosis (PTB) in Alberta, Saskatchewan, and Manitoba ("the Canadian prairies") is considerably higher in the Canadian-born Indigenous than the Canadian-born non-Indigenous people. This study aims to compare characteristics of Indigenous pulmonary TB transmitters with or without presence new infection or active disease in their contacts.

METHODS*:* Transmission events from 221 Canadian-born pulmonary tuberculosis transmitters were identified using conventional and molecular (DNA fingerprinting of *Mycobacterium tuberculosis* isolates using MIRU-VNTR typing) methods. Each transmitter was categorized by transmission outcome type (no transmission, newly infected contacts only, or at least 1 secondary case). Various geo-demographic, clinical, residential, and behavioral characteristics of the transmitters were identified from provincial TB registries and quantitative questionnaires. The association between case characteristics and transmission outcome was analyzed using multinomial logistic regression models.

RESULTS: In 2007 and 2008, 75 (33.9%) transmitters were linked to at least one secondary case, 100 (45.2%) to newly infected contacts only, and 46 (20.8%) to uninfected contacts. The independent predictors of secondary cases on the Prairies were diagnosis of AFB- smear positive (OR= 6.02, 95% CI 2.09-17.32) and cavitary disease (OR=3.64, 95% CI 1.29-10.28). Poor household ventilation was associated with infection only (OR= 3.00, 95% CI 1.10-8.24); whereas residency in reserve communities (OR= 3.55, 95% CI 1.10-11.44) was associated with at least one secondary case.

CONCLUSION: Transmission outcomes resulting in either infection or disease were largely due to advance pulmonary disease and residential conditions. Novel strategies that improve the timely diagnosis and treatment of active disease and new infection should be implemented particularly in reserve communities. Greater attention to housing conditions and pulmonary disease in Indigenous communities is necessary.

4.2 BACKGROUND

Despite a marked reduction in morbidity and mortality in the last century, the incidence of tuberculosis (TB) remains much higher in Canadian-born Indigenous compared to non-Indigenous people. In Alberta, Saskatchewan, and Manitoba (i.e. the 'Canadian Prairies'), the Registered Indian and Métis peoples are understood to account for TB transmission (1). Among the Indigenous pulmonary TB cases in this region, the factors that distinguish those who do and do not transmit are unknown.

The probability of TB infection or disease is primarily dependent upon host infectiousness, housing, and behavioral factors (2). Transmission of *Mycobacterium tuberculosis* (MTB), the causative agent of human tuberculosis, occurs through infectious aerosolized droplets (< 5µm) produced when a patient with active pulmonary tuberculosis (PTB) coughs (3,4). PTB is the most common phenotypic expression of human TB and is responsible for the overwhelming majority of transmission events on the Prairies. From a clinical perspective, the infectiousness of PTB increases with advanced disease when there is a higher acid-fast bacilli (AFB) load in the patient's sputum (5,6). At the community level, environmental determinants can elevate the level and duration of exposure to an infectious case, while other factors have the potential to weaken the host's immune system (7). Specifically, poor housing quality, number of close contacts, prevalence of smoking, and substance abuse are commonly studied factors understood to increase the number of individuals with infection or disease (7).

DNA fingerprinting of *M. tuberculosis* suggests that TB cases are more likely to be clustered within the same geographical location of the potential source, with larger clusters associated with a more infectious case (1,8,9). Although molecular methods are useful for identifying possible chains of transmission for culture-positive cases, they fail to include all cases and contacts involved in transmission. The combination of conventional and molecular epidemiological methods allows for a comprehensive analysis of transmission events on the Prairies. While it is known that the infectiousness of TB varies considerably between cases, the demographic and social context of the PTB cases must also be understood to account for why

some contacts are more likely to become infected or have active disease at the time of screening.

The characteristics of the potential transmitters and their contacts were extensively described in Chapter 3; however, the risk factors that are known to be associated with transmission and new infection have yet to be assessed on the Prairies. This study aims to bridge this knowledge gap by applying conventional and molecular epidemiological methods to assess the predictors of TB transmission. Specifically, this study will determine the likelihood of transmission resulting in infection and or secondary cases based on demographic, clinical, behavioral, and environmental characteristics of the 221 true transmitters identified in Chapter 3. The factors responsible for difference in transmission outcome will inform provincial TB control programs and community health leaders in their efforts to eliminate transmission and TB exposure in the Indigenous peoples.

4.3 METHODS

Study Participants

In 2007 and 2008, 221 Canadian-born adults (age >14 years) residing in Alberta, Saskatchewan, and Manitoba were diagnosed with culture-positive PTB disease and determined to be "true" transmitters (Chapter 3). These cases were identified systemically across the Prairies and their demographic, clinical, and laboratory characteristics were described (Appendix B). The cases hereafter referred to as transmitters, included First Nations (Registered Indians and Non-Registered Indian), Métis, Inuit and the non-Indigenous peoples. All transmitters were approached prospectively by a study coordinator in each province and invited to complete a quantitative questionnaire aimed at capturing household and behavioral characteristics. Of the 221 PTB transmitters, 163 (74%) gave informed consent for a quantitative questionnaire. The completion rates were lowest in Manitoba (65%) and approximately equal in Alberta (84%) and Saskatchewan (82%).

Transmission events were identified from the 221 transmitters and defined as a recently acquired MTB infection (with or without disease) directly from an infectious PTB transmitter

during 6 months prior to or 24 months after the date of diagnosis of the transmitter. Transmission events were required to have a conventional (including temporal and spatial) or molecular epidemiological link to the transmitter (Appendix D & E). Isolates from all transmitters were fingerprinted using 24-loci MIRU-VNTR in the National Microbiology Lab Winnipeg, Manitoba and the fingerprints were used to identify culture-positive secondary case contacts (Type I) and "unnamed" community contacts (Type III) based on a minimum of 23 loci fingerprint match. Culture-negative secondary cases (Type II) were identified through contact tracing and confirmed through clinical follow-up.

In this study, the transmitters were categorized into three groups based on their transmission event: 1) transmitters with no clinical or epidemiological evidence of transmission 2) transmitters causing one or more new infection but no secondary cases and 3) transmitters who caused infection and one or more secondary case. The transmission groups were determined according to the urgency and implications for TB control. It is understood that the occurrence of secondary case (active disease) is contingent on the level of infectiousness of the transmitter, closeness and duration of contact, and the underlying vulnerability of those exposed (age and immune status).

Measurements

Clinical, laboratory, and epidemiologic (conventional and molecular) data were used in conjunction to identify and describe the transmitters and their transmission events on the Prairies. Community health nurses and health representatives were responsible for conducting and recording the tuberculin skin tests (TST) in contacts. The demographic, community of residence, and clinical characteristics for each transmitter were extracted from provincial TB registries for analysis. Household and behavioral characteristics of the PTB transmitters were extracted from quantitative questionnaires and included the perceived household ventilation status, housing densities, proportion of household smokers, and mobility status over the 12 weeks immediately preceding diagnosis.

Statistical Analysis

The cases were assessed on the basis of demographic, geographic, clinical, household, and behavioral characteristics. The association between categorical independent and outcome variables was cross tabulated and analyzed with the Pearson's chi-square test or the Fisher's exact test if expected counts in 80% of the cells were less than 5. The total number of contacts obtained from contact tracing records was summed and the median number of contacts for transmitters in each outcome category was compared using the Kruskal-Wallis test. The risk factors for transmission were compared using multinominal logistic regression models with infected contacts and one or more secondary cases as the outcome categories and no transmission category as the reference. Independent variables were included in the final multivariate model based on clinical and statistical significance for transmission. All statistical analysis was completed using STATA 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP).

Ethics Approval

This project was undertaken in the context of a larger mixed method study: *The Determinants of Tuberculosis Transmission*, a CIHR and Health Canada funded project. This study was approved by University of Alberta (Health Research Ethics Board), Saskatoon, Regina, (Research Ethics Board), Manitoba (Health Research Ethics Board), and the Ethics Board of Health Canada. Additionally, informal approvals were received from Health Canada – First Nations and Inuit Health Branch (FNIHB) Headquarters and Assembly of First Nations. TB registry access agreements were signed with the respective provincial governments.

4.4 RESULTS

PTB Transmitter characteristics

According to the previous analysis, the clinical characteristics, community of residence, and median number of contacts of the potential transmitters were significantly associated with transmission (Table 3-1). The distribution of all possible transmission outcomes was illustrated in Figure 4-1. Of the 221 "true" transmitters identified in the Prairies, 46 (20.8%) had no

transmission events, 100 (45.2%) transmitters caused infection only and 75 (33.9%) caused one or more secondary case (Figure 4-1). The results of the univariate analysis derived from the multinominal logistic regression are shown in Table 4-1. In the univariate analysis, AFB-smear positivity and cavitary disease were strongly associated with at least one secondary case ($p<0.0001$)(Table 4-1). After controlling for all other covariates in the multinominal logistic regression analysis, as shown in Table 4-2, the odds of observing infection only (contacts) or a secondary case was 2.5 times and 6 times higher in smear positive transmitters compared to smear negative transmitters, respectively. Cavitary disease was 3.6 times more likely than non-cavitary disease to result in at least one secondary case, but was not associated with infection exclusively. In addition, the odds of transmission resulting in ≥ 1 secondary case were significantly greater for transmitters residing in the reserves compared to major metropolitan communities (OR=3.55, 95% CI: 1.10-11.44). The other Indigenous (Métis, non-Registered Indian, and Inuit) transmitters were not independently associated with any transmission outcomes; however, the odds of transmission increased drastically with considerable variation (OR= 12.97, 95% CI: 1.27 - 132.37) after adjusting for all other factors (Table 4-2). The Registered Indian transmitters on the contrary were independently associated with transmission events resulting in at least 1 secondary case in the univariate analysis but its statistical difference was nullified upon adjusting for all other factors.

There was significant interaction between age category and sex on the likelihood of transmission in the multi-nominal logistic regression. In the stratified analysis, transmission from females 15 to 34 years of age were approximately 3.15 and 2.82 times more likely to result in infection only or at least one secondary case compared to males respectively. The opposite effect was observed for transmitters >65 years of which females were 72% less likely to be associated with at least one secondary case (OR=0.28, 95% CI: 0.09-0.91) (Table 4-2).

Household and Behavior characteristics

Housing and behavioral risk factors for transmission outcome were analyzed in Table 4-3**.** The number of missing responses to household and behavioral inquiries varied moderately across each predicting variable. Some cases that were homeless or institutionalized,

could not respond to inquiries pertaining to household ventilation status (13.8%), proportion of household smokers (14.7%), and number of rooms (10.4%) (Table 4-3). Overall, the behavioral characteristics (household smokers, group activities, and mobility) did not have a significant impact on the difference in transmission outcomes across the prairies.

The final multivariate model in Table 4-4 was based on the most parsimonious covariates, which included community of residence, household ventilation, and persons per room. After adjusting for household characteristics, the transmitters that resided in reserve communities or reported poor to fair household ventilation were associated with secondary cases and infection respectively. The odds of transmission resulting in infection were observed to increase by approximately 3 fold (OR= 3.00, 95% CI: 1.10 – 8.24) in poorly ventilated and households compared to well-ventilated households. Similarly, residence in the reserve communities increased the odds for secondary cases by approximately 4 fold (OR=3.89, 95% CI: 1.27 – 11.94). The likelihood of observing a secondary case was 68% greater in households with >1 person per room compared to ≤ 1 person per room, however; the effect was not observed to be statistically significant (Table 4-4).

4.5 DISCUSSION

Despite the availability of better TB diagnosis and treatment in Canada, the transmission of *M. tuberculosis* is still an ongoing concern in the Indigenous peoples. This study has investigated risk factors for TB transmission outcome in the Registered Indian and Métis people in the Prairie Provinces. Overall, the likelihood of transmission was dependent upon residential and clinical characteristics of pulmonary tuberculosis transmitters.

Transmitters residing in the reserve communities, households with poor ventilation, and those diagnosed with AFB-smear positive or cavitary disease were significantly more likely to contribute to infection and secondary cases. This observation is consistent with what is known about TB in Indigenous people globally (11-13). Compared to metropolitan communities, substandard housing conditions and overcrowding are considerably more prevalent in Indigenous communities; thus creating a favorable environment for MTB to thrive and propagate. In households with poor ventilation, MTB contaminated aerosols can remain

suspended in the indoor air currents for a prolonged time, increasing the probability of exposure and re-infection of household contacts (7, 14, 15). Overall, the environmental characteristics assessed in this study yielded moderately imprecise point estimates. In a side analysis, the inclusion of smear positivity as a co-variate in context of household characteristics was observed to explain for the large variation in odds of transmission outcome. This suggests that smear positive transmitters were the primary driver of infection and secondary case in the prairies, whereas housing condition was seemingly a supporting factor for transmission.

Smear positivity and cavitary disease are defining characteristics for *M. tuberculosis* transmission from PTB patients (16). These individuals contribute the most to transmission due to the higher concentration of AFB present (>5000 CFU/mL) in respiratory secretions (sputum from cough or sneeze) compared to smear negative transmitters (17, 18). This clinical manifestation is common in individuals in whom disease has progressed to a more advanced stage, perhaps due the delay in diagnosis in addition to underlying co-morbidities (i.e. HIV-co-infection, diabetes mellitus), young age, or substance abuse (19, 20, 23, 24). The odds of transmission in this study were consistent with known epidemiological evidence that smear positive transmitters were approximately 5 to 6 times more infectious compared to smear negative patients (21,22). When placed in context with poor household conditions, the probability of infection and re-infection increases the odds of disease in their contacts compared to smear negative transmitters. Transmitters diagnosed later in the course of their disease are likely to have many more contacts therefore greater opportunity to transmit before treatment could be initiated.

This study has also investigated whether transmission outcome varied by sex and age.. In this study, older females ≥ 35 years were significantly less likely to result in a secondary case, an observation that was consistent with known age and sex distribution of tuberculosis (25-27). The contacts of older age transmitters (> 64 years) were presumably fewer and much older than the contacts of younger transmitters, reflecting fewer opportunities of transmission

Several unexpected yet critical results were noted in this study. Transmission outcome did not vary significantly by province despite prior evidence of high incidence of primary

disease in the Registered Indian children of Saskatchewan and on-going transmission in remote northern communities of Manitoba (28, 29). This observation indicates that transmission outcome is also dependent on characteristics of the susceptible population, which was not considered to be the primary focus of the current study. Although the Registered Indian persons comprise the majority of reserve communities, it was observed that the other Indigenous persons were far more likely to be associated with at least one secondary cases compared to any other the Canadian-born persons when adjusted for all factors. A possible explanation to this finding may be that the Métis, Non-registered Indian, and Inuit PTB transmitters account for only 17% of all transmitters in the study's sample thereby resulting in an imprecise estimate of transmission outcome.

Weaknesses in the study design stem primarily from unmeasured yet relevant predictors for TB transmission. The analysis partially explains the association between transmission outcome and transmitter characteristics, when it is well known that the outcome is also dependent upon contact immunity. Endogenous risk factors (i.e. HIV-AIDS, diabetes) and immunosuppressive behaviors (i.e alcoholism and substance abuse) of the susceptible contacts are able to accelerate the process of infection to overt disease. These characteristics were only available for contacts with active disease in the present study and could not be measured systematically in all contacts infected or not. Despite the general consensus that AFB-smear positivity is the standard characteristic of infectiousness, recent evidence claims that the generation of infectious cough aerosols in PTB patients may be a better predictor of transmission. Smear positive PTB subjects with higher concentration of AFB in their sputum were aerosol negative, suggesting that transmission capability is variable contradicting the current evidence that all smear-positive cases as equal transmitters clinically (30). Of the 221 source cases that were approached and encouraged to participate in the quantitative questionnaires, 58 (25%) did not participate. It is speculated that those cases that completed the questionnaire were more likely to be health-oriented and compared to those that chose not to complete upon request. This selection bias may likely under-estimate the true effect of household and behavioral risk factors. Finally, household measurements were restricted to participant responses and recollection, rather than an official accurate assessment. Errors in

recollection of household and behavioral status are likely to create a response bias in our study.

In spite of apparent limitations, this study has successfully combined conventional contact tracing and isolate DNA fingerprinting data to comprehensively quantify transmission outcomes in the prairies. The utilization of both approaches is necessary to compliment the methodological limitations of the other. Furthermore, the analysis conducted in this study was reassessed using a scoring distribution approach. In this former method, transmitters were awarded points based on the clinical and epidemiological evidence of their transmission events. The analysis revealed similar conclusions, suggesting that frequency and type (infected contact or secondary case) was determined mostly on clinical characteristics more so than the indirect effects of social circumstances in the Prairies.

This study has provided evidence that transmission of *M. tuberculosis* resulting in infection or secondary case is linked with advanced disease and inadequate household ventilation of pulmonary tuberculosis transmitters on the prairies. Considering the observations gleaned from this study and the known TB epidemiology of the Indigenous people, it is recommended that provincial contact tracing investigations should prioritize the contacts of pulmonary tuberculosis patients with clinically advanced disease in the reserve communities of the Prairie Provinces.

Table 4-1. Univariate analysis of demographic, geographic, and clinical predictors of transmission outcome from adult pulmonary tuberculosis (PTB) transmitters diagnosed in 2007 and 2008 (N=221)

	Transmission Outcome			
	Infected Contacts Only		≥ 1 Secondary Case	
	Unadjusted Odds Ratio (95% CI)	P-value	Unadjusted Odds Ratio (95% CI)	P-value
Demographic Characteristics				
Age				
15 to 34*	1		1	
≥35	0.97 (0.46-2.07)	0.95	0.43 (0.20 -0.92)	0.03
Sex				
Male*	1		1	
Female	1.27 (0.62-2.59)	0.51	1.10 (0.52-2.32)	0.81
Population Group				
Non-Indigenous	1		1	
Other Indigenous[1]	0.84(0.24 - 2.90)	0.78	3.11 (0.62 - 15.49)	0.17
Registered Indian	1.31 (0.48 - 3.61)	0.60	4.67 (1.13-19.34)	0.03
Geographical Characteristics				
Province				
Alberta*	1		1	
Saskatchewan	0.48 (0.15-1.51)	0.21	0.64 (0.18-2.25)	0.49
Manitoba	0.62 (0.20-1.88)	0.40	1.11 (0.33-3.72)	0.86
Community of Residence				
Major Metropolitan*	1		1	
Non-Major Metropolitan	2.37 (0.67-8.34)	0.18	1.5 (0.35 - 6.35)	0.58
Reserve	1.71 (0.75 - 3.91)	0.21	2.77 (1.14-6.72)	0.03
Métis Settlement	0.53 (0.17 -1.64)	0.27	0.67 (0.19-2.31)	0.52
Clinical Characteristics				
Chest Radiography				
Normal to Non-cavitary*	1		1	
Cavitary	1.73 (0.74 -4.08)	0.21	4.33 (1.81 - 10.36)	0.001
Unknown	1.08 (0.44 - 2.66)	0.86	0.29 (0.07 - 1.17)	0.08
AFB-Sputum Smear Positivity				
Negative*	1		1	
Positive	1.95 (0.96 - 3.95)	0.06	4.12 (1.87 - 9.05)	<0.0001

Odds ratio calculated with reference to the PTB cases that did not transmit

* Reference Category

1. Includes Métis, Non-Registered Indian, and Inuit transmitters

Table 4-2. Multivariate analysis of demographic, geographic, and clinical of transmission outcome from adult pulmonary tuberculosis (PTB) transmitters diagnosed in 2007 and 2008 (N=221)

	Infected Contacts Only		≥ 1 Secondary Case	
	Adjusted Odds Ratio (95% CI)	P-Value	Adjusted Odds Ratio (95% CI)	P-Value
Demographic Characteristics				
Age 15 to 34				
Males*	1		1	
Females	3.15 (0.69 - 14.3)	0.14	2.82 (0.57 - 13.9)	0.20
Age ≥35				
Males*	1		1	
Females	0.63 (0.24 - 1.60)	0.33	0.28 (0.09 - 0.91)	0.03
Population Group				
Non-Indigenous	1		1	
Other Indigenous[1]	3.25 (0.45 - 23.19)	0.24	12.97 (1.27 - 132.37)	0.03
Registered Indian	1.68 (0.41 - 6.83)	0.47	5.70 (0.92 - 35.41)	0.06
Geographical Characteristics				
Province				
Alberta*	1		1	
Saskatchewan	0.51 (0.12 - 2.19)	0.37	0.44 (0.08 - 2.43)	0.35
Manitoba	0.74 (0.18 - 3.07)	0.67	1.85 (0.35 - 9.67)	0.47
Community of Residence				
Major Metropolitan*	1		1	
Non-Major Metropolitan	2.54(0.67 - 9.65)	0.17	1.52 (0.28 - 8.16)	0.63
Reserve	2.61 (0.93 - 6.97)	0.06	3.55 (1.10 - 11.44)	0.03
Métis Settlement	0.36 (0.05 - 2.66)	0.33	0.34 (0.03 - 3.50)	0.37
Clinical Characteristics				
Chest Radiography				
Normal to Non-cavitary*	1		1	
Cavitary	1.62 (0.63 - 4.18)	0.31	3.64 (1.29 - 10.28)	0.02
Unknown	0.83 (0.29 - 2.42)	0.73	0.13 (0.03 - 0.62)	0.01
AFB-Sputum Smear Positivity				
Negative*	1		1	
Positive	2.51 (1.08 - 5.97)	0.04	6.02 (2.09 - 17.32)	0.001

Odds ratio calculated with reference to the PTB cases that did not transmit

* Reference Category

1. Includes Métis, Non-Registered Indian, and Inuit transmitters

Table 4-3. Household and behavioral characteristics of adult pulmonary tuberculosis (PTB) souce cases diagnosed in 2007 and 2008 based on transmission outcome

		Transmission Outcome			
	Total N(%)	No transmission N(%)	Infected Contacts Only N(%)	≥ 1 secondary case N(%)	P-Value*
Household Characteristics[1]	163(100)	31(100)	69(100)	63(100)	
Community of Residence					
Major Metropolitan*	40 (24.5)	11 (35.5)	19 (27.5)	10 (15.9)	0.07
Non-Major Metropolitan	20 (12.3)	3 (9.7)	12 (17.4)	5 (8)	
Reserve	84 (51.5)	12 (38.7)	30 (43.5)	42 (66.7)	
Métis Settlement	19 (11.7)	5 (16.1)	8 (11.6)	6 (9.5)	
Ventilation n(%)					
Good to Very Good	85 (52.2)	22 (71)	34 (49.3)	29 (46)	0.07
Poor to Fair	65 (40)	7 (22.6)	32 (46.4)	26 (41.3)	
Unknown or Inapplicable[Ψ]	13 (8.0)	2 (6.4)	3 (4.4)	8 (12.7)	
Persons per room (ppr) n(%)					
0 to 1	75 (46)	17 (54.8)	35 (50.7)	23 (36.5)	0.40
>1	71 (43.6)	12 (38.7)	27 (39.1)	32 (50.8)	
Unknown[Ψ]	17 (10.4)	2 (6.4)	7 (10.1)	8 (12.7)	
Behavioral Characteristics					
Proportion of members that smoke n(%)					
< 50%	86 (52.8)	16 (51.6)	36 (52.2)	34 (54)	0.95
≥ 50%	53 (32.5)	11 (35.5)	21 (30.4)	21 (33.3)	
Unknown or Inapplicable[Ψ]	24 (14.7)	4 (12.9)	12 (17.4)	8 (12.7)	
Participation in Group Activities n(%)					
No	110 (67.5)	17 (54.8)	49 (71)	44 (69.8)	0.42
Yes	45 (27.6)	12 (38.7)	18 (26)	15 (23.8)	
Unknown[Ψ]	8 (4.9)	2 (6.5)	2 (2.9)	4 (6.4)	
Mobility Status n(%)					
No Mobility	65 (39.9)	15 (48.4)	27 (39.1)	23 (36.5)	0.46
Within Community only	52 (31.9)	7 (22.6)	20 (29)	25 (39.7)	
Outside of Community	46 (28.2)	9 (29)	22 (31.9)	15 (23.8)	

* Fisher's Exact Test was used to calculate P-value

1. Characteristics and sample obtained from all source cases that have completed the *DTT* quantitative questionnaire

2. Refers to any travel, visit, or stay during 12 weeks before diagnosis

Ψ Unknown refers to cases who have chose to omit the inquiry or those who reside in prison and shelters of which household characteristics are suspected to vary daily

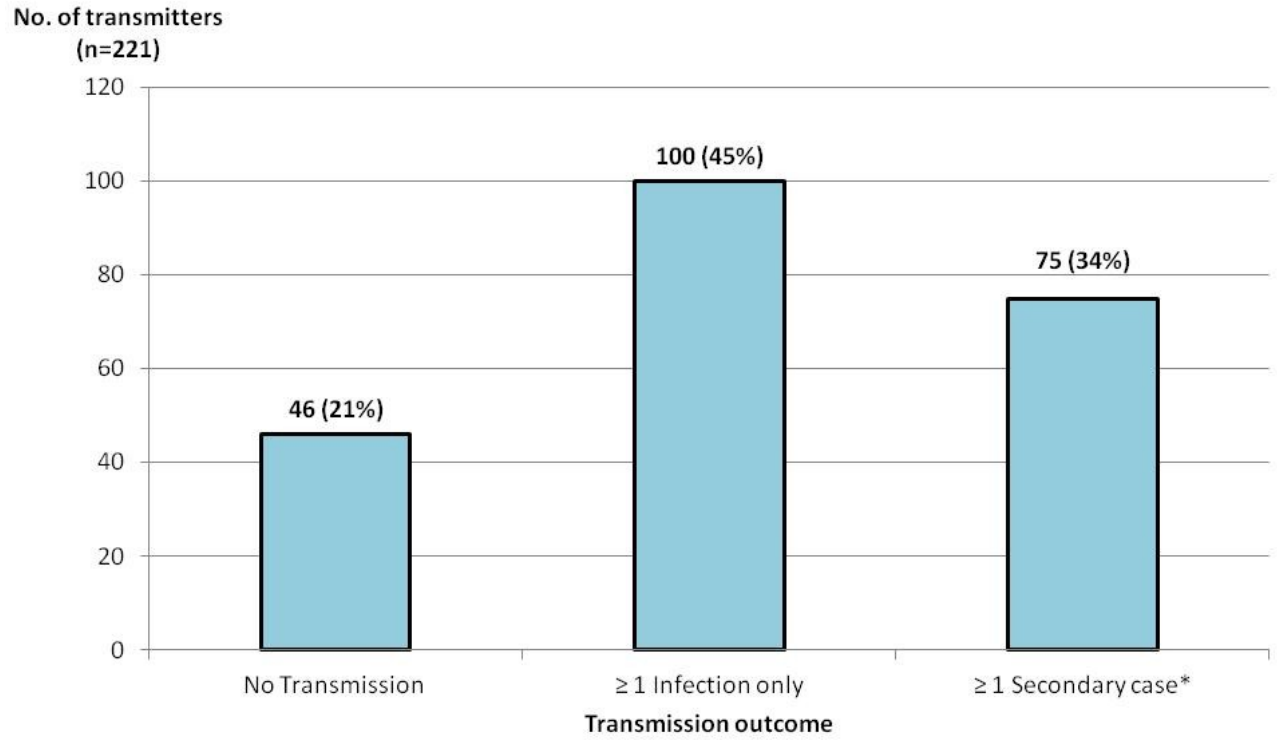
Table 4-4. Multivariate analysis of household and behavioral predictors of transmission outcome from adult pulmonary tuberculosis (PTB) transmitters diagnosed in 2007 and 2008 (N=163)

	Transmission Group			
	Infected Contacts Only		≥ 1 Secondary Cases	
Household Characteristics	Adjusted Odds Ratio (95% CI)	P-Value	Adjusted Odds Ratio (95% Confidence	P-Value
Community of Residence				
Major Metropolitan*	1		1	
Non-Major Metropolitan	2.66 (0.59 - 11.93)	0.20	2.08 (0.37 - 11.51)	0.40
Reserve	1.32 (0.47 - 3.72)	0.61	3.89 (1.27 - 11.94)	0.02
Métis Settlement	1.03 (0.26 - 4.16)	0.97	1.61 (0.35 - 7.45)	0.54
Ventilation				
Good to Very Good*	1		1	
Poor to Fair	3.00 (1.10 - 8.24)	0.03	2.25 (0.79 - 6.40)	0.13
Unknown or Inapplicable	0.61 (0.07 - 5.63)	0.67	2.19 (0.29 - 16.23)	0.44
Persons per room (ppr)				
0 to 1*	1		1	
>1	0.98 (0.39 - 2.49)	0.97	1.68 (0.65 - 4.36)	0.32
Unknown or Inapplicable	2.21 (0.30 - 16.37)	0.44	2.75 (0.16 - 1.29)	0.14

Odds ratio calculated with reference to the transmitters associated with no transmission events

* Denotes reference group

Figure 4-1. Outcome of MTB transmission from pulmonary tuberculosis (PTB) transmitters



CHAPTER 5: GENERAL DISCUSSION AND CONCLUSION

5.1 Overview of Thesis Research

This thesis has described the characteristics of cases and contacts involved in transmission of *M. tuberculosis* (MTB) in the Canadian-born people of the Prairie Provinces. Previous research pertaining to transmission characteristics is limited to population-based molecular studies, which do not account for all individuals affected by on-going transmission. (1-4). To bridge this knowledge gap, this project and thesis has taken a step to comprehensively identify infected contacts and secondary cases of potential TB transmitters by combining conventional and molecular approaches. The first objective was to combine individual level conventional epidemiology and molecular data to describe pulmonary tuberculosis (PTB) potential transmitters (source cases), infected contacts, and secondary cases among the Canadian-born population of the Prairies over a defined period of time. Key demographic, geographic, and clinical characteristics of these individuals were used to determine potential targets and priorities for TB elimination on the Prairies.

The PTB transmitters were further evaluated in the second objective to identify specific predictors of new infection and or secondary cases. In addition to basic population characteristics, the effect of poor housing conditions and high-risk behaviors on transmission outcome was also assessed. The study aimed to identify the important exogenous factors of the transmitters that contribute most to infection and secondary cases thus providing strategic avenues to disrupt the chains of transmission in the Indigenous peoples.

5.2 Summary of key findings

MTB transmission from 248 potential Canadian-born PTB transmitters diagnosed in 2007 and 2008 were quantified and described over 4.5 years (July 1, 2006 – December 31, 2010). Data derived from TB registries, contact-tracing investigations and isolate DNA fingerprinting identified 221 (89%) potential transmitters to be the source cases of 1189 infected contacts and secondary cases. Although recent TB infection occurred mostly within casual contacts of the transmitter, problematic secondary cases from those previously infected

were mostly identified in closer contacts, youth, and in the Métis Settlements. Remarkably, isolate DNA fingerprinting alone identified the majority (59%) of secondary cases to be unreported by contact investigations. Infected contacts and secondary cases were observed to occur mostly within the same population group, community and postal code of residence of the source. Compared to Alberta, transmission in Saskatchewan and Manitoba was common in Registered Indian people and in reserve communities. Lastly, a significant proportion of infected contacts resided in distant communities relative to the source case, highlighting the common yet significant role of mobility in inter-community transmission.

Transmission events resulting in at least one secondary case were associated with reserve communities and advanced pulmonary disease (i.e. AFB-smear positive and cavitary disease); whereas infection without active disease was most strongly associated with households with poor to fair ventilation. The sex of the transmitter was observed to modify the effect of age on the type of transmission event observed. Specifically, older females ≥ 35 years were approximately 70% less likely compared to males to transmit resulting in a secondary case. Behavioral risk factors and participation within group activities were speculated to be important for transmission but within limitations of the study, were not observed to be significantly significant.

5.3 Significance of Research

5.3.1 Contact Investigation

Conventional contact investigation (CCI) is an integral part of TB case management and disease diagnosis and prevention. In order to successfully interrupt MTB transmission, contacts of infectious transmitters must be promptly identified, assessed, and prioritized for treatment. It is understood that cases with advanced pulmonary disease (smear positive, cavitation, or cough) are the major drivers of transmission due to diagnostic delays and gaps in contact investigation (5-10). As observed in this study, smear positive pulmonary disease was associated with the majority of new infection and secondary cases. Effective contact identification and prompt treatment of infection at an earlier stage would prevent the

consequent progression to active disease thus eliminating future opportunities for transmission (11).

In this study, the data derived from CCI were used to identify and describe the contacts and culture-negative secondary cases that would have otherwise been omitted from strict molecular based studies. Tuberculin skin testing identified the majority of transmission to be manifest as new infection, suggesting that transmission studies that rely solely on molecular epidemiology have underestimated the true extent of transmission in the Prairie Provinces. Although these contacts were deemed non-infectious, they represent an important reservoir of potential TB cases. Without preventive therapy, approximately 10% of infected immunocompetant contacts are expected to develop active disease later in life of which 60 to 80% would be infectious (12,13). Considering this projection, it is expected that 98 of 982 infected contacts identified in this study would progress to active disease and 85 of these cases would present evidence of pulmonary tuberculosis.

Despite the expectation that transmission would mostly occur in close contacts, the analysis interestingly identified that the majority of newly infected individuals (ie. TST converters or new positives) were reported as casual contacts of the potential transmitter. The high proportion of contacts involved in transmission events may be a reflection of traditional Indigenous practices involving frequent socializing and casual interaction in the community. Although total transmission was most prevalent in casual contacts, secondary cases were more likely to be identified as close contacts of the potential transmitter. Furthermore, causal contact transmission was observed to occur more commonly in the same postal code of residence of the transmitter. In such situations, exposure to the transmitter was more likely to be ongoing resulting in possible repeated infection and faster progression to disease. This finding suggests that assigning conventional exposure status (“close” vs “casual other”) to contacts may not be the best indication for identifying overall transmission in the context of the Indigenous people, but rather a useful approach for identifying high-risk contacts that would benefit from preventive treatment.

5.3.2 Epidemiological risk factors for transmission

Host, residential, and behavioral factors have long been speculated to play a role in TB transmission, but little is known on the impact of these determinants on the Canadian-born population of the Prairies (14,15). These two transmission studies provide evidence that transmission from infectious PTB transmitter is linked between the characteristics of the host and his or her residence. Direct host factors of smear positive and cavitary disease in the Indigenous persons were the strongest independent predictors of transmission. In order to significantly reduce the pool of potential transmitters and potential transmission events, the prevention of advanced disease through prompt diagnosis and treatment must continue to be in the forefront of provincial TB control programs. Compared to metropolitan communities, the reserve communities are known to be associated with lower socioeconomic status and carry a greater burden of TB cases on the Prairies. The relatively poor social circumstance in reserve communities provides a broad explanation for the persistence of transmission (13,16-18). Residential characteristics of household overcrowding and household smokers were not statistically significant in the transmitters who completed a questionnaire, but are generally understood to be of clinical importance for on-going transmission. These characteristics are known to be more prevalent in reserve communities and have implications for greater exposure and susceptibility for infection and active disease. Similarly, households with poor ventilation were also more common in reserve communities but and were observed to be a more significant predictor for TB transmission. Once aerosolized in poorly ventilated conditions, MTB is able to persist in the air, thus increasing the probability of inhalation, possibly repeatedly, by household contacts (19-21).

5.4 Strengths and Limitations of Research Studies

The prospective nature of this study was advantageous to measuring transmission. Demographic, geographic, and clinical variables of exposure were assessed more accurately and efficiently as new cases and contacts were recruited in the study period. Additionally, the combination of conventional and molecular methodology was integrated into the study design to capture all cases and infected contacts presumed to be part of a chain of transmission on the

Prairies, consequently reducing selection bias. The limitations of conventional contact investigations and isolate DNA fingerprinting individually were offset by their combined application across the Prairies. Contact tracing investigations identified the majority of transmission to involve infected contacts that would not be identified by molecular methods alone. Likewise, isolate fingerprinting revealed that the majority of secondary cases were not identified by contact tracing, suggesting a potential gap in current contact investigations.

The limitations of these investigations must be acknowledged for future studies. In this study, missing data existed for demographic, social, and clinical characteristics of transmission. Due to missing data at the time of analysis, the majority of the secondary cases (n=36, 51%) in Saskatchewan were not categorized by age, sex, or population group at the time of writing, therefore; these the characteristics of these cases were not included in the analysis. The omission of these cases was expected to underestimate the true prevalence of transmission by at most 9% (36 of 388 transmission events) mostly in young Indigenous persons, the demographic in which most secondary cases are historically expected to occur (22-25). Approximately 5% to 15% of all potential transmitters did not respond or were unable to answer questions related to housing and behavioral characteristics. Upon further investigation, the majority of these individuals were identified as homeless or residents of correctional institutions on the Prairies. Despite the inability to measure residential and behavioral characteristics, it is presumed that these individuals would be exposed to over-crowded indoor situations in homeless shelters and prison cells (> 1 person per room or cell) with poor ventilation. Lastly, the complete clinical context was not available for all transmitters. It was noted that cough status was reported as “unknown” in 15% and 50%, respectively. This gap may have led to the misclassification of some potential transmitters as “true sources.” Since all clinical data was placed into context with conventional epidemiological data about person, place, and time relative to the infected contacts, it was presumed that the extent of misclassification would not be significant to alter the conclusions of the study.

Transmission characteristics were limited to available contact tracing and molecular data in this study. In accordance with the epidemiological criteria, the directionality of transmission was based on relative degree of infectiousness and the time of diagnosis compared to the

secondary case or contacts, with the most infectious cases likely to be the source case. Determining the order of transmission can be improved with higher discriminatory molecular methods in additional to conventional epidemiology. Recent development in whole-genome sequencing has proved useful in determining the direction of transmission (26). Inter-province transmission is likely to occur especially within communities situated near the provincial borders. Jurisdictional constraints make it difficult for contacts of a source case residing in a different province to be comprehensively assessed for inter-provincial transmission. Distance analysis was limited to the postal code of residence for all infected contacts and cases. Although postal codes may be useful in determining the community type, it may not be the most practical approach for accurate assessment of distance between cases and contacts. The reserve communities for example were identified within a single postal code covering large distances. Cases and contacts within the same reserve communities were identified within the same postal code but in actuality, could have resided geographically distant from one another. Theoretically, a postal code based distance analysis is more feasible in metropolitan settings, where a single postal code is more location-specific. Considering the high transmission in the reserve communities, transmission between cases and contacts residing at a distance from one another was likely to be underestimated in the analysis.

5.5 Future Directions and Recommendations

Considering the benefits and limitations of the epidemiological study of this caliber, substantial work is still required to capture the underlying social and clinical processes of transmission. As observed, contact tracing investigations and molecular fingerprinting methods provide considerable insight to identify transmission but together have limitations that may be resolved with other epidemiological methods. In addition to conventional and molecular approaches, target-specific methods using geographic information systems (GIS) and social network analyses may provide better resolution of transmission patterns at the community level. Practical examples have been demonstrated in a few studies that had successfully identified important individuals and locations associated with high transmission (26-30). When used appropriately, these methods may highlight specific location hot spots and contacts of

cases that are likely to benefit the most from TB treatment. Despite the method of choice, transmission data must be interpreted in context with conventional epidemiological data provided by contact investigations.

In light of the epidemiologic evidence of transmission, a few recommendations can be gleaned from this study. Preventing long diagnostic delays in cases and screening delays in contacts. In order to improve case finding and prevent contacts from progressing to infectious active disease, provincial TB program must establish a multi-disciplinary approach involving community leadership, education, and residential initiatives in order to provide a sustainable framework to eliminate TB transmission, whilst respecting traditional Indigenous values. Specifically, newer strategies are required to:

1. Reduce the prevalence of advanced pulmonary disease by intensifying case finding and contact investigations in high-incidence reserve communities of the Registered Indian people
2. Improve contact investigation outcomes by accounting for contact heterogeneity (mobility, co-morbidities) in addition to conventional exposure status (close vs. casual contacts)
3. Provide a community led initiative to improve the quality and sustainability of adequate housing in the reserve communities.

5.6 Conclusions

TB in the Canadian-born Indigenous people remains a public health concern in the Prairie Provinces. It is established that TB transmission is largely an issue in the Registered Indian population of the Prairies. Risk factors for transmission included exposure to pulmonary TB cases with advanced disease. Advanced pulmonary disease was strongly associated with greater number of infected contacts, and perhaps the strongest predictor of transmission overall. Indirect risk factors for transmission included residency on reserve and households of insufficient ventilation. Transmission generally occurred within the same community type as the transmitter but mobility of cases and or contacts was significant. Although the role of mobility is still unclear, it may potentially create challenges for TB control efforts to contain the

spread of new infection and disease. A targeted contact investigation in combination with modern epidemiological tools is suggested to identify contacts that are most susceptible to new infection and or progression to active disease.

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Chapter 1

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Chapter 2

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Chapter 5

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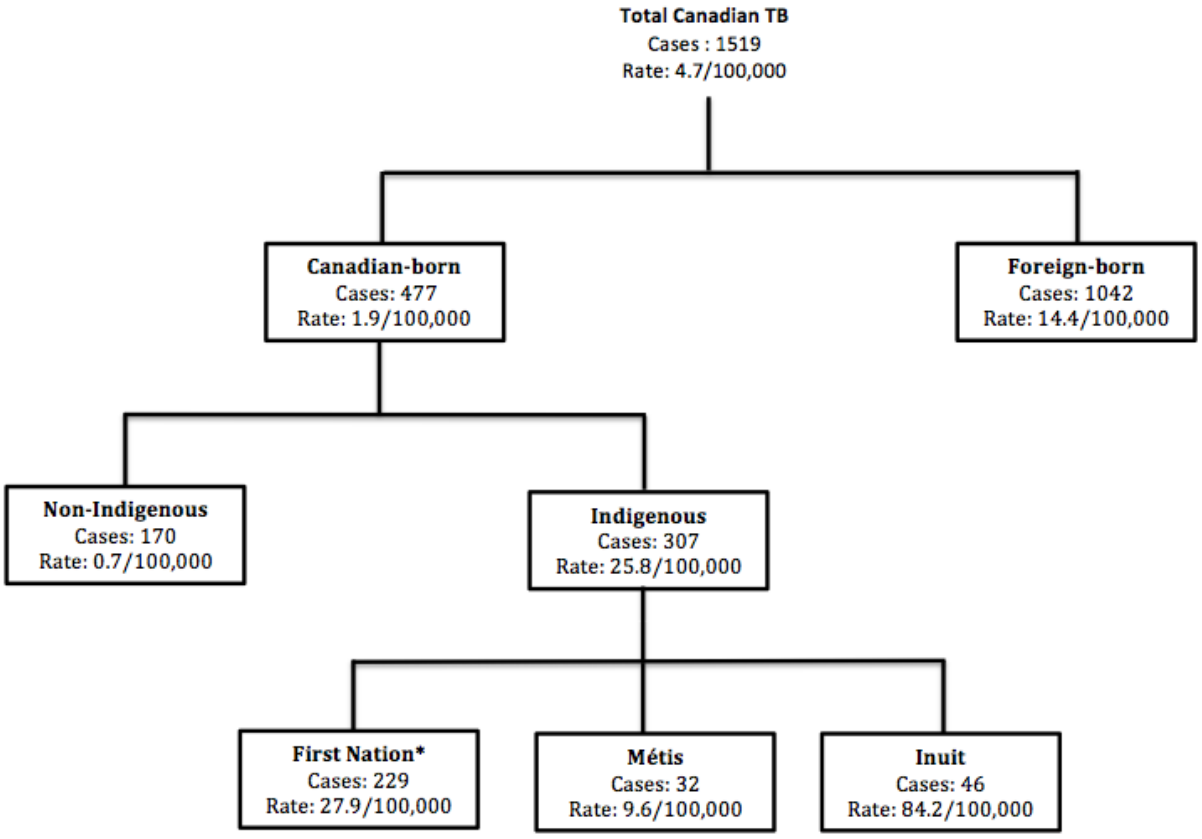
APPENDIX A

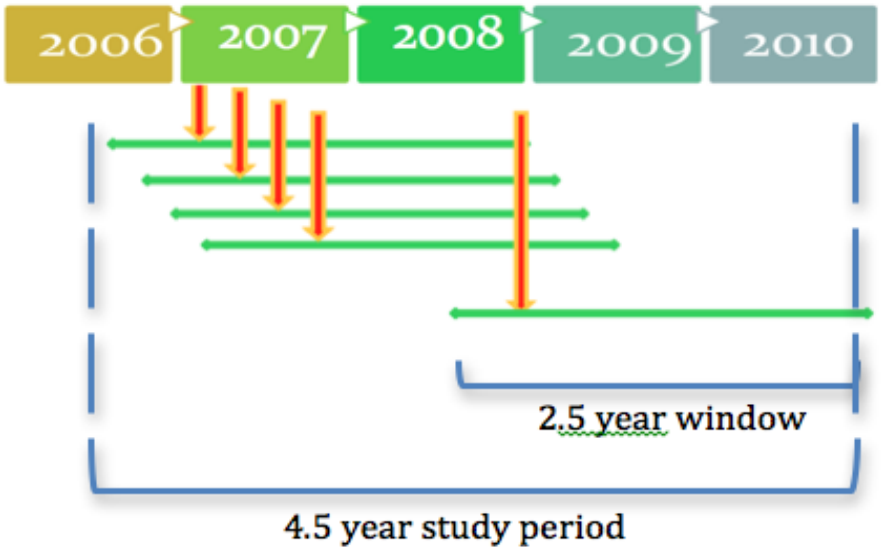
INCIDENCE OF TB IN CANADA BY POPULATION GROUP IN 2007



* First Nations Indigenous include the Status (Registered) and Non-Status Indian cases recognized in the Indian Act of 1876 (3)

APPENDIX B

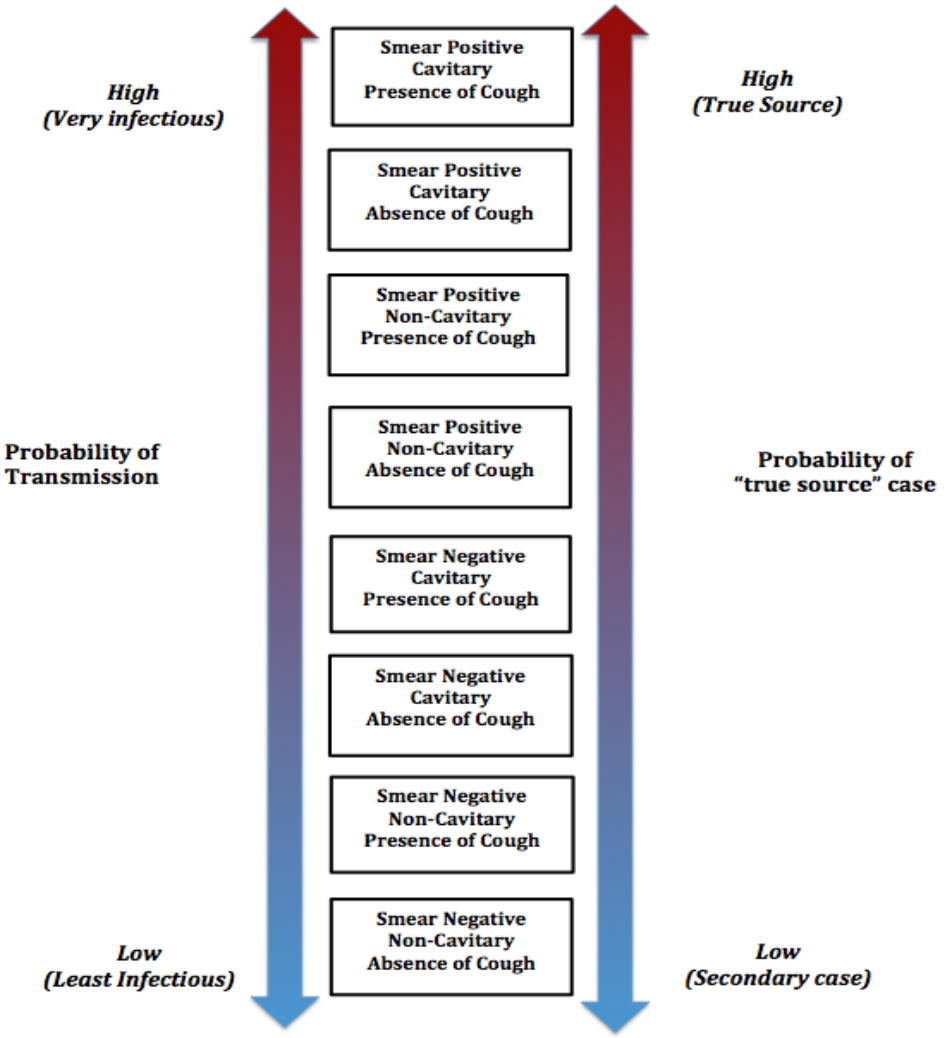
TRANSMISSION WINDOW OF POTENTIAL TRANSMITTERS DIAGNOSED IN 2007 AND 2008 IN ALBERTA, SASKATCHEWAN, AND MANITOBA



A 2.5 year (30 month) transmission window was examined for every Canadian-born adult PTB case diagnosed between 2007 and 2008 in order to capture all transmission events that led to early disease. This window began 6-months before and ended 24 months after the start date of treatment of each infectious case. It was assumed "potential transmitters" would be transmitting for less than 6 months before the start date of treatment. This period is necessary to identify index cases that may have been diagnosed prior to the transmitters. Index cases were required to have primary disease and a negligible capacity to transmit. Contacts of the source cases identified at the time of diagnosis had the greatest risk of developing disease within 24 months of being infected.

APPENDIX C

BASIC CLINICAL ASSUMPTIONS FOR IDENTIFYING SECONDARY CASES



A " Type I secondary pulmonary tuberculosis case" is understood to be relatively less infectious than the true source. Additionally, the case must be diagnosed either 6 months before (if 6 months before, the secondary case must have primary disease) or 24 months after the date of diagnosis of the source, listed as a contact of the source, and have an identical *M. tuberculosis* isolate. If multiple cases share the same exposure status as listed above, then attribution of a given secondary case to a given transmitter was decided after taking into account whether they were from the same community as the source, listed as a "close" contact, and diagnosed at an earlier time period. A secondary case could only be attributed to one source case

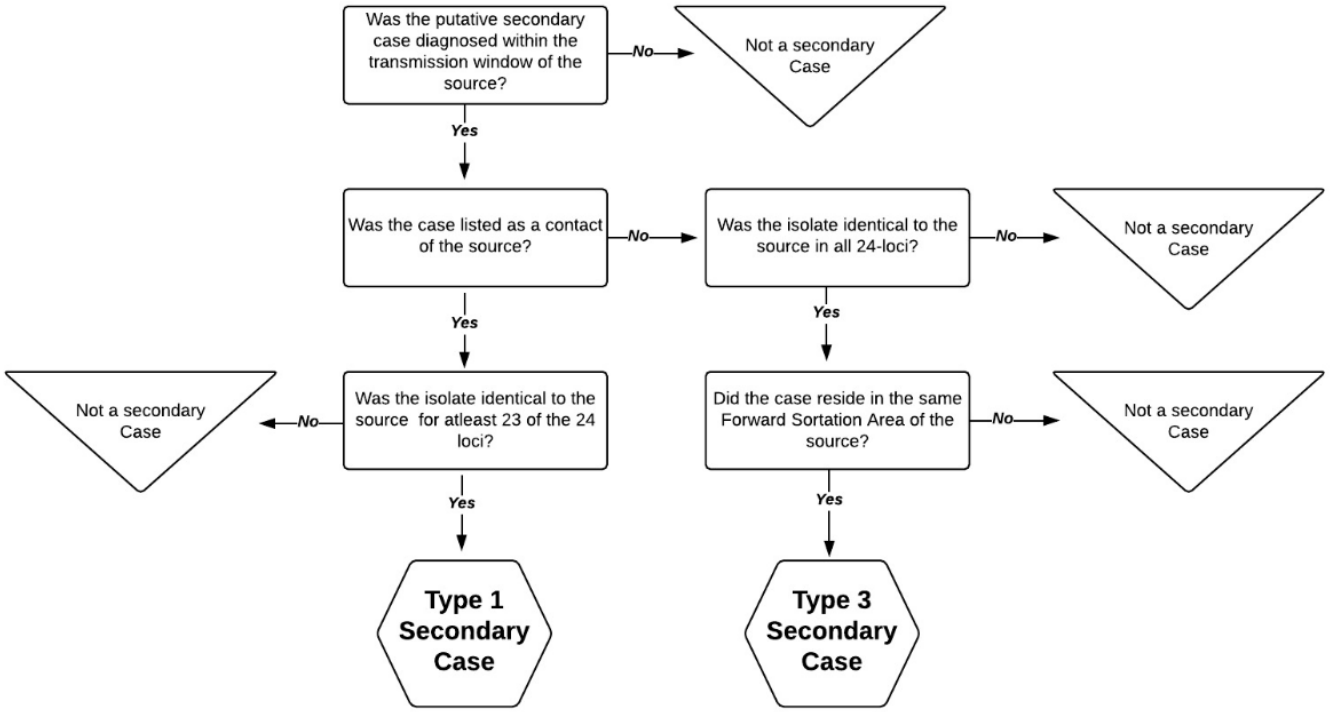
APPENDIX C (CONT'D)

CLINICAL CHARACTERISTICS OF ADULT PULMONARY TUBERCULOSIS SOURCE AND SECONDARY CASES: 2007 TO 2008

Source PTB characteristics	**Total Assessed** N (%)	**Source PTB** N (%)	**Secondary PTB** N (%)	P-value
Total No. Assessed	248 (100)	221 (100)	27 (100)	
AFB Sputum Smear Positivity				
Positive	144 (58.1)	137 (62)	7 (25.9)	<0.0001
Negative	104 (41.9)	84 (38)	20 (74.1)	
Chest Radiography				
Normal	16 (6.5)	8 (3.6)	8 (29.6)	<0.0001
Abnormal Non-Cavitary	108 (43.6)	93 (42.1)	15 (55.6)	
Abnormal Cavitary	88 (35.5)	87 (39.4)	1 (3.7)	
Unknown	36 (14.5)	33 (14.9)	3 (11.1)	
Symptomatology				
Presence of Cough	109 (44)	95(43)	14 (51.9)	<0.0001
Absence of Cough	32 (12.9)	20 (9.1)	12(44.4)	
Unknown	107 (43.2)	106 (48)	1(3.7)	

APPENDIX D

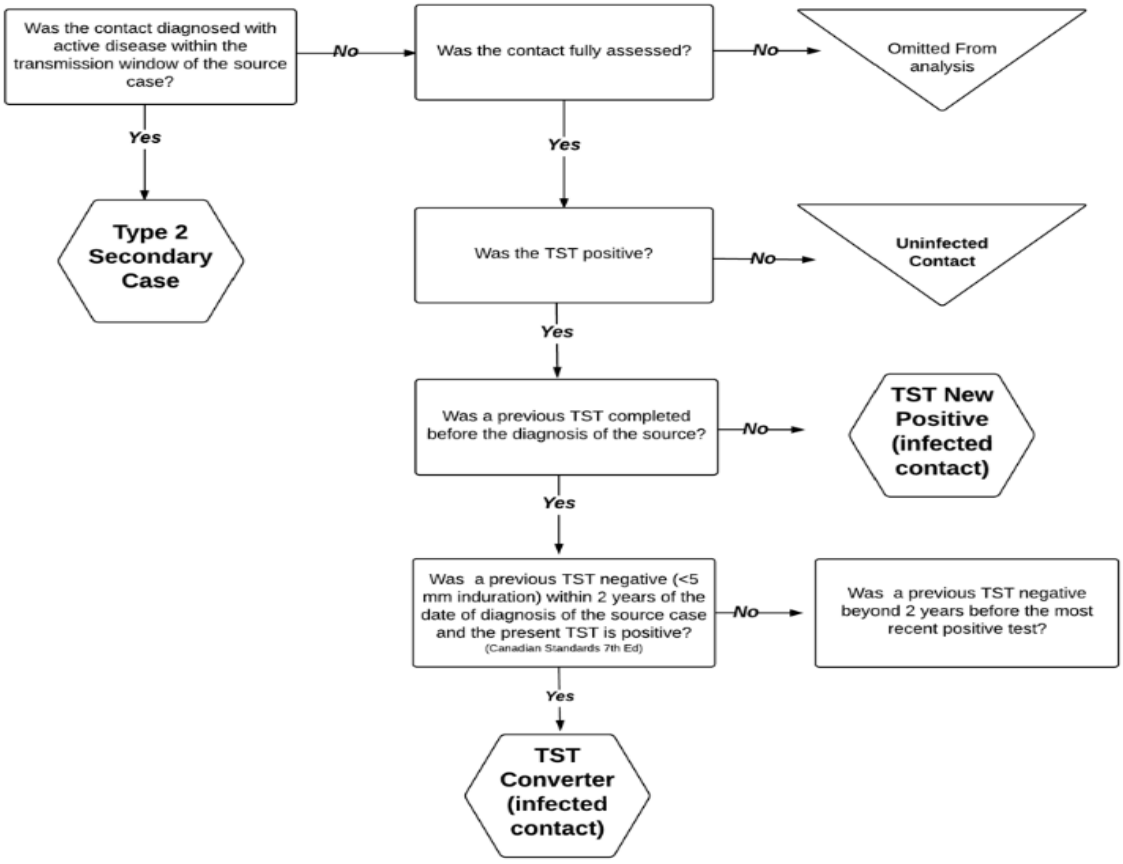
IDENTIFICATION STEPS OF CULTURE-POSITIVE SECONDARY CASES



If the "potential source" and the putative secondary case are listed as contacts of each other, and each is >14 years of age and neither has primary disease, then basic assumptions apply in deciding who is the true source case. If the true source case occurred before 2007 or after 2008, then the "potential source" reported in 2007 or 2008 cannot attribute the true source case to themselves as a secondary case. If the "potential transmitter" is smear-negative with minimal disease (i.e. is more appropriately considered to have primary disease) and is listed as a contact of a background case that is smear- positive, then the smear-positive case cannot be attributed to the smear-negative transmitter.

APPENDIX E

IDENTIFICATION OF CULTURE-NEGATIVE SECONDARY CASES AND INFECTED CONTACTS



If the putative Type II case is a contact of multiple "potential sources" then basic assumptions apply in attributing them to a particular "potential source". Rarely a notified culture-negative case may meet the definition of a type 2 secondary case of a "potential source" who has themselves already been labeled a secondary case (with primary disease) of another "potential source". Under such circumstances it is more appropriate to assign this "Type 2 secondary case" to the "true potential source" (ie. the "potential source" to whom the primary disease "potential source" was attributed); they thus become a special type 2 secondary case, their contact being a community contact