Strategies for Reducing Incidence of Tuberculosis Disease in a Low-Burden Setting

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

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Abstract

Pulmonary tuberculosis (TB) is a communicable disease that has an airborne route of transmission. It is a disease of poverty that exists in every country of the world. Within high-income, low TB burden settings, the disease increasingly affects vulnerable and underserved population groups who are hard to reach. In tandem, as TB becomes rarer, expertise in diagnosing and managing the disease declines. These two facts threaten TB elimination efforts because the delayed diagnosis of pulmonary TB can lead to transmission. Transmission can cause primary disease, or a latent TB infection (LTBI) that without appropriate precautions can reactivate at a later date, thereby causing future transmission. As such, within high-income countries already adept at identifying contacts and offering prophylaxis, it is making timelier diagnoses of pulmonary TB to interrupt transmission that is crucial. This work focuses on strategies aimed at improving current programming efforts in a high-income setting. The studies presented herein: 1) characterize the most infectious cases, with implications for raising clinical suspicion among all providers, 2) show that it is possible to 'predict' pulmonary TB among a cohort of people referred for TB services on the basis of readily available information from a targeted medical history, and, 3) identify a significant point of contact with the healthcare setting for undiagnosed pulmonary TB patients (the emergency department). This latter study suggests that, once validated, prediction algorithms for pulmonary TB may provide diagnostic tools that would have great application in settings where TB is frequently overlooked.

Preface

This thesis is an original work of Courtney Elizabeth Heffernan. Some of the work presented herein has been previously published, and are reproduced with the approval and support of my co-authors. Citations are provided below. Figures that are reproduced from publications are in those with Creative Commons Attribution non-Commercial Licenses; otherwise they are my own.

I have received ethics approvals from the University of Alberta Health Research Ethics Board for the three primary studies presented herein. Registration numbers are: **Pro00086712**, (Chapter 2), **Pro00035012** (Chapter 3), and **Pro00076709** (Chapter 4). Alberta Health Services (AHS) provided operational and administrative approvals. A data sharing agreement was executed for Chapter 4.

Grant support to the Tuberculosis Program Evaluation and Research Unit helped fund some of the work presented in this dissertation; details are provided below and within each chapter as appropriate.

Portions of the introduction have been reproduced (and edited for clarity) from the following commentary: **Heffernan C**, and Long R. Would program performance indicators and a nationally coordinated response accelerate the elimination of tuberculosis in Canada? *Can J Public Health* 2018; 110: 31–35

And, the following article: **Heffernan C**, Long R, Cardinal-Grant M, Heyd (née Lynn) A, Sparling L, Nokohoo M, Piche D, and Janvier D. Two Row Wampum, Human Rights, and the Elimination of Tuberculosis from High-Incidence Indigenous Communities. *Health Hum Rights*. 2019; 21(1):253–265.

For the latter article: CH and RL conceived of this manuscript. CH provided initial drafts. MCG, and AH provided important public health insights and critical reviews; LS, MN, DP, and DJ provided important cultural interpretation, insights, and local community knowledge critical to achieving the partnerships this paper describes. RL provided expert oversight, and critical reviews of all drafts. Funding was provided by: Canadian Institutes of Health Research (CIHR): grant numbers RN246253-337694, RN298107-379492, with partnership from the Saskatchewan Health Research Foundation (SHRF), Alberta Innovates (AI), and the Department of Medicine (DoM) in the Faculty of Medicine and Dentistry (FoMD) at the University of Alberta.

Chapter 2 is submitted for publication as: **Heffernan C**, Barrie J, Doroshenko A, Egedahl ML, Paulsen C, Senthilselvan A, and Long R. The prompt recognition of infectious pulmonary tuberculosis is critical to achieving elimination goals: a retrospective cohort study.

CH, and RL conceived of this study. CH analyzed and interpreted data and provided initial drafts, JB interpreted radiographs, and critical review, AD and AS provided assistance with statistical methods and critical reviews, MLE and CP abstracted and collated relevant clinical data and provided critical reviews, RL interpreted chest radiographs and provided expert oversight and critical reviews of all drafts.

Chapter 3 is published as: **Heffernan C,** Doroshenko A, Egedahl ML, Barrie J, Senthilselvan A, and Long R. Predicting pulmonary tuberculosis in immigrants: a retrospective cohort study. *ERJ Open Res* 2018; 4 00170-2017. DOI: 10.1183/23120541.00170-2017.

CH, and RL conceived of this study. CH analyzed and interpreted data and provided initial drafts; JB interpreted radiographs, and critical review; AD and AS provided assistance with statistical methods and critical reviews; MLE abstracted and collated relevant clinical data and provided critical reviews; and, RL provided expert oversight and critical reviews of all drafts. This work was supported by an open operating grant funded in 2015 by the University of Alberta University Hospital Foundation in the Medical Research Competition (UHFMRC), funding ID: RES0029110.

Chapter 4 is in preparation for submission for publication as: **Heffernan C**, Asadi L, Egedahl ML, Rowe BH, Barrie J, and Long R. Revisiting emergency department use by undiagnosed pulmonary tuberculosis patients: A population-based study. 2020.

CH and RL conceived of this study. CH analyzed, and interpreted data and provided initial drafts. BHR provided clinical guidance and critical reviews; JB interpreted radiographs, and provided critical reviews. LA, and MLE abstracted and collated relevant clinical data and provided critical reviews. RL provided expert oversight, and critical reviews of all drafts.

Dedication

Dedicated to the future version of self who was able to get the work completed.

Acknowledgements

My acknowledgments may appear long. This is because the pathway to a PhD has been long. The contents of my dissertation ought to prove short and sweet in comparison given the commitment, forged, no doubt, in a lake of fire, between my supervisor and his red pen.

I was raised by a young, single mother who is a high school dropout. In 1987, a year after my mother turned 25, she enrolled in University as a mature student with no imminent plans of getting a degree, and no major declared. In 1995, she earned a PhD in Cognitive Psychology. In 2008, she became a full professor while working as the Associate Dean of Graduate Studies and Research in the Faculty of Arts and Social Sciences at the institution where she is employed. She has been a Canada Research Chair, and her lab has had continuous support from Local, Provincial and National funding bodies; in 2019 she was made a fellow of the Canadian Society for Brain, Behaviour and Cognitive Science (CSBBCS). By bearing witness to my mother's journey, and also joining her in class when childcare was not within her means, I learned many important lessons for which I am truly grateful. These lessons include the promise of an education to propel you from other peoples' expectations of your abilities to your full potential; that it may take time to figure out what you want to be when you grow up, which is okay; and, that with a great education, you may exceed even the expectations you set for yourself. For these reasons, I express my gratitude for a high-quality education, which I believe to be a fundamental right. I acknowledge that this opportunity still does not exist for many.

My supervisor has taught, to a preternaturally impassive person, the value of having, and expressing your passion. To say that Richard is consumed by tuberculosis is both a punny joke, and an understatement. To say that his commitment to his patients, and ultimately, tuberculosis elimination is infectious, is… well… the same. Calvin Morriseau writes, in his book, *Into the Daylight*, of an Anishinaabe teaching: "It is the giving which beseeches the honour. It is the receiving which makes us humble". Under Richard's honourable supervision, I have been humbled.

My committee is rounded out by Drs. Alexander Doroshenko, James Talbot, and Paul Hackett. I have also received mentorship from Drs. Ambikaipakan Senthilselvan, Brian Rowe, and Giovanni Ferrara. To Drs. Doroshenko and Senthilselvan, thank you for your patience in teaching, and often re-teaching, the statistical and epidemiological methods I have used in my studies, and which are critically important to describing health inequities. Though these concepts do not come naturally to me, you have both generously shared your expertise. To Drs. Talbot, Rowe, and Ferrara, I thank you for the valuable lessons in time-tabling, priority setting, and for having passed along - as an implicit lesson – the importance of mirth in academia. To Dr. Hackett, I thank you for seeing in me a future colleague, and for pushing me to ask the questions I might otherwise have considered intractable problems. To my external reader - you have taken the time out of your schedule to read and comment on this work. That is important to me, and I thank you.

Since 2010 I have had the opportunity to work with so many wonderful staff, and trainees at the Tuberculosis Program Evaluation and Research Unit, all of whom have touched me and informed my studies either directly, or indirectly. These people include: Michael Jensen, Angela Lau, Derrick Kao, Lisa World, Betsy Varughese, Bill Chroniaris, Norah Landry, Kaelyn Boyes, Susan Lee-Ying, Smit Patel, Kathleen McMullin, Mannat Dhillon, John Niruban, Zhiwei Gao, Lisa Eisenbeis, Amber Lynn, John Cole, Mary Lou Egedahl, Leyla Asadi, Natalie Runham, Melissa Cardinal, and Sara Komarnisky. Of Mary Lou Egedahl, I would like to say a few extra words. Mary Lou has been instrumental to every one of my studies, and has assisted with data collection and research direction. Her work is integral to the basic functioning of the entire research unit. I could not have completed this (or any) work without her assistance.

I have many colleagues and partners outside of the TB PE & RU; all have been supportive and great to work with. They include, but are not limited to: Andrea Warman, Wadieh Yacoub, Ibrahim Kahn, Celine Czernick, Meenu Sharma, Sylvia Abonyi, and Maria Mayan. Most especially, I am grateful to the community partners with whom I have worked in Treaty 8 for nearly a decade. Everyone I have worked with at the community level has shown a great commitment to tuberculosis elimination efforts. It is inspiring in the face of so many competing demands – the presence of tuberculosis disease being a proxy for social and economic dysfunction. You remind me to, also, persist in the face of injustice.

I would be remiss not to mention the husband who has supported me throughout the past 13 years; he is a blessing, and also an amazing dog-walker. I thank him here for posterity in the event that he reads this tome. My step-father, and brother are also hugely supportive, and genuinely wonderful people.

I have received financial support throughout my PhD studies from the Canadian Institutes for Health Research (CIHR) administered through the Alberta Network Environments for Aboriginal Health Research (AB-NEAHR), the University Hospital Foundation (UHF), the Alberta Respiratory Centre (ARC), the Faculty of Graduate Studies and Research (FGSR) at the University of Alberta, the Alberta Lung Association (ALA), and the Respiratory Strategic Clinical Health Network (RHSCN). Financial support makes living while studying possible.

Finally, I should say a few words about my education in Philosophy. Philosophy is love, “philo”, in Greek, of wisdom, “sophia”. It is a discipline that teaches rigour, and *how to learn* rather than what to learn. Chief among those who taught me to love learning are Marcello Guarini, and Jeff Noonan. If you have read this far, then know that a love of learning has informed my entire student career, spanning 19 years (minus a five-year break, where I worked at... a University). One day I hope to impart this love onto the next generation of learners, and today I am a day closer to that goal.

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Chapter 1: Introduction

1.1 Background

Tuberculosis (TB) is among the top ten causes of death worldwide, and, in 2016, it surpassed HIV/AIDS to become the leading infectious source of mortality globally [1]. TB maintains this position today [2]. The principal disease causing agent is *Mycobacterium tuberculosis* (*M.tb*), which has, for practical purposes, a single host – humans [3, 4]. Although active disease can occur with any one, and/or multiple organ involvement, its most communicable form is disease in the lungs [5, 6]. This is because the organism spreads efficiently through the air via processes of aerosolization that include coughing, sneezing, singing, and playing wind instruments [6, 7]. Less common processes of aerosolization include irrigation of infected wounds, and irrigation of organs and the body during autopsy [8]. More recently, a non-aerosolization pathway has been implicated in the transmission of the pathogen; that is, in transplanted organs (bone marrow or solid organs) [9]. The transmission of TB by people who harbour disease in sites other than the lung is thus possible but very infrequent [10, 11]. Infection and the potential for subsequent progression to disease (reactivation) results when the organism is inhaled into the lower respiratory tract by someone in contact with a person exhaling/aerosolizing the organism in their presence [12]. In this way, the number one agency by which the organism is transmitted, and infection acquired is the biologically necessary function of breathing [13].

Sites of infection may be seeded in organs throughout the body by a 'silent bacillemia' [14, 15]. This is the name for the process whereby the organism is

drained from the lymphatics into the bloodstream, and is diffused throughout the body [15]. *M.tb,* however, is aerobic and prefers sites of high oxygen tension [16]. As a result, the disease very often reactivates in the upper lung zones where the environment is conducive to its replication [16, 17]. When the disease occurs in the lungs (and/or other organs in the respiratory tract) it is known as pulmonary TB (PTB). For the reasons described above, when PTB is not properly diagnosed, precautions against its transmission that rely on modifiable behaviours are not taken. As such, PTB represents the quintessential public health disease, and it is the focus of this dissertation.

This introductory chapter is designed as a narrative that describes the global and national (Canada) epidemiology of TB disease; the effects of migration on local epidemiology; current targets for TB elimination, and our national responsibility to meet those targets. I will briefly introduce the inherent weaknesses of elimination rhetoric; and, finally, describe the significance to public health of devising locally appropriate responses to the presence of this disease. The chapters that follow this introduction describe three studies that were undertaken within the context of TB elimination in the Prevention and Care Program of Alberta.

1.2 TB Epidemiology

It is estimated that between one quarter and one third of the world's population is infected with the bacillus *M.tb*, generating an enormous reservoir from which future cases may spring; infection being a necessary prerequisite for disease [18, 19, 20]. Undiagnosed or inadequately treated PTB cases continually replenish this reservoir. While the global population is ever growing, the absolute number of cases of TB (all

forms) estimated to occur, per year, has been relatively stable at 10 million (range: 9-11.1), with 7 million of those notified in 2018, up from 6.4 million notified in 2017 [2]. There is a gap between notified cases and the number of cases that are believed to exist because not every patient seeks treatment, and even if they do, not every patient receives an appropriate diagnosis [2]. Developing strategies to find and rapidly diagnose these missing cases is a high priority.

In 2018, there were 20 low-incidence countries that reported fewer than five cases per 100,000 population, while the 20 highest-burden countries held an 84% share in the global incidence of disease (~132/100,000 population)[1] [2]. Among this latter group, five reported an annual incidence of more than 500 cases [all forms of TB] per 100,000 population[2] [2]. The proportion of notified cases, globally, who have PTB is 85% (range across WHO regions: 76% - 92%) [2].

Pulmonary disease can represent both recent infection (developing within 12-24 months of infection), or the reactivation of a remotely acquired infection [21]. Since it is PTB that generates the seedbed of future cases, they are the cases who must be identified and receive treatment in a timely fashion in order to prevent transmission [22]. At the same time, LTBI should be identified and treated so that it does not progress to a state of disease with the potential to transmit [23]. It is

[1] Incidence data for 2018 are from: https://data.worldbank.org/indicator/SH.TBS.INCD (these data are updated as countries complete their reporting obligations, so the data here are not always reflected in the published annual reports from the WHO).
[2] China: 866/100,000 pop; India 2,690/100,000 pop; Indonesia 845/100,000 pop; Pakistan 562/100,000 pop; Philippines 591/100,000 pop. https://www.who.int/tb/publications/global_report/tb19_Report_country_profiles_15October2019.pdf?ua=1

recognized that these two very basic strategies- preventing transmission, and preventing reactivation - provide the foundation for good TB control [2, 24].

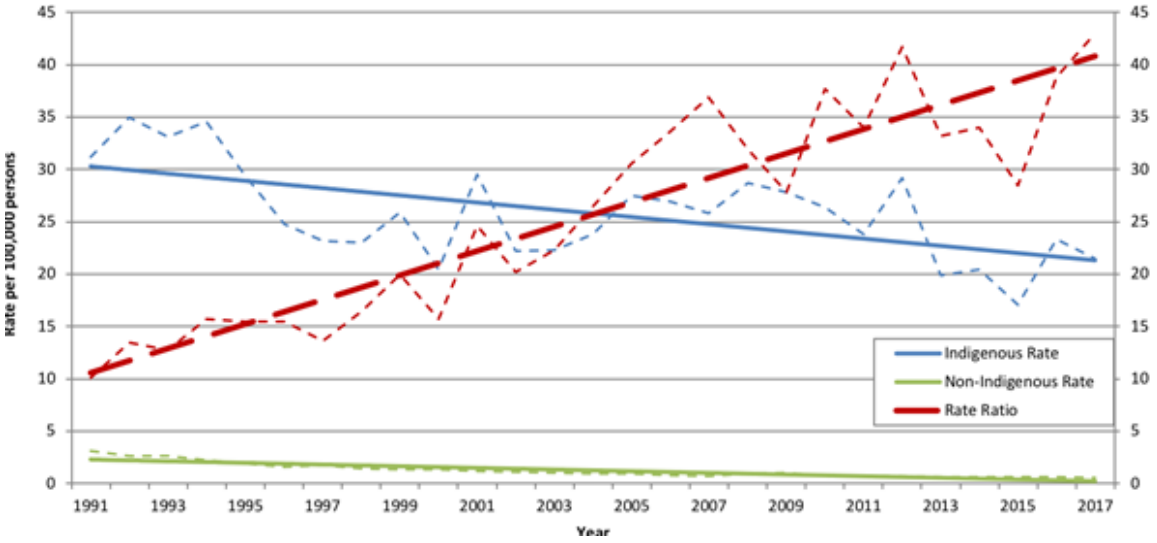
TB is a communicable disease of poverty that exploits conditions of socioeconomic inequity; there is much in-country and/or by population variability [25]. In other words, every country experiences inequitable distributions of wealth and national, population-specific measures of TB disease reflect this reality. TB in India, for example, is five times higher among the poorest quintile than the wealthiest [26]. Disparities in the experience of TB disease are perhaps most stark in high-income countries, where resources are available to effect successful TB prevention and care programs. Canada is one such example.

Canada is a high-income, low-incidence country, and the disease is now concentrated in two underserved population groups. While the overall rate of TB in Canada is low - 4.9 per 100,000 population in 2017 - among foreign-born persons and Indigenous peoples[3], it remains relatively high, at 14.7 and 21.5 per 100,000 population, respectively [27]. The rate of disease in the Canadian-born non-Indigenous population in the same period was 0.5 per 100,000 [27]. In other words, in 2017 the rate of TB disease in Canada was 29 times higher among foreign-born persons than the Canadian-born non-Indigenous population, and 43-fold higher among Indigenous Canadians than the Canadian-born non-Indigenous population. Between the latter two groups, the rate ratio – difference between the two rates –

[3] In 1982, the Constitution Act (Canadian Charter of Rights and Freedoms. Constitution Act, 1982(1)) was amended to recognize three culturally distinct groups of Indigenous peoples in Canada: First Nations, Métis and Inuit. Where I use the term "Indigenous peoples" throughout this text, I am referring to these three groups, generally, unless otherwise specified.

has been growing. This is the result of a diminishing burden of disease among Canadian-born non-Indigenous persons from 2.5 to <1 per 100,000 since 2010, and a less satisfactory decline in the burden of disease among Indigenous Canadians from 30 to 21.5 per 100,000 between 1991 and 2017 (see Figure 1). Meanwhile, the vast majority of cases, in absolute numbers, are notified among foreign-born persons in Canada (now representing >70% of cases per year [2017]) [27].

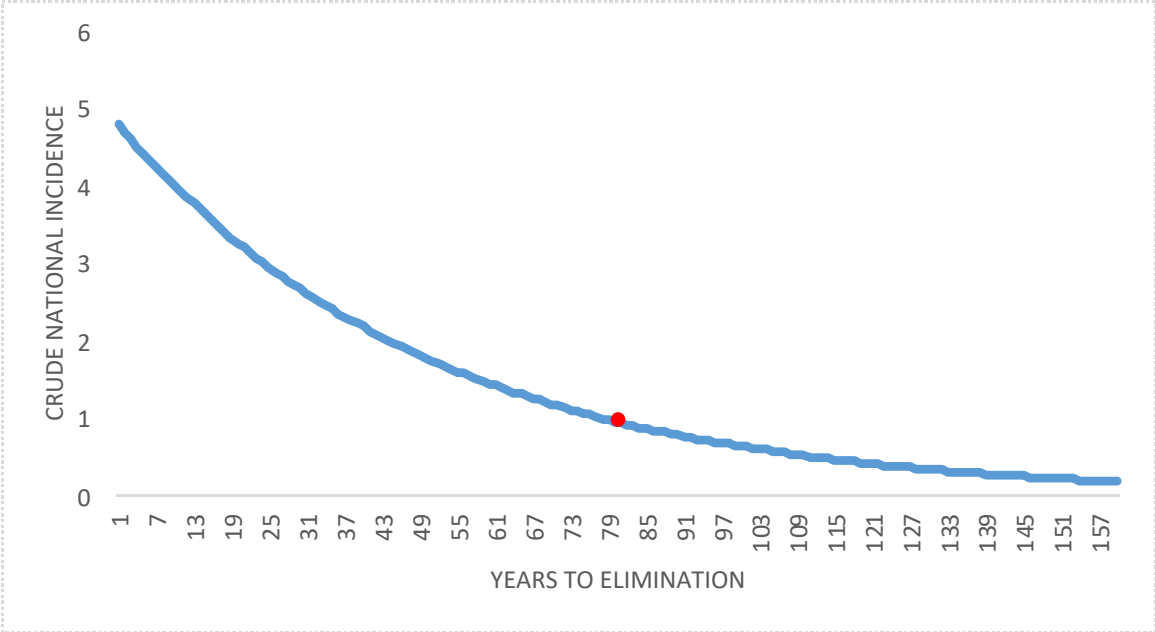
Figure 1: The incidence of TB in the Indigenous population of Canada divided by the incidence of TB in the Canadian-born non-Indigenous population of Canada – i.e., the rate ratio, over time (1991-2016).



1.3 Effects of Migration on Local Epidemiology

Models have demonstrated that once TB disease in the foreign-born population account for more than 70% of the total cases diagnosed in a country of low incidence, it will not be possible to achieve more than a 2% reduction in the incidence of disease per annum [28, 29]. In Canada, a 2% decline per year in the incidence of disease is not commensurate with an ability to achieve either elimination, or even pre-elimination targets defined below (see Figure 2).

Figure 2: 2017 annual TB incidence rate (4.9/100,000) in Canada declining at 2% per annum (pre-elimination target reached in 80 years (red circle); elimination target reached in 160 years)



An inability to achieve greater reductions is largely due to a failure by current programs to detect and subsequently treat imported prevalent latent TB infections (LTBI) [29, 30, 31]. Screening for LTBI among migrants to Canada has heretofore not been a priority effort because; the large prevalence of immigrants with actual infection and the lack of known markers for progression; previous mass vaccination coverage[4] (of bacille Calmette-Guérin [BCG]) in this population leads to false positive results in the most commonly administered test for LTBI: the tuberculin skin test (TST); and the cost implications of the subsequent duty to treat clients with positive test results, assuming they accept preventive therapy [32]. Accordingly, mass screening for LTBI among migrants to Canada would overwhelm

[4] BCG is among the most widely administered vaccines in the world: https://www.who.int/biologicals/areas/vaccines/bcg/en/

local programs and is not recommended. Evidence in support of targeted LTBI screening strategies among migrants is currently being developed [33, 34].

There are additional strains put on TB programs in low-incidence settings by migration. Firstly, many countries of high TB incidence (>150 cases per 100,000 population) also have elevated rates of high-risk medical conditions for the reactivation of LTBI including human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) [35]. The lifetime risk[5] of reactivating an LTBI is increased approximately 100 times in the presence of HIV/AIDS [32]. The treatment of active TB disease among persons with HIV is challenged by drug-drug (anti-TB/anti-retroviral) interactions of treatment, and the immune reconstitution inflammatory syndrome (IRIS) – a potentially life-threatening complication of anti-TB and ARV therapy - in patients with HIV/TB co-infection [36, 37]. Moreover, TB disease that occurs among HIV co-infected patients often has an atypical presentation that can delay diagnosis [32, 38]. Secondly, drug resistant – multidrug resistant (MDR) and extensively drug resistant (XDR) TB[6] - are more prevalent in areas with weak TB control, oftentimes overlapping with countries from which people are migrating. The importation of drug resistant TB represents a threat to in-country control [39, 40].

Resistance can be acquired or primary. The former is the result of inadequate or failed treatment, and the latter occurs when resistant organisms are transmitted.

[5] 10% - 5% within 5 years of infection, and the remaining 5% over the rest of the period of life.
[6] Multidrug resistant (MDR) – resistant to the two most powerful front line drugs (isoniazid, and rifampin) with, what is usually, full susceptibility to second line therapies, and extremely drug resistant (XDR) – isoniazid and rifampin resistance with resistance to any fluoroquinolone, and at least one second-line injectable drug (e.g. amikacin, capreomycin, or kanamycin).

Migrants with LTBI from a resistant organism can experience reactivation at a later date because of not receiving preventive therapy for the reasons described above. MDR and XDR-TB disease are associated with poorer patient outcomes and the treatment is long, difficult, and expensive not to mention associated with serious side-effects that can include permanent deafness [41, 42, 43].

1.4 Disease and Epidemiological Summary

TB disease, is, more than a clinical event, a marker of social inequity [44, 45]. Tellingly, malnutrition remains both a cause and effect [46]. As such, strategies to achieve elimination will have to incorporate complementary clinical/bio-medical and social components, including out-of-scope advocacy by leaders in the TB community to achieve equity in matters that relate to social justice [47]. In Canada, the population specific disparities in the experience of disease are believed to, generally, result from two phenomena.

Among the foreign-born from high-burden countries, most infections are acquired, prior to landing, in settings affected by the inequitable distribution of resources. Canadian funding of resources and programs overseas to resource limited countries can improve conditions, and programming[7], and is believed to be a cost-effective TB control measure for Canada [48]. At the same time, as the development of new tools or refinement of existing tools used to detect infection improve, and preventive regimens are shortened, recommendations for post-landing prevention of reactivation should also yield positive results [34].

[7] Including improvements to laboratory equipment and human resources to detect, properly diagnose and identify resistance, contact tracing and access to life-saving drugs.

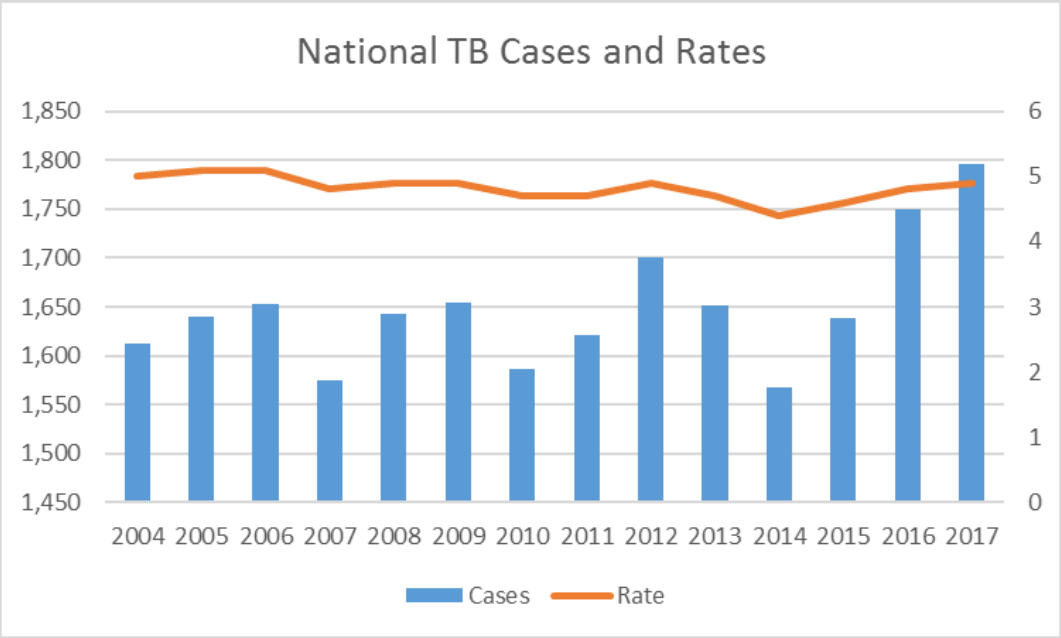
For Indigenous Canadians – transmission is still an important driver of TB epidemiology. Transmission in Canada is not believed to result from more virulent organisms, but rather source case, environmental, and contact characteristics. Highly infectious Indigenous source cases may, on average, experience longer delays in their diagnoses. The reported reasons for these delays include but are not limited to: access to care issues, racism by providers and mistrust of the healthcare system in general, a fraught history with TB disease specifically, and co-morbid conditions masking the presence of the disease due to its non-specific symptoms [49, 50, 51, 52]. Environmental conditions include poorly constructed and ventilated homes that are overcrowded [53]. Contacts may be especially vulnerable if they have a poor baseline health status with poor/naïve immunity due to illness, malnutrition, and young age [54, 55]. These factors mandate the need to address broader social determinants of health for Indigenous peoples in Canada [53, 56].

1.5 TB Elimination

Current TB elimination targets have been outlined in the World Health Organization (WHO) End TB Strategy (WHO 2014) [57]. Interim to achieving targets are 2020 milestones including that households are not catastrophically impoverished by a diagnosis of TB disease (not met by half the counties reporting), and that TB-related mortality is reduced 35% compared to 2015 deaths (not met by two thirds). For countries that are within an elimination phase, defined as having a national incidence of $<10/100{,}000$ population, the pre-elimination target is ten cases per million population by 2035, and the elimination target is 1 case per million by 2050 [2, 57].

Canada is within an elimination phase, and is a co-signatory to the aforementioned End TB Strategy. Unfortunately, with the disease now confined, almost exclusively, to Indigenous peoples and foreign-born migrants who are poorly positioned to advocate for themselves, and the rate having stayed between 4 and 5 per 100,000 for more than 15 years (see Figure 3), the chances of meeting these targets with existing programs and strategies, are virtually impossible.

Figure 3: National TB cases and corresponding rate of disease (2004-2017)



Directives aimed at TB elimination are not new to Canada. Over 20 years ago, a National Consensus Conference on TB recommended that the provinces and territories jointly declare a commitment to TB elimination, achievable by reducing the number of cases by 5% per annum [58]. In 2006, internationally established targets for the elimination of TB disease were supported by Canada; the national target was to achieve an incidence of 3.6/100,000 population by the year 2015 [59,

60]. The actual rate of disease in 2015 was 4.6 per 100,000 and in the last two years of reporting (2016 and 2017) the rate has increased – first to 4.8, and latterly to 4.9 per 100,000 population [27]. In summary, the incidence of TB in Canada has not changed since 2004, holding at ~5 cases (all forms) per 100,000 population per year despite multiple commitments over time to achieve specific targets. These include:

i) a failed commitment made in 1997 to achieve a 5% annual reduction in the number of cases

ii) a failed commitment in 2006 to reach a target incidence of 3.6/100,000 by 2015 (WHO Stop TB Strategy 2006-2015).

iii) a failed commitment (thus far) to make progress on the 2014 WHO END-TB pre-elimination targets (a case rate of 1/100,000 by 2035). This most recent commitment was reiterated at the first High Level Meeting on Tuberculosis of the UN General Assembly on September 26, 2018.

1.6 Weaknesses of Elimination Rhetoric

National surveillance reports – *Tuberculosis in Canada* – provide the data that was used to generate the figures, and related epidemiological profile for Canada described above. Significantly, however, the last *Tuberculosis in Canada* report was published in 2019, but only reports data for the year 2017 [27]. Delays in the provision of surveillance data is a critical barrier to achieving any targets, with programs operating so far ahead of the surveillance data that should be informing practice. Donald Ainslie (DA) Henderson, the American physician, educator and epidemiologist who directed the 10-year International effort to eradicate smallpox describes the significance of surveillance as such, "[it] is the ultimate outcome

measurement… [if] fewer cases due to the disease… is the ultimate objective of a control program" [61]. When surveillance is contemporary with associated clinical and public health interventions, it is *disease reporting for action* [62].

In 1998, Henderson delivered the Tuberculosis (TB) Pittsfield Lecture at the International Union Against Tuberculosis and Lung Disease, North America Region Conference (IUATLD-NAR), which is now published in the *International Journal Against Tuberculosis and Lung Disease* (IJTLD) as, *"The challenge of eradication: Lessons from past eradication campaigns"* [61]. This lecture is significant in that, less than 20 years prior to the WHO End TB Strategy, a speech was delivered by the leader of the only (at the time[8]) successful infectious disease eradication campaign (smallpox) to an audience of vested TB stakeholders; it was about the fallibility of making elimination the near-term goal of TB control programs [61, 63, 64].

Elimination of TB disease, he implied, is a rhetorical tool designed to garner political support and large transfers of resources to achieve targets on the basis of that support. At the same time, the actual goal - eliminating the pathogen through incidence reduction - is stymied by a number of factors that make it overly ambitious and impractical [61, 63]. Foremost, if reported at all, there is variability in the aspects of TB that are being monitored by countries, and even within countries. One example is that within Canada, there is no consensus on what constitutes the "date of diagnosis" for TB. Some jurisdictions define this date as the date on which anti-tuberculosis drugs have been initiated (as in Alberta), others define this date as

[8] Rinderpest was eradicated in 2011.

the date of collection of the specimen that ultimately grew the organism, or the date that a clinical diagnosis was made in the absence of a sample, and yet others have defined it as the date of onset of symptoms believed to be attributable to tuberculosis (by self-reporting). It is unclear if all jurisdictions, are therefore, striving to achieve the same targets, or, from what standing. Moreover, the tools available to effect TB control the world over exist, but their application has been challenged by socioeconomic and political realities external to TB programming [65, 66].

Socio-economic and political stability is important to achieving TB control. For example, treatment regimens may fail or be inadequate due to patients' inabilities to access drugs or, conversely, for programs to access patients. This can occur if drug supplies are limited, or if regional conflicts limit the movement of people. As a result, resistance can both be induced, and spread. The emergence of drug resistant TB has, in turn, created pressures to develop new drugs or trials to assess the safety and effectiveness of re-purposing existing drugs. Neither of these solutions resolves the conflict that necessitates new discoveries [67].

Mass delivery of a novel vaccine for TB would be affected by these same human factors, but its development is further complicated by scientific unknowns. A new vaccine, or vaccines, against TB, for example, should be effective both at preventing new infections from establishing, and, at preventing the progression of existing infections to active disease[9]. This is so, because between 1.9 and 2.5 billion people

[9] BCG, the existing vaccine, offers protection to vulnerable children against developing life-threatening forms of the disease, but does not prevent reinfection, or the development of pulmonary

are currently estimated to be infected. This existing reservoir alone has the potential to generate 100 million new TB cases among whom 85 million would be expected to have PTB [60]. Unfortunately, the development of new vaccines is hampered by blind spots in our understanding of the immunologic response to *M.tb*.

When contacts inhale *M.tb*; some will clear an infection before it establishes; others are infected but manage to contain the infection for a lifetime; among those who develop disease, few will develop primary disease rapidly and others will reactivate an infection in the presence of immune compromising conditions [68]. The immunological processes differentiating the first three of these four groups are not well established, and the final group is also heterogeneous. Immune compromise in the presence of *M.tb* can be highly variable; so, to what degree it is either a sufficient or necessary condition for reactivation is unknown [69]. Two related features are clear: infection by some natural form of the disease causing agent does not confer full immunity, and the variability in immunologic responses to *M.tb* are so poorly understood that the development of a vaccine that is analogous to the causative agent will be extremely challenging [68, 69].

Infection by *M.tb* in LTBI is also in the process of being re-examined. Where once "latent" infections were understood to be a static state in direct contrast to active, "patent", TB disease, it is now understood to be an active *process* associated with non-linear mycobacterial replication. In LTBI the period associated with latency (infection) is generally protracted, and there are no known markers or tools to

tuberculosis. It does, however, offer some protection against leprosy. Any new vaccine designed to replace BCG should include, or recognize the loss of, that benefit.

accurately predict progression (to active disease) [70, 71]. Finally, people with LTBI that progresses to pulmonary disease do not necessarily seek care because they experience limited or non-specific symptomatology. As a result, their diagnosis is almost invariably delayed. Delays in diagnosis and the initiation of anti-tuberculosis drugs increases the period of time that infectious persons can unknowingly transmit the organism to contacts.

From the combination of these factors it is obvious that, while resources are greatly needed to improve TB control programs, a focus on the rhetoric of elimination can actually hinder the ability to raise them. Elimination targets have been made and missed on so many occasions that the goodwill of political actors who supported past efforts may be stretched – i.e., renewed calls may cause apathy if the targets remain unattainable. The 2020 milestone for funding TB prevention and care is $13 billion (USD) annually by 2022; funding is short by 50% of this target. The 2020 milestone target for funding TB research is $2 billion (USD) annually by 2022; the latest data shows an inability to have achieved even half of that target ($906 million)[10] [2, 72]. In spite of all of these challenges, an obligation remains for nations, and the clinicians and researchers therein, to not turn a blind eye to this preventable and curable disease of poverty.

1.7 Organization of the Dissertation

This dissertation is organized into three main chapters (Chapters 2, 3 and 4) that represent three distinct studies. All three were designed to contribute to the

[10] Treatment Action Group (TAG) reports funding and R&D.

broader conversation of strategies for TB elimination relevant to high-income, low-incidence settings. Each was conducted within the TB Prevention and Care Program of Alberta, Canada.

By design, there is a strong emphasis on TB research in Alberta: the public health program is staffed by pulmonary and infectious disease specialists who hold joint academic appointments at either the University of Alberta, or the University of Calgary. There is a large body of translational research, and programmatic evaluations that, in turn, provide evidence in support of recommended changes/improvements. A single laboratory provides mycobacteriologic testing to the Province. In addition, there is a historical database linking conventional and molecular epidemiological information on all active cases from 1989 forward. This has allowed for the development and validation of methods for describing TB transmission [73, 74]. The strengths of the local program produce high quality data. The robustness of these data contributes to the generalizability of the findings from locally conducted studies to other settings that share similar socio-economic and epidemiological characteristics.

The first of my studies illuminates the typical presentation of the most infectious case – smear-positive PTB cases with typical radiographic findings (defined in Chapter 2). This chapter highlights strategies for a collaborative effort in the fight against TB disease to make timelier diagnoses.

The second study presented in this dissertation describes the potential for improving a diagnosis among those people who are suspected of having pulmonary TB on the basis of relevant risk factors that lower the threshold for suspicion of

disease. In follow-up to this study I have initiated a prospective validation of the constellation of risks that predict pulmonary TB disease, which is ongoing in an independent population.

Finally, I describe an important setting for discovery of patients who have undiagnosed PTB, and the potential for transmission therein – the emergency department. This study highlights *the place* where raising awareness for the prototypical infectious case would generate a large public health benefit.

These 3 studies are clinically, and bio-medically focused and so it is acknowledged that while the findings of each may contribute to positive public health outcomes; none are sufficient for achieving elimination, and each provides limited recommendations. The conclusion of this dissertation describes areas of future inquiry.

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Chapter 2: The prompt recognition of infectious pulmonary tuberculosis is critical to achieving elimination goals: A retrospective cohort study

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A version of this manuscript has been submitted for publication.

ABSTRACT

Introduction: All pulmonary tuberculosis (PTB) cases are presumed to be infectious to some degree. This spectrum of infectiousness is independently described by both the acid-fast bacilli smear and radiographic findings. Smear-positive patients with chest radiographic findings that are typical for adult-type PTB are presumed most infectious.

Hypothesis: Characterization of the presumed most infectious PTB case is possible by reference to readily available clinical features and laboratory results.

Methods: Retrospective cohort study of adult, culture-positive PTB cases (151 smear-positive; 162 smear negative) diagnosed between January 1, 2013 and April 30, 2017 in Canada. We describe cases according to demographic, clinical and laboratory features. We use multivariate multinomial logistic regression to estimate the relative risk ratio, with 95% confidence (RRR, and CI, respectively) of features associated with an outcome of smear-positive PTB, characterized by 'typical' chest radiograph findings.

Results: Being Canadian-born, symptomatic, having a subacute duration of symptoms, and broad-spectrum antibiotic prescriptions were all more commonly associated with smear-positive than smear-negative disease (36% vs 20%; 95% vs 63%; 88% vs 54%; and 59% vs 28%, respectively). After combining smear status

and radiographic features, we show that smear-positive patients with typical chest radiographs were younger, had a longer duration of symptoms (RRR 2.41; CI: 1.01, 5.74 and 2.93; CI: 1.20, 7.11, respectively) and were less likely to be foreign-born, or have a moderate-to-high risk factor for reactivation (RRR 0.40; CI: 0.17, 0.92 and 0.18; CI 0.04, 0.71, respectively) compared to smear-negative patients with atypical chest radiograph findings.

Conclusion: A clear picture of the presumed most infectious PTB case emerges from available historical and laboratory information; vigilance for this presentation by frontline providers will support elimination strategies aimed at reducing transmission.

2.1 Introduction

Elimination of tuberculosis (TB) requires a dual-pronged approach. Both interrupting transmission by promptly diagnosing and treating infection-spreading cases, and preventing TB among those already infected but who have not yet developed disease, are necessary. As TB becomes less common in high-income, low-incidence settings, the prompt diagnosis of infection-spreading cases by frontline physicians and nurses becomes increasingly difficult. These cases are mainly bacillary positive (smear-positive, culture-positive and smear-negative, culture-positive) pulmonary (hereafter "PTB"). Among culture-positive PTB cases, those with smear-positive disease are five to ten times more likely to generate a secondary case than those who are smear-negative [1-3]. In addition, among persons with smear-positive PTB, those with 'typical' findings on chest radiograph (defined below) are ten times more likely to generate a secondary case than smear-positive cases without such features [4]. Thus, both the smear status, and the presentation of disease on chest radiograph, contribute, independently, to transmission [4-7].

Six pieces of information from the medical history, and two readily available tests (the chest radiograph, and complete blood count) have emerged, both within the literature and clinical practice, as being critical to suspecting PTB as opposed to disease due to other respiratory pathogens, and subsequently ordering the collection of sputum or other specimens for mycobacteriologic examination [8,9]. The relative predictive value of each variable on an outcome of PTB in a specialized TB clinic has previously been shown [10]. What has not been shown is how well the

combination of these features differentiates the highly infectious case from the minimally infectious case, among whom the collection of a sputum is imperative for achieving public health goals.

The objective of this current study is to distinguish smear-positive, and smear-negative PTB by describing the relative frequency of the aforementioned variables of interest in a well-defined cohort of adult patients and further distinguishing their infectiousness by radiographic findings. While all PTB patients are presumed infectious to some degree, it is the smear-positive case with typical chest radiographic findings whose timely diagnosis offers the greatest potential for interrupting transmission, and impacting public health. Meeting this objective could establish a clinical threshold for frontline providers to consider the diagnosis and seek subsequent laboratory confirmation, which is important to TB elimination efforts [11].

2.2 Methods

This study was performed in Alberta – population over 4.25 million in 2016 (Statistics Canada) – one of four major immigrant-receiving provinces in Canada, the other three being British Columbia, Ontario, and Quebec. In Alberta, in 2016, the crude incidence rate of TB was 5.6 per 100,000 population. University-based pulmonary and infectious disease physicians staff three dedicated public health clinics that provide TB services to the province [9]. Language line (translation) services are available as necessary. Introduction of an assessment form into the two clinics supported by University of Alberta staff occurred in 2013. It records relevant information for each referred case. We identified a cohort of consecutive, adult (age

>14 years), culture-positive pulmonary cases diagnosed between January 1, 2013 and April 30, 2017 from these two clinics. We supplemented data collected through the assessment form with findings from the Provincial Laboratory for Public Health, which performs all mycobacteriology in the Province. Per standard of care, patients whose initial sputum specimens were smear-negative had three additional specimens collected at the time of reporting of the first positive culture to confirm that they were still smear-negative on the start date of treatment, which in Alberta, is the date of diagnosis. The initial isolate of each case was genotyped using Mycobacterial Interspersed Repetitive Units (MIRU), and laboratory cross contamination was excluded in all patients with a single, smear-negative, culture-positive specimen [12].

Basic demographic and clinical information is used to describe the cohort of patients in this study. These data included: age at diagnosis (15-64 years, >64 years); sex, population group (Canadian-born and foreign-born), disease type (new active vs. relapse/retreatment), and HIV status (positive, negative). We then examined the following eight explanatory variables, which we hypothesized would best describe the most infectious case of PTB.

Clinical characteristics included, as above, six pieces of information related to patient histories: 1) symptoms, 2) duration of symptoms, 3) absence of dyspnea, 4) broad-spectrum antibiotic prescriptions in the six months antedating diagnosis[11], 5)

[11] Broad spectrum antibiotics are indicative of a provider not suspecting TB disease; they are classes of drugs that provide effective therapeutic benefits against community acquired and/or nosocomial infections, but, as a general rule, are not effective against *Mycobacteria*, including *M.tb*. Similarly anti-tuberculosis drugs are not, generally, effective against other bacterial infections. One exception is the

epidemiologic risk of exposure to, or infection with, *Mycobacterium tuberculosis*, and 6) risk factors for the reactivation of latent TB infection (LTBI)[12]. Symptoms, if present, were reported as respiratory (dry cough, productive cough, hemoptysis, or chest pain), constitutional (fever, night sweats, weight loss or fatigue) or both [13]. The absence of dyspnea is known to favour a diagnosis of PTB over community-acquired pneumonia; parallel reductions in ventilation and perfusion at sites of PTB disease are known to preserve gas exchange [14-16]. We documented antibiotic prescriptions in individual records, and confirmed their prescription for respiratory complaints by cross-referencing the cohort against the provincial (Alberta Health) stakeholder registry, which, in turn, reports physician claims for the reimbursement of services provided.

Epidemiologic risks include: a history of TB, and whether it was adequately treated, a history of overt contact with PTB, and whether it was adequately assessed (e.g. tuberculin skin test [TST], or interferon gamma release assay [IGRA]) and treated, migration from a high incidence country of birth, or travel and work to/within a high incidence country, an occupational history (e.g. healthcare worker),

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fluroquinolones, but the action against *M.tb* by these drugs is not sustained and if TB is suspected they should not be administered as monotherapy. Other classes of broad spectrum antibiotics include: penicillin, macrolide, cephalosporin, and tetracycline.

[12] *High risk medical conditions for the reactivation of LTBI*: AIDS/HIV; transplantation (related to immune-suppressant therapy); silicosis; chronic renal failure requiring hemodialysis; carcinoma of head and neck; recent TB infection (≥ 2 years); abnormal chest radiograph – fibronodular disease. *Moderate risk medical conditions for the reactivation of LTBI:* tumour necrosis factor alpha inhibitors; diabetes mellitus (all types); treatment with glucocorticoids (≥15 mg/d prednisone); young age when infected (0-4 years). See: Menzies D, Alvarez G, Khan K. Treatment of latent tuberculosis infection. In: Menzies D, editor. Canadian tuberculosis standards 7th ed. Ottawa, ON: Her Majesty the Queen in Right of Canada; 2014: 1-32. Available from: http://canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-18.html

and/or social risk factors such as homelessness, incarceration and alcohol/substance misuse where non-overt exposures might occur. Supplement 1 provides a description of social factors including homelessness, incarceration, and alcohol/substance misuse. We reported the presence, or absence of one or more "moderate" or "high risk" factors for the reactivation of LTBI, as described in the Canadian TB Standards [17]. Finally, we report results of two routine laboratory tests performed at the time of diagnosis: the complete blood count (CBC), and the chest radiograph. The results of the CBC are grouped into four patterns based on the presence or absence of anemia, and or leukocytosis [18, 19].

An experienced chest radiologist, blind to the smear status of the patients, re-read the posterior-anterior (PA) and lateral (LAT) Digital Imaging and Communications in Medicine (DICOM) chest images performed at the time of diagnosis. In the context of this study, we divided frontal images into four quadrants by halving a perpendicular drawn from the apex of the lung to the dome of the hemi-diaphragm. Documented were the presence or absence of (1) parenchymal infiltrates and their dominant location – no distinction was made between infiltrates that were airspace, interstitial, nodular or some combination of these; (2) cavities, defined as a gas filled space within pulmonary consolidation, a mass, or a nodule; (3) adenopathy – hilar, mediastinal or both; and (4) pleural effusion.

As previously reported, we categorized patients as having "typical" vs. "atypical" radiographs based on the characteristics listed above [4,20]. For patients with infiltration localized to, or predominantly in the upper long zones, with or without cavitation, but with no discernable intrathoracic adenopathy, the

radiograph is “typical” for adult-type pulmonary TB. In patients with (1) no abnormality; (2) intrathoracic adenopathy with or without parenchymal disease; (3) a localized or predominant lower lung zone infiltrate, with or without cavitation; (4) an isolated pleural effusion; and (5) a miliary (diffuse micronodular) pattern, the radiograph is “atypical” for adult-type pulmonary TB. We report extent of disease on chest radiograph as normal, minimal, moderately advanced, far advanced, or miliary according to criteria established by the U.S. National Tuberculosis and Respiratory Disease Association [21].

Statistical Analysis: We describe cases by smear-status according to each of the aforementioned features. We tested the difference in proportions, by smear status, of each feature between two independent samples using the direct test, Fisher’s exact, or Chi-square as appropriate. Thereafter, we generated a combined outcome of smear-status and radiographic findings, creating an outcome for multinomial logistic regression that was a nominal variable with four responses: atypical smear-negative, typical smear-negative, atypical smear-positive, and typical smear-positive with atypical smear-negative as the baseline. The model includes all features and confounders considered clinically relevant to making a timely diagnosis of tuberculosis from a review of the literature. The total sample size of 313 in this study achieves 80% power or greater to detect an effect size (W) of 0.19 or greater for comparison of proportions between four groups using 3 degrees of freedom, and chi-square test with a significance level (alpha) of 0.05 [22]. We performed all statistical analyses using STATA 14, StataCorp 2015. There were no missing data within this cohort.

Approvals, Patient and Public Involvement: The University of Alberta's Research Ethics Board (HREB) approved this study (Study ID: Pro00086712). Analysis of anonymized, routinely collected surveillance data does not require direct patient contact and the HREB waived the need to require patient's informed consent. We did not involve patients and the public in this study given its retrospective design, but we anticipate that the findings presented herein will lead to benefits for future cohorts of patients.

2.3 Results

There were 313 patients in the cohort, 151 (48%) smear-positive and 162 (52%) smear-negative. Being Canadian-born was associated with a greater likelihood of having smear-positive than smear-negative disease (36% vs. 20%,); otherwise there were no statistically significant differences in the age, sex, disease type, drug resistance, or HIV status between these two groups (see Table 1). The leading countries of birth of foreign-born patients were the Philippines (38%), India (16%), Vietnam (5%), and Somalia (5%); Bhutan, Ethiopia and China each contributed 3% of foreign-born patients.

Table 1: Demographic and clinical characteristics of patients with PTB by smear-status

Characteristics	Total n	Smear Status[a] Positive n (%)	Smear Status[a] Negative n (%)	p-value
No. Assessed	**313**	**151**	**162**	
Age				
15-64 years	248	120 (79.4)	128 (79.0)	0.38
>64 years	65	31 (20.6)	34 (21.0)	
Sex				
Male	173	86 (57.0)	87 (53.8)	0.56
Female	140	65 (43.0)	75 (46.2)	
Population Group[c]				
Foreign-born	226	97 (64.3)	129 (79.7)	
Canadian-born	87	54 (35.7)	33 (20.3)	0.002
Disease Type				
New Active	280	135 (89.4)	145 (89.5)	
Relapse/Retreatment	33	16 (10.6)	17 (10.5)	0.97
HIV Status				
Negative	300	147 (97.4)	153 (94.5)	
Positive	13	4 (2.6)	9 (5.5)	0.19

[a]Smear-positive patients had to have one or more airway secretion specimens, on or before the start date of treatment, with a semi-quantitative smear size of 1^+ or greater.
[b]difference in proportions [(smear-positive) – (smear-negative)]; sample size was adequate to detect observable differences.
[c]Canadian-born, includes 61 Indigenous patients, and 26 Canadian-born non-Indigenous patients. Among the Foreign-born patients, 1 smear-positive, and 28 smear-negative, were referred to public health through the immigration medical screening surveillance mechanism.

[?]

As shown in Table 2, being symptomatic with either respiratory, constitutional, or both types of symptoms at the time of diagnosis was more likely in smear-positive than smear-negative patients (95% vs 63%). Cough (dry or productive), and hemoptysis were more common in smear-positive than smear-negative patients (83% vs. 45%, and 25% vs. 6%, respectively). Chest pain was equally uncommon in both groups (11% vs. 9%). Dyspnea was also relatively uncommon in both groups (28% vs. 14%). Each of the major constitutional symptoms was more common in smear-positive than smear-negative patients (weight loss, 50% vs 28%; fever, 45% vs. 20%; night sweats, 24% vs. 10%; and

fatigue, 21% vs. 12%). Finally, having a combination of respiratory and constitutional symptoms (70% vs. 28%) and a duration of symptoms ≥ 2 weeks (88% vs. 54%) were statistically significantly more common in smear-positive than smear-negative patients. Among smear-positive and smear-negative patients with any symptoms, 93% and 86%, respectively had symptoms for ≥ 2 weeks (data not shown).

Table 2: Symptoms and their duration in patients with PTB by smear-status

Characteristics	Total n	Smear Status		p-value[a]
		Positive n (%)	Negative n (%)	
No. Assessed	**313**	**151**	**162**	--
Symptomatic				
Yes	245	143 (94.7)	102 (63.0)	<0.001
No	68	8 (5.3)	60 (37.0)	
Symptoms				
Respiratory	217	133 (88.1)	84 (51.8)	<0.001
Cough (dry)	149	90 (59.6)	59 (36.4)	
Cough (productive)	50	36 (23.8)	14 (8.6)	
Hemoptysis	46	37 (24.5)	9 (5.5)	
Chest pain	31	17 (11.2)	14 (8.6)	
Absence of Dyspnea				
Yes	249	109 (72.2)	140 (86.4)	<0.001
No	64	42 (27.8)	22 (13.6)	
Constitutional	176	113 (74.8)	63 (38.8)	<0.001
Weight loss	121	76 (50.3)	45 (27.7)	
Fever	101	68 (45.0)	33 (20.3)	
Night sweats	52	36 (23.8)	16 (9.8)	
Fatigue	51	31 (20.5)	20 (12.3)	
Both[b]				
Yes	151	105 (69.5)	46 (28.4)	<0.001
No	162	46 (30.5)	116 (71.6)	
Duration of symptoms				
≥ 2 weeks	221	133 (88.0)	88 (54.3)	<0.001
< 2 weeks	92	18 (12.0)	74 (45.7)	

[a]difference in proportions [(smear-positive) – (smear-negative)]; sample size was adequate to detect observable differences.
[b]Patients with some combination of both respiratory and constitutional symptoms

We dichotomized possible combinations of antibiotic prescription, epidemiologic risk and reactivation risk, and describe their associations with an outcome of either smear-positive or smear-negative disease (Table 3).

Table 3: Broad spectrum antibiotic use, epidemiologic risk, reactivation risk, and laboratory features in patients with PTB by smear-status

Characteristics	Total n	Smear Status		p-value[a]
		Positive n (%)	Negative n (%)	
No. Assessed	**313**	**151**	**162**	--
Antibiotic use[b]				
Yes	124	86 (56.9)	38 (23.5)	<0.001
No	189	65 (43.1)	124 (76.5)	
Epidemiologic risk[c]				
Yes	301	144 (95.4)	157 (96.9)	0.48
No	12	7 (4.3)	5 (3.1)	
Reactivation risk[d]				
Yes	23	9 (5.9)	14 (8.6)	0.35
No	290	142 (94.1)	148 (91.4)	
Complete Blood Count[e]				
Normal hemoglobin; leukocytosis[f]	8	7 (4.6)	1 (0.6)	0.03
Normal hemoglobin; normal/low leukocyte count	139	46 (30.4)	93 (57.4)	<0.001
Anemia and leukocytosis[f]	36	25 (16.5)	11 (6.7)	0.01
Anemia and normal/low leukocyte count	130	73 (48.5)	57 (35.3)	0 .01
Chest Radiographs				
Typical appearance[g]	176	118 (78.1)	58 (35.8)	<0.001
Bilateral[h]	118	84 (55.6)	34 (21.1)	<0.001
Cavitary	103	93 (61.5)	10 (6.1)	<0.001
Extent: Moderate to far-advanced disease[i]	159	123 (81.4)	36 (22.2)	<0.001

[a]difference in proportions [(smear-positive) – (smear-negative)]; sample size was adequate to detect observable differences.
[b]Refers to broad-spectrum antibiotic use in the six months preceding the date of diagnosis (the start date of treatment).
[c]Epidemiologic risk for exposure to *Mycobacterium tuberculosis*.

A history of broad-spectrum antibiotic prescriptions for a respiratory complaint in the 6 months preceding the date of diagnosis was more likely among smear-positive patients (57% vs. 23%); of those, multiple prescriptions were also more likely among smear-positive patients (49% vs. 36% - data not shown). Macrolide, penicillin, and fluoroquinolone were, in order of frequency, the three major classes of antibiotics prescribed. If one assumes that antibiotic prescriptions for respiratory complaints, in the months immediately preceding their diagnosis, were due to PTB then there were missed opportunities to diagnose these patients. In absolute numbers, there were 291 antibiotic prescriptions in the 6 months antedating a TB diagnosis; 208 among persons ultimately diagnosed with smear-positive PTB and 83 among persons ultimately diagnosed with smear-negative PTB (data not shown).

Almost all patients in both groups (95%) had some epidemiologic risk. The distribution of social risk factors was similar in smear-positive and smear-negative patients. Notably, however, they were much more common among Canadian-born than among foreign-born patients (see supplement, Table 1). A moderate-to-high risk of reactivation was similarly uncommon in both smear-positive and smear-negative patients (6% vs 9%).

Anemia was more common in smear-positive than smear-negative cases (65% vs. 42%). Anemia was usually of the chronic disease, iron deficiency varieties, or both (data not shown). A leukocytosis was uncommon in both groups, but more uncommon in smear-negative cases (21% and 7%). The mean and median hemoglobin in smear-positive males and females was 127 and 126 g/L, and 112 and

112 g/L, respectively. In smear-negative males and females, it was 135 and 142 g/L, and 123 and 124 g/L, respectively. The mean and median leucocyte count was 8.6 x 10^9/L, and 7.8 x 10^9/L in smear-positive cases, and 7 x 10^9/L, and 7 x 10^9/L in smear-negative cases. The reference range for a normal hemoglobin is 135-175 g/L, and 120-160 g/L for males and females, respectively. The reference range for a normal leukocyte count is 4.0-11.0 x 10^9/L.

Chest radiographic features that are 'typical' for adult-type PTB, bilateral disease, cavitation, and moderate or far advanced disease were all more common in smear-positive than smear-negative patients (78% vs 36%; 56% vs. 21%; 62% vs 6%; and, 81% vs. 22%, respectively). Among smear-positive patients, those with cavitation had a statistically significantly higher semi-quantitative smear grade (3+ to 4+) vs. (1+ to 2+), 82% vs 46% than those without cavitation (data not shown). Only three patients, one smear-positive, and two smear-negative, had a miliary pattern.

Table 4 shows the findings of our multinomial logistic regression. An absence of dyspnea was more likely among smear-negative patients with typical chest radiograph findings than smear-negative patients with atypical chest radiograph findings; lower lung zone disease and dependent effusions – atypical findings on chest radiograph – are presumed to more negatively affect gas exchange (relative risk ratio [RRR] 4.71, 95% CI: 1.69, 13.18). Young age, and a subacute or chronic duration of symptoms were more greatly associated with smear-positive patients who have typical chest radiographs than smear-negative patients with atypical chest radiographs (RRR 2.41; CI: 1.01, 5.74, and 2.93; CI 1.20, 7.11, respectively),

while being foreign-born and having a moderate-to-high risk factor for reactivation were less commonly associated with smear-positive PTB with typical chest radiographs, than smear-negative PTB patients with atypical chest radiographs (RRR 0.40; CI: 0.17, 0.92, and 0.18; CI: 0.04, 0.71, respectively) (see Table 4, and supplemental Table 2). All major symptoms, respiratory and constitutional, were more commonly associated with typical presentation, cavitation, bilateral, and moderate to advanced disease on chest radiograph (see Table 3 in the supplement).

Table 4: Multivariate, multinomial regression of demographic and clinical characteristics to a combined smear, and radiographic outcome

	Smear-Negative			Smear-Positive			
	Atypical (Base)	Typical		Atypical		Typical	
Demographics and clinical characteristics	**n (%)**	**n (%)**	**RRR (95% CI)**	**n (%)**	**RRR (95% CI)**	**n (%)**	**RRR (95% CI)**
No. Assessed	**51**	**111**		**33**		**118**	
Age (years)							
>64	15 (23.1)	19 (29.2)	1.00	14 (21.5)	1.00	17 (26.2)	1.00
15-64	36 (14.5)	92 (37.1)	1.68 (0.71, 3.92)	19 (7.6)	0.56 (0.20, 1.55)	101 (40.7)	2.41 (1.01, 5.74)
Sex							
Female	22 (15.7)	53 (37.9)	1.00	13 (9.3)	1.00	52 (37.1)	1.00
Male	29 (16.8)	58 (33.5)	0.77 (0.38, 1.56)	20 (11.6)	1.15 (0.45, 2.93)	66 (38.2)	0.90 (0.44, 1.83)
Population Group							
Canadian-born	12 (13.8)	21 (24.1)	1.00	8 (9.2)	1.00	46 (52.9)	1.00
Foreign-born	39 (17.3)	90 (40.0)	1.00 (0.42, 2.37)	25 (11.0)	1.09 (0.36, 3.32)	72 (31.7)	0.40 (0.17, 0.92)
Absence of Dyspnea							
No	15 (23.4)	7 (11.0)	1.00	16 (25.0)	1.00	26 (40.6)	1.00
Yes	36 (14.4)	104 (41.8)	4.71 (1.69, 13.18)	17 (6.8)	0.59 (0.22, 1.60)	92 (37.0)	1.85 (0.79, 4.34)
Duration of Symptoms[a]							
< 2 wks	18 (19.5)	56 (60.9)	1.00	3 (3.3)	1.00	15 (16.3)	1.00
≥ 2 wks	33 (14.9)	55 (24.9)	0.68 (0.31, 1.75)	30 (13.6)	3.86 (0.93, 15.92)	103 (46.6)	2.93 (1.20, 7.11)
Antibiotics[b]							
No	35 (18.5)	89 (47.1)	1.00	13 (6.9)	1.00	52 (27.5)	1.00
Yes*	16 (12.9)	22 (17.7)	0.74 (0.31, 1.75)	20 (16.1)	2.14 (0.79, 5.82)	66 (53.2)	1.76 (0.79, 3.89)
Epidemiologic Risk[c]							
None/Low	24 (16.3)	45 (30.6)	1.00	17 (11.6)	1.00	61 (41.5)	1.00
Mod-High	27 (16.3)	66 (39.8)	0.89 (0.42, 1.87)	16 (9.6)	1.20 (0.46, 3.11)	57 (34.3)	0.77 (0.36, 1.61)
Reactivation Risk[d]							
None/Low	44 (15.2)	104 (35.9)	1.00	28 (9.7)	1.00	114 (39.3)	1.00
Mod-High	7 (30.4)	7 (30.4)	0.43 (0.13, 1.43)	5 (21.7)	1.24 (0.32, 4.80)	4 (17.4)	0.18 (0.04, 0.79)
CBC[e]							
Low Risk	5 (11.4)	7 (15.9)	1.00	5 (11.4)	1.00	27 (61.4)	1.00
High Risk	46 (17.1)	104 (38.7)	1.26 (0.36, 3.28)	28 (10.4)	0.64 (0.15, 2.61)	91 (33.8)	0.49 (0.16,1.48)

[a]the presence of 'symptoms', and the 'duration of symptoms' were considered collinear – here we report just on the duration of symptoms.

[b]one or more broad spectrum antibiotics prescribed in the six months prior to diagnosis.

c epidemiological risks none/low = no known occupational risk, travel history, migration from endemic nation, place of residence in a high incidence Indigenous community, recent contact with a known TB case plus no history of TB; OR, a past history of TB/LTBI that has been adequately treated.

Mod-high = occupational risk, travel history, migration from endemic nation, place of residence in a high incidence Indigenous community, recent contact with a known TB case and/or a positive TST/IGRA or a past history of TB that was inadequately treated or with no record of treatment.

d per the Canadian TB Standards, 7th Edition

e low risk = combined normal hemoglobin; leukocytosis and anemia; leukocytosis, and high risk = combined normal hemoglobin; normal/low leukocyte count and anemia; normal/low leukocyte count

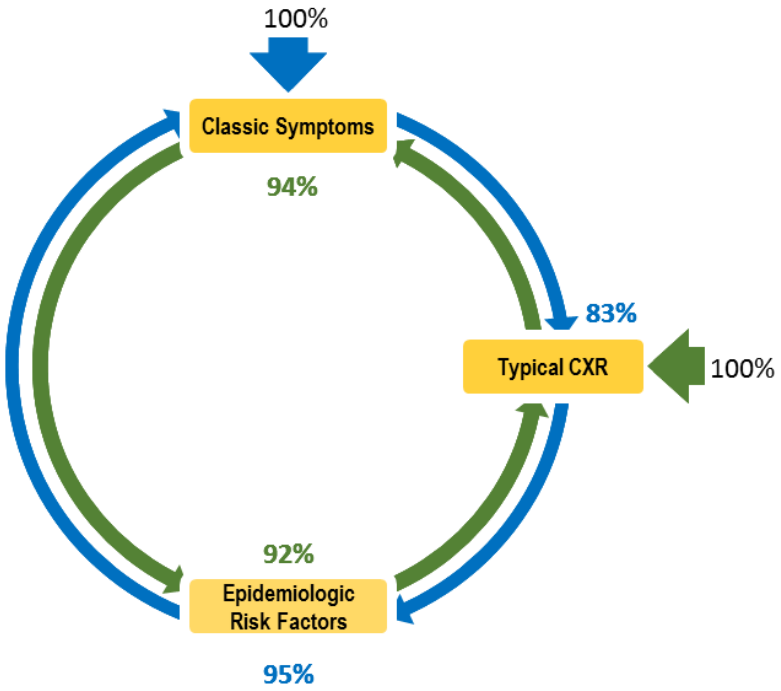
2.4 Discussion

It has previously been established that of the information readily available to front-line providers, three pieces are key to triggering suspicion of PTB. These include symptoms, especially if both respiratory and constitutional and subacute or chronic, and typical chest radiographic features; a public health trigger is an epidemiologic risk of having or acquiring LTBI (see Figure 1). Our study shows that although a public health risk was similarly common in smear-positive and smear-negative cases (95%, and 97%, respectively), clinical triggers (symptoms: 95% vs 63%, and typical chest radiographic features: 78% vs. 36%) were much more common in smear-positive cases. Since smear-positivity and typical radiographic features are presently the major determinants of infectiousness, and therefore the public health risk PTB poses, it is helpful to know where and how these patients enter the healthcare system (i.e., for management of classical TB symptoms, or with an abnormal chest radiograph) [1-4, 7]. Upon entry, the other variables of interest including broad-spectrum antibiotic prescription history, reactivation risk factors and the CBC findings are supportive in considering the likelihood of PTB and so should be a part of a targeted medical history.

Individually, each of the features identified in the multinomial logistic regression model as distinguishing (typical) smear-positive cases from (atypical) smear-negative cases has precedent in the literature including younger age [23, 24]; symptoms and their duration [25-27]; less likely to be foreign-born [14, 28]; and less likely to have a moderate to high risk factor for reactivation [29-32]. When combined, the features have utility for describing the prototypical smear-positive

patient with typical chest radiographic features: a young-middle aged male or female with an epidemiological risk for LTBI, and a subacute or chronic duration of symptoms, a history of broad-spectrum antibiotic prescriptions, rarely having a risk factor for reactivation, and with an anemia and a normal or low leucocyte count on CBC.

Figure 1: Diagnostic loop for smear-positive patients with typical chest radiographs



Legend: This figure depicts a diagnostic loop with two entry points: 1) report of one or more classical pulmonary tuberculosis symptoms, and 2) report of a chest radiograph abnormality that is considered 'typical' for adult type pulmonary tuberculosis. Proceeding clockwise, the percentages describe the proportion of patients with one or more symptom who had each of the other features; proceeding counter clockwise the percentages describe the proportion of patients who had a typical chest radiograph with each of the other features.

In the future, semi-quantitative results from the real-time PCR method, Xpert MTB/RIF assay, may replace smear-microscopy and its current role as a proximate measure of infectiousness [33, 34]. There is, however, no expectation that this technology will impact the picture of the prototypical infectious case described herein. By contrast, cough aerosol technology might. For reasons that are only

speculative at this time, some patients, whether smear-positive or smear-negative, are better able to generate an infectious aerosol than others [35]. Therefore, once available, this technology is expected to further clarify the picture of the most infectious cases. The earlier the detection of these cases, the lesser the transmission and the smaller the reservoir of LTBI, the seedbed of future cases.

It is a common misconception that smear-negative disease is early disease, and smear-positive disease is late disease and that the extent of disease on chest radiograph is an indication of its duration, i.e. that a minimal lesion is early disease and a moderate or advanced lesion is old or chronic disease. Years ago, Kurt Toman used data from longitudinal studies, and periodic x-ray surveys of large populations to dispel this idea [27]. He concluded that both types of disease – advanced smear-positive TB and minimal, only culture-positive TB – usually developed within the same timeframe; thus, making a diagnosis at first presentation an important piece of the elimination puzzle. A recent proof-of-concept study supports his findings of different phenotypic expressions of disease [20]. The proportion of smear-positive and smear-negative patients in our study that were asymptomatic (5% and 37%, respectively) is remarkably similar to what he reported across diverse ethnic groups many years ago [36-38].

Strengths of this study include the completeness of the data, made possible by the use of an assessment form and the centralized nature of the program, and the validation of key variables, for example, the attribution of smear status, radiographic features, and broad-spectrum antibiotic prescriptions. Consecutive patients in the jurisdiction and time period of the study were included. This may be

considered both a strength (reflecting programmatic realities and an unfiltered comparison of smear-positive and smear-negative disease) and a weakness (the pathway to diagnosis in smear-negative cases may be through active vs. passive case finding activities such as immigration medical surveillance) [39]. A limitation of this study includes the relatively small cohort, which is typical in low-incidence settings. A second limitation includes the retrospective study design, which affects the interpretation of the strength of relationship between clinical features and outcomes, though collection of the data evaluated in this study is by protocol and we are confident in their accuracy.

This study describes infectious TB cases in a high-income, low-incidence country where the disease is increasingly uncommon. We anticipate this description will contribute to the prompt submission of specimens for confirmation by mycobacteriologic testing. The prompt recognition of these cases is possible but takes a collaborative effort that includes frontline providers. Such input is understood to be a high-income, low-incidence country effort to follow the World Health Organization/Stop-TB Partnership roadmap to engage all care providers in TB prevention and care [11]. Limiting the potential for transmission will ultimately aid TB elimination efforts. Electronic recording of the readily available clinical features proposed in this work along with computer-aided detection of adult-type PTB on chest radiographs could conceivably automate this process.

2.5 References

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2.6 Supplement 1

Social risk factors in patients with PTB by population group

Social Risk Factors		CB n (%)	FB n (%)	Total n (%)
Homelessness, Incarceration, alcohol or substance misuse, or some combination of these*	yes	44 (50.6)	6 (2.7)	50 (16.0)
	no	43 (49.4)	220 (97.3)	263 (84.0)
Total		**87**	**226**	**313**

Abbreviations: CB Canadian-born; FB foreign-born

*refers to homeless at the time of diagnosis or at any time within the previous 12 months; incarceration = incarcerated at the time of diagnosis

2.7 Supplement 2

Univariate multinomial regression: associations of demographic and clinical characteristics to a combined smear, and radiographic outcome

Demographics and clinical characteristics	Smear-Negative			Smear-Positive			
	Atypical (Base)	Typical		Atypical		Typical	
	n (%)	n (%)	RRR (95% CI)	n (%)	RRR (95% CI)	n (%)	RRR (95% CI)
No. Assessed	**51**		**111**		**33**		**118**
Age (years)							
>64	15 (23.1)	19 (29.2)	1.00	14 (21.5)	1.00	17 (26.2)	1.00
15-64	36 (14.5)	92 (37.1)	2.01 (0.92, 4.39)	19 (7.6)	0.56 (0.22, 1.41)	101 (40.7)	2.47 (1.12, 5.46)
Sex							
Female	22 (15.7)	53 (37.9)	1.00	13 (9.3)	1.00	52 (37.1)	1.00
Male	29 (16.8)	58 (33.5)	0.83 (0.42, 1.61)	20 (11.6)	1.16 (0.47, 2.84)	66 (38.2)	0.96 (0.49, 1.86)
Population Group							
Canadian-born	12 (13.8)	21 (24.1)	1.00	8 (9.2)	1.00	46 (52.9)	1.00
Foreign-born	39 (17.3)	90 (40.0)	1.31 (0.59, 2.94)	25 (11.0)	0.96 (0.34, 2.68)	72 (31.7)	0.48 (0.22, 1.01)
Absence of Dyspnea							
No	15 (23.4)	7 (11.0)	1.00	16 (25.0)	1.00	26 (40.6)	1.00
Yes	36 (14.4)	104 (41.8)	6.19 (2.33, 16.39)	17 (6.8)	0.44 (0.17, 1.10)	92 (37.0)	1.47 (0.70, 3.09)
Duration of Symptoms[a]							
< 2 wks	18 (19.5)	56 (60.9)	1.00	3 (3.3)	1.00	15 (16.3)	1.00
≥ 2 wks	33 (14.9)	55 (24.9)	0.53 (0.27, 1.06)	30 (13.6)	5.45 (1.45, 20.38)	103 (46.6)	3.74 (1.70, 8.24)
Antibiotics[b]							
No	35 (18.5)	89 (47.1)	1.00	13 (6.9)	1.00	52 (27.5)	1.00
Yes*	16 (12.9)	22 (17.7)	0.54 (0.25, 1.14)	20 (16.1)	3.36 (1.34, 8.40)	66 (53.2)	2.77 (1.38, 5.55)
Epidemiologic Risk[c]							
None/Low	24 (16.3)	45 (30.6)	1.00	17 (11.6)	1.00	61 (41.5)	1.00
Mod-High	27 (16.3)	66 (39.8)	1.30 (0.66, 2.54)	16 (9.6)	0.83 (0.34, 2.01)	57 (34.3)	0.83 (0.43, 1.60)
Reactivation Risk[d]							
None/Low	44 (15.2)	104 (35.9)	1.00	28 (9.7)	1.00	114 (39.3)	1.00
Mod-High	7 (30.4)	7 (30.4)	0.42 (0.14, 1.27)	5 (21.7)	1.12 (0.32, 3.88)	4 (17.4)	0.22 (0.06, 0.79)
CBC[e]							
Low Risk	5 (11.4)	7 (15.9)	1.00	5 (11.4)	1.00	27 (61.4)	1.00
High Risk	46 (17.1)	104 (38.7)	1.61 (0.48, 5.35)	28 (10.4)	0.60 (0.16, 2.29)	91 (33.8)	0.36 (0.13, 1.01)

[a]the presence of 'symptoms', and the 'duration of symptoms' were considered collinear – here we report just on the duration of symptoms.

[b]one or more broad spectrum antibiotics prescribed in the six months prior to diagnosis.

c epidemiological risks none/low = no known occupational risk, travel history, migration from endemic nation, place of residence in a high incidence Indigenous community, recent contact with a known TB case plus no history of TB; OR, a past history of TB/LTBI that has been adequately treated.

Mod-high = occupational risk, travel history, migration from endemic nation, place of residence in a high incidence Indigenous community, recent contact with a known TB case and/or a positive TST/IGRA or a past history of TB that was inadequately treated or with no record of treatment.

d per the Canadian TB Standards, 7th Edition

e low risk = combined normal hemoglobin; leukocytosis and anemia; leukocytosis, and high risk = combined normal hemoglobin; normal/low leukocyte count and anemia; normal/low leukocyte count.

2.8 Supplement 3

Associations between radiographic indices of disease severity at the time of diagnosis and symptoms

Radiographic Indices of Disease Severity[a]	No. Assessed	Symptoms						
		Respiratory			Constitutional			Both[b]
		Dry Cough n (%)	Prod. Cough n (%)	Hemoptysis n (%)	Fever n (%)	Night Sweats n (%)	Weight Loss n (%)	n (%)
Cavitation								
Yes	103	65 (63.1)	24 (23.3)	30 (29.1)	45 (43.6)	25 (24.2)	57 (55.3)	74 (71.8)
No	210	84 (40.0)	26 (12.4)	16 (7.6)	56 (26.6)	27 (12.9)	64 (30.4)	77 (36.6)
Bilateral								
Yes	118	69 (58.4)	22 (18.6)	27 (22.8)	47 (39.8)	22 (18.6)	59 (50.0)	70 (59.3)
No	195	80 (41.0)	28 (14.4)	19 (9.7)	54 (27.6)	30 (15.4)	62 (31.7)	81 (41.5)
Moderate/ Far-Advanced								
Yes	159	97 (61.0)	36 (22.6)	37 (23.2)	67 (42.1)	37 (23.2)	82 (51.5)	106 (66.6)
No	154	52 (33.7)	14 (9.1)	9 (5.8)	34 (22.1)	15 (9.8)	39 (25.3)	45 (29.2)

[a]Radiographic indices are defined in the text. Those without 'bilateral' disease could have either unilateral disease, or no disease.
[b]"Both" refers to any combination of respiratory and constitutional symptoms

Chapter 3: Predicting Pulmonary Tuberculosis in Immigrants: A Retrospective Cohort Study

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A version of this manuscript is published: ERJ Open Res. 2018 Apr 20; 4 (2). DOI: 10.1183/23120541.00170-2017

ABSTRACT

Objective: Our objective was to investigate whether pulmonary tuberculosis (PTB) can be predicted from features of a targeted medical history and basic laboratory investigations in immigrants.

Methods: A retrospective cohort of 391 foreign-born adults referred to the Edmonton Tuberculosis Clinic (Edmonton, AB, Canada) was studied using multiple logistic regression analysis to predict PTB. Seven characteristics of disease were used as explanatory variables. Cross-validation assessed performance. Each predictor was tested on two outcomes: "culture-positive" and "smear-positive". Receiver operating characteristic (ROC) curves were generated and the area under the ROC curve (AUC) was quantified.

Results: Symptoms, subacute duration of symptoms, risk factors for reactivation of latent TB infection and anaemia were all associated with a positive culture (adjusted OR 1.79, 2.24, 1.72 and 2.28, respectively; $p<0.05$). Symptoms, inappropriate prescription of broad-spectrum antibiotics and a "typical" chest radiograph were associated with smear-positive PTB (adjusted OR 2.91, 1.55 and 12.34, respectively; $p<0.05$). ROC curve analysis was used to test each model, yielding AUC=0.91 for the

outcome “culture-positive” disease and AUC=0.94 for the outcome “smear-positive” disease.

Conclusion: PTB among the foreign-born can be predicted from a targeted medical history and basic laboratory investigations, raising suspicion of disease by clinicians in settings where the disease is relatively rare.

3.1 Introduction

Among the G7 (Group of Seven) Nations in 2015 there was a low tuberculosis (TB) incidence ranging from 3.2 per 100000 population in the USA to 17.1 per 100000 population in Japan [1]. In the same year, Canada reported the second lowest national TB incidence rate at 4.6 per 100000 population [2]. These low national incidence rates obscure disparate rates for vulnerable population subgroups. For example, in 2015 the TB incidence for the foreign-born in Canada was 14.8 per 100000, accounting for 71% of diagnosed cases, and the incidence among Indigenous peoples was 17.1 per 100000, while the rate for Canadian-born non-Indigenous persons was 0.6 per 100000 [2]. In the Western Canadian province of Alberta (population 4146000), foreign-born persons contributed ~90% of the 211 cases diagnosed with TB in 2015 ([3]; Provincial TB Consultant, Alberta Health Services, Edmonton, AB, Canada). The ability of Canada to meet global targets for TB pre-elimination, *i.e.* 1 case per 100000 population by 2035, is threatened given the high proportion of foreign-born cases in Canada and the knowledge that, with routine programming, the incidence of TB will not decline by >2% per year once the foreign-born contribute >70% of cases annually [4–6].

An observation important to TB elimination in high-resource, low-incidence settings is that expertise in managing the disease declines relative to the falling burden of disease [7, 8]. In countries like Canada, where universal, transferrable and equitable healthcare is presupposed, but where people can live remotely over vast geographic areas, managing the disease is becoming ever more challenging [7].

A tool that predicts the likelihood of pulmonary TB (PTB) may improve the efficiency of diagnosis by aiding the clinical decision-making process. More-timely PTB diagnoses result in reduced individual morbidity and mortality, and potentially diminish the pool of latently infected individuals by interrupting transmission [9]. Thus, the main objective of this study was to investigate whether PTB among foreign-born persons referred for TB services in Alberta could be predicted from the medical history, results of a complete blood count and a chest radiograph.

3.2 Methods

This retrospective cohort study was undertaken to derive predictions using multiple logistic regression for two main outcomes: culture-positive PTB disease (irrespective of smear status) and more infectious, smear-positive, culture-positive disease (hereafter "infectious PTB"). *A posteriori* considered features of disease were used as potential predictors, including the following routinely collected clinical, laboratory and radiographic information: 1) symptoms (respiratory and constitutional), 2) duration of symptoms, 3) relative absence of dyspnoea, 4) failure to respond to broad-spectrum antibiotics, 5) presence of epidemiological risk(s) of infection, 6) presence of moderate- or high-risk factor(s) for reactivation of latent TB infection (LTBI), and 7) complete blood count results. Chest radiograph features typical of PTB (*e.g.* new upper lung zone dominant infiltrate with or without cavitation but no discernible adenopathy) were also considered [9]. We tested the influence of each predictor on the outcomes, *i.e.* PTB and infectious PTB, to test the hypothesis that some variables would have a greater predictive value for each.

In Alberta, all TB services are delivered through three public health clinics: one in each of the major metropolitan areas of Calgary and Edmonton, and a Provincial TB Clinic serving clients from rural and remote areas of the province using public health networks and telehealth modalities [7]. Recruitment for this study was from the Edmonton TB Clinic (ETBC). Interpreter use was discretionary.

Consecutive foreign-born adults (aged >14 years) referred to the ETBC between January 1, 2013 and April 30, 2017 were considered eligible (n=391). This sample size was determined to be adequate to detect a change of $p_{(culture/smear=1)}$ from 0.25 to 0.33 or greater when a continuous predictor was increased 1 SD above the mean (equivalent to OR ≥1.5) with 80% power and 5% level of significance after allowing all other variables to have an R^2 of 0.15 with the continuous predictor [10]. Within the cohort, the top five countries of origin were the Philippines, India, Somalia, China and Vietnam, accounting for 317 of the 391 (81%) eligible adults.

Historical information for each member of the cohort was abstracted from public health records *via* the integrated public health information system retrospectively, and complemented by data gleaned from a standard patient intake form introduced into the ETBC at the outset of the study and by which some data were collected prospectively (see supplementary appendix S1). No members of the cohort had missing data for any of the explanatory variables. True disease status was defined as having a positive culture for *Mycobacterium tuberculosis* from airway secretions, while infectious PTB cases were determined to be culture-positive from airway secretions and, from that sample, have a positive acid-fast bacilli smear. Culture positivity was determined on the basis of one positive result as per the Canadian TB

standards, with every eligible member having at least two sputum specimens collected. Smear positivity was also determined on the basis of one positive result. Remaining members neither grew the organism nor were notified as having disease (n=221).

Each of the predictors was considered related to the outcomes, *i.e.* PTB (culture-positive) and infectious PTB (smear-positive), by some degree. The degree of association was represented by a score from 1 to 4. For example, symptoms ranged from "no symptoms" (score of 1), "one constitutional or one respiratory symptom excluding hemoptysis" (score of 2), "two constitutional, or two respiratory symptoms, or two with one of each, or three constitutional or respiratory symptoms excluding hemoptysis" (score of 3), or "three symptoms with any combination of respiratory and constitutional excluding hemoptysis, and hemoptysis with or without any other symptoms, or four symptoms" (score of 4) [9, 11]. Respiratory and constitutional TB symptoms are generally sensitive but lack specificity and, as such, symptoms alone should not be used for the purposes of TB diagnosis or screening. Dyspnea is an uncommon symptom of PTB and its absence was considered an independent predictor (see Results).

Predictors were coded, 1–4, and entered into an Excel spreadsheet (Microsoft, Redmond, WA, USA). These data were then imported into Stata version 14 (StataCorp, College Station, TX, USA) for further analysis. Stratification for each predictor is provided in supplementary appendix S2. Chest radiographs were re-read by an independent academic chest radiologist blind to the presence or absence

of active disease. The radiologist classified radiograph results as “typical” or “atypical” for adult-type PTB [12].

Prediction equations were obtained for both outcomes: PTB or infectious PTB, or not. Multiple logistic regression analysis was used to determine each prediction equation. Collinearity was assessed by using Kendall's τ_b, with none seen. Explanatory variables were treated as continuous, with the exception of sex and chest radiograph, which were dichotomised. Differences in mean age and proportion of males were tested by the two-tailed t-test and the Chi-squared test, respectively. Differences in the mean scores for each clinical feature were assessed using the Mann–Whitney U-test. Purposeful selection was used for model building, such that any predictors significant at $p \geq 0.20$ in univariate analysis were included in the final models. Goodness of fit was assessed using the Hosmer–Lemeshow statistic with a non-significant p-value indicating a good fit. The multiple logistic regression model was then considered to be the “prediction equation” for the outcome of interest. Receiver operating characteristic (ROC) curves were generated and the area under the ROC curve (AUC) was quantified for both PTB and infectious PTB diagnoses to assess the performance of the multiple logistic regression to correctly predict true disease status.

Model performance was examined by applying the leave-one-out cross-validation method to the full cohort [13, 14]. In this method, each observation is excluded one at a time, with a multiple logistic regression model fitted for the remaining observations; the predicted probability for each outcome (risk score) is then determined using the observed values for the deleted observation. The ROC

curve for the initial logistic regression is then compared with the sensitivity and specificity of a 2×2 table generated by cross-validation. The leave-one-out cross-validation method tends to yield a less optimistic prediction, and is routinely used as a test of internal validity and to estimate external validity [14]. All statistical tests were performed using Stata version 14.

Ethics approval: The Health Research Ethics Board panel at University of Alberta approved this study (approval Pro00035012). Alberta Health Services provided administrative and operational approvals. Patients were not involved in the design of this study, but future cohorts are expected to benefit from its results. Informed consent was not obtained because of the retrospective nature of the data used in this study. TB is a time-limited, curable disease so ongoing contact with the clinic is not likely. All data were anonymised and aggregated.

3.4 Results

The demographic and clinical profile of patients in this cohort are described in Table 1. There were 391 patients in this retrospective cohort, among whom all had some degree of suspicion for TB disease. Just over half of the cohort were male (51.4%), and the mean age was 45.4 years. With respect to the demographic characteristics of these patients, distribution was equal by age and sex for the outcomes PTB *versus* culture-negative (no disease) and for infectious PTB *versus* all others (smear-negative, culture-positive disease and culture-negative (no disease)). With respect to the clinical characteristics of these patients, there were significant differences in the mean scores observed between groups defined by their disease status.

Table 1: Demographic and clinical features by PTB diagnosis status and smear-status

	Culture +	Culture -	p-value	Smear +	All Others	p-value
Subjects	170	221		74	317	
Age	46.2±21.0	44.6±16.3	0.42	45.4±21.2	45.3±17.8	0.97
Males	90 (52.9)	111 (50.2)	0.59	41 (55.4)	160 (50.4)	0.44
Clinical characteristics*						
Symptoms	2.7± 1.14	1.1 ± 0.58	<0.001	3.3± 0.87	1.4± 0.92	<0.001
Duration of symptoms	3.0± 1.24	1.1± 0.72	<0.001	3.5± 0.89	1.6 ± 1.2	<0.001
Absence of dyspnea	3.7± 0.60	3.9± 0.22	<0.001	3.6 ± 0.64	3.9 ± 0.37	<0.001
Antibiotic use	1.9 ±1 .20	1.1± 0.53	<0.001	2.4± 1.2	1.2± 0.75	<0.001
Epi risk of acquiring MTB infection	2.5± 0.68	2.8± 0.92	0.007	2.3± 0.54	2.7± 0.87	0.002
Risk factor for reactivation of LTBI	1.4± 0.82	1.1± 0.51	<0.001	1.5± 0.74	1.1± 0.66	<0.001
CBC	2.9± 0.99	2.1± 0.64	<0.001	3.1 ± 1.01	2.3 ± 0.82	<0.001

Data are presented as n, mean± SD or n (%).
Abbreviations: MTB Mycobacterium tuberculosis; LTBI latent TB infection, MTB *Mycobacterium tuberculosis*; CBC complete blood count.
*refers to the mean of the score, ranging from 1 to 4, characterizing the association between the predictor and outcome from clinical experience.

The final multiple logistic regression model for the outcome PTB tested the seven aforementioned clinical characteristics as potential predictors (Table 2). Chest radiograph was not included because people without PTB generally do not have chest radiograph results that are "typical" of adult-type PTB. We therefore saw an unstable result for "typical" chest radiograph on PTB. Four predictors were found to have a statistically significant association with the outcome: 1) symptoms, 2) duration of symptoms, 3) risk factors for reactivation of LTBI and 4) complete blood count.

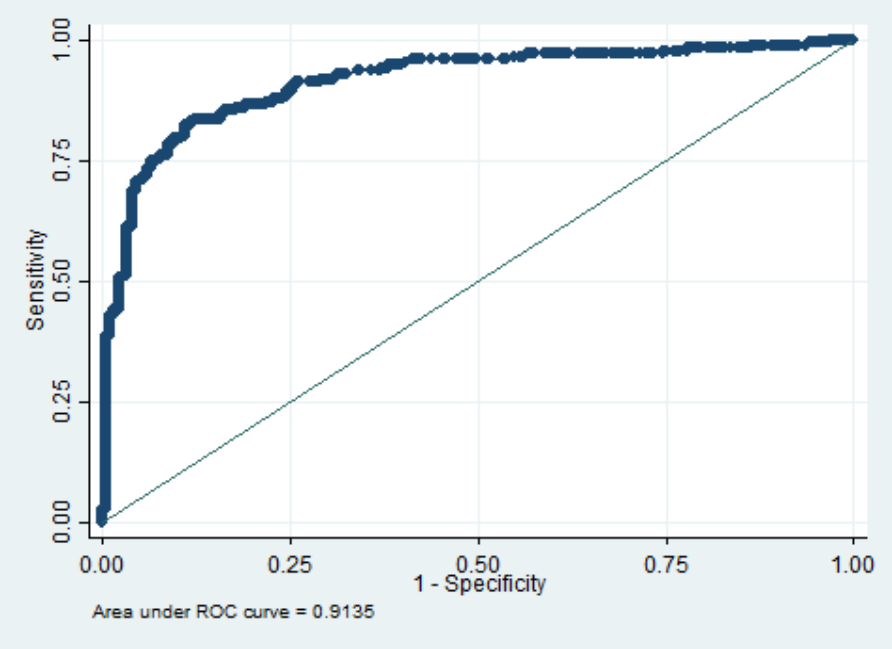
Table 2: Results from the multiple logistic regression model for culture status

Demographics	aOR (95% CI)	p-value
Age	0.98 (0.96, 1.00)	0.05
Male	1.13 (0.62, 2.07)	0.67
Clinical characteristics*		
Symptoms	1.79 (1.09, 2.96)	0.02
Duration of symptoms	2.24 (1.51, 3.34)	<0.001
Absence of dyspnea	0.85 (0.36, 2.00)	0.71
Antibiotic use	1.16 (0.77, 1.77)	0.46
Epi risk of acquiring MTB infection	1.06 (0.74, 1.51)	0.72
Risk factor for reactivation of LTBI	1.72 (1.08, 2.72)	0.02
CBC	2.28 (1.58, 3.31)	<0.001

Abbreviations: aOR adjusted Odds Ratio; LTBI latent TB infection, MTB *Mycobacterium tuberculosis*; CBC complete blood count.
*refers to the mean of the score, ranging from 1 to 4, characterizing the association between the predictor and outcome from clinical experience.

Persons with more symptoms suggestive of TB had greater odds of having PTB confirmed *via* culture (adjusted OR (aOR) 1.79, 95% CI 1.09–2.96). Moreover, those symptoms appeared to be subacute or chronic in nature ("duration") (aOR 2.24, 95% CI 1.51–3.34). Risk factors for the reactivation of LTBI ("risk factors") also increased the odds of disease (aOR 1.72, 95% CI 1.08–2.72). A chronic disease process was suggested by the association between the results of the complete blood count and a positive *M. tuberculosis* culture (aOR 2.28, 95% CI 1.58–3.31). All other predictors showed a positive relationship with PTB, with the exception of dyspnea, although they were found not to be statistically significant. The area under the ROC curve (AUC) for culture-positive-only PTB is 0.9135 (figure 1), suggesting a strong combined sensitivity and specificity of our multiple logistic regression model for PTB (disease) *versus* no disease.

Figure 1: Receiver operating characteristic (ROC) curve of the prediction equation for the outcome "culture-positive" (*i.e.* pulmonary tuberculosis). AUC: area under the ROC curve.



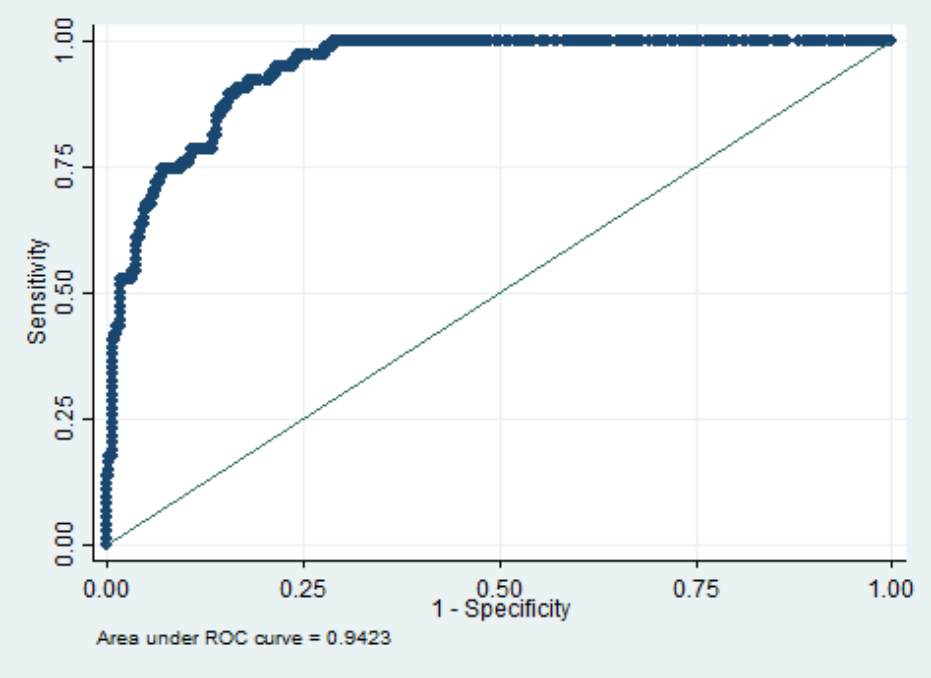
Among persons with culture-confirmed disease, having a typical chest radiograph increases the odds of having infectious PTB (aOR 12.34, 95% CI 5.32–28.62). Chest radiograph was included because infectious cases were compared with all others, including smear-negative, culture-positive PTB cases among whom some had "typical" chest radiograph results. Just as in the first multiple logistic regression, the predictor "symptoms" was found to have a statistically significant association with the outcome infectious PTB and so too was the predictor "antibiotics" (table 3). The explanatory variable "antibiotics" measured prescription history of broad-spectrum antibiotics in the 6 months preceding the date of diagnosis, with no appreciable or sustained relief of symptoms. Infectious PTB appears to be more strongly predicted than PTB alone (AUC=0.9423) (figure 2).

Table 3: Results from the multiple logistic regression model for infectious PTB (smear-positive, culture-positive disease)

Demographics	aOR (95% CI)	p-value
Age	1.00 (0.98, 1.02)	0.79
Male	1.23 (0.57, 2.65)	0.59
Clinical characteristics*		
Chest Radiograph	12.34 (5.32, 28.62)	<0.001
Symptoms	2.91 (1.80, 4.68)	<0.001
Duration of symptoms	0.94 (0.60, 1.46)	0.80
Absence of dyspnea	0.62 (0.30, 1.26)	0.18
Antibiotic use	1.55 (1.10, 2.18)	0.01
Epi risk of acquiring MTB infection	0.94 (0.52, 1.69)	0.84
Risk factor for reactivation of LTBI	1.35(0.86, 2.14)	0.18
CBC	1.45 (0.96, 2.18)	0.07

Abbreviations: aOR adjusted Odds Ratio; LTBI latent TB infection, MTB *Mycobacterium tuberculosis*; CBC complete blood count.
*refers to the mean of the score, ranging from 1 to 4, characterizing the association between the predictor and outcome from clinical experience.

Figure 2: Receiver operating characteristic (ROC) curve of the prediction equation for the outcome "smear-positive" (*i.e.* infectious pulmonary tuberculosis). AUC: area under the ROC curve.



Compared with the logistic regression model for the outcome PTB, with an AUC of ~0.91, cross-validation yielded a sensitivity of 83.8% and specificity of 87.3% (positive predictive value 91.4%, negative predictive value 77.0% and accuracy 85.1%). Compared with the logistic regression model for the outcome infectious PTB with an AUC of ~0.94, cross-validation yielded a sensitivity of 92.8% and specificity of 73.9% (positive predictive value 94.3%, negative predictive value 68.9% and accuracy 87.7%). Goodness of fit was tested using the Hosmer–Lemeshow statistic and both models were found to have a good fit ($p=0.18$ for "PTB" and $p=0.95$ for "infectious PTB"). A non-statistically significant result indicates failing to reject the null hypothesis that the data do not fully, or properly, describe the outcome of interest.

3.5 Discussion

This retrospective cohort study used consecutive referrals of foreign-born adults to the ETBC to determine if predicting who would ultimately have smear-negative, culture-positive and smear-positive, culture-positive disease is possible. Ideally the results of these models can be used to develop a tool to assist in the identification of PTB using clinically available tests and routinely collected information. We suggest a targeted medical history for patients referred to TB services or presenting with general respiratory complaints in primary care. A long duration of respiratory and/or constitutional symptoms, the results of a complete blood count suggesting anemia of chronic disease or micronutrient deficiency, with a normal or low leukocyte count suggesting a process other than community-acquired pneumonia, and risk factors relating to the reactivation of LTBI provide good predictive value of

culture-positive PTB [8, 16]. A documented failure to respond to prescription(s) of broad-spectrum antibiotics (previously defined) and chest radiograph features that are typical of adult-type PTB have additional predictive value for an outcome of infectious, smear-positive PTB. This constellation of features suggests that smear-positive cases may have had more contact with the healthcare system and that their diagnoses may have been delayed, thereby supporting the implementation of a valid instrument that helps make a more-timely diagnosis. We have not looked into whether these delays are associated with increased transmission, but foreign-born persons in Alberta have previously been reported not to transmit to the same extent as Canadian-born patients [15]. While the number of cases from the top five nationalities reported in this study has increased over time, the vast majority of these cases are likely the result of reactivation of latent infection acquired abroad.

With respect to the relative absence of dyspnea, all members of the cohort presented similarly. A relative absence of dyspnea in TB is understood to be due to parallel reductions in ventilation and perfusion in the diseased lung, with the result that gas exchange is relatively well preserved. It is an underappreciated clinical feature of PTB [9, 16]. The fact that dyspnea appears to be protective in our study group indicates that culture-positive PTB patients are very much like non-diseased persons, with neither group found to be dyspneic on examination in general. This feature, therefore, ought to be retained given its ability to offer clinically important information that can distinguish PTB from other respiratory illnesses (*e.g.* relative absence of dyspnea might support a differential diagnosis in favour of PTB over pneumonia in primary care) [16, 17]. “Risk factors” measured the moderate- and

high-risk factors for PTB in persons with LTBI as described in the 7th edition of the Canadian TB Standards, and previously defined in this text [18].

Among migrants, time since arrival in the new country is a classical predictor of progressing to active disease. Two papers published in low-incidence settings (Canada and the USA) suggest that this is likely due to active case-finding activities in persons referred by immigration authorities for medical surveillance post-arrival. If medical surveillance referrals are excluded, the risk of reactivation of LTBI among persons not referred for medical surveillance appears to be the same year over year [19, 20]. As such, it was not included as a predictor in these models, although recent arrivals who were referred for medical surveillance would be indirectly captured by two of the clinical characteristics contributing to the score. These include a high-risk lung scar on chest radiography (high medical risk factor for the reactivation of LTBI) and a past history of TB (part of the epidemiological risk characteristic). Among those not referred, time of arrival in Canada is not captured directly or indirectly.

There has been growing interest in using prediction models for TB. Recent papers have evaluated the significance of predicting a prognosis of PTB, best practices for screening and meta-analyses for ruling out (negative prediction) TB among HIV/AIDS co-infected individuals [21–24]. This is the first study to indicate the value of prediction in a low-incidence setting as a diagnostic aid for PTB among foreign-born persons. Suspicion would appear to be raised relative to the number of presenting clinical features. As such, it is theoretically possible to reach a threshold of suspicion (risk score) after which point sputum is collected, isolation is indicated

or an appropriate referral is made. If this is the case, clients may be triaged more appropriately, and loss to follow-up and delays in diagnosis (major contributors to the slow rate of decline in incidence) may be reduced.

Given the high proportion of foreign-born TB cases in Canada, assuming a 2% reduction in the incidence of TB per year is quite generous and, at that pace, our national pre-elimination target is >85 years away if TB programming does not change drastically [4–6]. While targeted screening efforts and overseas programme improvements are encouraged, technological innovation may assist the timeliness of diagnosis in the potential foreign-born cases already arrived [6, 25]. Our study findings corroborate the literature that, in low-incidence settings where TB is not often considered, patients presenting with infectious disease appear to have multiple missed opportunities to have their diagnosis made.

One limitation of this study is that the data are retrospective; validation with a prospectively collected dataset would strengthen the findings. However, because TB is relatively rare in high-income countries like Canada, collecting a sufficient sample of patients who are later confirmed to, in fact, have disease, prospectively, is logistically prohibitive. Leave-one-out cross-validation is considered to be a relatively sound method of overcoming this limitation with the results of our cross-validation showing strong internal validity [26]. Leave-one-out cross-validation is not without its own limitations, and the results it produces may be biased. It is, however, a powerful tool for estimating validation when data sets are too small to split into distinct training and validation groups, as is the case here. The external validity of these predictive models remains an open question and further testing is

required in future studies. Data for all patients were collected, in part, from a form that was introduced into the clinic for the purpose of quality improvement in TB client management and can be considered enhanced surveillance. This eliminated the possibility that we would have missing data for the members of our cohort. In other clinical settings, missing data could present a problem.

Globally, TB is a major cause of mortality with one person dying approximately every 18 seconds from the disease and its effects [27]. In Canada, the overall incidence is low; however, overrepresentation of cases by the foreign-born is a strong indication that in-country epidemiology reflects the epidemiology of disease in the country of origin among immigrants, refugees and visitors [6, 28]. While supporting TB programming in resource-limited settings remains a cost-effective way of reducing prevalence of infection among foreign-born persons arriving in Canada, data suggest that additional in-country interventions are required to reach elimination targets [29]. The foreign-born dominate the cases referred to the TB clinics in Alberta, but not all persons referred have TB. Identifying high-, medium- and low-risk referrals upon receipt by using a tool underwritten by these prediction models could be considered one such programmatic innovation.

Elimination of TB will be achieved by two mechanisms: 1) reducing the pool of latently infected persons through screening and use of preventive therapy, and 2) interrupting transmission wherever possible. From a public health perspective, identifying smear-positive cases is important because they present with the more communicable form of the disease. Using predictive features specific to the outcome "infectious PTB" provides an opportunity to halt the reproduction of the disease by

recommending more-timely treatment, thereby limiting their ability to transmit [30]. This work is recommended to aid a more-timely diagnosis and should not be used as a PTB diagnostic. The gold standard for PTB diagnosis is recovery of the organism in culture, although application of a risk score derived from prediction models may prompt the earlier collection of sputa. As such, we recommend that in the presence of 'respiratory' presenting complaints among patients to primary care, or upon referral to TB prevention and care, a targeted medical history or risk assessment form be designed to include the commonly collected clinical features presented in this work. Those tools may then be used to triage cases appropriately in order to more efficiently manage resources.

3.6 References

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3.7 Supplement 1

I. SYMPTOMS

1 { No Symptoms (out of 8 possible)

2 { One symptom (respiratory [R] or Constitutional [C]) not including hemoptysis

3 { Two symptoms (not including hemoptysis); 1R/1C, or 2R, or 2C
Three symptoms (not including hemoptysis) – all R or all C

4 { Three symptoms (not including hemoptysis); mix of R and C
Hemoptysis with or without other symptoms; or four or more symptoms (not including hemoptysis).

II. DYSPNEA

1 { Dyspnea at rest

2 { Dyspnea with minimal exertion (distinguished from fatigue)

3 { Dyspnea with heavy exertion (distinguished from fatigue)

4 { No dyspnea

III. DURATION OF SYMPTOMS ATTRIBUTED TO TB

1 { Asymptomatic

2 { Symptoms < 2 weeks

3 { Symptoms 2-4 weeks

4 { Symptoms 5 or more weeks

IV. FAILURE TO RESPOND TO BROAD SPECTRUM ANTIBIOTICS

1 { No prescriptions within the past 6 months.

2 { One prescription between 4-6 months of diagnosis.

3 { One prescription within the past 3 months

4 { Two or more prescriptions within the past 6 months.

V. EPIDEMIOLOGICAL RISK OF INFECTION

1 { No history of TB; no epidemiologic risk LTBI, negative historical IGRA
No history of TB; no epidemiologic risk LTBI, negative historical TST.
No history of TB; no epidemiologic risk LTBI; no IGRA or TST on record.

2 { Past history of TB or LTBI; adequately treated.
No history of TB, epidemiologic risk for LTBI (untreated); no TST or IGRA.

3 { No history of TB, epidemiologic risk for recent (<2 yr) LTBI (untreated); no TST or IGRA.
No history of TB, epidemiologic risk for LTBI (untreated); positive TST.
No history of TB, epidemiologic risk for LTBI (untreated); positive IGRA.

4 { No history of TB, epidemiologic risk for recent (< 2yr) LTBI; positive TST or IGRA.
Past history of TB, inadequately treated or no record of treatment.

VI. PRESENCE OF A HIGH OR MODERATE RISK FACTOR FOR REACTIVATION OF LTBI

1 { No risk factor.
One or more slight, low or very low risk factors.

2 { One moderate risk factor

3 { Two or more moderate risk factors
One high risk factor (other than HIV) with or without one moderate risk factor.

4 { One high risk factor (other than HIV) and two or more moderate risk factors.
Two high risk factors (other than HIV) with or without a moderate risk factor.
HIV or AIDS

VII. COMPLETE BLOOD COUNT

1 { Normal hemoglobin and leucocytosis.

2 { Normal hemoglobin, normal or low leucocyte count.

3 { Anemia and leucocytosis.

4 { Anemia and normal or low leucocyte count

VIII. CHEST RADIOGRAPH

Typical = new upper lung zone dominant infiltrate with or without cavitation but no discernible adenopathy.

Atypical = all others.

3.8 Supplement 2

Appendix 1. Assessment History Form

(Completed by _____)

I. Demographics

Date (dd/mm/yy): _____ Age (yrs): _____Wt(kg): _____

Current Address: _____Postal Code:_____

Previous Address (If <6 mo. at current address): _____

Referring Physician: _____

Family Physician (if different from referring physician):_____

Emergency Contact Name and Phone No:_____

Population Group: Status Indian ☐ Non-status Indian ☐ Foreign-born ☐
Métis ☐ Inuit ☐ Cdn-born non –aboriginal ☐

If Aboriginal: On-Reserve ☐ Off-reserve ☐

If Foreign-born: Country of birth: _____

If Foreign-born: Date of Arrival (dd/mm/yy): _____

Travel history within past 24 mos: Country (s) and length of stay: _____

_____

Homeless within past 12 mos: No ☐ Yes ☐ Incarcerated in past 24 mos: No ☐ Yes ☐

Work History/ Occupation: _____

II. TB History

No	Yes	Unknown	
☐	☐	☐	TB Contact /Exposure; If so when:_____
☐	☐	☐	Past History TB; Year: _____
☐	☐	☐	Past Treatment TB Disease: _____
☐	☐	☐	BCG Vaccination: _____
☐	☐	☐	Previous Mantoux: Size _____mm. Date: _____

III. Health History

Date of last CXR: _____

Current Medications: _____

Allergies: _____

Hospitalization(s) within past 12 mos:_____

LMP:_____ Recent live vaccine or viral Infection No ☐ Yes ☐

High or increased risk medical condition, etc.

No	Yes	
☐	☐	HIV /AIDS _____
☐	☐	Immuno-suppressant drugs (including corticosteroids/ TNF inhibitors) _____
		_____
☐	☐	Dialysis-dependent renal failure _____
☐	☐	Carcinoma of the head and neck _____
☐	☐	Diabetes (Specify if IDDM or NIDDM)_____
☐	☐	Recent (within the past yr.) Alcohol / Substance Abuse (specify) _____
☐	☐	Current Smoker (Pack / Day) _____
☐	☐	Hx of liver disease _____
☐	☐	Were antibiotics prescribed for a respiratory illness during the past 6 months?

If yes: Once ☐ Twice ☐ Three times ☐

IV. <u>Current Symptoms and Their Duration</u>

Symptom /Duration			Symptom /Duration		
No	Yes		No	Yes	
☐	☐	Cough _____	☐	☐	Dysuria_____
☐	☐	Sputum production _____	☐	☐	Nocturia _____
☐	☐	Hemoptysis _____	☐	☐	Headache _____
☐	☐	Chest Pain _____	☐	☐	Lymph Node Swelling _____
☐	☐	Dyspnea RR/Sa02: _____	☐	☐	Bone/Joint Problems _____
☐	☐	Fever _____	☐	☐	Nausea _____
☐	☐	Night Sweats _____	☐	☐	Vomiting _____
☐	☐	Weight Loss _____	☐	☐	Diarrhea _____
☐	☐	Fatigue _____	☐	☐	Other GI Problems _____

V. <u>If Client is a Presumptive or Suspect Active PTB Case</u>

No	Yes	
☐	☐	If productive cough, 3 spontaneous sputa for AFB smear & smear/culture
☐	☐	If dry cough or no cough, 2 induced sputa or 1 bronch wash for AFB smear/culture
☐	☐	TST / IGRA

Chapter 4: Quantifying the individual and public health consequences of a missed diagnosis of pulmonary TB in the emergency department: a population-based retrospective cohort study

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A version of this manuscript will be submitted for publication.

ABSTRACT

Objectives: To describe emergency department (ED) use by patients with pulmonary tuberculosis (PTB) in the months immediately preceding diagnostic confirmations. Herein we quantify both the individual, and public health consequences of a missed diagnosis in this setting.

Hypothesis: Patients with PTB who attended an ED prior to their diagnosis differ from those who did not.

Design: Population-based retrospective cohort study.

Setting: We undertook this study in EDs throughout the Province of Alberta, Canada, where TB is managed out of three public health clinics serving a population 4,252,900 with a crude TB incidence of 5.5/100,000 population in 2016.

Participants and outcome measures: We included patients with culture-confirmed PTB consecutively diagnosed over an 81-month period. ED visits were determined through administrative data holdings and divided, based on their most-responsible discharge diagnosis into respiratory (TB vs non-TB) and "other" groups. We systematically recorded sociodemographic details, and relevant investigations for each case. Outcomes included treatment outcome and evidence of transmission as measured by secondary cases among contacts of both attendees and non-attendees. We compared ED attendees to those without

ED presentation using chi-square tests for dichotomous outcomes and t-tests for continuous outcomes; we completed recursive partitioning for achieving a TB diagnosis in the ED.

Results: Overall, 711 culture-confirmed patients with PTB were identified; the median age was 44 years, and 395 (56%) were female. In the six months previous to a TB diagnosis, 378 (53%) made at least one ED visit. ED attendees experienced a median health-system delay of 20 days (IQR: 6, 178), contributed 3,812 hours of nosocomial exposure time, and generated 31 secondary cases of TB. Those who attended the ED had characteristics suggesting an underserved population. Many (51%), made multiple visits. Those who did were less likely to be foreign-born 67% vs 82% ($p<0.01$); more likely to report social risk factors, 15% vs 6% ($p<0.01$), have a rural residence 43% vs 21% ($p<0.01$), and were more likely to experience a TB-related death 9% vs 3% ($p = 0.05$) compared to PTB patients who attended the ED once.

Conclusions: The ED remains an important point of contact for PTB patients in Alberta; however, the diagnosis appears frequently missed, thereby delaying management. Complicating the diagnosis is the relatively low index of suspicion, atypical presentations and the overcrowding of many EDs settings. Missed diagnoses contribute to higher exposure to contagion by vulnerable groups, and increased number of preventable transmission events.

4.1 Introduction

The emergency department (ED) is a common place to seek care; a 2016 Commonwealth Fund survey indicated that Canadians seek care more often in an ED than 10 other comparator countries [1]. This creates two fundamental challenges for patients. First, the demand for emergent care is high and the atmosphere is crowded and high-stress for patients and staff alike. Second, underserved individuals without urgent needs can increase the demand for limited resources [2-4]. In turn, the throughput of EDs is extraordinarily high and the possibility of missing rare diagnoses therein increases [5]. Generally, the burden of a missed diagnosis falls squarely on the individual patient, resulting in increased morbidity and/or mortality. In some instances, however, there are both individual and public health consequences. This can occur when patients present to the ED with undiagnosed communicable diseases such as pulmonary tuberculosis (hereafter, referred to as PTB) [6-8].

Fundamentally, PTB is *the* transmissible form of the disease, with few exceptions [9-11]. While *Mycobacterium tuberculosis* (*M.tb*) can affect any organ, its presence in the lungs confers two advantages to the organism [12,13]. Firstly, *M.tb* is aerobic and therefore well adapted to highly oxygenated environments [14]. Secondly, transmission of PTB is achieved by processes that aerosolize the infecting bacilli such as coughing, and sneezing. Persons in close contact with someone who has PTB can subsequently inhale aerosols that, once established, complete a cycle of reproduction [15, 16]. Symptoms of PTB can indicate both the severity and duration of disease (i.e., weight loss, fever, night sweats, and fatigue), while some complete the transmission cycle (e.g., coughing, and sneezing). Unfortunately,

individually, and in combination, these classical symptoms are not specific to tuberculosis [17]. As such, while severe symptoms may lead patients to seek acute care, when the overall suspicion of PTB is low, diagnosis by symptomology alone is inaccurate and delayed [18, 19].

A study conducted in the city of Edmonton, Alberta, Canada in the 1990s showed that use of the ED by urban-dwelling tuberculosis patients pre-diagnosis was substantial; missed opportunities to diagnose TB patients in the ED have similarly been confirmed elsewhere [20, 21]. Herein, we revisited ED use by TB patients, this time province and program-wide in Alberta, by PTB patients alone, in the six-month period immediately preceding their diagnoses. Our purpose was to characterize those patients both detected and missed during an emergency room visit, and quantify both the individual, and public health consequences of missed diagnoses in this setting.

4.2 Methods

Design: A population-based retrospective cohort of consecutive, culture-confirmed PTB patients who did or did not attend an ED on one or more occasion(s) in the six-month period immediately preceding diagnosis. We explored missed opportunities for making timelier diagnoses with the potential to improve patient, and public health outcomes.

Setting: In Canada, each province and territory has its own TB prevention and care program. We performed this study in the Province of Alberta, which had a population of 4,252,900 (Statistics Canada), and a crude TB incidence rate of 5.5/100,000 population in 2016. The provision of all TB services in Alberta is via three dedicated public health clinics [22]. In Alberta, most TB cases arise from individuals who are foreign-born, and there is a low prevalence of HIV sero-positivity in line with other high-income, low TB-incidence

settings [23]. The province is one of the four major immigrant-receiving provinces in Canada.

Study Population: The cohort includes all culture-positive PTB cases diagnosed in Alberta between April 1 2010 and December 31 2016 and aged ≥ 17 years. We identified each case in the Integrated Public Health Information System (IPHIS), which is the repository for Alberta's Provincial TB registry, and the Provincial Laboratory for Public Health (ProvLab), which performs all mycobacteriology in the Province. The age criterion is based on the fact that 17 years is the lower limit for consideration as an 'adult' in emergency medicine in Alberta; it, and the culture-positive pulmonary criteria are based on the public health focus of the study with adolescent/adult-type pulmonary TB being the most communicable form of the disease. In Alberta, the date of diagnosis of TB is the start date of treatment, or the date of death for those diagnosed post-mortem. We reconstructed ED use histories of each case in the six months preceding their date of diagnosis by cross-referencing each notified case with the Alberta Health Services Data Integration, Measurement and Reporting (DIMR) system, using the personal health number (PHN).

We abstracted and tested demographic, clinical, mycobacteriologic and outcome information for associations to ED attendance. Demographic information included age at diagnosis, sex, population group (Canadian-born [Indigenous – including First Nations, Inuit and Métis, and non-Indigenous), and foreign-born, and place of residence (urban[1] vs. rural). In the TB program, identification of population-group is by self-report. Clinical information included disease type (new active vs. relapse/retreatment), disease site

[1] Urban is defined as either of the two major metropolitan areas in Alberta; i.e. the cities of Edmonton, and Calgary, populations 932,550 and 1,239,000 respectively in 2016.

(pulmonary alone vs. pulmonary plus extra-pulmonary), HIV status (positive vs. negative), presence or absence of diabetes, and the presence or absence of social risk factors[1]. Mycobacteriologic information included smear-status (positive vs. negative) and drug susceptibility test results (resistant [any first-line drug resistance] vs. fully susceptible). Outcome information included transmission events - whether the patient did or did not generate any secondary cases (see below) – and treatment outcome (survived vs. died[2]).

To determine whether ED attendees and non-attendees generated any secondary cases, we used conventional and molecular epidemiology. The latter included the DNA fingerprints[3] of initial isolates from all cohort cases, as well as all other culture-positive cases diagnosed in the province between October 1 2009 and December 31 2018. This window of time covers a period of time that extends from six months before the diagnosis of the first cohort case, to 24 months after the diagnosis of the last cohort case. We performed secondary case analyses according to an established protocol [24, 25]. We then compared all of the same demographic, clinical, mycobacteriologic, and outcome characteristics in ED attendees who had multiple versus those with single ED visits.

Using additional administrative data, we described the ED attendees according to the timing of their visits relative to their eventual TB diagnosis, the duration of their ED visit and diagnostic group as follows: "TB", "respiratory: not TB", and "other"[4]. Diagnostic groups

[1]The TB program of Alberta systematically performs HIV and hemoglobin A1C testing (the former using an opt-out approach) at the time of diagnosis. Social risk factors included any one of homelessness within the previous 12 months, a substance misuse disorder, or incarceration at the time of diagnosis.
[2] TB deaths are those that occur before or during treatment. They include those where TB was the primary or contributory cause of death, and those where death is unrelated to TB.
[3]Restriction Fragment-Length Polymorphism (RFLP), or 24-loci Mycobacterial Interspersed Repetitive Units (MIRU) – Variable Number Tandem Repeats (VNTR), or both.
[4] TB = any mention of tuberculosis; respiratory: not TB = respiratory complaint or illness with no mention of tuberculosis; other = any other illness or complaint.

were further confirmed by having the most responsible discharge diagnoses independently reviewed by an experienced university based pulmonologist (see Supplement 2 for the full list of diagnoses and groupings). We considered all ED visit time in hours from registration until discharge to be the ED nosocomial exposure time if it occurred in the "respiratory: not TB", or "other" diagnosed groups. We assumed that consideration of TB led to appropriate precautionary measures against transmission in the ED (e.g., respiratory isolation).

Finally, we generated a list of ED attendees whose last visit to the ED occurred within 30 days of their PTB diagnosis; we defined this group as 'diagnosable'. We cross-referenced this list to the Alberta Picture Archiving and Communication System (PACS) to determine whether there was a chest radiograph from that visit, or within 7 days prior to that visit. If there was, then a university-based chest radiologist re-read that radiograph to document the presence or absence of 'typical' features of adult-type PTB[1], and the presence or absence of cavitation. Thereafter we developed an explanatory model featuring important clinical, radiographic and epidemiologic predictors for achieving a PTB diagnosis in the ED among patients whose last visit occurred within 30 days of treatment initiation, and/or mycobacteriologic confirmation of disease using recursive partitioning [26].

We used all study variables to derive our decision tree using rpart (Recursive Partitioning and Regression Trees) package in R [27, 28]. The tree begins with a parent that is split into groups (nodes) beginning with two at the top that provide the most explanatory power, and which are most pure; repetition of this process occurs for each generation thereafter producing subsequent nodes until the tree terminates when there are no

[1] 'typical' for adult-type PTB: infiltration localized to or predominantly in the upper lung zones with or without cavitation – a gas-filled space within a pulmonary consolidation, mass, or nodule, but with no discernable intrathoracic adenopathy.

additional variables that can be added which provide further reductions in impurity [26, 29]. Our tree describes categorical observations as well as an associated probability of appearing in/achieving the outcome of interest. Our decision tree is descriptive, and we have not validated it here (see limitations).

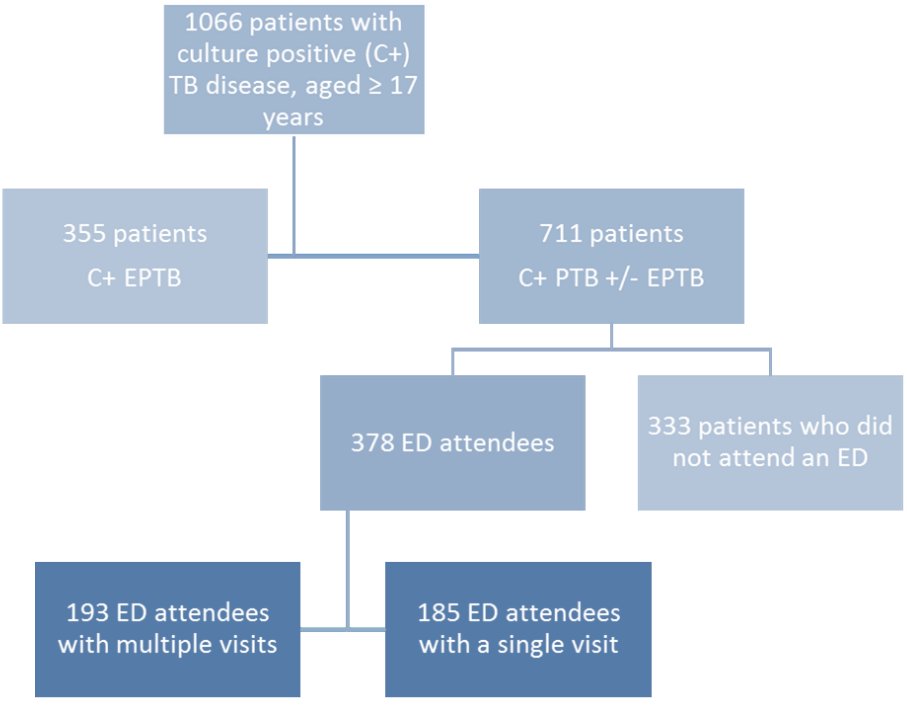
Statistical Analyses: We report continuous data as means and standard deviations (SD) or median and interquartile range (IQR), as appropriate. We report dichotomous data as counts and percentages. We used student t-test and Pearson's chi square to test for significant associations between patients' clinical and demographic characteristics and use of an ED. We similarly performed univariate tests to explore differences between patients with multiple vs. single ED visits. We performed statistical analyses using STATA 12.0 (STATA Corp., College Station, Texas, USA), and R (R Core Team, 2019) [27, 28].

Ethics approval: The Health Research Ethics Board (HREB) at University of Alberta approved this study (approval number: Pro00076709). Alberta Health Services (AHS) provided administrative and operational approvals. In addition, we obtained a data-sharing agreement from AHS for the abstraction of data from the administrative data holding - DIMR. Patients were not involved in the design of this study; however, we anticipate benefits to future cohorts of patients. The HREB waived the requirement for informed consent because of the retrospective nature of the data used in this study. TB disease is subacute and follow-up to obtain consent is not feasible. Anonymization of data occurred prior to analysis.

4.3 Results

Patients: Figure 1 (below) illustrates selection of the study cohort. As shown in Table 1, neither age nor sex were associated with attendance at an ED. ED attendees were more likely to report a rural place of residence, and were less likely to be foreign-born than non-attendees 32% vs 19%, and 75% vs 89% ($p < 0.01$ and $p < 0.01$, respectively). Of those who were foreign-born the five leading countries of origin were Philippines (25.3%); India (19.7%); Ethiopia (7.3%); Somalia (5.9%), and 4.2% of foreign-born patients were from both Afghanistan and Vietnam. Of the 94 Canadian-born attendees, 66 (70.2%) were Indigenous. Thirty-five percent of the Canadian-born and 3% foreign-born attendees reported one or more social risk factor (data not shown).

Figure 1. Selection of cohort – attendance at an emergency department (ED) by adult, culture-positive PTB patients in Alberta from April 1st 2010 to December 31st 2016



*Abbreviations: C+ culture-positive; EPTB extra-pulmonary TB; ED emergency department.

ED Attendees were more likely to have combined pulmonary and extra-pulmonary disease at diagnosis 21% vs 11% ($p < 0.01$), and more likely to have smear-positive disease at diagnosis 58% vs 39% ($p < 0.01$). Attendees and non-attendees were not more likely to be HIV seropositive (5%; $p = 0.07$), and/or diabetic (3%; $p = 0.37$) at diagnosis. Of the 22 HIV-positive ED attendees, 16 were known to be HIV positive and 6 were determined to be HIV positive at the time of their TB diagnosis (i.e., after their ED visit[s]). Of the 66 attendees with diabetes, 60 (91%) were known to be diabetic and 6 (9%) were determined to be diabetic at the time of their TB diagnosis.

Treatment outcomes were relatively poor among ED attendees. Most significantly, PTB patients who attended the ED were more likely to die than non-attendees 6% vs 1% ($p < 0.01$). The mean number of days between the first ED visit of patients who subsequently died and their date of diagnosis of PTB was 63 days. Of the 24 ED attendees who died either before or during TB treatment, TB either contributed, or directly caused the death of 22; these 22 patients made 65 visits (mean 2.9 visits). Of those visits, 18 ended with a "respiratory: not TB" diagnosis, and 47 resulted in an "other" diagnosis.

Better outcomes were observed among those patients who obtained a "TB" diagnosis in the ED. All but two of the 92 discharge diagnoses identified as "TB" occurred among patients whose treatment outcome was cure, or completed ($n = 349$); the other two occurred among patients who transferred out of Canada prior to treatment completion. The mean number of days between the first visits of patients cured or treatment complete, and their date of PTB diagnosis was 46 days.

Attendees and non-attendees were similarly likely to have generated a secondary case of TB, (5% vs. 4%; $p = 0.43$). Twenty-two attendees implicated in transmission of the

organism made 61 visits and contributed 276 hours of nosocomial exposure time (data not shown); they generated 31 secondary cases.

Table 1: Demographic and clinical characteristics associated with attendance at an ED by subsequently diagnosed TB patients

	Total	ED Attendee (%)	Non-Attendee (%)	p-value
No. Assessed	711	378 (100)	333 (100)	---
Age (mean [SD])	711	48.6 [20.9]	47.5 [19.2]	0.47
Sex				
Male	395	221 (58.4)	174 (52.2)	0.09
Female	316	157 (41.6)	159 (47.8)	
Population Group				
Canadian-Born	130	94 (24.8)	36 (10.8)	**<0.01**
Foreign-Born	581	284 (75.2)	297 (89.2)	
Place of Residence[a]				
Urban	522	255 (67.4)	267 (80.1)	**<0.01**
Rural	189	123 (32.6)	66 (19.9)	
Disease Site				
PTB Alone	592	298 (78.8)	294 (88.2)	**<0.01**
PTB+EPTB	119	80 (21.2)	39 (11.8)	
Smear Status				
Negative	357	155 (41.1)	202 (60.7)	**<0.01**
Positive	354	223 (58.9)	131 (39.3)	
Drug Resistance				
No	637	341 (90.3)	296 (88.9)	0.56
Yes	74	37 (9.7)	37 (11.1)	
HIV Status				
Negative	663	350 (92.5)	313 (93.9)	
Positive	35	22 (5.8)	13 (3.9)	0.07
Unknown[b]	13	6 (1.7)	7 (2.2)	
Diabetes				
No	595	312 (82.6)	283 (85.0)	0.37
Yes	116	66 (17.4)	50 (15.0)	
Social Risks				
No	656	336 (88.9)	320 (96.1)	**<0.01**
Yes	55	42 (11.1)	13 (3.9)	
Transmission				
No	674	356 (94.2)	318 (95.5)	0.43
Yes	37	22 (5.8)	15 (4.5)	
Outcome				
Survived	674	350 (92.5)	324 (97.2)	
Deceased	28	24 (6.3)	4 (1.2)	**<0.01**
Unknown[c]	9	4 (1.2)	5 (1.6)	

Abbreviations: PTB pulmonary TB; EPTB extra-pulmonary TB

[a]Place of Residence was the patient's "usual place of residence", or "where they lived most of the time" at diagnosis.

[b]Alberta implemented opt-out HIV-testing of all TB patients in 2003. Of the 13 patients whose HIV status was unknown, 6 people refused testing, 4 people were deceased, and 3 people were not offered testing for reasons that are unknown.

[c]All of the 9 patients whose treatment outcomes were unknown transferred outside of Canada prior to treatment completion.

Table 2 describes ED use by persons who attended multiple times vs. those with single visits.

Table 2: Characteristics associated with multiple vs. single ED visits

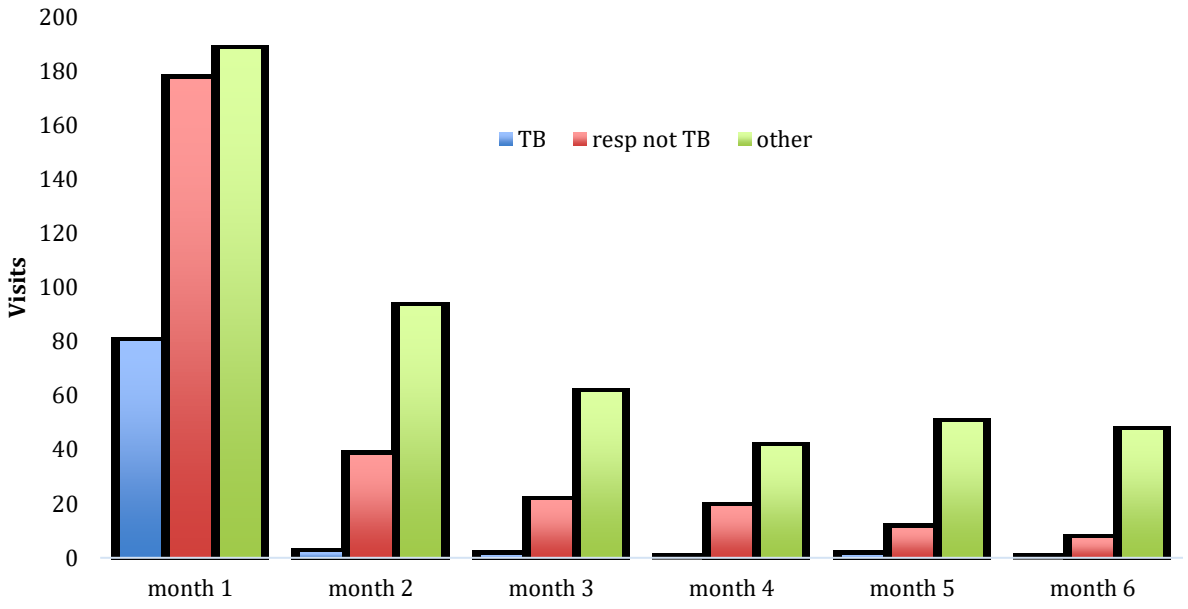
	Total	Multiple Visits (%)	Single Visits (%)	p-value
No. Assessed	378	193 (100)	185 (100)	---
Age (mean [SD])	378	49.8 [20.9]	47.2 [20.8]	0.22
Sex				
Male	221	112 (58.0)	109 (58.9)	0.86
Female	157	81 (42.0)	76 (41.1)	
Population Group				
Canadian-Born	94	62 (32.1)	32 (17.2)	**<0.01**
Foreign-Born	284	131 (67.9)	153 (82.8)	
Place of Residence[a]				
Urban	255	110 (56.9)	145 (78.3)	**<0.01**
Rural	123	83 (43.1)	40 (21.7)	
Disease Site				
PTB Alone	298	149 (77.2)	149 (80.5)	0.42
PTB+EPTB	80	44 (22.8)	36 (19.5)	
Smear Status				
Negative	155	87 (45.1)	68 (36.8)	0.10
Positive	223	106 (54.9)	117 (63.2)	
Drug Resistance				
No	37	16 (8.3)	21 (11.4)	0.31
Yes	341	177 (91.7)	164 (88.6)	
HIV Status				
Negative	350	179 (92.7)	171 (92.4)	
Positive	22	10 (5.1)	12 (6.4)	0.70
Unknown[b]	6	4 (2.2)	2 (1.2)	
Diabetes				
No	312	160 (83.0)	152 (82.2)	0.85
Yes	66	33 (17.0)	33 (17.8)	
Social Risks				
No	336	163 (84.5)	173 (93.6)	**<0.01**
Yes	42	30 (15.5)	12 (6.4)	
Transmission				
No	356	180 (93.3)	176 (95.2)	0.43
Yes	22	13 (6.7)	9 (4.8)	
Outcome				
Survived	350	173 (89.6)	177 (95.6)	
Deceased	24	18 (9.3)	6 (3.2)	**0.05**
Unknown[c]	4	2 (1.1)	2 (1.2)	

*Of those patients who had multiple ED visits, 29 (7.6%) attended both a major urban and a rural emergency department.
[a]Place of Residence was the patient's "usual place of residence", or "where they lived most of the time" at diagnosis.
[b]Of the six patients whose HIV status was unknown, one person refused testing, four people were deceased, and one person was not offered testing for reasons that are unknown.
[c]All of the four patients whose treatment outcomes were unknown transferred outside of Canada prior to treatment completion.

Attendees with multiple visits to the ED were less likely to be foreign-born (67% vs 82%; p <0.01), more likely to report a social risk (15% vs 6%), more likely to have a rural residence (43% vs 21%, p <0.01) and more likely to die during TB treatment (9% vs 3%; p= 0.05).

Visits: Figure 2 shows that visits to the ED increase closer to the date of diagnosis of TB with nearly 4 times as many visits occurring in the three months antedating a TB diagnosis than months 4, 5, and 6 combined (669 vs. 176 visits, respectively). Visits are slightly skewed towards time zero since 92 (10.8%) visits resulted in a most responsible discharge diagnosis properly characterized as TB, though the *trend* of increasing visits is maintained if those patients with a "TB" discharge diagnosis from the ED are removed from time 1 month (581 visits vs. 176, respectively). Four persons started treatment for their TB disease more than 30 days after someone in the ED suspected the disease.

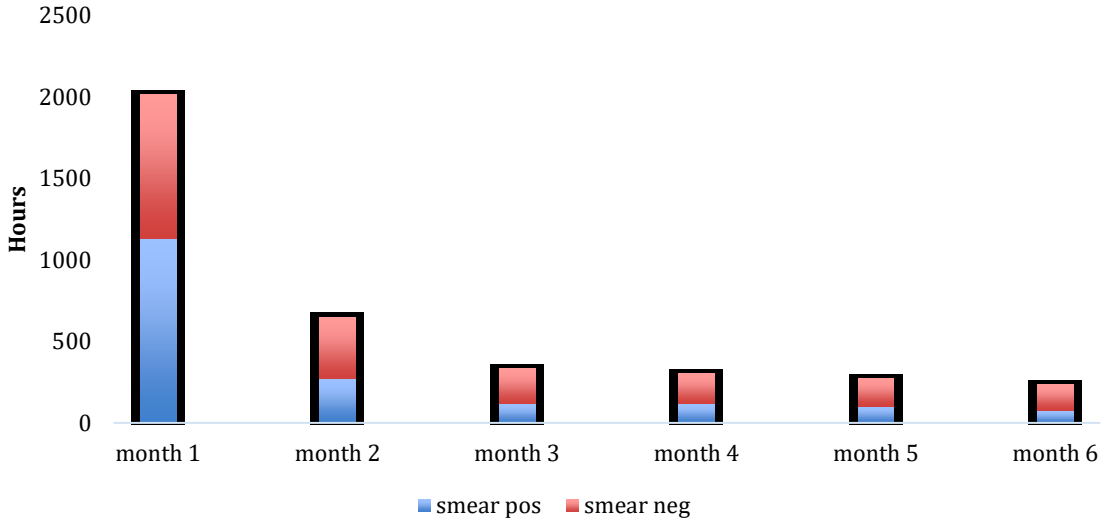
Figure 2. ED visits grouped according to discharge diagnosis by PTB patients, by month previous to TB diagnosis



Of those visits that ended with a "respiratory: not TB" diagnosis (n=273), the leading discharge diagnoses were pneumonia related (39%); cough or hemoptysis, not yet diagnosed (NYD) (15%); other respiratory symptoms (chest pain, dyspnea), NYD (14.2%); pleural effusion (6%); and, abnormal findings on chest radiograph, NYD (4%).

Delays: Figure 3 illustrates the cumulative unprotected hours (or nosocomial exposure time) of patients who received either a "respiratory: not TB", or "other" diagnoses discharge diagnoses within an ED by month and smear-status. The cumulative nosocomial exposure time in hours was 3,812 with 47.6% of those hours being contributed by persons who ended up being diagnosed with smear-positive PTB (the presumed most infectious form of the disease). In the month immediately preceding a PTB diagnosis there were 2,016 nosocomial exposure hours of which patients who were ultimately smear-positive contributed 56%.

Figure 3. Cumulative time in hours spent in ED by PTB patients whose ED discharge diagnosis was not TB-related



Nosocomial exposure time measures potential infectivity in a setting with many vulnerable contacts, but does not provide insight about risks outside of that place. As such,

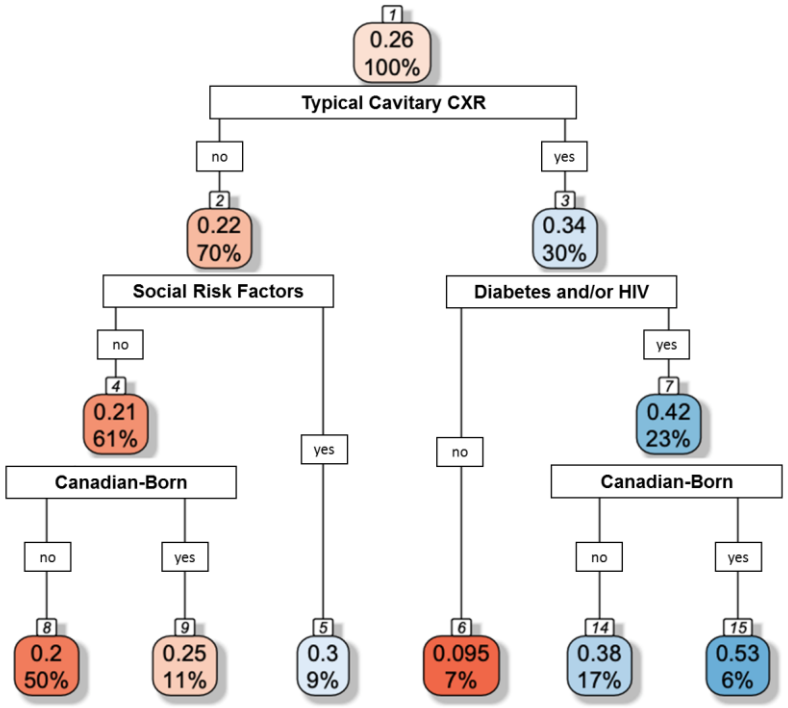
we calculated a measure of total health system delay in the cohort of patients who attended the ED. The median number of days from each patient's first visit to their eventual PTB diagnosis was 27 days (IQR: 7, 180). Since patients with complaints highly unlikely to raise the suspicion of PTB contributed many visits, we also calculated the health system delay among those patients who ever received a "respiratory: not TB" diagnosis as the time from their first visit that ended in a respiratory diagnostic code to confirmation of PTB. Among this latter group, the median delay in days was 20 days (IQR: 6, 178) (data not shown).

Diagnoses: Any diagnosis in a high-throughput setting requires agile decision-making by clinicians, and involves the consideration of many overlapping/interacting risk factors. If an outcome is rare then the ability to describe all possible interactions by regression in a study will be affected by diminishing cell counts. Within our data there were relatively few cases who achieved a TB diagnosis in the ED within a month of initiating anti-tuberculosis drugs (75/292). These patients, however, are well described by many demographic, epidemiological, and clinical data. In order to generate an explanatory model that could facilitate clinical decision-making we used recursive partitioning to describe the characteristics of patients whose TB was detected. The output of the model (see Figure 3 below) provides both the probability that features in branches of the tree are present in the outcome, and the proportion of the total number of observations from which they are selected.

Among patients who received a TB diagnosis in the ED, the probability of that diagnosis was highest among patients with the combined characteristics of having a typical chest radiograph featuring cavitation, a comorbid risk factor, and being Canadian-born (.52). These combined characteristics, however, were present in only 6% of the diagnosable

group. By contrast, most patients we defined as diagnosable were foreign-born, with no social risk factor and an absence of a typical chest radiograph with cavitation (either atypical, typical without cavitation, or no available result) (50%); the probability of these combined characteristics ever leading to a PTB diagnosis in the ED, however, was only .2.

Figure 4. Recursive Partitioning for Achieving a TB Diagnosis in the ED



top number is probability; bottom is proportion of categorized observations.
"yes" observations split down the right hand side of the tree; "no" observations appear down the left-side branches.

4.4 Discussion

In high-income countries with ready access to healthcare, the suite of services offered by hospitals including emergency services presents an opportunity to make a timely diagnosis of TB. If the suspicion of PTB is present, there are no technical barriers to making the diagnosis; however, there can be clinical challenges. We show that during the study period, the ED was a frequent place of contact for undiagnosed PTB patients in the province of

Alberta. However, while more than 50% of adult PTB patients accessed the ED in the months immediately prior to initiation of treatment making 845 visits, those patients made up a very small fraction (<0.007%) of the total adult ED visits in the Province (11,182,876) during the same time [30, 31]. This underscores the challenge of identifying a relatively rare outcome in a high throughput setting [4]. Our data, however, do suggest there are clues that should heighten the index of suspicion for a PTB diagnosis among clinicians.

Vigilance for the presence of TB is necessary for reducing exposure to contagion by others, and thus achieving elimination goals. In connection with elimination goals for low-burden settings, we interrogated our data for risks and indices of transmission. We present unprotected nosocomial exposure time (3,812 hours), and potentially preventable secondary cases among ED attendees (n=31). We did not evaluate cases for admissions from the ED to the hospital, but the ED is often a gateway to inpatient care. This represents additional risk since hospitals are host to vulnerable patients but preventing TB transmission only occurs when someone suspects the disease [32, 33].

Aside from transmission, we show that a missed diagnosis of PTB in the ED has myriad other adverse consequences, not the least of which is an increased likelihood of dying before or during treatment. Deaths in this group are multifactorial – patients who attended the ED were ultimately sicker. Attendees had more complicated forms of TB disease (combined pulmonary and extra-pulmonary disease; smear-positive vs. smear-negative disease), and more complex social needs; they, however, made more visits and ultimately suffered increased health system delays.

Recursive partitioning indicates that a diagnosis of PTB was relatively more probable among Canadian-born patients, as a group. We hypothesize this may be related to increased

awareness by providers of inequitable health outcomes between Indigenous and non-Indigenous Canadians, potential artefacts of improved Indigenous health research and increased media of the extraordinarily high TB rates among the Inuit in the Eastern Arctic region of Canada [34]. Probability of achieving a TB diagnosis greatly increases in the presence of typical chest radiographs showing cavitation, and a comorbid risk factor (diabetes and/or HIV) independent of population group, but these characteristics occur together infrequently. Significantly, as in other settings where migration from endemic areas greatly influences the epidemiology of disease in high-income countries, foreign-born persons now predominate the TB caseload in Alberta [35]. Unfortunately, our results suggest that diagnoses of foreign-born persons were less probable as compared to Canadian-born persons suggesting that the routine collection of epidemiological clues such as foreign birth, and/or travel history to and from high-incidence areas is a significant area of opportunity for making timelier diagnoses in this setting.

We are mindful of the following weaknesses of this study that affect the application of our findings. Since this study was retrospective, we do not have a fulsome picture of symptomatology or presenting complaints at ED visits. Our analyses were performed on the basis of the 'most responsible discharge diagnosis', but each patient visit may have 10 relevant diagnostic codes. We evaluated all diagnostic fields for evidence that TB was ever suspected, and there were 29 additional visits that had a query for TB. What to make of this finding is difficult to know because 14 of those visits were antedated by contact with TB services. We also applied a strict definition of a 'secondary case' that did not allow us to co-locate any in an ED with the patients identified as *source cases* (i.e., our definition of secondary cases that do not have a conventional epidemiological link [named contacts] are

limited to those that occur in the same forward sortation area, and within 24 months of the presumed source, the former of which almost assuredly excludes the hospital). It is significant, however, that the diagnosis of all secondary cases attributed to ED attendees occurred after their initial ED visits, and so, we infer, they were preventable. Finally, a significant limitation of recursive partitioning is that cut-points, or pre-defined outcomes can significantly alter the patterns that are detected within the data. For example, if we had extended our analysis to 45 days pre-treatment rather than 30 days we may have uncovered different interacting characteristics among patients whose TB was detected. The 30 day inclusion in this instance, however, is appropriate given the incremental increases in visits with the majority occurring within that period. The generation and validation of decision-trees across a range of possible outcomes would be helpful.

Notwithstanding these concerns, this study has several strengths. First, a centralized TB program provides complete and reliable data. Second, we report population, rather than hospital, based results. This suggests our findings are generalizable to other immigrant-receiving, low-TB incidence settings. In addition, while the retrospective nature of this study requires us to speculate as to the reasons these patients sought care in the ED, the confluence of characteristics observed suggests an underserved group aligned with the findings of prospective studies of ED use by TB patients, and the characteristics of vulnerable sub-groups disproportionately affected by TB in low-incidence settings. These characteristics include being foreign-born from a high-incidence country of origin, or Canadian-born Indigenous, HIV seropositive, having a social risk factor, having a rural residence, and presenting with both pulmonary and extra-pulmonary disease [36-38]. Finally, the analytic approach undertaken herein provides robust evidence of the role of

several important factors that should inform the delivery of emergency care by reference to epidemiological clues of PTB disease.

In conclusion, the ED remains an important place of contact with the healthcare system for PTB patients who will become even more difficult to identify the closer jurisdictions get to elimination. Given the demographic and social characteristics of patients who made multiple ED visits, the data suggest that there is a failing on the ground to adequate care outside of this setting. Increased access to primary care, and/or outreach by public health to especially vulnerable groups may generate two benefits – more rapid diagnoses of PTB with improved individual and public health outcomes, as well as concomitant reductions in ED demand.

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4.6 Supplement 1

Characteristics of "diagnosable" ED attendees, by diagnostic group; univariate analysis

	Total	TB n (%)	Resp n (%)	p-value	TB n (%)	Other n (%)	p-value
No. Assessed	292	75 (100)	110 (100)	---	75 (100)	107 (100)	
Age							
Mean (SD)	292	38 (16.6)	49 (20.3)	**<0.01**	38 (16.6)	51 (20.7)	**<0.01**
Sex							
Male	180	50 (66.7)	61 (55.5)	0.12	50 (66.7)	69 (64.5)	0.76
Female	112	25 (33.3)	49 (44.5)		25 (33.3)	38 (35.5)	
Population							
FB	217	51 (68.0)	81 (73.6)	0.40	51 (68.0)	85 (79.4)	0.08
CB	75	24 (32.0)	29 (26.4)		24 (32.0)	22 (20.6)	
Clinical Risk							
Yes	88	21 (28.0)	24 (21.8)	0.33	21 (28.0)	43 (40.2)	0.09
No	204	54 (72.0)	86 (78.2)		54 (72.0)	64 (59.8)	
Comorbid Risk							
Yes	66	12 (16.0)	23 (20.9)	0.40	12 (16.0)	31 (29.0)	**0.04**
No	226	63 (84.0)	87 (79.1)		63 (84.0)	76 (71.0)	
Social Risk							
Yes	38	13 (17.3)	14 (12.7)	0.38	13 (17.3)	11 (10.3)	0.16
No	254	62 (82.7)	96 (87.3)		62 (82.7)	96 (89.3)	
CXR Probability							
High	88	33 (44.0)	39 (35.5)	**0.03**	33 (44.0)	16 (15.0)	**<0.01**
Low/Other	159	42 (56.0)	71 (64.5)		42 (56.0)	46 (85.0)	
ED Type							
Referral	164	38 (50.7)	65 (59.1)	0.25	38 (50.7)	61 (57.0)	0.39
Other	128	37 (49.3)	45 (40.9)		37 (49.3)	46 (43.0)	

Abbreviations: FB foreign-born, CB Canadian-born; CXR probability: high = typical with cavitary disease; low/other = all others; ED type: referral = tertiary care/referral centre for TB cases; other = all others.

4.7 Supplement 2

Diagnostic group codes

MR_DX	Description	DX_Group
A099	Gastroe and colitis of unspec origin	Other
A403	Sepsis dt streptococcus pneumoniae	Other
A4188	Other specified sepsis	Other
A419	Sepsis unspec / Septicaemia unspecified	Other
B002	Herpes gingivostomatis pharyngotonsillit	Other
B023	Zoster ocular disease	Other
B029	Zoster without complication	Other
B07	Viral warts	Other
B182	Chronic viral hepatitis C	Other
B24	HIV disease	Other
B429	Sporotrichosis unspecified	Other
C189	Malgt neoplasm colon unspecified part	Other
C482	Malignant neoplasm peritoneum NOS	Other
C859	Nhl unspecified type	Other
C921	Chr myeloid leukaemia BCR/ABL pos / Chronic myeloid leukaemia	Other
C959	Leukaemia unspecified	Other
D119	Benign neoplasm major sal gland unspec	Other
D432	Neoplasm uncrt/unk beh brain NOS	Other
D489	Neoplasm uncertain or unknown beh NOS	Other
D508	Other iron deficiency anaemias	Other
D619	Aplastic anaemia unspecified	Other
D649	Anaemia unspecified	Other
D700	Neutropenia	Other
E110	Type 2 DM with coma	Other
E1110	Type 2 DM with ketoacidosis	Other
E1123	Type 2 DM w establish adv renal disease	Other
E1164	Type 2 DM w poor control	Other
E119	Type 2 DM no comp	Other
E1410	Unspec DM w ketoacidosis / DM NOS with ketoacidosis	Other
E149	DM NOS no comp / Unspec DM no comp	Other
E41	Nutritional marasmus	Other
E46	Unspecified protein-energy malnutrition	Other
E834	Disorders of magnesium metabolism	Other
E835	Disorders of calcium metabolism	Other
E860	Dehydration	Other
E871	Hypo-osmolality and hyponatraemia	Other
F050	Delirium not superimposed on dementia	Other

F058	Other delirium	Other
F059	Delirium unspecified	Other
F100	Ment/beh disrd dt alcohol use ac intox	Other
F101	Ment/beh disrd dt harmful alcohol use	Other
F102	Ment/beh disrd dt alcohol use dep syndr	Other
F103	Ment/beh disrd dt alco use withdrawal st	Other
F200	Paranoid schizophrenia	Other
F400	Agoraphobia	Other
G4090	Epilepsy unspecified n intr	Other
G439	Migraine unspecified	Other
G588	Other specified mononeuropathies	Other
G9388	Other specified disorders of brain	Other
H184	Corneal degeneration	Other
H579	Disorder of eye and adnexa unspecified	Other
H601	Cellulitis of external ear	Other
H609	Otitis externa unspecified	Other
H612	Impacted cerumen	Other
H669	Otitis media unspecified	Other
H919	Hearing loss unspecified	Other
I100	Benign hypertension	Other
I249	Acute ischaemic heart disease NOS	Other
I313	Pericardial effusion (noninflammatory)	Other
I471	Supraventricular tachycardia	Other
I480	Atrial fibrillation	Other
I4890	Atrial fib unspec	Other
I498	Other specified cardiac arrhythmias	Other
I620	Subdural haem (acute)(nontraumatic)	Other
I64	Stroke not spec haemorrhage or infarct	Other
I719	Aortic aneurysm unspec site w/o rupture	Other
I802	Phleb and thrombophleb oth deep vesl leg	Other
I889	Nonspecific lymphadenitis unspecified	Other
I959	Hypotension unspecified	Other
J029	Acute pharyngitis unspecified	Other
J051	Acute epiglottitis	Other
J069	Acute URTI unspecified	Other
J310	Chronic rhinitis	Other
K047	Periapical abscess without sinus	Other
K050	Acute gingivitis	Other
K219	Gastro-oesoph reflux dis w/o oesophagiti	Other
K226	Gastro-oesophageal laceration-haem syndr	Other
K228	Other specified diseases of oesophagus	Other

K292	Alcoholic gastritis	Other
K297	Gastritis unspecified	Other
K37	Unspecified appendicitis	Other
K409	Unil/unspec ing hernia w/o obs or gangr	Other
K566	Oth and unspec intestinal obstruction	Other
K603	Anal fistula	Other
K611	Rectal abscess	Other
K625	Haemorrhage of anus and rectum	Other
K628	Other specified diseases anus and rectum	Other
K648	Other specified haemorrhoids	Other
K649	Haemorrhoids unspecified	Other
K650	Acute peritonitis	Other
K658	Other peritonitis	Other
K701	Alcoholic hepatitis	Other
K720	Acute and subacute hepatic failure	Other
K746	Other and unspecified cirrhosis of liver	Other
K8010	Calc gallblad w oth chlcyst w/o obstrct	Other
K859	Acute pancreatitis, unspecified	Other
K920	Haematemesis	Other
K922	Gastrointestinal haemorrhage NOS	Other
L022	Cutan abscess furuncle and carbuncle tru	Other
L024	Cutan abscess furuncle and carbuncle lim	Other
L0311	Cellulitis of lower limb	Other
L032	Cellulitis of face	Other
L040	Acute lymphadenitis face head and neck	Other
L089	Local infection skin and subc tissue NOS	Other
L130	Dermatitis herpetiformis	Other
L270	Genl skin eruption dt drugs medicaments	Other
L309	Dermatitis unspecified	Other
L508	Other urticaria	Other
L509	Urticaria unspecified	Other
L600	Ingrowing nail	Other
L984	Chronic ulcer of skin NEC	Other
M0091	Pyogenic arthritis NOS shoulder	Other
M0093	Pyogenic arthritis unspecified forearm	Other
M0096	Pyogenic arthritis NOS lower leg	Other
M130	Polyarthritis, unspecified	Other
M1393	Arthritis unspecified forearm	Other
M1397	Arthritis unspecified ankle and foot	Other
M170	Primary gonarthrosis bilateral	Other
M199	Arthrosis, unspecified	Other

M2441	Rec disloc and sublux joint shoulder	Other
M2547	Effusion of joint ankle and foot	Other
M2550	Pain in a joint multiple sites	Other
M2551	Pain in a joint shoulder region	Other
M310	Hypersensitivity angiitis	Other
M4646	Unspecified discitis lumbar region	Other
M4782	Other spondylosis cervical region	Other
M5382	Other specified dorsopathies cervical	Other
M542	Cervicalgia	Other
M543	Sciatica	Other
M545	Low back pain	Other
M546	Pain in thoracic spine	Other
M548	Other dorsalgia	Other
M549	Dorsalgia, unspecified site	Other
M6268	Muscle strain other site	Other
M705	Other bursitis of knee	Other
M750	Adhesive capsulitis of shoulder	Other
M758	Other shoulder lesions	Other
M8668	Other chronic osteomyelitis other site	Other
M8998	Unspecified disorder of bone other site	Other
M940	Chondrocostal junction syndrome [Tietze]	Other
N12	Tubulo-interstitial nephritis NOS	Other
N179	Acute renal failure unspecified	Other
N23	Unspecified renal colic	Other
N289	Disorder of kidney and ureter NOS	Other
N390	Urinary tract infection site not spec	Other
N508	Oth spec disorder of male genital organs	Other
N814	Uterovaginal prolapse unspecified	Other
N840	Polyp of corpus uteri	Other
N939	Abnormal uterine and vaginal bleeding NO	Other
O021	Missed abortion	Other
O2000	Threatened abortion/antepartum	Other
O2090	Haemorrhage in early preg nos/antepartum	Other
O4690	Antepartum haem unspecified/antepart	Other
Q180	Sinus fistula and cyst of branchial clef	Other
Q182	Other branchial cleft malformations	Other
R002	Palpitations	Other
R040	Epistaxis	Other
R1011	Left upper quadrant pain	Other
R1012	Epigastric pain	Other
R1019	Upper abdominal pain, unspecified	Other

R1030	Right lower quadrant pain	Other
R1031	Left lower quadrant pain	Other
R1039	Lower abdominal pain, unspecified	Other
R104	Other and unspecified abdominal pain	Other
R113	Nausea with vomiting	Other
R14	Flatulence and related conditions	Other
R17	Unspecified jaundice	Other
R18	Ascites	Other
R21	Rash and other nonspecific skin eruption	Other
R220	Localized swelling mass and lump head	Other
R221	Localized swelling mass and lump neck	Other
R222	Localized swelling mass and lump trunk	Other
R224	Localized swelling mass lump lower limb	Other
R296	Tendency to fall NEC	Other
R318	Other and unspecified hematuria	Other
R4029	Coma, unspecified	Other
R410	Disorientation unspecified	Other
R42	Dizziness and giddiness	Other
R448	Oth/nos sym inv genl sensation perceptn	Other
R451	Restlessness and agitation	Other
R509	Fever unspecified	Other
R51	Headache	Other
R520	Acute pain	Other
R53	Malaise and fatigue	Other
R55	Syncope and collapse	Other
R5688	Other & unspec convulsions	Other
R590	Localized enlarged lymph nodes	Other
R630	Anorexia	Other
R634	Abnormal weight loss	Other
R64	Cachexia	Other
R9431	Abn cv funct study suggests NSTEMI	Other
S003	Superficial injury of nose	Other
S007	Multiple superficial injuries of head	Other
S008	Superficial injury of oth parts of head	Other
S009	Superficial injury of head part NOS	Other
S0100	Open wound of scalp uncomplicated	Other
S0110	Open wound eyelid and periocular area un	Other
S0151	Open wound lip and oral cavity complicat	Other
S0180	Open wounds oth parts head, uncomplicate	Other
S0260	Fracture of mandible, closed	Other
S060	Concussion	Other

S109	Superficial injury of neck part NOS	Other
S168	Oth and unspec inj muscle tendon neck le	Other
S202	Contusion of thorax	Other
S204	Oth superfic injuries back wall thorax	Other
S2908	Oth unspec inj musc and tendon thorax lv	Other
S3180	Opn wnd oth/unspec part abdomen, uncomp	Other
S3200	Fx of lumbar vertebra, L1 level, closed	Other
S3240	Fracture of acetabulum, closed	Other
S335	Sprain and strain of lumbar spine	Other
S4100	Open wound of shoulder, uncomplicated	Other
S4230	Fracture of shaft of humerus, closed	Other
S4340	Sprain & strain shldr jt NOS	Other
S498	Oth spec injuries shoulder and upper arm	Other
S499	Unspec injury shoulder and upper arm	Other
S5200	Fx of olecranon process of ulna, closed	Other
S5250	Colles' fracture, closed	Other
S6100	Opn wnd finger w/o damage nail, uncomp	Other
S6180	Opn wnd oth part wrist/hand, uncompl	Other
S6190	Opn wnd unspec part wrist/hand uncompl	Other
S6239	Fx unsp site other metacarpal bone, clsd	Other
S7210	Intertrochanteric fracture, closed	Other
S801	Contusion oth/unspec parts low leg	Other
S8180	Open wnds oth part of low leg, uncomplic	Other
S8260	Fracture of lateral malleolus, closed	Other
S898	Other specified injuries of lower leg	Other
S9130	Opn wnd oth parts foot, uncompl	Other
S9349	Sprain and strain of ankle, unspecified	Other
T095	Injury muscle and tendon of trunk, NOS	Other
T130	Superficial injury lower limb level NOS	Other
T149	Injury unspecified	Other
T264	Burn of eye and adnexa part unspecified	Other
T509	Poisn oth NOS drgs medicaments biol subs	Other
T510	Toxic effect of ethanol	Other
T814	Infection following a procedure NEC	Other
T886	Anaphyl shk dt adv eff drug proper admin	Other
T887	Nos adverse effect of drug or medicament	Other
Z017	Laboratory examination	Other
Z21	Asymptomatic HIV infection status	Other
Z228	Carrier of other infectious diseases	Other
Z478	Other spec orthopaedic follow-up care	Other
Z479	Orthopaedic follow-up care unspecified	Other

Z480	Attention to surg dressings and sutures	Other
Z488	Other specified surgical follow-up care	Other
Z509	Care inv use of rehab procedure NOS	Other
Z512	Other chemotherapy	Other
Z514	Preparatory care for subsequent Rx NEC	Other
Z5188	Other specified medical care NEC	Other
Z721	Alcohol use	Other
Z751	Pers waiting admssn facility elsewhere	Other
Z760	Issue of repeat prescription	Other
Z7688	Per encounter hlth serv oth spec circums	Other
A310	Pulmonary mycobacterial infection	Respiratory
B99	Other and unspecified infectious disease	Respiratory
C3490	Malgt neoplasm right bronc/lung unspec	Respiratory
C3491	Malgt neoplasm left bronc/lung unspec	Respiratory
C780	Secondary malignant neoplasm of lung	Respiratory
I269	Pulm embolism w/o acute cor pulmonale	Respiratory
I500	Congestive heart failure	Respiratory
J111	Influenza w oth resp manif virus not id	Respiratory
J129	Viral pneumonia unspecified	Respiratory
J159	Bacterial pneumonia unspecified	Respiratory
J180	Bronchopneumonia unspecified	Respiratory
J181	Lobar pneumonia unspecified	Respiratory
J188	Other pneumonia organism unspecified	Respiratory
J189	Pneumonia unspecified	Respiratory
J2088	Acute bronchitis dt other spec organisms	Respiratory
J22	Unspec acute lower respiratory infection	Respiratory
J40	Bronchitis not spec as acute or chronic	Respiratory
J440	COPD with acute lower resp infection	Respiratory
J441	COPD with acute exacerbation unspecified	Respiratory
J448	Other specified COPD	Respiratory
J449	COPD unspecified	Respiratory
J4590	Asthma, unspec w/o st status asthmaticus	Respiratory
J620	Pneumoconiosis due to talc dust	Respiratory
J81	Pulmonary oedema	Respiratory
J841	Oth interstitial pulm dis w fibrosis	Respiratory
J849	Interstitial pulmonary disease NOS	Respiratory
J851	Abscess of lung with pneumonia	Respiratory
J852	Abscess of lung without pneumonia	Respiratory
J869	Pyothorax without fistula	Respiratory
J90	Pleural effusion NEC	Respiratory
J939	Pneumothorax unspecified	Respiratory

J9690	Resp failure unspec type 1 [hypoxic]	Respiratory
J984	Other disorders of lung	Respiratory
J988	Other specified respiratory disorders	Respiratory
R042	Haemoptysis	Respiratory
R05	Cough	Respiratory
R060	Dyspnoea	Respiratory
R071	Chest pain on breathing	Respiratory
R073	Other chest pain	Respiratory
R074	Chest pain unspecified	Respiratory
R090	Asphyxia, unspecified	Respiratory
R091	Pleurisy	Respiratory
R591	Generalized enlarged lymph nodes	Respiratory
R91	Abn findings on diagnostic imaging lung	Respiratory
S2111	Open wound of front wall thorax complic	Respiratory
A1500	TB lung confrm by sputm w cavtn	TB: Respiratory
A151	TB of lung, confirm cult only	TB: Respiratory
A1521	TB lung confrm hist w/o cavtn	TB: Respiratory
A1531	TB lung confrm unsp means w/o cavtn	TB: Respiratory
A157	Primary respiratory tuberculosis / Prim resp TB conf bact and hist	TB: Respiratory
A158	Other respiratory tuberculosis / Other resp TB conf bact and hist	TB: Respiratory
A1620	TB lung w/o bact/his confrm w cavtn	TB: Respiratory
A1621	TB lung w/o bact/his confrm w/o cavtn	TB: Respiratory
A165	TB pleurisy w/o bact or hist conf	TB: Respiratory
A168	Other resp TB w/o bact or hist conf	TB: Respiratory
A1690	Resp TB unsp w/o bact/his confrm w cavt	TB: Respiratory
A1691	Resp TB unsp w/o bac/his confrm w/o cav	TB: Respiratory
A192	Acute miliary tuberculosis unspecified	TB: Respiratory
A199	Miliary tuberculosis unspecified	TB: Respiratory

Abbreviations: MR_DX most responsible discharge diagnosis; DX_Group diagnostic group

Chapter 5: CONCLUSION

5.1 Summary

This dissertation covered the development of three studies. Their purpose was to generate evidence in support of changed clinical activity, especially by primary care providers and nurse practitioners, to make timelier diagnoses of PTB. These clinical changes include targeting medical histories, or implementing a risk assessment for TB disease in low prevalence settings informed by the combined clinical characteristics of PTB patients shown here, and timelier requisitions of samples for microbiologic confirmation of disease. Each of these studies was dependent on having diagnostic and human resource capacity, and were thus possible because Alberta is a high-income, low-TB burden setting; generalization of findings is made cautiously to similar settings. Improvements to strategies inferred from these findings may be made, in practice, by the use of increasingly sophisticated technologies. For example, more sensitive and safer imaging techniques – e.g. low-dose CT scans vs. chest radiographs – and, improved medical histories facilitated by the development of integrated electronic medical records (EMRs). Since the focus herein has been on clinical interventions absent any recommendations about improvements to the social determinants of health, their overall influence on *TB elimination,* is limited. They still, however, offer important contributions.

These contributions can be summarized as: describing the features related to a spectrum of infectiousness that is independently defined by the pathology of disease in the lung (as depicted on chest radiograph) and the bacillary burden (as depicted by AFB smear); the development of a constellation of risk factors that has predictive value for identifying patients across the spectrum of infectivity (from no disease to the most

infectious state); and, finally identifying where (the emergency department) and how often patients with PTB seek care prior to achieving a diagnosis. By showing where diagnoses are missed (the ED), and how better to make them (by triaging patients according to a risk profile), an obvious intervention would be the development of an "app" or embedded (in the EMR) algorithm that automates requisition for a sputum triggered by results of a symptom inquiry and/or automated interpretation of a digital chest radiograph that is completed in the presence of the other clinically relevant (to making a timely diagnosis) features. With regards to the chest radiograph, we and others, have begun to take the computer engineering steps necessary to automate its reading.

In order to drive costs down and assure effectiveness of newly developed tools in the fight against TB (e.g. new drugs, diagnostics, etc…), high-income, low TB burden countries ought to shoulder the responsibility of testing, validating, and reporting on those innovations. This is in contrast to applying those tools in contexts where their failure may be guaranteed by a neglect to address the broader social determinants of health rather than anything intrinsic to the innovation itself[1] [1]. In other words, it is likely that our ability to achieve TB elimination is primarily dependent on making social progress apace with technological interventions.

The power of TB as a communicable disease is that it reaches far beyond individuals, bringing in to its orbit the families, friends, and contacts of sufferers; it both impacts, and is impacted by, socio-economic and political circumstance [2, 3]. As a result, solutions to this

[1] The author is aware that there are major ethical questions being raised about how to 'protect' newly developed drugs from becoming ineffective, i.e., should they be administered amid the same type of socio-political dysfunction that helped induce resistance to previously effective therapies? The answers are not in this dissertation, but they exist at the heart of TB prevention and care delivery and interconnected programs of research.

public health scourge have to be responsive to, or at least aware of, the human context within which the disease is spread. In other words, elimination will require a bio-social approach, if it is ever to be attainable [4].

5.2 ***Future Areas of Research***

- Most significantly, two of the three studies in this dissertation generate new evidence that can be used in *some way* by clinicians to make timelier diagnoses of PTB, though they are silent about precisely *how*. The third reconfirms that there exists, in the jurisdiction of Alberta, a setting where implementation of that evidence would have a high yield (the ED). Implementation science is an emerging field that can help to recommend strategies for, and facilitate the appropriate use of, evidence, in ways that will have practical benefits. For example, there is a new electronic medical record (EMR) – *Connect Care* - rolling out in phases across Alberta; it will be integrated across all patient visits, and services. As such, it may soon be possible to automate a prompt for the requisition of sputum if the convergence of demographic, epidemiological, and clinical features, perhaps linked to computer-aided detection/AI recognition of typical patterns on CXR, from a patient's record suggests suspicion of PTB is increased relative to some baseline. The toolkit that implementation science provides can help assess whether to integrate these prompts, how to integrate these prompts, and potentially whether providers see the clinical utility of them. This field of study offers the promise to bridge the gap between evidence and practice.

- There is a large body of literature surrounding delays in the diagnosis of tuberculosis [5-7]. Timelier diagnoses present an opportunity to interrupt transmission by reducing the

period of time infectious source cases can interface with contacts [8]. Unfortunately, most current definitions of "delay" describe the period of time between the onset of symptoms and diagnosis by culture confirmation, or initiation of anti-tuberculosis drugs [5]. The work in this dissertation shows that smear-negative cases of PTB are significantly less likely to report having any symptom and so these patients experience no 'delay' by the time anti-tuberculosis drugs are initiated no matter how long a patient has been living with microbiologically detectable disease that is still, to some degree, transmissible (though fortunately much less likely to transmit). These definitions of delay have contributed to an entrenched misunderstanding that 'advanced' smear-positive disease refers to the period of time a patient has been living with disease, and that it is the inevitable endpoint of smear-negative disease that has gone untreated. Older literature that is summarized by Kurt Toman, and a recent proof of concept paper from our research group refutes this [9, 10]. There are a number of possibilities forward from these observations. Firstly, a simple commentary clarifying the distinction between a delayed diagnosis, and advanced disease on the basis of the evidence we have generated would be a useful contribution to the literature with a potentially broad readership. Secondly, it appears that there may be different phenotypic expressions of the disease, and that infectious, smear-positive cases may develop at different speeds. As such, working in collaboration with an immunologist may further shed light on the host response to the organism to inform targeted preventive measures (i.e., immunological characteristics associated with rapid progression and which are identified among contacts might initiate the recommendation of preventive therapy in cases that otherwise may not have received a recommendation). There may also

potentially be new treatment strategies derived from these studies; i.e., it may be feasible to treat paucibacillary smear-negative disease, only intermittently excreting bacilli, in patients with a history of stable chest radiographs, with shorter-course regimens that have otherwise been reserved for the treatment of LTBI [10].

- In Alberta, the number of multi-drug resistant (MDR) cases of TB that are being diagnosed is growing [11, 12]. The management of their contacts is not standardized. Some are followed under medical surveillance by the program for the development of active disease, while others are recommended preventive therapy for LTBI with regimens informed by the drug susceptibility testing (DST) of the source case, and up to the discretion of the provider. As a result, the prevention of reactivation TB is by variable measures of intervention (from 'wait and see' to differing LTBI preventive therapeutic regimens that have levels of evidence in support of their use from low-grade to high [12-14]. Yet, there have been **no** secondary cases of MDR diagnosed in Alberta (from in-country transmissions) since 1990 (the first year from which we have molecular epidemiological information about organisms in Alberta). There appears to be some fitness cost to resistant organisms in terms of their transmissibility that warrants further investigation (this study is currently underway). In addition, a review of MDR-TB epidemiology in Alberta that emphasizes the strength of a centralized TB program may have important policy implications.

- As this dissertation has attempted to emphasize, "elimination" may be an overly ambitious goal. There have, however, been calls for low-incidence settings to strive for

zero annual transmissions. Alberta is a good jurisdiction to test the feasibility of implementing such a strategy. The vast majority of cases (~90% in 2017) in Alberta were diagnosed among foreign-born persons. The molecular epidemiology of TB shows a high proportion of unique isolates, and previous literature indicates that foreign-born patients with TB in Alberta transmit to a lesser degree than other patients. The combination of these findings suggests that most cases are already reactivation TB. This could potentially be assessed by looking at whether the proportion of secondary cases is declining relative to the number of source cases in Alberta, by population group, over time. It may also be possible to model the impacts of programmatic and clinical interventions that would be necessary to achieve zero transmissions (described, in part by the studies in this dissertation – i.e., timelier diagnoses are paramount). Concomitant monitoring of transmissions should occur. These can be recommended nationally in the Canadian TB Standards, and in Provincial program guidelines. A proposal has been submitted to the editor of the next edition of the Canadian TB Standards for a chapter on program performance indicators and monitoring; benchmarks for secondary cases could be a suggestion put forward to the community of national TB stakeholders.

- A 1964 paper described an outbreak of TB in what is now Arviat in Nunavut (previously Eskimo Point, Northwest Territories) [15]. There were over 80 active cases diagnosed in a population of less than 400, with more than 50% of households involved [15]. The outbreak was attributed to one highly infectious source case; environmental contributors included malnutrition and overcrowding. The settlement had also recently experienced viral outbreaks of influenza, measles, German measles, and mumps. It was

hypothesized that these viral infections facilitated the explosiveness of the TB outbreak. If this is so, the mechanisms are not clear – do respiratory viral illnesses make infection in the lung by TB more likely? If so is it by lung, or conducting airway, injury that allows an infection to establish itself more readily, replicate more rapidly, or be more readily transmissible? Do these viral infections contribute to a downregulation of the immune system that permits both LTBI and reactivation? Collaborations with virologists and immunologists could contribute to this area of inquiry that is going to be increasingly important as emerging viral respiratory illnesses occur in places with a high incidence of TB (e.g. new coronaviruses like Covid-19).

5.3 A Concluding Remark

A brief editorial commentary (the author is completely opining) concludes this work:

It is hubris for the International community to keep promoting TB elimination as attainable. The United Nations Sustainable Development Goals (SDGS), and their achievement are completely and directly upstream from TB elimination. They are aims for which the TB community should be more vociferously advocating since their failure precludes meaningful progress towards elimination. In addition, all levels of authority need to yield power, and make room for community-driven practices to produce positive outcomes for TB disease. This is especially so for vulnerable sub-groups disproportionately affected by TB in high-income, low-incidence settings whose self-determination and autonomy in matters of public health programming has been, heretofore, limited.

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