The Prevalence of Tuberculosis Infection Among Foreign-Born Canadians: A Modelling Study

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ABSTRACT

Background: Tuberculosis (TB) disproportionately impacts foreign-born persons living in Canada. Typically, they have acquired TB infection (TBI) in their country of origin and progress to TB disease during the months and years after landing. An understanding of TBI prevalence among foreign-born persons is necessary to further develop targeted TB prevention strategies, but prevalence is currently unknown. TBI prevalence was estimated among foreign-born Canadian permanent residents and citizens (foreign-born Canadians).

Methods: Annual risk of infection trends were generated using a previously developed Gaussian process regression model. These trends were used to estimate the probability of TB infection among people immigrating to Canada by age, year of birth, and year of immigration. These probabilities were combined with Canadian census data to estimate TBI prevalence and 95% uncertainty intervals (95%UI) among foreign-born Canadians originating from 168 countries in census years 2001, 2006, 2011, and 2016. TBI prevalence estimates were also stratified by age, TB disease incidence in country of origin, province/territory of residence, and prevalence of infection acquired within the two preceding years for the 2016 census year.

Results: Estimated TBI prevalence among foreign-born Canadians did not significantly change over time and was 25% (95%UI: 20-35%), 24% (20-33%), 23% (19-30%), and 22% (19-28%) for census years 2001, 2006, 2011, and 2016, respectively. In 2016, estimated prevalence increased with age at immigration from 8% (6-16%) among persons 0-14 years of age to 65% (50-74%) among persons ≥75 years. Prevalence also increased with TB disease incidence in the country of origin from 9% (5-22%) among those from countries with incidence of 0-9 cases per 100,000 persons to 35% (22-46%) among those from countries with incidence ≥200 cases per 100,000 persons. Estimated prevalence was lowest in Quebec, 19% (16-25%), and highest in Alberta and British Columbia, 24% (21-29%) and 24% (20-30%), respectively. Lastly, only an estimated 0.05% (0.04-0.07%) of foreign-born Canadians in 2016 had been infected in the previous two years.

Conclusions: Approximately one-quarter of foreign-born Canadians have TBI, a proportion that has remained relatively stable over time, and is similar to that estimated for foreign-born residents of other high-income countries. Despite this high estimated prevalence, only a small

minority of foreign-born persons were recently infected. TBI prevalence was higher among persons from countries with higher TB disease incidence and those who were older at immigration. These data may inform the development of TB prevention programs directed toward foreign-born persons.

ABRÉGÉ

Contexte : La tuberculose (TB) touche de manière disproportionnée les personnes nées à l'étranger et vivant au Canada. En général, ces personnes ont contracté une infection tuberculeuse latente (ITL) dans leur pays d'origine et progressent vers la tuberculose-maladie au cours des mois et des années qui suivent leur arrivée. Il est pertinent de comprendre la prévalence de l'infection tuberculeuse latente (ITL) chez les personnes nées à l'étranger afin d'élaborer des stratégies ciblées de prévention de la tuberculose, mais cette prévalence n'est pas connue à l'heure actuelle. Mes travaux ont estimé la prévalence de l'ITL chez les résidents permanents et les citoyens (Canadiens nés à l'étranger).

Méthodes : Les tendances annuelles du risque d'infection ont été générées à l'aide d'un modèle de régression par un processus gaussien élaboré antérieurement. Ces tendances ont été utilisées pour estimer la probabilité de l'infection tuberculeuse latente chez les personnes immigrant au Canada, en fonction de l'âge, de l'année de naissance et de l'année d'immigration. Ces probabilités ont été combinées aux données du recensement canadien pour estimer la prévalence de l'ITL et les intervalles d'incertitude à 95 % (II 95%) chez les Canadiens nés à l'étranger et originaires de 168 pays pendant les années de recensement 2001, 2006, 2011 et 2016. Les estimations de la prévalence de l'ITL ont également été stratifiées en fonction de l'âge, de l'incidence de la tuberculose dans le pays d'origine, de la province/territoire de résidence et de la prévalence de l'infection contractée au cours des deux années précédentes pour l'année de recensement 2016.

Résultats : La prévalence estimée de l'ITL chez les Canadiens nés à l'étranger n'a pas changé de façon significative au fil du temps et était de 25 % (II 95% : 20-35 %), 24 % (20-33 %), 23 % (19-30 %) et 22 % (19-28 %) pour les années de recensement 2001, 2006, 2011 et 2016, respectivement. En 2016, la prévalence estimée augmentait avec l'âge au moment de l'immigration, passant de 8 % (6-16 %) chez les personnes âgées de 0 à 14 ans à 65 % (50-74 %) chez les personnes âgées de ≥75 ans. La prévalence a également augmenté avec l'incidence de la tuberculose maladie dans le pays d'origine, passant de 9 % (5-22 %) chez les personnes originaires de pays ayant une incidence de 0 à 9 cas pour 100 000 personnes à 35 % (22-46 %)

chez les personnes originaires de pays ayant une incidence ≥200 cas pour 100 000 personnes. La prévalence estimée était la plus faible au Québec, 19 % (16-25 %), et la plus élevée en Alberta et en Colombie-Britannique, 24 % (21-29 %) et 24 % (20-30 %), respectivement. Enfin, on estime qu'en 2016, seulement 0,05 % (0,04-0,07 %) des Canadiens nés à l'étranger avaient été infectés au cours des deux années précédentes.

Conclusions : Environ un quart des Canadiens nés à l'étranger sont atteints d'une ITL, une proportion qui est demeurée relativement stable au fil du temps et qui est semblable à celle estimée parmi les résidents nés à l'étranger vivant dans d'autres pays à revenu élevé. Malgré cette prévalence élevé, une faible minorité de personnes nées à l'étranger a été récemment infectée. La prévalence de l'ITL est plus élevée chez les personnes originaires de pays où l'incidence de la tuberculose est plus élevée et chez celles qui étaient plus âgées au moment de l'immigration. Ces données peuvent contribuer à l'élaboration de programmes de prévention de la tuberculose destinés aux personnes nées à l'étranger.

CONTRIBUTION OF AUTHORS

Kevin Schwartzman, Jonathon Campbell, and Aria Ed Jordan conceived the thesis topic. Aria Ed Jordan created the code to clean relevant census data obtained from Statistics Canada and analyzed the census data, with some analytical support from Ntwali Placide Nsengiyumva. Rein M. G. J. Houben, Peter J. Dodd, Katie D. Dale, James M. Trauer, and Justin T. Denholm provided the annual risk of infection trajectory dataset and code for the analysis. Aria Ed Jordan created the code and analyzed the statistical data related to TB infection prevalence, with some analytical support from Jonathon Campbell. Aria Ed Jordan drafted the manuscript, with input from Kevin Schwartzman Jonathon Campbell. Aria Ed Jordan, Ntwali Placide Nsengiyumva, Rein M. G. J. Houben, Peter J. Dodd, Katie D. Dale, James M. Trauer, Justin T. Denholm, James C. Johnston, Faiz Ahmad Khan, Jonathon Campbell, and Kevin Schwartzman interpreted the data, critically revised the manuscript for important intellectual content; approved the final version submitted; and agreed to be accountable for all aspects of the work. Aria Ed Jordan drafted the thesis and approved the final draft. Kevin Schwartzman and Jonathon Campbell reviewed and edited the thesis and approved the final draft.

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

ARI — Annual Risk of Infection

BCG — Bacille Calmette-Guerin

CKD — Chronic Kidney Disease

COVID-19 — Coronavirus Disease 2019

IGRA — Interferon-Gamma Release Assay

IQR — Interquartile Range

HBC — High-Burden Country

HIV — Human Immunodeficiency Virus

Mtb – *Mycobacterium Tuberculosis*

N — Number

NHANES — National Health and Nutrition Examination Survey

PLHIV —People Living with HIV

ROI — Risk of Infection

RR/MDR — Rifampicin-Resistant/Multidrug Resistant

TB — Tuberculosis

TBI — Tuberculosis infection

TPT — Tuberculosis Preventive Treatment

TST — Tuberculin Skin Test

UI — Uncertainty Interval

WHO — World Health Organization

1 INTRODUCTION

Until the emergence of coronavirus disease 2019 (COVID-19), tuberculosis (TB) disease was the leading cause of death by an infectious agent, responsible for 1.6 million deaths in 2021.[1] Approximately 23% of the world's population is estimated to have TB infection (TBI), the precursor to TB disease.[2] An estimated 5-10% of those with TBI will progress to TB disease,[1] depending on various social factors and medical comorbidities.[3,4]

The World Health Organization (WHO) has set targets for TB disease elimination in low-incidence countries such as Canada, with a goal to reduce annual TB disease incidence to 10 cases per million population by 2035 and 1 case per million population by 2050.[5] To stay on track with this, a national target of 3.6 per 100,000 was set for 2015.[6] However, this target was not met as TB disease incidence in Canada declined steadily until 2007 and plateaued at approximately 5 per 100,000 persons annually.[7,8] The stagnation of TB disease incidence in Canada is the result of epidemiologic shifts and failure to adapt. While improvements in healthcare and living conditions reduced TB disease incidence in Canada overall, Indigenous communities and foreign-born persons remain disproportionately impacted.[9] Foreign-born persons, in particular, bear approximately 80% of the TB disease burden despite comprising 23% of the Canadian population.[8] This epidemiology mainly reflects TBI acquired abroad, with progression to TB disease post-arrival.[9]

With currently available drug regimens, treatment of TBI is effective and generally safe.[10,11] Hence in principle, ongoing screening and treatment for TBI will lead to TB disease prevention and, ultimately, elimination among foreign-born persons. However, current TBI diagnostics have a low predictive value for progression to TB disease and poor specificity among certain populations.[12–14] For these reasons, numerous people would need to be screened to prevent one person from developing TB disease.[15,16] However, widespread TBI screening and treatment programs would likely be cost-prohibitive [17] and could result in large numbers of people receiving TBI treatment with limited or no benefit.[18,19] The cost-

effectiveness and health impact of TB prevention programs could likely be improved if these are targeted toward those most like to have TBI. However, TBI prevalence among foreign-born Canadians has not been estimated. To support the development of targeted TB prevention programs in Canada, we aimed to estimate TBI prevalence and trends among foreign-born Canadians.

2 LITERATURE REVIEW

2.1 TUBERCULOSIS EPIDEMIOLOGY

2.1.1 Global

Before the coronavirus disease 2019 (COVID-19) pandemic, tuberculosis (TB) disease was the leading cause of death by a single infectious agent. After years of slow progress toward TB disease elimination, 2020 marked a rise in the number of TB-related deaths. It was the cause of an estimated 1.6 million deaths among an estimated 10.6 million people with TB disease, the most deaths since 2017. TB disease occurs because of progression of TB infection (TBI); individuals infected with *Mycobacterium tuberculosis* (Mtb) are said to have TBI, an asymptomatic condition. Modeling studies have estimated that 23% of the world's population has TBI,[2] and 5-10% of those with TBI will progress to TB disease.[1]

High-burden countries (HBCs) for TB are defined as the top 20 countries based on absolute numbers of incident TB disease plus the ten countries with the highest incidence rate per capita and that meet a minimum threshold of 10,000 TB cases per year.[20] The top 30 HBCs bear approximately 87% of the TB disease burden around the globe. Eight countries share approximately two-thirds of the global TB burden in absolute case numbers: India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh, and the Democratic Republic of the Congo.[1]

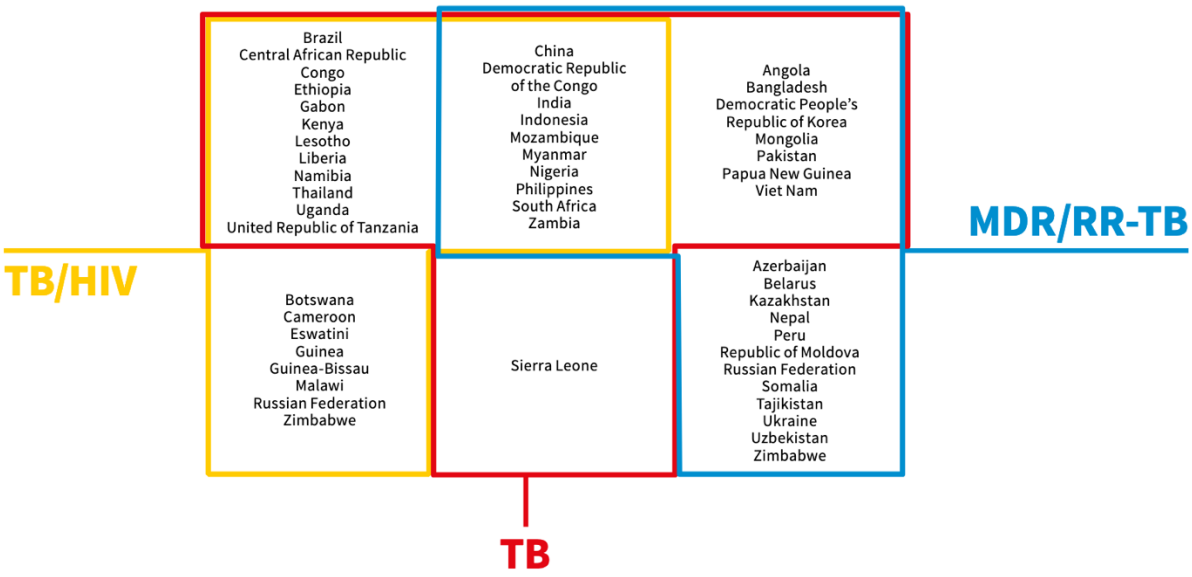

Figure 1. The three global lists of high-burden countries for TB disease, MDR-TB, HIV-TB co-infection (WHO Global tuberculosis report 2022)

For many HBCs, drug-resistant TB, such as rifampin-resistant (RR) and multi-drug resistant (MDR) TB, presents challenges to TB prevention and care strategies.[1] Most of the RR/MDR-TB burden is among former Soviet Union countries along with a few countries in Asia and sub-Saharan Africa. Detection of drug-resistant TB remains a considerable problem with most individuals undiagnosed and, thus, unable to receive proper treatment. In 2021, approximately 500,000 people were estimated to have developed RR/MDR-TB disease. Of those, RR/MDR-TB was detected in 166,991 people and 161,746 people initiated treatment for it. Detection and treatment are higher than 2020 but still lower than pre-COVID-19 levels. In addition to challenges in improving detection and treatment, RR/MDR-TB generally requires lengthier treatment, more expensive drugs that have a higher risk of toxicity, and that may not be consistently available, all leading to poorer treatment outcomes. In 2019, an estimated 60% of those on treatment for RR/MDR-TB were successfully treated. Strategies for mitigating the impacts of RR/MDR TB have included more efficient diagnostic technology, such as nucleic acid

amplification tests to improve detection and improve accessibility to all-oral, safer, and shorter treatment regimens to improve completion.[21–25]

In addition to the challenges presented by MDR-TB, human immunodeficiency virus (HIV)-TB co-infection is a key epidemiologic consideration. TB disease is the leading cause of death among persons living with HIV (PLHIV), a population at high risk of progression from TBI to TB disease. In 2020, an estimated 7% of incident TB disease and approximately 12% of TB mortality were among PLHIV.[1] Additionally, the odds of having RR-TB are 1.4 times higher among PLHIV compared to those without HIV, and of those with RR-TB, the odds of mortality were 2.4 times higher.[26,27] Overcoming barriers to HIV-TB prevention and care will require scaling up testing and tuberculosis preventive treatment (TPT), improving the accuracy of diagnostics, reducing treatment toxicity, and improving treatment adherence. TB-HIV co-infection is highest in parts of southern Africa, Asia, and South America, particularly resource-limited areas.[1]

As of 2019, 54 countries around the globe are categorized as low TB incidence countries, defined as an annual TB incidence of <100 per 1 million, i.e., < 10 per 100,000).[5] Although MDR/RR-TB and HIV-TB co-infection have major impacts, globally, in low-incidence countries such as Canada, the burden of TB is mainly concentrated in vulnerable groups such as persons experiencing houselessness, persons experiencing incarceration, Indigenous communities, persons living in densely populated areas, and migrants from higher-incidence countries.[9]

2.1.2 Tuberculosis in Canada

TB disease incidence in Canada declined steadily until it reached a plateau of 4.9 cases per 100,000 in 2007; it has remained essentially unchanged since at 4.7 per 100,000 in 2020.[8] This differs from the United States, another low-incidence country where TB disease incidence has further declined slowly but steadily.[28] The stagnation of TB disease incidence in Canada is the result of epidemiologic shifts occurring without the implementation of related prevention

strategies. This has resulted in TB disease disproportionately impacting vulnerable groups such as Indigenous communities and foreign-born persons. While TB disease within Indigenous communities often reflects ongoing transmission,[29–31] TB disease among foreign-born persons typically reflects progression of TBI acquired in their countries of origin, especially those arriving from moderate- to high-incidence countries (≥ 10 per 100,000 annually).[9]

Foreign-born persons in Canada bear approximately 80% of the TB disease burden despite only representing 23% of the Canadian population[8,32]. Furthermore, TB disease incidence among foreign-born persons is approximately 47.7 times greater than that of non-Indigenous, Canadian-born persons.[8]

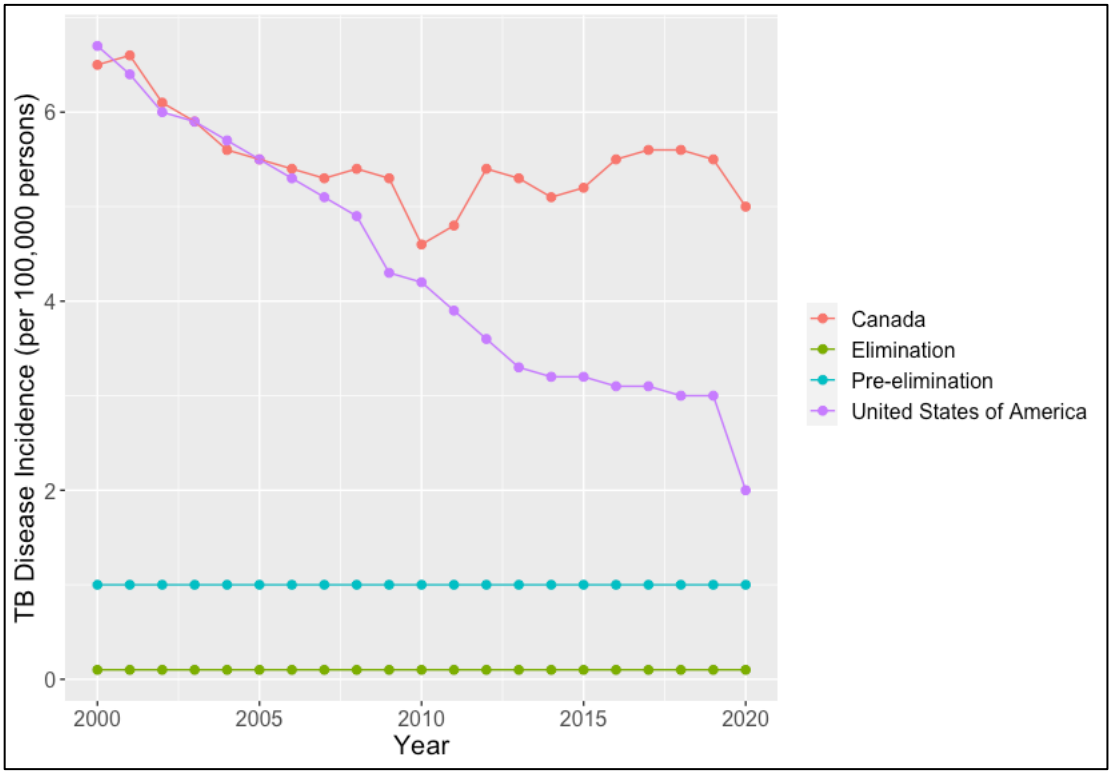

Figure 2. Yearly TB disease incidence trends for Canada and USA relative to previous pre-elimination and elimination targets. (Source: Canadian and US TB Reports)

**Pre-elimination is defined as incidence of <1 per 100,000 persons. Elimination is defined as <0.1 per 100,000 persons. (Source: World Health Organization)*

2.2 TB INFECTION IN CANADA

Countries with high TB disease incidence focus on its timely diagnosis and treatment as the top priority in reducing mortality and onward transmission. In contrast, low-incidence, high-income countries such as Canada must address TBI for TB elimination to become a reality.[33] The risk of acquiring TBI is highest among close contacts of individuals with smear-positive, pulmonary TB disease. Among close contacts, TBI prevalence is estimated to range from 30-70%, with the risk of acquisition varying by duration of exposure, proximity, infectiousness of the person with TB disease, and setting.[34–36] Foreign-born persons from countries with high TB disease incidence are at higher risk of TBI because they are more likely to have had close or casual contact with a person with TB disease.[37]

Only 0.10% of foreign-born persons were found to have TB disease during pre-arrival medical assessments and only 0.8-2.8% were identified as part of post-arrival surveillance of those with "high-risk" findings on chest X-ray.[9] More often, migrants arrive with TBI and, later, progress to TB disease depending on immunological and clinical characteristics such as age, HIV status, other comorbidities, and time since infection.[3] Provincial-level genotyping data have shown that the vast majority of migrants with TB disease have diverse, unique strains of *M. tb*. unrelated to local transmission i.e. not shared with others in the same area.[38–40] Despite this, there are no routine screening and treatment programs for TBI among foreign-born persons in Canada.

The development of cost-effective TBI screening and treatment programs will depend on multiple factors, with two key drivers being the prevalence of TBI among those screened, and the risk of TB disease progression among the subset with TBI. Large-scale screening of foreign-born persons is likely to be cost-prohibitive[17] and result in numerous individuals with

low risk of exposure or progression to TB disease receiving screening or treatment.[18,19] While current screening guidelines reflect risks of progression to TB disease,[9] lack of TBI prevalence data remains an obstacle to developing cost-effective TBI screening and treatment programs. To inform the development of cost-effective, targeted screening and treatment programs, prevalence estimates of TBI among foreign-born persons are crucial.

2.3 TOOLS FOR DIAGNOSING TBI

The tuberculin skin test (TST) and interferon gamma release assays (IGRAs) are the main tests available for TBI The TST and IGRAs assess the cell-mediated immune response to *Mtb*.[9] Both tests have similar sensitivity; however, IGRAs have higher specificity among persons who received the bacilli Calmette-Guérin (BCG) vaccination against tuberculosis after infancy and among individuals exposed to non-TB mycobacteria.[41] IGRAs are also associated with fewer losses to follow-up than the TST, as they do not require a return visit to clinic to obtain a result.[42] Because of these advantages, IGRA is the preferred test in some low-incidence countries under specific circumstances. However, the TST does not require sophisticated lab infrastructure and is far cheaper[9,43] and thus is more often used in low- and middle-income settings.

TST and IGRAs are both limited as diagnostic tests, to the extent that they measure the immunological response rather than the presence of *M. tb.* As such, their sensitivity is reduced in individuals with suppressed immune responses such as PLHIV.[9] Furthermore, the tests do not indicate when and how long an individual has been infected,[12,44] which is problematic as individuals with longstanding TBI are less likely to progress and may even self-clear infection.[45–47] Given these characteristics, both the TST and the IGRAs have poor predictive value for progression to TB disease.[12,48]

2.4 THE ANNUAL RISK OF INFECTION

The annual risk of infection (ARI) is a measure of TB transmission: specifically, the probability that a person within a given community acquires new tuberculosis infection or becomes reinfected over one calendar year.[49] In addition to being an important indicator of TB transmission, it is a key parameter for estimating TBI prevalence on a global, regional, and country-level scale.[2,50] The annual risk of infection can be estimated from TST or IGRA surveys or mathematically using other epidemiologic information such as local TB incidence. [49,51]

2.5 METHODS FOR ESTIMATING THE ARI AND TBI PREVALENCE

2.5.1 Estimating the ARI with TST and IGRA Surveys

TST and IGRA surveys have been used to estimate the ARI. While both tests can be used in cross-sectional surveys, TST can be advantageous in that serial testing can be conducted to measure test result conversion and hence provide a direct estimate of the ARI. This is not the case for IGRAs, as previous data have shown frequent and unexplained conversions and reversions during serial testing, without concomitant changes in exposures or suspected transmission.[9]

Tanzania and Kenya are two high-incidence countries that have used serial TST surveys to estimate the ARI.[52,53] Test positivity was estimated among schoolchildren ages 6-14 in both countries, focusing on those with no signs of previous BCG vaccination. The ARIs were estimated as ARI = $1 - (1 - \text{test positivity prevalence})^{1/\text{mean age of sample}}$. Estimates suggested that TB transmission had remained stable in Tanzania and increased in Kenya.

TST and IGRA surveys are typically conducted among children ages 5-14 as they are more accessible than adults. New infections can also more easily be tracked over time because children are less likely to be infected at baseline. Lastly, it is more reasonable to assume a constant ARI over a child's lifespan than an adult's.[49] However, a recent analysis argued that this approach may lead to a 2- to 6-fold underestimation of the ARI in countries with high TB

disease incidence, because TB disease is less common and less transmissible among children.[54] Additionally, by estimating ARI among children who are largely HIV-negative, it may underestimate the risks of infection faced by HIV-infected adults.[49]

Estimates of the ARI may also be biased because of TST and IGRA test limitations. In settings where BCG vaccination is common, and TST surveys are used, children vaccinated with BCG are often excluded from analysis; this may result in a less representative sample.[49] Recent studies also suggest that approximately 20% of people tested with TST or IGRA may not convert even after intense exposure to *Mtb*.[55,56] Lastly, some of those who test positive may revert in subsequent years.[57,58] These factors could lead to an underestimation of the ARI.[54]

2.5.2 Estimating the ARI Mathematically

The ARI can be estimated mathematically when TST or IGRA survey methods are not feasible. Observations in the mid-20th century highlighted a mathematical relationship between the prevalence of smear-positive TB and the annual risk of infection in a given population. In 1985, Styblo estimated this ratio to be a 1% increase in the ARI for every increase of 50 per 100,000 in the incidence of sputum smear-positive TB.[51] However, subsequent observation led to country-specific revisions of this ratio--reflecting the impact of HIV on TB epidemiology, and other changes in TB prevention and care.[59–61] These revised ratios are now more often used.

2.5.3 Handling Missing ARI Data

Statistical methodology also exists to estimate the ARI for periods of time where it may be missing or unknown. Gaussian process regression models use a Bayesian approach whereby the certainty of one variable is used to reduce uncertainty in others, based on an understanding of the covariance between one or more variables.[62] In time-series modeling studies, Gaussian process models can efficiently address interactions between covariates and account for time-

varying covariates, more than methods such as general linear mixed effect models and generalized estimating equations.[63,64] Limitations of Gaussian process regression models include that they can be computationally expensive and are prone to overfitting. However, they may be preferred when there is great uncertainty around parameters, such as the ARI which is difficult to directly measure.

2.5.4 Estimation of TBI Prevalence with Cross-Sectional Surveys

TBI prevalence can be estimated without knowledge of the ARI, using cross-sectional surveys. These surveys can provide subgroup-specific burden of disease data which can help with decision-making and allocation of TB prevention resources. Several low-incidence countries, including the United States, the United Kingdom, and the Netherlands, have used cross-sectional surveys to measure TBI prevalence.

The National Health and Nutrition Examination Survey in the United States estimated TBI prevalence among persons six years of age or older, during two survey periods. The TST was used for the 1999-2000 survey period, and both the TST and an IGRA for 2011-2012. Among US-born persons, prevalence was estimated at 2% between 1999-2000 and ranged from 1.5% to 2.8% between 2011-2012. Estimated prevalence among foreign-born persons during the 1999-2000 survey period was 18% and ranged from 16%-21% during the 2011-2012 survey period. Results did not change substantially between survey years for either group; test positivity was higher among those tested with IGRA.[65,66] Prevalence estimates among foreign-born persons in the US were similar to those from the United Kingdom, and the Netherlands, where estimated prevalence ranged from 17% to 20% over multiple survey periods from 2009 to 2019.[67,68]

Results from TST and IGRA surveys can also be pooled to estimate TBI prevalence more broadly;[69] however, they are difficult to apply to specific subpopulations, such as foreign-born persons, for whom less testing data may be available. One meta-analysis estimated TBI

prevalence globally based on TST and IGRA survey results published between 2005 and 2018. The analysis yielded pooled TBI prevalence estimates of 21% for TST-based studies and 24% for IGRA-based studies. The study also estimated TBI prevalence regionally, suggesting that prevalence was higher in parts of Sub-Saharan Africa, Southeast Asia, and the Eastern Mediterranean.

2.5.5 Mathematical Estimation of TBI Prevalence

TBI prevalence estimates over multiple survey periods are often desired for capturing trends. However, it is not always feasible to repeatedly conduct cross-sectional surveys. This can be overcome mathematically by using the ARI as a parameter for estimating TBI prevalence over time.

Houben and Dodd estimated TBI prevalence globally for the year 2014 and re-estimated prevalence for 1997 by estimating the ARI from surveys and mathematical methods.[2] They suggested that approximately 23% of people had TBI in 2014,[2] similar to the later meta-analysis conducted by *Cohen et al*.[69] Prevalence was similarly higher among those from parts of Africa, Southeast Asia, and the Eastern Mediterranean. By incorporating population data by country and age from the United Nations, they also found that prevalence increased with age and was highest among persons living in China, India, and Indonesia. They also estimated that global prevalence for 1997 had been 27%, using the revised ratios. This was lower than the previously accepted estimate of 32%, which reflected the original Styblo ratio.[70]

A modeling study examining the Australian population used the same methods as those from *Houben and Dodd* to analyze population-level trends over time and estimate TBI prevalence.[50] For each census year from 2006 to 2016, estimated TBI prevalence overall and among Australian-born persons did not change substantially, 5% and 0.4%, respectively. The estimated prevalence among foreign-born persons ranged from 17-18% over the same period. 2016 Australian census data indicated that from 1960 to 2016, migration from countries with

high TB disease incidence increased. Additionally, in 2016 the most frequent countries of origin with high TBI prevalence were China, India, the Philippines, and Viet Nam.

2.6 INTERPRETATION OF TBI PREVALENCE STUDIES IN LOW-INCIDENCE SETTINGS

Across all studies, estimated TBI prevalence was higher among persons from countries with higher TB disease incidence and people of older age. Prevalence among foreign-born persons was also substantially higher compared to non-foreign-born persons. Prevalence did not change substantially over time for any group.

A consistent finding from Australia and the United States was an increase in immigration from high-incidence countries over time. Prevalence among migrants in Australia and the United States likely remained unchanged despite increases in immigration from high-incidence countries because of factors such as global decreases in TB disease incidence or decreases in the age at which people immigrated.

Demographic changes and TBI prevalence trends among foreign-born persons in Canada are likely similar to those of other low-incidence settings. However, there are some differences in immigration patterns to Canada overall, and between Canadian provinces. These differences in size and demographic characteristics of the migrant population will likely influence time since infection and prevalence at the provincial level, which is relevant to the development of targeted TB prevention programs.

3 RESEARCH OBJECTIVES

The primary objective of my work was to estimate TBI prevalence among foreign-born persons in Canada, overall and by common countries of origin, age at immigration, and TB disease in country of origin between the years 2001 and 2016. Our secondary objective was to estimate TBI prevalence at the provincial level and by years since immigration based on the 2016 census. Our final objective was to estimate the number of people infected within the last two years –those at highest risk of progression to TB disease – in order to determine the number needed to be screened to prevent one case of TB disease. Each of these objectives will serve to inform the development of screening and treatment strategies directed toward migrants arriving in Canada with TBI.

4 MANUSCRIPT

The Prevalence of Tuberculosis Infection Among Foreign-Born Canadians: A Modelling Study

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Data sharing: All relevant data are in the main text or appendix. Code available on Github. https://github.com/Acesa2t

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Appendix: This manuscript has an appendix with supplemental information on methods and results, for on-line publication.

Keywords: Tuberculosis, Canada, immigrant health, modelling

ABSTRACT

Background: The prevalence of tuberculosis infection (TBI) is critical to designing tuberculosis (TB) prevention strategies, yet it is unknown in Canada. We estimated TBI prevalence among foreign-born Canadians.

Methods: Using a previously developed Gaussian process regression model, annual risk of infection trends abroad were constructed and used to estimate TBI prevalence by age and year of migration to Canada for persons from each of 168 countries. These stratified TBI prevalence estimates were combined with Canadian census data to estimate overall TBI prevalence among foreign-born residents during census years 2001, 2006, 2011, and 2016. We also estimated TBI prevalence according to age, WHO-estimated TB incidence in country of origin, and province/territory of residence. Finally, we estimated the prevalence of TBI acquired within the two preceding years.

Results: Estimated TBI prevalence among foreign-born Canadians overall was 25% (95% uncertainty interval [UI]: 20-35%), 24% (20-33%), 23% (19-30%), and 22% (19-28%) for census years 2001, 2006, 2011, and 2016, respectively. TBI prevalence increased with age at migration and TB incidence in the country of origin. In 2016, estimated TBI prevalence was lowest in Quebec (19%, 95% UI: 16-25) and highest in Alberta and British Columbia, at 24% each. Among all foreign-born Canadian residents with TBI in 2016, we estimated that only 1 in 440 were infected within the two preceding years.

Interpretation: Approximately 1 in 4 foreign-born Canadians has TBI; estimated prevalence has remained quite stable over the last two decades. However, a very small minority of people with TBI were infected within the last two years—the highest risk period for progression to TB disease. These data may inform future TBI screening policies.

INTRODUCTION

Before the COVID-19 pandemic, tuberculosis (TB) disease was the leading cause of death by a single infectious agent worldwide, and it remains the second leading cause. TB disease is preceded by TB infection (TBI), which traditionally has been identified by testing for immunoreactivity to the causative agent, *Mycobacterium tuberculosis*. An estimated 23% of the world's population has TB infection (TBI).[2] Depending on sociodemographic and medical characteristics, the World Health Organization (WHO) suggests that 5-10% of persons with TBI will progress to TB disease, the cause of 1.6 million deaths in 2021.[1,3]

The WHO has established targets for TB disease elimination in low-incidence countries such as Canada, with a goal to reduce annual TB disease incidence to 1 case per million population. TB disease incidence in Canada declined steadily through the second half of the 20th century but has remained essentially unchanged over the last decade. Despite a previous target of reducing TB incidence to 3.5 per 100,000 by 2015, TB incidence in Canada remained 4.7 per 100,000 in 2020. [6,8,9] The lack of further progress toward elimination is the result of epidemiologic shifts without the implementation of new prevention strategies

In Canada, TB disease disproportionately impacts foreign-born persons, who bear 80% of the TB disease burden, despite representing only 23% of the population.[8,9,32] TB disease among foreign-born persons is largely due to progression of TBI acquired within their countries of origin.[9] Tuberculosis preventive treatment (TPT) is highly effective at preventing progression to TB disease. However, implementation of TPT in Canada is limited.[71,72] With available TBI diagnostics, widespread TBI screening and treatment programs would likely be cost-prohibitive[17] and could result in the provision of treatment to large numbers of people who may derive minimal benefit.[18,19] Instead, targeting screening to those at highest risk of TBI would improve cost-effectiveness as well as health gains for treated individuals.[73] However, TBI prevalence among foreign-born Canadians is unknown. To support the design and

implementation of TB prevention programs, we estimated TBI prevalence and patterns among foreign-born Canadians.

METHODS

We used estimates of the annual risk of TBI—the probability someone would become infected with *M. tuberculosis* each year—from 168 countries between 1889 and 2016 to estimate the probability of TBI among people immigrating to Canada according to year of birth, age at arrival in Canada, and country of origin. We integrated Canadian census data from 2001, 2006, 2011, and 2016 to estimate the prevalence of TBI among foreign-born residents of Canada during each census year.

Data Sources

Annual Risk of Infection Data

We adapted a previously published approach to obtain country-specific estimates for the annual risk of TBI. In brief, estimated historic annual risks of infection (ARI) were constructed using two data sources. In-country tuberculin skin test (TST) surveys were used to directly estimate ARI where available (37 countries).[2,74] When TST surveys were unavailable, historic ARIs were estimated based on World Health Organization (WHO) estimates of the prevalence of smear-positive TB and the documented relationship between smear-positive pulmonary TB prevalence and annual infection risk,[60,75,76] while accounting for the impact of HIV infection in each country.[2] The delta method was used to propagate uncertainty and estimate variance around ARI estimates.[77] Countries were excluded from analysis if their population was below 500,000 people, if they could not be matched with TB disease incidence data, or if neither TST survey data nor adequate TB disease prevalence data were available. A total of 50 countries were excluded. The total number of people living in Canada from these 50 countries combined ranged from 66,670 (1.3% of all foreign-born residents) to 83,180 (1.1%) between the 2001 and 2016 census years, respectively (Table S1).[2] This left 168 countries of origin in our analysis.

Census Data

Canadian census data detailing the number of permanent residents and foreign-born Canadian citizens living in Canada (hereafter collectively referred to as foreign-born residents) were obtained from Statistics Canada for years 2001, 2006, 2011 and 2016.[78] These data include the number of permanent residents and citizens from each country (Table S2), further grouped into categories based on age and year of immigration (Table S3). Within each age and year of immigration category, we assumed a uniform distribution of people for each specific age and year of immigration. Temporary workers, visitors, and students were excluded.

Definitions

Annual TB disease incidence in country of origin per 100,000 person-years was categorized into groups of 0-9, 10-49, 50-99, 100-199, and ≥200 based on WHO global TB disease incidence estimates from 2016.[79,80] TB disease incidence estimates from 2016 were used as this was the final census year analyzed, and TB disease incidence data prior to year 2000 are considered unreliable.[81] Year of birth was calculated as the census year minus reported age. Year of immigration was considered the year in which individuals acquired permanent residence. Age at immigration was calculated as year of immigration minus year of birth. We categorized age during each census year and age at immigration as: <15 years, 15-34 years, 35-54 years, 55-74 years, ≥75 years.

Data Analysis

To account for uncertainty around ARI estimates, a Gaussian process regression model was used to simulate 200 log-scale ARI trends for each country and year from 1934 to 2014, conditioned on the available data. The ARI estimate for 2014 was used for the years 2015 and 2016, while the ARI estimate for 1934 was used for previous years back to 1889, giving ARI estimates based on country and year from 1889-2016.

For each of the 200 sampled log-scale ARI trends, probabilities of TBI for each combination of country, birth year, and migration year were generated as follows (see Appendix Figure S1 for further details). First, we calculated annual risks of TBI, assuming risks were uniform among

people from the same country, birth year, and migration year, by exponentiating each log-ARI. Second, we summed annual risks of infection for each country, birth year, and migration year to estimate the cumulative risk of infection for each census year (i.e., to 2001, 2006, 2011, and 2016)—accounting for annual risks of infection in country of origin before migration, as well as within Canada after migration. Since precise calendar dates of migration were unknown, we assumed that the average date of arrival for each cohort was the mid-point of the calendar year, resulting in the risk of infection during the year of migration being an average of the risk of infection in the country of origin and in Canada. Finally, using the cumulative risk of infection, we calculated the probability of TB infection for each combination of birth year, country of origin, and migration year.

For each census year, by summing relevant strata, we estimated the number of foreign-born residents living in Canada overall and by subgroups. These subgroups reflected categorization by age at immigration, age during each census year, TB disease incidence per 100,000 persons in country of origin, and the most frequent countries of origin across census years. Using our estimates of the probability of TBI, we estimated the prevalence of TBI for each census year overall, for each of these subgroups, and by time since immigration. Finally, for the 2016 census year only, we estimated the prevalence of TBI in Ontario, Quebec, Alberta, and British Columbia (the four largest immigrant-receiving provinces), and the rest of Canada, and estimated the prevalence of TBI acquired within the last 2 years. The point estimate and 95% uncertainty intervals (95% UI) for TBI estimates were calculated as the 50^{th}, 2.5^{th}, and 97.5^{th} percentile, respectively. Differences in median TBI prevalence across census years were tested using the Kruskal-Wallis test. All analyses were performed using R (version 4.0.2).

Ethics Approval

This study involved the use of publicly available, de-identified, aggregate data. Approval by a research ethics board was not required.

RESULTS

POPULATION COMPOSITION FROM 2001 TO 2016

During the 2016 census year, 7.5 million foreign-born residents lived in Canada. This represented an increase of 2.1 million (38%) since 2001. The median age (IQR) of foreign-born residents in each census year from 2001 to 2016 was 46 (32-58), 47 (32-61), 47 (32-61), and 48 (33-62) years, respectively; 74% had immigrated before the age of 35. In each of the census years, 52% of foreign-born residents were women while 48% were men. Between the 2001 and 2016 census years, the number of people immigrating from Europe decreased in absolute number and proportion, while those from Asia increased in both absolute number and proportion. In line with these trends, the proportion of foreign-born residents in Canada from countries with TB disease incidence ≥200 per 100,000 per year increased from 15% to 25% between 2001 and 2016, while the proportion from countries with TB incidence <10 per 100,000 decreased from 38% to 25% during the same period (Table 2).

From 2001 through 2016 census years, seven countries/jurisdictions (China, India, Italy, Philippines, the United Kingdom, the United States of America, and Hong Kong) were consistently among the ten most frequent places of origin for foreign-born residents. All except the United States of America, Italy, and the United Kingdom have TB disease incidence ≥50 per 100,000 persons, while TB disease incidence is ≥200 per 100,000 persons in India and the Philippines. In the 2016 census year, Pakistan, Viet Nam, and Iran also ranked among the ten most common countries of origin (Table 3); all three have TB disease incidence >100 per 100,000 persons.

ESTIMATED TBI PREVALENCE

The overall estimated TBI prevalence among foreign-born residents did not change substantially over time, with a prevalence of 25% (95% UI: 13-35%), 24% (95% UI: 14-33%), 23% (95% UI: 14-30%), and 22% (95% UI: 20-28%) in census years 2001, 2006, 2011, and 2016, respectively.

Between 2001 and 2016, estimated TBI prevalence decreased among foreign-born residents from India, China, Philippines, and the United States, ($p < 0.0001$ for each, Kruskal-Wallis test)—most substantially for China (Table 4).

In 2016, estimated TBI prevalence varied from 9% (95% UI: 5-22) among persons from countries with TB disease incidence of <10 per 100,000 persons to 35% (95% UI: 22-46) among persons from countries with incidence ≥200 per 100,000 persons. Similarly, it increased markedly with age at immigration, ranging from 8% (95% UI: 6-16) for those who had arrived at <15 years of age to 65% (95% UI: 50-74) for those who had arrived at ≥75 years of age (Table 5). Findings were generally similar in earlier census years (Appendix Table S4).

In 2016, 94% of all foreign-born residents resided in Ontario, Quebec, Alberta, or British Columbia (Appendix Table S5). In these four provinces, estimated TBI prevalence increased with age at immigration, while for the remaining provinces and territories, prevalence appeared similar among all those aged ≥15 years at immigration (Table 5). The estimated prevalence of TBI was lowest in Quebec (19%, 95% UI: 16-25) and highest in Alberta and British Columbia, at 24% (95% UI: 21-29%) and 24% (95% UI: 20-30%), respectively.

Estimated TBI prevalence increased with age during the 2016 census year from 2% (95% UI: 2-2%) among those aged <15 years in 2016 to 37% (95% UI: 27-54%) among those aged ≥75 years in 2016. Overall prevalence did not change substantially by time since arrival. However, when stratified by age during the census year, estimated prevalence decreased by time since arrival, reflecting lower values among those who entered Canada at younger age (Appendix Table S6).

As expected, the estimated prevalence of TBI acquired in the past two years increased with TB disease incidence in country of origin (Table 6). Overall, only an estimated 0.05% (95% UI: 0.04-0.07%) of foreign-born residents in 2016 had acquired TBI in the past two years. This increased to 0.6% (95% UI: 0.5-0.8%) when considering only those who immigrated in 2015 and 2016.

These data suggest that among all foreign-born residents with TBI, an estimated one in 440 had been infected within the last two years. For those with TBI who had arrived within the preceding two years, an estimated one in 39 had been infected within the last two years. To detect one person infected within the last two years among all foreign-born residents, 2,000 (95% UI: 1,429-2,500) would need to be tested. To detect one person infected within the last two years among only those foreign-born residents who had arrived in the last two years, 167 (95% CI: 125-200) would need to be tested.

INTERPRETATION

Our estimates suggest that almost one quarter of foreign-born residents in Canada have TBI, a proportion which did not substantially change between 2001 and 2016. However, despite the large number of people with TBI, only a small minority were likely to have been infected within the preceding two years—the highest risk period for progression to TB disease.[21]

Our TBI prevalence estimates are concordant with those from other low-incidence settings, notably an analysis that used similar methods to estimate TBI prevalence among migrants living in Australia.[50] They are also concordant with cross-sectional surveys. Using tuberculin skin tests, the U.S. National Health and Nutrition Examination Survey (NHANES) estimated TBI prevalence to be 18.1% and 20.5% among foreign-born persons in 1999-2000 and 2011-2012 respectively.[66,82,83] Other surveys in the United Kingdom and the Netherlands using interferon-gamma release assays estimated a TBI prevalence of approximately 20% among foreign-born persons between 2008 and 2012.[84,68]

The proportion of foreign-born residents in Canada from countries with TB disease incidence ≥50 per 100,000 persons increased to 55% by the 2016 census year, with a substantial increase in those from countries with incidence ≥200 per 100,000 persons. This was balanced by a decrease in estimated TBI prevalence among Canadians from some of the highest TB incidence countries, including China, India, and Viet Nam. This decline may potentially reflect the impact of both improved socioeconomic conditions and TB care programs in those countries. [4,79]

These results can help inform clinical and programmatic decision-making around TBI screening and treatment. They provide a provincial-level picture of TBI prevalence, which is relevant as healthcare policies fall within the provincial purview. They also have implications for the development of TBI screening and treatment programs. Our results reinforce earlier suggestions that screening and providing TPT to people who immigrated before adulthood will have limited public health impact as TBI prevalence among this group is low.[73,85] Even though

TBI prevalence among older persons is higher, the risk of adverse events with TPT—even newer rifamycin-based regimens—increases with age[86,87] and the likelihood the infection occurred within the previous 2 years is lower. Even if TBI testing targets persons from high-burden countries shortly after arrival, a small minority of persons found to have TBI will have been infected within the last two years. As the yield and cost-effectiveness of any TBI screening and treatment program increase with both pretest probability of TBI and risk of progression to TB in those with TBI,[18,19,73,84,85] our results are directly relevant to future TB prevention programming.

Strengths of this analysis include the use of robust, previously reported methodology for estimating risks of acquiring TB infection over time in many countries. We also accounted explicitly for uncertainty around these country- and time-based estimates of infection risk.

Limitations

Our analysis had several potential limitations. First, the source data assumed that individuals with positive TST results truly had had TBI and remained infected with viable mycobacteria for life, with no allowance for self-clearance. Hence we may have overestimated the prevalence of TBI, particularly in older age groups.[46,88,89] However, this is also a potential shortcoming of any analysis based on current immunological tests for TBI. Indeed, it has been argued that failure to account for self-clearance leads to an underestimate of the number of people who have recently acquired TBI, and of their ensuing risk for TB disease and subsequent transmission.[54] Second, we assumed that the ARI was consistent among persons within a given country in any given year, which obscures variation due to geography, mixing patterns, and other social factors.[51,90] For example, refugees are more likely to have TBI and to progress to TB disease than other migrants from the same countries.[38]

Similarly, we lacked census data stratified by immigration category (e.g. refugee, economic class, family reunification) as well as sex-stratified ARI data, making us unable to evaluate TBI according to immigration category or sex.[90] In tabulating TBI prevalence according to TB incidence in migrants' countries of origin, we relied on recent incidence estimates rather than

those corresponding to the dates they moved to Canada—as robust data were not consistently available before 2000. Hence some older foreign-born residents from countries with decreasing TB incidence faced higher past infection risks than current incidence estimates might imply. We did account for changing annual infection probabilities in our cumulative risk estimates. Finally, we could not estimate infection risks from 2016 to 2021, making us unable to evaluate any potential impact of the COVID-19 pandemic on TBI prevalence.

CONCLUSION

Approximately one quarter of foreign-born Canadians likely had TBI from 2001 to 2016, but few were recently infected. The composition of the Canadian foreign-born population has changed, with more persons from countries with high TB disease incidence, although estimated prevalence has dropped somewhat among immigrants from several key countries. These data can help inform future strategies to reduce the burden of TB disease among foreign-born Canadians.

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Table 1. Composition of the foreign-born Canadian population in census years 2001-2016.

Population	Census Year			
	2001	2006	2011	2016
Total Foreign-Born Residents	5,448,480	6,524,190	7,217,295	7,539,895
Sex, N (%)				
Female	2,825,870 (52)	3,389,085 (52)	3,763,070 (52)	3,953,825 (52)
Male	2,622,610 (48)	3,135,105 (48)	3,454,225 (48)	3,586,070 (48)
Age during census year				
Median (IQR) age, years	46 (32-58)	47 (32-61)	47 (32-61)	48 (33-62)
Age during census year, N (%)				
<15 years	301,470 (6)	336,705 (6)	372,190 (6)	373,960 (5)
15-34 years	1,207,909 (23)	1,369,695 (23)	1,493,443 (23)	1,608,233 (22)
35-54 years	2,011,356 (38)	2,184,035 (36)	2,400,517 (37)	2,642,352 (35)
55-74 years	1,189,814 (23)	1,478,539 (25)	1,519,770 (23)	1,963,148 (26)
≥75 years	565,341 (11)	666,871 (11)	706,630 (11)	877,517 (12)
Region of Origin, N (%)				
Americas	834,260 (15)	946,140 (15)	1,058,010 (16)	1,127,815 (15)
Europe	2,282,795 (42)	2,267,440 (37)	2,127,790 (31)	2,088,405 (28)
Africa	281,445 (5)	373,340 (6)	492,025 (7)	637,485 (8)
Asia	1,986,105 (37)	2,521,035 (41)	3,041,100 (45)	3,629,165 (48)
Oceania	47,825 (0.9)	52,625 (0.9)	54,530 (0.8)	56,920 (0.8)
TB Disease Incidence in Country of Origin in 2016, N (%)				
0-9 per 100,000 persons	2,017,280 (38)	2,019,465 (33)	1,884,040 (29)	1,890,965 (25)
10-49 per 100,000 persons	1,011,810 (19)	1,144, 505 (19)	1,257,380 (19)	1,480,190 (20)
50-99 per 100,000 persons	1,098,005 (21)	1,341,575 (22)	1,450,320 (22)	1,671,545 (22)
100-199 per 100,000 persons	332,735 (6)	411,935 (7)	473,735 (7)	579,945 (8)
≥200 per 100,000 persons	816,060 (15)	1,118,365 (19)	1,427,075 (22)	1,842,565 (25)
Age at Immigration, N (%)				
<15 years	1,613,358 (31)	1,828,028 (30)	2,253,488 (35)	2,504,326 (34)
15-34 years	2,291,796 (43)	2,655,510 (44)	2,626,257 (41)	3,007,347 (40)
35-54 years	1,140,530 (22)	1,303,154 (22)	1,349,278 (21)	1,643,312 (22)
55-74 years	205,982 (4)	225,683 (4)	240,426 (4)	279,984 (4)
≥75 years	24,224 (0.5)	23,470 (0.4)	23,101 (0.4)	30,241 (0.4)

Table 2. Number and proportion of foreign-born Canadians from top ten countries of origin in each census year

Census Year							
2001		**2006**		**2011**		**2016**	
Place of Origin	**N (%)**	**Place of Origin**	**N (%)**	**Place of Origin**	**N (%)**	**Place of Origin**	**N (%)**
India	314,265 (11)	India	443,120 (15)	India	538,325 (17)	India	668,565 (18)
China	332,235 (12)	China	465,940 (15)	China	533,035 (17)	China	649,260 (18)
Philippines	232,330 (8)	Philippines	302,860 (10)	Philippines	440,925 (14)	Philippines	588,310 (16)
United Kingdom	604,380 (22)	United Kingdom	574,740 (19)	United Kingdom	525,475 (16)	United Kingdom	499,125 (14)
United States of America	236,225 (9)	United States of America	247,870 (8)	United States of America	256,970 (8)	United States of America	253,700 (7)
Italy	315,215 (11)	Italy	296,250 (10)	Italy	255,350 (8)	Italy	236,635 (7)
Hong Kong	235,315 (8)	Hong Kong	215,080 (7)	Hong Kong	191,405 (6)	Hong Kong	208,945 (6)
Poland	180,150 (6)	Poland	169,740 (6)	Pakistan	155,330 (5)	Pakistan	202,250 (6)
Portugal	153,445 (6)	Viet Nam	159,940 (5)	Viet Nam	154,665 (5)	Viet Nam	169,265 (5)
Germany	173,515 (6)	Germany	170,165 (6)	Germany	150,085 (5)	Iran	154,430 (4)
Total	**2,777,075**	**Total**	**3,045,705**	**Total**	**3,201,565**	**Total**	**3,630,485**

Table 3. Estimated tuberculosis infection prevalence among foreign-born residents from the seven most frequent countries/jurisdictions of origin

Place of Origin	TB Infection Prevalence, % (95% UI)				Comparison, 2016 vs. 2001*
	Census 2001	Census 2006	Census 2011	Census 2016	
India	34 (22-47)	33 (23-45)	31 (23-41)	30 (23-39)	P<0.0001
China	46 (14-73)	38 (13-63)	31 (12-53)	28 (12-48)	P<0.0001
Philippines	54 (22-79)	51 (24-74)	47 (27-65)	45 (29-61)	P<0.0001
United Kingdom	3 (1-40)	3 (1-36)	3 (1-30)	3 (1-26)	P=0.565
United States of America	10 (1-54)	8 (1-47)	6 (1-37)	5 (1-35)	P< 0.0001
Italy	5 (1-58)	5 (1-57)	5 (1-54)	4 (1-45)	P=0.800
Hong Kong	20 (4-65)	19 (4-64)	19 (4-62)	19 (5-65)	P=0.940

UI = uncertainty interval
**P values from Kruskal-Wallis test*

Table 4. Estimated tuberculosis infection prevalence (95% uncertainty interval) among foreign-born persons by age at immigration and 2016 TB disease incidence per 100,000 persons in country of origin.

TB Incidence in Country of Origin	Age at Immigration <15	Age at Immigration 15-34	Age at Immigration 35-54	Age at Immigration 55-74	Age at Immigration ≥75	All
0-9 per 100,000 persons	6 (2-21)	11 (5-22)	13 (6-23)	17 (8-35)	22 (9-47)	9 (5-22)
10-49 per 100,000 persons	7 (4-15)	14 (9-24)	22 (15-31)	34 (23-52)	39 (24-61)	14 (9-22)
50-99 per 100,000 persons	7 (4-13)	21 (14-29)	39 (25-51)	60 (34-79)	72 (38-90)	24 (16-33)
100-199 per 100,000 persons	14 (7-24)	36 (23-50)	53 (38-66)	75 (50-89)	78 (58-93)	34 (22-46)
≥200 per 100,000 persons	12 (9-15)	35 (29-42)	54 (44-64)	67 (54-83)	75 (62-90)	35 (22-46)
All	8 (6-16)	22 (19-26)	37 (31-43)	55 (45-63)	65 (50-74)	22 (19-28)

Table 5. Estimated tuberculosis infection prevalence by age at immigration and province/territory of residence in 2016.

TB Infection Prevalence, % [95% UI)						
	Age at Immigration					
Province/Territory of Residence in 2016	**0-14**	**15-34**	**35-54**	**55-74**	**≥75**	**All**
Alberta	8 (6-14)	24 (21-28)	40 (35-46)	58 (49-67)	69 (56-79)	24 (21-29)
British Columbia	9 (7-18)	23 (19-29)	38 (32-48)	58 (45-71)	68 (50-79)	24 (20-30)
Ontario	8 (6-16)	22 (18-26)	36 (30-43)	53 (43-64)	63 (48-73)	22 (18-27)
Quebec	5 (5-15)	20 (16-25)	31 (27-38)	50 (42-61)	61 (48-72)	19 (16-25)
Other	7 (6-9)	25 (21-31)	36 (30-43)	29 (22-40)	35 (24-52)	22 (18-26)
All	8 (6-16)	22 (19-26)	37 (31-43)	55 (45-63)	65 (50-74)	22 (19-28)

UI = Uncertainty Interval

Table 6. Estimated prevalence of recently acquired tuberculosis infection among foreign-born residents.

TB Incidence in Country of Origin per 100,000 persons	All Foreign-Born Residents			Only Foreign-Born Residents Immigrating from 2015-2016		
	Prevalence of TBI Acquired in Past 2 Years (%, 95% UI)	Prevalence of TBI Overall (%, 95% UI)	Number of TB Infections to identify to detect one person infected in last 2 years*	Prevalence of TBI Acquired in Past 2 Years (%, 95% UI)	Prevalence of TBI Overall (%, 95% UI)	Number of TB Infections to identify to detect one person infected in last 2 years
0-9	0.02 (0.01 - 0.05)	9 (5-22)	450	0.04 (0.03 - 0.06)	3 (2-5)	75
10-49	0.03 (0.02 - 0.05)	14 (9-22)	467	0.1 (0.1 - 0.2)	8 (6-11)	80
50-99	0.04 (0.03 - 0.06)	24 (16-33)	600	0.3 (0.3 - 0.5)	22 (16-29)	74
100-199	0.07 (0.05 - 0.09)	34 (22-46)	486	0.7 (0.6 - 0.9)	29 (25-35)	42
≥200	0.12 (0.10 - 0.17)	35 (22-46)	292	1.2 (0.9 - 1.7)	37 (32-41)	31
All	0.05 (0.04 – 0.07)	22 (19-28)	440	0.6 (0.5 – 0.8)	23 (21-25)	39

UI = uncertainty interval

**Number of TB infections that must be diagnosed, to detect one person infected in the last 2 years = Prevalence of TBI overall/Prevalence of TBI acquired in past 2 years*

Appendix

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Methods (continued)

Table S1. List of countries excluded from analysis

Excluded Countries of Origin	
Aruba	Maldives
Anguilla	Marshall Islands
Andorra	Malta
Netherlands Antilles	Northern Mariana Islands
American Samoa	Montserrat
Antigua and Barbuda	New Caledonia
Bonaire, Sint Eustatius and Saba	Niue
Bahamas	Nauru
Belize	Palau
Bermuda	French Polynesia
Barbados	Samoa
Brunei Darussalam	San Marino
Cook Islands	Sao Tome and Principe
Curacao	Sint Maarten (Dutch part)
Cayman Islands	Seychelles
Dominica	Turks and Caicos Islands
Micronesia, Federated States of	Tokelau
Grenada	Timor-Leste
Greenland	Tonga
Guam	Tuvalu
Iceland	Saint Vincent and the Grenadines
Kiribati	Virgin Islands, British
Saint Kitts and Nevis	U.S. Virgin Islands
Saint Lucia	Vanuatu
Monaco	Wallis and Futuna

Table S2. Table of regions, countries, and special administrative regions included in the analysis

Regions	Countries	Special Administrative Regions
Americas Europe Africa Asia Oceania	Afghanistan Albania Algeria American Samoa Andorra Angola Anguilla Antigua and Barbuda Argentina Armenia Aruba Australia Austria Azerbaijan Bahamas Bahrain Bangladesh Barbados Belarus Belgium Belize Benin Bermuda Bhutan Bolivia Bosnia and Herzegovina Botswana Brazil Brunei Darussalam Bulgaria Burkina Faso Burma (Myanmar) Burundi Cabo Verde Cambodia Cameroon Cayman Islands Central African Republic Chad Chile	Hong Kong Macau

Regions	Countries	Special Administrative Regions
	China Colombia Comoros Congo, Democratic Republic of the Congo, Republic of the Cook Islands Costa Rica Croatia Cuba Cùte d'Ivoire Cyprus Czech Republic Denmark Djibouti Dominica Dominican Republic Ecuador Egypt El Salvador Equatorial Guinea Eritrea Estonia Ethiopia Federated States of Micronesia Fiji Finland France French Polynesia Gabon Gambia Georgia Germany Ghana Greece Greenland Grenada Guam Guatemala Guinea	

Regions	Countries	Special Administrative Regions
	Guinea-Bissau Guyana Haiti Honduras Hong Kong Hungary Iceland India Indonesia Iran Iraq Ireland Israel Italy Jamaica Japan Jordan Kazakhstan Kenya Kiribati Korea, North Korea, South Kuwait Kyrgyzstan Laos Latvia Lebanon Lesotho Liberia Libya Lithuania Luxembourg Macau Macedonia, Republic of Madagascar Malawi Malaysia Maldives Mali Malta Marshall Islands	

Regions	Countries	Special Administrative Regions
	Mauritania Mauritius Mexico Moldova Monaco Mongolia Montenegro Montserrat Morocco Mozambique Namibia Nepal Netherlands New Caledonia New Zealand Nicaragua Niger Nigeria Northern Mariana Islands Norway Oman Pakistan Palestine Panama Papua New Guinea Paraguay Peru Philippines Poland Portugal Puerto Rico Qatar Romania Russian Federation Rwanda Saint Kitts and Nevis Saint Lucia Saint Vincent and the Grenadines Samoa Sao Tome and Principe	

Regions	Countries	Special Administrative Regions
	Saudi Arabia Senegal Serbia Seychelles Sierra Leone Singapore Slovakia Slovenia Somalia South Africa, Republic of Spain Sri Lanka Sudan Suriname Swaziland Sweden Switzerland Syria Tajikistan Tanzania Thailand Timor-Leste Togo Tonga Trinidad and Tobago Tunisia Turkey Turkmenistan Uganda Ukraine United Kingdom United States Uruguay United Arab Emirates Uzbekistan Vanuatu Venezuela Viet Nam Virgin Islands, British Wallis and Futuna Yemen	

Regions	Countries	Special Administrative Regions
	Zambia Zimbabwe	

Table S3. Initial census data variables as provided by Statistics Canada.

Age Groups			
0 to 14 years			
15 to 24 years			
25 to 54 years			
55 to 64 years			
65 years and older			
Place of Birth			
Regions*			
Sub-Regions**			
Countries			
Special Administrative Regions			
Year of Immigration			
Census 2001†	**Census 2006†**	**Census 2011**	**Census 2016**
Before 1915	Same as Census 2001	Before 1971	Before 1981
1916 to 1920	2001 to 2006	1971 to 1980	1981 to 1990
1921 to 1925		1981 to 1990	1991 to 2000
1926 to 1930		1991 to 2000	2001 to 2010
1931 to 1935		2001 to 2011	2001 to 2005
1936 to 1940			2006 to 2010
1941 to 1945			2011 to 2016
1946 to 1950			
1951 to 1955			
1956 to 1960			
1961 to 1965			
1966 to 1970			
1970 to 1975			
1976 to 1980			
1981 to 1985			
1986 to 1990			
1991 to 1995			
1996 to 2001			

**Regions are defined as Americas, Europe, Africa, Asia, and Oceania.*
***Special Administrative Regions included Hong Kong and Macau.*
†The 2001 and 2006 census data were provided by Statistics Canada's Statistical Consultation Group

Between census years 2001 and 2016, TBI prevalence by age at immigration did not change substantially. Prevalence decreased by TB disease in country of origin for all groups, but most notably among foreign-born Canadians from countries with TB disease incidence of 100-199 per 100,000 persons from 46% in 2001 to 34% in 2016. Additionally, for census years 2001 and 2006, prevalence among persons from countries with incidence of 100-199 per 100,000 persons remained higher than that of those from countries with incidence ≥200 per 100,000; however, the difference in prevalence decreased between each census year (Table S4).

Table S4. Estimated tuberculosis infection prevalence by age at immigration and TB disease incidence in country of origin per 100,000 persons during census years 2001, 2006, 2011 and 2016.

TB Infection Prevalence in 2001 (%, 95% UI)						
	Age at Immigration <15	Age at Immigration 15-34	Age at Immigration 35-54	Age at Immigration 55-74	Age at Immigration ≥75	All
TB Incidence in Country of Origin per 100,000 persons						
0-9	6 (2-24)	15 (7-36)	21 (11-44)	25 (10-53)	31 (12-61)	13 (6-31)
10-49	7 (7-3-18)	22 (12-41)	33 (20-50)	45 (27-64)	49 (31-69)	21 (12-36)
50-99	8 (5-16)	28 (16-42)	48 (28-68)	71 (37-87)	75 (37-91)	32 (19-44)
100-199	15 (8-32)	50 (25-73)	69 (37-86)	83 (37-97)	86 (47-97)	46 (23-64)
200+	13 (10-19)	40 (29-54)	58 (42-72)	72 (52-89)	79 (58-94)	40 (29-52)
All	8 (6-18)	25 (19-37)	41 (33-50)	59 (45-70)	66 (51-76)	25 (20-35)
TB Infection Prevalence in 2006 (%, 95% UI)						
	Age at Immigration <15	Age at Immigration 15-34,	Age at Immigration 35-54	Age at Immigration 55-74	Age at Immigration ≥75	All
TB Incidence in Country of Origin per 100,000 persons						
0-9	6 (2-23)	15 (7-34)	18 (10-38)	23 (10-48	30 (12-60)	12 (6-28)
10-49	6 (3-15)	20 (11-35)	30 (19-44)	42 (27-60)	48 (31-65)	18 (11-31)
50-99	7 (4-12)	26 (15-38)	46 (28-64)	69 (36-86)	73 (42-89)	30 (18-41)
100-199	14 (8-29)	46 (24-66)	63 (38-80)	82 (42-95)	83 (55-95)	42 (23-58)
200+	12 (10-16)	38 (29-50)	57 (43-69)	71 (54-88)	79 (62-93)	39 (30-49)
All	8 (6-16)	25 (19-34)	40 (33-49)	59 (47-69)	67 (54-75)	24 (20-33)
TB Infection Prevalence in 2011 (%, 95% UI)						
	Age at Immigration <15	Age at Immigration 15-34	Age at Immigration 35-54	Age at Immigration 55-74	Age at Immigration ≥75	All
TB Incidence in Country of Origin per 100,000 persons						
0-9	7 (3-26)	12 (6-27)	15 (7-29)	20 (8-41)	25 (10-52)	10 (5-27)
10-49	7 (4-17)	16 (10-26)	25 (17-35)	38 (25-55)	42 (27-62)	16 (10-25)
50-99	7 (4-12)	22 (14-31)	42 (26-56)	63 (35-82)	71 (41-88)	26 (16-35)
100-199	14 (8-26)	39 (24-56)	57 (38-72)	78 (44-92)	81 (57-95)	37 (23-51)
200+	12 (10-15)	36 (29-46)	56 (45-68)	69 (54-84)	78 (63-92)	37 (30-46)
All	8 (6-18)	23 (19-29)	39 (33-46)	57 (46-66)	64 (52-73)	23 (19-30)
TB Infection Prevalence in 2016 (%, 95% UI)						

UI =

	Age at Immigration <15	Age at Immigration 15-34	Age at Immigration 35-54	Age at Immigration 55-74	Age at Immigration ≥75
TB Incidence in Country of Origin per 100,000 persons					
0-9	6 (2-21)	11 (5-22)	13 (6-23)	17 (8-35)	22 (9-47)
10-49	7 (4-15)	14 (9-24)	22 (15-31)	34 (23-52)	39 (24-61)
50-99	7 (4-13)	21 (14-29)	39 (25-51)	60 (34-79)	72 (38-90)
100-199	14 (7-24)	36 (23-50)	53 (38-66)	75 (50-89)	78 (58-93)
200+	12 (9-15)	35 (29-42)	54 (44-64)	67 (54-83)	75 (62-90)
All	8 (6-16)	22 (19-26)	37 (31-43)	55 (45-63)	65 (50-74)

uncertainty interval

Table S5. Numbers and ages of foreign-born Canadians in provinces of Alberta, British Columbia, Ontario, Quebec, and all other provinces and territories in 2016.

Province of Residence	**Foreign-Born Residents (N)**	**Median Age in 2016 (IQR)**	**Median Age at Immigration (IQR)**
Alberta	845,215	44 (30-57)	23 (10-35)
British Columbia	1,292,675	50 (35-65)	23 (10-36)
Ontario	3,852,150	49 (35-64)	22 (10-34)
Quebec	1,091,305	44 (30-57)	23 (10-35)
Other*	459,750	44 (29-59)	24 (8-43)
All	7,539,895	48 (33-62)	23 (10-35)

N = number, IQR = interquartile range

**Other is defined as Nova Scotia, New Brunswick, Manitoba, Prince Edward Island, Saskatchewan, Newfoundland and Labrador, Northwest Territories, Yukon, and Nunavut.*

Table S6. Estimated tuberculosis infection prevalence by age in census year and years since immigration

Tuberculosis Infection Prevalence in 2016 (%, 95% UI)						
Years Since Immigration	**Age in Census Year 2016**					
	0-14	**15-34**	**35-54**	**55-74**	**75+**	**All**
0-4	3 (3-3)	16 (15-17)	32 (28-36)	49 (40-59)	65 (49-75)	23 (21-25)
5-9	2 (1-2)	12 (11-13)	29 (26-33)	46 (39-55)	61 (49-70)	22 (20-25)
10-14	1 (1-1)	9 (9-10)	27 (24-32)	45 (37-53)	59 (48-68)	22 (19-25)
15-19	*N/A*	6 (6-7)	24 (20-28)	43 (34-52)	58 (47-68)	24 (20-28)
20+	*N/A*	4 (4-5)	14 (11-17)	25 (19-35)	33 (23-51)	22 (17-30)
All	2 (2-2)	10 (9-10)	23 (19-26)	29 (24-39)	37 (27-54)	22 (20-28)

UI = Uncertainty Interval

Figure S3. Data structure and corresponding equations.
Equation 1 shows estimation of cumulative risk of infection (ROI) among foreign-born persons immigrating to Canada. Subscripts b, o, m, c, and f refer to birth year, country of origin, migration year, Canada, and final census year of calculation, respectively.
Equation 2 shows how probability of infection among foreign-born persons was estimated using the cumulative ROI.

We simulated 200 log scale ARI trends for each country and year.

The following example describes how ARI trends are converted to a probability of infection in a given census year. We use a person born in hypothetical country X in the year 1996, who immigrated to Canada in the year 2000, and estimate their probability of infection in census year 2016.

The tables on the right show one simulated ARI trend for country-of-origin X and for Canada.

ARI for Time in Country-of-Origin X

Year	Log(ARI)
1996	-3.729
1997	-3.749
1998	-3.646
1999	-3.565
2000	-3.692

ARI for Time in Canada

Year	Log(ARI)
2000	-7.988
2001	-8.230
2002	-8.493
2003	-8.613
2004	-8.632
2005	-8.591
2006	-8.474
2007	-8.436
2008	-8.497
2009	-8.366
2010	-8.104
2011	-8.169
2012	-8.500
2013	-8.599
2014	-8.368
2015	-8.368
2016	-8.368

We then sum the annual ROI for each year spent in country X and in Canada. We halve the FROI for birth year and migration year as we assume both events occur 6 months into the year. This follows Equation 1, below.

ARI and ROI for Time in Country-of-Origin X

Year	Log(ARI)	ROI
1996	-3.729	0.024
1997	-3.749	0.024
1998	-3.646	0.026
1999	-3.565	0.028
2000	-3.692	0.025

ARI and ROI for Time in Canada

Year	Log(ARI)	ROI
2000	-7.988	0.0003
2001	-8.230	0.0003
2002	-8.493	0.0002
2003	-8.613	0.0002
2004	-8.632	0.0002
2005	-8.591	0.0002
2006	-8.474	0.0002
2007	-8.436	0.0002
2008	-8.497	0.0002
2009	-8.366	0.0002
2010	-8.104	0.0003
2011	-8.169	0.0003
2012	-8.500	0.0002
2013	-8.599	0.0002
2014	-8.368	0.0002
2015	-8.368	0.0002
2016	-8.368	0.0001

Equation 1:

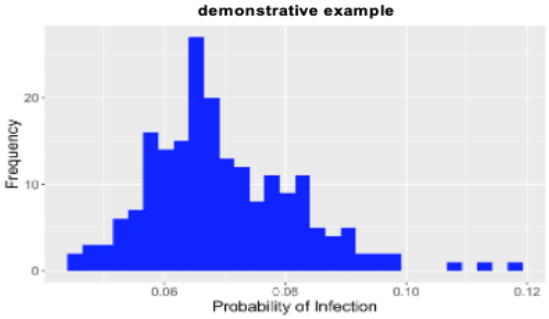
$$ROI_{cumulative} = \sum_{i=b+1}^{m-1} ROI_{io} + \sum_{i=m+1}^{f} ROI_{ic} + {}^{1}/_{2}\,ROI_{bo} + {}^{1}/_{2}\,ROI_{mo} + {}^{1}/_{2}\,ROI_{mc}$$

In this example, the cumulative ROI is equal to 0.07. The cumulative ROI is converted to a probability of infection according to Equation 2, below.

Equation 2: $Probability\ of\ Infection = 1 - e^{-ROI_{cumulative}}$

In this example, the probability of infection is equal to 6%. We repeat this calculation for all 200 simulated ARI trends, which provide a distribution for the probability of infection—shown in a histogram on the right. In this example, across 200 trends, we estimated the probability of infection to be 7 (95% UR 6% to 8%).

Histogram of estimated probability of infection for this demonstrative example



5 DISCUSSION

5.1 Summary of Results and Interpretation

To better inform tuberculosis prevention strategies and TB elimination efforts overall, TBI prevalence was estimated among all foreign-born Canadians and population trends were examined over census years 2001 to 2016. The estimates suggest that almost one-quarter of foreign-born Canadians have TBI. Although the proportion did not substantially change between 2001 and 2016, the relative reduction in TBI prevalence over this period was 12%. Over this same period, the relative reduction in TB disease incidence globally was 21%.[79] In Canada, incidence was 18%, but incidence plateaued as of 2007.[8] Globally, reductions in incidence were likely steeper because the epidemiologic impact of diagnosing and treating TB disease in moderate- to high-incidence countries is usually observed before its impact on TBI prevalence. Additionally, some people may remain infected with previously acquired TBI for much of their lives, though others will self-clear the infection.[46] Within the Canadian context, TB disease among foreign-born persons mainly reflects the acquisition of TBI abroad.[9] Thus, steeper decreases in incidence will likely be seen with the implementation of screening and treatment programs directed toward those with TBI.

TBI prevalence was consistently higher among persons from countries with higher TB disease incidence and those who were older when they immigrated. This is because those who spend a greater number of years in high-incidence and TB-endemic settings face higher potential risk and duration of exposure.[37]

Over the same period, the proportion of migrants from high-incidence countries also grew, accounting for majority of the foreign-born population by 2016. Population growth within Canada was particularly notable among people from China, India, and the Philippines. Estimated prevalence also declined significantly among persons from these countries, likely reflecting the impact of TB prevention and care programs[79] as well as socioeconomic improvements there.[4]

In 2016, only an estimated 0.05% of foreign-born Canadians were recently infected and therefore more likely to progress to TB disease accordingly. Not surprisingly, the estimated prevalence of recent infection was highest among foreign-born Canadians who had immigrated in 2015 or 2016 (0.6%) as well as those from countries with high TB disease incidence (1.2%).

In the major immigrant-receiving provinces, overall TBI prevalence was generally similar--although lowest in Quebec, reflecting more immigration from French-speaking countries compared to other provinces.[91] Prevalence was lower among foreign-born Canadians who had immigrated to the less populated provinces and territories at an older age. These persons more often originated from countries with low TB incidence.[91]

The results from this analysis support current TB prevention guidelines for clinicians by quantifying the extent to which persons of different ages from countries with different levels of TB disease incidence are impacted by TBI. The *Canadian TB Standards* recommend screening and treating patients from moderate- to high-incidence countries ≤ 65 years of age at immigration[9] as they tend to be at higher risk for TB disease, but at lower risk for treatment toxicity with the current rifamycin-based regimens than those over 65.[10,11] This has implications for the development of TBI screening and treatment programs. The probability of a person having TBI and the risk of adverse events with treatment are significant drivers of the yield, safety, and cost-effectiveness of screening and treatment programs.[11,18,19,42,92] Decades ago, for persons without other medical risk factors for progression, tuberculosis preventive treatment with isoniazid was typically prioritized for those < 35 years of age due to increased toxicity of this antibiotic in middle-aged and older adults.[93,94] This analysis has shown that prevalence is lower in younger adults, and especially children and adolescents < 15 years of age, indicating that focusing screening on younger persons may not have significant public health impact. With the development of newer rifamycin-based preventive treatment regimens, toxicity has been substantially reduced in older adults,[11] who also have higher TBI prevalence. Hence it has become easier for providers and policymakers to balance TBI prevalence, medical co-morbidities, and toxicity risks in older adults.

Indeed, risk of progression to TB disease is another key driver of cost-effectiveness for TB prevention programs. Persons at highest risk for progression include those with certain medical comorbidities—conditions that require immunosuppressant therapies, chronic kidney disease (CKD), and some cancers—and those who were recently infected.[3,95] Most foreign-born persons are <35 years of age when they immigrate, and thus, most develop medical comorbidities years after immigration, when they are older.[95,96] On the other hand, the subgroup with recent infection typically acquired their infection shortly before immigration and could theoretically benefit the most from screening and treatment shortly before or after arrival. However, the number estimated to be recently infected suggests that 2000 foreign-born persons with TBI would have to be screened to find one person recently infected with TBI and even more to find one person who will progress to TB disease. Reducing the number needed to screen is important for cost-effectiveness, especially considering expected increases in immigration. 272,707 people immigrated in 2016 and the Canadian government plans to increase the number to 450,000 by 2025 and 500,000 by 2050.[97] While the number needed to screen can be reduced by focusing on persons who recently arrived from high-incidence countries, reducing that number further will likely require the development of improved diagnostic tests with a higher predictive value for progression to TB disease. Such biomarkers are the subject of active investigation, though none is yet ready for clinical use.[98–100]

5.2 Strengths and Limitations

Strengths of this analysis include the source data which integrated serial TST survey data from some countries and the revised, country-specific relationship between the ARI and smear-positive TB disease to estimate the ARI more accurately in others. The analysis also accounted explicitly for uncertainty around these country- and time-based infection risk estimates.[2] Despite this uncertainty, the estimates are comparable to those from TST and IGRA surveys previously conducted among foreign-born persons in low-incidence countries. For example, in

countries such as the United States, United Kingdom, and the Netherlands, TBI prevalence ranged from 18-20% during different survey periods from 2001 to 2011. [65–68]

Limitations of this analysis included several underlying assumptions and limited data availability in some cases. The analysis assumed that individuals who acquire TBI remain infected lifelong, but more recent evidence argues that a substantial proportion of individuals may self-clear.[47,88] If self-clearance occurs, then this analysis will likely have overestimated TBI prevalence among older migrants who have spent more time in Canada. However, this limitation is common to any analysis built around TST or IGRA results, as evidence suggests that immunoreactivity does not wane until years after infection—if at all.[46] Second, the ARI during any particular year for all migrants from a given country, age, and year of migration was assumed to be constant; however, TB transmission can be heterogeneous within countries, and socioeconomic factors such as occupation, housing, income, and general population health influence transmission.[4,90,101] This is reflected in the fact that refugees have higher TB risks than other migrants from the same countries.[102]

Given the lack of data to estimate ARI from 2016 to 2021, the impact of the COVID-19 pandemic could not be addressed. It seems likely that TBI prevalence will increase among persons from high-incidence countries, as TB disease incidence increased during the pandemic.[1] However, between 2020 and 2021, there were tremendous fluctuations in the number of immigrants arriving in Canada,[32,103] which could impact overall TBI prevalence.

Reliable TB disease incidence data were unavailable prior to 2000, so TB disease incidence data in countries of origin could not be matched with migrants' specific years of immigration. Therefore 2016 country-level TB disease incidence estimates from WHO were used. Because TB disease incidence had gradually declined over time in many countries, TBI prevalence estimates

stratified by 2016 TB disease incidence in country of origin in some cases include persons from countries that previously had higher TB disease incidence. This does not change the overall findings but leads to higher prevalence estimates than might otherwise be anticipated for older persons in some of the lower incidence country of origin strata.

In 2018 people who were neither permanent residents nor Canadian citizens accounted for 45 % of the TB disease burden.[7] However, census classifications specific to temporary workers, visitors, and students were unavailable, so these groups could not be examined further. Risk of TB disease has also been shown to vary depending on immigration class[90]—business, skilled worker, caregiver, refugee—but this level of detail was also unavailable from the census. Lastly, sex-specific ARI estimates were unavailable, and thus, TBI prevalence could not be estimated by sex. Such estimates could be relevant to prevention efforts as (depending on the specific year) men are diagnosed with TB disease 1.1 to 1.4 times more often than women, reflecting many factors, including health behaviors.[7]

Lastly, a recent review[54] suggested that ARI estimates for high-incidence countries may be underestimated five- to ten-fold due to the limitations of TST and IGRA sensitivity as well as the use of diagnostic surveys among children, who typically face a lower risk of TB transmission. Based on their analysis, the proportion of persons with true "biologic" TBI who were recently infected has been underestimated, which could have substantial implications for screening programs.

5.3 Future Directions for Research

This analysis examined TBI prevalence among foreign-born Canadians, to better support the development of TB prevention strategies that could bring Canada closer to TB elimination. I hypothesize that the public health impact of TB prevention programs can be improved by balancing the screening and treatment of groups with higher prevalence of TBI, higher risk of progression to TB disease, lower risk of adverse events from treatment, and reducing barriers

to treatment for foreign-born persons. In a future cost-effectiveness analysis, the TBI prevalence estimates from this analysis and existing data will become inputs for a dynamic cohort model designed to evaluate this hypothesis. The model will be used to formally evaluate the impact of screening different subgroups (e.g., by age and time since immigration) and explore how culturally competent screening and treatment support and newer, safer TPT regimens impact the yield and cost-effectiveness of preventive programs.

The TBI prevalence estimates can also inform TBI screening and treatment efforts in other important ways. First, these estimates could be incorporated into a clinical risk calculator estimating the pre-test probability of TBI. This calculator could complement current risk calculators, which focus on the risk of TB disease based on TST and IGRA results (TSTin3D, PERISKOPE-TB) without considering which groups are most likely to have TBI in the first place. Second, estimating TBI prevalence among those with comorbidities could not be done with this analysis, but the TBI prevalence estimates could likely be incorporated into models that provide this information. Persons with TBI who have not been screened or treated in the past are still likely to progress to TB disease if, years after immigration, they acquire diseases such as HIV infection, chronic kidney disease, certain cancers, or conditions that require immunosuppressive therapy.[9] Thus, estimating TBI prevalence among those with comorbidities could be useful to clinical decision-making. These data could also inform routine immigration screening if the proportion of those with comorbidities who have been infected during the period just before immigration can be estimated. Although having comorbidities such as cancer during immigration is generally less common[104] prior data suggest that specific subgroups such as persons from Southeast Asia and Latin America are more likely to have diabetes, a key precursor to CKD.[96] Third, TST and IGRA tests are imperfect and have a poor predictive value for progression from TBI to TB disease.[9] TBI prevalence estimates could be used to evaluate hypothetical new diagnostic tests and determine what test properties would be necessary to improve targeted screening and treatment programs substantially.

The development of improved screening and treatment programs and guidelines directed toward foreign-born persons with TBI may help prevent progression to TB disease among migrants, but eliminating TB in Canada's foreign-born will also require reductions in TBI more broadly. This can only be achieved by reducing TB transmission in other countries .[105] Future modeling work can quantify the potential impact of reducing downstream TBI prevalence among foreign-born persons in Canada via improved TB prevention and care abroad. It can also forecast the time lag before Canada begins to experience reductions in TB disease that result from such decreases in TBI prevalence among arriving migrants.

6 CONCLUSION

Between 2001 and 2016, an estimated one-quarter of foreign-born Canadian citizens and permanent residents had TB infection, but only a small minority were recently infected. Prevalence increased with incidence in country of origin and older age at immigration but was generally similar across provinces. In line with existing recommendations, these data suggest that young and middle-aged adults from high-incidence countries and people who immigrated recently should likely be considered for screening and TPT. However, careful consideration regarding treatment toxicity should be made for the oldest adults. Lastly, results highlight the need for new diagnostic tools with greater predictive value for progression to TB disease, which would allow providers to focus TPT on the smaller group most likely to progress without it. These results serve to inform clinical and policy-level decision-making and, in turn, TB elimination efforts.

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