Demographic predictors of active tuberculosis in people migrating to British Columbia, Canada: a retrospective cohort study

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ABSTRACT

BACKGROUND: Canadian tuberculosis (TB) guidelines recommend targeting postlanding screening for and treatment of latent tuberculosis infection (LTBI) in people migrating to Canada who are at increased risk for TB reactivation. Our objectives were to calculate robust longitudinal estimates of TB incidence in a cohort of people migrating to British Columbia, Canada, over a 29-year period, and to identify groups at highest risk of developing TB based on demographic characteristics at time of landing.

METHODS: We included all individuals (n = 1 080 908) who became permanent residents of Canada between Jan. 1, 1985, and Dec. 31, 2012, and were resident in BC at any time between 1985 and 2013. Multiple administrative databases were linked to the provincial TB registry. We used recursive partitioning models to identify populations with high TB yield.

RESULTS: Active TB was diagnosed in 2814 individuals (incidence rate 24.2/100 000 person-years). Demographic factors (live-in caregiver, family, refugee immigration classes; higher TB incidence in country of birth; and older age) were strong predictors of TB incidence in BC, with elevated rates continuing many years after entry into the cohort. Recursive partitioning identified refugees 18–64 years of age from countries with a TB incidence greater than 224/100 000 population as a high-yield group, with 1% developing TB within the first 10 years.

INTERPRETATION: These findings support recommendations in Canadian guidelines to target postlanding screening for and treatment of LTBI in adult refugees from high-incidence countries. Because high-yield populations can be identified at entry via demographic data, screening at this point may be practical and high-impact, particularly if the LTBI care cascade can be optimized.

As tuberculosis (TB) transmission declines in regions of low TB incidence, TB is becoming concentrated in migrant populations.[1] In Canada, a country with low TB incidence, most cases of TB (about 70%) are diagnosed in people born outside of Canada, with many arriving from countries with a high TB incidence.[2]

Preimmigration medical screening is a cornerstone of TB prevention in Canada. Prospective permanent residents and temporary residents who will be staying in Canada for more than 6 months undergo a preimmigration medical examination that includes a history, physical examination and chest radiograph, and when indicated by radiograph abnormalities, sputum samples for smear and culture. Applicants with a diagnosis of active TB must receive treatment before they can obtain residency status.[2] Postimmigration surveillance of select individuals is also conducted, whereby people considered to be at high risk for TB (i.e., evidence of prior TB or abnormalities present on chest radiographs) are highlighted for follow-up surveillance by public health authorities in Canada.[2] However, a recent study found that less than 3% of active cases of TB in people migrating to Canada were detected by postimmigration surveillance.[3] Currently, no routine pre- or postimmigration screening and treatment programs for latent TB infection (LTBI) for people migrating to Canada are available.[2]

Scale-up of LTBI screening and treatment in high-risk populations postimmigration is a component strategy for achieving World Health Organization (WHO) targets for TB elimination in Canada.[4,5] However, with about 250 000 new permanent residents migrating to Canada annually, the large population of people who may qualify for LTBI screening and treatment is a substantial barrier to implementation.[6] National guidelines recommend targeting screening for LTBI in people migrating from high-incidence countries, particularly in adult refugees up to 50 years of age and those with other risk factors for increased TB reactivation.[2,4] However, many of these recommendations are based on weak evidence.[2] A

better understanding of who is at highest risk for active TB after immigration to Canada is needed.

Our objectives were to calculate robust longitudinal estimates of TB incidence in people migrating to British Columbia, Canada, over a 29-year period, and to identify groups at highest risk of TB based on demographic characteristics at the time of immigration.

Methods

Study population and data sources

This study is part of a larger project to describe risk factors for TB among people migrating to BC. The study setting, cohort, databases and linkage methods have been described previously.[7] Briefly, we derived our data from a permanent linkage between the Permanent Resident database (Immigration, Refugees and Citizenship Canada) and Population Data BC, a multiuniversity resource with a large collection of health services data.[8] For this analysis, we extracted data on demographics from the Permanent Resident database and the provincial Medical Services Plan (MSP), MSP registration dates, deaths from Vital Statistics records and TB testing from the provincial TB registry.[9–15] Data were linked using unique scrambled identification numbers.[16] Use of similar methods to link the Immigration, Refugees and Citizenship Canada database with Ontario health administrative databases has been found to have high linkage accuracy.[17]

We included all permanent residents landing in Canada between Jan. 1, 1985, and Dec. 31, 2012, and establishing residency in BC at any point between Jan. 1, 1985, and Dec. 31, 2013, in the cohort. We defined landing as the first date when an individual entered Canada with their permanent resident visa. Individuals were identified as resident in BC when they registered for MSP, the universal health insurance program administered by the government of BC. Enrolment in MSP is mandatory for all eligible BC residents and their dependents, and has a monthly fee; therefore, we considered MSP coverage a good proxy measure for residence in BC.

We started calculation of follow-up time at each individual's index date, which we defined as 90 days before the date of MSP registration. We censored follow-up at the earliest of first active TB diagnosis, end of MSP coverage, time of death or end of study (Dec. 31, 2013). Diagnosis of TB was based on data from the TB registry, and included all TB sites that were confirmed microbiologically or clinically.

Demographic risk factors

We included the following variables: age at index date, year of index date, gender, country of birth, incidence of TB in the country of birth and immigration class. We derived incidence rates of TB in the country of birth from annual country-level WHO data for incidence of TB (all forms of TB/100 000 population).[18] We further grouped incidence based on Canadian TB standards cut-points, where countries with a high TB incidence are classified as those with an incidence greater than 30/100 000 population.[19] We categorized immigration classes based on categories from Immigration, Refugees and Citizenship Canada:[20] family, refugee, other, and 3 types of economic immigration classes (business, skilled workers and live-in caregivers). Live-in caregivers are a specific skilled-worker stream that has been reported to have significantly higher TB incidence in Canada compared with other immigration classes.[3] All economic class applicants are able to sponsor themselves and their dependents within these immigration streams.

Statistical analysis

As a primary outcome, we calculated active TB incidence as the number of TB cases per 100 000 person-years at risk, with 95% confidence intervals (CIs) based on a Poisson distribution. We accounted for lapses in MSP registration by excluding lapsed periods from the person-years denominator.

We stratified outcomes by demographic characteristics and by elapsed time since index date. To describe the relation between TB incidence rates as a smooth function of the number of years since index date, we used a generalized additive model with a cubic regression spline for time. Because of variability in rates of TB incidence when denominators for person-years were small, we limited plots of rates of TB incidence to the first 20 years after the index date.

We also used recursive partitioning to help identify population groups with high TB incidence in the first 10 years after landing. Recursive partitioning is a data-driven method for multivariable analysis that can handle complex interactions among predictor variables, and predictor variables that may have a nonlinear association with the outcome.[21,22] For predictors, we included demographic variables identifiable at the time of immigration: age, gender, immigration class and incidence of TB in the country of birth. We focused our primary analysis on 10-year outcomes (because most cases of TB occurred within the first 10 years) that were limited to participants less than 65 years of age (because treatment for LTBI is not likely to be offered to people 65 yr of age or older) and who had an index year before 2004 (to allow for 10 yr of follow-up for each person). We visualized the results by plotting the 10-year Kaplan–Meier survival curves that were evaluated for each identified population group (i.e., the terminal nodes of the tree). As a sensitivity analysis, we ran a logistic regression model using categories and interactions identified by recursive partitioning, with little substantive change in results.

All analyses were conducted in R (version 3.2.5; The R Project for Statistical Computing), with 95% CIs that were calculated using the epitools package (version 0.5–7). Graphs were produced using the R ggplot2 (version 2.1.0) and survminer packages (version 0.2.4). Classification trees were constructed using the rpart (version 4.1–10) and rpart.plot (version 1.5.3) packages.

Ethics approval

This study received ethical approval from the Clinical Research Ethics Board of the University of British Columbia (H16–00265).

Results

Cohort characteristics

We included 1 080 908 individuals in the cohort (Table 1). Participants were followed for a median of 10 years (interquartile range

[IQR] 5–17 yr), with a total follow-up of 11.6 million person-years (Appendix 1, supplemental Figure 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170817/-/DC1).

The median age of the cohort population was 30 years (IQR 19–41 yr) at index date. Almost half of the individuals migrated through the skilled worker stream (41%); refugees accounted for

Table 1: Characteristics of people in the study cohort at index date, and incidence rates of tuberculosis during study follow-up

Characteristic	No. of people in the cohort (%) *n* = 1 080 908	No. of person-years (1000s) *n* = 11 640	No. of cases of TB in BC* *n* = 2814	No. of cases of TB/ 100 000 person-years (95% CI)
All				24.2 (23.3–25.1)
Age group, yr				
0–4	45 998 (4.3)	520	22	4.2 (2.7–6.4)
5–14	152 560 (14.1)	1756	129	7.3 (6.1–8.7)
15–34	453 538 (42.0)	4858	1132	23.3 (22.0–24.7)
35–54	327 781 (30.3)	3434	743	21.6 (20.1–23.2)
55–64	59 256 (5.5)	669	419	62.6 (56.8–68.9)
≥ 65	41 775 (3.9)	403	369	91.6 (82.5–101.4)
Sex				
Female	553 976 (51.3)	6071	1391	22.9 (21.7–24.1)
Male	526 932 (48.8)	5569	1423	25.6 (24.2–26.9)
Immigration class				
Business†	168 357 (15.6)	1915	240	12.5 (11.0–14.2)
Skilled worker†	440 778 (40.8)	4295	573	13.3 (12.3–14.5)
Live-in caregiver†	28 640 (2.7)	278	129	46.4 (38.7–55.1)
Refugee‡	86 803 (8.0)	1069	362	33.9 (30.5–37.5)
Family	326 106 (30.2)	3723	1387	37.3 (35.3–39.3)
Other§	30 224 (2.8)	359	123	34.3 (28.5– 40.9)
WHO Region of birth¶				
Southeast Asia	153 061 (14.2)	1631	698	42.8 (39.7–46.1)
Africa	31 161 (2.9)	320	101	31.6 (25.7–38.4)
Western Pacific	586 669 (54.3)	6476	1773	27.4 (26.1–28.7)
Eastern Mediterranean	84 057 (7.8)	778	134	17.2 (14.4–20.4)
The Americas	80 297 (7.4)	839	49	5.8 (4.3–7.7)
Europe	145 661 (13.5)	1595	59	3.7 (2.8–4.8)
TB rate in country of birth**				
0–30 cases/100 000 population	186 165 (17.2)	1733	37	2.1 (1.5–2.9)
31–100 cases/100 000 population	278 081 (25.7)	2582	249	9.6 (8.5–10.9)
101–200 cases/100 000 population	340 901 (31.5)	4067	952	23.4 (21.9–24.9)
> 200 cases/100 000 population	275 759 (25.5)	3257	1576	48.4 (46.0–50.8)
Index year				
1985–1994	299 501 (27.7)	5051	1386	27.4 (26.0–28.9)
1995–2004	443 941 (41.1)	5032	1084	21.5 (20.3–22.9)
2005–2013	337 466 (31.2)	1556	344	22.1 (19.8–24.6)

Note: BC = British Columbia, CI = confidence interval, TB = tuberculosis. Missing data: country of birth (*n* = 2).
*Includes respiratory (70%) and nonrespiratory (30%) TB sites.
†Economic immigration classes include both principal applicants and their dependents.
‡Includes government-assisted (46%), privately sponsored (26%), asylum (22%) and dependents abroad (6%).
§Includes retirees (57%), deferred removal orders and postdetermination refugee claimants in Canada (7%), permit holders applying for permanent residence (3%), and humanitarian and compassionate cases (36%).
¶Countries/territories in each WHO Health Region (based on most person-time spent in BC): Southeast Asia (India, Sri Lanka, Indonesia), Africa (South Africa, Kenya, Ethiopia), Western Pacific (China, Hong Kong, Philippines), Eastern Mediterranean (Iran, Pakistan, Afghanistan), Americas (United States, El Salvador, Mexico), Europe (United Kingdom and colonies, Poland, Germany) (Appendix 1, supplemental Table 1 [available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170817/-/DC1] provides a more extensive list).
**Values are World Health Organization estimates for an individual's year of index = number of TB cases (all forms)/100 000 population.

8% of the cohort population. Over half of the cohort population was born in the Western Pacific Region; 3 major source areas were China (including Taiwan, Hong Kong and Macao [34%]), India (12%) and Philippines (9%). Most people (83%) originated from high TB-incidence countries (i.e., incidence > 30/100 000 population, with 26% originating from countries with incidence > 200/100 000 population [Table 1]). The proportion of individuals migrating from countries with a TB incidence greater than 30/100 000 population peaked in 1994 (Figure 1). The proportion of skilled workers increased (22.4% during index years 1985–1994 v. 46.7% during index years 2005–2013) and the proportion of refugees decreased (11.7% v. 5.5%) across the 29-year study period (data not shown).

Tuberculosis outcomes

Active TB was diagnosed in 2814 people, for an incidence rate of 24.2/100 000 person-years over the study period (Table 1). Most cases (71%) were diagnosed in the first 10 years after the index date; rates of TB incidence declined sharply over the first 5 years and remained relatively stable after 10 years (Figure 2A).

Incidence of TB increased with older age at index date (Table 1), with the highest rates in individuals 65 years of age or older (91.6/100 000 person-years, 95% CI 82.5–101.4). Tuberculosis incidence was highest among the following classes: live-in caregiver (46.4/100 000 person-years, 95% CI 38.7–55.1), family (37.3/100 000 person-years, 95% CI 35.3–39.3) and refugee (33.9/100 000 person-years, 95% CI 30.5–37.5). Tuberculosis incidence rates increased in a dose–response manner with increasing TB incidence in the country of birth, whereby rates among individuals with a birth-country TB incidence of more than 200/100 000 population (48.4/100 000 person-years, 95% CI 46.0–50.8) were more than 21 times higher than those born in a country with a TB incidence of 0–30/100 000 population, (2.1/100 000 person-years, 95% CI 1.5–2.9). These patterns were observed over elapsed time since index date (Figure 2B, Figure 2C and Figure 2D) and across immigration time periods (data not shown).

Our analyses using recursive partitioning suggested 21 groups at risk of TB based on demographic characteristics (Appendix 1, supplementary Table 2). Kaplan–Meier curves for 10-year survival (Figure 3) for these groups showed that adult refugees who migrated from countries with a TB incidence of more than 224/100 000 population were among the most likely to be diagnosed with active TB, with about 1% developing TB within 10 years after the index date. At a TB incidence threshold of more than 224/100 000 population, about 0.7% of people aged 18–64 years in the family, live-in caregiver and other immigration classes developed TB within 10 years (Figure 3). Among individuals migrating within any immigration class from countries with a TB incidence of 132/100 000 population or less (Appendix 1, supplemental Table 2), the yield of TB cases was low (< 0.1% of 423 193 individuals (n = 396) developed TB within 10 yr).

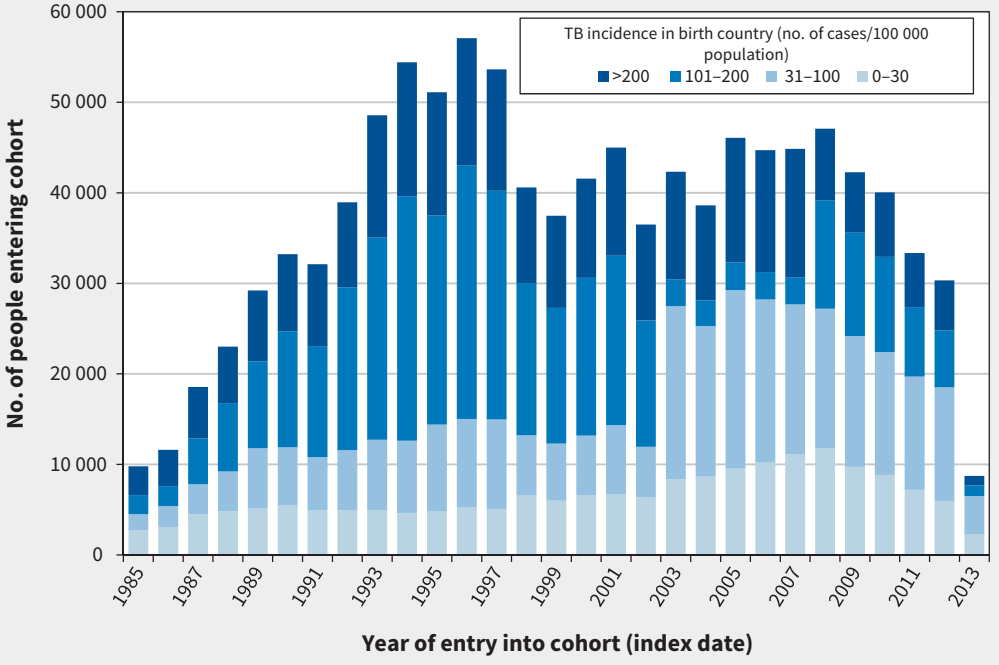

Figure 1: Number of people entering the study cohort each year from 1985 to 2013, stratified by the WHO-estimated TB incidence in the country of birth (n = 1 080 908). Note: TB = tuberculosis, WHO = World Health Organization.

Interpretation

Our cohort represents a near-complete capture of data for demographic characteristics, immigration and health service utilization for more than a million people migrating to BC over a 29-year period. Our study adds to the understanding of long-term TB incidence in migrant populations in Canada by showing that rates remain elevated up to 2 decades after migration. Demographic factors (i.e., live-in caregiver, family and refugee immigration classes; higher TB incidence in country of birth; and older age) were strong predictors of TB incidence in BC, with the differential rates observed across demographic factors continuing for many years after arrival. Refugees aged 18–64 years from countries with a TB incidence of more than 224/100 000 population had the highest TB yield.

Our findings parallel studies estimating person-years in calculations of TB rates.[23–26] For example, in a large study in the United States the rates remained elevated up to 19 years after arrival.[24]

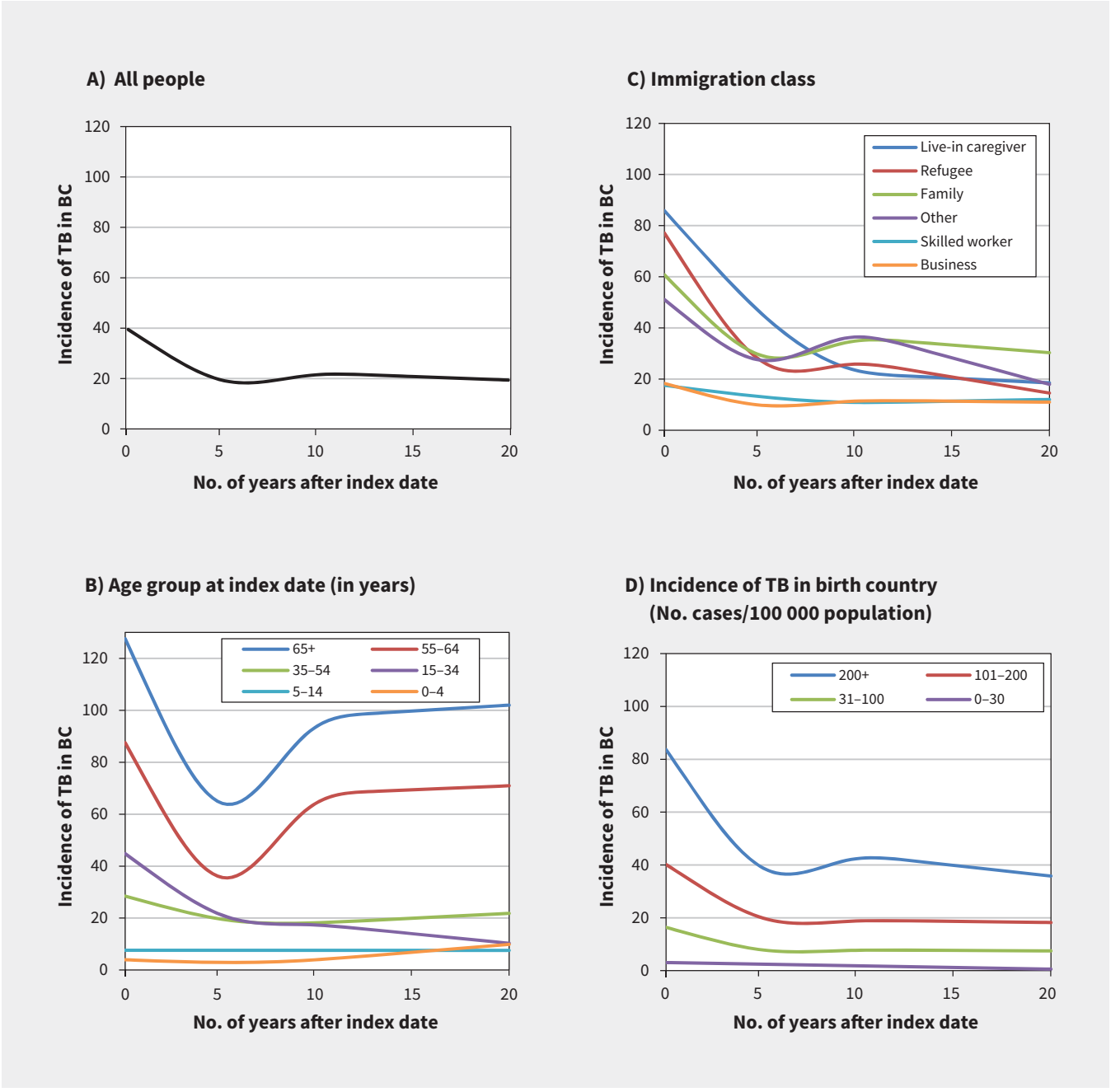

Figure 2: Incidence of TB among migrants in BC (no. of cases/100 000 person-years at risk), stratified by the number of years since index date and demographic characteristics. (A) All participants, (B) age group, (C) immigration class and (D) incidence of TB in the country of birth. Rates of TB incidence (no. of TB cases/100 000 person-years) modelled as a smooth function of the number of years since index date using generalized additive models, with time represented as a cubic regression spline (degrees of freedom = 4) with knots set to the 30th, 50th, 70th and 90th percentiles of time (in accumulated person-years). Note: BC = British Columbia, TB = tuberculosis.

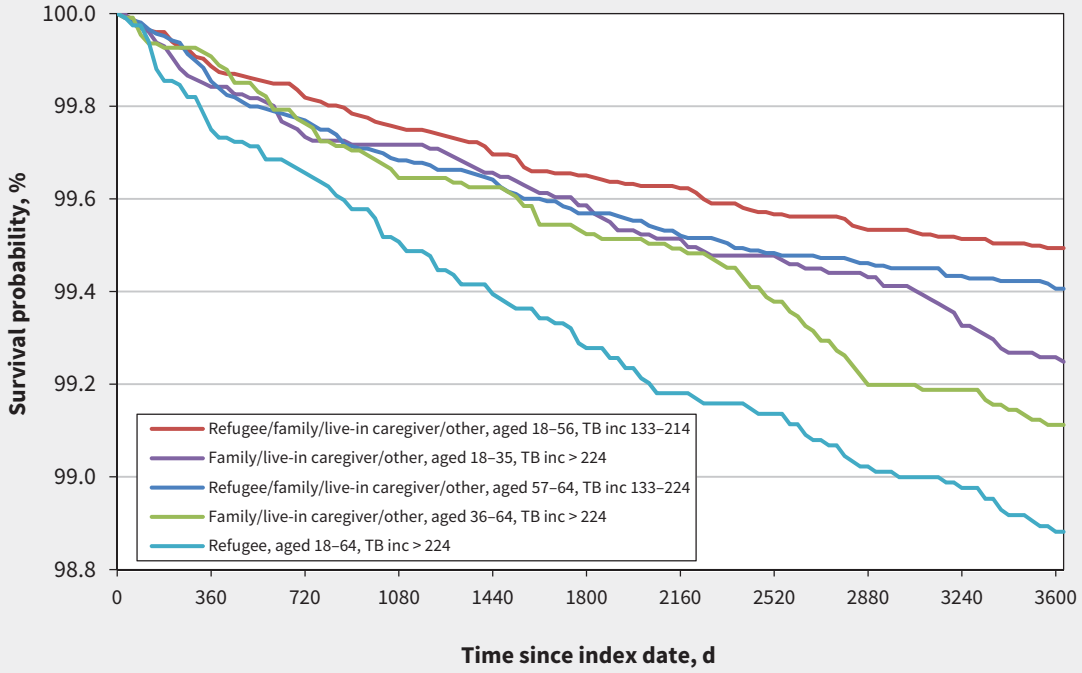

Figure 3: Kaplan–Meier curves of 10-year TB outcomes within population subgroups identified by recursive partitioning models (plot shows the groups with highest TB yield). Analysis included participants with index years from 1985 to 2003 and aged less than 65 years at index date (n = 676 294). Note: inc = World Health Organization estimate for TB incidence in country of birth in index year (no. of TB cases [all forms]/100 000 population), TB = tuberculosis.

Our finding that refugee and live-in caregiver classes had some of the highest TB rates among people migrating to BC complements previous Canadian findings.[3] Our study further adds to this recent cohort study reporting 2-year TB incidence among people migrating to Ontario[3] by including a longer follow-up time to assess TB incidence rates across years since immigration, by using MSP records to estimate time spent in province, by including a more detailed breakdown of immigration classes and by using recursive partitioning methods to determine the groups at highest risk of TB after immigration.

Limitations

The Immigration, Refugees and Citizenship Canada database includes only individuals who have received permanent landing status. Therefore, this study necessarily excluded temporary visitors and workers, some refugee applicants and undocumented migrants. Although temporary migrants account for a large proportion of people entering Canada,[2] it is unlikely that the epidemiologic patterns we observed would differ markedly between temporary versus permanent migrant populations. Second, it is possible that lapsed MSP coverage may not be a good proxy for leaving the province, and thus we may have estimated time spent in BC incorrectly. However, we found that TB rates were markedly lower during break periods for MSP coverage compared with nonbreak periods, which supports our assumption that participants were not in BC during these periods. In addition, we could not identify travel to a high-incidence country or family clusters; if new infections were acquired after immigration, the public health impact of LTBI screening at time of immigration may be overestimated. As well, the small number of deaths not related to TB (compared with TB cases diagnosed pre- or postmortem) suggests the potential for bias due to competing risks is negligible. Finally, as is typical with health administrative database studies, misclassification because of inaccurate health administrative data is possible.

Implications and knowledge gaps

Identifying higher-risk groups based on demographic factors at time of immigration is a first step toward improving LTBI screening and treatment programs for people migrating to Canada. Our results support recommendations to target postlanding LTBI screening and treatment to adult refugees originating from countries with a high TB incidence.[2,4,27] Although the public health impact may not be high given the relatively small population, LTBI screening of adult refugees from countries with a high TB incidence should be a feasible first step to implement (e.g., in BC, this represents up to an estimated 600 people annually). Many WHO European-region countries screen for both TB and LTBI in refugee centres.[28] In Canada, refugees who are assisted by the government are placed in a reception house until

permanent housing can be located; during this period, refugees receive a medical evaluation, which could provide an opportunity for LTBI screening.[29] High rates of LTBI screening and treatment completion have also been reported in a Canadian refugee clinic.[29] Notably, Canadian guidelines for TB recommend LTBI screening for refugees up to age 50 years and to age 65 years when sufficient monitoring for drug-related adverse events can be ensured.[4]

We did not investigate adverse events related to LTBI treatment; however, based on TB rates, our results support screening some groups up to the age of 65 years. As well, given the generally low rates of TB among people migrating from countries with a TB incidence below 132/100 000 population, this suggests a higher threshold for targeting LTBI screening and treatment programs in Canada, in particular when other medical risk factors are not present.

Provision of screening and treatment for LTBI among people who are migrating as domestic caregivers from countries with a high TB incidence may also be suggested, given consistent findings of higher TB rates after migration to Canada. Live-in caregivers to Canada migrate predominantly from settings with a high TB incidence[30] and often work in health care–related professions before immigration,[31] where TB exposure may be higher than in the general population.[32]

To achieve WHO elimination targets for Canada, other high-risk groups also need to be identified. Evaluation of TB risk associated with immune-suppressive comorbidities in this cohort is an important next research step. Evaluation of the cost-effectiveness of different LTBI programs is also needed. Although a number of studies from low-incidence countries suggest that LTBI screening in migrants from high-incidence countries is cost-effective,[5,33–35] there remains uncertainty about optimal thresholds for screening.[36] In addition, more research is needed to optimize the LTBI care cascade, because the impact of screening will be limited if treatment completion is poor.[37] For example, a recent systematic review suggested that fewer than one-fifth of people successfully completed LTBI screening and treatment programs.[38] Finally, more research is needed to understand TB-related outcomes and barriers to accessing health care among vulnerable migrant populations.[39,40]

Conclusion

With high-yield populations easily identified via demographic data, LTBI screening and treatment at entry may be practical and potentially high-impact, particularly if the LTBI care cascade can be optimized. Using demographic data alone, we found that adult refugees from countries with a high TB incidence had the highest rates of TB incidence within the first 10 years of cohort entry. Screening this vulnerable group may be a practical first step toward more comprehensive LTBI screening in migrant populations arriving in Canada.

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