Effectiveness of Canada's tuberculosis surveillance strategy in identifying immigrants at risk of developing and transmitting tuberculosis: a population-based retrospective cohort study

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Summary

Background In Canada, tuberculosis disproportionately affects the foreign-born population. The national tuberculosis medical surveillance programme aims to prevent these cases. Individuals referred for further in-country surveillance (referrals) have a history of active tuberculosis or have features of old, healed tuberculosis on chest radiograph; those not referred (non-referrals) do not undergo surveillance. We aimed to examine the risk of transmission arising from referrals versus non-referrals.

Methods We did this population-based retrospective cohort study of foreign-born migrants (aged 15–64 years) to Alberta, Canada, between Jan 1, 2002, and Dec 31, 2013. We obtained information about year of arrival and country of citizenship from Immigration, Refugees and Citizenship Canada, and data for tuberculosis cases and their contacts from the Alberta Tuberculosis Registry. The outcome of interest was culture-positive pulmonary tuberculosis. We compared the incidence of pulmonary tuberculosis and the odds of transmission among referrals versus non-referrals. By use of conventional and molecular epidemiological techniques, we defined transmission as either a secondary case or a tuberculin skin-test (TST) conversion among close contacts. We used multivariate logistic regression to determine the independent association between referral for tuberculosis surveillance and transmission.

Findings Between 2002 and 2013, there were 223 225 foreign-born migrants to Alberta, of whom 5500 (2%) were referrals and 217 657 (98%) were non-referrals. 3805 (69%) referrals and 115 226 (53%) non-referrals were from countries with a tuberculosis incidence of more than 150 per 100 000 populations, or sub-Saharan Africa. 234 foreign-born individuals were diagnosed with culture-positive pulmonary tuberculosis between Jan 1, 2004, and Dec 31, 2013. The incidence of culture-positive pulmonary disease was nine times higher in referrals (n=50) than all non-referrals (n=184; incidence rate ratio 9·1, 95% CI 6·7–12·5) and five times higher in referrals than non-referrals from high-risk countries (n=167; 5·0, 3·6–6·8). 71 total transmission events arose from the individuals with culture-positive pulmonary tuberculosis—three (4%) from referrals and 68 (96%) from non-referrals. No secondary cases were attributable to a referral source case, whereas 18 secondary cases were attributable to 11 different non-referral source cases. Three TST conversions were attributable to three different referral source cases compared with 50 conversions from 31 different non-referral source cases. That is, three (6%) referrals transmitted tuberculosis compared with 42 (22%) non-referrals (adjusted odds ratio of 0·19, 95% CI 0·054–0·66; p=0·009).

Interpretation Despite a much higher incidence of pulmonary tuberculosis in referrals than non-referrals, referrals were 80% less likely to transmit tuberculosis. Rather than a focus on referrals, Canada could consider screening and treatment of latent tuberculosis in all migrants from high-risk countries—a group that accounted for 100% of secondary cases.

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Introduction

Canada is a low tuberculosis-incidence country where rates have slowly decreased or plateaued over time. Nevertheless, tuberculosis disproportionately affects the foreign-born population, with an incidence in 2014 that was 23 times higher than that in the Canadian-born, non-Indigenous population.[1] In the province of Alberta, tuberculosis cases amomg the foreign-born population accounted for roughly 90% of incident cases in 2015 (unpublished). This proportion is alarming because when the proportion of cases in foreign-born individuals exceeds 70%, standard tuberculosis control programming is unlikely to achieve more than a 2% decrease in annual tuberculosis rates.[2] Such a rate of decline would preclude Canada from achieving its elimination targets.

Tuberculosis elimination efforts for the foreign-born population in Canada occur within the context of the tuberculosis medical surveillance programme. All permanent residents and some temporary residents undergo an immigration medical examination before

Research in context

Evidence before this study

Publication of WHO's framework towards tuberculosis elimination in low-incidence countries combined with the imperative of enhanced research into migrant health—resulting from unprecedented mass displacements—has fuelled interest in tuberculosis screening strategies. To gather evidence on the latest tuberculosis control and surveillance strategies used in low-incidence settings, we searched PubMed between December, 2015, and February, 2017, with two-term keywords "tuberculosis" and "migrant" and "immigrant" and "foreign born", and separately combined the two-term searches with "low incidence". In Canada's tuberculosis surveillance system, individuals identified as being high risk during pre-immigration screening and subsequently referred for further post-immigration surveillance are more likely to develop active tuberculosis than are those not referred. Furthermore, both nationally and internationally, immigrants from countries with a high incidence of tuberculosis are likewise at increased risk for a post-immigration tuberculosis diagnosis. The relatively small proportion of post-immigration transmissions arising from migrants has been shown consistently. However, investigators of only one other study have reported on the effect of a post-immigration surveillance programme on transmission in their country (the Netherlands).

Added value of this study

To our knowledge, this is the first study to use both conventional epidemiological techniques (contact tracing) and molecular epidemiological data to systematically examine the risk of transmission arising from individuals referred for further in-country surveillance (referrals) compared with those not referred (non-referrals). We found that referrals were less likely to transmit disease and noted that all (transmitted) secondary cases were attributable to non-referrals from high-risk countries, defined as countries with a tuberculosis incidence of more than 150 per 100 000 population, or sub-Saharan Africa. Our findings also showed that referrals were less likely to have smear-positive and cavitary disease, pointing to the more infectious nature of the disease in non-referrals.

Implications of all the available evidence

When the Canadian tuberculosis surveillance programme identifies an individual as high risk for active tuberculosis, they are indeed at increased risk of a post-immigration diagnosis of tuberculosis. By contrast, these individuals have a much lower risk of transmitting tuberculosis than do non-referrals. Either the surveillance programme is effective at diagnosing disease earlier, and earlier diagnosis leads to reduced risk of transmission, or we have identified individuals whose disease phenotype was, from the outset, at a lower risk of transmission. This alternate hypothesis should be explored with further research. Given that the main aim of tuberculosis public health programmes is prevention of transmission, expansion of latent tuberculosis testing to individuals most likely to result in post-immigration transmissions—ie, migrants from high-risk countries—should be considered.

arrival. This examination consists of a medical history, physical examination, mental examination, and four age-related routine tests: urinalysis, chest radiograph, syphilis serology, and HIV serology. If there is radiographic evidence of tuberculosis, three sputum mycobacterial smears (and cultures) are obtained. Applicants with active tuberculosis must complete treatment before entering Canada. Applicants with inactive or old, healed pulmonary tuberculosis on chest radiograph, or a history of tuberculosis, are referred by Immigration, Refugees and Citizenship Canada (IRCC) to provincial or territorial public health authorities for a tuberculosis surveillance medical evaluation.[3] These referrals are to report to a public health authority within 30 days of arrival. Non-referrals have no in-country surveillance. The steps undertaken by each local public health authority vary. In general, the surveillance medical evaluation begins with an assessment for active tuberculosis. If active disease is not identified, consideration is given to testing and treatment of latent infection, or annual surveillance with chest radiograph and sputum.

Previous studies[4,5] have shown that referrals are four to five times more likely to have active tuberculosis than are non-referrals. The primary aim of the referral system is to prevent transmission and identify individuals who might pose a public health threat; however, there are no Canadian estimates of the differences in transmission arising from referrals versus non-referrals. International data for the efficacy of in-country surveillance in prevention of transmission are equally sparse.[6] To address these gaps, we first determined the incidence of pulmonary tuberculosis in referrals and non-referrals, and then examined differences in transmission activity. We hypothesised that referrals would be less likely to transmit tuberculosis because of enhanced surveillance and earlier identification, despite being more likely to have active disease.[7,8]

Methods

Setting and datasets

Alberta is a province with a population of 4 108 300 people in 2014,[9] 10% of whom are foreign born.[10] There is a low prevalence of HIV. Tuberculosis incidence in 2014 was 4·7 per 100 0000 population.[1] We used two distinct datasets. The IRCC dataset contains annual, aggregated information about year of arrival and country of citizenship for all foreign-born permanent residents and refugees (excluding refugee claimants) aged 15–64 years who arrived in Alberta between Jan 1, 2002, and Dec 31, 2013. We obtained tuberculosis data from the

Alberta Tuberculosis Registry, extracted from the Integrated Public Health Information System. These data included information about all tuberculosis cases and their contacts in the province.[11]

This study was approved by the Health Research Ethics Board, Panel B, at the University of Alberta. Consent was not obtained because of the retrospective nature of these data. All patient data were anonymised and delinked before analysis.

Tuberculosis incidence

We used the IRCC dataset to determine the total number of foreign-born arrivals to Alberta from Jan 1, 2002, to Dec 31, 2013. The outcome of interest was culture-positive pulmonary tuberculosis and we identified all such cases diagnosed between 2002 and 2013 via the Alberta Tuberculosis Registry. From these data, we calculated crude incidence of culture-positive pulmonary tuberculosis and smear-positive pulmonary disease in Alberta during those 12 years within three groups: referrals, all non-referrals, and non-referrals from high-risk countries. Referrals were individuals who had been referred for tuberculosis surveillance via the immigration medical examination before a diagnosis of active disease. High-risk countries were defined as countries of citizenship with a tuberculosis incidence of more than 150 per 100 000 population, or sub-Saharan Africa. This definition was gleaned from UK tuberculosis programming recommendations for screening of latent infection screening in this subgroup.[12]

Tuberculosis transmission

We applied conventional and molecular epidemiological (DNA fingerprint) techniques to identify transmission events arising from the subgroup diagnosed with culture-positive pulmonary tuberculosis between Jan 1, 2004, and Dec 31, 2013. These patients are variably infectious and constitute potential source cases. In addition to information about whether the potential source case was a tuberculosis surveillance referral, the provincial registry also included demographic, clinical, and laboratory information. Demographic information consisted of age, sex, and immigration status (permanent resident or Canadian citizen; refugee or refugee claimant; or visitor, student, work, or "other" temporary visa). By use of WHO estimates for incidence of active tuberculosis,[13] incidence in the country of origin was considered to be the average incidence of tuberculosis in the year of immigration and the 2 years before immigration. Clinical information included HIV status, active disease type (new *vs* relapse or retreatment), and disease site. We defined disseminated disease as per the Canadian tuberculosis standards.[3] Laboratory information included smear and culture status and radiographic appearance. Treatment outcome describes whether an individual died before or during tuberculosis treatment and if death was related to tuberculosis.

Isolates of *Mycobacterium tuberculosis* from all culture-positive cases of tuberculosis diagnosed in Alberta were routinely DNA fingerprinted by use of standardised restriction fragment-length polymorphism, supplemented in isolates with five or fewer copies of the insertion sequence *6110*, by spoligotyping.[14,15]

We compiled contact lists for each potential source case. Routine contact tracing included the gathering of information about the number, type (close or casual), tuberculin skin test (TST), and disease status of contacts for all pulmonary tuberculosis cases. We defined close contacts as per the Canadian tuberculosis standards.[3] Assessment of close contacts included a symptom inquiry and TST 8–12 weeks after the final contact with the source case (if the contact was not already TST positive), a chest radiograph if symptomatic or TST positive, and sputum for acid-fast bacilli smear and culture if symptomatic or if chest radiograph was abnormal.[16]

Because of the relative infrequency of secondary cases arising from the foreign-born population[17] and the implications for tuberculosis perpetuation, we considered source cases to have resulted in transmission if at least one of their close contacts was found to have a TST conversion or was identified as a secondary case. We examined transmission only among close contacts because the effort that goes into identification and assessment of close contacts in Alberta is consistent across all cases. Additionally, because Alberta uses the stone-in-pond method of contact tracing (ie, the search among contacts for evidence of transmission by examination of close or high-risk contacts before casual or low-risk contacts), if transmission was not identified among close contacts, it would be unlikely that any would be seen among casual or "other" contacts.[18]

We defined TST conversion as a TST of 10 mm or greater when a previous test resulted in a reaction of less than 5 mm. If the previous result was between 5 mm and 9 mm, we deemed conversion to be an increase of 10 mm or more.[3] If interferon gamma release assay (IGRA; typically QuantiFERON-TB Gold) was done and the results were discrepant from the TST, IGRA results were used. Because of the little availability of IGRA during much of the study period, and the Canadian guideline endorsement of TST over IGRA in most cases, there was restricted use of IGRA. Tuberculosis cases were not included as TST converters.

We grouped secondary cases as type 1 or type 2 based on their conventional and molecular epidemiological links to the source case. Our group has previously reported on this method of transmission identification.[19,20] Type 1 secondary cases were individuals who were listed as a contact of the source case, diagnosed with active tuberculosis within a transmission window extending from 6 months to before 24 months after the date of diagnosis of the source case, and culture positive with an isolate of *M tuberculosis* that was a genotypic match to the

fingerprint of the putative source case. Type 2 secondary cases were close contacts of the source case who were diagnosed with active tuberculosis within the 30 month transmission window, but were culture negative (or cultures could not be obtained). All paediatric type 2 pulmonary cases were independently verified by a paediatric pulmonary radiologist specialising in paediatric tuberculosis diagnoses and masked to referral status. Secondary cases diagnosed before the date of diagnosis of the source case were only counted as a transmission event if they had primary disease. We defined the date of diagnosis of the source case as the start date of treatment.

To identify secondary cases, we cross-referenced contact lists against the Alberta Tuberculosis Registry from July 1, 2003, to Dec 31, 2015. Data were linked by use of tuberculosis registry number and name, and were verified by date of birth and country of birth, as necessary. A previously published analysis by our group[21] investigated secondary cases via DNA fingerprint data and spatial matching. In this study, we did not undertake such analysis because there is more uncertainty about the putative source and case linkage, and a difference in transmission between the groups is unlikely if such a difference is not first identified among close contacts.[21]

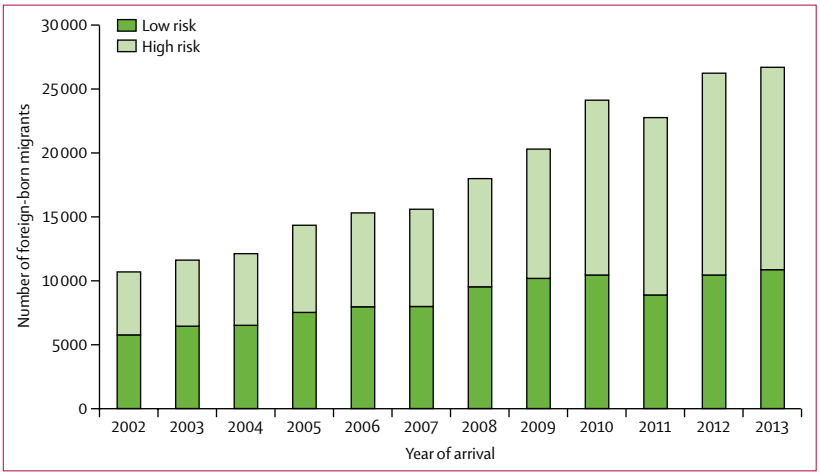

Figure 1: **Foreign-born migrants to Alberta according to tuberculosis risk category**

Statistical analysis

We calculated tuberculosis incidence per 100 000 person-years. Calculation of 95% CIs for rates assumed a Poisson distribution for case counts. We compared rates with incidence rate ratios and 95% CIs.

For transmission, we calculated demographic and clinical characteristics of referrals and non-referrals in addition to their respective findings from contact-tracing investigation. We used multivariate logistic regression to determine the independent association between referral for tuberculosis surveillance and transmission. We adjusted analysis for age, immigration status (permanent resident or citizen *vs* refugee), risk of tuberculosis in country of birth (high risk *vs* lower risk), and number of months in Canada. We did not include clinical or contact characteristics of source cases in our model because we deemed them to be on the causal pathway between tuberculosis surveillance referral and a transmission event.

We did sensitivity analysis assessing three different groups: individuals from high-risk countries, individuals who had been in Canada for 2 years or less, and a more inclusive cohort of temporary and permanent residents. All statistical analyses were done with SAS (version 9.4).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. LA, CH, and RL had full access to the raw data. The corresponding author (LH) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between 2002 and 2013, there were 223 225 foreign-born migrants to Alberta, of whom 5500 (2%) were referrals and 217 657 (98%) were non-referrals. Many referrals (n=3805) and non-referrals (n=115 226) were from high-risk countries. The proportion and absolute number of foreign-born arrivals from high-risk countries increased over time (figure 1). Both referrals and non-referrals were most frequently from the Philippines, India, or China (appendix p 1). The overall incidence of pulmonary tuberculosis for all foreign-born cases was 19 per

See Online for appendix

	Number of individuals	Cases of culture-positive pulmonary tuberculosis	Incidence of culture-positive pulmonary tuberculosis (per 100 000 person-years)	Incidence rate ratio (referrals over non-referrals)	Cases of smear-positive pulmonary tuberculosis	Incidence of smear-positive pulmonary tuberculosis (per 100 000 person-years)	Incidence rate ratio (referrals over non-referrals)
Referrals	5500	50	141 (105–184)	1 (ref)	11	31	1 (ref)
Non-referrals	217 675	184	15 (13–17)	9·1 (6·7–12·5)	103	9	4·0 (1·9–6·7)
Non-referrals from high-risk countries	115 226	167	28 (24–33)	5·0 (3·6–6·8)	93	16	2·0 (1·0–3·7)

Data in parentheses are 95% CIs.

Table 1: **Incidence of culture-positive pulmonary tuberculosis**

100 000 person-years (95% CI 17–22). The highest incidence was among referrals, followed by non-referrals from high-risk countries, and all non-referrals (table 1). Whereas the rate of culture-positive pulmonary tuberculosis was five times higher in referrals than non-referrals from high-risk countries, the rate of smear-positive pulmonary disease was only two times higher (table 1).

234 foreign-born individuals were diagnosed with culture-positive pulmonary tuberculosis between 2004 and 2013 (table 1). There were 50 (21%) referral and 184 (79%) non-referral source cases (table 1). Referrals had been in Canada for a median of 11 months before diagnosis, compared with 33 months in the non-referral group (table 2). 39 (78%) referrals were diagnosed during routine surveillance follow-up. Roughly 90% of individuals in both groups were from a high-risk country (appendix p 2).

Referrals presented with less advanced disease and with characteristics associated with decreased infectivity (table 2). No referrals had disseminated disease compared with nine (5%) non-referrals (table 2). Only three (6%) referrals had cavitary and only ten (20%) had smear-positive disease compared with 67 (36%) and 103 (56%) cases, respectively, among referrals (table 2). Referrals had fewer total contacts and fewer close contacts than did non-referrals (table 3).

71 total transmission events arose from the foreign-born individuals with culture-positive pulmonary tuberculosis—three (4%) from referrals and 68 (96%) from non-referrals (figure 2). Whereas no secondary cases were attributable to a referral source case, 18 secondary cases were attributable to 11 different non-referral source cases (figure 2). Eight type 1 and ten type 2 secondary cases were identified (figure 2). All but one of the type 2 secondary cases were paediatric cases. Three TST conversions were attributable to three different referral source cases (figure 2). All these referral source cases had been diagnosed through the surveillance process. 50 TST conversions arose from 31 different non-referral source cases (figure 2). That is, among the tuberculosis surveillance referrals, three (6%) of 50 transmitted *M tuberculosis* compared with 42 (23%) of 184 non-referrals (unadjusted odds ratio 0·22, 95% CI 0·065–0·75; p=0·01; figure 2, table 4). The independent association between being a referral and the lower likelihood of transmission persisted in multivariable adjusted analyses (table 4). Appendix p 3 shows results of univariate and multivariate analyses for the remainder of the variables included in the final model. 37 (83%) of 45 source cases resulting in any transmission and 11 (100%) of source cases resulting in a secondary case were from high-risk countries.

Our sensitivity analysis showed that, among foreign-born individuals in Canada for 2 years or less, referrals were significantly less likely to transmit tuberculosis than were non-referrals (table 4). The association persisted for individuals from high-risk countries and with inclusion of temporary residents (table 4).

Discussion

Our findings show that foreign-born individuals referred for further in-country surveillance were more likely to be

	IRCC referrals (n=50)	Non-referrals (n=184)
Sex		
Female	31 (62%)	81 (44%)
Male	19 (38%)	103 (56%)
Age (years)	37 (13)	36 (13)
Time in Canada (months)		
Mean (SD)	19 (23)	39 (31)
Median (range)	11 (1–21)	33 (0 to 77·5)
HIV positive	2 (4%)	20 (11%)
Immigration status		
Canadian citizen or landed immigrant	46 (92%)	161 (88%)
Refugee	4 (8%)	23 (13%)
Tuberculosis incidence in country of birth (per 100 000 population)		
<30	0	4 (2%)
30–99	5 (10%)	11 (6%)
100–149	5 (10%)	18 (10%)
150–199	13 (26%)	20 (11%)
>200	27 (54%)	131 (71%)
Cavitation on chest radiograph	3 (6%)	67 (36%)
Sputum smear-positivity	10 (20%)	103 (56%)
Disseminated tuberculosis	0	9 (5%)
Tuberculosis caused or contributed to death	0	0

Data are n (%) or mean (SD), unless otherwise specified. IRCC=Immigration, Refugees and Citizenship Canada.

***Table 2*: Baseline characteristics of foreign-born individuals with culture-positive pulmonary tuberculosis**

	IRCC referral contacts	Non-referral contacts
All named contacts	841	3098
Median (IQR)	3 (–2 to 8)	6 (–7 to 18)
Close contacts	216	1201
Median (IQR)	3 (0 to 6)	4 (–1 to 9)
Documented TST conversion*	3/216 (1%)	68/1201 (6%)
Newly Identified TST positivity	62/216 (29%)	416/1201 (35%)
Previously positive	10/216 (5%)	77/1201 (6%)
Incomplete†	16/216 (7%)	139/1201 (12%)

Data are n or n/N (%), unless otherwise specified. IRCC=Immigration, Refugees and Citizenship Canada. TST=tuberculin skin test. *Secondary cases were included among the TST converters. †Named close contacts who could not be contacted, did not return telephone calls or letters, or did not fully complete assessment.

***Table 3*: Characteristics of contacts of foreign-born migrants with culture-positive pulmonary tuberculosis**

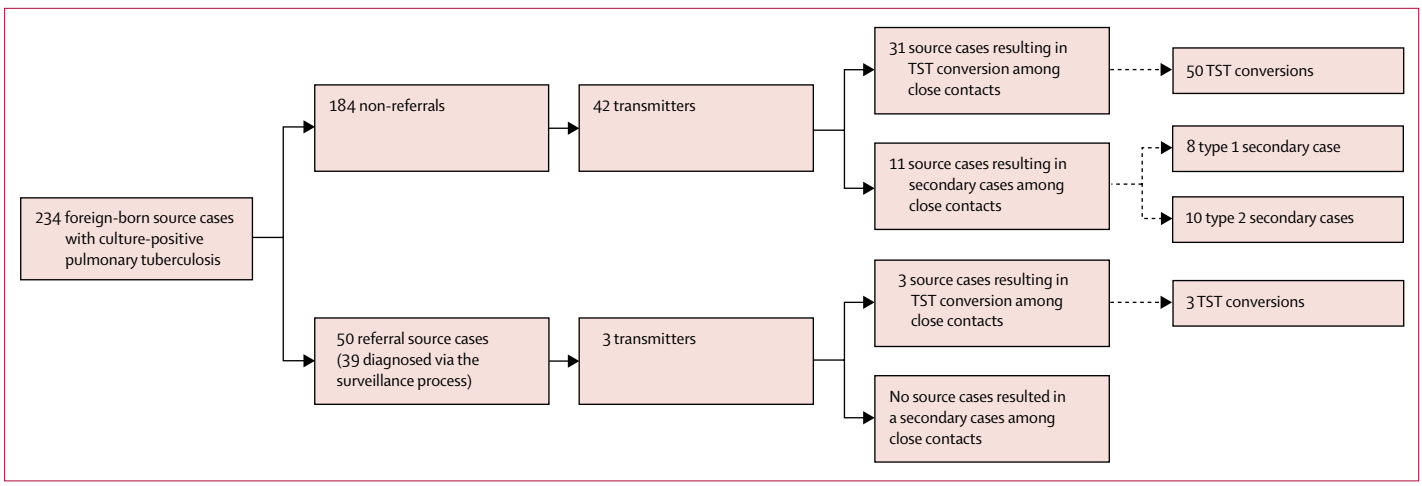

***Figure 2*: Transmission events arising from permanent residents who developed culture-positive pulmonary tuberculosis**
Dashed lines represent transmissions to close contacts. Secondary cases were not also counted as TST conversions. TST=tuberculin skin test.

	Referrals	Non-referrals	Odds ratio (95% CI)	p value
Unadjusted	3/50 (6%)	42/184 (23%)	0·22 (0·065–0·75)	0·01
Adjusted	3/50 (6%)	42/184 (23%)	0·19 (0·054–0·66)	0·009
Less than 2 years since arrival to Canada	3/38 (8%)	23/75 (31%)	0·19 (0·049–0·70)	0·01
From a high-risk country*	3/45 (7%)	36/167 (22%)	0·23 (0·064–0·80)	0·02
All foreign-born patients with pulmonary tuberculosis (including temporary residents)	6/78 (8%)	50/240 (21%)	0·31 (0·12–0·76)	0·01

Data are n/N (%), unless otherwise specified. *Countries with a tuberculosis incidence of more than 150 per 100 000 population, or sub-Saharan Africa.

***Table 4*: Transmission arising from referrals versus non-referrals (including sensitivity analyses)**

diagnosed with pulmonary tuberculosis than were all non-referrals and non-referrals from high-risk countries. However, referrals had a roughly 80% decreased risk of transmitting tuberculosis and did not result in any secondary cases.

Referrals, perhaps because they had lived in Canada for a shorter time before diagnosis, had fewer contacts than did non-referrals, which might be one reason why they were less likely to transmit tuberculosis. However, it is more likely that the decreased transmission is attributable to the lower incidence of smear-positive disease in referrals than non-referrals.[22] Why then were referrals less likely than non-referrals to be smear positive? One explanation might be earlier time to diagnosis. About 80% of the referrals were asymptomatic and were diagnosed during routine surveillance. Their time from symptom onset to diagnosis would have been much shorter than in non-referrals. Another Canadian study[7] found that time to diagnosis from symptom onset was 18 days earlier for compliant referrals than for non-referrals. Studies of nosocomial transmissions and outbreaks also point to an association between delayed diagnosis and increased transmission.[23,24] However, longer time to diagnosis did not predict tuberculosis transmission in contacts of US-born patients with pulmonary disease[25] nor was it associated with increased transmission to close contacts of foreign-born US patients.[26]

An alternative possibility is that the referral group represents a phenotypically distinct disease entity. Referrals either had evidence of old, healed tuberculosis on chest radiograph or a history of tuberculosis. They might have achieved some degree of accommodation[27] with their tuberculosis infection, which might render their active disease less severe and less infectious. This theory was originally posited by Toman in 1979,[28] when he noted that "[t]he hypothesis that all cases (of active pulmonary TB) could be detected at an early stage by x-raying the entire population at intervals of a few years (assumes) that tuberculosis in adults starts as a rule with a minimal lesion 'early infiltrate' that—without treatment—would all develop step by step into advanced, smear-positive tuberculosis. However, studies in populations under surveillance have shown that newly detected, smear-positive tuberculosis usually develops fast—ie, without passing through a clinically perceptible initial stage". A review of about 159 000 pulmonary tuberculosis cases showed that those with smear-negative disease were more likely to be foreign born.[29] The findings were attributed to the foreign-born population being more likely than the native-born population to have been diagnosed via screening. The possibility that reactivation of disease in foreign-born individuals might be of this different phenotype was not explored.

Our study has several limitations. The inability to reliably track the number of temporary residents in the province forced their exclusion from the main analyses. Nevertheless, we did sensitivity analyses including temporary residents and our transmission findings were unchanged. The IRCC dataset provided information about country of citizenship and the assumption was made that,

in most cases, country of citizenship at the time of immigration corresponded with country of birth. These definitions were used interchangeably. The assumption that country of citizenship is equivalent to country of birth might overestimate the number of foreign-born individuals from low-risk countries (to which migrants might have immigrated before entering Canada).

There might be concerns about the definition of transmission. Unfortunately, no standardised definition of tuberculosis transmission exists in the literature. Our definition might exclude secondary cases who were not named as contacts of the source case. Similarly, some might call the 30 month transmission window into question. However, our method has been previously published and described,[19,20] with sensitivity analyses corroborating its appropriateness. Findings from other studies[30,31] also suggest that this length of time is likely to capture most transmission events. Another limitation is that use of TST conversion as a marker of transmission in a population with a high proportion of BCG-vaccinated individuals might have identified BCG boosting rather than true conversion. If IGRA had been more widely used, or if we had chosen a cutoff of more than 15 mm for TST conversion, we might have identified fewer transmissions. However, we have adhered to the Canadian tuberculosis standards' definition of TST conversion and would not expect differential outcome misclassification between the two groups. We also appreciate that in our analysis of tuberculosis incidence, the denominator assumes no substantial emigration from or immigration into the province from elsewhere in Canada. Unfortunately, no national registries exist to allow us to consider in-country migration patterns after arrival. Finally, our data are specific to the province of Alberta. Although Quebec is more inclined to accept French speakers, immigration patterns and foreign-born tuberculosis epidemiology is similar across the major immigrant receiving provinces of Quebec, Ontario, Alberta, and British Columbia. However, implementation of the surveillance medical evaluation varies from province to province; therefore, some caution should be applied in extrapolation of our findings to the whole country.

To our knowledge, this is the first study assessing the effect of the national tuberculosis surveillance programme on transmission of tuberculosis in Canada—its primary aim. A large study of migrants to the UK found that those born in countries with higher tuberculosis incidence had a higher risk of reactivation. The investigators also reported minimal transmission.[32] The study did not examine differences between individuals who had undergone screening and those who had not been screened, instead focusing on the out-of-country screening process. Verver and colleagues[6] found that absence of tuberculosis screening and increased duration of stay in the Netherlands were risk factors for transmission, but that these risk factors were strongly correlated in multivariate analysis. By contrast, we found that even with adjustment for length of stay in Canada and even with sensitivity analyses assessing only individuals who had been in Canada for less than 2 years, referrals were less likely to transmit tuberculosis than non-referrals.

When Canada's surveillance system identifies an individual to be at risk for pulmonary tuberculosis, they are indeed at an increased risk of being diagnosed with the disease. However, the surveillance system did not identify roughly 80% of the foreign-born population who developed disease, nor did it identify the cases that accounted for the overwhelming majority of transmissions. Our findings agree with the UK recommendations to undertake screening for latent tuberculosis infection in individuals from countries with a tuberculosis incidence of more than 150 per 100 000 population or sub-Saharan Africa,[12] since this high-risk group accounted for 100% of secondary cases. Still, although more than 100 000 migrants were high risk, the number of secondary cases (n=18) was relatively low. Further research could improve the feasibility of screening this large group by clarifying who is at highest risk of developing and transmitting tuberculosis, and could be supplemented with economic evaluations examining the resource implications. Our results should also encourage investment in tuberculosis control in countries of origin, particularly in high-risk countries. For countries with a similar surveillance system and similar immigration sources, aspects of Canada's in-country surveillance system might be worth replicating.

Contributors

All authors participated in study conception, design, interpretation, critical revisions, and approved the final manuscript. LA did analyses and drafted the initial manuscript. CH, DM, and RL critically revised the manuscript. RL obtained funding and supervised the study.

Declaration of interests

We declare no competing interests.

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