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Preventing tuberculosis in the foreign-born population of Canada: a mathematical modelling study

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SUMMARY

BACKGROUND: Foreign-born persons in Canada contribute 67% of all tuberculosis (TB) cases annually, but represent only 21% of the total population. Molecular epidemiological studies suggest that most foreign-born TB cases result from the reactivation of latent tuberculous infection (LTBI) acquired before immigration.

OBJECTIVE: To estimate the effect on incidence of a prevention strategy that would screen selected immigrants at arrival for LTBI and offer preventive treatment to those who test positive.

DESIGN: A deterministic model was developed to quantify the incidence of active TB in immigrants to Canada and validated with national immigration and TB case data.

RESULTS: Model simulations suggested that it would be optimal to screen and treat LTBI in new immigrants from countries of birth with an estimated TB incidence rate in excess of 50 per 100 000 person-years. If this strategy had been implemented in 1986, the national TB incidence rate would have fallen by 18.5%, from 5.4 to 4.4 cases per 100 000 population by 2002.

CONCLUSION: This study suggests that screening and treating LTBI in foreign-born persons from high TB incidence countries is the most effective strategy in terms of total persons screened and treated and percentage reduction in national incidence.

KEY WORDS: latent tuberculous infection; TB prevention; modelling TB prevention

A GROWING PROPORTION of tuberculosis (TB) case patients in low TB incidence immigrant-receiving countries are foreign-born. In Canada, foreign-born persons now account for 67% of reported TB cases, despite comprising only 21% of the total population.[1,2] There is also a growing disparity in the rate of TB in foreign-born persons in Canada relative to the rate of TB in the Canadian-born non-Aboriginal population: the rate of TB in foreign-born persons was respectively 4 and 19 times greater than the Canadian-born non-Aboriginal population in 1981 and 2011.[2]

In molecular epidemiological studies, approximately 85% of the foreign-born TB cases reported in high-income immigrant-receiving countries result from reactivation of latent tuberculous infection (LTBI) acquired abroad before the immigrants' arrival.[3,4] One cost-effective strategy suggested for use by high-income countries to reduce TB-related morbidity and mortality among foreign-born persons is to fund expanded TB control programmes in high TB incidence countries.[5–7] Another is the implementation of targeted LTBI screening and treatment strategies within immigrant-receiving countries.

It is generally accepted that reducing TB in foreign-born persons is critically important to TB elimination in immigrant-receiving countries.[5,8] Nevertheless, targeted screening has not been routinely implemented because of concerns about false-positive tuberculin skin test (TST) results and suboptimal treatment acceptance and adherence rates.[9,10] These obstacles have been largely overcome with the use of interferon-gamma release assays (IGRAs) and short-course prophylaxis.[11] Another barrier reasonably relates to uncertainty about the cost-effectiveness of targeted screening. This study seeks to address this uncertainty by identifying a cost-effective screening strategy for LTBI among immigrants newly arrived in Canada using a deterministic mathematical model validated by national TB case and immigration data. Cost-effectiveness is described by a ratio that shows the number of persons screened and treated to avert one case of active TB.

METHODS

Deterministic mathematical model

Deterministic mathematical models are models with no random variation among parameter values. A

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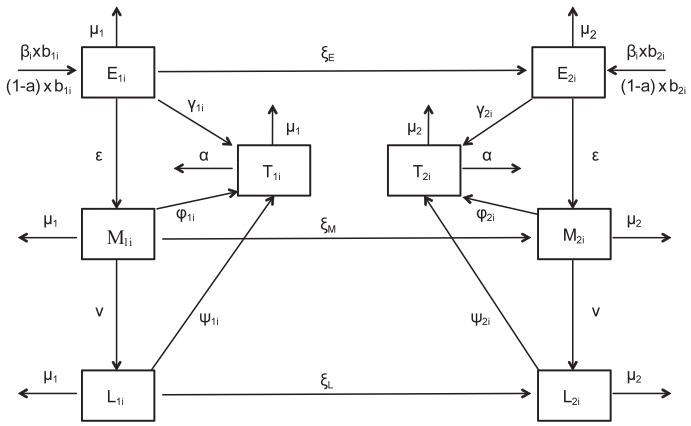

Figure 1 The overall schematic diagram of the LTBI model. The foreign-born population in Canada between 1986 and 2002 was stratified by three incidence groups denoted by *i* (low = L, <15; medium = Me, 15–50; and high = H, >50 cases/100 000). The two age groups for the foreign-born population are denoted by subscripts 1 (<35 years) and 2 (≥35 years). Compartments E, M, and L describe foreign-born persons who arrived within 2 years, 3–5 years and >5 years, respectively. The T compartment represents the foreign-born population that developed active TB disease. The parameter *b* describes the average number of people immigrating into Canada per year. The incidence rate per year of active TB from the progression of LTBI from E, M and L compartments is denoted by γ, φ and ψ. The parameter denotes the proportion of foreign-born persons who are successfully treated. Transitional parameters describe the annual percentage change due to advancing age (ξ_E, ξ_M and ξ_L) and time since arrival (ε and v). The μ rate describes the background mortality. Foreign-born persons who did not undergo screening (1-a) and those who have falsely negative sequential screening tests or did not adhere to preventive treatment (β) have different rates of progression from LTBI to active TB. Those who are falsely negative progress to active TB with a probability rather than an incidence rate (see Appendix, Probability of progression). TB = tuberculosis; LTBI = latent tuberculous infection.

deterministic mathematical model was developed using a system of ordinary differential equations (see Appendix, Methods)* to describe the reactivation of LTBI in foreign-born persons (Figure 1). Foreign-born persons were immigrants or convention refugees who were granted permanent residency and had arrived in Canada between 1986 and 2002.[8] Visitors, students, temporary workers and refugee claimants (those claiming refugee status while in Canada) were excluded due to data limitations.[8]

Based on previous findings,[8] strata were included to account for key predictive variables associated with TB incidence in foreign-born populations. Specifically, the population was stratified according to the demographic variables of age at arrival (age <35 or ≥35 years as denoted by subscripts 1 and 2, respectively), country of birth group (low, medium or high TB incidence countries) and time since arrival (E, ≤2 years; M, 3–5 years; and L, >5 years) (Table 1). Country of birth groupings used World Health Organization country-specific estimated rates of smear-positive pulmonary TB, such that low-, medium- and high-incidence countries were those with estimated rates of respectively <15, 15–50 and >50 cases per 100 000 person-years.[8] The T compartment described the foreign-born population that developed active TB disease. Local transmission of TB with progression to active disease was not considered, as it is a relatively infrequent cause of TB in foreign-born persons.[14,15]

Aging (ξ_E, ξ_M, and ξ_L), mortality (μ), increased time since arrival (ε and v) and the continual arrival of new immigrants (b) were considered by the model to account for changes in the foreign-born population over time as well as the transition from one strata to another (Table 1). Aging was based on the average age of the population (21 years) during the 17-year study period and the length of time people remained in each compartment (E, M and L). Parameters μ_1 and μ_2 represent mortality rates in the overall Canadian population.[12] The increased time since arrival was estimated using the length of time individuals remain in compartment E and M, which is 2 and 3 years, respectively, therefore $\varepsilon = 1/2$ and $v = 1/3$ year^{-1}. The continual arrival of new immigrants (b) is time-dependent, and was estimated from Citizenship and Immigration Canada (CIC) data.[8]

Table 1 outlines the aforementioned model parameters and initial conditions. The intervention parameter β describes the proportion of persons with false-negative TST results or those who did not adhere to

*The Appendix is available in the online version of this article at http://www.ingentaconnect.com/content/iuatld/ijtld/2014/00000018/00000004/00000007

Table 1 Definitions and estimated values for model parameters and initial conditions where E, M and L represent the foreign-born who arrived in Canada within 2 years, 3–5 years and >5 years, respectively, between 1986 and 2002

Parameter*	Definition†	Units	LIC	MIC	HIC
ε	Transition from E to M	$Year^{-1}$	1/2	1/2	1/2
ν	Transition from M to L	$Year^{-1}$	1/3	1/3	1/3
ξ_E	Transition from E_1 to E_2	$Year^{-1}$	1/14	1/14	1/14
ξ_M	Transition from M_1 to M_2	$Year^{-1}$	1/12	1/12	1/12
ξ_L	Transition from L_1 to L_2	$Year^{-1}$	1/9	1/9	1/9
α	Proportion of TB cases successfully treated		1.2	1.2	1.2
μ_1	Mortality rate (<35)‡	$Year^{-1}$	7.5×10^{-4}	7.5×10^{-4}	7.5×10^{-4}
μ_2	Mortality rate (≥35)	$Year^{-1}$	1.4×10^{-2}	1.4×10^{-2}	1.4×10^{-2}
p	Proportion of LTBI§		0.20	0.40	0.65
Se_1	TST sensitivity		0.77	0.77	0.77
Sp_1	TST specificity¶		0.97	0.78	0.59
Se_2	IGRA sensitivity		0.83	0.83	0.83
Sp_2	IGRA specificity		0.97	0.97	0.97
β	100% intervention	Effectiveness 0.60/0.75/ 0.93	0.12/0.10/0.08	0.24/0.20/0.15	0.39/0.33/0.25
β	75% intervention	Effectiveness 0.60/0.75/ 0.93	0.09/0.08/0.06	0.18/0.15/0.11	0.29/0.24/0.19
β	50% intervention	Effectiveness 0.60/0.75/ 0.93	0.06/0.05/0.01	0.12/0.10/0.08	0.20/0.16/0.12
Initial conditions (time = 0 ~ 1986)#					
E_1	Persons aged <35 years within 2 years of arrival	Number of foreign-born persons	18 615	36 435	26 465
E_2	Person aged ≥35 years within 2 years of arrival		8268	14 227	9503
T_1**	Person aged <35 years developing active TB		3	14	22
T_2	Person aged ≥35 years developing active TB		3	15	22

*Data sources: Citizenship and Immigration Canada and the Canadian Tuberculosis Reporting System (see text for details).
†Subscript numbers '1' and '2' refer to persons aged <35 and those aged ≥35 years, respectively.
‡Reference 12.
§Reference 13.
¶TST specificity is 59% for HIC (BCG-vaccinated) and 97% for LIC (non-BCG-vaccinated). Assume LIC is 97%, MIC is 78% (middle value), and HIC is 59%.
#The initial conditions for compartments M and L are zero since all individuals who arrived in 1986 were in compartment E.
**Total TB cases per year were aggregated; accordingly, an equal distribution was assumed in T_1 and T_2. Note: T_1 and T_2 compartments are not incident cases and are not reported.
LIC = low-incidence country; MIC = medium-incidence country; HIC = high-incidence country; LTBI = latent tuberculous infection; TST = tuberculin skin test; IGRA = interferon gamma release assay; TB = tuberculosis; BCG = bacille Calmette-Guérin.

preventive treatment (see Appendix, The intervention parameter β). Figure 2 describes incidence rates per 100 000 person-years for active TB (γ_1, γ_2, ψ_1, ψ_2, φ_1, and φ_2). The number of younger (b_1) and older (b_2) foreign-born persons arriving in Canada per year is given for each country of birth group. Linear and exponential functions were used to find γ_1, γ_2, ψ_1, ψ_2, φ_1, φ_2, b_1 and b_2 that best fit with the immigration data. Data points were excluded as outliers if they were outside 1.5x the interquartile range. Foreign-born persons either screened as falsely negative for LTBI or having incomplete treatment experience a probability of progression to active TB rather than an incidence rate progression. This was achieved by multiplying the incidence rate by $(1/p_i)_{L,Me,H}$, where p_i is the prevalence of LTBI in low-, medium- and high-incidence countries (see Appendix, Probability of progression). Transitional parameters (ξ_E, ξ_M, ξ_L, ε, and ν) describe the annual percentage change in the size of the foreign-born population between each compartment due to advancing age and time since arrival.

Modelling of prevention strategies

Following development and verification (see Appendix, Model validation), the model was used to estimate the potential impact of various prevention strategies on the reduction of active TB in foreign-born persons. This was achieved by adjusting the parameter β to reflect different prevention strategies being investigated. It also focused on different groups of foreign-born persons as characterised by age at arrival and the TB incidence rate in their country of birth.

All of the prevention strategies were based on the premise that screening for LTBI was initiated at the time of arrival due to the inverse relationship between TB incidence and time since arrival.[8,16,17] The approach optimises the early identification of individuals who may have progressed to active TB in the interval between the overseas immigration medical examination and arrival in Canada.[8,17–19] In terms of screening, sequential screening tests are more cost-effective than using IGRAs alone.[20] The model therefore assumed that foreign-born persons would be screened with a TST and, for those with a positive TST (induration ≥10 mm), secondarily screened with either the QuantiFERON®-TB Gold In-Tube assay (Cellestis Ltd, Carnegie, VIC, Australia) or the T-SPOT®.*TB* assay (Oxford Immunotec, Oxford, UK).[11] The parameter (β) related to screening is

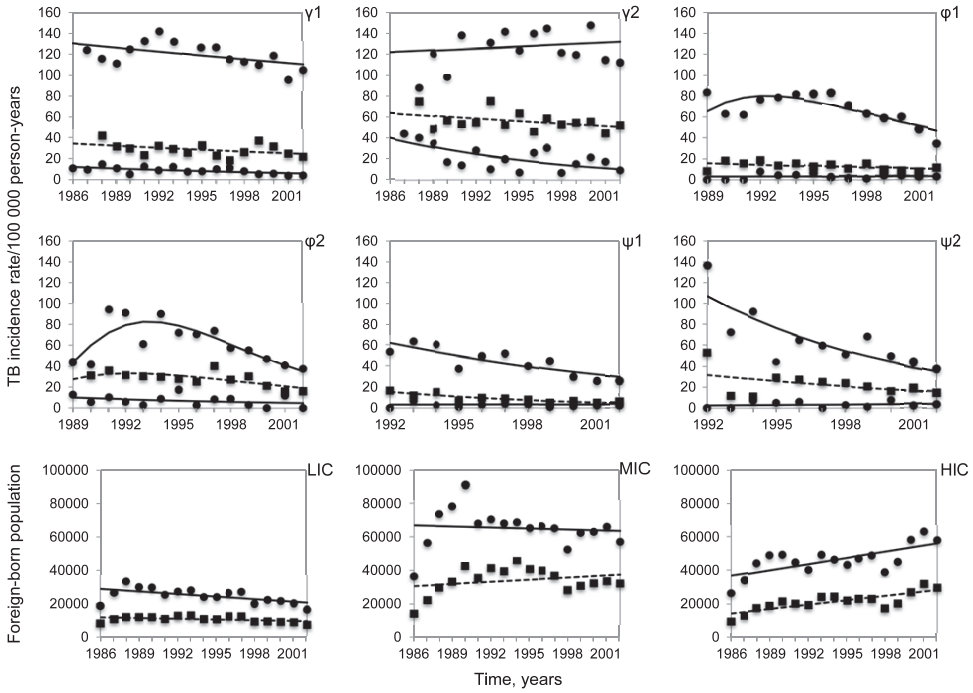

Figure 2 Time-dependent TB incidence rates and foreign-born population between 1986 and 2002 by country group (LIC, MIC and HIC), age (<35 and ≥35 years denoted by 1 and 2) and year of arrival (γ = within 2 years; φ = 3–5 years; ψ = >5 years of arrival). Note: For incidence plots, top, middle and lower functions represent HIC, MIC and LIC. TB = tuberculosis; LIC = low-incidence country; MIC = medium-incidence country; HIC = high-incidence country.

derived using the pooled sensitivities and specificities of the TST and IGRAs, specifically, a pooled TST sensitivity of 77% and specificity of 59% and 97% in populations that are respectively bacille Calmette-Guérin (BCG) vaccinated and non-BCG-vaccinated.[11,21] TST specificity was adjusted to account for foreign-born persons who arrived from countries that have a high TB incidence and predictably high rates of BCG vaccination.[22] In this study, the TST specificity was assumed to be 97% for low- and 59% for high-incidence countries. A median value of 78% for TST specificity was used for medium-incidence countries. For IGRAs, the model used a pooled sensitivity and specificity of respectively 83% and 97%, as these tests are not influenced by BCG vaccination.[11,21]

Furthermore, it was assumed that TST-positive individuals who were also IGRA-positive would be offered the standard prophylactic treatment regimen of daily isoniazid (INH) for 9 months.[18] As the effectiveness of the treatment for LTBI (INH) is known to be imperfect, treatment failure and adherence rates were considered in evaluating the strategies. Estimates for treatment efficacy assuming perfect adherence was 93%. For imperfect adherence rates of 81% and 65%, the treatment effectiveness was 75% and 60%.[9,10] In addition, age-related adverse events (mainly hepatotoxicity) due to INH in individuals aged ≥35 years were included in the model.[23] A prevention strategy that was not restricted by age was also investigated, as emerging preventive therapies are less likely to be associated with age-related adverse events.[24]

The number of people screened and treated per active TB case averted is a ratio (*r*) used to measure the cost-effectiveness of prevention strategies in this study. A calculation of the health-related costs of screening for LTBI and treating active TB is described in the Appendix.[20]

Data sources and materials

Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) and Mathematica 7.0 (Wolfram Research, Campaign, IL, USA) were used for data management and model simulation. Ethics approval was not required as the analysis was restricted to non-nominal, routinely collected surveillance data. Based on the study design, only foreign-born persons arriving in 1986 or later could have been beneficiaries of the modelled prevention strategies. The number of TB cases diagnosed between 1986 and 2002 among foreign-born persons who arrived in Canada before 1986 would therefore coincide with the actual number of cases reported in this group and previously described in Langlois-Klassen et al.[8] To

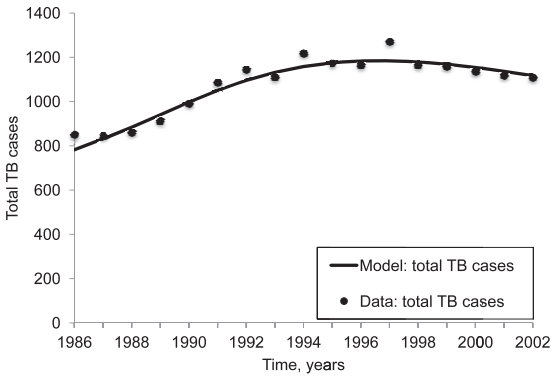

Figure 3 Total TB case data obtained from Citizenship and Immigration Canada and the Public Health Agency of Canada plotted with model results (post-1986) and pre-1986 TB cases. Post-1986 TB cases represent TB contributed by foreign-born individuals who arrived from 1986 to 2002. Pre-1986 represent TB cases in foreign-born persons who arrived before 1986. TB = tuberculosis.

estimate the total number of TB cases in the foreign-born population in Canada under any given prevention strategy, TB cases contributed by pre-1986 arrivals were added to the model estimates of TB cases among persons who arrived between 1986 and 2002. National TB incidence rates were estimated using Public Health Agency of Canada (PHAC) surveillance reports and model outcomes (see Appendix, Results).

RESULTS

After cross-validation, the coefficient of determination (R^2) for our model was determined to be high (98%), indicating that the model coincided well with the reported data (Figure 3, which compares model-derived total TB cases to reported total TB cases). Following the process of cross-validation, various prevention strategies were simulated using the mathematical model.

Summarised in Table 2 are nine different strategies (A to I), each at three different levels of effectiveness (60%, 75%, and 93%). For each strategy and each level of effectiveness, the model derived impact on the average annual percentage reduction in national incidence, the incidence rate in 2002 and the effectiveness ratio (r) is given. It can be seen that while strategy B resulted in the highest average annual percentage reduction in national incidence (4.1% at 93% effectiveness) and the lowest incidence rate in 2002 (3.9 cases per 100 000 population), it did so at an r value of 1000.5. Strategy D, on the other hand, while it did not result in as high an average

Table 2 A description and analysis of nine intervention strategies applied between 1986 and 2002 using the LTBI model

Intervention strategy	Description*	Effectiveness (*ef*)	Average annual reduction in national incidence %	Incidence rate in 2002 cases/100 000	Average screened and treated to avert 1 active TB case/year *r*
A	100% LIC, MIC and HIC	0.60	3.4	4.4	1723.1
		0.75	3.7	4.2	1379.8
		0.93	4.1	3.9	1113.6
B	100% MIC and HIC all ages	0.60	3.3	4.4	1548.0
		0.75	3.7	4.2	1239.6
		0.93	4.1	3.9	1000.5
C	100% MIC all ages	0.60	2.5	5.1	2532.8
		0.75	2.6	5.0	2028.3
		0.93	2.7	4.9	1637.0
D	100% HIC all ages	0.60	2.9	4.7	1054.8
		0.75	3.1	4.6	844.7
		0.93	3.4	4.4	681.7
E	75% HIC all ages	0.60	2.7	4.9	1054.8
		0.75	2.9	4.8	844.7
		0.93	3.1	4.6	681.7
F	50% HIC all ages	0.60	2.6	5.1	1054.8
		0.75	2.7	5.0	844.7
		0.93	2.8	4.9	681.7
G	100% HIC aged <35 years	0.60	2.7	4.9	1058.1
		0.75	2.8	4.8	847.3
		0.93	3.0	4.7	683.8
H	75% HIC aged <35 years	0.60	2.6	5.0	1058.1
		0.75	2.7	5.0	847.3
		0.93	2.8	4.9	683.8
I	50% HIC aged <35 years	0.60	2.4	5.2	1058.1
		0.75	2.5	5.1	847.3
		0.93	2.6	5.0	683.8
Baseline		—	2.2	5.4	—

*Test foreign-born people as they arrived in Canada between 1986 and 2002 and treat those who tested positive for LTBI with isoniazid daily for 9 months.
LIC = low-incidence country; MIC = medium-incidence country; HIC = high-incidence country; LTBI = latent tuberculous infection.

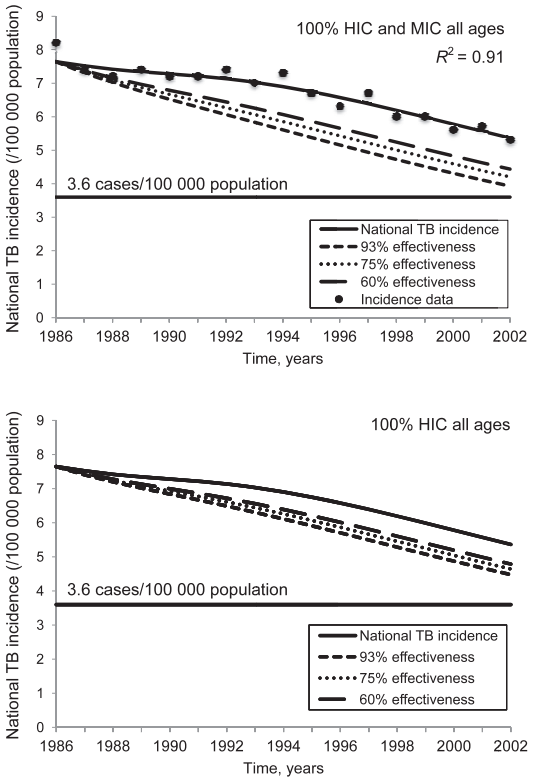

Figure 4 National TB incidence rates for screening and treating 100% of all foreign-born people from HIC and MIC (top) and 100% of foreign-born people from HIC only (bottom) at 93%, 75% and 60% effectiveness. TB = tuberculosis; MIC = medium-incidence country; HIC = high-incidence country.

annual percentage reduction in national incidence (3.4% at 93% effectiveness) or as low an incidence rate in 2002 (4.4 cases/100 000), resulted in the lowest *r* value (681.7). Strategy G, which was the same as strategy D except that it was limited to those aged <35 years and therefore safer, given that the treatment regimen consisted of daily INH for 9 months, resulted in a comparable *r* value (683.8), but a lower average annual percentage reduction in national incidence (3.0% at 93% effectiveness), and a higher incidence rate in 2002 (4.7 cases/100 000).

Depicted graphically in Figure 4 are the model-derived annual incidence rates between 1986 and 2002 using strategy B (upper panel) and strategy D (lower panel). Using data obtained from TB surveillance reports published by PHAC (see Appendix Results), the national incidence can be seen to compare favourably with model simulations (R^2 = 91%).

DISCUSSION

The treatment of LTBI has the potential to reduce the incidence of active TB.[25] Its cost-effectiveness has been studied in Canada.[20,26,27] Based on the strategies modelled here, the targeted screening and treatment of LTBI among foreign-born persons (all ages or those aged <35 years) from high-incidence countries on arrival is the optimal prevention strategy (Strategy D or Strategy G), based on their low effectiveness ratios. Other studies looking at the effectiveness of prevention strategies support the idea of focusing on foreign-born persons at higher risk of developing TB.[5,20,26] The optimal strategy based on our model also includes considerations of adverse events from INH treatment for people aged ≥ 35 years.[23] In anticipation of emerging therapies that are likely to be safer in older age groups, the optimal strategy (Strategy D) would achieve lower incidence rates in 2002 compared with Strategy G. Newer and shorter LTBI treatment regimens, such as 4 months of daily rifampicin[28] or 12 weeks of once-weekly INH+rifapentine,[24,29] suggest that the age-dependent TB prevention strategies and lower adherence estimates modelled in this study are quite conservative.

A post-hoc analysis was conducted to compare the effectiveness of a strategy that used the proposed screening method, TST+IGRA, with a strategy that used IGRA alone as the screening method (see Appendix Discussion). This analysis was limited to Strategy D. At 75% effectiveness, the incidence rate at the end of the study period (year 2002) would have been lower for the IGRA only (4.4 cases/100 000) than the TST+IGRA strategy (4.6 cases/100 000). The annual average reduction in incidence was increased by 0.3% in the IGRA-only approach, but required an additional investment of 3–4 million dollars per year. Although the proposed strategy (TST+IGRA) describes the most cost-effective approach,[20] the IGRA-only approach is not without benefit. The benefits include ease of test performance, greater specificity in populations with high rates of BCG vaccination and non-tuberculous mycobacteria, and limiting follow-up to those with positive test results.[30]

With respect to Canada's Stop TB goal of achieving an incidence rate (in lieu of prevalence) of 3.6 cases/100 000 by 2015,[31,32] model predictions suggest that, if Strategy D was used, a national incidence rate of 4.6 cases/100 000 (*ef* = 75%) would have been achieved in 2002. Reaching Stop TB goals in Canada requires not only the prevention of disease in the foreign-born, but also the interruption of transmission and prevention of disease in Canada's indigenous peoples.[2]

This study has certain limitations. First, the model did not directly account for the likely failure of standard treatment among foreign-born persons infected with INH-resistant strains. The effectiveness rate of 93% indirectly accounted for INH resistance given that the estimated prevalence of the latter is between 7% and 10% in the foreign-born population

of Canada.[17] In a post-hoc analysis that assumed an INH resistance rate of 7.9% in foreign-born persons with LTBI and an effectiveness rate of 85% (see Appendix, Discussion), there was little change in the average annual percentage reduction in national incidence. Newer and shorter LTBI treatment regimens would improve overall treatment effectiveness for this prevention strategy. Second, the foreign-born population in this study did not include refugee claimants whose incidence rates are not known for certain, although these are generally thought to be higher than landed immigrants. Finally, the effectiveness ratio, which described the number of foreign-born persons needing to be screened and treated to avert one case of active TB, did not include a detailed accounting of costs such as those related to drug resistance, treatment complications, administration and program implementation.[20,33] Its estimate was understood to be a relative measure that provides meaningful insight into strategies that require a closer examination.

CONCLUSION

Reducing TB among the foreign-born will ultimately have a positive impact on the health of immigrants, national TB rates and national TB elimination targets in Canada and other high-income immigrant-receiving countries. Using a deterministic mathematical model validated by national TB data, this study suggests that a strategy of screening and treating LTBI in foreign-born persons (all ages or those aged <35 years) from high-incidence countries at arrival would be optimal. Integrating epidemiological data in a mathematical model provides valuable insight into issues of public health importance.

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APPENDIX

METHODS

The ordinary differential equation system of the latent tuberculous infection model

$$\left\{\begin{aligned}
\frac{dE_{1i}}{dt} &= (1-a)b_{1i}(t)E_{1i}(t) - \mu_1 E_{1i}(t) - \xi_E E_{1i}(t) - \varepsilon E_{1i}(t) - \gamma_{1i}(t)E_{1i}(t)\\
\frac{dM_{1i}}{dt} &= \varepsilon E_{1i}(t) - \mu_1 M_{1i}(t) - \xi_M M_{1i}(t) - \phi_{1i}(t)M_{1i}(t) - \nu M_{1i}(t)\\
\frac{dL_{1i}}{dt} &= \nu M_{1i}(t) - \mu_1 L_{1i}(t) - \xi_L L_{1i}(t) - \psi_{1i}L_{1i}(t)\\
\frac{dT_{1i}}{dt} &= \gamma_{1i}(t)E_{1i}(t) + \phi_{1i}(t)M_{1i}(t) + \psi_{1i}L_{1i}(t) - \alpha T_{1i}(t) - \mu_1 T_{1i}\\
\frac{dE_{2i}}{dt} &= (1-a)b_{2i}(t)E_{2i}(t) - \mu_2 E_{2i}(t) + \xi_E E_{1i}(t) - \varepsilon E_{2i}(t) - \gamma_{2i}(t)E_{2i}(t)\\
\frac{dM_{2i}}{dt} &= \varepsilon E_{2i}(t) - \mu_2 M_{2i}(t) + \xi_M M_{1i}(t) - \phi_{2i}(t)M_{2i}(t) - \nu M_{2i}(t)\\
\frac{dL_{2i}}{dt} &= \nu M_{2i}(t) - \mu_2 L_{2i}(t) + \xi_L L_{1i}(t) - \psi_{2i}L_{2i}(t)\\
\frac{dT_{2i}}{dt} &= \gamma_{2i}(t)E_{2i}(t) + \phi_{2i}(t)M_{2i}(t) + \psi_{2i}L_{2i}(t) - \alpha T_{2i}(t) - \mu_2 T_{2i}
\end{aligned}\right\}_{i=L,Me,H}$$

Here, '*i*' represents a model stratified by country of birth group: low- (LIC), medium- (MIC) and high-incidence countries (HIC). The ordinary differential equation (ODE) system above represents foreign-born individuals who did not undergo screening. A similar ODE system representing foreign-born individuals who had false-negative sequential screening tests or did not complete preventive treatment was evaluated simultaneously. This system is presented below:

$$\left\{\begin{aligned}
\frac{dE^*_{1i}}{dt} &= \beta_i b_{1i}(t)E_{1i}(t) - \mu_1 E_{1i}(t) - \xi_E E_{1i}(t) - \varepsilon E_{1i}(t) - \frac{1}{p_i}\gamma_{1i}(t)E_{1i}(t)\\
\frac{dM^*_{1i}}{dt} &= \varepsilon E_{1i}(t) - \mu_1 M_{1i}(t) - \xi_M M_{1i}(t) - \frac{1}{p_i}\phi_{1i}(t)M_{1i}(t) - \nu M_{1i}(t)\\
\frac{dL^*_{1i}}{dt} &= \nu M_{1i}(t) - \mu_1 L_{1i}(t) - \xi_L L_{1i}(t) - \frac{1}{p_i}\psi_{1i}L_{1i}(t)\\
\frac{dT^*_{1i}}{dt} &= \frac{1}{p_i}\gamma_{1i}(t)E_{1i}(t) + \frac{1}{p_i}\phi_{1i}(t)M_{1i}(t) + \frac{1}{p_i}\psi_{1i}L_{1i}(t) - \alpha T_{1i}(t) - \mu_1 T_{1i}\\
\frac{dE^*_{2i}}{dt} &= \beta_i b_{2i}(t)E_{2i}(t) - \mu_2 E_{2i}(t) + \xi_E E_{1i}(t) - \varepsilon E_{2i}(t) - \frac{1}{p_i}\gamma_{2i}(t)E_{2i}(t)\\
\frac{dM^*_{2i}}{dt} &= \varepsilon E_{2i}(t) - \mu_2 M_{2i}(t) + \xi_M M_{1i}(t) - \frac{1}{p_i}\phi_{2i}(t)M_{2i}(t) - \nu M_{2i}(t)\\
\frac{dL^*_{2i}}{dt} &= \nu M_{2i}(t) - \mu_2 L_{2i}(t) + \xi_L L_{1i}(t) - \frac{1}{p_i}\psi_{2i}L_{2i}(t)\\
\frac{dT^*_{2i}}{dt} &= \frac{1}{p_i}\gamma_{2i}(t)E_{2i}(t) + \frac{1}{p_i}\phi_{2i}(t)M_{2i}(t) + \frac{1}{p_i}\psi_{2i}L_{2i}(t) - \alpha T_{2i}(t) - \mu_2 T_{2i}
\end{aligned}\right\}_{i=L,Me,H}$$

The intervention parameter β

The parameter β is described by:

$$\left.\begin{array}{l}\beta_i = a \times FN_i + a[(TP_i + FP_i) - (ef \times TP_i \times se2 + FP_i(1 - sp2) + FP_i \times sp2)] \\ = a \times FN_i + a[TP_i - (ef \times TP_i \times se2)]\end{array}\right\}_{i=L,Me,H}$$

$$where\ FN_i = p_i(1 - se1),\ FP_i = (1 - p_i)(1 - sp1),\ \&TP_i = p_i se1$$

where: FN = false-negatives; FP = false-positives; TP = true-positives; a = proportion of the foreign-born who were screened and treated; ef = effectiveness of treatment; p_i = proportion of the foreign-born with LTBI in 'i' incidence countries; se = sensitivity of screening test where 1 and 2 are tuberculin skin tests and interferon-gamma release assays; sp = specificity of the screening test.

Probability of progression

Probability of progression is defined as the number of active TB cases/total number of persons with LTBI. This was estimated by increasing the incidence by $1/p_i$ where p_i is the prevalence of LTBI in LIC, MIC and HIC.

$$Progression\ rate = Incidence$$

$$= \frac{\#\ of\ active\ TB\ cases}{Total\ population\ at\ risk}$$

$$Progression\ probability = \frac{\#\ of\ Active\ TB\ cases}{Total\ \#\ of\ people\ infected}$$

$$= \frac{1}{p_i} \times \frac{\#\ of\ active\ TB\ cases}{Total\ population\ at\ risk}$$

$$= \frac{1}{p_i} \times incidence$$

Model validation

The mathematical model was validated using national TB case and immigration data between 1986 and 2002. The TB case data obtained from the Canadian Tuberculosis Reporting System (CTBRS) and the immigrant data provided by Citizenship and Immigration Canada (CIC) was previously described by Langlois-Klassen et al.[1] Data from the CTBRS consisted of all foreign-born active TB cases diagnosed during the study period (isoniazid resistance in foreign-born new active cases was 7.9% between 2006 and 2010).[1] Cross-validation (hold-out method) was used to overcome the challenge of validating dependent data. As model parameters and initial conditions were estimated using the CTBRS and CIC data, the hold-out method used half the data set for model simulations and independently compared results with the other half. The primary outcome for cross-validation was total active TB cases per year. The coefficient of determination (R^2) was estimated to measure the strength of the validation, with high values indicating a better fit of the primary outcome during the study period

Estimation of national tuberculosis incidence

National TB case counts were calculated through the integration of model outcomes for TB cases among 1986–2002 arrivals with that of pre-1986 arrivals (see Data Sources and Materials) and Canadian-born population groups. TB incidence data for Canadian-born persons were obtained from Public Health Agency of Canada (PHAC) surveillance reports.[2–4] The case counts, excluding those contributed by the foreign-born population group, were estimated using PHAC surveillance reports. Case counts contributed by the foreign-born population group were estimated by adding the 1986–2002 arrivals using model simulations and the pre-1986 arrivals. National incidence rates were obtained by dividing the new total TB cases (PHAC surveillance reports, model simulations and estimates previously described by Langlois-Klassen et al.) by the total population obtained from surveillance reports (Table A.1).[1]

RESULTS

Calculation of national TB rate: surveillance report information

TB surveillance report data for 1986 to 2002 were used to estimate national TB incidence in Canada (Table A.1). The population at risk is estimated by dividing the total new and relapsed TB cases (column 2) by the reported TB incidence rate (column 3). The new national TB rate was estimated by combining all TB cases totals (column 5) with model outcomes divided by the population at risk for each calendar year.

Table A.1

Year (t)	Total TB cases (new and relapsed) *n*	National TB incidence rate /100 000 py	New foreign-born TB cases (those who immigrated from 1986 to 2002) *n*	All TB cases (excluding new cases contributed by the foreign-born population who immigrated from 1986 to 2002) *n*	References
1986 (0)	2145	8.2	79	2066	[2]
1987 (1)	1972	7.4	167	1805	[2]
1988 (2)	1947	7.2	234	1713	[2]
1989 (3)	2035	7.4	297	1738	[2]
1990 (4)	1997	7.2	383	1614	[2]
1991 (5)	2018	7.2	491	1527	[2]
1992 (6)	2108	7.4	632	1476	[2]
1993 (7)	2012	7.0	630	1382	[2]
1994 (8)	2106	7.3	753	1353	[5]
1995 (9)	1964	6.7	701	1263	[5]
1996 (10)	1877	6.3	760	1117	[5]
1997 (11)	1995	6.7	801	1194	[5]
1998 (12)	1809	6.0	751	1058	[5]
1999 (13)	1820	6.0	779	1041	[5]
2000 (14)	1723	5.6	746	977	[5]
2001 (15)	1772	5.7	693	1079	[5]
2002 (16)	1660	5.3	716	944	[5]

TB = tuberculosis.

DISCUSSION

Comparing the costs for active TB treatment and prevention programme costs for screening and treating LTBI among foreign-born people who arrive from HIC (Strategy D at 75% effectiveness) between 1986 and 2002. Total cases include all new foreign-born TB cases between 1986 and 2002 (Table A.2).

Treatment effectiveness using the LTBI model and assuming an isoniazid resistance rate of 7.9% in foreign-born persons in Canada. Optimal strategies are used to evaluate the overall impact on the national incidence rate in 2002 (Table A.3).

Table A.2

Screening strategy	Cost type*	1987 cost in millions $	1991 cost in millions $	1997 cost in millions $	2002 cost in millions $	Incidence rate in 2002 cases/100 000	Average reduction in incidence %
No strategy	Baseline cost for active TB treatment (pre-1986)	14.6	12.8	10.1	8.4	5.4	2.2
No strategy	Baseline cost for active TB treatment (1986–2002)	18.0	22.7	25.6	24.1		
TST+IGRA	Cost for active TB treatment under Strategy D	17.4	19.7	20.5	18.8	4.6	3.1
	Cost for LTBI prevention programme under Strategy D	15.7	18.2	21.9	25.0		
Cost savings for active TB treatment		0.6	3.0	5.1	5.3		
IGRA only	Cost for active TB treatment under Strategy D	17.2	19.0	19.2	17.5	4.4	3.4
	Cost for LTBI prevention programme under Strategy D	19.3	22.4	26.9	30.7		
Cost savings for active TB treatment		0.8	3.7	6.4	6.6		

*Costs for active TB treatment ($21 600) obtained from reference 6. Costs for TST and IGRA obtained from reference 7. TST and IGRA screening costs were assumed at respectively $13/test and $41/test. Cost for investigating a positive IGRA result was assumed to be $154/case with an LTBI treatment cost of $433/case.
TB = tuberculosis; TST = tuberculin skin test; IGRA = interferon-gamma release assay; LTBI = latent tuberculous infection.

Table A.3

Intervention strategy	Description	Effectiveness* (*ef*)	Average annual percentage reduction in national incidence %	Incidence rate in 2002 cases/100 000 population
D	100% HIC all ages	0.60	2.9	4.7
		0.75	3.1	4.6
		0.93	3.4	4.4
		0.55	2.9	4.8
		0.69	3.1	4.6
		0.85	3.3	4.5
G	100% HIC <35 years	0.60	2.7	4.9
		0.75	2.8	4.8
		0.93	3.0	4.7
		0.55	2.7	5.0
		0.69	2.8	4.9
		0.85	2.9	4.8

*Isoniazid resistance in foreign-born new active cases was 7.9% between 2006 and 2010.[8]
HIC = high-incidence country.

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RESUME

CONTEXTE : Au Canada, les personnes nées à l'étranger représentent 67% des cas de tuberculose (TB) annuels, alors qu'ils ne constituent que 21% de la population. Des études épidémiologiques moléculaires suggèrent que la majorité des patients tuberculeux nés à l'étranger ont eu une réactivation d'une infection tuberculeuse latente (LTBI) acquise avant leur immigration.

OBJECTIF : Estimer l'impact sur l'incidence d'une stratégie de prévention qui dépisterait une sélection d'immigrants à leur arrivée à la recherche d'une LTBI et proposer un traitement préventif à ceux qui seraient positifs.

SCHÉMA : Un modèle déterministe a été élaboré afin de quantifier l'incidence de la TB active chez les immigrants au Canada et validé grâce aux données nationales relatives à l'immigration et aux cas de TB.

RÉSULTATS : Les simulations réalisées grâce à ce modèle ont suggéré que la meilleure stratégie serait de dépister et de traiter la LTBI chez les immigrants nés dans des pays où l'incidence de la TB est estimée à >50/100 000 personnes-années. Si cette stratégie avait été mise en œuvre en 1986, en 2002 l'incidence nationale de la TB serait tombée de 5,4 à 4,4 cas/100 000 habitants, soit une diminution de 18,5%.

CONCLUSION : Cette étude suggère que dépister et traiter la LTBI chez des personnes nées dans des pays à forte incidence de TB est la stratégie la plus efficace en termes de nombre total de personnes dépistées et traitées et de réduction de l'incidence nationale de la TB.

RESUMEN

MARCO DE REFERENCIA: Las personas que residen en el Canadá nacidas en el extranjero representan el 67% de todos los casos de tuberculosis (TB) cada año, pero constituyen solo el 21% del total de la población. Los estudios de epidemiología molecular indican que la mayoría de los casos de TB en las personas nacidas en el extranjero proviene de la reactivación de una infección tuberculosa latente (LTBI) adquirida antes de la inmigración.

OBJETIVO: Calcular la repercusión en la incidencia de TB de una estrategia de prevención que consista en detectar sistemáticamente la LTBI en algunos inmigrantes y ofrecer el tratamiento preventivo a los que presentan un resultado positivo.

MÉTODO: Se aplicó un modelo determinista con el fin de cuantificar la incidencia de TB activa en los inmigrantes al Canadá y se validó el modelo con los datos del servicio nacional de inmigración y del registro de casos de TB.

RESULTADOS: Los modelos de simulación indicaron que sería óptimo practicar la detección sistemática y tratar la LTBI en los nuevos inmigrantes que nacieron en países que presentan una tasa de incidencia calculada por encima de 50/100 000 años-persona. Si esta estrategia se hubiese introducido en 1986, la tasa de incidencia nacional de TB en el 2002 habría sido un 18,5% más baja, con 5,4–4,4 casos/100 000 habitantes.

CONCLUSIÓN: Los resultados del presente estudio indican que la detección sistemática y el tratamiento de la LTBI en las personas nacidas en países con una alta incidencia de TB es la estrategia más eficaz con respecto al número de personas examinadas y tratadas y al porcentaje de disminución de la incidencia nacional de la TB.