PERSISTENT HIGH INCIDENCE OF TUBERCULOSIS AMONG IMMIGRANTS IN A LOW-INCIDENCE COUNTRY: IMPACT OF IMMIGRANTS WITH EARLY OR LATE LATENCY

Hongbin Guo and Jianhong Wu

Centre for Disease Modeling
Department of Mathematics and Statistics
York University, 4700 Keele Street
Toronto, ON, M3J 1P3, Canada

(Communicated by Jia Li)

Abstract. Spread of tuberculosis (TB) due to the immigration from some developing countries with high TB incidence to developed countries poses an increasing challenge in the global TB control. Here a simple compartmental TB model with constant immigration, early and late latency is developed in order to investigate the impact of new immigrants with latent TB on the overall TB incidence, and to compare the difference contributed by different proportions of latently-infected new immigrants with high or low risk to develop active TB shortly after arrival. The global dynamics of the system is completely classified, numerical simulations are carried out for different scenarios, and potential applications to public health policy are discussed.

1. **Introduction.** Tuberculosis is an airborne infectious disease that is preventable and curable. Only individuals with active TB bacteria in their lungs can infect others when they cough. The risk of developing active TB is greatest within the first several years following infection, however, sometimes disease can present many years after infection [9, 20, 24, 30]. About 10% people infected with TB bacilli will become sick with active TB in their lifetime without treatment [37]. Around 5% of infected will develop active TB many years later mainly through endogenous reactivation [2, 37].

Globally, there are estimated 9.2 million new cases of TB in 2006 [37]. 1.5 million people died from TB in 2006 [37] and the vast majority of TB deaths are in the developing countries. It was estimated that 2 billion people, one-third of the world total population, are infected with TB bacilli. This provides a huge pool for future TB epidemic. Global spread of tuberculosis due to the immigration from developing countries with high TB incidence to developed countries with low TB incidence poses an increasing challenge in TB control in many developed countries. In certain low TB incidence countries such as Australia, Canada and United States, increasing immigration contributes to a growing TB incidence and may have a significant impact on the local TB transmission patterns [10, 11, 12, 15, 16, 17, 18, 26, 36].

Mathematical models have been used significantly in our understanding of TB epidemics and the potential impact of control strategies, see [1, 2, 3, 7, 8, 31, 38, 39] and references therein. Although there has been remarkable progress in the development of a theoretical framework for the study of TB dynamics and the related epidemiological processes, two of the most important challenges for TB modeling raised in [8], namely immigration and ethnicity, have been largely ignored. Murphy *et al* [31] compared the TB epidemics in demographically distinct heterogenous populations between India and USA to investigate the effects of host genetics. McCluskey and van den Driessche [25] considered a TB model with latent and infective immigration, and Zhou *et al* [38] formulated a discrete model to investigate the TB epidemics for overall population in Canada.

In this paper, we develop a deterministic compartmental TB model with constant immigration to early and late latencies, in order to compare the different contributions of latently-infected new immigrants who have a high or low risk to develop active TB shortly after arrival. Our results show that early latent TB has a much more significant impact than late latent TB on the incidence of immigrant population, and in particular, early latent TB drives (even a small percentage) the TB incidence up quickly. It is therefore hoped that this qualitative study can contribute to the medical screening and following-up policy in developed countries with large number of immigrants.

The paper is organized as follows: the model formulation is presented in next section. In Section 3, we establish the global dynamics of the proposed model and give the proof of the global stability of endemic equilibrium based on a global Lyapunov function. In Section 4, numerical simulations are carried out for different scenarios using data from Canada. A summery is given in Section 5.

2. **Model formulation.** Over the past decade, most of one quarter million new immigrants who arrived in Canada annually are adults and more than 80% of them were from TB-endemic countries [6, 28, 29]. It is estimated that 40% of the new immigrants are positive for tuberculin skin test [28]. These immigrants with positive tuberculin skin test are at risk for future disease at different time scales. A proportion of them will develop TB quickly after entry and another fraction of them will develop TB at later time. Due to strict immigration medical checks before entry, new immigrants with active TB at arrival are rare (except for refugees [16]).

The percentage of new immigrants who develop TB after arrival is estimated in several studies [9, 10, 17, 18, 34]. In 1998 [16], it was estimated that 8% of foreign-born TB cases reported in Canada developed TB within the first year of arrival, 18% developed active TB within 2 years and 37% within five years. Another study from Australia is shown in Figure 1. A further comparison of percentages for new immigrants who develop active TB after arrival among the UK, Canada and Australia is given in Table 1, where strict immigration medical checks were carried out but a sharp proportion of annual new immigrants were screened to be latently infected, indicating the infection before entry. Thus a reasonable assumption is that a proportion of annual new immigrants are latently infected, and a small percentage of them are in the highest risk to develop TB after arrival.

We propose a simple ODE model that incorporates fast and slow routes to TB, early and late latency stages of latent TB infection (LTBI) as previously introduced in [39]. One novelty of our model is that different proportions of new immigrants to host countries are assumed to have different risks to develop TB within the first two
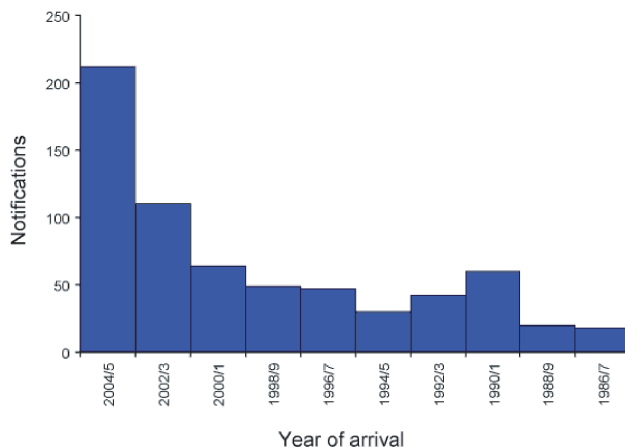
FIGURE 1. 2005 TB notification numbers of immigrants who develop TB after arrival in Australia, Figure adapted from [10].

Groups classification	Non-UK born 2000-2005, the UK	Foreign-born 2002, Canada	Overseas-born 2005, Australia
within 2 years' arrival	22%	25%	23%
3 or more years prior	78%	75%	74%
Total	100%	100%	100%

TABLE 1. Percentage of latently-infected immigrants who develop TB after entry in three different studies. This table is tabulated based on three different studies [10, 16, 18, 27].

years after arrival or at a later period of time. It is reported, at least in Canada, that TB transmission from the foreign-born population to others is small [19, 21], and is even smaller from others to the foreign-born [19, 21]. Therefore, in what follows, for the study of TB transmission, we consider the foreign-born population alone.

Using a compartmental approach, the total foreign-born population in a host country is partitioned into following compartments: susceptible individuals (X), early latent stage (E) and late latent stage (L) individuals, individuals with active TB (T), and recovered individuals (R). Only individuals in compartment T are infectious, and new infections result from contacts between a susceptible and an infectious individual within the immigrant population, with an incidence rate $\beta X(t)T(t)$. Here $X(t), E(t), L(t), T(t)$ and $R(t)$ denote the numbers of individuals in the respective compartments at time t. Once infected, individuals will progress through the early latent stage with an average rate ω within the first two years. A fraction p, $0 < p \leq 1$, of these individuals progress directly to the active TB stage, and the remaining $1-p$ fraction progresses to the late latent stage. Once there, the rate of slow progression to active TB due to reactivation is at a lower rate ν. The inputs to the susceptible, early latent stage and late latent stage compartments are $(1 - q_1 - q_2)\pi$, $q_1\pi$ and $q_2\pi$, respectively. Here π is the average number of annual new immigrants to the host country, and q_1, q_2 are percentages of new immigrants

who are in early latent (high risk) or late latent stages (low risk) to develop TB. Due to strict immigration policies, we assume that there are no new immigrants with active TB. The natural removal rates for all compartments X, E, L, T, R are d_X, d_E, d_L, d_T, d_R, respectively. α is the TB-caused death rate, and δ is the rate constant of recovery by nature or treatment. The dynamical transfer among the compartments is depicted in Figure 2. Here all parameters are assumed to be nonnegative. The model is described by the following system of ODEs:
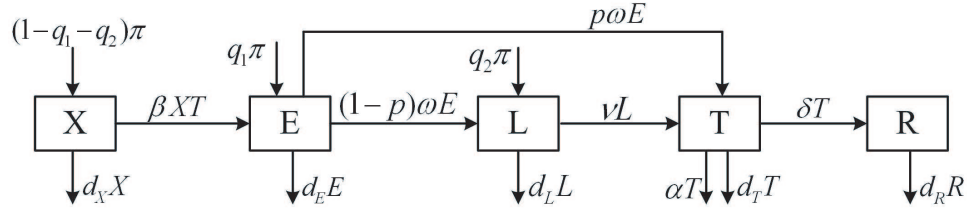

FIGURE 2. Schematic diagram of disease transmission and progression for the deterministic TB model (1) with new immigrants to early or late latency stage.

$$\begin{cases} X' = (1 - q_1 - q_2)\pi - \beta XT - d_X X, \\ E' = q_1\pi + \beta XT - (d_E + \omega)E, \\ L' = q_2\pi + (1 - p)\omega E - (d_L + \nu)L, \\ T' = p\omega E + \nu L - (d_T + \alpha + \delta)T, \end{cases} \tag{1}$$

and

$$R' = \delta T - d_R R.$$

Here we assume that $q_1^2 + q_2^2 \neq 0$. For $q_1 = q_2 = 0$, model (1) reduces to one in [39] and its global dynamics were established in [13]. If $q_1^2 + q_2^2 \neq 0$, model (1) becomes the so-called *immigration* models. The complete analysis for an SIR model with immigration into infective compartment appeared first in [4]. The usual disease-free equilibrium disappears and the basic reproduction number also loses its original meaning. And the system always has a unique endemic equilibrium which is globally asymptotically stable [4, 5]. An SEI model of TB with immigration into both latent and infectious classes was considered in [25] and the global stability of the endemic equilibrium was established for proportionate incidence. One epidemiological consequence of immigration models is that the disease always persists in the population. However, the quantitative impact of how new immigrants could exert on the disease incidence in the population is not clear and needs further explorations.

3. **Model analysis.**

3.1. **Equilibria and main results.** Since the variable R doesn't appear in other equations in (1), we will focus on system (1) and study its global behavior. It is easy to show that solutions of (1) starting from nonnegative initial conditions remains to be nonnegative for all $t \geq 0$. In what follows, we focus on these solutions. From the first equation of (1), in the absence of disease, we have

$$X' \leq (1 - q_1 - q_2)\pi - d_X X,$$

and thus $\limsup\limits_{t\to\infty} X(t) \leq (1 - q_1 - q_2)\pi/d_X$ along each solution to (1). Let $N = X + E + L + T$. Then

$$N' = (X + E + L + T)' \leq \pi - \bar{d}N - \alpha T - \delta T,$$

where $\bar{d} = \min\{d_X, d_E, d_L, d_T\}$. Therefore, $\limsup_{t\to\infty} N(t) \leq \pi/\bar{d}$. Consequently, model (1) can be studied in the following feasible region

$$\Gamma = \{(X, E, L, T) \in \mathbb{R}_+^4 \mid 0 \leq X \leq (1 - q_1 - q_2)\pi/d_X, 0 \leq X + E + L + T \leq \pi/\bar{d}\},$$

where $\mathbb{R}_+^4$ denotes the non-negative cone of $\mathbb{R}^4$ including its lower dimensional faces. It can be verified that Γ is positively invariant with respect to (1). We denote by $\overline{\Gamma}$ and $\overset{\circ}{\Gamma}$ the closure and the interior of Γ in $\mathbb{R}_+^4$, respectively.

An equilibrium of system (1) satisfies the following system of algebraic equations

$$\begin{cases} 0 = (1 - q_1 - q_2)\pi - \beta XT - d_X X, \\ 0 = q_1\pi + \beta XT - (d_E + \omega)E, \\ 0 = q_2\pi + (1 - p)\omega E - (d_L + \nu)L, \\ 0 = p\omega E + \nu L - (d_T + \alpha + \delta)T. \end{cases} \tag{2}$$

Solving X from the first equation in (2), we obtain

$$X = \frac{(1 - q_1 - q_2)\pi}{\beta T + d_X}. \tag{3}$$

Substituting the last equation into the third equation in (2) to cancel the L term, we have

$$q_2\pi\nu + (pd_L + \nu)\omega E = (d_L + \nu)(d_T + \alpha + \delta)T. \tag{4}$$

Combining (4) with the second equation in (2) and canceling E, we get

$$(pd_L + \nu)\omega[q_1\pi + \beta XT] + q_2\pi\nu(d_E + \omega) = (d_E + \omega)(d_L + \nu)(d_T + \alpha + \delta)T. \tag{5}$$

Substituting X in (3) into (5) yeilds

$$q_1\pi\omega(pd_L + \nu) + q_2\pi\nu(d_E + \omega) + (pd_L + \nu)\omega\beta T\frac{(1 - q_1 - q_2)\pi}{\beta T + d_X}$$
$$= (d_E + \omega)(d_L + \nu)(d_T + \alpha + \delta)T. \tag{6}$$

Then, we get a quadratic equation for T

$$f(T) \doteq a_1 T^2 + a_2 T + a_3 = 0,$$

where

$a_1 = -\beta(d_E + \omega)(d_L + \nu)(d_T + \alpha + \delta) < 0,$
$a_3 = d_X\pi[q_1\omega(pd_L + \nu) + q_2\nu(d_E + \omega)],$
$a_2 = \beta(1 - q_2)\pi(pd_L + \nu) + \beta q_2\pi\nu(d_E + \omega) - d_X[(d_E + \omega)(d_L + \nu)(d_T + \alpha + \delta)].$

Note that if $q_1^2 + q_2^2 \neq 0$, then $a_3 > 0$ and the quadratic equation $f(T)$ always has a positive solution

$$T_+^* = \frac{a_2 + \sqrt{a_2^2 - 4a_1 a_3}}{-2a_1} > 0$$

in $\overset{\circ}{\Gamma}$. Substituting this value into (2), we will get an endemic equilibrium $P^* = (X^*, E^*, L^*, T^*)$ in $\overset{\circ}{\Gamma}$, with $X^* > 0, E^* > 0, L^* > 0, T^* > 0$.

In [13], the case where $q_1 = q_2 = 0$ is considered. The basic reproduction number is given as $R_0 = \frac{\beta\pi\omega(\nu + pd_L)}{d_X(d_E + \omega)(d_L + \nu)(d_T + \alpha + \delta)}$. It was shown that if $R_0 \leq 1$, then system (1) always has a disease-free equilibrium which is globally asymptotically stable

(TB will die out eventually in the foreign-born population); if $R_0 > 1$, then system (1) has a unique endemic equilibrium which is globally asymptotically stable in the interior of Γ (TB will persist in the foreign-born population irrespective of any initial condition).

Here we consider the case where $q_1^2 + q_2^2 \neq 0$. Our main result is as follows:

Theorem 3.1. *Suppose that $q_1^2 + q_2^2 \neq 0$. Then system (1) always has a unique endemic equilibrium P^* which is globally asymptotically stable in $\overset{\circ}{\Gamma}$. All solutions with positive initial conditions will converge to the unique endemic equilibrium P^*, and any size of initial outbreak will become endemic in the foreign-born population.*

Proof of GAS of endemic equilibrium. The endemic equilibrium satisfies the following system of equations:

$$\begin{cases} (1 - q_1 - q_2)\pi = \beta X^* T^* + d_X X^*, \\ q_1 \pi + \beta X^* T^* = (d_E + \omega) E^*, \\ q_2 \pi + (1 - p)\omega E^* = (d_L + \nu) L^*, \\ p\omega E^* + \nu L^* = (d_T + \alpha + \delta) T^*. \end{cases} \tag{7}$$

Set $x(t) = (X(t), E(t), L(t), T(t)) \in \Gamma \subset \mathbb{R}_+^4$. Consider a Lyapunov function

$$\begin{aligned} V(x) &= A(X - X^* - X^* \ln \frac{X}{X^*}) + B(E - E^* - E^* \ln \frac{E}{E^*}) \\ &\quad + C(L - L^* - L^* \ln \frac{L}{L^*}) + D(T - T^* - T^* \ln \frac{T}{T^*}), \end{aligned}$$

where

$$A = B = \frac{(pd_L + \nu)\omega}{d_E + \omega}, \ C = \nu, \ D = d_L + \nu \tag{8}$$

are positive constants and (X^*, E^*, L^*, T^*) is the endemic equilibrium P^*. We note that the function $V(x)$ is positive definite with respect to $x^* = P^*$. The derivative of $V(t)$ along the solution $(X(t), E(t), L(t), T(t))$ of (1) is

$$V' = A(X' - \frac{X^*}{X}X') + B(E' - \frac{E^*}{E}E') + C(L' - \frac{L^*}{L}L') + D(T' - \frac{T^*}{T}T'). \tag{9}$$

Using (1) and the first equation of (7), we obtain

$$\begin{aligned} &X' - \frac{X^*}{X}X' \\ &= (1 - q_1 - q_2)\pi - \beta XT - d_X X - (1 - q_1 - q_2)\pi\frac{X^*}{X} + \beta X^* T + d_X X^* \\ &= \beta X^* T - \beta XT + d_X X^* \left(2 - \frac{X}{X^*} - \frac{X^*}{X}\right) + \beta X^* T^* - \frac{\beta X^* T^* X^*}{X} \\ &\leq \beta X^* T - \beta XT + \beta X^* T^* - \frac{\beta X^* T^* X^*}{X}, \end{aligned} \tag{10}$$

since $2 - \frac{X}{X^*} - \frac{X^*}{X} \leq 0$. Similarly, using (1), we have

$$\begin{aligned} E' - \frac{E^*}{E}E' &= q_1\pi + \beta XT - (d_E + \omega)E - q_1\pi\frac{E^*}{E} - \beta\frac{XTE^*}{E} + (d_E + \omega)E^*, \\ L' - \frac{L^*}{L}L' &= q_2\pi + (1 - p)\omega E - (d_L + \nu)L - q_2\pi\frac{L^*}{L} - (1 - p)\omega\frac{EL^*}{L} \\ &\quad + (d_L + \nu)L^*, \\ T' - \frac{T^*}{T}T' &= p\omega E + \nu L - (d_T + \alpha + \delta)T - p\omega\frac{ET^*}{T} - \nu\frac{LT^*}{T} \\ &\quad + (d_T + \alpha + \delta)T^*. \end{aligned} \tag{11}$$

Substituting (10) and (11) into (9) and using (8), we can rearrange V' as

$$
\begin{aligned}
V' = {}& [A\beta X^* - D(d_T + \alpha + \delta)]T + \Big[A\beta X^* T^* + Aq_1\pi + A(d_E + \omega)E^* \\
& + Cq_2\pi + C(d_L + \nu)L^* + D(d_T + \alpha + \delta)T^* \Big] \\
& + \Big[-A\frac{\beta X^* T^* X^*}{X} - A\frac{q_1\pi E^*}{E} - A\frac{\beta XTE^*}{E} - C\frac{q_2\pi L^*}{L} \\
& - C\frac{(1-p)\omega EL^*}{L} - D\frac{p\omega ET^*}{T} - D\frac{\nu LT^*}{T} \Big] \\
\doteq {}& V_1 + V_2 + V_3.
\end{aligned} \tag{12}
$$

Furthermore

$$
V_1 = [A\beta X^* - D(d_T + \alpha + \delta)]T = -\pi\,(Aq_1 + q_2\nu)\,\frac{T}{T^*}. \tag{13}
$$

This is achieved as follows: combining the last two equations of (7) and canceling the L^* yield

$$
q_2\pi\nu + (pd_L + \nu)\omega E^* = (d_L + \nu)(d_T + \alpha + \delta)T^*. \tag{14}
$$

Then combining (14) with the second equation of (7) and canceling the E^*, we have

$$
(pd_L + \nu)\omega[q_1\pi + \beta X^* T^*] + q_2\pi\nu(d_E + \omega) = (d_E + \omega)(d_L + \nu)(d_T + \alpha + \delta)T^*.
$$

Dividing both sides by $(d_E + \omega)T^*$ gives

$$
\frac{(pd_L + \nu)\omega}{(d_E + \omega)} \cdot \frac{q_1\pi + \beta X^* T^*}{T^*} + \frac{q_2\pi\nu}{T^*} = (d_L + \nu)(d_T + \alpha + \delta).
$$

Thus

$$
A\frac{q_1\pi}{T^*} + A\beta X^* + \frac{q_2\pi\nu}{T^*} = D(d_T + \alpha + \delta). \tag{15}
$$

Rewriting (15) as

$$
A\beta X^* - D(d_T + \alpha + \delta) = -\frac{Aq_1\pi}{T^*} - \frac{Cq_2\pi}{T^*}, \tag{16}
$$

then V_1 is obtained by multiplying T on (16).

Now we are in a position to simplify V_2. By (15), the second and third equations of (7) and using (8), V_2 becomes

$$
\begin{aligned}
V_2 \ & = 2A\beta X^* T^* + 2Aq_1\pi + 2Cq_2\pi + A(d_E + \omega)E^* + C(d_L + \nu)L^* \\
& = 3A\beta X^* T^* + 3Aq_1\pi + 2Cq_2\pi + C(d_L + \nu)L^* \\
& = 3A\beta X^* T^* + 3Aq_1\pi + 3Cq_2\pi + (1-p)C\omega E^*.
\end{aligned}
$$

Note that

$$
\begin{aligned}
(1-p)C\omega E^* \ & = \frac{(1-p)\nu}{pd_L + \nu}\frac{(pd_L + \nu)\omega}{d_E + \omega}(d_E + \omega)E^* \\
& = \frac{(1-p)\nu}{pd_L + \nu}A(d_E + \omega)E^* \\
& = \frac{(1-p)\nu}{pd_L + \nu}A(\beta X^* T^* + q_1\pi).
\end{aligned}
$$

Define

$$
a_1 = \frac{p(d_L + \nu)}{pd_L + \nu}, \ b_1 = \frac{(1-p)\nu}{pd_L + \nu}. \tag{17}
$$

Thus $a_1 > 0$, $b_1 > 0$, $a_1 + b_1 = 1$. Furthermore

$$\begin{aligned}
V_2 &= 3A\beta X^*T^* + 3Aq_1\pi + 3Cq_2\pi + Ab_1(\beta X^*T^* + q_1\pi) \\
&= (3 + b_1)(A\beta X^*T^* + Aq_1\pi) + 3Cq_2\pi \\
&= (3a_1 + 4b_1)(A\beta X^*T^* + Aq_1\pi) + 3Cq_2\pi.
\end{aligned} \tag{18}$$

From the second equation of (7), we define

$$\beta_1 = \frac{q_1\pi}{(d_E + \omega)E^*}, \;\; \beta_2 = \frac{\beta X^*T^*}{(d_E + \omega)E^*}, \text{ and } \beta_1 > 0, \beta_2 > 0, \beta_1 + \beta_2 = 1. \tag{19}$$

Combining the second and third equations of (7) and canceling the E^*, we have

$$\begin{aligned}
\nu(d_L + \nu)L^* &= \frac{(1-p)\nu\omega}{(d_E + \omega)}[q_1\pi + \beta X^*T^*] + q_2\pi\nu \\
&= \frac{(1-p)\nu}{pd_L + \nu} \cdot \frac{(pd_L + \nu)\omega}{(d_E + \omega)}[q_1\pi + \beta X^*T^*] + Cq_2\pi \\
&= b_1 A[q_1\pi + \beta X^*T^*] + Cq_2\pi.
\end{aligned}$$

Define

$$\eta_1 = \frac{b_1 A q_1\pi}{\nu(d_L + \nu)L^*}, \;\; \eta_2 = \frac{b_1 A\beta X^*T^*}{\nu(d_L + \nu)L^*}, \;\; \eta_3 = \frac{Cq_2\pi}{\nu(d_L + \nu)L^*}. \tag{20}$$

Thus $\eta_i > 0$, $i = 1, 2, 3$, and $\eta_1 + \eta_2 + \eta_3 = 1$. Now combing V_3 with V_1 in (13) and regrouping, we get

$$\begin{aligned}
&V_1 + V_3 \\
={}& -A\frac{\beta X^*T^*X^*}{X} - A\frac{q_1\pi E^*}{E} - A\frac{\beta XTE^*}{E} - C\frac{q_2\pi L^*}{L} - C\frac{(1-p)\omega EL^*}{L} \\
& - D\frac{p\omega ET^*}{T} - D\frac{\nu LT^*}{T} - A\frac{q_1\pi T}{T^*} - \frac{Cq_2\pi T}{T^*} \\
={}& -A(a_1 + b_1)\frac{\beta X^*T^*X^*}{X} - A(a_1 + b_1)\frac{q_1\pi E^*}{E} - A(a_1 + b_1)\frac{\beta XTE^*}{E} \\
& - C\frac{q_2\pi L^*}{L} - C(\beta_1 + \beta_2)\frac{(1-p)\omega EL^*}{L} - D(\beta_1 + \beta_2)\frac{p\omega ET^*}{T} \\
& - D(\eta_1 + \eta_2 + \eta_3)\frac{\nu LT^*}{T} - A(a_1 + b_1)\frac{q_1\pi T}{T^*} - \frac{Cq_2\pi T}{T^*} \\
={}& \left\{ -Ab_1\frac{\beta X^*T^*X^*}{X} - Ab_1\frac{\beta XTE^*}{E} - C\beta_2\frac{(1-p)\omega EL^*}{L} - D\eta_2\frac{\nu LT^*}{T} \right\} \\
& + \left\{ -Aa_1\frac{\beta X^*T^*X^*}{X} - Aa_1\frac{\beta XTE^*}{E} - D\beta_2\frac{p\omega ET^*}{T} \right\} \\
& + \left\{ -Ab_1\frac{q_1\pi E^*}{E} - Ab_1\frac{q_1\pi T}{T^*} - C\beta_1\frac{(1-p)\omega EL^*}{L} - D\eta_1\frac{\nu LT^*}{T} \right\} \\
& + \left\{ -Aa_1\frac{q_1\pi E^*}{E} - Aa_1\frac{q_1\pi T}{T^*} - D\beta_1\frac{p\omega ET^*}{T} \right\} \\
& + \left\{ -\frac{Cq_2\pi T}{T^*} - C\frac{q_2\pi L^*}{L} - D\eta_3\frac{\nu LT^*}{T} \right\} \\
\doteq{}& I_1 + I_2 + I_3 + I_4 + I_5.
\end{aligned} \tag{21}$$

Combining (21) with (18), we have

$$V' \leq \sum_{i=1}^{3} V_i = (3a_1 + 4b_1)(A\beta X^*T^* + Aq_1\pi) + 3Cq_2\pi + \sum_{i=1}^{5} I_i$$
$$= [4b_1 A\beta X^*T^* + I_1] + [3a_1 A\beta X^*T^* + I_2]$$
$$+ [4b_1 Aq_1\pi + I_3] + [3a_1 Aq_1\pi + I_4] + [3Cq_2\pi + I_5] \tag{22}$$
$$\doteq \sum_{i=1}^{5} J_i.$$

By applying the mean inequality

$$\frac{x_1 + x_2 + \cdots + x_n}{n} \geq \sqrt[n]{x_1 \cdot x_2 \cdots x_n}, \ (x_i \geq 0, i = 1, 2, \cdots, n),$$

we can show that $V' \leq V_1 + V_2 + V_3 \leq 0$. Using (8), (17), (19) and (20) and notation $\bar{\beta} \doteq \beta X^*T^*$, we obtain the following inequalities:

$$J_1 = 4b_1 A\bar{\beta} + I_1$$
$$\leq 4b_1 A\bar{\beta} - 4\sqrt[4]{Ab_1\beta X^*T^*X^* \cdot Ab_1\beta E^* \cdot C\beta_2(1-p)\omega L^* \cdot D\eta_2\nu T^*}$$
$$= 4b_1 A\bar{\beta} - 4\sqrt[4]{(Ab_1\bar{\beta})^2 \cdot (1-p)C\omega \cdot \beta_2 E^* \cdot D\nu\eta_2 L^*}$$
$$= 4b_1 A\bar{\beta} - 4\sqrt[4]{(Ab_1\bar{\beta})^2 \frac{(1-p)\nu}{pd_L + \nu} \cdot \frac{(pd_L + \nu)\omega}{d_E + \omega} \cdot \beta_2(d_E + \omega)E^* \cdot D\nu\eta_2 L^*} \tag{23}$$
$$= 4b_1 A\bar{\beta} - 4\sqrt[4]{(Ab_1\bar{\beta})^2 \cdot b_1 \cdot A \cdot \bar{\beta} \cdot b_1 A\bar{\beta}}$$
$$= 0;$$

$$J_2 = 3a_1 A\bar{\beta} + I_2$$
$$\leq 3a_1 A\bar{\beta} - 3\sqrt[3]{Aa_1\beta X^*T^*X^* \cdot Aa_1\beta E^* \cdot D\beta_2 p\omega T^*}$$
$$= 3a_1 A\bar{\beta} - 3\sqrt[3]{(Aa_1\bar{\beta})^2 \cdot pD\omega \cdot \beta_2 E^*}$$
$$= 3a_1 A\bar{\beta} - 3\sqrt[3]{(Aa_1\bar{\beta})^2 \cdot \frac{p(d_L + \nu)}{pd_L + \nu} \cdot \frac{(pd_L + \nu)\omega}{d_E + \omega} \cdot \beta_2(d_E + \omega)E^*} \tag{24}$$
$$= 3a_1 A\bar{\beta} - 3\sqrt[3]{(Aa_1\bar{\beta})^2 \cdot a_1 \cdot A \cdot \bar{\beta}}$$
$$= 0;$$

$$J_3 = 4b_1 Aq_1\pi + I_3$$
$$\leq 4b_1 Aq_1\pi - 4\sqrt[4]{Ab_1 q_1\pi E^* \cdot Ab_1 q_1\pi \cdot C\beta_1(1-p)\omega L^* \cdot D\eta_1\nu}$$
$$= 4b_1 Aq_1\pi - 4\sqrt[4]{[Ab_1 q_1\pi]^2 \cdot (1-p)C\omega \cdot \beta_1 E^* \cdot D\eta_1\nu L^*}$$
$$= 4b_1 Aq_1\pi \left(1 - \sqrt[4]{\frac{(1-p)\nu}{pd_L + \nu} \cdot \frac{(pd_L + \nu)\omega}{d_E + \omega} \cdot \beta_1(d_E + \omega)E^* \cdot \frac{\eta_1 D\nu L^*}{[Ab_1 q_1\pi]^2}}\right) \tag{25}$$
$$= 4b_1 Aq_1\pi \left(1 - \sqrt[4]{b_1 \cdot A \cdot q_1\pi \cdot Ab_1 q_1\pi/[Ab_1 q_1\pi]^2}\right)$$
$$= 0;$$

$$\begin{aligned}
J_4 &= 3a_1 A q_1 \pi + I_4 \\
&\leq 3a_1 A q_1 \pi - 3\sqrt[3]{Aa_1 q_1 \pi E^* \cdot Aa_1 q_1 \pi \cdot D\beta_1 p\omega} \\
&= 3a_1 A q_1 \pi - 3\sqrt[3]{[Aa_1 q_1 \pi]^2 \cdot pD\omega \cdot \beta_1 E^*} \\
&= 3a_1 A q_1 \pi - 3\sqrt[3]{[Aa_1 q_1 \pi]^2 \cdot \frac{p(d_L + \nu)}{pd_L + \nu} \cdot \frac{(pd_L + \nu)\omega}{d_E + \omega} \cdot \beta_1(d_E + \omega)E^*} \\
&= 3a_1 A q_1 \pi - 3\sqrt[3]{[Aa_1 q_1 \pi]^2 \cdot a_1 \cdot A \cdot q_1 \pi} \\
&= 0;
\end{aligned} \tag{26}$$

$$\begin{aligned}
J_5 &= 3C q_2 \pi + I_5 \\
&\leq 3C q_2 \pi - 3\sqrt[3]{C q_2 \pi L^* \cdot q_2 \pi \nu \cdot D\eta_3 \nu} \\
&= 3C q_2 \pi - 3\sqrt[3]{[C q_2 \pi]^2 \cdot \eta_3 D\nu L^*} \\
&= 3C q_2 \pi - 3\sqrt[3]{[C q_2 \pi]^2 \cdot C q_2 \pi} \\
&= 0.
\end{aligned} \tag{27}$$

Substituting (23)–(27) into (22), we conclude that

$$\frac{dV}{dt} \leq V_1 + V_2 + V_3 \leq 0, \text{ for all } X > 0, E > 0, L > 0, T > 0. \tag{28}$$

Furthermore, $V' = 0$ if and only if

$$X = X^*, \text{ and } \frac{E^*}{E} = \frac{L^*}{L} = \frac{T^*}{T}. \tag{29}$$

To find the largest invariant set in the set where $V' = 0$, we use (29) and set $X' = 0$ in the first equation of (1), and we see that $T = T^*$, and hence $E = E^*, L = L^*$. Namely, the largest invariant set where $V' = 0$ is the singleton $\{P^*\}$. By LaSalle's Invariance Principle [22], P^* is globally asymptotically stable with respect to Γ. This completes the proof.

4. **Numerical Simulation.** In order to quantitatively investigate the impact of new immigrants with LTBI on the TB incidence in an foreign-born population, we now conduct some scenario analysis using Canadian data.

We assume that the removal rates for all compartments are equal, i.e., $d_X = d_E = d_L = d_T = d_R$. Table 2 lists the parameter values used in the simulations. $(X_0, E_0, L_0, T_0) = (4431746, 9784, 1196551, 1094)$ is initial data used in simulations for foreign-born population in Canada [35] (Therefore, the latently infected population constitutes 21.4% of total foreign-born population within Canada in 2001 [24, 28]).

In literature, estimated proportions for new immigrants with LTBI in early or late stage are very limited. By varying q_1 and q_2 in simulations and keeping other parameters fixed, we are able to see how the magnitude of the TB incidence depends on different combinations of q_1 and q_2. The TB incidence rate (the number of new TB cases per 100,000 persons per year) was computed from $p\omega E + \nu L$ as in [33].

Assume that all new immigrants to Canada are susceptible (i.e. $q_1 = q_2 = 0$). The basic reproduction number for model (1) is calculated as $R_0 = 0.0032 < 1$. Without importation of new immigrants with LTBI, TB incidence rate in the foreign-born population will expect a steady decline, and TB will die out eventually under the current treatment measure. This is a baseline assumption in the subsequent simulations. Now we always assume that $q_1^2 + q_2^2 \neq 0$.

Parameter	Value	Definition	Source
π	$223,840$	average annual new immigrants to Canada.	[6]
β	10^{-8}	transmission rate within foreign-born population in Canada.	[2, 39]
d_X	0.039	removal rate of the foreign-born population.	estimate
p	0.05	5% high-risk LTBI immigrants develop TB within the first 2 years.	[2, 39]
v	0.0002	1% low-risk LTBI immigrants develop TB in the next 50 years.	[2, 39]
ω	0.40	all LTBI immigrants pass through latent stage in the first 2.5 years.	[39]
α	0.06	removal rate (TB-induced death 6%).	[15, 34]
δ	0.80	removal rate (treatment rate 80%).	[15, 34]

TABLE 2. Parameter values for simulations of the compartmental TB model (1) with early and late latently-infected new immigrants.

Effects of early and late latency.

I). $q_1 > 0$ & $q_2 = 0$. This assumes that all latently-infected new immigrants have a high risk to develop TB within the first two years after entry. Increase of q_1 will sharply increase TB incidence rate within a short period of time, see Figure 3a (left). When q_1 increases from 0% to 5% alone, the incidence goes up to 9 quickly. If q_1 reaches 10%, the incidence enhances to a much higher level. This shows that TB incidence is very sensitive to the percentage of new immigrants with early stage LTBI.

II). $q_1 = 0$ & $q_2 > 0$. This assumes that all latently-infected new immigrants have a low risk to develop TB within the first two years after arrival. TB incidence rate increases slowly by increasing q_2 during a relatively long period, see Figure 3a (right). When q_2 even reaches 40%, the incidence still remains around 10. This illustrates that new immigrants with late latent TB alone, though in a large proportion, can not sustain a high TB incidence level in foreign-born population.

III). $q_1 > 0$ & $q_2 > 0$. This reflects more of the reality that new immigrants mix up with both early and late stage LTBI. Figure 3b illustrates the relationship of TB incidence rate with varying q_1 and q_2 at the endemic equilibrium. We can see that the impact of q_1 on the TB incidence is much more significant than that of q_2. A small q_1 combing with a large q_2 seems enough to maintain a persistently high level of TB incidence. Therefore, estimating the values of q_1 and q_2 is of importance in understanding TB dynamics in the foreign-born population, this estimation is also helpful in guiding early TB detection and treatment for new immigrants with LTBI.

Effects of annual new immigrant level.
Now we fix $q_1 = 3\%$ and $q_2 = 37\%$ (this corresponds to a total 40% of annual new immigrants with LTBI) and vary the annual level of new immigrants (π). From half $(111,920)$ of the current average number $(223,840)$, to double of that $(447,680)$, the TB incidence in the foreign-born population changes little in a longer term but exhibits sharp variation in a shorter period (see Figure 4 (a)). Thus reducing the annual level of new immigrants may have a significant impact on the TB control in immigration countries over a relatively shorter period rather than over a longer period.
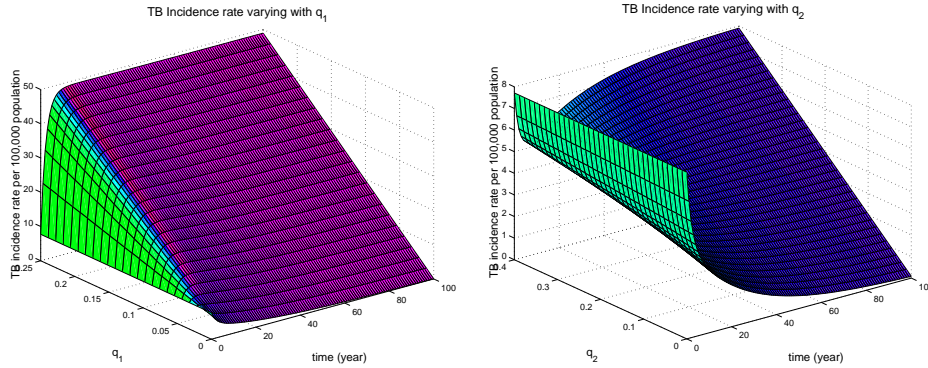
FIGURE 3A. Correlations between TB incidence in the foreign-born population and the percentage of latently-infected new immigrants, all having a high risk (left) or low risk (right) to develop TB within their first two years of arrival, respectively.
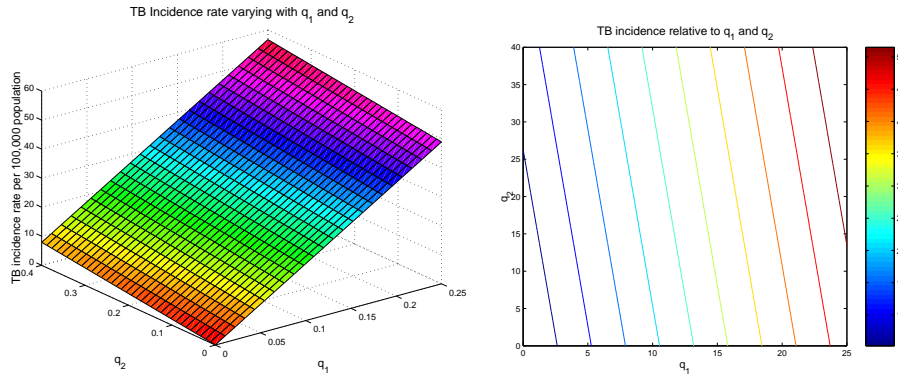

FIGURE 3B. TB incidence at the endemic equilibrium as a function of q_1 and q_2 in a 3D plot (left), and the corresponding 2D isocline (right).

Effect of transmission coefficient. Sensitivity analysis to the important parameter β on the TB incidence is carried out for a long period of time. Figure 4 (b) shows the relationship between TB incidence and the transmission coefficient β. It shows that TB incidence changes slightly as β increases, both in a short and a long term. We conclude that the persistent high TB incidence is driven, in mechanism, by the importation of new immigrants with LTBI rather than new infections occurring in foreign-born population.

5. **Summary.** TB spread by immigration is a very important research topic recently recognized due to the persistence of high incidence rate and gradually increasing percentage in the total TB cases, in most immigration countries with low TB incidence rate [9, 23, 30, 38]. In this paper, we studied a simple compartmental TB model with immigrants to different latencies, to investigate the impact of early and late LTBI new immigrants on the TB incidence rate of the foreign-born population in an immigration country. The proposed TB model always has a unique endemic equilibrium which is globally asymptotically stable, as long as there is
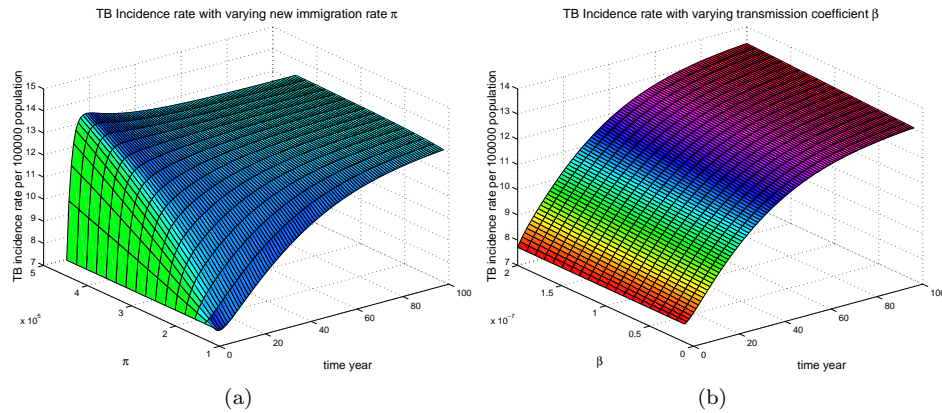
FIGURE 4. Correlation between the TB incidence rate in the foreign-born population and (a) the annual new immigrant level π, (b) the transmission coefficient β, respectively.

latently-infected immigrants to the host population. The proof of global stability of the endemic equilibrium is based on a global Lyapunov function (see e.g. [13, 14] and reference therein).

Using realistic data from Canada, one of immigration countries with low TB incidence, we carried out numerical simulations to compare the difference contributed by latently-infected new immigrants with high or low risk to develop active TB shortly after arrival, on the overall TB incidence rate of the foreign-born population according to different scenarios, such as different combinations of early and late latencies, the annual new immigrant levels and the sensitivity of transmission.

Our simulation results show that new immigrants in early latent stage (q_1) has a much more significant impact than those in late latent stage (q_2) on the TB incidence of foreign-born population in an immigration country. More specifically, importation of new immigrants with early stage LTBI drives the TB incidence fast and high in a short period of time. So it is of a high priority to identify and treat new immigrants with early stage LTBI. In the mean time, new immigrants with late stage LTBI would drive the TB incidence up slowly. Treatment of new immigrants with late LTBI is of a lower priority compared to those with early LTBI. Increasing or decreasing the level of annual new immigrants does not change much on the TB incidence in a long period of time, but a sharp variation is observable in a short period. Sensitivity analysis again verifies that the TB incidence is driven by the importation of LTBI rather than transmission of disease after entry. Our conclusions agree with those in the literature (see [9, 32]). Future research would be expected to explore the combinations of q_1 and q_2 for different foreign-born populations in different immigration countries by further stratifying the immigration population.

REFERENCES

[1] R. M. Anderson and R. M. May, "Infectious Diseases of Humans: Dynamics and Control," Oxford University Press, Oxford, 1992.

[2] S. M. Blower, A. R. Mclean, T. C. Proco, P. M. Small, P. C. Hopewell, M. A. Sanchez and A. R. Moss, *The intrinsic transmission dynamics of tuberculosis epidemics*, Nature Medicine, **1** (1995), 815–821.

[3] S. M. Blower, P. M. Small and P. C. Hopewell, *Control strategies for tuberculosis epidemics: New models for old problems*, Science, **273** (1996), 497–500.

[4] F. Brauer and P. van den Driessche, *Models for transmission of disease with immigration of infectives*, Math. Biosci., **171** (2001), 143–154.

[5] F. Brauer, P. van den Driessche and J. Wu, editors, "Mathematical Epidemiology," Lecture Notes in Mathematics, **1945**, Springer-Verlag, Berlin, 2008.

[6] Canada Immigration Center (CIC), *Facts and figures of immigration in Canada.* Available from: http://www.cic.gc.ca/english/resources/statistics/menu-fact.asp

[7] C. Castillo-Chavez and Z. Feng, *To treat or not to treat: The case of tuberculosis,* J. Math. Biol., **35** (1997), 629–656.

[8] C. Castillo-Chavez and B. Song, *Dynamical models of tuberculosis and their applications,* Math. Biosci. Eng., **1** (2004), 361–404.

[9] T. Cohen and M. Murray, *Incident tuberculosis among recent US immigrants and exogenous reinfection,* Emerg. Infec. Dises., **11** (2005), 725–728.

[10] Communicable Diseases Intelligence, *Tuberculosis notifications in Australia, 2005,* Commun. Dis. Intell., **31** (2007), 71–80.

[11] A. Fanning, *Globalization of tuberculosis,* Canadian Med. Asso. J., **158** (1998), 611–612.

[12] E. Geng, B. Kreiswirth, C. Driver, J. Li, J. Burzynski, P. DellaLatta, A. LaPaz and N. W. Schluger, *Changes in the transmission of tuberculosis in New York City from 1990–1999,* N. Engl. J. Med., **346** (2002), 1453–1458.

[13] H. Guo and M. Y. Li, *Mathematical analysis of a model for latent tuberculosis,* Canadian Appl. Math. Quart., **14** (2006), 185–197.

[14] H. Guo, M. Y. Li and Z. Shuai, *A graph-theoretic approach to the method of global Lyapunov functions,* Proc. Amer. Math. Soc., **136** (2008), 2793–2802.

[15] Health Canada, *Tuberculosis in Canada,* 2001. Available from: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/tbcan01/pdf/tbcan-2001-e.pdf

[16] Health Canada, *Canadian guidelines for the investigation and follow-up of individuals under medical surveillance for TB after arrival in Canada,* Canada Communicable Disease Report, **27** (2002), I57–I68.

[17] Health Protection Agency, *UK TB update,* 2007. Available from: http://www.hpa.org.uk.

[18] Health Protection Agency, *Recent trends in tuberculosis: 2000–2005,* Annual surveillance report, UK, 2006.

[19] E. Hemandez-Garduno, D. Kunimoto, L. Wang, M. Rodrigues, R. K. Elwood, W. Black, S. Mak and J. M. FitzGerald, *Predictors of clustering of tuberculosis in Greater Vancouver: A molecular epidemiology study,* Can. Med. Assoc. J., **167** (2002), 349–352.

[20] J. Inigo, D. Garcia de Viedma, A. Arce, E. Palenque, N. A. Rodriguez, E. Rodriguez, M. J. R. Serrano, S. Andres, E. Bouza and F. Chaves, *Analysis of changes in recent tuberculosis transmission patterns after a sharp increase in immigration,* J. Clinical Microbio., **45** (2007), 63–69.

[21] S. Kulaga, M. Behr, K. Musana, J. Brinkman, D. Menzies, P. Brassard, D. Kunimoto, T.-N. Tannenbaum, L. Thibert, L. Joseph, J.-F. Boivin and K. Schwartzman, *Molecular epidemiology of tuberculosis in Montreal,* CMAJ., **167** (2002), 353–354.

[22] J. P. LaSalle, "The Stability of Dynamical Systems," Regional Conference Series in Applied Mathematics, SIAM, Philadelphia, 1976.

[23] T. Lillebaek, A. B. Andersen, J. Bauer, A. Dirksen, S. Glismann, P. de Haas and A. Kok-Jensen, *Risk of Mycobacterium tuberculosis transmission in a low-incidence country due to immigration from high-incidence areas,* J. Clinical Microbio., **39** (2001), 855–861.

[24] T. Lillebaek, A. B. Andersen, A. Dirksen, E. Smith, L. T. Skovgaard and A. Kok-Jensen, *Persistent high incidence of tuberculosis in immigrants in a low-incidence country,* Emerging Infectious Disease, **8** (2002), 679–684.

[25] C. C. McCluskey and P. van den Driessche, *Global analysis of two tuberculosis models,* J. Dynam. Diff. Eqs., **16** (2004), 139–166.

[26] M. T. Mckenna, E. McCray and I. Onorato, *The epidemiology of tuberculosis among foreign-born persons in the United States, 1986 to 1993,* N. Engl. J. Med., **332** (1995), 1071–1076.

[27] M. E. McPherson, H. Kelly, M. S. Patel and D. Leslie, *Persistent risk of tuberculosis in migrants a decade after arrival in Australia,* Medical J. of Australia, **188** (2008), 528–531.

[28] D. Menzies, *Screening immigrants to Canada for tuberculosis: Chest radiography or tuberculin skin testing?,* Canadian Med. Asso. J., **169** (2003), 1035–1036.

[29] D. Menzies, *Controlling TB among foreign-born within industrialized countries: Expensive Band-Aids,* Am. J. Respiratory Crit. Care Med., **164** (2001), 914–915.

[30] M. B. Murray, *Molecular epidemiology and the dynamics of tuberculosis transmission among foreign-born people,* Canadian Med. Asso. J., **167** (2002), 355–356.

[31] B. M. Murphy, B. H. Singer, S. Anderson and D. Kirschner, *Comparing epidemic tuberculosis in demographically distict heterogenous populations,* Math. Biosci., **180** (2002), 161–185.

[32] S. Patel, A. E. Parsyan, J. Gunn, M. A. Barry, C. Reed, S. Sharnprapai and C. R. Horsburgh, *Risk of progression to active tuberculosis among foreign-born persons with latent tuberculosis,* Chest., **131** (2007), 1811–1816.

[33] T. C. Porco and S. M. Blower, *Quantifying the intrinsic transmission dynamics of tuberculosis*, Theor. Popu. Bio., **54** (1998), 117–132.

[34] Public Health Agency of Canada, *Tuberculosis in Canada 2002,* 2005. Available from: http://www.phac-aspc.gc.ca/publicat/tbcan02/index.html.

[35] Statistics Canada, *2001 Census of Canada,* Available from: http://www.statcan.ca/menu-en.htm.

[36] E. A. Talbot, M. Moore, E. McCray and N. J. Binkin, *Tuberculosis among foreign-born persons in the United States, 1993–1998,* J. Amer. Med. Asso., **284** (2000), 2894–2900.

[37] WHO, "Global Tuberculosis Control: Surveillance, Planning and Financing," World Heath Organization, Geneva, 2008.

[38] Y. Zhou, K. Khan, Z. Feng and J. Wu, *Projection of Canadian tuberculosis incidence with increasing immigration,* J. Theore. Bio., **254** (2008), 215–228.

[39] E. Ziv, C. L. Daley and S. M. Blower, *Early therapy for latent tuberculosis infection,* Amer. J. Epidemiol., **153** (2001), 381–385.

E-mail address: hguo@mathstat.yorku.ca, hongbin.guo@gmail.com
E-mail address: wujh@mathstat.yorku.ca