ELSEVIER Mathematical Biosciences 151 (1998) 135–154

Mathematical Biosciences
an international journal

Global stability of an age-structure model for TB and its applications to optimal vaccination strategies

Carlos Castillo-Chavez [a], Zhilan Feng [b,*]

[a] *Biometrics Unit, Cornell University, Ithaca, NY 14853, USA*
[b] *Department of Mathematics, Purdue University, West Lafayette, IN 47907-1395, USA*

Received 10 March 1998

Abstract

This article focuses on the study of an age-structure model for the disease transmission dynamics of tuberculosis in populations that are subjected to a vaccination program. We first show that the infection-free steady state is globally stable if the basic reproductive number $\mathscr{R}_0$ is below one, and that an endemic steady state exists when the reproductive number in the presence of vaccine is above one. We then apply the theoretical results to vaccination policies to determine the optimal age or ages at which an individual should be vaccinated. It is shown that the optimal strategies can be either one- or two-age strategies.

1. Introduction

Tuberculosis (TB) is a communicable disease primarily spread by the airborne route. The risk that a person may become infected is strongly associated with the probability of coming in contact with an actively infected individual as well as the closeness and duration of the contact [18]. There is evidence showing that TB case rates are highly age-dependent. Furthermore, it is also clear that mixing plays a key role in TB transmission, as it does for most communicable diseases. Approximately 100 million newborns and children received the

* Corresponding author. E-mail: zfeng@math.purdue.edu.

0025-5564/98/$19.00
PII: S0025-5564(98)10016-0

Bacillus of Calmette and Guérin (BCG) vaccine in 1992 through the World Health Organization [2]. More people alive today have been vaccinated with BCG than with any other vaccine. However, despite its wide usage, the effectiveness of BCG in preventing TB is controversial. Results of field trials of the vaccine have differed widely, some indicating protection rates as high as 70–80% while others show a strong evidence that the vaccine was completely ineffective [20]. Potential problems associated with the generalized use of the BCG vaccine in some populations are closely related to the fact that vaccinated individuals will test positive for TB. It, therefore, becomes nearly impossible to be able to detect the prevalence of a disease in a population like the Argentineans where most individuals are vaccinated.

Different vaccination policies have been adopted in different parts of the world. In Argentina, BCG is given both at birth and at age 15. Children are vaccinated between the ages of 12–14 in Queensland (Australia), and newborns are vaccinated in Burma (see Refs. [16,17]). In practice, the application of a vaccination policy is limited by many factors including the cost. Costs may be increased by variability in age-dependent compliance (at birth, the disease may be 'caught' by children in the hospitals). Various policies have been established in the past, and our objective here is to determine whether or not the policies being followed are 'optimal' in some sense.

In order to test the value of a strategy, we consider an age-dependent vaccination rate $\psi(a)$ into our age-structure TB model and calculate the corresponding effect of this rate on the reproductive number for the vaccine-dependent model. Since we are interested in vaccination policies, we first study the effects of age-dependent transmission rates on a model for TB dynamics in a population with or without a vaccination program. The formulation of an age-structure model for the transmission dynamics is straightforward; however, because those with TB who are being treated and vaccinated individuals can become infected again, it is not easy to study such a model. We denote the vaccine-dependent reproductive number by $\mathscr{R}(\psi)$ and obtain a formula for $\mathscr{R}(\psi)$. We establish conditions for the stability of the infection-free steady state distribution and for the existence of an endemic steady state. We also show that, in the absence of vaccine, the infection-free steady state is globally stable if the basic reproductive number $\mathscr{R}_0$ (it is shown to be larger than $\mathscr{R}(\psi)$) is below one. We use the results on the dynamics of our TB age-structure model to study the role of BCG on the epidemiological age-structure of a population. We consider two optimization problems (see Refs. [13,14]): reducing $\mathscr{R}(\psi)$ below a certain level $\mathscr{R}_*$ at minimal costs or minimizing the reproductive number $\mathscr{R}(\psi)$ with fixed resources. Following the approach used by Hadeler and Müller (implicit in the work on optimal harvesting models of Rorres and Fair [19]) we show that the optimal strategies for the two problems above have the form 'vaccinate at a single age' or 'vaccinate at precisely two age classes'. These are the policies followed in Argentina and many other countries. A detailed account on TB epidemiology can be found in Ref. [4].

This paper is organized as follows: Section 2 introduces an age-structure model to study the dynamics of TB in the presence of a vaccine. The reproductive numbers $\mathscr{R}(\psi)$ and $\mathscr{R}_0$ are computed in Section 3. Some local stabilities of the infection-free steady state are also studied in this section. In Section 4 we study the global stability properties of this model. In Section 5 we apply our results to vaccination policies and study the two optimization problems outlined above. Section 6 discusses our results and points to some future work.

2. The model

One of the typical features of TB is that the infectious agent has evolved a symbiotic relationship with the human host; only about 10% of those infected go on to develop the clinical disease. Most people will remain infected, which may lead to long-lasting partial immunity both to further infection and to reactivation of latent bacilli remaining from the original infection [18]. It is, therefore, important to include a latency period into a TB model. Since relapse (reactivation of a disease after an apparent cure) is one of the major risks to be considered in etiological epidemiology of TB [8], it is also necessary to incorporate such a feature in a TB model. We, therefore, assume that treated individuals can become infected again with a lower transmission rate than susceptibles. This may cause some difficulties in the analysis of the model as will be seen later.

In order to formulate an age-structure model for the transmission of TB, we need to introduce some notation. The population is divided into susceptible, vaccinated, exposed, infectious, and treated classes, where $s(t,a), v(t,a), l(t,a), i(t,a)$, and $j(t,a)$ denote the associated density functions with these respective epidemiological age-structure classes. We assume that all newborns are susceptible and that the mixing between individuals is proportional to their age-dependent activity level. We also assume that an individual may become infected only through contact with infectious individuals, that vaccination is partially effective (i.e., vaccinated individuals can become infected again but with a reduced transmission rate), that only susceptibles will be vaccinated (susceptibles can be recognized since they will test negative and TB exposed individuals will test positive), and that the disease-induced death rate can be neglected. The joint dynamics of the age-structure epidemiological classes are governed by the following initial boundary value problem:

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)s(t,a) = -\beta(a)c(a)B(t)s(t,a) - \mu(a)s(t,a) - \psi(a)s(t,a),$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)v(t,a) = \psi(a)s(t,a) - \mu(a)v(t,a) - \delta\beta(a)c(a)B(t)v(t,a),$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)l(t,a)=\beta(a)c(a)B(t)(s(t,a)+\sigma j(t,a)+\delta v(t,a))$$
$$-(k+\mu(a))l(t,a),$$
$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)i(t,a)=kl(t,a)-(r+\mu(a))i(t,a),$$
$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)j(t,a)=ri(t,a)-\sigma\beta(a)c(a)B(t)j(t,a)-\mu(a)j(t,a),$$
$$B(t)=\int_0^\infty \frac{i(t,a')}{n(t,a')}p(t,a,a')\,\mathrm{d}a',$$
$$p(t,a,a')=\frac{c(a')n(t,a')}{\int_0^\infty c(u)n(t,u)\,\mathrm{d}u},$$
$$s(t,0)=\Lambda,\qquad v(t,0)=l(t,0)=i(t,0)=j(t,0)=0,$$
$$s(0,a)=s_0(a),\qquad v(0,a)=v_0(a),\qquad l(0,a)=l_0(a),$$
$$i(0,a)=i_0(a),\qquad j(0,a)=j_0(a),$$
$$n(t,a)=s(t,a)+v(t,a)+l(t,a)+i(t,a)+j(t,a).$$

Λ is the recruitment/birth rate (assumed constant); $\beta(a)$ is the age-specific (average) probability of becoming infected through contact with infectious individuals, $c(a)$ is the age-specific per-capita contact/activity rate and $\mu(a)$ is the age-specific per-capita natural death rate (all of these functions are assumed to be continuous and to be zero beyond some maximum age); k is the per-capita rate at which individuals leave the latent class by becoming infectious and r is the per-capita treatment rate; σ and δ are the reductions in risk due to prior exposure to TB and vaccination, respectively, $0\leqslant\sigma\leqslant 1$, $0\leqslant\delta\leqslant 1$; and $p(t,a,a')$ gives the probability that an individual of age a has contact with an individual of age a' given that it has a contact with a member of the population. Here we assume proportionate mixing as introduced earlier by many authors including Hethcote and Yorke [15], Dietz and Schenzle [10], Anderson and May [1], and Castillo-Chavez et al. [6,7]. Hence, using the approach of Busenberg and Castillo-Chavez [3], we assume that $p(t,a,a')=p(t,a')$ as explicitly described above. The initial age distributions are assumed to be known and to be zero beyond some maximum age. The model (1) is well-posed and the proof is similar to that found in Ref. [7].

In the next section, we derive explicit expressions for $\mathscr{R}(\psi)$, a quantity that must exceed one for the disease to remain endemic (persist). In general, $\mathscr{R}(\psi)$ is called the net reproductive number which measures *the expected number of secondary infection produced by a 'typical' infected individual during its entire–death adjusted–period of infectiousness in an uninfected population.*

3. Calculation of $\mathscr{R}(\psi)$ and stability of the infection-free state

Notice that $n(t,a)$ satisfies the following equations:

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)n(t,a) = -\mu(a)n(t,a),$$
$$n(t,0) = \Lambda,$$
$$n(0,a) = n_0(a) = s_0(a) + v_0(a) + l_0(a) + i_0(a) + j_0(a).$$

Using the method of characteristic curves we can solve for n explicitly:

$$n(t,a) = n_0(a)\frac{\mathscr{F}(a)}{\mathscr{F}(a-t)}H(a-t) + \Lambda\mathscr{F}(a)H(t-a),$$

where

$$\mathscr{F}(a) = \exp\left\{-\int_0^a \mu(s)\,\mathrm{d}s\right\},$$
$$H(s) = 1, s \geqslant 0; \quad H(s) = 0, s < 0.$$

Hence,

$$n(t,a) \to \Lambda\mathscr{F}(a),$$
$$p(t,a) \to \frac{c(a)\mathscr{F}(a)}{\int_0^\infty c(b)\mathscr{F}(b)\mathrm{d}b} =: p_\infty(a), \quad t \to \infty. \tag{2}$$

Introducing the fractions

$$u(t,a) = \frac{s(t,a)}{n(t,a)}, \quad w(t,a) = \frac{v(t,a)}{n(t,a)}, \quad x(t,a) = \frac{l(t,a)}{n(t,a)},$$
$$y(t,a) = \frac{i(t,a)}{n(t,a)}, \quad z(t,a) = \frac{j(t,a)}{n(t,a)},$$

we get a simplified system of Eq. (1):

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)u(t,a) = -\beta(a)c(a)B(t)u(t,a) - \psi(a)u(t,a),$$
$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)w(t,a) = \psi(a)u(t,a) - \delta\beta(a)c(a)B(t)w(t,a),$$
$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)x(t,a) = \beta(a)c(a)B(t)(u(t,a) + \delta w(t,a) + \sigma z(t,a)) - kx(t,a),$$
$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)y(t,a) = kx(t,a) - ry(t,a),$$
$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)z(t,a) = ry(t,a) - \sigma\beta(a)c(a)B(t)z(t,a),$$

$$
\begin{aligned}
&B(t) = \int_0^\infty y(t,a)p(t,a)\,\mathrm{d}a,\\
&p(t,a) = \frac{c(a)n(t,a)}{\int_0^\infty c(u)n(t,u)\,\mathrm{d}u},\\
&u(t,0) = 1, \qquad w(t,0) = x(t,0) = y(t,0) = z(t,0) = 0.
\end{aligned}
\tag{3}
$$

Let $\mathscr{F}_\psi(a)$ denote the probability that a susceptible individual has not been vaccinated at age a. Then

$$
\mathscr{F}_\psi(a) = \exp\left\{ -\int_0^a \psi(b)\,\mathrm{d}b \right\}.
$$

The system (3) has the infection-free steady state

$$
\begin{aligned}
&u(a) = \mathscr{F}_\psi(a), \quad w(a) = 1 - \mathscr{F}_\psi(a), \quad x(a) = y(a) = z(a) = 0,\\
&n(a) = \Lambda\mathscr{F}(a).
\end{aligned}
\tag{4}
$$

To study the local stability of the infection-free equilibrium, we linearize Eq. (3) about Eq. (4) and consider exponential solutions of the form

$$
x(t,a) = X(a)\mathrm{e}^{\lambda t}, \quad y(t,a) = Y(a)\mathrm{e}^{\lambda t}, \quad B(t) = B_0\mathrm{e}^{\lambda t} + \mathrm{O}(\mathrm{e}^{2\lambda t}),
$$

where

$$
B_0 = \int_0^\infty Y(a)p_\infty(a)\,\mathrm{d}a \tag{5}
$$

is a constant and $p_\infty(a)$ is as in Eq. (2). Then the linear parts of the x and y equations in Eq. (3) are of the form

$$
\begin{aligned}
&\lambda X(a) + \frac{\mathrm{d}}{\mathrm{d}a}X(a) = \beta(a)c(a)B_0\mathscr{V}_\psi(a) - kX(a),\\
&\lambda Y(a) + \frac{\mathrm{d}}{\mathrm{d}a}Y(a) = kX(a) - rY(a),
\end{aligned}
$$

where

$$
\mathscr{V}_\psi(a) = \mathscr{F}_\psi(a) + \delta(1 - \mathscr{F}_\psi(a)). \tag{6}
$$

An expression for $Y(a)$ can be obtained by solving the above system:

$$
Y(a) = B_0\int_0^a \frac{k}{r-k}\beta(\alpha)c(\alpha)\left(\mathrm{e}^{(\lambda+k)(\alpha-a)} - \mathrm{e}^{(\lambda+r)(\alpha-a)}\right)\mathscr{V}_\psi(\alpha)\,\mathrm{d}\alpha. \tag{7}
$$

From Eqs. (5) and (7) we get

$$
B_0 = B_0\int_0^\infty\int_0^a \frac{k}{r-k}p_\infty(a)\beta(\alpha)c(\alpha)\left(\mathrm{e}^{(\lambda+k)(\alpha-a)} - \mathrm{e}^{(\lambda+r)(\alpha-a)}\right)\mathscr{V}_\psi(\alpha)\,\mathrm{d}\alpha\,\mathrm{d}a. \tag{8}
$$

By changing the order of integration, introducing $\tau = a - \alpha$, and dividing both sides by B_0 (since $B_0 \neq 0$) in Eq. (8) we get the characteristic equation

$$1 = \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\alpha+\tau)\beta(\alpha)c(\alpha)\left(e^{-(\lambda+k)\tau} - e^{-(\lambda+r)\tau}\right)\mathscr{V}_\psi(\alpha)\, d\tau\, d\alpha =: G(\lambda). \tag{9}$$

Now we are ready to define the net reproductive number as $\mathscr{R}(\psi) = G(0)$; i.e.,

$$\mathscr{R}(\psi) = \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\alpha+\tau)\beta(\alpha)c(\alpha)\left(e^{-k\tau} - e^{-r\tau}\right)\mathscr{V}_\psi(\alpha)\, d\tau\, d\alpha, \tag{10}$$

and establish the following result.

Theorem 3.1. *The infection-free steady-state (4) is locally asymptotically stable (l.a.s.) if* $\mathscr{R}(\psi) < 1$ *and unstable if* $\mathscr{R}(\psi) > 1$.

Proof. Noticing that

$$G'(\lambda) < 0, \qquad \lim_{\lambda\to\infty} G(\lambda) = 0, \qquad \lim_{\lambda\to-\infty} G(\lambda) = \infty,$$

we know that Eq. (9) has a unique negative real solution λ^* if, and only if, $G(0) < 1$, or $\mathscr{R}(\psi) < 1$. Also, Eq. (9) has a unique positive (zero) real solution if $\mathscr{R}(\psi) > 1$ ($\mathscr{R}(\psi) = 1$). To show that λ^* is the dominant real part of roots of $G(\lambda)$, we let $\lambda = x + iy$ be an arbitrary complex solution to Eq. (9). Note that

$$1 = G(\lambda) = |G(x + \mathrm{i}y)| \leqslant G(x),$$

indicating that $R\lambda \leqslant \lambda^*$. It follows that the infection-free steady state is l.a.s. if $\mathscr{R}(\psi) < 1$, and unstable if $\mathscr{R}(\psi) > 1$.

This completes the proof.

A natural question is whether $\mathscr{R}(\psi)$ in Eq. (10) gives the net reproductive number or it is only a threshold quantity. We show in Appendix A that such defined $\mathscr{R}(\psi)$ is indeed the net reproductive number as introduced by Diekmann and coworkers [9].

One may obtain a better understanding of the impact of vaccine by comparing the net reproductive number $\mathscr{R}(\psi)$ with $\mathscr{R}_0$, which is called the *basic* reproductive number (when a purely susceptible population is considered). We can obtain an expression for $\mathscr{R}_0$ in a similar way as the derivation of $\mathscr{R}(\psi)$ by considering Eq. (1) without vaccination; i.e., by assuming that $\psi(a) \equiv 0$ and neglecting the v equation. It can be shown that $\mathscr{R}_0 = \mathscr{R}(0)$; i.e.,

$$\mathscr{R}_0 = \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\alpha+\tau)\beta(\alpha)c(\alpha)\left(e^{-k\tau} - e^{-r\tau}\right) d\tau\, d\alpha. \tag{11}$$

Notice that $\mathscr{V}_\psi(a) < 1$ for all $a > 0$. Hence,

$$\mathscr{R}(\psi) \leqslant \mathscr{R}_0. \tag{12}$$

When the reproductive number is greater than one in the absence of vaccine; i.e., $\mathscr{R}_0 = \mathscr{R}(0) > 1$, vaccination programs can be used to reduce the reproductive number $\mathscr{R}(\psi)$ to values below one, thereby playing an important role in controlling or eliminating the disease.

4. Global stability of the infection-free state and existence of an endemic state

In Section 3 we showed that the infection-free steady state is unstable when $\mathscr{R}(\psi) > 1$. In fact, a non-trivial steady state appears at the same time as shown below.

Theorem 4.1. *There exists an endemic steady state of Eq. (3) when* $\mathscr{R}(\psi) > 1$.

The method commonly used to find an endemic steady state for age-structure models consists of obtaining explicit expressions for a time independent solution of Eq. (3) $(u^*(a), w^*(a), x^*(a), y^*(a), z^*(a))$ that satisfies

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}a}u^*(a) = -\beta(a)c(a)B^*u^*(a) - \psi(a)u^*(a),\\
&\frac{\mathrm{d}}{\mathrm{d}a}w^*(a) = \psi(a)u^*(a) - \delta\beta(a)c(a)B^*w^*(a),\\
&\frac{\mathrm{d}}{\mathrm{d}a}x^*(a) = \beta(a)c(a)B^*(u^*(a) + \sigma z^*(a) + \delta w^*(a)) - kx^*(a),\\
&\frac{\mathrm{d}}{\mathrm{d}a}y^*(a) = kx^*(a) - ry^*(a),\\
&\frac{\mathrm{d}}{\mathrm{d}a}z^*(a) = ry^*(a) - \sigma\beta(a)c(a)B^*z^*(a),
\end{aligned} \tag{13}$$

where

$$B^* = \int_0^\infty y^*(a)p_\infty(a)\,\mathrm{d}a. \tag{14}$$

For models where individuals only move forward ($\sigma = 0$) it is possible to solve the steady state equations recurrently (e.g., one can solve for $u^*(a)$ and $w^*(a)$ first, then solve for $x^*(a)$ independently of $y^*(a)$ and $z^*(a)$, and then for $y^*(a)$ and $z^*(a)$). We cannot follow this approach because there is a flow going back to the x class from the z class and, consequently, we are unable to obtain an explicit expression for $x^*(a)$.

Proof of Theorem 3.1. Using the x^* and y^* equations in Eq. (13) we have that

$$x^*(a) = \int_0^a \mathrm{e}^{-k(a-\alpha)}\beta(\alpha)c(\alpha)B^*h(\alpha, B^*)\,\mathrm{d}\alpha,$$

$$y^*(a) = \int_0^a e^{-r(a-\lambda)} k x^*(\lambda)\, d\lambda,$$

where

$$h(\alpha, B^*) = u^*(\alpha) + \delta w^*(\alpha) + \sigma z^*(\alpha),$$

and

$$u^*(\alpha) = \mathscr{F}_\psi(\alpha) \exp\left\{ -B^* \int_0^\alpha \beta(s) c(s)\, ds \right\},$$

$$w^*(\alpha) = \int_0^\alpha \exp\left\{ -B^* \int_s^\alpha \delta\beta(\lambda) c(\lambda)\, d\lambda \right\} \psi(s) u^*(s)\, ds,$$

$$z^*(\alpha) = \int_0^\alpha \exp\left\{ -B^* \int_s^\alpha \sigma\beta(\lambda) c(\lambda)\, d\lambda \right\} r y^*(s)\, ds.$$

Note that $h(\alpha, B^*)$ is the solution of an integral equation which involves only the known functions. In fact, $h(\alpha, B^*)$ satisfies the following Volterra integral equation with parameter B^*:

$$h(\alpha, B^*) = f(\alpha, B^*) + \int_0^\alpha g(\alpha, a, B^*) h(a, B^*)\, da,$$

where $f(\alpha, B^*) = u^*(\alpha) + \delta w^*(\alpha)$ which obviously contains only the known functions, and

$$g(\alpha, a, B^*) = \sigma B^* \beta(a) c(a) \frac{rk}{r-k} \int_a^\alpha \left(e^{r(a-s)} - e^{k(a-s)} \right) \exp\left\{ -B^* \int_s^\alpha \sigma\beta(u) c(u)\, du \right\} ds.$$

Note that all the known functions are continuous for $a \in [0, A)$ and $0 < A \leqslant \infty$. It can be shown that $f \in C([0, A) \times \mathbb{R}; \mathbb{R})$ is continuously differentiable with respect to B^* and that, for each $B^* \in \mathbb{R}$, the function $g(\cdot, \cdot, B^*)$ is a Volterra kernel of continuous type on $[0, A)$ (see Ref. [11]). Using the result of Gripenberg et al. Ref. [11], Chapter 13, Section 2, Theorem 1.2) we know that, for each $B^* > 0$, there is a unique solution $h(\alpha, B^*)$ defined on the maximal interval of existence $[0, A_{\max})$, and that $h(\alpha, B^*)$ depends continuously on B^*. Moreover, since $u + w + x + y + z = 1$, $h(\alpha, B^*)$ is bounded. It follows from Ref. [11] (Chapter 12, Section 1) that $A_{\max} = \infty$.

Then from the x^* and y^* equations we have that

$$y^*(a) = \int_0^a \frac{k}{r-k}(e^{k(\alpha-a)} - e^{r(\alpha-a)})\beta(\alpha)c(\alpha)B^*h(\alpha,B^*)\,d\alpha. \tag{15}$$

Substituting the above integral for y^* in Eq. (14), dividing the resulting equation by B^* (noticing that $B^* \neq 0$), and letting $\tau = a - \alpha$ we obtain

$$1 = \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\alpha+\tau)(e^{-k\tau} - e^{-r\tau})\beta(\alpha)c(\alpha)h(\alpha,B^*)\,d\tau\,d\alpha =: H(B^*). \tag{16}$$

We now see that an endemic steady state exists if Eq. (16) has a positive solution. After checking that $h(\alpha,0) = \mathscr{V}_\psi(\alpha)$, we get $H(0) = \mathscr{R}(\psi)$; hence, $H(0) > 1$. Since $u^* + w^* + x^* + y^* + z^* = 1$ and $u^*(a) > 0$, we know that $y^*(a) < 1$. Thus, we have from Eq. (15) that

$$\int_0^a \frac{k}{r-k}(e^{k(\alpha-a)} - e^{r(\alpha-a)})\beta(\alpha)c(\alpha)B^*h(\alpha,B^*)\,d\alpha < 1. \tag{17}$$

Then, for any $B^* > 0$, from Eqs. (16) and (17) we have

$$\begin{aligned} B^*H(B^*) &= \int_0^\infty p_\infty(a) \int_0^a \frac{k}{r-k}(e^{k(\alpha-a)} - e^{r(\alpha-a)})\beta(\alpha)c(\alpha)B^*h(\alpha,B^*)\,d\alpha\,da \\ &< \int_0^\infty p_\infty(a)\,da = 1. \end{aligned}$$

In particular, for $B^* = 1$ we have $H(1) < 1$, but $H(0) > 1$. Since $H(B^*)$ is a continuous function of B^*, we conclude that $H(B^*) = 1$ has a positive solution $\tilde{B}^*$ on $(0,1)$. This solution may not be unique since $H(B^*)$ may not be monotone ($H(B^*)$ depends on $h(\alpha,B^*)$ which is defined implicitly). It follows that when $\mathscr{R}(\psi) > 1$, there exists an endemic steady state distribution which is given by the unique solution of Eq. (13) corresponding to $\tilde{B}^*$.

This finishes the proof.

Since $\mathscr{R}(\psi) > 1$ is the only sufficient condition in which an endemic steady state can exist and since we have shown only the local stability of the infection-free steady state when $\mathscr{R}(\psi) < 1$, we may ask whether or not there exists an endemic equilibrium when $\mathscr{R}(\psi) < 1$. While we cannot rule out the possibility, the following result shows that there is no endemic steady state when $\mathscr{R}_0 < 1$ (see Eqs. (11) and (12) for the relation between $\mathscr{R}(\psi)$ and $\mathscr{R}_0$).

Theorem 4.2. *The infection-free equilibrium of Eq. (3) is globally asymptotically stable if* $\mathscr{R}_0 < 1$.

Proof. Let $\mathscr{I}(t,a)$ denote the rate at which uninfected individuals of age a are infected at time t. Then

$$\begin{aligned}\mathscr{I}(t,a) &= \beta(a)c(a)B(t)(u(t,a)+\delta w(t,a)+\sigma z(t,a))\\ &\leqslant \beta(a)c(a)B(t),\end{aligned} \tag{18}$$

where $B(t)$ is given in Eq. (3). Here we have used the fact that $u(t,a)+w(t,a)+z(t,a)\leqslant 1$ and the assumption $\sigma\leqslant 1$, $\delta\leqslant 1$. Integrating Eq. (3) along characteristic lines we get

$$x(t,a) = \int_0^a \mathrm{e}^{-ks}\mathscr{I}(t-s,a-s)\,\mathrm{d}s, \quad a<t, \tag{19}$$

$$y(t,a) = k\int_0^a \mathrm{e}^{-rs}x(t-s,a-s)\,\mathrm{d}s, \quad a<t.$$

Replacing x by the integral in Eq. (19) we get that, for $a<t$,

$$\begin{aligned}y(t,a) &= k\int_0^a \mathrm{e}^{-rs}\int_0^{a-s}\mathrm{e}^{-k\lambda}\mathscr{I}(t-s-\lambda,a-s-\lambda)\,\mathrm{d}\lambda\,\mathrm{d}s\\ &= k\int_0^a\int_0^{a-s}\mathrm{e}^{-rs}\mathrm{e}^{-k(a-s-\alpha)}\mathscr{I}(t-a+\alpha,\alpha)\,\mathrm{d}\alpha\,\mathrm{d}s \quad (\alpha=a-s-\lambda)\\ &= k\int_0^a\int_0^{a-\alpha}\mathrm{e}^{-rs}\mathrm{e}^{-k(a-s-\alpha)}\mathscr{I}(t-a+\alpha,\alpha)\,\mathrm{d}s\,\mathrm{d}\alpha\\ &= \frac{k}{r-k}\int_0^a\left(\mathrm{e}^{-k(a-\alpha)}-\mathrm{e}^{-r(a-\alpha)}\right)\mathscr{I}(t-a+\alpha,\alpha)\,\mathrm{d}\alpha.\end{aligned} \tag{20}$$

Hence, by Eqs. (18) and (20) we obtain the inequality

$$\begin{aligned}\mathscr{I}(t,a) \leqslant \beta(a)c(a)\int_0^\infty p(t,a)\frac{k}{r-k}\int_0^a\left(\mathrm{e}^{-k(a-\alpha)}-\mathrm{e}^{-r(a-\alpha)}\right)\\ \mathscr{I}(t-a+\alpha,\alpha)\,\mathrm{d}\alpha\,\mathrm{d}a.\end{aligned} \tag{21}$$

Let

$$W(a) = \limsup_{t\to\infty}\mathscr{I}(t,a).$$

Then taking the limit supreme when $t\to\infty$ on both sides of Eq. (21) and using Fatou's Lemma we get

$$W(a)\leqslant\beta(a)c(a)\int_0^\infty p_\infty(a)\frac{k}{r-k}\int_0^a\left(\mathrm{e}^{-k(a-\alpha)}-\mathrm{e}^{-r(a-\alpha)}\right)W(\alpha)\,\mathrm{d}\alpha\,\mathrm{d}a, \tag{22}$$

where $p_\infty(a)$ is as in Eq. (2). Let C denote the constant

$$C = \int_0^\infty p_\infty(a)\frac{k}{r-k}\int_0^a \left(e^{-k(a-\alpha)} - e^{-r(a-\alpha)}\right) W(\alpha)\,d\alpha\,da. \tag{23}$$

Then Eq. (22) can be written as

$$W(a) \leqslant C\beta(a)c(a),$$

and thus Eq. (23) yields

$$C \leqslant C\int_0^\infty \int_0^a p_\infty(a)\frac{k}{r-k}\left(e^{-k(a-\alpha)} - e^{-r(a-\alpha)}\right)\beta(\alpha)c(\alpha)\,d\alpha\,da. \tag{24}$$

If we change the order of integration in Eq. (24) and let $\tau = a - \alpha$, then the double integral is actually $\mathscr{R}_0$. Hence, Eq. (24) becomes

$$C \leqslant C\mathscr{R}_0,$$

and $C = 0$ if $\mathscr{R}_0 < 1$. It follows that if $\mathscr{R}_0 < 1$, then $W(a) = 0$ and, therefore,

$$\lim_{t\to\infty} \sup \mathscr{I}(t,a) = 0.$$

From Eqs. (19) and (20) we see that

$$\lim_{t\to\infty} x(t,a) = 0, \qquad \lim_{t\to\infty} y(t,a) = 0.$$

It is then easy to show that

$$\lim_{t\to\infty} u(t,a) = \mathscr{F}_\psi(a), \qquad \lim_{t\to\infty} w(t,a) = 1 - \mathscr{F}_\psi(a), \qquad \lim_{t\to\infty} z(t,a) = 0.$$

This finishes the proof.

Theorem 4.2 shows that there is no endemic steady state for parameter values such that $\mathscr{R}_0 < 1$. However, it is not clear if an endemic steady state exists in the case when $\mathscr{R}(\psi) < 1$ but $\mathscr{R}_0 > 1$. It is possible a backwards bifurcation of endemic steady states exists for some parameter values that satisfy $\mathscr{R}(\psi) < 1 < \mathscr{R}_0$ (see Refs. [5,12]).

5. Optimal vaccination strategies

Generally speaking, the effect of subjecting a population to a vaccination program is to reduce its reproductive number and to increase the average age of first infection. Ideally, in a vaccination program, one would like to eliminate or eradicate a disease, but vaccinations often can only prevent major epidemic outbreaks. Since elimination is usually highly unlikely, we often try to

find ways of reducing the prevalence or incidence of a particular disease. By lowering the reproductive number, we reduce the prevalence and incidence of a disease. In Ref. [10], a simpler formula was derived which can be used to determine the function $\psi(a)$ needed to reduce $\mathscr{R}(\psi)$ below 1. Their approximation was constructed for diseases where the length of the infectious period is short. TB has a long and variable period of infectiousness. Therefore, we consider instead the approach used by Hadeler and Müller [14] in the case of HIV, and look at the effectiveness of vaccination policies that are driven by reductions of the reproductive number.

Consider the functional defined by

$$F(\psi) = \mathscr{R}_0 - \mathscr{R}(\psi).$$

Then

$$F(\psi) = \int_0^\infty \int_0^\infty \beta(\alpha)c(\alpha)p(\alpha+\tau)\frac{k}{r-k}(\mathrm{e}^{-k\tau} - \mathrm{e}^{-r\tau})(1 - \mathscr{V}_\psi(\alpha))\,\mathrm{d}\tau\,\mathrm{d}\alpha, \quad (25)$$

where $\mathscr{V}_\psi(\alpha)$ is as in Eq. (6). Note that $F(\psi)$ gives a measure of the reduction in the reproductive number by the vaccination strategy ψ.

We next formulate two optimization problems by considering costs that are associated with the vaccination strategies. Let $s_\psi(a)$ denote the density function of susceptibles describing the steady demographic state in the absence of disease, then

$$s_\psi(a) = \Lambda\mathscr{F}(a)\mathscr{F}_\psi(a).$$

Let $C(\psi)$ be the total cost associated with the vaccination strategy ψ, and assume that $C(\psi)$ depends linearly on the number of vaccinations (see Ref. [14]). Then we can write

$$C(\psi) = \int_0^\infty \kappa(a)\psi(a)s_\psi(a)\,\mathrm{d}a,$$

where $\kappa(a)$ is a positive function representing the costs associated with one vaccination at age a. For future use, we note that

$$C(\psi) = \int_0^\infty \Lambda\kappa(a)\psi(a)\mathscr{F}(a)\exp\left\{-\int_0^a \psi(s)\,\mathrm{d}s\right\}\mathrm{d}a. \quad (26)$$

Two optimization problems can be defined as follows. Let $\mathscr{R}_*$ and C_* be two constants.

(I) Find a vaccination strategy $\psi(a)$ that minimizes $C(\psi)$ constrained by $\mathscr{R}(\psi) \leqslant \mathscr{R}_*$.

(II) Find a vaccination strategy $\psi(a)$ that minimizes $\mathscr{R}(\psi)$ constrained by $C(\psi) \leqslant C_*$.

The difficulty associated with these optimization problems is due to the fact that $C(\psi)$ and $F(\psi)$ are non-linear functionals of ψ. Hadeler and Müller [14] showed how to overcome this difficulty. In order to make both $C(\psi)$ and $F(\psi)$ linear functionals we apply the transformation

$$\phi(a) = -\frac{\mathrm{d}}{\mathrm{d}a}\exp\left\{-\int_0^a \psi(s)\,\mathrm{d}s\right\} = \psi(a)\exp\left\{-\int_0^a \psi(s)\,\mathrm{d}s\right\}.$$

Denote $\bar{F}(\phi) = F(\psi), \bar{C}(\phi) = C(\psi)$. Then, seeing that

$$1 - \mathscr{V}_\psi(a) = (1-\delta)(1-\mathscr{F}_\psi(a)) = (1-\delta)\int_0^a \phi(s)\,\mathrm{d}s$$

(see Eq. (6)), and also noting that

$$\begin{aligned}\bar{F}(\phi) &= \int_0^\infty\int_0^\infty \beta(\alpha)c(\alpha)p(\alpha+\tau)\frac{k}{r-k}(\mathrm{e}^{-k\tau}-\mathrm{e}^{-r\tau})(1-\delta)\int_0^\alpha \phi(s)\,\mathrm{d}s\,\mathrm{d}\tau\,\mathrm{d}\alpha\\ &= \int_0^\infty\left\{\int_a^\infty\int_0^\infty (1-\delta)\beta(\alpha)c(\alpha)p_\infty(\alpha+\tau)\frac{k}{r-k}(\mathrm{e}^{-k\tau}-\mathrm{e}^{-r\tau})\,\mathrm{d}\tau\,\mathrm{d}\alpha\right\}\\ &\quad \phi(a)\,\mathrm{d}a\end{aligned}$$

(see Eq. (25)), we arrive at

$$\bar{F}(\phi) = \int_0^\infty K(a)\phi(a)\,\mathrm{d}a,$$

$$\bar{C}(\phi) = \int_0^\infty B(a)\phi(a)\,\mathrm{d}a$$

(see also Eq. (26)), where

$$\begin{aligned}K(a) &= \int_a^\infty\int_0^\infty (1-\delta)\beta(\alpha)c(\alpha)p_\infty(\alpha+\tau)\frac{k}{r-k}(\mathrm{e}^{-k\tau}-\mathrm{e}^{-r\tau})\,\mathrm{d}\tau\,\mathrm{d}\alpha,\\ B(a) &= \Lambda\kappa(a)\mathscr{F}(a).\end{aligned} \tag{27}$$

Hence, we have replaced two non-linear functionals with the linear functionals given by $\bar{F}(\phi)$ and $\bar{C}(\phi)$. If we let

$$Q(\phi) = \int_0^\infty \phi(a)\,\mathrm{d}a,$$

then it is easy to see that $Q(\phi) \leqslant 1$.

Letting $\rho = \mathscr{R}_0 - \mathscr{R}_*$ we are able to replace (I) by the following linear optimization problem:

$$\begin{array}{ll} \text{minimize} & \bar{C}(\phi) \\ \text{subject to} & f(\phi) \leqslant 0, \\ & \phi \geqslant 0, \end{array} \tag{28}$$

where

$$f(\phi) = \begin{pmatrix} f_1(\phi) \\ f_2(\phi) \end{pmatrix} = \begin{pmatrix} \rho - \bar{F}(\phi) \\ Q(\phi) - 1 \end{pmatrix},$$

and $f(\phi) \leqslant 0$ is equivalent to $f_i(\phi) \leqslant 0$ $(i = 1, 2)$. After using (formally) the Saddle Point Theorem of Kuhn and Tucker for the convex optimization problem (see Ref. [21]) we can show that Eq. (28) is mathematically equivalent to (P1) in Ref. [14]. Hence, using the same arguments we arrive at the following conclusion.

Result 5.1. There are two possible optimal vaccination strategies in (I):

(i) one-age strategy: vaccinate the susceptible population at exactly age A;

(ii) two-age strategy: vaccinate part of the susceptible population at age A_1 and the remaining susceptibles at a later age A_2.

For the two vaccination strategies, the optimal ages can be calculated in the following way: Note that $K(a)$ (see Eq. (27)) is a strictly decreasing function with $K(0) = \mathscr{R}_0 > \rho$ and $K(a) \to 0$ as $a \to \infty$. Hence, we can find $A_* > 0$ such that $K(A_*) = \rho$. Let A be the minimum of the quotient $B(a)/K(a)$. (See Ref. [14] for discussions about the existence of A.) If $A \in [0, A_*]$, then it gives an optimal age for the one-age strategy. If $A \in (A_*, \infty)$, then the optimal two-age strategy is found by minimizing the expression $C(A_1, A_2)$ on $A_1 \in [0, A_*]$ and $A_2 \in [A_*, \infty)$, where

$$C(A_1, A_2) = \frac{\rho - K(A_2)}{K(A_1) - K(A_2)} B(A_1) + \frac{K(A_1) - \rho}{K(A_1) - K(A_2)} B(A_2).$$

For (II), a similar conclusion to Result 5.1 can be obtained; i.e., the optimal vaccination strategy is either one- or two-age, and the optimal ages can be determined.

6. Discussion

In this paper we introduced an age-structure model to study the dynamics of TB and problems related to optimal vaccination strategies. First we calculated the reproductive numbers and studied the disease transmission dynamics with and without vaccine. We proved the global stability of the infection-free steady state for $\mathscr{R}_0 < 1$. A threshold condition is given by $\mathscr{R}(\psi) = 1$ in the sense that

the infection-free state is l.a.s if $\mathscr{R}(\psi) < 1$ and unstable if $\mathscr{R}(\psi) > 1$. Also an endemic steady state exists when $\mathscr{R}(\psi) > 1$. We have not shown whether or not endemic steady states exist for parameters that satisfy $\mathscr{R}(\psi) < 1 < \mathscr{R}_0$. This may suggest the existence of a backwards bifurcation of nontrivial equilibria for some parameter values in that range. We then studied cost-related optimal vaccination strategy problems and found that the optimal strategies have the form of one- or two-age strategies which can be found by minimizing functions of one or two variables. We did not include the infection age dependent infectivity which seems to play a role in the transmission of TB.

In Argentina, individuals are vaccinated for TB at birth and at age 15 years. Are these in agreement with the optimal vaccination strategies computed here? These questions cannot be answered until information on $\mathscr{R}_0$, the cost function, and, more importantly, $\psi(a)$, are available. Our results agree with those of Rorres and Fair [19], but this is not surprising since 'harvesting' is mathematically equivalent to 'vaccinating'.

We have followed the approach of Hadeler and Müller [13,14] when formulating the optimization problems and finding vaccination strategies. Nevertheless, our studies of the model that incorporates several characteristics of TB help understand the role that key epidemiological parameters play in the maintenance of the disease – including the role of the parameters associated with relapses, imperfect vaccines, and long periods of latency. More specifically, Hadeler and Müller's model has three variables which are susceptibles, vaccinated, and infected. They identify recovered with vaccinated. In our model vaccinated and treated individuals may have different infection rates. This is one of the important features of TB since the protection rates of TB vaccines against TB reinfection seem to be much higher than that of treatments. Such models allow one to address questions associated with the effectiveness of TB vaccines (such as the BCG vaccine) and the impact of relapse of the disease on the dynamics of TB within age-structure populations. Also our model includes a latent class which seems important in modeling TB transmission dynamics since TB has relatively long periods of latency and only a small proportion of latents will become infectious.

The incorporation of these realistic features of TB into our model has caused some difficulties in the analysis, especially in proving the global stability result and the existence of an endemic steady state. For example, allowing treated individuals to return to the infected class due to reactivation of the disease makes it impossible to solve the steady state equations recurrently (see Section 4) which is the method commonly used for age-structure models. In fact, in order to show the existence of an endemic steady state of Eq. (3), it is necessary to show first the existence, uniqueness, and continuity (with respect to a parameter) of the solution of a Volterra integral equation with a parameter.

On the other hand Hadeler and Müller's model is a homogeneous system, and they show the linear stability of the uninfected state which describes expo-

nential growth of the total population whereas the proportions of age remain constant. This seems to be more general than results where the uninfected state is time independent which is the case in our model (we do not have a homogeneous system). Our contribution consists of looking at a model where individuals are allowed to 'return' to previously visited classes, studying some global stability properties of this age-structure model, proving the existence of an endemic steady state when the commonly used method does not apply, and showing how to compute the optimal vaccination strategies in such situations. Clearly, a one- or two-age optimal vaccination strategy may become the rule in these types of models.

Acknowledgements

We thank Karl Hadeler and Johannes Müller for useful discussions. We thank Horst Thieme and Jorge Velasco-Hernandez for helpful suggestions, and two anonymous referees for comments which improved the manuscript. This research was partially supported by NSF grant DEB-925370 (Presidential Faculty Fellowship Award) to Carlos Castillo-Chavez and by the US Army Research Office through the Mathematical Science Institute of Cornell University (contract DAAL03-91-0027).

Appendix A

In this appendix we provide an alternative calculation of the net reproductive number $\mathscr{R}(\psi)$ defined in Eq. (10) using the approach developed by Diekmann and coworkers [9].

Diekmann's notation lets $S(a)$ denote the density function of susceptibles used to describe the *steady demographic state* in the absence of disease. Diekmann defines $A(\tau, a, \alpha)$ as the expected infectivity of an individual infected τ units of time ago while at age α towards an uninfected individual of age a while the population is in a steady demographic state. The function $A(\tau, a, \alpha)$ combines information on the probability (per unit of time) that contacts between certain ages take place and the probability that, given a contact, the disease agent is actually transmitted. Under the special assumption of *proportionate-mixing* $A(\tau, a, \alpha)$ can be written in the form $A(\tau, a, \alpha) = f(a)g(\tau, \alpha)$. Under these assumptions Diekmann gives the following formula for the reproductive number $\mathscr{R}$:

$$\mathscr{R} = \int_0^\infty \int_0^\infty f(\alpha)g(\tau, \alpha)S(\alpha)\, \mathrm{d}\tau\, \mathrm{d}\alpha.$$

In our model the population (in a steady demographic state) consists of both susceptibles $s(a)$ and vaccinated individuals $v(a)$ which may have a reduced infection rate ($0 < \delta < 1$). In this case the above formula can be generalized to

$$\mathscr{R} = \int_0^\infty \int_0^\infty f(\alpha)g(\tau,\alpha)(s(\alpha) + \delta v(\alpha))\,\mathrm{d}\tau\,\mathrm{d}\alpha. \tag{A.1}$$

To make use of Eq. (A.1) to calculate the reproductive number for system (1) with the vaccination function ψ, we consider a demographic steady state $(s(a), v(a), 0, 0, 0)$ of system (1) with every one uninfected and temporarily ignore the fact that $s(a)$ and $v(a)$ decrease due to the infection process (see Ref. [9]). For simplicity we first consider the case $\mu(a) = \mu$ (a constant). The results hold also for non-constant death rate $\mu(a)$. Let

$$\mathscr{F}_\psi(a) = \mathrm{e}^{-\Phi(a)}, \qquad \Phi(a) = \int_0^a \psi(u)\,\mathrm{d}u.$$

Clearly, we have that

$$s(a) = \Lambda \mathrm{e}^{-\mu a}\mathscr{F}_\psi(a), \qquad v(a) = \Lambda \mathrm{e}^{-\mu a}(1 - \mathscr{F}_\psi(a)). \tag{A.2}$$

We need to compute the remaining elements required in Eq. (A.1). We observe that

$$p_\infty(a) = \frac{c(a)n(a)}{\int_0^\infty c(u)n(u)\,\mathrm{d}u},$$

where $n(a)$ denotes the density function of the total population at the steady state. Let $\gamma(\tau,\alpha)$ be the probability that an individual of age $\alpha+\tau$ who was infected τ time units ago is in class i, and let $u \in (0,\tau)$ denote the probability that an individual of age $\alpha+\tau$ who was infected τ time units ago is in class l at time u after infection. Furthermore, we observe that the probability of remaining in l class times the probability of being still alive at age $\alpha+u$, given that the individual was alive at age α, is

$$\mathrm{e}^{-ku}\frac{\mathrm{e}^{-\mu(\alpha+u)}}{\mathrm{e}^{-\mu\alpha}} = \mathrm{e}^{-(\mu+k)u},$$

and we observe that the density function for entering class i is therefore given by

$$k\mathrm{e}^{-(\mu+k)u}. \tag{A.3}$$

In order to be in class i with infection age τ one should

(i) have entered i at some time $u \in (0,\tau)$,

(ii) have remained in i in the interval (u,τ).

The probability that (ii) holds is

$$\mathrm{e}^{-(\mu+r)(\tau-u)}. \tag{A.4}$$

From Eqs. (A.3) and (A.4) we have

$$\gamma(\tau,\alpha)=\int_0^{\tau} k\mathrm{e}^{-(\mu+k)u}\mathrm{e}^{-(r+\mu)(\tau-u)}\,\mathrm{d}u=\frac{k}{r-k}(\mathrm{e}^{-k\tau}-\mathrm{e}^{-r\tau})\mathrm{e}^{-\mu\tau}.$$

(Note that $\gamma(\tau,\alpha)>0$ for all $r>0,k>0$.) Hence using the definition of $A(\tau,a,\alpha)$ we have

$$\begin{aligned}A(\tau,a,\alpha)&=\beta(a)c(a)p_\infty(\alpha+\tau)\frac{\gamma(\tau,\alpha)}{n(\alpha+\tau)}\\&=\beta(a)c(a)p_\infty(\alpha+\tau)\frac{k}{r-k}(\mathrm{e}^{-k\tau}-\mathrm{e}^{-r\tau})\mathrm{e}^{\mu\alpha}\frac{1}{\Lambda}\\&=:f(a)g(\tau,\alpha),\end{aligned}\tag{A.5}$$

where

$$f(a)=\beta(a)c(a),$$

$$g(\tau,\alpha)=p_\infty(\alpha+\tau)\frac{k}{r-k}(\mathrm{e}^{-k\tau}-\mathrm{e}^{-r\tau})\mathrm{e}^{\mu\alpha}\frac{1}{\Lambda}.$$

Using Eqs. (A.1) and (A.2) we get

$$\begin{aligned}\mathscr{R}&=\int_0^{\infty}\int_0^{\infty} f(\alpha)g(\tau,\alpha)(s(\alpha)+\delta v(\alpha))\,\mathrm{d}\tau\,\mathrm{d}\alpha\\&=\int_0^{\infty}\int_0^{\infty}\beta(\alpha)c(\alpha)p_\infty(\alpha+\tau)\frac{k}{r-k}(\mathrm{e}^{-k\tau}-\mathrm{e}^{-r\tau})\mathscr{V}_\psi(\alpha)\,\mathrm{d}\tau\,\mathrm{d}\alpha,\end{aligned}\tag{A.6}$$

where

$$\mathscr{V}_\psi(\alpha)=\mathscr{F}_\psi(\alpha)+\delta(1-\mathscr{F}_\psi(\alpha)).$$

The reproductive number $\mathscr{R}$ in Eq. (A.6) is exactly the same as $\mathscr{R}(\psi)$ defined in Eq. (10).

References

[1] R.M. Anderson, R.M. May, Spatial, temporal, and genetic heterogeneity in host populations and the design of immunization programmes, IMA J. Math. Appl. Med. Biol. 1 (1984) 233.
[2] B.R. Bloom, Tuberculosis: Pathogenesis, Protection, and Control, ASM, Washington, DC, 1994.
[3] S. Busenberg, C. Castillo-Chavez, A general solution of the problem of mixing subpopulations, and its application to risk- and age-structure epidemic models for the spread of AIDS, IMA J. Math. Appl. Med. Biol. 8 (1991) 1.
[4] C. Castillo-Chavez, Z. Feng, To treat or not to treat: the case of tuberculosis, J. Math. Biol. 35 (1997) 629.
[5] C. Castillo-Chavez, Z. Feng, A TB model with exogenous reinfection, Biometrics Unit Tech. Report, BU-1388-M, Cornell University, 1997.

[6] C. Castillo-Chavez, H.W. Hethcote, V. Andreason, S.A. Levin, W. Liu, Cross-immunity in the dynamics of homogeneous and heterogeneous populations, in: L. Gross, T.G. Hallam, S.A. Levin (Eds.), Mathematical Ecology, World Scientific, Singapore, 1988, p. 303.
[7] C. Castillo-Chavez, H.W. Hethcote, V. Andreason, S.A. Levin, W. Liu, Epidemiological models with age structure, proportionate mixing, and cross-immunity, J. Math. Biol. 27 (1989) 233.
[8] G.W. Comstock, G.M. Cauthen, Epidemiology of tuberculosis, in: L.B. Reichman, E.S. Hershfield (Eds.), Tuberculosis: A Comprehensive International Approach, Marcel Dekker, New York, 1993, p. 23.
[9] O. Diekmann, J.A.P. Heesterbeek, J.A.J. Metz, On the definition and computation of the basic reproduction ratio in models for infectious diseases in heterogeneous populations, J. Math. Biol. 28 (1990) 365.
[10] K. Dietz, D. Schenzle, Proportionate mixing models for age-dependent infection transmission, J. Math. Biol. 22 (1985) 117.
[11] G. Gripenberg, S.-O. Londen, O. Staffans, Volterra integral and functional equations, Cambridge University, Cambridge, 1990.
[12] K.P. Hadeler, C. Castillo-Chavez, A core group model for disease transmission, Math. Biosci. 128 (1995) 41.
[13] K.P. Hadeler, J. Müller, Vaccination in age structured population I: the reproduction number, in: D. Mollison (Ed.), Epidemic Models: Their Structure and Relation to Data, Cambridge University, Cambridge, 1996, p. 90.
[14] K.P. Hadeler, J. Müller, Vaccination in age structured populations II: optimal vaccination strategies, in: V. Isham, G. Medley (Eds.), Models for Infectious Human Diseases: Their Structure and Relation to Data, Cambridge University, Cambridge, 1996, p. 102.
[15] H.W. Hethcote, J.A. Yorke, Gonorrhea transmission dynamics and control, Lect. Notes Biomath., vol. 56, Springer, Berlin, 1984.
[16] T.T. Myint, H. Win, H.H. Aye, T.O. Kyaw-Mint, Case-control study on evaluation of BCG vaccination of newborn in Rangoon, Burma, in: Annals of Tropical Pediatrics, vol. 7, UK, 1987, p. 159.
[17] A. Patel, F. Schofield, V. Siskind, E. Abrahams, J. Parker, Case-control evaluation of a school-age BCG vaccination programme in subtropical Australia, Bullet. World Health Organization 69 (4) (1991) 425.
[18] L.B. Reichman, E.S. Hershfield, Tuberculosis: A Comprehensive International Approach, Marcel Dekker, New York, 1993.
[19] C. Rorres, W. Fair, Optimal harvesting policy for an age-specific population, Math. Biosci. 24 (1975) 31.
[20] A.A. Saylers, D.D. Whitt, Bacterial Pathogenesis: A Molecular Approach, ASM, Washington, DC, 1994.
[21] J. Stoer, Chr. Witzgall, Convexity and optimization in finite dimension I, Springer, Berlin, 1970.