Optimal vaccination strategies for TB in age-structure populations

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Abstract. This article focuses on the study of optimal vaccination strategies for tuberculosis. Two vaccination programs are considered within an age structure population in order to determine the optimal age or ages at which an individual should be vaccinated. We look at two scenarios. First, we begin with the goal of reducing the basic reproductive numbers down to a fixed level at a minimal cost. Secondly, we determine what are the best ways to minimize the basic reproductive number with fixed resources. It is shown that the optimal strategies are either one-age strategies or two-age strategies. In the process an age-structure model is introduced. The basic reproductive numbers for cases with or without vaccination are calculated using the approach of "next generation operator" for heterogeneous mixing models. Conditions for the stability of the infection-free steady state in the absence of vaccination are also derived.

Key words: Tuberculosis, Age-structure, Proportionate Mixing, Vaccination Strategies, Optimization, Dynamical systema, Differential Equations

Introduction

Tuberculosis (TB) is a communicable disease primarily spread by the airborne route. The risk that a person may become infected is strongly associate with the probability of

coming in contact with an actively infected individual as well as the closeness and the duration of the contact (Reichman 1993). There are evidences 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. Because 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 where there is no vaccine. The formulation of an age-structure model for the transmission dynamics is straightforward, however, because TB treated individuals can become infected again, it is not easy to study such a model. Here, we use the "next generation operator" approach of Diekmann and co-workers (see Diekmann *et al.*1990; Heesterbeek 1992) to determine the threshold for our heterogeneous mixing population. We obtain a formula for the basic reproductive number $\mathcal{R}_0$; conditions for the stability of the infection-free steady state distribution; and establish necessary and sufficient conditions for the existence of an endemic steady state. We use the results on the dynamics of our TB age-structure model to study the role of the *Bacillus of Calmette and Guérin* (BCG) vaccine for TB on the epidemiological age-structure of a population.

Approximately 100 million newborns and children received the BCG vaccine in 1992 through the World Health Organization (WHO, 1992; Bloom1994). 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% to 80% while others presenting a strong evidence that the vaccine was completely ineffective in preventing TB (Saylers 1994). Potential problems associated with the generalized use of the BCG vaccine in some populations are closely associated to the fact that vaccinated individuals will test positive for TB. It becomes therefore nearly impossible to be able to detect the prevalence of a disease in a population like the Argentinean population where most individuals are vaccinated.

Different vaccination policies have been adopted in different parts of the world. In Argentina, BCG is given to children both at birth and at age of 15. Children are vaccined at age of 12-14 in Queensland (Australia) and newborns are vaccinated in Burma (see Patel *et al* 1991; Myint *et al* 1987). In practice the application of a vaccination policy is

limited by many factors including the costs associated with its application. Costs may be increased by variability in age-dependent compliance (at birth, children may be "caught" in the hospitals and hence, the per-capita vaccine cost may be relatively low). Various vaccination policies have been established in the past and our objective here is to determine whether or not current vaccination policies are "optimal" in some sense. Here we assume that the vaccine is somewhat effective. An assumption that it may have to be weaken if definite studies show that the vaccine is totally ineffective or if it is established that it only provides only temporary protection. However, we believe that our study will throw some light on how to handle the "real" problem. In order to test the value of a strategy, we introduce an age-dependent effective 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. We denote the vaccine-dependent reproductive number by $\mathcal{R}(\psi)$ and consider two optimization problems following earlier work on HIV vaccination policies (see Hadeler and Müeller 1993a; 1993b): reducing $\mathcal{R}(\psi)$ below a certain level $\mathcal{R}_*$ at minimal costs or minimizing the basic reproductive number $\mathcal{R}(\psi)$ with fixed resources. Following the approach used by Hadeler and coworkers (to some degree implicit in the work on optimal harvesting models of Rorres and Fair 1975, albeit the mathematical approach in Hadeler's group is more general) we show that the optimal strategies for the above two problems have the form "vaccinate at a single age class" or "vaccinate at precisely two age classes". These results agree qualitatively with the policies followed in Argentina and many other countries (a detailed account on the epidemiology of TB for modelers can be found in Castillo-Chavez and Feng, 1996).

This paper is organized as follows: Section 1 introduces an age-structure model to study the dynamics of TB in the absence of a vaccine. The basic reproductive number $\mathcal{R}_0$ is computed in Section 2. In Section 3 we study role of $\mathcal{R}_0$ on the dynamics and stability properties of this vaccine-free model. In Section 4 we modify our model through the introduction of an age-dependent per-capita vaccination rate into our "null" age-structure model and study the two optimization problems outlined above. Section 5 discuss our results and points to some future work.

1. The model in the absence of vaccine

In order to formulate an age-structure model for the transmission of TB we need to introduce some notation. The age-structured population under consideration is divided into four epidemiological classes: susceptible, exposed, infectious, and treated. We let $s(t,a), l(t,a), i(t,a)$ and $j(t,a)$ denote the associated density functions with these respective epidemiological age-structured classes. The transfer diagram that graphically illustrates the flow of individuals is that of Fig.1. We assume that all newborns are susceptible, that the mixing between individuals is proportional to their age-dependent activity levels, 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:

$$
\begin{aligned}
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})s(t,a) = -\beta(a)c(a)B(t)s(t,a) - \mu s(t,a),\\
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})l(t,a) = \beta(a)c(a)B(t)s(t,a) - (k+\mu)l(t,a) + \sigma\beta(a)c(a)B(t)j(t,a),\\
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})i(t,a) = kl(t,a) - (r+\mu)i(t,a),\\
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})j(t,a) = ri(t,a) - \sigma\beta(a)c(a)B(t)j(t,a) - \mu j(t,a),\\
&B(t) = \int_0^\infty \frac{i(t,a')}{n(t,a')}p(t,a,a')da',\\
&p(t,a,a') = \frac{c(a')n(t,a')}{\int_0^\infty c(u)n(t,u)du} \equiv p(t,a'),\\
&s(t,0) = \Lambda,\quad l(t,0) = i(t,0) = j(t,0) = 0,\\
&s(0,a) = s_0(a),\quad l(0,a) = l_0(a),\quad i(0,a) = i_0(a),\quad j(0,a) = j_0(a),\\
&n(t,a) = s(t,a) + l(t,a) + i(t,a) + j(t,a),
\end{aligned}
\tag{1.1}
$$

where Λ is the recruitment/birth rate (assumed constant); $\beta(a)$ is the age-specific (average) probability of becoming infected through contacts with infectious individuals; $c(a)$ is the age-specific per-capita contact/activity rate; μ is the per-capita natural death rate; k is the per-capita rate at which individuals leave the latent class by becoming infectious; r is the per-capita treatment rate; σ is the reduction in risk due to prior exposure to TB, $0 \leq \sigma \leq 1$; $p(t,a,a')$ gives the probability that an individual of age a has a contact with

an individual of age a' given that it has a contact with a member of our population. We assume that individuals mix according to the proportionate mixing model as priorly introduced by many researchers including Hethcote and Yorke (1984), Dietz and Schenzle (1985), Anderson and May (1984), Castillo-Chavez *et al.* (1988, 1989). If we assume that $p(t, a, a') \equiv p(t, a')$ then using the approach of Busenberg and Castillo-Chavez (1991), we obtain the above expression for age-dependent mixing. The initial age distributions are assumed to known and to be zero beyond some maximum age. We assumed that an individual may be infected only through contacts with infectious individuals, and that treated individuals can become infected again. The model (1.1) is well-posed. The proof is similar to that found is standard (see Castillo-Chavez *et al.*, 1989).

$\mathcal{R}_0$ is defined as *the expected number of secondary infectious generated by a "typical" infected individual during its entire–death adjusted–period of infectiousness on a population of purely susceptibles in demographic steady-state when it is invaded by an infectious agent.* In the next section we derive explicit expressions for the basic reproductive number $\mathcal{R}_0$, a quantity that must exceed one for the disease to remain endemic (persist). The method commonly used to calculate $\mathcal{R}_0$ for age-structure models consists of obtaining first expressions for its steady-state age distributions $(s^*(a), l^*(a), i^*(a), j^*(a))$ with $B(t) = B^*$ (a constant). The expression for $i^*(a)$ and B^* are then substituted into the equation for $B(t)$. The resulting characteristic equation is then used to define $\mathcal{R}_0$. We cannot follow this approach because there is a flow going back to the l class from the j class and, consequentely, we are unable to obtain an explicit expression for $i^*(a)$. Such an expression – when computable – can be found from models where individuals only move forward ($\sigma = 0$). For such models (the case $\sigma = 0$ in our model) it is possible to solve the steady state equations recurrently (e.g., one can solve for $s^*(a)$ first, then solve for $l^*(a)$ independently of $i^*(a)$ and $j^*(a)$, and then for $i^*(a)$ and $j^*(a)$), the initial step towards the application of the usual procedure.

Diekmann and collaborators (see Diekmann *et al.* 1990; Heestebeek 1992) introduced the method of the "next generation operator" to calculate $\mathcal{R}_0$ for heterogeneous populations. Diekmann and collaborators gave a mathematical definition of $\mathcal{R}_0$ that it is in complete analogy with the usual one. They introduce an operator which, when acting on

an initial distribution of infectives, gives the distribution of secondary cases. $\mathcal{R}_0$ is defined as the *spectral radius* of this operator. Their method works nicely for System (1.1) as it will be shown in the next section.

2. Calculation of $\mathcal{R}_0$

Diekmann and coworkers consider (as we do) a heterogeneously mixing population where individuals are characterised by age a. We let $s(a)$ denote the density function used to describe the *steady demographic state* in the absence of disease. $A(\tau, a, \alpha)$ gives 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 $A(\tau, a, \alpha) = f(a)g(\tau, \alpha)$. Proportionate mixing is quite appropriate in the modeling of communicable diseases such as TB. This assumption which is sociologically acceptable makes the computation of $\mathcal{R}_0$ possible. However, the use of this assumption in models for sexually-transmitted diseases while common is not appropriate (see Castillo-Chavez et *al.*, 1995).

We can now state the following important result.

Lemma 1. (*Diekmann*) *Under assumptions above,* $\mathcal{R}_0$ *is given by the formula*

$$\mathcal{R}_0 = \int_0^\infty \int_0^\infty g(\tau, \alpha)s(\alpha)f(\alpha)d\tau d\alpha. \tag{2.1}$$

To make use of the formula (2.1) to calculate $\mathcal{R}_0$ for System (1.1), weconsider the demographic steady state $(s(a), 0, 0, 0)$ of System (1.1) where every one is susceptible. We also temporarily ignore the fact that $s(a)$ decreases due to the infection process (for the justification see Diekmann *et al.* 1990). Then $s(a) = n(a) = \Lambda e^{-\mu a}$. We need to compute

the remaining factors required in Equation (2.1). We observe that

$$p(a) = \frac{c(a)n(a)}{\int_0^\infty c(u)n(u)du}, \tag{2.2}$$

and 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. We also 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 the l class times the probability of being still alive at age $\alpha + u$, given that the individual was alive at age α, is:

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

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

$$ke^{-(\mu+k)u}. \tag{2.3}$$

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

$$e^{-(\mu+r)(\tau-u)}. \tag{2.4}$$

From (2.3) and (2.4) we have that

$$\begin{aligned}\gamma(\tau, \alpha) &= \int_0^\tau ke^{-(\mu+k)u}e^{-(r+\mu)(\tau-u)}du \\ &= \frac{k}{r-k}(e^{-k\tau} - e^{-r\tau})e^{-\mu\tau}.\end{aligned}$$

Remark: $\gamma(\tau, \alpha) > 0$ for all $r > 0, k > 0$.

Hence using the definition of $A(\tau, a, \alpha)$ we have

$$\begin{aligned}A(\tau, a, \alpha) &= \beta(a)c(a)p(\alpha+\tau)\frac{\gamma(\tau, \alpha)}{n(\alpha+\tau)} \\ &= \beta(a)c(a)p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau} - e^{-r\tau})e^{\mu\alpha}\frac{1}{\Lambda} \\ &=: f(a)g(\tau, \alpha),\end{aligned} \tag{2.5}$$

where

$$f(a) = \beta(a)c(a),$$
$$g(\tau,\alpha) = p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau}-e^{-r\tau})e^{\mu\alpha}\frac{1}{\Lambda}$$

Noticing that $s(\alpha) = \Lambda e^{-\mu\alpha}$, we conclude from Lemma 1 that

$$\begin{aligned}\mathcal{R}_0 &= \int_0^\infty \int_0^\infty g(\tau,\alpha)S(\alpha)f(\alpha)d\tau d\alpha \\ &= \int_0^\infty \int_0^\infty \beta(a)c(\alpha)p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau}-e^{-r\tau})d\tau d\alpha.\end{aligned} \tag{2.6}$$

Equation (2.6) gives the basic reproductive number or $\mathcal{R}_0$ for our age-structured model that governs the dynamics of TB in the absence of a vaccination policy. We use this threshold quantity in the next section to study some of the properties of System (1.1); the properties that are relevant to our study of optimal vaccination policies.

3. Stability of the infection-free state and existence of an endemic state

We find the relationship between the generation process (transmission of the disease) and the development of the epidemic in real time following the work of Diekmann (1989 and 1990). We let $\mathcal{I}(t,a)$ denote the rate at which uninfected individuals of age a are infected at time t and observe that individuals with infection age τ were actually infected at time $t-\tau$. These infected individuals have at time t an infectivity given by $A(\tau,a,.)$ that can be directed towards uninfected individuals (those in classes s and j) of age a. Therefore, $A(\tau,a,\alpha)\mathcal{I}(t-\tau,\alpha)$ gives the infective pressure per unit of time on the uninfected individuals of age a from infected individuals with infection age τ at time t. Integrating over all possible ages α and and all infection ages τ gives the total infective pressure. Finally, we arrive at the following relation between $\mathcal{I}(t,a)$ and its history:

$$\mathcal{I}(t,a) = (s(t,a)+j(t,a))\int_0^\infty \int_0^\infty A(\tau,a,\alpha)\mathcal{I}(t-\tau,\alpha)d\alpha d\tau. \tag{3.1}$$

Using Expression (3.1) we can establish the following result:

Result 1: *(a) The disease-free equilibrium of System (1.1) is stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$. (b) When $\mathcal{R}_0 > 1$, there exists a unique endemic steady state age distribution.*

Proof: (a). The infection-free state is given by

$$s(t,a) = s(a) = \Lambda e^{-\mu a}, \quad j(t,a) = 0, \quad \mathcal{I}(t,a) = 0. \tag{3.2}$$

For solutions to (3.1) of the form $\mathcal{I}(t,a) = \eta(a)e^{\lambda t}$ the linearization of (3.1) about the infection-free state (3.2) gives

$$\eta(a)e^{\lambda t} = s(a)\int_0^\infty \int_0^\infty A(\tau,a,\alpha)\eta(\alpha)e^{\lambda(t-\tau)}d\alpha d\tau. \tag{3.3}$$

Substituting the expressions for $s(a)$ given in Equation (3.2) and for $A(\tau,a,\alpha)$ given in Equation (2.5) in Equation (3.3) leads to

$$\eta(a) = e^{-\mu a}\int_0^\infty \int_0^\infty \beta(a)c(a)p(\alpha+\tau)\frac{k}{r-k}\left(e^{-k\tau}-e^{-r\tau}\right)e^{\mu\alpha}\eta(\alpha)e^{-\lambda\tau}d\alpha d\tau. \tag{3.4}$$

Equation (3.4) is separable, that is, it can be written as the following product

$$\eta(a) = \phi(\eta)e^{-\mu a}\beta(a)c(a), \tag{3.5}$$

where

$$\phi(\eta) = \int_0^\infty \int_0^\infty p(\alpha+\tau)\frac{k}{r-k}\left(e^{-k\tau}-e^{-r\tau}\right)e^{\mu\alpha}\eta(\alpha)e^{-\lambda\tau}d\alpha d\tau$$

is a positive constant depending on η. Replacing $\eta(a)$ in (3.4) by (3.5) and dividing the resulting equation by $\phi(\eta)e^{-\mu a}\beta(a)c(a)$ we arrive at the following characteristic equation:

$$1 = \int_0^\infty \int_0^\infty \beta(\alpha)c(\alpha)p(\alpha+\tau)\frac{k}{r-k}\left(e^{-k\tau}-e^{-r\tau}\right)e^{-\lambda\tau}d\alpha d\tau. \tag{3.6}$$

Let $G(\lambda)$ denote the RHS of (3.6) as a function of λ and observe that $G(0) = \mathcal{R}_0$, $G'(\lambda) < 0$ for all $\lambda \in \mathbf{R}$, and that

$$\lim_{\lambda\to\infty} G(\lambda) = 0, \quad \lim_{\lambda\to-\infty} G(\lambda) = \infty.$$

Hence $G(\lambda) = 1$ has a unique negative real root if and only if $\mathcal{R}_0 < 1$ and a unique positive (zero) real root λ^* if $\mathcal{R}_0 > 1$ ($\mathcal{R}_0 = 1$). Let $\lambda = x + iy$ be another root. Since

$$1 = G(\lambda) = |G(x+iy)| \le G(x)$$

then $\Re\lambda \le \lambda^*$. It follows that the disease-free steady state is l.a.s. if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

Proof: (b). Let $(s^*(a), l^*(a), i^*(a), j^*(a))$ denote an endemic steady state distribution for System (1.1) and let $n^*(a) \equiv s^*(a) + l^*(a) + i^*(a) + j^*(a)$. It is easy to see that $n^*(a) = n(a) = \Lambda e^{-\mu a}$. We assume that $B(t) \to B^*$ as $t \to \infty$ where

$$B^* = \int_0^\infty \frac{i^*(a')}{n^*(a')} p^*(a') da',$$

and where $p^*(a) = p(a)$ is given by (3.2). Hence the age specific force of infection (that is, the age specific rate of becoming infected) is given by $B^*\beta(a)c(a)$. The survival function

$$\mathcal{F}(a) = e^{-\int_0^a B^*\beta(u)c(u)du} \tag{3.7}$$

gives the probability that a susceptible individual remains uninfected if alive (in classes s and j) and, hence

$$s^*(a) = \Lambda \mathcal{F}(a) e^{-\mu a}. \tag{3.8}$$

Because $B^*\beta(a)c(a)s^*(a)$ gives the age specific incidence rate then consistency requires that

$$\begin{aligned} B^*\beta(a)c(a) &= \int_0^\infty \int_0^\infty A(\tau, a, \alpha) B^*\beta(\alpha)c(\alpha)(s^*(\alpha) + j^*(\alpha)) d\alpha d\tau \\ &= \int_0^\infty \int_0^\infty \beta(a)c(a)p(\alpha+\tau)\frac{k}{r-k}\left(e^{-k\tau} - e^{-r\tau}\right)\frac{e^{\mu\alpha}}{\Lambda} B^* c(\alpha)(s^*(\alpha) + j^*(\alpha)) d\alpha d\tau. \end{aligned} \tag{3.9}$$

First $B^* = 0$ is always a solution of Equation (3.9) and this naturally corresponds to the disease-free state. Any other positive solution of Equation (3.9) corresponds to an endemic equilibrium. As an equation for B^*, Equation (3.9) provides a necessary and sufficient condition for the existence of an endemic equilibrium solution

Assuming that $B^* > 0$ and dividing both sides of (11) by $B^*\beta(a)c(a)$ we get

$$1 = \int_0^\infty \int_0^\infty \beta(\alpha)c(\alpha)p(\alpha+\tau)\frac{k}{r-k}\left(e^{-k\tau} - e^{-r\tau}\right) h(B^*) d\alpha d\tau, \tag{3.10}$$

where

$$\begin{aligned} h(\alpha, B^*) &= s^*(\alpha, B^*) + j^*(\alpha, B^*), \\ s^*(\alpha, B^*) &= \Lambda e^{-\mu\alpha - \int_0^\alpha B^*\beta(u)c(u)du}, \\ j^*(\alpha, B^*) &= \int_0^\alpha e^{-\mu(\alpha+s) - \int_s^\alpha B^*\beta(u)c(u)du} r i^*(s) ds. \end{aligned} \tag{3.11}$$

We let $H(B^*)$ denote the function on the RHS of (3.10)—a function of B^*. Note that as a function of B^*, $s^*(\alpha, B^*) \to 0$ as $B^* \to \infty$. Also note that since $i^*(\alpha)$ is bounded by Λ for all $\alpha \in [0, a]$, $j^*(\alpha, B^*) \to 0$ as $B^* \to \infty$ for all $a \in [0, \infty)$. It follows that $h(\alpha, B^*) \to 0$ and hence $H(B^*) \to 0$ as $B^* \to \infty$. Since $H(B^*)$ is a continuous function of B^*, we conclude that $H(B^*) = 1$ has a unique positive solution when $H(0) = \mathcal{R}_0 > 1$.
This finishes the proof.

4. Optimal vaccination strategies

Generally speaking, the effect of subjecting a population to a vaccination program is to reduce its basic reproductive number and to increase its average age of first infection (Dietz, 1975). The goals of a vaccination program are multiple. Ideally, one would like to eliminate or erradicate a disease. Often, vaccinations can only prevent major epidemic outbreaks. Elimination is usually highly unlikely. Hence, we often try to find ways of reducing the prevalence or the incidence of a particular disease. The reduction of the reproductive number provides an approach towards the reduction of the prevalence and incidence of a disease. Following the work of Hadeler and Müeller (1993a; 1993b) on models for HIV vaccination, we proceed to look at the effectiveness of vaccination policies that are driven by reductions on the basic reproductive number. In order to discuss these concepts, we must introduce a model with per capita age-dependent vaccination rates.

We assume that susceptibles in the same age-structure population model are vaccinated at an age-dependent per capita vaccination rate given by the function $\psi(a)$ (similar results can be obtained in the case where susceptibles cannot be recognized and thus every one is vaccinated, see Hadeler and Müeller (1993b). We also assume that vaccination lasts forever. Let $\mathcal{R}(\psi)$ be the basic reproduction number in the presence of the vaccination strategy ψ. Note that for the calculation of $\mathcal{R}(\psi)$ we only need to consider the equation for s since the population is assumed to be at demographic equilibrium and consisting of only susceptible individuals. The equation for s now has the following form:

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

with the same boundary condition $s(t,0) = \Lambda$. Let $s_\psi(a)$ denote the density function describing the steady demographic state in the absence of disease, and let

$$\mathcal{F}_v(a) = e^{-\Phi(a)}, \quad \Phi(a) = \int_0^a \psi(u)du.$$

Clearly, we have that

$$s_\psi(a) = \Lambda e^{-\mu a}\mathcal{F}_v(a). \tag{4.1}$$

We derive a formula for $\mathcal{R}(\psi)$ using the same approach used to derive the expression for $\mathcal{R}_0$ in Section 2 (details are ommited). We arrive at the following expression for $\mathcal{R}(\psi)$:

$$\mathcal{R}(\psi) = \int_0^\infty \int_0^\infty \beta c(\alpha)p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau} - e^{-r\tau})\mathcal{F}_v(\alpha)d\tau d\alpha. \tag{4.2}$$

Since $\psi(a) \geq 0$, comparisons between the formula for $\mathcal{R}_0$ (see (2.6)) and Formula (4.2) show that

$$\mathcal{R}(\psi) \leq \mathcal{R}_0, \quad \mathcal{R}(0) = \mathcal{R}_0. \tag{4.3}$$

A little algebra shows that

$$\mathcal{R}(\psi) = \mathcal{R}_0 + F(\psi), \tag{4.4}$$

where

$$F(\psi) = \int_0^\infty \int_0^\infty \beta c(\alpha)p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau} - e^{-r\tau})(1-\mathcal{F}_v(\alpha))d\tau d\alpha. \tag{4.5}$$

Remark: *The quantity $F(\psi)$ is the reduction in the reproductive number that can be achieved when the vaccination strategy ψ is applied.*

When $\mathcal{R}_0 > 1$, one would like to choose a vaccination strategy ψ which makes $F(\psi)$ large, and thus possibly reduces $\mathcal{R}(\psi)$ to values below which would lead to the elimination of the disease. In Dietz and Schenzle (1985), a formula is derived to compute the $\psi(a)$ needed to reduce $\mathcal{R}(\psi)$ below 1. However, their approximation was constructed for diseases where the length of the infectious period is short. Because TB has a long and variable

periods of infectiousness, we follow instead, the approach used by Hadeler and Müeller (1993b) in their study of potential HIV vaccination policies.

In practice the application of vaccination strategies is limited by costs. We assume that the costs associated with one vaccination at age a are given by a positive number $\kappa(a)$, and let the total cost associated with the vaccination program depend linearly on the number of vaccinations (see Hadeler and Müeller (1993b)). Vaccination here–as with Hadeler and Müeller (1993b)–means a transition from the susceptible state to the vaccinated state. Vaccinnes which do not lead to the vaccinated class (vaccine efficacy and failure) are assumed to have been incorporated into the cost function κ. Let $C(\psi)$ be the total cost associated with the vaccination steategy ψ, then

$$C(\psi) = \int_0^\infty \kappa(a)\psi(a)s_\psi(a)da, \tag{4.6}$$

where $s_\psi(a)$ is given by (4.1).

Following Hadeler and Müeller (1993b), we define two optimization problems.

(I) Find a vaccination strategy $\psi(a)$ that minimizes $C(\psi)$ constrained by $\mathcal{R}(\psi) \leq \mathcal{R}_*$;

(II) Find a vaccination strategy $\psi(a)$ that minimizes $\mathcal{R}(\psi)$ constrained by $C(\psi) \leq \kappa_*$;

where (explicitly)

$$C(\psi) = \int \Lambda\kappa(a)e^{-\mu a}\psi(a)e^{-\int_0^a \psi(s)ds}da.$$

These optimization problems are stated in terms of $C(\psi)$ and $F(\psi)$ that is, in terms of non-linear functionals of ψ. To make both $C(\psi)$ and $F(\psi)$ linear functionals the following transformation is used (Hadeler and Müeller, 1993b).

$$\phi(a) = -\frac{d}{da}e^{\int_0^a \psi(s)ds} = \psi(a)e^{-\int_0^a \psi(s)ds}. \tag{4.7}$$

If we let $\bar{F}(\phi) \equiv F(\psi)$ and $\bar{C}(\phi) \equiv C(\psi)$; observe that

$$1 - \mathcal{F}_v(\psi) = 1 - e^{-\int_0^a \psi(s)ds} = \int_0^a \phi(s)ds;$$

and exchange the order of integrations in (4.5) to arrive at

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

Hence we can proceeed to reformulate our optimization problems using the linear functionals

$$\begin{aligned}\bar{F}(\phi) &= \int_0^\infty K(a)\phi(a)da, \\ \bar{C}(\phi) &= \int_0^\infty B(a)\phi(a)da,\end{aligned} \tag{4.8}$$

where

$$\begin{aligned}K(a) &= \int_a^\infty \int_0^\infty \beta c(\alpha) p(\alpha+\tau) \frac{k}{r-k}(e^{-k\tau} - e^{-r\tau}) d\tau d\alpha, \\ B(a) &= \Lambda \kappa(a) e^{-\mu a}.\end{aligned} \tag{4.9}$$

Let

$$Q(\phi) = \int_0^\infty \phi(a) da$$

and let $\rho = \mathcal{R}_0 - R_*$. Then observing that $Q(\phi) \leq 1$, we are able to replace Problem (I) with the following linear optimization problem:

$$\begin{aligned}&\text{Minimize} \quad \bar{C}(\phi) \quad \text{subject to} \\ &f(\phi) \leq 0, \\ &\phi \geq 0,\end{aligned} \tag{4.10}$$

where

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

We apply the Kuhn-Tucker Theorem for convex optimization problems because both $C(\phi)$ and $f(\phi)$ are linear and hence convex. Therefore ϕ is a solution to (4.10) if and only if there exists a non-negative vector (*Lagrange multipliers*) $Y = (\eta, \xi)^T \geq 0$ such that the *Lagrange function*

$$L(\phi, Y) = C(\phi) + Y^T f(\phi)$$

and Y satisfy the following conditions:

$$(D_\phi L(\phi, Y))\phi = 0, \qquad Y^T f(\phi) = 0. \tag{4.11}$$

The Saddle Point Theorem of Kuhn and Tucker requires a necessary condition for ϕ to be an optimal solution to (4.10), namely, that (ϕ, Y) is a saddle point of L. If this assumption is satisfied then

$$D_\phi L(\phi, Y) \geq 0. \tag{4.12}$$

Noticing that

$$\big(D_\phi L(\phi, Y)\big)\phi_0 = \int_0^\infty \big(B(a) - \eta(a)K(a) - \xi\big)\phi_0(a)da \tag{4.13}$$

for any $\phi_0 \geq 0$, we get from (4.12) that

$$B(a) - \eta K(a) - \xi \geq 0, \quad \text{for almost all } \ a \geq 0. \tag{4.14}$$

Using (4.13) we can rewrite conditions (4.11) as follows:

$$\bar{C}(\phi) - \eta\bar{F}(\phi) - \xi Q(\phi) = 0, \qquad \eta(\rho - \bar{F}(\phi)) = 0, \qquad \xi(\bar{C}(\phi) - 1) = 0. \tag{4.15}$$

Conditions (4.14), (4.15) give formally the same conditions as those described in Hadeler and Müeller (1993b, Equations (15a)-(15f)). Problem (I) is mathematically equivalent to their roblem (P1) (Hadeler and Müeller, 1993b). Hence, using Hadeler and Müeller's results (Hadeler and Müeller, 1993b) led to the following conclusion:

Result 2: *In a 'generic' situation the optimal vaccination strategy in Problem (I) is either a one-age strategy with vaccination at exactly one age A, or it is a two-age strategy where part of the population is vaccinated at an age A_1 while the remaining susceptible individuals are vaccinated at a later age A_2.*

Remarks:

1 The one-age strategy occurs when $Q(\phi) < 1$ in which case, necessarily, ϕ is a delta function concentrated at the minimum of the function $B(a)/K(a)$. When $Q(\phi) = 1$, there is a two-age strategy as the optimal ϕ is a convex combination of two delta functions. Hadeler and Müeller (1993b) results also provide a way of calculating the optimal ages for these two vaccination strategies.

2 The word "generic" is used in the same sense as in Hadeler and Müeller (1993b). For arbitrary positive continuous functions $B(a)$ and $K(a)$ nothing can be said about the set where the quotient assumes its minimum. However, for almost all functions the minimum is assumed at a single point. This argument can be made mathematically rigorous by fixing a topology that guarantees the existence of an open dense set where this quotient assumes its minimum at a single point. Hence generically the quotient assumes its minimum at a single point. The case $Q(\phi) = 1$ demands a similar argument but not applied to the ratio $B(a)/K(a)$ but to the function $B(a) - \eta K(a)$.

For these two vaccination strategies the corresponding total costs can be calculated using the following formulas

$$
\begin{aligned}
C(A) &= \frac{B(A)}{K(A)}\rho, \\
C(A_1, A_2) &= \frac{\rho - K(A_2)}{K(A_1) - K(A_2)} B(A_1) + \frac{K(A_1) - \rho}{K(A_1) - K(A_2)} B(A_2),
\end{aligned}
\tag{4.16}
$$

respectively for one-age and two-age strategy.

To determine the optimal ages, we note that $K(a)$ is a strictly decreasing function with $K(0) = \mathcal{R}_0 > \rho$ and $K(a) \to 0$ as $a \to \infty$. Hence we can find a $A_* > 0$ such that $K(A_*) = \rho$. The following result can be used to calculate the optimal ages.

Result 3. *The minimum A of the quotient $B(a)/K(a)$, if $A \in [0, A_*]$, 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 $A_1 \in [0, A_*], A_2 \in [A_*, \infty)$.*

A similar conclusion to Result 1 can be obtained for Problem (II), i.e., the optimal vaccination strategy is either a one-age strategy or a two-age strategy. To determine the

optimal ages in this case, we define

$$\mathcal{M}^* = \{a : a \geq 0, B(a) \geq \kappa^*\}$$

$$\mathcal{N}^* = \{(A_1, A_2) : A_2 \geq A_1 \geq 0, 0 \leq (\kappa^* - B(A_1))/(B(A_2) - B(A_1)) \leq 1\}.$$

Result 4. *For Problem (II) the optimal age for the one-age strategy is found by minimizing* $K(A)/B(A)$ *on* $\mathcal{M}^*$ *and the optimal ages for the two-age strategy are found by minimizing the expression*

$$F(\psi) = K(A_1)\frac{B(A_2) - \kappa^*}{B(A_2) - B(A_1)} + K(A_2)\frac{\kappa^* - B(A_1)}{B(A_2) - B(A_1)}$$

on $\mathcal{N}^*$.

5. Discussion

In this paper we introduced an age-structure model for the dynamics of TB to study age-dependent optimal vaccination strategies. First we calculated the basic reproductive number using the approach of the "next generation operator" and studied the disease transmission dynamics in the absence of a vaccination policy. We proceeded to study cost related optimal vaccination strategy problems. We found that optimal strategies have the form of one-age strategies or of two-age strategies. The optimal strategies are determined by minimizing functions of one or two variables. Our model has many limitations. For example, we did not consider infection age depedent infectivity which may play a role in the transmission of TB. We also assumed permanent immunity which may not be realistic for the BCG vaccine.

We have looked at a complex mathematical model for TB dynamics that it is not realistic enough to capture the major difficulties associated with the study of the optimal vaccination strategies associated with the use of BCG vaccine. The main difficult may be that the BCG vaccine is not be very effective. In Argentina, individuals are vaccinated at birth and at age of 15. Is this policy in agreement with the optimal vaccination strategies computed in this article? We cannot answer this question until information on $\mathcal{R}_0$, the cost function, and more importantly $\psi(a)$ becomes available.

Our results agree with those of Rorres and Fair (1975) who obtained the same qualitative results in the context of a resource management problem that involved an age-structured population. This is not surprising as "harvesting" is mathematically equivalent to "vaccinating" in our model. We followed mostly the approach of Hadeler and Müeller (1993a, 1993b) throughout our paper after our computation of $\mathcal{R}_0$. Our contribution consists on looking at a model where individuals are allowed to "return" to previously visited epidemiological classes and showing how to compute the optimal vaccination strategies in such situations by combining the approaches of Diekman, Hadeler and their various collaborators. Clearly, one or two-age optimal vaccination strategies seem the rule for this type of models.

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