Key words. Tuberculosis, epidemic model, optimal control theory, treatment strategies.

AMS subject classifications. 49M05, 92D30.

EXTENDED ABSTRACT. We apply optimal control theory to a tuberculosis model given by a system of ordinary differential equations. Optimal control strategies are proposed to minimize the cost of interventions. Numerical simulations are given using data from Angola.

Mycobacterium tuberculosis is the cause of most occurrences of tuberculosis (TB) and is usually acquired via airborne infection from someone who has active TB. It typically affects the lungs (pulmonary TB) but can affect other sites as well (extra pulmonary TB). Approximately 10% of people infected with mycobacterium tuberculosis develop active TB disease. Therefore, approximately 90% of people infected remain latent. Latent infected TB people are asymptomatic and do not transmit TB, but may progress to active TB through either endogenous reactivation or exogenous reinfection [11, 12]. Without treatment, mortality rates are high, but the anti-TB drugs developed since 1940 dramatically reduce mortality rates, and in clinical cases, cure rates of 90% have been documented [14]. However, TB remains a major health problem. In 2010 there were an estimated 8.5–9.2 million cases and 1.2–1.5 million deaths. TB is one of the leading causes of death from an infectious disease worldwide [14].

One can distinguish three types of TB treatment: vaccination to prevent infection; treatment to cure active TB; treatment of latent TB to prevent endogenous reactivation [3]. The treatment of active infectious individuals can have different timings [5]. In this work we consider treatment with the duration of six months. In these treatments one of the difficulties to their success is to make sure that the patients complete the treatment. Indeed, after two months, patients no longer have symptoms of the disease and feel healed, and many of them stop taking the medicines. When the treatment is not concluded, the patients are not cured and reactivation can occur and/or the patients may develop resistant TB. One way to prevent patients of not completing the treatment is based on supervision and patient support. In fact, this is proposed by the Direct Observation Therapy (DOT) of World Health Organization (WHO) [13]. These measures are very expensive since the patients need to stay longer in the hospital or specialized people are to be payed to supervise patients till they finish their treatment. On the other hand, it is recognized that the treatment of latent TB individuals reduces the changes of reactivation, even if it is still unknown how treatment influences reinfection [3].
Angola is one of the countries in the world with the fastest economic growth, and is very rich in natural resources: oil, diamonds, hydroelectric potential, and rich agricultural land. However, Angola remains a poor country and a third of the population depends on subsistence agriculture. Angola established the National Program for the Control of Tuberculosis in 1981, but the civil war destroyed 70 percent of the country’s health facilities, leaving a substantial proportion of the population vulnerable to TB. In 2007 the Ministry of Health confirmed that only in 8.6 percent of the health units the national program was implemented. Moreover, the internal transport and distribution mechanisms of TB drugs was precarious and 40 percent of clinics have experienced stockouts in TB drugs [16]. Between 2002 and 2005 treatment success rates were between 68 and 74 percent, in 2008 the success rate is still within that range, still below the WHO target of 85 percent [16].

Optimal control is a branch of mathematics developed to find optimal ways to control a dynamic system [1, 2, 7]. While the usefulness of optimal control theory in epidemiology is nowadays well recognized [6, 8, 9], results in tuberculosis are a rarity [4]. Our aim is to study optimal strategies for the minimization of the number of active TB infectious and persistent latent TB individuals, taking into account the cost of the measures for the treatments of these individuals. For that, we study the mathematical model for TB dynamics presented in [3], where reinfection and post-exposure interventions are considered. We modify the model of [3] adding two controls $u_1(t)$ and $u_2(t)$, which are functions of time $t$, and two real positive parameters, $\epsilon_1$ and $\epsilon_2$. The resulting model is given by the following system of nonlinear ordinary differential equations:

$$
\begin{align*}
\dot{S}(t) &= \mu N - \frac{\beta}{N} I(t) S(t) - \mu S(t) \\
\dot{L}_1(t) &= \frac{\beta}{N} I(t) (S(t) + \sigma L_2(t) + \sigma_R R(t)) - (\delta + \tau_1 + \mu)L_1(t) \\
\dot{I}(t) &= \phi \delta L_1(t) + \omega L_2(t) + \omega_R R(t) - (\tau_0 + \epsilon_1 u_1(t) + \mu)I(t) \\
\dot{L}_2(t) &= (1 - \phi) \delta L_1(t) - \sigma \frac{\beta}{N} I(t) L_2(t) - (\omega + \epsilon_2 u_2(t) + \tau_2 + \mu)L_2(t) \\
\dot{R}(t) &= (\tau_0 + \epsilon_1 u_1(t)) I(t) + \tau_1 L_1(t) + (\tau_2 + \epsilon_2 u_2(t)) L_2(t) - \sigma_R \frac{\beta}{N} I(t) R(t) \\
&\quad - (\omega_R + \mu) R(t).
\end{align*}
$$

The population is divided into five categories (i.e., the control system (1) has five state variables): susceptible ($S$); early latent ($L_1$), i.e., individuals recently infected (less than two years) but not infectious; infected ($I$), i.e., individuals who have active TB and are infectious; persistent latent ($L_2$), i.e., individuals who were infected and remain latent; and recovered ($R$), i.e., individuals who were previously infected and treated. The control $u_1$ represents the effort that prevents the failure of treatment in active TB infectious individuals $I$, e.g., supervising the patients, helping them to take the TB medications regularly and to complete the TB treatment. The control $u_2$ alters the fraction of persistent latent individuals $L_2$ that is put under treatment. The parameters $\epsilon_1$, $\epsilon_2 \in (0, 1)$, $i = 1, 2$, measure the effectiveness of the controls $u_i$, $i = 1, 2$, respectively, i.e., these parameters measure the efficacy of treatment interventions for active and persistent latent TB individuals, respectively. We assume that at birth all individuals are equally susceptible and differentiate as they experience infection and respective therapy. Moreover, the total population, $N$, with $N = S + L_1 + I + L_2 + R$, is assumed to be constant, i.e., the rate of birth and death, $\mu$, are equal and there are no disease-related deaths. Following WHO’s Global Health Observatory with respect to the year of 2009 in Angola, we consider $\mu = 1/52 \text{ yr}^{-1}$ corresponding to a life expectancy at birth of 52 years [15]. The values of the other rates and parameters...
of the model (1) are taken from [3] and the references cited therein, taking into account the specificities of the situation of TB in Angola in the choice of the values for some of these rates. The basic reproduction number $R_0$ for system (1) in the absence of controls, is proportional to the transmission coefficient $\beta$ (see [3]). The endemic threshold $ET$ at $R_0 = 1$ indicates the minimal transmission potential that sustains endemic disease, i.e., when $R_0 < 1$ the disease dies out; and for $R_0 > 1$ the disease may become endemic. In our simulations we take increasing values for $\beta$ with $R_0 > 1$.

The total simulation duration, $T$, is fixed and we take $T = 5$, in years. We consider the optimal control problem of determining a quintuple $(S^*(\cdot), I_1^*(\cdot), I_2^*(\cdot), L_2^*(\cdot), R^*(\cdot))$, satisfying (1), the initial conditions $S(0), L_1(0), I(0), L_2(0)$ and $R(0)$ (suitably chosen), associated to an admissible control pair $(u_1^*(\cdot), u_2^*(\cdot)) \in \Omega$ on the time interval $[0, T]$, where $\Omega = \{(u_1(\cdot), u_2(\cdot)) \in (L^\infty(0, T))^2 \mid 0 \leq u_1(t), u_2(t) \leq 1, \forall t \in [0, T]\}$, and minimizing the cost functional

$$J(u_1(\cdot), u_2(\cdot)) = \int_0^T \left[I(t) + L_2(t) + \frac{W_1}{2}u_1^2(t) + \frac{W_2}{2}u_2^2(t)\right] dt,$$

that is,

$$J(u_1^*(\cdot), u_2^*(\cdot)) = \min_{\Omega} J(u_1(\cdot), u_2(\cdot)).$$

The constants $W_1$ and $W_2$ are a measure of the relative cost of the interventions associated to the controls $u_1$, $u_2$, respectively. We prove that the problem has an unique solution, and finally we apply to it the celebrated Pontryagin Maximum Principle [7].

Optimal control strategies are proposed to minimize the number of active TB infectious and persistent latent individuals in Angola, taking into account the cost of the measures for the treatment of these individuals. We show that optimal control strategies reduce effectively both the fraction of active infectious and persistent latent individuals. For details see [10].

REFERENCES


http://apps.who.int/ghodata/?theme=country