Mathematical Modeling of Drug Resistance in Tuberculosis Transmission and Optimal Control Treatment

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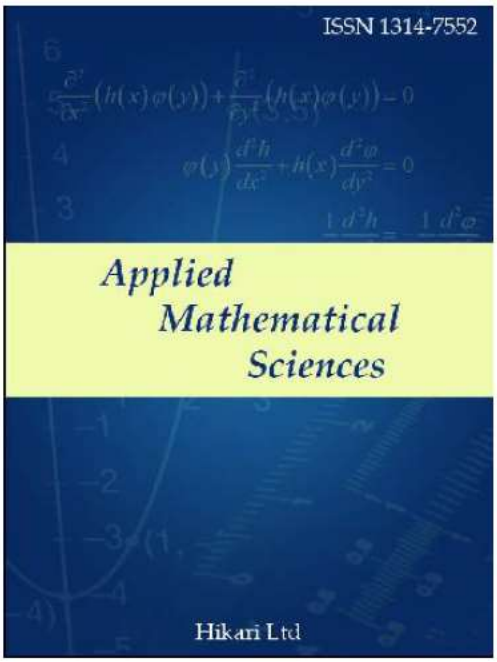
Applied Mathematical Sciences, Vol. 8, 2014, no. 92, 4547 - 4559
HIKARI Ltd, www.m-hikari.com
http://dx.doi.org/10.12988/ams.2014.46492



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ISSN 1312-885X (Print)
ISSN 1314-7552 (Online)

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Published by Hikari Ltd

Applied Mathematical Sciences, Vol. 8, 2014, no. 89 – 92

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HIKARI Ltd, www.m-hikari.com
http://dx.doi.org/10.12988/ams.2014.46492

Mathematical Modeling of Drug Resistance in Tuberculosis Transmission and Optimal Control Treatment

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Abstract

Tuberculosis is caused by Mycobacterium tuberculosis. The disease is still one of the major killer of humans. We derive and analyzed mathematical modeling of drug resistance in tuberculosis transmission. We use control on treatment to reduce of the number of infected population. For model without control optimal, we have the basic reproduction number for the sensitive and resistant tuberculosis infection in the first area and tuberculosis infection in the second area. This number determine the existence and stability of equilibria. Then, the Pontryagin Maximum Principle is applied to derive necessary conditions for the optimal control of the tuberculosis disease. Finally, numerical simulations are performed to describe the analytical results.

Keywords: mathematical model, tuberculosis, optimal control, resistance.

1 Introduction

Tuberculosis (TB) is a deadly infectious disease caused by Mycobacterium tuberculosis (MTB). There is about one-third of the world's population has latent TB, which means people have been infected by MTB but are not (yet) ill with

disease and cannot transmit the disease. TB is spread from person to person through the air. When people with pulmonary TB cough, sneeze or spit, they propel the TB germs into the air. Someone needs to breathe just a few of these germs to be infected. In 2011, 8.7 million people fell ill with TB and 1.4 million died from TB. Standard anti-TB drugs have been used for decades, and resistance to the medicines is growing. Disease strains that are resistant to a single anti-TB drug have been documented in every country surveyed [11]. Hence, a good understanding of the effectiveness of the treatment and control strategies in different regions of the world still needed

Study of the spread of TB disease have been conducted by several researchers [1,4,5,10]. Other forms of mathematical models can be used to control the spread of disease is to formulate the application of optimal control to prevent and control TB disease with minimum costs [6]. In [8], the authors have developed a model of the spread of tuberculosis by vaccination and treatment in patients with TB. While in [10], the authors have extended a model of the spread of TB disease by observing the migration of healthy subpopulations in the two regions without the factor of resistance to anti- TB drugs. Therefore, in this paper will be constructed a mathematical model that describes the dynamics of the spread of TB by a factor of resistance to anti-TB drugs and also the migration of healthy sub-population in the two regions. In addition, we further carried out qualitative optimal control analysis to reduce the number of TB patients with the resistance factor. We use Pontryagin Maximum Principle to find the necessary conditions for the optimal control of the tuberculosis disease.

2. Model Formulation

In this paper, we extended the model of tuberculosis that has been developed in [10]. Model of tuberculosis SIR by a factor of migration in human populations are vulnerable and transmission does not occur during the migration process. This model consists of two major subpopulations. Each subpopulation is divided into three classes based on the epidemiology status that is susceptible (S_i), infected (I_i), and recovered(R_i), with $i = 1,2$. For the class of subpopulations infected first divided into two classes, namely class -infected sensitive (I_s) and resistant to the class of anti- TB drugs (I_r). Recruitment in each subpopulation

only in the susceptible class at a constant rate Λ_i, with $i = 1,2$.

Natural mortality is proportional to the population size of each region with the rate μ_1 and μ_2 on the first and second regions, respectively. Additional mortality due to TB disease only affects the class I_s, I_r , and I_2 with the rate of the first region d_1 and the second region d_2. Transmission of MTB occur after adequate contact between vulnerable populations with the infected population in each subpopulation. In each unit of time, susceptible individuals have an average contact $\beta_s I_s, \beta_r I_r$, and $\beta_2 I_2$ that will be sufficient to transmit the disease. Thus the rate of the population is susceptible to infection $\beta_s S_1 I_s, \beta_r S_1 I_r$, and $\beta_2 S_2 I_2$. Each individual is infected were given treatment (u) with cure rate for treatment are α_s and α_r, respectively healing rate of the population is infected with sensitive and resistant to the treatment. While the natural healing rate of diseased individuals is constant γ_r, γ_s and γ_2. All parameters and variables used in the nonnegative value in order to have biological significance.

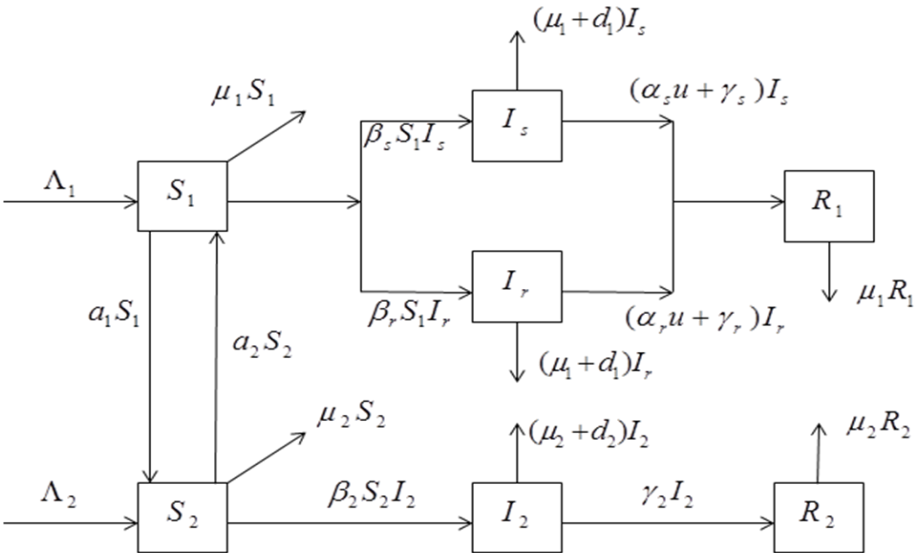

Figure 1. Transmission diagram for tuberculosis disease

Based on the assumption and transmission diagram, we can develop the model population as follows:

$$\begin{aligned}
\frac{dS_1}{dt} &= \Lambda_1 - \beta_s S_1 I_s - \beta_r S_1 I_r - \mu_1 S_1 - a_1 S_1 + a_2 S_2 \\
\frac{dI_S}{dt} &= \beta_s S_1 I_s - (\alpha_s u + \gamma_s) I_s - (\mu_1 + d_1) I_s \\
\frac{dI_r}{dt} &= \beta_r S_1 I_r - (\alpha_r u + \gamma_r) I_r - (\mu_1 + d_1) I_r \\
\frac{dR_1}{dt} &= (\alpha_s u + \gamma_s) I_s + (\alpha_r u + \gamma_r) I_r - \mu_1 R_1 \\
\frac{dS_2}{dt} &= \Lambda_2 - \beta_2 S_2 I_2 - \mu_2 S_2 - a_2 S_2 + a_1 S_1 \\
\frac{dI_2}{dt} &= \beta_2 S_2 I_2 - (\alpha_2 u + \gamma_2) I_2 - (\mu_2 + d_2) I_2 \\
\frac{dR_2}{dt} &= (\alpha_2 u + \gamma_2) I_2 - \mu_2 R_2
\end{aligned} \tag{1}$$

Model (1) has the biological domain as follows: $\Omega = \left\{ \left(S_1, I_s, I_r, R_1, S_2, I_2, R_2 \right) \in \Re_+^7 \right\}$.

3. Model Analysis

First, we analyze the model (1) without control function *u*, that is, without treatment. Let defined the parameter

$$R_0 = \max\{R_{0s}, R_{0r}, R_{02}\}, \text{ with}$$

$$R_{0s} = \frac{\beta_s (\Lambda_1 \mu_2 + \Lambda_1 a_2 + \Lambda_2 a_2)}{(\gamma_s + \mu_1 + d_1)(\mu_1 a_2 + \mu_2 a_1 + \mu_1 \mu_2)}$$

$$R_{0r} = \frac{\beta_r (\Lambda_1 \mu_2 + \Lambda_1 a_2 + \Lambda_2 a_2)}{(\gamma_r + \mu_1 + d_1)(\mu_1 a_2 + \mu_2 a_1 + \mu_1 \mu_2)}$$

$$R_{02} = \frac{\beta_2 (\Lambda_1 a_1 + \Lambda_2 \mu_1 + \Lambda_2 a_1)}{(\gamma_2 + \mu_2 + d_2)(\mu_1 a_2 + \mu_2 a_1 + \mu_1 \mu_2)}$$

The parameter R_0 is called the basic reproduction ratio. Parameters R_{0s}, R_{0r}, and R_{02} is called basic reproduction ratio for the sensitive, resistant TB infection in the first area and TB infection in second area, respectively. In this study, R_0 obtained by constructing a matrix that generates a new number of infected individuals. This matrix is called the Next Generation Matrix [2].

Model (1) has six equilibriums (with respect to coordinate $(S_1, I_s, I_r, R_1, S_2, I_2, R_2)$), these are

a. $E_1 = (S_{11}, 0, 0, 0, S_{21}, 0, 0)$ is called disease-free equilibrium in both regions, with

$$S_{11} = \frac{\Lambda_1 \mu_2 + \Lambda_1 a_2 + \Lambda_2 a_2}{\mu_1 a_2 + \mu_2 a_1 + \mu_1 \mu_2}, \quad S_{22} = \frac{\Lambda_1 a_1 + \Lambda_2 \mu_1 + \Lambda_2 a_1}{\mu_1 a_2 + \mu_2 a_1 + \mu_1 \mu_2}$$

b. $E_2 = (S_{12}, 0, 0, 0, S_{22}, I_{22}, R_{22})$ is called the disease-free equilibrium in the first

area, but endemic in the second area, with

$$S_{12}=\frac{a_2d_2+a_2\mu_2+\Lambda_1\beta_2+a_2\gamma_2}{(a_1+\mu_1)\beta_2}, S_{22}=\frac{\gamma_2+\mu_2+d_2}{\beta_2}$$

$$I_{22}=\frac{(\mu_1\Lambda_2+\Lambda_1a_1+\Lambda_2a_1)\left(1-\frac{1}{R_{02}}\right)}{(a_1+\mu_1)(\gamma_2+\mu_2+d_2)}, R_{22}=\frac{\gamma_2(\mu_1\Lambda_2+\Lambda_1a_1+a_2a_1)\left(1-\frac{1}{R_{02}}\right)}{\mu_2(a_1+\mu_1)(\gamma_2+\mu_2+d_2)}$$

The equilibrium E_2 exists if and only if $R_{02}>1$.

c. $E_3=(S_{13},I_{s3},0,R_{13},S_{23},0,0)$ is called the disease-free equilibrium in second area but infective sensitive endemic in the first area, with

$$S_{13}=\frac{\gamma_S+\mu_1+d_1}{\beta_S},\ I_{S3}=\frac{(\Lambda_1\mu_2+\Lambda_1a_2+\Lambda_2a_2)\left(1-\frac{1}{R_{0S}}\right)}{(\gamma_S+\mu_1+d_1)(\mu_2+a_2)}$$

$$R_{13}=\frac{\gamma_S(\Lambda_1\mu_2+\Lambda_1a_2+\Lambda_2a_2)\left(1-\frac{1}{R_{0S}}\right)}{(\gamma_S+\mu_1+d_1)(\mu_2+a_2)}, S_{23}=\frac{\Lambda_2\beta_S+a_1(\gamma_S+\mu_1+d_1)}{\beta_S(\mu_2+a_2)}.$$

The equilibrium E_3 exists if and only if $R_{0s}>1$.

d. $E_4=(S_{14},0,I_{r4},R_{14},S_{24},0,0)$ is called the disease-free equilibrium in second area but resistant endemic in the first area, with

$$S_{14}=\frac{\gamma_r+\mu_1+d_1}{\beta_r},\ I_{r4}=\frac{(\Lambda_1\mu_2+\Lambda_1a_2+\Lambda_2a_2)\left(1-\frac{1}{R_{0r}}\right)}{(\gamma_r+\mu_1+d_1)(\mu_2+a_2)}$$

$$R_{14}=\frac{\gamma_r(\Lambda_1\mu_2+\Lambda_1a_2+\Lambda_2a_2)\left(1-\frac{1}{R_{0r}}\right)}{(\gamma_r+\mu_1+d_1)(\mu_2+a_2)}, S_{24}=\frac{\Lambda_2\beta_r+a_1(\gamma_r+\mu_1+d_1)}{\beta_r(\mu_2+a_2)}.$$

The equilibrium E_4 exists if and only if $R_{0r}>1$.

e. $E_5=(S_{15},I_{S5},0,R_{15},S_{25},I_{25},R_{25})$ is called sensitive endemic equilibrium in the first area and endemic in the second area, with

$$S_{15}=\frac{\gamma_S+\mu_1+d_1}{\beta_S},\quad I_{S5}=-\frac{1}{\beta_S}(a_1+\mu_1)+\frac{\Lambda_1\beta_2+a_2(\gamma_2+\mu_2+d_2)}{\beta_2(\gamma_S+\mu_1+d_1)}$$

$$R_{15}=-\frac{\gamma_S}{\beta_S\mu_1}(a_1+\mu_1)+\frac{\gamma_S\Lambda_1\beta_2+\gamma_S a_2(\gamma_2+\mu_2+d_2)}{\beta_2\mu_1(\gamma_S+\mu_1+d_1)}$$

$$S_{25}=\frac{\gamma_2+\mu_2+d_2}{\beta_2},I_{25}=-\frac{1}{\beta_2}(a_2+\mu_2)+\frac{\Lambda_2\beta_S+a_1(\gamma_S+\mu_1+d_1)}{\beta_S(\gamma_2+\mu_2+d_2)}$$

$$R_{25}=-\frac{\gamma_2}{\beta_2\mu_2}(a_2+\mu_2)+\frac{\gamma_2\Lambda_2\beta_S+\gamma_2 a_1(\gamma_S+\mu_1+d_1)}{\beta_S\mu_2(\gamma_2+\mu_2+d_2)}.$$

The equilibrium E_5 exists if and only if it satisfies the following conditions

- $\frac{1}{\beta_s}(a_1+\mu_1)<\frac{\Lambda_1\beta_2+a_2(\gamma_2+\mu_2+d_2)}{\beta_2(\gamma_s+\mu_1+d_1)}$
- $\frac{1}{\beta_2}(a_2+\mu_2)<\frac{\Lambda_2\beta_s+a_1(\gamma_s+\mu_1+d_1)}{\beta_s(\gamma_2+\mu_2+d_2)}$

f. $E_6=(S_{16},0,I_{r6},R_{16},S_{26},I_{26},R_{26})$ is called resistant endemic equilibrium in the first area and endemic in the second area, with

$$S_{16}=\frac{\gamma_r+\mu_1+d_1}{\beta_r},\quad I_{r6}=-\frac{1}{\beta_r}(a_1+\mu_1)+\frac{\Lambda_1\beta_2+a_2(\gamma_2+\mu_2+d_2)}{\beta_2(\gamma_r+\mu_1+d_1)}$$

$$R_{16}=-\frac{\gamma_r}{\beta_r\mu_1}(a_1+\mu_1)+\frac{\gamma_r\Lambda_1\beta_2+\gamma_r a_2(\gamma_2+\mu_2+d_2)}{\beta_2\mu_1(\gamma_r+\mu_1+d_1)}$$

$$S_{26}=\frac{\gamma_2+\mu_2+d_2}{\beta_2},I_{26}=-\frac{1}{\beta_2}(a_2+\mu_2)+\frac{\Lambda_2\beta_r+a_1(\gamma_r+\mu_1+d_1)}{\beta_r(\gamma_2+\mu_2+d_2)}$$

$$R_{26}=-\frac{\gamma_2}{\beta_2\mu_2}(a_2+\mu_2)+\frac{\gamma_2\Lambda_2\beta_r+\gamma_2 a_1(\gamma_r+\mu_1+d_1)}{\beta_r\mu_2(\gamma_2+\mu_2+d_2)}.$$

The equilibrium E_6 exists if and only if it satisfies the following conditions

- $\frac{1}{\beta_r}(a_1+\mu_1)<\frac{\Lambda_1\beta_2+a_2(\gamma_2+\mu_2+d_2)}{\beta_2(\gamma_r+\mu_1+d_1)}$
- $\frac{1}{\beta_2}(a_2+\mu_2)<\frac{\Lambda_2\beta_r+a_1(\gamma_r+\mu_1+d_1)}{\beta_r(\gamma_2+\mu_2+d_2)}$.

A criterion for the stability of the disease-free equilibrium is given in the following theorem.

Theorem 1.

Disease-free equilibrium is locally asymptotically stable if and only if $R_0<1$.

Proof. Local stability of the disease-free equilibrium E_1 is determined by the eigenvalues of the Jacobian matrix of the model (1) at E_1. We get the eigenvalues are

$$\lambda_1 = -\mu_1, \lambda_{2=} -\mu_2 \quad ,$$

$$\lambda_3 = \frac{1}{\mu_1 a_2 + \mu_2 a_1 + \mu_1\mu_2}(1-\frac{1}{R_{0s}}), \lambda_4 = \frac{1}{\mu_1 a_2 + \mu_2 a_1 + \mu_1\mu_2}(1-\frac{1}{R_{0r}}), \quad ,$$

$$\lambda_5 = \frac{1}{\mu_1 a_2 + \mu_2 a_1 + \mu_1\mu_2}(1-\frac{1}{R_{02}}),$$

$$\lambda_6 = -\frac{1}{2}(\mu_1+\mu_2+a_1+a_2) + \frac{1}{2}\sqrt{(\mu_1+\mu_2)^2 + (a_1+a_2)^2 + 2a_1\mu_1 + 2a_2\mu_2 - 2\mu_2 a_1 - 4\mu_1\mu_2}$$

$$\lambda_7 = \frac{1}{2}(\mu_1+\mu_2+a_1+a_2) - \frac{1}{2}\sqrt{(\mu_1+\mu_2)^2 + (a_1+a_2)^2 + 2a_1\mu_1 + 2a_2\mu_2 - 2\mu_2 a_1 - 4\mu_1\mu_2}.$$

While that calculation is obtained that both λ_6 and λ_7 are negative. From these results can be concluded that the equilibrium E_1 is locally asymptotically stable if only if $R_0 < 1$, with $R_0 = \max\{R_{0s}, R_{0r}, R_{02}\}$. □

Next, we will be reviewed the stability of the five endemic equilibriums E_i, for $i \in \{2,3,\ldots,6\}$. From the calculation, the eigenvalues of the Jacobian matrix at the point E_i, for $i \in \{2,3,\ldots,6\}$, is difficult to determine analytically. Hence, the stability of the endemic equilibriums will be performed numerically. We use three initial values for simulations. It aims to find out where the convergence of each solution given initial value. Numerically, the endemic equilibrium E_2 is tend to locally asymptotically stable if $R_{02} > 1$, as given in Figure 2.

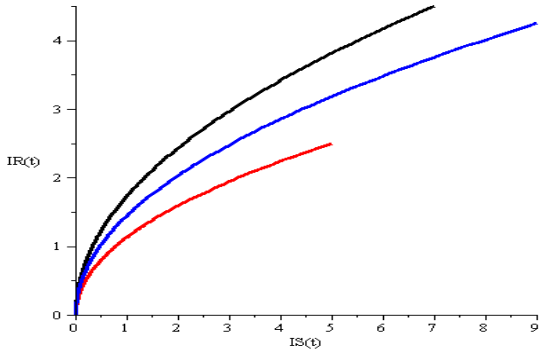

Figure 2. Phase portrait of model (1) for E_2

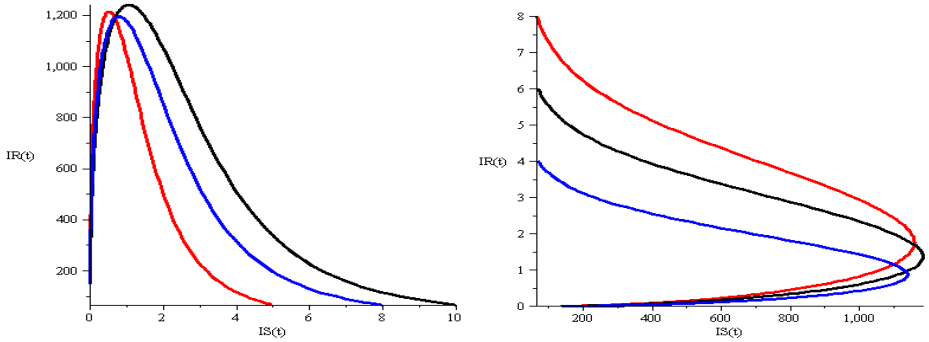

Figure 3. Phase portrait of model (1) for E_3 (left) and E_4 (right)

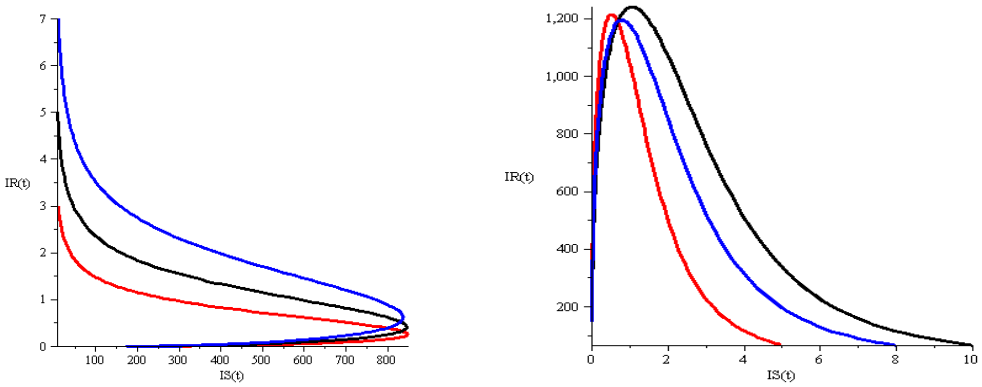

Figure 4. Phase portrait of model (1) for E_5 (left) and E_6 (right).

Based on Figure 3 and Figure 4, it is shown that each of the three different initial values, all the graphs tend to converge to the endemic equilibriums. Thus, the stability of endemic equilibriums E_3- E_6 can be expressed in the following conjectures.

Conjecture 1.

The endemic equilibrium E_3 *is locally asymptotically stable if* $R_{0s} > 1$. *The endemic equilibrium* E_4 *is locally asymptotically stable if* $R_{0r} > 1$.

Conjecture 2.

The endemic equilibrium E_5 *is locally asymptotically stable if* $R_{0s} > 1$, $R_{02} > 1$ $\frac{1}{\beta_s}(a_1 + \mu_1) < \frac{\Lambda_1\beta_2 + a_2(\gamma_2 + \mu_2 + d_2)}{\beta_2(\gamma_s + \mu_1 + d_1)}$, *and*

$\frac{1}{\beta_2}(a_2+\mu_2)<\frac{\Lambda_2\beta_s+a_1(\gamma_s+\mu_1+d_1)}{\beta_s(\gamma_2+\mu_2+d_2)}$. *The endemic equilibrium* E_6 *is locally asymptotically stable if* $R_{0r}>1$, $R_{02}>1$,

$$\frac{1}{\beta_r}(a_1+\mu_1)<\frac{\Lambda_1\beta_2+a_2(\gamma_2+\mu_2+d_2)}{\beta_2(\gamma_r+\mu_1+d_1)},\ \frac{1}{\beta_2}(a_2+\mu_2)<\frac{\Lambda_2\beta_r+a_1(\gamma_r+\mu_1+d_1)}{\beta_r(\gamma_2+\mu_2+d_2)}.$$

4. Analysis of Optimal Control

The application of optimal control in this study is to minimize the number of individuals infected with TB through treatment with minimal cost. The optimal control strategy can be achieved by minimizing the following objective function:

$$J(u)=\int_0^{t_f}\left\{I_s+I_r+I_2+\frac{1}{2}cu^2\right\}dt \qquad (2)$$

where c is weighting constant for attempt treatment. The greater the value c will imply more expensive implementation costs for treatment. We seek an optimal control u^* such that

$$J(u^*)=\min_{\Gamma} J(u), \qquad (3)$$

where $\Gamma=\{u\,|\,0\le u\le 1\}$.

Consider again the objective function (2) to the model (1). Necessary conditions to determine the optimal control u^* so that satisfy the conditions (3) with the constraint (1) will be solved by the Pontriyagin Maximum Principle [9]. This principle is to convert equation (1) - (3) to minimize the problem to the Hamiltonian function:

$$\begin{aligned}H=&I_s+I_r+I_2+\frac{1}{2}cu^2+\lambda_1(\Lambda_1-\beta_sS_1I_s-\beta_rS_1I_r-\mu_1S_1-a_1S_1+a_2S_2)\\&+\lambda_2(\beta_sS_1I_s-(\alpha_su+\gamma_s)I_s-(\mu_1+d_1)I_s)+\lambda_3(\beta_rS_1I_r-(\alpha_ru+\gamma_r)I_r-(\mu_1+d_1)I_r)\\&+\lambda_4((\alpha_su+\gamma_s)I_s+(\alpha_ru+\gamma_r)I_r-\mu_1R_1)+\lambda_5(\Lambda_2-\beta_2S_2I_2-\mu_2S_2-a_2S_2+a_1S_1)\\&+\lambda_6(\beta_2S_2I_2-(\alpha_2u+\gamma_2)I_2-(\mu_2+d_2)I_2)+\lambda_7((\alpha_2u+\gamma_2)I_2-\mu_2R_2).\end{aligned}$$

Furthermore, adjoint equations or co-state equations can be written as:

$$
\begin{aligned}
\dot{\lambda}_1 &= \lambda_1(\beta_s I_s + \beta_r I_r + \mu_1 + a_1) - \lambda_2\beta_s I_s - \lambda_3\beta_r I_r - \lambda_5 a_1 \\
\dot{\lambda}_2 &= -1 + \lambda_1\beta_s S_1 + \lambda_2(-\beta_s S_1 + \alpha_s u + \gamma_s + \mu_1 + d_1) - \lambda_4(\alpha_s u + \gamma_s) \\
\dot{\lambda}_3 &= -1 + \lambda_1\beta_r S_1 + \lambda_3(-\beta_r S_1 + \alpha_r u + \gamma_r + \mu_1 + d_1) - \lambda_4(\alpha_r u + \gamma_r) \\
\dot{\lambda}_4 &= \lambda_4\mu_1 \qquad (4) \\
\dot{\lambda}_5 &= -\lambda_1 a_2 + \lambda_5(\beta_2 I_2 + \mu_2 + a_2) - \lambda_6\beta_2 I_2 \\
\dot{\lambda}_6 &= -1 + \lambda_5\beta_2 S_2 + \lambda_6(-\beta_2 S_2 + \alpha_2 u + \gamma_2 + \mu_2 + d_2) - \lambda_7(\alpha_2 u + \gamma_2) \\
\dot{\lambda}_7 &= \lambda_7\mu_2
\end{aligned}
$$

with final condition $\lambda_i(t_f) = 0, \quad i = 1,\ldots,7.$

By applying Pontryagin's Maximum Principle and the existence result of the optimal control [3, 9], we obtain the following theorem.

Theorem 2. The optimal control u^* that minimizes $J(u)$ over Γ is given by

$$u^* = \min\{\max\{0, \Delta_1 + \Delta_2 + \Delta_3\}, 1\}$$

where $\Delta_1 = \frac{\alpha_s I_s}{c}(\lambda_2 - \lambda_4)$, $\Delta_2 = \frac{\alpha_r I_r}{c}(\lambda_3 - \lambda_4)$, $\Delta_3 = \frac{\alpha_2 I_2}{c}(\lambda_6 - \lambda_7)$, and λ_i is the solutions of the co-state equation (4) for $i = 1, 2, \ldots 7$.

Proof. Using the same argument as in Theorem 4.1 of [9], the co-states equations (4) is obtained by differentiating the Hamiltonian function, then the systems can be written as $\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S_1}, \ldots, \frac{d\lambda_7}{dt} = -\frac{\partial H}{\partial R_2}$, with transversality conditions $\lambda_i(t_f) = 0, \quad i = 1,\ldots,7,$ where t_f is the final time.

The optimal control is obtained by equating to the zero the derivative of the Hamiltonian with respect to the control, we have

$$0 = \frac{\partial H}{\partial u} = cu - \lambda_2\alpha_s I_s - \lambda_3\alpha_r I_r + \lambda_4(\alpha_s I_s + \alpha_r I_r) - \lambda_6\alpha_2 I_2 + \lambda_7\alpha_2 I_2.$$

Solving *u** for subject the constrains, the optimal control can be derived. □

5. Numerical Simulation

In this section, we present the numerically the optimal solution to the optimal control treatment on tuberculosis transmission with drug resistance by the fourth order Runge-Kutta [7]. The state system is solved forward in time with initial conditions $x(0)$ = (4100, 7, 5, 4, 4110, 8, 4), while the co-state system is solved backward in time. For numerical simulation, we use the following parameters: Λ_1 = 100; Λ_2=110; β_s = 0.001/year; β = 0.001/year; β_2 = 0.002/year;

$\frac{1}{\mu_1} = \frac{1}{\mu_2}$ = 65 year; γ_s = 0.15/ year; γ_r = 0.2/year; γ_2 = 0.15/year; a_1 = 0.5/year; a_2 =0.5001/year; d_1 = 0.0575/year; d_2 = 0.05751/ year; α_s = 0.8182/year; α_r = 0.5/year; α_2 = 0.8183/year and weight control c = 80.

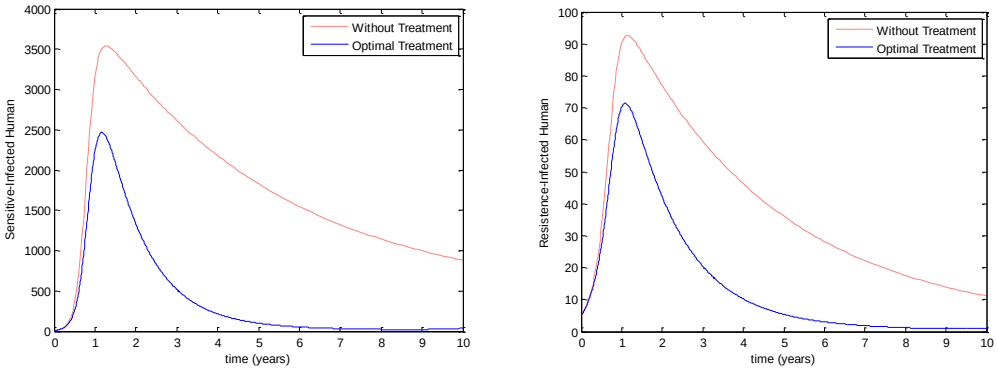

Figure 5. The dynamic of sensitive infected I_s (left) and resistant I_r (right)

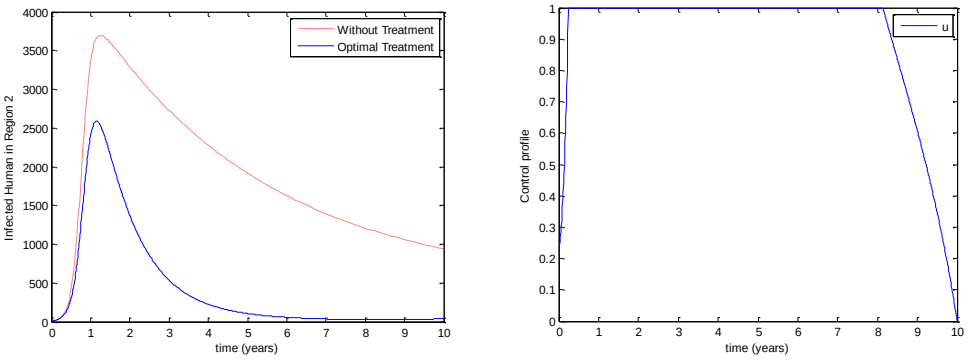

Figure 6. The dynamic of sensitive infected I_2 (left) and optimal control profile u (right)

The dynamic of the sensitive and resistance infected population in the first region are given in Figure 5. We see in Figure 5 that there is a significant difference in the number of sensitive infected I_s and drug resistant individuals I_r between the case with control and case without control. We also observe in the left of Figure 6 that the number sensitive infected I_2 decreases with control compared to the situation where there is no control. The profile of the optimal control u^* could be seen in the right of Figure 6. From this Figure, we see that to reduce the number of individuals infected with TB in the first and the second regions in 10 years, the treatment should be hold intensively almost 8 years and then reduced to near zero at the end of the 10-th year.

6. Conclusion

In this paper we have constructed a mathematical model of drug resistant in the tuberculosis disease transmission that include treatment measure as optimal control. For the model without control, we obtained three basic reproduction ratios corresponding to the sensitive and resistant TB infection in the first region and the sensitive TB infection in the second region. These ratios determine the existence and stability of the equilibrium of the model. Using Pontryagin Maximum Principle, we derived and analyzed the condition for optimal control which minimize the both sensitive and resistant infective in the first region and the sensitive only in the second region. The numerical simulations with and without control show that the control strategy has a positive impact in reducing the spread of the disease.

Acknowledgements.

Part of this research is financially supported by the Hibah Riset Berskala Nasional, FSAINTEK, DIPA Unversitas Airlangga/ BOPTN 2013 according to SK Rektor No 6091/UN3/KR/2013.

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Received: June 5, 2014