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Optimal Control for TB disease with vaccination assuming endogeneous reactivation and exogeneous reinfection

N Anggriani[1], **B C Wicaksono, A K Supriatna**
Department of Mathematics
Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran
Jl. Raya Bandung-Sumedang km 21 Jatinangor 45363, Indonesia

[1]E-mail: nursanti.anggriani@unpad.ac.id and nsanti_a@yahoo.co.id

Abstract. Tuberculosis (TB) is one of the deadliest infectious disease in the world which caused by *Mycobacterium tuberculosis*. The disease is spread through the air via the droplets from the infectious persons when they are coughing. The World Health Organization (WHO) has paid a special attention to the TB by providing some solution, for example by providing BCG vaccine that prevent an infected person from becoming an active infectious TB. In this paper we develop a mathematical model of the spread of the TB which assumes endogeneous reactivation and exogeneous reinfection factors. We also assume that some of the susceptible population are vaccinated. Furthermore we investigate the optimal vaccination level for the disease.

1. Introduction

Tuberculosis (TB) is among the fatal diseases known globally. It is estimated 9.6 millions new TB cases reported in 2014 [1]. Meanwhile, Indonesia is the third rank in regards to this new TB prevalence compared to other countries globally. In fact, TB vaccine is already available in the market. Since 1906 BCG (Bacille Calmette-Guerin) vaccine has been available. However the occurence of TB is still increasing from time to time. This is alarming, hence many effort have been explored to attack the TB transmission from various view of points, including from theoretical view point via the utilization of mathematical modeling to understand and to control the TB. Recently some mathematical models of TB transmission have been developed [2,3]. In this paper, based on earlier model [4] we derived a pulmonary and non-pulmonary transmission of TB as in [5]. Here we develop the mathematical model of the spread of the TB which assumes endogeneous reactivation and exogeneous reinfection factors. Here we also assume that some of the susceptible population are vaccinated, since vaccination is still common method in TB elimination [6]. These complexities are considred simultaneously in the model to give a better insight into the analysis of the optimal control of the TB transmission.

2. Model Formulation

Here we assume that human population is divided into seven compartments as the following: the number of susceptible compartment individual in time t is denoted by $S(t)$, the number of latent compartment individual in time t is denoted by $L(t)$, the number of vaccinated compartment individual

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in time t is denoted by V(t), the number of infectious/pulmonary *TB* compartment individual in time t is denoted by $I_i(t)$, the number of non-infectious/extra pulmonary *TB* compartment individual in time t is denoted by $I_n(t)$, the number of recovered from infectious *TB* compartment individual in the time t is denoted by $R_i(t)$ and the number of recovered from non-infectious *TB* compartment individual in the time t is denoted by $R_i(t)$. The model is represented by the diagrams shown in Figure 1, with the description of the parameters given in Table 1. The model assumes that the recruitment rate is coming from the birth (there is no immigration factor), individual who are vaccinated goes to L if they are not immune. Each compartment will experience natural death but to compartment infectious and non-infectious an extra factor of death caused by TB is added. The causes of TB disease are also assumed to be affected by endogeneous reactivation or exogeneous reinfection.

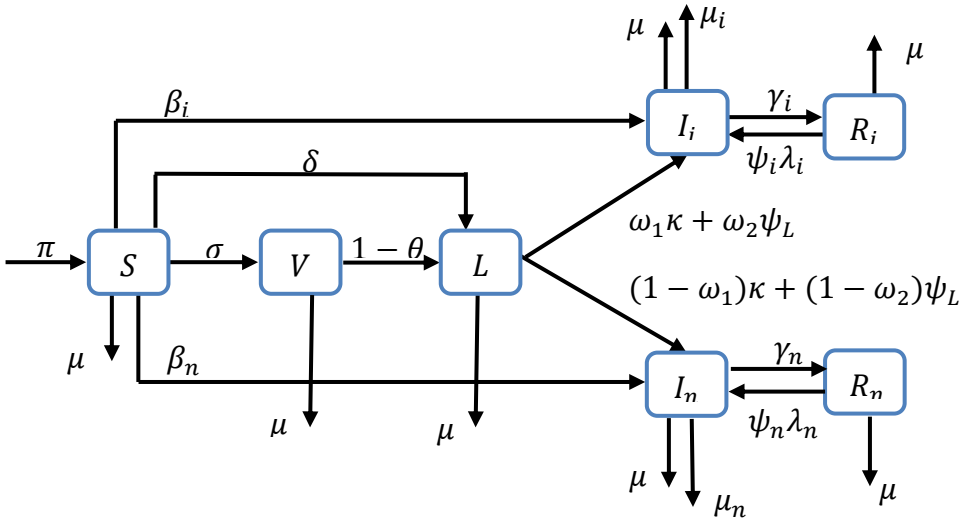


Figure 1. Schematic diagram of the TB disease transmission with endogeneous reactivation I_i and exogeneous reinfection I_n.

Based on the schematic diagram in Figure 1, we obtain the mathematical model of the TB disease transmission as follows:

$$\frac{dS}{dt} = \pi - \delta S I_i - \beta_i S I_i - \beta_n S I_i - \sigma S - \mu S \quad (1)$$

$$\frac{dV}{dt} = \sigma S - (1-\theta) V I_i - \mu V \quad (2)$$

$$\frac{dL}{dt} = \delta S I_i + (1-\theta) V I_i - \kappa L - \psi_L L I_i - \mu L \quad (3)$$

$$\frac{dI_i}{dt} = \beta_i S I_i + (\omega_1 \kappa + \omega_2 \psi_L I_i) L + \lambda_i \psi_i R_i I_i - \gamma_i I_i - \mu_i I_i - \mu I_i \quad (4)$$

$$\frac{dI_n}{dt} = \beta_n S I_i + ((1-\omega_1)\kappa + (1-\omega_2)\psi_L I_i) L + \lambda_n \psi_n R_n I_i - \gamma_n I_n - \mu_n I_n - \mu I_n \quad (5)$$

$$\frac{dR_i}{dt} = \gamma_i I_i - \lambda_i \psi_i R_i I_i - \mu R_i \quad (6)$$

$$\frac{dR_n}{dt} = \gamma_n I_n - \lambda_n \psi_n R_n I_i - \mu R_n \quad (7)$$

Table 1. Definition of parameters used in model

Parameter	Description
π	Birth rate
μ	Natural mortality rate
μ_i	Mortality rate of the infectious TB
μ_n	Mortality rate of the non-infectious TB
β_i	Transmission rate from susceptible compartment to infectious compartment I_i
β_n	Transmission rate from susceptible compartment to non-infectious compartment I_n
δ	Transmission rate from susceptible compartment to exposed compartment
σ	Vaccination rate for the susceptible
θ	Vaccination effectiveness
ψ_L, ψ_i, ψ_n	Rate of exogenous reinfection L, I_i, and I_n
ω_1	Fraction of exposed infectious TB
ω_2	Fraction of exposed non-infectious TB
κ	Rate of endogenous reactivation
γ_i	Recovery rate from infectious TB, I_i
γ_n	Recovery rate from non-infectious TB, I_n
λ_i	Transmission rate from recovered (R_i) compartment to I_i compartment
λ_n	Transmission rate from recovered (R_n) compartment to I_n compartment

2.1 *Equilibrium and the Reproduction Number*

From the model (1-7), we have two equilibrium points, i.e nonendemic,

$$(S, V, L, I_i, I_n, R_i, R_n) \quad \left(\frac{\pi}{(\sigma+\mu)}, \frac{\pi\sigma}{\mu(\sigma+\mu)}, 0,0,0,0,0\right)$$

and endemic point

$$S^* \quad \frac{\pi}{\beta_n I_i+\beta_i I_i+\delta I_i+\mu+\sigma},$$

$$V^* \quad -\frac{\sigma\pi}{a^*-b^*} \quad \frac{\sigma\pi}{(b^*-a^*)},$$

$$L^* \quad \frac{I_i\pi(\sigma\theta+\delta I_i\theta-\delta\mu-\delta I_i-\sigma)}{(a^*-b^*)(k+\psi_l I_i+\mu)},$$

$$R_i^* \quad \frac{\gamma_i I_i}{\lambda_i\psi_i I_i+\mu},$$

$$R_n^* \quad \frac{\gamma_n I_n}{\lambda_n\psi_n I_i+\mu},$$

with

$$a^* \quad \delta I_i^2\theta + \beta_i I_i^2\theta + \beta_n I_i^2\theta + \sigma I_i\theta + \mu I_i\theta$$

$$b^* \quad \delta I_i^2 + \delta I_i\mu + \beta_i I_i^2 + \beta_i I_i\mu + \beta_n I_i^2 + \beta_n I_i\mu + \sigma I_i + \sigma\mu + \mu I_i + \mu^2$$

The Reproduction Number for model (1 - 7) is given by :

$$\mathcal{R}_0 \quad \left(\frac{\beta_i\pi}{\sigma+\mu} + \frac{\omega_1 k(\mu\delta\pi+(1-\theta)\pi\sigma)}{\mu(\sigma+\mu)(k+\mu)}\right)\left(\frac{1}{\gamma_i+\mu_i+\mu}\right).$$

3. Model Analysis

In this section we analyze the model by assuming that there is a program of vaccination to the susceptibe population. We define the following objective function:

$$J(u) \quad \int_{t_0}^{t_1}(A_1 I_i(t) + A_2 I_n(t) + C_1 u_1^2(t) + C_2 u_2^2(t))dt$$

where t_1 is the final time and the coefficients A_1, A_2 are the weight factors for infectious population, u_1, u_2 are the rate of the vaccination and the effectiveness control with C_1 and C_2 are the balancing cost factor due to scale the importance of I. The constraints of the optimization problem for the Eqs. (1-7) are :

$t_0 < t < t_1,\ 0 \le u_1(t) \le 1,\ 0 \le u_2(t) \le 1,\ S(0) \quad S_0 \ge 0,\ V(0) \quad V_0 \ge 0,\ L(0) \quad L_0 \ge 0,$
$I_i(0) \quad I_{i0} \ge 0, I_n(0) \quad I_{n0} \ge 0, R_i(0) \quad R_{i0} \ge 0,$

Here we assume that there is a sufficient fund such that we are able to undertake a full vaccination program by vaccinating all susceptible in the human population, $u_1 = 1$. Hence, the Hamiltonian of the problem is given by

$$H \quad f(t,x,u) + \lambda g(t,x,u)$$
$$H \quad A_1 I_i(t) + A_2 I_n(t) + C_1 u_1^2(t) + C_2 u_2^2(t) + \lambda_1(\pi - \delta S I_i - \beta_i S I_i - \beta_n S I_i - u_1 S - \mu S) + \lambda_2(u_1 S - (1-u_2) V I_i - \mu V) + \lambda_3(\delta S I_i + (1-u_2) V I_i - \kappa L - \psi_L L I_i - \mu L) + \lambda_4(\beta_i S I_i + (\omega_1 \kappa + \omega_2 \psi_L I_i) L + \lambda_i \psi_i R_i I_i - \gamma_i I_i - \mu_i I_i - \mu I_i) + \lambda_5\big(\beta_n S I_i + \big((1-\omega_1)\kappa + (1-\omega_2)\psi_L I_i\big) L + \lambda_n \psi_n R_n I_i - \gamma_n I_n - \mu_n I_n - \mu I_n\big) + \lambda_6(\gamma_i I_i - \lambda_i \psi_i R_i I_i - \mu R_i) + \lambda_7(\gamma_n I_n - \lambda_n \psi_n R_n I_i - \mu R_n)$$

with $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6$, and λ_7 *co-state* variable or the Lagrange multiplier of the optimization problem. The necessary conditions that an optimal control must satisfy come from the Pontryagin's Maximum Principle. To accomplish this, we define the Hamiltonian H for the control problem as above, and define the state vector variables:

$$\dot{x}(t) \quad \begin{bmatrix} \dot{S}(t) \\ \dot{V}(t) \\ \dot{L}(t) \\ \dot{I}_\iota(t) \\ \dot{I_n}(t) \\ \dot{R}_\iota(t) \\ \dot{R_n}(t) \end{bmatrix}, \text{ and the vector variables for the co state equation : } \dot{\lambda}(t) \quad \begin{bmatrix} \dot{\lambda_1}(t) \\ \dot{\lambda_2}(t) \\ \dot{\lambda_3}(t) \\ \dot{\lambda_4}(t) \\ \dot{\lambda_5}(t) \\ \dot{\lambda_6}(t) \\ \dot{\lambda_7}(t) \end{bmatrix}.$$

Then the necessary conditions are:

$$\dot{S} \quad \frac{\partial H}{\partial \dot{\lambda_1}} \quad \pi - \delta S I_i - \beta_i S I_i - \beta_n S I_i - u_1 S - \mu S$$
$$\dot{V} \quad \frac{\partial H}{\partial \dot{\lambda_2}} \quad u_1 S - (1-u_2) V I_i - \mu V$$
$$\dot{L} \quad \frac{\partial H}{\partial \dot{\lambda_3}} \quad \delta S I_i + (1-u_2) V I_i - \kappa L - \psi_L L I_i - \mu L$$
$$\dot{I}_\iota \quad \frac{\partial H}{\partial \dot{\lambda_4}} \quad \beta_i S I_i + (\omega_1 \kappa + \omega_2 \psi_L I_i) L + \lambda_i \psi_i R_i I_i - \gamma_i I_i - \mu_i I_i - \mu I_i$$
$$\dot{I_n} \quad \frac{\partial H}{\partial \dot{\lambda_5}} \quad \beta_n S I_i + \big((1-\omega_1)\kappa + (1-\omega_2)\psi_L I_i\big) L + \lambda_n \psi_n R_n I_i - \gamma_n I_n - \mu_n I_n - \mu I_n$$
$$\dot{R}_\iota \quad \frac{\partial H}{\partial \dot{\lambda_6}} \quad \gamma_i I_i - \lambda_i \psi_i R_i I_i - \mu R_i$$
$$\dot{R_n} \quad \frac{\partial H}{\partial \dot{\lambda_7}} \quad \gamma_n I_n - \lambda_n \psi_n R_n I_i - \mu R_n$$

with co-state equation :

$$\dot{\lambda_1} = -\frac{\partial H}{\partial S} = \lambda_1(\delta I_i + \beta_i I_i + \beta_n I_i + u_1 + \mu) - \lambda_2 u_1 - \lambda_3 \delta I_i - \lambda_4 \beta_i I_i - \lambda_5 \beta_n I_i$$
$$\dot{\lambda_2} = -\frac{\partial H}{\partial V} = \lambda_2\big((1-u_2)I_i + \mu\big) - \lambda_3((1-u_2)I_i)$$
$$\dot{\lambda_3} = -\frac{\partial H}{\partial L} = \lambda_3(\kappa + \psi_L I_i + \mu) - \lambda_4(\omega_1\kappa + \omega_2\psi_L I_i) - \lambda_5\big((1-\omega_1)\kappa + (1-\omega_2)\psi_L I_i\big)$$
$$\dot{\lambda_4} = -\frac{\partial H}{\partial I_i} = -A_1 + \lambda_1(\delta S + \beta_i S + \beta_n S) + \lambda_2\big((1-u_2)V\big) - \lambda_3(\delta S + (1-u_2)V - \psi_L L) - \lambda_4(\beta_i S + \omega_2\psi_L L + \lambda_i\psi_i R_i - \gamma_i - \mu_i - \mu) - \lambda_5(\beta_n S + (1-\omega_2)\psi_L L + \lambda_n\psi_n R_n) - \lambda_6(\gamma_i - \lambda_i\psi_i R_i) + \lambda_7(\lambda_n\psi_n R_n)$$
$$\dot{\lambda_5} = -\frac{\partial H}{\partial I_n} = -A_2 + \lambda_5(\gamma_n + \mu_n + \mu) - \lambda_7\gamma_n$$
$$\dot{\lambda_6} = -\frac{\partial H}{\partial R_i} = -\lambda_4(\lambda_i\psi_i I_i) + \lambda_6(\lambda_i\psi_i I_i + \mu)$$
$$\dot{\lambda_7} = -\frac{\partial H}{\partial R_n} = -\lambda_5(\lambda_n\psi_n I_i) + \lambda_7(\lambda_n\psi_n I_i + \mu)$$

The optimal condition can be achieved via the Pontryagin Maximum Principle, i.e., $\frac{\partial H}{\partial u_1} = 0$, which gives :

$2C_1u_1 - \lambda_1 S + \lambda_2 S = 0$,
$2C_1u_1 = \lambda_1 S - \lambda_2 S$,
$u_1 = \frac{\lambda_1 S - \lambda_2 S}{2C_1} = \frac{(\lambda_1 - \lambda_2)S}{2C_1}$,

with the conditions $0 \le u_1 \le 1$. Then finally we have:

$$u_1 = max\left\{min\left(\frac{(\lambda_1-\lambda_2)S}{2C_1}, 1\right), 0\right\}.$$

Similarly, $\frac{\partial H}{\partial u_2} = 0$ which gives:

$2C_2u_2 + \lambda_2(VI_i) - \lambda_3(VI_i) = 0$
$2C_2u_2 = \lambda_3(VI_i) - \lambda_2(VI_i)$
$u_2 = \frac{\lambda_3(VI_i) - \lambda_2(VI_i)}{2C_2} = \frac{(\lambda_3 - \lambda_2)VI_i}{2C_2}$

with the conditions $0 \le u_2 \le 1$. Then finally we have:

$$u_2 = max\left\{min\left(\frac{(\lambda_3-\lambda_2)VI_i}{2C_2}, 1\right), 0\right\}.$$

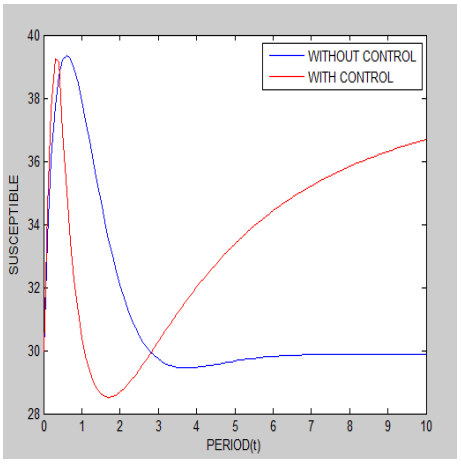
Here the sufficient conditions for both control giving the minimum objective value are $\frac{\partial^2 H}{\partial u_1^2} = 2C_1 \ge 0$ and $\frac{\partial^2 H}{\partial u_2^2} = 2C_2 \ge 0$. In the next section we provide a numerical example of the result above to show that the controls are really exist.

4. Numerical Simulation

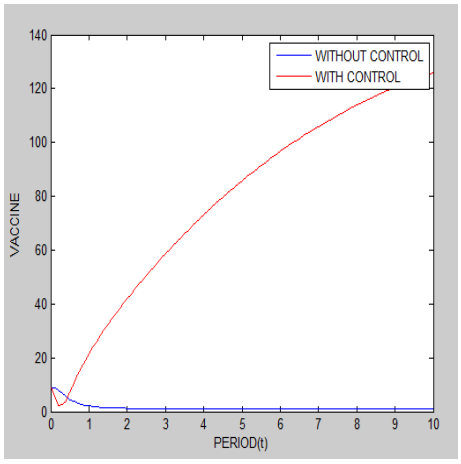
Numerical simulation is done to illustrate the theory above. Here we choose the parameters values described in Table 2 to run the simulation in the model. The results are presented in Figure 2(a) to 2(h).

Table 2. The values of parameters used in the subsequent simulation of the model.

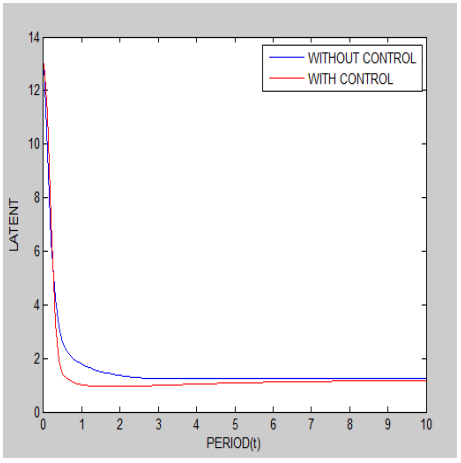
Parameter	Value
μ	0.2509710694
μ_i	0.6587000003
μ_n	0.5000000000
λ_i	0.7100995912
λ_n	0.5000000000
γ_i	0.2200000000
γ_n	0.2100000000
ω_1	0.1600000000
ω_2	0.7800000000
β_i	0.0027308696
β_n	0.0050000000
ψ	0.8500000000
δ	0.02883022718
κ	0.2522000000



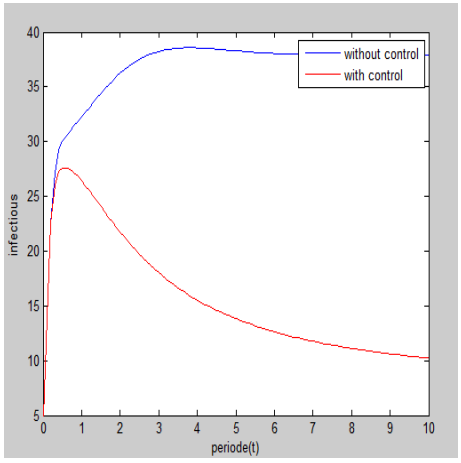
(a)



(b)



(c)



(d)

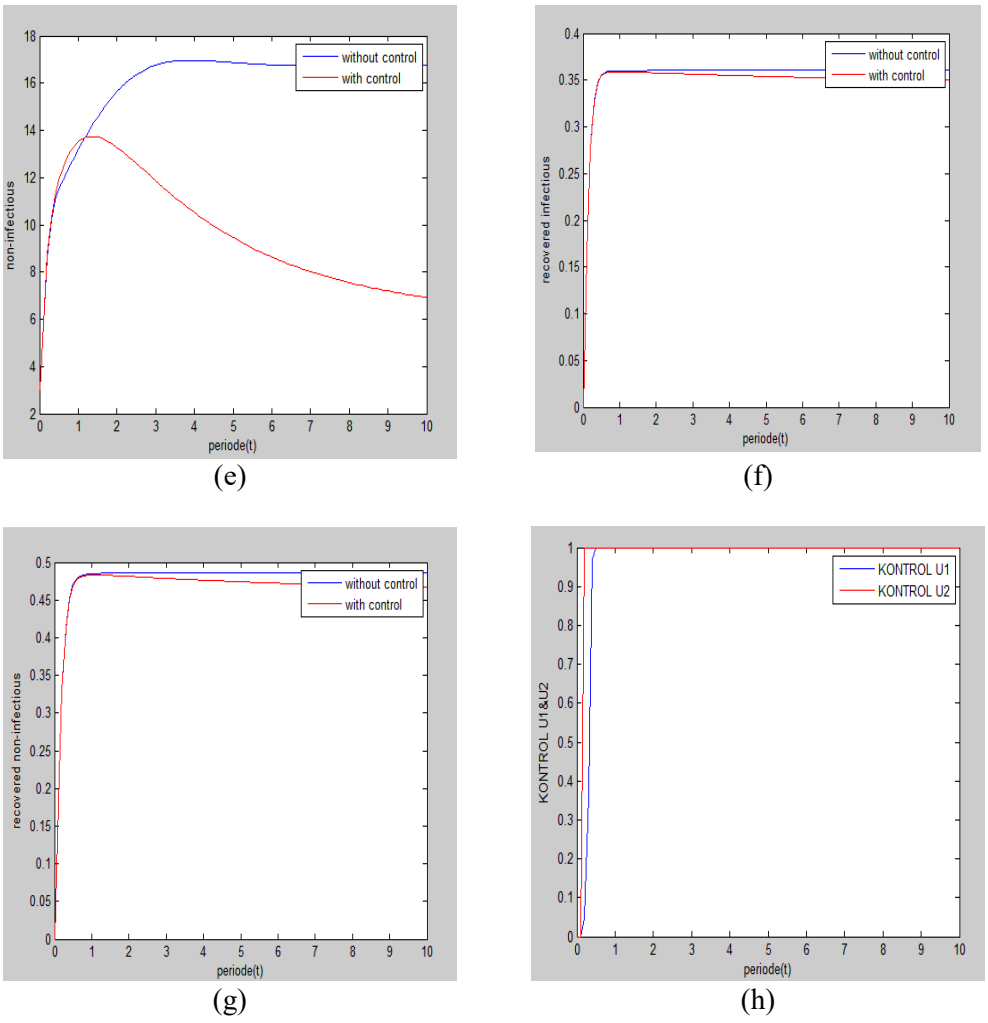


Figure 2. The results of the simulation for the data set given in Table 1.

Figure 2(a) shows the trajectory for the susceptible class. Figure 2(b) shows the trajectory for the vaccinated class. Figure 2(c) shows the trajectory for the latent. Figure 2(d) shows the trajectory for the infectious TB class. Figure 2(e) shows the trajectory for the non-infectious TB Class. Figure 2(f) shows the trajectory for the recovered from th infectious TB class and figure 2(g) for the non-infectious TB class. The control profiles are given in figure 2(h). The resulting Ro upon the implementation of the controls is 0.48. In the simulation we use the values: $A_1 = 1$, $A_2 = 1$, $C_1 = 1$, $C_2 = 1$. The results presented in the figure above indicate that when there is no vaccination, the basic reproduction number (R_0) is certainly greater than one. However, when we apply vaccination control program with the control profiles given by figure 2(h) then the basic reproduction number reduces to just 0.48. This shows the success of the control program as indicated by figure 2(d) and 2(c) for the decrease of the population in the infected compartment.

5. Conclusion

In this paper we have developed a mathematical model for the transmission of tuberculosis disease with the effect of control, i.e. by taking into account the factor of BCG vaccine, and considering the endogeneous reactivation and exogeneous reinfection. The optimal control to the TB disease by BCG vaccine aims to reduce the number of population of active TB by taking into account the lowest possible cost. Optimal control dynamic models of disease control tuberculosis vaccine in this paper

concluded that vaccination is better done optimally to the susceptible population if the vaccine is highly effective. Otherwise, the effect of vaccination will not be optimal.

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