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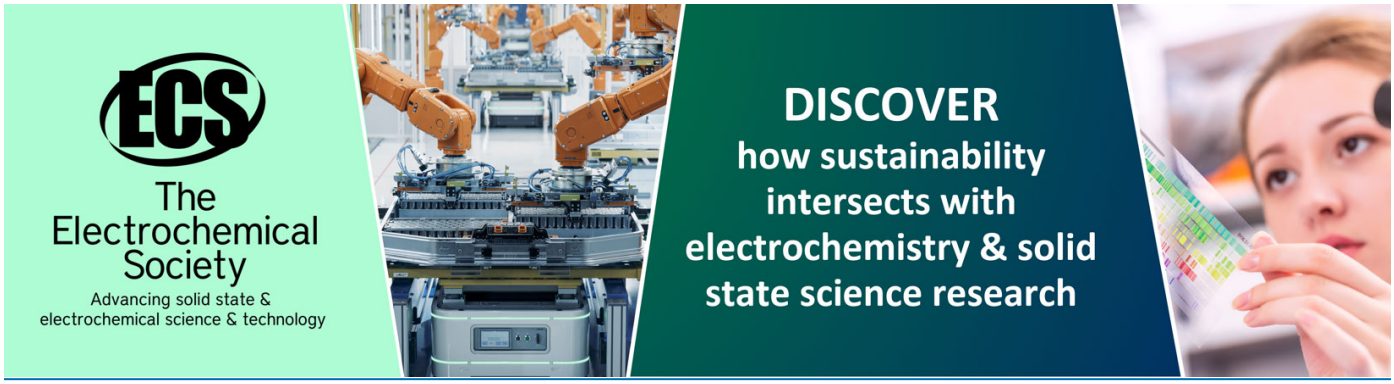


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# Two-strain Tuberculosis Transmission Model under Three Control Strategies

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**Abstract.** In 1997, Castillo-Chavez and Feng developed a two-strain tuberculosis (TB) model, which is typical TB and resistant TB. Castillo-Chavez and Feng's model was then subsequently developed by Jung et al. (2002) by adding two control variables. In this work, Jung et al.'s model was modified by introducing a new control variable so that there are three controls, namely chemoprophylaxis and two treatment strategies, with the application of three different scenarios related to the objective functional form and control application. Pontryagin maximum principle was applied to derive the differential equations system as a condition that must be satisfied by the optimal control variables. Furthermore, the fourth-order Runge-Kutta method was exploited to determine the numerical solution of the optimal control problem. In this numerical solution, it is shown that the controls treated on TB transmission model provide a good effect because latent and infected individuals are decreasing, and the number of individuals that is treated effectively is increasing.

## 1. Introduction

Since 1993, WHO said that tuberculosis (TB) was one of global emergency issues. Since 2003 until 2011, it was estimated that there are still approximately 9.5 million new cases of TB at present, and almost 0.5 million people died because of TB around the world[3]. Meanwhile, controlling TB offers new challenges such as TB/HIV co-infection, drug-resistant TB, and other challenges with a higher complexity for humanity.

In human beings, TB is caused by *Mycobacterium tuberculosis* bacteria (Mtb) and it is an airborne transmitted disease. Mtb droplets are released into the air by sneezing or coughing infectious individuals, and so TB can be transmitted by it. TB is not highly infectious and so occasional contacts with an infectious individual that rarely leads to infection. TB is described as a slow disease because of its long and variable latency period distribution and its short and relatively narrow infectious period distribution. Latent stage of TB is a phase where Mtb lives inside a person's body but don't make them feel any pain, don't show TB symptoms, and can't spread the disease. However, if the bacteria inside their body became active and developed, they can be infected with active TB[2]. Individuals who are latently infected are neither clinically ill nor capable of transmitting TB[1]. Most latently infected individuals do not become infectious (active TB).

Treatment on latent TB plays an important role in reducing the risk of TB become active. Every effort must be done to initiate an appropriate treatment and to make sure the treatment is done completely to individuals with latent TB. It is really important for infected individuals that are being

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treated to consume their medicine as prescribed. If an individual stop consuming their medicine before the preferred time, the disease will relapse, and if they don't consume it regularly, the bacteria that still living inside their body will be resistant to the drugs. This condition can lead to a new disease called resistant TB, and this will be harder and require much more expenses to be treated.

TB transmission can be controlled by reducing the number of patients and doing actions that can prevent susceptible individuals become infected by infectious individuals. One of the prevention that can be done is applying chemoprophylaxis, that is giving drugs and therapy routinely to prevent the infection on latently infected individuals, and also avoid the disease transmission on infected individuals. Incomplete TB treatment can cause the disease to relapse, even on recovered individuals.

In 1997, Castillo-Chavez and Feng developed a two-strain TB transmission model, that is typical TB and resistant TB. Typical TB is a TB disease in general, while the resistant TB is caused by infectious individuals who didn't obey and complete their treatment so that the disease inside is resisting the drugs that were given. Afterwards, this model is developed by Jung *et. al* (2002) by adding two control variables.

In this paper, the authors integrated the models developed [4] and [1]. The model is taken from [4], and then added one control variable from [1] to the model in [4], then a model with three control variables, that are chemoprophylaxis and two treatment strategies, is obtained. This model represents the rate of typical TB and resistant TB transmission, and with these controls will be studied what are the impacts to the transmission model.

## 2. Mathematical model

### *2.1. Tuberculosis transmission model*

The tuberculosis model from Jung *et. al* (2002) divides the total human population into the following sub-groups that are susceptible individuals $S$, those latently infected with typical TB and resistant TB respectively $L_1$ and $L_2$, those infected with typical TB and resistant TB respectively $I_1$ and $I_2$, and those who are treated (effectively) $T$. The total population size at time $t$ is given by $N(t) = S(t) + L_1(t) + I_1(t) + L_2(t) + I_2(t) + T(t)$.

The state system is the following system of six differential equations in [4] and the relapse parameter $q^*$ is added to it:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 S\frac{I_1}{N} - \beta^* S\frac{I_2}{N} - \mu S,\\
\frac{dL_1}{dt} &= \beta_1 S\frac{I_1}{N} - (\mu + k_1)L_1 + pr_2 I_1 + \beta_2 T\frac{I_2}{N} - \beta^* L_1\frac{I_2}{N},\\
\frac{dI_1}{dt} &= k_1 L_1 - (\mu + d_1)I_1 - r_2 I_1 + q^* T,\\
\frac{dL_2}{dt} &= qr_2 I_1 - (\mu + k_2)L_2 + \beta^*(S + L_1 + T)\frac{I_2}{N},\\
\frac{dI_2}{dt} &= k_2 L_2 - (\mu + d_2)I_2,\\
\frac{dT}{dt} &= \big(1 - (p+q)\big)r_2 I_1 - (q^* + \mu)T - \beta_2 T\frac{I_1}{N} - \beta^* T\frac{I_2}{N},
\end{aligned} \tag{1}$$

with initial conditions:

$$S(0) = S_0, L_1(0) = L_{10}, I_1(0) = I_{10}, L_2(0) = L_{20}, I_2(0) = I_{20}, T(0) = T_0, \tag{2}$$

and $S(t_f), L_1(t_f), I_1(t_f), L_2(t_f), I_2(t_f), T(t_f)$ are undetermined.

We assume that an individual may be infected only through contacts with infectious individuals. It is also assumed that susceptible humans are recruited into the population at per capita rate $\Lambda$. $\beta_1$ and

$\beta_2$ are the rates at which susceptible and treated individuals become infected by an infectious individual with typical TB, respectively. $\beta^*$ is the rate at which an uninfected individual becomes infected by one resistant-TB infectious individual. The per capita natural death rate is $\mu$ while the per capita disease induced death rates are $d_1$ and $d_2$ for the typical TB and resistant TB, respectively. The rates at which an individual leaves the two latent classes by becoming infectious are $k_1$ and $k_2$. Some treated individuals relapse back into the infective state at rate $q^*$. $r_1$ and $r_2$ are the treatment rates of individuals with latent and infectious typical TB, respectively, and $p+q$ is the proportion of those treated infectious individuals who did not complete their treatment $(p+q \leq 1)$. Some treated individuals relapse back into the infective state at rate $q^*$.

There are three control strategies used to control the spread of the two-strain TB; applying chemoprophylaxis to latently infected individuals of typical TB, treatments for infected individuals of typical TB, and treatments for treated individuals to reduce the probability of disease relapse. With these controls, model (1) becomes:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 S\frac{I_1}{N} - \beta^* S\frac{I_2}{N} - \mu S,\\
\frac{dL_1}{dt} &= \beta_1 S\frac{I_1}{N} - (\mu + k_1)L_1 - u_1 r_1 L_1 + (1-u_2)pr_2 I_1 + \beta_2 T\frac{I_1}{N} - \beta^* L_1\frac{I_2}{N},\\
\frac{dI_1}{dt} &= k_1 L_1 - (\mu + d_1)I_1 - r_2 I_1 + (1-u_3)q^* T,\\
\frac{dL_2}{dt} &= (1-u_2)qr_2 I_1 - (\mu + k_2)L_2 + \beta^*(S + L_1 + T)\frac{I_2}{N},\\
\frac{dI_2}{dt} &= k_2 L_2 - (\mu + d_2)I_2,\\
\frac{dT}{dt} &= u_1 r_1 L_1 + \big(1-(1-u_2)(p+q)\big)r_2 I_1 - \big((1-u_3)q^* + \mu\big)T - \beta_2 T\frac{I_1}{N}\\
&\qquad - \beta^* T\frac{I_2}{N}.
\end{aligned} \tag{3}$$

The coefficient $u_1$ represents a routine therapy for individuals latently infected with typical TB who are carrying on treatments, $1-u_2$ represents the effort that prevents the failure of the treatment in typical TB infectious individuals, such as supervising individuals who are undergoing treatments, and $1-u_3$ represents the effort that prevents the disease relapse of treated individuals. Basically, model (1) can be obtained by assigning $u_1 = u_2 = u_3 = 0$.

*2.2. Analysis of optimal control*

The optimal control problem faced is to determine the control functions $u_1, u_2$, and $u_3$ that are carrying the system from initial state $(S_0, L_{10}, I_{10}, L_{20}, I_{20}, T_0)$ to an undetermined terminal state $\left(S_{t_f}, L_{1t_f}, I_{1t_f}, L_{2t_f}, I_{2t_f}, T_{t_f}\right)$. Optimal control $u_1^*, u_2^*$, and $u_3^*$ are seek to be found so that it minimize the objective function:

$$J(u_1, u_2, u_3) = \int_0^{t_f} [aL_1 + bI_1 + cL_2 + dI_2 + C_1 u_1^2 + C_2 u_2^2 + C_3 u_3^2]\, dt, \tag{4}$$

with coefficients $a, b, c$, and $d$ are non-negative, and $C_1, C_2$, and $C_3$ are positive constants which are weight parameters on controls. The objective function is to minimize the latent and infectious individuals with typical TB and resistant TB. Therefore, the optimal control problem can be expressed as:

$$\min J,$$

with dynamical system constraints (3), the state variables initial values are known and the terminal values are independent from the following control variables:

$$0 \le a_1 \le u_1 \le b_1 \quad (5)$$
$$0 \le a_2 \le u_2 \le b_2 \quad (6)$$
$$0 \le a_3 \le u_3 \le b_3 \quad (7)$$

The necessary conditions that an optimal control must satisfy come from the Pontryagin's maximum principle. In general, Hamiltonian function $H$ is defined as follows:

$$\begin{aligned} H = {} & aL_1 + bI_1 + cL_2 + dI_2 + C_1u_1^2 + C_2u_2^2 + C_3u_3^2 + p_1\left(\Lambda - \beta_1 S\frac{I_1}{N} - \beta^* S\frac{I_2}{N} - \mu S\right) \\ & + p_2\left(\beta_1 S\frac{I_1}{N} - (\mu + k_1)L_1 - u_1r_1L_1 + (1-u_2)pr_2I_1 + \beta_2 T\frac{I_1}{N} - \beta^* L_1\frac{I_2}{N}\right) \\ & + p_3(k_1L_1 - (\mu + d_1)I_1 - r_2I_1 + (1-u_3)q^*T) \\ & + p_4\left((1-u_2)qr_2I_1 - (\mu + k_2)L_2 + \beta^*(S + L_1 + T)\frac{I_2}{N}\right) + p_5(k_2L_2 - (\mu + d_2)I_2) \\ & + p_6\left(u_1r_1L_1 + \big(1 - (1-u_2)(p+q)\big)r_2I_1 - ((1-u_3)q^* + \mu)T - \beta_2 T\frac{I_1}{N}\right. \\ & \left. - \beta^* T\frac{I_2}{N}\right), \end{aligned}$$

with $p_1(t), p_2(t), p_3(t), p_4(t), p_5(t)$, and $p_6(t)$ are adjoin functions to be determined.

The optimality conditions from Pontryagin's maximum principle is used to obtain the controls $u_1^*, u_2^*$, and $u_3^*$, so it gives:

$$\frac{\partial H}{\partial u_1} = 0 \Leftrightarrow 2C_1u_1 - p_2r_1L_1 + p_6r_1L_1 = 0,$$
$$\frac{\partial H}{\partial u_2} = 0 \Leftrightarrow 2C_2u_2 - p_2pr_2I_1 - p_4qr_2I_1 + p_6(p+q)r_2I_1 = 0,$$
$$\frac{\partial H}{\partial u_3} = 0 \Leftrightarrow 2C_3u_3 - p_3q^*T + p_6q^*T = 0,$$

hence, the controls obtained are:

$$u_1^*(t) = \frac{(p_2 - p_6)r_1L_1(t)}{2C_1},$$
$$u_2^*(t) = \frac{p_2p + p_4q - p_6(p+q)r_2I_1(t)}{2C_2},$$
$$u_3^*(t) = \frac{(p_3 - p_6)q^*T(t)}{2C_3}.$$

Since the optimal control problems above are using bounds on the controls, we conclude for control $u_1$:

$$u_1^* = \begin{cases} a_1 & ; \quad \dfrac{(p_2 - p_6)r_1L_1}{2C_1} \le a_1 \\ \dfrac{(p_2 - p_6)r_1L_1}{2C_1} & ; \quad a_1 < \dfrac{(p_2 - p_6)r_1L_1}{2C_1} < b_1 \\ b_1 & ; \quad \dfrac{(p_2 - p_6)r_1L_1}{2C_1} \ge b_1 \end{cases}$$

In compact form

$$u_1^* = \min\left\{\max\left\{a_1, \frac{(p_2 - p_6)r_1 L_1}{2C_1}\right\}, b_1\right\}.$$

Similarly, for control $u_2$ and $u_3$ we have

$$u_2^* = \min\left\{\max\left\{a_2, \frac{p_2 p + p_4 q - p_6(p+q)r_2 I_1}{2C_2}\right\}, b_2\right\}, \tag{8}$$

and

$$u_3^* = \min\left\{\max\left\{a_3, \frac{(p_3 - p_6)q^* T}{2C_3}\right\}, b_3\right\}.$$

Then the adjoin system based on (4) can be written as:

$$\begin{aligned}
\dot{p_1} &= p_1\left(\beta_1 \frac{I_1}{N} + \beta^* \frac{I_2}{N}\right) - p_2\beta_1 \frac{I_1}{N} - p_4\beta^* \frac{I_2}{N}, \\
\dot{p_2} &= -1 + p_2\left(\mu + k_1 + u_1 r_1 + \beta^* \frac{I_2}{N}\right) - p_3 k_1 - p_4\beta^* \frac{I_2}{N} - p_6 u_1 r_1, \\
\dot{p_3} &= -1 + p_1\beta_1 \frac{S}{N} - p_2\left(\beta_1 \frac{S}{N} + (1-u_2)pr_2 + \beta_2 \frac{T}{N}\right) + p_3(\mu + d_1 + r_2) \\
&\quad - p_4(1-u_2)qr_2 - p_6\left(1 - (1-u_2)(p+q))r_2 + \beta_2 \frac{T}{N}\right), \\
\dot{p_4} &= -1 + p_4(\mu + k_2) - p_5 k_2, \\
\dot{p_5} &= -1 - p_1\beta^* \frac{S}{N} + p_2\beta^* \frac{L_1}{N} - p_4\beta^* \frac{S + L_1 + T}{N} + p_5(\mu + d_2) + p_6\beta^* \frac{T}{N}, \\
\dot{p_6} &= -p_2\beta_2 \frac{I_1}{N} - p_3 q^* - p_4\beta^* \frac{I_2}{N} + p_6\left((1-u_3)q^* + \mu + \beta_2 \frac{I_1}{N} + \beta^* \frac{I_2}{N}\right).
\end{aligned} \tag{9}$$

with transversality conditions:

$$p_1(t_f) = 0, p_2(t_f) = 0, p_3(t_f) = 0, p_4(t_f) = 0, p_5(t_f) = 0, p_6(t_f) = 0. \tag{10}$$

## 3. Numerical results and discussion

In this section, the optimal treatment strategies for the two-strain TB model will be studied numerically. For solving the optimality system we use an iterative method, starting from solving the state equation using a forward fourth order Runge-Kutta scheme. Because of the transversality conditions (10), the adjoin system is solved by a backward fourth order Runge-Kutta scheme using the current iteration solution of the state equations. All numerical solutions are carried out using Scilab.

There are three scenarios examined in this problem associated with the objective functions formulation and controls application, as described in table 1. These scenarios aim to see the impacts of the objective functions formulation to the controls effectiveness and population dynamics in some compartments.

**Table 1.** Scenarios of the objective function formulation and controls application.

| Scenarios | Coefficients | | | | Controls | | |
|---|---|---|---|---|---|---|---|
| | $a$ | $b$ | $c$ | $d$ | $u_1$ | $u_2$ | $u_3$ |
| I | 0 | 0 | 1 | 1 | on | on | off |
| II | 1 | 1 | 0 | 0 | on | on | on |
| III | 1 | 1 | 1 | 1 | on | on | on |

With these different scenarios, the effectiveness of the controls will be demonstrated. Time observed is 5 years, and the numerical parameters used in the system are adopted from [4] and [1] with $N = 12000$, given in table 2.

**Table 2(a), (b) and (c).** Parameters and their values.

| Parameters | Values |
|---|---|
| $\Lambda$ | 171.6 |
| $\beta_1$ | 13 |
| $\beta_2$ | 13 |
| $\beta^*$ | 0.0131 |
| $\mu$ | 0.0143 |
| $d_1$ | 0 |
| $d_2$ | 0 |

| Parameters | Values |
|---|---|
| $k_1$ | 0.5 |
| $k_2$ | 1 |
| $r_1$ | 2 |
| $r_2$ | 1 |
| $p$ | 0.4 |
| $q$ | 0.1 |
| $q^*$ | 0.005 |

| Parameters | Values |
|---|---|
| $S(0)$ | 7,600 |
| $L_1(0)$ | 3,600 |
| $I_1(0)$ | 400 |
| $L_2(0)$ | 200 |
| $I_2(0)$ | 100 |
| $T(0)$ | 100 |

Coefficients used in all scenarios are given in table 3 below.

**Table 3.** Coefficients and their values.

| Coefficients | Values |
|---|---|
| $a_1$ | 0.05 |
| $b_1$ | 0.95 |
| $a_2$ | 0.05 |
| $b_2$ | 0.95 |
| $C_1$ | 50 |
| $C_2$ | 500 |
| $C_3$ | 55 |

For the first scenario, the objective function is to minimize the number of the latent and infectious individuals of resistant TB, and control $u_3$ is deactivated. The optimal control problem formed is:

$$\min J(u_1, u_2) = \int_0^{t_f} [L_2 + I_2 + C_1 u_1^2 + C_2 u_2^2]\, dt,$$

subject to system (3). Meanwhile the optimal control problem for the second scenario can be written as:

$$\min J(u_1, u_2, u_3) = \int_0^{t_f} [L_1 + I_1 + C_1 u_1^2 + C_2 u_2^2 + C_3 u_3^2]\, dt,$$

subject to system (3). The above equation is expressing the population to be minimized are the latent and actively infectious individuals from typical TB, and all controls are activated. And in the last scenario, all latent and infectious individuals from both typical TB and resistant TB is minimized, and all controls are activated with each lower and upper bounds. The optimal control problem for this scenario is given by:

$$\min J(u_1, u_2, u_3) = \int_0^{t_f} [L_1 + I_1 + L_2 + I_2 + C_1 u_1^2 + C_2 u_2^2 + C_3 u_3^2]\, dt,$$

subject to system (3).

Figure 1 to 3 shows the impacts of the scenarios applied to the system. From all scenarios, it can be concluded that there are considerable differences between the presence and the absence of controls. With the first scenario, the total number of individuals $L_2 + I_2$ at the final time $t_f = 5$ years is 453 in the case with control and 1,498 without control. Meanwhile, with the second scenario, the total number of individuals $L_1 + I_1$ at final time $t_f$ is 8,432 with control and 11,412 without control. With

the last scenario, the total number of individuals $L_1 + I_1 + L_2 + I_2$ after 5 years is 8,966 with control and 13,304 without control. So the total cases prevented at the end of control program are 1,045 for the first scenario, 2,980 for the second scenario, and 4,388 for the third scenario. From these results, it can be concluded that the third scenario is the best strategy for our problem.

Figure 4 illustrates the optimal control strategies for the third scenario. The control $u_1$ is applied over the most for 5 years, while the control $u_2$ and $u_3$ are applied at the upper bound during almost 3.6 years and then it decreases to the lower bound until the fifth year.

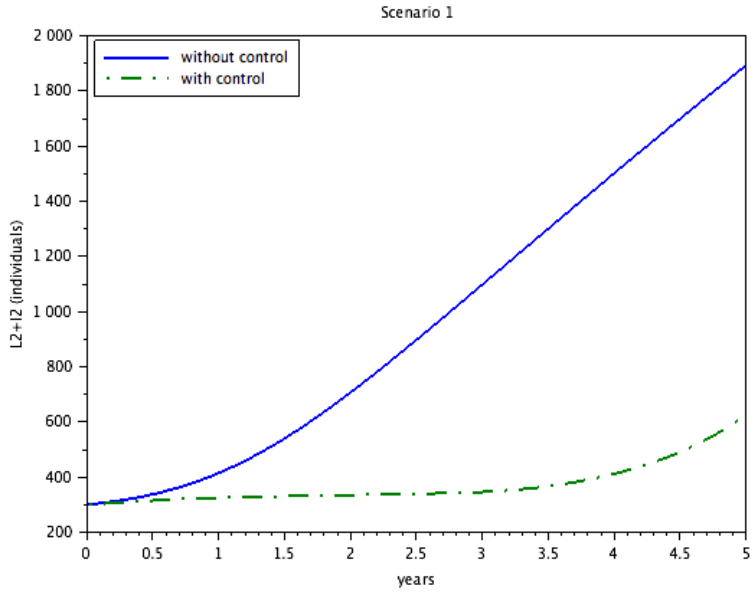


**Figure 1.** The population dynamics with and without control in scenario 1.

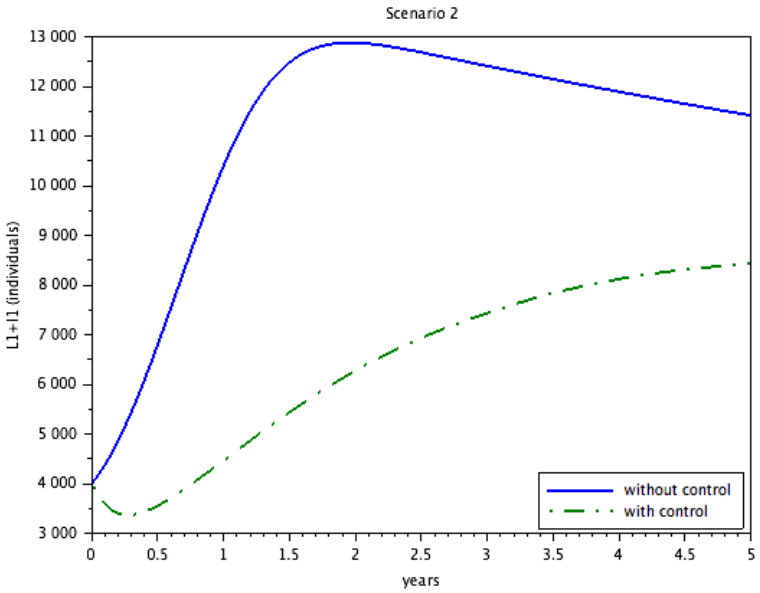


**Figure 2.** The population dynamics with and without control in scenario 2.

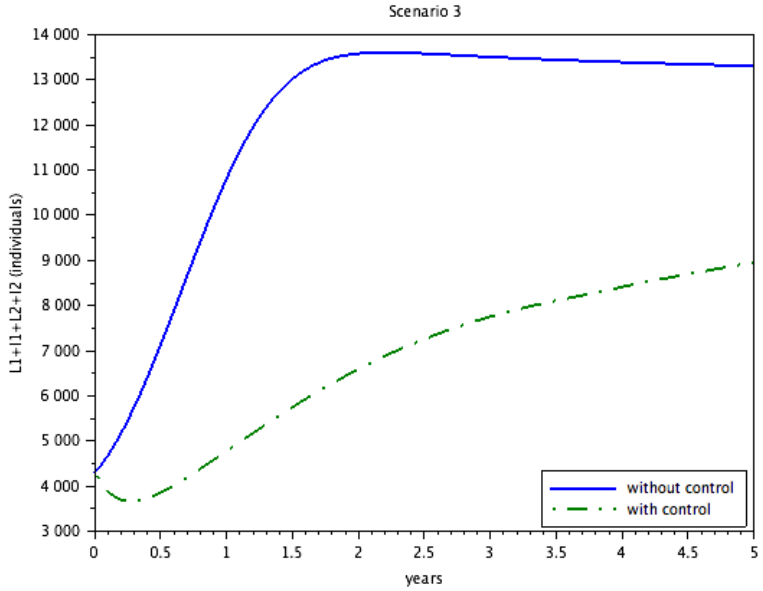


**Figure 3.** The population dynamics with and without control in scenario 3.

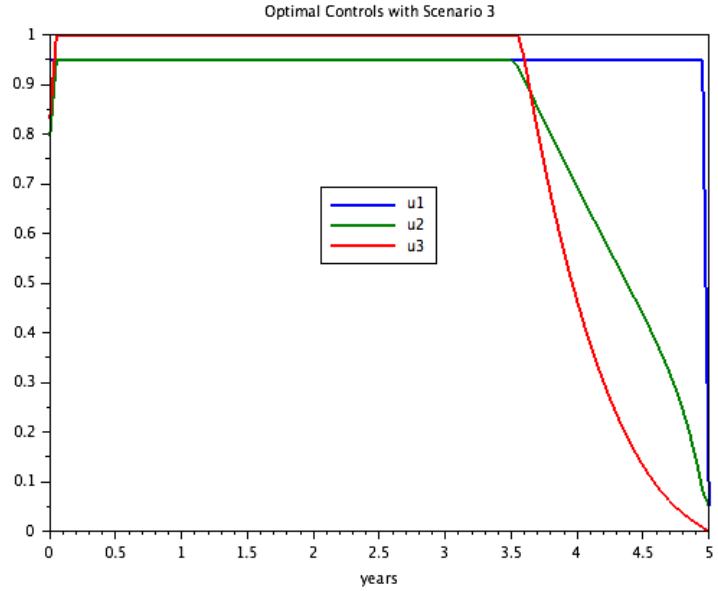


**Figure 4.** The optimal control strategy for scenario 3.

## 4. Conclusion

In conclusion, the application of controls on two-strain TB transmission model gives positive influences for it reduces the number of latent and infected individuals from both typical TB and resistant TB. From three scenarios studied, the best scenario is the third one, so we can say that minimizing the population with susceptible, latently infected and actively infected with typical TB, and treated individuals plays an important role in giving those positive influences.

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