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A mathematical model for the response of immune cells to mycobacterium tuberculosis

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Abstract

Tuberculosis (TB) is an infectious disease that is a problem almost all over the world. In 2019, the World Health Organization (WHO) reported 10 million new infections each year, with an average of 1.2 million people dying from the disease. Vaccination to healthy people is an effort to protect against infection with this disease. In this paper, a mathematical model of the interaction of the immune response against Mycobacterium tuberculosis by administering the vaccine is a system of ordinary differential equations with four variables. Furthermore, an analysis of local stability to the equilibrium point is carried out. The results obtained indicate that the disease-free equilibrium point is globally asymptotically stable if $R_0 \leq 1$ and unstable if $R_0 > 1$. The sensitivity analysis showed that the infection rate and the bacterial growth rate were the two most influencing factors for the infection's survival. This study's results are expected to be a reference for doctors and paramedics so that the number of tuberculosis cases can be reduced.

Keywords

Mycobacterium tuberculosis, macrophage, a mathematical model

1. Introduction

Tuberculosis (TB) is an infectious disease caused by the bacteria Mycobacterium tuberculosis, which can attack the lungs or other body organs. Tuberculosis is one of the top 10 causes of death worldwide. WHO (2019) reported that, India is the largest contributor to TB cases in the world, amounting to 27%. Five other countries that account for nearly two-thirds of total global TB cases are China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%) [1].

TB is characterized by early fever symptoms, a relatively long cough, coughing up blood, and chest pain [2]. This disease is transmitted through the air containing the bacteria Mycobacterium tuberculosis, not through direct contact. When people with active TB experience coughing, sneezing, screaming, or singing, the bacteria will be carried out of the lungs into the air. Transmission occurs when a person inhales air containing the bacteria Mycobacterium tuberculosis and then reaches the lungs' alveoli. When bacteria enter the human body, the immune system will try to resist and destroy them. The immune response plays a role in controlling the development of Mycobacterium tuberculosis in macrophages and T lymphocytes [3].

Macrophages originate from monocytes, which are part of white blood cells. These macrophages include phagocytic cells (eating cells). Cells damaged by bacteria will produce chemical signals that function to call phagocytes (macrophages) to eat or destroy these bacteria. T lymphocytes are white blood cells that are part of the immune system. The role of T lymphocytes is to recognize harmful foreign objects that enter the body or antigens. With memory T lymphocytes, antigens that have entered the body can be easily identified and destroyed more quickly [4].

Mathematical models can be applied to understand tuberculosis dynamics. Several mathematical models have been developed to study tuberculosis's dynamics, as in [5 - 10]. Ibarguen-Mondragon et al. [5] have modeled immunological cells in tuberculosis. Furthermore, Ibarguen et al. [6] extended the assumption of bacterial population growth by forming a system of ordinary differential equations, a model of the interaction between uninfected macrophages, infected macrophages, T cells, and

Mycobacterium tuberculosis bacteria to control tuberculosis. We performed numerical simulations by entering values in the model parameters to estimate the likelihood of disease. Shi et al. [7] extended the previous model to consider chemotherapy drug administration. They were using assumptions that the rate of chemotherapy drug administration is constant (fixed), and the rate of chemotherapy drug administration varies.

Meanwhile, Magombedze et al. [8] developed a tuberculosis model with the infection's location in the lungs. Zhang et al. [9] established a tuberculosis model and then performed global stability and bifurcation analysis for disease-free equilibrium points. Also, Adi & Thobirin [10] compiled a model of the interaction of macrophage cells and Tb bacteria and found a backward bifurcation condition. This paper constructs a dynamic model of tuberculosis in a within-host, an extension of the Adi & Thobirin model in [10], taking vaccination into account.

We organize the paper as follows. In Section 2, we formulate our model and establishing the properties of solutions. We then discuss the existence of equilibria and the stability of the disease-free equilibrium point in Section 3. In section 4, we provide some numerical simulations to support the theoretical results. Finally, the discussion and conclusion are given in Section 5.

2. Mathematical model

To construct a mathematical model of the immune response of tuberculosis bacteria, the population was divided into uninfected macrophages (M_u), infected macrophages (M_i), Mycobacterium tuberculosis (B) and T cells (T). It is assumed that uninfected macrophages reproduce with a growth or recruitment rate of uninfected macrophages of Λ_u and die with a natural mortality rate of uninfected macrophages of μ_u. When bacteria enter the body, uninfected macrophages will get a signal to come to cells that are attacked by bacteria. There is a possibility that uninfected macrophages are unable to clean the bacteria so that uninfected macrophages will become infected macrophages with an infected rate of β. The infected macrophages were killed by T cells of α_T and the infected macrophages exploded due to the proliferation of bacteria outside the threshold for infected macrophages of b.

Mycobacterium tuberculosis bacteria multiply in infected macrophages to a threshold and then explode and release the bacteria. Therefore, it is assumed that the growth rate of rbM_i with r is the rate of bacteria reproducing in infected macrophages. The released bacteria will become extracellular, then infect macrophages or be eaten (killed) by uninfected macrophages γ and the natural death rate of bacteria is μ_B. T cell population using the logistic equation $(1-T)k_1M_i$ where k_1 is the growth rate of T cells, which is limited and can be stimulated by bacteria $\frac{c_B BT}{e_B T+1}$ and died with a natural death rate μ_T.

From the above assumptions, the TB model is written as follows

$$\begin{aligned}
\frac{dM_u}{dt} &= \Lambda_u - \beta B M_u - \mu_u M_u \\
\frac{dM_i}{dt} &= \beta B M_u - b M_i - \alpha_T M_i T \\
\frac{dB}{dt} &= rb M_i - \gamma M_u B - \mu_B \\
\frac{dT}{dt} &= (1-T)k_1 M_i + \frac{c_B BT}{e_B T+1} - \mu_T T
\end{aligned} \tag{1}$$

The following theorem verifies that all solutions with nonnegative initial conditions remain nonnegative for all $t > 0$. So the model of the system (1) has biological meaning.

Theorem 1. *The set*

$$\Omega = \left\{(M_u, M_i, B, T) \in \mathbb{R}^4_+ \;\middle|\; M_u + M_i \le \frac{\Lambda_u}{\mu_u}, B \le \frac{rb\Lambda_u}{\mu_u}, T \le \frac{\Lambda_u}{\mu_T \mu_u}\left(k_1 + \frac{rbc_B}{e_B}\right)\right\},$$

is a positive invariant and attracting set for equation (1).

Proof. From the first and second equation of (1), we find

$$\begin{aligned}
\frac{dM_u}{dt} + \frac{dM_i}{dt} &= \Lambda_u - \mu_u \mathrm{M}_u - b\mathrm{M}_i \\
&\le \Lambda_u - \bar{\mu}_u(\mathrm{M}_u + \mathrm{M}_i)
\end{aligned}$$

with $\bar{\mu}_u = \min\{\mu_u, b\}$. We have

$$0 \le (M_u + M_i)(t) \le \frac{\Lambda_u}{\bar{\mu}_u} = M_{max}.$$

From the third equation of (1), we find

$$\frac{dB}{dt} = rbM_i - \gamma M_u B - \mu_B B \le rb\frac{\Lambda_u}{\bar{\mu}_u} - \mu_B B$$

Then, we have

$$B(t) \le \frac{rbM_{max}}{\mu_B} = B_{max}.$$

Lastly, from the fourth equation of (1), we have

$$\frac{dT}{dt} = (1-T)k_1 M_i + \frac{c_B BT}{e_B T + 1} - \mu_T T$$
$$\le (1-T)k_1 \frac{\Lambda_u}{\bar{\mu}_u} + \frac{c_B}{e_B}\frac{rbM_{max}}{\mu_B} - \mu_T T.$$

Hence,

$$\limsup_{t\to\infty} T(t) \le \frac{1}{\mu_T}\left(k_1 M_{max} + \frac{c_B}{e_B}B_{max}\right).$$

Therefore, all solutions of model (1) that starting in Ω remain in Ω for all $t \ge 0$. ■

3. Existence and stability of equilibrium points

The system (1) always have s disease-free equilibrium point $E_0 = \left(\frac{\Lambda_u}{\mu_u}, 0,0,0\right)$. Then, applying the next generation matrix procedures, we find the basic reproduction number

$$R_0 = \frac{r\beta\Lambda_u}{\gamma\Lambda_u + \mu_u\mu_B}.$$

Furthermore, we have the following theorem.

Theorema 2. *If $R_0 < 1$ then the system (1) has an only disease-free equilibrium point $E_0 = \left(\frac{\Lambda_u}{\mu_u}, 0,0,0\right)$ and if $R_0 > 1$ then the system (1) has two equilibrium points, that is, the disease-free equilibrium point $E_0 = \left(\frac{\Lambda_u}{\mu_u}, 0,0,0\right)$ and the disease equilibrium point $E_1 = (M_u^*, M_i^*, B^*, T^*)$.*

Proof. Solving the system (1) by setting the right-hand side equal to zero, we get

$$M_u^* = \frac{\Lambda_u}{\beta B + \mu_u},\ M_i^* = \frac{B}{rb}\left[\gamma\frac{\Lambda_u}{\beta B + \mu_u} + \mu_B\right], T_1^* = \frac{k_1 B}{rb}\left[\gamma\frac{\Lambda_u}{\beta B + \mu_u} + \mu_B\right],$$

and B^* is a positive real root of

$$a_1 B^4 + a_2 B^3 + a_3 B^2 + a_4 B = 0,$$

where

$$a_1 = \frac{\beta^2 k_1 (\mu_B)^2 \alpha_T}{(rb)^2}$$
$$a_2 = 2\frac{\beta k_1 \gamma \Lambda_u \alpha_T \mu_B}{(rb)^2} + \frac{\beta^2 \mu_B}{r} + \frac{\beta k_1 \mu_u (\mu_B)^2 \alpha_T}{(rb)^2} + \frac{\beta \mu_u k_1 (\mu_B)^2 \alpha_T}{(rb)^2}$$
$$a_3 = \frac{rb^2\beta}{(rb)^2}(\gamma\Lambda_u + \mu_u\mu_B)(1-R_0) + \frac{k_1(\gamma\Lambda_u)^2\alpha_T}{(rb)^2} + 2\frac{k_1\gamma\Lambda_u\alpha_T\mu_u\mu_B}{(rb)^2} + \frac{\beta\mu_u\mu_B}{r} + \frac{k_1(\mu_u\mu_B)^2\alpha_T}{(rb)^2}$$
$$a_4 = \frac{\mu_u}{r}(\gamma\Lambda_u + \mu_u\mu_B)(1-R_0).$$

We find $B = 0$ or

$$a_1 B^3 + a_2 B^2 + a_3 B + a_4 = 0. \quad (2)$$

If $B = 0$ we have a disease-free equilibrium point, $E_0 = \left(\frac{\Lambda_u}{\mu_u}, 0,0,0\right)$.

The coefficient a_1 and a_2 always positive. If $R_0 < 1$, the coefficient a_3 and a_4 also positive, so there no positive real root. Consequently, system (1) has no disease equilibrium point. If $R_0 > 1$, then the coefficient a_3 can be positive or negative, while a_4 is negative. Hence, there is one change of coefficient sign of (2) and according to Descartes's rule of sign, there is at least one positive root of (2). We find that, in addition to E_0, the system (1) at least has one positive disease equilibrium point. This completes the proof.

■

Next, the following theorem shows the equilibrium point's stability determined by the sign of real part eigenvalues of the Jacobian matrix of system (1) at the equilibrium point.

Theorema 3. *The disease-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. The Jacobian matrix of system (1) at $E_0 = \left(\frac{\Lambda_u}{\mu_u}, 0,0,0\right)$ is

$$J_0 = \begin{bmatrix} -\mu_u & 0 & -\frac{\beta \Lambda_u}{\mu_u} & 0 \\ 0 & -b & \frac{\beta \Lambda_u}{\mu_u} & 0 \\ 0 & rb & -\frac{\gamma \Lambda_u}{\mu_u} - \mu_B & 0 \\ 0 & k_1 & 0 & -\mu_T \end{bmatrix}.$$

The characteristic polynomial of J_0 is

$$p(\lambda) = (\lambda + \mu_u)(\lambda + \mu_T)\left(\lambda^2 + \left(b + \mu_B + \frac{\gamma \Lambda_u}{\mu_u}\right)\lambda + \left(\frac{b\gamma \Lambda_u}{\mu_u} + b\mu_B\right)(1 - R_0)\right) = 0. \quad (3)$$

The roots of (3) are $\lambda_1 = -\mu_u < 0$, $\lambda_2 = -b < 0$, and the other two roots are determined by the quadratic equation

$$\lambda^2 + \left(b + \mu_B + \frac{\gamma \Lambda_u}{\mu_u}\right)\lambda + \left(\frac{b\gamma \Lambda_u}{\mu_u} + b\mu_B\right)(1 - R_0) = 0. \quad (4)$$

We find that both roots of equation (4) have a negative real part if $R_0 < 1$. If $R_0 > 1$, the equation (4) has one root with a positive real part. Hence, E_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

■

We then prove the global stability of E_0 when $R_0 \leq 1$.

Theorema 4. *The disease-free equilibrium E_0 is globally asymptotically stable if $R_0 \leq 1$.*

Proof. Consider the Lyapunov function

$$V = \beta \Lambda_u B + (\gamma \Lambda_u + \mu_u \mu_B) M_i$$

The derivative V given by

$$\begin{aligned} \frac{dV}{dt} &= \beta \Lambda_u (rbM_i - \gamma M_u B - \mu_B B) + (\gamma \Lambda_u + \mu_u \mu_B)(\beta B M_u - bM_i - \alpha_T M_i T) \\ &= r\beta \Lambda_u bM_i - \gamma \beta \Lambda_u M_u B - \beta \Lambda_u \mu_B B + \gamma \Lambda_u \beta B M_u - b\gamma \Lambda_u M_i - \gamma \Lambda_u \alpha_T M_i T \\ &\quad + \mu_u \mu_B \beta B M_u - \mu_u \mu_B bM_i - \mu_u \mu_B \alpha_T M_i T \\ &\leq (\gamma \Lambda_u + \mu_u \mu_B) bM_i (R_0 - 1) + \mu_B \beta \mu_u B \left(M_u - \frac{\Lambda_u}{\mu_u}\right). \end{aligned}$$

Since $M_u \leq \frac{\Lambda_u}{\mu_u}$, we have $\frac{dV}{dt} \leq 0$ as long as $R_0 \leq 1$. Furthermore, we can see from the system (1) that as t tend to infinity, $M_u \to \frac{\Lambda_u}{\mu_u}, M_i \to 0, B \to 0$, and $T \to 0$. Hence, the maximum invariant set in $\left\{M_u, M_i, B, T \in \Omega : \frac{dV}{dt} = 0\right\}$, is the singleton $E_0 = \left(\frac{\Lambda_u}{\mu_u}, 0,0,0\right)$. Thus, by following Lasalle's Invariance Principle in [11], we have that E_0 is globally asymptotically stable. ■

For the stability of disease equilibrium E_1, we claim the following theorem.

Theorema *Let* $A = \beta B^* + \mu_u$; $J = \beta B^*$; $C = \gamma B^*$; $D = b + \alpha_T T^*$; $E = rb$; $F = \beta M_u^*$; $G = \gamma M_u^* + \mu_B$; $H = \frac{e_B c_B T^{*2} + c_B T^*}{(e_B T^* + 1)^2}$; $I = \alpha_T M_i^*$. *The disease equilibrium point* E_1 *is locally asymptotically stable if* $k_1 M_i^* - \frac{c_B B^*}{(e_B T^* + 1)^2} - k_1 I T^* - k_1 I > 0$, $DG + AD + AG - CF - EF > 0$, *and* $ADG + FJE - CDF - AEF > 0$.

Proof. The characteristic equation for the Jacobian matrix of system (1) at E_1 is

$$\lambda^4 + P_1\lambda^3 + P_2\lambda^2 + P_3\lambda + P_4, \tag{5}$$

where

$$P_1 = k_1 M_i^* - \frac{c_B B^*}{(e_B T^* + 1)^2} + \mu_T + G + D + A$$

$$P_2 = k_1 M_i^*(G + D + A) - \frac{c_B B^*}{(e_B T^* + 1)^2}(G + D + A) + \mu_T(G + D + A) + (DG + AD + AG) - (k_1 I T^* - k_1 I) - (CF - EF)$$

$$P_3 = k_1 M_i^*(DG + AD + AG) - \frac{c_B B^*}{(e_B T^* + 1)^2}(DG + AD + AG) + \mu_T(DG + AD + AG) + ADG$$
$$- (k_1 A I T^* - k_1 A I + k_1 G I T^* - k_1 G I) - \left(CF k_1 M_i^* - CF\frac{c_B B^*}{(e_B T^* + 1)^2} + CF\mu_T + CDF\right) + EHI + FJE$$
$$- \left(EF k_1 M_i^* - EF\frac{c_B B^*}{(e_B T^* + 1)^2} + EF\mu_T + AEF\right)$$

$$P_4 = \left(ADG k_1 M_i^* - ADG\frac{c_B B^*}{(e_B T^* + 1)^2} + ADG\mu_T\right) + (-k_1 FIC + k_1 FICT^*) - (-k_1 AGI + k_1 AGIT^*)$$
$$- \left(CDF k_1 M_i^* - CDF\frac{c_B B^*}{(e_B T^* + 1)^2} + CDF\mu_T\right) + AEHI + \left(FJE k_1 M_i^* - FJE\frac{c_B B^*}{(e_B T^* + 1)^2} + FJE\mu_T\right)$$
$$- \left(AEF k_1 M_i^* - AEF\frac{c_B B^*}{(e_B T^* + 1)^2} + AEF\mu_T\right).$$

According to Routh-Hurwitz stability criteria, all roots of (5) have a negative real part if $P_1 > 0, P_2 > 0, P_3 > 0, P_4 > 0$ and $P_1 P_2 P_3 > P_3^2 + P_1^2 P_4$, that is $k_1 M_i^* - \frac{c_B B^*}{(e_B T^* + 1)^2} - k_1 I T^* - k_1 I > 0$, $DG + AD + AG - CF - EF > 0$, *and* $ADG + FJE - CDF - AEF > 0$.

■

4. Numerical results

In this section, we present the numerical results of the system (1). We also provide the sensitivity of the basic reproduction number R_0 to know the relative importance parameter in the disease.

4.1 Numerical simulation

The parameter values used in the numerical simulation were obtained from the literature [9] given in Table 1.

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Table 1. Parameter values being used

Parameter	Values	Unit
Λ_u	$1000 - 5000$	ml.day^{-1}
β	$8{,}25 \times 10^{-9} - 2 \times 10^{-5}$	day^{-1}
μ_u	$0{,}0033 - 0{,}01$	day^{-1}
b	$0{,}11 - 0{,}4$	day^{-1}
α_T	$0{,}1 - 0{,}5$	day^{-1}
r	$0{,}055 - 0{,}1$	day^{-1}
γ	$1{,}25 \times 10^{-7}(10^{-8}, 10^{-9})$	ml. day^{-1}
μ_B	0,012	day^{-1}
k_1	0,484848	day^{-1}
c_B	5×10^{-3}	day^{-1}
e_B	10^{-4}	day^{-1}
μ_T	$0{,}01 - 0{,}3333$	day^{-1}

We take the set of parameter values $\Lambda_u = 1000, \beta = 2 \times 10^{-6}, \mu_u = 0.01, b = 0.11, \alpha_T = 0.1, r = 0.1, \gamma = 1.25 \times 10^{-7}, \mu_B = 0.012, \mu_T = 0.1$. With these values, we have $R_0 = 0.8163 < 1$. Figure 1 shows that with a different initial condition, the solution converges to the disease-free equilibrium point $E_0 = (100000,0,0,0)$. On the other hand, by choosing $\beta = 2 \times 10^{-5}$ and keeping all others parameter values, we have $R_0 = 8.163 > 1$, and we show the stability of the disease equilibrium point $E_1 = (13065,4123,3327,1)$ (Figure 2).

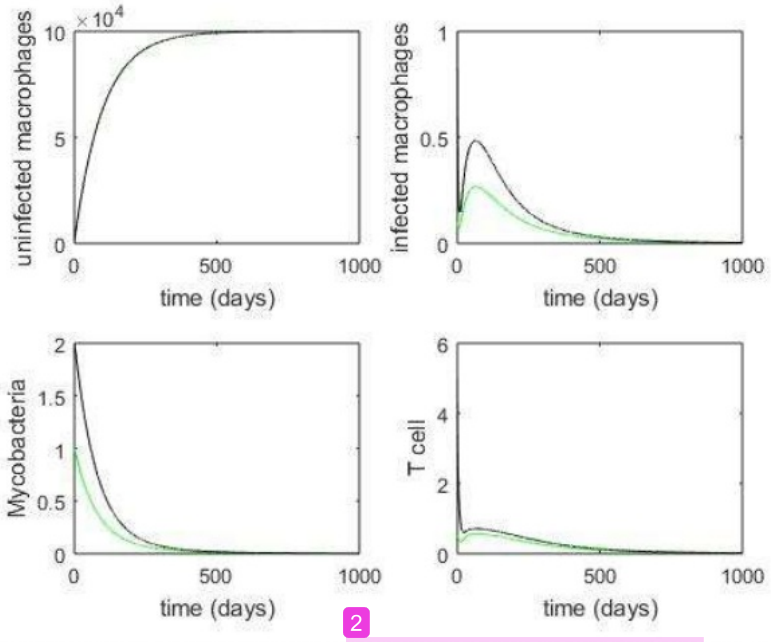

Figure 1. Time series solution with different initial conditions of the system (1) with $R_0 = 0.8163$.

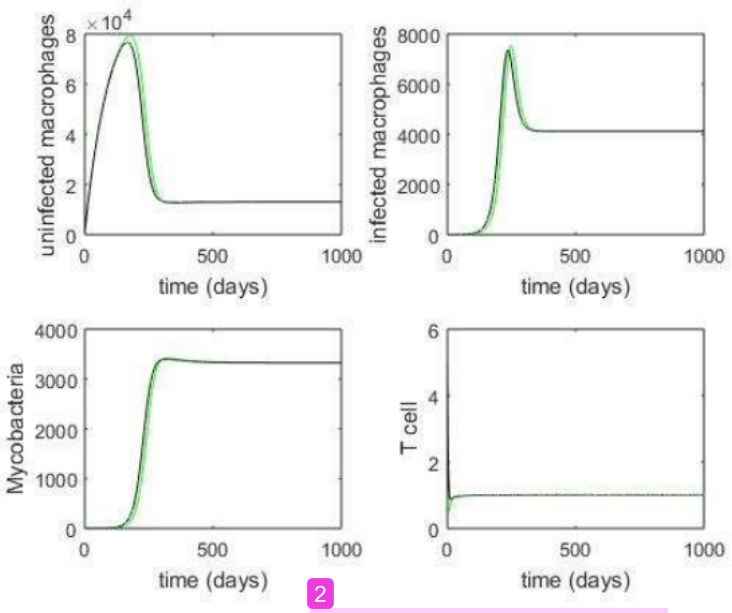

Figure 2. Time series solution with different initial conditions of the system (1) with $R_0 = 8.163 > 1$.

4.2 Sensitivity analysis of R_0

In order to discover the key parameters that have a high impact on disease, we present the sensitivity indices of R_0 to the given set of parameters. We follow the methods in [12] to calculate the sensitivity index, which is defined as the ratio of relative change on R_0 to the relative change on a parameter p as

$$\Gamma_p^{R_0} = \frac{\partial \Gamma}{\partial p} \times \frac{p}{\Gamma}. \tag{6}$$

We note that the maximum value of $\Gamma_p^{R_0}$ is 1, which implies that an increase (decrease) of p by a % increase (decrease) R_0 by a %. The sensitivity indices for the set of parameter values are presented in Table 2.

Table 2. The sensitivity indices of R_0

Parameter	Indeks Sensitivity
r	$+1,0000$
β	$+1,0000$
Λ_u	$+0,9057$
γ	$-0,0943$
μ_u	$-0,9057$
μ_B	$-0,9057$

Table 2 shows that the most sensitive parameters are the infection rate and the rate of bacterial proliferation. Therefore, sensitivity analysis can predict the appropriate intervention strategy to prevent and control the disease's spread described by the model. In Figure 3, we show the effect of changing parameter β on the number of infected macrophages. From Table 2, we know that the sensitivity index of β, $\Gamma_p^{R_0} = 1$. We find that, if β increase by 10 % from 6×10^{-6} to 6.6×10^{-6}, then R_0 increase by 10 % from $R_0 = 2.44898$ to $R_0 = 2.693878$.

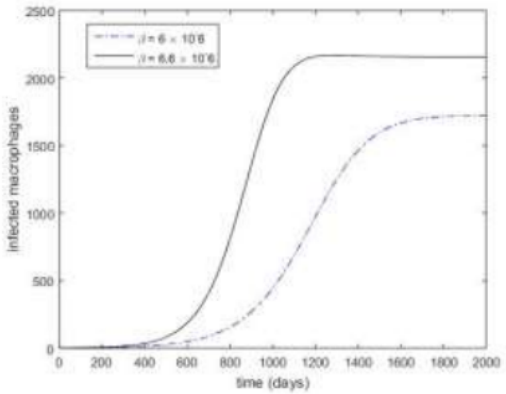

Figure 3. The changing effects of the infection rate β on the number on infected macrophages.

Considering the initial conditions $M_u(0) = 750, M_i(0) = 10, B(0) = 2$, and $T(0) = 5$ the results of the simulation are given in Figure 3.

5. Conclusion

In this study, we present a theoretical and quantitative analysis of the within-host TB model, taking into account the immune response and vaccination. From the mathematical model the interaction of the immune response to Mycobacterium tuberculosis, two equilibrium points are obtained, namely the disease-free equilibrium point and the infected equilibrium point. The global asymptotically stable disease-free equilibrium point if $R_0 \leq 1$ and the disease equilibrium point is stable if $R_0 > 1$. From the sensitivity analysis, it is known that the most influential parameters in the spread of tuberculosis are the infection rate (β) and bacterial proliferation (r). Medically, TB treatment can be done by paying attention to the two most sensitive parameters. A more in-depth analysis will be carried out for future research.

Acknowledgments

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