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Research article

A within-host model on the interaction dynamics between innate immune cells and Mycobacterium tuberculosis

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Abstract: Tuberculosis is the leading cause of death worldwide from a single infectious agent; it has also been declared a threat to humanity by the World Health Organization. New insights indicate that the innate immune response plays a crucial role in determining the outcome of the infection. In this study, we assessed the role of macrophages in the innate immune response through a simple mathematical model. Our results confirm that macrophages provide the primary protective response against *Mycobacterium tuberculosis*. However, they also highlight the importance of other innate cells in the outcome of infection. Specifically, our findings suggest that, in addition to macrophage activity, the involvement of other innate immune cells is essential for eliminating or controlling bacterial progression, ultimately leading to an adaptive immune response.

Keywords: tuberculosis; innate immune response; within-host model; ordinary differential equation; qualitative analysis; normalized sensitivity index

1. Introduction

Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium tuberculosis* (Mtb). It is both preventable and generally curable. However, in 2022, TB was the second leading cause of death worldwide due to a single infectious agent, following coronavirus disease (COVID-19). Current statistics are encouraging, showing a decline in the incidence, prevalence, and mortality rates over the years. Between 2015 and 2022, the incidence rate decreased by 8.9%, and TB-related deaths fell by 19% during the same period [1]. Despite these improvements, the situation remains concerning,

with approximately a quarter of the world's population estimated to be infected with Mtb, and over 10 million people falling ill with TB each year [1].

After an individual is infected with Mtb, the risk of developing TB disease is highest in the first 2 years (approximately 5%), after which it decreases. Without treatment, the mortality rate from TB is high (approximately 50%). With the treatments currently recommended by WHO (a 4- to 6-month course of anti-TB drugs), approximately 85% of people with TB can be cured [1]. The above allows us to assume that one in two sick people not treated with any medication overcomes the disease thanks to their immune system (a complex network of cells, tissues, organs, and substances they produce, which help the body fight infections and other diseases).

Defense mechanisms against substances that are considered harmful or foreign are divided into innate immune response and acquired immune response. The role of adaptive or acquired immunity in controlling Mtb infection is well-studied, and the protective role of T and B lymphocytes in anti-tuberculosis immunity is widely recognized [2]. However, following exposure to Mtb, it typically takes 4 to 6 weeks for a human host, and 2 to 3 weeks for mice, to develop antigen-specific T-cell responses in the lymph nodes [3]. Therefore, the non-specific innate immune response plays a pivotal role in protecting the host before the onset of adaptive immunity and even leads to early clearance of bacteria [3].

Innate immunity constitutes the first defense against harmful substances or antigens that try to enter the body, which also includes barriers such as the skin, mucous membranes, tears, and stomach acid [2, 4]. In TB, the innate immune response is crucial in determining the course of infection. The processes of transmission, infection, and development of TB are well-defined [3].

Transmission of Mtb begins when an infected individual expels microdroplets containing the infectious bacillus into the environment, which are then inhaled by an uninfected individual. Infectious bacilli can persist for up to 3 hours in closed, non-ventilated environments, and those that overcome the intrinsic barriers of the innate immune response (skin, mucous membranes, tears) enter the respiratory tract, which serves as a means of transport, generally to the pulmonary alveoli [3, 5]. It is important to note that there are many cells of the innate immune system that participate in the response against TB; however, the precise mechanisms of TB immunopathology have not yet been fully understood [3].

Once Mtb overcomes the first barriers, it encounters the alveolar epithelial cells (AEC), which are the first to interact with any pathogen that attempts to enter the respiratory tract. AECs are also known to be vital for host defenses against Mtb, and although knowledge about their immunopathological functions in TB has increased considerably, they are still not fully elucidated [3, 6].

In the alveoli, bacteria are detected, recognized, phagocytosed, and processed by antigen-presenting cells (APCs). The first line of defense against Mtb are alveolar macrophages (AM). Through the expression of several cell surface receptors, the macrophage recognizes, binds, and internalizes foreign particles, including Mtb. These cells phagocytose the Mtb by placing it inside a vacuole called a phagosome, which fuses with a bag of enzymes called a lysosome, giving rise to the phagolysosome [4].

Through a complex process, the enzymes of the phagolysosome control or eliminate the bacteria and also generate a signaling cascade that involves the production of cytokines and chemokines. This stimulate the activation of the antimicrobial activities of the phagocytes and recruitment of other cells of the immune system to the site of infection. However, bacilli that are not destroyed manipulate

phagosome maturation to prevent phagolysosome formation and evade their removal. Furthermore, the phagosome binds to other vesicles with nutrients necessary for its replication inside the AM, converting the infected macrophage into a niche for bacterial replication [7].

In an attempt to deprive Mtb of its chosen cellular niche, macrophages infected with attenuated strains of Mtb can undergo apoptosis in a manner involving tumor necrosis factor-alpha, $TNF-\alpha$, (proinflammatory cytokine secreted in the immune system by monocytes and macrophages, T and B lymphocytes, NK cells, and polymorphonuclear leukocytes). This cell death process also results in reduced survival of mycobacteria and leads to the priming of Mtb-specific CD8 T-cells [8, 9].

Macrophage apoptosis may contribute to the innate immune response against this intracellular infection by containing and limiting the growth of bacilli, as has been observed for other infectious agents, and may therefore be part of a successful host defense mechanism [10]. On the other hand, TNF induces mitochondrial reactive oxygen species (ROS) to cause necrosis of Mtb-infected macrophages. Necrosis of infected macrophages constitutes a critical pathogenic event in TB by releasing mycobacteria into the extracellular environment, permissive for Mtb population growth [11].

Neutrophils play a specific role of great clinical importance in TB, although controversial studies have established a close correlation between the development of TB and tissue infiltration by neutrophils. However, the functions of circulating neutrophils in the development of tuberculosis is largely unknown [11]. Through animal models and in vitro experiments with human cells, it has been suggested that endothelial cells (EC) also participate in the immunopathology of TB. In vitro studies have shown that human ECs succumb to Mtb infection, and can help in the dissemination of bacteria through the bloodstream and lymph [3]. Also, ECs produce ROS, nitrogen intermediates (RNI), and antimicrobial peptides such as defensins to control bacterial growth [3]. Similarly, it has been verified that other cells that also participate in the innate immune response are eosinophils, dendritic cells, inflammatory monocytes, natural killer cells, and innate lymphoid cells, among others [3, 4].

As observed, Mtb interacts with various innate immune cells, however the immunopathology arising from these interactions is not fully determined. In this regard, further research is needed to understand the immunopathology of TB. It is well documented that macrophages exert an important role in innate immune response against Mtb but they are also a niche for Mtb replication and propagation [6,7,12,13]. However, new studies have revealed that other cells such as dendritic cells, neutrophils and monocytes also play a key role in the immunopathology of TB [14, 15].

Mathematical models had been used to gain insights in within-host dynamics of TB, mainly, related to adaptive immunity [16–19]. Currently, it is known that the innate immune response is critical to the outcome of Mtb infection, since it can control bacterial progression or substantially influence the subsequent adaptive response of the host. In the literature, researchers have analyzed several aspects of the innate immune response against *Mycobacterium tuberculosis* throughout of mathematical modeling. In [20], the authors formulated and analyzed a model to describe the dynamics of innate immunology of macrophages against *Mycobacterium tuberculosis*. In [21], the authors formulated a system of ordinary differential equations that describes the interaction dynamics between Mtb, iron, lipids, and nitric oxide in the early phase of macrophage infection. They incorporated the bactericidal property of nitric oxide and the cellular regulation of iron and lipids to analyze the role they play in the outcome of infection. In [22], the authors developed a spatiotemporal model of the initial and innate response to tuberculosis. The model consists of coupled reaction-diffusion-advection equations governing the dynamics of macrophages (resting and

infected), bacteria (extracellular and intracellular), and a chemokine released by the bacteria, each of which affects final granuloma size. The model describes the migration of uninfected macrophages to the site of infection (pulmonary alveoli) and their subsequent phagocytosis of bacteria. It aims to capture clearance by innate immunity or disease progression through granuloma growth. In [23], the early immune response to Mtb infection in the lungs was modeled by means of coupled reaction-diffusion-transport equations with chemotaxis. The results and conclusions are similar to those presented in [22]. Other computational approaches have also addressed the role of early innate immunity in TB [21, 24–26].

In this work, we are interested in evaluating and comparing the response of macrophages with respect to the response of other cells of the innate immune system against TB. To this end, we formulate and analyze, at theoretical and numerical levels, a non-linear system of ordinary differential equations that describes the interaction between macrophages, the other cells of the innate immune system, and Mtb. We believe this is the first model that incorporates the dynamics of all innate immune cells against Mtb.

2. Model formulation

In order to characterize some aspects of TB immunology at the cellular level, in the context of the innate immune response, and focus on the role played by macrophage responses in the outcome of infection, in this section, we formulate a model that describes the dynamics of interaction between innate immune cells and *Mycobacterium tuberculosis* at the site of infection.

Since there are different innate immune cells that participate in the response against Mtb [3], we will group all the innate cells that act against TB into a single population that we will denote by C. We also consider the population of macrophages, M, which is divided into uninfected macrophages, M_U (macrophages that have not had contact with Mtb or that phagocytize Mtb and eliminate it efficiently), and infected macrophages, M_I (macrophages that phagocytose the bacteria but do not have the capacity to eliminate it, and the bacteria also reproduce inside it). Similarly, we consider the population of bacteria, B, which will be divided into two subpopulations: the population of internal bacteria, B_I (bacteria that have been phagocytosed by innate cells), and the population of external bacteria, B_E (bacteria that have not been phagocytosed or that have gone from internal to external due to the necrotic death of their host cells).

The cell population of the innate immune system at time t is represented by $C(t)$, which is composed of the subgroups of alveolar epithelial cells, endothelial cells, macrophages, neutrophils, eosinophils, monocytes, dendritic cells, natural killer cells, invariant natural killer T lymphocytes and innate lymphoid cells. All of these cells play a role in the immunopathology of TB that favors the host and/or the bacteria. Unfortunately, for most of them, the functions they perform and the mechanisms they carry out are still a matter of research; available results come from individual studies, and the hypotheses established based on them must be empirically validated [3, 4, 15].

We assume that the site of infection are the pulmonary alveoli and that infectious bacilli have been transported there. At this site, resident cells recruited from the bone marrow via the thymus or lymph nodes, among others, have initiated an innate immune response. As mentioned in the previous section, the set of cells that participate in this response is quite broad. However, at this stage of the infection, none of them show a specific response to the antigen [3, 4].

We suppose that innate cells are recruited at a constant rate, Λ_C, and die at per capita natural death rate, μ_C. Since cells produced by the thymus and lymph differentiate into different types of innate immune cells, and we want to compare the macrophages response with respect to the response of the rest of the innate cells, we assume that a portion of innate cells differentiate into uninfected macrophages at a rate α.

Since a portion of the bacteria phagocytosed by macrophages is eliminated by them, and the other turns them into their reproduction niche, we assume that uninfected macrophages phagocytose Mtb at a rate ε, of which a fraction ν becomes infected. Other innate cells participate directly or indirectly in the death of infected macrophages [3,4]; for this reason, we assume that the innate cells eliminates the population of infected macrophages at a rate λ. Necrosis is classified by NCCD-201 as accidental cell death, and Mtb-infected macrophage necrosis occurs when the Mtb kills infected macrophages [27, 28]. This process is a key part of the Mtb infection cycle, allowing the bacteria to spread and evade the host's immune response. In TB, the internal bacteria, in addition to reproducing within the macrophage, induce its death by necrosis, releasing necrotic tissue, and a certain amount of bacteria into the environment [3, 28]. As a consequence, we assume that the natural death of infected macrophages is by necrosis, which occurs at a per capita rate $\mu_{MI}(B_I)$, which is a function that depends on the internal bacteria. Consequently, the number of infected macrophages that die by necrosis is $\mu_{MI}(B_I)M_I$, and in turn, these necrotic macrophages release on average r bacilli into the extracellular environment. This implies that the amount of external bacteria released into the environment would be proportional to the number of macrophages that die by necrosis, $r\mu_{MI}(B_I)$. To date, the most appropriate functional response for $\mu_{MI}(B_I)$ has not been empirically determined. However, there is experimental evidence that the amount of foreign bacteria produced by macrophage necrosis is proportional to the number of infected macrophages [29]. For this reason, in this model, we will assume that infected macrophages die by necrosis at a constant rate μ_{MI}. In addition, bacteria phagocytosed by macrophages are eliminated at a rate, κ.

Since there are other innate cells such as dendritic cells, neutrophils, or monocytes that phagocytose and eliminate Mtb [3, 4], we assume that extracellular bacteria are eliminated by these innate cells at a rate η. We also assume that internal bacteria replicate inside an infected macrophage at a rate β, following a saturation kinetics with carrying capacity of the infected macrophages denoted by K_I. Finally, μ_{MU}, μ_{BE}, and μ_{BI} denote the per capita natural death rates (reciprocal of the half-life) of uninfected macrophages, and intracellular and extracellular bacteria, respectively.

From the above assumptions, we obtain the following system of ordinary differential equations

$$\begin{aligned}
\frac{dC}{dt} &= \Lambda_C - \alpha C - \mu_C C \\
\frac{dM_U}{dt} &= \alpha C - \varepsilon\nu B_E M_U - \mu_{MU} M_U \\
\frac{dM_I}{dt} &= \varepsilon\nu B_E M_U - \lambda M_I C - \mu_{MI} M_I \\
\frac{dB_E}{dt} &= r\mu_{MI} M_I - \varepsilon\kappa B_E M_U - \eta B_E C - \mu_{BE} B_E \\
\frac{dB_I}{dt} &= \beta\left(1 - \frac{B_I}{K_I}\right) M_I - \mu_{BI} B_I.
\end{aligned} \tag{2.1}$$

The set of biological interest is given by

$$\Omega = \left\{ \begin{pmatrix} C \\ M_U \\ M_I \\ B_E \\ B_I \end{pmatrix} \in \mathbb{R}^5_+ : 0 \leq C \leq \frac{\Lambda_C}{\alpha + \mu_C}, 0 \leq M_U + M_I \leq \frac{\alpha \Lambda_C}{\mu_M(\alpha + \mu_C)}, 0 \leq B_E + B_I \leq \frac{\bar{\alpha}}{\mu_B} \right\}, \tag{2.2}$$

where $\mu_M = \min\{\mu_{MU}, \mu_{MI}\}$, $\mu_B = \min\{\mu_{BE}, \mu_{BI}\}$, and $\bar{\alpha} = \dfrac{\alpha(r\mu_{MI} + \beta)\Lambda_C}{\mu_M(\alpha + \mu_C)}$. The following lemma ensures that system (2.1) makes biological sense; that is, all solutions starting at Ω remain there for all $t \geq 0$.

Lemma 2.1. *The set Ω defined in (2.2) is positively invariant for solutions of the system (2.1).*

Proof. Let us start by verifying the existence of the solution to the initial value problem defined by the system (2.1) and $x_0 = (C(0), M_U(0), M_I(0), B_E(0), B_I(0)) \in \Omega$. Since the vector field defined by the right-hand side of (2.1) is $C^1(\mathbb{R}^5_+)$, then the fundamental theorem of existence and uniqueness guarantees the existence of a solution $x(t) \in \mathbb{R}^5_+$ in the interval $[0, \sigma]$ [30]. Furthermore, if the compact set $\bar{\Omega} \in \mathbb{R}^5_+$ satisfies $\{y \in \mathbb{R}^5 : y = f(t) \text{ for some } t \in [0, \sigma)\}$, then by the extension theorem $\sigma = \infty$ (Corollary 2, page 91, [30]). Now, suppose that $x_0 \in \Omega$, then we have

$$0 \leq C(0) \leq \frac{\Lambda_C}{\alpha + \mu_C}, 0 \leq M_U(0) + M_I(0) \leq \frac{\alpha \Lambda_C}{\mu_M(\alpha + \mu_C)}, 0 \leq B_E(0) + B_I(0) \leq \frac{\bar{\alpha}}{\mu_B}.$$

On the other hand, the solution of the first equation of the system (2.1) is given by

$$C(t) = \frac{\Lambda_C}{\alpha + \mu_C} + \left(C(0) - \frac{\Lambda_C}{\alpha + \mu_C} \right) e^{-(\alpha + \mu_C)t},$$

since $0 \leq C(0) \leq \Lambda_C/(\alpha + \mu_C)$, then $0 \leq C(t) \leq \Lambda_C/(\alpha + \mu_C)$ for all $t \geq 0$. Adding the second and third equations of the system (2.1), we have

$$\frac{dM_U}{dt} + \frac{dM_I}{dt} = \alpha C - \mu_{MU} M_U - \lambda M_I C - \mu_{MI} M_I,$$

since $\mu_M \leq \mu_{MU}$ and $\mu_M \leq \mu_{MI}$, then from the previous equation we obtain the following inequality

$$\frac{dM_U}{dt} + \frac{dM_I}{dt} \leq \alpha \frac{\Lambda_C}{\alpha + \mu_C} - \mu_M(M_U + M_I) - \lambda M_I C \leq \frac{\alpha \Lambda_C}{\alpha + \mu_C} - \mu_M(M_U + M_I),$$

or equivalently

$$\frac{d(M_U + M_I)}{dt} + \mu_M(M_U + M_I) \leq \frac{\alpha \Lambda_C}{\alpha + \mu_C}.$$

The solution of the above inequality satisfies

$$M_U(t) + M_I(t) \leq \frac{\alpha \Lambda_C}{\mu_U(\alpha + \mu_C)} + \left(M_U(0) + M_I(0) - \frac{\alpha \Lambda_C}{\mu_M(\alpha + \mu_C)} \right) e^{-\mu_M t},$$

since $0 \le M_U(0) + M_I(0) \le \dfrac{\alpha\Lambda_C}{\mu_M(\alpha+\mu_C)}$, then $0 \le M_U(t) + M_I(t) \le \dfrac{\alpha\Lambda_C}{\mu_M(\alpha+\mu_C)}$ for all $t \ge 0$. Adding the fourth and fifth equations of (2.1) we have

$$\frac{dB_E}{dt} + \frac{dB_I}{dt} = r\mu_{MI}M_I + \beta\left(1 - \frac{B_I}{K_I}\right)M_I - \varepsilon\kappa B_E M_U - \eta B_E C - \mu_{BE}B_E - \mu_{BI}B_I,$$

since $\mu_B \le \mu_{BE}$, $\mu_B \le \mu_{BI}$, $M_I < \alpha\Lambda_C/\mu_M(\alpha+\mu_C)$, then we obtain the following inequality

$$\frac{d(B_E + B_I)}{dt} + \mu_B(B_E + B_I) < \bar{\alpha},$$

where $\bar{\alpha} = \dfrac{\alpha(r\mu_{MI}+\beta)\Lambda_C}{\mu_M(\alpha+\mu_C)}$. The solution of the above inequality satisfies

$$B_E(t) + B_I(t) < \frac{\bar{\alpha}}{\mu_B} + \left(B_E(0) + B_I(0) - \frac{\bar{\alpha}}{\mu_B}\right)e^{-\mu_B t}.$$

Therefore, if $B(0) \le \bar{\alpha}/\mu_B$, then $B(t) \le \bar{\alpha}/\mu_B$ for all $t \ge 0$. □

3. Qualitative analysis of the model

3.1. Equilibrium solutions

Taking the left-hand side of (2.1) equal to the zero vector gives the following system of algebraic equations

$$\begin{aligned}
\Lambda_C - \alpha C - \mu_C C &= 0\\
\alpha C - \varepsilon\nu B_E M_U - \mu_{MU}M_U &= 0\\
\varepsilon\nu B_E M_U - \lambda M_I C - \mu_{MI}M_I &= 0\\
r\mu_{MI}M_I - \varepsilon\kappa B_E M_U - \eta B_E C - \mu_{BE}B_E &= 0\\
\beta\left(1 - \frac{B_I}{K_I}\right)M_I - \mu_{BI}B_I &= 0.
\end{aligned} \tag{3.1}$$

From the first equation of (3.1), we obtain $C = C^*$, where

$$C^* = \frac{\Lambda_C}{\alpha + \mu_C}. \tag{3.2}$$

Substituting (3.2) in the second equation of (3.1), we obtain

$$M_U = \frac{\alpha C^*}{\varepsilon\nu B_E + \mu_{MU}}. \tag{3.3}$$

From the third equation of (3.1), we obtain

$$M_I = \frac{\varepsilon\nu B_E M_U}{\lambda C^* + \mu_{MI}}$$

$$= \frac{\varepsilon\nu B_E}{\lambda C^* + \mu_{MI}} \frac{\alpha C^*}{\varepsilon\nu B_E + \mu_{MU}}. \tag{3.4}$$

Substituting (3.2), (3.3), and (3.4) in the fourth equation of (3.1), we obtain

$$r\mu_{MI} \frac{\varepsilon\nu B_E}{\lambda C^* + \mu_{MI}} \frac{\alpha C^*}{\varepsilon\nu B_E + \mu_{MU}} - \varepsilon\kappa B_E \frac{\alpha C^*}{\varepsilon\nu B_E + \mu_{MU}} - \eta B_E C^* - \mu_{BE} B_E = 0.$$

The solutions of the above equation are given by $B_E = 0$ and $B_E = B_E^*$, where

$$B_E^* = \left[\frac{\kappa\alpha C^*}{\nu(\eta C^* + \mu_{BE})} + \frac{\mu_{MU}}{\varepsilon\nu} \right] (R_0 - 1), \tag{3.5}$$

and

$$R_0 = \frac{r\mu_{MI}\varepsilon\nu\alpha C^*}{(\lambda C^* + \mu_{MI}) \left[\varepsilon\kappa\alpha C^* + \mu_{MU}(\eta C^* + \mu_{BE}) \right]}. \tag{3.6}$$

If $B_E = 0$, we obtain the free-infection equilibrium

$$E_0 = \left(C^*, \frac{\alpha C^*}{\mu_{MU}}, 0, 0, 0 \right). \tag{3.7}$$

Now, substituting (3.5) in the Eqs (3.3) and (3.4) we obtain

$$\begin{aligned} M_U^* &= \frac{\alpha C^*}{\varepsilon\nu B_E^* + \mu_{MU}} \\ M_I^* &= \frac{\varepsilon\nu B_E^*}{\lambda C^* + \mu_{MI}} \frac{\alpha C^*}{\varepsilon\nu B_E^* + \mu_{MU}}. \end{aligned} \tag{3.8}$$

Substituting (3.8) in the fifth equation of (3.1), we obtain $B_I = B_I^*$, where

$$B_I^* = \frac{\beta M_I^*}{\frac{\beta}{K_I} M_I^* + \mu_{BI}}. \tag{3.9}$$

As a consequence, if $R_0 > 1$, there exists a non-trivial equilibrium

$$E_1 = (C^*, M_U^*, M_I^*, B_E^*, B_I^*). \tag{3.10}$$

The following theorem summarizes the results of the existence of equilibria.

Teorem 3.1. *If $R_0 \leq 1$, then E_0 defined in (3.7) is the only equilibrium in Ω. If $R_0 > 1$, in addition to E_0, there exists the infected equilibrium E_1 defined in (3.10).*

3.2. Stability of equilibrium solutions

In this section, we will analyze the stability of equilibrium solutions. The linearization of the system (2.1) around an equilibrium solution $\bar{x}$ is given by $x = J(\bar{x})x$, where the Jacobian matrix J evaluated at

x is given by

$$J(x) = \begin{pmatrix} -(\alpha+\mu_C) & 0 & 0 & 0 & 0 \\ \alpha & -(\varepsilon\nu B_E + \mu_{MU}) & 0 & -\varepsilon\nu M_U & 0 \\ -\lambda M_I & \varepsilon\nu B_E & -(\lambda C + \mu_{MI}) & \varepsilon\nu M_U & 0 \\ -\eta B_E & -\varepsilon\kappa B_E & r\mu_{MI} & -(\varepsilon\kappa M_U + \eta C + \mu_{BE}) & 0 \\ 0 & 0 & \beta\left(1 - \dfrac{B_I}{K_I}\right) & 0 & -\left(\dfrac{\beta M_I}{K_I} + \mu_{BI}\right) \end{pmatrix}. \tag{3.11}$$

From (3.11), we verify that the Jacobian matrix evaluated in trivial equilibrium E_0 is given by

$$J(E_0) = \begin{pmatrix} -(\alpha+\mu_C) & 0 & 0 & 0 & 0 \\ \alpha & -\mu_{MU} & 0 & -\dfrac{\varepsilon\nu\alpha C^*}{\mu_{MU}} & 0 \\ 0 & 0 & -(\lambda C^* + \mu_{MI}) & \dfrac{\varepsilon\nu\alpha C^*}{\mu_{MU}} & 0 \\ 0 & 0 & r\mu_{MI} & -\left(\dfrac{\varepsilon\kappa\alpha C^*}{\mu_{MU}} + \eta C^* + \mu_{BE}\right) & 0 \\ 0 & 0 & \beta & 0 & -\mu_{BI} \end{pmatrix}. \tag{3.12}$$

The eigenvalues of $J(E_0)$ defined in (3.12) are given by $-(\alpha+\mu_C)$, $-\mu_{MU}$, $-\mu_{BI}$, and the roots of the following quadratic equation

$$\varsigma^2 + \left(\lambda C^* + \mu_{MI} + \frac{\varepsilon\kappa\alpha C^*}{\mu_{MU}} + \eta C^* + \mu_{BE}\right)\varsigma + \frac{1}{\mu_{MU}}(\lambda C^* + \mu_{MI})(\varepsilon\kappa\alpha C^* + \mu_{MU}(\eta C^* + \mu_{BE}))(1 - R_0) = 0.$$

The above implies that E_0 is locally asymptotically stable in Ω when $R_0 < 1$. Similarly, it is verified that the eigenvalues of $J(E_1)$ are $-(\alpha+\mu_C)$, $-(\beta M_I^*/K_I + \mu_{BI})$ and the roots of the following polynomial

$$\varsigma^3 + a_2\varsigma^2 + a_1\varsigma + a_0, \tag{3.13}$$

where

$$\begin{aligned} a_2 &= \varepsilon\kappa M_U^* + \eta C^* + \mu_{BE} + \lambda C^* + \mu_{MI} + \varepsilon\nu B_E^* + \mu_{MU} \\ a_1 &= (\varepsilon\kappa M_U^* + \eta C^* + \mu_{BE} + \lambda C^* + \mu_{MI})(\varepsilon\nu B_E^* + \mu_{MU}) - \varepsilon\nu M_U^* \varepsilon\kappa B_E^* \\ a_0 &= \varepsilon\nu M_U^* \left[r\mu_{MI}\varepsilon\nu B_E - \varepsilon\kappa B_E^*(\lambda C^* + \mu_{MI})\right] \\ &= \varepsilon\nu M_U^*(\lambda C^* + \mu_{MI})(\eta C^* + \mu_{BR})\frac{B_E^*}{M_U}. \end{aligned}$$

Since the coefficients of the cubic polynomial (3.13) do not change sign, then from the rule of the signs of Descartes, it is verified that all its roots have a negative real part. Therefore, the equilibrium E_1 is locally asymptotically stable in Ω. The following theorem summarizes the results of the existence of equilibria.

Teorem 3.2. *If $R_0 < 1$, then E_0 defined in (3.7) is locally asymptotically stable in Ω. If $R_0 > 1$, E_0 is unstable, and E_1 defined in (3.10) is locally asymptotically stable in Ω.*

4. Sensitivity analysis of parameters and numerical simulations

In the previous section, it was verified that the result of the infection depends on the basic radius of offspring R_0 defined in (3.6). We observe that R_0 depends on almost all the parameters of the model. In this sense, an interesting question is which parameters of the model (2.1) influence the most values of R_0. To answer this question, it is necessary to perform a sensitivity analysis that determines the uncertainty of the model outputs based on the uncertainty of its inputs.

There are various theoretical and numerical methods to perform this type of analysis. In our case, we have an initial value problem defined by a system of nonlinear ordinary differential equations whose inputs are the model parameters and the initial conditions; and also, the behavior of the model outputs is conditioned by the value of R_0. As such, good method to perform the analysis consists of using the normalized sensitivity index to determine the sensitivity of R_0 with respect to each of the parameters that define it.

Let p be a parameter, and the normalized sensitivity index $\Upsilon_p^{R_0}$ is given by the following partial derivative

$$\Upsilon_p^{R_0} = \frac{p}{R_0}\frac{\partial R_0}{\partial p}. \tag{4.1}$$

From (4.1), we verify that

$$\begin{aligned}
\Upsilon_{\Lambda_C}^{R_0} &= \frac{\mu_{MU}\mu_{BE}}{\mu_{MU}\mu_{BE} + (\varepsilon\kappa\alpha + \mu_{MU}\eta)\, C^*} - \frac{\lambda C^*}{\lambda C^* + \mu_{MI}} \\
\Upsilon_{\alpha}^{R_0} &= 1 + \frac{\alpha}{\alpha + \mu_C}\left[\frac{\lambda C^*}{\lambda C^* + \mu_{MI}} - \frac{\varepsilon\kappa(\alpha + \mu_C)C^* + \mu_{MU}\mu_{BE}}{\mu_{MU}\mu_{BE} + (\varepsilon\kappa\alpha + \mu_{MU}\eta)\, C^*}\right] \\
\Upsilon_{\mu_C}^{R_0} &= -\frac{\mu_C}{\alpha + \mu_C}\left[\frac{\mu_{MU}\mu_{BE}}{\mu_{MU}\mu_{BE} + (\varepsilon\kappa\alpha + \mu_{MU}\eta)\, C^*} + \frac{\lambda C^*}{\lambda C^* + \mu_{MI}}\right] \\
\Upsilon_{\varepsilon}^{R_0} &= 1 - \frac{\varepsilon\kappa\alpha C^*}{\mu_{MU}\mu_{BE} + (\varepsilon\kappa\alpha + \mu_{MU}\eta)\, C^*} \\
\Upsilon_{\nu}^{R_0} &= 1 \\
\Upsilon_{\mu_{MU}}^{R_0} &= -\frac{\mu_{MU}\eta C^* + \mu_{MU}\mu_{BE}}{\mu_{MU}\mu_{BE} + (\varepsilon\kappa\alpha + \mu_{MU}\eta)\, C^*} \\
\Upsilon_{\lambda}^{R_0} &= -\frac{\lambda C^*}{\lambda C^* + \mu_{MI}} \\
\Upsilon_{\mu_{MI}}^{R_0} &= 1 - \frac{\mu_{MI}}{\lambda C^* + \mu_{MI}} \\
\Upsilon_{r}^{R_0} &= 1 \\
\Upsilon_{\kappa}^{R_0} &= -\frac{\varepsilon\kappa\alpha C^*}{\mu_{MU}\mu_{BE} + (\varepsilon\kappa\alpha + \mu_{MU}\eta)\, C^*} \\
\Upsilon_{\eta}^{R_0} &= -\frac{\mu_{MU}\eta C^*}{\mu_{MU}\mu_{BE} + (\varepsilon\kappa\alpha + \mu_{MU}\eta)\, C^*} \\
\Upsilon_{\mu_{BE}}^{R_0} &= -\frac{\mu_{MU}\mu_{BE}}{\mu_{MU}\mu_{BE} + (\varepsilon\kappa\alpha + \mu_{MU}\eta)\, C^*}.
\end{aligned} \tag{4.2}$$

From (4.2) we verify that sensitivity indices are within the ranges presented in Table 1.

Table 1. Range of normalized sensitivity indices.

Índice	$\Upsilon_{\Lambda_C}^{R_0}$	$\Upsilon_{\alpha}^{R_0}$	$\Upsilon_{\mu_C}^{R_0}$	$\Upsilon_{\varepsilon}^{R_0}$	$\Upsilon_{\nu}^{R_0}$	$\Upsilon_{\mu_{MU}}^{R_0}$	$\Upsilon_{\lambda}^{R_0}$	$\Upsilon_{\mu_{MI}}^{R_0}$	$\Upsilon_{r}^{R_0}$	$\Upsilon_{\kappa}^{R_0}$	$\Upsilon_{\eta}^{R_0}$	$\Upsilon_{\mu_{BE}}^{R_0}$
Rango	$(-1, 1)$	$(-\infty, 2)$	$(-2, 0)$	$(0, 1)$	1	$(-1, 0)$	(-1.0)	$(0, 1)$	1	$(-1, 0)$	$(-1, 0)$	$(-1, 0)$

From Table 1 we observe that $\Upsilon_{\Lambda_C}^{R_0} \in (-1, 1)$, $\Upsilon_{\alpha}^{R_0} \in (-\infty, 2)$, $\Upsilon_{\mu_C}^{R_0} \in (-2, 0)$, $\Upsilon_{\nu}^{R_0} = \Upsilon_{r}^{R_0} = 1$, $\{\Upsilon_{\mu_{MU}}^{R_0}, \Upsilon_{\lambda}^{R_0}, \Upsilon_{\kappa}^{R_0}, \Upsilon_{\eta}^{R_0}, \Upsilon_{\mu_{BE}}^{R_0}\} \in (-1, 0)$ and $\{\Upsilon_{\varepsilon}^{R_0}, \Upsilon_{\mu_{MI}}^{R_0}\} \in (0, 1)$. The above indicates that the parameters μ_C, μ_{MU}, λ, κ, η, and μ_{BE} have a positive impact on infection control, in the sense that if the value of any of these parameters increases, then the value of R_0 decreases. On the other hand, an increase in any of the parameters ν, r, μ_{MI} o ε leads to an increase in the value of R_0.

Due to the form of the expressions that define $\Upsilon_{\Lambda_C}^{R_0}$ and $\Upsilon_{\alpha}^{R_0}$, it was not possible to determine a smaller range; however, we can conclude that the parameters Λ_C, α, and μ_C can have positive or negative effects on infection control. Note that, if we do not consider the three previous parameters, the parameters that most influence the outcome of the infection are r and ν.

Table 2. Parameter ranges.

Parameter	Description	Values	References
Λ_C	Recruitment rate of innate cells	50–120 cell/h	[31]
α	Differentiation rate of macrophages	0.02–0.06 h^{-1}	[32]
ε	Phagocytosis rate of macrophages	0.1–0.8	[31]
ν	Macrophage infection rate	0.2–0.8	[31]
$\varepsilon\nu$	Effective macrophage infection rate	0.02–0.64 (h· cell)$^{-1}$	[31]
r	Nnumber of bact. released by necrotic M_I	1–50 cell	[31]
κ	Bacterial elimination rate by macrophages	0.001–0.01	[31]
$\varepsilon\kappa$	Effective bacterial killing rate by macrophages	0.0001–0.008 (h· cell)$^{-1}$	[31]
η	Bacterial elimination rate by innate cells	0.003–0.03 (h· cell)$^{-1}$	[31]
β	B_I replication rate within M_I	0.0032–0.032 h^{-1}	[31]
λ	M_I elimination rate by innate cells	0.001–0.01 (h· cell)$^{-1}$	[31]
μ_C	Natural death rate of C	0.0067–0.0083 h^{-1}	[31]
μ_{MU}	Natural death rate of M_U	0.0032–0.0051 h^{-1}	[32]
μ_{MI}	M_I death rate due to necrosis	0.0101–0.0139 h^{-1}	[31]
μ_{BE}	Natural death rate of B_E	0.002–0.02 h^{-1}	[13]
μ_{BI}	Natural death rate of B_I	0.002–0.03 h^{-1}	[13]
K_I	Carrying capacity of macrophages	10–100 cell	[31]

Let us observe that the rate of differentiation of innate cells into macrophages, α, is the parameter that most influences the outcome of the infection (an increase of 5% in this parameter would generate an increase in R_0 between 5.6% and 7.85%), followed by the parameters ν, r, Λ_C, and μ_{MI}. It is also observed that when the phagocytic rate of macrophages has a high impact on the variation of R_0, the rate of bacterial elimination by macrophages has a low impact, and vice versa. The incidence of the parameters μ_C and μ_{BE} on the variation of R_0 is almost zero. Finally, the minimum value of μ_{MU} has a greater impact on the result of the infection than its maximum value.

Table 3. Sensitivity indices evaluated at extreme values of the parameters in Table 2.

Index	$\Upsilon_{\Lambda_C}^{R_0}$	$\Upsilon_{\alpha}^{R_0}$	$\Upsilon_{\mu_C}^{R_0}$	$\Upsilon_{\varepsilon}^{R_0}$	$\Upsilon_{\nu}^{R_0}$	$\Upsilon_{\mu_{MU}}^{R_0}$	$\Upsilon_{\lambda}^{R_0}$	$\Upsilon_{\mu_{MI}}^{R_0}$	$\Upsilon_{r}^{R_0}$	$\Upsilon_{\kappa}^{R_0}$	$\Upsilon_{\eta}^{R_0}$	$\Upsilon_{\mu_{BE}}^{R_0}$
Minimum	−0.99	1.57	−0.24	0.83	1	−0.83	−0.99	0.99	1	−0.17	−0.83	-2.95×10^{-4}
Maximum	−0.99	1.12	−0.12	0.24	1	−0.24	−0.99	0.99	1	−0.76	−0.24	-9.17×10^{-5}

Table 4. Index values.

Índice	$\Upsilon_{\Lambda_C}^{R_0}$	$\Upsilon_{\alpha}^{R_0}$	$\Upsilon_{\mu_C}^{R_0}$	$\Upsilon_{\varepsilon}^{R_0}$	$\Upsilon_{\nu}^{R_0}$	$\Upsilon_{\mu_{MU}}^{R_0}$	$\Upsilon_{\lambda}^{R_0}$	$\Upsilon_{\mu_{MI}}^{R_0}$	$\Upsilon_{r}^{R_0}$	$\Upsilon_{\kappa}^{R_0}$	$\Upsilon_{\eta}^{R_0}$	$\Upsilon_{\mu_{BE}}^{R_0}$
Figure 1	−0.89	1.74	−0.11	0.95	1	−0, 95	−0.90	0.90	1	−0.05	−0.94	-7×10^{-3}
Figure 2	−0.99	0.89	−0.12	0.01	1	−0, 01	−0.99	0.99	1	−0.99	−0.01	-1.2×10^{-4}

Figures 1 and 2 were made with data from Table 2 and show graphs of the temporal behavior of the cell population. In Figure 1, it can be seen that in the first 10 hours, a large number of innate cells differentiate into macrophages, almost quintupling their initial population, all with the purpose of counteracting the spread of the infection. However, their response was insufficient because both the population of bacteria and infected macrophages increased considerably.

In contrast, in Figure 2, it can be seen that the initial population of macrophages declines very rapidly, and, although at the beginning the populations of external bacteria and infected macrophages grow rapidly, after 2 hours these decrease to less than 10 bacteria and 10 infected macrophages. Table 4 shows the values of sensitivity indices for the simulations presented in Figures 1 and 2.

It is important to highlight that although in Figure 1 it can be seen that at the beginning the population of uninfected macrophages grows, and in Figure 2 this population decreases from the beginning, the sensitivity analysis reveals that the innate immune response of uninfected macrophages was better in the second simulation. Indeed, the magnitude of $\Upsilon_{\kappa}^{R_0}$ was larger in the second simulation, indicating that more bacteria were eliminated in the second simulation than in the first one.

In a similar way, indicating that more uninfected macrophages were killed in the first simulation than in the second one (Figure 2), and decreased steadily in the first simulation (Figure 1). Since the magnitude of $\Upsilon_{\eta}^{R_0}$ was larger in the first simulation and the magnitude of $\Upsilon_{\alpha}^{R_0}$ was smaller in the second simulation, parameter analysis suggests that its incidence was significantly higher in the first one.

The infection and replication rates have a high impact on the outcome of the infection, but they have the same incidence in both cases. Although the recruitment of bone marrow cells is low in the first simulation and high in the second one, the level of incidence on the outcome of the infection is similar in both cases. The incidence level of both the death rate of innate cells that do not differentiate into infected macrophages as well as the death rate of external cells did not have a significant impact on bacterial progression.

5. Discussion

Microbiological processes at any level, and in particular at the cellular level, are extremely complex and require contributions from different areas of knowledge to advance in their understanding. Our model is a very simple approximation to the interaction dynamics of innate cells (divided between macrophages and the rest of the innate cells without specifying) and *Mycobacterium tuberculosis*, at

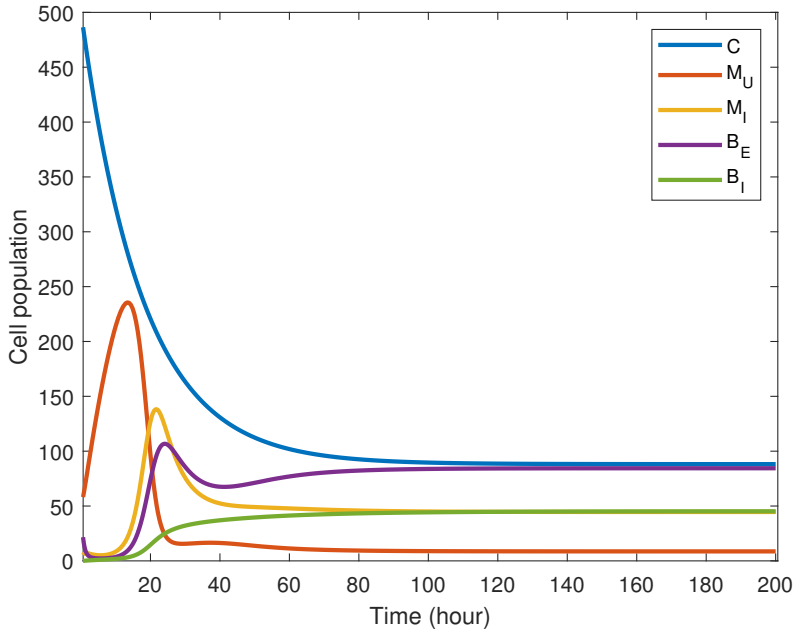

Figure 1. Initial conditions $(500, 50, 0, 50, 0)$. Values of the parameters: $\Lambda_C = 5$, $\alpha = 0.05$, $\varepsilon = 0.01$, $\nu = 0.6$, $r = 50$, $\kappa = 0.001$, $\eta = 0.003$, $\beta = 0.032$, $\lambda = 0.001$, $\mu_C = 0.0067$, $\mu_{MU} = 0.0032$, $\mu_{MI} = 0.0101$, $\mu_{BE} = 0.002$, $\mu_{BI} = 0.03$, $K_I = 50$.

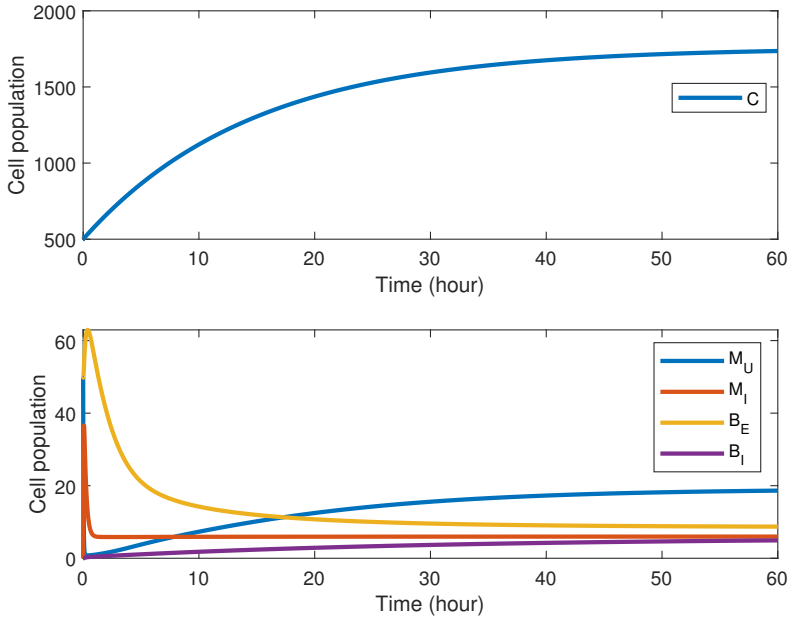

Figure 2. Initial conditions $(500, 50, 0, 50, 0)$. Values of the parameters: $\Lambda_C = 120$, $\alpha = 0.06$, $\varepsilon = 0.8$, $\nu = 0.8$, $r = 50$, $\kappa = 0.01$, $\eta = 0.001$, $\beta = 0.032$, $\lambda = 0.01$, $\mu_C = 0.0083$, $\mu_{MU} = 0.0051$, $\mu_{MI} = 0.0556$, $\mu_{BE} = 0.02$, $\mu_{BI} = 0.03$, $K_I = 50$.

the beginning of the Mtb infection.

Qualitative analysis reveals a forward bifurcation in which the infection-free equilibrium E_0 loses its stability when $R_0 = 1$ and emerges a stable coexistence equilibrium E_1. Note that the progression of the infection will depend on a condition very similar to that used in epidemiology for the spread of an infectious disease in a population of host individuals. The key quantity is the basic offspring proportion R_0 defined in (3.6), which is interpreted as the number of secondary infections arising from a macrophage during its lifetime when all other innate cells are not infected. The fact that R_0 depends on all the parameters of the model except for three parameters associated with internal bacteria dynamics suggests that both macrophages and the rest of innate cells must perform their effector functions appropriately to counteract Mtb pathogenesis. It was verified that the parameters associated with macrophages immunopathology (ε, ν, r, κ, μ_{MU}, μ_{MI} and α) significantly impact the interaction dynamics. The results above corroborates that macrophages play a fundamental role in the control or dissemination of the bacillus, during the first stage of infection. In addition, the analysis provides new insights that suggest focusing our attention on the rest of the innate cells that participate in the activation of the innate immune response against TB, since the parameters associated with these cells Λ_C, α, μ_C, λ, and η are as relevant as those of the macrophages in the variation of R_0.

The parameter α represents the differentiation rate of cells produced by the bone marrow into mature macrophages capable of performing their effector functions against any pathogen, in particular against Mtb. In reality, this parameter is an oversimplification homeostasis, a process with many unknown aspects at the biological level, but that begins with the production of stem cells in the bone marrow and involves the transition to other cells (such as the differentiation of promonocytic cells into mature monocytes); this process in turn includes self-regulation mechanisms, among other factors. Note that this parameter is associated with responses from macrophages and other innate cells. With the largest range among all the sensitivity indices $(-\infty, 2)$, the results suggest that it can contribute to either reducing or increasing bacterial progression. Indeed, if $\Upsilon_\alpha^{R_0} \in (-\infty, 0)$ contributes to reducing the value of R_0, which will decrease the number of secondary infections. On the other hand, if $\Upsilon_\alpha^{R_0} \in (0, 2)$ increases secondary infections. Under the set of parameters used to perform the simulations in Figures 1 and 2, positive sensitivity indices were obtained for α. As a consequence, for both cases, the differentiation rate contributed to the progression of the infection. By carrying out a similar procedure, it is verified that the recruitment rate of innate cells Λ_C can contribute to the decrease or increase of infection. In fact, in the numerical simulations of Figures 1 and 2, it positively affects the control of infection.

At the experimental level, there is a large body of literature supporting the theoretical results obtained here, which highlight that Mtb infection can be eliminated by the innate immune system before an adaptive immune response is initiated; this innate protection requires a variety of robust cell-autonomous responses from many different types of host immune cells [6].

For centuries, TB research has focused on the role of adaptive immunity in TB, leaving aside innate immunity. However, advances in recent decades have shown that the innate immune response determines the outcome of the infection. In this sense, scientific and academic production on the innate immunology of TB has increased, and generated new perspectives. However, there are still many gaps. In this article, we have formulated and analyzed a model whose results corroborate the importance of the innate response of macrophages in TB, and also suggest that other innate cells are also very important during primary infection.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare there is no conflict of interest.

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