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EXISTENCE OF MULTIPLE-STABLE EQUILIBRIA FOR A MULTI-DRUG-RESISTANT MODEL OF MYCOBACTERIUM TUBERCULOSIS

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Abstract. The resurgence of multi-drug-resistant tuberculosis in some parts of Europe and North America calls for a mathematical study to assess the impact of the emergence and spread of such strain on the global effort to effectively control the burden of tuberculosis. This paper presents a deterministic compartmental model for the transmission dynamics of two strains of tuberculosis, a drug-sensitive (wild) one and a multi-drug-resistant strain. The model allows for the assessment of the treatment of people infected with the wild strain. The qualitative analysis of the model reveals the following. The model has a disease-free equilibrium, which is locally asymptotically stable if a certain threshold, known as the *effective reproduction number*, is less than unity. Further, the model undergoes a backward bifurcation, where the disease-free equilibrium coexists with a stable endemic equilibrium. One of the main novelties of this study is the numerical illustration of tri-stable equilibria, where the disease-free equilibrium coexists with two stable endemic equilibrium when the aforementioned threshold is less than unity, and a bi-stable setup, involving two stable endemic equilibria, when the effective reproduction number is greater than one. This, to our knowledge, is the first time such dynamical features have been observed in TB dynamics. Finally, it is shown that the backward bifurcation phenomenon in this model arises due to the exogenous re-infection property of tuberculosis.

1. **Introduction.** Tuberculosis (TB), an infectious disease caused by the bacterium *Mycobacterium tuberculosis*, affects at least two billion people (one-third of the world's population) and is the second greatest contributor of adult mortality amongst infectious diseases, causing approximately two million deaths a year worldwide [31, 33, 36]. The recent World Health Organization's (WHO) report on global TB control [36] shows that although the number of TB cases was stable or

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falling in 5 of 6 WHO regions in 2004, the number of cases in Africa continues to grow (where the TB epidemic is still driven by the spread of HIV). Overall, more than 80% of all TB patients live in 22 countries mostly in sub-Saharan Africa and Asia. In the United States, about 10 to 15 million people have latent TB.

TB is an airborne-transmitted disease. Tubercle bacilli, which reside in the lungs of infectious individuals, are the causative agent of its transmission. They spread in the air when infectious individuals sneeze, cough, speak or sing. A susceptible individual may become infected with TB if he or she inhales bacilli from the air. The particles containing *Mycobacterium tuberculosis* are so small that normal air currents not only keep them airborne but also transport them throughout rooms or buildings [35]. Individuals who regularly share space with those with active TB (the infectious stage of the disease) have a higher risk of becoming infected than those who do not. Bacilli become established in the alveoli of the lungs from where they spread throughout the body. Initially infected individuals typically undergo a long and varied period of latency before the onset of active disease.

The high burden of TB infections in regions within Asia, Africa, and some parts of Europe (notably the Russian Federation and other eastern European nations) necessitated a global effort, spear-headed by WHO, for the effective control of the TB epidemic worldwide. This resulted in a number of global initiatives such as the "Stop TB Partnership," "International Standards of Tuberculosis Care and the Patient's Charter" and "Global Plan to Stop TB." The key components of these initiatives are to achieve the Millennium Development Goal (of halting, and beginning to reverse the incidence of TB by 2015), providing access to quality TB diagnosis and treatment (based on the use of antibiotics) for all and, subsequently, saving millions of lives.

One of the major advances in TB control was the introduction of antibiotics. Its widespread use has dramatically reduced mortality. For instance, a 70% reduction in mortality was observed in the USA from 1945 to 1955 [3, 13, 23]. Nowadays, most forms of TB can be successfully treated. This, however, requires the use of multiple drugs and complex treatment regimens for a lengthy period of time, up to about nine months. The incomplete compliance to treatment and administration of improper treatment regimens (wrong treatment) have resulted in the emergence of a multi-drug resistant TB (MDR-TB) (see [8] and the references therein). The MDR-TB is transmitted from individual to individual in the same way the natural TB strain is transmitted, and cannot be treated using the currently available antibiotics. The tragedy of the death of a former First Lady of the United States (Mrs. Eleanor Roosevelt) was due to the MDR-TB [12, 26]. The emergence of MDR-TB has undoubtedly made the global effort of elimination of TB more difficult.

According to a 1999 report from the Open Society Institute of Harvard Medical School [19, 24], the highest percentage of tuberculosis infections that are multi-drug resistant was in Latvia (accounting for as high as 22.1%). Following the percentage for India (13.3%), Estonia ranked third with an MDR-TB percentage of 11.7%. Estonia's case is not surprising. An increase in tuberculosis morbidity, accompanied by an appearance of MDR-TB, has been documented in Estonia since the early 1990s. After a decline in incidence from 417 per 100,000 population in 1953

to 26 per 100,000 in 1992, the incidence showed a steady increase, which reached 52 per 100,000 in 1999. This two-fold increase in morbidity was followed by an increase in drug-resistant TB (particularly MDR-TB), resulting in a serious public health problem for Estonia. In 1994 and 1998, MDR-TB comprised 10% and 14% of the new pulmonary cases detected, placing Estonia among the countries with the highest MDR-TB rates in the world. The WHO's annual report clearly shows an increasing trend for the incidence of MDR-TB globally [36].

Mathematical models have been used to address the transmission dynamics of TB (see [7] for a comprehensive review). Exogenous reinfection was first incorporated in a model for the transmission dynamics of TB in [17]. An essential dynamical feature of the model in [17] is the phenomenon of backward bifurcation (see, for instance, [6, 7, 14, 21, 29, 30, 34]), where a stable disease-free equilibrium co-exists with a stable endemic equilibrium when the associated reproduction threshold is less than unity (albeit some of the modelling assumptions made in [17] were questioned in [22].) Two early models for the transmission dynamics of two TB strains were developed in [4, 8]; but these models did not include the exogenous reinfection property of TB disease. Further, some TB modelling studies have considered exogenous re-infection and drug-resistant or multi-drug resistant TB, using the mass action law for the incidence rate [5, 11, 15, 18, 27]. Although such formulations (using mass action law for the incidence rate) allows for mathematical tractability (models with standard incidence rate are more difficult to analyse qualitatively), data suggests that standard incidence formulation is more suited for modelling human diseases (see [1, 2, 20] and the references therein). It is, therefore, instructive to study the transmission dynamics of multiple TB strains, in the presence of exogenous reinfection, using standard incidence rate (Sharomi et al. [30] established the existence of backward bifurcation in a single strain TB model with exogenous re-infection and standard incidence rate). This is the main focus of this study.

The emergence of MDR-TB in some parts of Europe, the Americas, Asia, and Africa motivates this study. A mathematical model is designed and used, in this paper, to assess the epidemiological impact of the emergence and transmission of MDR-TB on the global effort to effectively control the burden of tuberculosis. The model incorporates key aspects of TB disease such as the exogenous reinfection and the endogenous reactivation of latent TB cases. The model is analyzed qualitatively and numerically to obtain important epidemiological thresholds, such as the basic reproduction numbers (which govern the persistence or elimination of disease in a given population), as well as determining some types of bifurcations the model can undergo. It is shown that the model can have two or three stable attractors via a backward bifurcation, and that the backward bifurcation is a consequence of the exogenous reinfection feature of TB.

2. **Model formulation.** In this study, we assume a homogenously mixing population and then model the rate of generation of new TB cases (both drug-sensitive and drug-resistant strains) using standard incidence rate. The model to be designed monitors the temporal dynamics of the sub-populations of susceptible individuals ($S(t)$), individuals exposed to wild type TB ($L_W(t)$), individuals exposed

to drug resistant TB ($L_R(t)$), individuals infectious with wild type ($I_W(t)$), and individuals infectious with resistant TB ($I_R(t)$) so that the total population is $N(t) = S(t) + L_W(t) + L_R(t) + I_W(t) + I_R(t)$. The model is given by

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{\beta(I_W + I_R)}{N}S - \mu S + (1-q_1)\tau_1 L_W + (1-q_2)\tau_2 I_W,\\
\frac{dL_W}{dt} &= \frac{\beta(1-\rho)I_W}{N}S - \frac{\beta_1 I_W}{N}L_W - \mu L_W - \kappa_1 L_W - \tau_1 L_W,\\
\frac{dL_R}{dt} &= \frac{\beta(1-\rho)I_R}{N}S + q_1\tau_1 L_W + q_2\tau_2 I_W - \frac{\beta_1 I_R}{N}L_R - \mu L_R - \kappa_2 L_R,\\
\frac{dI_W}{dt} &= \frac{\beta\rho I_W}{N}S + \frac{\beta_1 I_W}{N}L_W + \kappa_1 L_W - \mu I_W - d_1 I_W - \tau_2 I_W,\\
\frac{dI_R}{dt} &= \frac{\beta\rho I_R}{N}S + \frac{\beta_1 I_R}{N}L_R + \kappa_2 L_R - \mu I_R - d_2 I_R,
\end{aligned} \tag{1}$$

where Λ is the recruitment rate of individuals into the community by birth or immigration (assumed susceptible), β is the rate of TB transmission from infectious individuals to susceptible individuals, μ is the natural death rate, $0 \leq \rho \leq 1$ is the probability of primary progression from latent to active TB (proportion of fast progressors to active TB), β_1 represents the transmission rate associated with exogenous reinfection of both strains, κ_1 and κ_2 represent the endogenous reactivation rates of wild type and resistant type, respectively. Furthermore, d_i $(i = 1, 2)$ represent the death rates of infectious individuals with wild type and resistant type, respectively. Treatment is offered to individuals with the wild strain at the rates τ_1 and τ_2 for those in the latent and infectious stages, respectively. The parameter q_1 represents the proportion of latent-TB individuals who do not complete their treatment and develop drug-resistant TB; the remaining fraction, $1 - q_1$, denotes the proportion of successfully treated individuals with latent-TB. Similarly, q_2 represents the proportion of those infectious individuals who do not complete their treatment and develop multi-drug-resistant TB; and $1 - q_2$ denotes the remaining fraction of individuals with active TB who are successfully treated. Successfully treated individuals are moved to the susceptible class, where they can acquire further infection.

3. **Effective reproduction number.** The model has a disease-free equilibrium (DFE) given by

$$\mathcal{E}_0 := (S^*, L_W^*, I_W^*, L_R^*, I_R^*) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right). \tag{2}$$

The linear stability of $\mathcal{E}_0$ is obtained by using the next generation matrix [34] for the system (1). Using the notation in [34], the non-negative matrix F and the non-singular matrix V, for the new infection terms and the remaining transfer terms respectively, are given (at the disease-free equilibrium) by

$$F = \begin{pmatrix} 0 & \beta(1-\rho) & 0 & 0 \\ 0 & \beta\rho & 0 & 0 \\ 0 & 0 & 0 & \beta(1-\rho) \\ 0 & 0 & 0 & \beta\rho \end{pmatrix} = \begin{pmatrix} F_1 & 0 \\ 0 & F_2 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \mu+\kappa_1+\tau_1 & 0 & 0 & 0 \\ -\kappa_1 & \tau_2+\mu+d_1 & 0 & 0 \\ -q_1\tau_1 & -q_2\tau_2 & \mu+\kappa_2 & 0 \\ 0 & 0 & -\kappa_2 & \mu+d_2 \end{pmatrix} = \begin{pmatrix} V_1 & 0 \\ V_3 & V_2 \end{pmatrix},$$

where $F_1 = F_2 = \begin{pmatrix} 0 & \beta(1-\rho) \\ 0 & \beta\rho \end{pmatrix}$, $V_1 = \begin{pmatrix} \mu+\kappa_1+\tau_1 & 0 \\ -\kappa_1 & \tau_2+\mu+d_1 \end{pmatrix}$, $V_2 = \begin{pmatrix} \mu+\kappa_2 & 0 \\ -\kappa_2 & \mu+d_2 \end{pmatrix}$, and $V_3 = \begin{pmatrix} -q_1\tau_1 & -q_2\tau_2 \\ 0 & 0 \end{pmatrix}$.

The *effective reproduction number*, denoted by $\mathcal{R}_{eff}$, is then given by $\mathcal{R}_{eff} = \rho(FV^{-1})$ where ρ denotes the spectral radius (dominant eigenvalue).

It can then be shown that the positive eigenvalues of the matrix FV^{-1} are

$$\mathcal{R}_W = \rho(F_1V_1^{-1}) = \frac{\beta(1-\rho)\kappa_1}{(\mu+\kappa_1+\tau_1)(\mu+d_1+\tau_2)} + \frac{\beta\rho}{\mu+d_1+\tau_2}, \tag{3}$$

and

$$\mathcal{R}_L = \rho(F_2V_2^{-1}) = \frac{\beta(1-\rho)\kappa_2}{(\mu+\kappa_2)(\mu+d_2)} + \frac{\beta\rho}{\mu+d_2}, \tag{4}$$

so that $\mathcal{R}_{eff} = \rho(FV^{-1}) = \max\{\mathcal{R}_W, \mathcal{R}_L\}$. Thus, using Theorem 2 of [34], we have established the following result.

Lemma 1. *The disease-free equilibrium $\mathcal{E}_0$ of the system (1) is locally asymptotically stable if $\mathcal{R}_{eff} < 1$ and unstable if $\mathcal{R}_{eff} > 1$.*

The effective reproduction number ($\mathcal{R}_{eff}$) measures the average number of new infections generated by a typical infectious individual in a community where intervention strategies (treatment) are administered. In the absence of treatment ($\tau_1 = \tau_2 = 0$), expressions (3) and (4) reduce to

$$\mathcal{R}_{0W} = \frac{\beta(\rho\mu+\kappa_1)}{(\mu+d_1)(\mu+\kappa_1)}, \quad \mathcal{R}_{0L} = \frac{\beta(\mu\rho+\kappa_2)}{(\mu+d_2)(\mu+\kappa_2)},$$

so that $\mathcal{R}_0 = \max\{\mathcal{R}_{0W}, \mathcal{R}_{0L}\}$. The threshold quantity $\mathcal{R}_0$ is the *basic reproduction number of infection*, which represents the average number of new infections generated by a single infective individual in a completely susceptible population.

It should be mentioned that each term in $\mathcal{R}_{eff}$ has an epidemiological implication. Take, for instance, the terms in $\mathcal{R}_W$. The rate of infection is $\beta(1-\rho)$ and $\kappa_1/(\mu+\kappa_1+\tau_1)$ is the expected fraction progressing from L_W to I_W and $1/(\mu+d_1+\tau_2)$ is the expected time in I_W. A similar interpretation follows for $\mathcal{R}_L$.

The effective reproduction number ($\mathcal{R}_{eff}$) is then the larger of the two reproduction numbers ($\mathcal{R}_W$ and $\mathcal{R}_L$).

4. **Bifurcation analysis.** To explore the possibility of a backward bifurcation in the model (1), we introduce the following simplification. Let $\alpha_2 = \mu+\kappa_1+\tau_1$, $\alpha_3 = \mu+d_1+\tau_2$, $\alpha_4 = \mu+\kappa_2$ and $\alpha_5 = \mu+d_2$. It can be seen that $\mathcal{R}_W = \dfrac{\beta\rho}{\alpha_3}+\dfrac{\kappa_1\beta(1-\rho)}{\alpha_2\alpha_3}$ and $\mathcal{R}_L = \dfrac{\beta\rho}{\alpha_5} + \dfrac{\kappa_2\beta(1-\rho)}{\alpha_4\alpha_5}$. We then re-label the variables by $S = x_1$, $L_w = x_2$, $I_w = x_3$, $L_r = x_4$, and $I_r = x_5$, so that $N = x_1 + x_2 + x_3 + x_4 + x_5$. Further, by introducing the vector notation $X = (x_1, x_2, x_3, x_4, x_5)^T$, the model (1) can be written in the form $\frac{dX}{dt} = F(X)$, where $F = (f_1, f_2, f_3, f_4, f_5)^T$, as follows:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda - \frac{\beta(x_3+x_5)}{N}x_1 - \mu x_1 + (1-q_1)\tau_1 x_2 + (1-q_2)\tau_2 x_3,\\
\frac{dx_2}{dt} &= f_2 = \frac{\beta(1-\rho)x_3}{N}x_1 - \frac{\beta_1 x_3}{N}x_2 - \alpha_2 x_2,\\
\frac{dx_3}{dt} &= f_3 = \frac{\beta\rho x_3}{N-x_6}x_1 + \frac{\beta_1 x_3}{N}x_2 + \kappa_1 x_2 - \alpha_3 x_3,\\
\frac{dx_4}{dt} &= f_4 = \frac{\beta(1-\rho)x_5}{N}x_1 + q_1\tau_1 x_2 + q_2\tau_2 x_3 - \frac{\beta_1 x_5}{N}x_4 - \alpha_4 x_4,\\
\frac{dx_5}{dt} &= f_5 = \frac{\beta\rho x_5}{N}x_1 + \frac{\beta_1 x_5}{N}x_4 + \kappa_2 x_4 - \alpha_5 x_5.
\end{aligned} \tag{5}$$

The Jacobian of system (5) at the DFE is given by

$$J = \begin{pmatrix}
-\mu & (1-q_1)\tau_1 & (1-q_2)\tau_2 & -\beta & -\beta\\
0 & -\alpha_2 & \beta(1-\rho) & 0 & 0\\
0 & \kappa_1 & \beta\rho-\alpha_3 & 0 & 0\\
0 & q_1\tau_1 & q_2\tau_2 & -\alpha_4 & \beta(1-\rho)\\
0 & 0 & 0 & \kappa_2 & \beta\rho-\alpha_5
\end{pmatrix}. \tag{6}$$

The following theorem ([7, 14, 34]) will be used to determine whether or not the system (5) exhibits a backward bifurcation at $\mathcal{R}_{eff} = 1$.

Theorem 1. *Consider the following general system of ordinary differential equations with a parameter ϕ*

$$\frac{dx}{dt} = f(x,\phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \text{ and } f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}),$$

where 0 is an equilibrium point of the system (that is, $f(0,\phi) \equiv 0$ for all ϕ) and

1. *$A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ is the linearization matrix of the system around the equilibrium 0 with ϕ evaluated at 0;*
2. *zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;*
3. *matrix A has a right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.*

Let f_k be the kth component of f and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \tag{7}$$

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \tag{8}$$

Then the local dynamics of the system around the equilibrium point 0 is totally determined by the signs of a and b. Particularly, if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

4.1. **Case 1: $\mathcal{R}_W > \mathcal{R}_L$.** Consider, first of all, the case where $\mathcal{R}_W > \mathcal{R}_L$, so that $\mathcal{R}_{eff} = 1$ gives $1 = \mathcal{R}_W > \mathcal{R}_L$. Suppose, further, that β is chosen as the bifurcation parameter. Solving for β from $\mathcal{R}_{eff} = 1$ gives $\beta = \beta^* = \dfrac{\alpha_2\alpha_3}{\alpha_2\rho + \kappa_1(1-\rho)}$. For our convenience, we let J_β denote the value of J when $\beta = \beta^*$.

4.1.1. *Eigenvectors of J_β.* For the case $\mathcal{R}_{eff} = 1 = \mathcal{R}_W > \mathcal{R}_L$, it is easy to show that the Jacobian matrix J_β has a right eigenvector given by $w = (w_1, w_2, w_3, w_4, w_5)^T$, where

$$\begin{aligned}
w_2 &= \frac{\beta^*(1-\rho)}{\alpha_2} w_3, \quad w_3 > 0 \text{ is free,} \\
w_5 &= \frac{q_1\tau_1 w_2 + q_2\tau_2 w_3}{\alpha_4(\alpha_5 - \beta^*\rho) - \beta^*(1-\rho)\kappa_2}\kappa_2, \quad w_4 = \frac{\alpha_5 - \beta^*\rho}{\kappa_2} w_5, \\
w_1 &= \frac{(1-q_1)\tau_1 w_2 + (1-q_2)\tau_2 w_3 - \beta^* w_4 - \beta^* w_5}{\mu}.
\end{aligned}$$

Using the fact that $\mathcal{R}_L < 1$ in this case, it can then be shown that $\alpha_5 - \beta^*\rho > 0$ and $\alpha_4(\alpha_5 - \beta^*\rho) - \beta^*(1-\rho)\kappa_2 > 0$. Therefore, $w_i > 0$ for $i \geq 2$. It is not necessary to require $w_1 > 0$ (see Remark 1 in [7]). Furthermore, the Jacobian, J_β, has a left eigenvector given by $v = (0, \frac{\kappa_1}{\alpha_2} v_3, v_3, 0, 0)$ for any $v_3 > 0$.

4.1.2. *Computations of a and b.* For the system (5), the associated non-zero second partial derivatives of F are

$$\begin{aligned}
&\frac{\partial^2 f_2}{\partial x_2 \partial x_3} = -\frac{\beta^*(1-\rho)\mu}{\Lambda} - \frac{\beta_1 \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_3} = -\frac{2\beta^*(1-\rho)\mu}{\Lambda}, \\
&\frac{\partial^2 f_2}{\partial x_3 \partial x_4} = -\frac{\beta^*(1-\rho)\mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_5} = -\frac{\beta^*(1-\rho)\mu}{\Lambda}, \\
&\frac{\partial^2 f_3}{\partial x_3 \partial x_3} = -\frac{2\beta^*\rho\mu}{\Lambda}, \quad \frac{\partial^2 f_3}{\partial x_3 \partial x_4} = -\frac{\beta^*\rho\mu}{\Lambda}, \\
&\frac{\partial^2 f_3}{\partial x_3 \partial x_5} = -\frac{\beta^*\rho\mu}{\Lambda}, \quad \frac{\partial^2 f_3}{\partial x_2 \partial x_3} = -\frac{\beta^*\rho\mu}{\Lambda} + \frac{\beta_1 \mu}{\Lambda}.
\end{aligned}$$

It follows from (7) that

$$a = v_2 \sum_{i,j=1}^{n} w_i w_j \frac{\partial^2 f_2}{\partial x_i \partial x_j} + v_3 \sum_{i,j=1}^{n} w_i w_j \frac{\partial^2 f_3}{\partial x_i \partial x_j}.$$

To determine the sign of the coefficient a, the partial derivatives above are substituted into (7) so that (upon rearrangement)

$$a\left(\frac{1}{v_2}\right)\left(\frac{\Lambda}{\mu}\right)(2w_3) = -\beta^*\left(1+\frac{\mu+\tau_1}{\kappa_1}\rho\right)(w_2+w_3+w_4+w_5) + w_2\beta_1\left(\frac{\mu+\tau_1}{\kappa_1}\right),$$

from which it follows that $a > 0$ iff

$$w_2\beta_1\left(\frac{\mu+\tau_1}{\kappa_1}\right) > \beta^*\left(1+\frac{\mu+\tau_1}{\kappa_1}\rho\right)(w_2+w_3+w_4+w_5).$$

Using the expressions for w_i, the last inequality is simplified to

$$\beta_1 > \beta^*\left(\rho+\frac{\kappa_1}{\mu+\tau_1}\right)\left(1+\frac{\alpha_2}{\beta^*(1-\rho)}+\frac{(\alpha_5-\beta^*\rho+\kappa_2)\left(q_1\tau_1+q_2\tau_2\frac{\alpha_2}{\beta^*(1-\rho)}\right)}{\alpha_4(\alpha_5-\beta^*\rho)-\beta^*(1-\rho)\kappa_2}\right).$$

For the sign of b, it can be shown that the associated non-vanishing derivatives of F are

$$\frac{\partial f_2}{\partial\beta} = \frac{(1-\rho)x_1x_3}{N}, \quad \frac{\partial f_3}{\partial\beta} = \frac{\rho x_1x_3}{N}, \quad \frac{\partial^2 f_2}{\partial\beta\partial x_3} = 1-\rho, \quad \frac{\partial^2 f_3}{\partial\beta\partial x_3} = \rho,$$

and $b = v_2w_3\dfrac{\partial^2 f_2}{\partial\beta\partial x_3} + v_3w_3\dfrac{\partial^2 f_3}{\partial\beta\partial x_3} = v_2w_3(1-\rho+\dfrac{\alpha_2}{\kappa_1}\rho) = v_2w_3(1+\dfrac{\mu+\tau_1}{\kappa_1}\rho) > 0.$
Thus, we have established the following result.

Theorem 2. *If*

$$\beta_1 > \beta^*\left(\rho+\frac{\kappa_1}{\mu+\tau_1}\right)\left(1+\frac{\alpha_2}{\beta^*(1-\rho)}+\frac{(\alpha_5-\beta^*\rho+\kappa_2)\left(q_1\tau_1+q_2\tau_2\frac{\alpha_2}{\beta^*(1-\rho)}\right)}{\alpha_4(\alpha_5-\beta^*\rho)-\beta^*(1-\rho)\kappa_2}\right) \tag{9}$$

and

$$\frac{\rho}{\alpha_3}+\frac{\kappa_1(1-\rho)}{\alpha_2\alpha_3} > \frac{\rho}{\alpha_5}+\frac{\kappa_2(1-\rho)}{\alpha_4\alpha_5}, \tag{10}$$

then a backward bifurcation occurs at $\mathcal{R}_{eff} = 1$.

It is worth noting from the inequality (9) of the above theorem that the model cannot undergo a backward bifurcation if $\beta_1 = 0$. In other words, as in other models of TB dynamics [17], this study shows that exogenous reinfection is necessary for a backward bifurcation to occur. Figure 1 depicts the backward bifurcation phenomenon for this case using an arbitrary set of parameter values.

TABLE 1. Parameter values for illustrating tri-stable steady states when $\mathcal{R}_L < \mathcal{R}_W = \mathcal{R}_{eff} < 1$ ($\mathcal{R}_W = 3.7566\beta, \mathcal{R}_L = \frac{32}{9}\beta$)

d_1	d_2	Λ	β_1	μ	κ_1	κ_2	ρ	τ_1	τ_2	q_1	q_2
.01	.01	1	5	.14	.25	.1	.2	.03	.03	.04	.04

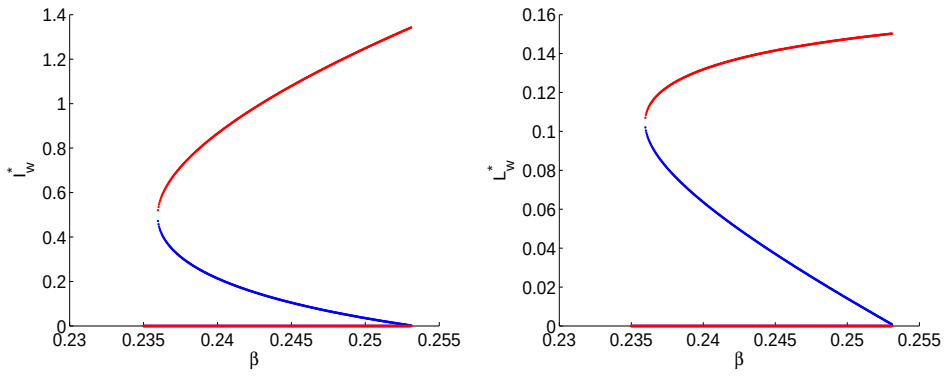

FIGURE 1. Illustration of a backward bifurcation for $\mathcal{R}_L < \mathcal{R}_W$. Plot of L_w at equilibrium (L_w^*) versus the parameter β (red indicates stable equilibria, and blue indicates unstable equilibria) using the parameter values $d_1 = d_2 = .01$, $\Lambda = 1$, $\mu = .14$, $\kappa_1 = .3$, $\kappa_2 = .0001$, $\rho = 0.2$, $\tau_1 = \tau_2 = .03$, $q_1 = q_2 = .04$, $\beta_1 = 5$ and $\beta \in [0.2350, 0.2531]$ (corresponding to $\mathcal{R}_{eff} \in [0.9278, 0.9992]$ and $\mathcal{R}_W = 3.9480\beta > \mathcal{R}_L = 1.3371\beta$).

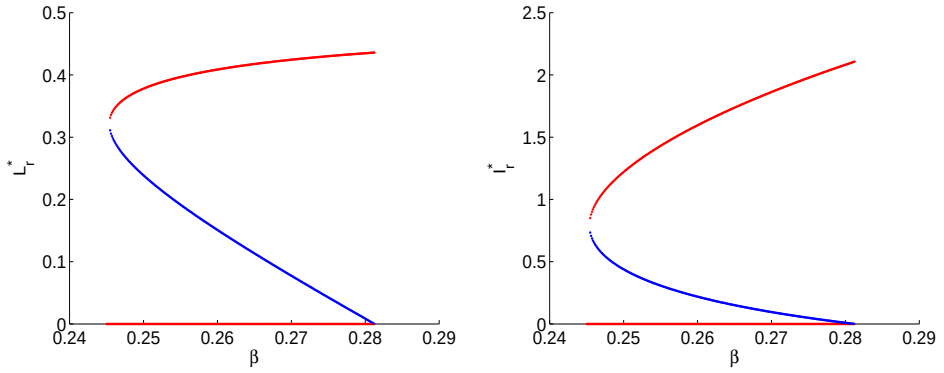

FIGURE 2. Illustration of a backward bifurcation for $\mathcal{R}_L > \mathcal{R}_W$. Plot of L_r at equilibrium (L_r^*) versus the parameter β (red indicates stable equilibria, and blue indicates unstable equilibria) using the parameter values $d_1 = d_2 = .01$, $\Lambda = 1$, $\mu = .14$, $\kappa_1 = .1$, $\kappa_2 = .1$, $\rho = 0.2$, $\tau_1 = \tau_2 = .03$, $q_1 = q_2 = .04$, $\beta_1 = 1.5$ and $\beta \in [0.2450, 0.2813]$ (corresponding to $\mathcal{R}_{eff} \in [0.8711, 1]$ and $\mathcal{R}_L = 3.5555\beta > \mathcal{R}_W = 2.7572\beta$).

4.2. **Case 2:** $1 = \mathcal{R}_L > \mathcal{R}_W$**.** Here, we explore the possibility for a backward bifurcation when $1 = \mathcal{R}_L > \mathcal{R}_W$, so that $\mathcal{R}_{eff} = 1$. We keep β as the bifurcation parameter. When $1 = \mathcal{R}_L > \mathcal{R}_W$, $\mathcal{R}_{eff} = 1$ gives $\beta^* = \dfrac{\alpha_4\alpha_5}{\alpha_4\rho + \kappa_2(1-\rho)}$.

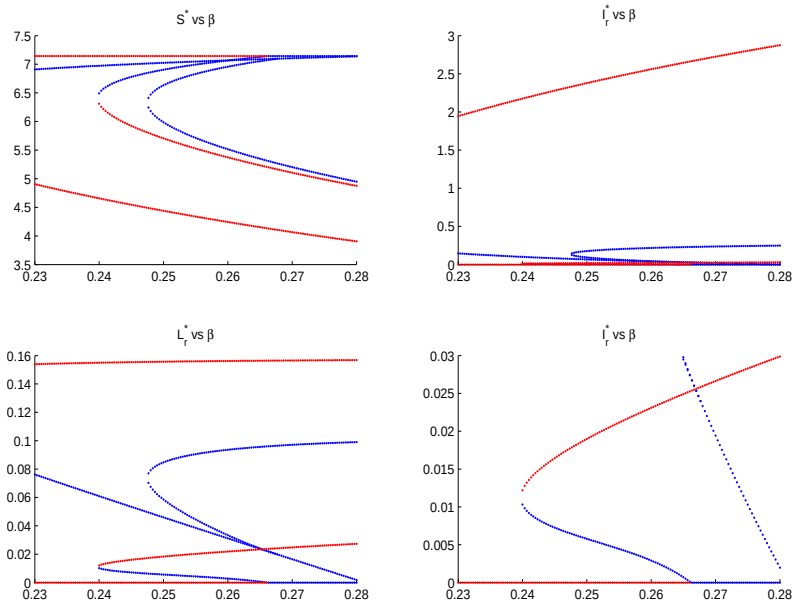

FIGURE 3. Plot of equilibrium values versus the parameter β. Red indicates stable equilibria, and blue indicates unstable equilibria. The lower right panel repeats the one above it but in a smaller scale to show two small stable steady states. Other parameter values can be found from Table 1 and $\mathcal{R}_{eff} = \mathcal{R}_W = 3.7566\beta > \mathcal{R}_L = 3.5555\beta$.

TABLE 2. Parameter values for illustrating bistable steady states when $\mathcal{R}_W < \mathcal{R}_L = \mathcal{R}_{eff} > 1$ ($\mathcal{R}_W = 2.7572\beta, \mathcal{R}_L = \frac{32}{9}\beta$)

d_1	d_2	Λ	β_1	μ	κ_1	κ_2	ρ	τ_1	τ_2	q_1	q_2
.01	.01	1	2	.14	.1	.1	.2	.03	.03	.04	.04

4.2.1. *Eigenvectors of J_β.* In this case, it can be shown that a right eigenvector for J_β is $w = (w_1, w_2, w_3, w_4, w_5)^T$, where

$$w_2 = w_3 = 0, \quad w_5 > 0 \text{ is free,}$$
$$w_4 = \frac{\alpha_5 - \beta^*\rho}{\kappa_2} w_5, \quad w_1 = \frac{w_5}{\mu}\left(1 - \frac{\beta^*(\alpha_5 - \beta^*\rho)}{\kappa_2}\right).$$

and a left eigenvector is $v = (v_1, v_2, v_3, v_4, v_5)$, where

$$v_1 = 0, \quad v_5 > 0 \text{ is free, } v_4 = \frac{\kappa_2}{\alpha_4} v_5,$$
$$v_2 = \frac{\kappa_2 v_5}{\alpha_2\alpha_3\alpha_4(1 - \mathcal{R}_0^w)}\left((\alpha_3 - \beta^*\rho)q_1\tau_1 + \kappa_2 q_2\tau_2\right),$$
$$v_3 = \frac{\kappa_2 v_5}{\alpha_2\alpha_3\alpha_4(1 - \mathcal{R}_0^w)}\left(\beta^*(1-\rho)q_1\tau_1 - \alpha_2 q_2\tau_2\right).$$

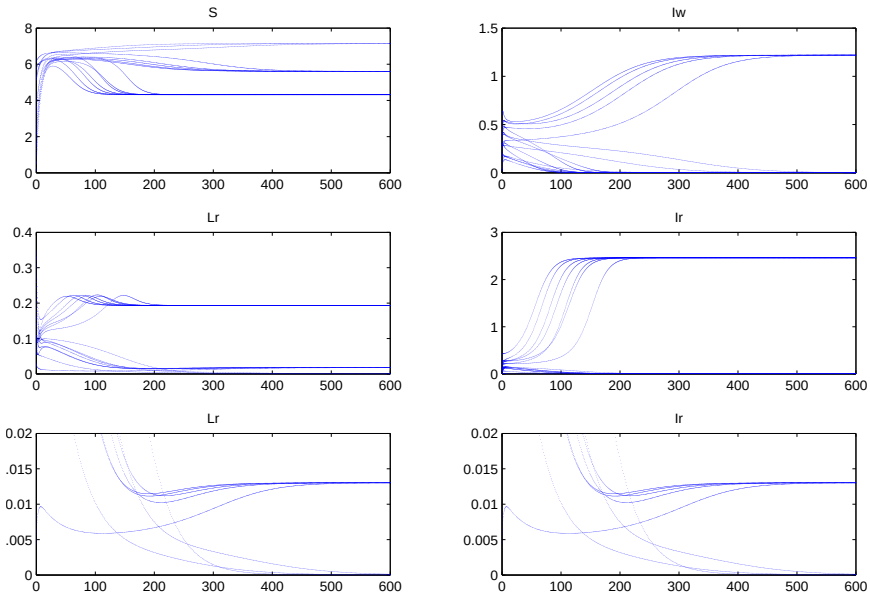

FIGURE 4. Illustration of tri-stable steady states. Plot of solutions generated by 30 randomly-chosen sets of initial values. The parameter β is set to equal to .26 and other parameters are as given in Table 1. The bottom two panels repeat the corresponding middle ones but in a smaller scale to show two small stable steady states.

4.2.2. *Computations of a and b.* Noting that $w_2 = w_3 = 0$ in this case, most of the second partial derivatives vanish at the DFE with $\beta = \beta^*$. The only non-zero second derivatives are

$$\frac{\partial^2 f_4}{\partial x_4 \partial x_5} = -\frac{\beta^*(1-\rho)\mu}{\Lambda} - \frac{\beta_1 \mu}{\Lambda}, \quad \frac{\partial^2 f_4}{\partial x_5^2} = -2\frac{\beta^*(1-\rho)\mu}{\Lambda}, \quad \frac{\partial^2 f_5}{\partial x_4 \partial x_5} = -\frac{\beta^*\rho\mu}{\Lambda} + \frac{\beta_1 \mu}{\Lambda}$$

and $\dfrac{\partial^2 f_5}{\partial x_5^2} = -2\dfrac{\beta^*\rho\mu}{\Lambda}$.

In this case, the coefficient a takes the form

$$a = 2v_4 \frac{\partial^2 f_4}{\partial x_4 \partial x_5} w_4 w_5 + v_4 \frac{\partial^2 f_4}{\partial x_5 \partial x_5} w_5 w_5 + 2v_5 \frac{\partial^2 f_5}{\partial x_4 \partial x_5} w_4 w_5 + v_5 \frac{\partial^2 f_5}{\partial x_5 \partial x_5} w_5 w_5$$

so that

$$a \frac{2}{v_4 w_4 w_5} \frac{\Lambda}{\mu} = \frac{\mu}{\kappa_2}\beta_1 - \beta^* \left((1-\rho)\left(1 + \frac{\kappa_2}{\alpha_5 - \beta^*\rho}\right) + \rho\left(\frac{\alpha_4}{\kappa_2} + \frac{\alpha_4}{\alpha_5 - \beta^*\rho}\right)\right).$$

Thus, if $\beta_1 > \beta^* \dfrac{(\kappa_2 + \mu\rho)(\alpha_5 - \beta^*\rho + \kappa_2)}{\mu(\alpha_5 - \beta^*\rho)}$, then $a > 0$. Similarly, the coefficient b is given by

$$b = v_4 \frac{\partial^2 f_4}{\partial x_5 \partial \beta} w_5 + v_5 \frac{\partial^2 f_5}{\partial x_5 \partial \beta} w_5 = v_4 w_5 (1-\rho) + v_5 w_5 \rho > 0.$$

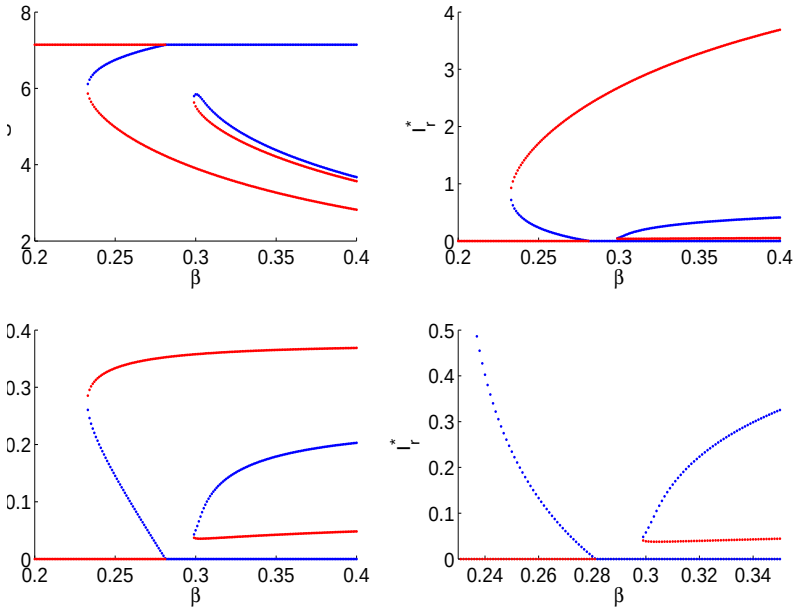

FIGURE 5. Bistable when $\mathcal{R}_{eff} > 1$. Plot of equilibrium values versus β. Red indicates stable equlibria and blue indicates unstable equilibria. Other parameter values can be found in Table 2. The lower right panel repeats the one above it but in a smaller scale to show two small stable steady states.

Combining this and the condition for $a > 0$ above, we have established the following result.

Theorem 3. *If*

$$\beta_1 > \beta^* \frac{(\kappa_2 + \mu\rho)(\alpha_5 - \beta^*\rho + \kappa_2)}{\mu(\alpha_5 - \beta^*\rho)} \tag{11}$$

and

$$\frac{\rho}{\alpha_3} + \frac{\kappa_1(1-\rho)}{\alpha_2\alpha_3} < \frac{\rho}{\alpha_5} + \frac{\kappa_2(1-\rho)}{\alpha_4\alpha_5}, \tag{12}$$

then a backward bifurcation occurs at $\mathcal{R}_{eff} = 1$.

Again, we can conclude that, for this case, the exogenous reinfection is necessary for the occurrence of the backward bifurcation because (11) cannot hold when $\beta_1 = 0$.

The backward bifurcation phenomenon for Case 2 is illustrated in Figure 2.

5. Tri-stable and bi-stable solutions: numerical illustration.

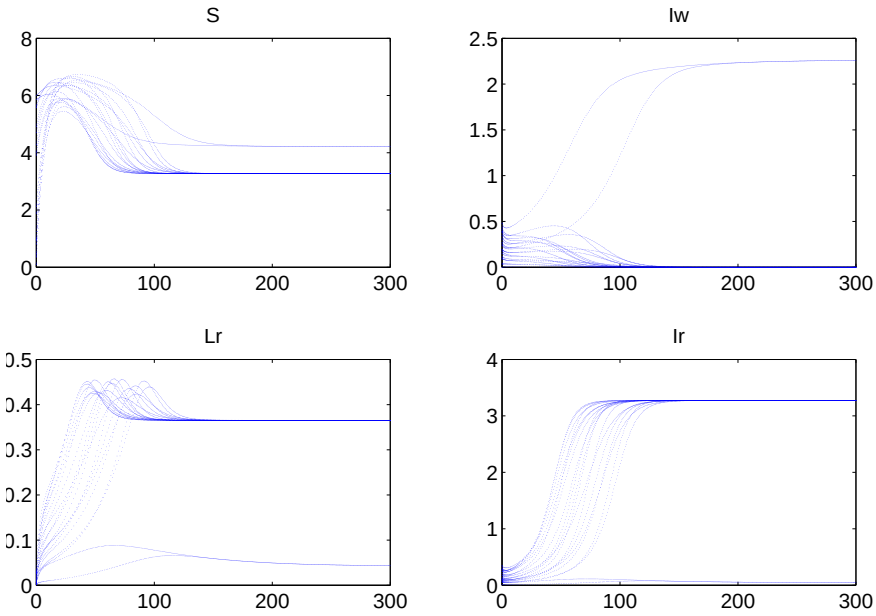

FIGURE 6. Plot of solutions generated by 20 randomly-chosen sets of initial values using $\beta = .35$ and and other parameters as given in Table 2.

5.1. **Tri-stable solutions.** Owing to the complexity of the model, its full dynamics analysis is not feasible at this stage. Hence, we resort to numerical simulations using the arbitrary set of parameter values in Table 1. It is worth stating that since the focus of this paper is to illustrate the various types of dynamics the model can undergo, parameter values are chosen with this purpose in mind (and, it may well be possible that some may not be within their realistic ranges). Simulating the model with this set of parameter values using $\beta \in [0.24, 0.28]$ (so that $\mathcal{R}_{eff}(\beta) \in [0.9016, 1.0519]$) gives seven feasible equilibria for $0.245 \leq \beta \leq 0.265$ ($0.9024 \leq \mathcal{R}_{eff}(\beta) \leq .9955$) (Table 3). Three of these equilibria are locally asymptotically stable (Figure 3). Figure 4 depicts these tri-stable solutions for randomly-chosen sets of initial values with $\beta = 0.26$ and other parameters as in Table 1. The epidemiological implication of this (tri-stability) phenomenon is that the classical requirement of the reproduction number ($\mathcal{R}_{eff}$) less than unity, although necessary, is no longer sufficient for disease elimination. The presence of the two stable endemic equilibria when $\mathcal{R}_{eff} < 1$ requires $\mathcal{R}_{eff}$ to be much less than one (outside the backward bifurcation range) to ensure disease elimination. To our knowledge, this is the first time such a feature (tri-stability for $\mathcal{R}_{eff} < 1$) is illustrated in TB dynamics, and possibly in the transmission dynamics of any other epidemic.

5.2. **Bi-stable solutions for $\mathcal{R}_{eff} > 1$.** Figure 3 shows that the multiple steady states exist even when $\mathcal{R}_{eff}$ crosses unity. We present these dynamics by using

another set of parameter values, given in Table 2. Using $\beta \in [0.3, 0.4]$, four feasible equilibria were obtained; two unstable and two stable (Figure 5). Simulating the model with the parameters in Table 2 with $\beta = 0.35$ and randomly-chosen sets of initial conditions shows the existence of two stable (bi-stable) endemic equilibria (Figure 6). Bi-stable equilibria for $\mathcal{R}_{eff} > 1$ have been observed in a model of dengue dynamics [28].

6. **Conclusions and discussion.** A deterministic model for the transmission dynamics of wild and multi-drug resistant strains of mycobacterium tuberculosis is designed and analyzed. The theoretical analysis and numerical simulations (using arbitrary set of parameters) of the model show the following.

(i) The classical epidemiological requirement of having the reproduction number ($\mathcal{R}_{eff}$) less than unity, while necessary, is not sufficient for disease elimination owing to the phenomenon of backward bifurcation, which occurs at $\mathcal{R}_{eff} = 1$ (for the cases $\mathcal{R}_L > \mathcal{R}_W$ and $\mathcal{R}_W > \mathcal{R}_L$). The disease can persist even when the reproduction threshold is less than unity. The disease will also persist when $\mathcal{R}_{eff} > 1$;
(ii) The model can exhibit bifurcations involving three stable equilibria (the disease-free equilibrium and two stable endemic equilibria) when the associated effective reproduction number is less than unity;
(iii) The model can have two stable endemic equilibria when the effective reproduction number exceeds unity;
(iv) To the authors' knowledge, this is the first time the phenomena of tri-stability (for $\mathcal{R}_{eff} < 1$) and bi-stable endemic equilibria for $\mathcal{R}_{eff} > 1$ are observed for a model of the transmission dynamics of TB; further, this may be the first time tri-stable equilibria (for $\mathcal{R}_{eff} < 1$) are illustrated for any human disease;
(v) The occurrence of the backward bifurcation phenomenon necessarily requires the exogenous reinfection.

Overall, the prospect of eliminating MDR-TB in a population seems plausible if the use of treatment can make the effective reproduction number less than unity and outside the backward bifurcation range. It is of interest to extend this work to determine (i) whether or not such dynamical behaviors (tri-stability for $\mathcal{R}_{eff} < 1$ and bi-stability for $\mathcal{R}_{eff} > 1$) can be obtained with more reasonable sets of parameter values, and (ii) determine what other types of bifurcations the model can undergo at $\mathcal{R}_{eff} = \mathcal{R}_W = \mathcal{R}_L = 1$.

It should be stated that in modeling the exogenous reinfection property of multiple strains of tuberculosis, the model (1) does not include the possibility of cross-infection between strains. This is because the paper is focussed on illustrating the rich qualitative dynamics of the MDR-TB using a relatively simple model. It is quite plausible to expect more complicated dynamics (rich bifurcations) if the model (1) is extended to incorporate cross-infection.

It is worth emphasizing that in performing the bifurcation analysis and numerical simulations of the model, the associated parameters of the model were not restricted. Tables 1 and 2 and Figures 1 and 2 actually shows that conditions (9) and (10) (or (11) and (12)) are achievable. However, because of the uncertainty of actual real

parameter values, one may not certainly predict that the bi-stable or tri-stable situations could happen in real-life. Like in the case of the single strain models of TB, the presence of backward bifurcation may be based on using an unrealistic set of parameter values [22]. Further, under the hypothesis that individuals with latent TB have partial immunity against exogenous reinfection [32], the associated backward bifurcation conditions (9) or (11) may not hold for realistic parameter values. Consider, for example, the model with only the resistant strain (for a simple case). Consider also the case when all new infected individuals enter the latent stage the resistant strain only for a simple case of $\rho = 0$ (that is, fast TB cases are ignored). Take inequality (11) for example. For the model with resistant strain only, given a contact between an infectious individual with resistant strain and an individual with latent TB with resistant strain, the reinfection probability is β_1; and given a contact between an infectious individual with resistant strain and a susceptible individual, the primary infection probability is $\beta\frac{k_2}{k_2+\mu}$. If individuals with latent TB have partial immunity against exogenous reinfection [32], then we have

$$\beta_1 < \beta\frac{\kappa_2}{\kappa_2+\mu}. \tag{13}$$

If $\rho = 0$, inequality (11) becomes

$$\beta_1 > \beta\frac{\kappa_2(\alpha_5+\kappa_2)}{\mu\alpha_5}. \tag{14}$$

Rearranging (14) as

$$\beta_1 > \beta\frac{\kappa_2(\alpha_5+\kappa_2)}{\mu\alpha_5} = \beta\frac{\kappa_2}{\kappa_2+\mu}\left(\frac{\kappa_2+\mu}{\mu}\right)\left(\frac{\alpha_5+\kappa_2}{\alpha_5}\right) > \beta\frac{\kappa_2}{\kappa_2+\mu}. \tag{15}$$

Thus, obviously, (15) contradicts (13). Therefore, we conclude that if we assume that individuals with latent TB infection have partial immunity against reinfection (that is, if (13) holds), then the presence of multi-stable steady states is impossible.

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TABLE 3. Tri-stable steady states when $\mathcal{R}_{eff} < 1$. For each β value, there are three locally asymptotically stable and four unstable equilibria. All other parameters are as given in Table 1.

β	$\mathcal{R}_{eff}$	S^*	L_w^*	I_w^*	L_r^*	I_r^*	Stability Status
0.2450	0.9204	7.1429	0	0	0	0	Stable
		4.5453	0	0	0.1553	2.2794	Stable
		7.0008	0	0	0.0534	0.0828	Unstable
		5.9235	0.1441	0.9722	0.0161	0.0164	Stable
		6.7796	0.0787	0.2517	0.0071	0.0073	Unstable
0.2500	0.9392	7.1429	0	0	0	0	Stable
		4.4394	0	0	0.1557	2.3779	Stable
		7.0251	0	0	0.0460	0.0670	Unstable
		5.7053	0.1512	1.1645	0.0183	0.0190	Stable
		5.9868	0.1296	0.7020	0.0847	0.1770	Unstable
		6.6325	0.0791	0.2539	0.0585	0.0940	Unstable
		6.9047	0.0575	0.1575	0.0056	0.0058	Unstable
0.2550	.9579	7.1429	0	0	0	0	Stable
		4.3392	0	0	0.1559	2.4712	Stable
		7.0475	0	0	0.0385	0.0530	Unstable
		5.5280	0.1558	1.3218	0.0202	0.0211	Stable
		5.7134	0.1414	0.9150	0.0905	0.2027	Unstable
		6.8312	0.0520	0.1373	0.0444	0.0635	Unstable
		6.9940	0.0388	0.0943	0.0043	0.0045	Unstable
0.2600	.9767	7.1429	0	0	0	0	Stable
		4.2440	0	0	0.1562	2.5598	Stable
		7.0682	0	0	0.0312	0.0406	Unstable
		5.3732	0.1591	1.4596	0.0219	0.0231	Stable
		5.5152	0.1480	1.0757	0.0936	0.2180	Unstable
		6.9575	0.0302	0.0697	0.0334	0.0440	Unstable
		7.0659	0.0212	0.0465	0.0028	0.0029	Unstable
0.2640	.9917	7.1429	0	0	0	0	Stable
		4.1712	0	0	0.1563	2.6276	Stable
		7.0837	0	0	0.0253	0.0316	Unstable
		5.2607	0.1612	1.5601	0.0231	0.0246	Stable
		5.3806	0.1517	1.1874	0.0953	0.2269	Unstable
		7.0358	0.0143	0.0303	0.0258	0.0323	Unstable
		7.1165	0.0075	0.0153	0.0012	0.0012	Unstable
0.2650	.9955	7.1429	0	0	0	0	Stable
		4.1535	0	0	0.1564	2.6441	Stable
		7.0875	0	0	0.0238	0.02948	Unstable
		5.2338	0.1617	1.5842	0.0234	0.0249	Stable
		5.3492	0.1525	1.2137	0.0956	0.2288	Unstable
		7.0531	0.0104	0.0218	0.0241	0.02978	Unstable
		7.1286	0.0041	0.0082	0.0007	0.00071	Unstable

TABLE 4. Bi-stable steady states when $\mathcal{R}_{eff} > 1$. For each β value, there are four steady states, two are locally asymptotically stable and the remaining two are unstable. All other parameters are as given in Table 2.

β	$\mathcal{R}_{eff}$	S^*	L_w^*	I_w^*	L_r^*	I_r^*	Stability Status
0.3100	1.1022	7.1429	0	0	0	0	Unstable
		3.7582	0	0	0.3598	2.8231	Stable
		5.0756	0.3852	1.4980	0.0362	0.0382	Stable
		5.4215	0.3466	1.0143	0.1139	0.1625	Unstable
0.3200	1.1378	7.1429	0	0	0	0	Unstable
		3.6212	0	0	0.3615	2.9494	Stable
		4.7967	0.3979	1.7435	0.0378	0.0396	Stable
		5.0669	0.3671	1.2389	0.1420	0.2235	Unstable
0.3300	1.1733	7.1429	0	0	0	0	Unstable
		3.4950	0	0	0.3630	3.0659	Stable
		4.5731	0.4060	1.9415	0.0394	0.0412	Stable
		4.7978	0.3798	1.4202	0.1587	0.2658	Unstable
0.3400	1.2089	7.1429	0	0	0	0	Unstable
		3.3780	0	0	0.3642	3.1740	Stable
		4.3816	0.4119	2.1117	0.0409	0.0428	Stable
		4.5751	0.3888	1.5761	0.1703	0.2986	Unstable
0.3500	1.2444	7.1429	0	0	0	0	Unstable
		3.2692	0	0	0.3652	3.2745	Stable
		4.2125	0.4164	2.2626	0.0424	0.0443	Stable
		4.3827	0.3956	1.7145	0.1789	0.3253	Unstable
0.3600	1.2800	7.1429	0	0	0	0	Unstable
		3.1677	0	0	0.3661	3.3684	Stable
		4.0603	0.4200	2.3986	0.0437	0.0457	Stable
		4.2124	0.4010	1.8398	0.1857	0.3477	Unstable
0.3700	1.3156	7.1429	0	0	0	0	Unstable
		3.0726	0	0	0.3669	3.4564	Stable
		3.9216	0.4229	2.5227	0.0449	0.0471	Stable
		4.0592	0.4054	1.9544	0.1912	0.3669	Unstable
0.3800	1.3511	7.1429	0	0	0	0	Unstable
		2.9834	0	0	0.3676	3.5390	Stable
		3.7942	0.4254	2.6370	0.0461	0.0484	Stable
		3.9197	0.4090	2.0603	0.1958	0.3835	Unstable
0.3900	1.3867	7.1429	0	0	0	0	Unstable
		2.8995	0	0	0.3682	3.6168	Stable
		3.6763	0.4274	2.7428	0.0472	0.0496	Stable
		3.7916	0.4121	2.1588	0.1996	0.3981	Unstable
0.4000	1.4222	7.1429	0	0	0	0	Unstable
		2.8203	0	0	0.3688	3.6902	Stable
		3.5666	0.4292	2.8414	0.0482	0.0508	Stable
		3.6732	0.4148	2.2507	0.2029	0.4111	Unstable