SECTION 3

MATHEMATICAL AND STATISTICAL MODELS IN LIFE AND CLIMATE SCIENCE APPLICATIONS

5

A MODEL FOR THE SPREAD OF TUBERCULOSIS WITH DRUG-SENSITIVE AND EMERGING MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT STRAINS

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5.1 INTRODUCTION

Tuberculosis (TB) is a global issue, being the second highest cause of infectious disease-induced mortality after HIV/AIDS [21]. It is a disease of poverty that strikes mostly vulnerable populations [24]. If treatment is available and treatment regimens are followed seriously, most individuals recover. The same is not true of individuals with active TB who are not treated; in this case, tuberculosis is fatal in up to 50% of cases [16]. This further accentuates inequalities when facing the disease.

Because of the immense impact it has had on society for hundreds of years, TB has been the object of a considerable volume of work. The complexity of TB transmission and the diversity of patient life histories it involves, in particular the potential lifelong incubation period, mean that TB has been the object of many mathematical modeling

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studies. It is beyond the scope of the present work to review these studies; see, for example, Refs. [1, 11, 25] and the references therein.

One aspect of TB epidemiology that has recently become very important is concernsdrug resistance. As often with the use of drugs, selective pressure on *Mycobacterium tuberculosis* (the causative agent of TB) due to the use of antituberculosis drugs has led to the emergence of antituberculosis drugs-resistant strains [26]. The situation further evolved in recent years, with the detection of mycobacteria in the 1990s, resistant to more than one of the drugs typically used to combat the infection. A *M. tuberculosis* strain is called multidrug resistant (MDR) if it is resistant at least to isoniazid and rifampicin [9]. The incidence of MDR-TB is not homogeneous. In a 2004 study [17], it was noted that the incidence of MDR-TB was generally low save for a few hot spots in China, Estonia, Latvia, and Russia. In 2010, the situation remained similar, with more countries reporting imported cases [31]. Further evolutions in drug resistance were noted in the 2000s, with mycobacteria resistant to second-line antituberculosis drugs [27]. The definition of extensively drug resistant (XDR) strains was then specified to consist of strains resistant to rifampicin and isoniazid, any fluoroquinolone, and one of the three injectable drugs, capreomycin, kanamycin, and amikacin [9]; see in particular the reviews in Refs. [18, 22]. Drug-resistant TB (M/XDR-TB for short) makes it a considerable challenge to control TB, since treatment is less efficacious for a patient infected with MDR-TB [18] and can even be unsuccessful for patients with XDR-TB.

Although several mathematical models have considered multiple strains of TB (see a review in Ref. [14]), few consider explicitly MDR- and XDR-TB and their emergence in a population as a consequence of treatment. The model in Ref. [4] uses a variation on previous models for TB and considers both nosocomial and community propagation. The models in Refs. [6, 13] are in the spirit of the model presented here: they consider multiple strains of TB and the evolution between these strains. They were, however, the object of little analytical work. The model in Ref. [7] considers a simple mechanism for the emergence of resistance: individuals with active drug-sensitive TB are treated at the rate ϕ; of those, a proportion r develops drug-resistant TB because of treatment failure (the remaining $1 - r$ are removed from the system).

In the present work, we formulate a model for the spread of drug-resistant (MDR and XDR) tuberculosis in a population. We assume that drug resistance can emerge as a consequence of treatment. The model is derived from earlier models given in Ref. [10]. Conditions are investigated which lead to the existence of a so-called backward bifurcation, where subthreshold endemic equilibria exist. The global stability of the disease-free equilibrium (DEF) is established when parameter values preclude the existence of a backward bifurcation.

5.1.1 Model formulation

The population of interest is divided into eight compartments depending on the epidemiological status of individuals. The number in each compartment at time t is given by the following variables.

1. $S(t)$ is the susceptible population, individuals who have never encountered TB.
2. $L_s(t)$ are the individuals infected with the drug-sensitive TB strain but who are in a latent stage, that is, who are neither showing symptoms nor infecting others.
3. $L_m(t)$ individuals are latently infected with MDR-TB.
4. $L_x(t)$ individuals are those who are latently infected with XDR-TB.

   Individuals in all three latent stages L_s, L_m, and L_x make up the so-called *latent tuberculosis infections* (LTBI). It is assumed that LTBI with a drug-sensitive strain are treated, while latent infections with multidrug-resistant or extensively resistant strains are not treated.
5. $I_s(t)$ are individuals infected with the drug-sensitive TB strain who are infectious to others (and most likely, showing symptoms as well).
6. $I_m(t)$ are those individuals who are infectious with the MDR-TB strain.
7. $I_x(t)$ individuals are infectious with the XDR-TB strain.

   Individuals in all three infectious stages I_s, I_m, and I_x make up the so-called *active TB* cases. All active TB cases are offered treatment.
8. $R(t)$ are those individuals for whom treatment was successful.

If this does not lead to ambiguities, we omit the time dependence of state variables. The total population N is given by

$$N = S + L_s + L_m + L_x + I_s + I_m + I_x + R.$$

We assume that flows between classes take the form indicated in the flow diagram in Figure 5.1. We formulate the model by reasoning as follows. Rather than stating all hypotheses at a time, we state them when they are needed. To simplify notation, we use the generic index $r \in \{s, m, x\}$ in state variables and parameters to refer to strains.

Susceptible population. The evolution of the number of susceptible individuals in the population is governed by the following equation:

$$S' = b - dS - \beta_s \frac{SI_s}{N} - \beta_m \frac{SI_m}{N} - \beta_x \frac{SI_x}{N}, \tag{5.1a}$$

where b is the rate at which new individuals join the susceptible population (recruitment) and β_r are coefficients indicating the rates at which new infections arise given contacts between susceptible and infectious individuals in the different infectious classes. Note that incidence is here assumed to be proportional.

When a susceptible individual becomes infected with TB, that person leaves the S compartment and transitions to the LTBI or active TB compartments corresponding to the strain harbored by the individual that infected them, that is, to compartment L_r or I_r, respectively. A proportion λ_r of new infections by strain r transitions to LTBI compartment L_r, the remaining $1 - \lambda_r$ moves directly to infectious compartment I_r through so-called *fast infections*. This first infection with TB is called a *primary infection*.

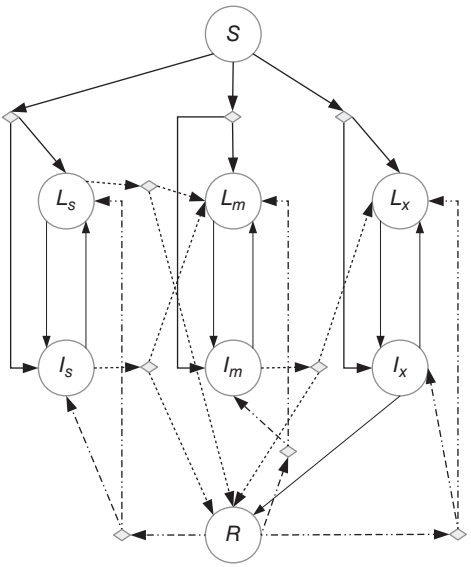

FIGURE 5.1 Simplified flow diagram of the model with drug-sensitive (L_s, I_s), MDR (L_m, I_m), and XDR (L_x, I_x) TB strains. Because of notational burden, birth and death are not shown and rates are not indicated. Diamonds indicate that the given flow is further divided between the indicated outcomes. Plain thick arrows indicate primary infections. Dash-dotted thick arrows indicate infections of previously successfully treated patients. Dotted arrows indicate treatment pathways that potentially lead to an increase in the resistance of the myobacteria in a given patient. Finally, thin plain arrows indicate other flows within the system, including exogenous reinfection.

Individuals latently infected with the drug-sensitive strain. The number $L_s(t)$ of drug-sensitive LTBI is increased by primary infections with the drug-sensitive strain I_s at the rate $\lambda_s \beta_s S I_s / N$ and by natural recovery of individuals in the drug-sensitive infectious compartment I_s at the per capita rate γ_s. Treatment, natural death, and natural progression to the infectious stage (due to a weakening immune system) also decrease the population in the L_s compartment.

Our model also incorporates *exogeneous reinfection*. Exogeneous reinfection is an important process in TB transmission; it happens when an individual already bearing the mycobacterium gets infected again [12, 30]. Here, we assume that two types of individuals can be subject to reinfection: latently infected and treated patients. Exogeneous reinfection of L_s individuals occurs because of contacts with individuals carrying the same strain I_s or a different strain I_m or I_x, following which the reinfected individual transitions from L_s to the corresponding infectious compartment, leading to a decrease of L_s at the rate $\alpha_{sr}\beta_r$. Similarly, a treated individual that comes in contact with an infectious individual can become reinfected. We assume that treatment reduces the probability of such a reinfection; we take the efficiency of treatment to be $1 - \sigma_s \in (0, 1)$. Thus, exogeneous reinfection of treated individuals increases L_s at the rate $\sigma_s \lambda_s \beta_s R I_s / N$.

$$L_s' = \lambda_s\beta_s(S+\sigma_s R)\frac{I_s}{N} + \gamma_s I_s - \{d+\varepsilon_s+t_{\ell s}\}L_s - (\alpha_{ss}\beta_s I_s + \alpha_{sm}\beta_m I_m + \alpha_{sx}\beta_x I_x)\frac{L_s}{N}. \tag{5.1b}$$

Individuals latently infected with the M/XDR-TB strains. As with the drug-sensitive case, the number L_m of individuals latently infected with MDR-TB increases when individuals in the S compartment are infected with MDR-TB. Reinfection of L_s individuals by an MDR-TB strain occurs at the rate $\alpha_{sm}\beta_m L_s I_m/N$, decreasing the population in L_s at that rate and increasing that in L_m at the rate $\lambda_m\alpha_{sm}\beta_m L_s I_m/N$, with the remaining $(1-\lambda_m)\alpha_{sm}\beta_m L_s I_m/N$ making a fast transition to I_m.

Individuals also become latently infected with the MDR-TB strain when they develop resistance to drugs. This occurs to individuals infected with the drug-sensitive strain at rates $(1-p_1)t_{\ell s}$ and $(1-p_2)t_{is}$ for latently infected and infectious individuals, respectively. The number of individuals in L_m decreases because of reinfection with I_x and exogenous reinfection at the rates $\alpha_{mx}\beta_x$ and $\alpha_{mm}\beta_m$, respectively. Note that we assume that L_m individuals, being already infected by an MDR-TB strain, cannot be exogenously reinfected by an individual carrying a drug sensitive strain, as this would "downgrade" the strain they are carrying.

We assume that while treatment is offered to drug-sensitive strain carriers both in the LTBI and active TB stages, it is only offered to MDR-TB and MDR-TB-infected individuals with active TB, not to those with LTBI. Contrary to other treatment rates, the rate t_{ix} of treatment of active XDR TB infections is the rate of successful treatment, not just the rate of treatment.

The rate of change of L_m is then given by

$$L_m' = \lambda_m\beta_m(S+\sigma_m R)\frac{I_m}{N} + \lambda_m\alpha_{sm}\beta_m\frac{L_s I_m}{N} + \gamma_m I_m + (1-p_1)t_{\ell s}L_s + (1-p_2)t_{is}I_s - (\alpha_{mm}\beta_m I_m + \alpha_{mx}\beta_x I_x)\frac{L_m}{N} - \{d+\varepsilon_m\}L_m \tag{5.1c}$$

and the rate of change of L_x is

$$L_x' = \lambda_x\beta_x(S+\sigma_x R)\frac{I_x}{N} + \lambda_x\beta_x(\alpha_{sx}L_s + \alpha_{mx}L_m)\frac{I_x}{N} + \gamma_x I_x + (1-p_3)t_{im}I_m - \alpha_{xx}\beta_x\frac{L_x I_x}{N} - \{d+\varepsilon_x\}L_x. \tag{5.1d}$$

Individuals infectious with drug-sensitive TB. To describe the rate of change of the number of individuals in infectious compartment I_s, we note that natural recovery, natural death, death due to TB, and failure of treatment that causes resistance to drugs in I_s are the only reasons to leave I_s at rates γ_s, d_s, δ_s, and t_s, respectively. All other flows, that is, exogenous reinfection in L_s, fast infection in S or R, and

individuals who become infectious in L_s, feed into I_s at rate $\alpha_{ss}\beta_s$, $(1-\lambda_s)\beta_s$ and ε_s respectively.

$$I_s' = (1-\lambda_s)\beta_s(S+\sigma_s R)\frac{I_s}{N} + \alpha_{ss}\beta_s\frac{L_s I_s}{N} + \varepsilon_s L_s - \{d+\delta_s+t_{is}+\gamma_s\}I_s. \tag{5.1e}$$

Individuals infectious with M/XDR-TB. Exogenous reinfection in L_m, fast infection or reinfection in S, R or L_s, and individuals who become infectious in L_m feed into I_m at the corresponding rates; see Table 5.1. Natural recovery, natural death, death

TABLE 5.1 Model parameters

Parameter	Interpretation
	Demography
b	Birth/recruitment rate
d	*per capita* natural death rate
	Disease dynamics
β_r	Transmission coefficient for strain r
λ_r	Proportion of newly infected individuals developing LTBI with strain r
$1-\lambda_r$	Proportion of newly infected individuals progressing to active TB with strain r due to fast infection
ε_r	*per capita* rate of endogenous reactivation of L_r
$\alpha_{r_1 r_2}$	Proportion of exogenous reinfection of L_{r_1} due to contact with I_{r_2}
γ_r	*per capita* rate of natural recovery to the latent stage L_r
δ_r	*per capita* rate of death due to TB of strain r
	Treatment related
$t_{\ell s}$	*per capita* rate of treatment for L_s
t_{ir}	*per capita* rate of treatment for I_r. Note that t_{ix} is the rate of successful treatment of I_x
$1-\sigma_r$	Efficiency of treatment in preventing infection with strain r
p_1	Probability of treatment success for L_s
$1-p_1$	Proportion of treated L_s moved to L_m due to incomplete treatment or lack of strict compliance in the use of drugs
p_2	Probability of treatment success for I_s
$1-p_2$	Proportion of treated I_s moved to L_m due to incomplete treatment or lack of strict compliance in the use of drugs
p_3	Probability of treatment success for I_m
$1-p_3$	Proportion of treated I_m moved to L_x due to incomplete treatment or lack of strict compliance in the use of drugs

The notation $r, r_1, r_2 \in \{s, m, x\}$ is used.

due to TB, and failure in treatment that causes resistance to drugs in I_m lead to the decrease in I_m.

$$\begin{aligned} I_m' = {} & (1-\lambda_m)\beta_m(S+\sigma_m R)\frac{I_m}{N} + \alpha_{mm}\beta_m\frac{L_m I_m}{N} + (1-\lambda_m)\beta_m\alpha_{sm}\frac{L_s I_m}{N} \\ & + \varepsilon_m L_m - \{d+\delta_m+t_{im}+\gamma_m\} I_m. \end{aligned} \tag{5.1f}$$

Similarly, the rate of change of I_x is given by

$$\begin{aligned} I_x' = {} & \alpha_{xx}\beta_x\frac{L_x I_x}{N} + (1-\lambda_x)\beta_x\left(\frac{SI_x}{N} + \sigma_x\frac{RI_x}{N} + \alpha_{sx}\frac{L_s I_x}{N} + \alpha_{mx}\frac{L_m I_x}{N}\right) \\ & + \varepsilon_x L_x - \{d+\delta_x+t_{ix}+\gamma_x\} I_x. \end{aligned} \tag{5.1g}$$

Treated individuals. Finally the rate of change of R depends positively on the proportion of individuals in L_s, I_s, I_m, and I_x who successfully got treated and negatively on reinfection with the sensitive, MDR and XDR strains, and natural death.

$$\begin{aligned} R' = {} & p_1 t_{\ell s} L_s + p_2 t_{is} I_s + p_3 t_{im} I_m + t_{ix} I_x \\ & - (\sigma_s\beta_s I_s + \sigma_m\beta_m I_m + \sigma_x\beta_x I_x)\frac{R}{N} - dR. \end{aligned} \tag{5.1h}$$

Table 5.1 lists all parameters and their interpretation. Model (5.1) is considered together with nonnegative initial conditions.

5.1.2 Mathematical Analysis

To simplify notation, define $\mathcal{X} := (S, L_s, L_m, L_x, I_s, I_m, I_x, R)^T$. Where needed, we write x_i, $i = 1, \ldots, 8$, the components of $\mathcal{X}$ (with the order the same as that in $\mathcal{X}$). We denote

$$\mathcal{I} := (L_s, L_m, L_x, I_s, I_m, I_x)^T$$

the infected variables.

5.1.2.1 Basic properties of solutions

Proposition 5.1 *Given nonnegative initial conditions, solutions to* (5.1) *exist and are unique for all $t \geq 0$. Furthermore, the positive orthant $\mathbb{R}^8_+$ is positively invariant under the flow of* (5.1).

Proof: Since the vector field in (5.1) consists of sums of constants and rational polynomial functions of the state variables and that we show later that the total population N is positive, it is differentiable. Hence solutions to (5.1) exist and are unique.

To prove the nonnegativity of solutions, first consider S; setting $S = 0$ in (5.1a), we get

$$S' = b > 0.$$

This implies that for nonnegative initial conditions, $S(0) \geq 0$, $S(t)$ is positive for all $t > 0$. For all other state variables, the vector field is nonnegative on the boundary of the orthant. It follows that solutions remain nonnegative for nonnegative initial conditions. As $S(t) > 0$ for all $t > 0$, we have $N(t) > 0$ for all $t > 0$.

From now on, we assume that $S(0) > 0$. Note that it is also easy to show that if initial conditions are positive, solutions remain positive for all t.

Proposition 5.2 *Given nonnegative initial conditions, solutions to* (5.1) *are bounded for all* $t \geq 0$*. Furthermore, the closed set*

$$\Omega := \left\{ \mathcal{X} \in \mathbb{R}^8_+ : S + L_s + L_m + L_x + I_s + I_m + I_x + R \leq \frac{b}{d} \right\} \tag{5.2}$$

attracts the flow of (5.1) *for any initial condition in* $\mathbb{R}^8_+$.

Proof: To establish boundedness, remark that the rate of change of the total population is given by

$$N' = b - dN - \delta_s I_s - \delta_m I_m - \delta_x I_x \leq b - dN. \tag{5.3}$$

This implies that $N(t)$ is bounded above by solutions of the differential equation $\Psi' = b - d\Psi$, that is, $N(t) \leq \max(\Psi(0), b/d)$, with, for all sufficiently large t, $N(t) \leq b/d$. Whence, since $\mathcal{X}$ is nonnegative, $\mathcal{X}$ is also bounded. Now consider Ω given by (5.2). We have that Ω is positively invariant. Moreover, for any solution outside Ω, that is, $N \geq b/d$, by (5.3), $N' < 0$. Thus Ω attracts all solutions of (5.1) with initial condition in $\mathbb{R}^8_+$.

5.1.2.2 Nature of the disease-free equilibrium The system is at an equilibrium if the time derivatives in (5.1) are zero. An equilibrium is a DFE if $\mathcal{I} = 0$. From (5.1h), this implies that $R = 0$. Thus, at a DFE, (5.1) is such that $S = N = b/d$; the DFE is unique and given by

$$\mathcal{E}_{\mathrm{DFE}} = \left(\frac{b}{d}, 0, 0, 0, 0, 0, 0, 0 \right). \tag{5.4}$$

5.1.2.3 Local asymptotic stability of the DFE The local asymptotic stability of the DFE is investigated using the next-generation method [15, 29]. The aim of the method is to produce a number, the *basic reproduction number*, usually denoted $\mathcal{R}_0$, that governs the local asymptotic stability of the DFE. To derive a formula for $\mathcal{R}_0$ using the next-generation method, we follow Ref. [29] and write the dynamics of the

infected classes $\mathcal{I}$ as $\mathcal{I}' = \mathcal{F} - \mathcal{V}$, where $\mathcal{F}$ has the new infections into the infected classes and here takes the form

$$\mathcal{F} := \begin{pmatrix} \lambda_s \beta_s (S + \sigma_s R) \dfrac{I_s}{N} \\ \lambda_m \beta_m (S + \sigma_m R) \dfrac{I_m}{N} \\ \lambda_x \beta_x (S + \sigma_x R) \dfrac{I_x}{N} \\ (1-\lambda_s) \beta_s (S + \sigma_s R) \dfrac{I_s}{N} \\ (1-\lambda_m) \beta_m (S + \sigma_m R) \dfrac{I_m}{N} \\ (1-\lambda_x) \beta_x (S + \sigma_x R) \dfrac{I_x}{N} \end{pmatrix}.$$

The vector $-\mathcal{V}$ (not shown here) has all other flows within and out of the infected classes $\mathcal{I}$. The matrix of new infections F and the matrix of transfers between compartments V are the Jacobian matrices obtained by taking the Fréchet derivatives of $\mathcal{F}$ and $\mathcal{V}$ with respect to the infected variables $\mathcal{I}$ and evaluating them at the DFE. They take the form

$$F = \begin{pmatrix} 0 & F_{12} \\ 0 & F_{22} \end{pmatrix}, \qquad V = \begin{pmatrix} V_{11} & V_{12} \\ V_{21} & V_{22} \end{pmatrix}, \tag{5.5}$$

where

$$F_{12} = \begin{pmatrix} \lambda_s \beta_s & 0 & 0 \\ 0 & \lambda_m \beta_m & 0 \\ 0 & 0 & \lambda_x \beta_x \end{pmatrix},$$

$$F_{22} = \begin{pmatrix} (1-\lambda_s)\beta_s & 0 & 0 \\ 0 & (1-\lambda_m)\beta_m & 0 \\ 0 & 0 & (1-\lambda_x)\beta_x \end{pmatrix},$$

$$V_{11} = \begin{pmatrix} d + \varepsilon_s + t_{\ell s} & 0 & 0 \\ -(1-p_1)t_{\ell s} & d + \varepsilon_m & 0 \\ 0 & 0 & d + \varepsilon_x \end{pmatrix},$$

$$V_{12} = \begin{pmatrix} -\gamma_s & 0 & 0 \\ -(1-p_2)t_{is} & -\gamma_m & 0 \\ 0 & -(1-p_3)t_{im} & -\gamma_x \end{pmatrix},$$

$$V_{21} = \begin{pmatrix} -\varepsilon_s & 0 & 0 \\ 0 & -\varepsilon_m & 0 \\ 0 & 0 & -\varepsilon_x \end{pmatrix},$$

$$V_{22} = \begin{pmatrix} d+\delta_s+t_{is}+\gamma_s & 0 & 0 \\ 0 & d+\delta_m+t_{im}+\gamma_m & 0 \\ 0 & 0 & d+\delta_x+t_{ix}+\gamma_x \end{pmatrix}.$$

Then the basic reproduction number $\mathcal{R}_0$ for system (5.1) is the spectral radius of the next-generation matrix FV^{-1} and is given by

$$\mathcal{R}_0 = \rho(FV^{-1}) = \max(\mathcal{R}_{0s}, \mathcal{R}_{0m}, \mathcal{R}_{0x}), \tag{5.6}$$

where

$$\mathcal{R}_{0s} = \frac{\beta_s(\varepsilon_s + (1-\lambda_s)(d+t_{\ell s}))}{(\varepsilon_s+d+t_{\ell s})(t_{is}+\delta_s+d)+\gamma_s(t_{\ell s}+d)}$$
$$\mathcal{R}_{0m} = \frac{\beta_m(\varepsilon_m + (1-\lambda_m)d)}{(\varepsilon_m+d)(t_{im}+\delta_m+d)+d\gamma_m}$$

and

$$\mathcal{R}_{0x} = \frac{\beta_x(\varepsilon_x + (1-\lambda_x)d)}{(\varepsilon_x+d)(t_{ix}+\delta_x+d)+d\gamma_x}$$

are the basic reproduction numbers for the drug-sensitive, MDR and XDR strains, respectively.

The method in Ref. [29] thus transforms the problem of local asymptotic stability of the DFE of (5.1) into that of the local asymptotic stability of $\mathcal{I} = 0$ in the reduced model $\mathcal{I}' = \mathcal{F} - \mathcal{V}$. The linearization of the latter problem at $\mathcal{I} = 0$, with the noninfected variables (S and R here) taking their values at the DFE, then leads to the linear system $\mathcal{I}' = (F-V)\mathcal{I}$. It is proved in Ref. [29] that for matrices F and V obtained with this method, there holds that

$$\max\{\Re(\lambda), \lambda \in \mathrm{Sp}(F-V)\} < 0 \Leftrightarrow \max\{|\lambda|, \lambda \in \mathrm{Sp}(FV^{-1})\} < 1,$$

where $\mathrm{Sp}(M)$ is the spectrum of matrix M. Thus the local asymptotic stability of the DFE is governed by the location inside the complex unit ball of the eigenvalues of FV^{-1}. This is summarized in the next result.

Lemma 5.1 *The DFE* (5.4) *of* (5.1) *is locally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$*, where* $\mathcal{R}_0$ *is defined by* (5.6)*.*

5.1.2.4 Existence of subthreshold endemic equilibria Lemma 5.1 establishes conditions under which the DFE is locally asymptotically stable and unstable. This

does not provide a full picture of the behavior near $\mathcal{R}_0 = 1$, though. Indeed, the direction and stability of the branch of equilibria that bifurcates at $\mathcal{R}_0 = 1$ are unknown without further analysis.

The classic situation is depicted in Figure 5.2, with a negative (and therefore biologically irrelevant) equilibrium entering the positive orthant at $\mathcal{R}_0 = 1$ and exchanging stability with the DFE through a transcritical bifurcation. The situation depicted in Figure 5.3 has come to be known as a "backward bifurcation" after the seminal work of Hadeler and van and Driessche [19]. In this case, as $\mathcal{R}_0$ increases from small values, the system first undergoes a saddle-node bifurcation when $\mathcal{R}_0 = \mathcal{R}_c$, where $\mathcal{R}_c < 1$ is some critical value. Then as $\mathcal{R}_0$ continues to increase, the lower unstable branch of equilibria

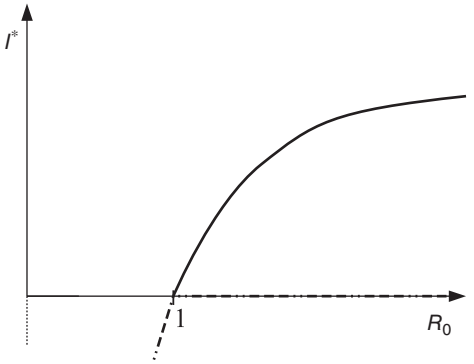

FIGURE 5.2 Forward bifurcation. The two most common bifurcation scenario at $\mathcal{R}_0 = 1$, where the value of $I^* = \|\mathcal{I}^*\|$ is plotted as a function of $\mathcal{R}_0$. Thick continuous lines indicate that the equilibrium is locally asymptotically stable and dashed lines indicate an unstable equilibrium.

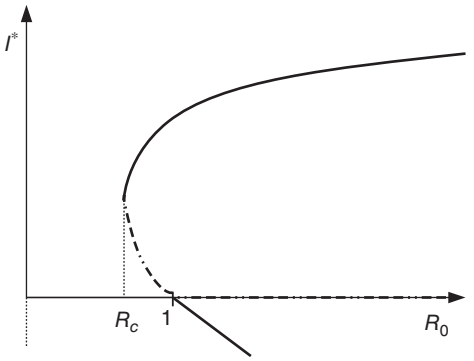

FIGURE 5.3 Backward bifurcation. The two most common bifurcation scenario at $\mathcal{R}_0 = 1$, where the value of $I^* = \|\mathcal{I}^*\|$ is plotted as a function of $\mathcal{R}_0$. Thick continuous lines indicate that the equilibrium is locally asymptotically stable and dashed lines indicate an unstable equilibrium.

undergoes a transcritical bifurcation and leaves the positive orthant. Castillo-Chavez and Song [11] and van den Driessche and Watmough [29] have provided methods to characterize the direction of the bifurcation that takes place at $\mathcal{R}_0 = 1$.

The model from which the current system is derived is studied in Ref. [10]. In that case, it is shown that under certain conditions, the system undergoes a backward bifurcation. As the present model is a refinement of this model, such behavior can be expected here.

In the absence of exogeneous reinfection by the XDR-TB strain ($\alpha_{xx} = 0$) or when the proportion $1 - \lambda_x$ of infected individuals making a fast transition to I_x is large, there is no backward bifurcation. Otherwise, conditions can be obtained under which such a bifurcation occurs. This is shown in the following theorem.

Theorem 5.1 *If* $\alpha_{xx} = 0$ *or*

$$\alpha_{xx} \leq 1 - \lambda_x, \tag{5.7}$$

then (5.1) *undergoes a forward bifurcation at* $\mathcal{R}_0 = 1$. *Otherwise, the model has a backward bifurcation at* $\mathcal{R}_0 = 1$ *if*

$$\begin{aligned}(\alpha_{xx} + \lambda_x - 1)(\lambda_x\beta_x + \gamma_x)d\left(1 - \frac{\varepsilon_x}{(\varepsilon_x + d)^2} + \frac{\varepsilon_x}{(\varepsilon_x + d)}\right)\\ > \lambda_x(1 - \sigma_x)\left(\frac{\varepsilon_x}{(\varepsilon_x + d)} + t_{ix}\right) + (1 - \lambda_x)d\end{aligned} \tag{5.8}$$

Proof: The proof uses the center manifold techniques of Refs. [11, 29]. Consider the model when $\mathcal{R}_0 = 1$, and using β_x as the bifurcation parameter, then

$$\beta_x = \frac{d^2 + (t_{ix} + \delta_x + \varepsilon_x + \gamma_x)\,d + \varepsilon_x\,(t_{ix} + \delta_x)}{(\varepsilon_x + (1 - \lambda_x)d)}. \tag{5.9}$$

Checking the eigenvalues of the Jacobian of model (5.1) evaluated at the DFE, $\mathcal{E}^*$, and β_x shows that 0 is a simple eigenvalue and all other eigenvalues have a negative real parts. Hence we can use Ref. [11, theorem 4.1]. The Jacobian of model (5.1) has a right eigenvector $\mathbf{w}$ (corresponding to the zero eigenvalue) given by

$$\mathbf{w} = \left[-\frac{k\beta_x}{d}, 0, 0, \frac{k(\lambda_x\beta_x + \gamma_x)}{d + \varepsilon_x}, 0, 0, k > 0, \frac{kt_{ix}}{d}\right]^T, \tag{5.10}$$

and a left eigenvector $\mathbf{v}$ given by

$$\mathbf{v} = \left[-\frac{k\beta_x}{d}, 0, 0, \frac{k(\lambda_x\beta_x + \gamma_x)}{d + \varepsilon_x}, 0, 0, k > 0, \frac{kt_{ix}}{d}\right]^T, \tag{5.11}$$

where k is a positive parameter.

To use Ref. [11, theorem 4.1], it is convenient to write the vector field in (5.1) as

$$\mathcal{X}' = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8)^T.$$

Using this notation, the parameter a used in Ref. [11, theorem 4.1] takes the form

$$\begin{aligned} a &:= \sum_{i,j,k=1}^{8} v_k \varepsilon_i \varepsilon_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(\mathcal{E}^*, \beta_x), \\ &= \frac{2v_7 k^2 \beta_x d}{b} \left[-(\lambda_x \beta_x + \gamma_x) \frac{\lambda_x + \alpha_{xx}}{(d+\varepsilon_x)^2} - \frac{\lambda_x}{(d+\varepsilon_x)} - (\lambda_x \beta_x + \gamma_x) \frac{1 - \lambda_x - \alpha_{xx}}{(d+\varepsilon_x)} \right. \\ &\qquad \left. - t_{ix} \lambda_x \beta_x \frac{1-\sigma_x}{d(d+\varepsilon_x)} - (1-\lambda_x) - t_{ix}(1-\lambda_x) \frac{1-\sigma_x}{d} \right], \end{aligned}$$

which is strictly negative if $\alpha_{xx} = 0$ or inequality (5.7) holds. The parameter b in Ref. [11, theorem 4.1] takes the form

$$b = \sum_{i,k=1}^{8} v_k \varepsilon_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_x}(\mathcal{E}^*, \beta_x) = v_7 k \frac{d(1-\lambda_x) + \varepsilon_x}{d + \varepsilon_x} > 0.$$

Therefore, by Ref. [11, theorem 4.1], (5.1) has a forward bifurcation at $\mathcal{R}_0 = 1$. If condition (5.7) is broken, then (5.1) undergoes a backward bifurcation if condition (5.8) holds.

Theorem 5.1 shows that (5.1) undergoes a backward bifurcation only if the XDR strain itself undergoes a backward bifurcation, regardless of the type of bifurcations of the other two strains. Indeed, as can be noticed in the model, there is directed movement of individuals between the strains, starting with drug-sensitive TB and terminating with the XDR strain. Because of that movement, whether or not the first two strains are in backward bifurcation, the whole model develops a backward bifurcation only if the terminal strain undergoes a backward bifurcation.

5.1.2.5 Global stability of the DFE when the bifurcation is "forward" We now investigate the global asymptotic stability of the DFE under conditions that preclude a backward bifurcation.

Theorem 5.2 *Assume that*

$$0 \le \alpha_{xx} \le 1 - \lambda_x, \tag{A_1}$$
$$0 \le \alpha_{mm} \le 1 - \lambda_m, \tag{A_2}$$
$$0 \le \alpha_{ss} \le 1 - \lambda_s. \tag{A_3}$$

Then the DFE (5.4) *of* (5.1) *is globally asymptotically stable when* $\mathcal{R}_0 < 1$.

Proof: We prove the global stability of the DFE by showing that if $\mathcal{R}_0 < 1$, then $\lim_{t\to\infty} \mathcal{X}(t) = \mathcal{E}_{\mathrm{DFE}}$. The attractivity of $\mathcal{E}_{\mathrm{DFE}}$, together with the local asymptotic stability of the DFE implied by the fact that $\mathcal{R}_0 < 1$, gives the result.

Since (5.1) is not of type K, a standard comparison theorem is not applicable. Let $\tau_n \to \infty$ be a sequence such that $L_s(\tau_n) \to L_s^\infty := \limsup_{t\to\infty} L_s(t)$. Thus, $L_s(\tau_n)' \to 0$ using lemma 2.1 in Ref. [28]. Then Equation 5.1b gives

$$\begin{aligned}0 &= \lambda_s\beta_s\frac{S(\tau_n)+\sigma_s R(\tau_n)}{N(\tau_n)}I_s(\tau_n) - \alpha_{ss}\beta_s\frac{L_s(\tau_n)}{N(\tau_n)}I_s(\tau_n) - \alpha_{sm}\beta_m\frac{I_m(\tau_n)}{N(\tau_n)}L_s(\tau_n)\\ &\quad - \alpha_{sx}\beta_x\frac{I_x(\tau_n)}{N(\tau_n)}L_s(\tau_n) - \{d+\varepsilon_s+t_{\ell s}\}L_s^\infty + \gamma_s I_s(\tau_n)\\ &\le \lambda_s\beta_s\frac{S(\tau_n)+\sigma_s R(\tau_n)}{N(\tau_n)}I_s(\tau_n) - \{d+\varepsilon_s+t_{\ell s}\}L_s^\infty + \gamma_s I_s(\tau_n).\end{aligned}$$

Since $\frac{S(t)+\sigma_s R(t)}{N(t)} < 1$ and $I_s(t) \le I_s^\infty$ at any t, it follows that

$$L_s^\infty \le \frac{\lambda_s\beta_s+\gamma_s}{d+\varepsilon_s+t_{\ell s}}I_s^\infty. \tag{5.12}$$

Now let $s_n \to \infty$ be a sequence such that $I_s(s_n) \to I_s^\infty$; this again implies that $I_s(s_n)' \to 0$ [28, lemma 2.1]. Then Equation 5.1e gives

$$\begin{aligned}0 &= \alpha_{ss}\beta_s\frac{L_s(\tau_n)}{N(\tau_n)}I_s^\infty + (1-\lambda_s)\beta_s\frac{S(\tau_n)+\sigma_s R(\tau_n)}{N(\tau_n)}I_s^\infty + \varepsilon_s L_s(s_n)\\ &\quad - \{d+\delta_s+t_{is}+\gamma_s\}I_s^\infty.\end{aligned}$$

Using Assumption (A_3),

$$\begin{aligned}0 &\le (1-\lambda_s)\beta_s\frac{S(\tau_n)+\sigma_s R(\tau_n)+L_s(\tau_n)}{N(\tau_n)}I_s^\infty + \varepsilon_s L_s(s_n)\\ &\quad - \{d+\delta_s+t_{is}+\gamma_s\}I_s^\infty.\end{aligned}$$

For simplicity, define $a_1 := (d+\delta_s+t_{is}+\gamma_s)$ and $a_2 := (d+\varepsilon_s+t_{\ell s})$. The fact that for all t, $\frac{S(t)+\sigma_s R(t)+L_s(t)}{N(t)} < 1$ and $L_s(t) \le L_s^\infty$, together with Equation 5.12, implies that

$$\begin{aligned}0 &\le \left[(1-\lambda_s)\beta_s - a_1 + \frac{\lambda_s\beta_s\varepsilon_s+\gamma_s\varepsilon_s}{a_2}\right]I_s^\infty\\ &\le \left[a_2(1-\lambda_s)\beta_s - a_1a_2 + \lambda_s\beta_s\varepsilon_s+\gamma_s\varepsilon_s\right]\frac{1}{a_2}I_s^\infty\\ &\le \frac{\mathcal{R}_{0s}-1}{a_2(a_1a_2-\varepsilon_s\gamma_s)}I_s^\infty.\end{aligned} \tag{5.13}$$

Since $\mathcal{R}_0 = \max\{\mathcal{R}_{0s},\mathcal{R}_{0m},\mathcal{R}_{0x}\}$, $\mathcal{R}_0 < 1$ implies that $\mathcal{R}_{0s} < 1$. Therefore, (5.13) implies that $I_s^\infty = 0$. Hence, $\lim_{t\to\infty} I_s(t) = 0$. Similarly, using Assumptions (A_1) and (A_2), we can prove the following inequalities involving I_m and I_x:

$$\begin{aligned} 0 &\leq \frac{\mathcal{R}_{0m}-1}{a_3(a_3a_4-\varepsilon_m\gamma_m)}I_m^\infty \\ 0 &\leq \frac{\mathcal{R}_{0x}-1}{a_5(a_5a_6-\varepsilon_x\gamma_x)}I_x^\infty, \end{aligned} \tag{5.14}$$

where

$$a_3 := d+\varepsilon_m, \qquad a_4 := d+t_{im}+\delta_m+\gamma_m, \tag{5.15a}$$

$$a_5 := d+\varepsilon_x, \qquad a_6 := d+t_{ix}+\delta_x+\gamma_x. \tag{5.15b}$$

The inequalities (5.14) imply that $I_m^\infty = I_x^\infty = 0$ when $\mathcal{R}_0 < 1$; therefore, $\lim_{t\to\infty} I_m(t) = \lim_{t\to\infty} I_x(t) = 0$. As a consequence, using (5.3), the total population $N(t)$ converges to b/d. To finish the proof, we study system (5.1) after N, I_s, I_m, and I_x have converged, thereby reducing (5.1) to the following system

$$S' = b-dS \tag{5.16a}$$

$$L_s' = -\{d+\varepsilon_s+t_{\ell s}\}L_s \tag{5.16b}$$

$$L_m' = -\{d+\varepsilon_m\}L_m + (1-p_1)t_{\ell s}L_s \tag{5.16c}$$

$$L_x' = -\{d+\varepsilon_x\}L_x \tag{5.16d}$$

$$R' = p_1t_{\ell s}L_s - dR. \tag{5.16e}$$

System (5.16) is linear and clearly limits to $(b/d,0,0,0,0)$. Finally, when $\mathcal{R}_0 < 1$, the DFE is locally asymptotically stable. As a consequence, the DFE is globally asymptotically stable when $\mathcal{R}_0 < 1$.

In the absence of exogenous reinfection, it was established in Ref. [10] that under certain conditions, the DFE of a drug-sensitive TB model and of a two-strains TB model was globally asymptotically stable. With exogenous reinfection, in Ref. [10] a drug-sensitive TB strain only model was considered; a backward bifurcation phenomenon because of exogenous reinfection was shown to exist. Theorem 5.2 shows that even with exogenous reinfection occurring, in the case of (5.1), there is a range of values of the exogenous reinfection parameter for which the model undergoes a forward bifurcation with all solutions going to the DFE. Outside that range, the system can undergo a backward bifurcation if (5.8) holds, as established in Theorem 5.1.

5.1.2.6 Strain-specific global stability in "forward" bifurcation cases Conditions in Theorem 5.2 mean that while the existence of a backward bifurcation in system (5.1) depends on the existence of a backward bifurcation in the terminal XDR strain (Theorem 5.1), the global asymptotic stability of the DFE of model (5.1) requires the DFE to be globally asymptotically stable for each strain. In view of this, we now investigate the global asymptotic stability of the DFE in specific strains. We show only the case of the XDR-TB strain, the drug-resistant and MDR-TB strains proceed similarly. The submodel for XDR-TB in the absence of the other strains is easily shown to live on the invariant hyperplane $\{\mathcal{X} \in \mathbb{R}_+^8; L_s = L_m = I_s = I_m = 0\}$

and takes the following form

$$S' = b - dS - \beta_x \frac{SI_x}{N}, \tag{5.17a}$$

$$L_x' = \lambda_x\beta_x(S+\sigma_x R)\frac{I_x}{N} - \alpha_{xx}\beta_x\frac{L_xI_x}{N} - \{d+\varepsilon_x\}L_x + \gamma_x I_x, \tag{5.17b}$$

$$I_x' = (1-\lambda_x)\beta_x(S+\sigma_x R)\frac{I_x}{N} + \alpha_{xx}\beta_x\frac{L_xI_x}{N} + \varepsilon_x L_x - \{d+\delta_x+t_{ix}+\gamma_x\}I_x, \tag{5.17c}$$

$$R' = t_{ix}I_x - \sigma_x\beta_x\frac{RI_x}{N} - dR. \tag{5.17d}$$

Theorem 5.3 *Under assumption* (A_1)*, the DFE* $(b/d,0,0,0)$ *of the XDR-TB submodel* (5.17) *is globally asymptotically stable when* $\mathcal{R}_{0x} < 1$.

Proof: Similarly to the proof of Theorem 5.2, we prove the global stability of the DFE by showing that, if $\mathcal{R}_0 < 1$, then

$$\lim_{t\to\infty} S(t) = \frac{b}{d}, \lim_{t\to\infty} I_x(t) = \lim_{t\to\infty} L_x(t) = \lim_{t\to\infty} R(t) = 0.$$

Here again, (5.17) is not of type K and a standard comparison theorem cannot be used. Let $\tau_n \to \infty$ be the sequence such that $L_x(\tau_n) \to L_x^\infty$. Then $L_x(\tau_n)' \to 0$ using lemma 2.1 in Ref. [28]. Then equation 5.17b gives

$$0 \le \lambda_x\beta_x I_x(\tau_n) - \{d+\varepsilon_x\}L_x^\infty + \gamma_x I_x(\tau_n),$$

that is,

$$L_x^\infty \le \frac{\lambda_x\beta_x+\gamma_x}{d+\varepsilon_x} I_x^\infty. \tag{5.18}$$

Now let $s_n \to \infty$ be a sequence such that $I_x(s_n) \to I_x^\infty$, implying that $I_x(s_n)' \to 0$ [28, lemma 2.1]. Then Equation 5.17c gives

$$0 < \alpha_{xx}\beta_x\frac{L_x(s_n)}{N(s_n)}I_x^\infty + (1-\lambda_x)\beta_x\frac{S(s_n)+\sigma_x R(s_n)}{N(s_n)}I_x^\infty + \varepsilon_x L_x(s_n) - \{d+\delta_x+t_{ix}+\gamma_x\}I_x^\infty.$$

Using Assumption (A_3), it follows from $\left(\frac{S(t)+\sigma_s R(t)+L_s(t)}{N(t)}\right) < 1$, $L_s(t) \le L_s^\infty$ and Equation 5.18 that

$$0 \le \frac{\mathcal{R}_{0x}-1}{a_5(a_5a_6-\varepsilon_s\gamma_s)}I_s^\infty, \tag{5.19}$$

where a_5 and a_6 are given by (5.15b). If $\mathcal{R}_{0x} < 1$, then $I_x^\infty = 0$. Hence $\lim_{t\to\infty} I_x(t) = 0$. Moreover, the total population N converges to b/d. We then study (5.17) after convergence of N and I_x, reducing it to the following model

$$\begin{aligned} S' &= b - dS \\ L_x' &= -\{d + \varepsilon_x\} L_x \\ R' &= -dR. \end{aligned} \tag{5.20}$$

The proof is finished by remarking that (5.20) is linear and limits to $(b/d, 0, 0)$.

The same method of proof can be used to show that the disease-free equilibria for the drug sensitive and MDR-TB subsystems are globally asymptotically stable under assumptions (A_3) and (A_2) when $\mathcal{R}_{0s} < 1$ and $\mathcal{R}_{0m} < 1$, respectively.

5.2 DISCUSSION

In this chapter, a model to study the emergence and propagation of drug-resistant TB, both MDR and XDR, is developed and analyzed. The most important results proved are as follows:

1. System (5.1) has a globally asymptotically stable DFE when $\mathcal{R}_0 < 1$ under suitable conditions (Theorem 5.2).
2. If condition (A_1) in Theorem 5.2 does not hold, system (5.1) can undergo a backward bifurcation. The existence of subthreshold endemic equilibria is governed by the bifurcation structure of the "top level" model, namely, that for XDR-TB.

Note that the model presented here has not been validated in the usual sense. Indeed, in epidemiology, validating models is a hard task. There are many factors that contribute to this difficulty. The data available to carry out the task is of varying quality. For instance, TB data of relatively good quality is mostly available for countries with strong healthcare systems, which see very few "homegrown" M/XDR-TB cases (most are imported), so estimating the rates of treatment-induced progression from drug-sensitive TB to MDR-TB and onward to XDR-TB is hard. Validation is further complicated because estimating parameters of the contact rate function is, at best, guesswork. Indeed, even for a disease such as TB that has been studied intensely for over a century, while the general mechanisms of transmission are well known, the specifics are to a large extent unknown. For instance, it is known that repeated and prolonged contacts favor the person-to-person transmission of TB. But a quantification of what constitutes this type of contacts is unknown. As a consequence, this model, like most that came before it and many that will follow, remains largely an intellectual exercise. However, this does not make it irrelevant. Mathematical epidemiology

has contributed a lot to the understanding of disease transmission processes and their control; see, for instance, the discussions in Refs. [3, 20]. The contribution of the present model is in laying out a potential scenario for the occurrence and spread of M/XDR-TB in a population and the elucidation of some of the basic properties of this model.

Our mathematical analysis revealed the potential presence of subthreshold endemic equilibria. Despite having been investigated since before the work of Hadeler and van der Driessche [19], little progress has been made in the understanding of the reasons for the presence of such subthreshold endemic equilibria in epidemic models (other than the mathematical reasons, which are straightforward and have to do with the degree of the multivariable polynomial, one must solve to find endemic equilibria). We know of no work that would satisfactorily address the pressing question of the determination of the direction of a bifurcation in real data; given the quality of epidemic data and the uncertainty on parameters, it is in general impossible to decide whether one is observing an endemic situation with $\mathcal{R}_0 < 1$ or $\mathcal{R}_0 > 1$. The situation is not as clear cut as it was which led to the publication [23], since backward bifurcations were identified in more realistic models in more feasible parameter regions, but, in our view, backward bifurcations are mostly anecdotal. Their presence should however be established, they forbid most type of global stability analysis; to the best of our knowledge, the work by Arino et al. [2] is the only work in which it was proved that when $\mathcal{R}_c < \mathcal{R}_0 < 1$, all solutions not starting on the stable manifold of the unstable subthreshold equilibrium are attracted to one of the locally stable equilibria.

This is a preliminary analysis. The model is quite complicated with a large number of nonlinearities, and considerations beyond the simple case of the disease-free equilibrium for all three strains are quite involved and will be considered in further work. Further work will also involve parametrizing the model and, if possible, comparing it with data.

Note. It has come to the authors' attention during revisions of this manuscript that the model studied here is very similar to a model of Bhunu [5], with some subtle differences. The model in Ref. [5] adds the possibility for individuals with active XDR-TB to be quarantined but does not consider treatment of individuals latently infected with the drug-sensitive strain nor natural recovery of individuals with active TB. Also, we assume that any type of reinfection, not only of treated individuals, can lead to slow or fast progression to infectiousness. These differences imply that while the classical analysis ($\mathcal{R}_0$ and nature of the bifurcation at $\mathcal{R}_0 = 1$) proceeds quite similarly, there are little differences in the results. Also, Bhunu [5] considered boundary equilibria, which are barely discussed here in Theorem 5.3. On the other hand, our results in the case of $\mathcal{R}_0 < 1$ are global when a backward bifurcation is ruled out. Thus, the analyses here and in Ref. [5] complement each other. The fact that two models starting with the same basic building blocks (the SLIR TB model [8], the SLIT model [10] and their progeny) and description of the epidemiology of M/XDR-TB are so similar is also encouraging and should probably be interpreted as a first step in the validation of the model of Bhunu (and ours).

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