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Research Article

Modelling the Role of Diagnosis, Treatment, and Health Education on Multidrug-Resistant Tuberculosis Dynamics

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Tuberculosis, an airborne disease affecting almost a third of the world's population remains one of the major public health burdens globally, and the resurgence of multidrug-resistant tuberculosis in some parts of sub-Saharan Africa calls for concern. To gain insight into its qualitative dynamics at the population level, mathematical modeling which require as inputs key demographic and epidemiological information can fill in gaps where field and lab data are not readily available. A deterministic model for the transmission dynamics of multi-drug resistant tuberculosis to assess the impact of diagnosis, treatment, and health education is formulated. The model assumes that exposed individuals develop active tuberculosis due to endogenous activation and exogenous re-infection. Treatment is offered to all infected individuals except those latently infected with multi-drug resistant tuberculosis. Qualitative analysis using the theory of dynamical systems shows that, in addition to the disease-free equilibrium, there exists a unique dominant locally asymptotically stable equilibrium corresponding to each strain. Numerical simulations suggest that, at the current level of control strategies (with Malawi as a case study), the drug-sensitive tuberculosis can be completely eliminated from the population, thereby reducing multi-drug resistant tuberculosis.

1. Introduction

Tuberculosis (TB) is a bacterial infection that is fatal if untreated timely [1]. It is an airborne disease caused by the *mycobacterium tuberculosis* and primarily affects the lungs (it can also affect the central nervous system, the lymphatic system, the brain, spine, and the kidneys). Approximately one-third of the world's population is affected [2]. In 1993, concerned with the rising cases of deaths and the new infection rate which were occurring at one per second, the World Health Organization (WHO) declared TB as a global emergency. This resurgence has been closely linked with environmental and social changes that compromised people's immune system [3]. Out of the 1.7 billion people estimated to be infected with TB, 1.3 billion lived in developing countries [2].

Active TB individuals can infect on average 10–15 other people per year if left untreated [12]. TB progression from inactive (latent) infection to active infection varies from one person to another. People suffering from AIDS have a greater risk of developing active TB with about 50% chance of developing active TB within 2 months and a 5 to 10% chance of developing active TB each year thereafter [1]. TB is treatable and curable if it is diagnosed and treated before it becomes severe [13]. WHO stresses that treatment for TB should not be undertaken unless the diagnosis is confirmed [14]. Currently five drugs are available: isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin [13]. A combination of these drugs is required to prevent the development of drug-resistance, requiring 6–9 months of continued treatment to be effective [15].

Multidrug-resistant tuberculosis (MDR-TB) is a form of TB that is resistant to at least the two main first-line anti-TB drugs, isoniazid and rifampicin [1]. There were an estimated 0.5 million cases of MDR-TB in 2007 worldwide [14]. Drug-resistant strains are far more difficult but not

impossible to treat, despite being too expensive [12]. The most important factor in preventing drug-resistant TB is to ensure full compliance with anti-TB treatment [1]. It is recommended that patients take the pills in the presence of a medical professional, an approach referred to as the directly observed therapy strategy (DOTS).

Given the scarcity of complete data, partial data obtained from the Malawi National TB Control Program [4] will be used for numerical simulations. Other parameter values are from the literature or simply assumed for the purpose of illustration. Malawi which endorsed the DOTS program since 1984 is a landlocked country in Central-Southern Africa, sharing common borders with Tanzania, Zambia, and Mozambique. The country has an estimated total population of 12.8 million and has a surface area of 118,480 km^2, a quarter of which is occupied by Lake Malawi [4]. In July 2007, there was a commitment to treat all known MDR-TB cases in Malawi. By October 2007, some patients were identified, retested and a recommendation was made to start them on second-line treatment under DOTS. However, the effectiveness of the whole exercise is yet to be established as field and lab data are not yet available. Even when available, the data may not reflect the true picture because some hospitals do not collect monthly sputum specimens for checking conversion to negativity [4]. According to the 2007 tuberculosis case finding statistics, 26,299 cases were reported countrywide [4]. This is 3% less than the cases that were reported in 2006. For 2007/2008, WHO estimates that TB case detection rate for Malawi was 46%. Since TB-infected people progress faster to active TB if they are HIV positive, all TB patients are tested for HIV. Out of the 26,299 TB patients registered for anti-TB treatment, 22,744 (86%) were tested for HIV and 15,491 (68%) were found to be HIV positive [4].

Two-strain TB models that considered different interventions have been developed [5, 16, 17]. There are fundamental differences with this study. In addition to treatment, individuals are further classified based on their knowledge about health information (education) on the importance of completing their TB dosage. Also, infectious drug-sensitive individuals are diagnosed for any development of drug-resistance. Since much remains unknown about the transmission of drug-resistant TB strains, another novelty of this study is the consideration of two cases whereby an individual can get infected with MDR-TB. The first case is when latently infected individuals with drug sensitive TB come into adequate contact with an infectious MDR-TB individual and transmission takes place. The second one is when a drug sensitive TB individual can be reinfected with MDR-TB, which might also be due to incomplete treatment. Furthermore, fast and slow progression to active TB as well as endogenous re-activation and exogenous re-infection for both drug sensitive and resistant strains is accounted for.

This paper is organized as follows. In Section 2, we formulate and analyze the model. The potential impact of the various control strategies is numerically investigated in Section 3. In Section 4, we discuss the relevance of the results and possible future work.

2. Model Construction and Analysis

We consider a two-strain TB model with three interventions. The model is defined as a set of nonlinear ordinary differential equations based upon specific biological and intervention assumptions about the transmission dynamics of MDR-TB. The host population is subdivided into various classes according to their disease status: susceptible individuals (S), individuals exposed to drug sensitive TB only (E_s), infectious individuals with drug sensitive TB (I_s), individuals exposed to MDR-TB (E_r), infectious individuals with MDR-TB (I_r), and individuals who have recovered from the disease (R). Susceptible individuals are recruited at a constant rate, Λ. These individuals will be infected with the tubercle bacillus if they come into effective contact with an active TB case at a rate λ_i, where the subscript $i = s, r$ denotes sensitive and MDR strains, respectively. The force of infection λ_i is defined as $\lambda_i = (c\beta_i I_i)/N$, where β_i is the probability that an individual is infected by one infectious individual, and c is the percapita contact rate.

Progression from respective exposed classes to infectious classes is due to exogenous re-infection and endogenous reactivation. Thus, due to exogenous re-infection, individuals in E_s and E_r classes progress to active TB classes, I_s and I_r, at the rate $\gamma_s\lambda_s$ and $\gamma_r\lambda_r$, respectively (γ_r is the re-infection rate of exposed individuals with MDR-TB γ_s is similarly defined). Latently infected individuals with drug sensitive and MDR-TB strains will progress to active classes I_s and I_r at the rates k_1 and k_2, respectively, due to endogenous reactivation. Individuals in I_s and I_r classes are treated at the rate ϕ_s and ϕ_r, respectively (realistically, it is possible that $\phi_s = \phi_r$). They then progress to recovered class, R, if successfully treated. However, some individuals in I_s class will recover naturally at a rate φ and move to R class. Also, exposed individuals in E_s and infectious individuals in I_s can acquire MDR-TB if they are in contact with infectious MDR-TB individuals at a rate λ_r and will then enter I_r class.

Infectious individuals in I_s class receive treatment at a rate ϕ_r, a proportion p of which responds positively to the treatment, whereas a proportion q partially responds to the treatment and as such they go back to E_s class. The remaining proportion $(1 - (p + q))$ will not complete the treatment which may result in the development of MDR-TB and these individuals move to E_r class. In addition, health education is offered to infectious individuals with drug sensitive strains only at a rate a. This is due to the nature of the disease, that is, one is diagnosed with drug sensitive TB (at a rate σ in this case) which later progress to MDR-TB if treatment compliance is disregarded [13]. Both ϕ_r and σ also describe a consequence of incomplete treatment, and as such, treatment rate ϕ_r is also a result of a diagnosis.

Susceptible individuals who become infected progress faster to active drug sensitive TB, that is, from S to I_s class at a rate ρ_s and to resistant strain class I_r, at a rate ρ_r; this might be due to other immunocompromised factors such as HIV and malaria that weakens individuals' immune systems leaving them very vulnerable to TB attack. Thus, $(1-\rho_s)$ and $(1-\rho_r)$ denote slow progression to active drug sensitive and MDR strains, respectively. We assume that recovery is non

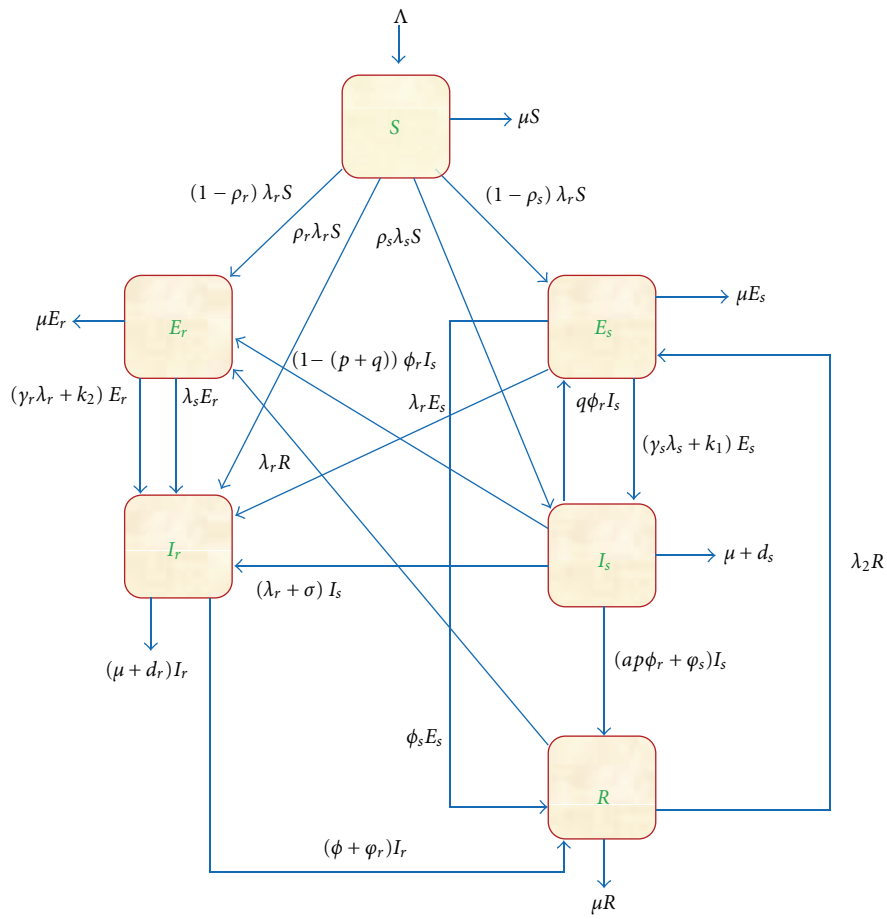

Figure 1: Compartmental diagram and flows for a two-strain tuberculosis transmission model with diagnosis, treatment, and health education.

permanent and as such recovered individuals are infected with drug sensitive TB at a rate λ_s, move to E_s class where they become infected with MDR-TB at a rate λ_r to move into the E_r class. Furthermore, infectious individuals in I_s class die due to the disease at a rate d_s and those in I_r class die at a rate d_r. All individuals in different subgroups die naturally at a rate μ. A schematic diagram of the model is depicted in Figure 1, and the associated parameters are described in Table 1.

With the pervious assumptions, terminology and interrelations between the parameters and variables as described by Figure 1, the dynamics of the MDR-TB model can be described by the following deterministic system of nonlinear ordinary differential equations:

$$\begin{aligned}
S'(t) &= \Lambda - (\lambda_s + \lambda_r)S - \mu S,\\
E_s'(t) &= ((1-\rho_s)S + R)\lambda_s - (\gamma_s\lambda_s + \lambda_r)E_s\\
&\quad - (\phi_s + k_1 + \mu)E_s + q\phi_r I_s,\\
I_s'(t) &= \rho_s\lambda_s S + (\gamma_s\lambda_s + k_1)E_s - \lambda_r I_s\\
&\quad - (d_s + ap\phi_r + \varphi_s + \sigma + \mu)I_s,\\
E_r'(t) &= ((1-\rho_r)S + R)\lambda_r + (1-(p+q))\phi_r I_s\\
&\quad - (\lambda_s + \gamma_r\lambda_r + k_2 + \mu)E_r,\\
I_r'(t) &= \rho_r\lambda_r S + (\lambda_s + \gamma_r\lambda_r + k_2)E_r + \lambda_r E_s\\
&\quad + \lambda_r I_s + \sigma I_s - (d_r + \phi + \varphi_r + \mu)I_r,\\
R'(t) &= (ap\phi_r + \varphi_s)I_s + \phi_s E_s + (\phi + \varphi_r)I_r\\
&\quad - (\lambda_s + \lambda_r)R - \mu R,
\end{aligned} \tag{1}$$

where the force of infection $\lambda_s = c\beta_s(I_s/N)$, $\lambda_r = c\beta_r(I_r/N)$. The initial conditions are $S(0) = S^0, E_s(0) = E_s^0, I_s(0) = I_s^0, E_r(0) = E_r^0, I_r(0) = I_r^0, R(0) = R^0$. The total population N (say) of system (1) is given by $N = S + E_s + I_s + E_r + I_r + R$. Model system (1) monitors a human population; therefore, all its associated parameters and state variables are assumed to be nonnegative for all $t > 0$. Thus, the feasible solutions of system (1) are well-defined in

$$\Gamma = \left\{(S(t), E_s(t), I_s(t), E_r(t), I_r(t), R(t)) \in \mathbb{R}_+^6 : N \le \frac{\Lambda}{\mu}\right\}, \tag{2}$$

which is positively invariant and attracting and it is sufficient to consider solutions in Γ [18]. Furthermore, existence, uniqueness, and continuation of results for system (1) hold in this region. Also, all solutions of model system (1) starting in Γ remain in Γ for all $t \geq 0$.

2.1. The Disease-Free Equilibrium and Its Stability. In the absence of infection (i.e., $E_s^* = E_r^* = I_s^* = I_r^* = 0$), model system (1) has a disease-free equilibrium E_0 given by

$$E_0 = (S^0, E_s^0, I_s^0, E_r^0, I_r^0, R^0) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0\right). \quad (3)$$

The potential intensity of transmission and the dynamics of a disease are often investigated in terms of the reproductive number, which represents the mean number of secondary cases a typical single infected individual will generate in a totally naive/susceptible population during his/her entire period of infectiousness. The linear stability of the disease-free equilibrium E_0 is investigated using the next generation matrix for system (1) [19]. To this effect, we compute the effective reproduction number R_e, the threshold for endemic persistence and epidemic spread of the disease. This is an important nondimensional quantity in epidemiology as it sets the threshold for predicting a disease outbreak and for evaluating its control strategies [20]. Therefore, whether a disease becomes persistent or dies out in a community depends on the size of this threshold parameter. Mathematically, R_e is the spectral radius of the next-generation matrix [19]. The next-generation matrix calculation (see details in Appendix A) shows that the effective reproduction number (or epidemic threshold) is

$$R_e = \max\{R_s, R_r\}, \quad (4)$$

where

$$R_s = \frac{c\beta_s(\mu\rho_s + \phi_s\rho_s + k_1)}{(\phi_s + k_1 + \mu)(d_s + a\phi_r + \varphi_s + \sigma + \mu) - q\phi_r k_1},$$
$$R_r = \frac{c\beta_r(k_2 + \mu\rho_r)}{(k_2 + \mu)(d_r + \phi + \varphi_r + \mu)}. \quad (5)$$

R_s and R_r are, respectively, the reproduction numbers for drug-sensitive TB strain only and MDR-TB strain only. R_e measures the average number of new infections generated by a typical infectious individual in a community where intervention strategies are in place. Thus, in the absence of diagnosis, treatment, and health education (i.e., $\phi_s = \phi_r = \phi = a = \sigma = 0$), (A.7) reduces to

$$R_{0s} = \frac{c\beta_s(k_1 + \mu\rho_s)}{(k_1 + \mu)(d_s + \varphi_s + \sigma + \mu)},$$
$$R_{0r} = \frac{c\beta_r(k_2 + \mu\rho_r)}{(k_2 + \mu)(d_r + \varphi_r + \sigma + \mu)}, \quad (6)$$

$R_0 = \max\{R_{0s}, R_{0r}\}$. The threshold quantity R_0 is the basic reproduction number of infection representing the average number of new infections generated by a single infective individual in a completely naive population. Each term in R_s and R_r has an epidemiological interpretation. For the drug-sensitive reproduction number,

(i) $k_1/(\phi_s + k_1 + \mu)$ is the expected fraction of individuals that will progress from E_s class to I_s;

(ii) $1/(d_s + a\phi_r + \varphi_s + \sigma + \mu)$ is the expected time infectious individuals with drug-sensitive TB spend in I_s class.

A similar interpretation caters for the drug-resistant reproduction number. Thus, from [19] the following result holds.

Theorem 1. *The disease-free equilibrium E_0 of model system (1) is locally asymptotically stable if $R_e < 1$, that is, $R_s < 1$ and $R_r < 1$, and unstable if $R_e > 1$, that is, $R_s > 1$ and $R_r > 1$.*

2.2. The Endemic Equilibria. For system (1), there are three possible endemic equilibria; two boundary equilibrium points which are E_1 (exists only when drug-sensitive strain is present) and E_2 (exists only when drug-resistant strain is present) and the equilibrium point E_3 which exists when both strains are present or coexist.

2.2.1. The Drug-Sensitive TB-Only Endemic Equilibrium. This is obtained by setting classes $E_r = I_r = 0$. This reduces system (1) to

$$\begin{aligned}
S'(t) &= \Lambda - \lambda_s S - \mu S,\\
E_s'(t) &= ((1-\rho_s)S + R)\lambda_s - \gamma_s\lambda_s E_s\\
&\quad - (\phi_s + k_1 + \mu)E_s + q\phi_r I_s,\\
I_s'(t) &= \rho_s\lambda_s S + (\gamma_s\lambda_s + k_1)E_s\\
&\quad - (d_s + a\phi_r + \varphi_s + \sigma + \mu)I_s,\\
R'(t) &= (ap\phi_r + \varphi_s)I_s + \phi_s E_s - (\lambda_s + \mu)R.
\end{aligned} \quad (7)$$

The drug-sensitive TB-only equilibrium in terms of the equilibrium value of the force of infection λ_s^* is given by $E_1 = (S^*, E_s^*, I_s^*, R^*, 0, 0)$, where

$$S^* = \frac{\Lambda}{\lambda_s^* + \mu}, \qquad E_s^* = \frac{a_1\lambda_s^{*2} + a_2\lambda_s^*}{(\lambda_s^* + \mu)(b_1\lambda_s^{*2} + b_2\lambda_s^* + b_3)},$$
$$I_s^* = \frac{\rho_s\lambda_s^*\Lambda(b_1\lambda_s^{*2} + b_2\lambda_s^* + b_3) + (\gamma_s\lambda_s^* + k_1)(a_1\lambda_s^{*2} + a_2\lambda_s^*)}{(d_s + a\phi_r + \varphi_s + \sigma + \mu)(\lambda_s^* + \mu)(b_1\lambda_s^{*2} + b_2\lambda_s^* + b_3)},$$
$$R^* = \frac{\lambda_s^*(a_3\lambda_s^{*2} + a_4\lambda_s^* + a_5)}{(d_s + a\phi_r + \varphi_s + \sigma + \mu)(\lambda_s^* + \mu)(b_1\lambda_s^{*2} + b_2\lambda_s^* + b_3)}, \quad (8)$$

with

$$\begin{aligned}
a_1 &= \Lambda[(1-\rho_s)(d_s + a\phi_r + \varphi_s + \sigma + \mu) \\
&\quad + q\phi_r\rho_s - (ap\phi_r + \varphi_s)\rho_s], \\
a_2 &= \mu\Lambda[(1-\rho_s)(d_s + a\phi_r + \varphi_s + \sigma + \mu) + q\phi_r\rho_s], \\
a_3 &= b_1(ap\phi_r + \varphi_s)\Lambda\rho_s + a_1 ap\phi_r\gamma_s, \\
a_4 &= b_2(ap\phi_r + \varphi_s)\Lambda\rho_s + a_1[(ap\phi_r + \varphi_s)k_1 \\
&\qquad + \phi_s(d_s + a\phi_r + \varphi_s + \sigma + \mu)] \\
&\quad + a_2(ap\phi_r + \varphi_s)\gamma_s, \\
a_5 &= b_3(ap\phi_r + \varphi_s)\Lambda\rho_s \\
&\quad + a_2[(ap\phi_r + \varphi_s)k_1 + \phi_s(d_s + a\phi_r + \varphi_s + \sigma + \mu)], \\
b_1 &= \gamma_s(d_s + a\phi_r + \varphi_s + \sigma + \mu) - \gamma_s q\phi_r - (ap\phi_r + \varphi_s)\gamma_s, \\
b_2 &= (d_s + a\phi_r + \varphi_s + \sigma + \mu)(\phi_s + k_1 + \mu) \\
&\quad + \mu\gamma_s(d_s + a\phi_r + \varphi_s + \sigma + \mu) - q\phi_r(\mu\gamma_s + k_1) \\
&\quad - ((ap\phi_r + \varphi_s)k_1 + \phi_s(d_s + a\phi_r + \varphi_s + \sigma + \mu)), \\
b_3 &= \mu(d_s + a\phi_r + \varphi_s + \sigma + \mu)(\phi_s + k_1 + \mu) - \mu q\phi_r k_1.
\end{aligned} \tag{9}$$

Substituting E_1 into the relationship $\lambda_s^* = (c\beta_s I_s^*)/N$, we obtain the drug-sensitive TB-only endemic equilibrium that satisfies the following polynomial:

$$\lambda_s^* h(\lambda_s^*) = \lambda_s^*(A_1\lambda_s^{*2} + B_1\lambda_s^* + C_1) = 0, \tag{10}$$

where

$$\begin{aligned}
A_1 &= a_1[\mu(d_s + a\phi_r + \varphi_s + \sigma + \mu) + k_1] \\
&\quad + a_2[(d_s + a\phi_r + \varphi_s + \sigma + \mu) + \gamma_s] \\
&\quad + b_2\Lambda[(d_s + a\phi_r + \varphi_s + \sigma + \mu) + \rho_s] \\
&\quad + b_1\mu\Lambda(d_s + a\phi_r + \varphi_s + \sigma + \mu) + a_4 \\
&\quad - c\beta_s(\rho_s\Lambda b_1 + a_1\gamma_s), \\
B_1 &= a_2[k_1 + \mu(d_s + a\phi_r + \varphi_s + \sigma + \mu)] \\
&\quad + b_3\Lambda(d_s + a\phi_r + \varphi_s + \sigma + \mu + \rho_s) \\
&\quad + b_2\Lambda\mu(d_s + a\phi_r + \varphi_s + \sigma + \mu) \\
&\quad + a_5 - c\beta_s(b_3\rho_s\Lambda + a_2k_1), \\
C_1 &= ((d_s + a\phi_r + \varphi_s + \sigma + \mu + \rho_s)(\phi_s + k_1 + \mu) - k_1 q\phi_r) \\
&\quad \times (1 - R_s).
\end{aligned} \tag{11}$$

The solution $\lambda_s^* = 0$ in (10) corresponds to the disease-free equilibrium and $h(\lambda_s^*) = 0$ corresponds to the existence of multiple equilibria. The coefficient A_1 is always positive and C_1 is positive if R_s is less than unity and negative if R_s is greater than unity. Thus, we have established the following result.

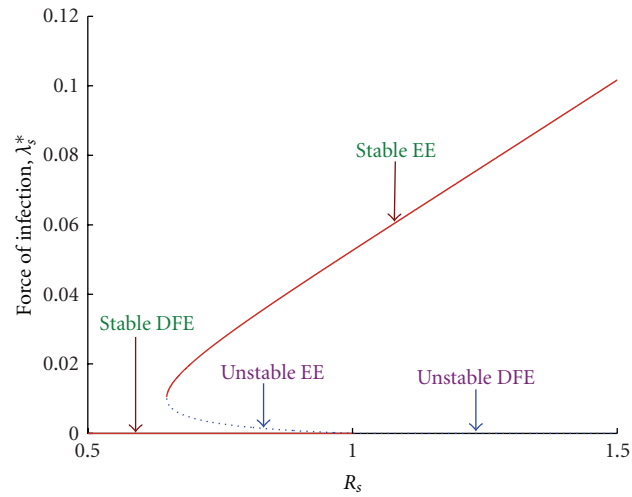

FIGURE 2: Backward bifurcation diagram of the force of infection λ_s^* for drug sensitive TB only model (7), against the drug sensitive TB reproduction number, R_s which occurs at $R_s = 1$ for an arbitrary set of parameter values. The acronyms EE and DFE represent endemic equilibrium and disease-free equilibrium, respectively.

Theorem 2. *The drug sensitive TB only model system* (7) *has*

(i) *precisely one unique endemic equilibrium if* $C_1 < 0 \Leftrightarrow R_s > 1$,

(ii) *precisely one unique endemic equilibrium if* $B_1 < 0$ *and* $C_1 = 0$ *or* $B_1^2 - 4A_1C_1 = 0$,

(iii) *precisely two endemic equilibria if* $C_1 > 0$, $B_1 < 0$ *and* $B_1^2 - 4A_1C_1 > 0$,

(iv) *otherwise, there is no endemic equilibrium.*

Condition (iii) implies that the dynamical phenomenon of backward bifurcation where a stable endemic equilibrium coexists with a stable disease-free equilibrium when the associated reproduction number is less than unity. This has important implications for disease control. In such a scenario, the classical requirement of the reproduction number being less than unity becomes only a necessary, but not a sufficient condition for disease elimination. To find the backward bifurcation point, we set the discriminant $B_1^2 - 4A_1C_1$ to zero. Making R_s the subject of formula, we obtain

$$R_s^c = 1 - \frac{B_1^2}{4A_1((d_s + a\phi_r + \varphi_s + \sigma + \mu)(\phi_s + k_1 + \mu) - k_1 q\phi_r)}. \tag{12}$$

Hence, it can be shown that backward bifurcation occurs for values of R_s in the range $R_s^c < R_s < 1$ (see Figure 2). Figure 2 shows a backward bifurcation diagram of model system (7). From the diagram, we observe that if $R_s < 1$ and then increases to unity, the number of TB cases increases abruptly thus, the disease-free equilibrium coexist with the endemic equilibrium implying that; the disease can invade

the population to a relatively high endemic level. In addition, decreasing R_s to its former level will not necessarily make the disease disappear. This is a consequence of the exogenous re-infection feature of TB. Hence, exogenous re-infection is capable of sustaining TB even when the reproduction number is below one [21]. However, backward bifurcation is illustrated by specific choice of parameters which may not be epidemiologically realistic.

2.2.2. The Drug-Resistant TB Only Endemic Equilibrium. This is obtained by setting $E_s = I_s = 0$ in model system (1). Hence, system (1) becomes

$$\begin{aligned} S'(t) &= \Lambda - \lambda_r S - \mu S, \\ E_r'(t) &= (1-\rho_r)\lambda_r S + \lambda_r R - (\gamma_r\lambda_r + k_2 + \mu)E_r, \\ I_r'(t) &= \rho_r\lambda_r S + (\gamma_r\lambda_r + k_2)E_r - (d_r + \phi + \varphi_r + \mu)I_r, \\ R'(t) &= (\phi + \varphi_r)I_r - (\lambda_r + \mu)R, \end{aligned} \tag{13}$$

so that $N = S + E_r + I_r + R$. Therefore, the drug-resistant TB only equilibrium in terms of the equilibrium value of the force of infection λ_r^* is given by $E_2 = (S^{**}, 0, 0, E_r^{**}, I_r^{**}, R^{**}) = (S^{**}, E_r^{**}, I_r^{**}, R^{**})$, where

$$\begin{aligned} S^{**} &= \frac{\Lambda}{\lambda_r^* + \mu}, \\ E_r^{**} &= \frac{(1-\rho_r)\Lambda\lambda_r^*(m_4\lambda_r^{*2} + m_5\lambda_r^* + m_6)}{(\gamma_r\lambda_r^* + k_2 + \mu)(\lambda_r^* + \mu)(m_4\lambda_r^{*2} + m_5\lambda_r^* + m_6)} \\ &\quad + \frac{\phi\lambda_r^*(m_1\lambda_r^{*2} + m_2\lambda_r^* + m_3)}{(\gamma_r\lambda_r^* + k_2 + \mu)(\lambda_r^* + \mu)(m_4\lambda_r^{*2} + m_5\lambda_r^* + m_6)}, \\ I_r^{**} &= \frac{m_1\lambda_r^{*2} + m_2\lambda_r^* + m_3}{m_4\lambda_r^{*2} + m_5\lambda_r^* + m_6}, \\ R^{**} &= \frac{\phi(m_1\lambda_r^{*2} + m_2\lambda_r^* + m_3)}{(\lambda_r^* + \mu)(m_4\lambda_r^{*2} + m_5\lambda_r^* + m_6)}, \end{aligned} \tag{14}$$

with

$$\begin{aligned} m_1 &= \Lambda\gamma_r, \qquad m_2 = \mu\Lambda\rho_r, \\ m_3 &= \Lambda k_2, \qquad m_4 = \gamma_r(d_r + \mu), \\ m_5 &= (d_r + \phi + \varphi_r + \mu)(k_2 + \mu + \mu\gamma_r) - (\phi + \varphi_r)k_2, \\ m_6 &= \mu(k_2 + \mu)(d_r + \phi + \varphi_r + \mu). \end{aligned} \tag{15}$$

Substituting E_2 into the equation $\lambda_r^* = (c\beta_r I_r^{**})/N$, we obtain an endemic equilibrium of the drug-resistant TB only that satisfies the polynomial given by

$$\lambda_r^* g(\lambda_r^*) = \lambda_r^*(A\lambda_r^{*2} + B\lambda_r^* + C) = 0, \tag{16}$$

where

$$\begin{aligned} A &= m_4\Lambda(k_2 + \mu) + m_5\Lambda(\gamma_r + (1-\rho_r)) \\ &\quad + m_1(k_2 + \mu)(\phi + \varphi_r + \mu) \\ &\quad + m_2((\phi + \varphi_r) + \gamma_r\mu + k_2 + \mu + (\phi + \varphi_r)\gamma_r) + m_3\gamma_r \\ &\quad - c\beta_r((\mu\gamma_r + k_2 + \mu)m_1 + m_2\gamma_r), \\ B &= m_5\Lambda(k_2 + \mu) + m_6\Lambda(\gamma_r + (1-\rho_r)) \\ &\quad + m_2(k_2 + \mu)(\phi + \varphi_r + \mu) \\ &\quad + m_3(\phi + \mu\gamma_r + k_2 + \mu + (\phi + \varphi_r)\gamma_r) \\ &\quad - c\beta_r(m_1(k_2 + \mu)\mu + m_2(\mu\gamma_r + k_2 + \mu) + m_3\gamma_r), \\ C &= \mu(k_2 + \mu)(d_r + \phi + \varphi_r + \mu)(\mu\gamma_r + k_2 + \mu)(1 - R_r). \end{aligned} \tag{17}$$

The root $\lambda_r^* = 0$ in (16) corresponds to E_0 (its stability has already been established) and $g(\lambda_r^*) = 0$ can be analyzed for the possibility of existence of multiple equilibria. It is worth mentioning here that the coefficient A is always positive and C is positive if $R_r < 1$ and negative if $R_r > 1$, hence, the following result.

Theorem 3. *The drug-resistant TB only model* (13) *has*

(1) *precisely one unique endemic equilibrium if* $C < 0 \iff R_r > 1$,

(2) *precisely one unique endemic equilibrium if* $B < 0$ *and* $C = 0$ *or* $B^2 - 4AC = 0$,

(3) *precisely two endemic equilibria if* $C > 0$, $B < 0$ *and* $B^2 - 4AC > 0$,

(4) *otherwise there is no endemic equilibrium.*

The backward bifurcation point can be found by setting the discriminant $B^2 - 4AC$ to zero. Then, making R_r the subject of the formula, we obtain

$$R_r^c = 1 - \frac{B^2}{4A\mu(k_2 + \mu)(d_r + \phi + \varphi_r + \mu)(\mu\gamma_r + k_2 + \mu)}, \tag{18}$$

from which it can be shown that backward bifurcation occurs for values of R_r in the range $R_r^c < R_r < 1$. The following result provides a condition for the existence of the drug-resistant TB only endemic equilibrium point, E_2.

Theorem 4. *The drug-resistant TB only endemic equilibrium* E_2 *exists whenever* $R_r > 1$.

Proof. Solving for λ_r^* in (16), we obtain

$$\lambda_r^* = \frac{-B + \sqrt{B^2 - 4AC}}{2A}. \tag{19}$$

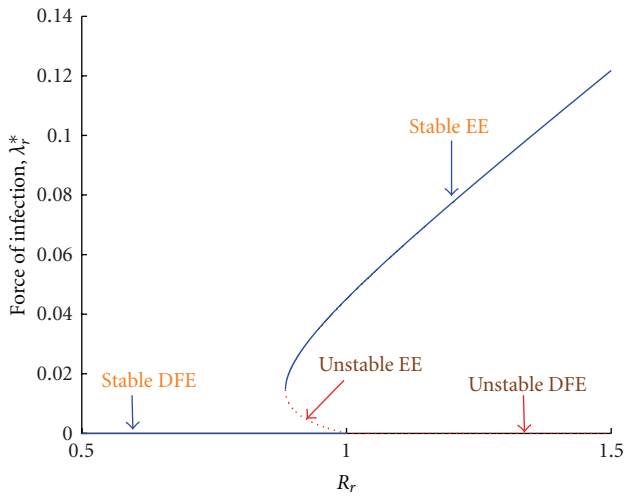

Figure 3: Backward bifurcation diagram of the drug-resistant TB only model (13), for an arbitrary set of parameter values. EE and DFE represent endemic equilibrium and disease-free equilibrium, respectively.

The disease is endemic when $\lambda_r^* > 0$ which occurs if and only if

$$B^2 - 4AC > B^2 \Longrightarrow 4A\mu(k_2+\mu)(d_r+\phi+\varphi_r+\mu) \times (\mu\gamma_r + k_2 + \mu)(1-R_r) < 0 \Longrightarrow R_r > 1. \tag{20}$$

Thus, E_2 exists whenever $R_r > 1$. □

Again, using the Center Manifold theory [22], the local asymptotic stability of E_2 is established (see details in Appendix B). The bifurcation diagram of the drug-resistant TB only model is illustrated in Figure 3.

Figure 3 illustrates a case of a backward bifurcation of system (13). As R_r approaches unity, it can be seen from the diagram that the number of secondary transmission suddenly increases giving rise to a situation whereby the disease-free equilibrium coexist with the endemic equilibrium.

2.2.3. Two-Strain Model: Drug Sensitive and MDR-TB Endemic Equilibrium. Having analyzed the dynamics of the two submodels, the full drug sensitive and MDR-TB model is now considered. Its endemic equilibrium occurs when both drug sensitive and MDR-TB strains circulate in the community and is denoted by

$$E_3 = (S^{***}, E_s^{***}, I_s^{***}, E_r^{***}, I_r^{***}, R^{***}). \tag{21}$$

It is a daunting task to explicitly express E_3 in terms of the equilibrium value of the force of infection λ_{rs}^*. As in the previous sections, it can be shown, using the next-generation method that the associated reproduction number for the full model is $R_e = \max\{R_s, R_r\}$, where R_s and R_r are, respectively, the reproduction numbers of drug sensitive and drug-resistant TB only sub-models given earlier. $R_e = \max\{R_s, R_r\}$ implies that the two TB strains (drug sensitive and drug-resistant) escalate each other and competitive exclusion may occur.

If $R_e = \max\{R_s, R_r\}$, then from Theorem 2, the drug sensitive TB only sub-model has a backward bifurcation for values of R_s such that $R_s^c < R_s < 1$ and Theorem 3 showed that the drug-resistant TB only sub-model exhibits backward bifurcation for values of R_r such that $R_r^c < R_r < 1$. Thus, the two-strain model will also exhibit the phenomenon of backward bifurcation whenever $R_e < 1$, and consequently, the coexistence endemic equilibrium E_3 is only locally asymptotically stable when $R_e > 1$.

The existence of multiple endemic equilibria is of general interest far beyond tuberculosis epidemiology. An important principle in theoretical biology is that of competitive exclusion which states that no two species can forever occupy the same ecological niche [23]. The system studied has the requisite in which the principle of competitive exclusion holds. Since model (1) exhibits the phenomenon of backward bifurcation thereby implying that the two-strain model is only locally stable, the strain with the large reproduction number colonizes the other strain [24].

3. Model Simulations

Graphical representations to support the analytical results are provided using a set of parameter values given in Table 1. These values were obtained from the National Tuberculosis Control Programme secretariat (Lilongwe, Malawi). Incomplete data from the National TB Control Program proves to be a major challenge, and the actual values of most of the parameters are not readily available [25]. Therefore, we use values from the literature for the purpose of illustration. We simulate both the drug sensitive and MDR-TB dynamics in the absence of any intervention and when the interventions are present as well as the effect of varying each intervention parameter on the number of infected populations. All figures are generated using the parameter values presented in Table 1 and the following initial conditions $S^0 = 14000, E_s^0 = 10500, I_s^0 = 7500, E_r^0 = 6500, I_r^0 = 5500, R = 4000$. The rationale behind this particular choice of the initial conditions is to capture the dynamics of the epidemic in a small community. TB is a disease with slow dynamics and consequently, TB epidemics must be studied and assessed over extremely long windows in time [26]. The time unit throughout is *per year*.

(a) Absence of any Intervention Strategy. In the absence of interventions, the susceptible population initially decreases and then increases to its carrying capacity as shown by Figure 4(a). On the other hand, the populations of latent drug sensitive TB, infectious drug sensitive TB, latent drug-resistant TB, and infectious drug-resistant TB decrease to an endemic level with increasing time as shown by Figures 4(b), 4(c), 4(d), and 4(e), respectively. This indicates that as long as there are no interventions to control the spread of the disease, the disease will not clear from the population since the basic

Table 1: Model Parameter Values.

Description	Symbol	Value	Source
Recruitment rate	Λ	$\mu * 10^5$	Assumed
Natural mortality rate	μ	0.02	[4]
Contact rate	c	2	[5]
DS TB induced death rate	d_s	0.3	[4]
MDR-TB induced death rate	d_r	0.5	[4]
Probability of being infected with drug sensitive TB	β_s	0.4	[6]
Probability of being infected with MDR-TB	β_r	0.5	[5]
Progression rate to active sensitive TB	k_1	0.03	[7]
Progression rate to active MDR-TB	k_2	0.05	[7]
Fast progression rate to active drug sensitive TB	ρ_s	0.2	Assumed
Fast progression rate to active MDR-TB	ρ_r	0.1	[8]
Re-infection rate of exposed individuals with sensitive TB	γ_s	0.4	[9]
Re-infection rate of exposed individuals with MDR-TB	γ_r	0.02	[9]
Natural immunity rate of infectious individuals with sensitive TB	φ_s	0.15	[10]
Natural immunity rate of infectious individuals with MDR-TB	φ_r	0.2	[10]
Treatment rate of latently infected individuals with sensitive TB	ϕ_s	0.2	[4]
Treatment rate of infectious individuals with sensitive TB	ϕ_r	0.3	[4]
Treatment rate of infectious individuals with MDR-TB	ϕ	0.09	[4]
Education rate of infectious individuals with sensitive TB	a	0.6	[4]
Rate of diagnosis	σ	0.3	[11]
Rate of recovery from active TB	p	0.8	[5]
Regression rate to latency after treatment	q	0.2	Assumed

reproduction number $R_0 = 1.4286 > 1$. This result supports the theorem on local stability of endemic equilibrium.

(b) With Control Strategies (Presence of Interventions). When interventions are introduced, improved trends of the populations are observed. For instance, in Figure 5(a), the susceptible population increases compared to the case when no interventions are available. Further improved trends can also be seen in Figures 5(b)–5(f). Figures 5(b) and 5(c) indicate that individuals infected with drug sensitive TB decrease and eventually diminish to zero as a result of the interventions. This means that, if the disease threshold is below unity ($R_e = 0.2987$), both drug sensitive and resistant strains can be eliminated. Figure 5(e) depicts the time series plot of the population density of infectious individuals with drug-resistant TB which decreases but does not tend to zero. This simply means that the interventions in place are not enough to completely eradicate the epidemic from the population. The observed decrease of the number of drug-resistant TB individuals may be the result of abrupt reductions in the rates of disease progression [27].

MDR-TB which is difficult to treat, spreads fastest in areas with poor adherence to second-line drug. This poor adherence is frequently caused by shortages of second-line drugs which are quite expensive and as such minimal treatment is offered to those infected. Figure 5(f) shows that the recovered population increases as a result of the interventions unlike in Figure 4(f). In other words, we observe that the introduction of treatment, diagnosis, and health education in a TB stricken community reduces the impact of MDR-TB but cannot completely clear it from the community, because higher levels of treatment may lead to an increase of the epidemic size, and the extend to which this occurs depends on the factors such as drug efficacy and resistance development [28]. Figure 6(a) shows that diagnosis of infectious individuals with drug sensitive TB to determine whether or not the infection has developed resistance to drugs is very crucial in MDR-TB control. More infectious individuals with sensitive TB needs effective treatment that should correlate with the diagnosis levels. In addition, diagnosis is very important to detect the number of people who have developed resistant strains and are eligible to the second-line treatment to prevent the infection from a possible spread. As for the sick individuals with MDR-TB, treatment of the infection is paramount as indicated by Figure 6(b). Also, from Figure 6(b), education campaigns alone cannot curb or reduce the infection but work hand in hand with treatment as well as diagnosis. In other words, Figure 6 suggests that all individuals diagnosed with MDR-TB should be educated on the importance of treatment compliance and completion.

3.1. Dynamics of the Populations under Different Interventions

3.1.1. The Effect of Treatment on MDR-TB Dynamics. It is assumed under this scenario that treatment is given to latent and infectious individuals with drug sensitive TB as well as infectious individuals with MDR-TB. We then investigate the impact of each of these control measures on all the infected populations of both strains. As the treatment rate

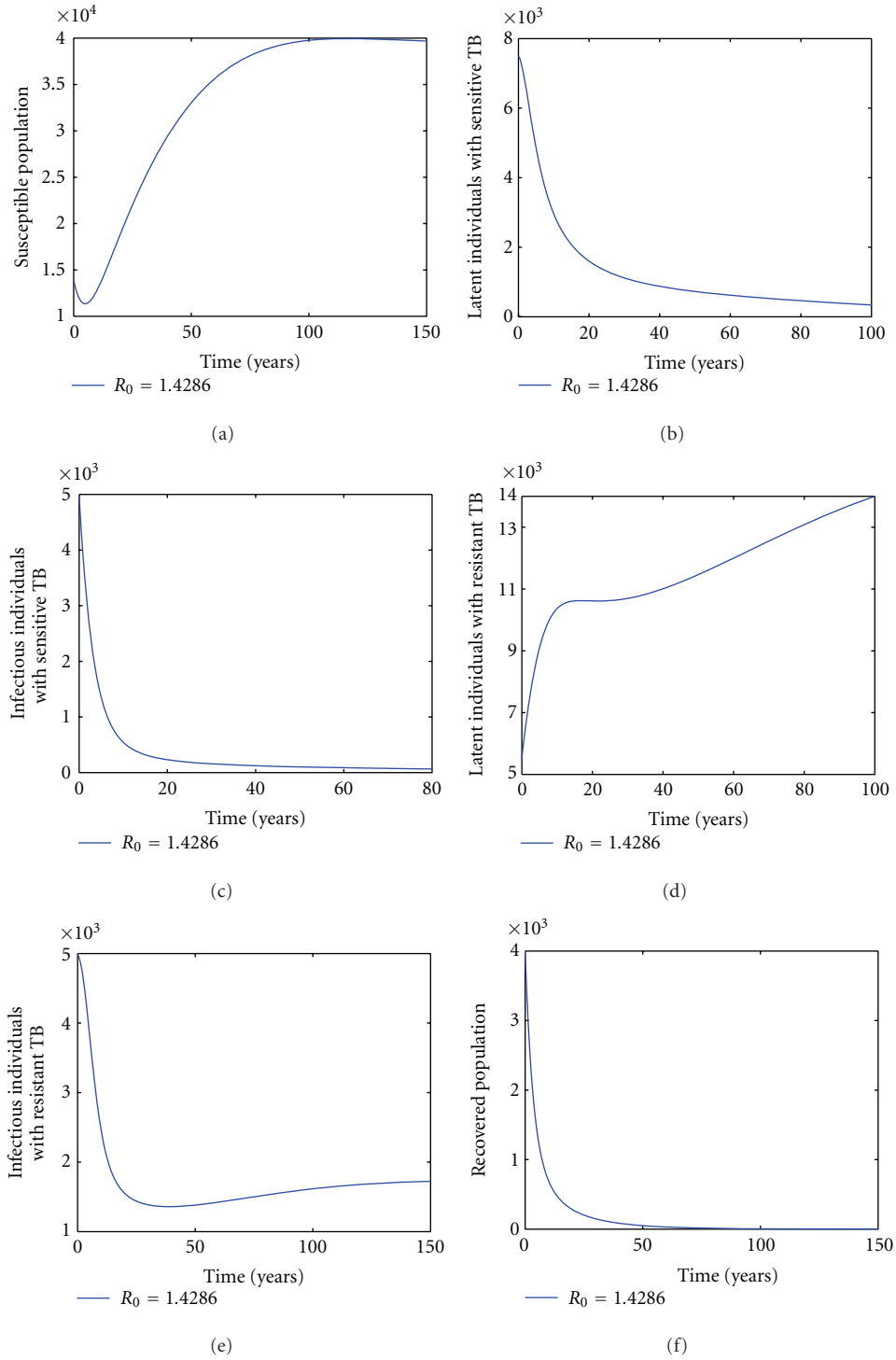

FIGURE 4: Time series of the dynamics of (a) susceptibles (b) latent individuals with sensitive TB, (c) infectious individuals with sensitive TB, (d) latent individuals with resistant TB, (e) infectious individuals with resistant TB and (f) recovered population (without interventions) when $R_0 = 1.4286$.

of latent individuals with drug sensitive TB, ϕ_s, increases, R_e decreases so are the infectious populations with both strains. Thus, treating more latent individuals with drug sensitive TB can eliminate drug sensitive TB (Figures 7(a) and 7(c)). This is the case because as more latent individuals with drug sensitive TB are treated, then only a few of them will progress to active infection. Also, increasing ϕ_s reduces the number of infectious individuals with MDR-TB since

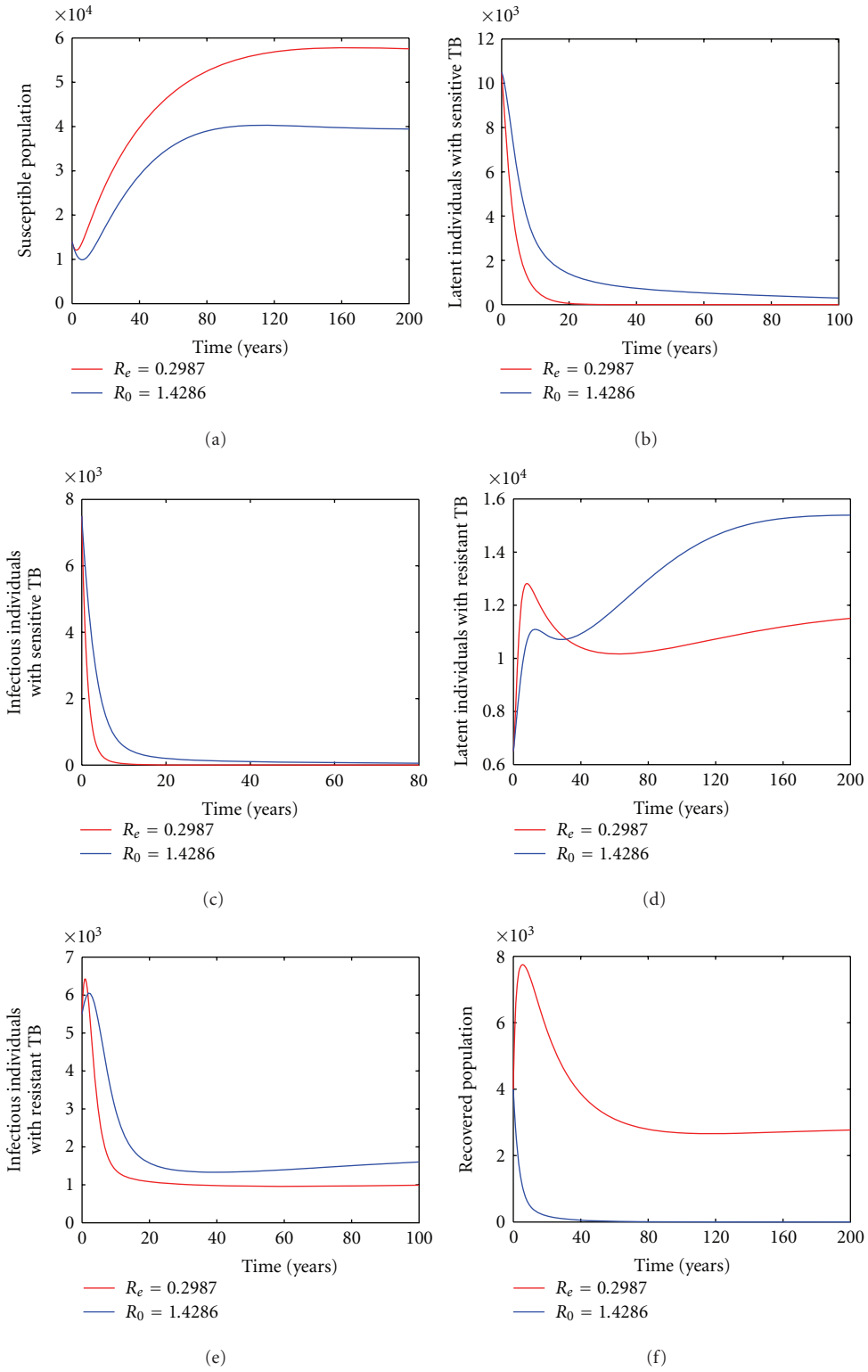

Figure 5: Time series plots when interventions are introduced: $R_e = 0.2987$ and $R_0 = 1.4286$ of (a) susceptible population, (b) latent individuals with sensitive TB, (c) infectious individuals with sensitive TB, (d) latent individuals with resistant TB, (e) infectious individuals with resistant TB, and (f) recovered population. The blue curve represents the dynamics of the populations without interventions and the red one with interventions.

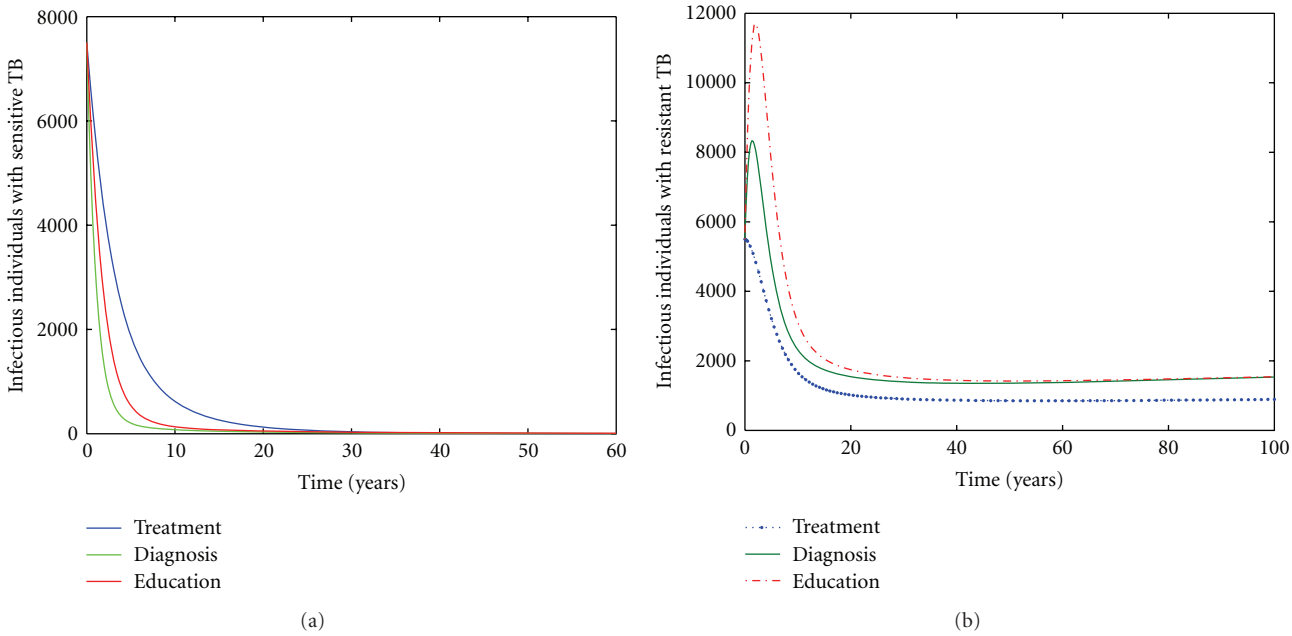

Figure 6: Impact of the different interventions under study on the dynamics of (a) infectious population with drug-sensitive TB and (b) infectious population with drug-resistant TB.

the treatment will prevent the infection from developing resistance to the drugs. Although, this is the case, MDR-TB may not completely be eradicated from the population due to re-infection and relapse as illustrated in Figure 7(d), and also due to the fact that treatment efficacy is less than 100%. Figures 8(a) and 8(b) show that increasing ϕ_r reduces both R_e and the latent and infectious populations with drug sensitive TB to zero over time. Treating more infectious individuals with drug sensitive TB prevents the infection from developing resistance to drugs and hence reduces the number of infectious population with MDR-TB as shown in Figure 8(d). However, Figure 8(d) also shows that, at this level of treatment, MDR-TB cannot be absolutely wiped out of the society which confirms the complexity of the disease. Figures 9(a) and 9(b) show that as the treatment rate of infectious individuals with MDR-TB, ϕ, increases, R_r reduces to less than unity and decreasing trends for latent and infectious individuals with MDR-TB are observed although they do not decay to zero due to the continuous development of resistance as treatment is not fully (or 100%) effective.

3.1.2. The Effect of Diagnosis on MDR-TB Dynamics. Figure 10 shows that increasing the value of σ reduces R_e and also decreases the infectious populations with drug sensitive and MDR-TB. From Figure 10(a), drug sensitive TB can be completely eliminated from the population if more people are diagnosed. This is mainly the case because usually diagnosis leads to treatment which reduces the infection (Figures 7, 8, and 9). On the contrary, diagnosis of more infectious individuals with drug sensitive TB is not a guarantee of eliminating MDR-TB as it only reduces the number of infectious individuals with MDR-TB but does not wipe the infection out of the population as illustrated by Figure 10(b). Therefore, increase in diagnosis should be correlated with increase in treatment to ensure treatment for all infectious individuals after they are detected.

3.1.3. The Effect of Health Education on MDR-TB Dynamics. Figure 11 illustrates the importance of health education in the fight against MDR-TB. It is observed in Figure 11(a) that when more people receive health education on the importance of adhering to the doctor's recommendation on how to take their TB regimens, the infectious population with drug sensitive TB decreases and eventually decays to zero. Also, this strategy reduces R_e to further smaller values. Consequently, health education slightly reduces infectious individuals with MDR-TB as shown in Figure 11(b). This is possible because treatment adherence and compliance reduce the likelihood of the infection developing drug-resistance. However, Figure 11(b) also indicates that education alone is not enough to completely eliminate MDR-TB from the community as not all people will follow these rational instructions. In addition, exogenous re-infection and regression also make the efforts to root out MDR-TB difficult but not impossible. Thus, preventing re-infection and regression are viable. Figure 12 shows that as more infectious individuals with drug sensitive TB receive health education, the number of recovered population increases. This supports the fact that education has a positive impact on TB dynamics as depicted in Figure 11. Thus, educating more infectious individuals with drug sensitive TB increases the number of people recovering from the infection which is a positive development for the management of MDR-TB. Therefore, stepping up TB information/awareness campaigns should be given prominence in TB control programmes.

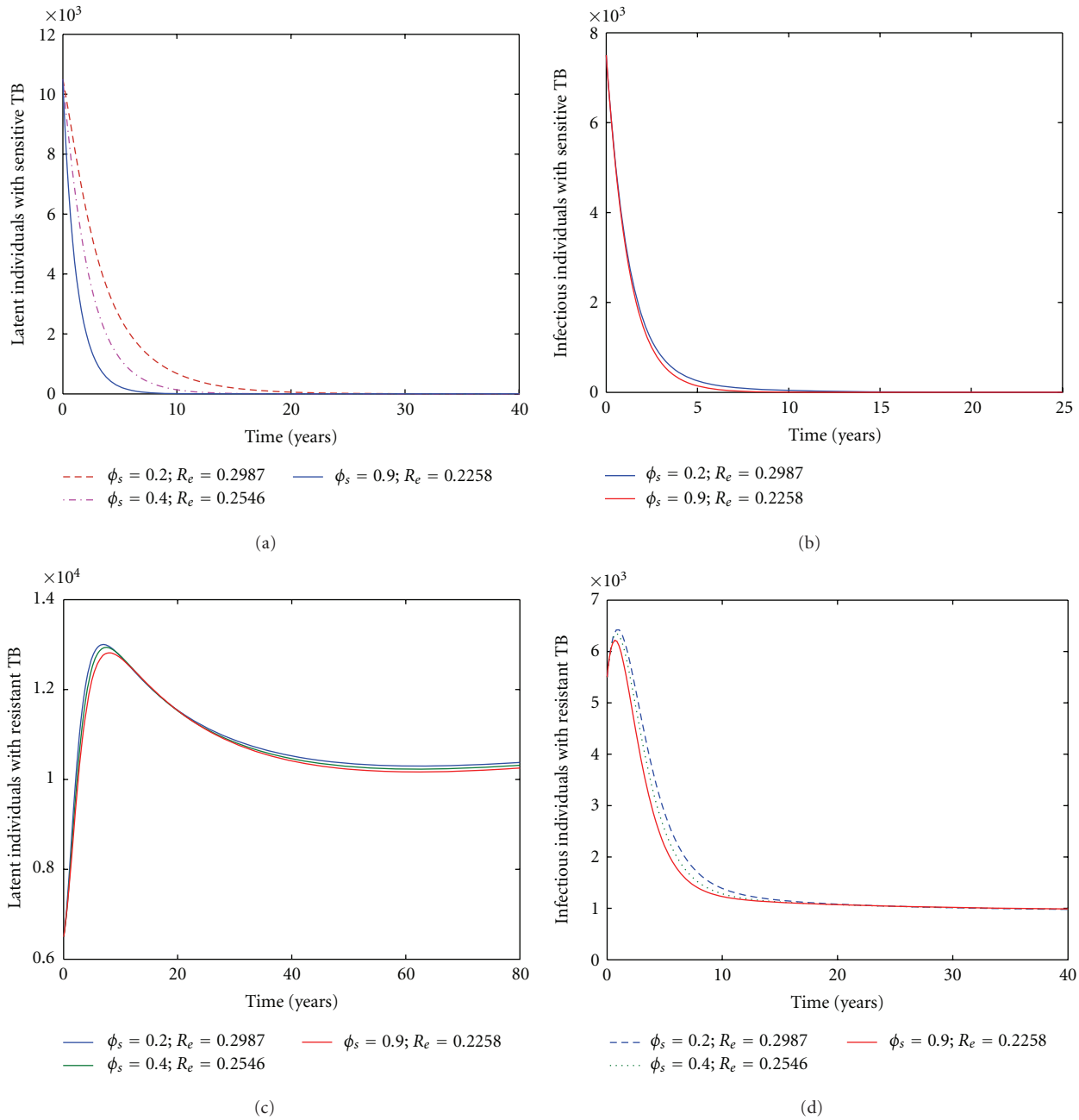

FIGURE 7: Impact of varying ϕ_s on R_e and on the number of (a) latent population with drug sensitive TB, (b) infectious population with drug sensitive TB, (c) latent population with MDR-TB, and (d) infectious population with MDR-TB.

4. Discussion and Conclusion

A two-strain TB model with diagnosis, treatment, and health education is formulated and analyzed. The main objective of this theoretical study was to assess the impact of these control strategies on the transmission dynamics of MDR-TB (with Malawi as a case study). We note however that the results presented are general and can be applied to other settings because neither the model, nor the parameters values represent characteristics unique of Malawi. The effective reproduction number was computed and used to compare the effect of each intervention strategy on the MDR-TB dynamics.

Using the theory of dynamical systems, qualitative analysis shows that the model has two equilibria the disease-free equilibrium and endemic equilibrium. Using the next-generation operator approach, it was found that, whenever the threshold that describes endemic persistence of the disease, $R_e < 1$ (i.e., $R_s < 1$ and $R_r < 1$), the disease-free equilibrium is locally asymptotically stable and becomes unstable whenever $R_e > 1$ ($R_s > 1$ and $R_r > 1$). The existence and stability of the endemic equilibrium was determined

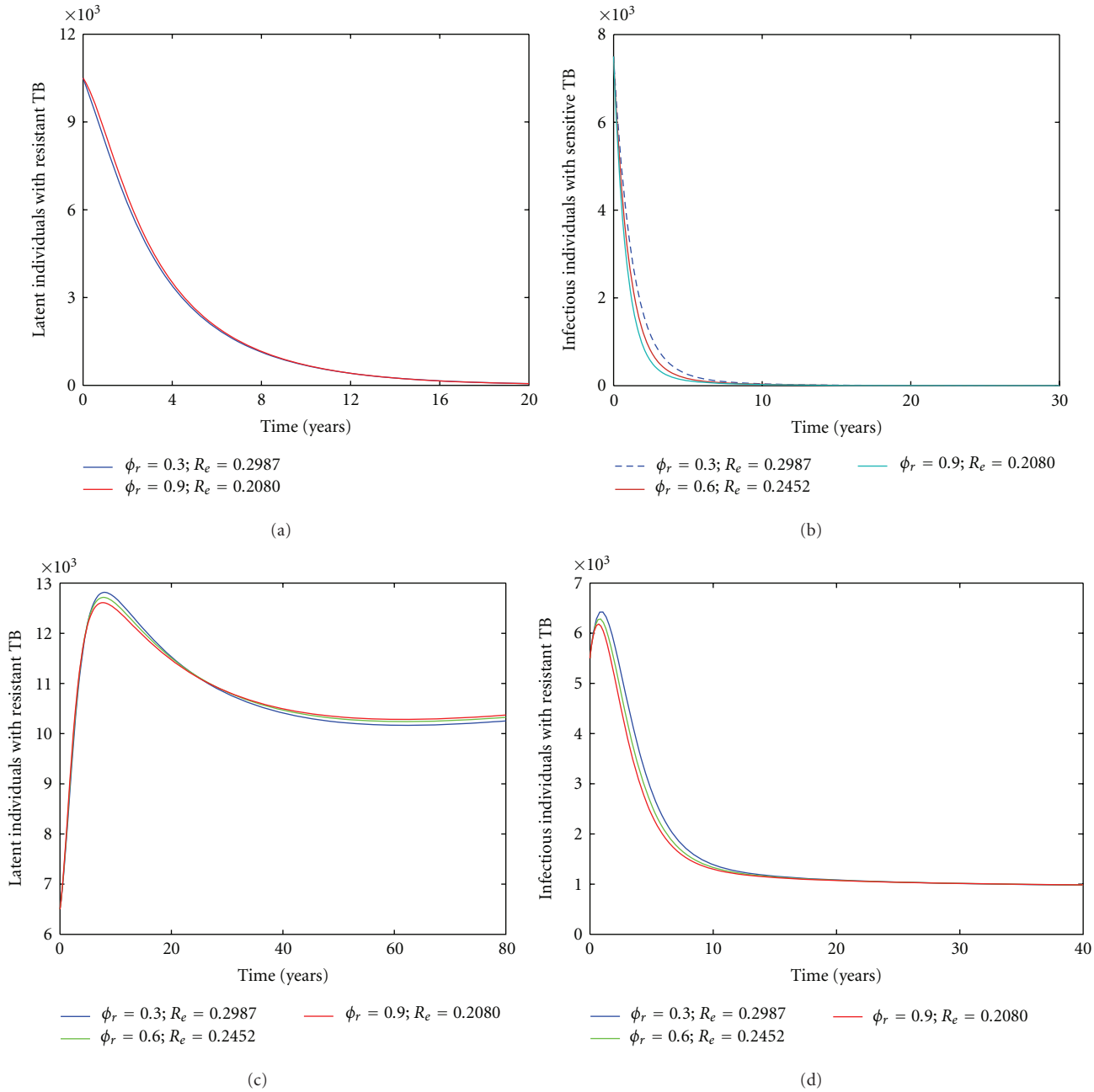

FIGURE 8: Impact of varying ϕ_r on R_e and on the number of (a) latent population with drug sensitive TB, (b) infectious population with drug sensitive TB, (c) latent population with MDR-TB and (d) infectious population with MDR-TB.

using the Center Manifold theory [22]. Near the threshold $R_e = 1$, there exists a stable endemic equilibrium which is locally asymptotically stable for $R_e > 1$. In the absence of interventions, the effective reproduction number, R_e, reduces to the basic reproduction number R_0. As customary in epidemiological models, the disease-free and endemic equilibria are found and their stability is investigated depending on the system parameters. Because of the occurrence of backward bifurcation in some parameter regimes, the system exhibits a bistability between a disease-free and endemic steady states. Whether the parameter values for which this phenomenon arises are biologically realistic remains a conjecture as field data will be needed to parameterize such occurrence. The Centre Manifold theory was used to determine the local asymptotic stability of the endemic equilibrium. Our results provide a perspective for understanding the complexity of MDR-TB, and the model can be applied in most settings where MDR-TB is present.

Numerical simulations suggest that, in the absence of any intervention, both TB strains cannot be eliminated from

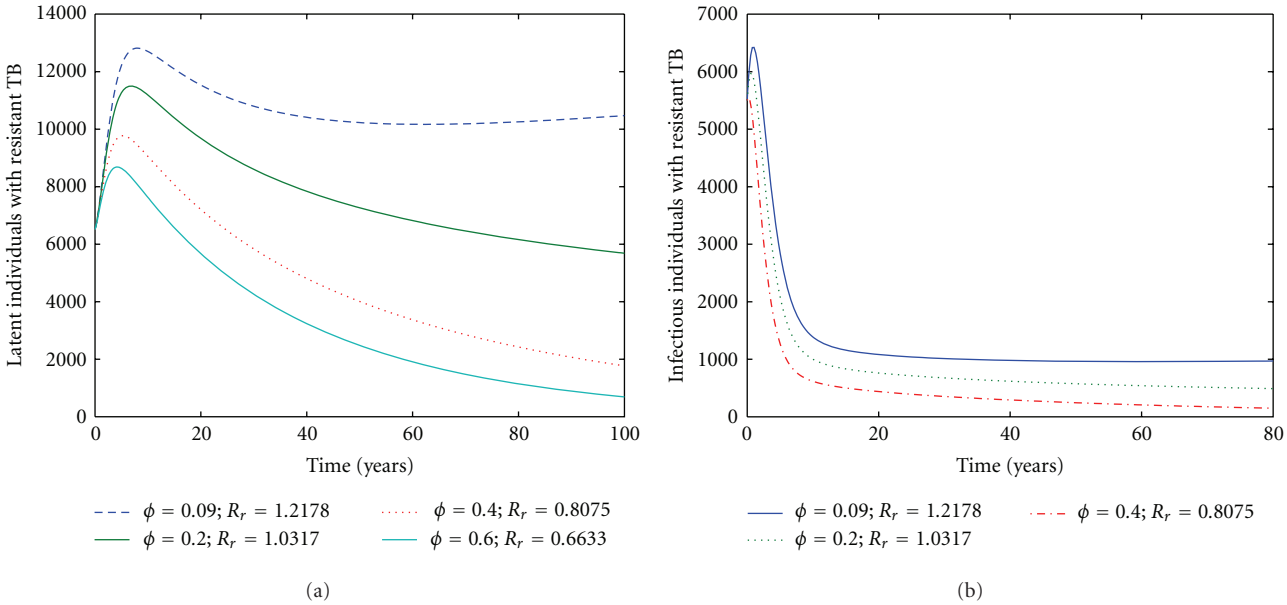

Figure 9: Impact of varying ϕ on the value of R_r and the dynamics of the number of (a) latent population with MDR-TB and (b) infectious population with MDR-TB.

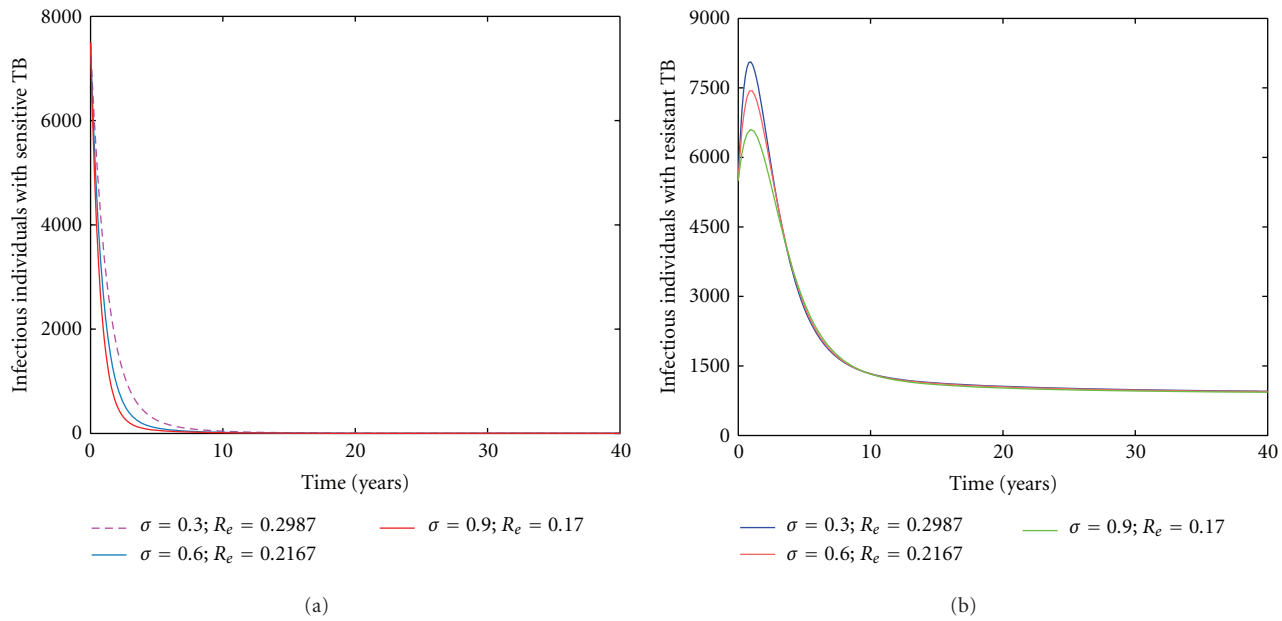

Figure 10: Impact of varying σ on the value of R_e and the dynamics of the number of (a) infectious population with drug sensitive TB and (b) infectious population with MDR-TB with respect to time.

the population as $R_0 > 1$, and the disease persists at an endemic equilibrium. A critical factor in addressing MDR-TB is primary prevention through DOTS and management of patients requiring second-line drug-regimen. Treatment of latent and infectious individuals with sensitive TB showed that ordinary TB can be completely eradicated. Thus, effective treatment for latent and infectious individuals with ordinary TB results in a reduction of MDR-TB, since the emergence of most MDR-TB cases is due to failure to provide TB drugs on time, as identifying latently infected individuals with sensitive and putting them on treatment is crucial in reducing new cases of resistant TB [29]. Also effective chemoprophylaxis and treatment of infectives result in a reduction of MDR-TB cases since most MDR-TB cases are a result of inappropriate treatment [5]. Treatment for infectious individuals with MDR-TB alters TB epidemics because it reduces the spread of MDR-TB strains and this supports the analytical results. Hence, a decrease in MDR-TB

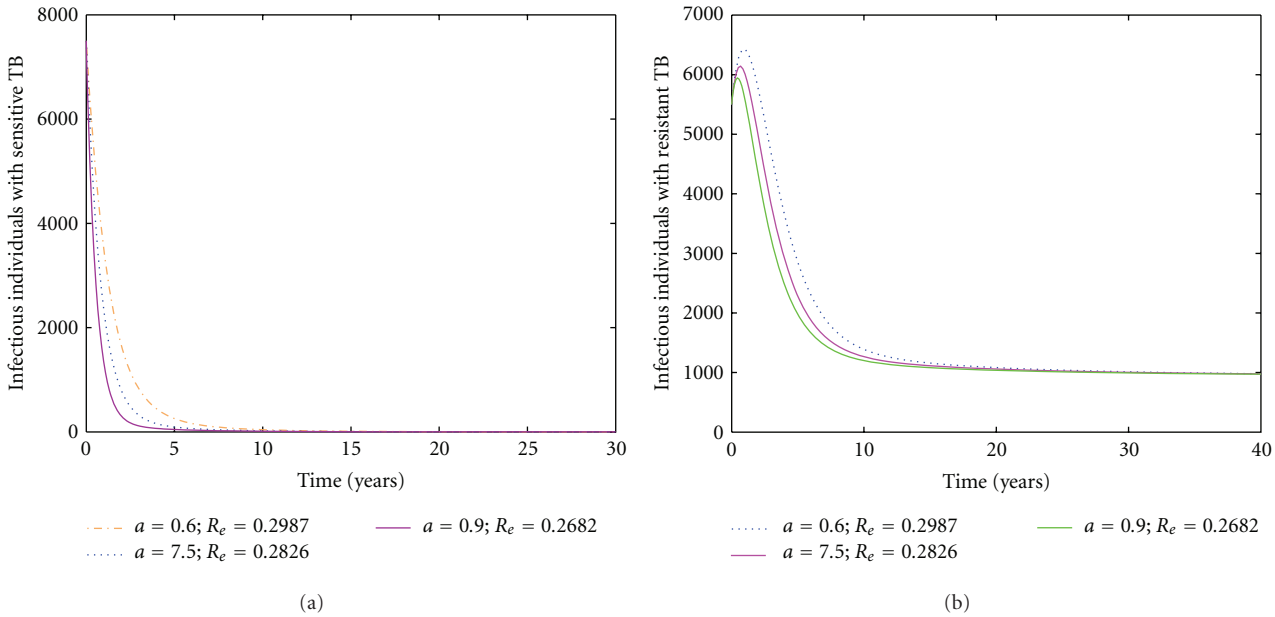

Figure 11: Impact of varying a on the value of R_e and the dynamics of the number of (a) infectious population with drug sensitive TB and (b) infectious population with MDR-TB.

cases implies a decrease in MDR-TB-related deaths as MDR-TB kills more people than ordinary TB.

Diagnosis also plays an important role in MDR-TB reduction. As the proportion of TB patients being presented for diagnosis is increased, the rate of treatment should be correlated to the number of diagnosed infected individuals so as to reduce the burden of TB [6]. Significant increase in the detection rate of infectious individuals in Nigeria has been recommended because DOTS failed to reduce the incidence rate in the country due to failure to adequately detect a huge number of active TB cases which are primarily responsible for the spread of the infection [30]. As more people go for TB diagnosis, MDR-TB decreases due to the fact that those diagnosed with the disease are placed on DOTS. Drug-resistant TB will remain a serious threat to our communities as long as many members of our society do not have regular access to medical care [31]. Health education is another important aspect in the fight against MDR-TB. Results showed that, if more people receive health education, then the burden of MDR-TB can be reduced since MDR-TB cases also arise due to noncompliance with TB treatment. Information/awareness campaigns are viable in order to sensitize people on the importance of completing their TB dosages. Despite the role of the control strategies in reducing the burden of MDR-TB, numerical simulations also show that at the current level of TB treatment, diagnosis and health education, MDR-TB can only be reduced significanly.

Incomplete data from the National TB Control Program proves to be a major challenge in deriving estimates for the key biological parameters to calibrate the model to Malawi. Nevertheless, resorting to the literature, fundamental parameters values mimicking the epidemic in the region were used as a basis for illustration. Although several assumptions are made in the process, our results are driven by the model formulation and its structure; however, they are applicable to the Malawi context and other settings with similar epidemic trend. In summary, adequate treatment of sensitive TB will result in a reduction of MDR-TB in Malawi as most MDR-TB cases come from failure to properly administer TB drugs. Furthermore, diagnosis and health education of infectives with sensitive TB is important in the reduction of new MDR-TB cases due to adherence and compliance to treatment. Scaling up diagnosis, treating, and TB education will help in reducing the burden of the disease. Treatment rate of infected individuals should be correlated to the number of diagnosed individuals, and policies should be put in place to minimize loss to follow up. MDR-TB eradication remains a challenge to National Tuberculosis Control Programs in most developing countries, hence strengthening control strategies is paramount to curtailing TB spread, especially as the incidence rate of MDR-TB seems to be on the increase.

Finally, we identify some limitations of this study. A more realistic perspective could have been achieved by including, vaccination of susceptible population, immigrants, and new born; efficacy of MDR-TB drugs and information campaigns; controlling the disease with a possible minimal cost and side effects using control theory; estimating the cost-effectiveness of these control measures. Most parameter values are obtained from different sources giving rise to parameter uncertainty regarding their exact value. Our results which are driven by the model structure and its formulation are sensitive to the choice of parameter values. However, it is worth stressing that the main goal of this work was to provide a theoretical framework where the emergence of drug-resistant and MDR-TB can be addressed using a dynamical model. We focused on the population-level dynamics and potential benefits associated with implementation of various control strategies. It is our hope that

the theoretical results obtained from this study will stimulate further interest in developing more complex models, be it agent based or network.

Appendices

A. Computation of the Effective Reproduction Number R_e

Following [19], the associated matrices $\mathcal{F}_i$ for new infections terms and $\mathcal{V}_i$ for the remaining transition terms are, respectively, given by

$$\mathcal{F}_i = \begin{bmatrix} [(1-\rho_s)S+R]\lambda_s \\ \rho_s\lambda_s S \\ [(1-\rho_r)S+R]\lambda_r \\ \rho_r\lambda_r S \\ 0 \\ 0 \end{bmatrix}, \tag{A.1}$$

$$\mathcal{V}_i = \begin{bmatrix} (\gamma_s\lambda_s+\lambda_r)E_s+(\phi_s+k_1+\mu)E_s-q\phi_r I_s \\ (d_s+a\phi_r+\varphi_s+\sigma+\mu)I_s+\lambda_r I_s-(\gamma_s\lambda_s+k_1)E_s \\ (k_2+\mu)E_r+(\gamma_r\lambda_r+\lambda_s)E_r-(1-(p+q))\phi_r I_s \\ (d_r+\phi+\varphi_r+\mu)I_r-(E_s+I_s)\lambda_r-(\lambda_s+k_2+\gamma_r\lambda_r)E_r-\sigma I_s \\ \mu S+(\lambda_s+\lambda_r)S-\Lambda \\ \mu R+(\lambda_s+\lambda_r)R-ap\phi_r I_s-\phi_s E_s-\phi I_r \end{bmatrix}. \tag{A.2}$$

Evaluating the partial derivatives of (A.1) at E_0 and bearing in mind that system (1) has four infected classes, namely, E_s, I_s, E_r, and I_r, we obtain

$$F = \begin{bmatrix} 0 & (1-\rho_s)c\beta_s & 0 & 0 \\ 0 & \rho_s c\beta_s & 0 & 0 \\ 0 & 0 & 0 & (1-\rho_r)c\beta_r \\ 0 & 0 & 0 & \rho_r c\beta_r \end{bmatrix} = \begin{bmatrix} F_1 & 0 \\ 0 & F_2 \end{bmatrix}, \tag{A.3}$$

where

$$F_1 = \begin{bmatrix} 0 & (1-\rho_s)c\beta_s \\ 0 & \rho_s c\beta_s \end{bmatrix} \qquad F_2 = \begin{bmatrix} 0 & (1-\rho_r)c\beta_r \\ 0 & \rho_r c\beta_r \end{bmatrix}. \tag{A.4}$$

Similarly, partial differentiation of (A.2) with respect to E_s, I_s, E_r, and I_r at E_0 gives

$$V = \begin{bmatrix} (\phi_s+k_1+\mu) & -q\phi_r & 0 & 0 \\ -k_1 & (d_s+a\phi_r+\varphi_s+\sigma+\mu) & 0 & 0 \\ 0 & -(1-(p+q))\phi_r & k_2+\mu & 0 \\ 0 & -\sigma & -k_2 & (d_r+\phi+\varphi_r+\mu) \end{bmatrix} = \begin{bmatrix} V_1 & 0 \\ V_3 & V_2 \end{bmatrix}, \tag{A.5}$$

where

$$V_1 = \begin{bmatrix} (\phi_s+k_1+\mu) & -q\phi_r \\ -k_1 & (d_s+a\phi_r+\varphi_s+\sigma+\mu) \end{bmatrix},$$
$$V_2 = \begin{bmatrix} k_2+\mu & 0 \\ -k_2 & (d_r+\phi_r+\varphi_r+\mu) \end{bmatrix}, \tag{A.6}$$
$$V_3 = \begin{bmatrix} 0 & -(1-(p+q))\phi_r \\ 0 & -\sigma \end{bmatrix}.$$

The effective reproduction number, denoted by R_e, is given by $R_e = \rho(FV^{-1})$, where ρ denotes the spectral radius (or the dominant eigenvalue of matrix FV^{-1}). The dominant eigenvalues of matrix FV^{-1} are given by

$$R_s = (F_1V_1^{-1}) = \frac{c\beta_s(\mu\rho_s+\phi_s\rho_s+k_1)}{(\phi_s+k_1+\mu)(d_s+a\phi_r+\varphi_s+\sigma+\mu)-q\phi_r k_1}, \tag{A.7}$$
$$R_r = (F_2V_2^{-1}) = \frac{c\beta_r(k_2+\mu\rho_r)}{(k_2+\mu)(d_r+\phi+\varphi_r+\mu)}.$$

Therefore, $R_e = \rho(FV^{-1}) = \max\{R_s, R_r\}$, where R_s and R_r are, respectively, the reproduction numbers for drug sensitive TB strain only and MDR-TB strain only. R_e measures the average number of new infections generated by a typical infectious individual in a community where intervention strategies are in place. Thus, in the absence of diagnosis, treatment and health education (i.e., $\phi_s = \phi_r = \phi = a = \sigma = 0$), (A.7) reduces to

$$R_{0s} = \frac{c\beta_s(k_1+\mu\rho_s)}{(k_1+\mu)(d_s+\varphi_s+\mu)},$$
$$R_{0r} = \frac{c\beta_r(k_2+\mu\rho_r)}{(k_2+\mu)(d_r+\varphi_r+\mu)}, \tag{A.8}$$

and $R_0 = \max\{R_{0s}, R_{0r}\}$.

B. Proof of the Stability of the EE

B.1. The Bifurcation Theorem. This Theorem is proven in Castillo-Chavez and Song [32].

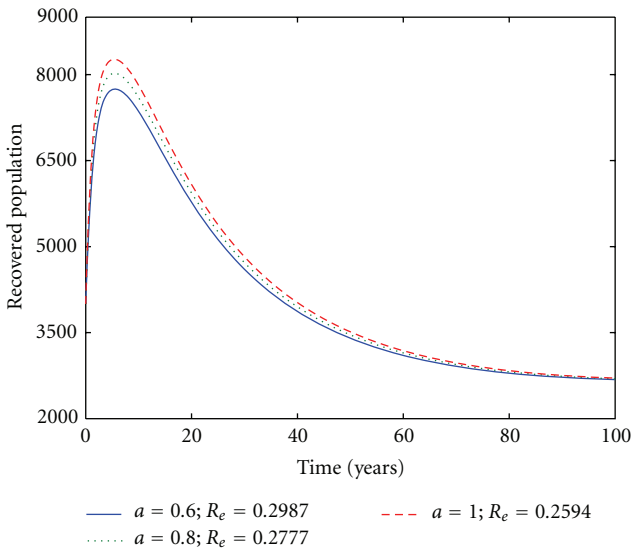

FIGURE 12: Impact of health education on the dynamics of recovered population.

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

$$\frac{dx}{dt} = f(x,\phi), \quad f : \mathbb{R}^n \times \mathbb{R} \longrightarrow \mathbb{R}^n,\ f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}), \tag{B.1}$$

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

(i) *$A = D_x f(0,0) = [(\partial f_i/\partial x_j)(0,0)]$ is the linearization matrix of the system around the equilibrium 0 with ϕ evaluated at 0;*

(ii) *zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;*

(iii) *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

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

The local dynamics of system (B.1) around 0 is governed by the signs of a and b.

(i) $a > 0$, $b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium.

(ii) $a < 0$, $b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium.

(iii) $a > 0$, $b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears.

(iv) $a < 0$, $b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

Particularly if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

B.2. Proof of Local Asymptotic Stability of E_2. Again, using the Center Manifold theory [22], the local asymptotic stability of E_2 is established. To this effect, the following change of variables is made; $S = x_1, E_r = x_2, I_r = x_3, R = x_4$ (note that $E_s = I_s = 0$ at this point) so that $N = x_1 + x_2 + x_3 + x_4$. Using vector notation $X = [x_1, x_2, x_3, x_4]^T$, the system (13) can be written in the form

$$\frac{dX}{dt} = F = (f_1, f_2, f_3, f_4), \tag{B.3}$$

such that

$$\begin{aligned}
x_1'(t) &= f_1 = \Lambda - \frac{c\beta_r x_3 x_1}{N} - \mu x_1,\\
x_2'(t) &= f_2 = \frac{c\beta_r x_3[(1-\rho_r)x_1 + x_4]}{N} - \frac{\gamma_r c\beta_r x_3 x_2}{N}\\
&\quad - (k_2+\mu)x_2,\\
x_3'(t) &= f_3 = \frac{c\beta_r \rho_r x_3 x_1}{N} + \frac{\gamma_r c\beta_r x_3 x_2}{N} + k_2 x_2\\
&\quad - (d_r + \phi + \varphi_r + \mu)x_3,\\
x_4'(t) &= f_4 = (\phi + \varphi_r)x_3 - \frac{c\beta_r x_3 x_4}{N} - \mu x_4.
\end{aligned} \tag{B.4}$$

The Jacobian matrix of (B.4) at E_r^0 is given by

$$J(E_r^0) = \begin{bmatrix} -\mu & 0 & -c\beta_r & 0\\ 0 & -(k_2+\mu) & (1-\rho_r)c\beta_r & \\ 0 & k_2 & c\beta_r\rho_r - (d_r+\phi+\varphi_r+\mu) & 0\\ 0 & 0 & (\phi+\varphi_r) & -\mu \end{bmatrix}. \tag{B.5}$$

From (B.5), it can be shown that the the reproduction number is

$$R_r = \frac{c\beta_r(k_2+\mu\rho_r)}{(k_2+\mu)(d_r+\phi+\varphi_r+\mu)}. \tag{B.6}$$

If β_r is the bifurcation point and if we consider the case when $R_r = 1$ and then solve for β_r, we obtain

$$\beta_r = \beta_* = \frac{(k_2+\mu)(d_r+\phi+\varphi_r+\mu)}{c(k_2+\mu\rho_r)}. \tag{B.7}$$

System (B.5) with $\beta_r = \beta_*$ has a simple zero eigenvalue, hence we can use the center manifold theory in the analysis

of the dynamics of system (B.5) near $\beta_r = \beta_*$. The Jacobian matrix (B.5) near $\beta_r = \beta_*$ has a right eigenvector associated with the zero eigenvalue given by $w = [w_1, w_2, w_3, w_4]^T$, where

$$w_1 = -\frac{c\beta_* w_3}{\mu},$$
$$w_2 = \frac{(1-\rho_r)c\beta_* w_3}{k_2+\mu} = \frac{(d_r+\phi+\varphi_r+\mu-c\beta_*\rho_r)w_3}{k_2},$$
$$w_3 = w_3 > 0, \qquad w_4 = \frac{(\phi+\varphi_r)w_3}{k_2}. \tag{B.8}$$

The left eigenvector of (B.5) associated with the zero eigenvalue at $\beta_r = \beta_*$ is given by $v = [v_1, v_2, v_3, v_4]^T$, where

$$v_1 = v_4 = 0, \qquad v_3 = v_3 > 0,$$
$$v_2 = \frac{k_2 v_3}{k_2+\mu} = \frac{(d_r+\phi+\varphi_r+\mu-c\beta_*\rho_r)v_3}{(1-\rho_r)c\beta_*}. \tag{B.9}$$

We use Theorem 2.5 in [32] to find the conditions for the occurrence of backward bifurcation.

Computations of a and b. For system (B.4), the partial derivatives of F associated with a at E_0^r are given by

$$\frac{\partial^2 f_2}{\partial x_3 \partial x_2} = -\frac{\mu c\beta_*[(1-\rho_r)+\gamma_r]}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_3 \partial x_3} = -\frac{2(1-\rho_r)\mu c\beta_*}{\Lambda},$$
$$\frac{\partial^2 f_3}{\partial x_3 \partial x_2} = -\frac{\mu c\beta_*(\rho_r-\gamma_r)}{\Lambda}, \qquad \frac{\partial^2 f_3}{\partial x_3 \partial x_3} = -\frac{2\rho_r\mu c\beta_*}{\Lambda}. \tag{B.10}$$

Following (B.10), we have

$$\begin{aligned} a &= v_2 \sum_{i,j=1}^{n} w_i w_j \frac{\partial^2 f_2}{\partial x_i \partial x_j}(0,0) + v_3 \sum_{i,j=1}^{n} w_i w_j \frac{\partial^2 f_3}{\partial x_i \partial x_j}(0,0), \\ &= v_2\left[-\frac{w_3 w_2 \mu c\beta_*((1-\rho_r)+\gamma_r)}{\Lambda} - \frac{2w_3^2(1-\rho_r)\mu c\beta_*}{\Lambda}\right] \\ &\quad + v_3\left[-\frac{w_3 w_2 \mu c\beta_*(\rho_r-\gamma_r)}{\Lambda} - \frac{2w_3^2\rho_r\mu c\beta_*}{\Lambda}\right], \\ &= \frac{2\mu c\beta_* v_3 w_3^2}{\Lambda(k_2+\mu)^2}[\gamma_r(1-\rho_r)\mu c\beta_* - (1-\rho_r)\mu c\beta_*\rho_r \\ &\qquad -(k_2+\mu)(2\rho_r(k_2+\mu)+(1-\rho_r)k_2)]. \end{aligned} \tag{B.11}$$

We see from (B.11) that $a < 0$ whenever $m < n$ and $a > 0$ whenever $m > n$, where

$$m = \gamma_r(1-\rho_r)\mu c\beta_*,$$
$$n = (1-\rho_r)\mu c\beta_*\rho_r + (k_2+\mu)(2\rho_r(k_2+\mu)+(1-\rho_r)k_2). \tag{B.12}$$

The nonzero partial derivatives of F associated with b at E_0^r are given by

$$\frac{\partial^2 f_2}{\partial x_3 \partial \beta_*} = (1-\rho_r)c, \qquad \frac{\partial^2 f_3}{\partial x_3 \partial \beta_*} = c\rho_r. \tag{B.13}$$

It follows from (B.13) that,

$$\begin{aligned} b &= v_2 \sum_{i=1}^{n} w_i \frac{\partial^2 f_2}{\partial x_i \partial \beta_*}(0,0) + v_3 \sum_{i=1}^{n} w_i \frac{\partial^2 f_3}{\partial x_i \partial \beta_*}(0,0), \\ &= v_2 w_3(1-\rho_r)c + v_3 w_3 \rho_r c, \\ &= \frac{c v_3 w_3[k_2(1-\rho_r)+\rho_r(k_2+\mu)]}{k_2+\mu} > 0. \end{aligned} \tag{B.14}$$

Therefore, $b > 0$ and $a < 0$ or $a > 0$ depending on whether $m < n$ or $m > n$. We have therefore, established the following result.

Theorem B.2. *If $m > n$, $a > 0$, then model system (13) has a backward bifurcation at $R_r = 1$, otherwise $a < 0$ and a unique endemic equilibrium E_2 is locally asymptotically stable for $R_r > 1$ but close to 1.*

B.3. Existence of Backward Bifurcation of the Full Model. From model system (1), we make the following change of variables, that is, $S = x_1, E_s = x_2, I_s = x_3, E_r = x_4, I_r = x_5, R = x_6$, such that $N = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$. Further, by using vector notation $X = [x_1, x_2, x_3, x_4, x_5, x_6]^T$, system (1) can be written in the form $dX/dt = F(X)$, where $F = (f_1, f_2, f_3, f_4, f_5, f_6)$ as follows:

$$\begin{aligned} S'(t) &= f_1 = \Lambda - (\lambda_s+\lambda_r)x_1 - \mu x_1, \\ E_s'(t) &= f_2 = ((1-\rho_s)x_1 + x_6)\lambda_s - (\gamma_s\lambda_s+\lambda_r)x_2 \\ &\qquad - (\phi_s + k_1 + \mu)x_2 + q\phi_r x_3, \\ I_s'(t) &= f_3 = \rho_s\lambda_s x_1 + (\gamma_s\lambda_s + k_1)x_2 - \lambda_r x_3 \\ &\qquad - (d_s + a\phi_r + \sigma + \varphi_s + \mu)x_3, \\ E_r'(t) &= f_4 = ((1-\rho_r)x_1 + x_6)\lambda_r + (1-(p+q))\phi_r x_3 \\ &\qquad - (\lambda_s + \gamma_r\lambda_r + k_2 + \mu)x_4, \\ I_r'(t) &= f_5 = \rho_r\lambda_r x_1 + (\lambda_s + \gamma_r\lambda_r + k_2)x_4 + \lambda_r x_2 \\ &\qquad + \lambda_r x_3 + \sigma x_3 - (d_r + \phi + \varphi_r + \mu)x_5, \\ R'(t) &= f_6 = (ap\phi_r + \varphi_s)x_3 + \phi_s x_2 \\ &\qquad + (\phi + \varphi_r)x_5 - (\lambda_s + \lambda_r)x_6 - \mu x_6, \end{aligned} \tag{B.15}$$

where $\lambda_s = c\beta_s x_3/N$ and $\lambda_r = c\beta_r x_5/N$. The Jacobian matrix of system (B.15) at E_0 is given by

$$J(E_0) = \begin{bmatrix} -\mu & 0 & 0 & 0 & 0 & 0 \\ 0 & -(\phi_s + k_1 + \mu) & (1-\rho_s)c\beta_s + q\phi_r & 0 & 0 & 0 \\ 0 & k_1 & g_1 & 0 & 0 & 0 \\ 0 & 0 & g_2 & -(k_2+\mu) & g_3 & 0 \\ 0 & 0 & \sigma & k_2 & g_4 & 0 \\ 0 & \phi_s & (ap\phi_r + \varphi_s) & 0 & (\phi + \varphi_r) & -\mu \end{bmatrix} \tag{B.16}$$

where

$$g_1 = -(d_s + a\phi_r + \sigma + \varphi_s + \mu) + c\beta_s\rho_s,$$
$$g_2 = (1 - (p+q))\phi_r,$$
$$g_3 = (1-\rho_r)c\beta_r, \qquad g_4 = -(d_r + \phi + \varphi_r + \mu) + \rho_r c\beta_r. \tag{B.17}$$

It can be shown that the eigenvalues of (B.16) are expressed in terms of $R_e = \max\{R_s, R_r\}$, where R_s and R_r are the reproduction numbers of drug sensitive and drug-resistant TB only sub-models respectively as seen earlier. $R_e = \max\{R_s, R_r\}$ implies that the two TB strains (drug sensitive and drug-resistant) escalate each other. Thus, when the two reproduction numbers exceed unity, that is, $R_s > 1$ and $R_r > 1$, there is always coexistence (endemic case) of these two strains regardless of which reproduction number is greater as shown in Theorem 4. If $R_e = \max\{R_s, R_r\}$, then from Theorem 2, the drug sensitive TB only sub-model has a backward bifurcation for values of R_s such that $R_s^c < R_s < 1$ and Theorem 3 showed that the drug-resistant TB only sub-model exhibits backward bifurcation for values of R_r such that $R_r^c < R_r < 1$. Thus, the coexistence model of TB will also exhibit the phenomenon of backward bifurcation whenever $R_e = 1$

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