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Abstract. In this paper, we investigate the effect of the emergence of TB drug-resistant within a human population. We first propose a drug resistance in a tuberculosis transmission model with two strains of *Mycobacterium tuberculosis*: those that are sensitive to anti-tuberculosis drugs and those that are resistant. After, we present the theoretical results of the model. More precisely, we compute the disease-free equilibrium and derive the basic reproduction number $\mathscr{R}_0$ that determines the outcome of the disease. We show that there exists a threshold parameter ξ such that the disease-free equilibrium is globally asymptotically stable in a feasible region whenever $\mathscr{R}_0 \leq \xi < 1$, while when $\xi < \mathscr{R}_0 < 1$, the model exhibits the phenomenon of backward bifurcation and if $\mathscr{R}_0 > 1$, the disease-free equilibrium is unstable and there exists an unique endemic equilibrium which is stable. Conditions for the coexistence of sensitive and resistant strains are derived. We also show that the model undergoes the Hopf-bifurcation with respect to the transmission rates. A dynamically consistent non standard finite difference scheme is developed to illustrate and validate theoretical result. The motivation comes to the fact the classical Runge-Kutta scheme cannot preserve the positivity of solutions of the model.

Keywords: Tuberculosis; Drug resistance; Mathematical models; Stability; Hopf-bifurcation; Non standard finite difference scheme.

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1. INTRODUCTION

Tuberculosis (TB) remains a major health problem, especially in Africa and especially in the sub-Saharan countries. The World Health Organization (WHO) estimates that in 2015, 10.4 million people have contracted the disease and 1.8 million have died (including 0.4 million with HIV). More than 95% of TB deaths occur in low and middle income countries [1].

Tuberculosis is an infectious and contagious disease caused by the infection with *Mycobacterium tuberculosis*. TB is transmitted from person to person by air. When a person with pulmonary tuberculosis coughs, sneezes or spits, they throw tubercle bacilli into the air. One need to inhale only a few to get infected. According to the report of WHO [1], approximately one-third of the world's population has latent tuberculosis, i.e. they have been infected with the tubercle bacillus but are not (yet) sick and can not transmit the disease [1,2]. Throughout their lives, individuals infected with tubercle bacilli have 10% chance of developing the disease. On the other hand, the risk is much higher for those who have a deficient immune system, such as people living with HIV, reary alcohol drinking, malnourished or with diabetes. TB is the leading cause of death among HIV-positive people: by 2015, 35% of HIV-positive deaths were due to TB. When active tuberculosis occurs, symptoms (cough, fever, night sweats or weight loss) may remain mild for many months, which can lead to delay in referral and transmission of the bacillus to others. A subject with active TB can infect 10 to 15 other people a year during his close contacts. In the absence of treatment, an average of 45% of HIV-negative tuberculosis patients will die, as will virtually all those who are also HIV-positive. The WHO estimates that by 2020, one billion people will contract TB and 35 million will die [6,7]. Africa is also at the receiving end of TB. At least 1.5 million TB cases are diagnosed every year on this continent. TB greatly contributes in numerous deaths of people leaving with HIV/AIDS in Africa. Individuals infected with HIV are particularly susceptible to acquiring TB infection, TB increases an individual's rate of progression from asymptomatic HIV to AIDS, and shortens survival time [6-8].

Tuberculosis is a disease that can be cured. For drug-susceptible active tuberculosis, a standard 6-month treatment with 4 anti-tuberculosis medicines is administered through the provision of information, surveillance and patient support provided by a trained health worker or volunteer. Drug resistant tuberculosis (MDR-TB) is a form of the disease caused by a bacillus that is not responsive to isoniazid and rifampicin, the two most effective first-line anti-tuberculosis drugs. MDR-TB can be treated and cured with second-line drugs. Without this support, adherence may be difficult and the disease can spread [9]. Drug resistance can either be acquired during treatment or transmitted from individuals infected with drug-resistant strains. An individual develops acquired drug resistant TB (ADR-TB) due to treatment failure. Spread of TB via individuals infected with drug resistant TB causes the newly-infected individuals to develop transmitted drug resistant TB. Acquired drug resistance always initiates an epidemic of drug-resistant TB, but if the drug-resistant pathogen is transmissible, the risk of primary drug resistance increases over time. However, these therapeutic options are more limited and require long-term (up to two years) treatment of both expensive and toxic drugs. In some cases, severe resistance may develop; we are talking about highly drug-resistant tuberculosis, which is an even more serious form of MDR-TB due to bacilli that do not respond to the most effective second-line drugs, often leaving patients without any other therapeutic option. By 2015, WHO estimates that approximately 480,000 people have developed MDR-TB worldwide [9-11].

The dynamics of tuberculosis is complex due to the multiple interactions between the human host and *Mycobacterium tuberculosis*, the increasing HIV epidemic in the early 1990s leading to HIV/TB co-infection, the emergence of drug resistant TB, immigration to the US from developing countries, increased mass transportation, malnutrition, heavy alcohol drinking, smoking, co infection with diabetes mellitus but also indoor air pollution from solid fuels. A deep understanding of the disease dynamics would have a significant impact on the effective prevention and control strategies [12,13]. Mathematical modeling and numerical simulations have the potential, and offer a promising way, to achieve this. Many efforts have been and are still being devoted to the modeling of this disease. As in the study of many other infectious diseases, modeling efforts on TB have mainly focused on mean-field compartmental models, either deterministic or stochastic, and agent-based models [14-34]. Recent global reports of multidrug

resistant and extensively drug-resistant tuberculosis have renewed concerns that antibiotic resistance may undermine progress in tuberculosis control [35-47]. Including MDR tuberculosis in mathematical models is relatively new and there are very few models with this aspect. However none of the works mentioned above has considered the global stability of the disease-free equilibrium, and the Hopf bifurcation analysis.

Motivated by the above discussion, this paper investigates the impact of drug resistance as a competition between multiples types of strains of Mycobacterium tuberculosis: those that are sensitive to anti-tuberculosis drugs and those that are resistant. We first present a deterministic model for the dynamical transmission of TB that captures the essential biological and epidemiological features of the disease such as exogenous reinfections and drug resistance. Drug resistant is modelled by the competition between two types of strains: sensitive and resistant to drugs. We present the mathematical analysis of the model. More precisely, we compute the disease-free equilibrium and derive the basic reproduction number $\mathscr{R}_0$ that determines the outcome of the disease. We show that there exists a threshold parameter ξ such that when $0 < \mathscr{R}_0 < \xi < 1$, the disease-free equilibrium is globally asymptotically stable, while when $\xi < \mathscr{R}_0 < 1$, the model exhibits the phenomenon of backward bifurcation. Sufficient conditions for the existence and local stability of the interior and boundaries equilibria are also presented. We also describe how coexistence of boundaries equilibria is shaped by the outcome of the drug resistance. Two coexistence thresholds have been calculated: the first separates the region where resistant strain only persists from the region of coexistence and the second marks the shift from the region of coexistence to persistence of resistant strain alone. Theoretical results are illustrated using numerical simulations based on a dynamically consistent non standard finite difference scheme. We also show that the model undergoes the Hopf-bifurcation with respect to TB transmission rates. The existence of Hopf-bifurcation has been counterchecked by the software Matcont (MATLAB package for numerical bifurcation analysis).

The paper is organized as follows. A TB model with two-strains is formulated in Section 2. In Section 3, we present the quantitative and qualitative analysis of the model. In section 4, we propose a numerical scheme based on a dynamically consistent non standard finite difference scheme to verify the effectiveness and the efficiency of theoretical results.

2. MODEL CONSTRUCTION

In this section, we process with the construction of a mathematical model for the drug resistance of TB. The resistant cases may emerge when individuals are infected with a resistant strain (primary resistance) or as a result of treatment failure (acquired resistance). We specify drug-resistant and drug-sensitive strains by adding subscripts r and s to model variables and parameters. We consider two strains of TB: the regular TB (sensitive TB or strain 1) and the resistant TB (strain 2). We consider a finite population of N people divided in five classes: S who have not Infected, E_s regular TB who have infected but not infectious, E_r resistant TB who have infected but not infectious, I_s regular TB with active disease and I_r resistant TB with active TB. The subscripts s and r stand for sensitive strain and resistant strains, respectively. Thus, the total population at time t is

$$(1) \qquad N(t) = S(t) + E_s(t) + I_s(t) + E_r(t) + I_r(t).$$

We assume that infected individuals in the active stage of TB can transmit only same strain of the disease and that at certain rate latent individuals with regular strain develop resistant strain because of incomplete treatment. Furthermore, we assume that the treatment rate of resistant infectious with TB is small than the treatment rate for regular infectious with TB. We also assume that a fraction of infectious individuals with active sensitive TB progress into the infectious class of resistant strain due to treatment failure. This corresponds to cases of acquired resistance.

The flowchart of the model is depicted in Fig.1.

Susceptible individuals acquire TB infection following effective contact with TB infected individuals in the infectious stage with strain sensitive (i.e. those in I_s class) or with TB infected individuals in the infectious stage with strain resistant, (i.e. those in I_r class) with the forces of infection λ_s and λ_r defined, respectively by

$$(2) \qquad \lambda_s = \beta_s \frac{I_s}{N} \qquad \text{and} \qquad \lambda_r = \beta_r \frac{I_r}{N},$$

where β_s and β_r are the average proportions of susceptible infected by one infectious individual of the strain sensitive and resistant per contact per unit of time respectively.
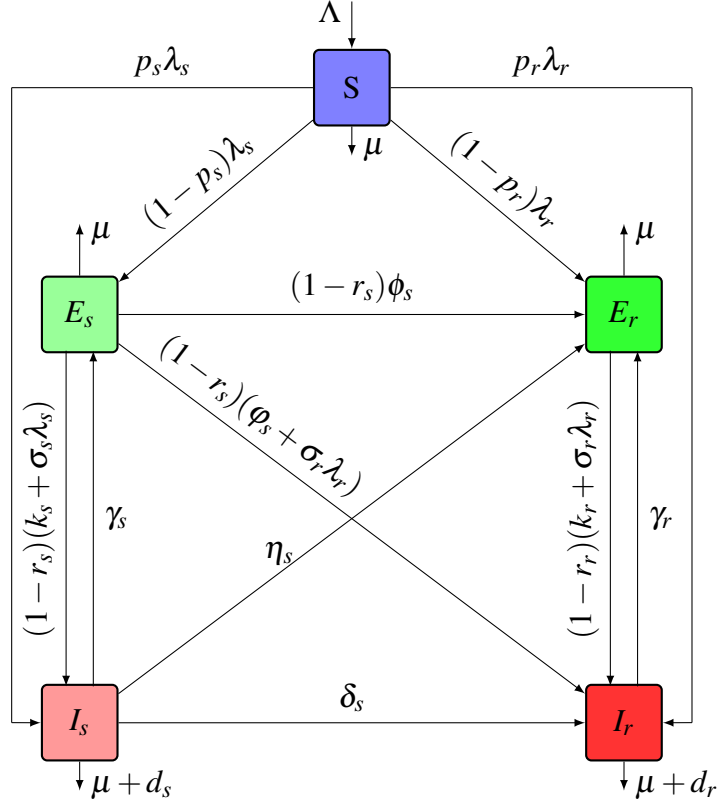
FIGURE 1. Structure of the model.

The transfer diagram in Fig.1 can be represented by the following system of differential equations:

(3)
$$
\begin{cases}
\dot{S} &= \Lambda - (\lambda_s + \lambda_r + \mu)S, \\
\dot{E_s} &= \lambda_s(1 - p_s)S + \gamma_s I_s - (1 - r_s)(\sigma_s \lambda_s + \sigma_r \lambda_r)E_s - A_1 E_s, \\
\dot{E_r} &= \lambda_r(1 - p_r)S + \gamma_r I_r - (1 - r_r)\sigma_r \lambda_r E_r + (1 - r_s)\phi_s E_s + \eta_s I_s - A_3 E_r, \\
\dot{I_s} &= \lambda_s p_s S + (1 - r_s)k_s E_s + (1 - r_s)\sigma_s \lambda_s E_s - A_2 I_s, \\
\dot{I_r} &= \lambda_r p_r S + (1 - r_r)(k_r + \sigma_r \lambda_r)E_r + (1 - r_s)(\varphi_s + \sigma_r \lambda_r)E_s + \delta_s I_s - A_4 I_r,
\end{cases}
$$

where

$$
\begin{aligned}
A_1 &= (1 - r_s)(k_s + \phi_s + \varphi_s) + \mu, \quad A_2 = \gamma_s + \delta_s + \eta_s + \mu + d_s, \\
A_3 &= k_r(1 - r_r) + \mu \quad \text{and} \quad A_4 = \gamma_r + \mu + d_r.
\end{aligned}
$$

The recruitment is Λ, p_s and p_r are the proportions of newly infected individuals who are assumed to undergo fast progression directly to infectious classes I_s and I_r respectively; while

the remainder are latently infected and enter the exposed classes E_s and E_r respectively; r_s and r_r, are respectively, the per-capita chemoprophylaxis treatment rates of TB latently individuals in the E_s, E_r classes, $k_s(1-r_s)$ and $k_r(1-r_r)$, are respectively the rates at which TB infected individuals with strains 1 and 2 leave the latent classes E_r and E_s, to the infectious classes I_s and I_r; the per-capita natural death rate is denotes by μ; d_r and d_s stand for the per-capita disease induced death rates with strains 1 and 2; γ_s and γ_r are respectively the per-capita treatment rates for TB infectious with strains 1 and 2, $\phi_s(1-r_s)E_s$ the proportions of those TB treated infected individuals with strain 1 who did not complete their chemoprophylaxis treatment and develop resistant TB; $\eta_s I_s$ and $\delta_s I_s$ are the proportions of those TB treated infected individuals with strain 1 who did not complete their treatment and develop resistant TB; σ_s and σ_r are, factors reducing the risk of infection as a result of acquiring TB immunity for individuals in the E_s, E_r classes respectively.

Table 1 summarizes the model variables and their units.

Table 1: Variables and parameters with units of model system (3)

Symbol	Description	Units
$S(t)$	Susceptible individuals	individual
$E_s(t)$	TB-latently infected individuals with sensitive strain	individual
$I_s(t)$	TB-infectious with sensitive strain	individual
$E_r(t)$	TB-latently infected individuals with resistant strain	individual
$I_r(t)$	TB-infectious with resistant strain	individual

3. QUANTITATIVE AND QUALITATIVE ANALYSIS

In this section, we present the theoretical analysis of system (3).

3.1. Basic properties.

Herein, we study the basic properties of solutions of system (3), which are essential in the proof of stability results. We have the following result.

Theorem 1. *System (3) is a dynamical system on the biologically feasible compact domain:*

$$(4) \qquad \Omega = \left\{ (S, E_s, E_r, I_s, I_r) \in \mathbb{R}_+^5, \quad N_\# \leq N(t) \leq S_0 \right\},$$

where

$$S_0 = \frac{\Lambda}{\mu} \quad and \quad N_\# = \frac{\Lambda}{\mu + d_s + d_r}.$$

Proof: The proof is provided in two steps.

Step 1: We show that the solution $S(t)$, $E_s(t)$, $E_r(t)$, $I_s(t)$ and $I_r(t)$ of system (3) correspond-ing to initial conditions such that $S(0)$, $E_s(0)$, $E_r(0)$, $I_s(0)$ and $I_r(0)$ are non negative. Assume that $\bar{t} = \sup\{t > 0 : S > 0, E_s > 0, E_r \geq 0, I_s \geq 0, I_r \geq 0\} \in [0,t]$. Thus, $\bar{t} > 0$ and it follows from the first equation of system (3), that

$$\frac{dS}{dt} = \Lambda - (\mu + \lambda(t))S,$$

where $\lambda(t) = \lambda_s(t) + \lambda_r(t)$. The above equation can be rewritten as

$$\frac{d}{dt}\left[S(t)\exp\left\{\mu t + \int_0^t \lambda(s)ds\right\}\right] \geq \Lambda\exp\left\{\mu t + \int_0^t \lambda(s)ds\right\}.$$

Hence,

$$S(\bar{t})\exp\left\{\mu\bar{t} + \int_0^{\bar{t}} \lambda(s)ds\right\} - S(0) \geq \int_0^{\bar{t}} \Lambda\exp\left\{\mu u + \int_0^u \lambda(w)dw\right\}du,$$

so that

$$\begin{aligned}
S(\bar{t}) \geq\ & S(0)\exp\left\{-\left(\mu\bar{t} + \int_0^{\bar{t}} \lambda(s)ds\right)\right\} \\
& + \exp\left\{-\left(\mu\bar{t} + \int_0^{\bar{t}} \lambda(s)ds\right)\right\} \times \int_0^{\bar{t}} \Lambda\exp\left\{\mu u + \int_0^u \lambda(w)dw\right\}du > 0.
\end{aligned}$$

Similarly, it can be shown that $E_s(t) > 0$, $E_r(t) > 0$, $I_s(t) > 0$ and $I_r(t) > 0$ for all $t > 0$.

Step 2: We prove that the total population at time t, $N(t)$ satisfies the boundedness property

$$N_\# \leq N(t) \leq S_0 \quad whenever \quad N_\# \leq N(t_0) \leq S_0.$$

Adding all the equations in the differential system (3) gives

$$(5) \qquad\qquad \dot{N}(t) = \Lambda - \mu N(t) - d_s I_s(t) - d_r I_r(t).$$

From Eq.(5), one has that

$$(6) \qquad\qquad \Lambda - (\mu + d_s + d_r)N(t) \leq \dot{N}(t) \leq \Lambda - \mu N(t).$$

Applying the Gronwall inequality to Eq.(6) gives

$$\frac{\Lambda}{\mu + d_s + d_r}\left(1 - e^{-(\mu + d_s + d_r)t}\right) + S(0)e^{-(\mu + d_s + d_r)t} \leq N(t) \leq S(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t}),$$

which implies that $N_\# \leq N(t) \leq S_0$.

Combining *Step 1* and *Step 2*, Theorem 1 follows from the classical theory of dynamical systems. This concludes the proof.

$\square$

3.2. The disease-free equilibrium (DFE) and its stability.

The global behaviour of system (3) crucially depends on the basic reproduction number $\mathscr{R}_0$, i.e. an average number of secondary cases produced by a single infective individual which is introduced into an entirely susceptible population.

The DFE of system (3) is

$$(7) \qquad\qquad Q_0 = (S_0, 0, 0, 0, 0),$$

where $S_0 = \Lambda/\mu$. The basic reproduction number $\mathscr{R}_0$ is computed using the next generation operator method developed in van den Driessche and Watmough [48,49] which is the dominant eigenvalue of the next generation matrix. Using the method of van den Driessche and Watmough [49], the basic reproduction number $\mathscr{R}_0$ (see Appendix A for the calculation of $\mathscr{R}_0$) of system (3) is

$$(8) \qquad\qquad \mathscr{R}_0 = \max\{\mathscr{R}_{0_s}, \mathscr{R}_{0_r}\},$$

where

$$(9) \quad \mathscr{R}_{0_s} = \frac{\beta_s[p_s\mu + p_s(1 - r_s)(\phi_s + \varphi_s) + k_s(1 - r_s)]}{A_1 A_2 - \gamma_s k_s(1 - r_s)} \quad \text{and} \quad \mathscr{R}_{0_r} = \frac{\beta_r[p_\mu + k_r(1 - r_r)]}{A_3 A_4 - \gamma_r k_r(1 - r_r)},$$

with

$$A_1 A_2 - \gamma_s k_s(1 - r_s) = k_s(1 - r_s)(\delta_s + \eta_s + \mu + d_s) + ((1 - r_s)(\phi_s + \varphi_s) + \mu)A_2 \quad \text{and}$$

$$A_3 A_4 - \gamma_r k_r(1 - r_r) = k_r(1 - r_r)(\mu + d_r) + \mu(\gamma_r + \mu + d_r).$$

The threshold parameters $\mathscr{R}_{0_s}$ and $\mathscr{R}_{0_r}$ can be interpreted as the average number of secondary infectious cases that an infectious individual (with a sensitive or a resistant strain, respectively) would generate in an otherwise uninfected population.

The relevance of the basic reproduction number is due to the following result established in [49].

Lemma 1. *The DFE Q_0 of system (3) is locally asymptotically stable (LAS) if $\mathscr{R}_0 < 1$, and unstable if $\mathscr{R}_0 > 1$.*

The biological implication of Lemma 1 is that, a sufficiently small flow of infected individuals will not generate an outbreak of the disease unless $\mathscr{R}_0 > 1$. For a better control of the disease, the global asymptotic stability (GAS) of the DFE is needed. To do so, we use the result of Kamgang and Sallet [50] for the global stability of the disease-free equilibrium for a class of epidemiological models.

Following Kamgang and Sallet [50], system (3) can be rewritten in the following form:

$$(10) \qquad \begin{cases} \dot{x}_1 = A_1(x)(x_1 - x_1^0) + A_{12}(x)x_2, \\ \dot{x}_2 = A_2(x)x_2, \end{cases}$$

where $x_1 = S$ represents the uninfected class (susceptible class) and $x_2 = (E_s, I_s, E_r, I_r)^T$ represent the infected classes (TB-latently infected individuals with sensitive strain, TB-infectious with sensitive strain, TB-latently infected individuals with resistant strain, and TB-infectious with resistant strain), $x = (x_1, x_2)^T$ denotes the all states of system (3), $x_1^0 = \Lambda/\mu$ the non-zero component of the disease-free equilibrium,

$$A_1(x) = -\mu, \qquad A_{12}(x) = \left(0, -\beta_s \frac{S}{N}, 0, -\beta_r \frac{S}{N} \right)$$

and

$$A_2(x) = \begin{pmatrix} -P_1 - A_1 & \gamma_s + \beta_s(1 - p_s)\dfrac{S}{N} & 0 & 0 \\ (1 - r_s)(k_s + \sigma_s \lambda_s) & \beta_s p_s \dfrac{S}{N} - A_2 & 0 & 0 \\ (1 - r_s)\phi_s & 0 & P_2 & P_3 \\ (1 - r_s)(\varphi_s + \sigma_r \lambda_r) & \delta_s & P_4 & P_5 \end{pmatrix},$$

with

$$P_1 = (1 - r_s)(\sigma_s \lambda_s + \sigma_r \lambda_r), \qquad P_2 = -(1 - r_r)\sigma_r \lambda_r - A_3, \qquad P_3 = \gamma_r + \beta_r(1 - p_r)\frac{S}{N},$$

$$P_4 = (1 - r_r)(k_r + \sigma_r \lambda_r) \quad \text{and} \quad P_5 = \beta_r p_r \frac{S}{N} - A_4.$$

The following conditions $\mathbf{H_1}$-$\mathbf{H_5}$ below must be met to guarantee the global asymptotic stability of Q_0.

$\mathbf{H_1}$: System (10) is defined on a positively invariant set $\mathscr{D}$ of Ω and it is dissipative on $\mathscr{D}$.

$\mathbf{H_2}$: The sub-system $\dot{x}_1 = A_1(x_1,0)(x_1 - x_1^0)$ is globally asymptotically stable at the equilibrium x_0^1 on the canonical projection of $\mathscr{D}$ on Ω.

$\mathbf{H_3}$: The matrix $A_2(x)$ is Metzler (A Metzler matrix is a matrix with off-diagonal entries nonnegative [51,52]) and irreducible for any given $x \in \mathscr{D}$.

$\mathbf{H_4}$: There exists an upper-bound matrix $\overline{A}_2$ for $\mathscr{M} = \{A_2(x),\ x \in \mathscr{D}\}$ with the property that either $A_2 \in \mathscr{M}$ (i.e. $A_2 = \max\limits_{\mathscr{D}} \mathscr{M}$), then for any $\overline{x} \in \mathscr{D}$ such that $\overline{A}_2 = A_2(\overline{x}), \overline{x} \in \mathscr{D} \times \{0\}$ (i.e. the points where the maximum is realized are contained in the disease-free sub-manifold).

$\mathbf{H_5}$: $\alpha(\overline{A}_2) \leq 0$ where $\alpha(\overline{A}_2)$ denotes the largest real part of the eigenvalues of $\overline{A}_2$.

If the conditions $\mathbf{H_1} - \mathbf{H_5}$ are satisfied, then the DFE Q_0 is globally asymptotically stable in $\mathscr{D}$.

The result of the Kamgang-Sallet approach [50] uses the algebraic structure of system (10), namely the fact that $A_1(x)$ and $A_2(x)$ are Metzler matrices. Since in the said approach, the matrix $A_2(x)$ is required to be irreducible, we further restrict the domain of system to

$$\mathscr{D} = \{(x_1, x_2) \in \Omega,\ x_1 \neq 0\}. \tag{11}$$

The set $\mathscr{D}$ is positively invariant because only the initial point of any trajectory can have $x_1 = 0$ (see Theorem 1). Indeed, from the first and second equations of system (10), one has $S' > 0$ whenever $S = 0$. Thus,

$$A_2(x)\ \text{is Metzler and irreducible for all}\ x \in \mathscr{D}. \tag{12}$$

The sub-system:

$$\dot{x}_1 = A_1(x_1, 0)(x_1 - x_1^0),$$

can be expressed as

$$\dot{S} = -\mu \left(S - \frac{\Lambda}{\mu} \right). \tag{13}$$

Thus, $x_1^0 = S_0$ is a GAS equilibrium of the reduced system (13) on the sub-domain $\{x \in \mathscr{D},\ x_2 = 0\}$. Then, the hypothesis H_2 is satisfied. The result of Kamgang and Sallet (see [50], Theorem 4.3) gives the GAS of the DFE of a dissipative system of the form (10) which satisfies (12) and

hypothesis H_2 provided there exists a matrix $A_2(x)$ with the following additional properties:

$$(14) \quad \begin{cases} A_2(x) \leq \bar{A}_2, \quad x \in \mathscr{D}, \\ \text{if} \quad A_2(\bar{x}) = \bar{A}_2 \quad \text{for some} \quad \bar{x} = (\bar{x}_1, \bar{x}_2)^T \in \mathscr{D} \quad \text{then} \quad \bar{x}_2 = 0, \\ \alpha(\bar{A}_2) \leq 0. \end{cases}$$

Note that since $-(1-r_s)(\sigma_s\lambda_s + \sigma_r\lambda_r) < 0$, $-(1-r_r)\sigma_r\lambda_r < 0$ and $\dfrac{S}{N} \leq \dfrac{S_0}{N_\#}$, the upper bound $\bar{A}_2(x)$ of $A_2(x)$ is

$$\bar{A}_2 = \begin{pmatrix} A & 0 \\ C & D \end{pmatrix},$$

where

$$A = \begin{pmatrix} -A_1 & \gamma_s + \beta_s(1-p_s)\dfrac{S_0}{N_\#} \\ (1-r_s)(k_s + \beta_s\sigma_s) & \beta_s p_s \dfrac{S_0}{N_\#} - A_2 \end{pmatrix}, \quad C = \begin{pmatrix} (1-r_s)\phi_s & 0 \\ (1-r_s)(\varphi_s + \beta_r\sigma_r)\dfrac{S_0}{N_\#} & \delta_s \end{pmatrix}$$

and

$$D = \begin{pmatrix} -A_3 & \gamma_r + \beta_r(1-p_r) \\ (1-r_r)(k_r + \beta_r\sigma_r) & \beta_r p_r \dfrac{S_0}{N_\#} - A_4 \end{pmatrix}.$$

The equality $A_2(x) = \bar{A}_2$ holds only when $S = N$ which implies that $x_2 = 0$. Therefore, the first and second conditions in (14) hold. Note that $\bar{A}_2$ is a Metzler matrix which satisfies the stability condition of Kamgang and Sallet [50].

Since $\bar{A}_2$ is a triangular matrix, its stability is associated with the stability of the matrices A and D.

Using Kamgang and Sallet's result [50], the sub-matrice A and D are stable Metzler matrice if

$$(15) \qquad\qquad \mathscr{R}_0 = \max\{\mathscr{R}_{0_s}, \mathscr{R}_{0_r}\} < \xi,$$

where

$$(16) \qquad\qquad \xi = \min\{\xi_s, \xi_r\},$$

with

$$
\xi_s = \frac{N_\#}{S_0}\left(1 - \frac{\beta_s \sigma_s (1-r_s)(\gamma_s N_\# + \beta_s S_0 (1-p_s))}{N_\#(A_1 A_2 - \gamma_s k_s (1-r_s))}\right) < 1,
$$

(17)

$$
\xi_r = \frac{N_\#}{S_0}\left(1 - \frac{\beta_r \sigma_r (1-r_r)\left[\gamma_r N_\# + \beta_r (1-p_r) S_0\right]}{N_\#(A_3 A_4 - \gamma_r k_r (1-r_r))}\right) < 1.
$$

We can now apply Theorem 4.3 in Kamgang and Sallet [50] and conclude that under the condition (15), the disease-free equilibrium $(x_1^0, 0)$ of system (3) is GAS in $\mathscr{D}$. From Eq. (11), for the points of $\mathscr{D}$ where $x_1 = 0$, and from Eq. (15) the disease-free equilibrium is GAS on Ω.

We have established the following result for the global stability of the DFE Q_0.

Theorem 2. *The disease free equilibrium point Q_0 of system (3) is GAS if $\mathscr{R}_0 \leq \xi < 1$ and unstable if $\mathscr{R}_0 > 1$ in Ω. However, when $\xi \leq \mathscr{R}_0 < 1$, the backward bifurcation phenomenon occurs, i.e. the DFE may coexists with two endemic equilibria, one asymptotically stable and one unstable.*

3.3. Endemic equilibria and their stabilities.

3.3.1. *Steady states.*

System (3) has one disease-free equilibrium, $Q_0 = (S_0, 0, 0, 0, 0, 0, 0)$ and endemic equilibria of the form $Q_s^* = (S_s^*, E_s^*, I_s^*, 0, 0)$, $Q_r^* = (S_r^*, 0, 0, E_r^*, I_r^*)$ and $Q^* = (S^*, E_s^*, I_s^*, E_r^*, I_r^*)$, corresponding, respectively, to states with only sensitive TB strain, only resistant TB strain and with both two TB strains (sensitive and resistant strains) are present. We point out that the sensitive TB strain (free-TB resistant strain) equilibrium point Q_s^* exists if and only if $\mathscr{R}_{0_s} > 1$, while the existence of the resistant TB strain (free-TB sensitive strain) equilibrium point Q_r^* will depends of the threshold parameter $\mathscr{R}_{0_r}$.

3.3.2. *Stability of boundary equilibria and coexistence.*

Herein, we study the existence and stability of boundary equilibria of system (3). We first study the existence and stability of the boundary endemic equilibrium point when only resistant TB strain persists in the host population.

Let $Q_r^* = (S_r^*, 0, 0, E_r^*, I_r^*)$ be the endemic equilibrium without TB sensitive strain with S_r^*, E_r^*, $I_r^* > 0$. In this case, $\beta_s = 0$ (so that $\lambda_s = 0$) and S_r^*, E_r^* and I_r^* satisfies the following system of equations:

(18)
$$\begin{cases} \Lambda - \lambda_r^* S_r^* - \mu S_r^* = 0, \\ (1 - p_r)\lambda_r^* S_r^* - \sigma_r(1 - r_r)\lambda_r^* E_r^* + \gamma_r I_r^* - A_3 E_r^* = 0, \\ p_r \lambda_r^* S_r^* + \sigma_r(1 - r_r)\lambda_r^* E_r^* + k_r(1 - r_r)E_r^* - A_4 I_r^* = 0, \end{cases}$$

where $N_r^* = S_r^* + E_r^* + I_r^*$ and

(19)
$$\lambda_r^* = \beta_r \frac{I_r^*}{N_r^*},$$

is the force of infection at the steady state Q_r^*. From Eq. (18), one has

$$S_r^* = \frac{\Lambda}{\mu + \lambda_r^*}, \qquad E_r^* = \frac{\lambda_r^* S_r^* [(1 - p_r)A_4 + \gamma_r p_r]}{A_3 A_4 - \gamma_r k_r(1 - r_r) + \sigma_r(1 - r_r)(A_4 - \gamma_r)\lambda_r^*} \qquad \text{and}$$

(20)
$$I_r^* = \frac{\lambda_r^* S_r^* [k_r(1 - r_r) + \mu p_r + \sigma_r(1 - r_r)\lambda_r^*]}{A_3 A_4 - \gamma_r k_r(1 - r_r) + \sigma_r(1 - r_r)(A_4 - \gamma_r)\lambda_r^*}.$$

Substituting Eq. (20) into Eq. (19), it can be shown that the non-zero boundary endemic equilibrium with only resistant TB strain of system (3) satisfies the following equation in term of λ_r^*:

(21)
$$a_2(\lambda_r^*)^2 + a_1(\lambda_r^*) + a_0 = 0,$$

where

$$\begin{aligned} a_2 &= \sigma_r(1 - r_r), \\ a_1 &= \sigma_r(1 - r_r)(\mu + d_r - \beta_r) + (1 - p_r)(\mu + d_r) + \gamma_r + p_r \mu + k_r(1 - r_r), \\ a_0 &= \mathscr{R}_r^*(1 - \mathscr{R}_{0r}) \qquad \text{and} \qquad \mathscr{R}_r^* = \mu(\mu + d_r + \gamma_r) + k_r(1 - r_r)(\mu + d_r). \end{aligned}$$

Thus, the positive endemic equilibrium point Q_r^* is obtained by solving for λ_r^* from the quadratic equation (21) and substituting the result (positive values of λ_r^*) into the expressions in Eq. (19). Clearly, the coefficients a_2 of Eq. (21) is always positive, and a_0 is positive or negative if $\mathscr{R}_{0r}$ is less than or greater than unity, respectively. Thus, the number of possible real roots of the polynomial (21) can have depends on the signs of a_2, a_1 and a_0. We have the following result.

Lemma 2. *System (3) with only resistant TB strain has*

(i): *a unique endemic equilibrium when $a_0 < 0$, i.e., $\mathscr{R}_{0_r} > 1$,*

(ii): *a unique endemic equilibrium when $a_1 < 0$, and $a_0 = 0$ or $a_1^2 - 4a_2a_0 = 0$,*

(iii): *two endemic equilibria when $a_0 > 0$, $a_1 < 0$ and $a_1^2 - 4a_2a_0 > 0$,*

(iv): *no endemic equilibria in the other cases.*

Now, we derive a threshold condition for the coexistence which is equivalent to a threshold condition for the sensitive TB endemicity in a population where resistant strains are at the equilibrium. To do so, we compute the region of stability of the boundary equilibrium point Q_r^* when $\mathscr{R}_{0_r} > 1$ (so that system (3) has only one sensitive TB-free equilibrium). We measure the capacity of the sensitive TB strain to invade a population where resistant TB strain is already endemic (cases (i), (ii) and (iii) of Lemma 2). Then, $Q_r^* = (S_r^*, E_r^*, I_r^*, 0, 0)$ corresponds to the equilibrium free of sensitive TB strain. Applying the method of van den Driessche in [49] once again, the basic reproduction ratio of the sensitive TB in a population where resistant TB strain is fixed (see Appendix B for details) is

$$(22) \qquad \mathscr{R}_{0_s}(Q_r^*) = \frac{\beta_s S_r^* [k_s(1 - r_s) + p_s(\mu + (1 - r_s)(\phi_s + \varphi_s) + \sigma_r \lambda_r^*)]}{N_r^* [A_1 A_2 - \gamma_s k_s(1 - r_s) + A_2 \sigma_r \lambda_r^*(1 - r_s)]},$$

where $N_r^* = S_r^* + E_r^* + I_r^*$ and $\lambda_r^* = \beta_r \dfrac{I_r^*}{N_r^*}$. The corresponding result for the stability of boundary equilibrium point Q_r^* is expressed by Lemma 3, stated below.

Lemma 3. *If $\mathscr{R}_{0_r} > 1$, the boundary endemic equilibrium Q_r^* of system (3) is stable if $\mathscr{R}_{0_s}(Q_r^*) < 1$ and unstable if $\mathscr{R}_{0_s}(Q_r^*) > 1$.*

Lemma 3 gives a condition for the coexistence, now equivalent to a threshold condition for the sensitive TB endemicity in a population where the resistant strains is at the equilibrium, $\mathscr{R}_{0_s}(Q_r^*) = 1$: only resistant TB strains persist for $\mathscr{R}_{0_s}(Q_r^*) < 1$, while for $\mathscr{R}_{0_s}(Q_r^*) > 1$ sensitive strains can invade a population where resistant strains are fixed, that is, to say coexistence is possible.

Now, we study the existence and stability of endemic equilibria when only sensitive TB strains persists in the host population.

Let $Q_s^* = (S_s^*, E_s^*, I_s^*, 0, 0)$ be the endemic equilibrium without resistant TB strain with $S_s^*, E_s^*, I_s^* > 0$. In this case, $\beta_r = 0$ (so that $\lambda_r = 0$) and S_s^*, E_s^* and $I_s^* > 0$ satisfies the following

system of equations:

(23)
$$\begin{cases} \Lambda - \lambda_s^* S_s^* - \mu S_s^* = 0, \\ (1-p_s)\lambda_s^* S_s^* - (1-r_s)\sigma_s\lambda_s^* E_s^* + \gamma_s I_s^* - A_1 E_s^* = 0, \\ p_s\lambda_s^* S_s^* + (1-r_s)\sigma_s\lambda_s^* E_s^* + (1-r_r)k_s E_s^* - A_2 I_s^* = 0, \end{cases}$$

where $N_s^* = S_s^* + E_s^* + I_s^*$ and

(24)
$$\lambda_s^* = \beta_s \frac{I_s^*}{N_s^*},$$

is the force of infection at the steady state Q_s^*. From Eq. (23), one has that

$$S_s^* = \frac{\Lambda}{\mu + \lambda_s^*}, \qquad E_s^* = \frac{\lambda_s^* S_s^*[(1-p_s)A_2 + \gamma_s p_s]}{A_1 A_2 - \gamma_s k_s(1-r_s) + (1-r_s)(A_4 - \gamma_s)\sigma_s\lambda_s^*} \qquad \text{and}$$

(25)

$$I_s^* = \frac{\lambda_s^* S_s^*[k_s(1-r_s) + \mu p_s + (1-r_s)\sigma_s\lambda_s^*]}{A_1 A_2 - \gamma_s k_s(1-r_s) + (1-r_s)(A_4 - \gamma_s)\sigma_s\lambda_s^*}.$$

Substituting the expressions of S_s^*, E_s^* and I_s^* given in Eq. (25) in Eq. (24), it can be shown that the non-zero boundary equilibria without resistant TB strain of system (3) satisfies the following second order polynomial in term of λ_s^*:

(26)
$$b_2(\lambda_s^*)^2 + b_1(\lambda_s^*) + b_0 = 0,$$

where

$$\begin{aligned} b_2 &= \sigma_s(1-r_s), \\ b_1 &= \sigma_s(1-r_s)(\mu + d_s - \beta_s) + (1-p_s)(\mu + d_s) + \gamma_s + p_s\mu + k_s(1-r_s), \\ b_0 &= \mathscr{R}_s^*(1-\mathscr{R}_{0_s}) \qquad \text{and} \qquad \mathscr{R}_s^* = \mu(\mu + d_s + \gamma_s) + k_s(1-r_s)(\mu + d_s). \end{aligned}$$

Thus, positive endemic equilibria Q_s^* can be obtained by solving for λ_s^* from the quadratic equation (26) and replacing positive values of λ_s^* into the force of infection at defined as in Eq. (24). Note that the coefficients b_2 in Eq. (26) is always positive, while b_0 is positive or negative if $\mathscr{R}_{0_s}$ is less than or greater than unity, respectively. Thus, the number of possible real roots of the polynomial (26) can have depends on the signs of b_2, b_1 and b_0. We have the following result.

Lemma 4. *System (3) with only sensitive TB strain has*

    (i): *a unique endemic equilibrium when $b_0 < 0$, i.e., $\mathscr{R}_{0_s} > 1$,*

(ii): *a unique endemic equilibrium when $b_1 < 0$, and $b_0 = 0$ or $b_1^2 - 4b_2b_0 = 0$,*

(iii): *two endemic equilibria when $b_0 > 0$, $b_1 < 0$ and $b_1^2 - 4b_2b_0 > 0$,*

(iv): *no endemic equilibria in the other cases.*

Remark 1. *The cases (iii) of Lemma 2 and 4 indicate the possibility of backward bifurcation (where a locally asymptotically stable DFE co-exists with a locally asymptotically stable endemic equilibrium when $\mathscr{R}_0 < 1$ [53-56]), in system (3) with sensitive TB strain alone when $\mathscr{R}_{0_s} < 1$ and with resistant TB strain alone when $\mathscr{R}_{0_r} < 1$.*

Now, let us compute the region of stability of the boundary equilibrium Q_s^* when $\mathscr{R}_{0_s} > 1$ (so that system (3) has only one sensitive TB strain free equilibrium). We use the same reasoning as before. Suppose that the resistant TB strain can invade a population where the sensitive TB strain is already endemic (cases (i), (ii) and (iii) of Lemma 4). Then, the boundary endemic equilibrium point $Q_s^* = (S_s^*, E_s^*, I_s^*, 0, 0)$ corresponds to the equilibrium free of resistant TB strain. Applying the method of van den Driessche [49] once again, the basic reproduction ratio of the sensitive TB strain in a population where the sensitive TB strain is fixed (see Appendix C for details) is

$$(27) \qquad \mathscr{R}_{0_r}(Q_s^*) = \frac{\beta_r S_s^* [k_r(1 - r_r) + \mu p_r]}{N_s^* [A_3 A_4 - \gamma_r k_r(1 - r_r) + A_3(1 - r_s)\beta_r \sigma_r E_s^*]},$$

where λ_s^* and $N_s^* = S_s^* + E_s^* + I_s^*$ are defined in Eqs. (25) and (24)-(26), respectively.

The corresponding result for the stability of the boundary equilibrium Q_s^* is expressed by Lemma 5, stated below.

Lemma 5. *If $\mathscr{R}_{0_s} > 1$, the boundary endemic equilibrium Q_s^* of system (3) is stable whenever $\mathscr{R}_{0_r}(Q_s^*) < 1$ and unstable whenever $\mathscr{R}_{0_r}(Q_s^*) > 1$.*

The local stability of the endemic equilibrium of system (3) is given in Theorem 3 and proved in Appendix D.

Theorem 3. *The endemic equilibria Q_s^* and Q_r^* of system (3) are locally asymptotically stable when $\mathscr{R}_{0_s} > 1$ and $\mathscr{R}_{0_r} > 1$ but with $\mathscr{R}_0$ near 1 if condition (50) given in Appendix D is satisfied.*

3.4. Hopf bifurcation.

Herein, we study the Hopf bifurcation of system (3) around the endemic equilibria $Q_s^* = (S_s^*, E_s^*, I_s^*, 0, 0)$ and $Q_r^* = (S_r^*, 0, 0, E_r^*, I_r^*)$.

The variational matrix at Q_s^* is

$$J(Q_s^*) = \begin{pmatrix} -m_1 & 0 & -m_2 \\ m_3 & -m_4 & m_5 - m_6 \\ m_7 & m_8 & m_6 + m_9 \end{pmatrix},$$

where

$$m_1 = \lambda_s + \mu, \ m_2 = \frac{\beta_s S_s^*}{N_s}, \ m_3 = (1 - p_s)\lambda_s^*, \ m_4 = (1 - r_s)\sigma_s \lambda_s^* + A_1, \ m_5 = (1 - p_s)\beta_s \frac{S_s^*}{N_s} + \gamma_s;$$

$$m_6 = (1 - r_s)\sigma_s \beta_s \frac{E_s^*}{N_s}, \ m_7 = \lambda_s^* p_s, \ m_8 = (1 - r_s)(k_s + \sigma_s \lambda_s^*) \quad and \quad m_9 = \beta_s p_s \frac{S_s^*}{N_s} - A_2.$$

The characteristic equation of the variational matrix $J(Q_s^*)$ is

$$(28) \qquad\qquad x^3 + B_1 x^2 + B_2 x + B_3 = 0,$$

where

$$B_1 = m_1 + m_4 - m_6 - m_9, \ B_2 = m_1(m_4 - b) + m_2 m_7 - c, \ B_3 = -m_1 c + d;$$

$$a = m_5 - m_6, \ b = m_6 + m_9, \ c = am_8 + bm_4 \quad and \quad d = m_2(m_3 m_8 + m_4 m_7).$$

The Routh-Hurtwitz criteria gives a set of necessary and sufficient conditions for the roots of Eq. (28) to have negative real part, that is

$$B_1 > 0, \quad B_3 > 0, \quad and \quad B_1 B_2 - B_3 > 0.$$

Considering β_s as the bifurcating parameter, we shall derive the transversality conditions for Hopf bifurcation around the endemic equilibrium point Q_s^*. We have the following result:

Theorem 4. *The endemic equilibrium point $Q_s^* = (S_s^*, E_s^*, I_s^*, 0, 0)$ undergoes the Hopf bifurcation as β_s varies over $\mathbb{R}$.*

Let $h :]0, +\infty[\to \mathbb{R}$ be a continuously differentiable function of β_s defined

$$(29) \qquad\qquad h(\beta_s) = B_1(\beta_s)B_2(\beta_s) - B_3(\beta_s).$$

Let β_0 be a positive root of $h(\beta_s) = 0$. Then, the subsystem of system (3) enters into the Hopf bifurcation around Q_s^* at $\beta_s = \beta_0 \in]0, +\infty[$ if and only if

(1) $B_i(\beta_s) > 0$ $i = 1, 2, 3$;

(2) $h(\beta_s) = 0$ *which gives two purely imaginary eigenvalues of the variational matrix $J(Q_s^*)$;*

(3) $B_1' B_2 + B_1 B_2' - B_3' \neq 0$, *and all other eigenvalues haspurely negative real parts.*

Proof: Using the condition $h(\beta_s) = 0$ the characteristic equation (28) takes the following form:

$$(x + B_1)\left(x^2 + B_2\right) = 0.$$

The roots of the above equation are, x_i for $i = 1, 2, 3$. Let the pair of purely imaginary roots at $\beta_s = \beta_0$ are x_1 and x_2, that is, $x_1 = \bar{x}_2$, then one has

(30) $$x_{1,2} = \pm\sqrt{B_2} = \pm\omega_0 \quad \text{and} \quad x_3 = -B_1 = -\omega < 0.$$

Now, we need to verify the transversality condition, to complete the discussion.

Since $h(\beta_s)$ is continuously differentiable function of all its roots, then there exists an open interval $\beta_s \in]\beta_0 - \varepsilon, \beta_0 + \varepsilon[$, where x_1 and x_2 are complex conjugate for β_s. Suppose their general forms in this neighbourhood are

$$x_1(\beta_s) = \alpha_1(\beta_s) + i\alpha_2(\beta_s) \quad and \quad x_2(\beta_s) = \alpha_1(\beta_s) - i\alpha_2(\beta_s).$$

The transversality condition is given by $\left[\dfrac{dx_i}{d\beta_s}(\beta_s)\right]_{\beta_s = \beta_0} \neq 0 \quad for \quad i = 1, 2$. Substituting $x_i(\beta_s) = \alpha_1(\beta_s) \pm \alpha_2(\beta_s)$ into the characteristic equation (28) and after differentiation, separating the real and imaginary parts, one has

(31) $$M_1(\beta_s)\, \alpha_1'(\beta_s) - M_2(\beta_s)\, \alpha_2'(\beta_s) + M_3(\beta_s) \;=\; 0,$$

(32) $$M_2(\beta_s)\, \alpha_1'(\beta_s) + M_1(\beta_s)\, \alpha_2'(\beta_s) + M_4(\beta_s) \;=\; 0,$$

where

$$M_1(\beta_s) \;=\; 3\left(\alpha_1^2 - \alpha_2^2\right) + 2B_1\alpha_1 + B_2, \quad M_2(\beta_s) = 2\alpha_2(3\alpha_1 + A_1);$$

$$M_3(\beta_s) \;=\; B_1'(\alpha_1^2 - \alpha_2^2) + B_2'\alpha_1, \quad \text{and} \quad M_4(\beta_s) = 2B_1'\alpha_1\alpha_2 + B_2'\alpha_2.$$

At $\beta_s = \beta_0$, one has

$$M_1(\beta_0) = -2B_2, \ M_2(\beta_0) = 2B_1\sqrt{B_2}, \ M_3(\beta_0) = -B_1'B_2, \ and \ M_4(\beta_0) = B_2'\sqrt{B_2}.$$

Solving the system (31)-(32) for $\alpha_1'(\beta_s)$ at $\beta_s = \beta_0$, one has

$$
(33) \quad
\begin{aligned}
\left[\frac{dx_i}{d\beta_s}(\beta_s)\right]_{\beta_s=\beta_0} &= \alpha_1'(\beta_0) = -\frac{M_1(\beta_0)M_3(\beta_0) + M_2(\beta_0)M_4(\beta_0))}{M_1(\beta_0)^2 + M_2(\beta_0)^2} \quad i = 1, 2; \\
&= -\frac{B_1'B_2 + B_1B_2' - B_3'}{2B_2 + 2B_1^2} \neq 0; \\
\Rightarrow \quad M &= B_1'B_2 + B_1B_2 - B_3' \neq 0.
\end{aligned}
$$

Thus, the transversality condition holds and the system (3) undergoes Hopf bifurcation at $\beta_s = \beta_0$. Hence, the contact rate β_s crosses its critical/threshold value, $\beta_s = \beta_0$, then all the individuals start oscillating around the endemic equilibrium point Q_s^*. This completes the proof. $\square$

Remark 2. *We have identical result at the endemic equilibrium point $Q_r^* = (S_r^*, 0, 0, E_r^*, I_r^*)$.*

Now, we shall derive the direction of the Hopf bifurcation, stability and period of bifurcating periodic solutions for system (3). We used the Poincar method to write system (3) into the normal form following the procedure outlined by Hassard [57]. Now, we compute the index number I from the Hopf bifurcation theorem [58], employing the central manifold theory [53]. For the sake of simplicity, we replace the current variables to the new variables (n_1, n_2, n_3) by considering the following transformations

$$n_1 = S - S^*, \quad n_2 = E_s - E_s^* \quad \text{and} \quad n_3 = I_s - I_s^*.$$

Then, system (3) can be written in the following matrix form:

$$(34) \qquad\qquad\qquad \dot{X} = AX + B,$$

where A represents the linear part and B stands for the non-linear part of system (3), one has

$$
X = \begin{pmatrix} n_1 \\ n_2 \\ n_3 \end{pmatrix}, \qquad
B = \begin{pmatrix} -\dfrac{\beta_s}{N_s} n_1 n_3 \\ (1-p_s)\dfrac{\beta_s}{N_s} n_1 n_3 - (1-r_s)\sigma_s \dfrac{\beta_s}{N_s} n_2 n_3 \\ p_s \dfrac{\beta_s}{N_s} n_1 n_3 - (1-r_s)\sigma_s \dfrac{\beta_s}{N_s} n_2 n_3 \end{pmatrix} \qquad \text{and}
$$

$$A = \begin{pmatrix} -\lambda_s^* - \mu & 0 & -\beta_s \dfrac{S^*}{N_s} \\ (1-p_s)\lambda_s^* & -(1-r_s)\sigma_s\lambda_s^* - A_1 & (1-p_s)\beta_s \dfrac{S^*}{N_s} - (1-r_s)\sigma_s\beta_s \dfrac{E_s^*}{N_s} + \gamma_s \\ p_s\lambda_s^* & (1-r_s)(k_s+\sigma_s\lambda_s^*) & p_s\beta_s \dfrac{S^*}{N_s} + (1-r_s)\sigma_s\beta_s \dfrac{E_s^*}{N_s} - A_2 \end{pmatrix}.$$

With this in mind, there exists a transformation matrix P that reduces the matrix A in the form:

$$P^{-1}AP = \begin{pmatrix} 0 & -\omega_0 & 0 \\ \omega_0 & 0 & 0 \\ 0 & 0 & -\omega \end{pmatrix},$$

where the nonsingular matrix P is given by

$$P = \begin{pmatrix} 1 & 0 & 1 \\ p_{21} & p_{22} & p_{23} \\ p_{31} & p_{32} & p_{33} \end{pmatrix},$$

with

$$p_{21} = a23a_{11} + \omega_0^2 - \beta_s^2 p_s \frac{S^* I_s^*}{N_s^2}, \quad p_{22} = a_{11} - a_{33},$$

$$p_{23} = (a_{11} - \omega)(a_{33} + \omega) - \beta_s^2 p_s \frac{S^* I_s^*}{N_s^2}, \quad p_{31} = -a_{11}, \ p_{32} = \omega_0 \quad \text{and} \quad p_{33} = \omega - a_{11}.$$

In order, to obtain the normal form for Eq. (34), we use the transformation $X = PY$. In this case, one has that

$$\dot{Y} = TY + R,$$

where

$$T = P^{-1}AP, \quad R = P^{-1}f = \begin{pmatrix} R_1(y_1, y_2, y_3) \\ R_2(y_1, y_2, y_3) \\ R_3(y_1, y_2, y_3) \end{pmatrix} \quad \text{and} \quad f = \begin{pmatrix} f_1(y_1, y_2, y_3) \\ f_2(y_1, y_2, y_3) \\ f_3(y_1, y_2, y_3) \end{pmatrix},$$

with

$$f_1(y_1, y_2, y_3) = -\frac{\beta_s}{N_s}(y_1 + y_3)(p_{31}y_1 + p_{32}y_2 + p_{33}y_3),$$

$$f_2(y_1, y_2, y_3) = (1 - p_s)\frac{\beta_s}{N_s}(y_1 + y_3)(p_{31}y_1 + p_{32}y_2 + p_{33}y_3)$$

$$- (1 - r_s)\frac{\beta_s \sigma_s}{N_s}(p_{21}y_1 + p_{22}y_2 + p_{23}y_3)(p_{31}y_1 + p_{32}y_2 + p_{33}y_3),$$

$$f_3(y_1, y_2, y_3) = \frac{\beta_s p_s}{N_s}(y_1 + y_3)(p_{31}y_1 + p_{32}y_2 + p_{33}y_3)$$

$$+ (1 - r_s)\frac{\beta_s \sigma_s}{N_s}(p_{21}y_1 + p_{22}y_2 + p_{23}y_3)(p_{31}y_1 + p_{32}y_2 + p_{33}y_3).$$

Consider the 2-dimensional central manifold at the origin given by

$$(35) \qquad\qquad y_3 = f(y_1, y_2) = ay_1^2 + by_1y_2 + cy_2^2 + \dots$$

Hence, the system $\dot{Y} = TY + R$ restricted to the central manifold is

$$\begin{pmatrix} \dot{y}_1 \\ \dot{y}_2 \end{pmatrix} = \begin{pmatrix} 0 & -\omega_0 \\ \omega_0 & 0 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + \begin{pmatrix} g_1(y_1, y_2) \\ g_2(y_1, y_2) \end{pmatrix},$$

where

$$g_1(y_1, y_2) = R_1(y_1, y_2, f(y_1, y_2)) \qquad \text{and} \qquad g_2(y_1, y_2) = R_2(y_1, y_2, f(y_1, y_2)).$$

The index number I can be computed as follows [58]:

$$I(y_1, y_2) = \frac{1}{16}\left[\frac{\partial^3 g_1}{\partial y_1^3} + \frac{\partial^3 g_1}{\partial y_1 \partial y_2^2} + \frac{\partial^3 g_2}{\partial y_1^2 \partial y_2} + \frac{\partial^3 g_2}{\partial y_2^3}\right] - \frac{1}{16\omega_0}\left[\frac{\partial^2 g_1}{\partial y_1^2}\frac{\partial^2 g_2}{\partial y_1^2} - \frac{\partial^2 g_1}{\partial y_2^2}\frac{\partial^2 g_2}{\partial y_2^2}\right]$$

$$+ \frac{1}{16\omega_0}\left[\frac{\partial^2 g_1}{\partial y_1 \partial y_2}\left(\frac{\partial^2 g_1}{\partial y_1^2} + \frac{\partial^2 g_1}{\partial y_2^2}\right) - \frac{\partial^2 g_2}{\partial y_1 \partial y_2}\left(\frac{\partial^2 g_2}{\partial y_1^2} + \frac{\partial^2 g_2}{\partial y_2^2}\right)\right].$$

Now, using [58], we have the following result.

Theorem 5. *The direction of bifurcation are above (bellow) as if MI < 0 (MI > 0).*

4. NUMERICAL STUDIES

Herein, we perform numerical simulation of system (3). To do so, the parameter values used for numerical simulation are given in Table 2.

Table 2 Numerical values of the parameters of system (3)

Parameter	Description	Values/Units	Reference
Λ	Recruitment rate of susceptible individuals	397800 year^{-1}	Assumed
β_s	Transmission rate of sensitive TB	variable	Assumed
β_r	Transmission rate of resistant TB	variable	Assumed
p_s	Proportion of individuals that develop sensitive active TB	0.7 year^{-1}	Assumed
p_r	Proportion of individuals that develop resistant active TB	0.55 year^{-1}	Assumed
k_s	Endogenous reactivation rate of sensitive latent TB	0.0013 year^{-1}	[10]
k_r	Endogenous reactivation of rate resistant latent TB	0.0014 year^{-1}	[10]
r_s	Effective chemoprophylaxis rate of sensitive latent TB	0 year^{-1}	[10]
r_r	Effective chemoprophylaxis rate of resistant latent TB	0 year^{-1}	[10]
σ_s	Reinfection parameters of sensitive latent TB	0.7 year^{-1}	Assumed
σ_r	Reinfection parameters of resistant latent TB	0.8 year^{-1}	Assumed
ϕ_s	Progression rate from sensitive latent TB to resistant latent TB	0	Assumed
δ_s	Progression rate from sensitive active TB to resistant active TB	0.0015 year^{-1}	Assumed
φ_s	Progression rate from sensitive latent TB to resistant active TB	0 year^{-1}	Assumed
η_s	Progression rate from sensitive active TB to resistant latent TB	0.0035 year^{-1}	Assumed
μ	Natural death rate	0.01986 year^{-1}	[48]
d_s	Death rate induced by sensitive active TB	0.05575 year^{-1}	[10]
d_r	Death rate induced by resistant active TB	0.06 year^{-1}	[10]
γ_s	Recovery rate of sensitive active TB cases	0.7311 year^{-1}	[10]
γ_r	Recovery rate of resistant active TB cases	0.7 year^{-1}	[10]

4.1. Sensitivity analysis.

Herein, we perform the sensitivity analysis in order to determine the most sensitive parameters, that is the parameters that most influence the output variable of the model. This can help us to predict the effect of each parameter on the model results and classify them according to their degree of sensitivity. To do so, we use the eFast sensitivity method. This method highlights the effects of the first order called main effects and the total effects that combine the main effects and all the interaction effects of the parameters on the outputs of the model. It is a global

sensitivity technique based on the decomposition or partitioning of the variance. The variance of the model output is decomposed into components resulting from the individual effects of parameters as well as their interactions [59,60].

Figure 2 gives the different correlations of the variables of system (3) according to the different parameters of system (3). According to the sensitivity analysis method the parameters μ have a strongest impact on all variable. the parameter d_r have the important impact on resistant strain variables (E_r and I_r). the parameter p_e have a strongest impact on the variable I_s. Finally all the variables have the same impact on the variable E_s.
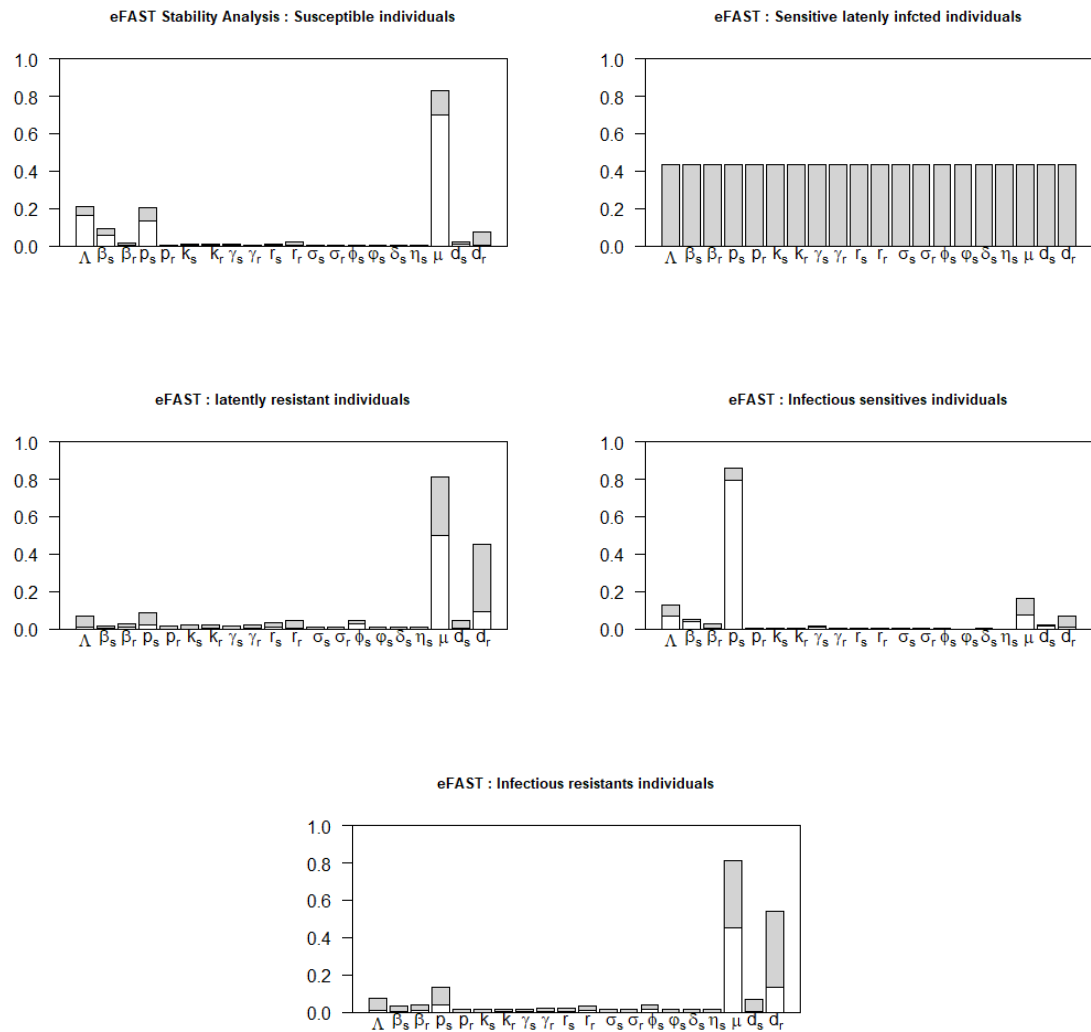
FIGURE 2. eFAST Sensibility analysis of system (3).

4.2. Non-standard finite difference scheme.

For numerical simulation, we use the non standard finite difference (NSFD) for the numerical approximation of system (3). The motivation comes the fact classical Runge-Kutta scheme cannot preserve the positivity of solution of system (3).

Figure 3 presents the numerical results obtained with the standard Runge-Kutta scheme of four order. From this figure, one can observe the presence of negative solution which are not in adequacy with the positivity of solution of system (3). So, in the following we present a numerical scheme that preserves the properties of system (3) such as the positivity, the boundedness property of solutions and replicate the global asymptotic stability of the disease-free equilibrium.
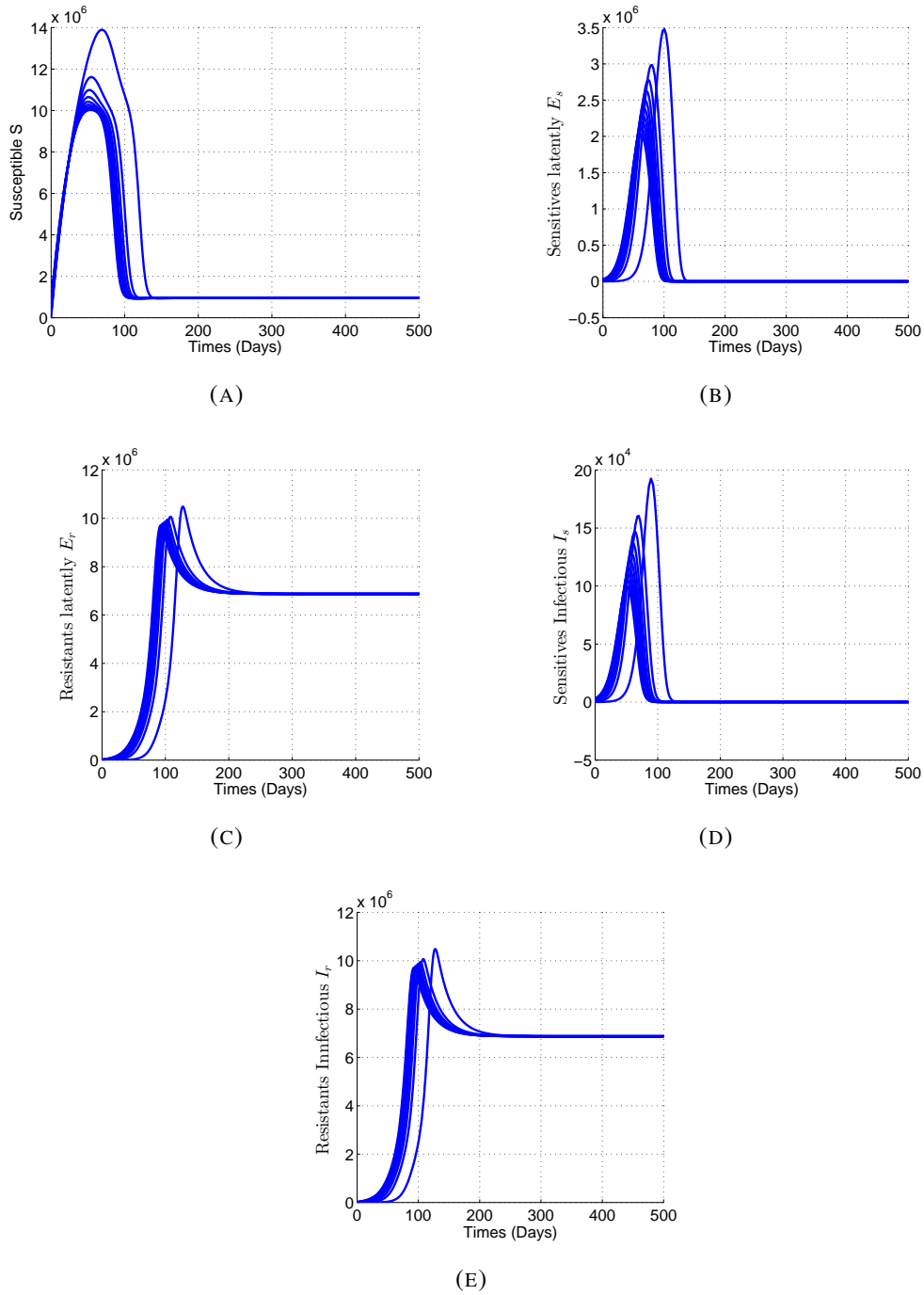
FIGURE 3. Simulation of system (3) using Runge Kutta scheme of four order when $\beta_s = 1.8$, $\beta_r = 1.4$ (so that $\mathscr{R}_{0_s} = 1.1616 > 1$, $\mathscr{R}_{0_r} = 1.1059 > 1$ and $\mathscr{R}_0 => 1$). (A) Susceptible individuals S; (B) latently infected individuals with sensitive strain E_s; (C) latently infected individuals with resistant strain E_r; (D) infectious with sensitive strain I_s, and (E) infectious with resistant strain I_r. All other parameter values are as in Table 2.

We replace the continuous time variable $t \in [0, \infty[$ by discrete nodes $t_n = n\Delta t, n \in \mathbb{N}$ where Δt is the step size. We wish to find approximate solutions $S^n, E_s^n, E_r^n, I_s^n, I_r^n$ of S, E_s, E_r, I_s, I_r at time $t = t_n$.

We propose the following NSFD scheme:

$$
(36) \quad
\begin{cases}
\dfrac{S^{n+1} - S^n}{\phi(\Delta t)} = \Lambda - (\lambda_s^n + \lambda_r^n + \mu)S^{n+1}, \\[2ex]
\dfrac{E_s^{n+1} - E_s^n}{\phi(\Delta t)} = \lambda_s^n(1 - p_s)S^{n+1} - (1 - r_s)(\sigma_s \lambda_s^n + \sigma_r \lambda_r^n)E_s^{n+1} \\[1ex]
\qquad\qquad + \gamma_s I_s^{n+1} - A_1 E_s^{n+1}, \\[2ex]
\dfrac{E_r^{n+1} - E_r^n}{\phi(\Delta t)} = \lambda_r^n(1 - p_r)S^{n+1} - (1 - r_r)\sigma_r \lambda_r^n E_r^{n+1} + (1 - r_s)\phi_s E_s^{n+1} \\[1ex]
\qquad\qquad + \gamma_r I_r^{n+1} + \eta_s I_s^{n+1} - A_3 E_r^{n+1}, \\[2ex]
\dfrac{I_s^{n+1} - I_s^n}{\phi(\Delta t)} = \lambda_s^n p_s S^{n+1} + (1 - r_s)k_s E_s^{n+1} + (1 - r_s)\sigma_s \lambda_s^n E_s^{n+1} - A_2 I_s^{n+1}, \\[2ex]
\dfrac{I_r^{n+1} - I_r^n}{\phi(\Delta t)} = \lambda_r^n p_r S^{n+1} + (1 - r_r)\sigma_r \lambda_r^n E_r^{n+1} + (1 - r_s)\left(\varphi_s + \sigma_r \lambda_r^n\right)E_s^{n+1} \\[1ex]
\qquad\qquad + (1 - r_r)k_r E_r^{n+1} + \delta_s I_s^{n+1} - A_4 I_r^{n+1},
\end{cases}
$$

where

$$
\lambda_s^n = \beta_s \frac{I_s^n}{N^n}, \quad \lambda_r^n = \beta_r \frac{I_r^n}{N^n}, \quad N^n = S^n + E_s^n + E_r^n + I_s^n + I_r^n,
$$

A_1, A_2, A_3 and A_4 are defined in Eq.(3) The numerical scheme (36) is called a non-standard finite difference method [61], because the non-linear terms are approximated in a non local way by using more than one mesh point: λS and λE are approximated by $\lambda^n S^{n+1}$ and $\lambda^n E^{n+1}$ (where λ denotes λ_s or λ_r while E denotes E_s or E_r) and the standard denominator Δt of the discrete derivatives is replaced by a more complex positive function $\phi(\Delta t)$ defined as follow

$$
(37) \qquad\qquad \phi = \phi(\Delta t) = \Delta t + \mathcal{O}((\Delta t)^2).
$$

The denominator function should reflect the essential qualitative features of the original contin-uous model. The numerical scheme (36) is an implicit non-standard finite difference method. we have the following result.

Proposition 1. *The numerical scheme (36) is consistent for the system (3).*

   Proof: The consistency error is

$$\xi^n = R(x^n) - \tilde{R}(x^n) = \mathcal{O}(\phi(\Delta t)),$$

where $R(x^n)$ denotes the approximation of x at the point t_n and $\tilde{R}(x^n)$ the approximation given by the numerical scheme at the point t_n. with this in mind, one has

$$
\begin{aligned}
\xi^n &= \mathcal{O}(\phi(\Delta t)), \\
&= \mathcal{O}(\Delta t + \mathcal{O}((\Delta t)^2), \\
&= \mathcal{O}(\Delta t) \to 0 \ \text{ when } \ \Delta t \to 0.
\end{aligned}
$$

Thus, the numerical schema (36) is consistent for the system (3). This completes the proof. □

Proposition 2. *The numerical scheme (36) is implicit therefore unconditionally stable.*

   Proof: The numerical scheme (36) can be rewritten as

$$(38) \qquad\qquad\qquad\qquad AX^{n+1} = BX^n + C,$$

where

$$A = \begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix},$$

with

$$A_{11} = \begin{pmatrix} 1 + \phi\left(\lambda_s^n + \lambda_r^n + \mu\right) & 0 & 0 \\ -\phi(1 - p_s)\lambda_s^n & 1 + \phi\left((1 - r_s)(\sigma_s\lambda_s^n + \sigma_r\lambda_r^n) + A_1\right) & 0 \\ -\phi(1 - p_r)\lambda_r^n & -\phi(1 - r_s)\phi_s & 1 + \phi\left((1 - r_r)\sigma_r\lambda_r^n + A_3\right) \end{pmatrix},$$

$$A_{12} = \begin{pmatrix} 0 & 0 \\ -\phi\gamma_s & 0 \\ -\phi\eta_s & -\phi\gamma_r \end{pmatrix}, \quad A_{21} = \begin{pmatrix} -\phi p_s\lambda_s^n & -\phi(1-r_s)(k_s + \sigma_s\lambda_s^n) & 0 \\ -\phi p_r\lambda_r^n & -\phi(1-r_s)(\varphi_s + \sigma_r\lambda_r^n) & -\phi(1-r_r)(k_r + \sigma_r\lambda_r^n) \end{pmatrix},$$

$$A_{22} = \begin{pmatrix} 1 + \phi A_2 & 0 \\ -\phi\delta_s & 1 + \phi A_4 \end{pmatrix},$$

$$B = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}, \quad C = \begin{pmatrix} \phi\Lambda \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad and \quad X^n = \begin{pmatrix} S^n \\ E_s^n \\ E_r^n \\ I_s^n \\ I_r^n \end{pmatrix}.$$

From Eq. (38), we has $X^{n+1} = A^{-1}X^n + A^{-1}C$. The matrix A is a column strictly diagonally dominated, thus one has deduce that A is $M-matrix$ for $x^n \in \Omega$; so all its eigenvalues are within the unit circle $\rho(A^{-1}) < 1$. This concludes the proof.

$\square$

We have the following result.

Proposition 3. *The discrete system (36) preserves the positivity of the solutions of the continuous model (3).*

Proof: Equation (38) can be written in the following form :

$$AX^{n+1} = F,$$

where A is defined as in Eq. (38) and

$$F = \begin{pmatrix} S^n + \phi\Lambda \\ E_s^n \\ E_r^n \\ I_s^n \\ I_r^n \end{pmatrix}.$$

Note that A is $M - matrice$ which implies that $A^{-1} \geq 0$. Therefore, the numerical scheme of (36) preserves the non negativity of the solutions of the continuous system (3). This concludes the proof   □

Proposition 4. *The disease-free equilibrium of system (3) is preserved and the solutions of system (3) are bounded.*

Proof: Adding all equations of discrete system (36), one has

$$\text{(39)} \qquad \frac{N^{n+1} - N^n}{\phi(\Delta t)} = \Lambda + \mu N^{n+1} - d_s I_s^{n+1} - d_r I_r^{n+1}.$$

This is equivalent to

$$\text{(40)} \qquad (1 + \phi(\Delta t)) N^{n+1} + \phi(\Delta t) d_s I_s^{n+1} + \phi(\Delta t) d_r I_r^{n+1} = (1 + \phi(\Delta t)\mu) N^n + \phi(\Delta t)\Lambda.$$

On the other hand, one has

$$0 \; < \; I_s^{n+1} < N^{n+1} \quad \Rightarrow \quad 0 < \phi(\Delta t) d_s I_s^{n+1} < \phi(\Delta t) d_s N^{n+1},$$

$$0 \; < \; I_r^{n+1} < N^{n+1} \quad \Rightarrow \quad 0 < \phi(\Delta t) d_r I_r^{n+1} < \phi(\Delta t) d_r N^{n+1}.$$

Adding member to member, one obtains

$$0 < \phi(\Delta t) \left(d_s I_s^{n+1} + d_r I_r^{n+1} \right) < \phi(\Delta t)(d_s + d_r) N^{n+1}.$$

Therefore, the sequence N^{n+1} satisfies the inequalities:

$$\text{(41)} \qquad \qquad \qquad \underline{F}(N^n) \leq N^{n+1} \leq \bar{F}(N^n),$$

where

$$\underline{F}(N^n) = \frac{(1 + \phi(\Delta t)\mu) N^n + \phi(\Delta t)\Lambda}{1 + \phi(\Delta t)(d_s + d_r + \mu)} \quad \text{and} \quad \bar{F}(N^n) = \frac{(1 + \phi(\Delta t)\mu) N^n + \phi(\Delta t)\Lambda}{1 + \phi(\Delta t)\mu}.$$

The fixed points of $\underline{F}(x)$ and $\bar{F}$ are respectively $N_\#$ and S_0. Thus, the disease free equilibrium is retained. The boundary of system comes from the fact that $N_\#$ and S_0 are respectively the fixed points of $\underline{F}(x)$ and $\bar{F}(x)$. This concludes the proof.   □

Proposition 5. *The domain Ω defined in Eq.(4) is positively invariant for the discrete dynamic system (36).*

Proof: Since the solutions are positive and bounded, any trajectory that begins in the domain Ω can not leave the domain Ω. This concludes the proof. □

We have the following result about the stability of the DFE of system (36).

Theorem 6. *If the values of the parameters of system (3) are such that when $\mathscr{R}_0 < \xi < 1$, then the disease-free equilibrium point (DFE) of the discrete dynamic system (36) is globally asymptotically stable in the domain Ω.*

Proof: The proof of this theorem is essentially based on Theorem 3 of [61].

The discrete dynamic system (36) can be written in the following form:

$$(42) \qquad \begin{cases} x_1^{n+1} = g(x_1^n, x_2^n), \\ P(x^n)x_2^{n+1} = Q(x_1^{n+1})x_2^n, \end{cases}$$

where $x = (x_1, x_2)$, $x_1^{n+1} = S^{n+1}$, $x_2^{n+1} = \left(E_s^{n+1}, E_r^{n+1}, I_s^{n+1}, I_r^{n+1}\right)$,

$$P(x^n) = \begin{pmatrix} (1+\phi Z_1) & -\phi\gamma_s & 0 & 0 \\ -\phi(1-r_s)(k_s+\sigma_s\lambda_s^n) & 1+\phi A_2 & 0 & 0 \\ -\phi(1-r_s)\phi_s & -\phi\eta_s & 1+\phi Z_2 & -\phi\gamma_r \\ -\phi(1-r_s)(\varphi_s+\sigma_r\lambda_r^n) & -\phi\delta_s & -\phi(1-r_r)(k_r+\sigma_r\lambda_r^n) & 1+\phi A_4 \end{pmatrix},$$

$$Q(x_1^{n+1}) = \begin{pmatrix} 1 & \phi\beta_s(1-p_s)\dfrac{S^{n+1}}{N^{n+1}} & 0 & 0 \\ 0 & 1+\phi\beta_s p_s\dfrac{S^{n+1}}{N^{n+1}} & 0 & 0 \\ 0 & 0 & 1 & \phi\beta_r(1-p_r)\dfrac{S^{n+1}}{N^{n+1}} \\ 0 & 0 & 0 & 1+\phi\beta_r p_r\dfrac{S^{n+1}}{N^{n+1}} \end{pmatrix},$$

with

$$Z_1 = (1-r_s)(\sigma_s\lambda_s^n + \sigma_r\lambda_r^n) + A_1 \qquad \text{and} \qquad Z_2 = (1-r_r)\sigma_r\lambda_r^n + A_3.$$

Since the matrix $P(x^n)$ is an M-matrix, it comes that $(P(x^n))^{-1} \geq 0$ and consequently one has

$$x_2^{n+1} = (P(x^n))^{-1}Q(x_1^{n+1})x_2^n.$$

Let's start with $M(x^n) = (P(x^n))^{-1}Q(x_2^{n+1})$, using Theorem 3 in [61], $M(x^n)$ is a irreducible matrix and admits $\overline{M} = (P(Q_0))^{-1}Q(x_2^{n+1})$ as a majorant.

On the other hand, the matrix $\bar{A}_2$ verifies the following relation:

$$Q(Q_0) - P(Q_0) = \phi\bar{A}_2.$$

With this in mind, one has that

$$\overline{M} = I + \phi P(Q_0)^{-1}\bar{A}_2.$$

Since the matrix $\bar{A}_2$ is irreducible, then the matrix M is also irreducible. Using the positivity properties of matrices [51,52] and the relation $\alpha(\bar{A}_2) < 0$, one can deduce that $\alpha(\overline{M}) < 0$. It follows that the disease free equilibrium is globally asymptotically stable for the discrete dynamic system (36). This completes the proof. □

Now, we present numerical results of the general dynamics of system (3). More precisely, we illustrate the theoretical results reported in Theorem 2, Lemma 3 and 4 using the numerical scheme of discrete dynamic system (36). The parameter values used for numerical simulations are given in Table 4. These values were chosen arbitrarily to satisfy the stability conditions of the disease-free equilibrium point of system (3).

Figure 4 shows the convergence to the disease-free equilibrium Q_0 of system (3) when $\beta_s = 0.3$ and $\beta_r = 0.45$ (so that $\mathcal{R}_{0_s} = 0.1936 < \xi_s = 0.8281 < 1$ and $\mathcal{R}_{0_r} = 0.3555 < \xi_r = 0.8847$ and $\mathcal{R}_0 \leq \xi$). It illustrates that the disease disappears when $\mathcal{R}_0 \leq \xi < 1$ and TB is controllable within the host population.
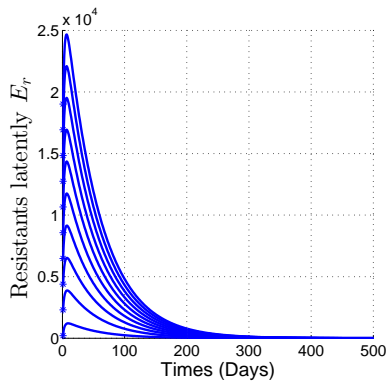
The backward bifurcation phenomenon is illustrated by simulating system (3) with the parameter values of Table 2. The associated backward bifurcation diagram is depicted in Fig. 5.
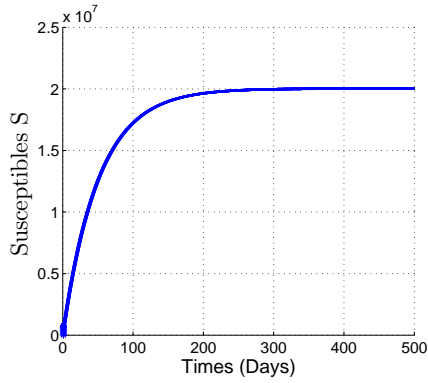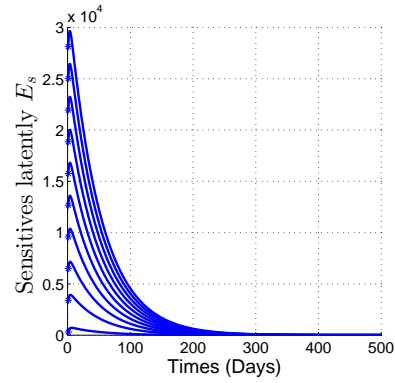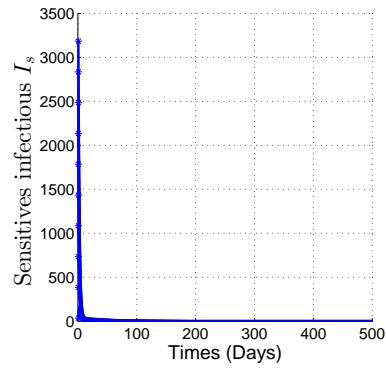
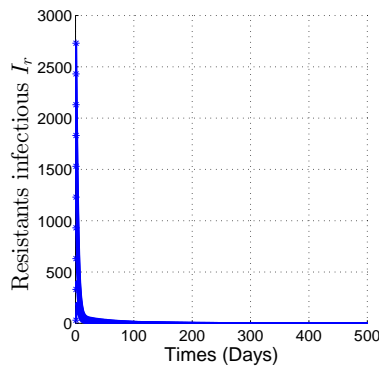FIGURE 4. Simulation of system (3) when $\beta_s = 0.3$ and $\beta_r = 0.45$ (so that $\mathscr{R}_{0_s} = 0.1936 < \xi_s = 0.8281 < 1$ and $\mathscr{R}_{0_r} = 0.3555 < \xi_r = 0.8847$ and $\mathscr{R}_0 \le \xi$). (A) Susceptible individuals S; (B) latently infected individuals with sensitive strain E_s; (C) latently infected individuals with resistant strain E_r; (D) infectious with sensitive strain I_s and (E) infectious with resistant strain I_r. All other parameter values are as in Table 2.
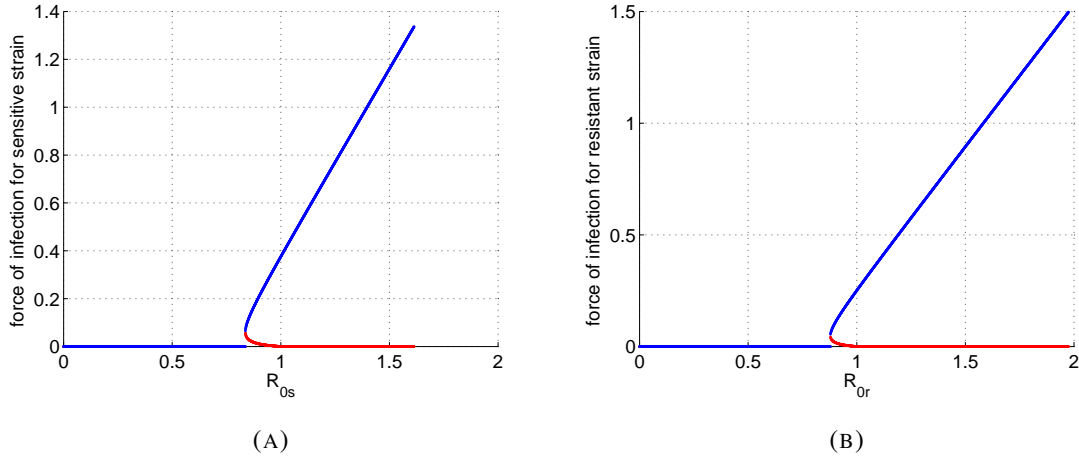
FIGURE 5. Bifurcation diagram of system (3).

The trajectories of system (3) when $\beta_s = 1.5$ and $\beta_r = 1.2$ (so that $\xi_s = 0.8281 \leq \mathscr{R}_{0_s} = 0.9680 < 1$, $\xi_r = 0.8847 \leq \mathscr{R}_{0_r} = 0.9479$ and $\xi \leq \mathscr{R}_0 < 1$) is depicted in Figure 6. This clearly shows that when $\xi \leq \mathscr{R}_0 < 1$, the profiles can converge to either the disease-free equilibrium or an endemic equilibrium point, depending on the initial sizes of the population (owing to the phenomenon of backward bifurcation). It is worth stating that, for the set of parameter values used, the simulations have to be run for a long-time period (in hundred of years). The epidemiological significance of the phenomenon of backward bifurcation is that the classical requirement of $\xi \leq \mathscr{R}_0 < 1$ is, although necessary, no longer sufficient for disease eradication. In such a scenario, the disease elimination would depend on the initial sizes of the population (state variables) of the model. That is, the presence of backward bifurcation in the TB transmission model (3) suggests that the feasibility of controlling TB when $\xi \leq \mathscr{R}_0 < 1$ could depend on the initial sizes of the population. The backward bifurcation phenomenon is usually due to the exogenous reinfections rates of σ_s and σ_r. So, it is important to perform Monte-Carlos simulation on the exogenous reinfection rates of σ_s and σ_r to see how it affects the disease free equilibrium when $\xi \leq \mathscr{R}_0 < 1$ for a fixed population size. Using parameter values as in Fig 6, Figure 6 present the Monte Carlos simulation of system (3), from this figure it clearly appears that for random generation of σ_s and σ_r the trajectories of system (3) converge to the DFE.
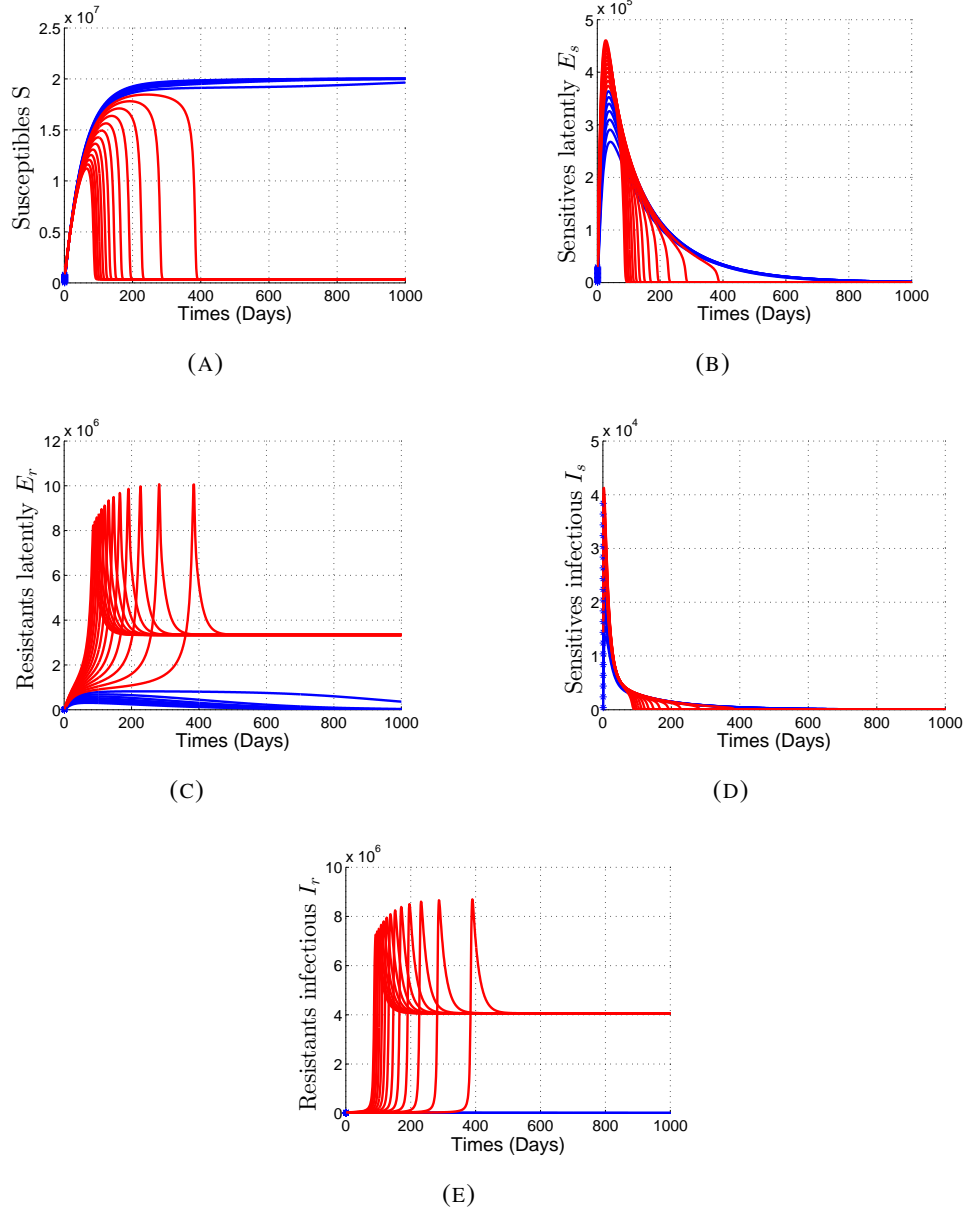
FIGURE 6. Simulation of model system (3) when $\beta_s = 1.5$ and $\beta_r = 1.2$ ((so that $\xi_s = 0.8281 \leq \mathscr{R}_{0_s} = 0.9680 < 1$, $\xi_r = 0.8847 \leq \mathscr{R}_{0_r} = 0.9479$ and $\xi \leq \mathscr{R}_0 < 1$). (A) Susceptible individuals S; (B) latently infected individuals with sensitive strain E_s; (C) latently infected individuals with resistant strain E_r; (D) infectious with sensitive strain I_s and (E) infectious with resistant strain I_r. All other parameter values are as in Table 2.
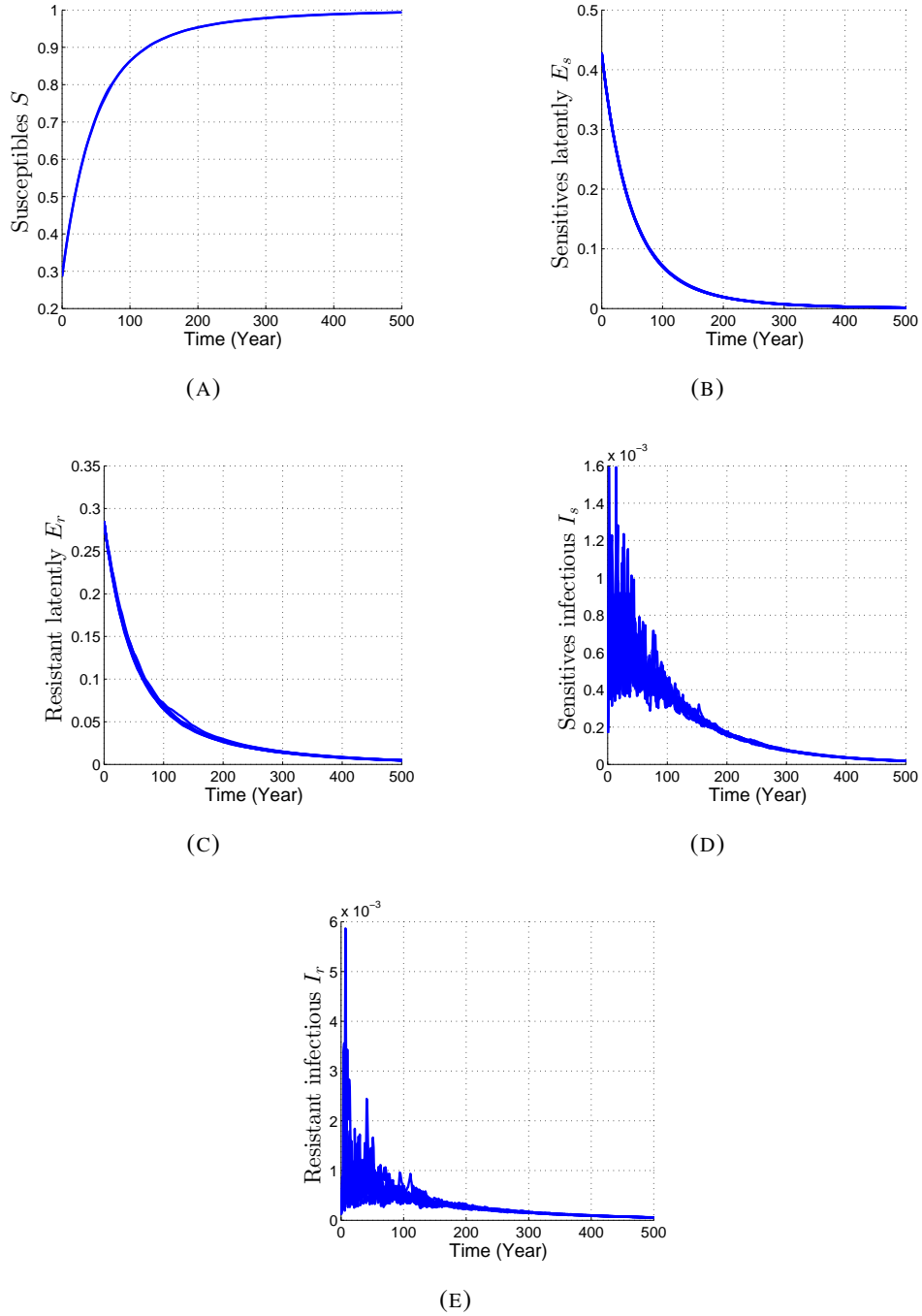
FIGURE 7. Monte-Carlos simulation of system (3) when $\beta_s = 1.5$ and $\beta_r = 1.2$ (so that $\mathcal{R}_{0_s} = 0.9680$, $\mathcal{R}_{0_r} = 0.9479$, $\xi_s = 0.8281$ and $\xi_r = 0.8847$). (A) Susceptible individuals S; (B) latently infected individuals with sensitive strain E_s; (C) latently infected individuals with resistant strain E_r; (D) infectious with sensitive strain I_s and (E) infectious with resistant strain I_r. All other parameter values are as in Table 2.

Figure 8 shows the convergence to the endemic equilibrium Q^* of the trajectories of system (3), when $\beta_s = 1.8$ and $\beta_r = 1.4$ (so that $\mathcal{R}_{0_s} = 1.1616$, and $\mathcal{R}_{0_r} = 1.1059$ and $\mathcal{R}_0 > 1$). It illustrates that TB persists within the host population when $\mathcal{R}_0 > 1$ and the disease becomes endemic and uncontrollable.

The local stability of the boundary endemic equilibrium Q_r^* when $\beta_s = 0.8$ and $\beta_r = 1.4$ (so that $\mathcal{R}_{0_s} = 0.5163 < 1$, $\mathcal{R}_{0_r} = 1.1059 > 1$, and $\mathcal{R}_{0_s}(Q_r^*) = 0.0607 < 1$) is show in Fig 9. Numerical results when $\beta_s = 4.2$, $\beta_r = 1.8$ and $d_r = 0.3$ (so that $\mathcal{R}_{0_s} = 3.9351 > 1$, $\mathcal{R}_{0_r} = 1.0715 > 1$, and $\mathcal{R}_{0_s}(Q_r^*) = 1.0452 > 1$) are depicted in Figure 10. Further, these figures illustrate that when $\mathcal{R}_{0_s} < 1$, $\mathcal{R}_{0_r} > 1$, and $\mathcal{R}_{0_s}(Q_r^*) < 1$, only the resistant strain persists within the host population, while when $\mathcal{R}_{0_s} > 1$, $\mathcal{R}_{0_r} > 1$, and $\mathcal{R}_{0_s}(Q_r^*) > 1$, the sensitive strain invades the host population.

Figures 11 and 12 depict the time evolution of system (3) using various initial conditions when $\beta_s = 1.8$ and $\beta_r = 0.8$ (so that $\mathcal{R}_{0_s} = 1.6975 > 1$, $\mathcal{R}_{0_r} = 0.632 < 1$, and $\mathcal{R}_{0_r}(Q_s^*) = 0.0885 < 1$), and $\beta_s = 2$, $\beta_r = 4.2$ and $d_s = 0.35$ (so that $\mathcal{R}_{0_s} = 1.3491 > 1$, $\mathcal{R}_{0_r} = 4.6545 > 1$, and $\mathcal{R}_{0_r}(Q_s^*) = 1.0315 > 1$), respectively. As predicted by Lemma 5 when $\mathcal{R}_{0_s} > 1$, $\mathcal{R}_{0_r} = 0.632 < 1$, and $\mathcal{R}_{0_r}(Q_s^*) < 1$ only sensitive strain persists in the host population, while when $\mathcal{R}_{0_s} > 1$, $\mathcal{R}_{0_r} > 1$, and $\mathcal{R}_{0_r}(Q_s^*) = 1.0315 > 1$, the resistant strain invades the host population where the sensitive strain is at the equilibrium.

We now numerically investigate that system (3) undergoes the Hopf bifurcation around the endemic equilibrium point $Q_s^* = (S_s^*, E_s^*, I_s^*, 0, 0)$ with respect to the transmission rate β_s. Using the software MATCONT, we found that system (3) undergoes the Hopf bifurcation for the threshold value $\beta_s = 2.289638 \approx 2.29$ of the transmission rate. In this case, Hopf bifurcation occurs at $H = (73.637118, 39.419053, 18.197512, 0, 0)$. The associated bifurcation diagram is shown in Fig 13. To add more evidence on the occurrence of the Hopf bifurcation.

Figure 14 shows the existence of an asymptotically stable periodic solution when β_s crosses the threshold value $\beta_s = 2.29$, $\sigma_s = 9.7$ and $\gamma_s = 6.7311$. It is evident that the occurrence of periodic oscillating solutions is relevant in tuberculosis models, as it indicates that the disease levels may oscillate around the endemic equilibrium point Q_s^* even in absence of any treatment.
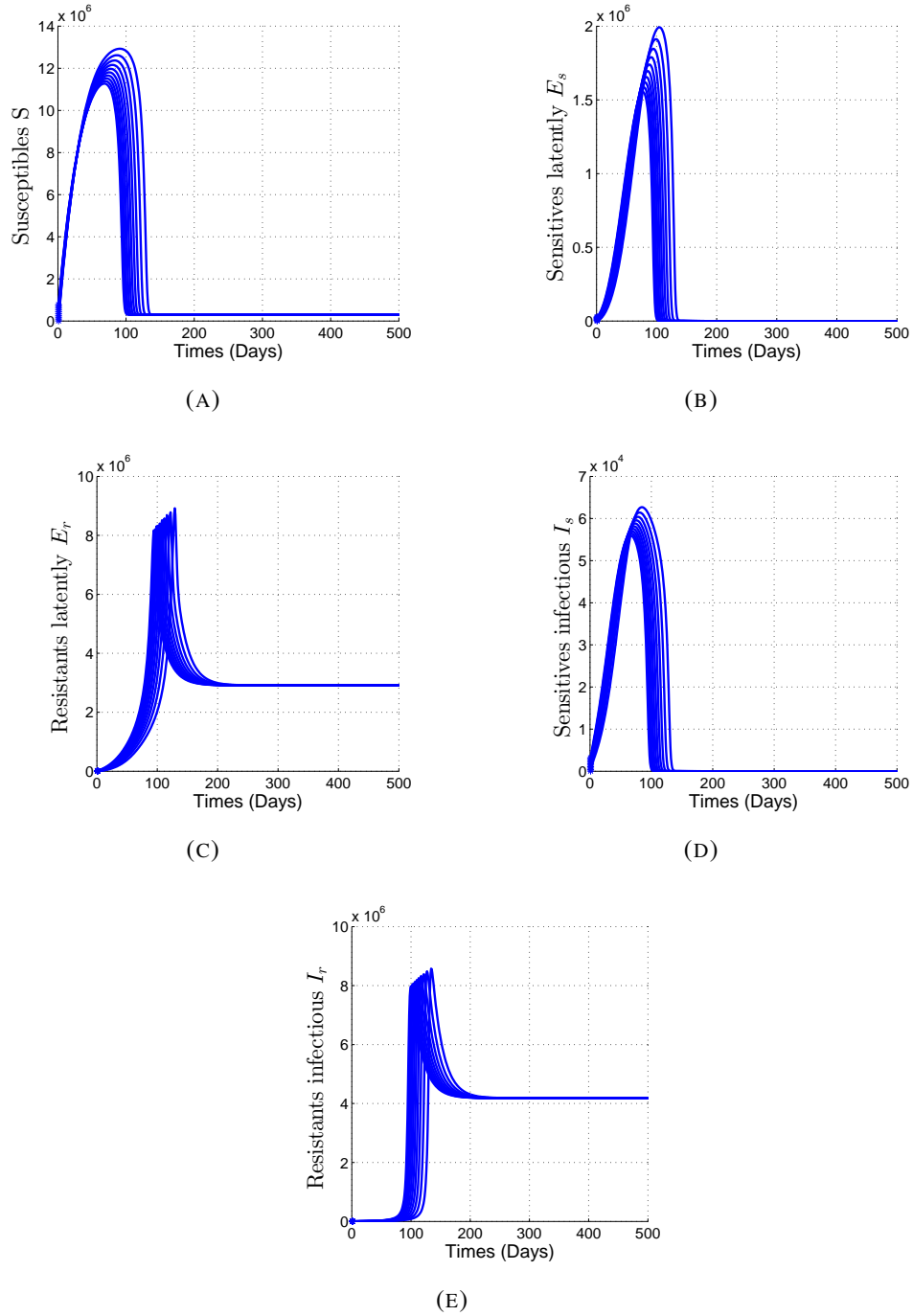
FIGURE 8. Simulation of system (3) using various initial conditions when $\beta_s = 1.8$ and $\beta_r = 1.4$ (so that $\mathscr{R}_{0_s} = 1.1616$, and $\mathscr{R}_{0_r} = 1.1059$ and $\mathscr{R}_0 > 1$). (A) Susceptible individuals S; (B) latently infected individuals with sensitive strain E_s; (C) latently infected individuals with resistant strain E_r; (D) infectious with sensitive strain I_s and (E) infectious with resistant strain I_r. All other parameter values are as in Table 2.
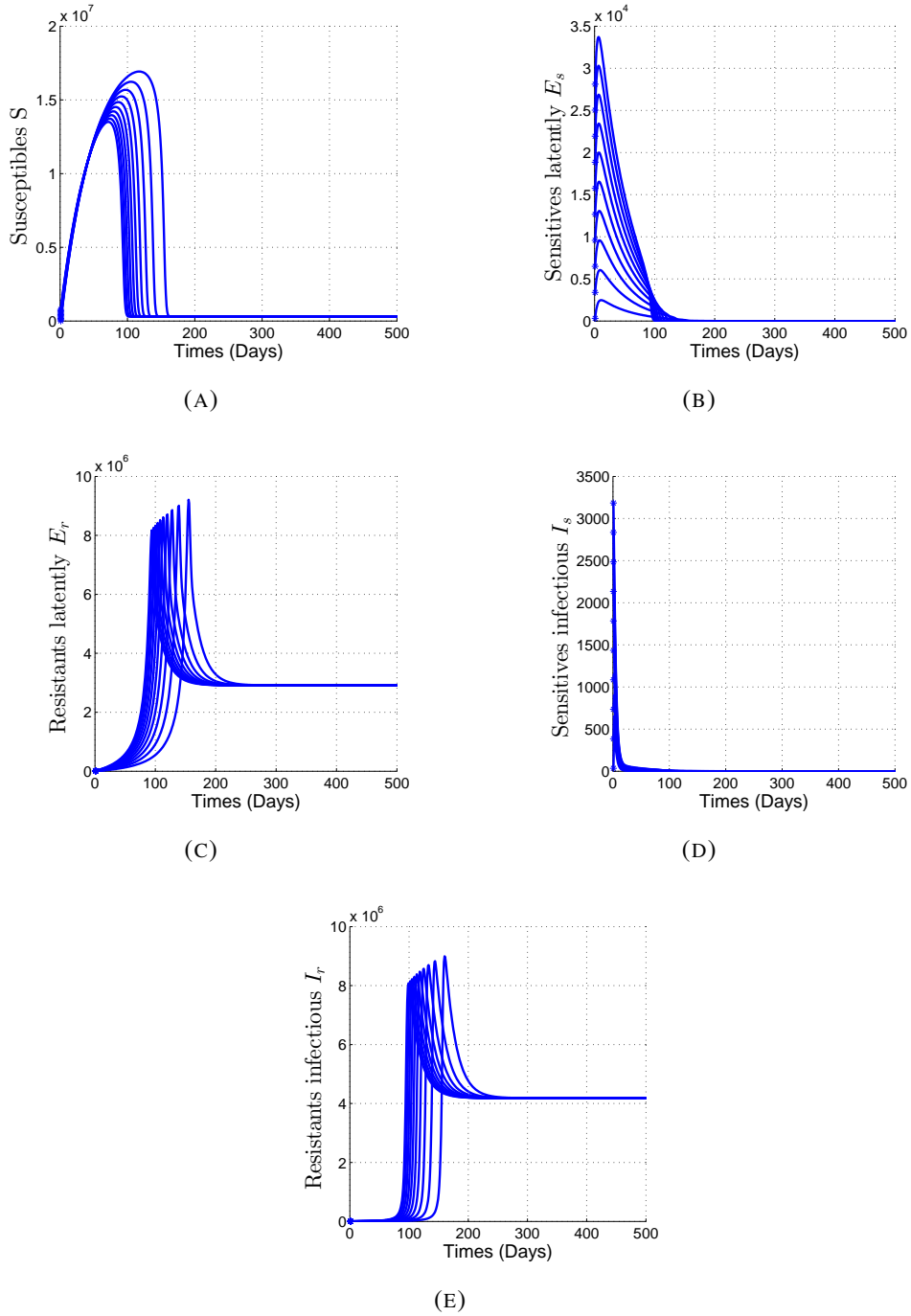
FIGURE 9. Simulation of system (3) where resistant TB is already endemic using various initial conditions when $\beta_s = 0.8$ and $\beta_r = 1.4$ (so that $\mathscr{R}_{0_s} = 0.5163 < 1$, $\mathscr{R}_{0_r} = 1.1059 > 1$, and $\mathscr{R}_{0_s}(Q_r^*) = 0.0607 < 1$). (A) Susceptible individuals S; (B) latently infected individuals with sensitive strain E_s; (C) latently infected individuals with resistant strain E_r; (D) infectious with sensitive strain I_s and (E) infectious with resistant strain I_r. All other parameter values are as in Table 2.
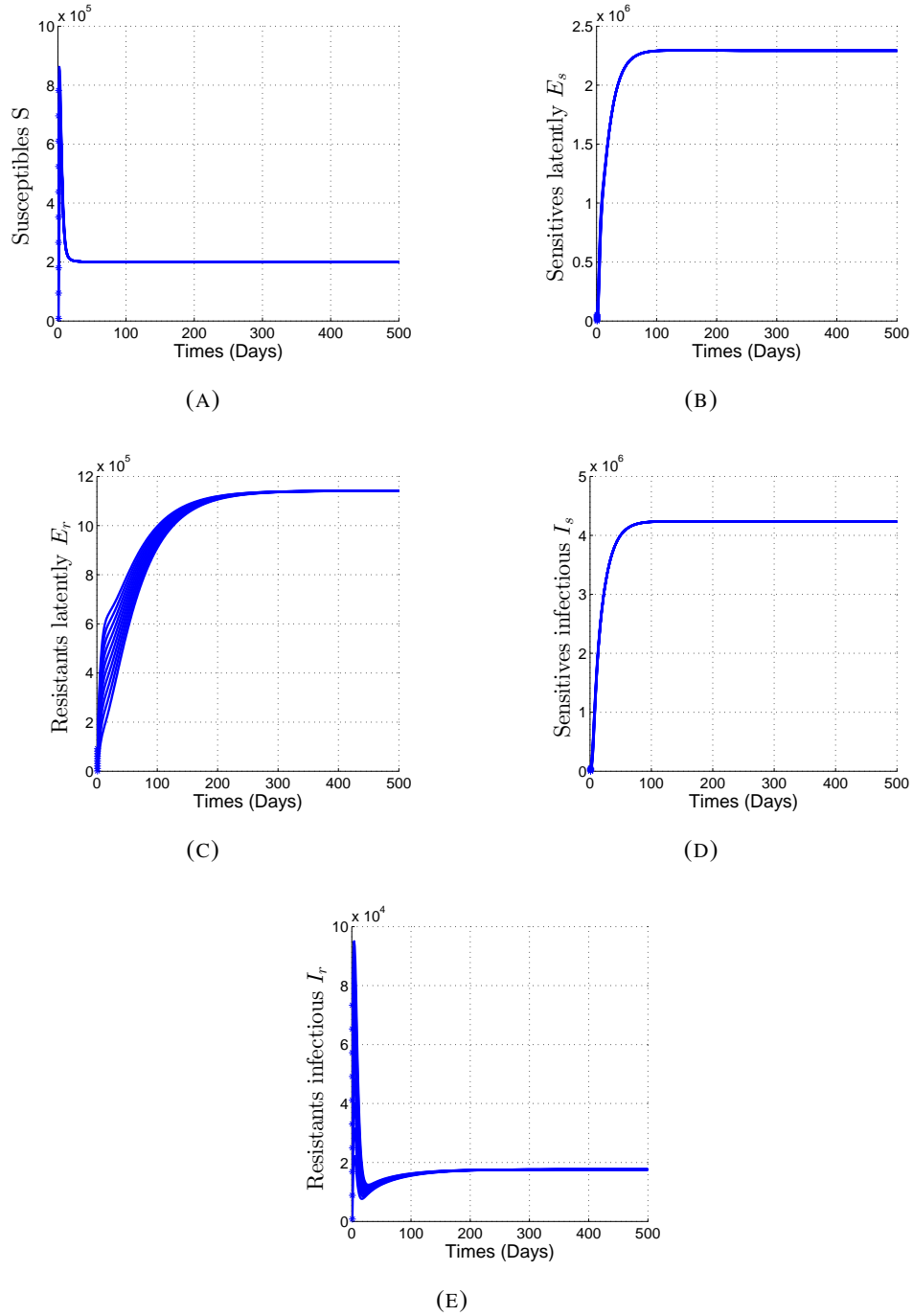
FIGURE 10. Simulation of system (3) where resistant TB is already endemic using various initial conditions when $\beta_s = 4.2$, $\beta_r = 1.8$ and $d_r = 0.3$ (so that $\mathscr{R}_{0_s} = 3.9351 > 1$, $\mathscr{R}_{0_r} = 1.0715 > 1$, and $\mathscr{R}_{0_s}(Q_r^*) = 1.0452 > 1$). (A) Susceptible individuals S; (B) latently infected individuals with sensitive strain E_s; (C) latently infected individuals with resistant strain E_r, (D) infectious with sensitive strain I_s and (E) infectious with resistant strain I_r. All other parameter values are as in Table 2.
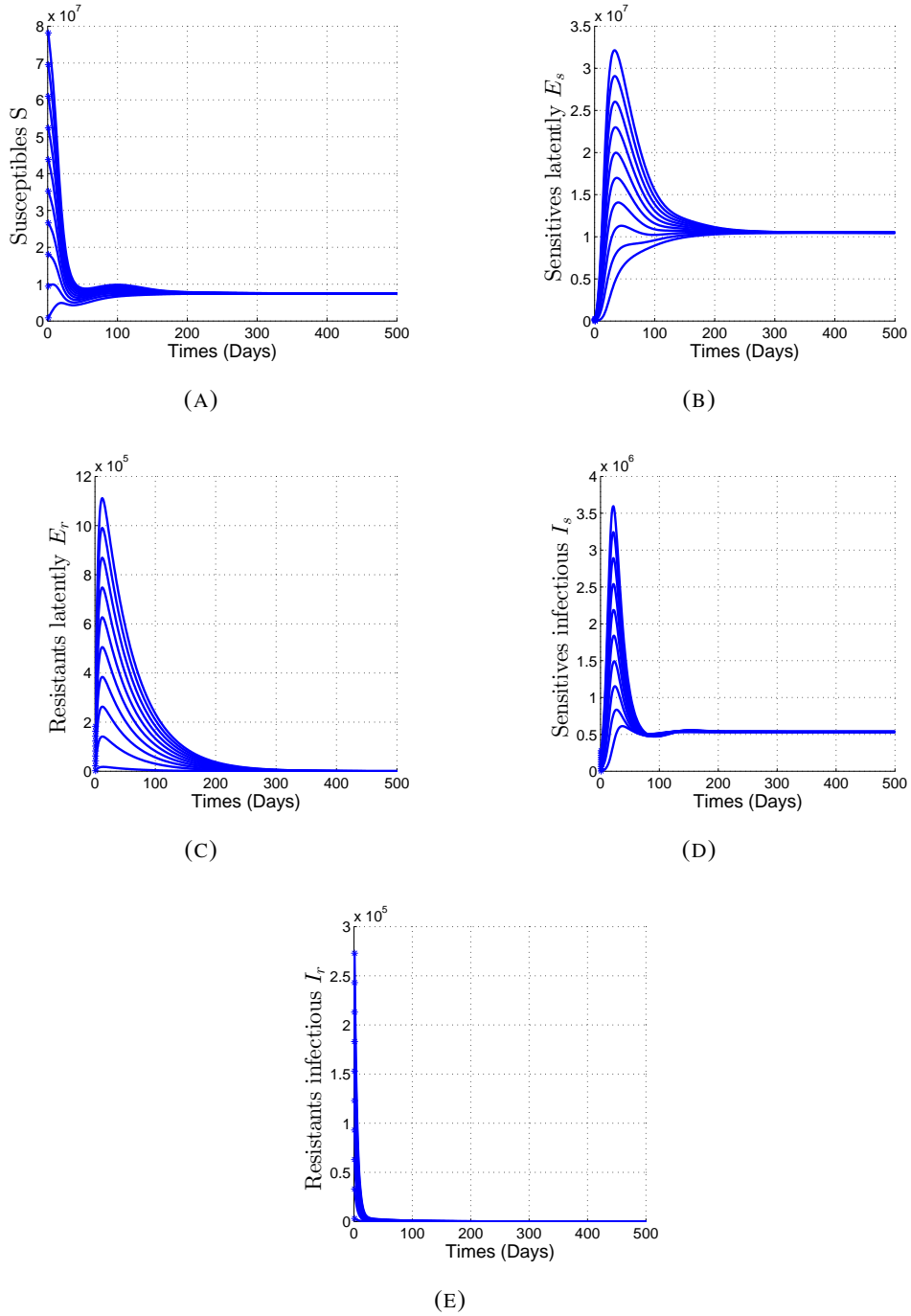
FIGURE 11. Simulation of system (3) where resistant TB is already endemic using various initial conditions when $\beta_s = 1.8$ and $\beta_r = 0.8$ (so that $\mathscr{R}_{0_s} = 1.6975 > 1$, $\mathscr{R}_{0_r} = 0.6320 < 1$, and $\mathscr{R}_{0_r}(Q_s^*) = 0.0885 < 1$). (A) Susceptible individuals S; (B) latently infected individuals with sensitive strain E_s; (C) latently infected individuals with resistant strain E_r; (D) infectious with sensitive strain I_s and (E) infectious with resistant strain I_r. All other parameter values are as in Table 2.
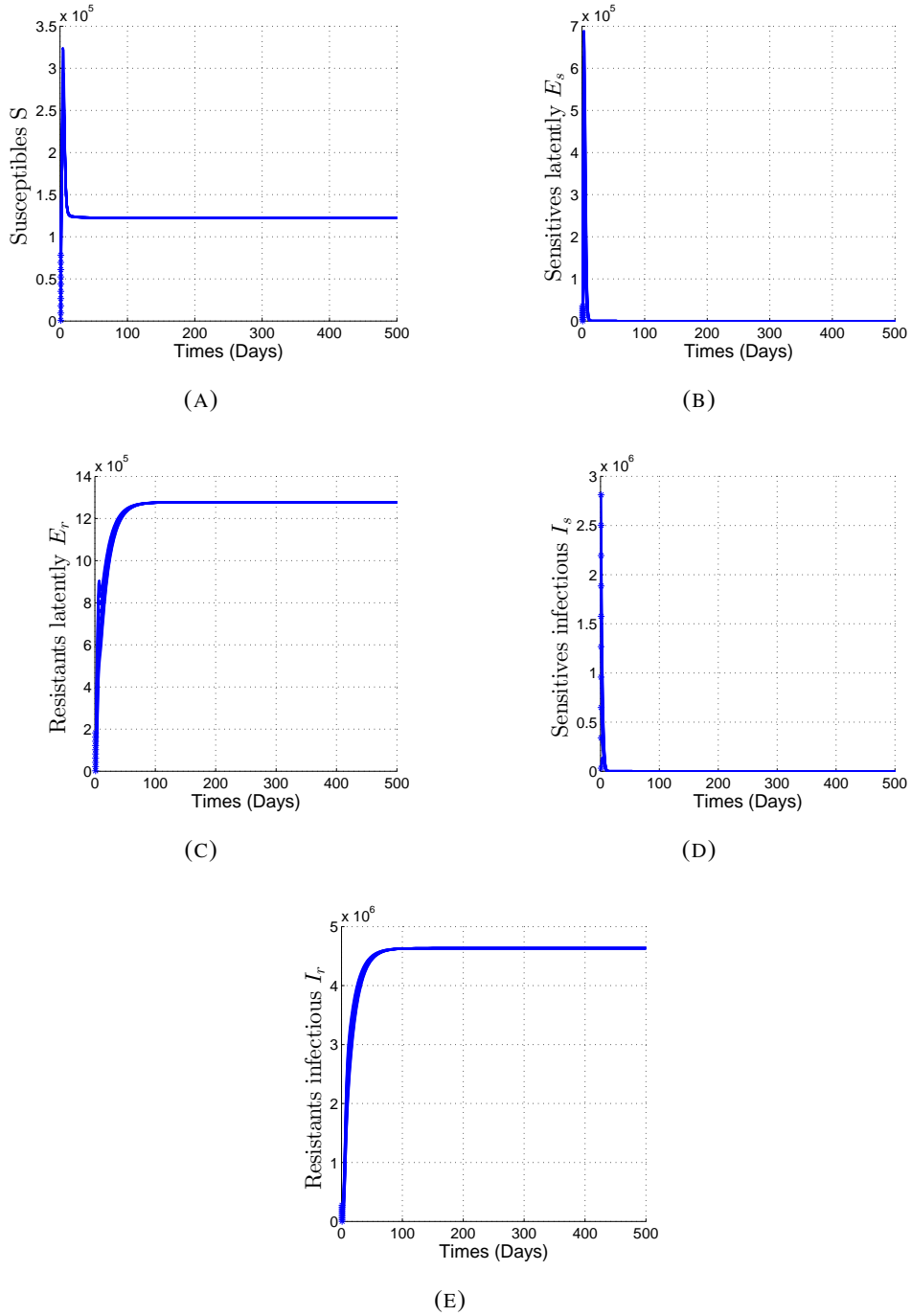
FIGURE 12. Simulation of system (3) where resistant TB is already endemic using various initial conditions when $\beta_s = 2$, $\beta_r = 4.2$ and $d_s = 0.35$ (so that $\mathscr{R}_{0_s} = 1.3491 > 1$, $\mathscr{R}_{0_r} = 4.6545 > 1$, and $\mathscr{R}_{0_r}(Q_s^*) = 1.0315 > 1$). (A) Susceptible individuals S; (B) latently infected individuals with sensitive strain E_s; (C) latently infected individuals with resistant strain E_r; (D) infectious with sensitive strain I_s and (E) infectious with resistant strain I_r. All other parameter values are as in Table 2.
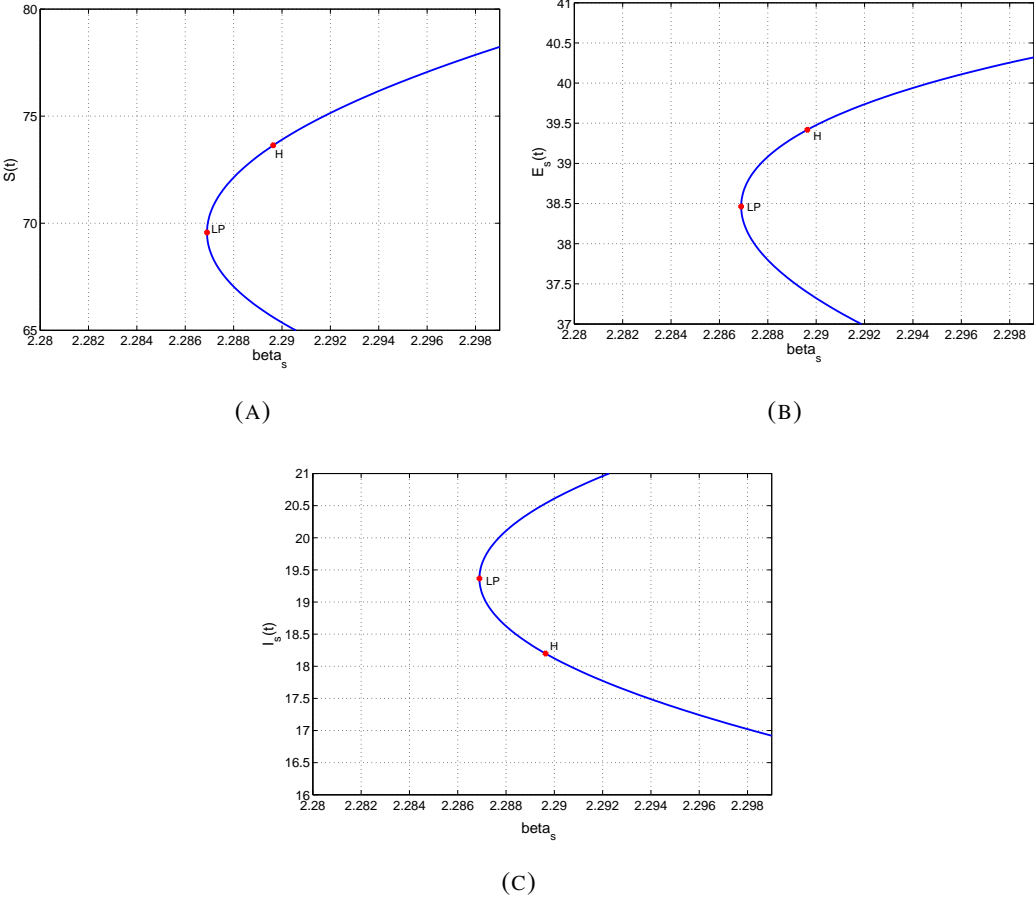
(A)

(B)

(C)

FIGURE 13. Bifurcation diagram of system (3) when $\beta_s = 1.12$, $\sigma_s = 9.7$ and $\gamma_s = 6.7311$. The Hopf bifurcation occurs for $\beta_s = 2.29$, which has been labeled by "H". All other parameter values are as in Table 2.

5. CONCLUSION

In this paper, we addressed the problem of drug resistance as a competition between two types of *Mycobacterium tuberculosis* strains. We first formulated a TB model with two strains: : those that are sensitive to anti-tuberculosis drugs and those that are resistant. We presented the theoretical analysis of the model. More precisely, we computed the disease-free equilibrium and derived the basic reproduction number $\mathscr{R}_0$. By using a result of Kamgang and Sallet [50], we shown that there exists a threshold parameter ξ such that if $\mathscr{R}_0 < \xi$, the disease-free equilibrium is globally asymptotically stable, while if $\xi < \mathscr{R}_0 < 1$, the phenomenon of backwards bifurcation occurs. We also shown that if $\mathscr{R}_0 > 1$, the disease-free equilibrium is unstable and
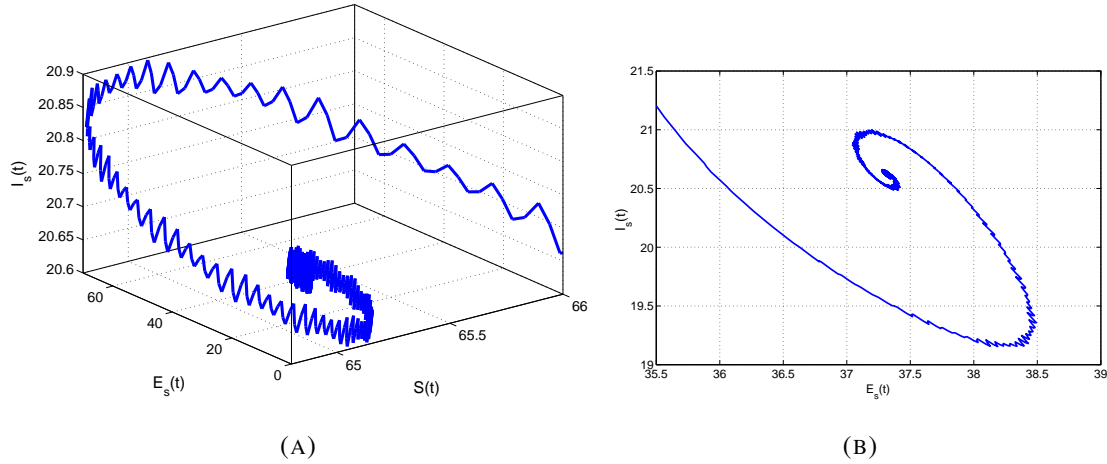
FIGURE 14. Existence of an asymptotically stable periodic solution when β_s crosses the threshold value $\beta_s = 2.29$, $\sigma_s = 9.7$ and $\gamma_s = 6.7311$. All other parameters are as in Table 2

there exists a unique endemic equilibrium which is stable with $\mathscr{R}_0$ close to 1. The coexistence and stability of the associated equilibria are discussed. We also showed that the TB transmission model undergoes the Hopf-bifurcation with respect to the transmission rates β_s and β_r. We also presented a dynamically consistent non-standard finite difference scheme to numerically study the model. The non-standard finite difference scheme has the advantage that it preserves some properties of the model that is not the case for the classical Runge-Kutta scheme. Numerical results have been presented to illustrate and validate theoretical results.

APPENDIX A: CALCULATION OF THE BASIC REPRODUCTION RATIO FOR SYSTEM (3)

Herein, we compute the basic reproduction ratio (8) of system (3). To do so, it is important to distinguish new infections from all other class transitions in the population when to compute the basic reproduction ratio. The infected classes are E_s, E_r, I_s, and I_r. Using the method of Van den Driessche and Watmough [49], system (3) can written in the following form:

$$\dot{x} = f(x) = \mathscr{F}(x) - \mathscr{V}(x) = \mathscr{F}(x) - (\mathscr{V}^-(x) - \mathscr{V}^+(x)),$$
(43)

where $x = (E_s, E_r, I_s, I_r, S)$, $\mathscr{F}$ is the rate of appearance of new infections in each class, $\mathscr{V}^+$ is the rate of transfer into each class by all other means and $\mathscr{V}^-$ is the rate of transfer out of each class. Hence,

$$\mathscr{F}(x) = (\lambda_s(1-p_s)S,\ \lambda_r(1-p_r)S,\ \lambda_r p_r S,\ \lambda_r p_r S, 0)^T$$

and

$$\mathscr{V}(x) = \begin{pmatrix} -\gamma_s I_s + (1-r_s)(\sigma_s \lambda_s + \sigma_r \lambda_r)E_s + A_1 E_s \\ -\gamma_r I_r + (1-r_r)\sigma_r \lambda_r E_r - (1-r_s)\phi_s E_s - \eta_s I_s + A_3 E_r \\ -(1-r_s)k_s E_s - (1-r_s)\sigma_s \lambda_s E_s + A_2 I_s \\ -(1-r_r)(k_r + \sigma_r \lambda_r)E_r + (1-r_s)(\varphi_s + \sigma_r \lambda_r)E_s - \delta_s I_s + A_4 I_r \\ 0 \end{pmatrix}.$$

The jacobian matrices of $\mathscr{F}$ and $\mathscr{V}$ at the disease-free equilibrium $Q_0 = (0,0,0,0,\Lambda/\mu)$ are

$$D\mathscr{F}(Q_0) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix} \qquad \text{and} \qquad D\mathscr{V}(Q_0) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix},$$

where

$$F = \begin{pmatrix} 0 & 0 & \beta_s(1-p_s) & 0 \\ 0 & 0 & 0 & \beta_r(1-p_r) \\ 0 & 0 & \beta_s p_s & 0 \\ 0 & 0 & 0 & \beta_r p_r \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} A_1 & 0 & -\gamma_s & 0 \\ -(1-r_s)\phi_s & A_3 & -\eta_s & -\gamma_r \\ -k_s(1-r_s) & 0 & A_2 & 0 \\ -\varphi_s(1-r_s) & -k_r(1-r_r) & -\delta_s & A_4 \end{pmatrix},$$

with A_1, A_2, A_3 and A_4 defined as in Eq. (3).

Following van den Driessche and Watmough [49], the basic reproduction ratio is defined as the dominant eigenvalue of the next generation matrix, FV^{-1}:

$$\mathscr{R}_0 = \max\{\mathscr{R}_{0_s}, \mathscr{R}_{0_r}\},$$
(44)

where

$$\mathscr{R}_{0_s} = \frac{\beta_s[p_s\mu + p_s(1-r_s)(\phi_s + \varphi_s) + k_s(1-r_s)]}{A_1 A_2 - \gamma_s k_s(1-r_s)} \quad \text{and} \quad \mathscr{R}_{0_r} = \frac{\beta_r[p_\mu + k_r(1-r_r)]}{A_3 A_4 - \gamma_r k_r(1-r_r)}.$$

APPENDIX B: CALCULATION OF THE COEXISTENCE THRESHOLD FOR THE RESISTANT ENDEMIC EQUILIBRIUM Q_r^*

Herein, we calculate the coexistence threshold for the resistant endemicity Q_r^*. To do so, we consider the case only when the sensitive TB is transmissible, in a population where resistant TB is at equilibrium. The infected compartments are E_s and I_s. Following Van den Driessche and Watmough [49], we can write system (3) as in Eq. (43) where $x = (E_s, I_s, S, E_r, I_r)^T$ with

$$\mathscr{F}_s = \begin{pmatrix} (1-p_s)\lambda_s S \\ p_s \lambda_s S \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \mathscr{V}_s = \begin{pmatrix} -\gamma_s I_s + (1-r_s)(\sigma_s \lambda_s + \sigma_r \lambda_r)E_s + A_1 E_s \\ -(1-r_s)k_s E_s - (1-r_s)\sigma_s \lambda_s E_s + A_2 I_s \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

The Jacobian matrice of $\mathscr{F}_s$ and $\mathscr{V}_s$ at the disease-free equilibrium $Q_r^* = (0,0,S_r^*, E_r^*, I_r^*)^T$ are

$$F_s = \begin{bmatrix} 0 & \beta_s(1-p_s)\dfrac{S_r^*}{N_r^*} \\ 0 & \beta_s p_s \dfrac{S_r^*}{N_r^*} \end{bmatrix} \quad \text{and} \quad V_s = \begin{bmatrix} A_1 + (1-r_s)\sigma_r \lambda_r^* & -\gamma_s \\ -k_s(1-r_s) & A_2 \end{bmatrix}.$$

The basic reproduction ratio of the sensitive strains in a population where resistant strains are fixed is then the spectral radius of the next generation matrix, $F_s V_s^{-1}$:

$$(45) \qquad \mathscr{R}_{0_s}(X_r) = \frac{\beta_s S_r^*[k_s(1-r_s) + p_s(\mu + (1-r_s)(\phi_s + \varphi_s) + \sigma_r \lambda_r^*)]}{N_r^*[A_1 A_2 - \gamma_s k_s(1-r_s) + A_2 \sigma_r \lambda_r^*(1-r_s)]},$$

where

$$\lambda_r^* = \beta_r \frac{I_r^*}{N_r^*}, \qquad \text{and} \qquad N_r^* = S_r^* + E_r^* + I_r^*.$$

APPENDIX C: CALCULATION OF THE COEXISTENCE THRESHOLD FOR THE SENSITIVE ENDEMIC EQUILIBRIUM Q_s^*

Here, we show how to calculate the coexistence threshold for the sensitive endemicity Q_s^*. To do so, consider the case only when the sensitive TB is transmissible, in a population where resistant TB is at equilibrium. The infected compartments are E_r and I_r. Following Van den Driessche and Watmough [49], system (3) can be written as in (43) with $x = (E_r, I_r, S, E_s, I_s)^T$, one has

$$\mathscr{F}_r = \begin{pmatrix} (1-p_r)\lambda_r S \\ p_r \lambda_r S \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \mathscr{V}_r = \begin{pmatrix} -\gamma_r I_r + (1-r_r)\sigma_r \lambda_r E_r + A_3 E_r \\ -(1-r_r)k_r E_r - (1-r_r)\sigma_r \lambda_r E_r + A_4 I_r + (1-r_s)\sigma_r \lambda_r E_s \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

The Jacobian matrice of $\mathscr{F}_r$ and $\mathscr{V}_r$ at the disease (sensitive-TB)-free equilibrium is $Q_s^* = (0,0,S_s^*,E_s^*,I_s^*)^T$. are

$$F_r = \begin{bmatrix} 0 & \beta_r(1-p_r)\dfrac{S_s^*}{N_s*} \\ 0 & \beta_r p_r \dfrac{S_s^*}{N_s^*} \end{bmatrix} \quad \text{and} \quad V_r = \begin{bmatrix} A_3 & -\gamma_r \\ -k_r(1-r_r) & A_4 + (1-r_s)\beta_r \sigma_r \dfrac{E_s^*}{N_s^*} \end{bmatrix},$$

The basic reproduction ratio of the sensitive strains in a population where resistant strains are fixed is then the spectral radius of the next generation matrix, $F_r V_r^{-1}$:

$$(46) \qquad \mathscr{R}_{0_r}(X_s) = \frac{\beta_r S_s^*[k_r(1-r_r) + \mu p_r]}{N_s^*[A_3 A_4 - \gamma_r k_r(1-r_r) + A_3(1-r_s)\beta_r \sigma_r E_s^*]},$$

where

$$\lambda_s^* = \beta_s \frac{I_s^*}{N_s^*}, \qquad and \qquad N_s^* = S_s^* + E_s^* + I_s^*.$$

APPENDIX D: PROOF OF THEOREM 3

In. this Appendix, we gives the proof of Theorem 3. In order to analyze the stability of the endemic equilibrium point, we make use of the Centre Manifold theory as described by Theorem 4.1 of Castillo-Chavez and Song [34], to establish the local asymptotic stability of the TB endemic equilibrium. In particular, Theorem 3.5 reproduced below for convenience, will be used to show that when $\mathscr{R}_0 > 1$, there exists a unique endemic equilibrium of system (3) which is locally asymptotically stable for $\mathscr{R}_0$ near 1 under some conditions.

Theorem 7. *[34] Consider the following general system of ordinary differential equations with a parameter ϕ:*

$$(47) \qquad \frac{dz}{dt} = f(z, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \quad and \quad f \in \mathscr{C}^2 (\mathbb{R}^n, \mathbb{R}),$$

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

(1) $A = D_z f(0,0) = \dfrac{\partial f_i}{\partial z_j}(0,0)$ is the linearization matrix of system (47) around the equilibrium 0 with evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts,

(2) Matrix A has a right eigenvector u and a left eigenvector v (each corresponding to the zero eigenvalue).

Let f_k be the kth component of f and

$$\mathbf{a} = \sum_{k,i,j}^n v_k u_i u_j \frac{\partial^2 f_k}{\partial z_i \partial z_j}(0,0) \quad and \quad \mathbf{b} = \sum_{k,i}^n v_k u_i \frac{\partial^2 f_k}{\partial z_i \partial \phi}(0,0),$$

then, the local dynamics of system around the equilibrium point 0 is totally determined by the signs of a and b.

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

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

(3) **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;*

(4) **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 $\phi = 0$.*

Let us first make the following simplification and change of variables. Let $x_1 = S$, $x_2 = E_s$, $x_3 = I_s$, $x_4 = E_r$ and $x_5 = I_r$ so that $N = x_1 + x_2 + x_3 + x_4 + x_5$. Further, by using vector notation $x = (x_1, x_2, x_3, x_4, x_5)^t$, system (3) can be written in the form $x' = f(x)$, with $f = (f_1, f_2, f_3, f_4, f_5)^t$, as follows:

$$(48) \quad \begin{cases} \dot{x}_1 & = \quad f_1 = \Lambda - (\lambda_s + \lambda_r + \mu)x_1, \\ \dot{x}_2 & = \quad f_2 = \lambda_s(1 - p_s)x_1 + \gamma_s x_3 - (1 - r_s)(\sigma_s \lambda_s + \sigma_r \lambda_r)x_2 - A_1 x_2, \\ \dot{x}_3 & = \quad f_3 = \lambda_s p_s x_1 + (1 - r_s)k_s x_2 + (1 - r_s)\sigma_s \lambda_s x_2 - A_2 x_3, \\ \dot{x}_4 & = \quad f_4 = \lambda_r(1 - p_r)x_1 + \gamma_r x_5 - (1 - r_r)\sigma_r \lambda_r x_4 + (1 - r_s)\phi_s x_2 + \eta_s x_3 - A_3 x_4, \\ \dot{x}_5 & = \quad f_5 = \lambda_r p_r x_1 + (1 - r_r)(k_r + \sigma_r \lambda_r)x_4 + (1 - r_s)(\varphi_s + \sigma_r \lambda_r)x_2 + \delta_s x_3 - A_4 x_5, \end{cases}$$

where

$$\lambda_s = \frac{\beta_s x_3}{x_1 + x_2 + x_3 + x_4 + x_5} \quad \text{and} \quad \lambda_r = \frac{\beta_r x_5}{x_1 + x_2 + x_3 + x_4 + x_5},$$

with A_1, A_2, A_3 and A_4 defined as in system (3).

The Jacobian of system (3), at the DFE $Q_0 = (S_0, 0, 0, 0, 0)$, is given by

$$J(Q_0) = \begin{pmatrix} -\mu & 0 & -\beta_s & 0 & -\beta_r \\ 0 & -A_1 & \beta_s(1 - p_s) + \gamma_s & 0 & 0 \\ 0 & (1 - r_s)k_s & \beta_s p_s - A_2 & 0 & 0 \\ 0 & (1 - r_s)\phi_s & \eta_s & -A_3 & \beta_r(1 - p_r) + \gamma_r \\ 0 & (1 - r_s)\varphi_s & \delta_s & k_r(1 - r_r) & \beta_r p_r - A_4 \end{pmatrix},$$

The reproduction number of the transformed (linearized) system (48) is the same than of the original system given as in Eq. (8). Therefore, choosing β_s and β_r as a bifurcation parameter

and solving equation $\mathscr{R}_0 = 1$ (i.e $\mathscr{R}_{0_s} = 1$ and $\mathscr{R}_{0_r} = 1$), one has

$$\beta_s = \beta_s^* = \frac{A_1 A_2 - \gamma_s k_s (1 - r_s)}{p_s \mu + p_s (1 - r_s)(\phi_s + \varphi_s) + k_s (1 - r_s)} \quad \text{and} \quad \beta_r = \beta_r^* = \frac{A_3 A_4 - \gamma_r k_r (1 - r_r)}{p \mu + k_r (1 - r_r)}.$$

It follows that the Jacobian $J(Q_0)$ of system (48) at the DFE Q_0, with $\beta_s = \beta_s^*$ and $\beta_r = \beta_r^*$, has a simple zero eigenvalue (with all other eigenvalues having negative real parts). Hence, the Centre Manifold theory [53] can be used to analyse the dynamics of system (48). Now, Theorem 3.3.2 of [34], can be used to show that the unique endemic equilibrium of system (48) is locally asymptotically stable for $\mathscr{R}_0$ near 1.

For the case $\mathscr{R}_0 = 1$ ($\mathscr{R}_{0_s} = 1$ and $\mathscr{R}_{0_r} = 1$), it can be shown that the right eigenvector (corresponding to the zero eigenvalue) of Jacobian of system (48) at $\beta_s = \beta_s^*$ and $\beta_r = \beta_r^*$, is given by $U = (u_1, u_2, u_3, u_4, u_5)^T$, where,

$$(49) \quad u_1 = -\frac{1}{\mu}(\beta_s u_3 + \beta_r u_5) < 0, \quad u_2 = B_s u_3 > 0, \quad u_4 = B u_3 + B_r u_5 > 0, \quad u_3, u_5 > 0,$$

with

$$B_s = \frac{\beta_s(1 - p_s) + \gamma_s}{A_1}, \quad B_r = \frac{\beta_r(1 - p_r) + \gamma_r}{A_3} \quad \text{and} \quad B = B_s \frac{\phi_s(1 - r_s)}{A_3} + \frac{\eta_s}{A_3}.$$

Similarly, the components of the left eigenvectors of Jacobian of system (48) (corresponding to the zero eigenvalue), denoted by $V = (v_1, v_2, v_3, v_4, v_5)^T$, are given by,

$$v_1 = 0, \quad v_2 = C_s v_3 + C v_5 > 0, \quad v_4 = C_r v_5 > 0, \quad v_3, v_5 > 0,$$

where

$$C_s = \frac{k_s(1 - r_s)}{A_1}, \quad C_r = \frac{k_r(1 - r_r)}{A_3} \quad \text{and} \quad C = C_r \frac{\phi_s(1 - r_s)}{A_1} + \frac{\varphi_s(1 - r_s)}{A_1}.$$

Computation of b: For the sign of b, it can be shown that the associated non-vanishing partial derivatives of f are

$$\frac{\partial^2 f_1}{\partial x_3 \partial \beta_s}(Q_0, \beta_s^*) = -1, \quad \frac{\partial^2 f_1}{\partial x_5 \partial \beta_r}(Q_0, \beta_r^*) = -1, \quad \frac{\partial^2 f_2}{\partial x_3 \partial \beta_s}(Q_0, \beta_s^*) = 1 - p_s,$$

$$\frac{\partial^2 f_3}{\partial x_3 \partial \beta_s}(Q_0, \beta_s^*) = p_s, \quad \frac{\partial^2 f_4}{\partial x_5 \partial \beta_r}(Q_0, \beta_r^*) = 1 - p_r \quad \text{and} \quad \frac{\partial^2 f_5}{\partial x_5 \partial \beta_r}(Q_0, \beta_r^*) = p_r$$

Substituting the respective partial derivatives into the expression of **b**, one has

$$
\begin{aligned}
\mathbf{b} &= v_2 \sum_{i=1}^{5} u_i \frac{\partial^2 f_2}{\partial x_i \partial \beta_s} + v_3 \sum_{i=1}^{5} u_i \frac{\partial^2 f_3}{\partial x_i \partial \beta_s} + v_4 \sum_{i=1}^{5} u_i \frac{\partial^2 f_4}{\partial x_i \partial \beta_r} + v_5 \sum_{i=1}^{5} u_i \frac{\partial^2 f_5}{\partial x_i \partial \beta_r}, \\
&= v_2 u_3 (1 - p_s) + v_3 u_3 p_s + v_4 u_5 (1 - p_r) + v_5 u_5 p_r \\
&= ((1 - p_s)C_s + p_s) u_3 v_3 + (1 - p_s)C u_3 v_5 + ((1 - p_r)C_r + p_r) u_5 v_5 > 0.
\end{aligned}
$$

Computation of a: For system (48), the associated non-zero partial derivatives of f (at the DFE Q_0) are given by

$$
\frac{\partial^2 f_1}{\partial x_3 \partial x_2} = \frac{\partial^2 f_1}{\partial x_3 \partial x_4} = \frac{\beta_s}{S_0}, \quad \frac{\partial^2 f_1}{\partial x_5 \partial x_2} = \frac{\partial^2 f_1}{\partial x_5 \partial x_4} = \frac{\beta_r}{S_0}, \quad \frac{\partial^2 f_1}{\partial x_3^2} = 2\frac{\beta_s}{S_0}, \quad \frac{\partial^2 f_1}{\partial x_5^2} = 2\frac{\beta_r}{S_0},
$$

$$
\frac{\partial^2 f_1}{\partial x_3 \partial x_5} = \frac{\beta_r}{S_0} + \frac{\beta_s}{S_0}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = -\frac{\beta_s (1 - p_s)}{S_0} - \frac{\beta_s \sigma_s (1 - r_s)}{S_0}, \quad \frac{\partial^2 f_2}{\partial x_5 \partial x_2} = -\frac{\beta_r \sigma_r (1 - r_r)}{S_0},
$$

$$
\frac{\partial^2 f_2}{\partial x_3^2} = -2\frac{\beta_s (1 - p_s)}{S_0}, \quad \frac{\partial^2 f_2}{\partial x_4 \partial x_3} = \frac{\partial^2 f_2}{\partial x_5 \partial x_3} = -\frac{\beta_s (1 - p_s)}{S_0}, \quad \frac{\partial^2 f_3}{\partial x_3 \partial x_2} = -\frac{\beta_s p_s}{S_0} + \frac{\beta_s \sigma_s (1 - r_s)}{S_0},
$$

$$
\frac{\partial^2 f_3}{\partial x_3^2} = -2\frac{\beta_s p_s}{S_0}, \quad \frac{\partial^2 f_3}{\partial x_4 \partial x_3} = \frac{\partial^2 f_3}{\partial x_5 \partial x_3} = -\frac{\beta_s p_s}{S_0}, \quad \frac{\partial^2 f_4}{\partial x_5 \partial x_4} = -\frac{\beta_r (1 - p_r)}{S_0} - \frac{\beta_r \sigma_r (1 - r_r)}{S_0},
$$

$$
\frac{\partial^2 f_4}{\partial x_5^2} = -2\frac{\beta_r (1 - p_r)}{S_0}, \quad \frac{\partial^2 f_4}{\partial x_2 \partial x_5} = \frac{\partial^2 f_4}{\partial x_3 \partial x_5} = -\frac{\beta_r (1 - p_r)}{S_0}, \quad \frac{\partial^2 f_5}{\partial x_5 \partial x_4} = -\frac{\beta_r p_r}{S_0} + \frac{\beta_r \sigma_r (1 - r_r)}{S_0},
$$

$$
\frac{\partial^2 f_5}{\partial x_5^2} = -2\frac{\beta_r p_r}{S_0}, \quad \frac{\partial^2 f_5}{\partial x_2 \partial x_5} = -\frac{\beta_r p_r}{S_0} + \frac{\beta_r \sigma_r (1 - r_s)}{S_0} \quad \text{and} \quad \frac{\partial^2 f_5}{\partial x_3 \partial x_5} = -\frac{\beta_r p_r}{S_0}.
$$

Substituting the respective partial derivatives into the expression of **a**, one has

$$
\begin{aligned}
\mathbf{a} &= v_2 \sum_{i,j=1}^{5} u_i u_j \frac{\partial^2 f_2}{\partial x_i \partial x_j} + v_3 \sum_{i,j=1}^{5} u_i u_j \frac{\partial^2 f_3}{\partial x_i \partial x_j} + v_4 \sum_{i,j=1}^{5} u_i u_j \frac{\partial^2 f_4}{\partial x_i \partial x_j} + v_5 \sum_{i,j=1}^{5} u_i u_j \frac{\partial^2 f_5}{\partial x_i \partial x_j}, \\
&= -(H_1 - \beta_s \sigma_s (1 - r_s) B_s) u_3^3 v_3 - H_2 u_3^2 v_5 - H_3 u_3 v_3 u_5 - (H_4 - \beta_r \sigma_r (1 - r_r) B) u_5^2 v_5 \\
&\quad - (H_5 - \beta_r \sigma_r ((1 - r_s) B_s + (1 - r_r) B)) u_3 u_5 v_5,
\end{aligned}
$$

where

$$H_1 = \beta_s B_s C_s((1-p_s)+\sigma_s(1-r_s))+\beta_s(1-p_s)C_s(2+B)+\beta_s p_s(2+B+B_s),$$

$$H_2 = \beta_s B_s C((1-p_s)+\sigma_s(1-r_s))+\beta_s(1-p_s)C(2+B),$$

$$H_3 = \beta_s(1-p_s)(1+C_s B_r)+\beta_r \sigma_r(1-r_r)B_s C_s+\beta_s p_s(1+B_r),$$

$$H_4 = \beta_r B_r C_r((1-p_r)+\sigma_r(1-r_r))+\beta_r(1-p_r)C_r(2+B_s)+\beta_r p_r(2+B),$$

$$H_5 = \beta_r(1-p_r)(B+1)+\beta_r p_r(B+B_s+1)+\beta_r \sigma_r(1-r_r)(B+CB_s+1)+\beta_s(1-p_s)C.$$

The bifurcation coefficient $\mathbf{a} < 0$ if

$$(50) \qquad \sigma_s < \frac{H_1}{\beta_s(1-r_s)B_s} \quad \text{and} \quad \sigma_r < \min\left\{\frac{H_4}{\beta_r(1-r_r)B}, \frac{H_5}{\beta_r((1-r_s)B_s+(1-r_r)B)}\right\}.$$

In this case, we have $a < 0$ and $b > 0$. All conditions of Theorem 47 are satisfied and it should be noted that we use β_s and β_r as the bifurcation parameter, in place of ϕ in Theorem 7. Thus, it follows that the endemic equilibrium is locally asymptotically stable. This concludes the proof. $\square$

Conflict of Interests

The authors declare that there is no conflict of interests.

REFERENCES

[1] W.H.O. Report, Global tuberculosis control: epidemiology, strategy, financing, World Health Organization, Geneva, (2009).

[2] G. L. Snider, Tuberculosis then and now: A personal perspective on the last 50 years, Ann. Intern. Med. 126 (1997), 237-243.

[3] CDC. National Tuberculosis Surveillance System Highlights. http://www.cdc.gov/tb/; http://www.cdc.gov:80/tb/statistics/surv/surv2008/default.htm (2008).

[4] L. Wilson, The historical decline of tuberculosis in Europe and America: its causes and significance, J. Hist. Med. Allied Sci. 45 (2015), 366-396.

[5] WHO/IUATLD, Global Project on Anti-tuberculosis Drug Resistance Surveillance. Anti-Tuberculosis Drug Resistance in the World: third global report. WHO/HTM/TB/2004.343, (2004).

[6] Integrating HIV/AIDS and TB Efforts. The challenge for the Presidents 783 AIDS Initiative. Open Society Institute, New York Public Health Programs. 784 http://www.soros.org/initiatives/health/articles publications/publications/ 785 integrating tb 20040218, (2004).

[7] Global Fund Against AIDS, TB and Malaria. The Global Tuberculosis Epidemic. Geneva, Switzerland, (2004).

[8] AVERT.ORG. AIDS, HIV & tuberculosis (TB). 2006a. Retrieved September 9, (2006), http://www.avert.org/tuberc.htm.

[9] S. Bonhoeffer. Managing antibiotic resistance: what models tell us. In: U. Dieckmann, J. A. J. Metz, M. W. Sabelis, K. Sigmund, Adaptive Dynamics and Infectious Diseases: In Pursuit of Virulence Management Cambridge University Press, Cambridge, UK, (2002), 326-338.

[10] C. Y. Chiang, L. W. Riley, Exogenous reinfection in tuberculosis. Lancet Infect. Dis. 5 (2005), 629-636.

[11] J. Crofton, P. Chaulet, D. Mahaler. Guidelines for the management of drug resistant tuberculosis. WHO/TB/96.21 (Rev/1) vol. 8, (1997).

[12] W. O. Kermack, A. G. McKendrick. A contribution to the mathematical theory of epidemics. Proc. Roy. Soc. A115 (1927), 700-721.

[13] R. M. Anderson, R. M. May, Infectious Disease of Humans, Dynamics and Control. Oxford University Press, London/New York, (1992).

[14] C. Ozcaglar, A. Shabbeer, S. L. Vandenberg, B. Yener, K. P. Bennett, Epidemiological models of Mycobacterium tuberculosis complex infections, Math. Biosci. 236 (2012), 77-96.

[15] C. Colijn, T. Cohen, M. Murray, Mathematical Models of Tuberculosis: accomplishments and future challenges, in: Proceedings of BIOMAT International Symposium on Mathematical and Computational Biology, World Scientific Publisher, (2006), 123.

[16] J. P. Aparicio, A.F. Capurro, C. Castillo-Chavez, Transmission and dynamics of tuberculosis on generalized households, J. Theor. Biol. 206 (2000), 327.

[17] T. C. Porco, S.M. Blower, Quantifying the Intrinsic Transmission Dynamics of Tuberculosis, Theor. Popul. Biol. 5 (4) (1998), 117-132.

[18] B. M. Murphy, B. H. Singer, S. Anderson, S. Kirschner, Comparing epidemic tuber- culosis in demographically distinct heterogeneous populations, Math. Biosci. 180 (2002), 161-185.

[19] Z. Feng, C. Castillo-Chavez, A. F. Capurro, A model for tuberculosis with exogenous reinfection, Theor. Popul. Biol. 57 (3) (2000), 235-247.

[20] J. P. Aparicio, C. Castillo-Chavez, Mathematical modelling of tuberculosis epidemics, Math. Biosci. Eng. 6 (2) (2009), 209-237.

[21] J. P. Aparicio, A. F. Capurro, C. Castillo-Chavez, Markers of disease evolution: the case of tuberculosis, J. Theor. Biol. 215 (2) (2002), 227-237.

[22] Z. Feng, W. Huang, C. Castillo-Chavez, On the role of variable latent periods in mathematical models for tuberculosis, J. Dyn. Differ. Equations, 13 (2001), 425-452.

[23] D. Okuonghae, A. Korobeinikov, Dynamics of tuberculosis: the effect of direct observation therapy strategy (DOTS) in Nigeria, Math. Model. Natural Phenomena, 2 (1) (2007), 113-128.

[24] C. Beggs, C. Noakes, P. Sleigh, L. Fletcher, K. Siddiqi, The transmission of tuberculosis in confined spaces: an analytical review of alternative epidemiological models, Int. J. Tuberculosis Lung Dis. 7 (11) (2003), 1015-1026.

[25] S. Bowong, J. J. Tewa, Global analysis of a dynamical model for transmission of tuberculosis with a general contact rate, Commun. Nonlinear Sci. Numer. Simulat. 15 (2010), 3621-3631.

[26] E. Vynnycky, P. Fine, The long-term dynamics of tuberculosis and other diseases with long serial: The implications of and for changing reproduction numbers, Epidemiol. Infect. 121 (1998), 309-324.

[27] K. Styblo, Epidemiology of Tuberculosis: Selected Papers, Royal Netherlands Tuberculosis Association (1991).

[28] J. W. Raleigh, R. H. Wichelhausen, Exogenous reinfection with mycobacterium tuberculosis conrmed by phage typing. Am. Rev. Respir. Dis. 108 (1973), 636-642.

[29] D. J. Gerberry, Practical aspects of backward bifurcation in a mathematical model for tuberculoisis, J. Theor. Biol. 388 (2016), 15-36.

[30] P. K. Mondal, T. K. Kar, Optimal treatment control and bifurcation analysis of a tuberculosis model with eect of multiple re-infections, Int. J. Dynam. Control. 5 (2) (2017), 367-380.

[31] T. K. Kar, P. K. Mondal, Global dynamics of a tuberculosis epidemic model and influence of backward bifurcation. J. Math. Model. Algor. 11 (2012), 433-459.

[32] C. Castillo-Chavez, Z. Feng, Mathematical Models for the Disease Dynamics of Tuberculosis, World Scientific Press, (1998).

[33] M. Maliyoni, P. M. M. Mwamtobe, S. D. Hove-Musekwa, J. M. Tchuenche, Modelling the Role of Diagnosis, Treatment, and Health Education on Multidrug-Resistant Tuberculosis Dynamics, ISRN Biomath. 2012 (2012), Article ID 459829.

[34] C. Castillo-Chavez, B. Song, Dynamical models of tuberculosis and their applications. Math. Biosci. Eng. 1 (2004), 361-404.

[35] D. J. Austin, M. Kakehashi, R. M. Anderson, The transmission dynamics of antibiotic-resistant bacteria: the relationship between resistance in commensal organisms and antibiotic consumption. Proc. R. Soc. London B, 264 (1997), 1629-1638.

[36] S. M. Blower, T. Chou, Modeling the emergence of the hot zones tuberculosis and the amplification dynamics of drug resistance. Nature Med. 10 (2004), 1111-1116.

[37] Z. Feng, M. Iannelli, F. A. Milner, A two strains tuberculosis model with age of infection. SIAM. J. Appl. Math. 65 (2002), 1634-1656.

[38] P. Rodriguesa, M. Gabriela, M. Gomesa, C. Rebeloc, Drug resistance in tuberculosis a reinfection model. Theor. Popul. Biol. 71 (2007), 196-212.

[39] S. M. Blower, J. Gerberding, Understanding, predicting and controlling the emergence of drug tuberculosis: a theoretical framework. J. Mol. Med. 76 (1998), 624-636.

[40] E. Jung, S. Lenhart, Z. Feng, Optimal control of treatments in a two-strain tuberculosis model, Discr. Contin. Dyn. Syst. B, 2 (4) (2002), 473-482.

[41] Z. Feng, M. Iannelli, F. A. Milner, A two-strain tuberculosis model with age of infection, SIAM J. Appl. Math. 62 (5) (2002), 1634-1656.

[42] A. B. Gumel, B. Song, Existence of multiple-stable equilibria for a multi-drug-resistant model of mycobacterium tuberculosis, Math. Biosci. Eng. 5 (3) (2002), 437-455.

[43] C. P. Bhunu, W. Garira, A two strain tuberculosis trans- mission model with therapy and quarantine, Math. Model. Anal. 14 (3) (2009), 291-312.

[44] M. Ronoh, R. Jaroudi, P. Fotso, V. Kamdoum, A Mathematical Model of Tuberculosis with Drug Resistance Effects. Appl. Math. 7 (12) (2016), 1303-1316.

[45] J. Trauer, J. Denholm, E. McBryde, Construction of a Mathematical Model for Tuberculosis Transmission in Highly Endemic Regions of the Asia-Pacific. J. Theor. Biol. 358 (2014), 74-84.

[46] F. B., Agusto, J. Cook, P. D. Shelton, M.G. Wickers, Mathematical Model of mdr-tb and xdr-tb with Isolation and Lost to Follow-Up. Abstr. Appl. Anal. 2015 (2015), Article ID 828461.

[47] T. Cohen, M. Murray, Modelling Epidemics of Multidrug-Resistant m. Tuberculosis of Heterogeneous Fitness. Nature Med. 10 (2004), 1117-1121.

[48] O. Diekmann, J. A. P. Heesterbeek, J. A. P. Metz, On the definition and computation of the basic reproduction ratio $\mathscr{R}_0$ in the model of infectious disease in heterogeneous populations. J. Math. Biol. 2 (1990), 265-382.

[49] P. van den Driessche, J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Bios. 180 (2002), 29-28.

[50] J. C. Kamgang, G. Sallet, Computation of threshold conditions for epidemiological models and global stability of the disease-free equilibrium (DFE), Math. Biosci. 213 (2008), 1-12.

[51] A. Berman, R. J. Plemmons, Nonnegative Matrices in the Mathematical Sciences, SIAM, (1994).

[52] H. W. Hethcote, The mathematics of infectious diseases, SIAM Rev. 42 (2000), 599-653.

[53] J. Carr. Applications Centre Manifold theory. Springer-Verlag New York, (1981).

[54] J. Dushoff, W. Huang, C. Castillo-Chavez. Backwards bifurcations and catastro- phe in simple models of fatal diseases. J. Math. Biol. 36 (1998), 227-248.

[55] J. Arino, C. C. McCluskey, P. van den Driessche., Global result for an epidemic model with vaccination that exhibits backward bifurcation. SIAM J. Appl. Math. 64 (2003), 260-276.

[56] F. Brauer. Backward bifurcation in simple vaccination models. J. Math. Anal. Appl. 298 (2004), 418-431.

[57] B. D. Hassard, N. Kazarino, Y. Wan, Theory and Application of Hopf Bifurcation, CUP archive (1981).

[58] Y. Chang, G. Chen, Complex dynamics in Chen's system. Chaos, Solitons Fractals, 27 (2006), 75-86.

[59] A. Saltelli et al., A quantitative modelindependent method for global sensitivity analysis of model output, technometrics. J. Stat. Phys. Chem. Eng. Sci. 41 (1) (1999), 39-56.

[60] M. Muma, S. J. Gumiere, A. N. Rousseau, Analyse de sensibilite globale du modele CATHY aux proprietes hydrodynamiques du sol dun micro-bassin agricole draine. Hydrol. Sci. J. 59 (8) (2014), 1606-1623

[61] R. Anguelov, Y. Dumont, J. M. S Lubuma, M. Shillor, Dynamically consistent nonstandard finite difference scheme for epidemiological models, J. Comput. Appl. Math. 255 (2014), 161-182.

[62] Y. Dumont, F. Chiroleu Vector-control for the chikungunya disease, Math. Biosci. Eng. 7 (2010), 315-345.

[63] M. F. Boni, M. W. Feldman, Evolution of antibiotic resistance by human and bacterial niche construction. Evolution 59 (2005), 477-491.