# Analysis of a tuberculosis model with undetected and lost-sight cases

D.P. Moualeu, A. Nana Yakam, S. Bowong, A. Temgoua

# Analysis of a tuberculosis model with undetected and lost-sight cases

**D. P. Moualeu**[1,3]**, A. Nana Yakam**[2,3]**, S. Bowong**[2,3,†]**, A. Temgoua**[2]

[1] Institute for Horticultural Production Systems,

Vegetable Systems Modelling Section

Faculty of Natural Sciences, Leibniz Universität Hannover,

Herrenhäuser Str. 2, D-30419 Hannover

[2] Department of Mathematics and Computer Science, Faculty of Science,

University of Douala, PO Box 24157 Douala, Cameroon

[3] UMI 209 IRD/UPMC UMMISCO, Bondy, France and

Project-Team GRIMCAPE, LIRIMA and The African Center of Excellence in Information and

Communication Technologies (CETIC), University of Yaounde I, Cameroon

[†] Corresponding author Email: sbowong@gmail.com, Tel: +237 678 00 97 81

## Abstract

A deterministic model of tuberculosis (TB) in sub-Saharan Africa including undetected and lost-sight cases is presented and analyzed. The model is shown to exhibit the phenomenon of backward bifurcation, when a stable disease-free equilibrium co-exists with one or more stable endemic equilibrium points when the associated basic reproduction number ($\mathcal{R}_0$) is less than unity. Analyzing the model obviously reveals that exogenous reinfection plays a key role on the existence of backward bifurcation. However, an analysis of the ranges of exogenous reinfection suggested that backward bifurcation occurs only for very high and unrealistic ranges of the exogeneous reinfection rate. Random perturbation of reinfection rates was performed to gain insight into the role of this latter on the stability of the disease free equilibrium.

**Keywords** : Nonlinear dynamical systems; Tuberculosis; Mathematical models; Stability; Bifurcation.

## 1  Introduction

The global burden of tuberculosis (TB) has increased over the past two decades, despite widespread implementation of control strategies including

BCG (Bacillus Calmette-Guerrin) vaccination and the World Health Organization's (WHO) DOTS strategy which focuses on case finding and short-course chemotherapy cause of death. TB is the second largest cause of death from an infectious agent after HIV/AIDS in developing countries [19]. In the modern era, TB is recognized as a disease that preys upon social disadvantage [8, 7]. It remains a worldwide emergency mostly affecting poor countries and to this old and persistent threat, the multidrug-resistant TB is a emergency adding further challenges. Despite predictions of a decline in global incidence, the number of new cases continues to grow, approaching 10 million in 2010 [20].

TB has a latent or incubation period during which the individual is said to be infected but not infectious. This period was modeled either by incorporating as a delay effect or by introducing an exposed class. Therefore, second infection or reinfection occurs in an individual in both high and low-incidence regions, which is already experiencing an infection with another agent. This parameter plays an important role on TB dynamics.

Some authors proposed mathematical models of TB including reinfection and assumed that the rate of reinfection is a multiple of the rate of first infection [45, 47, 48, 49, 52, 5, 22, 29]. Exposed individuals who have been previously infected (in dormant stage) or recovered individuals may acquire new infection from another infectious individual due to low immunity of persons. Therefore, individuals in the latent stage of TB progress into active stage due to exogenous reinfection and recovered individual may progress to Latently infected class [45, 47, 48, 49, 52, 5, 22, 29]. Studies confirmed that reinfection in areas with a low incidence of tuberculosis is possible, although less common than in high-incidence geographical regions, indicating that higher prevalence of *M. tuberculosis* represents the major risk for tuberculosis reinfection.

The challenge of TB control in developing countries is due to the increase of TB incidence by a high level of undiagnosed infectious population and lost sight population with respect to diagnosed infectious cases. Undiagnosed infectious population means people who have not yet been to a hospital for diagnosis or have not been detected, but have a pulmonary TB [4, 51] when lost sight population are people who have been diagnosed as having active TB, begun their treatment and quitted before the end.

3

Lost-sight population are the most likely to develop multi-drug resitance [50]. Compared to existing results [15, 9, 38, 3, 1, 18, 32, 43, 22] and references therein, our work differs from these studies in that our model, in addition to undiagnosed infectious and lost sight population, also considers the aspects of exogenous reinfections, disease relapse as well as primary active TB cases, natural recovery and traditional medicine or self-medication (practiced in Sub-Saharan Africa). Also, it is recognized that undiagnosed population, lost sight population and exogenous reinfections are important components of TB transmission in Sub-Saharan Africa. For the new mathematical model, the infective class is divided into three subgroups with different properties: i) diagnosed infectious population, ii) undiagnosed infectious population and iii) lost sight population. According to the National Committee of Fight against TB of Cameroon (NCFT) [40], about 8% of diagnosed infectious that begin their therapy treatment never returned to the hospital for the rest of sputum examinations and treatment, and then become lost sight. This class of TB epidemiological models can be extended to many classes of infective individuals and data for many other African countries.

For many epidemiological models, a threshold condition that indicates whether an infection introduced into a population will be eliminated or become endemic was defined [13]. The basic reproduction number $\mathcal{R}_0$ is defined as the average number of secondary infections produced by an infected individual in a completely susceptible population [24]. In models with only two steady states and a transcritical bifurcation, $\mathcal{R}_0 > 1$ implies that the endemic state is stable (e.g. the infection persists), and $\mathcal{R}_0 \leq 1$ implies that the uninfected state is stable (e.g. the infection will die out). The co-existence of disease-free equilibrium and endemic equilibrium points when the basic reproduction number ($\mathcal{R}_0 < 1$) is typically associated with the backward or subcritical bifurcation. This phenomenon was found in many epidemiological settings (see for instance, [21, 23, 30, 44] and references therein). The epidemiological implication of is that the classical requirement of having the associated reproduction number less than unity, while necessary is not a sufficient condition for disease control. Results showed that a threshold level of reinfection exists in all cases of the model. Beyond this threshold, the dynamics of the model are described by a backward bifurcation. However, uncertainty analysis of the parameters showed that this threshold is too

4

high to be attained in a realistic epidemic [44]. In our previous works, we analysed optimal control strategies for the model and estimated parameters corresponding to data recorded in Cameroon [37, 35, 36]. Here, we intend to discuss the role of exogenous reinfection on the existence of backward bifurcation in the TB model. In this paper, we determine the basic reproduction ratio, and discuss the existence and the stability of the endemic equilibrium and the disease free equilibrium (DFE). Some discussion about the TB persistence condition was deduced.

## 2  The Proposed Model

### 2.1  The model formulation

A finite total population at time $t$ denoted by $N(t)$ was considered and sub-divided into mutually exclusive sub-populations of

  S  susceptible: healthy people not yet exposed to TB,

  E  latently infected: exposed to TB but not infectious,

  I  diagnosed infectious: have active TB confirmed after a sputum examination in a hospital,

  J  undiagnosed infectious: have not yet been to a hospital for diagnosis but are active for confirmation by a sputum examination,

  L  lost sight: people who have been diagnosed as having active TB, begun their treatment and quitted before the end,

  R  recovered: people cured after treatment in the hospital.

In some countries, reliable TB tests are often missing or too expensive [31]. Hence, TB diagnosis based on a single sputum examination can often only be classified as "probable" or "presumed", and cannot detect cases of less infectious forms of TB [50]. Therefore, the model is based on the following assumptions, established from behaviors of people in different epidemiological classes.

5

1. *Mtb transmission from diagnosed infectious to susceptible population, due to education on the infection is limited. It was therefore modeled using a standard incidence or frequency-dependent force of infection.*

2. *Mtb transmission from undiagnosed infectious to susceptible population, due to their level of education on the disease was modeled by a density-dependent force of infection.*

These arguments abide on the fact that diagnosed infectious people are in most cases hospitalized for at least 2 months or are advised to lessen their infectiousness in their residing neighborhood. Their distribution in the population is not necessarily homogeneous. Since undiagnosed infectious remain inside the population, there is an unlimited possibility of contacts with the susceptible population [4]. We therefore assume a density dependent force of infection for hospital inmates [6].

All recruitment is into the susceptible class and occurs at an average scale $\Lambda$. The fixed survey for non-disease related death is $\mu$, thus $1/\mu$ is the average lifetime. Diagnosed infectious, undiagnosed infectious and lost sight population have additional constant death rates due to the disease, defined by $d_1$, $d_2$ and $d_3$, respectively. Transmission of Mtb occurs due to adequate contacts among susceptible and an active TB case. Thus, susceptible individuals acquire Mtb infection from individuals with active TB and lost sight at a rate $\nu(I, J, L)$ given by

$$\nu(I, J, L) = \beta_1 \frac{I}{N} + \beta_2 \frac{L}{N} + \beta_3 J, \tag{1}$$

where $\beta_i$, $i = 1, 2, 3$, are the effective contact rates with diagnosed, lost sight and undiagnosed infectious population sufficient to transmit infection to susceptible people. The effective contact rates $\beta_i$ in a given population for tuberculosis are measured in effective contacts per unit time. This may be expressed as the product of the total contact rate per unit time $(\eta_i)$ by the risk of infection $(\phi_i)$ given contact between an infectious and a susceptible individual,

$$\beta_i = \eta_i \phi_i.$$

This risk is called the transmission risk.

A proportion $p$ of the latently-infected individuals develop fast active TB and the remainder $(1 - p)$ develop latent TB and enter the latent class

6

$E$. Among latently-infected individuals developing active TB, a fraction $f$ is assumed to undergo a fast progression directly to the diagnosed infectious class $I$, while the remainder $(1 - f)$ enters the undiagnosed infectious class $J$. We set $p_1 = pf$ and $p_2 = p(1 - f)$. Once latently infected with Mtb, an individual will remain so for life unless reactivation occurs. Latently infected individuals are assumed to acquire some immunity as a result of infection, which reduces the risk of subsequent infection but does not fully prevent it.

Due to endogenous reactivation, a fraction $1 - r_1$ of latently infected individuals who did not receive effective chemoprophylaxis become infectious with a constant rate $k$, and get re-infected after effective contact with individuals in the active TB classes or lost sight at a rate

$$\lambda_e = \sigma_1 \nu(I, J, L), \tag{2}$$

where $\sigma_1$ is the factor reducing the risk of infection as a result of acquiring immunity for latently infected individuals. Among latently infected individuals who become infectious, the fraction $h$ is diagnosed and treated under the "Stop TB" program, while the remaining $1 - h$ is not diagnosed and becomes undiagnosed infectious $J$. We assume that after some time suffering from TB, some undiagnosed infectious decide to go to hospital with a rate $\theta$. Also, we assume that among diagnosed infectious who had begun their treatment therapy, a fraction $r_2$ of $I$ has taken all the dose and has made all the sputum examinations and will be declared cured from the disease. Some diagnosed infectious who have not finished their dose of drugs and sputum examinations or whose treatment was unsuccessful, will not return to the hospital for the rest of sputum examinations and check-up. They will enter the class of lost sight $L$ at a constant rate $\alpha$. Lost sight can return to the hospital at a constant rate $\delta$.

As suggested by Murray et al. [39], recovered individuals can only have partial immunity. Hence, they can undergo a TB reactivation or relapse with a constant rate $\gamma$. The remainder can be reinfected (exogenously) after an effective contact with individuals in the active TB classes and lost sight at a rate

$$\lambda_r = \sigma_2 \nu(I, J, L), \tag{3}$$

where $\sigma_2$ is the factor reducing the risk of infection as a result of acquiring partial immunity for recovered individuals. Due to their own immunity, tra-

7

ditional medicine, natural recovery and drugs bought in the street (practiced in sub-Saharan Africa), a fraction of lost sight and undiagnosed infectious can spontaneously recover at constant rates $\rho$ and $\omega$, respectively and enter the latent class $E$ and recovered class $R$ respectively.

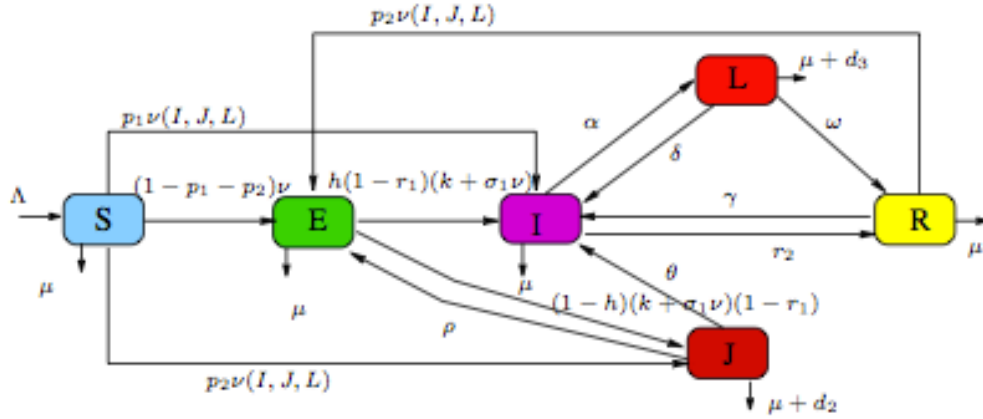The transfer diagram of the model is shown in Fig. 1.



Figure 1: Transfer diagram of the TB model.

A description of the parameters is summarized in Table 1.

Keeping in view the above facts, the mathematical model is formulated as follows:

$$
\begin{cases}
\dot{S} &= \Lambda - \nu(I,J,L)S - \mu S, \\
\dot{E} &= (1 - p_1 - p_2)\nu(I,J,L)S + \rho J + \sigma_2 \nu(I,J,L)R \\
& \quad -\sigma_1(1 - r_1)\nu(I,J,L)E - A_1 E, \\
\dot{I} &= p_1 \nu(I,J,L)S + \delta L + \theta J + \gamma R + h(1 - r_1)(k + \sigma_1 \nu(I,J,L))E \\
& \quad -A_2 I, \\
\dot{J} &= p_2 \nu(I,J,L)S + (1 - h)(1 - r_1)(k + \sigma_1 \nu(I,J,L))E - A_3 J, \\
\dot{L} &= \alpha I - A_4 L, \\
\dot{R} &= r_2 I + \omega L - \sigma_2 \nu(I,J,L)R - A_5 R,
\end{cases}
\tag{4}
$$

where

$$
\begin{aligned}
& A_1 = \mu + k(1 - r_1), && A_2 = \mu + d_1 + r_2 + \alpha, \\
& A_3 = \mu + d_2 + \theta + \rho, && A_4 = \mu + d_3 + \delta + \omega && \text{and} && A_5 = \gamma + \mu.
\end{aligned}
$$

The parameter values of model (4) are given in Table 1.

8

| Parameters | Symbol | Estimate /yr | Source |
|---|---|---|---|
| Recruitment rate of susceptible | $\Lambda$ | 679685 | [37, 41] |
| Transmission rate | $\beta_1, \beta_2$ | $1, 4$ | [37, 11] |
| Transmission rate | $\beta_3$ | $6.05681 \cdot 10^{-06}$ | [37] |
| Fast route to infectious class | $p_1$ | $9.36432 \cdot 10^{-04}$ | [37] |
| Fast route to undiagnosed infectious class | $p_2$ | $2.43736 \cdot 10^{-02}$ | [37] |
| Reinfection parameter of latently infected individuals | $\sigma_1$ | $2.38390 \cdot 10^{-04}$ | [37] |
| Reinfection parameter of recovered individuals | $\sigma_2$ | $0.7 \cdot (p_1 + p_2)$ | [37, 3] |
| Slow route to active TB | $k$ | $3.31390 \cdot 10^{-04}$ | [37] |
| Natural mortality | $\mu$ | $1/53.6$ | [37, 11, 41] |
| TB mortality of diagnosed infectious | $d_1$ | 0.139 | [37, 11] |
| TB mortality of undiagnosed infectious | $d_2$ | 0.413 | [37] |
| TB mortality of lost sight | $d_3$ | 0.20 | [37] |
| Chemoprophylaxis of latently infected individuals | $r_1$ | 0 | [37, 42] |
| Detection rate of active TB | $h$ | 0.828248 | [37] |
| Recovery rate of diagnosed infectious | $r_2$ | 0.758821 | [37, 42] |
| Recovery rate of lost sight | $\omega$ | 0.5 | [37] |
| Recovery rate of undiagnosed infectious | $\rho$ | 0.131140 | [37] |
| Relapse of recovered individuals | $\gamma$ | $8.51257 \cdot 10^{-02}$ | [37] |
| Diagnosed infectious route to the lost sight class | $\alpha$ | 0.216682 | [37] |
| Lost sight route to the diagnosed infectious class | $\delta$ | 0.39 | [37] |
| Diagnosed rate | $\theta$ | 0.495896 | [37] |

Table 1: Numerical values of the parameters of the TB model (4)

## 2.2 Basic properties

Since model (4) monitors a human population, all its associated parameters and state variables should be non-negative and bounded for all $t \geq 0$. It is shown in this section that the model is mathematically well-posed and epidemiologically reasonable [24].

The following result shows that state variables are non-negative and dissipative.

**Lemma 2.1.** *Let the initial values be* $S(0) > 0$, $E(0) \geq 0$, $I(0) \geq 0$,

9

$J(0) \geq 0$, $L(0) \geq 0$ and $R(0) \geq 0$. Then, solutions $(S, E, I, J, L, R)$ of model (4) are non-negative for all $t > 0$. Furthermore,

$$\limsup_{t \longrightarrow \infty} N(t) \leq \frac{\Lambda}{\mu},$$

with $N(t) = S(t) + E(t) + I(t) + J(t) + L(t) + R(t)$.

The proof of this Lemma follows from an obvious adjustment of the result in [33, 34]. The following steps establish the positive invariance of the set

$$\Omega_\varepsilon = \left\{ (S, E, I, J, L, R) \in \mathbb{R}_+^6, \quad N(t) \leq \frac{\Lambda}{\mu} + \varepsilon \right\}, \quad \varepsilon > 0, \quad (5)$$

i.e. solutions remain in $\Omega_\varepsilon$ for all $t \geq 0$. This implies that the trajectories of model (4) are bounded. On the other hand, integrating the differential inequality $\dot{N} \leq \Lambda - \mu N$ yields

$$N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t}).$$

In particular $N(t) \leq \frac{\Lambda}{\mu}$ if $N(0) \leq \frac{\Lambda}{\mu}$. On the other hand, if $N(0) \geq \frac{\Lambda}{\mu}$, then $\Lambda - \mu N(0) \leq 0$, and

$$\dot{N}(0) \leq \Lambda - \mu N(0) \leq 0,$$

i.e. the total population $N(t)$ will decrease until

$$N(t) \leq \frac{\Lambda}{\mu}.$$

Thus, the region $\Omega_\varepsilon$ is a compact forward invariant set for model system (4), and for $\varepsilon > 0$ this set is absorbing. So, we limit our study to this region for $\varepsilon > 0$. The prevalent existence, uniqueness and continuation results hold for model system (4) in $\Omega_\varepsilon$.

## 2.3 The basic reproduction number

The global behavior of the TB model crucially depends on the basic reproduction number, i.e., an average number of secondary cases produced by a single infective individual, who is introduced into an entirely susceptible population. Model system (4) has an evident equilibrium $Q_0 = (x_0, 0)$ with $x_0 = \Lambda/\mu$ when there is no disease in the population. This equilibrium point is the disease-free equilibrium, obtained by setting the right hand sides of

10

equations in model (4) to zero. We calculate the basic reproduction number $\mathcal{R}_0$, using the next generation method developed in [46]. To this end, let us write system (4) in the form

$$\begin{cases} \dot{x} &= \varphi(x) - \nu(I,J,L)x, \\ \dot{y} &= \mathcal{F}(x,y) - \mathcal{V}(x,y), \end{cases} \tag{6}$$

where $\mathcal{F}(x,y) = \nu(I,J,L)B_1 x$, $\mathcal{V}(x,y) = \nu(I,J,L)[B_2\langle e_1 \mid y\rangle + B_3\langle e_5 \mid y\rangle] + A\,y$, $\langle . \mid .\rangle$ is the usual scalar product and $A$ is the constant matrix

$$A = \begin{bmatrix} -A_1 & 0 & \rho & 0 & 0 \\ kh(1-r_1) & -A_2 & \theta & \delta & \gamma \\ k(1-h)(1-r_1) & 0 & -A_3 & 0 & 0 \\ 0 & \alpha & 0 & -A_4 & 0 \\ 0 & r_2 & 0 & \omega & -A_5 \end{bmatrix},$$

with $A_1$, $A_2$, $A_3$, $A_4$ and $A_5$ defined as above in Eq. (4).

The Jacobian matrices of $\mathcal{F}(x,y)$ and $\mathcal{V}(x,y)$ at the DFE of are

$$F = \frac{\partial \mathcal{F}}{\partial y}(Q_0) = B_1\left(e_1 + \frac{\Lambda}{\mu}e_2\right) \quad \text{and} \quad V = \frac{\partial \mathcal{V}}{\partial y}(Q_0) = -A,$$

where

$$e_1 = (0, \beta_1, \beta_2, 0, 0), \quad e_2 = (0, 0, 0, \beta_3, 0), \quad e_3 = (1, 0, 0, 0, 0),$$

$$e_4 = (0, 0, 0, 0, 1), \quad B_1 = (1 - p_1 - p_2, p_1, p_2, 0, 0)^T,$$

$$B_2 = (-\sigma_1(1 - r_1), h\sigma_1(1 - r_1), \sigma_1(1 - h)(1 - r_1), 0, 0)^T \quad \text{and}$$

$$B_3 = (-\sigma_2(1 - \gamma), 0, 0, 0, \sigma_2(1 - \gamma))^T.$$

Thus, using the matrix transformation of [28, 25, 26, 27], the basic reproduction number is the spectral radius of $FV^{-1}$:

$$\mathcal{R}_0 = \left\langle e_1 + \frac{\Lambda}{\mu}e_2 \mid (-A^{-1})B_1 \right\rangle. \tag{7}$$

We use the expression $(-A^{-1})$ to emphasize that $(-A^{-1}) \geq 0$ because the matrix $A$ is Metzler stable.

The following result is established (from [46]):

**Lemma 2.2.** : *The disease-free equilibrium $Q_0$ of model (4) is locally asymptotically stable whenever $\mathcal{R}_0 < 1$, and instable if $\mathcal{R}_0 > 1$.*

11

From a biological point of view, Lemma 2.2 implies that TB can be eliminated from the community (when $\mathcal{R}_0 \leq 1$) if the initial sizes of the population are in the basin of attraction of $Q_0$. But if $\mathcal{R}_0 > 1$ the infection will be able to spread in a population. Generally, the larger the value of $\mathcal{R}_0$, the harder it is to control the epidemic.

## 3 Bifurcation analysis

Herein, the number of equilibrium solutions of model (4) is investigated. Let $Q^* = (x^*, y^*)$ be any arbitrary equilibrium of model (4). To find existence conditions for an endemic equilibrium of tuberculosis in the population (steady state with $y^*$ non zero), the equations in model(4) are set to zero, i.e.,

$$\begin{cases} \varphi(x^*) - x^*\nu^* = 0, \\ \\ \nu^*[x^*B_1 + \langle e_3 \mid y^* \rangle B_2 + \langle e_4 \mid y^* \rangle B_3] + A\,y^* = 0, \end{cases} \quad (8)$$

with

$$\nu^* = \frac{\langle e_1 \mid y^* \rangle}{N^*} + \langle e_2 \mid y^* \rangle, \quad (9)$$

is the force of infection at the steady state.

Multiplying the second equation of (8) by $-A^{-1}$, one obtains

$$y^* = \nu^*[x^*(-A^{-1})B_1 + \langle e_3 \mid y^* \rangle(-A^{-1})B_2 + \langle e_4 \mid y^* \rangle(-A^{-1})B_3]. \quad (10)$$

Then, one can deduce that

$$\begin{array}{rcl} \langle e_1 \mid y^* \rangle & = & \nu^*[x^*R_{01} + a_1\langle e_3 \mid y^* \rangle + a_2\langle e_4 \mid y^* \rangle], \\ \langle e_2 \mid y^* \rangle & = & \nu^*[x^*R_{02} + a_3\langle e_3 \mid y^* \rangle + a_4\langle e_4 \mid y^* \rangle], \\ \langle e_3 \mid y^* \rangle & = & \nu^*[x^*a_5 + a_6\langle e_3 \mid y^* \rangle + a_7\langle e_4 \mid y^* \rangle], \\ \langle e_4 \mid y^* \rangle & = & \nu^*[x^*a_8 + a_9\langle e_3 \mid y^* \rangle + a_{10}\langle e_4 \mid y^* \rangle], \end{array} \quad (11)$$

where

$$R_{01} = \langle e_1 \mid (-A^{-1})B_1 \rangle, \quad R_{02} = \langle e_2 \mid (-A^{-1})B_1 \rangle, \quad a_1 = \langle e_1 \mid (-A^{-1})B_2 \rangle,$$

$$a_2 = \langle e_1 \mid (-A^{-1})B_3 \rangle, \quad a_3 = \langle e_2 \mid (-A^{-1})B_2 \rangle, \quad a_4 = \langle e_2 \mid (-A^{-1})B_3 \rangle,$$

$$a_5 = \langle e_3 \mid (-A^{-1})B_1 \rangle, \quad a_6 = \langle e_3 \mid (-A^{-1})B_2 \rangle, \quad a_7 = \langle e_3 \mid (-A^{-1})B_3 \rangle,$$

$$a_8 = \langle e_4 \mid (-A^{-1})B_1 \rangle, \quad a_9 = \langle e_4 \mid (-A^{-1})B_2 \rangle \text{ and } a_{10} = \langle e_4 \mid (-A^{-1})B_3 \rangle.$$

12

Using the last two equation of (11), one can deduce that

$$
\begin{aligned}
\langle e_3 \mid y^* \rangle &= \frac{\nu^* x^* [a_5 + (a_7 a_8 - a_5 a_{10})\nu^*]}{-a_7 a_9 (\nu^*)^2 + (1 - a_6 \nu(I, J, L)^*)(1 - a_{10}\nu^*)}, \\
\langle e_4 \mid y^* \rangle &= \frac{\nu^* x^* [a_8 + (a_5 a_9 - a_6 a_8)\nu^*]}{-a_7 a_9 (\nu^*)^2 + (1 - a_6 \nu^*)(1 - a_{10}\nu^*)}.
\end{aligned}
\tag{12}
$$

From the first equation of (8), one has

$$
x^* = \frac{\Lambda}{\mu + \nu^*}
\tag{13}
$$

Combining equations (9), (11), (12) and (13), one can deduce that the total population size at the steady state is given by

$$
N^* = \frac{\Lambda \left( F_2 (\nu^*)^2 + F_1 \nu^* + R_{01} \right)}{H_3 (\nu^*)^3 - (\mu H_3 - \Lambda C_2 - (a_6 + a_{10}))(\nu^*)^2 + (1 - \mu(a_6 + a_{10}) - \Lambda C_1)\nu^* + \mu - \mu R_{02}},
\tag{14}
$$

where

$$
\begin{aligned}
F_2 &= R_{01}(a_{10}a_6 - a_7 a_9) + a_1(a_7 a_8 - a_5 a_{10}) + a_2(a_5 a_9 - a_8 a_6), \\
F_1 &= -R_{01}(a_6 + a_{10}) + a_1 a_5 + a_2 a_8, \\
C_2 &= R_{02}(a_{10}a_6 - a_7 a_9) + a_3(a_7 a_8 - a_5 a_{10}) + a_4(a_5 a_9 - a_8 a_6), \\
C_1 &= R_{02}(a_6 + a_{10}) + a_3 a_5 + a_4 a_8, \\
H_3 &= (a_6 a_{10} - a_7 a_9).
\end{aligned}
$$

Let $w_1 = (0, 1, 0, 0, 0)^T$, $w_2 = (0, 0, 1, 0, 0)^T$ and $w_3 = (0, 0, 0, 1, 0)^T$. Then, from Eq. (10), one can deduce that

$$
\begin{aligned}
I^* = \langle w_1 \mid y^* \rangle &= \nu^* [x^* \langle w_1 \mid (-A^{-1})B_1 \rangle + \langle w_1 \mid (-A^{-1})B_2 \rangle \langle e_3 \mid y^* \rangle \\
&\quad + \langle w_1 \mid (-A^{-1})B_3 \rangle \langle e_4 \mid y^* \rangle], \\
J^* = \langle w_2 \mid y^* \rangle &= \nu^* [x^* \langle w_2 \mid (-A^{-1})B_1 \rangle + \langle w_2 \mid (-A^{-1})B_2 \rangle \langle e_3 \mid y^* \rangle \\
&\quad + \langle w_2 \mid (-A^{-1})B_3 \rangle \langle e_4 \mid y^* \rangle], \\
L^* = \langle w_3 \mid y^* \rangle &= \nu^* [x^* \langle w_3 \mid (-A^{-1})B_1 \rangle + \langle w_3 \mid (-A^{-1})B_2 \rangle \langle e_3 \mid y^* \rangle \\
&\quad + \langle w_3 \mid (-A^{-1})B_3 \rangle \langle e_4 \mid y^* \rangle].
\end{aligned}
\tag{15}
$$

Now, using the total population dynamics at the steady state, one has

$$
N^* = \frac{\Lambda}{\mu} - \frac{d_1}{\mu} I^* - \frac{d_2}{\mu} J^* - \frac{d_3}{\mu} L^*.
\tag{16}
$$

Combining Eqs. (12), (15) and (16) yields

$$
N^* = \frac{\Lambda}{\mu} \frac{(\nu^*)^3 (H_3 - D_2) + (\nu^*)^2 (\mu H_3 - D_1 - (a_6 + a_{10})) + \nu^* (1 - \mu(a_6 + a_{10}) - g_0) + \mu}{H_3 (\nu^*)^3 + (H_3 \mu - (a_6 + a_{10}))(\nu^*)^2 + (1 - \mu(a_6 + a_{10}))\nu^* + \mu},
\tag{17}
$$

13

where

$$
\begin{aligned}
g_0 &= d_1\langle w_1 \mid (-A^{-1})B_1\rangle + d_2\langle w_2 \mid (-A^{-1})B_1\rangle + d_3\langle w_3 \mid (-A^{-1})B_1\rangle, \\
g_1 &= d_1\langle w_1 \mid (-A^{-1})B_2\rangle + d_2\langle w_2 \mid (-A^{-1})B_2\rangle + d_3\langle w_3 \mid (-A^{-1})B_2\rangle, \\
g_2 &= d_1\langle w_1 \mid (-A^{-1})B_3\rangle + d_2\langle w_2 \mid (-A^{-1})B_3\rangle + d_3\langle w_3 \mid (-A^{-1})B_3\rangle, \\
D_1 &= -g_0(a_6 + a_{10}) + a_5 g_1 + a_8 g_2, \\
D_2 &= g_2(a_9 a_5 - a_6 a_8) + g_1(a_7 a_8 - a_5 a_{10}) + g_0(a_6 a_{10} - a_7 a_9).
\end{aligned}
$$

Equating Eqs. (14) and (17), it can be shown that the non-zero equilibria of model (4) satisfies the following equation in term of $\nu^*$:

$$
E_6(\nu^*)^6 + E_5(\nu^*)^5 + E_4(\nu^*)^4 + E_3(\nu^*)^3 + E_2(\nu^*)^2 + E_1(\nu^*) + E_0 = 0, \quad (18)
$$

where

$$
\begin{aligned}
E_6 &= H_3(H_3 - D_2), \\
E_5 &= H_3(\mu H_3 - D_1 - (a_6 + a_{10})) + (H_3 - D_2)(\mu H_3 - (a_6 + a_{10}) - \Lambda C_2) - \mu F_2 H_3, \\
E_4 &= H_3(1 - \mu(a_6 + a_{10}) - g_0) + (\mu H_3 - (a_6 + a_{10}) - \Lambda C_2)(\mu H_3 - (a_6 + a_{10}) - D_1) \\
&\quad + (H_3 - D_2)(1 - (a_6 + a_{10}) - \Lambda C_1) - \mu F_2(\mu H_3 - (a_6 + a_{10}) - \Lambda C_2) - \mu F_1 H_3, \\
E_3 &= \mu H_3 + (1 - \mu(a_6 + a_{10}) - g_0)(\mu H_3 - (a_6 + a_{10}) - \Lambda C_2) + (H_3 - D_2)(\mu - \Lambda R_{02}) \\
&\quad - \mu F_2(1 - \mu(a_6 + a_{10}) - \Lambda C_1) - \mu F_1(\mu H_3 - (a_6 + a_{10}) - \Lambda C_2), \\
E_2 &= (1 - (a_6 + a_{10}) - \Lambda C_1)(1 - \mu(a_6 + a_{10}) - g_0) + (\mu - \Lambda R_{02})(\mu H_3 - (a_6 + a_{10}) - D_1) \\
&\quad - \mu^2 F_2 + \mu(\mu H_3 - (a_6 + a_{10}) - \Lambda C_2) - \mu F_1(1 - (a_6 + a_{10}) - \Lambda C_1) \\
&\quad - \mu R_{01}(\mu H_3 - (a_6 + a_{10}) - \Lambda C_2), \\
E_1 &= \mu(1 - (a_6 + a_{10}) - \Lambda C_1) + (\mu - \Lambda R_{02})(1 - \mu(a_6 + a_{10}) - g_0) - \mu^2 F_2 \\
&\quad - (1 - (a_6 + a_{10}) - \Lambda C_1)\mu R_{01}, \\
E_0 &= \mu^2(1 - \mathcal{R}_0).
\end{aligned}
$$

The positive endemic equilibrium point $Q^*$ are obtained by finding $\nu^*$ from the polynomial equation (18) and substituting the numerical results (positive values of $\nu^*$) into the expressions of the state variables at the steady state. Clearly, the coefficient $E_0$ of equation (18) is positive or negative whenever $\mathcal{R}_0$ is less or greater than unity, respectively. Thus, the number of possible real roots of the polynomial equation (18) depends on the signs of $E_6$, $E_5$, $E_4$, $E_3$, $E_2$, $E_1$ and $E_0$. This can be analyzed using the Descartes Rule of Signs on the function:

$$
f(\nu^*) = E_6(\nu^*)^6 + E_5(\nu(I,J,L)^*)^5 + E_4(\nu(I,J,L)^*)^4 + E_3(\nu(I,J,L)^*)^3 + E_2(\nu(I,J,L)^*)^2 + E_1(\nu^*) + E_0,
$$

given in Eq. (18). We claim the following result.

**Lemma 3.1.** *The TB model (4)*

**(i)** *could have a unique endemic equilibrium wherever $\mathcal{R}_0 > 1$;*

14

**(ii)** *could have more than one endemic equilibrium wherever $\mathcal{R}_0 > 1$;*

**(iii)** *could have a unique endemic equilibrium wherever $\mathcal{R}_0 < 1$;*

**(iv)** *could have one or more endemic equilibria wherever $\mathcal{R}_0 < 1$.*

The existence of multiple endemic equilibria when $\mathcal{R}_0 < 1$ suggests the possibility of a backward bifurcation (see, [12, 2, 21] and references therein), where a stable disease-free equilibrium co-exists with a stable endemic equilibrium when the basic reproduction number is less than unity. This is explored below via numerical simulations. The function `roots` of Matlab is used to find the root of the polynomial (18).
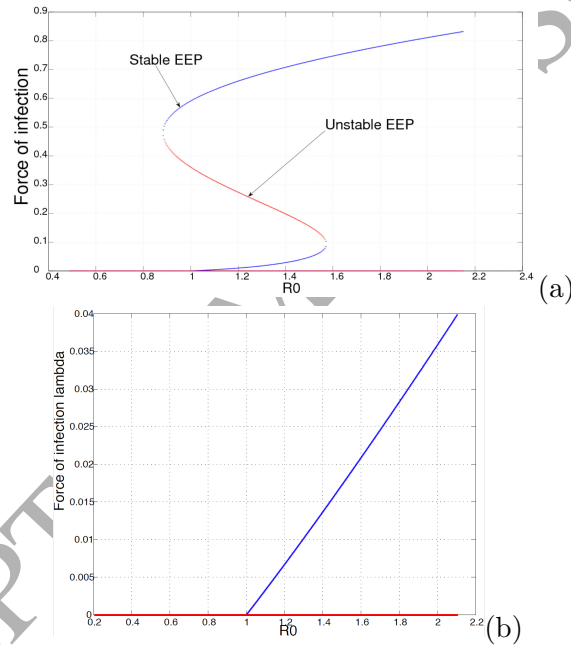


Figure 2: Bifurcation diagram for model (4). (a) $\sigma_1 = 2.38390 \cdot 10^{-4}$ and (b) $\sigma_1 = 0.015$. The notation EEP stands for endemic equilibrium point.

The bifurcations which occurs for different signs of $\sigma_1$ are shown in Fig. 2. The notation EE stands for endemic equilibrium point. Figures 2 (a) and (b) show respectively, the force of the infection as a function of the basic reproduction number $\mathcal{R}_0$ generating forward bifurcation when $\sigma_1 = 2.38390 \cdot 10^{-4}$ as well as multiple supercritical endemic equilibria when $\sigma_1 = 0.015$ using the parameter values in Table 1 (except for $\beta_3$, which vary). From

15

Fig. 2 (b), it clearly appears that there are three equilibrium points in $\Omega_\varepsilon$: a locally asymptotically stable disease-free equilibrium point on the boundary of the positive orthant of $\mathbb{R}_+^6$, and two endemic equilibrium points inside the positive orthant. Linear stability analysis (through analysis of the jacobian matrix at this point) shows that the "larger" endemic equilibrium point is locally asymptotically stable, while the "smaller" point is unstable. Further linear analysis with an increased value of $\beta_3$, (with $\mathcal{R}_0 > 1.155$) shows that the DFE is unstable, and there is one locally asymptotically stable endemic equilibrium point.

The epidemiological significance of the phenomenon of backward bifurcation is that the classical requirement of $\mathcal{R}_0 < 1$ is, although necessary, no longer sufficient for disease eradication. In such a scenario, disease elimination would depend on the initial sizes of the population (state variables) of the model. The presence of backward bifurcation in TB transmission model (4) suggests that the feasibility of controlling TB when $\mathcal{R}_0 < 1$ could be dependent on the initial sizes of the population. Further, as a consequence, it is instructive to try to determine the "cause" of the backward bifurcation phenomenon in model (4). The role of reinfection on backward bifurcation is investigated in the following section.

Now, let us investigate the role of exogenous reinfections. This corresponds to the case where there is no exogenous reinfection in the population, that is , $\sigma_1 = \sigma_2 = 0$, $B_2 = B_3 = 0$ . Then, model (4) becomes

$$\begin{cases} \dot{x} & = \varphi(x) - \nu(I, J, L)x, \\ \dot{y} & = \nu(I, J, L)B_1 x + A\, y, \end{cases} \tag{19}$$

where $\varphi(x)$, $B_1$, $\nu(I, J, L)$ and $A$ are defined as in Eq. (4).

The above model has the same disease-free equilibrium $Q_0$. Apart this equilibrium state, the model can also have a unique positive endemic equilibrium state. In the absence of exogenous reinfection $\sigma_1 = \sigma_2 = 0$ (i.e, $B_2 = B_3 = 0$), the coefficients $E_0$, $E_1$, $E_2$, $E_3$, $E_4$, $E_5$ and $E_5$ in equation (18) reduce to

$E_6 = E_5 = E_4 = E_3 = 0, \quad E_2 = 1 - g_0, \quad E_1 = \mu + (\mu(1 - \mathcal{R}_0)(1 - g_0),$
$E_0 = \mu^2(1 - \mathcal{R}_0).$

In this case, the force of infection at the steady state satisfies the quadratic equation

$$E_2(\nu^*)^2 + E_1\nu^* + E_0 = 0. \tag{20}$$

16

It is worth noting that the coefficient $E_0$ is positive if $\mathcal{R}_0 < 0$, and negative if $\mathcal{R}_0 > 1$. Thus, the number of possible real roots of equation (21) depends on the signs of $E_2$, $E_1$ and $E_0$. This can be analyzed using the Descartes Rule of Signs on the polynomial $g(\nu^*) = E_2(\nu^*)^2 + E_1\nu^* + E_0$.

From the equality $\nu(I, J, L) = \beta_1 \dfrac{I}{N} + \beta_2 \dfrac{L}{N} + \beta_3 J$, one can deduce that

$$0 \leq \nu^* \leq \left(\beta_1 + \beta_2 + \beta_3 \frac{\Lambda}{\mu}\right).$$

In this case, the force of infection at the steady state satisfies the quadratic equation

$$E_2(\nu^*)^2 + E_1\nu^* + E_0 = 0. \tag{21}$$

It is worth noting that the coefficient $E_0$ is positive if $\mathcal{R}_0 < 0$, and negative if $\mathcal{R}_0 > 1$. Thus, the number of possible real roots of equation (21) depends on the signs of $E_2$, $E_1$ and $E_0$. This can be analyzed using the Descartes Rule of Signs on the polynomial $g(\nu^*) = E_2(\nu^*)^2 + E_1\nu^* + E_0$.

A simple calculation proves that $g_0 < \mathcal{R}_0$ when $d_1 < \beta_1$, $d_2 < \beta_2$ and $d_3 < \beta_3 \Lambda/\mu$. This means that the contact rate to get the infection is higher than the mortality rate of the infection. Since this condition is fulfilled, $\mathcal{R}_0 \leq 1$ leads to the positivity of $E_0$, $E_1$ and $E_2$. The previous equation does not have a nonnegative solution if $\nu^* > 0$ from the Descartes Rule of Sign.

If $\mathcal{R}_0 > 1 > g_0$ or $E_1 < 0$ (e.g. $(1 - \mathcal{R}_0)(1 - g_0) < 1$), then, because $E_0 < 0$, and $g_0 < 1$, the polynomial has one positive root by Descarte's Rule of Sign.

From the equality $\nu(I, J, L) = \beta_1 \dfrac{I}{N} + \beta_2 \dfrac{L}{N} + \beta_3 J$, one can deduce that

$$0 \leq \nu^* \leq \left(\beta_1 + \beta_2 + \beta_3 \frac{\Lambda}{\mu}\right).$$

If $\mathcal{R}_0 > g_0 > 1$, then $E_1 > 0$, $E_0 < 0$, and $E_2 < 0$; by Descartes rule of sign, there are two positive solutions. The solution in the interval $\left[0, \beta_1 + \beta_2 + \beta_3 \dfrac{\Lambda}{\mu}\right]$ is the suitable.

Hence, when $\sigma_1 = \sigma_2 = 0$, no endemic equilibrium exists whenever $\mathcal{R}_0 < 1$. It follows then that, owing to the absence of multiple endemic equilibria for model (4) with $\sigma_1 = \sigma_2 = 0$ and $\mathcal{R}_0 < 1$, a backward bifurcation is unlikely to happen for model (4). The absence of multiple endemic

17

equilibria suggests that the disease-free equilibrium of model (4) is globally asymptotically stable when $\mathcal{R}_0 < 1$.

We claim the following result about the global stability of the DFE of model (4) whenever $\sigma_1 = \sigma_2 = 0$.

**Theorem 3.2.** *Consider model (4) with $\sigma_1 = \sigma_2 = 0$. Then, the DFE is globally asymptotically stable in $\Omega_\varepsilon$ whenever $\mathcal{R}_0 \leq 1$.*

The proof of Theorem 3.2 is given in Appendix A.

Figure 3 shows the time series of of susceptible individuals (S), latently infected individuals (E), diagnosed infectious (I), undiagnosed infectious (J), lost sight (L) and recovered individuals (R) of model (4) when $\beta_3 = 0.2605681 \cdot 10^{-6}$ (so that $\mathcal{R}_0 = 0.4424$) using various initial conditions. All other parameters are as in Table 1. It illustrates the convergence of the trajectories of the model (4) without exogenous reinfection to the disease free equilibrium when $\mathcal{R}_0 \leq 1$. This means that after long time of decreasing, TB will die out in the absence of exogenous reinfection. This figure also shows that reaching a disease free equilibrium, will take more decades than meet the endemic equilibrium point. This is certainly due to the fact that some latently infected individuals might not develop the disease over their life time. In fact, the high number of latent makes the class persistent throughout the simulation and allows therefore longer time to reach the DFE.

The local stability of the endemic equilibrium of the model (4) without exogenous reinfection is stated in Theorem 3.3 below and proved in Appendix B.

**Theorem 3.3.** *The endemic equilibrium of model without exogenous reinfection (4) is locally asymptotically stable for $\mathcal{R}_0 > 1$ but close to 1.*

The time evolution of the fraction of susceptible individuals (S), latently infected individuals (E), diagnosed infectious (I), undiagnosed infectious (J), lost sight (L) and recovered individuals (R) of system (4) using various initial values when $\beta_3 = 1.26 \cdot 10^{-06}$ and $\sigma_1 = \sigma_2 = 0$ (so that $\mathcal{R}_0 = 1.6079$) is shown in Figure 4. Various initial states are used to see numerically the impact of varying initial values on the stability of the endemic equilibrium. The figure illustrates the convergence of the trajectories of model (4) without exogenous reinfections to a local endemic equilibrium.
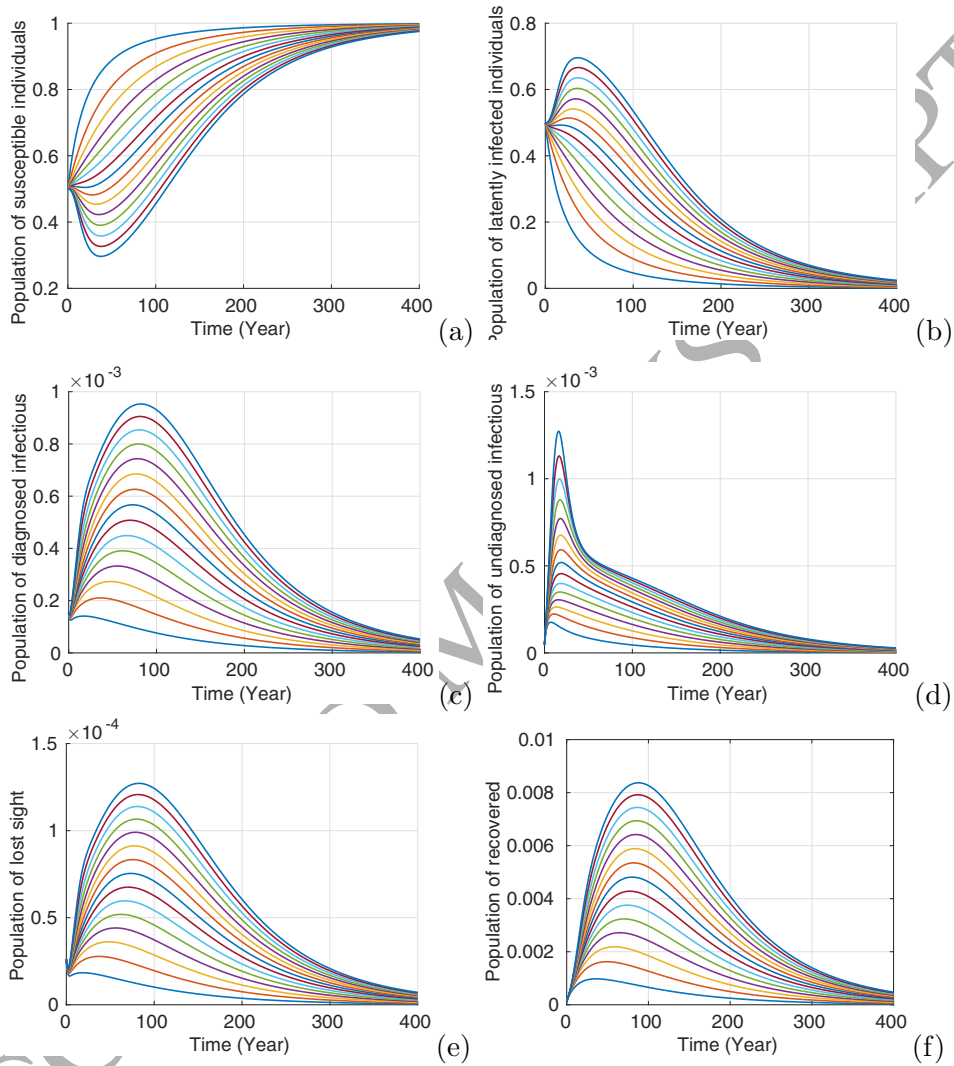
18

Figure 3: Simulation results of model (4) showing the global asymptotic stability of the DFE for the fraction of population in each class using various initial conditions when $\beta_3 = 0.26 \cdot 10^{-6}$ and $\sigma_1 = \sigma_2 = 0$ (so that $\mathcal{R}_0 = 0.44$).
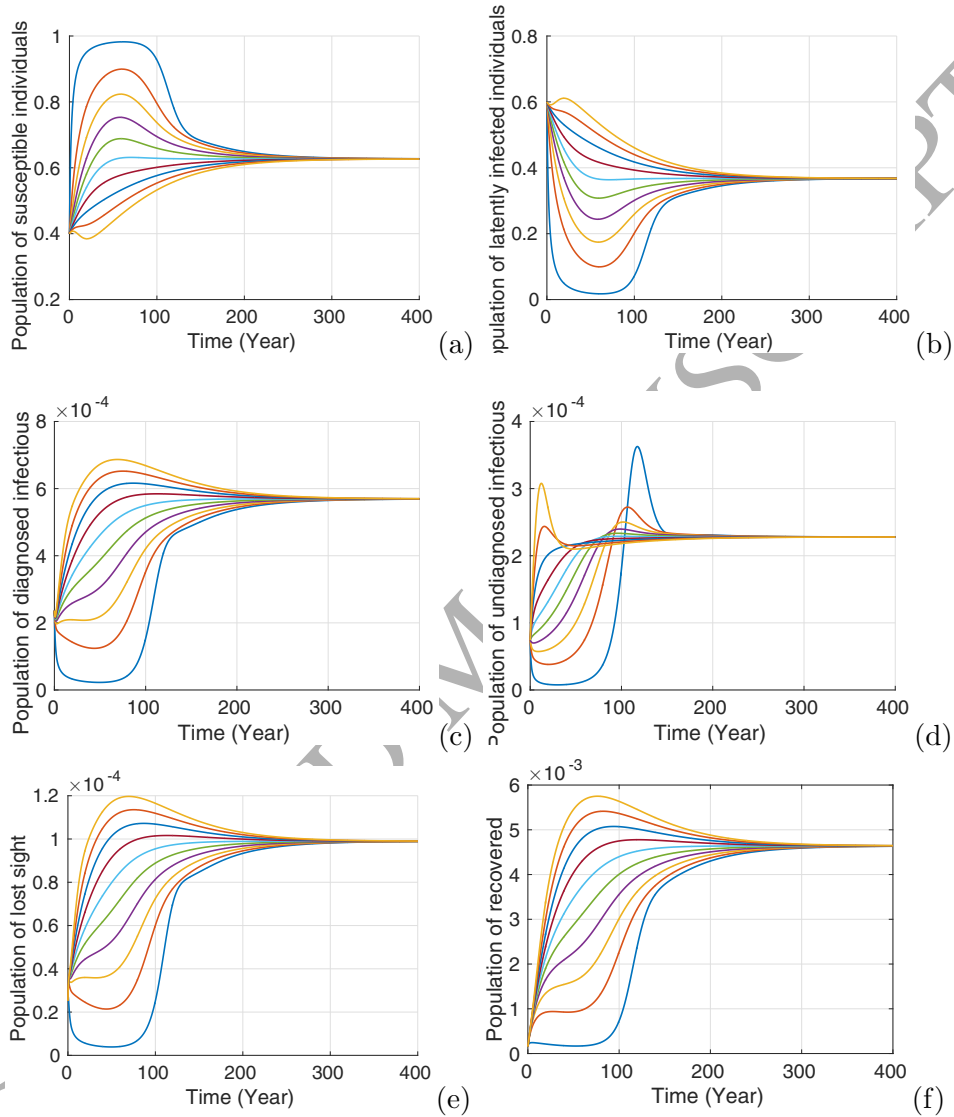
19

Figure 4: Time series of model (4) showing the local stability of the endemic equilibrium of the fraction of population in each class for various initial conditions when $\beta_3 = 1.26 \cdot 10^{-06}$ and $\sigma_1 = \sigma_2 = 0$ (so that $\mathcal{R}_0 = 1.6079$). All other parameters are defined as in Table 1.

20

# 4 The model with stochasticity

We performed Monte-Carlos simulation on the reinfection rates $\sigma_1$ and $\sigma_2$ to see how it affects the disease free equilibrium when $\mathcal{R}_0 < 1$ for a fixed population size. Using parameter values as in Fig. 3, it comes out that for random generation of $\sigma_i$, the disease could converge to an endemic equilibrium or a disease free equilibrium (Figure 5 ). It illustrates the existence of backward bifurcation in the presence of exogenous reinfection.

Analysis of the model with data from Cameroon, as estimated in [37], did not reveal any backward bifurcation. Considering exogenous reinfection as a random phenomena with changes every years due to different reasons, Figure 6 presents result of 50 times numerical simulations of the model. Here, we considered the exogenous reinfection as random perturbation in the system at each time steps. The stop criterium was the positivity of the system. It appears that TB dies out in all run after relatively long run. This result supports that for various exogenous reinfection and when $\mathcal{R}_0 < 1$, the disease might still die out.

# 5 Discussion and conclusion

In this paper, we presented a comprehensive, continuous and realistic deterministic model for the transmission dynamics of tuberculosis in sub-Saharan Africa whose object is to determine the role of TB diagnosis, treatment and lack information about the epidemiological status of certain patients. In contrast to many TB models in the literature, the model includes three infective classes emanating from diagnosed and undiagnosed infectious and lost sight. The undiagnosed and lost sight subclasses are of particular importance in modeling TB in developing countries since it reflects better the social reality. In particular the proportion of individuals that are diagnosed is very important factor for intervention strategies. The parameter can be used can be used to measure successes of educational campaigns that encourage individuals to go for TB screening. It can also be a measure of the level of awareness of the implications of not having TB diagnosis.

The model was rigorously analyzed to gain insight into its qualitative dynamics. It was mainly found that the model exhibits the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists
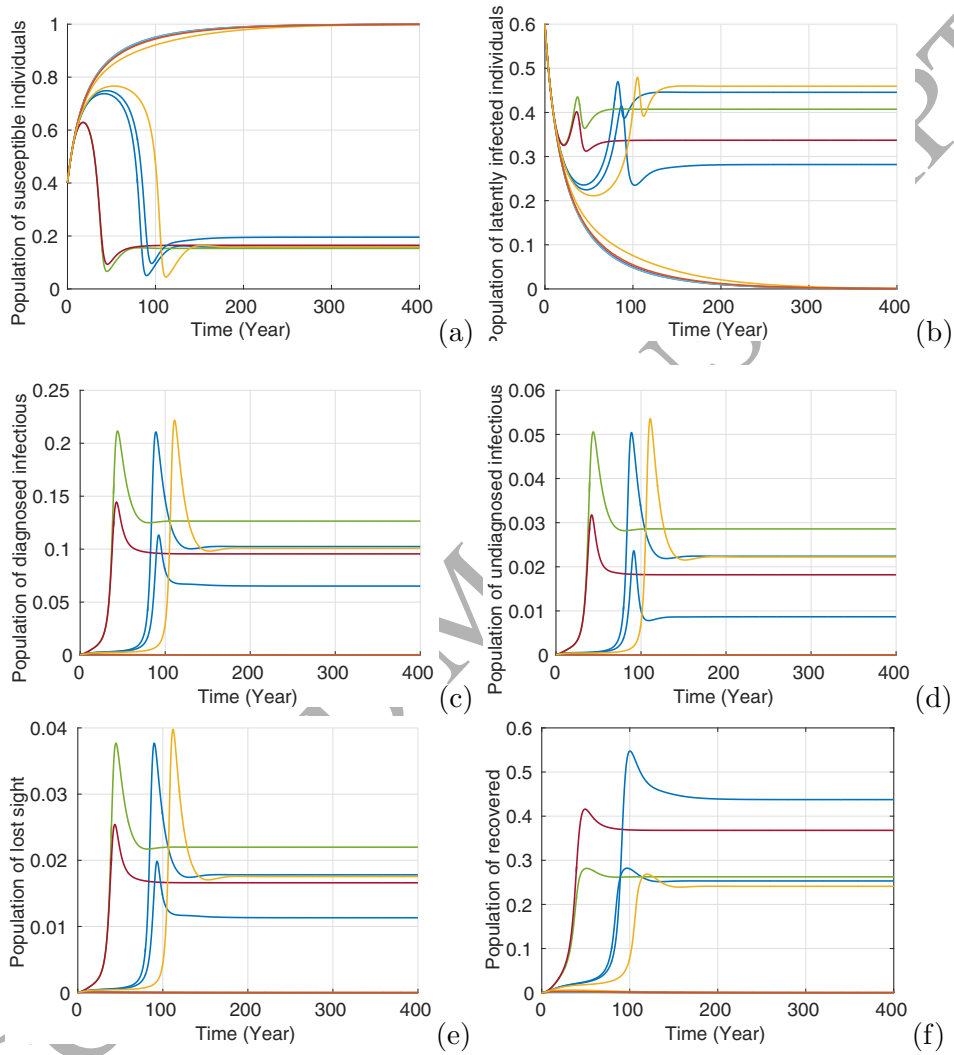
21

Figure 5: Monte-Carlos simulation of model (4) showing the instability of the DFE for various random values of $\sigma_1$ and $\sigma_2$ when $\beta_3 = 0.26 \cdot 10^{-06}$ ($\mathcal{R}_0 = 0.44$).
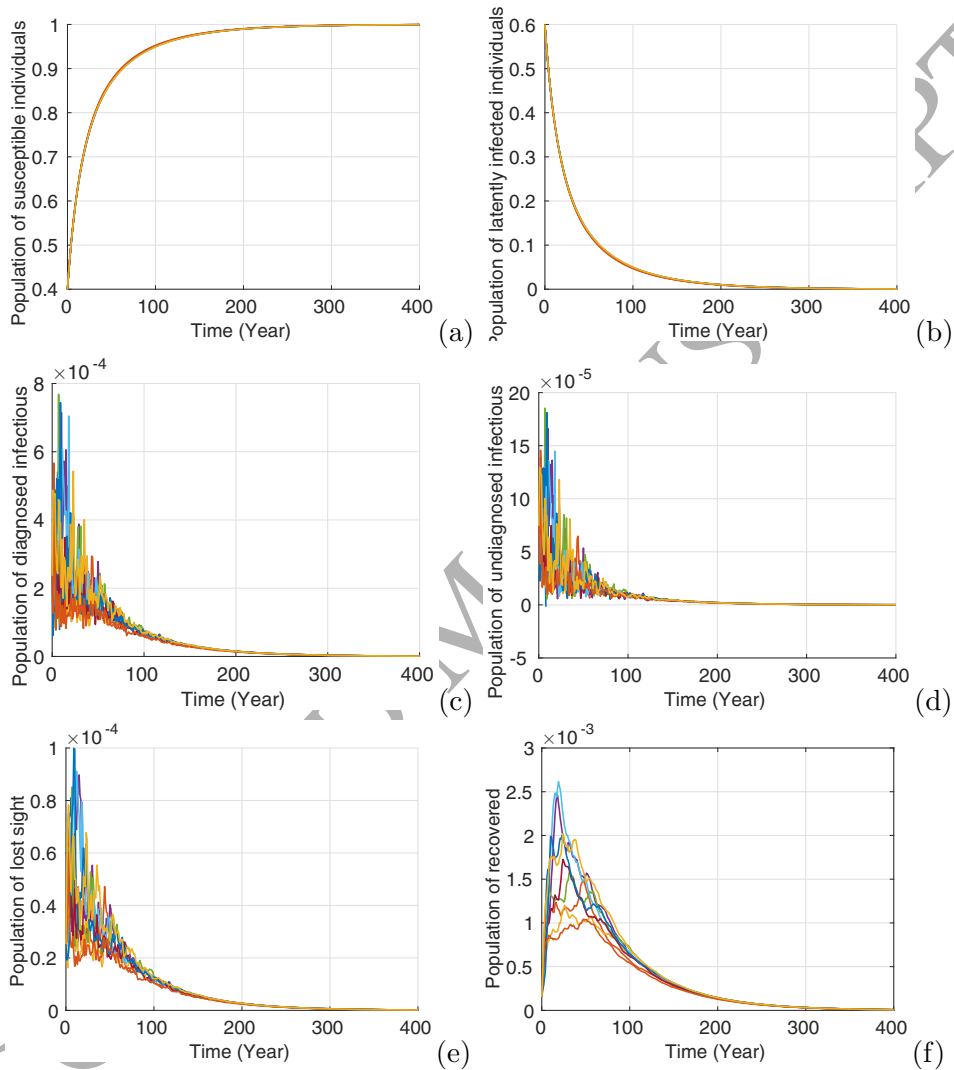
22

Figure 6: Monte-Carlos simulation of model (4) showing stability of the DFE for various random values of $\sigma_1$ and $\sigma_2$ when $\beta_3 = 0.26 \cdot 10^{-06}$ ($\mathcal{R}_0 = 0.4424$).

23

with a stable endemic equilibrium, when the basic reproduction ratio is less than unity. However, backward bifurcation dynamics feature is caused by the re-infection of latently infected and recovered individuals had mainly occur for values that over ten times than estimations from Cameroon's data.

Numerical analysis allowed us to observe that to reach a disease free equilibrium, it will take more decades than reaching endemic equilibrium point, because the latently infected population will take more time to reach zero due to the high number and the slow flow to other classes. For high values, potentially unrealistic of the reinfection rate, backward bifurcation was effective and lead to a convergence to a disease endemic equilibrium. However, for random values of the reinfection rate at each computation state, the disease dies out. This means that backward bifurcation only occurs for constant and high values of reinfection rates. Since the effect of drug resistance is an important aspect on TB propagation, this study might be extended to account drug resistances and specific HIV/AIDS coinfection classes.

## Appendix A: Proof of Theorem 3.2

The local stability of $Q_0$ is classic by the result of van den Driessche and Watmough [46]. Since we are interested in the global asymptotic behavior of model (4), we will show that there exists $T > 0$ such that, if $\mathcal{R}_0 < 1$, the solutions of model system (4) without exogenous reinfections tend to the DFE $Q_0 = (S_0, 0, 0, 0, 0)$ when $t \to \infty$, $\forall t > T$. Indeed, from the first equation of model (4) without exogenous reinfections, one has

$$\dot{S} \leq \Lambda - \mu S. \tag{22}$$

This suggests the linear comparison system:

$$\dot{S} = \Lambda - \mu S. \tag{23}$$

The linear comparison system (23) has a unique positive equilibrium $S_0$ which is globally asymptotically stable. By the comparison theorem for cooperative systems, one has that

$$\limsup_{t \to \infty} S(t) \leq \lim_{t \to \infty} S(t) = S_0. \tag{24}$$

Thus, for any $\sigma > 0$, there exists a sufficiently large $T > 0$ such that $S(t) \leq S_0 + \sigma$, for all $t > T$.

Since $\mathcal{R}_0$ depend of $S_0$, we set $F = F(S_0)$, $S_0^\sigma = S_0 + \sigma$ and $F_\sigma = F(S_0^\sigma) = F(S_0 + \sigma) = [F_1 + (S_0 + \sigma)F_2]B$. Since the spectral radius of $F_\sigma V^{-1}$ is a continuous function of $\sigma$, we can choose $\sigma$ as small as possible such that if $\rho(FV^{-1}) < 1$, so $\rho(F_\sigma V^{-1}) < 1$.

Now, since $S(t) \leq S_0 + \sigma$ for all $t > T$ and $\dfrac{S(t)}{N(t)} \leq 1$, replacing $S(t)$ by $S_0 + \sigma$ in model (4) without exogenous reinfections, we have the following comparison linear system in $E$, $I$, $J$, $L$ and $R$ :

$$\begin{cases} \dot{E} &= (1 - p_1 - p_2)(\beta_1 I + \beta_2 L + \beta_3 J(S_0 + \sigma)) + \rho J - A_1 E, \\ \dot{I} &= p_1(\beta_1 I + \beta_2 L + \beta_3 J(S_0 + \sigma)) + \delta L + \theta J + \gamma R + h(1 - r_1)k - A_2 I, \\ \dot{J} &= p_2(\beta_1 I + \beta_2 L + \beta_3 J(S_0 + \sigma)) + (1 - h)(1 - r_1)k - A_3 J, \\ \dot{L} &= \alpha I - A_4 L, \\ \dot{R} &= r_2 I + \omega L - A_5 R, \end{cases} \tag{25}$$

Model system (25) can be written in the following compact form:

$$\dot{y} = (F_\sigma - V)\, y, \tag{26}$$

25

where $y$ is defined as in model (6). Note that $y = (0, 0, 0, 0, 0)$ is the unique equilibrium of the linear comparison system (26) which is globally asymptotically stable, since it is well known that if $s(F_\sigma - V)$ is the stability modulus of the matrix $(F_\sigma - V)$ defined as the maximal real part of the eigenvalues of $(F_\sigma - V)$, then from [46], $s(F_\sigma - V) < 0$ is equivalent to $\rho(F_\sigma V^{-1}) < 1$. Therefore, all solutions of the linear comparison system (26) converge to the trivial solution $y = (0, 0, 0, 0, 0)$ when $t \to \infty$, with $t > T$. It is obvious to see that $F_\sigma - V$ as the Jacobian of model (26) is a M-matrix and irreducible. Thus, by the comparison theorem for monotone dynamical systems [10], we can conclude that the $E, I, J, R$ components of model (4) also converge to zero when $t \to \infty$, with $t > T$. Putting this last zero solution into the first equation of model (4) without exogenous reinfections gives the linear system (23) which admits a unique positive equilibrium $S_0$ which is globally asymptotically stable. Finally, by the asymptotically autonomous systems theory [17], we can conclude that the $S$-component of the solution of system (4) without exogenous reinfections converges to $S_0$. This proves the global asymptotic stability of the DFE $Q_0 = (S_0, 0, 0, 0, 0, 0)$ when $\mathcal{R}_0 < 1$, and this completes the proof. □

## Appendix B: Proof of Theorem 3.3

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 [16], stated below (Theorem 5.1 for convenience), to establish the local asymptotic stability of the TB endemic equilibrium in the absence of reinfection.

**Theorem 5.1.** *[16]: Consider the following general system of ordinary differential equations with a parameter $\phi$:*

$$\frac{dz}{dt} = f(z, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \quad and \quad f \in C^2(\mathbb{R}^n, \mathbb{R}), \tag{27}$$

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

1. *$A = D_z f(0, 0) = \left( \dfrac{\partial f_i}{\partial z_j}(0, 0) \right)$ is the linearization matrix of system (27) around the equilibrium 0 with $\phi$ evaluated at 0. Zero is a simple eigenvalue of $A$ and other eigenvalues of $A$ have negative real parts;*

26

2. *Matrix $A$ has a right eigen-vector $u$ and a left eigen-vector $v$ (each corresponding to the zero eigenvalue).*

Let $f_k$ be the $k^{th}$ component of $f$ and

$$
\begin{aligned}
a &= \sum_{k,i,j=1}^{n} v_k u_i u_j \frac{\partial^2 f_k}{\partial z_i \partial z_j}(0,0),\\
b &= \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial z_i \partial \phi}(0,0),
\end{aligned}
$$

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

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

2. $a < 0$, $b < 0$. 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 $\phi$ 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 $x_1 = S$, $x_2 = E$, $x_3 = I$, $x_4 = J$, $x_5 = L$ and $x_6 = R$ so that $N = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$. Further, by using vector notation $x = (x_1, x_2, x_3, x_4, x_5, x_6)^T$, the TB model (4) without exogenous reinfections can be written in the form $\dot{x} = f(x)$, with $f = (f_1, f_2, f_3, f_4, f_5, f_6)^T$, as follows:

$$
\begin{cases}
x_1' &= f_1 = \Lambda - (\mu + \nu(I,J,L))x_1,\\
x_2' &= f_2 = (1-p_1-p_2)\nu(I,J,L)x_1 + \rho J - A_1 x_2,\\
x_3' &= f_3 = p_1\nu(I,J,L)x_1 + h(1-r_1)kx_2 + \delta x_5 + \gamma x_6 - A_2 x_3,\\
x_4' &= f_4 = p_2\nu(I,J,L)x_1 + (1-h)(1-r_1)kx_2 - A_3 x_4,\\
x_5' &= f_5 = \alpha x_3 - A_4 x_5,\\
x_6' &= r_2 x_3 + \omega x_5 - A_5 x_6,
\end{cases}
\tag{28}
$$

27

where $\nu(I, J, L) = \dfrac{\beta_1 x_3 + \beta_2 x_5}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6} + \beta_3 x_4$, with $A_1$, $A_2$, $A_3$, $A_4$ and $A_5$ defined as in model (4).

The Jacobian of the system (4), at the DFE $Q_0$, for all $\beta_3$ is given by

$$J_{\beta_3}(Q_0) = \begin{pmatrix} -\mu & 0 & -\beta_1 & -\tilde{\beta}_3 & -\beta_2 & 0 \\ 0 & -A_1 & \beta_1(1 - p_1 - p_2) & (1 - p_1 - p_2)\tilde{\beta}_3 + \rho & (1 - p_1 - p_2)\beta_2 & 0 \\ 0 & hk(1 - r_1) & p_1\beta_1 - A_2 & p_1\tilde{\beta}_3 + \theta & \beta_2 p_1 + \delta & \gamma \\ 0 & (1 - h)k(1 - r_1) & p_2\beta_1 & p_2\tilde{\beta}_3 - A_3 & \beta_2 p_2 & 0 \\ 0 & 0 & \alpha & 0 & -A_4 & 0 \\ 0 & 0 & r_2 & 0 & \omega & -A_5 \end{pmatrix}.$$

with $\tilde{\beta}_3 = \beta_3 N_0$.

The reproduction number of the transformed (linearized) model (28) is the same as that of the original model given by (7). Therefore, choosing $\beta_3$ as a bifurcation parameter and solving equation in $\beta_3$ when $\mathcal{R}_0 = 1$, we obtain

$$\beta_3 = \beta_3^* = \frac{1 - \langle e_1 \mid (-A^{-1})B_1 \rangle}{\langle N_0 e_2' \mid (-A^{-1})B_1 \rangle}.$$

where $e_2' = (0, 0, 0, 1, 0)$. It follows that the Jacobian $J(Q_0)$ of system (28) at the DFE $Q_0$, with $\beta_3 = \beta_3^*$, denoted by $J_{\beta_3^*}$ has a simple zero eigenvalue (with all other eigenvalues having negative real parts). Hence, the Centre Manifold theory [14] can be used to analyse the dynamics of the model (28). Now, the theorem 5.1 (cf. [16], can be used to show that the unique endemic equilibrium of the model (28) (or, equivalently, (4)) is locally asymptotically stable for $\mathcal{R}_0$ near 1.

**Eigenvectors of $J_{\beta_3^*}$:** For the case when $\mathcal{R}_0 = 1$, it can be shown that the Jacobian of system (28) at $\beta_3 = \beta_3^*$ (denoted by $J_{\beta_3^*}$) has a right eigenvector (corresponding to the zero eigenvalue), given by $U = (u_1, u_2, u_3, u_4, u_5, u_6)^T$, where,

$$u_1 = -\frac{1}{\mu}\left(\left(\beta_1 + \beta_2\frac{B_4}{C_4}\right)u_3 + \tilde{\beta}_3 u_4\right) < 0,$$

$$u_2 = \frac{1}{A_1}\left((1 - p_1 - p_2)\left(\beta_1 + \frac{\beta_2\alpha}{A_4}\right) + (\tilde{\beta}_3(1 - p_1 - p_2) + \rho)\frac{B_4}{C_4}\right)u_3 > 0, \ u_3 > 0,$$

$$u_4 = \frac{B_4}{C_4}u_3 > 0, \quad u_5 = \frac{\alpha}{A_4}u_3 > 0, \quad \text{and} \quad u_6 = \frac{r_2 A_4 + \omega\alpha}{A_4 A_5}u_3 > 0$$

(29)

with $B_4 = \left[p_2 + (1 - p_1 - p_2)\dfrac{(1 - h)k(1 - r_1)}{A_1}\right]\left(\beta_1 + \dfrac{\beta_2\alpha}{A_4}\right)$

and $C_4 = A_3 - \left(\tilde{\beta}_3 p_2 + \dfrac{\tilde{\beta}_3(1 - p_1 - p_2) + \rho}{A_1}(1 - h)(1 - r_1)k\right).$

28

Similarly, the components of the left eigenvectors of $J_{\beta^*}$ (corresponding to the zero eigenvalue), denoted by $V = (v_1, v_2, v_3, v_4, v_5, v_6)^T$, are given by,

$$v_1 = 0, \quad v_2 = \frac{h(1-r_1)k}{A_1}v_3 + \frac{(1-h)(1-r_1)k}{A_1}v_4, \quad v_3 = v_3 > 0,$$

$$v_4 = \frac{(\theta + \tilde{\beta}_3 p_1)A_1 + h(1-r_1)k(\rho + \tilde{\beta}_3(1-p_1-p_2))}{\tilde{\beta}_3((1-h)(1-r_1)k((1-p_1-p_2)+\rho)+p_2 A_1)+A_1 A_3}v_3 > 0,$$

$$v_5 = \left((1-p_1-p_2)\frac{\beta_2}{A_4}\frac{h(1-r_1)k}{A_1} + \frac{\beta_2 p_1 N_0 + \delta}{A_4}\right)v_3$$

$$+ \left(\frac{\beta_2(1-p_1-p_2)}{A_4}\frac{(1-h)(1-r_1)k}{A_1} + \frac{\beta_2 p_2}{A_4}\right)v_4 > 0,$$

and $\quad v_6 = \frac{\gamma}{A_5}v_3 > 0$

$$(30)$$

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

$$\frac{\partial^2 f_1}{\partial x_4 \partial \beta_3^*} = -N_0, \quad \frac{\partial^2 f_2}{\partial x_4 \partial \beta_3^*} = (1-p_1-p_2)N_0, \quad \frac{\partial^2 f_3}{\partial x_4 \partial \beta_3^*} = p_1 N_0, \quad \frac{\partial^2 f_3}{\partial x_4 \partial \beta_3^*} = p_2 N_0$$

Substituting the respective partial derivatives into the expression

$$b = v_2 \sum_{i=1}^{6} u_i \frac{\partial^2 f_2}{\partial x_i \beta^*} + v_3 \sum_{i=1}^{6} u_i \frac{\partial^2 f_3}{\partial x_i \beta^*} + v_4 \sum_{i=1}^{6} u_i \frac{\partial^2 f_4}{\partial x_i \beta^*},$$

gives

$$b = u_4 N_0(v_2(1-p_1-p_2) + v_3 p_1 + v_4 p_2) > 0. \quad (31)$$

**Computation of** $a$: For model (28), the associated non-zero partial derivatives of $f$ (at the DFE $Q_0$) are given by

$$\frac{\partial^2 f_1}{\partial x_3 \partial x_1} = -\frac{\beta_1}{N_0^2}, \quad \frac{\partial^2 f_1}{\partial x_4 \partial x_1} = -\beta_3, \quad \frac{\partial^2 f_1}{\partial x_5 \partial x_1} = -\frac{\beta_2}{N_0^2},$$

$$\frac{\partial^2 f_2}{\partial x_3 \partial x_2} = -(1-p_1-p_2)\frac{\beta_1}{N_0}, \quad \frac{\partial^2 f_2}{\partial x_5 \partial x_2} = -(1-p_1-p_2)\frac{\beta_2}{N_0},$$

$$\frac{\partial^2 f_3}{\partial x_2 \partial x_3} = -p_1\frac{\beta_1}{N_0}, \quad \frac{\partial^2 f_3}{\partial x_3^2} = -2p_1\frac{\beta_1}{N_0^2}, \quad \frac{\partial^2 f_3}{\partial x_4 \partial x_3} = -p_1\frac{\beta_1}{N_0}, \quad \frac{\partial^2 f_3}{\partial x_5 \partial x_3} = -(\beta_1+\beta_2)\frac{p_1}{N_0},$$

$$\frac{\partial^2 f_3}{\partial x_6 \partial x_3} = -p_1\frac{\beta_1}{N_0}, \quad \frac{\partial^2 f_4}{\partial x_1 \partial x_4} = \beta_3 p_2, \quad \frac{\partial^2 f_4}{\partial x_3 \partial x_4} = -\beta_1 p_2 \frac{1}{N_0}, \quad \frac{\partial^2 f_4}{\partial x_5 \partial x_4} = -\beta_2 p_2 \frac{1}{N_0}$$

29

Then, it follows that

$$
\begin{aligned}
a &= -2\left(v_2 u_2 (1 - p_1 - p_2)\frac{1}{N_0}(u_3\beta_1 + u_5\beta_2)\right) \\
&\quad - 2\left(v_3 u_3 p_1 \frac{1}{N_0}\left[(u_2 + \frac{u_3}{N_0} + u_4 + u_5 + u_6)\beta_1 + \beta_2 u_5\right]\right) \\
&\quad - 2v_4 u_4 p_2\left[-u_1\beta_3 + \beta_1 u_3 + \beta_2 u_5\right],
\end{aligned}
$$

so that the bifurcation coefficient $a < 0$ since $u_1 < 0$. Thus, we have $a < 0$ and $b > 0$. All conditions of Theorem 5.1 are satisfied and it should be noted that we use $\beta_3^*$ as the bifurcation parameter, in place of $\phi$ in Theorem 5.1). Thus, it follows that the endemic equilibrium is locally asymptotically stable. This concludes the proof.

$\square$

# References

[1] J. Aparicio, A. F. Capurro, and C. Castillo-Chavez. Markers of disease evolution: the case of tuberculosis. *J. Theo. Biol.*, 215:227–237, 2002.

[2] J. Arino, C. C. McCluskey, and P. van den Driessche. Global result for an epidemic model with vaccination that exihibits backward bifurcation. *SIAM Journal on Applied Mathematics*, 64:260–276, 2003.

[3] N. Bacaër, R. Ouifki, C. Pretorius, R. Wood, and B. Williams. Modeling the joint epidemics of TB and HIV in a South African township. *J Math Biol*, 57(4):557–93, Oct. 2008.

[4] Y. Balabanova, V. Tchernyshev, I. Tsigankov, S. Maximova, N. Mikheeva, L. Fedyukovitch, S. Kuznetsov, I. Fedorin, and F. Drobniewski. Analysis of undiagnosed tuberculosis-related deaths identified at post-mortem among hiv-infected patients in russia: a descriptive study. *BMC Infectious Diseases*, 11(1):276, 2011.

[5] A. Bandera, A. Gori, L. Catozzi, A. Esposti, G. Marchetti, C. Molteni, G. Ferrario, L. Codecasa, V. Penati, A. Matteelli, and F. Franzetti. Molecular epidemiology study of exogenous reinfection in an area with a low incidence of tuberculosis. *J. Clin. Microbiol.*, 39:2213–2218, 2001.

[6] M. Begon, M. Bennett, R. G. Bowers, N. P. French, S. M. Hazel, and J. Turner. A clarification of transmission terms in host-microparasite models : numbers, densities and areas. *Epidemiol. Infect.*, 129:147–153, 2002.

[7] S. R. Benatar. Facing ethical challenges in rolling out antiretroviral treatment in resource-poor countries: Comment on "they call it 'patient selection' in khayelitsha". *Cambridge Quarterly of Healthcare Ethics*, 15:322–330, 2006.

[8] S. R. Benatar, A. S. Daar, and P. A. Singer. Global health challenges: The need for an expanded discourse on bioethics. *Public Library of Science Medicine PLOS*, 2(7):100–102, 2005.

[9] C. Bhunu, W. Garira, Z. Mukandavire, and M. Zimba. Tuberculosis transmission model with chemoprophylaxis and treatment. *Bulletin of Mathematical Biology*, 70(4):1163–1191, 2008. 10.1007/s11538-008-9295-4.

[10] G. Birkhoff and G.-C. Rota. *Ordinary Differential Equations*. John Wiley and Sons new York, 3rd edition, 1978.

[11] S. M. Blower, P. Small, and P. Hopewell. Control strategies for tuberculosis epidemics: new method for old problem. *Science*, 273:497–500, 1996.

[12] F. Brauer. Backward bifurcation in simple vaccination models. *Journal of Mathematical Analysis and Application*, 298:418–431, 2004.

[13] F. Brauer and C. Castillo-Chavez. *Mathematical Models in Population Biology and Epidemiology*. Springer-Verlag New York, Inc.,, 2001.

[14] J. Carr. *Applications Centre Manifold theory*. Springer-Verlag New York, 1981.

[15] C. Castillo-Chavez and Z. Feng. To treat or not to treat: the case of tuberculosis. *J. Math. Biol.*, 35:629–635, 1997.

[16] C. Castillo-Chavez and B. Song. Dynamical models of tuberculosis and their applications. *Math. Biosci. Eng.*, 1:361–404, 2004.

[17] C. Castillo-Chavez and H. R. Thieme. Asymptotically autonomous epidemic models. In A. et al, editor, *Mathematical Population Dynamics: Analysis of heterogeneity Theory of epidemics*, volume 1, pages 33–50. Wuerz, Winnipeg, 1995.

[18] C. Chintu and A. Mwinga. An african perspective of tuberculosis and hiv/aids. *Lancet*, 353:997–1005, 1999.

[19] C. Dye, S. Schele, P. Dolin, V. Pathania, and M. Raviglione. For the who global surveillance and monitoring project. global burden of tuberculosis estimated incidence and prevalence and mortality by country. *JAMA*, 282:677–686, 1999.

[20] C. Dye and B. G. Williams. The population dynamics and control of tuberculosis. *Science*, 328(5980):856–61, May 2010.

[21] E. H. Elbasha and A. Gumel. Theoretical assesssment of public health impact of imperfect prophylatics hiv-1 vaccines with therapeutic benefits. *Bulletin of Mathematical Biology*, 68:577–614, 2006.

[22] Z. Feng, C. Castillo-Chavez, and A. F. Capurro. A model for tuberculosis with exogenous reinfection. *Theor Popul Biol*, 57(3):235–47, May 2000.

[23] K. Hadeler and P. van den Driessche. Backward bifurcation in epidemic control. *Math. Biosci.*, 146:15–35, 1997.

[24] H. W. Hethcote. The mathematics of infectious diseases. *SIAM Review*, 42:599–653, 2000.

[25] A. Iggidr, J. C. Kamgang, G. Sallet, and J. J. Tewa. Global analysis of new malaria intrahost models with a competitive exclusion principle. *SIAM J. App. Math.*, 1:260–278, 2007.

[26] A. Iggidr, J. Mbang, and G. Sallet. Stability analysis of within-host parasite models with delays. *Math. Biosci.*, 209:51–75, 2007.

[27] A. Iggidr, J. Mbang, G. Sallet, and J. J. Tewa. Multi-compartment models. *Discrete Contin. Dyn. Syst. Ser. B*, 1:506–519, 2007.

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

[29] T. K. Kar and P. K. Mondal. Global dynamics of a tuberculosis epidemic model and the influence of backward bifurcation. *J Math Model Algor*, 11:433–459, 2012.

[30] C. Kribs-Zaleta and J. Halesco-Hernandez. A simple vaccination model with multiple endemic states. *Math. Biosci.*, 164:183–201, 2000.

[31] V. Kumar, A. K. Abbas, N. Fausto, and R. N. Mitchell. *Basic Pathology (8th ed.)*, volume ISBN 978-1-4160-2973-1. Saunders Elsevier, 2007.

[32] D. Moualeu, S. Bowong, and Y. Emvudu. Global properties of a tuberculosis model with n latents classes. *JAMI*, 29(5-6):1097–116, 2011.

[33] D. P. Moualeu, S. Bowong, and Y. Emvudu. Analysis of the impact of diabetes on the dynamics transmission of tuberculosis. *Mathematical modeling of natural phenomena*, 7(03):117–146, 2012.

[34] D. P. Moualeu, J. Mbang, R. Ndoundam, and S. Bowong. Modeling and analysis of hiv and hepatitis c co-infections. *Journal of Biological Systems*, 19(04):683–723, 2011.

[35] D. P. Moualeu, M. Weiser, R. Ehrig, and P. Deuflhard. Optimal control for a tuberculosis model with undetected cases in cameroon. *Communications in Nonlinear Science and Numerical Simulation*, 20(3):986–1003, 2015.

[36] D. P. Moualeu-Ngangue. *A Mathematical Tuberculosis Model in Cameroon*. PhD thesis, FU Berlin, 2013.

[37] D. P. Moualeu-Ngangue, S. Röblitz, R. Ehrig, and P. Deuflhard. Parameter identification in a tuberculosis model for cameroon. *PloS one*, 10(4):e0120607, 2015.

[38] B. Murphy, B. H. Singer, and D. Kirschner. On the treatment of tuberculosis in hetergeneous populations. *J. Theor. Biol.*, 223:391–404, 2003.

[39] C. Murray, K. Styblo, and A. Rouillon. Tuberculosis in developing countries: burden, intervention, and cost. *Bull. Int. Union Tuberc. Lung Dis.*, 65:6–24, 1990.

[40] NCFT. *Guide de personnel de la santé*. National Comity of Fight Againts Tuberculosis, Ministère de la Santé Publique du Cameroun, 2001.

[41] NIS. Rapport sur la présentation des résultats définitifs. Technical report, National Institute of Statistics, Bureau Central des Recensements et des Etudes de Population, 2010.

[42] P. Nunn, B. G. Williams, K. Floyd, C. Dye, G. Elzinga, and M. C. Raviglione. Tuberculosis control in the era of HIV. *Nat. Rev. Immunol.*, 5:819–826, 2005.

[43] D. Okuonghae and A. Korobeinikov. Dynamics of tuberculosis: The effect of direct observation therapy strategy (dots) in nigeria. *Math. Mod. Nat. Phen.*, 2:101–113, 2007.

[44] B. S. Singer and D. E. Kirchner. Influence of backward bifurcation on interpretation of r0 in a model of epidemic tuberculosis with reinfection. *Math. Biosc. and Engeneering*, 1(1):81–91, 2004.

[45] P. Uys, P. van Helden, and J. Hargrove. Tuberculosis reinfection rate as a proportion of total infection rate correlates with the logarithm of the incidence rate: a mathematical model. *J. R. Soc. Interface*, 6:11–15, 2009.

[46] P. van den Driessche and J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math. Biosc.*, 180:29–28, 2002.

[47] van Rie, W. A., M. R., Richardson, T. Victor, R. Gie, D. Enarson, N. Beyers, and P. van Helden. Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. *N. Engl. J. Med.*, 341:1174–1179, 1999.

[48] S. Verver, R. Warren, N. Beyers, M. Richardson, van der Spuy, M. G.D., Borgdorff, D. Enarson, M. Behr, and P. van Helden. Rate of reinfection tuberculosis after successful treatment is higher than rate of new tuberculosis. *Am. J. Respir. Crit. Care Med.*, 171:1430–1435, 2005.

[49] W. Wang. Backward bifurcation of an epidemic model with treatment. *Math. Biosci.*, 201:58–71, 2006.

[50] WHO. Global tuberculosis control: surveillance, planning, financing. Technical report, World Health Organization, Geneva, Switzerland, 2012.

[51] R. Wood, K. Middelkoop, L. Myer, A. D. Grant, and A. W. et al. Undiagnosed tuberculosis in a community with high hiv prevalence: implications for tuberculosis control. *Am J Respir Crit Care Med*, 175(1):87–93, Jan. 2007.

[52] H. Yang. The effects of re-infection in directly transmitted infections modeled with vaccination. *IMA J. Math. Appl. Med. Biol.*, 19:113–135, 2002.