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GLOBAL STABILITY OF A TUBERCULOSIS MODEL WITH n LATENT CLASSES†

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Abstract. We consider the global stability of a general tuberculosis model with two differential infectivity, n classes of latent individuals and mass action incidence. This system exhibits the traditional threshold behavior. There is always a globally asymptotically stable equilibrium state. Depending on the value of the basic reproduction ratio $\mathcal{R}_0$, this state can be either endemic ($\mathcal{R}_0 > 1$), or infection-free ($\mathcal{R}_0 \leq 1$). The global stability of this model is derived through the use of Lyapunov stability theory and LaSalle's invariant set theorem. Both the analytical results and numerical simulations suggest that patients should be strongly encouraged to complete their treatment and sputum examination.

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1. Introduction

Tuberculosis (TB) is primarily a disease of the respiratory system with variable degrees of infectiousness. It can follow after infection by the airborne bacteria germ *Mycobacterium tuberculosis*. Bacilli only live in the air for approximately 2 hours so individuals who have intense contacts with TB bacilli in poorly ventilated areas are the most likely to become infected. Thus, TB morbidity and mortality rates are strongly affected by living conditions. Infectiousness of the source case, duration and frequency of exposure, and characteristics of shared environments, all contribute to the overall risk of transmission [1-8]. It is also known that factors such as endogenous reactivation, emergence of multi-drug resistant TB, and increase in HIV incidence in the recent years call for improved control strategies for TB. Another issue that is essential to the epidemiology of TB is exogenous re-infections, where a latently-infected individual acquires a

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new infection from another infectious (see [7] and references therein). A number of theoretical studies have been carried out on the mathematical modelling of TB transmission dynamics [8-12].

On the other hand, it is well known that the duration of latency varies greatly from case to case [9]. It is possible for a infected human to become active within a few months of infection. It is also possible that activation may occur several years or decades after exposure has taken place. Until such time, the individual suffers no ill-effects of the disease, and cannot transmit the disease to others [9,10]. Also, the risk of activation seems to decrease over time [1,10]. One way in which this can be modeled is to include a sequence of several latent classes through which latently infected individuals can pass. Each latent class can be assigned its own activation rate.

However, TB infected individuals, generally classified as "infective", play a major role in the transmission of TB. In this work, we divided the infective class into two subgroups with different properties: infectious and lost sight. Indeed, in sub-Saharan Africa, some infectious that begun their effective therapy in the hospital never return to the hospital during for the rest of sputum examinations and check-up. This can be due to negligence, lack of information about TB, long duration of treatment regimen, poverty, mentality, etc... In this case, the health personal do not know their epidemiological status, i.e., if they died, recovered or are still infectious. These infective individuals are called lost sight [6]. According to the National Committee of Fight against Tuberculosis of Cameroon [11], about 10% of infectious individuals that begun their therapy of treatment never return to the hospital for the rest of sputum examinations and treatment, and then become lost sight. Thus, this lack of epidemiological status of some patients can affect the spread of TB in a population.

In this paper, we explore the role of the lack of epidemiological status of some patients in the hospital on the transmission dynamics of tuberculosis by formulating a mathematical model taking into cognisance the variability of the duration of latency and that some lost sight are still infectious. This tuberculosis model has two differential infectivity and n latent classes. Comparing to existing results [2-8], our work differs from these studies in that our model in addition to lost sight, also considers the aspects of disease relapse as well as primary active TB cases and the variation of the duration of latency. We completely analyze the stability behavior of the model. The global dynamics of the model is resolved through the use of Lyapunov functions. We use the same Lyapunov functions as those used recently in Refs. [6,12-16] to demonstrate the global stability of the endemic equilibrium of SEIR, SEIS, and SIR models. However, to our knowledge, no studies so far have described TB with differential infectivity and n latent classes. Numerical studies are presented to validate the analytical results.

2. The model

We consider a finite population of N people. We assume that latently infected individuals (inactive TB) have variable (typically long) latency period. At any given time, an individual is in one of the following states: susceptible, latently infected with n stages (i.e., exposed to TB but are not infectious), infectious individuals (i.e., have active TB), lost sight (i.e., the health personal do not know their epidemiological status) and recovered (i.e., cured after a therapy of treatment). We denote these states by S, E, I, L and R, respectively. All recruitment is into the susceptible class, and occurs at a constant rate Λ. Transmission of *M. tuberculosis* occurs following adequate contacts between a susceptible individual and infectious or lost sight individuals. After adequate contacts with infectious or lost sight individuals, a susceptible individual becomes infected but not yet infectious. This individual remains in the latently infected classes for a certain latent period through n stages $E_1, \ldots, E_n$. We use the standard mass balance incidence expressions $\beta_1 SI$ and $\beta_2 SL$ to indicate successful transmission of *M. tuberculosis* due to nonlinear contact dynamics in the population. Once latently infected with *M. tuberculosis*, an individual will remain so for life unless reactivation occurs. We assume that chemoprophylaxis of latently infected individuals reduces their reactivation at a constant rate r_i. Latently infected individuals who do not received effective chemoprophylaxis progress to the next stage of latently infected class with a constant rate $k_i(1 - r_i)$. We assume that latently infected individuals leave the subclass E_i to the infectious class I at a constant rate α_i. After receiving an effective therapy, infectious individuals can recover from the disease with a constant rate r and entering the recovered class R. As suggested by Styblo [24], recovered individuals still have the bacterium in their body and can undergo a reactivation of the disease with a constant rate γ. We also assume that among infectious individuals who do not recovered, some of them who begun their treatment will not return to the hospital during their period of treatment for the examination of sputum at a constant rate $\phi(1 - r)$ and enters the lost sight class L. After some time, some of them will continue to suffer of the disease and will return to the hospital at a constant rate δ and the remaining can recover because of natural recover and traditional medicine (practiced in sub-Saharan Africa) at a constant rate $\varepsilon(1 - \delta)$ and enters the recovered class R. Individuals with active TB induce a death rate μ, thus $1/\mu$ is the average lifespan. Latently infected, infectious and lost sight individuals have addition death rates due to infection and disease with constant rates d_i, d_I and d_L, respectively.

Thus, the corresponding transfer diagram is

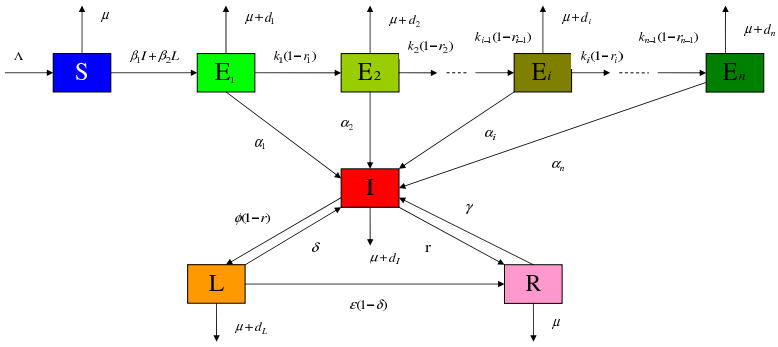

FIGURE 1. A transfer diagram for a TB model with two differential infectivity and n latent classes.

The corresponding equations are

$$\begin{cases} \dot{S} = \Lambda - S(\beta_1 I + \beta_2 L) - \mu S, \\ \dot{E}_1 = S(\beta_1 I + \beta_2 L) - [\mu + d_1 + \alpha_1 + k_1(1 - r_1)]E_1, \\ \quad \vdots \\ \dot{E}_i = k_{i-1}(1 - r_{i-1})E_{i-1} - [\mu + d_i + \alpha_i + k_i(1 - r_i)]I_i, \;\; i = 2, \ldots, n-1, \\ \quad \vdots \\ \dot{E}_n = k_{n-1}(1 - r_{n-1})E_{n-1} - [\mu + d_n + \alpha_n]E_n, \\ \dot{I} = \sum_{i=1}^{n} \alpha_i E_i + \gamma R + \delta L - [\mu + d_I + r + \phi(1 - r)]I, \\ \dot{L} = \phi(1 - r)I - [\mu + d_L + \delta + \varepsilon(1 - \delta)]L, \\ \dot{R} = rI + \varepsilon(1 - \delta)L - (\mu + \gamma)R. \end{cases} \tag{1}$$

3. Properties of the model

System (1) can be written in the following compact form:

$$\begin{cases} \dot{x} = \varphi(x) - x\langle \beta \mid y \rangle, \\ \dot{y} = x\langle \beta \mid y \rangle B + A\, y, \end{cases} \tag{2}$$

where $x = S \in \mathbb{R}_{\geq 0}$ is a state representing the compartment of non transmitting individuals (susceptible), $y = (E_1, \cdots, E_n, I, L, R)^T \in \mathbb{R}^{n+3}_{\geq 0}$ is the vector representing the state compartment of different infected individuals (latently-infected, infectious, lost sight and recovered individuals), $\varphi(x) = \Lambda - \mu\, x$ is a function that depends on x, $\beta = (0, \cdots, 0, \beta_1, \beta_2, 0) \in \mathbb{R}^{n+3}$ and $B = (1, 0, \cdots, 0)^T \in \mathbb{R}^{n+3}$, $\langle . \mid . \rangle$ is the usual scalar product in $\mathbb{R}^{n+3}_{\geq 0}$ and A is a $(n+3) \times (n+3)$ constant

matrix defined as

$$A=\begin{bmatrix} -a_1 & \dots & 0 & 0 & 0 & 0 & 0 \\ k_1(1-r_1) & \dots & 0 & 0 & 0 & 0 & 0 \\ \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \dots & k_{n-1}(1-r_{n-1}) & -a_n & 0 & 0 & 0 \\ \alpha_1 & \dots & \cdots & \alpha_n & -a_I & \delta & \gamma \\ 0 & \dots & \dots & 0 & \phi(1-r) & -a_L & 0 \\ 0 & \dots & \dots & 0 & r & \varepsilon(1-\delta) & -a_R \end{bmatrix},$$

with

$$a_i=\mu+d_i+\alpha_i+k_i(1-r_i),\quad i=1,\cdots,n-1,\qquad a_n=\mu+d_n+\alpha_n,$$
$$a_I=\mu+d_I+r+\phi(1-r),\qquad a_L=\mu+d_L+\delta+\varepsilon(1-\delta)\text{ and }\ a_R=\mu+\gamma.$$

It should be pointed out that A is a Metzler matrix, that is, a matrix with off-diagonal entries nonnegative [16-18].

3.1. Positivity and boundedness of solutions. For system (1) to be epidemiologically meaningful, it is important to prove that all its state variables are non-negative for all time. In other word, solutions of system (1) with positive initial data remain positive for all time $t>0$. This can be verified as follows. Suppose, for example, the variable E_1 becomes zero for some time $\bar{t}>0$, i.e., $E_1(\bar{t})=0$, while all other variables are positive. Then, from the E_1 equation, we have $dE_1(\bar{t})/dt>0$. Thus, $E_1(t)\geq 0$ for all $t>0$. Similarly, it can be shown that all variables remain nonnegative for all $t>0$.

3.2. Invariant region. Model system (1) will be analyzed in a suitable region as follows. That is all solutions are uniformly bounded in a proper subset $\Omega_\rho\subset\mathbb{R}^{n+3}_{\geq 0}$. Let $(S,E_i,I,L,R)\in\mathbb{R}^{n+3}_{\geq 0}$ be any solution with non-negative initial conditions.

Model system (1) has a varying population size ($N=0$) and therefore a trivial equilibrium is not feasible. Adding all equations in the differential system (1) gives

$$\dot{N}(t)=\Lambda-\mu N(t)-d_1\,I(t)-d_2\,L(t). \tag{3}$$

From Eq. (3), one can deduce that $\dot{N}(t)\leq\Lambda-\mu N(t)$. It then follows that $\lim\limits_{t\to+\infty}N(t)\leq\dfrac{\Lambda}{\mu}$ which implies that the trajectories of model (1) are bounded. On the other hand, from Eq. (3), one has $N(t)\leq N(0)e^{-\mu t}+\dfrac{\Lambda}{\mu}(1-e^{-\mu t})$. In particular $N(t)\leq\dfrac{\Lambda}{\mu}$ if $N(0)\leq\dfrac{\Lambda}{\mu}$. Then, the region:

$$\Omega_\rho=\left\{(S,E_i,I,R,L)\in\mathbb{R}^{n+4}_{\geq 0},\quad N(t)\leq\frac{\Lambda}{\mu}+\rho\right\}, \tag{4}$$

is a compact forward invariant set for system (1) and that for $\rho>0$ this set is absorbing. So, we limit our study to this region for $\rho>0$.

3.3. Local stability of the disease-free equilibrium (DFE). System (2) has an evident equilibrium $P_0 = (x_0, 0)$ with $x_0 = \Lambda/\mu$ when there is no disease. This equilibrium point is the disease free equilibrium. We calculate the basic reproduction number, $\mathcal{R}_0$, using the next generation approach, developed by van den Driessche and Watmough [19]. Using the technique reported in [19], the basic reproduction number of system (2) is

$$\mathcal{R}_0 = x_0 \langle \beta \mid (-A^{-1})\, B \rangle. \tag{5}$$

We use the expression of $(-A^{-1})$ to put the emphasis on the fact that $(-A^{-1}) \geq 0$ because the matrix A is Metzler stable. Using the expressions of β and B defined as in Eq. (2) and after the computation of $(-A^{-1})$, the basic reproduction number (5) may be rewritten as

$$\mathcal{R}_0 = \frac{a_R\, \mathcal{R}_0^1 [\beta_1\, a_L + \beta_2\, \phi(1-r)] x_0}{\phi(1-r)\mathcal{R}_0^2 + a_L\, [(\mu+\gamma)(\mu+d_I) + \mu\, r]}, \tag{6}$$

where

$$\mathcal{R}_0^1 = \frac{\alpha_1}{a_1} + \sum_{i=2}^{n} \left[\alpha_i \frac{\prod_{l=1}^{i-1} k_l (1-r_l)}{\prod_{j=1}^{i} a_j} \right] \text{ and } \mathcal{R}_0^2 = \mu[\mu + d_L + \varepsilon(1-\delta)] + \gamma(\mu + d_L).$$

Now, let us determine, using the threshold quantity $\mathcal{R}_0$, whether or not lost sight can influence the propagation of tuberculosis in the host population. From Eq. (6), it is evident that

$$\lim_{\phi \to 1} \mathcal{R}_0 = \frac{a_R\, \mathcal{R}_0^1 [\beta_1\, a_L + \beta_2\, (1-r)] x_0}{(1-r)\mathcal{R}_0^2 + a_L\, [(\mu+\gamma)(\mu+d_I) + \mu\, r]} > 0, \tag{7}$$

where $\mathcal{R}_0^1$ and $\mathcal{R}_0^2$ are defined as in Eq. (5). Thus, a sufficiently effective TB treatment program can lead to effective disease control if it results in making the right-hand side of (7) less than unity.

Further sensitivity analysis on the rate at which infectious individuals become lost sight is carried out by computing the partial derivative of $\mathcal{R}_0$ with respect to the parameter ϕ giving

$$\frac{\partial \mathcal{R}_0}{\partial \phi} = \frac{a_R a_L \mathcal{R}_0^1 x_0 [\beta_2\, [(\mu+\gamma)(\mu+d_I) + \mu\, r] - \beta_1 \mathcal{R}_0^2]}{[\phi(1-r)\mathcal{R}_0^2 + a_L\, [(\mu+\gamma)(\mu+d_I) + \mu\, r]]^2}. \tag{8}$$

From the above equation, $\dfrac{\partial \mathcal{R}_0}{\partial \phi} < 0$ if

$$\beta_2 < \Delta = \frac{\beta_1 \mathcal{R}_0^2}{(\mu+\gamma)(\mu+d_I) + \mu\, r}. \tag{9}$$

Thus, the rate at which infectious individuals become lost sight will have positive impact in reducing the propagation of TB only if $\beta_2 < \Delta$. Such a rate at which infectious individuals become lost sight will fail to reduce TB propagation if

$\beta_2 = \Delta$, and will have detrimental impact in the host population (increase $\mathcal{R}_0$) if $\beta_2 > \Delta$. This result is summarized below:

Lemma 3.1. *The rate at which infectious individuals become lost sight ϕ will have a positive impact if $\beta_2 < \Delta$, no impact if $\beta_2 = \Delta$ and will have a detrimental impact if $\beta_2 > \Delta$ on the propagation of TB in the host population.*

It is worth emphasizing that the quantity Δ decreases when the treatment rate of infectious individuals r increases. So, this quantity can be make as small as possible by increasing the treatment rate of infectious individuals. Note that if condition (9) do not hold (this corresponds to lower values of the treatment rate), then the use of the corresponding treatment strategy would increase TB propagation in the host population (since $\mathcal{R}_0 > 1$). That is, the use of drug will increase the disease propagation if it fails to reduce the infectiousness of those treated below a certain threshold ($\beta_2 < \Delta$). So, the best way to control the disease is to take care of all infectious individuals in health centers to avoid lost sight and then to increase the successful of treatment. This is, not the case in developing countries where the organization of health centers is practically non existent.

The following result is established (from Theorem 2 of [19]):

Lemma 3.2. *The disease-free equilibrium Q_0 of system (1) is locally asymptotically stable whenever $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

Biologically speaking, Lemma 3.2 implies that TB can be eliminated from the community (when $\mathcal{R}_0 < 1$) if the initial size of the population of the model are in the basin of attraction of P_0.

3.4. Equilibria. Let $P^* = (x^*, y^*)$ be the positive endemic equilibrium of system (2). Then, the positive endemic equilibrium (steady state with $y^* > 0$) can be obtained by setting the right hand side of all equations in system (2) equal to zero, that is,

$$\begin{cases} \varphi(x^*) - x^* \langle \beta \mid y^* \rangle = 0, \\ x^* \langle \beta \mid y^* \rangle \, B + A \, y^* = 0. \end{cases} \tag{10}$$

From the second equation of Eq. (10), one has $y^* = x^*(-A^{-1})B\langle \beta \mid y^* \rangle$. Then, one can deduce that

$$\langle \beta \mid y^* \rangle = x^* \langle \beta \mid (-A^{-1})B \rangle \langle \beta \mid y^* \rangle.$$

The case $\langle \beta \mid y^* \rangle = 0$ implies that $\varphi(x^*) = 0$ and $-Ay^* = 0$. Since A is nonsingular, this gives the disease-free equilibrium P_0. For the other case, simplifying by $\langle \beta \mid y^* \rangle$ gives

$$x^* = \frac{1}{\langle \beta \mid (-A^{-1})\, B \rangle} = \frac{x_0}{\mathcal{R}_0} > 0.$$

With $\mathcal{R}_0 > 1$, one has $x^* < x_0$, $\varphi(x^*) > 0$ and

$$y^* = (-A^{-1})\, B\, \varphi(x^*).$$

Hence, system (2) has a unique endemic equilibrium $P^* = (x^*, y^*)$ where x^* and y^* are given by

$$x^* = \frac{1}{\langle \beta \mid (-A^{-1})\, B \rangle} \qquad \text{and} \qquad y^* = (-A^{-1})\, B\, \varphi(x^*). \tag{11}$$

Using the expressions of β and B defined as in Eq. (2) and the expression of $(-A^{-1})$ obtained after a calculation, the endemic equilibrium of system (1) is given by

$$\begin{cases} S^* = \dfrac{\Lambda}{\mu \mathcal{R}_0}, \qquad E_1^* = \dfrac{\Lambda(\mathcal{R}_0 - 1)}{a_1 \mathcal{R}_0}, \\ E_i^* = \dfrac{\prod\limits_{l=1}^{i-1} k_l(1 - r_l)}{\prod\limits_{j=2}^{i} a_j} \dfrac{\Lambda(\mathcal{R}_0 - 1)}{a_1 \mathcal{R}_0}, \ \texttt{for}\ i = 2, 3, \cdots, n, \\ I^* = \dfrac{a_L \mu(\mathcal{R}_0 - 1)}{\beta_1\, a_L + \beta_2\, \phi(1 - r)}, \qquad L^* = \dfrac{\phi(1 - r)\mu(\mathcal{R}_0 - 1)}{\beta_1\, a_L + \beta_2\, \phi(1 - r)}, \\ R^* = \dfrac{\mu[r\, a_L + \varepsilon(1 - \delta)\phi(1 - r)](\mathcal{R}_0 - 1)}{a_R\, [\beta_1\, a_L + \beta_2\, \phi(1 - r)]}. \end{cases} \tag{12}$$

3.5. Global stability of the disease-free equilibrium. We have the following result about the global stability of the disease-free equilibrium P_0.

Theorem 3.3. *If $\mathcal{R}_0 \leq 1$, system (1) has no positive equilibrium states and the disease-free equilibrium P_0 is globally asymptotically stable in Ω_ρ.*

Proof. Consider the following LaSalle-Lyapunov candidate function:

$$V(x, y) = \frac{1}{x_0}(x - x_0 \ln x) + \beta^T\, (-A^{-1})\, y - \frac{1}{x_0}(x_0 - x_0 \ln x_0). \tag{13}$$

It is easy to see that at the disease free equilibrium P_0, the fonction $V(x, y)$ reaches its global minimum in Ω_ρ, and hence $V(x, y)$ is a Lyapunov function since we know that $\beta^T\, (-A)^{-1} > 0$. Its time derivative along the trajectories of system (2) satisfies

$$\begin{aligned} \dot{V}(x, y) &= \frac{1}{x_0}\left[\varphi(x) - x\langle \beta \mid y \rangle - \frac{x_0}{x}\varphi(x) + x_0 \langle \beta \mid y \rangle\right] - \beta^T\, A^{-1}\, x \langle \beta \mid y \rangle\, B - \beta^T\, y \\ &= \frac{1}{x_0}\left[\frac{(x - x_0)}{x}\varphi(x) - x\, \beta^T\, y + x_0\, \beta^T\, y\right] - x\, \beta^T\, y\, \beta^T\, A^{-1}\, B - \beta^T\, y \\ &= \frac{(x - x_0)}{x_0\, x}\varphi(x) - \frac{x\, \beta^T\, y}{x_0} - x\, \beta^T\, y \frac{\mathcal{R}_0}{x_0} = \frac{(x - x_0)}{x_0\, x}\varphi(x) + \frac{x\, \beta^T\, y}{x_0}(\mathcal{R}_0 - 1). \end{aligned} \tag{14}$$

Recalling that at the disease-free equilibrium, one has $\Lambda = \mu x_0$. With this in mind, Eq. (14) becomes

$$\dot{V}(x, y) = \frac{-\mu(x - x_0)^2}{x_0\, x} + \frac{x}{x_0}(\beta_1\, I + \beta_2\, L)(\mathcal{R}_0 - 1). \tag{15}$$

Thus, $\mathcal{R}_0 \leq 1$ ensures that $\dot{V}(x, y) \leq 0$ for all $x, y \geq 0$, and that $\dot{V}(x, y) = 0$ holds when $\mathcal{R}_0 = 1$ for $x = x_0$. It is easy to verify that the disease-free equilibrium state P_0 is the only fixed point of the system in the space $x = x_0$,

and hence, system (2) has no equilibria in Ω_ρ apart from P_0. Then, by the Lyapunov-LaSalle's asymptotic stability theorem [20-22], the equilibrium state P_0 is globally asymptotically stable in Ω_ρ and then in the nonnegative orthant $\mathbb{R}^{n+4}_{\geq 0}$ (see [22], Theorem 3.7.11, page 346). This achieves the proof. □

3.6. Global stability of the endemic equilibrium. The global stability of the endemic equilibrium is given by the Theorem 3.4, stated above.

Theorem 3.4. *If $\mathcal{R}_0 > 1$, the positive endemic equilibrium state P^* of model system (1) defined in Eq. (12) is globally asymptotically stable on the set Ω_ρ whenever*

$$\frac{L^*}{L} \leq \frac{R^*}{R} \leq \frac{I^*}{I} \leq 1 \quad \textit{and} \quad \frac{E^*_{i+1}}{E_{i+1}} \leq \frac{I^*}{I} \leq \frac{E^*_i}{E_i} \leq 1, \quad i = 1, \ldots, n-1. \tag{16}$$

Proof. Consider the following Lyapunov function:

$$\begin{aligned} U(S, E_i, L, R) = (S - S^* \ln S) + \sum_{i=1}^{n} A_i (E_i - E^*_i \ln E_i) + B(I - I^* \ln I) \\ + C(L - L^* \ln L) + D(R - R^* \ln R), \end{aligned} \tag{17}$$

where

$$\begin{aligned} A_1 &= 1, \quad B = \frac{a_n \prod\limits_{j=1}^{n-1} \dfrac{a_j}{k_j(1-r_j)}}{\alpha_n + \sum\limits_{l=1}^{n-1} \dfrac{\alpha_l}{k_l(1-r_l)} \prod\limits_{k=l+1}^{n-1} \dfrac{a_k}{k_k(1-r_k)}}, \\ A_i &= \prod_{j=1}^{i-1} \frac{a_j}{k_j(1-r_j)} - \left(\sum_{l=1}^{i-1} \frac{\alpha_l}{k_l(1-r_l)} \prod_{k=l+1}^{i-1} \frac{a_k}{k_k(1-r_k)} \right) B, \quad i = 2, \ldots, n, \\ D &= \frac{\gamma}{a_R} B \quad \text{and} \quad C = \frac{1}{a_L} \left[\beta_2 S^* + \left(\delta + \frac{\varepsilon\gamma(1-\delta)}{a_R} \right) B \right]. \end{aligned} \tag{18}$$

In Eq. (17), S^*, E^*_i, I^*, L^* and R^* are solutions of system (1) at the endemic equilibrium, that is,

$$\begin{cases} \Lambda = \beta_1 S^* I^* + \beta_2 S^* L^* + \mu S^*, \\ a_1 E^*_1 = \beta_1 S^* I + \beta_2 S^* L^*, \\ \quad \vdots \\ a_i E^*_i = k_{i-1}(1 - r_{i-1}) E^*_{i-1}, \qquad i = 2, \ldots, n, \\ a_I I^* = \sum\limits_{i=1}^{n} \alpha_i E^*_i + \gamma R^* + \delta L^*, \\ a_L L^* = \phi(1-r) I^*, \\ a_R R^* = r I^* + \varepsilon(1-\delta) L^*. \end{cases} \tag{19}$$

The time derivative of this function with respect to system (1) satisfies

$$\begin{aligned}\dot{U} = &-\mu\frac{(S-S^*)^2}{S} + (A_1-1)(\beta_1 SI + \beta_2 SL) + \left(1-\frac{S^*}{S}\right)(\beta_1 S^* I^* + \beta_2 S^* L^*)\\ &+ A_1\beta_1 S^* I^*\left(1-\frac{S}{S^*}\frac{I}{I^*}\frac{E_1^*}{E_1}\right) + A_1\beta_2 S^* L^*\left(1-\frac{S}{S^*}\frac{I}{I^*}\frac{E_1^*}{E_1}\right)\\ &+ \sum_{i=2}^{n} A_i k_{i-1}(1-r_{i-1})E_{i-1}^*\left(1-\frac{E_{i-1}}{E_{i-1}^*}\frac{E_i^*}{E_i}\right) + B\sum_{i=1}^{n}\alpha_i E_i^*\left(1-\frac{E_i}{E_i^*}\frac{I^*}{I}\right)\\ &+ B\gamma R^*\left(1-\frac{R}{R^*}\frac{I^*}{I}\right) + B\delta L^*\left(1-\frac{L}{L^*}\frac{I^*}{I}\right) + C\phi(1-r)I^*\left(1-\frac{I}{I^*}\frac{L^*}{L}\right)\\ &+ DrI^*\left(1-\frac{I}{I^*}\frac{R^*}{R}\right) + D\varepsilon(1-\delta)L^*\left(1-\frac{L}{L^*}\frac{R^*}{R}\right) + (-Da_R + B\gamma)R\\ &+ [\beta_1 S^* - Ba_I + C\phi(1-r) + Dr]I + [\beta_2 S^* - Ca_L + D\varepsilon(1-\delta) + B\delta]I\\ &+ \sum_{i=2}^{n} A_i k_{i-1}(1-r_{i-1})E_{i-1} - a_n A_n E_n + B\sum_{i=1}^{n}\alpha_i E_i - a_1 A_1 E_1 - \sum_{i=2}^{n} a_i A_i E_i.\end{aligned} \tag{20}$$

Now, let $(u_1, u_2, u_3, u_4, v_i) = \left(\dfrac{S^*}{S}, \dfrac{I^*}{I}, \dfrac{L^*}{L}, \dfrac{R^*}{R}, \dfrac{E_i^*}{E_i}\right)$. Then, Eq. (20) becomes

$$\begin{aligned}\dot{U} = &-\mu\frac{(S-S^*)^2}{S} + (A_1-1)(\beta_1 SI + \beta_2 SL) + (1-u_1)(\beta_1 S^* I^* + \beta_2 S^* L^*)\\ &+ A_1\beta_1 S^* I^*\left(1-\frac{v_1}{u_1 u_2}\right) + A_1\beta_2 S^* L^*\left(1-\frac{v_1}{u_2 u_3}\right) + A_2 k_1(1-r_1)E_1^*\left(1-\frac{v_2}{v_1}\right)\\ &+ \sum_{i=2}^{n-1} A_{i+1}k_i(1-r_i)E_i^*\left(1-\frac{v_{i+1}}{v_i}\right) + B\sum_{i=1}^{n}\alpha_i E_i^*\left(1-\frac{u_2}{v_i}\right)\\ &+ B\gamma R^*\left(1-\frac{u_2}{u_4}\right) + B\delta L^*\left(1-\frac{u_2}{u_3}\right) + C\phi(1-r)I^*\left(1-\frac{u_3}{u_2}\right)\\ &+ DrI^*\left(1-\frac{u_4}{u_2}\right) + D\varepsilon(1-\delta)L^*\left(1-\frac{u_4}{u_3}\right)\\ &+ [\beta_1 S^* - Ba_I + C\phi(1-r) + Dr]I + [\beta_2 S^* - Ca_L + D\varepsilon(1-\delta) + B\delta]L\\ &+ (-Da_R + B\gamma)R + \sum_{i=1}^{n-1}[-a_i A_i + B\alpha_i + A_{i+1}k_i(1-r_i)]E_i\\ &+ (-a_n A_n + B\alpha_n)E_n.\end{aligned} \tag{21}$$

The coefficients A_i, B, C and D are chosen such that the coefficients of $\beta_1 SI + \beta_2 SL$, L, R, E_i and E_n are equal to zero, that is,

$$\begin{cases} A_1 - 1 = 0,\\ \beta_2 S^* - Ca_L + D\varepsilon(1-\delta) + B\delta = 0,\\ -Da_R + B\gamma = 0,\\ -a_i A_i + B\alpha_i + A_{i+1}k_i(1-r_i) = 0, \qquad i = 1, 2, \ldots, n-1,\\ -A_n a_n + B\alpha_n = 0. \end{cases} \tag{22}$$

Solving the above equations yields the expressions of A_i, B, C and D given as in Eq. (18). Replacing the expressions of A_i, B, C and D given in Eq. (18) into

Eq. (21) gives

$$\begin{aligned}\dot{U} = &-\mu\frac{(S-S^*)^2}{S} + \beta_1 S^* I^* \left(2 - u_1 - \frac{v_1}{u_1 u_2}\right) + \beta_2 S^* L^* \left(2 - u_1 - \frac{v_1}{u_2 u_3}\right) \\ &+ \sum_{i=1}^{n-1} A_{i+1} k_i (1-r_i) E_i^* \left(1 - \frac{v_{i+1}}{v_i}\right) + B\sum_{i=1}^{n} \alpha_i E_i^* \left(1 - \frac{u_2}{v_i}\right) \\ &+ B\gamma R^* \left(1 - \frac{u_2}{u_4}\right) + B\delta L^* \left(1 - \frac{u_2}{u_3}\right) + C\phi(1-r) I^* \left(1 - \frac{u_3}{u_2}\right) \\ &+ DrI^* \left(1 - \frac{u_4}{u_2}\right) + D\varepsilon(1-\delta) L^* \left(1 - \frac{u_4}{u_3}\right).\end{aligned} \tag{23}$$

Multiplying the second, third, fourth and fifth equations of Eq. (22) by L^*, R^*, E_i^*, $i = 1, \ldots, n-1$ and E_n^*, respectively, and using the expressions of $a_L L^*$, $a_R R^*$, $a_i E_i^*$ and $a_n E_n^*$ defined as in Eq. (19), one has

$$\begin{cases} \beta_2 S^* L^* - C\phi(1-r) I^* + D\varepsilon(1-\delta) L^* + B\delta L^* = 0, \\ -DrI^* - D\varepsilon(1-\delta) L^* + B\gamma R^* = 0, \\ -\beta_1 S^* I^* - \beta_2 S^* L^* + B\alpha_1 E_1^* + a_2 A_2 k_1 (1-r_1) E_1^* = 0, \\ -A_i k_{i-1}(1-r_{i-1}) E_{i-1}^* + B\alpha_i E_i^* + A_{i+1} k_i (1-r_i) E_i^* = 0,\ i = 2, \ldots, n-1, \\ -A_n k_{n-1}(1-r_{n-1}) E_{n-1}^* + B\alpha_n E_n^* = 0. \end{cases} \tag{24}$$

Let $F_1(u)$, $F_2(u)$, $F_3(u)$ and $G_i(u)$ $(i = 1, \ldots, n)$ where $u = (u_1, u_2, u_3, v_i)^T$ be $n+3$ functions to be determined later. Then, multiplying the first, second, third, fourth and fifth equations of Eq. (24) by $F_1(u)$, $F_2(u)$, $F_3(u)$, $G_1(u)$, $G_i(u)$ $(i = 2, \ldots, n-1)$ and $G_n(u)$, respectively, yields

$$\begin{cases} \beta_2 S^* L^* F_1(u) - C\phi(1-r) I^* F_1(u) + D\varepsilon(1-\delta) L^* F_1(u) + B\delta L^* F_1(u) = 0, \\ -DrI^* F_2(u) - D\varepsilon(1-\delta) L^* F_2(u) + B\gamma R^* F_2(u) = 0, \\ -\beta_1 S^* I^* G_1(u) - \beta_2 S^* L^* G_1(u) + \displaystyle\sum_{i=1}^{n-1} A_{i+1} k_i (1-r_i) E_i^* (G_i(u) - G_{i+1}(u)) \\ \quad + \displaystyle\sum_{i=1}^{n} \alpha_i E_i^* G_i(u). \end{cases} \tag{25}$$

Adding Eq. (25) to the right hand side of Eq. (23) yields

$$\begin{aligned}\dot{U} = &-\mu\frac{(S-S^*)^2}{S} + \beta_1 S^* I^* \left(2 - u_1 - \frac{v_1}{u_1 u_2} - G_1\right) \\ &+ \beta_2 S^* L^* \left(2 - u_1 - \frac{v_1}{u_2 u_3} - G_1 + F_1\right) \\ &+ \sum_{i=1}^{n-1} A_{i+1} k_i (1-r_i) E_i^* \left(1 - \frac{v_{i+1}}{v_i} + G_i - G_{i+1}\right) \\ &+ B\sum_{i=1}^{n} \alpha_i E_i^* \left(1 - \frac{u_2}{v_i} + G_i\right) + B\gamma R^* \left(1 - \frac{u_2}{u_4} + F_2\right) \\ &+ B\delta L^* \left(1 - \frac{u_2}{u_3} + F_1\right) + C\phi(1-r) I^* \left(1 - \frac{u_3}{u_2} - F_1\right) \\ &+ DrI^* \left(1 - \frac{u_4}{u_2} - F_2\right) + D\varepsilon(1-\delta) L^* \left(1 - \frac{u_4}{u_3} + F_1 - F_2\right).\end{aligned} \tag{26}$$

Now, we shall choose the functions $F_1(u)$, $F_2(u)$, $F_3(u)$ and $G_i(u)$, which make $\dot{U}$ non positive. To do so, the functions $F_1(u)$, $F_2(u)$, $F_3(u)$ and $G_i(u)$ are chosen such that the coefficients of $C\phi(1-r)I^*$, DrI^* and $\alpha_i E_i^*$ are equal to zero, that is,

$$F_1 = 1 - \frac{u_3}{u_2}, \qquad F_2 = 1 - \frac{u_4}{u_2} \qquad \text{and} \qquad G_i = -1 + \frac{u_2}{v_i} \ \ (i = 1, \ldots, n). \tag{27}$$

After plugging the expressions of $F_1(u)$, $F_2(u)$, $F_3(u)$ and $G_i(u)$ given as in Eq. (27) into Eq. (26), one finally obtains

$$\begin{aligned}
\dot{U} = &-\mu\frac{(S-S^*)^2}{S} + \beta_1 S^* I^* \left(3 - u_1 - \frac{v_1}{u_1 u_2} - \frac{u_2}{v_1}\right) \\
&+ \beta_2 S^* L^* \left(4 - u_1 - \frac{v_1}{u_1 u_3} - \frac{u_2}{v_1} - \frac{u_3}{u_2}\right) \\
&+ \sum_{i=1}^{n-1} A_{i+1} k_i (1 - r_i) E_i^* \left(1 - \frac{v_{i+1}}{v_i} + \frac{u_2}{v_i} - \frac{u_2}{v_{i+1}}\right) \\
&+ B\gamma R^* \left(2 - \frac{u_2}{u_4} - \frac{u_4}{u_2}\right) + B\delta L^* \left(2 - \frac{u_2}{u_3} - \frac{u_3}{u_2}\right) \\
&+ D\varepsilon(1-\delta) L^* \left(1 - \frac{u_4}{u_3} - \frac{u_3}{u_2} + \frac{u_4}{u_2}\right).
\end{aligned} \tag{28}$$

Now let

$$F = 1 + \frac{u_4}{u_2} - \frac{u_4}{u_3} - \frac{u_3}{u_2} \quad \text{and} \quad H_i = 1 + \frac{u_2}{v_i} - \frac{v_{i+1}}{v_i} - \frac{u_2}{v_{i+1}}, \quad i = 1, \ldots, n-1. \tag{29}$$

The next step is to show that the functions F and H_i are non-positive for all $u_1, u_2, u_3, v_i \in \mathbb{R}_{\geq 0}$.

By using Appendix 2 in Appendix with $w = 2$, $y_1 = u_3$, $y_2 = u_4$ and $Y = u_2$, when $u_3 \leq u_4 \leq u_2 \leq 1$ one has $1 + \frac{u_4}{u_2} - \frac{u_4}{u_3} - \frac{u_3}{u_2} \leq 0$, i.e., $F \leq 0$. Also, using the same lemma with $w = 2$, $y_1 = v_{i+1}$, $y_2 = u_2$ and $Y = v_i$, then if $v_{i+1} \leq u_2 \leq v_i \leq 1$ one obtains $1 + \frac{u_2}{v_i} - \frac{v_{i+1}}{v_i} - \frac{u_2}{v_{i+1}} \leq 0$, i.e., $H_i \leq 0$. Thus $\dot{U} \leq 0$ and Eq. (28) implies that $\dot{U}$ is less than or equal to zero with equality only if $S = S^*$. Therefore, $\dot{U} \leq 0$ for all $S, E_i, I, L, R \geq 0$, provided that $S^*, E_i^*, I^*, L^*, R^*$ are positive, where the equality $\dot{U} = 0$ holds only on the straight line $S = S^*$, $E_i^*/E_i = I^*/I = L^*/L = R^*/R$. It is easy to see that for system (1), P^* is the only equilibrium state on this line. Therefore, by Lyapunov-LaSalle asymptotic stability theorem [20-22], the positive endemic equilibrium state P^* is globally asymptotically stable in $\Omega_\rho \subset \mathbb{R}_{\geq 0}^{n+4}$, except on the S-axis which is the stable manifold for the fixed point P_0. This achieves the proof. □

Remark 1. It is possible for inequality (16) to fail, in which case the global stability of P^* may not be possible.

TABLE 1. Estimation of parameters

Parameters	Estimated value	Source
Λ	1000/yr	Assumed
β_1	Variable	Assumed
β_2	Variable	Assumed
μ	0.0101/yr	[23]
k_1	0.5/yr	Assumed
r_1	0/yr	[11]
α_1	0.003/yr	Assumed
α_2	0.005/yr	Assumed
r	0.8182/yr	[11]
ϕ	0.2/yr	[11]
δ	0.1/yr	[11]
γ	0.002/yr	[11]
ε	0.001/yr	Assumed
d_I	0.022722/yr	[11]
d_L	0.020/yr	[11]
d_1	0.001/yr	Assumed
d_2	0.002/yr	Assumed

4. Numerical simulations

To illustrate the various theoretical results contained in this paper, system (1) is simulated with two latent classes ($n = 2$) and parameter values using real data of the situation of TB in Cameroon and summarize in the following table.

Numerical results are reported in Figs. 2-6.

Figure 2 presents the basic reproduction ratio $\mathcal{R}_0$ as a function of the parameter at which infectious individuals become lost sight ϕ. In this figure the line blue stands for $\beta_2 < \Delta$ and the line red for $\beta_2 > \Delta$. As predicted by Lemma 3.2, when the parameter ϕ increases, one can see that for $\beta_2 < \Delta$ the basic reproduction ratio decreases while for $\beta_2 > \Delta$, the basic reproduction ratio increases

Figure 3 presents the trajectory plot of model system (1) with $n = 2$ using various initial conditions when $\beta_1 = 0.000009$, $\beta_2 = 0.000015$ and $n = 2$ (so that $\mathcal{R}_0 = 0.591$). From this figure, one can see that the trajectories of system (1) with $n = 2$ converge to the disease-free equilibrium. This means that the disease disappears in the host population when $\mathcal{R}_0 \leq 1$.

Figure 4 gives the trajectory plot when $\beta_1 = 0.0001$, $\beta_2 = 0.0005$ and $n = 2$ (so that $\mathcal{R}_0 = 9.0570$) using various initial conditions. It illustrates that the trajectories of model system (1) with $n = 2$ converge to the unique endemic equilibrium point. Thus, when $\mathcal{R}_0 > 1$, the disease persists in the host population as shown in Theorem 3.4.

Figure 5 shows the impact of varying the parameter ϕ in system (1) with $n = 2$ when $\beta_1 = 0.0001$, $\beta_2 = 0.0005$ and $n = 2$. The model was simulated with the

following initial conditions $S(0) = 57414$, $E_1(0) = 478$, $E_2(0) = 150$, $I(0) = 283$, $L(0) = 204$ and $R(0) = 2567$. From this figure, one can see that as the value of ϕ increases, the population of susceptible decreases (see Fig. 5(a)), while the population of latently-infected, infectious, lost sight and recovered increases (see Figs. 5(b)-(f)). This demonstrates that lost sight play an important on the spread of TB in a population. This pattern is also observed for the model of the basic reproduction ratio $\mathcal{R}_0$. Care then should be taken to prevent the failure of treatment, the abandon of treatment, the rest of the sputum examination and the relapse of the disease after treatment.

Figure 6 presents the mean prevalence of the infection as a function of the number of latent classes n. It clearly appears that the prevalence of the infection increases with the number of latent classes.

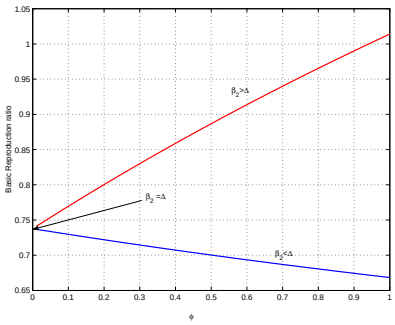

FIGURE 2. Basic reproduction ratio $\mathcal{R}_0$ as a function of ϕ.

5. Conclusion

In this paper, we have give a complete analysis of a tuberculosis model with two differential infectivity, n classes of latently infected individuals and mass balance incidence. In contrast to many TB models in the literature, we have included two infective classes emanating from infectious and lost sight. By analyzing this model, we found that it is globally asymptotically stable and possesses the only globally stable equilibrium state. Depending on the basic reproduction ratio, this steady state is either the endemic or the disease-free. The global stability of the infection-free equilibrium state implies that for any initial level of infection, the disease will eventually fade out from the population when the condition for this stability, namely $\mathcal{R}_0 \leq 1$, holds. The condition $\mathcal{R}_0 > 1$ implies that the disease will persist in a population.

In numerical analysis, we have used the basic reproduction ratio $\mathcal{R}_0$ to determine the role of lost sight on the spread of TB in a population. We have observed that to reach a disease-free equilibrium, it will take more decades than reaching endemic equilibrium point, because some latently infected individuals

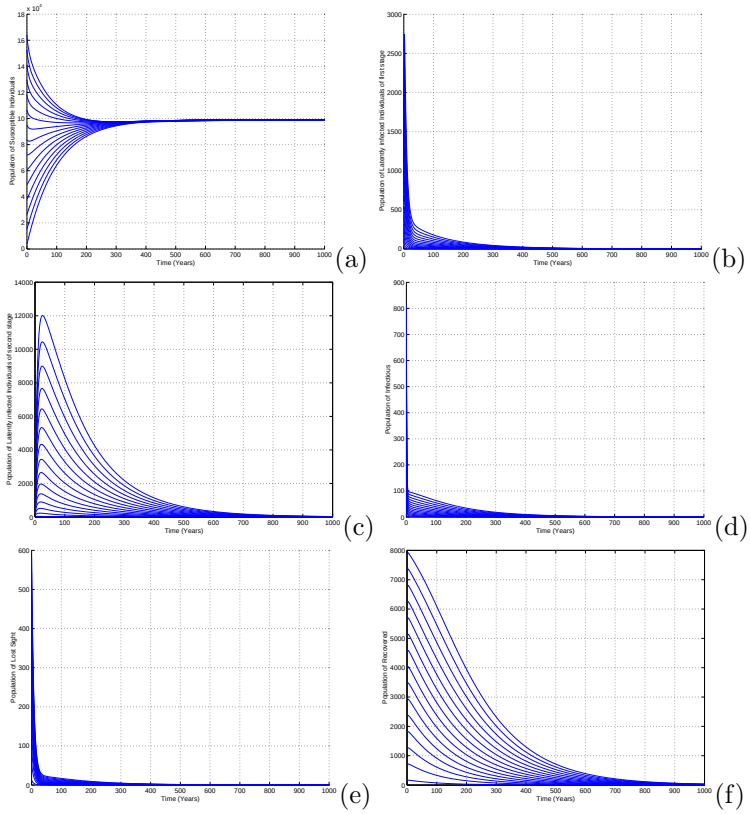

FIGURE 3. Trajectories of system (1) for different initial conditions when $\beta_1 = 0.000009$, $\beta_2 = 0.000015$ and $n = 2$ (so that $\mathcal{R}_0 = 0.591$).

might not develop disease over their life time. By increasing the value of ϕ, (the proportional of TB patients who never return in the hospital for the rest of sputum examinations and check-up), we have observed that the population of lost sight increases. This illustrates the fact that if the TB patients understand the importance to take all dose of their drugs and to make all sputum examinations during the period of their treatment, the number of recovered individuals will increase, hence the TB epidemic and death related to TB will decrease.

Appendix : Useful inequalities

In this appendix, we give inequalities which are necessary to demonstrate that the time derivative of the Lyapunov function $U(S, E_i, I, L, R)$ is non-positive. A key tool is the Arithmetic-Geometric Means Inequality, which we state here.

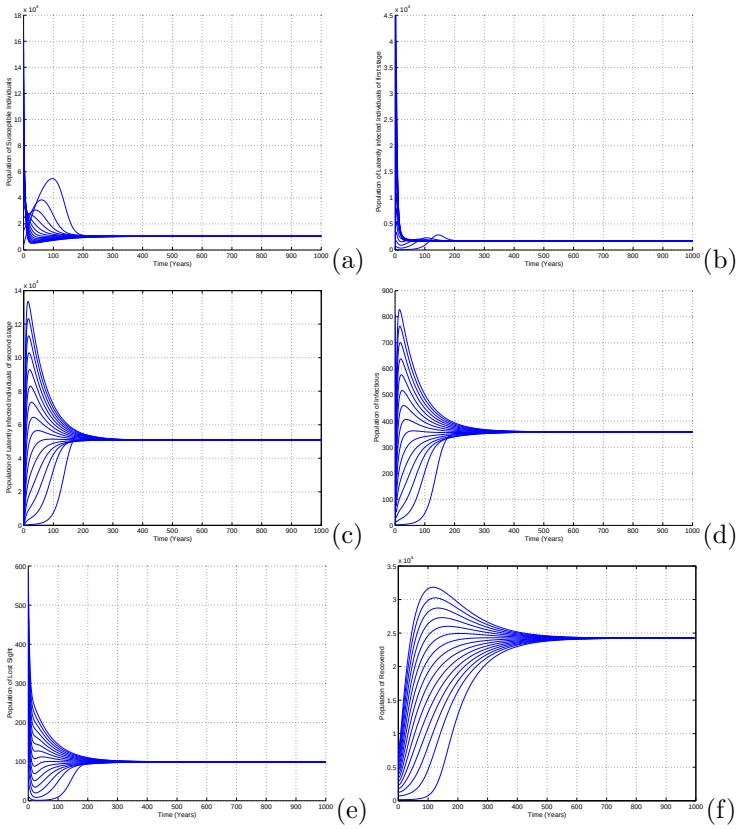

FIGURE 4. Trajectories of system (1) for different initial conditions when $\beta_1 = 0.0001$, $\beta_2 = 0.0005$ and $n = 2$ (so that $\mathcal{R}_0 = 9.0570$).

Appendix 1 (Arithmetic-Geometric Means Inequalit). Let $z_1, \ldots, z_w$ be positive real numbers. Then,

$$\sqrt[w]{z_1 \ldots z_w} \leq \frac{z_1 + \ldots + z_w}{w}. \tag{30}$$

Furthermore, exact equality only occur if $z_1 = \ldots = z_w$.

An immediate consequence of the Arithmetic-Geometric Means Inequality follows.

Appendix 2 ([13]). Let $y_1 \leq \ldots \leq y_w \leq Y$ be positive real numbers. Then

$$\frac{y_w}{Y} + (w-1) - \left(\frac{y_1}{Y} + \frac{y_2}{y_1} + \ldots + \frac{y_w}{y_{w-1}} \right) \leq 0. \tag{31}$$

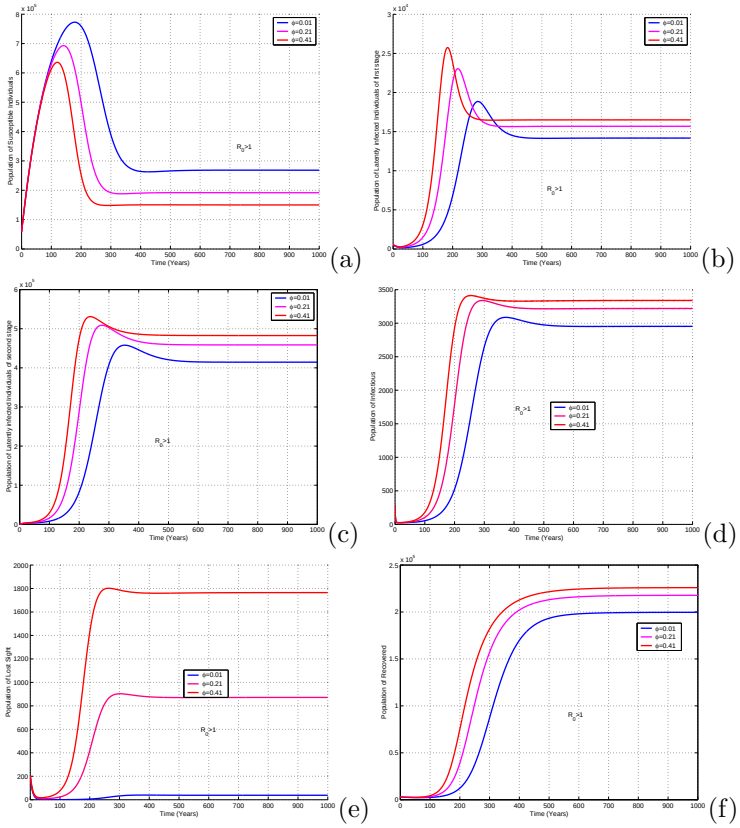

FIGURE 5. Time series of (a) susceptible individuals, (b) latently-infected individuals in the first stage of infection, (c) latently-infected individuals in the second stage of infection, (d) infectious individuals, (e) lost sight and (f) recovered individuals showing the impact of varying ϕ when $\beta_1 = 0.0001$, $\beta_2 = 0.0005$ and $n = 2$.

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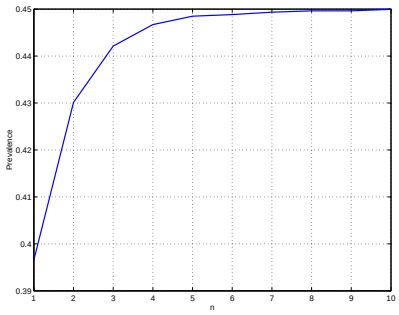

FIGURE 6. Mean prevalence of the infection as a function of the number of latent classes n.

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