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Global properties of a tuberculosis model with lost sight and multi-compartment of latents

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Abstract. A tuberculosis (TB) model with lost sight and multiple latent classes is considered and studied. We derive the basic reproduction ratio $\mathcal{R}_0$. There is always a globally asymptotically stable equilibrium state. Depending on the value of $\mathcal{R}_0$, this state can be either endemic ($\mathcal{R}_0 > 1$), or infection-free ($\mathcal{R}_0 \leq 1$). The global asymptotic stability of equilibria is established using Lyapunov functions that combine quadratic, Volterra-type and linear functions. The theory is supported by numerical simulations.

Keywords: TB, mathematical models, basic reproduction number, stability.
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1 Introduction

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

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ing BCG vaccination and the World Health Organization's DOTS strategy which focuses on case finding and short-course chemotherapy [20, 22, 44, 45, 48, 49]. This rise has been attributed to the spread of HIV, the collapse of public health programs and the emergence of drug-resistant strains of *Mycobacterium tuberculosis*. At present, about 95% of the estimated 8 million new cases of TB occurring each year are in developing countries, where 80% occurs among people between the ages of 15-59 years [20]. In sub-Saharan Africa, TB is the leading cause of mortality and in developing countries, it accounts for an estimated 2 million deaths which accounts for a quarter of avoidable adult deaths [22, 45]. TB was assumed to out in developed countries until the number of TB cases began to increase in the 1980. With this return, we face the paradox of a well-known bacteria, fully treatable with efficient and affordable drugs according to internationally recommended guidelines, which yet causes increasing human suffering and death. As the world is experiencing the devastating effects of HIV/AIDS epidemic, it is now necessary to ask why we have so far failed to control TB and to define the limits of the global TB control programs [4]. Currently, half of the people living with HIV are TB co-infected and three quarters of all dually infected people live in sub-Saharan Africa. In sub-Saharan Africa, the face of HIV/AIDS is TB, HIV/AIDS and TB fuel one another. Preventive therapy of TB in HIV infected individuals is highly recommended [18, 47] and could dramatically reduce the impact of HIV on TB epidemiology, but its implementation is limited in developing countries because of complex logistical and practical difficulties [11, 47].

Furthermore, as for many infectious diseases, it is well known that the duration of latency of TB varies greatly from case to case [20, 44]. For example, it is possible 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 [20, 48, 49]. Also, the risk of activation seems to decrease over time [20]. This leads to the questions whether this diversity of the length of the infective period affects the system dynamics of TB, and whether the classic compartmental models in mathematical epidemiology, which postulate that all the hosts are identical, are adequate to describe the spread of TB. The simplest way to explore this issue is to assume that there are several alternative paths for an infected host. We point out that, the residence time in an epidemiological status or in a compartment is generally not fixed. There are several ways to introduce the residence time into an epidemiological compartment. One can use delays where the residence time is represented by

a probability density function. One technique for representing this delay, when the function is a convex linear combination of Erlang functions, is to introduce additional compartments [28]. This technique is called "linear chain trick" or "method of stages". Thus, one can introduce compartments for phenomenological reasons, to simulate a delay, in addition to biological reasons. For example, introducing a latent compartment corresponds to an epidemiological reason, but we can add compartments in order to have a residence time corresponding to an Erlang function.

In this work, we divided the infective class into two subgroups with different properties: infectious and lost sight. Indeed, in sub-Saharan Africa, some diagnosed infectious that begun their effective therapy treatment in the hospital never return to the hospital for the sputum examinations and check up. The reasons could be negligence, lack of information about TB, long duration of treatment regimen, poverty, mentality, etc. In this case, the health personal does not know their epidemiological status, i.e., if they died, recovered or are still infectious. We call these infective individuals lost sight. It should be pointed out that according to the Direct Observation Therapy Strategy (DOTS) applied in most developing countries, a patient with pulmonary tuberculosis must make three sputum examinations during his treatment and will be considered cured when the last result of the examination of sputum is negative. According to the National Committee of Fight against Tuberculosis of Cameroon (1998), about 8% of detected infectious that begun their therapy 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 lost sight can have some effects on the spread of TB. Indeed, what is happening with lost sight? How are these affect the dynamics of TB? So this epidemiological feature cannot be neglected in the mathematical modeling of TB in developing countries like sub-Saharan Africa.

The dynamics of TB are complex due to a combination of various factors of societal order such as social and environmental factors, malnutrition, heavy alcohol drinking, smoking, HIV, diabetes mellitus but also Indoor air pollution from solid fuels. It is worth emphasizing that mathematical analysis of biomedical and disease transmission models can contribute to the understanding of the mechanisms of those processes and to design potential therapies (see [2, 3, 15, 24, 46] and the references therein). Unfortunately, a frequent focus in qualitative mathematical epidemiology is to determine the long-term dynamics exhibited by a given model. Since the publication of the result of Korobeinikov and Maini [29], the "Volterra-like" Lyapunov functions has been used to address the stability of high-dimensional systems

with mass action. Global stability of epidemic models is always mathematically challenging [1, 8, 23, 25, 26, 30, 33, 34] The difficulty is to choose the coefficients of the Lyapunov function and to prove that its time derivative is nonnegative. A number of theoretical studies have been carried out on the mathematical modelling of TB transmission dynamics [5–7, 10, 12–14, 16, 17, 21, 27, 35, 36, 40, 41, 43]. However, all of them are based on differential or partial differential equations [5–7, 10, 12–14, 16, 17, 21, 27, 35, 36, 40, 41, 43] and they exhibit some drawbacks: they do not take into account the duration of the period of latency and the population of lost of sight.

This paper builds on the existing works mentioned above and fills some of the gaps observed there . We formulate and analyze a TB mathematical model that incorporates the key epidemiological and biological features of the disease such as multiple latent classes and lost sight. Multiple classes of latent may be justified by the fact that the duration of latency varies from individual to individual on the understanding that every latently infected individual can become infectious depending on its hygiene rule. The model is completely analyzed. We compute the disease-free equilibrium and the reproduction number $\mathcal{R}_0$. We do an in-depth analysis of the global asymptotic stability of the disease-free equilibrium and endemic equilibria. In this regard, another feature of this work is the construction of new Lyapunov functions of gradual complexity. More precisely, we prove that when $\mathcal{R}_0 \leq 1$, the disease-free equilibrium is globally asymptotically stable, while when $\mathcal{R}_0 > 1$, the disease-free equilibrium is unstable and there exists a unique endemic equilibrium which is globally asymptotically stable. Numerical simulations are presented to support the theory and to get insight on the role of lost sight on the dynamics of TB within a population of sub-Saharan Africa.

The paper is organized as follows. After the formulation of the model in Section 2, we present its quantitative and qualitative analysis in Section 3. Numerical simulations are provided to illustrate and validate theoretical results. The last Section is devoted to concluding remarks on how our findings fit in the literature and on possible extensions.

2 Model description

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 (i.e., have active TB), lost sight (i.e., the health

personal do not know their epidemiological status) and recovered (i.e., have been cured after a therapy of treatment). We will denote these states by S, E_i, I, L and R, respectively. Thus, the total population at time t is

$$N = S + \sum_{i=1}^{n} E_i + I + L + R. \tag{1}$$

All recruitment is into the susceptible class, and occurs at a constant rate Λ. Transmission of *M. tuberculosis* occurs following adequate contact between a susceptible individual and infectious or lost sight. On adequate contact with infectious or lost sight, a susceptible individual becomes infected but not yet infectious. This individual remains in the latently infected class 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. To account for treatment, we define by $r_i E_i$ as the fraction of latently infected individuals receiving effective chemoprophylaxis. We assume that the chemoprophylaxis of latently infected individuals reduces their reactivation at a constant rate r_i. Thus, a fraction $1 - r_i$ of latently infected individuals does not receive effective chemoprophylaxis and progress to the next stage of latently infected class with a constant rate k_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 can spontaneously recover from the disease with a constant rate r, entering the recovered class R. Recovered individuals may have the bacterium in their body and can undergo a reactivation of the disease with a constant rate γ. We also assume that among the fraction $1-r$ of infectious who does not recover, some of them who begun their treatment will not return to the hospital for the rest of examination of sputum, check up, etc. at a constant rate ϕ 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. Because of natural recover and traditional medicine that is practiced in sub-Saharan Africa, a fraction $1 - \delta$ of lost sight who does not continue to have disease can recover at a constant rate ε and enters the recovered class R. The constant rate for non-disease related death is μ, thus $1/\mu$ is the average lifetime. Latently infected, infectious and lost sight have addition death rates due to infection and disease with constant rates d_i, d_I and d_L, respectively.

The corresponding transfer diagram is depicted in Fig. 1.

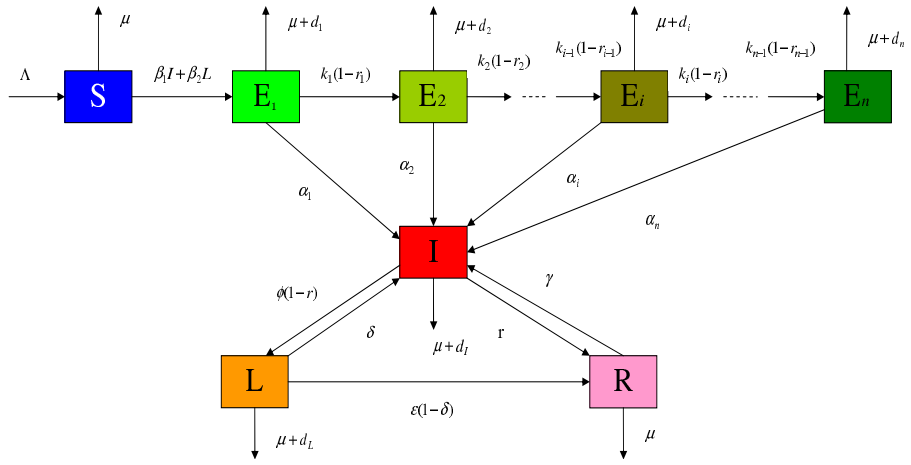

Figure 1: Flowchart of the transmission of tuberculosis with two infectious stages and n latent classes.

The corresponding equations are

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

Model system (2) can be written in the following compact form:

$$\begin{cases} \dot{x} &= \varphi(x) - x\langle \beta \mid y \rangle, \\ \dot{y} &= x\langle \beta \mid y \rangle \, B + A\, y, \end{cases} \tag{3}$$

where $x = S \in \mathbb{R}_{\ge 0}$, $y = (E_1, \ldots, E_n, I, L, R)^T \in \mathbb{R}^{n+3}_{\ge 0}$, $\varphi(x) = \Lambda - \mu\, x$ is a function that depends on x, $\beta = (0, \ldots, 0, \beta_1, \beta_2, 0)^T \in \mathbb{R}^{n+3}$ and $B = (1, 0, \ldots, 0)^T \in \mathbb{R}^{n+3}$, $\langle . \mid . \rangle$ is the usual scalar product in $\mathbb{R}^{n+3}$ and A is a $(n+3) \times (n+3)$ constant matrix defined as

$$A = \begin{bmatrix} -a_1 & 0 & 0 & 0 & 0 & \dots & 0 & 0 \\ \tilde{k}_1 & -a_2 & 0 & 0 & 0 & \dots & 0 & 0 \\ 0 & \tilde{k}_2 & -a_3 & 0 & 0 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \ddots & \ddots & \vdots & \vdots \\ 0 & \vdots & 0 & \tilde{k}_{n-1} & -a_n & 0 & 0 & 0 \\ \alpha_1 & \alpha_2 & \alpha_3 & \dots & \alpha_n & -a_I & \delta & \gamma \\ 0 & 0 & 0 & \dots & 0 & \phi(1-r) & -a_L & 0 \\ 0 & 0 & 0 & \dots & 0 & r & \varepsilon(1-\delta) & -a_R \end{bmatrix},$$

with

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

3 Mathematical analysis

3.1 Basic properties

Herein, we study the basic properties of model system (2), which are essential in the proofs of stability results. We have the following result.

Theorem 1. *Model system (2) is a dynamical system on the biologically feasible compact domain:*

$$\Omega = \left\{ (S, E_1, \dots, E_n, I, L, R) \in \mathbb{R}^{n+4}_{\geq 0},\quad N(t) \leq \frac{\Lambda}{\mu} \right\}. \tag{4}$$

Proof. The proof is provided in two steps.

Step 1: We show that the solution $(S(t),\ E_1(t), \dots, E_n(t),\ I(t),\ L(t),\ R(t))$ of model system (2) corresponding to initial conditions such that $S(0) > 0$, $E_1(0), \dots, E_n(0) > 0$, $I(0) > 0$, $L(0) > 0$ and $R(0) > 0$ are non negative. Assume that $\bar{t} = \sup\{t > 0 :\ S > 0,\ E_i > 0,\ 1 \leq i \leq n,\ I \geq 0,\ L \geq 0,\ R \geq 0\} \in [0, t]$. Thus, $\bar{t} > 0$ and it follows from the first equation of system (2), one has

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

where $\lambda(t) = \beta_1 I(t) + \beta_2 L(t)$. The above equation can be rewritten as,

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

Hence,

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

so that

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

Similarly, it can be shown that $E_i(t)>0$, $1\leq i\leq n$, $I(t)>0$, $L(t)>0$ and $R(t)>0$ for all $t>0$.

Step 2: We prove that the total population at time t, $N(t)$ satisfies the boundedness property $0\leq N(t)\leq\dfrac{\Lambda}{\mu}$ whenever $\quad 0\leq N(0)\leq\dfrac{\Lambda}{\mu}$.

By adding all equations in model system (2), one has

$$\dot{N}=\Lambda-\mu N-d_I\,I-d_L\,L-\sum_{i=1}^{n}d_iE_i\leq\Lambda-\mu N. \tag{5}$$

Applying the Gronwall inequalities to Eq. (5) yields

$$N(t)\leq\frac{\Lambda}{\mu}+\left(N(0)-\frac{\Lambda}{\mu}\right)e^{-\mu t},\qquad\forall\ t\geq 0, \tag{6}$$

which implies that $0\leq N(t)\leq\Lambda/\mu$ for all $t\geq 0$ if $N(0)\leq\Lambda/\mu$.

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

3.2 The disease-free equilibrium and its stability

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

Model system (3) has an evident equilibrium $Q_0=(x_0,0)$ with $x_0=\Lambda/\mu$ when there is no disease. We compute the basic reproduction number, $\mathcal{R}_0$, using the next generation approach, developed in [49].

Using notations of van den Driessche and Watmough [19], the jacobian matrices F and V, for the new infection and the remaining transfer at the disease-free equilibrium Q_0, are, respectively, given by

$$F = x_0 B\beta \qquad \text{and} \qquad V = -A.$$

Then, the basic reproduction ratio is defined, following van den Driessche and Watmough [49], as the spectral radius of the next generation matrix, FV^{-1}:

$$\mathcal{R}_0 = x_0 \langle \beta \mid (-A^{-1})\, B \rangle > 0. \tag{7}$$

We use the expression $(-A^{-1})$ to put the emphasis on the fact that $(-A^{-1}) \geq 0$ because the matrix A is Metzler stable. Using the expression of B, β defined as in model system (3) and after the computation of $-A^{-1}$, the basic reproduction ratio for system (2) is given by

$$\mathcal{R}_0 = \frac{a_1 a_R\, \mathcal{R}_0^{(1)} [\beta_1\, a_L + \beta_2\, \phi(1-r)] x_0}{\phi(1-r)\mathcal{R}_0^{(2)} + a_L\, [(\mu+\gamma)(\mu+d_I) + \mu\, r]}, \tag{8}$$

where

$$\mathcal{R}_0^{(1)} \;=\; \frac{\alpha_1}{a_1} + \sum_{i=2}^{n} \left[\alpha_i \frac{\prod_{l=1}^{i-1} k_l(1-r_l)}{\prod_{j=1}^{i} a_j} \right],$$

and

$$\mathcal{R}_0^{(2)} \;=\; \mu[\mu + d_L + \varepsilon(1-\delta)] + \gamma(\mu + d_L).$$

Now, let us determine the role of lost sight in the transmission of TB within a community of sub-Saharan Africa using the basic reproduction ratio $\mathcal{R}_0$. Suppose that there is no lost sight in the host population, that is, $\phi = \delta = \varepsilon = 0$. In this case, the basic reproduction ratio (8) reduces to

$$\mathcal{R}_0^0 = \frac{\beta_1\, a_1 a_R\, \mathcal{R}_0^{(1)} x_0}{(\mu+\gamma)(\mu+d_I) + \mu\, r}. \tag{9}$$

From Eqs. (8) and (9), one can deduce that

$$\mathcal{R}_0^0 < \mathcal{R}_0. \tag{10}$$

From the above Eq. (10), one can observe that the parameters ϕ, δ and ε influence the propagation of the disease in the host population. This means that lost sight play an important role in the propagation of TB within a host population of sub-Saharan Africa.

Further sensitivity analysis on the rate at which infectious become lost sight is carried out by computing the partial derivative of $\mathcal{R}_0$ with respect to the parameter ϕ. From Eq. (8), one has

$$\frac{\partial \mathcal{R}_0}{\partial \phi} = \frac{a_1 a_R a_L \mathcal{R}_0^{(1)} x_0 [\beta_2 \left[(\mu+\gamma)(\mu+d_I)+\mu\, r\right] - \beta_1 \mathcal{R}_0^{(2)}]}{[\phi(1-r)\mathcal{R}_0^{(2)} + a_L \left[(\mu+\gamma)(\mu+d_I)+\mu\, r\right]]^2}. \tag{11}$$

With this in mind, one can show that $\dfrac{\partial \mathcal{R}_0}{\partial \phi} < 0$ if

$$\beta_2 < \Delta = \frac{\beta_1 \mathcal{R}_0^{(2)}}{(\mu+\gamma)(\mu+d_I)+\mu\, r}. \tag{12}$$

Thus, the rate at which infectious become lost sight will a have positive impact in reducing the propagation of TB only if $\beta_2 < \Delta$ (i.e. $\mathcal{R}_0$ is a decrease function of ϕ). Also, that rate at which infectious 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 $\beta_2 > \Delta$ (i.e $\mathcal{R}_0$ is an increase function of ϕ). This result is summarized below:

Lemma 1. *The rate at which infectious become lost sight ϕ will a have 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 r increases. So, this quantity can be made as small as possible by increasing the treatment rate of infectious. Note that if the condition (12) does not hold (this happen for small values of the treatment rate of infectious r), 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, in order to better control the disease, we have to take care of all infectious detected in the health centers to avoid that some patients disappear during the treatment period. This will increase the successful of treatment of infectious.

For the numerical simulations, we consider only two classes of latently infected individuals. The parameter values used for numerical simulations are given in Table 1.

The following numerical results demonstrate the role of β_2, ϕ and δ on the basic reproduction number $\mathcal{R}_0$. We begin by investigating how the basic reproduction number $\mathcal{R}_0$ depends on β_2 and ϕ when $\beta_1 = 0.00005$

Table 1: Numerical values for the parameters of model system (2) with two latent classes.

Symbol	Description	Values/Units	Reference
Λ	Recruitment rate	5000 individual year^{-1}	Assumed
β_1	TB transmission rate of infectious	variable	
β_2	TB transmission rate of lost sight	variable	
μ	Naturally mortality rate	0.0101 year^{-1}	[38]
k_1	Progression rate from the first stage of latency to the second stage of latency	0.5 year^{-1}	Assumed
r_1	Chemoprophylaxis rate of infected individuals in the first stage of latency	0 year^{-1}	[37]
r_2	Chemoprophylaxis rate of infected individuals of the second stage of latency	0 year^{-1}	[37]
α_1	Progression rate from the first stage of latency to infectious	0.003 year^{-1}	Assumed
α_2	Progression rate from the second stage of latency to infectious	0.005 year^{-1}	Assumed
r	Effective therapy rate of infectious	0.8182 year^{-1}	[37]
ϕ	Progression rate from infectious to lost sight	0.2 year^{-1}	[14]
δ	Rate at which lost sight return to the hospital	0.1 year^{-1}	Assumed
γ	Relapse rate of recovered individuals	0.002 year^{-1}	[37]
ε	Recovered rate of lost sight	0.001 year^{-1}	Assumed
d_1	Additional death rate in the first stage of latency	0.001 year^{-1}	Assumed
d_2	Additional death rate in the second stage of latency	0.002 year^{-1}	Assumed
d_I	Death rate of infectious	0.022722 year^{-1}	[37]
d_L	Death rate of lost sight	0.020 year^{-1}	Assumed

using parameter values in Table 1. The illustration in Fig. 2(a) shows that the increase of the transmission coefficient of lost sight and the progression rate from infectious to lost sight results in an increase in $\mathcal{R}_0$. Figure 2(b) presents the 3-D plot showing the effects of β_2 and δ on the basic reproduction ratio $\mathcal{R}_0$. One can observe that $\mathcal{R}_0$ decreases if β_2 decreases even in the case of large values of δ. This means that if the TB transmission coefficient β_2 is sufficiently small TB infection could be eliminated even if $\delta = 0$. Figure 2(c) shows the effects of δ and ϕ on the basic reproduction ratio $\mathcal{R}_0$ when $\beta_1 = 0.0006$ and $\beta_2 = 0.000001$. One can also observe that

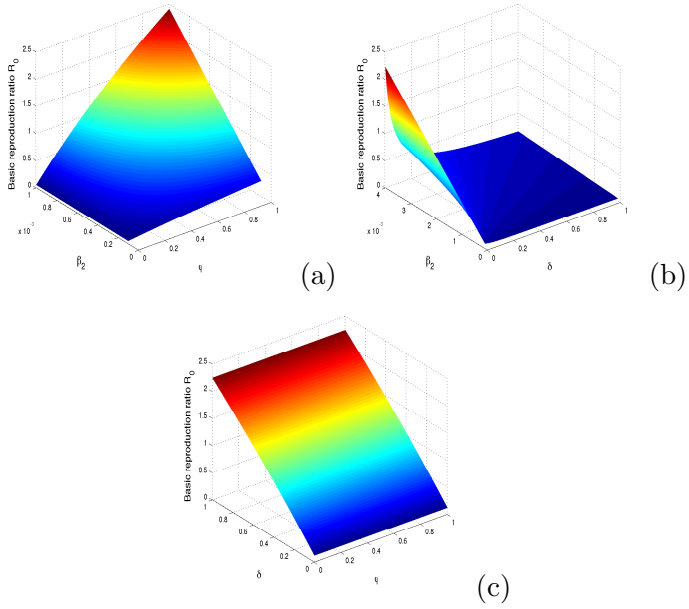

Figure 2: Graphs of the basic reproduction ratio $\mathcal{R}_0$ of model system (2) with two latent classes in dependence on some parameters: (a) $\mathcal{R}_0$ in term of β_2 and ϕ when $\beta_1 = 0.00005$; (b) $\mathcal{R}_0$ in term of β_2 and δ when $\beta_1 = 0.0006$ and (c) $\mathcal{R}_0$ in term of ϕ and δ when $\beta_1 = 0.0025$ and $\beta_2 = 0.000001$. All other parameter values are as in Table 1.

for the chosen parameter values, if the progression rate from infectious to lost sight ϕ does not exceed 0.4 ($\phi < 0.4$), then TB can be controlled irrespective of the value of ϕ. The infection will equally persist for $\phi > 0.4$.

Now, it is convenient to define the region (the stable manifold of the DFE, Q_0):

$$\Omega_0 = \{(S, E_1, \ldots, E_n, I, L, R) \in \Omega :, \;\; E_1 = \ldots = E_n = I = L = R = 0\}.$$

The relevance of the basic reproduction number is due to the following result established in [19].

Lemma 2. *The disease-free equilibrium Q_0 of model system (3) is locally asymptotically stable whenever $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The biological implication of Lemma 2 is that, a sufficiently small flow of infected individuals will not generate an outbreak of the disease unless $\mathcal{R}_0 > 1$. For a better control of the disease, the global asymptotic stability

(GAS) of the DFE is needed. We claim the following result about the global stability of the disease-free equilibrium Q_0 of model system (3).

Theorem 2. *The disease-free equilibrium Q_0 of model system (3) is globally asymptotically stable in Ω whenever $\mathcal{R}_0 \leq 1$. This implies the global asymptotic stability of the disease-free equilibrium Q_0 on the nonnegative orthant $\mathbb{R}^{n+4}_{\geq 0}$. This means that the disease naturally dies out.*

Proof. Consider the following LaSalle-Lyapunov candidate function:

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

where β and A are defined as in model system (3). It is easy to see that at the disease-free equilibrium Q_0, the function $V(x,y)$ reaches its global minimum in Ω, and hence $V(x,y)$ is a Lyapunov function since $\beta^T (-A^{-1}) > 0$. Its time derivative along the trajectories of model system (3) is

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

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

$$\dot{V}(x,y) = -\frac{(x - x_0)^2}{x_0\, x} + \frac{x\,\beta^T y}{x_0}(\mathcal{R}_0 - 1). \tag{15}$$

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 Q_0 is the only fixed point of the system in the space $x = x_0$, and hence, the system has no equilibria in Ω apart Q_0. Then, by the

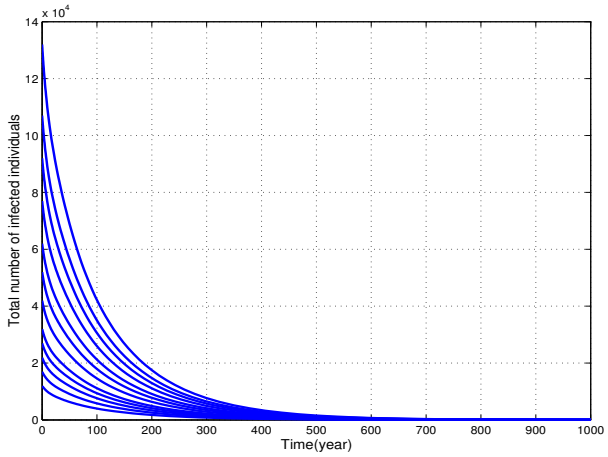

Figure 3: Simulation of model system (2) with $n = 2$ using various initial conditions when $\beta_1 = 0.000005$ and $\beta_2 = 0.000001$ (so that $\mathcal{R}_0 = 0.1462 < 1$). All other parameter values are as in Table 1.

Lyapunov-LaSalle's [31, 32] asymptotic stability theorem, the equilibrium state Q_0 is globally asymptotically stable in Ω. This proves the global asymptotic stability on Ω and then in the nonnegative orthant $\mathbb{R}^{n+4}_{\geq 0}$ (see Bhatia and Szegö [9], Theorem 3.7.11, page 346). This achieves the proof. □

Figure 3 shows the convergence of the total number of infected individuals to the disease-free equilibrium Q_0 of model system (2) with two latent classes using various initial conditions when $\beta_1 = 0.000005$, $\beta_2 = 0.000001$ (so that $\mathcal{R}_0 = 0.1462$). All other parameter values are as in Table 1. It illustrates that the disease disappears in the host population when $\mathcal{R}_0 \leq 1$ and the disease is controllable.

3.3 The endemic equilibrium point and its stability

Let $Q^* = (x^*, y^*)$ be the positive endemic equilibrium of model system (3). Then, the positive endemic equilibrium (steady state with $y > 0$) can be obtained by setting the right hand side of all equations in model system (3) to zero, giving

$$\begin{cases} \varphi(x^*) = x^* \langle \beta \mid y^* \rangle, \\ x^* \langle \beta \mid y^* \rangle \, B = -A \, y^*. \end{cases} \tag{16}$$

From the second equation of (16), one has $y^* = x^*(-A^{-1})B\langle \beta \mid y^* \rangle$. Plugging this expression of y^* in the second equation of (16) gives $\langle \beta \mid y^* \rangle =$

$x^*\langle\beta \mid (-A^{-1}B\rangle\langle\beta \mid y^*\rangle$. The case $\langle\beta \mid y^*\rangle = 0$ implies that $\varphi(x^*) = 0$ or $-Ay^* = 0$. Since A is nonsingular, this gives the disease-free equilibrium Q_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 using the first equation of (16), one obtains $y^* = (-A^{-1})\, B\, \varphi(x^*)$.Hence, the endemic equilibrium for model system (3) is given by

$$x^* = \frac{1}{\langle\beta \mid (-A^{-1})\, B\rangle} = \frac{x_0}{\mathcal{R}_0} \qquad \text{and} \qquad y^* = (-A^{-1})\, B\, \varphi(x^*). \tag{17}$$

Thus, we have established the following result.

Lemma 3. *2 When $\mathcal{R}_0 > 1$, there exists a unique endemic equilibrium point $Q^* = (x^*, y^*)$ for the system (3) where x^* and y^* are defined as in Eq. (17) which is in the nonnegative orthant $\mathbb{R}^{n+4}_{\geq 0}$.*

The explicit expressions of the endemic equilibrium for model system (2) are given in Appendix A.

The global stability of the endemic equilibrium of model system (2) is given by Theorem 3, stated below and proved in Appendix B.

Theorem 3. *The unique endemic equilibrium $Q^* = (S^*, E_1^*, \ldots, E_n^*, I^*, L^*, R^*)$ given as in Eq. (19) of the TB model (2) is globally asymptotically stable in $\Omega \setminus \Omega_0$ whenever $\mathcal{R}_0 > 1$ and*

$$\frac{E_1^*}{E_1} \leq \frac{E_2^*}{E_2} \leq \cdots \leq \frac{E_n^*}{E_n} \leq \frac{I^*}{I} \leq \frac{R^*}{R}. \tag{18}$$

The convergence to the endemic equilibrium Q^* for model system (2) for the total number of infected individuals when $\beta_1 = 0.00005$ and $\beta_2 = 0.00001$ (so that $\mathcal{R}_0 = 2.8146$) are depicted in Fig. 4. All other parameter values are as in Table 1. It illustrates that when $\mathcal{R}_0 > 1$, the disease persists in the host population as established in Theorem 3.

4 Concluding remarks

In this work, we considered a TB model where the following epidemiological facts have been incorporated: (a) a more general demographic structure, (b) multiple classes of latent, (c) mass action incidence and (d) the population of lost sight, which can simulate the process of disease control.

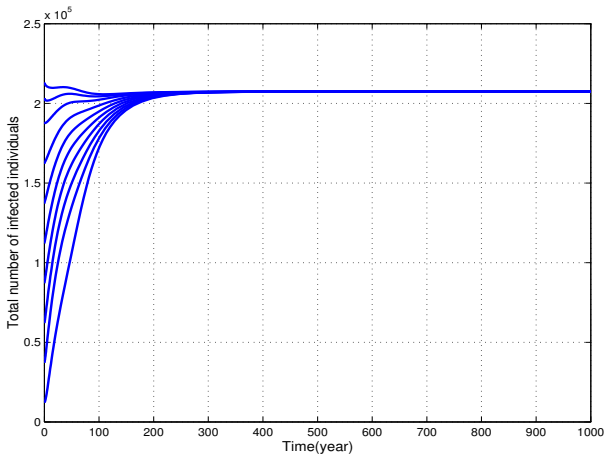

Figure 4: Simulation of model system (2) with $n = 2$, using various initial conditions when $\beta_1 = 0.00005$ and $\beta_2 = 0.00001$ (so that $\mathcal{R}_0 = 2.8146 > 1$). All other parameters are as in Table 1.

The model has been rigorously analyzed to gain insight into its dynamical features. We derived the basic reproduction number $\mathcal{R}_0$. Theoretical analysis of the basic reproduction number $\mathcal{R}_0$ revealed that infectious who become lost sight will have positive impact in reducing the propagation of TB. Thus, in order to better control the disease, we have to take care of all infectious in the health centers to avoid lost sight and then to increase the successful of treatment of infectious. This can be done by taking all the contact details of patients diagnosed with active TB at the health center (telephone number, place of residence, address of service, telephone number of a close relative, etc.). This would make it possible to find them in case they did not show up at the health center to monitor their treatment. We computed equilibria and study their stabilities. The model has a globally-asymptotically stable disease-free equilibrium whenever $\mathcal{R}_0 \leq 1$, while when $\mathcal{R}_0 > 1$, there exists a unique endemic equilibrium which is globally asymptotically stable in the nonnegative orthant. A big deal in the proof of the global results has been the construction of Lyapunov functions that combine linear and Volterra-type Lyapunov functions (Theorems 2 and 3). Thus, we have successfully applied to a TB model with multiple classes of latents, lost of sight and mass action incidence.

Different improvements and extensions of the model on which we are still working include: (i) including the class of undetected infectious which also play an important role on the spread of TB in sub-Saharan Africa; (ii) introducing of the mobility of the population, (iii) introducing drug

resistance, (iv) introducing time-dependent parameters and (v) designing of Nonstandard Finite Difference Schemes that can preserve the properties of the considered model.

Appendix A: Endemic equilibrium of model system (2)

In this appendix, we give the explicit expressions of the endemic equilibrium of model system (2).

To do so, 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 model system (2) is given by

$$\begin{cases} S^* &= \dfrac{x_0}{\mathcal{R}_0} = \dfrac{\Lambda}{\mu\mathcal{R}_0}, \qquad E_1^* = \dfrac{\Lambda(\mathcal{R}_0-1)}{a_1\mathcal{R}_0}, \\ E_i^* &= \dfrac{\prod\limits_{l=1}^{i-1} k_l(1-r_l)}{\prod\limits_{j=2}^{i} a_j}\,\dfrac{\Lambda(\mathcal{R}_0-1)}{a_1\mathcal{R}_0}, \qquad \text{for} \qquad i=2,3,\ldots,n, \\ I^* &= \dfrac{a_L\mu(\mathcal{R}_0-1)}{\beta_1\, a_L+\beta_2\,\phi(1-r)}, \qquad L^* = \dfrac{\phi(1-r)\mu(\mathcal{R}_0-1)}{\beta_1\, a_L+\beta_2\,\phi(1-r)}, \\ R^* &= \dfrac{\mu[r\, a_L+\varepsilon(1-\delta)\phi(1-r)](\mathcal{R}_0-1)}{a_R\,[\beta_1\, a_L+\beta_2\,\phi(1-r)]}. \end{cases} \tag{19}$$

Appendix B: Proof of Theorem 3

Herein, we give the proof of Theorem 3 on the global asymptotic stability of the endemic equilibrium $Q^* = (S^*, E_i^*, I^*, L^*, R^*)$ where S^*, E_i^*, $1 \le i \le n$, I^*, L^* and R^* are defined as in Eq. (19) of model system (2).

Consider the following Lyapunov function:

$$\begin{aligned} U(S,E_i,L,R) \;=\; & (S - S^*\ln S) + \sum_{i=1}^{n} A_i(E_i - E_i^*\ln E_i) \\ & + B(I - I^*\ln I) + C(L - L^*\ln L) + D(R - R^*\ln R), \end{aligned} \tag{20}$$

where A_i, B, C and D are positive constants to be determined later.

Differentiating this function with respect to time yields

$$\begin{aligned}
\dot{U} = & \left(1-\frac{S^*}{S}\right)\dot{S}+\sum_{k=1}^{n}A_i\left(1-\frac{E_i^*}{E_i}\right)\dot{E}_i+B\left(1-\frac{I^*}{I}\right)\dot{I} \\
& +C\left(1-\frac{L^*}{L}\right)\dot{L}+D\left(1-\frac{R^*}{R}\right)\dot{R} \\
= & \left(1-\frac{S^*}{S}\right)[\Lambda-\beta_1 SI-\beta_2 SL-\mu S] \\
& +A_1\left(1-\frac{E_1^*}{E_1}\right)[\beta_1 SI+\beta_2 SL-a_1E_1] \\
& +\sum_{i=2}^{n}A_i\left(1-\frac{E_i^*}{E_i}\right)[k_{i-1}(1-r_{i-1})E_{i-1}-a_iE_i] \\
& +B\left(1-\frac{I^*}{I}\right)\left[\sum_{i=1}^{n}\alpha_iE_i+\gamma R+\delta L-a_II\right] \\
& +C\left(1-\frac{L^*}{L}\right)[\phi(1-\delta)I-a_LL] \\
& +D\left(1-\frac{R^*}{R}\right)[rI+\varepsilon(1-\delta)L-a_RR] \\
= & \left(1-\frac{S^*}{S}\right)(\Lambda-\beta_1 SI-\beta_2 SL-\mu S)+A_1\beta_1 SI+A_1\beta_2 SL \\
& -A_1a_1E_1-A_1\beta_1 SI\frac{E_1^*}{E_1}-A_1\beta_2 SL\frac{E_1^*}{E_1} \\
& +A_1a_1E_1^*+\sum_{i=2}^{n}A_ik_{i-1}(1-r_{i-1})E_{i-1}-\sum_{i=2}^{n}A_ia_iE_i \\
& -\sum_{i=2}^{n}A_ik_{i-1}(1-r_{i-1})E_{i-1}\frac{E_i^*}{E_i}+\sum_{i=2}^{n}A_ia_iE_i^*+B\sum_{i=1}^{n}\alpha_iE_i \\
& +B\gamma R+B\delta L-Ba_II-B\sum_{i=1}^{n}\alpha_iE_i\frac{I^*}{I}-B\gamma R\frac{I^*}{I}-B\delta L\frac{I^*}{I} \\
& +Ba_II^*+C\phi(1-r)I-Ca_LL-C\phi(1-r)I\frac{L^*}{L} \\
& +Ca_LL^*+DrI+D\varepsilon(1-\delta)L-Da_RR-DrI\frac{R^*}{R} \\
& -D\varepsilon(1-\delta)L\frac{R^*}{R}+Da_RR^*,
\end{aligned} \tag{21}$$

where a_i, a_I, a_L and a_R are defined as in Eq. (2). By considering Eq. (2) at the positive endemic equilibrium $Q^*=(S^*,E_1^*,\ldots,E_n^*,I^*,L^*,R^*)$, one has

$$\begin{cases}
\Lambda = \beta_1S^*I^*+\beta_2S^*L^*+\mu S^*, \\
a_1E_1^* = \beta_1S^*I+\beta_2S^*L^*, \\
\quad\vdots \\
a_iE_i^* = k_{i-1}(1-r_{i-1})E_{i-1}^*, \qquad i=2,\ldots,n, \\
a_II^* = \sum_{i=1}^{n}\alpha_iE_i^*+\gamma R^*+\delta L^*, \\
a_LL^* = \phi(1-r)I^*, \\
a_RR^* = rI^*+\varepsilon(1-\delta)L^*.
\end{cases} \tag{22}$$

After plugging Eq. (22) into Eq. (21), one has

$$\begin{aligned}
\dot{U} \;=\; & -\mu\frac{(S-S^*)^2}{S} + (A_1-1)(\beta_1 SI + \beta_2 SL) \\
& + \left(1-\frac{S^*}{S}\right)(\beta_1 S^* I^* + \beta_2 S^* L^*) + A_1\beta_1 S^* I^* \left(1 - \frac{S}{S^*}\frac{I}{I^*}\frac{E_1^*}{E_1}\right) \\
& + A_1\beta_2 S^* L^* \left(1 - \frac{S}{S^*}\frac{I}{I^*}\frac{E_1^*}{E_1}\right) \\
& + \sum_{i=2}^{n} A_i k_{i-1}(1-r_{i-1})E_{i-1}^* \left(1 - \frac{E_{i-1}}{E_{i-1}^*}\frac{E_i^*}{E_i}\right) \\
& + B\sum_{i=1}^{n}\alpha_i E_i^* \left(1 - \frac{E_i}{E_i^*}\frac{I^*}{I}\right) + B\gamma R^* \left(1 - \frac{R}{R^*}\frac{I^*}{I}\right) \\
& + B\delta L^* \left(1 - \frac{L}{L^*}\frac{I^*}{I}\right) + C\phi(1-r)I^* \left(1 - \frac{I}{I^*}\frac{L^*}{L}\right) \\
& + DrI^* \left(1 - \frac{I}{I^*}\frac{R^*}{R}\right) + D\varepsilon(1-\delta)L^* \left(1 - \frac{L}{L^*}\frac{R^*}{R}\right) \\
& + (-Da_R + B\gamma)R + [\beta_1 S^* - Ba_I + C\phi(1-r) + Dr]I \\
& + [\beta_2 S^* - Ca_L + D\varepsilon(1-\delta) + B\delta]I + \sum_{i=2}^{n} A_i k_{i-1}(1-r_{i-1})E_{i-1} \\
& - a_n A_n E_n + B\sum_{i=1}^{n}\alpha_i E_i - a_1 A_1 E_1 - \sum_{i=2}^{n} a_i A_i E_i.
\end{aligned} \tag{23}$$

Now, let $(u_1, u_2, u_3, u_4, v_i) = \left(\frac{S^*}{S}, \frac{I^*}{I}, \frac{L^*}{L}, \frac{R^*}{R}, \frac{E_i^*}{E_i}\right)$. Then, Eq. (23) becomes

$$\begin{aligned}
\dot{U} \;=\; & -\mu\frac{(S-S^*)^2}{S} + (A_1-1)(\beta_1 SI + \beta_2 SL) \\
& + (1-u_1)(\beta_1 S^* I^* + \beta_2 S^* L^*) + A_1\beta_1 S^* I^* \left(1 - \frac{v_1}{u_1 u_2}\right) \\
& + A_1\beta_2 S^* L^* \left(1 - \frac{v_1}{u_2 u_3}\right) + A_2 k_1(1-r_1)E_1^* \left(1 - \frac{v_2}{v_1}\right) \\
& + \sum_{i=2}^{n-1} A_{i+1} k_i (1-r_i) E_i^* \left(1 - \frac{v_{i+1}}{v_i}\right) + B\sum_{i=1}^{n}\alpha_i E_i^* \left(1 - \frac{u_2}{v_i}\right) \\
& + B\gamma R^* \left(1 - \frac{u_2}{u_4}\right) + B\delta L^* \left(1 - \frac{u_2}{u_3}\right) \\
& + C\phi(1-r)I^* \left(1 - \frac{u_3}{u_2}\right) \\
& + DrI^* \left(1 - \frac{u_4}{u_2}\right) + D\varepsilon(1-\delta)L^* \left(1 - \frac{u_4}{u_3}\right)
\end{aligned} \tag{24}$$

$$
\begin{aligned}
&+[\beta_1 S^* - Ba_I + C\phi(1-r) + Dr]I \\
&+[\beta_2 S^* - Ca_L + D\varepsilon(1-\delta) + B\delta]L + (-Da_R + B\gamma)R \\
&+\sum_{i=1}^{n-1}[-a_i A_i + B\alpha_i + A_{i+1}k_i(1-r_i)]E_i \\
&+(-a_n A_n + B\alpha_n)E_n. \qquad (25)
\end{aligned}
$$

The coefficients A_i, B, C and D are chosen such that the coefficients of I, L, R and E_i are equal to zero, that is,

$$
\begin{cases}
A_1 - 1 = 0, \\
\beta_1 S^* - Ba_I + C\phi(1-r) + Dr = 0, \\
\beta_2 S^* - Ca_L + D\varepsilon(1-\delta) + B\delta = 0, \\
-Da_R + B\gamma = 0, \\
-a_i A_i + B\alpha_i + A_{i+1}k_i(1-r_i) = 0, \qquad i = 1, 2, \ldots, n-1, \\
-A_n a_n + B\alpha_n = 0.
\end{cases} \qquad (26)
$$

At this point, it is important to mention that when the second equation of (26) is satisfied, then all equations of (26) are also satisfied. Indeed, multiplying the second equation of (26) by I^* and using the expression of $a_I I^*$ defined as in Eq. (22), one has

$$
\begin{aligned}
\beta_1 S^* I^* - Ba_I I^* + C\phi(1-r)I^* + DrI^* = &-B\sum_{i=1}^{n}\alpha_i E_i^* - B\gamma R^* \\
&-B\delta L^* + \beta_1 S^* I^* \\
&+C\phi(1-r)I^* + DrI^*. \qquad (27)
\end{aligned}
$$

On the other hand, from Eq. (22), one has

$$
\begin{aligned}
a_1 A_1 E_1^* - A_1\beta_1 S^* I - A_1\beta_2 S^* L^* + \sum_{i=2}^{n} a_i A_i E_i^* - \sum_{i=2}^{n} A_i k_{i-1}(1-r_{i-1})E_{i-1}^* \\
+Ca_L L^* - C\phi(1-r)I^* + Da_R R^* - DrI^* - D\varepsilon(1-\delta)L^* = 0. \qquad (28)
\end{aligned}
$$

Adding Eq. (28) in the right hand side of Eq. (27) gives

$$
\begin{aligned}
\beta_1 S^* I^* - Ba_I I^* + C\phi(1-r)I^* + DrI^* &= (1-A_1)(\beta_1 I^* + \beta_2 L^*)S^* \\
&+ (-B\gamma + Da_R)R^* + [-\beta_2 S^* - B\delta - D\varepsilon(1-\delta) + Ca_L]L^* \\
&+ \sum_{i=1}^{n-1}[-B\alpha_i + a_i A_i - A_{i+1}k_i(1-r_i)]E_i^* \\
&+ (-B\alpha_n + a_n A_n)E_n^* = 0. \qquad (29)
\end{aligned}
$$

Therefore, we only consider the following system of equations:

$$\begin{cases} A_1 - 1 = 0, \\ \beta_2 S^* - C a_L + D\varepsilon(1-\delta) + B\delta = 0, \\ -D a_R + B\gamma = 0, \\ -a_i A_i + B\alpha_i + A_{i+1} k_i (1 - r_i) = 0, \quad 1 \le i \le n-1, \\ -A_n a_n + B\alpha_n = 0. \end{cases} \tag{30}$$

Using the fourth equation of (30), one can easily prove that

$$A_i = \prod_{j=1}^{i-1} \frac{a_j}{k_j(1-r_j)} - \left(\sum_{l=1}^{i-1} \frac{\alpha_l}{k_l(1-r_l)} \prod_{k=l+1}^{i-1} \frac{a_k}{k_k(1-r_k)} \right) B, \qquad 2 \le i \le n.$$

Now, using the expression of A_n obtained from the above equation and plugging it in the last equation of (30) gives

$$B = \frac{a_n \prod_{j=1}^{n-1} \frac{a_j}{k_j(1-r_j)}}{\alpha_n + \sum_{l=1}^{n-1} \frac{\alpha_l}{k_l(1-r_l)} \prod_{k=l+1}^{n-1} \frac{a_k}{k_k(1-r_k)}}.$$

Thus, the solutions of (30) are given by

$$\begin{aligned} A_1 &= 1, \qquad B = \frac{a_n \prod_{j=1}^{n-1} \frac{a_j}{k_j(1-r_j)}}{\alpha_n + \sum_{l=1}^{n-1} \frac{\alpha_l}{k_l(1-r_l)} \prod_{k=l+1}^{n-1} \frac{a_k}{k_k(1-r_k)}}, \\ A_i &= \prod_{j=1}^{i-1} \frac{a_j}{k_j(1-r_j)} - \left(\sum_{l=1}^{i-1} \frac{\alpha_l}{k_l(1-r_l)} \prod_{k=l+1}^{i-1} \frac{a_k}{k_k(1-r_k)} \right) B, \quad 2 \le i \le n, \\ D &= \frac{\gamma}{a_R} B \qquad \text{and} \qquad C = \frac{1}{a_L} \left[\beta_2 S^* + \left(\delta + \frac{\varepsilon\gamma(1-\delta)}{a_R} \right) B \right]. \end{aligned} \tag{31}$$

Replacing the expressions of A_i, B, C and D given in (31) into Eq. (25),

one obtains

$$\begin{aligned}\dot{U} = & -\mu\frac{(S-S^*)^2}{S} + \beta_1 S^* I^* \left(2 - u_1 - \frac{v_1}{u_1 u_2}\right) \\ & + \beta_2 S^* L^* \left(2 - u_1 - \frac{v_1}{u_2 u_3}\right) \\ & + \sum_{i=1}^{n-1} A_{i+1} k_i (1-r_i) E_i^* \left(1 - \frac{v_{i+1}}{v_i}\right) + B \sum_{i=1}^{n} \alpha_i E_i^* \left(1 - \frac{u_2}{v_i}\right) \\ & + B\gamma R^* \left(1 - \frac{u_2}{u_4}\right) + B\delta L^* \left(1 - \frac{u_2}{u_3}\right) + C\phi(1-r) I^* \left(1 - \frac{u_3}{u_2}\right) \\ & + DrI^* \left(1 - \frac{u_4}{u_2}\right) + D\varepsilon(1-\delta) L^* \left(1 - \frac{u_4}{u_3}\right). \end{aligned} \tag{32}$$

At present, multiplying the second, third, fourth, fifth and sixth equations of (30) by L^*, R^*, E_i^*, $1 \le i \le n-1$ and E_n^*, and using the expressions of $a_L L^*$, $a_R R^*$, $a_i E_i^*$ and $a_n E_n^*$ defined as in Eq. (22), one has

$$\begin{cases} \beta_2 S^* L^* - C\phi(1-r) I^* + D\varepsilon(1-\delta) L^* + B\delta L^* = 0, \\ -DrI^* - D\varepsilon(1-\delta) L^* + B\gamma R^* = 0, \\ -\beta_1 S^* I^* - \beta_2 S^* L^* + B\alpha_1 E_1^* + a_2 A_2 k_1 (1-r_1) E_1^* = 0, \\ -A_i k_{i-1}(1-r_{i-1}) E_{i-1}^* + B\alpha_i E_i^* + A_{i+1} k_i (1-r_i) E_i^* = 0, \\ \qquad\qquad 2 \le i \le n-1, \\ -A_n k_{n-1}(1-r_{n-1}) E_{n-1}^* + B\alpha_n E_n^* = 0. \end{cases} \tag{33}$$

Now, 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 (33) 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

$$\begin{cases} \beta_2 S^* L^* F_1(u) - C\phi(1-r) I^* F_1(u) + D\varepsilon(1-\delta) L^* F_1(u) \\ \qquad\qquad + B\delta L^* F_1(u) = 0, \\ -DrI^* F_2(u) - D\varepsilon(1-\delta) L^* F_2(u) + B\gamma R^* F_2(u) = 0, \\ -\beta_1 S^* I^* G_1(u) - \beta_2 S^* L^* G_1(u) + B\alpha_1 E_1^* G_1(u) \\ \qquad\qquad + a_2 A_2 k_1 (1-r_1) E_1^* G_1(u) = 0, \\ -A_i k_{i-1}(1-r_{i-1}) E_{i-1}^* G_i(u) + B\alpha_i E_i^* G_i(u) \\ \qquad\qquad + A_{i+1} k_i (1-r_i) E_i^* G_i(u) = 0, \quad 2 \le i \le 2, \\ -A_n k_{n-1}(1-r_{n-1}) E_{n-1}^* G_n(u) + B\alpha_n E_n^* G_n(u) = 0. \end{cases} \tag{34}$$

By adding the three last equations of (34), one obtains

$$
\begin{aligned}
&-\beta_1 S^* I^* G_1(u) - \beta_2 S^* L^* G_1(u) + B\alpha_1 E_1^* G_1(u) + a_2 A_2 k_1 (1-r_1) E_1^* G_1(u) \\
&- \sum_{i=2}^{n-1} A_i k_{i-1}(1-r_{i-1}) E_{i-1}^* G_i(u) + B \sum_{i=2}^{n-1} \alpha_i E_i^* G_i(u) \\
&+ \sum_{i=2}^{n-1} A_{i+1} k_i (1-r_i) E_i^* G_i(u) - A_n k_{n-1}(1-r_{n-1}) E_{n-1}^* G_n(u) + B\alpha_n E_n^* G_n(u) \\
&= -\beta_1 S^* I^* G_1(u) - \beta_2 S^* L^* G_1(u) \\
&+ \sum_{i=1}^{n-1} A_{i+1} k_i (1-r_i) E_i^* (G_i(u) - G_{i+1}(u)) + \sum_{i=1}^{n} \alpha_i E_i^* G_i(u).
\end{aligned}
$$

With this in mind, Eq. (34) becomes:

$$
\left\{
\begin{array}{l}
\beta_2 S^* L^* F_1(u) - C\phi(1-r) I^* F_1(u) + D\varepsilon(1-\delta) L^* F_1(u) \\
\qquad\qquad + B\delta L^* F_1(u) = 0, \\
-DrI^* F_2(u) - D\varepsilon(1-\delta) L^* F_2(u) + B\gamma R^* F_2(u) = 0, \\
-\beta_1 S^* I^* G_1(u) - \beta_2 S^* L^* G_1(u) \\
\quad + \sum_{i=1}^{n-1} A_{i+1} k_i (1-r_i) E_i^* (G_i(u) - G_{i+1}(u)) + \sum_{i=1}^{n} \alpha_i E_i^* G_i(u) = 0.
\end{array}
\right. \tag{35}
$$

Adding Eq. (35) to the right hand side of Eq. (32) yields

$$
\begin{aligned}
\dot{U} \;=\; & -\mu \frac{(S-S^*)^2}{S} \\
& + \beta_1 S^* I^* \left(2 - u_1 - \frac{v_1}{u_1 u_2} - G_1\right) \\
& + \beta_2 S^* L^* \left(2 - u_1 - \frac{v_1}{u_1 u_3} - G_1 + F_1\right) \\
& + \sum_{i=1}^{n-1} A_{i+1} k_i (1-r_i) E_i^* \left(1 - \frac{v_{i+1}}{v_i} + G_i - G_{i+1}\right) \\
& + B \sum_{i=1}^{n} \alpha_i E_i^* \left(1 - \frac{u_2}{v_i} + G_i\right) + B\gamma R^* \left(1 - \frac{u_2}{u_4} + F_2\right) \\
& + B\delta L^* \left(1 - \frac{u_2}{u_3} + F_1\right) + C\phi(1-r) I^* \left(1 - \frac{u_3}{u_2} - F_1\right) \\
& + DrI^* \left(1 - \frac{u_4}{u_2} - F_2\right) + D\varepsilon(1-\delta) L^* \left(1 - \frac{u_4}{u_3} + F_1 - F_2\right).
\end{aligned} \tag{36}
$$

Now, we shall choose the functions $F_1(u)$, $F_2(u)$ and $G_i(u)$, which make $\dot{U}$ non positive. To do so, the functions $F_1(u)$, $F_2(u)$ and $G_i(u)$ are chosen such that the coefficients of $C\phi(1-r)I^*$, $B\gamma R^*$ and $A_{i+1}k_i(1-r_i)E_i^*$ are

equal to zero, that is,

$$G_i(u) = \frac{v_{i+1}}{v_i} + \frac{v_{i+2}}{v_{i+1}} + \cdots + \frac{v_n}{v_{n-1}} + \frac{u_2}{v_n} - (n+1-i), \quad i = 1, \ldots, n-1$$

$$G_n(u) = \frac{u_2}{v_n} - 1, \qquad F_1(u) = -\frac{u_3}{u_2} + 1 \qquad \text{and} \qquad F_2(u) = \frac{u_2}{u_4} - 1. \tag{37}$$

After plugging the expressions of $F_1(u)$, $F_2(u)$ and $G_i(u)$ given as in Eq. (37) into Eq. (36), one obtains

$$\begin{aligned}
\dot{U} = \; & -\mu\frac{(S-S^*)^2}{S} \\
& +\beta_1 S^* I^* \left(-u_1 - \frac{v_1}{u_1 u_2} - \frac{v_2}{v_1} - \frac{v_3}{v_2} - \cdots - \frac{v_n}{v_{n-1}} - \frac{u_2}{v_n} + (n+2)\right) \\
& +\beta_2 S^* L^* \left(-u_1 - \frac{v_1}{u_1 u_3} - \frac{v_2}{v_1} - \frac{v_3}{v_2} - \cdots - \frac{v_n}{v_{n-1}} - \frac{u_2}{v_n} - \frac{u_3}{u_2} + (n+3)\right) \\
& +B\sum_{i=1}^{n} \alpha_i E_i^* \left(1 - \frac{u_2}{v_i} + \frac{v_{i+1}}{v_i} + \frac{v_{i+2}}{v_{i+1}} + \cdots + \frac{v_n}{v_{n-1}} + \frac{u_2}{v_n} - (n-i+1)\right) \\
& +B\delta L^* \left(2 - \frac{u_2}{u_3} - \frac{u_3}{u_2}\right) + DrI^* \left(2 - \frac{u_4}{u_2} - \frac{u_2}{u_4}\right) \\
& +D\varepsilon(1-\delta)L^* \left(3 - \frac{u_4}{u_3} - \frac{u_3}{u_2} - \frac{u_2}{u_4}\right).
\end{aligned} \tag{38}$$

Since the arithmetic mean exceeds the geometric mean, the following inequalities hold:

$$\begin{aligned}
& n + 2 - u_1 - \frac{v_1}{u_1 u_2} - \frac{v_2}{v_1} - \frac{v_3}{v_2} - \cdots - \frac{v_n}{v_{n-1}} - \frac{u_2}{v_n} \leq 0, \\
& n + 3 - u_1 - \frac{v_1}{u_1 u_3} - \frac{v_2}{v_1} - \frac{v_3}{v_2} - \cdots - \frac{v_n}{v_{n-1}} - \frac{u_2}{v_n} - \frac{u_3}{u_2} \leq 0, \\
& 2 - \frac{u_2}{u_3} - \frac{u_3}{u_2} \leq 0, \quad 2 - \frac{u_4}{u_2} - \frac{u_2}{u_4} \leq 0, \quad \text{and} \quad 3 - \frac{u_4}{u_3} - \frac{u_3}{u_2} - \frac{u_2}{u_4} \leq 0.
\end{aligned} \tag{39}$$

Now, let

$$H_i = 1 - \frac{u_2}{v_i} + \frac{v_{i+1}}{v_i} + \frac{v_{i+2}}{v_{i+1}} + \cdots + \frac{v_n}{v_{n-1}} + \frac{u_2}{v_n} - (n-i+1), \quad i = 1, ..., n. \tag{40}$$

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

Using Lemma 5 in Appendix B with $w = n-i+2$, $y_1 = v_i, \ldots, y_{w-1} = v_n$ and $y_w = u_2$, we have $y_1 \leq \ldots \leq y_w$ and one obtains,

$$\frac{v_{i+1}}{v_i} + \frac{v_{i+2}}{v_{i+1}} + \ldots + \frac{v_n}{v_{n-1}} + \frac{u_2}{v_n} - (n-i+1) \leq \frac{u_2}{v_i} - 1.$$

Then, one can deduce that

$$\begin{aligned} H_i &= 1 - \frac{u_2}{v_i} + \left(\frac{v_{i+1}}{v_i} + \frac{v_{i+2}}{v_{i+1}} + \ldots + \frac{v_n}{v_{n-1}} + \frac{u_2}{v_n} - (n-i+1) \right) \\ &\leq 1 - \frac{u_2}{v_i} + \frac{u_2}{v_i} - 1 = 0, \end{aligned}$$

i.e., $H_i \leq 0$. Thus $\dot{U} \leq 0$ and Eq. (38) 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 model system (2), Q^* is the only equilibrium state on this line. Therefore, by Lyapunov-LaSalle asymptotic stability theorem [9, 31, 32], the positive equilibrium state Q^* is globally asymptotically stable in the positive region $\Omega \subset \mathbb{R}^{n+4}_{\geq 0}$, except on the S-axis which is the stable manifold for the fixed point Q_0. This achieves the proof.

□

Appendix B: Useful inequalities

In this appendix, we give inequalities which are necessary to demonstrate that the time derivative of the Lyapunov functions are non-positive. A key tool is the Arithmetic-Geometric Means Inequality, which we state here.

Lemma 4. *(Arithmetic-Geometric Means Inequality): Let $z_1, \ldots, z_w$ be positive real numbers. Then,*

$$\sqrt[w]{z_1 \ldots z_w} \leq \frac{z_1 + \ldots + z_w}{w}. \tag{41}$$

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

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

Proposition 1. *Let $y_1, \ldots, y_w$ be positive real numbers such as $y_1 \ldots y_w = 1$. Then*

$$w - (y_1 + y_2 + \cdots + y_w) \leq 0, \tag{42}$$

Furthermore, exact equality only occur if $y_1 = \ldots = y_w$

We also have the following result

Lemma 5. *Let $y_1 \leq \cdots \leq y_w$ be positive real numbers. Then*

$$0 \leq \frac{y_2}{y_1} + \cdots + \frac{y_w}{y_{w-1}} - (w-1) \leq \frac{y_w}{y_1} - 1. \tag{43}$$

We have the following result

Lemma 6. *Let $y_1 \leq y_2 \leq \cdots \leq y_w$ be positive real numbers. Then*

$$0 \leq \frac{y_1}{y_2} + \cdots + \frac{y_{w-1}}{y_w} - (w-1) \leq \frac{y_1}{y_w} - 1. \tag{44}$$

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