

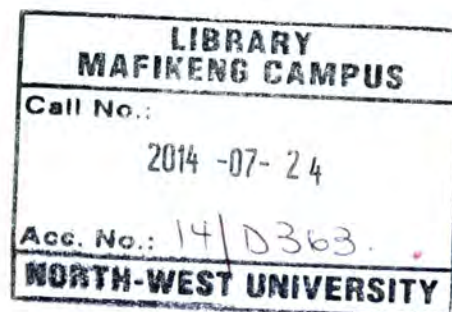
Mathematical analysis of tuberculosis models with differential infectivity, general contact rates, migration and staged progression

By

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Declaration

I, STELLA MUGISHA, student number 23717564, declare that this dissertation for the degree of Master of Science in Applied Mathematics at The North-West University, Mafikeng Campus, hereby submitted, has not previously been submitted by me for a degree at this or any other university, that this is my own work in design and execution and that all material contained herein has been duly acknowledged.

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Date:

This dissertation has been submitted with my approval as a university supervisor and I certify that the requirements for the applicable Master of Science degree rules and regulations have been fulfilled.

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Dedication

To my boys, Andrew, Matthew and Mark.

Acknowledgements

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Abstract

This study covers four fundamental features of tuberculosis dynamics (variable contact rates, differential infectivity, migration and staged progression). The first model under consideration covers the general contact rates and differential infectivity. The second model explores migration and staged progression. In this model, the spread of tuberculosis is studied through a two-patch epidemiological system $SE_1 \cdots E_n I$. The study proves that when the basic reproduction ratio is less than unity in the models, the disease-free equilibrium is globally asymptotically stable and when the basic reproduction ratio is greater than unity, a unique endemic equilibrium exists and happens to be globally asymptotically stable under certain conditions.

Direct and indirect Lyapunov methods as well as LaSalle's invariant set principle are used to investigate the stability of endemic equilibria.

Numerical simulations are provided to illustrate the theoretical results.

List of acronyms and abbreviations

S	:	Susceptibles
E	:	Exposed
I	:	Infectives
R	:	Recovered
L	:	Loss
TB	:	Tuberculosis
ODEs	:	Ordinary differential equations
PDEs	:	Partial differential equations
IVP	:	Initial value problem
HIV	:	Human immuno-deficiency virus
DFE	:	Disease-free equilibrium
M. tuberculosis	:	Mycobacterium tuberculosis.

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Chapter 1

Introduction

Despite the availability of effective treatment, tuberculosis remains a major global cause of morbidity and mortality, with around one-third of the world's population believed to be infected. It is estimated that in 2004, 1.7 million people died due to the disease and 8.9 million new cases of infection were recorded. The highest incidence of the disease is in sub-Saharan Africa, partly due to interactions with HIV, which has fuelled dramatic rises in incidence of the disease in many countries. Other factors may contribute to TB epidemic including the elimination of TB control programmes, drug use, poverty and immigration [3, 4]. Humans are the natural reservoir for *M. tuberculosis*, which is spread from person to person *via* airborne droplets [13, 14, 21]. *M. tuberculosis* may need only a low infectious dose to establish infection [5]. Factors that affect the transmission of *M. tuberculosis* include the number, viability, and virulence of organisms within sputum droplet nuclei and most importantly, time spent in close contact with an infectious person. Socio-economic status, family size, crowding, malnutrition and limited access to health-care or effective treatment also influence transmission. Infection with *M. tuberculosis* is dependent on non-linear contact processes that are determined by population size and density, as well as other factors. Demographic characteristics of a population, therefore, play a significant role in the development and progression of a TB epidemic. People who are infected with TB, do not feel sick, do not have any symptoms and cannot spread TB. However they may develop TB at later stage. The symptoms of active TB of the lung are coughing, sometimes with sputum or blood, chest pains, weakness, weight loss, fever and night sweats. Latently infected individuals (inactive TB) become infectious (active TB) after a variable (typically long) latency period. Latent periods range from months to decades. Most infected individuals never progress towards the active TB state. Treatment requires long-term use of antibiotics (at least 6 months is recommended for short course therapy), but is generally highly effective, including those with HIV, provided the patient is adherent. Lack of adherence can result in bacterium acquiring drug resistance. Transmission of drug-resistant strains is a significant problem in many parts of the world.

1.1 Motivation

In order to model the progress of an epidemic in a large population comprising individuals in various fields, the population diversity must be reduced to a few key characteristics relevant to the infection under consideration. For example, for most common childhood diseases that confer long-lasting immunity, it makes sense to divide the population into those who are susceptible to the disease, those who are infected and those who have recovered and considered immune. These subdivisions of the population are called compartments. Diseases that confer immunity have a different compartmental structure from diseases without immunity. The terminology *SIR* is used to describe a disease which confers immunity against re-infection, to indicate that the passage of individuals is from the susceptible class *S* to the infective class *I* to the removed class *R*. On the other hand, the terminology *SIS* is used to describe a disease with no immunity against re-infection, to indicate that the passage of individuals is from the susceptible class to the infective class and then back to the susceptible class. Other possibilities include *SEIR* and *SEIS* models, with an exposed period between being infected and becoming infective, and *SIRS* models, with temporary immunity on recovery from infection. The independent variable in our compartmental models is the time t and the rates of transfer between compartments are expressed mathematically as derivatives with respect to time of the sizes of the compartments and as a result, the models are formulated as differential equations. Mathematical models for tuberculosis have proven to be useful tools in assessing the epidemiological consequences of medical or behavioural interventions (which may cause many direct and indirect effects) because they contain explicit mechanisms that link individuals with a population-level outcome such as incidence or prevalence (see [1] to [46] and references therein).

The next section presents definitions of some of the concepts that will be used throughout this study.

1.2 Definition of concepts

Equations of the form

$$\frac{du}{dt} = f(t, u) \quad (1.1)$$

where f is continuous and X -valued on a set $\mathcal{U} \in \mathbb{R} \times X$ are used to describe continuous evolution systems. Here, $u(t) \in X$ is the state of the system at time t and f is a given vector field on X . The space X is the state space of the system; a point in X specifies the instantaneous state of the system. It is assumed that X is a Banach space. When X is finite dimensional, the evolution equation is a system of ordinary differential equations (ODE's). Partial differential equations (PDE's) can be regarded as evolution equations on an infinite dimensional state space. In this case, the solution $u(t) \equiv u(t, x)$ belongs to a function space in x at each instant of time t .

Definition 1.2.1. (*Initial value problem*)

An initial value problem (IVP) for equation (1.1) is given by

$$\begin{cases} \frac{du}{dt} = f(t, u) \\ u(t_0) = u_0 \end{cases} \quad (1.2)$$

where f is continuous and X -valued on a set $\mathcal{U} \in \mathbb{R} \times X$, with $(t_0, u_0) \in \mathcal{U}$.

Definition 1.2.2. (*Solution*)

A function $\phi(t)$ is a solution to the ODE (1.1) if it satisfies this equation, that is, if

$$\frac{d\phi(t)}{dt} = f(t, \phi(t)) \quad (1.3)$$

for all $t \in \mathcal{I} \subset \mathbb{R}$, an open interval such that $(t, \phi(t)) \in \mathcal{U}$ for all $t \in \mathcal{I}$.

Definition 1.2.3. (*Integral form of the solution*)

The function

$$\phi(t) = u_0 + \int_{t_0}^t f(s, \phi(s)) ds \quad (1.4)$$

is called the integral form of the solution to the IVP (1.2).

Definition 1.2.4. (*Lipschitz condition*) A vector-valued function $f(t, x)$ is said to satisfy a Lipschitz condition in a region \mathcal{R} in (t, x) -space if, for some constant L (called the Lipschitz constant), we have

$$\|f(t, x) - f(t, y)\| \leq L\|x - y\|, \quad (1.5)$$

whenever $(t, x) \in \mathcal{R}$ and $(t, y) \in \mathcal{R}$.

Epidemiological models are in general, formulated in terms of nonlinear systems of ordinary differential equations. Accordingly we set $X = \mathbb{R}^n$ in the rest of this proposal. The equation in IVP (1.2) is rewritten as

$$\frac{dx}{dt} = f(t, x); \quad x(t) \in \mathbb{R}^n. \quad (1.6)$$

It is assumed that $f(t, x)$ satisfies the standard conditions for the existence and uniqueness of solutions. Such conditions are, for instance, that $f(t, x)$ is Lipschitz continuous with respect to x , uniformly in t and piecewise continuous in t .

Definition 1.2.5. (*Stability*)

A solution $\phi(t)$ of (1.6) is stable if $\forall \epsilon, \forall t_0 \geq 0, \exists \delta(\epsilon, t_0) > 0$ such that whenever any solution $\psi(t)$ of (1.6) satisfies $\|\psi(t_0) - \phi(t_0)\| < \delta$, we have $\|\psi(t) - \phi(t)\| < \epsilon, \forall t \geq t_0$.

Definition 1.2.6. (*Asymptotic stability*) A solution $\phi(t)$ of (1.6) is asymptotically stable if it is stable and $\exists \delta_0 > 0$ such that whenever any solution $\psi(t)$ of (1.6) satisfies $\|\psi(t_0) - \phi(t_0)\| < \delta_0$, the identity

$$\lim_{t \rightarrow \infty} \|\psi(t) - \phi(t)\| = 0$$

holds.

Definition 1.2.7. (*Invariant set*)

A set K of points in phase space is invariant with respect to the system (1.6) if every solution starting in K remains in K for all future time.

1.3 Aims and objectives of the study

Despite the fact that the infectious agent that causes tuberculosis was discovered in 1882, many aspects of the natural history and transmission dynamics of TB are still not fully understood. This is reflected in differences in the structures of mathematical models of TB, which in turn, produce differences in the predicted impacts of interventions. Gaining a greater understanding of TB transmission dynamics requires further empirical laboratory and field work, mathematical modelling and interaction between them. Modelling can be used to quantify uncertainty due to different gaps in our knowledge to help identify research priorities.

The purpose of this study is to explore four important aspects of Tuberculosis dynamics that are not adequately discussed in the literature and to develop large models incorporating these components. The aims and objectives of the study are described in the following subsections:

- (a) Motivated by [13, 14], the study aims at investigating the global properties of a deterministic model for tuberculosis transmission dynamics with two differential infectivity with a general contact rate incorporating constant recruitment, vaccination, slow and fast progression, effective chemoprophylaxis (given to latently infected individuals) and therapeutic treatments (given to infectious). The study introduces a new epidemiological class known as hidden (loss of record) class. Loss of record refers to infectious individuals who began effective therapy in the hospital and never returned for sputum examinations due to long duration of treatment regimen, poverty and mentality. In this case, health officers do not usually know their status. One reason to introduce this new epidemiological class is because this phenomenon is common and occurs especially in Southern Africa. The study intends to analyse the stability behaviour of the model. The study will compute the basic reproduction ratio R_0 , investigate the global asymptotic stability of the disease-free equilibrium (DFE) and check the stability of the endemic equilibria on the non-negative orthant under certain assumptions. The global dynamics of the model will be resolved through the use of Lyapunov functions. Furthermore some

coefficients will be allowed to be time-dependent in order to extend earlier results. Numerical methods will be used in order to test the validity of the generalised model.

- (b) The second aspect of the research is based on [36] and consists of the study of tuberculosis through a two-patch epidemiological system $SE_1 \cdots E_n I$ which incorporates migration from one patch to another just by susceptible individuals. The model used is considered with bilinear incidence and migration between two patches, where infected and infectious individuals cannot migrate from one patch to another due to medical reasons. The existence and uniqueness of the associated endemic equilibria are discussed. Quadratic forms and Lyapunov functions are used to show that when the basic reproduction ratio is less than one, the disease-free equilibrium (DFE) is globally asymptotically stable, and when it is greater than one, there exists in each case, a unique endemic equilibrium (boundary equilibria and endemic equilibrium) which is globally asymptotically stable. Numerical simulation results are provided to illustrate the theoretical results. In this portion, the stability of a $2n+4$ -dimensions system will be investigated using Lyapunov-LaSalle functions and quadratic forms.

The dissertation is structured as follows: Chapter 1 provides a brief background for the study, discusses the preliminary tools and introduces the fundamental aspects of this research work. Chapter 2 discusses tuberculosis models with two differential infectivity and general contact rates. In chapter 3, the study investigates the global properties of tuberculosis models with staged progression and migrations. Chapter 4 presents numerical simulations of the models discussed in the study as well as a general conclusion.

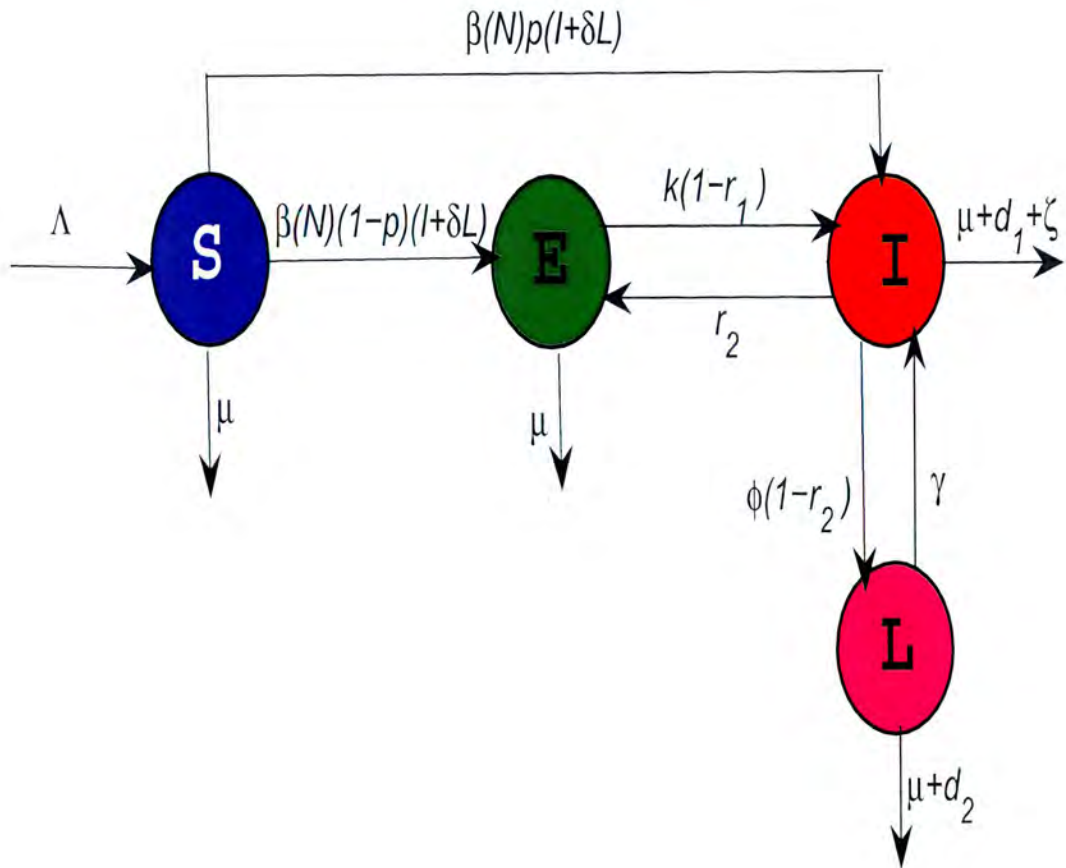
Chapter 2

General rates and differential infectivity

2.1 Model formulation

In this chapter, a general model for the spread of tuberculosis with variable contact rates and differential infectivity is derived. A diagrammatic representation of the spread of the disease is presented in Fig 2.1. The population is sub-divided into four classes: susceptible, latently infected (exposed), infectious and hidden (loss of sight) with the average number of individuals in each compartment denoted by S , E , I and L respectively. All recruitment is into the susceptible class, and occurs at a constant rate Λ . The rate constant for non-disease related death is μ , thus $1/\mu$ is the average lifetime. Infectious and loss of sight have additional death rates due to the disease with rates constant d_1 and d_2 , respectively. Since it is not known whether loss of sight would recover, die or still be infectious, it is assumed that a fraction δ of them is still infectious and can transmit the disease to susceptible. Transmission of M. tuberculosis occurs following adequate contact between a susceptible and an infectious individual or a loss of sight that continues to harbour the disease. It is assumed that infected individuals are not infectious and thus, not capable of transmitting the bacteria. The standard mass balance incidence expressions βSI and $\beta\delta SL$ are used to indicate successful transmission of M. tuberculosis due to non-linear contact dynamics in the population by infectious and loss of sight respectively. A fraction p of the newly infected individuals are assumed to undergo fast progression directly to the infectious class, while the remainder are latently infected and enter the latent class. Once latently infected with M. Tuberculosis, an individual will remain in this condition for life unless reactivation occurs. To account for treatment, $r_1 E$ is defined as the fraction of infected individuals receiving effective chemoprophylaxis, and r_2 as the rate of effective per capita therapy. It is assumed that chemoprophylaxis of latently infected individuals E reduces their reactivation at rate r_1 .

Figure 2.1: Model of tuberculosis with general contact rates and differential infectivity.



Thus, a fraction $(1 - r_1)E$ of infected individuals who do not receive effective chemo-

prophylaxis become infectious with rate constant k , so that $1/k$ is the average latent period. Thus, individuals leave the class E to I at rate $k(1 - r_1)$. After receiving an effective therapy, infectious individuals can spontaneously recover from the disease with rate constant r_2 , entering the infected class. A fraction $\phi(1 - r_2)I$ of infectious individuals who began their treatment will not return to hospital for sputum examination. After some time, some of them will return with the disease in hospital at constant rate γ . It is assumed that the emigration only affects the class of infectious I so that the fraction ζI of infectious leaves the class I without therapy treatment due to poverty and mentality. Since TB latent individuals are not capable of transmitting the disease, it is assumed that a susceptible individual may become infected only through contact with infectious individuals. In each unit time, a susceptible individual has an average $\beta(N)I$ contacts that would suffice to transmit the infection where $N = S + E + I$ is the total population size. Thus, the rate at which susceptible individuals are infected is $\beta(N)SI$.

The dynamical system described by Fig 2.1 is given by the following differential system:

$$\begin{aligned}\dot{S} &= \Lambda - \beta(N)S(I + \delta L) - \mu S, \\ \dot{E} &= \beta(N)(1 - p)S(I + \delta L) + r_2 I - [\mu + k(1 - r_1)]E, \\ \dot{I} &= \beta(N)pS(I + \delta L) + k(1 - r_1)E + \gamma L - [\mu + d_1 + \zeta + \phi(1 - r_2) + r_2]I, \\ \dot{L} &= \phi(1 - r_2)I - (\mu + d_2 + \gamma)L.\end{aligned}\tag{2.1}$$

Parameters Λ , μ , d_1 , d_2 , k , r_1 and r_2 are assumed to be positive and all other parameters are non-negative with $p \in [0, 1]$. Since the model (2.5) monitors human populations, it is further assumed that all the state variables are non-negative at time $t = 0$. It then follows from the differential equations that the variables are non-negative for all $t \geq 0$. Furthermore, adding all equations in (2.5) gives

$$\dot{N} = \Lambda - \mu N - (d_1 + \delta)I - d_2 L.\tag{2.2}$$

Consequently, in the absence of tuberculosis infection, $N \rightarrow \Lambda/\mu$ as $t \rightarrow \infty$ and Λ/μ is an upper bound of $N(t)$ provided that $N(0) \leq \Lambda/\mu$. Also, if $N(0) > \Lambda/\mu$, then N will decrease to this level. Thus, the following feasible region:

$$\mathfrak{D} = \{(S, E, I, L) \in R_{\geq 0}^4, 0 \leq S + E + I + L \leq \frac{\Lambda}{\mu} + \varepsilon\},\tag{2.3}$$

is a compact forward positively invariant set for $\varepsilon > 0$ and that for $\varepsilon > 0$ this set is absorbing. Furthermore, each solution of $R_{\geq 0}^4$ approaches \mathfrak{D} so that the study restricts its analysis to this region. In this region, the usual existence, uniqueness and continuation results hold for the system. In general, the model cannot be reduced to a lower dimensional model without making additional assumptions on the parameters.

2.2 Analysis of models with general contact rates

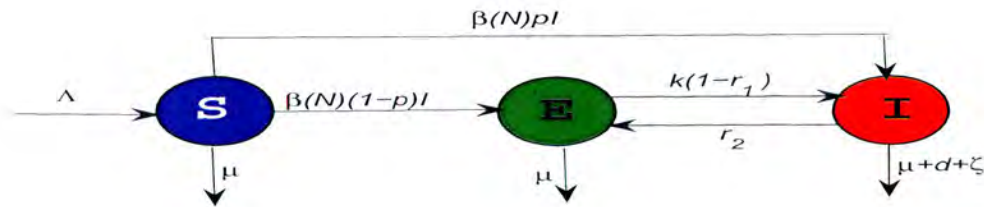
In this section, focus is on models with variable contact rates $\beta(N)$. The hidden (loss of sight) class L is ignored and it is assumed that the contact rate $\beta(N)$ is a non-negative C^2 function of the total population $N \geq 0$ (see Fig 2.2). It is further assumed that

$$\beta(N) > 0; \quad \beta'(N) \leq 0; \quad \text{and} \quad (N\beta(N))' \geq 0. \quad (2.4)$$

Remark 1. It is easy to notice that $\beta(N) = \frac{c}{N}$ corresponds to the standard incidence rate, that $\beta(N) = \beta$ corresponds to the mass action incidence rate, and that $\beta(N) = \beta C(N)$ corresponds to the saturating contact rate, where

$$C(N) = \frac{bN}{1 + bN + \sqrt{1 + 2bN}}.$$

Figure 2.2: Model of tuberculosis with general contact rates.



This leads to the following system of differential equations for the rate change with respect to time of the numbers of susceptible, latently infected and infectious individuals:

$$\begin{cases} \dot{S} &= \Lambda - \beta(N)SI - \mu S, \\ \dot{E} &= \beta(N)(1-p)SI + r_2I - [\mu + k(1-r_1)]E, \\ \dot{I} &= \beta(N)pSI + k(1-r_1)E - (\mu + d_1 + \zeta + r_2)I. \end{cases} \quad (2.5)$$

2.2.1 Basic reproduction ratio

Many epidemiological models have a threshold condition which can be used to determine whether an infection will be eliminated from the population or become endemic. The

basic reproduction number \mathfrak{R}_0 , is defined as the average number of secondary infections produced by an infected individual in a completely susceptible population. Indeed, \mathfrak{R}_0 is simply a normalised bifurcation (transcritical) condition for epidemiological models, such that $\mathfrak{R}_0 > 1$ implies that the endemic steady state is stable (i.e., the infection persists) and, $\mathfrak{R}_0 \leq 1$ implies that the uninfected steady state is stable (i.e., the infection can be eliminated from the population). The model has a disease-free equilibrium (DFE), obtained by setting the right hand side of Eq. (2.5) to zero and $I = 0$, given by $P_0 = (S_0, 0, 0)$ with $S_0 = \Lambda/\mu$. The stability of this equilibrium will be investigated using the next generation operator [43, 44, 45, 46]. Using the notation in Ref. [46] on the system (2.5), the matrices F and V , for the new infection terms and the remaining transfer terms are, respectively given by

$$F = \begin{bmatrix} 0 & \beta(S_0)S_0(1-p) \\ 0 & \beta(S_0)S_0p \end{bmatrix}$$

and

$$V = \begin{bmatrix} \mu + k(1-r_1) & -r_2 \\ -k(1-r_1) & d + r_2 \end{bmatrix},$$

where $d = \mu + d_1 + \zeta$. The spectral radius or the largest eigenvalue of its next generation operator is given by

$$\mathfrak{R}_0 = \rho(FV^{-1}) = \frac{\beta(S_0)S_0[\mu p + k(1-r_1)]}{d[\mu + k(1-r_1)] + \mu r_2}, \quad (2.6)$$

where ρ represents the spectral radius (the dominant eigenvalue in magnitude) of FV^{-1} . The threshold quantity \mathfrak{R}_0 is the basic reproduction number for TB infection. It measures the average number of new TB infections generated by a single infectious individual in a completely susceptible population. Consequently, the disease-free equilibrium P_0 of the basic model (2.5) is locally asymptotically stable (LAS) whenever $\mathfrak{R}_0 < 1$ and unstable if $\mathfrak{R}_0 > 1$. This implies that TB can be eliminated from the community (when $\mathfrak{R}_0 < 1$) if the sizes of the population of system (2.5) are in the basin of attraction of the disease-free equilibrium P_0 .

2.2.2 Global stability of the disease-free equilibrium

The following theorem provides the global stability of the disease-free equilibrium.

Theorem 2.2.1. *The disease-free equilibrium P_0 of model (2.5) is globally asymptotically stable in the non-negative orthant $R_{\geq 0}^3$ when $\mathfrak{R}_0 \leq 1$.*

Proof. Consider the following Lyapunov-LaSalle function:

$$V(E, I) = k(1-r_1)E + [\mu + k(1-r_1)]I. \quad (2.7)$$

Its time derivative along the solutions of system (2.5) satisfies

$$\begin{aligned}\dot{V}(E, I) &= k(1 - r_1)\dot{E} + [\mu + k(1 - r_1)]\dot{I} \\ &= k(1 - r_1)[\beta(N)(1 - p)SI + r_2I - [\mu + k(1 - r_1)]E] \\ &\quad + [\mu + k(1 - r_1)][\beta(N)pSI + k(1 - r_1)E - (d + r_2)I] \\ &= [\beta(N)S[p\mu + k(1 - r_1)] - r_2\mu - d[\mu + k(1 - r_1)]]I.\end{aligned}\tag{2.8}$$

Now, using Eq. (2.4), it gives $\beta(N)S \leq \beta(S)S \leq \beta(S_0)S_0$. With this in mind, (2.8) becomes

$$\begin{aligned}\dot{V}(E, I) &\leq [r_2\mu + [\mu + k(1 - r_1)]d]\left(\frac{\Lambda\beta(S_0)[p\mu + k(1 - r_1)]}{\mu[\mu + k(1 - r_1)]d + r_2\mu} - 1\right)I, \\ &= [r_2\mu + [\mu + k(1 - r_1)]d](\mathfrak{R}_0 - 1)I.\end{aligned}\tag{2.9}$$

Thus, $\dot{V}(E, I) \leq 0$ if $\mathfrak{R}_0 \leq 1$. Furthermore, $\dot{V}(E, I) = 0$ if and only if $\mathfrak{R}_0 = 1$ or $I = 0$. Then, the largest compact invariant set in $\{(S, E, I) \in R^3 \geq 0, \dot{V}(E, I) = 0\}$ is the singleton $\{P_0\}$. Therefore, by the LaSalle-Lyapunov theorem [40], all trajectories that start in \mathfrak{D} approach P_0 when $t \rightarrow \infty$. Since \mathfrak{D} is absorbing, this proves the global asymptotic stability on the non-negative orthant $R_{\geq 0}^3$ for $\mathfrak{R}_0 \leq 1$. It should be emphasized that the need to consider a positively invariant compact set is to establish the stability of P_0 since $V(E, I)$ is not positive definite. Generally, the LaSalle's invariance principle only proves the attractivity of the equilibrium. Considering \mathfrak{D} permits to conclude for the stability [39, 40, 41]. This fact is often overlooked in the literature using LaSalle's invariance principle. This concludes the proof. \square

2.2.3 Existence and uniqueness of endemic equilibrium

This section presents a result concerning the existence and uniqueness of endemic equilibrium for the model formulated above. This will be achieved by using the basic reproduction ratio \mathfrak{R}_0 . Let $P^* = (S^*, E^*, I^*)$ be the positive endemic equilibrium of model (2.5). Then, the positive endemic equilibrium (steady state with $I > 0$) can be obtained by setting the right hand side of each of the three differential equations in model (2.5) equal to zero, giving

$$\begin{cases} \Lambda - \beta(N^*)S^*I^* - \mu S^* = 0, \\ \beta(N^*)(1 - p)S^*I^* + r_2I^* - [k(1 - r_1) + \mu]E^* = 0, \\ \beta(N^*)pS^*I^* + k(1 - r_1)E^* - (d + r_2)I^* = 0, \end{cases}\tag{2.10}$$

and

$$\Lambda - \mu N^* - (d_1 + \zeta)I^* = 0.\tag{2.11}$$

Using Eq. (2.11), the first and second equations of (2.10), S^* , E^* and I^* in terms of N^*

can easily be expressed in the form:

$$\begin{aligned} S^* &= \frac{\Lambda(d_1 + \zeta)}{\beta(N^*)(\Lambda - \mu N^*) + \mu(d_1 + \zeta)}, \quad I^* = \frac{\Lambda - \mu N^*}{d_1 + \zeta} \quad \text{and} \\ E^* &= \frac{(\Lambda - \mu N^*)}{\mu + k(1 - r_1)} \left[\frac{\beta(N^*)\Lambda(1 - p)}{\beta(N^*)(\Lambda - \mu N^*) + \mu(d_1 + \zeta)} + \frac{r_2}{d_1 + \zeta} \right] \end{aligned} \quad (2.12)$$

Substituting (2.12) in the third equation of (2.10) yields

$$(\Lambda - \mu N^*)F(N^*) = 0. \quad (2.13)$$

where

$$F(N^*) = \beta(N^*)\Lambda(d_1 + \zeta)[p\mu + k(1 - r_1)] - \beta(N^*)(\Lambda - \mu N^*) + \mu(d_1 + \zeta)[r_2\mu + [\mu + k(1 - r_1)]d].$$

Clearly, $\Lambda - \mu N^* = 0$ is a fixed point of (2.10), which corresponds to the disease-free equilibrium P_0 . Since $N^* \in [0, S_0]$, one has

$$\begin{aligned} F(0) &= -\beta(0)\Lambda(d_1 + \zeta)\mu(1 - p) - \mu[\beta(0)\Lambda + \mu(d_1 + \zeta)][r_2 + \mu + k(1 - r_1)] \\ &\quad - \mu(d_1 + \zeta)^2[\mu + k(1 - r_1)], \\ F(S_0) &= \mu(d_1 + \zeta)[r_2\mu + d[\mu + k(1 - r_1)]](\mathfrak{R}_0 - 1). \end{aligned}$$

Clearly, it appears that $F(0) < 0$. It is now a trivial matter to observe that $F(S_0) > 0$ when $\mathfrak{R}_0 > 1$. The existence follows from the intermediate value theorem. Now, $F(N^*)$ is monotone increasing, so that $F(N^*) = 0$ has only one positive root in the interval $[0, S_0]$. Thus, the following result is established.

Lemma 2.2.2. *When $\mathfrak{R}_0 > 1$, the model (2.5) has a unique endemic equilibrium $P^* = (S^*, E^*, I^*)$ with S^* , E^* and I^* all non-negative.*

2.2.4 Global stability of the endemic equilibrium

Herein, the global stability of the endemic equilibrium P^* of system (2.5) is studied and the following result obtained:

Theorem 2.2.3. *If $\mathfrak{R}_0 > 1$, the unique endemic equilibrium P^* of the model (2.5) is globally asymptotically stable in $\mathfrak{D} \setminus \{E = I = 0\}$ whenever*

$$\frac{S}{S^*} \leq \frac{E}{E^*} \quad \text{and} \quad \frac{S}{S^*} \leq \frac{I}{I^*}. \quad (2.14)$$

Proof. Consider the following Lyapunov function candidate [29, 30, 31, 32, 33, 34, 35, 38]:

$$U(S, E, I) = (S - S^* \ln(S)) + A(E - E^* \ln(E)) + B(I - I^* \ln(I)), \quad (2.15)$$

where A and B are positive constants to be determined later. Differentiating this function with respect to time yields

$$\begin{aligned}
 \dot{U}(S, E, I) &= (1 - \frac{S^*}{S})\dot{S} + A(1 - \frac{E^*}{E})\dot{E} + B(1 - \frac{I^*}{I})\dot{I}, \\
 &= (1 - \frac{S^*}{S})(\Lambda - \beta(N)SI - \mu S) \\
 &\quad + A(1 - \frac{E^*}{E})[\beta(N)(1-p)SI + r_2I - [\mu + k(1-r_1)]E] \\
 &\quad + B(1 - \frac{I^*}{I})[\beta(N)pSI + k(1-r_1)E - (d+r_2)I].
 \end{aligned} \tag{2.16}$$

Considering (2.10), it can be deduced that

$$\begin{aligned}
 \Lambda &= \beta(N^*)S^*I^* + \mu S^*, \quad \mu + k(1-r_1) = \beta(N^*)(1-p)\frac{S^*I^*}{E^*} + r_2\frac{I^*}{E^*}, \\
 d + r_2 &= \beta(N^*)pS^* + k(1-r_1)\frac{E^*}{I^*}.
 \end{aligned} \tag{2.17}$$

With this in mind, (2.16) becomes

$$\begin{aligned}
 \dot{U}(S, E, I) &= (1 - \frac{S^*}{S})[\beta(N^*)S^*I^* + \mu S^* - \beta(N)SI - \mu S] \\
 &\quad + A(1 - \frac{E^*}{E})[\beta(N)(1-p)SI + r_2I - \beta(N^*)(1-p)S^*I^*\frac{E}{E^*} - r_2I^*\frac{E}{E^*}] \\
 &\quad + B(1 - \frac{I^*}{I})[\beta(N)pSI + k(1-r_1)E - \beta(N^*)pS^*I - k(1-r_1)E^*\frac{I}{I^*}], \\
 &= -\frac{\mu(S-S^*)^2}{S} + \beta(N^*)S^*I^*(1 - \frac{\beta(N)SI}{\beta(N^*)S^*I^*})(1 - \frac{S^*}{S}) \\
 &\quad + A(1 - \frac{E^*}{E})[(1-p)\beta(N^*)S^*I^*(\frac{\beta(N)SI}{\beta(N^*)S^*I^*} - \frac{E}{E^*}) + r_2I^*(\frac{I}{I^*} - \frac{E}{E^*})] \\
 &\quad + B(1 - \frac{I^*}{I})[p\beta(N^*)S^*I^*(\frac{\beta(N)SI}{\beta(N^*)S^*I^*} - \frac{I}{I^*}) + k(1-r_1)E^*(\frac{E}{E^*} - \frac{I}{I^*})].
 \end{aligned} \tag{2.18}$$

Now, using (2.10) results in

$$E^* = \frac{1}{\mu + k(1-r_1)}[\beta(N^*)(1-p)S^*I^* + r_2I^*].$$

Then, (2.18) may be rewritten as follows:

$$\begin{aligned}
& \dot{U}(S, E, I) \\
&= -\frac{\mu(S - S^*)^2}{S} + \beta(N^*)S^*I^* \left[\left(1 - \frac{S^*}{S}\right) \left(-\frac{\beta(N)SI}{\beta(N^*)S^*I^*} + 1\right) \right. \\
&\quad + A(1-p) \left(1 - \frac{E^*}{E}\right) \left(\frac{\beta(N)SI}{\beta(N^*)S^*I^*} - \frac{E}{E^*}\right) + Bp \left(1 - \frac{I^*}{I}\right) \left(\frac{\beta(N)SI}{\beta(N^*)S^*I^*} - \frac{I}{I^*}\right) \\
&\quad + \frac{Bk(1-r_1)(1-p)}{\mu + k(1-r_1)} \left(1 - \frac{I^*}{I}\right) \left(\frac{E}{E^*} - \frac{I}{I^*}\right) \left. \right] + r_2I^* \left[A \left(1 - \frac{E}{E^*}\right) \left(\frac{I}{I^*} - \frac{E}{E^*}\right) \right. \\
&\quad + \left. \frac{Bk(1-r_1)}{\mu + k(1-r_1)} \left(1 - \frac{I^*}{I}\right) \left(\frac{E}{E^*} - \frac{I}{I^*}\right) \right].
\end{aligned} \tag{2.19}$$

Now, let

$$(x, y, z, w) = \left(\frac{S}{S^*}, \frac{E}{E^*}, \frac{I}{I^*}, \frac{N}{N^*} \right)$$

and

$$g(w) = \frac{\beta(wN^*)}{\beta(N^*)}.$$

Then

$$\begin{aligned}
\dot{U}(S, E, I) &= -\mu \frac{(S - S^*)^2}{S} + \\
&\quad \beta(N^*)S^*I^* \left[\left(1 - \frac{1}{x}\right) (-g(w)xz + 1) + A(1-p) \left(1 - \frac{1}{y}\right) (g(w)xz - y) \right. \\
&\quad + Bp \left(1 - \frac{1}{z}\right) (g(w)xz - z) + \frac{Bk(1-r_1)(1-p)}{\mu + k(1-r_1)} \left(1 - \frac{1}{z}\right) (y - z) \left. \right] \\
&\quad + r_2I^* \left[A \left(1 - \frac{1}{y}\right) (z - y) + \frac{Bk(1-r_1)}{\mu + k(1-r_1)} \left(1 - \frac{1}{z}\right) (y - z) \right], \\
&= -\mu \frac{(S - S^*)^2}{S} + f(x, y, z, w),
\end{aligned} \tag{2.20}$$

where

$$\begin{aligned}
f(x, y, z, w) &= \beta(N^*)S^*I^*f_1(x, y, z, w) + r_2I^*f_2(z, w), \\
f_1(x, y, z, w) &= \left(1 - \frac{1}{x}\right) (-g(w)xz + 1) + A(1-p) \left(1 - \frac{1}{y}\right) (g(w)xz - y) \\
&\quad + Bp \left(1 - \frac{1}{z}\right) (g(w)xz - z) + \frac{Bk(1-r_1)(1-p)}{\mu + k(1-r_1)} \left(1 - \frac{1}{z}\right) (y - z) \\
f_2(z, w) &= A \left(1 - \frac{1}{y}\right) (z - y) + \frac{Bk(1-r_1)}{\mu + k(1-r_1)} \left(1 - \frac{1}{z}\right) (y - z).
\end{aligned} \tag{2.21}$$

The constants A and B can be chosen in the form $A = A(p)$ and $B = B(p)$ such that the function f is non-positive for all $x, y, z, w \in \mathbb{R}_{\geq 0}$ so that the time derivative of $U(S, E, I)$ is less than zero. In order to cancel the coefficients of y and z in the expressions of f_1 and f_2 , respectively, it is possible to choose

$$A = \frac{k(1-r_1)}{\mu p + k(1-r_1)} \quad \text{and} \quad B = \frac{\mu + k(1-r_1)}{\mu p + k(1-r_1)}. \quad (2.22)$$

Substituting (2.22) into (2.21) and rearranging gives

$$\begin{aligned} f_1(x, y, z, w) &= 1 + g(w)z - \frac{1}{x} + \frac{k(1-r_1)(1-p)}{p\mu + k(1-r_1)} \left(2 - g(w)\frac{xz}{y} - z - \frac{y}{z} \right) + \\ &\quad \frac{p[\mu + k(1-r_1)]}{p\mu + k(1-r_1)} (1 - z - g(w)x), \\ f_2(y, z) &= \frac{k(1-r_1)}{p\mu + k(1-r_1)} \left(2 - \frac{y}{z} - \frac{z}{y} \right). \end{aligned} \quad (2.23)$$

From the second equation of (2.23), using the arithmetic-geometric means inequality, it clearly appears that the function f_2 is less or equal to zero with equality at $y = z$. On the other hand, differentiating the function f_1 with respect to p yields

$$\frac{\partial f_1}{\partial p}(x, y, z, w) = -\frac{k(1-r_1)[\mu + k(1-r_1)]}{[\mu p + k(1-r_1)]^2} \left(1 + g(w)x - g(w)\frac{xz}{y} - \frac{y}{z} \right).$$

If x, y, z, w are fixed, then $\frac{\partial f_1}{\partial p}$ has a constant sign for $p \in [0, 1]$. Thus, f_1 is maximised at $p = 0$ or at $p = 1$. Suppose that $p = 1$, then, filling it into the first equation of (2.23) yields

$$f_1(x, y, z, w) = 2 + (z - x)g(w) - z - \frac{1}{x}.$$

Using (2.4), one has $g(w) \leq 1$. Then, if $x \leq z$, the above equation becomes

$$f_1(x, w, z, w) \leq 2 - x - \frac{1}{x}, \quad (2.24)$$

which is less than or equal by the arithmetic-geometric mean inequality, with equality if and only if $x = 1$. Similarly, if $p = 0$, then the function $f_1(x, y, z, w)$ becomes

$$f_1(x, y, z, w) = 3 + g(w)z \left(1 - \frac{x}{y} \right) - z - \frac{1}{x} - \frac{y}{z}$$

Using (2.4) yields $g(w) \leq 1$. Then, if $x \leq y$, it follows that

$$f_1(x, y, z, w) \leq 3 - \frac{xz}{y} - \frac{1}{x} - \frac{y}{z}, \quad (2.25)$$

which is also less than or equal to zero by arithmetic-geometric mean inequality, with equality if and only if $x = 1$ and $y = z$. Thus, $\dot{U}(S, E, I)$ is less or equal to zero with equality only if $S = S^*$ and $y = z$. LaSalle's extension [39, 40, 41] implies that solutions of (2.5) which intersect the interior of \mathfrak{D} limit to an invariant set contained in $\Omega = \{(S, E, I) \in R_{\geq 0}^3, S = S^*, E/E^* = I/I^*\}$. Then, it follows that the only invariant set contained in Ω is the set consisting of the endemic equilibrium point P^* . Therefore, all solutions of system (2.5) which intersect the interior of $\mathfrak{D} \setminus \{E = I = 0\}$ limit to P^* . Then, it could be concluded that the endemic equilibrium P^* is globally asymptotically stable on $\mathfrak{D} \setminus \{E = I = 0\}$ for all non-negative initial conditions if inequalities (2.14) are satisfied. This ends the proof. \square

Remark 2. It is possible for inequalities (2.14) to fail, in which case, the global stability of the endemic equilibrium of model (2.5) has not been established. The local stability result and numerical simulations, however, seem to support the idea that the endemic equilibrium of model (2.5) is still global asymptotically stable even in these cases.

2.3 Analysis of models with differential infectivity

In this section, the focus is on differential infectivity and it is assumed that the contact rate β is constant (see Fig 2.3). The system of non-linear ordinary differential equations governing the evolution process reads:

$$\begin{cases} \dot{S} &= \Lambda - \beta S(I + \delta L) - \mu S, \\ \dot{E} &= \beta(1 - p)S(I + \delta L) + r_2 I - [\mu + k(1 - r_1)]E, \\ \dot{I} &= \beta p S(I + \delta L) + k(1 - r_1)E + \gamma L - [\mu + d_1 + \phi(1 - r_2) + r_2]I, \\ \dot{L} &= \phi(1 - r_2)I - (\mu + d_2 + \gamma)L. \end{cases} \quad (2.26)$$

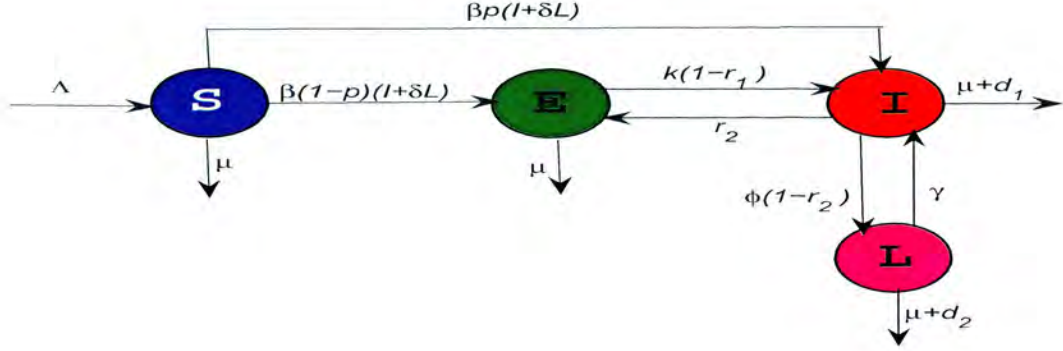
The basic reproduction ratio of this epidemiological system will be computed analytically. Furthermore, conditions for the existence and uniqueness of non-trivial equilibria and threshold conditions for asymptotical stability will be investigated.

2.3.1 Positive invariance of the nonnegative orthant

Without loss of generality, it is assumed that the dynamic of system (1) without infection is asymptotically stable. In other words, for the system

$$\dot{S} = \Lambda - \mu S,$$

Figure 2.3: Model of tuberculosis with differential infectivity.



there exists a unique constant $S^* > 0$ such that

$$\Lambda = \mu S^*, \quad \Lambda - \mu S > 0 \quad \text{for } 0 \leq S < S^*, \quad \text{and} \quad \Lambda - \mu S < 0 \quad \text{for } S > S^*. \quad (2.27)$$

The following result is established:

Proposition 2.3.1. *The non-negative orthant \mathbb{R}_+^4 is positively invariant for the system (2.26).*

Proof. The positive invariance of the nonnegative orthant by (2.26) is immediate with the assumption on the model. This system can be rewritten in the following form:

$$\begin{cases} \dot{x} = \varphi(x) - x \langle \beta_1 \mid y \rangle, \\ \dot{y} = (x B \beta_1^T + A) y, \end{cases} \quad (2.28)$$

where $\langle \cdot \mid \cdot \rangle$ is the usual scalar product in \mathbb{R}_+^3 ,

$$x = S, \quad y = \begin{pmatrix} y_1 \\ y_2 \\ y_3 \end{pmatrix} = \begin{pmatrix} E \\ I \\ L \end{pmatrix}, \quad \beta_1 = (0 \ \beta, \ \delta \beta)^T, \quad B = \begin{pmatrix} 1-p \\ p \\ 0 \end{pmatrix}, \quad \varphi(x) = \Lambda - \mu x,$$

and the matrix A is given by

$$A = \begin{pmatrix} -(k(1-r_1) + \mu) & r_2 & 0 \\ k(1-r_1) & -(\mu + d_1 + \phi(1-r_2) + r_2) & \gamma \\ 0 & \phi(1-r_2) & -(\mu + d_2 + \gamma) \end{pmatrix}.$$

Note that $(x B \beta_1^T + A)$ is a Metzler matrix if $x \geq 0$ (A Metzler matrix is a matrix with off-diagonal entries non-negative [14, 15, 16]). With the hypothesis (2.27), $\varphi(0) > 0$ and the half line \mathbb{R}_+ is positively invariant by $\dot{x} = \varphi(x) - x \langle \beta_1 \mid y \rangle$. Since it is well known that a linear Metzler system lets invariant the nonnegative orthant, this proves the positive invariance of the nonnegative orthant \mathbb{R}_+^3 for the system (2.26). This achieves the proof. \square

2.3.2 Boundedness and dissipativity of the trajectories

From the model (2.26), if the total population is denoted by $N(t)$, then

$$N(t) = S(t) + E(t) + I(t) + L(t)$$

and

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

Thus, this yields

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

It follows that $\lim_{t \rightarrow +\infty} N(t) = \frac{\Lambda}{\mu} = x^*$.

It is straightforward to prove that for $\varepsilon \geq 0$ the simplex:

$$\Omega_\varepsilon = \left\{ (S, E, I, L) \in \mathbb{R}_+^4, \quad N(t) \leq \frac{\Lambda}{\mu} + \varepsilon \right\}, \quad (2.29)$$

is a compact forward invariant set for the system (2.26) and that for $\varepsilon > 0$, this set is absorbing. Thus the study is limited to this simplex for $\varepsilon > 0$.

2.3.3 Basic reproduction ratio

The system (2.26) has an evident equilibrium $DFE = (S^*, 0, 0, 0)$ with $S^* = \Lambda/\mu$ when there is no disease. This equilibrium point is the disease free equilibrium (DFE).

The basic reproduction ratio, \mathfrak{R}_0 is calculated using the next generation approach, developed in Van den Driessche and Watmough [46]. The basic reproduction number is defined as the dominant eigenvalue of the next generation matrix. In order to find the basic reproduction number, it is important to distinguish new infections from all other class transitions in the population. The infected classes are I , L and E . Following Van den Driessche and Watmough [46], system (2.26) could be written as

$$\dot{x} = f(x) = \mathcal{F}(x) - \mathcal{V}(x) = \mathcal{F}(x) - (\mathcal{V}^-(x) - \mathcal{V}^+(x)), \quad (2.30)$$

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

$$\mathcal{F}(x) = (\beta(1-p)(I + \delta L)S, \beta p(I + \delta L)S, 0, 0)^T,$$

and

$$\mathcal{V}(x) = \begin{pmatrix} A_1 E - r_2 I \\ A_2 I - k(1-r_1)E - \gamma L \\ A_3 L - \phi(1-r_2)I \\ 0 \end{pmatrix}.$$

The jacobian matrices of \mathcal{F} and \mathcal{V} at the disease-free equilibrium $DFE = (0, 0, 0, \Lambda/\mu)$ can be partitioned as

$$D\mathcal{F}(DFE) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, \quad D\mathcal{V}(DFE) = \begin{bmatrix} V & 0 \\ J_1 & J_2 \end{bmatrix},$$

where F and V correspond to the derivatives of \mathcal{F} and \mathcal{V} with respect to the infected classes:

$$F = \begin{bmatrix} 0 & \beta(1-p)S^* & \beta(1-p)\delta S^* \\ 0 & \beta p S^* & \beta p \delta S^* \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} A_1 & -r_2 & 0 \\ -k(1-r_1) & A_2 & -\gamma \\ -\phi(1-r_2) & A_3 & 0 \end{bmatrix}.$$

The basic reproduction number is defined, following Van den Driessche and Watmough [46], as the spectral radius of the next generation matrix, FV^{-1} :

$$\mathfrak{R}_0 = \frac{\beta S^* [p\mu - k(1-r_1)] [\mu + r_2 + \gamma + \delta\phi(1-r_2)]}{[\mu + k(1-r_1)] [(\mu + d_1)(\mu + d_2 + \gamma) + \phi(1-r_2)(\mu + d_2) + r_2\mu(\mu + d + \gamma)]}. \quad (2.31)$$

2.3.4 Global stability of the disease-free equilibrium

The following result about the global stability of the disease-free equilibrium is obtained:

Theorem 2.3.2. *When $\mathfrak{R}_0 \leq 1$, then the DFE is globally asymptotically stable in Ω_ϵ ; this implies the global asymptotic stability of the DFE on the nonnegative orthant \mathbb{R}_+^4 . This means that the disease naturally dies out.*

Proof. Let us consider the following LaSalle-Lyapunov candidate function:

$$V_{DFE}(t) = AE + BI + CL, \quad (2.32)$$

where A , B and C are positive constants to be determined later. Its time derivative along the trajectories of (1) satisfies

$$\begin{aligned}
\dot{V}_{DFE}(t) &= A\dot{E} + B\dot{I} + C\dot{L}, \\
&= A[\beta(1-p)S(I + \delta L) + r_2I - [\mu + k(1-r_1)]E], \\
&+ B[\beta pS(I + \delta L) + k(1-r_1)E + \gamma L - [\mu + d_1 + \phi(1-r_2) + r_2]I] \\
&+ C[\phi(1-r_2)I - (\mu + d_2 + \gamma)L], \\
&= [-A[\mu + k(1-r_1)] + Bk(1-r_1)]E \\
&+ [A\beta(1-p)S + Ar_2 + B\beta pS - B[\mu + d_1 + \phi(1-r_2) + r_2]] \\
&+ [A\beta(1-p)\delta S + B\beta p\delta S + B\gamma - C(\mu + d_2 + \gamma)]L + C\phi(1-r_2)I.
\end{aligned} \tag{2.33}$$

The constants A , B and C are chosen such that the coefficients of E and L are equal to zero. Thus, it could tediously be proven that

$$A = k(1-r_1), \quad B = \mu + k(1-r_1) \tag{2.34}$$

and

$$C = \frac{\beta\delta S^*[p\mu + k(1-r_1)] + \gamma[\mu + k(1-r_1)]}{\mu + d_2 + \gamma}. \tag{2.35}$$

Since $S \leq S^*$, substituting the positive constants A , B and C given in (2.34) and (2.35) yields

$$\dot{V}_{DFE}(t) \leq \frac{1}{D(\mu + d_2 + \gamma)}(R_0 - 1)I, \tag{2.36}$$

where

$$D = [\mu + k(1-r_1)][(\mu + d_1)(\mu + d_2 + \gamma) + \phi(1-r_2)(\mu + d_2)] + r_2\mu(\mu + d_2 + \gamma).$$

So, $\dot{V}_{DFE}(t) \leq 0$ when $\mathfrak{R}_0 \leq 1$. By LaSalle's invariance principle, the largest invariant set in Ω_ε , contained in $\{(S, E, I, L) \in \mathbb{R}_+^4 \mid \dot{V}_{DFE}(t) = 0\}$ is reduced to the DFE. This proves the global asymptotic stability on Ω_ε ([32, Theorem 3.7.11, page 346]). Since Ω_ε is absorbing, this proves the global asymptotic stability on the non-negative orthant when $\mathfrak{R}_0 \leq 1$. The need to consider a positively invariant compact set to establish the stability of the DFE is emphasized since the function $V_{DFE}(t)$ is not positive definite. Generally, the LaSalle's invariance principle only proves the attractivity of the equilibrium; considering Ω_ε permit to conclude for the stability [30-32]. This fact is often overlooked in the literature using LaSalle's invariance principle. This concludes the proof. □

2.3.5 Existence and uniqueness of the endemic equilibrium

A result concerning the existence and uniqueness of endemic equilibrium for the model formulated above is presented herein. This will be achieved by using the basic reproduction ratio \mathfrak{R}_0 .

Let $EE = (S^*, E^*, I^*, L^*)$ be the positive endemic equilibrium of model (2.26). Then, the positive endemic equilibrium (steady state with $I, L > 0$) can be obtained by setting the right hand side of equations in the model (2.26) equal to zero, giving

$$\begin{cases} \Lambda - \beta S^*(I^* + \delta L^*) - \mu S^* = 0, \\ \beta(1-p)S^*(I^* + \delta L^*) + r_2 I^* - A_1 E^* = 0, \\ \beta p S^*(I^* + \delta L^*) + k(1-r_1)E^* + \gamma L^* - A_2 I^* = 0, \\ \phi(1-r_2)I^* - A_3 L^* = 0, \end{cases} \quad (2.37)$$

where

$$A_1 = \mu + k(1-r_1), \quad A_2 = \mu + d_1 + \phi(1-r_2) + r_2 \quad \text{and} \quad A_3 = \mu + d_2 + \gamma.$$

Using the first, second and fourth equations of (2.37),

$$S^* = \frac{\Lambda A_3}{\mu A_3 + \beta[A_3 + \delta\phi(1-r_2)]I^*},$$

$$E^* = \frac{I^*}{A_1} \left[\frac{\beta p \Lambda [A_3 + \phi(1-r_2)]}{\mu A_3 + \beta[A_3\mu + \beta[A_3 + \delta\phi(1-r_2)]]I^*} + r_2 \right],$$

and

$$L^* = \frac{\phi(1-r_2)I^*}{A_3}$$

are obtained.

Now, substituting the above expressions of S^* , E^* and L^* in the third equation of (2.37), the following equation of second degree is obtained:

$$I^*(-aI^* + b) = 0,$$

with

$$a = \beta[D[\mu + d_2 + \gamma + \varepsilon\phi(1-r_2)] + k(1-r_1)r_2(\mu + d_2 + \gamma)],$$

$$b = \frac{\mu + d_2 + \gamma}{\mu D}(R_0 - 1),$$

where D is defined as in (2.36). Then, it can be observed that the above equation has two solutions: $I^* = 0$ which corresponds to the disease free-equilibrium and $I^* = \frac{b}{a}$.

Thus, if $\mathfrak{R}_0 > 1$, $b > 0$ and $I^* = \frac{b}{a} > 0$. Thus, the endemic equilibrium is defined by

$$\begin{aligned} S^* &= \frac{\Lambda A_3 a}{\mu A_3 a + \beta[A_3 + \varepsilon\phi(1 - r_2)]b}, \\ E^* &= \frac{a}{bA_1} \left[\frac{\beta p \Lambda[A_3 + \phi(1 - r_2)]a}{\mu A_3 a + \beta[A_3\mu + \beta[A_3 + \delta\phi(1 - r_2)]]b} + r_2 \right], \\ I^* &= \frac{b}{a} \quad \text{and} \quad L^* = \frac{\phi(1 - r_2)b}{aA_3}, \end{aligned} \quad (2.38)$$

Thus, the following result is established:

Lemma 2.3.3. *When $\mathfrak{R}_0 > 1$, there exists a unique endemic equilibrium point $EE = (S^*, E^*, I^*, L^*)$ for the system (2.26) where S^* , E^* , I^* and L^* are defined as in (2.38) which is in the non-negative orthant \mathbb{R}_+^4 .*

2.3.6 Global stability of the endemic equilibrium

Theorem 2.3.4. : *When $\mathfrak{R}_0 > 1$, the endemic equilibrium $EE = (S^*, E^*, I^*, L^*)$ is globally asymptotically stable in Ω_ε implying the global asymptotic stability in the non-negative orthant. This implies that the disease is uncontrollable.*

Proof. If we consider the system (2.26) when $\mathfrak{R}_0 > 1$, there exists a unique endemic equilibrium (S^*, E^*, I^*, L^*) given as in (2.38). In order to establish the condition for global asymptotic stability of this endemic equilibrium, the following Lyapunov function candidate is considered:

$$V_{EE}(t) = (S - S^* \ln S) + a_1(E - E^* \ln E) + a_2(I - I^* \ln I) + a_3(L - L^* \ln L), \quad (2.39)$$

where a_1 , a_2 and a_3 are positive constants to be determined. Differentiating this function with respect to time yields

$$\begin{aligned} \dot{V}_{EE}(t) &= \left(1 - \frac{S^*}{S}\right) \dot{S} + a_1 \left(1 - \frac{E^*}{E}\right) \dot{E} + a_2 \left(1 - \frac{I^*}{I}\right) \dot{I} + a_3 \left(1 - \frac{L^*}{L}\right) \dot{L}, \\ &= \left(1 - \frac{S^*}{S}\right) [\Lambda - \mu S - \beta S(I + \delta L)] \\ &\quad + a_1 \left(1 - \frac{E^*}{E}\right) [\beta(1 - p)S(I + \delta L) + r_2 I - A_1 E] \\ &\quad + a_2 \left(1 - \frac{I^*}{I}\right) [\beta p S(I + \delta L) + k(1 - r_1)E + \gamma L - A_2 I] \\ &\quad + a_3 \left(1 - \frac{L^*}{L}\right) [\phi(1 - r_2)I - A_3 L]. \end{aligned} \quad (2.40)$$

By considering equation (2.37),

$$\begin{aligned}
 \Lambda &= \mu S^* + \beta S^*(I^* + \delta L), \\
 A_1 E^* &= r_2 I^* + \beta(1-p)S^*(I^* + \delta L^*), \\
 A_2 I^* &= \gamma L^* + k(1-r_1)E^* + \beta p S^*(I^* + \delta L^*), \\
 A_3 L^* &= \phi(1-r_2)I^*
 \end{aligned} \tag{2.41}$$

is obtained. With this in mind,

$$\begin{aligned}
 \dot{V}_{EE}(t) &= \left(1 - \frac{S^*}{S}\right) [\mu S^* + \beta S^*(I^* + \delta L^*) - \mu S - \beta S(I + \delta L)] \\
 &+ a_1 \left(1 - \frac{E^*}{E}\right) [\beta(1-p)S(I + \delta L) + r_2 I] - a_1 A_1 E + a_1 r_2 I^* \\
 &+ a_2 \left(1 - \frac{I^*}{I}\right) [\beta p S(I + \delta L) + k(1-r_1)E + \gamma L] - a_2 A_2 I + a_2 \gamma L^* \\
 &+ a_2 \beta p S^*(I^* + \delta L^*) + a_3 \left(1 - \frac{L^*}{L}\right) \phi(1-r_2)I - a_3 A_3 L + a_3 \phi(1-r_2)I^* \\
 &+ a_1 \beta(1-p)S^*(I^* + \delta L^*) + a_2 k(1-r_1)E^*.
 \end{aligned} \tag{2.42}$$

It follows that

$$\begin{aligned}
 \dot{V}_{EE}(t) &= -\mu \frac{(S - S^*)^2}{S} + \beta S^* I^* \left(1 - \frac{S^*}{S}\right) + \beta \delta S^* L^* \left(1 - \frac{S^*}{S}\right) \\
 &+ \beta \delta [a_1(1-p) + a_2 p - 1] S L + [a_1 r_2 + a_3 \phi(1-r_2) - a_2 A_2 + \beta S^*] I \\
 &+ [-a_3 A_3 + a_2 \gamma + \beta \delta S^*] L + [-a_1 A_1 + a_2 k(1-r_1)] E \\
 &+ \beta [a_1(1-p) + a_2 p - 1] S I + a_2 k(1-r_1) E^* \left(1 - \frac{E}{E^*} \frac{I^*}{I}\right) \\
 &+ a_3 \phi(1-r_2) I^* \left(1 - \frac{I}{I^*} \frac{L^*}{L}\right) + a_2 \gamma L^* \left(1 - \frac{L}{L^*} \frac{I^*}{I}\right) + a_1 r_2 I^* \left(1 - \frac{E^*}{E} \frac{I}{I^*}\right) \\
 &- a_1 \beta(1-p) S^* \frac{E^*}{E} \frac{S}{S^*} \left(I^* \frac{I}{I^*} + \delta L^* \frac{L}{L^*}\right) - a_2 \beta p S^* \frac{I^*}{I} \frac{S}{S^*} \left(I^* \frac{I}{I^*} + \delta L^* \frac{L}{L^*}\right) \\
 &+ a_1 \beta(1-p) S^*(I^* + \delta L^*) + a_2 \beta p S^*(I^* + \delta L^*).
 \end{aligned} \tag{2.43}$$

Now, let $(x, y, z, w) = \left(\frac{S^*}{S}, \frac{E^*}{E}, \frac{I^*}{I}, \frac{L^*}{L}\right)$, then

$$\begin{aligned}
\dot{V}_{EE}(t) = & -\mu \frac{(S - S^*)^2}{S} + \beta S^* I^* (1 - x) + a_1 \beta (1 - p) S^* (I^* + \delta L^*) + \beta \delta S^* L^* (1 - x) \\
& + \beta S^* [a_1 (1 - p) + a_2 p] (I^* + \delta L^*) + [-a_1 A_1 + a_2 k (1 - r_1)] E \\
& + [a_1 r_2 + a_3 \phi (1 - r_2) - a_2 A_2 + \beta S^*] I + \beta [-1 + a_1 (1 - p) + a_2 p] S I \\
& + \beta \delta [-1 + a_1 (1 - p) + a_2 p] S L + a_1 r_2 I^* \left(1 - \frac{y}{z}\right) + a_2 \phi (1 - r_2) \left(1 - \frac{w}{z}\right) \\
& + a_2 k (1 - r_1) E^* \left(1 - \frac{z}{y}\right) - a_1 \beta (1 - p) S^* \frac{y}{x} \left(I^* \frac{1}{z} + \delta L^* \frac{1}{w}\right) \\
& - a_2 \beta p S^* \frac{z}{x} \left(I^* \frac{1}{z} + \delta L^* \frac{1}{w}\right) + a_2 \gamma L^* \left(1 - \frac{z}{w}\right) + [-a_3 A_3 + a_2 \gamma + \beta \delta S^*] L.
\end{aligned} \tag{2.44}$$

The positive constants a_1 , a_2 and a_3 are chosen such that the coefficients of SI , SL , E , I and L are equal to zero, that is,

$$\begin{cases} -1 + a_1(1 - p) + a_2 p = 0, \\ -a_1 A_1 + a_2 k(1 - r_1) = 0, \\ -a_3 A_3 + a_2 \gamma + \beta \delta S^* = 0, \\ a_1 r_2 + a_3 \phi(1 - r_2) - a_2 A_2 + \beta S^* = 0. \end{cases} \tag{2.45}$$

Using (2.37), it can be easily shown that the fourth equation of (2.45) is satisfied provided the first and third equations of (2.45) are satisfied. Therefore, only the following equations are considered:

$$\begin{cases} a_1(1 - p) + a_2 p = 1, \\ a_1 A_1 = a_2 k(1 - r_1), \\ -a_3 A_3 + a_2 \gamma + \beta \delta S^* = 0. \end{cases} \tag{2.46}$$

Solving the above equations yields

$$a_1 = \frac{k(1 - r_1)}{(1 - p)k(1 - r_1) + pA_1}, \quad a_2 = \frac{A_1}{(1 - p)k(1 - r_1) + pA_1} \quad \text{and} \quad a_3 = \frac{\beta \delta S^* + a_2 \gamma}{A_3}. \tag{2.47}$$

Replacing the above expressions of a_1 , a_2 and a_3 in (2.44) implies

$$\begin{aligned}
\dot{V}_{EE}(t) = & -\mu \frac{(S - S^*)^2}{S} + \beta S^* I^* (2 - x) + \beta \delta S^* L^* (2 - x) - a_1 \beta (1 - p) S^* I^* \frac{y}{xz} \\
& - a_1 \beta (1 - p) \delta S^* L^* \frac{y}{xw} - a_2 \beta p S^* I^* \frac{1}{x} - a_2 \beta p \delta S^* L^* \frac{z}{xw} \\
& + a_1 r_2 I^* \left(1 - \frac{y}{z}\right) + a_3 \phi (1 - r_2) I^* \left(1 - \frac{w}{z}\right) + a_2 k (1 - r_1) E^* \left(1 - \frac{z}{y}\right) \\
& + a_2 \gamma L^* \left(1 - \frac{z}{w}\right).
\end{aligned} \tag{2.48}$$

Recalling that $a_1(1 - p) + a_2 p = 1$, the above equation becomes

$$\begin{aligned}
\dot{V}_{EE}(t) = & -\mu \frac{(S - S^*)^2}{S} + [a_1(1 - p) + a_2 p] \beta S^* I^* (2 - x) \\
& + [a_1(1 - p) + a_2 p] \beta \delta S^* L^* (2 - x) - a_1 \beta (1 - p) S^* I^* \frac{y}{xz} \\
& - a_1 \beta (1 - p) \delta S^* L^* \frac{y}{xw} - a_2 \beta p S^* I^* \frac{1}{x} - a_2 \beta p \delta S^* L^* \frac{z}{xw} \\
& + a_1 r_2 I^* \left(1 - \frac{y}{z}\right) + a_3 \phi (1 - r_2) I^* \left(1 - \frac{w}{z}\right) + a_2 k (1 - r_1) E^* \left(1 - \frac{z}{y}\right) \\
& + a_2 \gamma L^* \left(1 - \frac{z}{w}\right), \\
= & -\mu \frac{(S - S^*)^2}{S} + a_1 \beta (1 - p) S^* I^* \left(2 - x - \frac{y}{xz}\right) + a_2 \beta p S^* I^* \left(2 - x - \frac{1}{x}\right) \\
& + a_1 \beta (1 - p) \delta S^* L^* \left(2 - x - \frac{y}{xw}\right) + a_2 \beta p \delta S^* L^* \left(2 - x - \frac{z}{xy}\right) \\
& + a_1 r_2 I^* \left(1 - \frac{y}{z}\right) + a_2 k (1 - r_1) E^* \left(2 - \frac{z}{y}\right) \\
& + a_3 \phi (1 - r_2) I^* \left(1 - \frac{w}{z}\right) + a_2 \gamma L^* \left(1 - \frac{z}{w}\right).
\end{aligned} \tag{2.49}$$

Multiplying the second equation of (2.46) by E^* and the second equation of (2.41) by a_1

gives

$$\begin{cases} a_1 A_1 E^* = a_2 k(1 - r_1) E^*, \\ a_1 A_1 E^* = a_1 r_2 I^* + a_1 \beta(1 - p) S^* (I^* + \delta L^*). \end{cases}$$

Hence, it clearly appears that

$$-a_1 \beta(1 - p) S^* (I^* + \delta L^*) - a_1 r_2 I^* + a_2 k(1 - r_1) E^* = 0.$$

Multiplying the above equation by $F_1(u)$ where $u = (x, y, z, w)^T$ and $F_1(u)$ a function to be determined later, yields

$$-a_1 \beta(1 - p) S^* (I^* + \delta L^*) F_1(u) - a_1 r_2 I^* F_1(u) + a_2 k(1 - r_1) E^* F_1(u) = 0. \quad (2.50)$$

Also, multiplying the third equation of (18) by L^* and the fourth equation of (14) by a_3 yields

$$\begin{cases} a_3 \Lambda_3 L^* = a_2 \gamma L^* + \beta \delta S^* L^*, \\ a_3 \Lambda_3 L^* = a_3 \phi(1 - r_2) I^*. \end{cases}$$

Thus, it can be deduced that

$$-a_3 \phi(1 - r_2) I^* + a_2 \gamma L^* + \beta \delta S^* L^* = 0.$$

Also, multiplying the above equation by $F_2(u)$ where $u = (x, y, z, w)^T$ and $F_2(u)$ a function to be determined later and using $a_1(1 - p) + a_2 p = 1$ gives

$$-a_3 \phi(1 - r_2) I^* F_2(u) + a_2 \gamma L^* F_2(u) + [a_1(1 - p) + a_2 p] \beta \delta S^* L^* F_2(u) = 0. \quad (2.51)$$

Thus, plugging (2.50) and (2.51) into (2.49) yields

$$\begin{aligned} \dot{V}_{EE}(t) &= -\mu \frac{(S - S^*)^2}{S} + a_1 \beta(1 - p) S^* I^* \left(2 - x - \frac{y}{xz} - F_1(u) \right) \\ &+ a_1 \beta(1 - p) \delta S^* L^* \left(2 - x - \frac{y}{xw} - F_1(u) + F_2(u) \right) \\ &+ a_2 \beta p S^* I^* \left(2 - x - \frac{1}{x} \right) + a_2 \beta p \delta S^* L^* \left(2 - x - \frac{z}{xw} + F_2(u) \right) \\ &+ a_1 r_2 I^* \left(1 - \frac{y}{z} - F_1(u) \right) + a_2 k(1 - r_1) E^* \left(1 - \frac{z}{y} + F_1(u) \right) \\ &+ a_3 \phi(1 - r_2) I^* \left(1 - \frac{w}{z} - F_2(u) \right) + a_2 \gamma L^* \left(1 - \frac{z}{w} + F_2(u) \right). \end{aligned} \quad (2.52)$$

Next, the functions $F_1(u)$ and $F_2(u)$ are chosen such that the coefficients of E^* and L^* are equal to zero. In this case,

$$F_1(u) = \frac{z}{y} - 1 \quad \text{and} \quad F_2(u) = 1 - \frac{w}{z}. \quad (2.53)$$

It follows that

$$\begin{aligned}
\dot{V}_{EE}(t) = & -\mu \frac{(S - S^*)^2}{S} + a_1 \beta (1 - p) S^* I^* \left(3 - x - \frac{y}{xz} - \frac{z}{y} \right) \\
& + a_1 \beta (1 - p) \delta S^* L^* \left(4 - x - \frac{y}{xw} - \frac{z}{y} - \frac{w}{z} \right) \\
& + a_2 \gamma L^* \left(2 - \frac{z}{w} - \frac{w}{z} \right) + a_2 \beta p S^* I^* \left(2 - x - \frac{1}{x} \right) \\
& + a_1 r_2 I^* \left(2 - \frac{y}{z} - \frac{z}{y} \right) + a_2 \beta p \delta S^* L^* \left(3 - x - \frac{z}{xw} - \frac{w}{z} \right).
\end{aligned} \tag{2.54}$$

Using the arithmetic-geometric means inequality, it can be observed that $\dot{V}_{EE}(t)$ is less or equal to zero with equality only if $S = S^*$ and $y = z = w$. By LaSalle's invariance principle, it can be concluded that the endemic equilibrium is globally asymptotically stable in Ω_ε . Since Ω_ε is absorbing, this proves the global asymptotic stability in the non-negative orthant. This concludes the proof. \square

Chapter 3

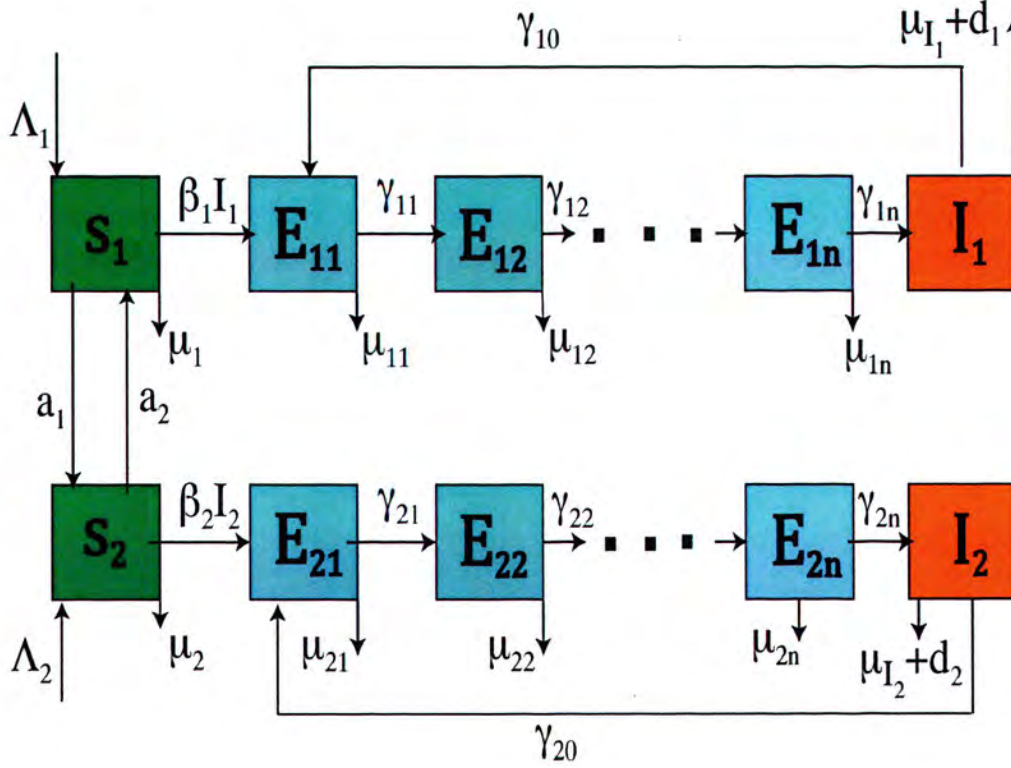
Models with staged progression and migration

3.1 Model formulation

A model for tuberculosis dynamics in two sub-populations is considered in this chapter. The disease in each population is described by $SE_1 \cdots E_n IS$ compartmental models, with staged progression to the disease. There is one class of susceptible individuals (S_i), n classes of latently infected individuals (E_i) and one class of infectious individuals (I_i), with $i = 1, 2$. The subscript i stands for population i . It is assumed that the transmission does not occur during migration. The recruitment in each population is only in the susceptible class and occurs at a constant rate Λ_i ; only the susceptible individuals are concerned by migrations at rate a_i between the two populations. The infectious individuals do not migrate from one population to another, for medical reasons. The force of mortality is a constant μ_i , $i = 1, 2$, for susceptible classes, μ_{ij} , $i = 1, 2$, $j = 1, 2, \dots, n$, for latently infected classes and μ_{I_i} , $i = 1, 2$, for infectious classes the additional death rate due to disease affects only the class I_i and has a constant rate d_i , $i = 1, 2$. It is assumed that there is no chemoprophylaxis for latently infected individuals. The initiation of therapeutics immediately removes individuals from the class of active status I_i and places them into the susceptible class S_i at rate γ_{i0} . As TB confers temporary immunity, the recovered individual returns to the susceptible class after an immune period.

The new infections occur after adequate contact between the susceptible and infectious individuals. Here, latently-infected individuals are not infectious. The rate at which the susceptible are infected is $\beta_i I_i S_i$. This could model for instance dynamics in crowded areas. The transfer diagramme of the model is captured in Fig 3.1: This yields the

Figure 3.1: Model of tuberculosis with migration and staged progression



following set of differential equations:

$$\left\{ \begin{array}{l} \dot{S}_1 = \Lambda_1 - (\mu_1 + a_1) S_1 - \beta_1 I_1 S_1 + a_2 S_2 + \gamma_{10} I_1, \\ \dot{E}_{11} = \beta_1 I_1 S_1 - (\mu_{11} + \gamma_{11}) E_{11}, \\ \dot{E}_{12} = \gamma_{11} E_{11} - (\mu_{12} + \gamma_{12}) E_{12}, \\ \vdots \\ \dot{E}_{1n} = \gamma_{1,n-1} E_{1,n-1} - (\mu_{1n} + \gamma_{1n}) E_{1n}, \\ \dot{I}_1 = \gamma_{1n} E_{1n} - (\mu_{I_1} + d_1 + \gamma_{10}) I_1, \\ \dot{S}_2 = \Lambda_2 - (\mu_2 + a_2) S_2 - \beta_2 I_2 S_2 + a_1 S_1 + \gamma_{20} I_2, \\ \dot{E}_{21} = \beta_2 I_2 S_2 - (\mu_{21} + \gamma_{21}) E_{21}, \\ \dot{E}_{22} = \gamma_{21} E_{21} - (\mu_{22} + \gamma_{22}) E_{22}, \\ \vdots \\ \dot{E}_{2n} = \gamma_{2,n-1} E_{2,n-1} - (\mu_{2n} + \gamma_{2n}) E_{2n}, \\ \dot{I}_2 = \gamma_{2n} E_{2n} - (\mu_{I_2} + d_2 + \gamma_{20}) I_2. \end{array} \right. \quad (3.1)$$

System (3.1) can be represented as

$$\begin{cases} \dot{x}_1 &= \phi_1(x) - \beta_1 x_1 \langle e_{n+1}^1 \mid Y_1 \rangle + \gamma_{10} y_{1,n+1} \\ \dot{Y}_1 &= \beta_1 x_1 \langle e_{n+1}^1 \mid Y_1 \rangle e_1^1 + A_1 Y_1 \\ \dot{x}_2 &= \phi_2(x) - \beta_2 x_2 \langle e_{n+1}^1 \mid Y_2 \rangle + \gamma_{20} y_{2,n+1} \\ \dot{Y}_2 &= \beta_2 x_2 \langle e_{n+1}^1 \mid Y_2 \rangle e_1^1 + A_2 Y_2 \end{cases} \quad (3.2)$$

where $\langle \cdot \mid \cdot \rangle$ is the scalar usual product in \mathbb{R}_+^{n+1} , $x = (x_1, x_2)^T$, $Y_1 = (E_{11}, E_{12}, \dots, E_{1n}, I_1)^T = (y_{11}, y_{12}, \dots, y_{1n}, y_{1,n+1})^T$, $Y_2 = (E_{21}, E_{22}, \dots, E_{2n}, I_2)^T = (y_{21}, y_{22}, \dots, y_{2n}, y_{2,n+1})^T$, (e_i^1) is the canonical basis of \mathbb{R}_+^{n+1} , $\phi_1(x) = \varphi_1(x_1) + a_2 x_2$, $\phi_2(x) = \varphi_2(x_2) + a_1 x_1$, $\varphi_1(x_1) = \Lambda_1 - (\mu_1 + a_1)x_1$, $\varphi_2(x_2) = \Lambda_2 - (\mu_2 + a_2)x_2$, the matrices A_1 and A_2 are Metzler stable [15, 37] and given by

$$A_1 = \begin{pmatrix} -\alpha_{11} & 0 & 0 & 0 & 0 \\ \gamma_{11} & -\alpha_{12} & 0 & 0 & 0 \\ 0 & \gamma_{12} & -\alpha_{13} & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & \gamma_{1,n-1} & -\alpha_{1n} & 0 \\ 0 & \cdots & 0 & \gamma_{1n} & -\alpha_{1,n+1} \end{pmatrix}$$

and

$$A_2 = \begin{pmatrix} -\alpha_{21} & 0 & 0 & 0 & 0 \\ \gamma_{21} & -\alpha_{22} & 0 & 0 & 0 \\ 0 & \gamma_{22} & -\alpha_{23} & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & \gamma_{2,n-1} & -\alpha_{2n} & 0 \\ 0 & \cdots & 0 & \gamma_{2n} & -\alpha_{2,n+1} \end{pmatrix}$$

respectively, where $\alpha_{11} = (\mu_{11} + \gamma_{11})$, $\alpha_{12} = (\mu_{12} + \gamma_{12})$, $\alpha_{13} = (\mu_{13} + \gamma_{13})$, \dots , $\alpha_{1n} = (\mu_{1n} + \gamma_{1n})$, $\alpha_{n+1} = (\mu_{I_1} + d_1 + \gamma_{10})$, $\alpha_{21} = (\mu_{21} + \gamma_{21})$, $\alpha_{22} = (\mu_{22} + \gamma_{22})$, $\alpha_{23} = (\mu_{23} + \gamma_{23})$, \dots , $\alpha_{2n} = (\mu_{2n} + \gamma_{2n})$, $\alpha_{2n+1} = (\mu_{I_2} + d_2 + \gamma_{20})$.

3.2 Mathematical properties

3.2.1 Positivity of the solutions

Since the variables considered here are non-negative quantities, it is necessary to ensure that their values are always non-negative.

Theorem 3.2.1. : *The non-negative orthant \mathbb{R}_+^{2n+4} is positively invariant by (3.1). This means that every trajectory which begins in the positive orthant will stay inside.*

Proof. System (3.2) can be written in the following form:

$$\begin{cases} \dot{x}_1 &= \phi_1(x) - \beta_1 x_1 \langle e_{n+1}^1 \mid Y_1 \rangle + \gamma_{10} y_{1,n+1}, \\ \dot{x}_2 &= \phi_2(x) - \beta_2 x_2 \langle e_{n+1}^1 \mid Y_2 \rangle + \gamma_{20} y_{2,n+1}, \\ \dot{Y}_1 &= \left(\beta_1 x_1 (e_{n+1}^1)^T e_1^1 + A_1 \right) Y_1, \\ \dot{Y}_2 &= \left(\beta_2 x_2 (e_{n+1}^1)^T e_1^1 + A_2 \right) Y_2, \end{cases} \quad (3.3)$$

where A_1, A_2 are Metzler matrices. Since $x_i(t) \geq 0$, the matrices $\left(\beta_1 x_1 (e_{n+1}^1)^T e_1^1 + A_1 \right)$ and $\left(\beta_2 x_2 (e_{n+1}^1)^T e_1^1 + A_2 \right)$ are Metzler matrices. It is well known that a linear Metzler system lets the nonnegative orthant invariant [15].

On $x_i = 0$, $\dot{x}_i = \Lambda_i + \gamma_{i,0} y_{i,n+1} > 0$. Then, no trajectory can pass through the set $x_i = 0$. This proves the positive invariance of the non-negative orthant \mathbb{R}_+^{2n+4} by (3.1). \square

3.2.2 Boundedness of the trajectories

From the system (3.1),

$$\dot{N}(t) = S_1(t) + E_{11}(t) + \cdots + E_{1n}(t) + I_1(t) + S_2(t) + E_{21}(t) + \cdots + E_{2n}(t) + I_2(t)$$

and

$$\dot{N}(t) \leq \Lambda_1 + \Lambda_2 - \mu N(t),$$

where $\mu = \min(\mu_{ij})$.

It follows that $\lim_{t \rightarrow +\infty} N(t) \leq \frac{\Lambda_1 + \Lambda_2}{\mu}$. The following lemma is thus obtained.

Lemma 3.2.2. *The simplex*

$$\Gamma_\varepsilon = \left\{ \begin{array}{l} (S_1, E_{11}, \dots, E_{1n}, I_1, S_2, E_{21}, \dots, E_{2n}, I_2) \in \mathbb{R}_+^{2n+4} \mid \\ S_1 + E_{11} + \cdots + E_{1n} + I_1 + S_2 + E_{21} + \cdots + E_{2n} + I_2 \leq \frac{\Lambda_1 + \Lambda_2}{\mu} + \varepsilon \end{array} \right\}, \quad (3.4)$$

is a compact forward invariant set for (3.1) and that for $\varepsilon > 0$ this set is absorbing, and so the study is limited to this simplex for $\varepsilon > 0$.

In the simplex Γ_ε , Eq.(3.1) is mathematically well-posed.

Lemma 3.2.3. : *The simplex*

$$\gamma_\varepsilon = \{(x, y) \in \Gamma_\varepsilon \mid x \leq x^*\}, \quad (3.5)$$

is a compact forward invariant set for Eq.(3.1).

3.2.3 Local Stability of the Disease-Free Equilibrium (DFE)

Many epidemiological models have a threshold condition which can be determined whether an infection will be eliminated from the population or become endemic [30]. The basic reproduction number \mathfrak{R}_0 , is defined as the average number of secondary infections produced by an infected individual in a completely susceptible population [12]. As discussed in [30, 31], \mathfrak{R}_0 is a simply normalised bifurcation (transcritical) parameter for epidemiological models, such that \mathfrak{R}_0 implies that the endemic steady state is stable (i.e., the infection persists), and \mathfrak{R}_0 implies that the uninfected steady state is stable (i.e., the infection can be eliminated from the population).

There is a trivial equilibrium $x^* = (x_1^*, x_2^*)^T$ of Eq.(3.2), which is the solution of $Dx + \Lambda = 0$. Eq.(3.1) has a Disease-Free Equilibrium given by $(S_1^*, 0, \dots, 0, S_2^*, 0, \dots, 0)$, which always exists in the non-negative orthant \mathbb{R}_+^{2n+4} . The explicit expressions of S_1^* and S_2^* are

$$S_1^* = \frac{(\mu_{21} + a_2)\Lambda_1 + a_2 \Lambda_2}{\mu_{11}\mu_{21} + \mu_{11}a_2 + \mu_{21}a_1} \quad S_2^* = \frac{(\mu_{11} + a_1)\Lambda_2 + a_1 \Lambda_1}{\mu_{11}\mu_{21} + \mu_{11}a_2 + \mu_{21}a_1}.$$

Lemma 3.2.4. : *Using the same method as in [46], the basic reproduction ratio of (3.1) is $\mathfrak{R}_0 = \max_{i=1,2}(\mathfrak{R}_0^i)$, where \mathfrak{R}_0^i is the basic reproduction of population i .*

Proof. Let us consider a $SE_1 \cdots E_n IS$ model of one population with staged progression as in [32]; it is easy to observe that the basic ratio is

$$\mathfrak{R}_0^i = \beta_i S_i^* \frac{\gamma_{i1} \gamma_{i2} \cdots \gamma_{in}}{\alpha_{i1} \alpha_{i2} \cdots \alpha_{in}} \frac{1}{\alpha_{I_i}}.$$

For the evolution equation (3.1), the basic reproduction ratio of each population is separately given by

$$\mathfrak{R}_0^1 = \beta_1 \frac{\gamma_{11} \gamma_{12} \cdots \gamma_{1n}}{\alpha_{11} \alpha_{12} \cdots \alpha_{1n}} \frac{1}{\alpha_{I_1}} \frac{(\mu_2 + a_2)\Lambda_1 + a_2 \Lambda_2}{\mu_1 \mu_2 + \mu_1 a_2 + \mu_2 a_1} \quad (3.6)$$

and

$$\mathfrak{R}_0^2 = \beta_2 \frac{\gamma_{21} \gamma_{22} \cdots \gamma_{2n}}{\alpha_{21} \alpha_{22} \cdots \alpha_{2n}} \frac{1}{\alpha_{I_2}} \frac{(\mu_1 + a_1)\Lambda_2 + a_1 \Lambda_1}{\mu_1 \mu_2 + \mu_1 a_2 + \mu_2 a_1}. \quad (3.7)$$

In order to use the same method as in [46] for (3.2) to compute the basic reproduction ratio, the expression $\mathcal{F}(x)$ derived from the other compartment due to the contamination

and the expression $\mathcal{V}(x)$ resulting from the other compartments due to any other reason are

$$\mathcal{F}(x) = \begin{pmatrix} \beta_1 I_1 S_1 \\ \gamma_{11} E_{11} \\ \gamma_{12} E_{12} \\ \dots \\ \gamma_{1n} E_{1n} \\ \beta_2 I_2 S_2 \\ \gamma_{21} E_{21} \\ \gamma_{22} E_{22} \\ \dots \\ \gamma_{2n} E_{2n} \\ 0 \\ 0 \end{pmatrix}$$

and

$$\mathcal{V}(x) = \begin{pmatrix} -\alpha_{11} E_{11} \\ -\alpha_{12} E_{12} \\ \dots \\ -\alpha_{1n} E_{1n} \\ -\alpha_{21} E_{21} \\ -\alpha_{22} E_{22} \\ \dots \\ -\alpha_{2n} E_{2n} \\ \Lambda_1 - (\mu_1 + a_1) S_1 - \beta_1 I_1 S_1 + a_2 S_2 + \gamma_{10} I_1 \\ \Lambda_2 - (\mu_2 + a_2) S_2 - \beta_2 I_2 S_2 + a_1 S_1 + \gamma_{20} I_2 \end{pmatrix},$$

with $x = (E_{11}, \dots, E_{1n}, I_1, E_{21}, \dots, E_{2n}, I_2, S_1, S_2)$. Then, the Jacobian matrices at DFE are

$$D\mathcal{F}(x^*) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad D\mathcal{V}(x^*) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix}$$

where

$$F = \begin{pmatrix} 0 & 0 & \cdots & 0 & \beta_1 S_1^* & 0 & 0 & 0 & 0 & 0 \\ \gamma_{11} & 0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 & 0 \\ 0 & \gamma_{12} & 0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & \gamma_{1,n-1} & 0 & 0 & \cdots & 0 & 0 & 0 & 0 \\ 0 & 0 & \cdots & \gamma_{1n} & 0 & 0 & \cdots & 0 & 0 & 0 \\ 0 & \cdots & 0 & 0 & 0 & 0 & 0 & \cdots & 0 & \beta_2 S_2^* \\ 0 & 0 & \cdots & 0 & 0 & \gamma_{21} & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 & 0 & \gamma_{22} & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & 0 & 0 & 0 & 0 & \cdots & \gamma_{2,n-1} & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 & 0 & 0 & \cdots & \gamma_{2n} & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} -\alpha_{11} & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & 0 & 0 \\ 0 & -\alpha_{12} & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & -\alpha_{1,n-1} & 0 & 0 & 0 & \cdots & 0 & 0 & 0 \\ 0 & 0 & \cdots & -\alpha_{1n} & 0 & 0 & \cdots & 0 & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 & -\alpha_{21} & 0 & \cdots & 0 & 0 \\ 0 & 0 & 0 & \cdots & 0 & 0 & -\alpha_{22} & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -\alpha_{2,n-1} & 0 \\ 0 & 0 & \cdots & 0 & 0 & 0 & 0 & \cdots & 0 & -\alpha_{2n} \end{pmatrix},$$

The next generation matrix is $-FV^{-1}$. It can be observed that since \mathfrak{R}_0 is the largest eigenvalue of the next generation matrix,

$$\mathfrak{R}_0 = \max(\mathfrak{R}_0^1, \mathfrak{R}_0^2). \quad (3.8)$$

□

Lemma 3.2.5. : *The disease-free equilibrium of (3.1) is locally asymptotically stable whenever $\mathfrak{R}_0 < 1$, and unstable if $\mathfrak{R}_0 > 1$.*

This lemma shows that if $\mathfrak{R}_0 < 1$, a small flow of infectious individuals will not generate large outbreaks of the disease. To eradicate the disease independently of the initial total number of infectious individuals, a global asymptotic stability property has to be established for the DFE when $\mathfrak{R}_0 < 1$.

3.2.4 Global stability of the disease-free equilibrium(DFE)

The following theorem exists about stability of the DFE when $\mathfrak{R}_0^1 \leq 1$ and $\mathfrak{R}_0^2 \leq 1$.

Theorem 3.2.6. : *When $\mathcal{R}_0 \leq 1$ (this implies $\mathfrak{R}_0^1 \leq 1$ and $\mathfrak{R}_0^2 \leq 1$), then the DFE is globally asymptotically stable in Γ_ϵ . This implies the global asymptotic stability of the DFE on the non-negative orthant \mathbb{R}_+^{2n+4} , i.e., the disease naturally dies out in both two patches.*

Proof. Let us consider the compact form of the system, given by (3.2).

Consider the following Lyapunov candidate function which is similar to those which can be found in [36, 13, 14] :

$$V_{DFE}(t) = \langle e_{n+1}^1 | (-A_1)^{-1} Y_1 \rangle + \langle e_{n+1}^1 | (-A_2)^{-1} Y_2 \rangle \quad (3.9)$$

where $(A_1)^{-1} > 0$ and $(A_2)^{-1} > 0$ since A_1 and A_2 are stable Metzler matrices. This function is non-negative since the matrices $(A_1)^{-1}$ and $(A_2)^{-1}$ are non-singular. Its time derivative along the trajectories of (3.2) gives

$$\begin{aligned} \dot{V}_{DFE}(t) &= \langle e_{n+1}^1 | (-A_1)^{-1} \dot{Y}_1 \rangle + \langle e_{n+1}^1 | (-A_2)^{-1} \dot{Y}_2 \rangle \\ &= \beta_1 x_1 \langle e_{n+1}^1 | (-A_1)^{-1} e_1^1 \rangle \langle e_{n+1}^1 | Y_1 \rangle - \langle e_{n+1}^1 | Y_1 \rangle \\ &+ \beta_2 x_2 \langle e_{n+1}^1 | (-A_2)^{-1} e_1^1 \rangle \langle e_{n+1}^1 | Y_2 \rangle - \langle e_{n+1}^1 | Y_2 \rangle \\ &= \left(\mathfrak{R}_0^1 \frac{x_1}{x_1^*} - 1 \right) \langle e_{n+1}^1 | Y_1 \rangle + \left(\mathfrak{R}_0^2 \frac{x_2}{x_2^*} - 1 \right) \langle e_{n+1}^1 | Y_2 \rangle. \end{aligned}$$

In γ_ϵ , we have $x_i \leq x_i^*$. This derivative can be written as

$$\dot{V}_{DFE}(t) \leq (\mathfrak{R}_0^1 - 1) y_{1,n+1} + (\mathfrak{R}_0^2 - 1) y_{2,n+1} \leq 0.$$

Then, we have $\dot{V}_{DFE}(t) \leq 0$. This proves the global asymptotic stability on Γ_ϵ (see [41], Theorem 3.7.11, page 346). Since Γ_ϵ is absorbing, this proves the global asymptotic stability on the non-negative orthant when $\mathfrak{R}_0^1 \leq 1$ and $\mathfrak{R}_0^2 \leq 1$. This achieves the proof that the DFE is globally asymptotically stable. □

3.2.5 Existence of endemic equilibria

Definition 3.2.7. : *An equilibrium of (3.1) is called boundary equilibrium if exactly one population disappears at this equilibrium.*

Theorem 3.2.8. : *The following results hold about existence of endemic equilibria.*

1. *A unique boundary equilibrium $E_1DF_2 = (\bar{S}_1^*, \bar{E}_{11}^*, \dots, \bar{E}_{1n}^*, \bar{I}_1^*, \bar{S}_2^*, 0, \dots, 0)$ exists in the non-negative orthant when $\mathfrak{R}_0^1 > 1$ and $\mathfrak{R}_0^2 \leq 1$. This means the disease dies out in the second population while it is still endemic in the first population.*
2. *A unique boundary equilibrium $DF_1E_2 = (\bar{S}_1^*, 0, \dots, 0, \bar{S}_2^*, \bar{E}_{21}^*, \dots, \bar{E}_{2n}^*, \bar{I}_2^*)$ exists in the non-negative orthant when $\mathfrak{R}_0^1 \leq 1$ and $\mathfrak{R}_0^2 > 1$. This means the disease is still endemic in the second population while it dies out in the first population.*
3. *A unique endemic equilibrium $(\bar{S}_1, \bar{E}_{11}, \dots, \bar{E}_{1n}, \bar{I}_1, \bar{S}_2, \bar{E}_{21}, \dots, \bar{E}_{2n}, \bar{I}_2)$ exists in the non-negative orthant when $\mathfrak{R}_0^1 > 1$ and $\mathfrak{R}_0^2 > 1$. This means the disease is still endemic in both populations.*

Proof. For the first part of the theorem, let us consider Eq.(3.1) at equilibrium with $y_{1,n+1} \neq 0$ and $y_{2,n+1} = 0$. Then we have

$$\left\{ \begin{array}{l} \Lambda_1 - (\mu_1 + a_1) \bar{S}_1^* + a_2 \bar{S}_2^* + \gamma_{10} \bar{I}_1^* = \beta_1 \bar{I}_1^* \bar{S}_1^*, \\ \beta_1 \bar{I}_1^* \bar{S}_1^* = (\mu_{11} + \gamma_{11}) \bar{E}_{11}^*, \\ \gamma_{11} \bar{E}_{11}^* = (\mu_{12} + \gamma_{12}) \bar{E}_{12}^*, \\ \vdots \\ \gamma_{1,n-1} \bar{E}_{1,n-1}^* = (\mu_{1n} + \gamma_{1n}) \bar{E}_{1n}^*, \\ \gamma_{1n} \bar{E}_{1n}^* = (\mu_{I_1} + d_1 + \gamma_{10}) \bar{I}_1^*, \\ \Lambda_2 - (\mu_2 + a_2) \bar{S}_2^* + a_1 \bar{S}_1^* = 0, \end{array} \right. \quad (3.10)$$

or equivalently

$$\left\{ \begin{array}{l} \phi_1(\bar{x}^b) = \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b - \gamma_{10} \bar{y}_{1,n+1}^b, \\ -A_1 \bar{Y}_1 = \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b e_1^1, \\ \phi_2(\bar{x}^b) = 0. \end{array} \right. \quad (3.11)$$

The second equation of (3.11) yields

$$\bar{Y}_1 = \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b (-A_1)^{-1} e_1^1. \quad (3.12)$$

Then, equation (3.12) implies $\langle e_{n+1}^1 \mid \bar{Y}_1 \rangle = \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b \langle e_{n+1}^1 \mid (-A_1)^{-1} e_1^1 \rangle$. Since $\langle e_{n+1}^1 \mid \bar{Y}_1 \rangle = \bar{y}_{1,n+1}^b$, it follows that

$$\bar{y}_{1,n+1}^b = \beta_1 \bar{x}_1^b \langle e_{n+1}^1 \mid (-A_1)^{-1} e_1^1 \rangle \bar{y}_{1,n+1}^b$$

and since $\bar{y}_{1,n+1}^b \neq 0$, it results in

$$\bar{x}_1^b = \frac{1}{\beta_1 \langle e_{n+1}^1 \mid (-A_1)^{-1} e_1^1 \rangle} = \frac{x_1^*}{\mathfrak{R}_0^1}. \quad (3.13)$$

The third equation of (3.11) gives $\phi_2(\bar{x}^b) = 0$, which is equivalent to $\Lambda_2 - (\mu_2 + a_2) \bar{x}_2^b + a_1 \bar{x}_1^b = 0$. This then results in

$$\bar{x}_2^b = \frac{\Lambda_2}{(\mu_2 + a_2)} + \frac{a_1}{(\mu_2 + a_2)} \bar{x}_1^b. \quad (3.14)$$

The first equation of (3.11) gives

$$\bar{y}_{1,n+1}^b = \frac{\phi_1(\bar{x}^b)}{\beta_1 \bar{x}_1^b - \gamma_{10}} = \frac{\varphi_1(\bar{x}_1^b) + a_2 \bar{x}_2^b}{\beta_1 \bar{x}_1^b - \gamma_{10}}. \quad (3.15)$$

It can then be deduced from (3.12), (3.13) and (3.15) that

$$\bar{Y}_1 = \beta_1 \frac{x_1^*}{\mathfrak{R}_0^1} \frac{\varphi_1(\bar{x}_1^b) + a_2 \bar{x}_2^b}{\beta_1 \bar{x}_1^b - \gamma_{10}} (-A_1)^{-1} e_1^1. \quad (3.16)$$

When $\mathfrak{R}_0^1 > 1$, it results from equation (3.13) that $\bar{x}_1^b < x_1^*$, and then $\varphi_1(\bar{x}_1^b) > 0$, since the function φ_1 models the dynamics of the first population when there is no disease. The condition $\mathfrak{R}_0^1 > 1$ is equivalent to

$$\beta_1 \frac{\gamma_{11} \gamma_{12} \cdots \gamma_{1n}}{\alpha_{11} \alpha_{12} \cdots \alpha_{1n} \alpha_{I_1}} \bar{x}_1^b > 1,$$

which implies

$$\beta_1 \bar{x}_1^b > \frac{\alpha_{11} \cdots \alpha_{1n}}{\gamma_{11} \cdots \gamma_{1n}} (\mu_{I_1} + d_1 + \gamma_{10}) > (\mu_{I_1} + d_1 + \gamma_{10}) > \gamma_{10}.$$

This yields $\beta_1 \bar{x}_1^b - \gamma_{10} > 0$. Since A_1 is a Metzler stable matrix, $(-A_1) > 0$.

Therefore, $\bar{x}_1^b > 0$, $\bar{Y}_1 > 0$, $\bar{y}_{1,n+1}^b > 0$ and $\bar{x}_2^b > 0$. The boundary equilibrium $E_1 D F_2$ given by (3.17) is a boundary endemic equilibrium.

When $\mathfrak{R}_0^1 > 1$ and $\mathfrak{R}_0^2 \leq 1$, the first boundary equilibrium exists and is given by

$$\left\{ \begin{array}{l} \bar{x}_1^b = \frac{1}{\beta_1 \langle e_{n+1}^1 \mid (-A_1)^{-1} e_1^1 \rangle} = \frac{x_1^*}{\mathfrak{R}_0^1} > 0, \\ \bar{Y}_1 = \beta_1 \frac{x_1^*}{\mathfrak{R}_0^1} \frac{\varphi_1(\bar{x}_1^b) + a_2 \bar{x}_2^b}{\beta_1 \bar{x}_1^b - \gamma_{10}} (-A_1)^{-1} e_1^1 > 0, \\ \bar{y}_{1,n+1}^b = \frac{\phi_1(\bar{x}^b)}{\beta_1 \bar{x}_1^b - \gamma_{10}} = \frac{\varphi_1(\bar{x}_1^b) + a_2 \bar{x}_2^b}{\beta_1 \bar{x}_1^b - \gamma_{10}} > 0, \\ \bar{x}_2^b = \frac{\Lambda_2}{(\mu_2 + a_2)} + \frac{a_1}{(\mu_2 + a_2)} \bar{x}_1^b > 0. \end{array} \right. \quad (3.17)$$

For the second part of the theorem, let us consider Eq.(3.1) at equilibrium with $y_{1,n+1} = 0$ and $y_{2,n+1} \neq 0$. This results in

$$\left\{ \begin{array}{l} \Lambda_1 - (\mu_1 + a_1) \bar{S}_1^* + a_2 \bar{S}_2^* = 0, \\ \Lambda_2 - (\mu_2 + a_2) \bar{S}_2^* + a_1 \bar{S}_1^* + \gamma_{20} \bar{I}_2^* = \beta_2 \bar{I}_2^* \bar{S}_2^*, \\ \beta_2 \bar{I}_2^* \bar{S}_2^* = (\mu_{21} + \gamma_{21}) \bar{E}_{21}^*, \\ \gamma_{21} \bar{E}_{21}^* = (\mu_{22} + \gamma_{22}) \bar{E}_{22}^*, \\ \vdots \\ \gamma_{2,n-1} \bar{E}_{2,n-1}^* = (\mu_{2n} + \gamma_{2n}) \bar{E}_{2n}^*, \\ \gamma_{2n} \bar{E}_{2n}^* = (\mu_{I_2} + d_2 + \gamma_{20}) \bar{I}_2^*, \end{array} \right. \quad (3.18)$$

or equivalently

$$\left\{ \begin{array}{l} \phi_2(\bar{x}^b) = \beta_2 \bar{x}_2^b \bar{y}_{2,n+1}^b - \gamma_{20} \bar{y}_{2,n+1}^b, \\ -A_2 Y_2 = \beta_2 \bar{x}_2^b \bar{y}_{2,n+1}^b e_1^1, \\ \phi_1(\bar{x}^b) = 0. \end{array} \right. \quad (3.19)$$

The second equation of (3.19) gives

$$\bar{Y}_2 = \beta_2 \bar{x}_2^b \bar{y}_{2,n+1}^b (-A_2)^{-1} e_1^1. \quad (3.20)$$

Then, equation (3.20) implies $\langle e_{n+1}^1 \mid \bar{Y}_2 \rangle = \beta_2 \bar{x}_2^b \bar{y}_{2,n+1}^b \langle e_{n+1}^1 \mid (-A_2)^{-1} e_1^1 \rangle$. Since $\langle e_{n+1}^1 \mid \bar{Y}_2 \rangle = \bar{y}_{2,n+1}^b$, it results in

$$\bar{y}_{2,n+1}^b = \beta_2 \bar{x}_2^b \langle e_{n+1}^1 \mid (-A_2)^{-1} e_1^1 \rangle \bar{y}_{2,n+1}^b$$

and since $\bar{y}_{2,n+1}^b \neq 0$, it yields

$$\bar{x}_2^b = \frac{1}{\beta_2 \langle e_{n+1}^1 | (-A_2)^{-1} e_1^1 \rangle} = \frac{x_2^*}{\mathfrak{R}_0^2}. \quad (3.21)$$

The third equation of (3.19) gives $\phi_1(\bar{x}^b) = 0$, which is equivalent to $\Lambda_1 - (\mu_1 + a_1) \bar{x}_1^b + a_2 \bar{x}_2^b = 0$. This yields

$$\bar{x}_1^b = \frac{\Lambda_1}{(\mu_1 + a_1)} + \frac{a_2}{(\mu_1 + a_1)} \bar{x}_2^b. \quad (3.22)$$

The first equation of (3.19) gives

$$\bar{y}_{2,n+1}^b = \frac{\phi_2(\bar{x}^b)}{\beta_2 \bar{x}_2^b - \gamma_{20}} = \frac{\varphi_2(\bar{x}_2^b) + a_1 \bar{x}_1^b}{\beta_2 \bar{x}_2^b - \gamma_{20}}. \quad (3.23)$$

It can then be deduced from (3.20), (3.21) and (3.23) that

$$\bar{Y}_2 = \beta_2 \frac{x_2^*}{\mathfrak{R}_0^2} \frac{\varphi_2(\bar{x}_2^b) + a_1 \bar{x}_1^b}{\beta_2 \bar{x}_2^b - \gamma_{20}} (-A_2)^{-1} e_1^1. \quad (3.24)$$

When $\mathfrak{R}_0^2 > 1$, it is observed from equation (3.21) that $\bar{x}_2^b < x_2^*$, and then $\varphi_2(\bar{x}_2^b) > 0$, since the function φ_2 models the dynamics of the second population when there is no disease. The condition $\mathfrak{R}_0^2 > 1$ is equivalent to

$$\beta_2 \frac{\gamma_{21} \gamma_{22} \cdots \gamma_{2n}}{\alpha_{21} \alpha_{22} \cdots \alpha_{2n} \alpha_{I_2}} \frac{1}{\alpha_{I_2}} \bar{x}_2^b > 1,$$

which implies

$$\beta_2 \bar{x}_2^b > \frac{\alpha_{21} \cdots \alpha_{2n}}{\gamma_{21} \cdots \gamma_{2n}} (\mu_{I_2} + d_2 + \gamma_{20}) > (\mu_{I_2} + d_2 + \gamma_{20}) > \gamma_{20}.$$

This yields $\beta_2 \bar{x}_2^b - \gamma_{20} > 0$. Since A_2 is a Metzler stable matrix, $(-A_2) > 0$.

Therefore, $\bar{x}_2^b > 0$, $\bar{Y}_2 > 0$, $\bar{y}_{2,n+1}^b > 0$ and $\bar{x}_1^b > 0$. The boundary equilibrium $DF_1 E_2$ given by (3.25) is a boundary endemic equilibrium.

When $\mathfrak{R}_0^1 \leq 1$ and $\mathfrak{R}_0^2 > 1$, the second boundary equilibrium exists and is given by

$$\left\{ \begin{array}{l} \bar{x}_2^b = \frac{1}{\beta_2 \langle e_{n+1}^1 | (-A_2)^{-1} e_1^1 \rangle} = \frac{x_2^*}{\mathfrak{R}_0^2} > 0, \\ \bar{Y}_2 = \beta_2 \frac{x_2^*}{\mathfrak{R}_0^2} \frac{\varphi_2(\bar{x}_2^b) + a_1 \bar{x}_1^b}{\beta_2 \bar{x}_2^b - \gamma_{20}} (-A_2)^{-1} e_1^1 > 0, \\ \bar{y}_{2,n+1}^b = \frac{\phi_2(\bar{x})}{\beta_2 \bar{x}_2^b - \gamma_{20}} = \frac{\varphi_2(\bar{x}_2^b) + a_1 \bar{x}_1^b}{\beta_2 \bar{x}_2^b - \gamma_{20}} > 0, \\ \bar{x}_1^b = \frac{\Lambda_1}{(\mu_1 + a_1)} + \frac{a_2}{(\mu_1 + a_1)} \bar{x}_2^b > 0. \end{array} \right. \quad (3.25)$$

For the third part of the theorem, the equilibrium has to be computed when both infectious individuals of the two populations co-exist. This means $I_1 \neq 0$ and $I_2 \neq 0$. This equilibrium is called endemic equilibrium. The endemic equilibrium $EE = (\bar{x}_1, \bar{Y}_1, \bar{x}_2, \bar{Y}_2)$ of Eq.(3.2) should satisfy

$$\left\{ \begin{array}{l} \phi_1(\bar{x}) = \beta_1 \bar{x}_1 \bar{y}_{1,n+1} - \gamma_{10} \bar{y}_{1,n+1} \\ \beta_1 \bar{x}_1 \bar{y}_{1,n+1} e_1^1 + A_1 \bar{Y}_1 = 0 \\ \phi_2(\bar{x}) = \beta_2 \bar{x}_2 \bar{y}_{2,n+1} - \gamma_{20} \bar{y}_{2,n+1} \\ \beta_2 \bar{x}_2 \bar{y}_{2,n+1} e_1^1 + A_2 \bar{Y}_2 = 0 \end{array} \right. \quad (3.26)$$

The second equation of (3.26) gives $\bar{Y}_1 = \beta_1 \bar{x}_1 \bar{y}_{1,n+1} (-A_1)^{-1} e_1^1$ and using the scalar usual product,

$$\langle e_{n+1}^1 | \bar{Y}_1 \rangle = \beta_1 \langle e_{n+1}^1 | (-A_1)^{-1} e_1^1 \rangle \bar{x}_1 \bar{y}_{1,n+1}.$$

Since $\langle e_{n+1}^1 | \bar{Y}_1 \rangle = \bar{y}_{1,n+1}$ and $\bar{y}_{1,n+1} \neq 0$,

$$\bar{x}_1 = \frac{1}{\beta_1 \langle e_{n+1}^1 | (-A_1)^{-1} e_1^1 \rangle} = \frac{x_1^*}{\mathfrak{R}_0^1} \quad (3.27)$$

The last equation of (3.26) gives $\bar{Y}_2 = \beta_2 \bar{x}_2 \bar{y}_{2,n+1} (-A_2)^{-1} e_1^1$ and using the scalar usual product,

$$\langle e_{n+1}^1 | \bar{Y}_2 \rangle = \beta_2 \langle e_{n+1}^1 | (-A_2)^{-1} e_1^1 \rangle \bar{x}_2 \bar{y}_{2,n+1}.$$

Since $\langle e_{n+1}^1 | \bar{Y}_2 \rangle = \bar{y}_{2,n+1}$ and $\bar{y}_{2,n+1} \neq 0$,

$$\bar{x}_2 = \frac{1}{\beta_2 \langle e_{n+1}^1 | (-A_2)^{-1} e_1^1 \rangle} = \frac{x_2^*}{\mathfrak{R}_0^2}. \quad (3.28)$$

When $\mathfrak{R}_0^1 > 1$ and $\mathfrak{R}_0^2 > 1$, then $\varphi_1(\bar{x}_1) > 0$ and $\varphi_2(\bar{x}_2) > 0$.

The first equation of (3.26) implies $\phi_1(\bar{x}) = \beta_1 \bar{x}_1 \bar{y}_{1,n+1} - \gamma_{10} \bar{y}_{1,n+1}$, with $\phi_1(\bar{x}) = \varphi_1(\bar{x}_1) + a_2 \bar{x}_2$. Then,

$$\bar{y}_{1,n+1} = \frac{\varphi_1(\bar{x}_1) + a_2 \bar{x}_2}{\beta_1 \bar{x}_1 - \gamma_{10}}, \quad (3.29)$$

where $\beta_1 \bar{x}_1 - \gamma_{10} > 0$. The third equation of (3.26) implies $\phi_2(\bar{x}) = \beta_2 \bar{x}_2 \bar{y}_{2,n+1} - \gamma_{20} \bar{y}_{2,n+1}$, with $\phi_2(\bar{x}) = \varphi_2(\bar{x}_2) + a_1 \bar{x}_1$. Then,

$$\bar{y}_{2,n+1} = \frac{\varphi_2(\bar{x}_2) + a_1 \bar{x}_1}{\beta_2 \bar{x}_2 - \gamma_{20}}, \quad (3.30)$$

where $\beta_2 \bar{x}_2 - \gamma_{20} > 0$. Since $\bar{Y}_1 = \beta_1 \bar{x}_1 \bar{y}_{1,n+1} (-A_1)^{-1} e_1^1$ with \bar{x}_1 and $\bar{y}_{1,n+1}$ given as in (3.27) and (3.29),

$$\bar{Y}_1 = \beta_1 \frac{x_1^*}{\mathfrak{R}_0^1} \frac{\varphi_1(\bar{x}_1) + a_2 \bar{x}_2}{\beta_1 \bar{x}_1 - \gamma_{10}} (-A_1)^{-1} e_1^1. \quad (3.31)$$

Since $\bar{Y}_2 = \beta_2 \bar{x}_2 \bar{y}_{2,n+1} (-A_2)^{-1} e_1^1$ with \bar{x}_2 and $\bar{y}_{2,n+1}$ given as in (3.28) and (3.30),

$$\bar{Y}_2 = \beta_2 \frac{x_2^*}{\mathfrak{R}_0^2} \frac{\varphi_2(\bar{x}_2) + a_1 \bar{x}_1}{\beta_2 \bar{x}_2 - \gamma_{20}} (-A_2)^{-1} e_1^1. \quad (3.32)$$

When $\mathfrak{R}_0^1 > 1$ and $\mathfrak{R}_0^2 > 1$, the endemic equilibrium exists and is given by

$$\left\{ \begin{array}{l} \bar{x}_1 = \frac{x_1^*}{\mathfrak{R}_0^1} > 0, \\ \bar{Y}_1 = \beta_1 \frac{x_1^*}{\mathfrak{R}_0^1} \frac{\varphi_1(\bar{x}_1) + a_2 \bar{x}_2}{\beta_1 \bar{x}_1 - \gamma_{10}} (-A_1)^{-1} e_1^1 > 0, \\ \bar{y}_{1,n+1} = \frac{\varphi_1(\bar{x}_1) + a_2 \bar{x}_2}{\beta_1 \bar{x}_1 - \gamma_{10}} > 0, \\ \bar{x}_2 = \frac{x_2^*}{\mathfrak{R}_0^2} > 0, \\ \bar{Y}_2 = \beta_2 \frac{x_2^*}{\mathfrak{R}_0^2} \frac{\varphi_2(\bar{x}_2) + a_1 \bar{x}_1}{\beta_2 \bar{x}_2 - \gamma_{20}} (-A_2)^{-1} e_1^1 > 0, \\ \bar{y}_{2,n+1} = \frac{\varphi_2(\bar{x}_2) + a_1 \bar{x}_1}{\beta_2 \bar{x}_2 - \gamma_{20}} > 0. \end{array} \right. \quad (3.33)$$

□

3.2.6 Global stability of boundaries equilibria

The stability of endemic equilibria always presents a number of challenges. For (3.1), the following stability results hold.

Theorem 3.2.9. 1. When $\mathfrak{R}_0^1 > 1$ and $\mathfrak{R}_0^2 \leq 1$, there exists a boundary equilibrium

$$E_1 D F_2 = (\bar{S}_1^*, \bar{E}_{11}^*, \dots, \bar{E}_{1n}^*, \bar{I}_1^*, \bar{S}_2^*, 0, \dots, 0)$$

which is globally asymptotically stable if a sufficient mild condition given by

$$\begin{aligned} & a_2 \left(1 + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \right) (x_2 - \bar{x}_2^b) \\ & \leq \left[(\mu_1 + a_1) \left(1 + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \right) + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \beta_1 y_{1,n+1} \right] (x_1 - \bar{x}_1^b) \end{aligned}$$

is satisfied. This implies that the disease is endemic in the first population while it will die out in the second population.

2. When $\mathfrak{R}_0^1 \leq 1$ and $\mathfrak{R}_0^2 > 1$, there exists a boundary equilibrium

$$D F_1 E_2 = (\bar{S}_1^*, 0, \dots, 0, \bar{S}_2^*, \bar{E}_{21}^*, \dots, \bar{E}_{2n}^*, \bar{I}_2^*)$$

which is globally asymptotically stable if a sufficient mild condition given by

$$\begin{aligned} & a_1 \left(1 + \frac{\gamma_{20}}{\beta_2 \bar{x}_2^b - \gamma_{20}} \right) (x_1 - \bar{x}_1^b) \\ & \leq \left[(\mu_2 + a_2) \left(1 + \frac{\gamma_{20}}{\beta_2 \bar{x}_2^b - \gamma_{20}} \right) + \frac{\gamma_{20}}{\beta_2 \bar{x}_2^b - \gamma_{20}} \beta_2 y_{2,n+1} \right] (x_2 - \bar{x}_2^b) \end{aligned}$$

is satisfied.

This implies that the disease is endemic in the first population while it will die out in the second population.

Proof. The approach used in [14] could be followed. Consider the following Lyapunov function candidate, which is almost the same as in [36, 13]:

$$V_{E_1 D F_2}^1(t) = (x_1 - \bar{x}_1^b \ln x_1) + \sum_{i=1}^{n+1} v_{1i} (y_{1i} - \bar{y}_{1i}^b \ln y_{1i}) + \langle e_{n+1}^1 \mid (-A_2)^{-1} Y_2 \rangle \quad (3.34)$$

where v_{11}, \dots, v_{1n} and $v_{1,n+1}$ are positive constants that will be given below. Differen-

tiating $V_{E_1DF_2}^1(t)$ with respect to time gives

$$\begin{aligned}
 \dot{V}_{E_1DF_2}^1(t) &= \phi_1(x) \frac{(x_1 - \bar{x}_1^b)}{x_1} + \gamma_{10} y_{1,n+1} \frac{(x_1 - \bar{x}_1^b)}{x_1} - \beta_1 x_1 y_{1,n+1} + \beta_1 \bar{x}_1^b y_{1,n+1} \\
 &+ v_{11} \left[\beta_1 x_1 y_{1,n+1} - \alpha_{11} y_{11} - \beta_1 x_1 y_{1,n+1} \frac{\bar{y}_{11}^b}{y_{11}} + \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b \right] \\
 &+ v_{12} \left[\gamma_{11} y_{11} - \alpha_{12} y_{12} - \gamma_{11} y_{11} \frac{\bar{y}_{12}^b}{y_{12}} + \gamma_{11} \bar{y}_{11}^b \right] \\
 &+ v_{13} \left[\gamma_{12} y_{12} - \alpha_{13} y_{13} - \gamma_{12} y_{12} \frac{\bar{y}_{13}^b}{y_{13}} + \gamma_{12} \bar{y}_{12}^b \right] \\
 &\vdots \\
 &+ v_{1n} \left[\gamma_{1,n-1} y_{1,n-1} - \alpha_{1n} y_{1n} - \gamma_{1,n-1} y_{1,n-1} \frac{\bar{y}_{1n}^b}{y_{1n}} + \gamma_{1,n-1} \bar{y}_{1,n-1}^b \right] \\
 &+ v_{1,n+1} \left[\gamma_{1n} y_{1n} - \alpha_{1,n+1} y_{1,n+1} - \gamma_{1n} y_{1n} \frac{\bar{y}_{1,n+1}^b}{y_{1,n+1}} + \gamma_{1n} \bar{y}_{1n}^b \right] \\
 &+ \left(\mathfrak{R}_0^2 \frac{x_2}{\bar{x}_2^b} - 1 \right) y_{2,n+1}
 \end{aligned}$$

Let us choose the coefficients of our function as

$$\begin{cases} v_{12} \gamma_{11} \bar{E}_{11}^* = v_{11} (\mu_{11} + \gamma_{11}) \bar{E}_{11}^* \\ v_{13} \gamma_{12} \bar{E}_{12}^* = v_{12} (\mu_{12} + \gamma_{12}) \bar{E}_{12}^* \\ \vdots \\ v_{1n} \gamma_{1,n-1} \bar{E}_{1,n-1}^* = v_{1,n-1} (\mu_{1,n-1} + \gamma_{1,n-1}) \bar{E}_{1,n-1}^* \\ w_1 \gamma_{1n} \bar{E}_{1n}^* = v_{1n} (\mu_{1n} + \gamma_{1n}) \bar{E}_{1n}^* \end{cases}$$

or equivalently

$$\begin{cases} v_{11} = 1 \\ v_{12} \gamma_{11} = v_{11} \alpha_{11} \\ v_{13} \gamma_{12} = v_{12} \alpha_{12} \\ \vdots \\ v_{1,n+1} \gamma_{1n} = v_{1n} \alpha_{1n} \\ \beta_1 \bar{x}_1^b = v_{1,n+1} \alpha_{1,n+1} \end{cases} .$$

By the endemic relations,

$$\begin{cases} v_{12} (\mu_{12} + \gamma_{12}) \bar{E}_{12}^* = v_{11} (\mu_{11} + \gamma_{11}) \bar{E}_{11}^* \\ v_{13} (\mu_{13} + \gamma_{13}) \bar{E}_{13}^* = v_{12} (\mu_{12} + \gamma_{12}) \bar{E}_{12}^* \\ \vdots \\ v_{1n} (\mu_{1n} + \gamma_{1n}) \bar{E}_{1n}^* = v_{1,n-1} (\mu_{1,n-1} + \gamma_{1,n-1}) \bar{E}_{1,n-1}^* \\ v_{1,n+1} (\mu_{I_1} + d_1 + \gamma_{10}) \bar{I}_1^* = v_{1n} (\mu_{1n} + \gamma_{1n}) \bar{E}_{1n}^* \end{cases}$$

or equivalently

$$\begin{cases} \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b = \alpha_{11} \bar{y}_{11}^b \\ \gamma_{11} \bar{y}_{11}^b = \alpha_{12} \bar{y}_{12}^b \\ \gamma_{12} \bar{y}_{12}^b = \alpha_{13} \bar{y}_{13}^b \\ \vdots \\ \gamma_{1n} \bar{y}_{1n}^b = \alpha_{n+1} \bar{y}_{1,n+1}^b \end{cases}.$$

Then,

$$\begin{aligned} \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b &= v_{11} \alpha_{11} \bar{y}_{11}^b = v_{12} \alpha_{12} \bar{y}_{12}^b = \cdots = v_{1n} \alpha_{1n} \bar{y}_{1n}^b = v_{1,n+1} \alpha_{n+1} \bar{y}_{1,n+1}^b \\ &= v_{12} \gamma_{11} \bar{y}_{11}^b = v_{13} \gamma_{12} \bar{y}_{12}^b = \cdots = v_{1n} \gamma_{1,n-1} \bar{y}_{1,n-1}^b = v_{1,n+1} \gamma_{1,n} \bar{y}_{1,n}^b \end{aligned} \quad (3.35)$$

The derivative of $V_{E_1 D F_2}^1(t)$ becomes

$$\begin{aligned} \dot{V}_{E_1 D F_2}^1(t) &= \phi_1(x) \frac{(x_1 - \bar{x}_1^b)}{x_1} + \gamma_{10} y_{n+1} \frac{(x_1 - \bar{x}_1^b)}{x_1} - \beta_1 x_1 y_{1,n+1} + \\ &\left(\Re_0^2 \frac{x_2}{\bar{x}_2^b} - 1 \right) y_{2,n+1} + \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b \left[(n+1) - \frac{x_1 y_{1,n+1} \bar{y}_{11}^b}{\bar{x}_1^b \bar{y}_{1,n+1} y_{11}} - \sum_{k=1}^n \frac{y_{1k} \bar{y}_{1,k+1}^b}{\bar{y}_{1k}^b y_{1,k+1}} \right]. \end{aligned}$$

Using the relation $\beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b = \phi_1(\bar{x}) + \gamma_{10} \bar{y}_{1,n+1}^b$, the expression $\beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b \frac{(x_1 - \bar{x}_1^b)}{x_1}$ can be added and subtracted. This yields

$$\beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b - \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b \frac{\bar{x}_1^b}{x_1} - \phi_1(\bar{x}) \frac{(x_1 - \bar{x}_1^b)}{x_1} - \gamma_{10} \bar{y}_{1,n+1}^b \frac{(x_1 - \bar{x}_1^b)}{x_1}.$$

Therefore,

$$\begin{aligned} & \dot{V}_{E_1 DF_2}^1(t) \\ = & (\phi_1(x) - \phi_1(\bar{x})) \frac{(x_1 - \bar{x}_1^b)}{x_1} + \gamma_{10} (y_{1,n+1} - \bar{y}_{1,n+1}^b) \frac{(x_1 - \bar{x}_1^b)}{x_1} + \left(\mathfrak{R}_0^2 \frac{x_2}{\bar{x}_2^b} - 1 \right) y_{2,n+1} \\ & + \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b \left[(n+1) - \frac{x_1 y_{1,n+1} \bar{y}_{11}^b}{\bar{x}_1^b \bar{y}_{1,n+1} y_{11}} - \sum_{k=1}^n \frac{y_{1k} \bar{y}_{1,k+1}^b}{\bar{y}_{1k}^b y_{1,k+1}} \right]. \end{aligned}$$

Making use of the identity

$$\phi_1(x) - \phi_1(\bar{x}) = -(\mu_1 + a_1)(x_1 - \bar{x}_1^b) + a_2(x_2 - \bar{x}_2^b)$$

and the relation

$$\Lambda_1 = (\mu_1 + a_1)\bar{x}_1^b + \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b - \gamma_{10} \bar{y}_{1,n+1}^b + a_2 \bar{x}_2^b$$

yields

$$\dot{x}_1 = -[(\mu_1 + a_1) + \beta_1 y_{1,n+1}] (x_1 - \bar{x}_1^b) - (y_{1,n+1} - \bar{y}_{1,n+1}^b)(\beta_1 \bar{x}_1^b - \gamma_{10}) + a_2 (x_2 - \bar{x}_2^b).$$

Next another function

$$V_{E_1 DF_2}^2(t) \equiv \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} (x_1 - \bar{x}_1^b \ln x_1)$$

is considered. It follows that

$$\begin{aligned} \dot{V}_{E_1 DF_2}^2(t) = & -\frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} [(\mu_1 + a_1) + \beta_1 y_{1,n+1}] \frac{(x_1 - \bar{x}_1^b)^2}{x_1} + \\ & \frac{a_2 \gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \frac{(x_1 - \bar{x}_1^b)(x_2 - \bar{x}_2^b)}{x_1} - \gamma_{10} (y_{1,n+1} - \bar{y}_{1,n+1}^b) \frac{(x_1 - \bar{x}_1^b)}{x_1}. \end{aligned}$$

Considering the summation

$$V_{E_1 DF_2}(t) = V_{E_1 DF_2}^1(t) + V_{E_1 DF_2}^2(t)$$

results in

$$\begin{aligned} \dot{V}_{E_1 DF_2}(t) = & - \left[(\mu_1 + a_1) \left(1 + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \right) + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \beta_1 y_{1,n+1} \right] \frac{(x_1 - \bar{x}_1^b)^2}{x_1} \\ & + a_2 \left[1 + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \right] \frac{(x_1 - \bar{x}_1^b)(x_2 - \bar{x}_2^b)}{x_1} + \left(\mathfrak{R}_0^2 \frac{x_2}{\bar{x}_2^b} - 1 \right) y_{2,n+1} \\ & + \beta_1 \bar{x}_1^b \bar{y}_{1,n+1}^b \left[(n+2) - \frac{\bar{x}_1^b}{x_1} - \frac{x_1 y_{n+1} \bar{y}_{11}^b}{\bar{x}_1^b \bar{y}_{n+1} y_{11}} - \sum_{k=1}^n \frac{y_{1k} \bar{y}_{1,k+1}^b}{\bar{y}_{1k}^b y_{1,k+1}} \right]. \end{aligned}$$

Thus, as shown in the previous section for the stability of disease-free equilibrium, $\left(\Re_0^2 \frac{x_2}{\bar{x}_2^b} - 1\right) \leq 0$ in γ_ε . Then, sufficient condition to have $\dot{V}_{E_1DF_2}(t) \leq 0$ is

$$\begin{aligned} & a_2 \left[1 + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \right] \frac{(x_1 - \bar{x}_1^b)(x_2 - \bar{x}_2^b)}{x_1} \\ & \leq \left[(\mu_1 + a_1) \left(1 + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \right) + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \beta_1 y_{1,n+1} \right] \frac{(x_1 - \bar{x}_1^b)^2}{x_1}. \end{aligned}$$

This sufficient condition can simply be written as

$$\begin{aligned} & a_2 \left(1 + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \right) (x_2 - \bar{x}_2^b) \\ & \leq \left[(\mu_1 + a_1) \left(1 + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \right) + \frac{\gamma_{10}}{\beta_1 \bar{x}_1^b - \gamma_{10}} \beta_1 y_{1,n+1} \right] (x_1 - \bar{x}_1^b), \end{aligned}$$

with $\beta_1 \bar{x}_1^b - \gamma_{10} > 0$. The LaSalle's invariance principle could be used to conclude that when this sufficient condition is satisfied, the first boundary equilibrium is globally asymptotically stable. The proof of the second part of the theorem uses the same approach with the functions

$$V_{DF_1E_2}^1(t) = (x_2 - \bar{x}_2^b \ln x_2) + \sum_{i=1}^{n+1} v_{2i} (y_{2i} - \bar{y}_{2i} \ln y_{2i}) + \langle e_{n+1}^1 \mid (-A_1)^{-1} Y_1 \rangle$$

and

$$V_{DF_1E_2}^2(t) = \frac{\gamma_{20}}{\beta_2 \bar{x}_2^b - \gamma_{20}} (x_2 - \bar{x}_2^b \ln x_2).$$

□

3.2.7 Global stability of endemic equilibrium

Lemma 3.2.10. *Let $Q(x, y)$ be a quadratic function of the form:*

$$Q(x, y) = u_1 k_1 \bar{x}_2 (\mu_1 + a_1) x^2 - (a_2 u_1 k_1 \bar{x}_2 + a_1 u_2 k_2 \bar{x}_1) x y + u_2 k_2 \bar{x}_1 (\mu_2 + a_2) y^2, \quad (3.36)$$

where u_1 and u_2 are positive constants. Then, there exists positive values of u_1 and u_2 such that $Q(x, y)$ is positive definite.

Proof. The quadratic function $Q(x, y)$ is positive definite if the discriminant

$$\Delta = (a_2 u_1 k_1 \bar{x}_2 + a_1 u_2 k_2 \bar{x}_1)^2 - 4 u_1 u_2 k_1 k_2 \bar{x}_1 \bar{x}_2 (\mu_1 + a_1) (\mu_2 + a_2),$$

is non-positive. Using the fact that $2(\mu_1 + a_1)(\mu_2 + a_2) - a_1 a_2 > 0$,

$$\Delta = (a_2 u_1 k_1 \bar{x}_2)^2 + (a_1 u_2 k_2 \bar{x}_1)^2 - 2 u_1 u_2 k_1 k_2 \bar{x}_1 \bar{x}_2 [2(\mu_1 + a_1)(\mu_2 + a_2) - a_1 a_2]$$

is obtained. Therefore, the positive constants u_1 and u_2 could be chosen in such a way that $\Delta < 0$ and this concludes the proof of the lemma. □

Theorem 3.2.11. *This result holds for the system (3.1):*

When $\mathfrak{R}_0^1 > 1$ and $\mathfrak{R}_0^2 > 1$, then there exists a unique endemic equilibrium

$$EE = (\bar{S}_1, \bar{E}_{11}, \dots, \bar{E}_{1n}, \bar{I}_1, \bar{S}_2, \bar{E}_{21}, \dots, \bar{E}_{2n}, \bar{I}_2)$$

which is globally asymptotically stable when a mild condition (3.40) given by

$$[u_1 k_1 (\mu_1 + a_1) - u_2 a_1 k_2] X_1 + [u_2 k_2 (\mu_2 + a_2) - u_1 a_2 k_1] X_2 \geq 0$$

is satisfied. This implies that the disease is endemic in both first and second populations and then, cannot be controlled.

Proof. Let us consider the following Lyapunov candidate function:

$$\begin{aligned} V_{EE}^1(t) = & u_1 (x_1 - \bar{x}_1 \ln x_1) + u_1 \sum_{i=1}^{n+1} v_{1i} (y_{1i} - \bar{y}_{1i} \ln y_{1i}) + u_2 (x_2 - \bar{x}_2 \ln x_2) \\ & + u_2 \sum_{i=1}^{n+1} v_{2i} (y_{2i} - \bar{y}_{2i} \ln y_{2i}). \end{aligned} \quad (3.37)$$

The derivative of $V_{EE}^1(t)$ is given by

$$\begin{aligned} \dot{V}_{EE}^1(t) = & u_1 \phi_1(x) \frac{(x_1 - \bar{x}_1)}{x_1} + u_1 \gamma_{10} y_{1,n+1} \frac{(x_1 - \bar{x}_1)}{x_1} - u_1 \beta_1 x_1 y_{1,n+1} + u_1 \beta_1 \bar{x}_1 y_{1,n+1} \\ & + u_1 v_{11} \left[\beta_1 x_1 y_{n+1} - \alpha_{11} y_{11} - \beta_1 x_1 y_{1,n+1} \frac{\bar{y}_{11}}{y_{11}} + \beta_1 \bar{x}_1 \bar{y}_{1,n+1} \right] \\ & + \sum_{k=1}^n u_1 v_{1,k+1} \left[\gamma_{1k} y_{1k} - \alpha_{k+1} y_{1,k+1} - \gamma_{1k} y_{1k} \frac{\bar{y}_{1,k+1}}{y_{1,k+1}} + \gamma_{1k} \bar{y}_{1k} \right] \\ & + u_2 \phi_2(x) \frac{(x_2 - \bar{x}_2)}{x_2} + \gamma_{20} y_{2,n+1} \frac{(x_2 - \bar{x}_2)}{x_2} - \beta_2 x_2 y_{2,n+1} + \beta_2 \bar{x}_2 y_{2,n+1} \\ & + u_2 v_{21} \left[\beta_2 x_2 y_{2,n+1} - \alpha_{21} y_{21} - \beta_2 x_2 y_{2,n+1} \frac{\bar{y}_{21}}{y_{21}} + \beta_2 \bar{x}_2 \bar{y}_{2,n+1} \right] \\ & + \sum_{k=1}^n u_2 v_{2,k+1} \left[\gamma_{2k} y_{2k} - \alpha_{2,k+1} y_{2,k+1} - \gamma_{2k} y_{2k} \frac{\bar{y}_{2,k+1}}{y_{2,k+1}} + \gamma_{2k} \bar{y}_{2k} \right]. \end{aligned}$$

Choosing for $i = 1, 2$, the coefficients of this function as

$$\begin{cases} v_{i2} \gamma_{i1} \bar{E}_{i1} = v_{i1} (\mu_{i1} + \gamma_{i1}) \bar{E}_{i1} \\ v_{i3} \gamma_{i2} \bar{E}_{i2} = v_{i2} (\mu_{i2} + \gamma_{i2}) \bar{E}_{i2} \\ \vdots \\ v_{in} \gamma_{i,n-1} \bar{E}_{i,n-1} = v_{i,n-1} (\mu_{i,n-1} + \gamma_{i,n-1}) \bar{E}_{i,n-1} \\ v_{i,n+1} \gamma_{in} \bar{E}_{in} = v_{in} (\mu_{in} + \gamma_{in}) \bar{E}_{in} \end{cases}$$

or equivalently

$$\begin{cases} v_{i1} = 1 \\ v_{i2} \gamma_{i1} = v_{i1} \alpha_{i1} \\ v_{i3} \gamma_{i2} = v_{i2} \alpha_{i2} \\ \vdots \\ v_{i,n+1} \gamma_{in} = v_{in} \alpha_{in} \\ \beta_i \bar{x}_i = v_{i,n+1} \alpha_{i,n+1} \end{cases}$$

yields

$$\begin{cases} \beta_i \bar{x}_i \bar{y}_{i,n+1} = \alpha_{i1} \bar{y}_{i1} \\ \gamma_{i1} \bar{y}_{i1} = \alpha_{i2} \bar{y}_{i2} \\ \gamma_{i2} \bar{y}_{i2} = \alpha_{i3} \bar{y}_{i3} \\ \vdots \\ \gamma_{in} \bar{y}_{in} = \alpha_{i,n+1} \bar{y}_{i,n+1} \end{cases} \quad (3.38)$$

by the endemic relations. It follows that

$$\begin{aligned} \beta_i \bar{x}_i \bar{y}_{i,n+1} &= v_{i1} \alpha_{i1} \bar{y}_{i1} = v_{i2} \alpha_{i2} \bar{y}_{i2} = \cdots = v_{in} \alpha_{in} \bar{y}_{in} = v_{i,n+1} \alpha_{i,n+1} \bar{y}_{i,n+1} \\ &= v_{i2} \gamma_{i1} \bar{y}_{i1} = v_{i3} \gamma_{i2} \bar{y}_{i2} = \cdots = v_{in} \gamma_{i,n-1} \bar{y}_{i,n-1} = v_{i,n+1} \gamma_{i,n} \bar{y}_{i,n}. \end{aligned} \quad (3.39)$$

The derivative of $V_{EE}^1(t)$ becomes

$$\begin{aligned} \dot{V}_{EE}^1(t) = & u_1 \phi_1(x) \frac{(x_1 - \bar{x}_1)}{x_1} + u_1 \gamma_{10} y_{1,n+1} \frac{(x_1 - \bar{x}_1)}{x_1} \\ & + u_2 \phi_2(x) \frac{(x_2 - \bar{x}_2)}{x_2} + u_2 \gamma_{20} y_{2,n+1} \frac{(x_2 - \bar{x}_2)}{x_2} \\ & + u_1 \beta_1 \bar{x}_1 \bar{y}_{1,n+1} \left[(n+1) - \frac{x_1 y_{1,n+1} \bar{y}_{11}}{\bar{x}_1 \bar{y}_{1,n+1} y_{11}} - \sum_{k=1}^n \frac{y_{1k} \bar{y}_{1,k+1}}{\bar{y}_{1k} y_{1,k+1}} \right] \\ & + u_2 \beta_2 \bar{x}_2 \bar{y}_{2,n+1} \left[(n+1) - \frac{x_2 y_{2,n+1} \bar{y}_{21}}{\bar{x}_2 \bar{y}_{2,n+1} y_{21}} - \sum_{k=1}^n \frac{y_{2k} \bar{y}_{2,k+1}}{\bar{y}_{2k} y_{2,k+1}} \right]. \end{aligned}$$

Using the relation $\beta_i \bar{x}_i \bar{y}_{i,n+1} = \phi_i(\bar{x}) + \gamma_{i0} \bar{y}_{i,n+1}$, the expression

$$\beta_1 \bar{x}_1 \bar{y}_{1,n+1} \frac{(x_1 - \bar{x}_1)}{x_1} + \beta_2 \bar{x}_2 \bar{y}_{2,n+1} \frac{(x_2 - \bar{x}_2)}{x_2}$$

can be added and subtracted. It follows that

$$\begin{aligned} & u_1 \beta_1 \bar{x}_1 \bar{y}_{1,n+1} - u_1 \beta_1 \bar{x}_1 \bar{y}_{1,n+1} \frac{\bar{x}_1}{x_1} - u_1 \phi_1(\bar{x}) \frac{(x_1 - \bar{x}_1)}{x_1} - u_1 \gamma_{10} \bar{y}_{1,n+1} \frac{(x_1 - \bar{x}_1)}{x_1} \\ & + u_2 \beta_2 \bar{x}_2 \bar{y}_{2,n+1} - u_2 \beta_2 \bar{x}_2 \bar{y}_{2,n+1} \frac{\bar{x}_2}{x_2} - u_2 \phi_2(\bar{x}) \frac{(x_2 - \bar{x}_2)}{x_2} - u_2 \gamma_{20} \bar{y}_{2,n+1} \frac{(x_2 - \bar{x}_2)}{x_2}. \end{aligned}$$

Therefore,

$$\begin{aligned} \dot{V}_{EE}^1(t) = & u_1 (\phi_1(x) - \phi_1(\bar{x})) \frac{(x_1 - \bar{x}_1)}{x_1} + u_1 \gamma_{10} (y_{1,n+1} - \bar{y}_{1,n+1}) \frac{(x_1 - \bar{x}_1)}{x_1} \\ & + u_1 \beta_1 \bar{x}_1 \bar{y}_{1,n+1} \left[(n+1) - \frac{x_1 y_{1,n+1} \bar{y}_{11}}{\bar{x}_1 \bar{y}_{1,n+1} y_{11}} - \sum_{k=1}^n \frac{y_{1k} \bar{y}_{1,k+1}}{\bar{y}_{1k} y_{1,k+1}} \right] \\ & + u_2 (\phi_2(x) - \phi_2(\bar{x})) \frac{(x_2 - \bar{x}_2)}{x_2} + u_2 \gamma_{20} (y_{2,n+1} - \bar{y}_{2,n+1}) \frac{(x_2 - \bar{x}_2)}{x_2} \\ & + u_2 \beta_2 \bar{x}_2 \bar{y}_{2,n+1} \left[(n+1) - \frac{x_2 y_{2,n+1} \bar{y}_{21}}{\bar{x}_2 \bar{y}_{2,n+1} y_{21}} - \sum_{k=1}^n \frac{y_{2k} \bar{y}_{2,k+1}}{\bar{y}_{2k} y_{2,k+1}} \right]. \end{aligned}$$

Since $\phi_1(x) - \phi_1(\bar{x}) = -(\mu_1 + a_1)(x_1 - \bar{x}_1) + a_2(x_2 - \bar{x}_2)$ and $\phi_2(x) - \phi_2(\bar{x}) = -(\mu_2 + a_2)(x_2 - \bar{x}_2) + a_1(x_1 - \bar{x}_1)$, let us get the other form of \dot{x}_1 and \dot{x}_2 . Then,

$$\dot{x}_1 = -[(\mu_1 + a_1) + \beta_1 y_{1,n+1}](x_1 - \bar{x}_1) - (y_{1,n+1} - \bar{y}_{1,n+1})(\beta_1 \bar{x}_1 - \gamma_{10}) + a_2(x_2 - \bar{x}_2),$$

and

$$\dot{x}_2 = -[(\mu_2 + a_2) + \beta_2 y_{2,n+1}](x_2 - \bar{x}_2) - (y_{2,n+1} - \bar{y}_{2,n+1})(\beta_2 \bar{x}_2 - \gamma_{20}) + a_1(x_1 - \bar{x}_1),$$

where we used the fact that $\Lambda_1 = (\mu_1 + a_1)\bar{x}_1 + \beta_1 \bar{x}_1 \bar{y}_{1,n+1} - \gamma_{10} \bar{y}_{1,n+1} + a_2 \bar{x}_2$.

Let us consider now another function

$$V_{EE}^2(t) = u_1 \frac{\gamma_{10}}{\beta_1 \bar{x}_1 - \gamma_{10}}(x_1 - \bar{x}_1 \ln x_1) + u_2 \frac{\gamma_{20}}{\beta_2 \bar{x}_2 - \gamma_{20}}(x_2 - \bar{x}_2 \ln x_2).$$

Then,

$$\begin{aligned} \dot{V}_{EE}^2(t) = & -u_1 \frac{\gamma_{10}}{\beta_1 \bar{x}_1 - \gamma_{10}} [(\mu_1 + a_1) + \beta_1 y_{1,n+1}] \frac{(x_1 - \bar{x}_1)^2}{x_1} \\ & + u_1 \frac{a_2 \gamma_{10}}{\beta_1 \bar{x}_1 - \gamma_{10}} \frac{(x_1 - \bar{x}_1)(x_2 - \bar{x}_2)}{x_1} \\ & - u_1 \gamma_{10} (y_{1,n+1} - \bar{y}_{1,n+1}) \frac{(x_1 - \bar{x}_1)}{x_1} - u_2 \gamma_{20} (y_{2,n+1} - \bar{y}_{2,n+1}) \frac{(x_2 - \bar{x}_2)}{x_2} \\ & - u_2 \frac{\gamma_{20}}{\beta_2 \bar{x}_2 - \gamma_{20}} [(\mu_2 + a_2) + \beta_2 y_{2,n+1}] \frac{(x_2 - \bar{x}_2)^2}{x_2} \\ & + u_2 \frac{a_1 \gamma_{20}}{\beta_2 \bar{x}_2 - \gamma_{20}} \frac{(x_1 - \bar{x}_1)(x_2 - \bar{x}_2)}{x_2} \end{aligned}$$

The final function used is $V_{EE}(t) = V_{EE}^1(t) + V_{EE}^2(t)$. The derivative of this function gives

$$\begin{aligned} \dot{V}_{EE}(t) = & -u_1 \left[(\mu_1 + a_1) \left(1 + \frac{\gamma_{10}}{\beta_1 \bar{x}_1 - \gamma_{10}} \right) + \frac{\gamma_{10}}{\beta_1 \bar{x}_1 - \gamma_{10}} \beta_1 y_{1,n+1} \right] \frac{(x_1 - \bar{x}_1)^2}{x_1} \\ & + u_1 a_2 \left[1 + \frac{\gamma_{10}}{\beta_1 \bar{x}_1 - \gamma_{10}} \right] \frac{(x_1 - \bar{x}_1)(x_2 - \bar{x}_2)}{x_1} \\ & + u_2 a_1 \left[1 + \frac{\gamma_{20}}{\beta_2 \bar{x}_2 - \gamma_{20}} \right] \frac{(x_1 - \bar{x}_1)(x_2 - \bar{x}_2)}{x_2} \\ & - u_2 \left[(\mu_2 + a_2) \left(1 + \frac{\gamma_{20}}{\beta_2 \bar{x}_2 - \gamma_{20}} \right) + \frac{\gamma_{20}}{\beta_2 \bar{x}_2 - \gamma_{20}} \beta_2 y_{2,n+1} \right] \frac{(x_2 - \bar{x}_2)^2}{x_2} \\ & + u_1 \beta_1 \bar{x}_1 \bar{y}_{1,n+1} \left[(n+2) - \frac{\bar{x}_1}{x_1} - \frac{x_1 y_{1,n+1} \bar{y}_{11}}{\bar{x}_1 \bar{y}_{1,n+1} y_{11}} - \sum_{k=1}^n \frac{y_{1k} \bar{y}_{1,k+1}}{\bar{y}_{1k} y_{1,k+1}} \right] \\ & + u_2 \beta_2 \bar{x}_2 \bar{y}_{2,n+1} \left[(n+2) - \frac{\bar{x}_2}{x_2} - \frac{x_2 y_{2,n+1} \bar{y}_{21}}{\bar{x}_2 \bar{y}_{2,n+1} y_{21}} - \sum_{k=1}^n \frac{y_{2k} \bar{y}_{2,k+1}}{\bar{y}_{2k} y_{2,k+1}} \right]. \end{aligned}$$

Let us set $k_1 = \left(1 + \frac{\gamma_{10}}{\beta_1 \bar{x}_1 - \gamma_{10}}\right)$, $k_2 = \left(1 + \frac{\gamma_{20}}{\beta_2 \bar{x}_2 - \gamma_{20}}\right)$, $X_1 = x_1 - \bar{x}_1$ and $X_2 = x_2 - \bar{x}_2$. Then, $\dot{V}_{EE}(t)$ can be written as

$$\begin{aligned} \dot{V}_{EE}(t) = & -\frac{1}{x_1 x_2} \left[u_1 k_1 (\mu_1 + a_1) x_2 X_1^2 - (u_1 a_2 k_1 x_2 + u_2 a_1 k_2 x_1) X_1 X_2 \right] \\ & -\frac{1}{x_1 x_2} \left[u_2 k_2 (\mu_2 + a_2) x_1 X_2^2 \right] \\ & -u_1 \frac{\gamma_{10}}{\beta_1 \bar{x}_1 - \gamma_{10}} \beta_1 y_{1,n+1} \frac{(x_1 - \bar{x}_1)^2}{x_1} - u_2 \frac{\gamma_{20}}{\beta_2 \bar{x}_2 - \gamma_{20}} \beta_2 y_{2,n+1} \frac{(x_2 - \bar{x}_2)^2}{x_2} \\ & +u_1 \beta_1 \bar{x}_1 \bar{y}_{1,n+1} \left[(n+2) - \frac{\bar{x}_1}{x_1} - \frac{x_1 y_{1,n+1} \bar{y}_{11}}{\bar{x}_1 \bar{y}_{1,n+1} y_{11}} - \sum_{k=1}^n \frac{y_{1k} \bar{y}_{1,k+1}}{\bar{y}_{1k} y_{1,k+1}} \right] \\ & +u_2 \beta_2 \bar{x}_2 \bar{y}_{2,n+1} \left[(n+2) - \frac{\bar{x}_2}{x_2} - \frac{x_2 y_{2,n+1} \bar{y}_{21}}{\bar{x}_2 \bar{y}_{2,n+1} y_{21}} - \sum_{k=1}^n \frac{y_{2k} \bar{y}_{2,k+1}}{\bar{y}_{2k} y_{2,k+1}} \right]. \end{aligned}$$

Using the fact that $X_1 = x_1 - \bar{x}_1$ and $X_2 = x_2 - \bar{x}_2$, one obtains

$$\begin{aligned} \dot{V}_{EE}(t) = & -\frac{1}{x_1 x_2} \left[u_1 k_1 \bar{x}_2 (\mu_1 + a_1) X_1^2 - (u_1 a_2 k_1 \bar{x}_2 + u_2 a_1 k_2 \bar{x}_1) X_1 X_2 \right] \\ & -\frac{1}{x_1 x_2} \left[u_2 k_2 \bar{x}_1 (\mu_2 + a_2) X_2^2 \right] \\ & -\frac{X_1 X_2}{x_1 x_2} \left[u_1 k_1 (\mu_1 + a_1) X_1 - (u_2 a_1 k_2 X_1 + u_1 a_2 k_1 X_2) + u_2 k_2 (\mu_2 + a_2) X_2 \right] \\ & -u_1 \frac{\gamma_{10}}{\beta_1 \bar{x}_1 - \gamma_{10}} \beta_1 y_{1,n+1} \frac{(x_1 - \bar{x}_1)^2}{x_1} - u_2 \frac{\gamma_{20}}{\beta_2 \bar{x}_2 - \gamma_{20}} \beta_2 y_{2,n+1} \frac{(x_2 - \bar{x}_2)^2}{x_2} \\ & +u_1 \beta_1 \bar{x}_1 \bar{y}_{1,n+1} \left[(n+2) - \frac{\bar{x}_1}{x_1} - \frac{x_1 y_{1,n+1} \bar{y}_{11}}{\bar{x}_1 \bar{y}_{1,n+1} y_{11}} - \sum_{k=1}^n \frac{y_{1k} \bar{y}_{1,k+1}}{\bar{y}_{1k} y_{1,k+1}} \right] \\ & +u_2 \beta_2 \bar{x}_2 \bar{y}_{2,n+1} \left[(n+2) - \frac{\bar{x}_2}{x_2} - \frac{x_2 y_{2,n+1} \bar{y}_{21}}{\bar{x}_2 \bar{y}_{2,n+1} y_{21}} - \sum_{k=1}^n \frac{y_{2k} \bar{y}_{2,k+1}}{\bar{y}_{2k} y_{2,k+1}} \right]. \end{aligned}$$

Using lemma (3.2.10) for $\dot{V}_{EE}(t)$, gives

$$u_1 k_1 \bar{x}_2 (\mu_1 + a_1) X_1^2 - (u_1 a_2 k_1 \bar{x}_2 + u_2 a_1 k_2 \bar{x}_1) X_1 X_2 + u_2 k_2 \bar{x}_1 (\mu_2 + a_2) X_2^2 \geq 0.$$

Then, the sufficient condition to have $\dot{V}_{EE}(t) \leq 0$ is

$$[u_1 k_1(\mu_1 + a_1) - u_2 a_1 k_2] X_1 + [u_2 k_2(\mu_2 + a_2) - u_1 a_2 k_1] X_2 \geq 0. \quad (3.40)$$

If this sufficient condition is satisfied, LaSalle's invariance principle can be used to conclude that the endemic equilibrium is globally asymptotically stable in the non-negative orthant \mathbb{R}_+^{2n+4} . \square

Chapter 4

Numerical simulations and conclusion

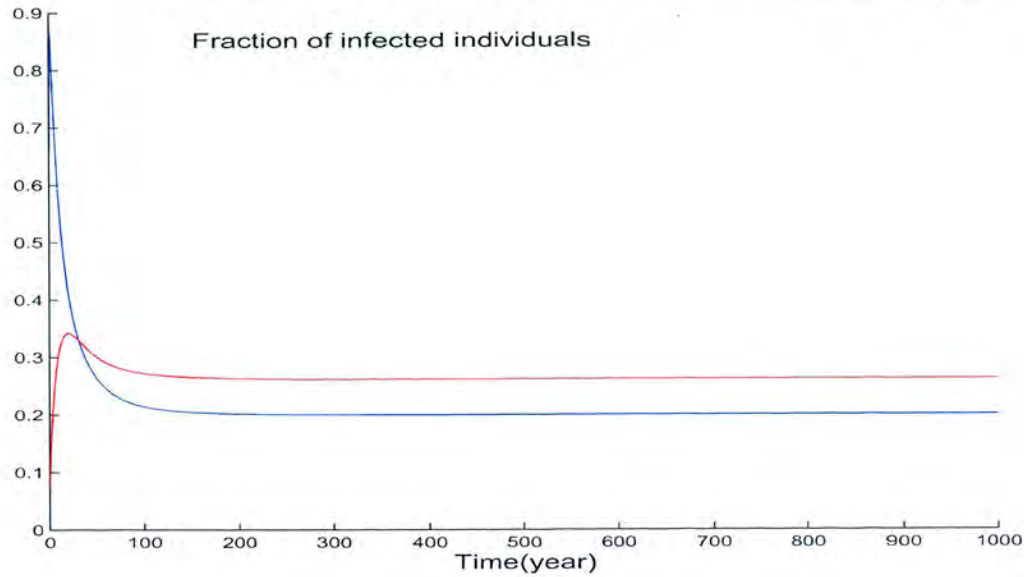
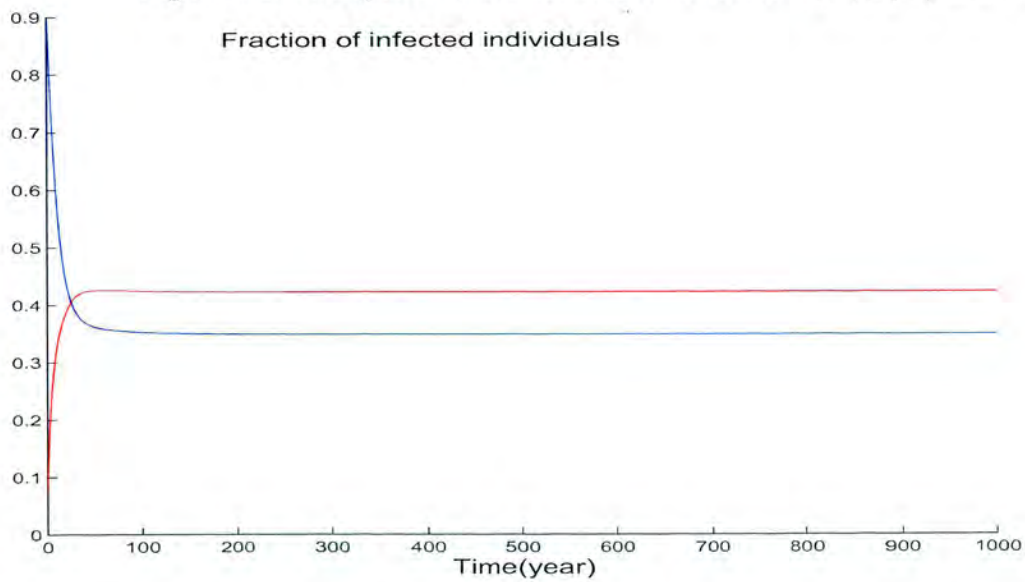
4.1 Models with general contact rates and differential infectivity

To illustrate the theoretical results contained in chapter 2, numerical simulations will be performed using the parameter value/range in the following table.

Table 1: Description and estimation of parameters

Parameters	Description	value/range
Λ	Recruitment rate	100 (year)^{-1}
$\beta(N)$	Transmission coefficient	variable
δ	Fraction of hidden infectious individuals	0.3
p	Proportion of newly infected individuals that have fast progression to the infectious class	0.4
μ	Naturally death rate	0.012
k	Rate of progression from infection to infectious	0.006
r_1	Rate of effective chemoprophylaxis	0.05
r_2	Rate of effective therapy	0.8188
ϕ	Rate at which infectious become loss of sight	0.02
γ	Rate at which loss of sight return to the hospital	0.01
d_1	Death rate of infectious individuals	0.02274
d_2	Death rate of loss of sight	0.27

The figures obtained from the simulations can be visualised in the following figures:

Figure 4.1: Susceptible and infectious individuals $S, I, \beta(N) = 2$.Figure 4.2: Susceptible and infectious individuals $S, I, \beta(N) = 2N$.

4.2 Model with staged progression and migration

The parameter values used in simulating the evolution system of ordinary differential equations investigated in chapter 3 is presented below:

Table 2 : Numerical values for the parameters of the model

Parameters	Description	Estimated value/range
Λ_1	Recruitment rate into the S_1 class	100/yr
Λ_2	Recruitment rate into the S_2 class	110/yr
β_1	Transmission coefficient of infectious individuals in the first sub-population	variable
β_2	Transmission coefficient of infectious individuals in the second sub-population	variable
μ_1	Force of mortality in the first sub-population	0.019896/yr
μ_2	Force of mortality in the second sub-population	0.019897/yr
k_1	Rate of progression from the E_1 class to I_1 class	0.00013/yr
k_2	Rate of progression from the E_2 class to I_2 class	0.00023/yr
r_1	Rate of effective chemoprophylaxis in E_1 class	0/yr
r_2	Rate of effective chemoprophylaxis in E_2 class	0/yr
γ_1	Rate of effective therapy in I_1 class	0.8182/yr
γ_2	Rate of effective therapy of in I_2 class	0.8183/yr
a_1	Rate of migration of individuals from susceptible class S_1 to susceptible class S_2	0.07/yr
a_2	Rate of migration of individuals from the susceptible class S_2 to the susceptible class S_1	0.0701/yr
b_1	Rate of migration of individuals from the latent class E_1 to the latent class E_2	0.05/yr
b_2	Rate of migration of individuals from the latent class E_2 to the latent class E_1	0.0501/yr
c_1	Rate of migration of individuals from the infectious class I_1 to the infectious class I_2	0.02/yr
c_2	Rate of migration from the infectious class I_2 to the infectious class I_1	0.0201/yr
d_1	Additional death rate in the I_1 class	0.0575/yr
d_2	Additional death rate in the I_2 class	0.05751/yr
p_1	Fast progression to the I_1 class	0.015/yr
p_2	Fast progression to the I_2 class	0.016/yr

4.3 Discussions and conclusion

Figures 4.1 and 4.2 show the dynamics of the susceptible and the infectious individuals as time evolves. It can be observed that the systems progress to endemic equilibria both with constant transmission rate (Fig 4.1) and in the case of variable linear transmission rate (Fig 4.2). Note that infectious individual increase tremendously and reach a peak,

Figure 4.3: Path 1 (Infected individuals)

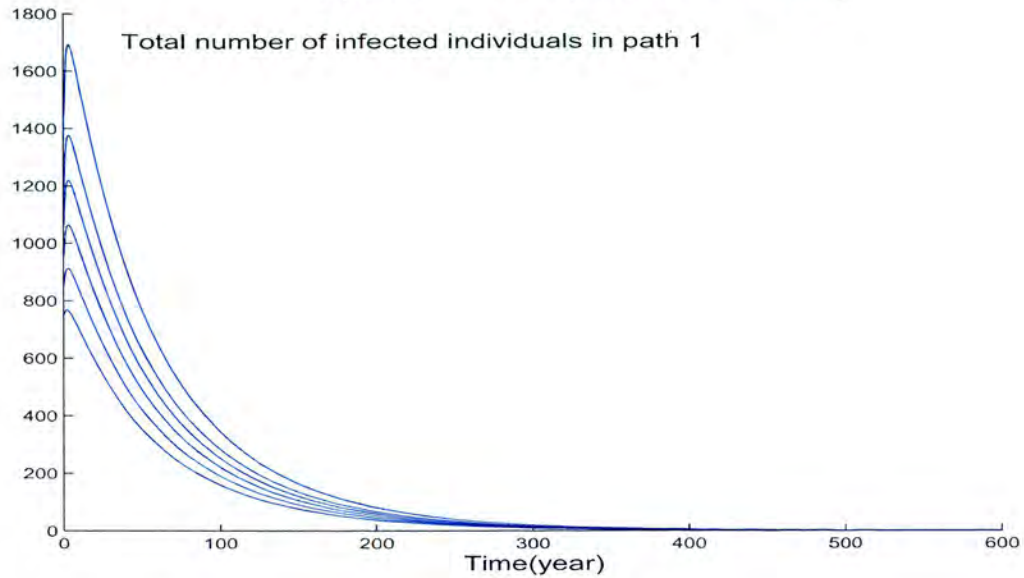
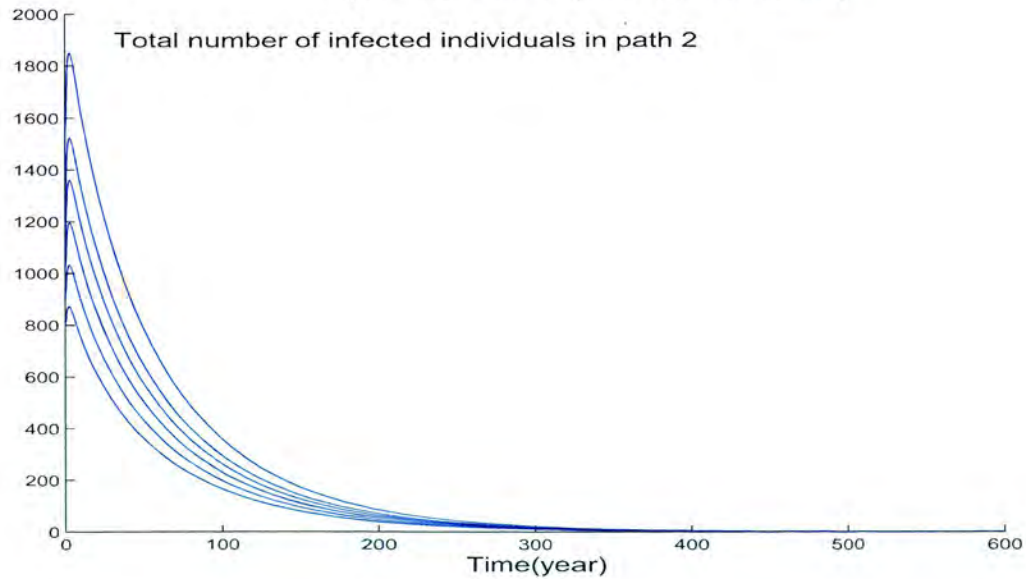


Figure 4.4: Path 2 (Infected individuals)



then decrease and stabilise in case of constant transmission rates. However, in the situation of variable transmission rate, the infectious individuals simply increase as time goes on and eventually stabilise. It should be noted that in both situations, the disease-free equilibria are unstable while the endemic equilibria are globally asymptotically stable.

Figures 4.3 and 4.4 project the opposite scenario of the previous figures. In these graphs, the overall behaviour of the infectious individuals is captured with time. The Scenario

is performed for several initial values for the infected individuals. The figures clearly show that the disease-free equilibria are globally asymptotically stable and the endemic equilibria unstable.

This study explored four important aspects of TB dynamics that were not properly discussed in the literature and developed two large models that incorporate these components.

- (a) Literature review, preliminaries and general introduction were considered in Chapter 1.
- (b) Chapter 2 considered tuberculosis models that incorporate general contact rates, constant recruitment, slow and fast progression, mass balance incidence, two differential infectivity, effective chemoprophylaxis and therapeutic treatments. The well-posedness of the models was investigated. The Lyapunov stability theory and Laplace invariance principle were used to explore the stability nature of the disease-free and endemic equilibria. A fairly good agreement was obtained between the analytical and numerical results.
- (c) Chapter 3 consisted of the study of tuberculosis through a two-patch epidemiological system $SE_1 \cdots E_n I$ which incorporates migrations from one patch to another just by susceptible individuals. The model was considered with bilinear incidence and migration between two patches, where infected and infectious individuals could not migrate from one patch to another for medical reasons. The existence and uniqueness of the associated endemic equilibria were discussed. Quadratic forms and Lyapunov functions were used to show that when the basic reproduction ratio is less than one, the disease-free equilibrium (DFE) is globally asymptotically stable, and when it is greater than one, there is a unique endemic equilibrium (boundary equilibria and endemic equilibrium) which is globally asymptotically stable. The long-term dynamics of this system was completely investigated. The model has at most four equilibria, depending on the values of parameters \mathcal{R}_0^i , $i = 1, 2$. The influence of parameters \mathcal{R}_0^i is significant on the spread of tuberculosis. The boundary equilibrium in this case is globally asymptotically stable. When these parameters are greater than unity, tuberculosis becomes endemic in each population. The endemic equilibrium, which is a unique equilibrium with both populations is globally asymptotically stable. Numerical simulation results were provided to illustrate the theoretical results.

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