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Structured Models and Bifurcations in Distributed Delay Differential Equations

''THESIS''

« Presented and argued for the partial Doctorate /PhD in Mathematics »

Mathematics and Modeling

By

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02T032
Master degree

Under the direction of

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ATTESTATION DE CORRECTION DE LA THESE DE DOCTORAT/Ph.D

Nous, Professeur **ANDJIGA Nicolas Gabriel** et Professeur **EMVUDU Yves**, respectivement président et examinateur du jury de Doctorat/Ph.D de Monsieur **DJIDJOU DEMASSE Ramses Emeric** (matricule **02T032**) préparé sous la direction du Professeur **BOWONG Samuel** et du Professeur **TEWA Jean-Jules**, et la supervision du Professeur **DOSSA Marcel** sur le sujet « **Modèles structurés et Bifurcation dans les équations différentielles à retard distribué** », soutenu le jeudi 25 Juin 2015 en vue de l'obtention du grade de Docteur/Ph.D en Mathématiques de l'Université de Yaoundé 1 attestons que toutes les corrections demandées par le jury de soutenance ont été effectuées.

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To Carole Anastasie Ngah-Zoa

Contents

Abstract / Résumé

Abstract

This work deals with a recent within-host malaria infection model with multistrain for the parasites and a spatial modeling of anopheles mosquito dynamics population. In this work, we also consider models of infectious disease into the host population structured by age. Namely, Hepatitis B virus (HBV) model and Susceptible-Infected-Lost of sight (SIL) model for the spread of a directly transmitted infectious disease taking into account demographic process and vertical transmission of the disease.

The work is organized into five majors chapters: **1.** General introduction, **2.** Biology of Malaria and Hepatitis B Virus, **3.** Hepatitis B virus and within-host malaria models, **4.** Within-host malaria infection and Anopheles mosquito dynamics, **5.** Population Models Structured by Age (Hepatitis B and SIL models). The true chapters of this work are Chapters 4 and 5.

Fundamentals tools of this work are Hille-Yosida operator, Strongly continuous semigroup, Integrated semigroup, Invariant manifold, Bifurcation, Lyapunov stability, linearized stability and Numerical analysis. For each model, we derived the existence of a unique maximal bounded dissipative semiflow. We also performed the asymptotic behavior of the models with respect to a specific threshold parameter.

Thematic results are provided for Within-host malaria infection, Anopheles mosquito dynamics, HBV and HIV dynamics in age-structured population.

For example, for within-host multi-strain malaria infection dynamics, our study allowed for the observation of competitive suppression, the reduction of parasites numbers due to the presence of another parasite, and competitive release, the improved performance of a parasite after the removal of a competitor. These studies demonstrated that the presence of two parasites led to the reduction in density of at least one parasite.

Résumé

Dans cette thèse, nous étudions un récent modèle intra-hôte de paludisme à plusieurs souches et la dynamique spatiale des anophèles moustiques. Nous étudions aussi deux modèles épidémiques pour une population hôte structuré en âge. Plus précisément, un modèle de l'hépatite viral B et un modèle SIL (Susceptible-Infectés-Perdus de vue) prenant en compte la transmission verticale de la maladie.

Ce travail est organisé en cinq chapitres majeurs: **1.** Introduction Générale, **2.** Biologie du Paludisme et de l'Hépatite Virale B, **3.** Les modèles d'Hépatite virale B et intra-hôte de paludisme, **4.** L'infection intra-hôte de paludisme et Dynamique spatiale des anophèles moustiques, **5.** Modèles de population structurés en âge (modèles SIL et d'hépatite B). L'essentiel de ce travail est donné par les Chapitres **4** et **5.**

Les outils fondamentaux de ce travail sont les opérateurs de Hille-Yosida, les semi-groupes fortement continus, les semi-groupes intégrés, la théorie de bifurcation, stabilité au sens de Lyapunov, la stabilité linéaire et l'analyse numérique. Pour chaque model, nous démontrons l'existence et l'unicité d'un unique flow borné, dissipatif et régulier. Nous étudions aussi le comportement asymptotique de chaque model suivant un paramètre seuil spécifique.

Les résultats thématiques sont donnés pour la dynamique d'infection intra-hôte multi-souches de paludisme, la dynamique spatiale des anophèles moustiques, la dynamique d'hépatite virale B et de VIH dans une population structurée en âge.

Par exemple, pour l'infection intra-hôte multi-souches de paludisme, notre étude démontre l'élimination compétitive des souches plasmodiales, la réduction du nombre de parasites dus à la présence d'une autre souche plasmodiale. Cette étude a démontré que la présence de deux parasites conduit à la réduction de la densité d'au moins un parasite.

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Chapter One

General Introduction

In this new century mankind faces ever more challenging environmental and public health problems, such as pollution, invasion by exotic species, the emergence of new diseases or the emergence of diseases into new regions (West Nile virus, SARS, Anthrax, etc.), the resurgence of existing diseases (influenza, malaria, TB, HIV/AIDS, etc.), and the antibiotic-resistant infections (malaria, etc.). Mathematical models have been successfully used to study many biological, epidemiological and medical problems, and nonlinear and complex dynamics have been observed in all of those contexts. Mathematical studies have helped us not only to better understand these problems but also to find solutions in some cases, such as the prediction and control of SARS outbreaks, understanding HIV infection, and the investigation of antibiotic-resistant infections in hospitals.

This work deals with a recent within-host malaria infection model with multistrain for the parasites and a spatial modeling of anopheles mosquito dynamics population. In this work, we also consider models of infectious disease into the host population structured by age. Namely, Hepatitis B virus (HBV) and Susceptible-Infected-Lost of sight (SIL) models.

1.1 Type of diseases.

The Oxford English Dictionary defines a disease as "a condition of the body, or of some part or organ of the body, in which its functions are disturbed or deranged; a morbid physical condition; a departure from the state of health, especially when caused by structural change." The fine-scale classification of diseases varies drastically between different scientific disciplines. Medical doctors and veterinary clinicians, for example, are primarily interested in treating human patients or animals and, as such, are most concerned about the infection's pathophysiology (affecting, for example, the central

nervous system) or clinical symptoms (for example, secretory diarrhea). Microbiologists, on the other hand, focus on the natural history of the causative organism: What is the etiological agent (a virus, bacterium, protozoan, fungus, or prion)? and what are the ideal conditions for its growth? Finally, epidemiologists are most interested in features that determine patterns of disease and its transmission.

Diseases can be either infectious or noninfectious. Infectious diseases (such as influenza) can be passed between individuals, whereas noninfectious diseases (such as arthritis) develop over an individual's lifespan. The epidemiology of noninfectious diseases is primarily a study of risk factors associated with the chance of developing the disease (for example, the increased risk of lung cancer attributable to smoking). In contrast, the primary risk factor for catching an infectious disease is the presence of infectious cases in the local population.

Infectious diseases (both macro- and microparasitic) can be subdivided into two further categories, depending on whether transmission of infection is direct or indirect. Direct transmission is when infection is caught by close contact with an infectious individual. The great majority of microparasitic diseases, such as influenza, measles, and HIV, are directly transmitted, although there are exceptions such as cholera, which is waterborne. Generally, directly transmitted pathogens do not survive for long outside the host organism. In contrast, indirectly transmitted parasites are passed between hosts via the environment; most macroparasitic diseases, such as those caused by helminths and schistosomes, are indirectly transmitted, spending part of their life cycle outside of their hosts.

Worldwide there are about 1,415 known human pathogens of which 217 (15%) are viruses or prions and 518 (38%) are bacteria or rickettsia; hence around 53% are microparasites (Cleaveland et al. 2001[34]). Of these pathogens, 868 (61%) are zoonotic and can therefore be transmitted from animals to humans. Around 616 pathogens of domestic livestock are known, of which around 18% are viral and 25% bacterial. However, if we restrict our attention to the 70 pathogens listed by the Office International des Epizooties (which contain the most prominent and infectious livestock diseases), we find that 77% are microparasites (Cleaveland et al. 2001[34]). The lower number of known livestock pathogens compared to human pathogens probably reflects to some degree our natural anthropocentric bias. Similarly, very few infectious diseases of wildlife

are known or studied in any detail, and yet wildlife reservoirs may be important sources of novel emerging human infections. It is therefore clear that the study of microparasitic infectious diseases encompasses a huge variety of hosts and diseases.

1.2 Characterization of diseases.

The progress of an infectious microparasitic disease is defined qualitatively in terms of the level of pathogen within the host, which in turn is determined by the growth rate of the pathogen and the interaction between the pathogen and the host's immune response. Figure 1.1 shows a much simplified infection profile. Initially, the host is *susceptible* to infection: No pathogen is present; just a low-level nonspecific immunity within the host. At time 0, the host encounters an infectious individual and becomes infected with a microparasite; the abundance of the parasite grows over time. During this early phase the individual may exhibit no obvious signs of infection and the abundance of pathogen may be too low to allow further transmission–individuals in this phase are said to be in the *exposed class*. Once the level of parasite is sufficiently large within the host, the potential exists to transmit the infection to other susceptible individuals; the host is *infectious*. Finally, once the individual's immune system has cleared the parasite and the host is therefore no longer infectious, they are referred to as *recovered*. [120].

This fundamental classification (as susceptible, exposed, infectious, or recovered) solely depends on the host's ability to transmit the pathogen. This has two implications. First, the disease status of the host is irrelevant–it is not important whether the individual is showing symptoms; an individual who feels perfectly healthy can be excreting large amounts of pathogen (Figure 1.1). Second, the boundaries between exposed and infectious (and infectious and recovered) are somewhat fuzzy because the ability to transmit does not simply switch on and off. This uncertainty is further complicated by the variability in responses between different individuals and the variability in pathogen levels over the infectious period; it is only with the recent advances in molecular techniques that these within-host individual-level details are beginning to emerge.

Although such qualitative descriptions of disease dynamics allow us to understand the behavior of infection within an individual and may even shed some light on potential transmission, if we are to extrapolate from the individual-level dynamics to the

population-scale epidemic, numerical values are required for many of the key parameters. Two fundamental quantities govern the population-level epidemic dynamics: the *basic reproductive ratio*, R_0, and the timescale of infection, which is measured by the infectious period for SIS and SIR infections or by a mixture of exposed and infectious periods in diseases with SEIR dynamics (for details, see [120], Chapter 2). The basic reproductive number is one of the most critical epidemiological parameters because it defines the average number of secondary cases an average primary case produces in a totally susceptible population. Among other things, this single parameter allows us to determine whether a disease can successfully invade or not, the threshold level of vaccination required for eradication, and the long-term proportion of susceptible individuals when the infection is endemic.

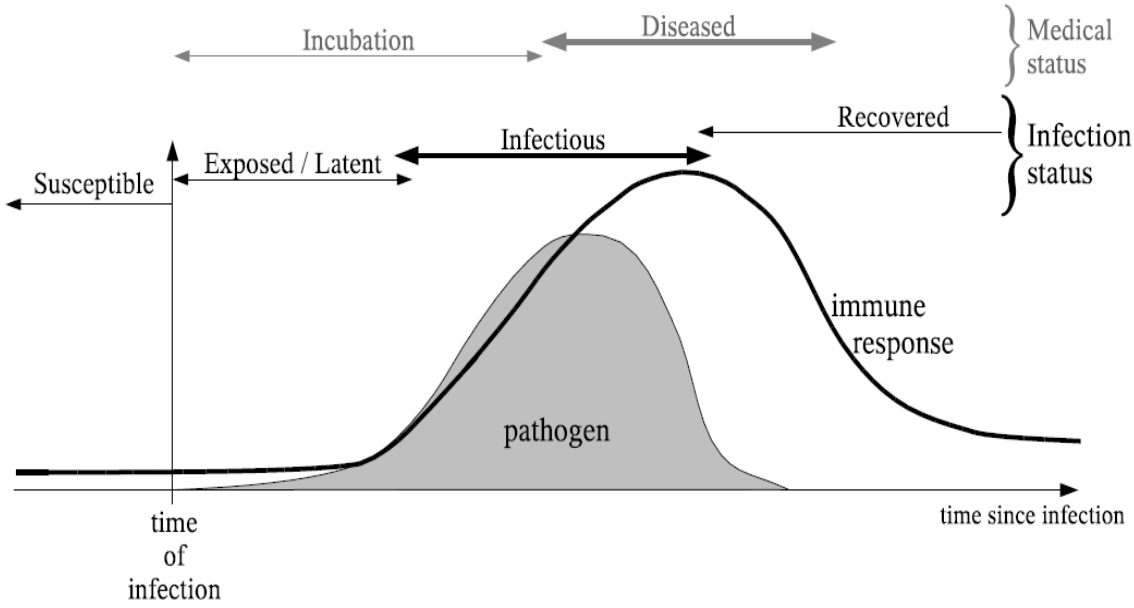


Figure 1.1: A caracature of the time-line of infection, showing the dynamics of the pathogen (gray area) and the host immune response (black line) as well as labeling the various infection classes: susceptible, exposed, infectious, and recovered. Note that the diseased period, when symptoms are experienced, is not necessarily correlated with any particular infection class. (Ref. Keeling et al. 2008[120])

1.3 What are mathematical models?

Recent years have seen an increasing trend in the number of publications, both in highprofile journals and more generally, that utilize mathematical models (Figure 1.2). This is associated with an increased understanding of what models can offer in terms of prediction and insight. Any model can be typically thought of as a conceptual tool that explains how an object (or system of objects) will behave. A mathematical model uses the language of mathematics to produce a more refined and precise description of the system. In epidemiology, models allow us to translate between behavior at various scales, or extrapolate from a known set of conditions to another. As such, models allow us to predict the population-level epidemic dynamics from an individual-level knowledge of epidemiological factors, the long-term behavior from the early invasion dynamics, or the impact of vaccination on the spread of infection.

By definition, all models are "wrong," in the sense that even the most complex will make some simplifying assumptions. It is, therefore, difficult to express definitively which model is "right," though naturally we are interested in developing models that capture the essential features of a system. Ultimately, we are faced with a rather subjective measure of the usefulness of any model.

Formulating a model for a particular problem is a trade-off between three important and often conflicting elements: accuracy, transparency, and flexibility, [120]. *Accuracy*, the ability to reproduce the observed data and reliably predict future dynamics, is clearly vital, but whether a qualitative or quantitative fit is necessary depends on the details of the problem. A qualitative fit may be sufficient to gain insights into the dynamics of an infectious disease, but a good quantitative fit is generally necessary if the model is used to advise on future control policies. Accuracy generally improves with increasing model complexity and the inclusion of more heterogeneities and relevant biological detail. Clearly, the feasibility of model complexity is compromised by computational power, the mechanistic understanding of disease natural history, and the availability of necessary parameters. Consequently, the accuracy of any model is always limited. *Transparency* comes from being able to understand (either analytically or more often numerically) how the various model components influence the dynamics and interact. This is usually achieved by successively adding or removing components and building

upon general intuitions from simpler models. As the number of model components increases, it becomes more difficult to assess the role of each component and its interactions with the whole. Transparency is, therefore, often in direct opposition to accuracy (Figure 1.3). *Flexibility* measures the ease with which the model can be adapted to new situations; this is vital if the model is to evaluate control policies or predict future disease levels in an ever-changing environment. Most mechanistic models (such as those within this book) are based on well-understood disease transmission principles and are therefore highly flexible, whereas "black-box" time-series tools (such as neural nets) that may be able to accurately reproduce a given time series of reported cases are less amenable to modification.

1.4 What is a good model?

According to Keeling et al. 2008 [120], no model is perfect, and no model can accurately predict the detailed outcome of an infection process. However, two key points define a good model. First, a model should be suited to its purpose–that is, it should be as simple as possible, but no simpler-having an appropriate balance of accuracy, transparency, and flexibility (Figure 1.3). A model that is designed to help us understand the behavior of an infectious disease should concentrate on the characteristics that are of interest while simplifying all others. A model built for accurate prediction should provide a comprehensive picture of the full dynamics, and include all the relevant features of the disease and host, although determining which factors are relevant and which may be safely ignored is a complex and skilled process. Second, the model should be parameterizable (where necessary) from available data. Thus, although a predictive model requires the inclusion of many features, it is important that they can all be parameterized from available data. Hence, in many situations–such as at the start of an emerging (novel) epidemic–it may be impossible to produce a good predictive model. In contrast, if we are interested only in understanding an epidemic pattern, there is far less need for a model to accurately represent a particular scenario, and so parameterization and availability of data are less important. Therefore, it is clear that what constitutes a good model is context dependent.

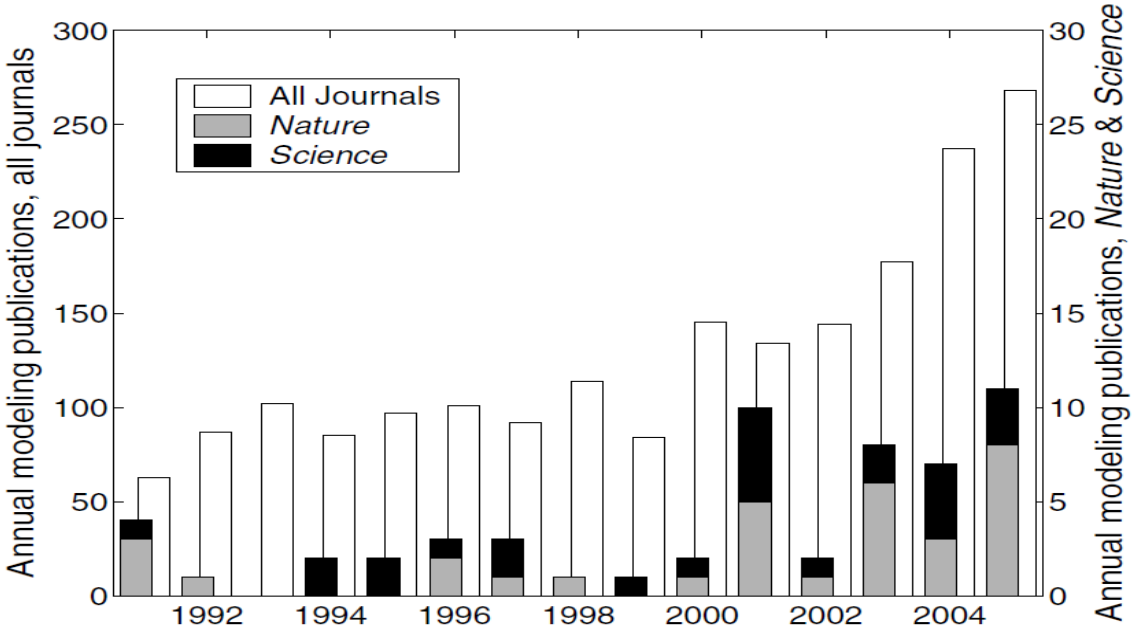


Figure 1.2: An indication of the increasing importance and use of mathematical models in the epidemiological literature. White bars show the approximate number of publications in the entire scientific literature that utilize models of infectious diseases. (Data are obtained from ISI Web of Science, and include all publications that contain in their title or abstract the words "epidemic," and "infect*," and either "model*" or "simulat*.") The gray and black bars show the number of these publications to be found in Nature and Science respectively, providing some indication of the high impact of such work. (These papers were identified from their title and abstract.) Note the different scales for general papers and those in Nature or Science. (Ref. Keeling et al. 2008[120])

1.5 Aged-structured models

Structured population models distinguish individuals from one another according to characteristics such as age, size, location, status, and movement, to determine the birth, growth and death rates, interaction with each other and with environment, infectivity, etc. The goal of structured population models is to understand how these characteristics affect the dynamics of these models and thus the outcomes and consequences of the biological and epidemiological processes Magal et al. 2008[148].

Mathematical models of populations incorporating age structure, or other structuring of individuals with continuously varying properties, have an extensive history. The

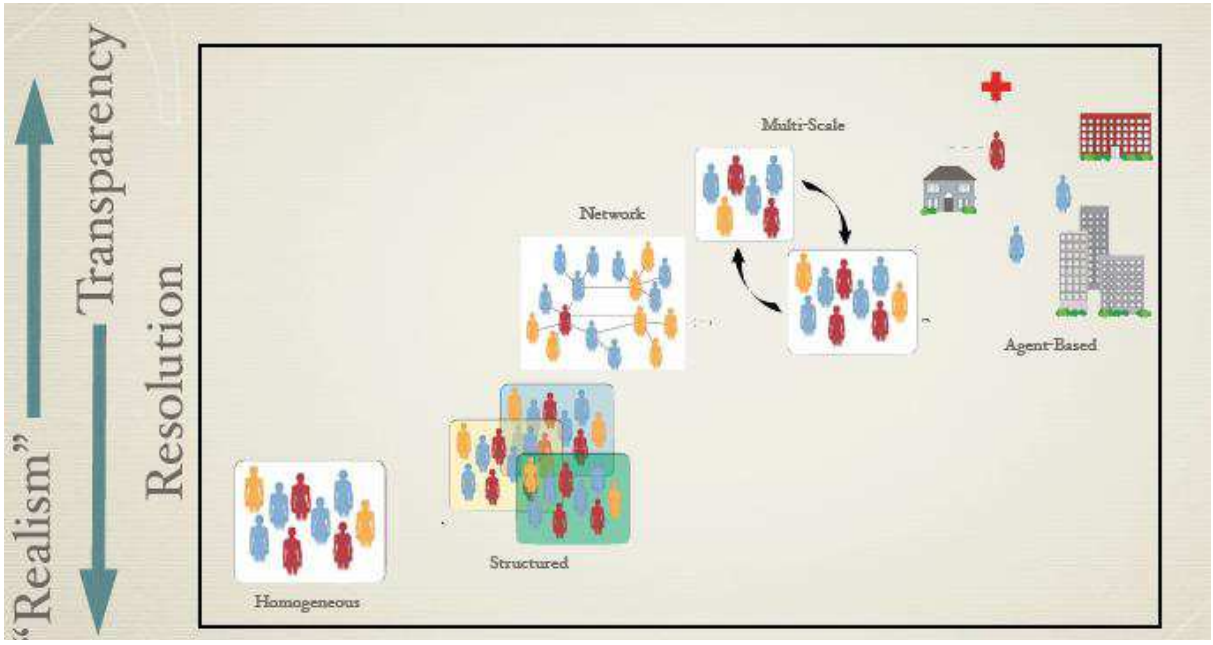


Figure 1.3: Realism versus Transparency.

earliest models of age structured populations, due to Sharpe and Lotka in 1911 [194] and McKendrick in 1926[154] established a foundation for a partial differential equations approach to modeling continuum age structure in an evolving population. At this early stage of development, the stabilization of age structure in models with linear mortality and fertility processes was recognized, although not rigorously established [138, 139]. Rigorous analysis of these linear models was accomplished later in 1941 by Feller [51], in 1963 by Bellman and Cooke [15], and others, using the methods of Volterra integral equations and Laplace transforms. Many applications of this theory have been developed in demography: Coale [37], Inaba [112], Keyfitz [125], Pollard [184], biology: Arino [10], Ayati [12], Bell and Anderson [13], Cushing [38], Gyllenberg [90], Von Foerster [207], and epidemiology: Busenberg and Cooke [25], Castillo-Chavez and Feng [28], Feng, Huang, Castillo-Chavez [71], Feng, Li, Milner [72], Hoppensteadt [102], Kermack and McKendrick [124], to name only a few.

A new impetus of research in age structured models arose with the pioneering work of Gurtin and MacCamy in 1974 [89] for nonlinear age structured models. Their technology, which utilized a nonlinear Volterra integtral equations approach, established the existence, uniqueness, and convergence to equilibrium of solutions to non-

linear versions of the Sharpe-Lotka-McKendrick model. A rapid expansion of research in nonlinear models ensued in both theoretical developments and biological applications. A comprehensive treatment of this approach is given by Iannelli [108]. The increasingly complex mathematical issues involved in nonlinearities in age structured models led to the development of new technologies, and one of the most useful of these has been the method of semigroups of linear and nonlinear operators in Banach spaces. This functional analytic approach was developed by many researchers, including [14, 26, 35, 49, 50, 86, 87, 109, 140, 141, 186, 200, 201, 202, 203, 211].

In the semigroup approach, an evolving age structured population is viewed as a dynamical system in a state space such as $X = L^1((0, a_1), \mathbb{R})$, where $a_1 \leq \infty$ is the maximum age of individuals. The initial stage at time $t = 0$ is a given age distribution $\phi(a), a \in (0, a_1)$, where $\phi \in X$. The age distribution at a later time $t > 0$ is given by $(S(t)\phi)(a)$, where $S(t)$, $t \geq 0$ is a linear or nonlinear semigroup of operators in X. The function $p(t, a) = (S(t)\phi)(a)$ is viewed as the age density of the population at time t, in the sense that the total population at any time t in a specific age range $(\tilde{a}, \hat{a}) \subset (0, a_1)$ is

$$\int_{\tilde{a}}^{\hat{a}} p(t, a)da.$$

If the initial data ϕ is sufficiently smooth, then $p(t, a)$ satisfies the linear partial differential equation model (I.1):

$$\begin{aligned} \frac{\partial}{\partial t}p(t,a) + \underbrace{\frac{\partial}{\partial a}p(t,a)}_{\text{aging}} &= \underbrace{-\mu(a)p(t,a)}_{\text{mortality}},\ a \in (0, a_1), t > 0; \\ p(t, 0) &= \underbrace{\int_0^{a_1} \beta(a)p(t,a)da}_{\text{birth rate at time t}},\ t > 0; \\ p(0, a) &= \phi(a), a \in (0, a_1), \phi \in X. \end{aligned}$$

The mortality process is controlled by the age-dependent *mortality modulus* $\mu(a)$. The reproductive process is controlled by the age dependent *fertility modulus* $\beta(a)$. If the initial state $\phi \in X$ is not sufficiently regular, then the formula $p(t, a) = (S(t)\phi)(a)$ is viewed as a generalized solution of (I.1). The advantage of the semigroup approach is that it enables description of the population processes as a dynamical system in the state space X. Nonlinear version of (I.1), as first investigated in [89], allow the mortality and fertility moduli to depend on the density $p(t, a)$ or a functional of density, such as the

total population $\int_0^{a_1} p(t,a)da$ at time t [52, 61, 211, 212, 214].

1.6 Layout of this work.

This thesis is organized into five majors chapters (including this introduction). To help with a rapid understanding of each chapter, crucial synopsis of the main points are highlighted throughout the chapter as follows:

1. General Introduction

This chapter introduces the basic concepts and ideas of modeling, as well as providing a brief overview of epidemiological characteristics and behavior. We also gives a brief description of mathematical models of populations incorporating age structure, or other structuring of individuals with continuously varying properties.

2. Biology of Malaria and Hepatitis B Virus

The emergence and spread of antimalarial drug resistance poses a severe and increasing public health threat. All the most effective drugs that we have had in the last few decades have been one by one rendered useless by the remarkable ability of this parasite to mutate and develop resistance. The *P. falciparum* parasite is now resistant to all of the used antimalarial drugs, even to the latest artemisinin-based combination treatments. Failures in prophylaxis or treatments induce the re-emergence of parasite related morbidity and mortality.

On the other hand, hepatitis B virus is a general term meaning *inflammation of the liver* and can be caused by a variety of different viruses such as hepatitis A, B, C, D and E. Of the many viral causes of human hepatitis few are of greater global importance than hepatitis B virus. More than 2 000 million people alive today have been infected with HBV at some time in their lives. Of these, about 350 million remain infected chronically and become carriers of the virus.

3. Models of Hepatitis B virus and within-host malaria.

Mathematical models associated to within-host *P. falciparum* malaria infection have been proposed since the pioneer work of Anderson, May and Gupta [2]. This model was intended to explain experimental observations, namely parasitaemia, that is, the concentration of parasitized red blue cells and also the decrease of the uninfected red blue cells leading to anaemia. Such ideas have been further developed in [4, 78, 98,

101, 103, 191, 134]. However all these works do not take into account an important characteristic of *P. falciparum* which is sequestration of merozoites with the pRBC and their ruptures. Such an issue has been considered using discrete age-structured systems of equations (see for instance [79, 80, 81, 159]) with constant red blue cells population assumption. We refer to Iggidr et al. [111] for a mathematical study of a discrete age-structured model with varying red blue cells concentration.

For HBV infection, many mathematical models have been proposed to investigate the transmission dynamics of HBV in various countries and regions in the world; covering many topics: sexual transmission of HBV which includes heterogeneous mixing with respect to age and sexual activity[5]; relation between the age at infection with HBV and the development of the carrier state[68]; HBV transmission in developing countries[158, 67, 215]; the long-term effectiveness of the vaccination[221]; determined the prevalence of infection[160]. Age-structured models have also been used to model the transmission dynamics of HBV by some researchers; see for instance Edmunds et al.[68], McLean and Blumberg[158], Zhao, Xu, and Lu[221], Zou, Ruan and Zhang[222].

4. Within-host malaria infection and Anopheles mosquito dynamics. This first true chapter is subdivided in two sections. The first section deals with an age-structured malaria within-host model and the second section deals with an advection-reaction mathematical model for the dynamics of the malaria vector.

For the age-structured malaria within-host model, taking into account multi-strains interaction, we provide a global analysis of the model depending upon some epidemic threshold $\mathcal{T}_0$. When $\mathcal{T}_0 \leq 1$, then the disease free equilibrium is globally asymptotically stable and the parasites are cleared. On the contrary if $\mathcal{T}_0 > 1$, the model exhibits the competition exclusion principle. Roughly speaking, only the strongest strain survives while the other strains go to extinct. Under some additional parameter conditions we prove that the endemic equilibrium corresponding to the strongest strain is globally asymptotically stable.

Despite the enormous global burden of malaria, after more than a century of research we still have a poor understanding of the mechanistic link between environmental variables, such as temperature and malaria risk. Hence, this chapter also develop and analyze an advection-reaction mathematical model for the dynamics of the malaria vector, taking into account environmental parameters (such as temperature). We derive

the existence of positive solutions to the seasonal model and the mosquito extinction results. We also derive persistence results to the seasonal model: the weak persistence results and the strong persistence results.

5. Population Models Structured by Age: Hepatitis B and SIL models

This chapter is organized in two sections and deals with two population models structured by age. The first section is concerned by a mathematical SIL (Susceptible-Infected-Lost of sight) model for the spread of a directly transmitted infectious disease in an age-structured population; taking into account the demographic process and the vertical transmission of the disease. For the SIL model, we first establish the mathematical well-posedness of the time evolution problem by using the semigroup approach. Next we prove that the basic reproduction ratio R_0 is given as the spectral radius of a positive operator, and an endemic state exist if and only if the basic reproduction ratio R_0 is greater than unity, while the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$. We also show that the endemic steady states are forwardly bifurcated from the disease-free steady state when R_0 cross the unity. Finally we examine the conditions for the local stability of the endemic steady states.

The second section of the chapter is concerned by and age-structured model for the transmission of hepatitis B virus, with differential infectivity: symptomatic infection and asymptomatic infection. The model is completely analyzed. We compute the basic reproduction number $\mathcal{R}_0$. We investigate the existence of equilibria and study their stability. We found that the model exhibits a forward bifurcation, that is, if $\mathcal{R}_0 \leq 1$, there exists a disease-free equilibrium which is globally asymptotically stable, while if $\mathcal{R}_0 > 1$, the disease-free equilibrium is unstable and there exists a unique endemic which is globally asymptotically stable. Numerical results are presented to illustrate analytical results. Through numerical simulation, we found that a control strategy of HBV consist in a combination of immunization of newborns, immunization of susceptible individuals (at least young adults), and reduction of perinatal infection.

Chapter Two

Biology of Malaria and Hepatitis B Virus.

2.1 Malaria biology

Malaria is one of the most severe public health problems worldwide. It is a leading cause of death and disease in many developing countries, where young children and pregnant women are the groups most affected. According to the World Health Organization's World Malaria Report 2012 and the Global Malaria Action Plan: 3.3 billion people (half the world's population) live in areas at risk of malaria transmission in 106 countries and territories. In 2010, malaria caused an estimated 216 million clinical episodes, and 655,000 deaths [169]. An estimated 91% of deaths in 2010 were in the African Region [216], followed by 6% in the South-East Asian Region and 3% in the Eastern Mediterranean Region (3%). About 86% of deaths globally were in children. Malaria imposes substantial costs to both individuals and governments. Direct costs (for example, illness, treatment, premature death) have been estimated to be at least US$ 12 billion per year. The costs are many times more than that in lost economic growth.

2.1.1 Epidemiology

The majority of malaria cases (65%) occur in children under 15 years old [167]. About 125 million pregnant women are at risk of infection each year; in Sub-Saharan Africa, maternal malaria is associated with up to 200,000 estimated infant deaths yearly [96]. There are about 10,000 malaria cases per year in Western Europe, and 1300-1500 in the United States [199]. About 900 people died from the disease in Europe between 1993 and 2003 [121]. Both the global incidence of disease and resulting mortality have declined in recent years. According to the WHO, deaths attributable to malaria in 2010 were

reduced by over a third from a 2000 estimate of 985,000, largely due to the widespread use of insecticide-treated nets and artemisinin-based combination therapies [104].

The geographic distribution of malaria within large regions is complex, and malaria-afflicted and malaria-free areas are often found close to each other [85]. Malaria is presently endemic in a broad band around the equator, in areas of the Americas, many parts of Asia, and much of Africa; in Sub-Saharan Africa, 85-90% of malaria fatalities occur [130] (see Figure 2.1).

Malaria is prevalent in tropical and subtropical regions because of rainfall, consistent high temperatures and high humidity, along with stagnant waters in which mosquito larvae readily mature, providing them with the environment they need for continuous breeding.

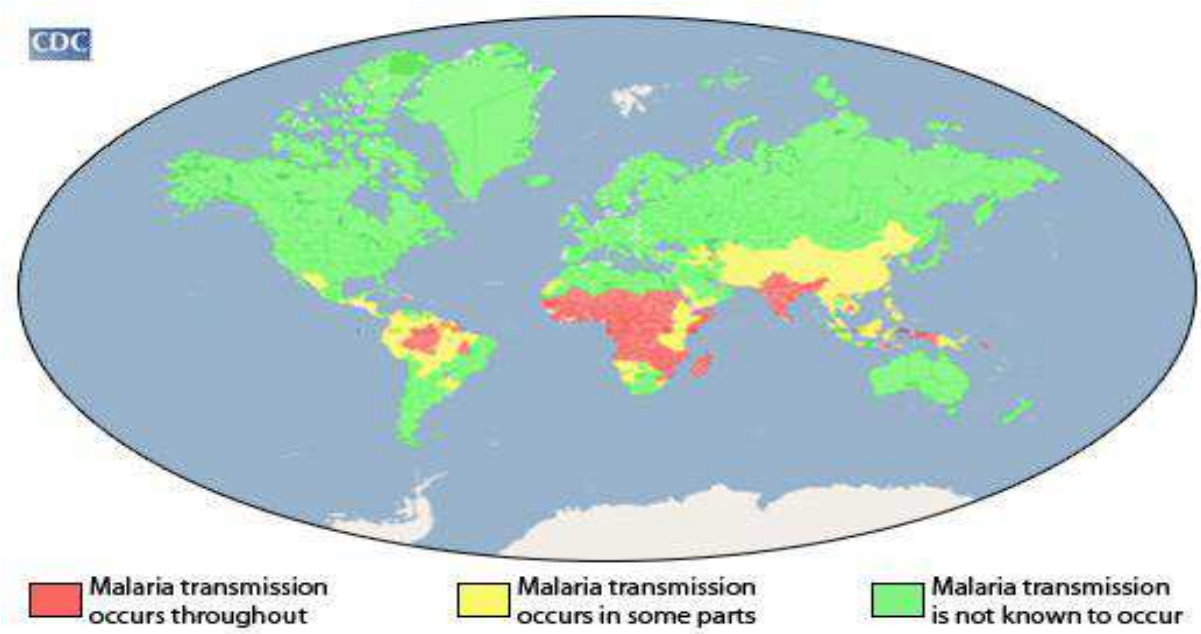


Figure 2.1: Approximation of the parts of the world where malaria transmission occurs.

Five species of *Plasmodium* can infect and be transmitted by humans. The vast majority of deaths are caused by *P. falciparum* and *P. vivax*, while *P. ovale*, and *P. malariae* cause a generally milder form of malaria that is rarely fatal. The zoonotic species *P. knowlesi*, prevalent in Southeast Asia, causes malaria in macaques but can also cause severe infections in humans. Malaria is typically diagnosed by the microscopic examination of blood using blood films, or with antigen-based rapid diagnostic tests.

Modern techniques that use the polymerase chain reaction to detect the parasite's DNA have also been developed, but these are not widely used in malaria-endemic areas due to their cost and complexity.

2.1.2 Life cycle

The pathogenesis of human *P. falciparum* infection is a complex process (see Figure 2.2). In the life cycle of *Plasmodium*, a female Anopheles mosquito (the definitive host) transmits a motile infective form (called the sporozoite) to a vertebrate host such as a human (the secondary host), thus acting as a transmission vector. A sporozoite travels through the blood vessels to liver cells (hepatocytes), where it reproduces asexually (tissue schizogony), producing thousands of merozoites; this is the starting point of the erythrocytic phase (we refer to [75] for mechanistic mechanism of the release). During this phase, the free merozoites infect new red blood cells and initiate a series of asexual multiplication cycles (blood schizogony) that produce 8 to 32 new infective merozoites, at which point the cells burst and the infective cycle begins anew.[131] Other merozoites develop into immature gametes, or gametocytes. When a fertilized mosquito bites an infected person, gametocytes are taken up with the blood and mature in the mosquito gut. The male and female gametocytes fuse and form zygotes (ookinetes), which develop into new sporozoites. The sporozoites migrate to the insect's salivary glands, ready to infect a new vertebrate host. The sporozoites are injected into the skin, alongside saliva, when the mosquito takes a subsequent blood meal [41].

Only female mosquitoes feed on blood; male mosquitoes feed on plant nectar, and thus do not transmit the disease. The females of the Anopheles genus of mosquito prefer to feed at night. They usually start searching for a meal at dusk, and will continue throughout the night until taking a meal [11]. Malaria parasites can also be transmitted by blood transfusions, although this is rare [177].

The blood stage of the parasites is mainly responsible for the clinical symptoms of the infection. The rupture of the parasitized red bood cells (pRBC) causes clinical fever. Moreover *P. falciparum* infection is the most frequent acquired red blood cells (RBC) disorders in the world (see [84], we also refer to the review paper of Buffet et al [23] and the references therein), that may also lead to severe symptoms such as anaemia or cerebral malaria (see [77]).

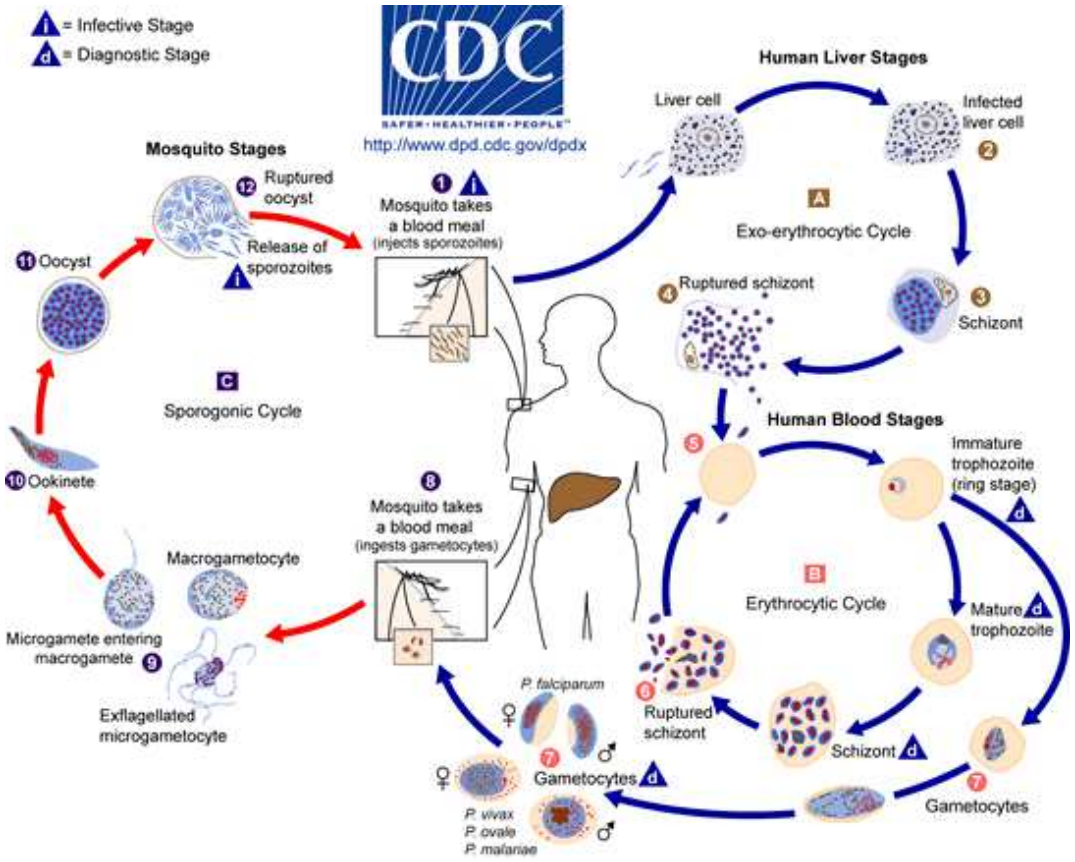


Figure 2.2: Malaria life cycle

2.1.3 Resistance to malaria drugs.

Despite a need, no effective vaccine currently exists, although efforts to develop one are ongoing. Several medications are available to prevent malaria in travellers to malaria-endemic countries (prophylaxis). A variety of antimalarial medications are available. Severe malaria is treated with intravenous or intramuscular quinine or, since the mid-2000s, the artemisinin derivative artesunate, which is superior to quinine in both children and adults and is given in combination with a second anti-malarial such as mefloquine. Resistance has developed to several antimalarial drugs and many drugs are out of use; for example, chloroquine-resistant *P. falciparum* has spread to most malarial areas, and emerging resistance to artemisinin has become a problem in some parts of Southeast Asia.

The emergence and spread of antimalarial drug resistance poses a severe and increasing public health threat. All the most effective drugs that we have had in the last few

decades have been one by one rendered useless by the remarkable ability of this parasite to mutate and develop resistance. The *P. falciparum* parasite is now resistant to all of the used antimalarial drugs, even to the latest artemisinin-based combination treatments (see Figure 2.3). Failures in prophylaxis or treatments induce the re-emergence of parasite related morbidity and mortality. Knowledge about resistance mechanisms involved may allow the development of new drugs that minimize or circumvent drug resistance, may allow the identification of new targets for drug development and to identify molecular markers for malaria resistance surveillance. Resistance is often associated with 1) inhibition of alteration of key enzymes that are targets for antimalarial drugs or 2) alteration of drug accumulation into the parasite which results from reduced uptake of the drug, an increased efflux, or a combination of the two processes [185].

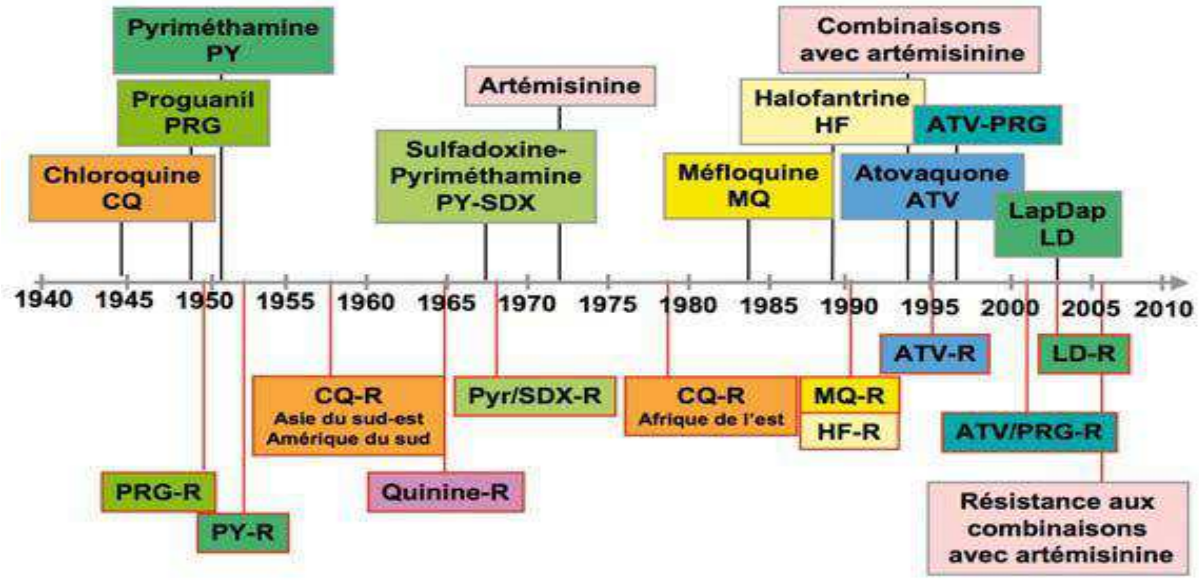


Figure 2.3: Introduction of malaria drugs and development of resistance (R) of *P. falciparum*.

2.2 HBV biology

Hepatitis B virus (HBV) infection is widespread in many parts of the world, especially in Africa, Southeast Asia, the Middle East, South and Western Pacific islands, the

interior Amazon River basin, and certain parts of the Caribbean (Centers for Disease Control and Prevention (CDC[30])). By the estimation of the World Health Organization (WHO[217]), about 2 billion people have been infected with HBV. An estimate of 600,000 persons die each year due to the acute or chronic consequences of the virus (WHO [217]).

Approximately 5% of all acute HBV infections progress to chronic infection, with the risk of chronic HBV infection decreasing with age. As many as 90% of infants who acquire HBV infection from their mothers at birth become chronically infected. Of children who become infected with HBV between 1 year and 5 years of age, 30% to 50% become chronically infected. By adulthood, the risk of acquiring chronic HBV infection is approximately 5% (see Fig. 2.4).

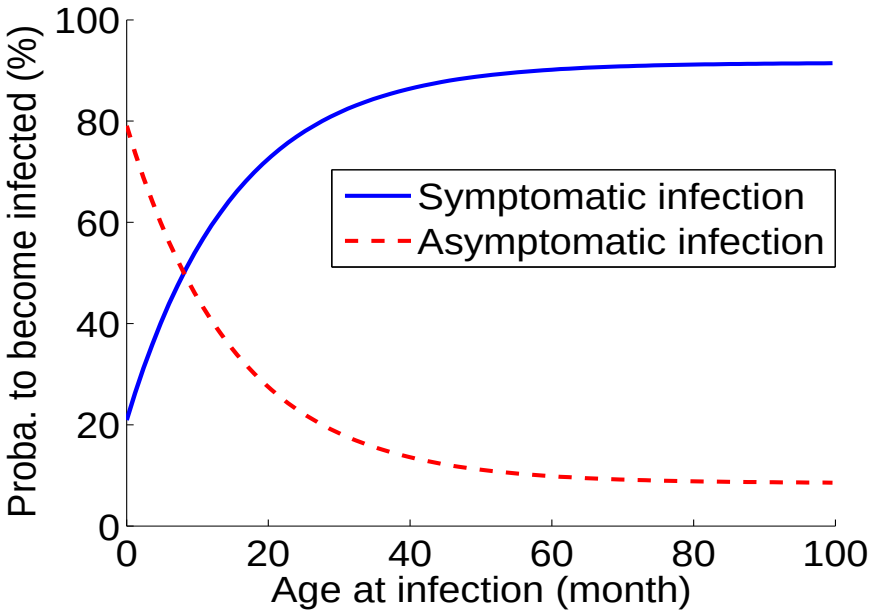


Figure 2.4: Outcome of HBV infection by age at infection

2.2.1 Epidemiology

Reservoir

Although other primates have been infected in laboratory conditions, HBV infection affects only humans. No animal or insect hosts or vectors are known to exist (CDC).

Transmission

The virus is transmitted by parenteral or mucosal exposure to hepatitis B surface antigen(HBsAg)-positive body fluids from persons who have acute or chronic HBV infection. The highest concentrations of virus are in blood and serous fluids; lower titers are found in other fluids, such as saliva and semen. Saliva can be a vehicle of transmission through bites; however, other types of exposure to saliva, including kissing, are unlikely modes of transmission. There appears to be no transmission of HBV via tears, sweat, urine, stool, or droplet nuclei. One of the most important route of transmission is by sexual contact, either heterosexual or homosexual, with an infected person. Fecal-oral transmission does not appear to occur. However, transmission occurs among men who have sex with men, possibly via contamination from asymptomatic rectal mucosal lesions.

Perinatal transmission from mother to infant at birth is very efficient. If the mother is positive for both HBsAg and hepatitis B e antigen (HBeAg), 70%-90% of infants will become infected in the absence of postexposure prophylaxis. The risk of perinatal transmission is about 10% if the mother is positive only for HBsAg. As many as 90% of these infected infants will become chronically infected with HBV.

The frequency of infection and patterns of transmission vary in different parts of the world. Approximately 45% of the global population live in areas with a high prevalence of chronic HBV infection (8% or more of the population is HBsAg positive), 43% in areas with a moderate prevalence (2% to 7% of the population is HBsAg positive), and 12% in areas with a low prevalence (less than 2% of the population is HBsAg positive). Source: CDC.

Communicability

Persons with either acute or chronic HBV infection should be considered infectious any time that HBsAg is present in the blood. When symptoms are present in persons with acute HBV infection, HBsAg can be found in blood and body fluids for 1-2 months before and after the onset of symptoms.

2.2.2 Public health policy against HBV

Hepatitis B vaccines have been available in the United States since 1981. However, the impact of vaccine on HBV disease has been less than optimal.

The apparent lack of impact from the vaccine can be attributed to several factors. From 1981 until 1991, vaccination was targeted to persons in groups at high risk of acquiring HBV infection. A large proportion of persons with HBV infection (25% to 30%) deny having any risk factors for the disease. These persons would not be identified by a targeted risk factor screening approach.

A comprehensive strategy to eliminate hepatitis B virus transmission was recommended in 1991 by WHO; it includes prenatal testing of pregnant women for HBsAg to identify newborns who require immunoprophylaxis for prevention of perinatal infection and to identify household contacts who should be vaccinated, routine vaccination of infants, vaccination of adolescents, and vaccination of adults at high risk for infection. Recommendations to further enhance vaccination of adults at increased risk of HBV infection were published in 2006.

Routine infant immunization

This routine infant vaccination is to vaccinate their new-borns from a young age. Great efforts should be given to routine vaccination of infants, because most chronic infections are acquired during the earliest childhood, especially in countries with medium or high endemicity. It is also a high priority in countries with low endemicity, because it is the only strategy to avoid infection of all age groups (children, adolescents and adults). In these countries, the majority of chronic infections are acquired during adolescence or adulthood, but infections that occur during childhood play an important role in maintaining the burden of chronic infection.

Prevention of perinatal transmission of hepatitis B

Perinatal HBV transmission can be prevented by identifying HBV-infected (i.e., Hepatitis B surface antigen [HBsAg]-positive) pregnant women and providing Hepatitis B immune globulin and Hepatitis B vaccine to their infants within 12 hours of birth.

Preventing perinatal HBV transmission is an integral part of the national strategy

to eliminate Hepatitis B. Generally, it consist on: (i) Universal screening of pregnant women for HBsAg during each pregnancy; (ii) Case management of HBsAg-positive mothers and their infants; (iii) Provision of immunoprophylaxis for infants born to infected mothers, including Hepatitis B vaccine and Hepatitis B immune globulin and (iv) Routine vaccination of all infants with the Hepatitis B vaccine series, with the first dose administered at birth.

The major obstacle is that screening pregnant women and infants research to infected mothers are operations that require significant resources, which is sometimes expensive for most countries with high prevalence. Prevention of perinatal transmission of hepatitis B is of major importance because an estimated 90% of children infected at birth become chronic in adulthood.

Catch-up Immunization Schedule

Catch-up strategies targeted at older age groups or groups with risk factors for acquiring HBV infection should be considered as a supplement to routine infant vaccination in countries of intermediate or low hepatitis B endemicity. In such settings, a substantial proportion of the disease burden may be attributable to infections acquired by older children, adolescents and adults. In countries of high endemicity, large-scale routine vaccination of infants rapidly reduces the transmission of HBV. In these circumstances, catch-up vaccination of older children and adults has relatively little impact on chronic disease because most of them have already been infected.

It is particularly important that the catch-up vaccination in older age classes does not impede efforts to achieve full immunization of infants and to prevent mother to child transmission of the virus by administering to the last dose of vaccine at birth (WHO).

Chapter Three

Hepatitis B virus and within-host models.

3.1 Within-host models.

The within-host models describe the parasites dynamics and their interaction with the host cells. For example *P. falciparum* attacks uninfected red blood cells and H.I.V. attacks auxiliary lymphocytes CD4+T.

There has been numerous works on pathogen within-host dynamics in *P. falciparum* infection. We refer to [4, 47, 78, 79, 80, 81, 98, 101, 103, 151, 156, 157, 164, 191]. We also refer to the survey paper of Molineaux and Dietz in [165] and the references therein as well as the following recent papers on this topic [111, 205, 134, 189, 18, 163]. Mathematical models associated to within-host *P. falciparum* malaria infection have been proposed since the pioneer work of Anderson, May and Gupta [2]. This model was intended to explain experimental observations, namely parasitaemia, that is, the concentration of parasitized red blue cells and also the decrease of the uninfected red blue cells leading to anaemia. Such ideas have been further developed in [4, 78, 98, 101, 103, 191]. We also refer to Li et al [134] for a mathematical model with immune response yielding to sustained oscillations. However all these works do not take into account an important characteristic of *P. falciparum* which is sequestration of merozoites with the pRBC and their ruptures [111]. Such an issue has been considered using discrete age-structured systems of equations (see for instance [79, 80, 81, 159]) with constant red blue cells population assumption. We refer to Iggidr et al. [111] for a mathematical study of a discrete age-structured model with varying red blue cells concentration.

3.1.1 Anderson-May-Gupta's models

The original Anderson-May-Gupta's (AMG) model is the following

$$\begin{cases} \dot{x} = & \Lambda - \mu_x x - \beta x m, \\ \dot{y} = & \beta x m - \mu_y - \rho_y y I, \\ \dot{m} = & r\mu_y y - \mu_m - \beta x m - \rho_m I m, \\ \dot{I} = & \rho_m I m + \rho_y I y - \mu_I I, \end{cases} \tag{3.1}$$

where in x denotes the concentration of uninfected red blood cells (uRBC), while y denotes the concentration of parasitized red blue cells (pRBC). Finally m and I denotes the concentration of free merozoites in the blood stream and immune effectors respectively. The parameters μ_x, μ_y, μ_m and μ_I are the death rates of uRBC, pRBC, free merozoites respectively and immune effectors. The parameter β is the contact rate between uRBC and merozoites. Uninfected blood cells are recruited at a constant rate Λ from the bone marrow and have a natural life-expectation of $1/\mu_x \approx 120$ days. Death of a pRBC results in the release of an average number of r merozoites. The parameters ρ_y is the removal rate of pRBC by immune effectors and ρ_m is the proliferation rate of immune effectors by free merozoites.

3.1.2 Hetzel-Anderson's model

The model of Hetzel-Anderson (HA) can be consider as an extension of AMG's model, according to the immune effectors dynamics.

$$\begin{cases} \dot{x} = & \Lambda - \mu_x x - \beta x m, \\ \dot{y} = & \beta x m - \mu_y - \rho_y y I, \\ \dot{m} = & r\mu_y y - \mu_m - \beta x m - \rho_m I m, \\ \dot{I} = & \rho_m I m + \rho_y I y - \mu_I I - \mu_I I^2, \end{cases} \tag{3.2}$$

The more general AMG's model, given in Tewa et al. [205], is defined by

$$\begin{cases} \dot{x} = & f(x) - \mu_x x - \beta x m, \\ \dot{y} = & \beta x m - \mu_y - \rho_y y I, \\ \dot{m} = & r\mu_y y - \mu_m - u\beta x m - v\beta y m - \rho_m m I, \\ \dot{I} = & \psi(y, m, I), \end{cases} \tag{3.3}$$

where the function $f(x) - \mu_x x$ is of class C^1 and models the recruitment rate of uRBC from borne marrow while the parameters u and v can only take the values 0 or 1. I

denotes the concentration of immune effectors and the function ψ represents the production of immune effectors in reaction to the parasites. From model (3.3) they observe that the immune response against merozoites is more difficult to observe than immune response against pRBC. Another observation is that the immune response increase when the parasites persist.

3.1.3 Barbara Hellriegel's model [98]

Hellriegel's model differs of the AMG and HA models by the following: without parasites, that is pRBC and free merozoites, the immune response will not disappear. The model of Hellriegel also takes into account multistrains malaria infections. The model reads as

$$\begin{cases} \dot{x} = & \Lambda - \mu_x x - \beta_1 m_1 x - \beta_2 m_2 x, \\ \dot{y}_1 = & \beta_1 m_1 x - (c_1 + \mu_y) y_1 - (k_{11} I_1 + k_{12} I_2) y_1, \\ \dot{y}_2 = & \beta_2 m_2 x - (c_2 + \mu_y) y_2 - (k_{21} I_1 + k_{22} I_2) y_2, \\ \dot{g}_1 = & c_1 y_1 - \alpha_y g_1 - (l_{11} I_1 + l_{12} I_2) g_1, \\ \dot{g}_2 = & c_2 y_2 - \alpha_y g_2 - (l_{21} I_1 + l_{22} I_2) g_2, \\ \dot{m}_1 = & r\mu_y y_1 - \mu_m m_1 - \beta_1 m_1 x - (h_{11} I_1 + h_{12} I_2) m_1, \\ \dot{m}_2 = & r\mu_y y_2 - \mu_m m_2 - \beta_2 m_2 x - (h_{21} I_1 + h_{22} I_2) m_2, \\ \dot{I}_1 = & (\sigma_1 m_1 + \gamma_1 y_1 + \lambda_1 g_1) I_1 - \mu_I I_1 + \frac{\epsilon}{2}, \\ \dot{I}_2 = & (\sigma_2 m_2 + \gamma_2 y_2 + \lambda_2 g_2) I_2 - \mu_I I_2 + \frac{\epsilon}{2}, \end{cases} \tag{3.4}$$

Wherein g is the gametocytes concentration.

3.1.4 The models of McKenzie et al. [156, 157, 155, 151]

McKenzie's et al models consider the dynamics of pRBC and gamatocytes. Denoting the pRBC concentration and the gametocytes concentration respectively by y and g; the model reads as

$$\begin{cases} \dot{y} = & ay - cyI - f_i(y, I), \\ \dot{g} = & f_1(y, I) - pg, \\ \dot{I} = & f_2(y, I) - cIy - qI, \end{cases} \tag{3.5}$$

wherein I denotes the concentration of immune effectors and

$$f_1(y(.), I(.)) \in \left\{ g_a y(.); g_b I(.) y(.); g_c y^2(.) \right\},$$

and

$$f_2(y(.), I(.)) \in \{s_1 y(.); s_2 I(.) yv; s_3 y(.)(I(. - \tau)\}\,.$$

3.1.5 Discrete age-structured models

The models of Gravenor and Kwiatkowski [80, 81] consider a discrete age-structured of the pRBC dynamics. The model is a catenary compartmental model. If we distinguish k stages, the linear model is given by

$$\begin{cases} \dot{y}_1 = & r\gamma_k - (\mu_1 + \gamma_1)y_1, \\ \dot{y}_2 = & \gamma_1 y_1 - (\mu_2 + \gamma_2)y_2, \\ \dots & \\ \dot{y}_i = & \gamma_{i-1} y_{i-1} - (\mu_i + \gamma_i)y_i, \\ \dots & \\ \dot{y}_k = & \gamma_{k-1} y_{k-1} - (\mu_k + \gamma_k)y_k. \end{cases} \tag{3.6}$$

The state y_i denotes the concentration of pRBC of class i. The rate transmission from compartment i to the following $i+1$ is γ_i and the mortality of class i is μ_i. In the last stage k the rupture of the erythrocyte releases r merozoites which invade fresh erythrocytes giving $r\gamma_k$ erythrocytes in stage 1.

In [111], Iggidr et al. considered an extension of model (3.6) as follows

$$\begin{cases} \dot{x} = & f(x) - \mu_x - \beta x m, \\ \dot{y}_1 = & \beta x m - (\mu_1 + \gamma_1)y_1, \\ \dot{y}_2 = & \gamma_1 y_1 - (\mu_2 + \gamma_2)y_2, \\ \dots & \\ \dot{y}_i = & \gamma_{i-1} y_{i-1} - (\mu_i + \gamma_i)y_i, \\ \dots & \\ \dot{y}_k = & \gamma_{k-1} y_{k-1} - (\mu_k + \gamma_k)y_k, \\ \dot{m} = & r\gamma_k y_k - \mu_m - u\beta x m. \end{cases} \tag{3.7}$$

Note that in this latter work multistrain competitive interaction is also considered and the authors derived the so-called competitive exclusion principle. Here we will extend these results to an age-structured model.

3.1.6 Within-in host HIV models

Earlier models of virus infection were commonly defined by ordinary differential equations (ODEs) (Nowak and May [176]; Perelson and Nelson [181]). In 1989, Perelson et al. has published two popular within-host HIV models (see [181]). Perelson et al. model is the following:

$$\begin{cases} \dot{T} = s - rT\left(1 - \dfrac{T + T_L}{T_{max}}\right) k_1 VT - \mu_T T, \\ \dot{T}_L = k_1 VT - \mu_T T_L - k_2 T_L, \\ \dot{T}_A = k_2 T_L - \mu_b T_A - kVT, \\ \dot{V} = \mu_b N T_A - k_1 VT - \mu_V - cV - kVT. \end{cases} \tag{3.8}$$

The general class of Perelson models is describe as follows (see [182]):

$$\begin{cases} \dot{T} = f(T) - kVT, \\ \dot{T}^* = kVT - \beta T^*, \\ \dot{V} = \beta N T^* - cV - ukVT, \end{cases} \tag{3.9}$$

wherein T is the concentration of uninfected red blood cells, T^* is the concentration of parasitized red blood cells and V is the concentration of free parasites in the blood. The parameter u takes the value 0 or 1.

For $f(T) = \delta - \alpha T + pT\left(1 - \frac{T}{T_{max}}\right)$ we obtain Perelson-Nelson model [181]. And for $f(T) = \delta - \alpha T$ we derive Nowak-May model [176]. Parameters α, β and c are respectively the rate of natural mortality of uninfected red blood cells, infected red blood cells and free parasites. k is the contact rate between free parasite and uninfected red blood cells. δ is the constant rate of lymphocytes production T, p is the growth rate in logistic equation and T_{max} is the carrying capacity of red blood cells population.

In [182], Perelson et al. estimated the average life span of a productively infected cell, the maturation time of HIV virion, the viral productive rate, and the loss rate of infected cells according to a set of viral load data collected from infected patients. Considering the latent period between initial infection of a cell and production of subsequent virus particles in reality, Herz et al. [99] first incorporated a discrete delay into their HIV infection model and showed that this intracellular delay would substantially shorten the estimates for the half-life of free virus obtained from clinical data. The incorporation of time delay in virus infection dynamics leads to a class of delay differential

equation (DDE) models. Thereafter, models of HIV infection dynamics combining drug treatment and discrete or distributed delays have generally been studied analytically and numerically by Perelson and collaborators [162, 171, 170] and other researchers [39, 105, 135, 137].

Recently, Nelson et al. [172] developed an age-structured model of HIV infection, in which the production rate of viral particles and the death rate of productively infected cells are allowed to vary and depend on two general functions of age, $p(a)$ and $\beta(a)$, respectively. Nelson's age-structured model without drug treatment is formulated as follows:

$$\begin{aligned} \dot{T}(t) &= s - \alpha T(t) - kV(t)T(t), \\ \frac{\partial i(t,a)}{\partial t} &+ \frac{\partial i(t,a)}{\partial a} = -\beta(a)i(t,a), \\ \dot{V}(t) &= \int_0^\infty p(a)i(t,a)da - cV(t), \end{aligned} \tag{3.10}$$

with the boundary condition

$$i(t,0) = kV(t)T(t).$$

Here, $i(t,a)$ denotes the density of infected T cells of infection age a (i.e., the time that has elapsed since an HIV virion has penetrated cell) at time t.

Huang et al. [105] recently study the basic age-structured population model describing the HIV infection process, which is defined by PDEs (based on Nelson's age-strutured model). By using the direct Lyapunov method and constructing suitable Lyapunov functions, they established (Huang at al) dynamical properties of the age-structured model without (or with) drug treatment. The results show that the global asymptotic stability of the infection-free steady state and the infected steady state depends only on the basic reproductive number determined by the burst size. Further, they (Huang at al.) establish mathematically that the typical ODE and DDE (delay differential equation) models of HIV infection are equivalent to two special cases of PDE models.

3.2 Hepatitis B virus models.

In this section we summarize some well know hepatitis B virus (HBV) in the literature. Some of them are due to Cvjetanovic et al., 1984 et 1987 ; Pasquini and Cvjetanovic,

1987 ; Pasquini et al., 1987 ; Williams et al., 1996 ; Garuz et al., 1997; Medley et al., 2001 ; Kretzschmar et al., 2002.

3.2.1 Anderson-May model

It is probably the first mathematical model for the transmission of HBV using ODEs (Ordinary Differential Equations). In [3], Anderson and May introduced a HBV model with differential infectivity. They assume that a proportion $(1-\pi)$ of susceptible population would develop carrier infection and then recovered, while the fraction π of susceptible population would develop chronic infection. Dividing the total population into tree subclasses: susceptible S, carrier infected I, chronic infected C; Anderson-May model is the following.

$$\begin{cases} \dot{S} = \mu N - (\beta_1 I + \beta_2 C)S - \mu S, \\ \dot{I} = \pi_1(\beta_1 I + \beta_2 C)S - (\mu + \gamma_1)I, \\ \dot{C} = \pi_2(\beta_1 I + \beta_2 C)S - (\mu + \gamma_2)I, \\ \dot{R} = \gamma_1 I + \gamma_2 C - \mu R, \end{cases} \tag{3.11}$$

wherein $\pi_1 + \pi_2 = 1$, and β_i is probability that an infective individual, I $(i = 1)$ or C $(i = 2)$, will have contact with and successfully infect a susceptible individual. γ_i is the rate moving from infectious to recovered. μ is the natural mortality rate and N is total population (which is assume to be constant). Anderson-May model is an element of the general models with differential infectivity (see [107]).

In [3], Anderson et al. also consider a second model of HBV infection taking into account the vertical transmission of the disease (from infected mother to their newborn). They (Anderson et al.) distinguish susceptible individuals according to their reaction to infection and they assume that asymptomatic carriers will give rise to a proportion ν asymptomatic carriers. Then the model assume that susceptible population is subdivided in two groups with proportions π_1 and π_2 $(\pi_1 + \pi_2 = 1)$. The model is

formulated as follows:

$$\begin{cases} \dot{S}_1 = \pi_1\mu N - \pi_1\mu\nu C - (\beta_1 I + \beta_2 C)S_1 - \mu S_1, \\ \dot{S}_2 = \pi_2\mu N - \pi_2\mu\nu C - (\beta_1 I + \beta_2 C)S_2 - \mu S_2, \\ \dot{I} = (\beta_1 I + \beta_2 C)S_1 - (\mu + \gamma_1)I, \\ \dot{C} = (\beta_1 I + \beta_2 C)S_2 - (\mu + \gamma_2)I + \mu\nu C, \\ \dot{R} = \gamma_1 I + \gamma_2 C - \mu R, \end{cases} \tag{3.12}$$

and where S_1 is for susceptible individual which will develop carrier infection, and S_2 I=is for susceptible individual which will develop chronic infection.

3.2.2 Edmunds et al. model [68]

Their model focuses on the study of correlation between the age of infection of hepatitis B virus and probability from becoming chronic. They thus establish a model gives a probability law to become chronic with respect to the age. Thus, they proposed the following model:

$$\begin{cases} p(a) = \exp(-ra^s), \quad a \geq 6(\text{ months}), \\ p_{pert} = 0.885(95\%C.L0.84 - 0.93), \quad a \leq 6(\text{ months}). \end{cases} \tag{3.13}$$

Parameters of the model is estimated from maximum likelihood principle, and using the data of the epidemiological surveillance of hepatitis B in Gambia: $r = 0.645$ and $s = 0.455$.

3.2.3 Medley et al. model (Williams et al., 1996; Medley et al. 2001) [67, 160, 215]

Williams et al. [215] have proposed a mathematical model applied to UK data. This deterministic model, structured in 12 age classes, takes into account the vertical and sexual transmissions of hepatitis B virus. They consider separately the dynamics of the epidemic in erosexuels and male homosexuals population. The host population is separated into six compartments: susceptibles, latently infected, acute infected, immune after infection, chronic infected and immune following vaccination. Different vaccination strategies is simulated in the model: Mass vaccination of infants is the least efficient, while vaccination of new-born, from infected mother, is more efficient. Mass vaccination

of adolescents is efficient faster than mass vaccination of infants. A second paper of William et al.(Williams1996) indicates that 40 years is needed to have a good efficiency of the mass vaccination programm of infants against HBV.

In 2001, Medley et al. [160], have a study of the role of age in carrying on the level of endemicity: over this age is higher and less endemism is important. These authors also analyzed the role of influx of virus carriers by immigration from highly endemic countries. It seems essential role in countries with low endemicity, particularly in the circulation of hepatitis B, but also the risk that carry viruses pose to the host region to move to a level of endemicity more high. This risk may justify less efficient short-term strategies targeted at populations at risk, but still interesting strategies mass immunization in terms of public health in the long term.

3.2.4 Age-structured models

Age-structured models have also been used to model the transmission dynamics of HBV by some researchers; see for instance Edmunds et al.[68], McLean and Blumberg[158], Zhao, Xu, and Lu[221], Zou, Ruan and Zhang[222].

Recently, Zou, Ruan and Zhang[223] have proposed a mathematical model for the transmission of HBV with susceptible, latently infected, acutely infectious, carrier, recovered, and immune following vaccination. The variables and model structure are described in Figure 3.1. By determining the basic reproduction number, they (Zou et al.) study the existence and stability of the disease-free and endemic steady state solutions of the model. They also provided numerical simulations to find optimal strategies for controlling the transmission of HBV. The analytical results and numerical simulations of the model suggest that the optimal control strategy is a combination of immunization of newborns and retroactive immunization of susceptible adults. But, to analyzed the model Zou et al. ignored the perinatal infection of HBV (vertical transmission of the disease) and deaths directly related to HBV. These assumptions are not entirely realistic in many part of the world. In fact, HBV prevalence is highest in sub-Saharan Africa and East Asia. Most people in these regions become infected with the hepatitis B virus during birth (and childhood) with a high risk (90% at birth) of progressing to chronic infection (WHO[217] and CDC[30]). Moreover, about 600,000 people die every year due to the acute or chronic consequences of hepatitis B (WHO[217]); that is deaths directly

related to HBV should not be neglected.

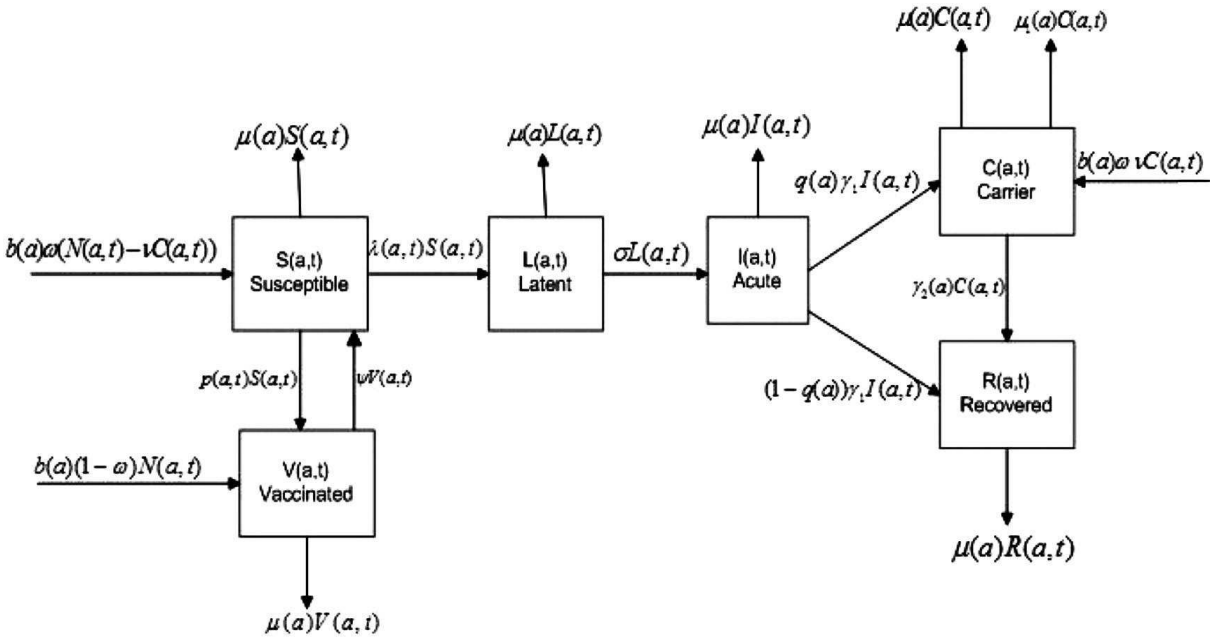


Figure 3.1: Flowchart of HBV transmission in a population (Ref. Zou et al. 2010[223])

Chapter Four

Within-host malaria infection and Anopheles mosquito dynamics.

This chapter is organized in two parts and deals with within-host model for malaria infection and advection-reaction model for anopheles mosquito dynamics population. Section 4.2 is concerned by an age-structured within-host model for multi-strain malaria infections. Section 4.3 is devoted to a mathematical modeling of anopheles mosquito dynamics population allowing migration.

4.1 Introduction

The global burden of malaria has increased over the past two decades, despite widespread implementation of control measures including bed nets, new drugs and the World Health Organization's strategy which focuses on case finding.

The malaria parasite is transmitted between people by the female *Anopheles* mosquitoes and more than 60 species are known to be able to transmit the infection. As a disease vector, some *Anopheles* species are more significant than others because of variations in susceptibility to the parasite or the propensity of the mosquito to bite humans and to enter houses when looking for a blood meal (see [16], [179]). Both the male and female *Anopheles* mosquitoes feed on nectar. However, only the female *Anopheles* mosquitoes feed on animal blood, since blood is needed to provide proteins for the development of their eggs. Thus, the transmission of malaria, from human to human, is essentially driven by the human biting habit of the mosquito. When the mosquito interacts with a human, it can either infect or be infected depending on the disease status of both the mosquito and the human.

On the other hand, natural parasitic infections are often diverse, containing multiple parasite species and/or distinct genotypes of the same species[187]. Parasites of the

Plasmodium genus are no exception. Infections of multiple strains or species of parasites have been widely reported [209, 118, 95, 119] and it may be typical in highly endemic regions [119, 129]. Growth relationships between parasite types within a single host have significant evolutionary implications for selection of fitness and drug resistance traits that can greatly impact public health [188].

There are many reports of multiple infections of human malaria [43, 60, 210, 106, 95]. Wargo et al.[210] found that when a mixed infection containing a drug resistant and drug sensitive clone is treated with drug, the removal of the sensitive parasite, which in the absence of drug competitively suppresses the drug resistant clone, leads to competitive release and allows for the expansion of the drug resistant parasite. We also refer to the recent paper of [208] where the authors perform in vivo experiments to describe and quantify the interaction of a two-strain infection. The same authors concluded that a deeper understanding of the dynamic growth responses of multiple strain *P. falciparum* infections, with and without drug pressure, can improve the understanding of the role of parasite interactions in the spread of drug resistant parasites, perhaps suggesting different treatment strategies [208].

To summarize the blood stage of the *P. falciparum* consists in the multiplication of the number of parasites and the resulting clinical symptoms. This blood stage also induces a strong competition between the different strains of the parasites that is responsible for the survival and spread of some particular strains and genetic traits. As consequence of this selection pressure drug resistance or sensitivity may spread into the whole population. In this section we consider an age-structured intra-host model for *P. falciparum* infection with n different strains for the parasites. The age-structure will allow us to have a good description of the pRBC rupture and of the merozoites release phenomenon. The model we shall consider reads as

$$\begin{cases} \dfrac{dx(t)}{dt} = \Lambda - \mu_x x(t) - x(t)\displaystyle\sum_{j=1}^{n} \beta_j m_j(t); \\ \dfrac{\partial \omega_j(t,a)}{\partial t} + \dfrac{\partial \omega_j(t,a)}{\partial a} = -(\mu_j(a) + \mu_x)\omega_j(t,a); \\ \dfrac{dm_j(t)}{dt} = \displaystyle\int_0^{\infty} \rho_{y,j}(a)\omega_j(t,a)da - \mu_{m,j} m_j(t) - \delta_j \beta_j x(t) m_j(t); \\ \omega_j(t,0) = \beta_j x(t) m_j(t); \;\; j \in \{1, 2, \cdots, n\}. \end{cases} \tag{4.1}$$

In (4.1), the RBC population is split into two classes, $x(t)$ denotes the concentration

of uninfected red blood cells (uRBC) at time t, while $\omega_j(t,a)$ denotes the age-specific concentration of pRBC at time t and parasitized since a time a by a specific j-strain. Finally $m_j(t)$ denotes the concentration of free specific j-merozoites in the blood stream. We briefly sketch the interpretation of the parameters arising in (4.1). Parameters μ_x, $\mu_{m,j}$ respectively denotes the natural death rates for uRBC and for free specific j-merozoites. Function $\mu_j(a)$ denotes the exit rate of pRBC due to the j-parasites at age a. The parameter β_j describes the contact rate between uRBC and free specific j-merozoites while Λ denotes the recruitment rate of uRBC from the bone marrow. The rupture of pRBC at age a results in the release of an average number $r_j(a)$ of specific j-merozoites into the blood stream; so that pRBC infected by a specific j-strain then produce j-merozoites at age a with the rate $\rho_{y,j}(a) := r_j(a)\mu_j(a)$. Together with this description, the quantity

$$\int_0^\infty \rho_{y,j}(a)\omega_j(t,a)da,$$

corresponds to the number of specific j-merozoites produced by pRBC at time t. In the literature the parameter δ_j takes the values $\delta_j = 0$ when the loss of merozoites when they enter a RBC is ignored or takes the value $\delta_j = 1$ when this loss is not ignored. System (4.1) is supplemented together with initial data those properties will described below: for each $j \in \{1, 2, \cdots, n\}$:

$$x(0) = x_0 \geq 0,\ \omega_j(0,.) = \omega_{0,j}(.),\ m_j(0) = m_{0,j} \geq 0. \tag{4.2}$$

There has been numerous works on pathogen within-host dynamics in *P. falciparum* infection. We refer to [4, 47, 78, 79, 80, 81, 98, 101, 103, 151, 156, 157, 164, 191]. We also refer to the survey paper of Molineaux and Dietz in [165] and the references therein as well as the following recent papers on this topic [111, 205, 134, 189, 18, 163]. Let us observe that the one-strain System (4.1) (namely with $n = 1$) has been rigorously and recently studied by Huang et al. [105] in the context HIV infection model (and with $\delta = 0$).

Mathematical models associated to within-host *P. falciparum* malaria infection have been proposed since the pioneer work of Anderson, May and Gupta [2]. This model was intended to explain experimental observations, namely parasitaemia, i.e., the concentration of pRBC and also the decrease of the uRBC leading to anaemia. Such ideas have been further developed in [4, 78, 98, 101, 103, 191]. We also refer to Li et al

[134] for a mathematical model with immune response yielding to sustained oscillations. However all these works do not take into account an important characteristic of *P. falciparum* which is sequestration of merozoites with the pRBC and their ruptures [111]. Such an issue has been considered using discrete age-structured systems of equations (see for instance [79, 80, 81, 159]) with constant RBC population assumption. We refer to Iggidr et al. [111] for a mathematical study of a discrete age-structured model with varying RBC concentration. Note that in this latter work multi-strain competitive interaction is also considered and the authors derived the so-called competitive exclusion principle. This principle is well known in the context of theoretical ecology and states that two competitive species cannot indefinitely occupy the same ecological niche [22, 24, 27, 53, 98, 152, 153].

Despite the enormous global burden of malaria, after more than a century of research we still have a poor understanding of the mechanistic link between environmental variables, such as temperature and malaria risk (Lafferty 2009[128]; Paaijmans et al. 2009[178]; Alonso et al. 2011[1]). Temperature is fundamentally linked to malaria mosquito and parasite vital rates (see [166] [44]), and understanding the role of temperature in malaria transmission is particularly important in light of climate change.

Knowledge of the population dynamics of the malaria vector is fundamental to the understanding of malaria epidemiology and the spread of insecticide resistance. Therefore, studies on the population structure of malaria vectors have important implications for the prediction and assessment of the effects of many vector control strategies. Due to global warming, there is a risk of the emergence of malaria in new regions (where malaria has not been endemic). Thus, the complete understanding of the malaria vector population dynamics is necessary for gaining insight into the disease spread and the design of effective vector control strategies. According to all malaria models, little has been done with regard to the studies on the population dynamics of malaria vectors: A deterministic differential equation model for the population dynamics of the human malaria vector, Ngwa 2006[174]; A delay ordinary deterministic differential equation model for the population dynamics of the malaria vector subject to two forms of the vector birth rate function (the Verhulst-Pearl logistic growth function and the Maynard-Smith-Slatkin function), Ngwa et al. 2010 [175]; Temporal models or/and taking into account one-dimensional spatial components on mosquito population dynamics and SIT

(Sterile Insect Technology is a nonpolluting method of control of the invading insects that transmit disease), Manoranjan et al. 1986[149], Lewis et al. 1993[133]; The control of the disease by the release of sterile or treated males in order to reduce the wild population of anopheles mosquito, Anguelov et al.[6]; A mathematical model to simulate mosquito dispersal and its control taking into account environmental parameters, like wind, temperature, or landscape elements Dufourd et al. 2013 [59].

In [59], Dufourd et al. have first consider a temporal compartmental approach and then include the spatial component that leads to a system of coupled diffusion-advection-reaction-like equations to model mosquito dispersal. For the temporal model, they (Dufourd et al.) derive some theoretical results (existence and uniqueness of a solution, existence of equilibria, local and global stability) and give some illustration. But for the diffusion-advection-reaction equations, they only derive a fast algorithm using appropriate numerical methods to illustrate the dynamic of the system.

The aim of this work is: firstly, to perform a mathematical analysis of System (4.1) and to obtain a generic competitive exclusion principle result. In an other context, let us mention that the one-strain System (4.1) (namely with $n = 1$) has been rigorously and recently studied by Huang et al [105] in the context HIV infection model (and with $\delta = 0$). Secondly, to develop and analyze an advection-reaction mathematical model for the dynamics of the malaria vector, taking into account environmental parameters (such as temperature).

This chapter is organized as follows.

✓ Section 4.2 deals with the mathematical analysis of with-in host malaria model (4.1). In Section 4.2.1, we describe the main results that will be proved in this work. Sections 4.2.2 and 4.2.4 are devoted to deriving preliminary results and remarks on (4.1)-(4.2) that will be used to study the long term behaviour of the problem. Section 4.2.5 is concerned with the proof of the first part of Theorem 4.2.1 below, that roughly speaking states that when the epidemic threshold (explicitly expressed using the parameters of the system) $\mathcal{T}_0 \leq 1$, then all the strains asymptotically die out and the parasites cannot survive. Finally Section 4.2.6 deals with the proof of the second part of Theorem 4.2.1, that roughly speaking say that when $\mathcal{T}_0 > 1$ and under some additional assumptions on the different strains, then the competitive exclusion principle holds true, that is that only the strongest strain (using a suitable order) is asymptotically surviving.

✓ In sections 4.3, an advection-reaction mathematical model for the dynamics of the malaria vector, taking into account environmental parameters (like temperature) is developed and analyzed. Section 4.3.1 is devoted to the mathematical model formulation, including: the description of the model parameters and the state variables for dynamics of the malaria vector. Then in section 4.3.2, we derive the existence of positive solutions to the seasonal model. For the study of the long term behavior of the model, three threshold parameters $\mathcal{R}^{\diamondsuit}$, $\mathcal{R}_{\diamondsuit}$ and $\mathcal{R}_*$ (explicitly expressed using the parameters of the model) are provided. In section 4.3.3, the mosquito extinction results is formulated; that is when $\mathcal{R}^{\diamondsuit} < 1$, then the mosquito population die out. In sections 4.3.4-4.3.5, we also derive persistence results to the seasonal model: the weak persistence results when $\mathcal{R}_{\diamondsuit} > 1$ and the strong persistence results when $\mathcal{R}_* > 1$.

4.2 Age-structured within-host model for multi-strain malaria infections

In this section we propose an age-structured malaria within-host model taking into account multi-strains interaction. We provide a global analysis of the model depending upon some epidemic threshold $\mathcal{T}_0$. When $\mathcal{T}_0 \leq 1$, then the disease free equilibrium is globally asymptotically stable and the parasites are cleared. On the contrary if $\mathcal{T}_0 > 1$, the model exhibits the competition exclusion principle. Roughly speaking, only the strongest strain survives while the other strains go to extinct. Under some additional parameter conditions we prove that the endemic equilibrium corresponding to the strongest strain is globally asymptotically stable.

4.2.1 Main results

In this section we will state the main results of this work. In order to deal with system (4.1)-(4.2) we first provide a parameter reduction by introducing the following unknown functions

$$y_j(t,a) = \omega_j(t,a)e^{\int_0^a \mu_j(l)dl}.$$

Therefore, by introducing the vector valued functions $\mathbf{y}(t,a) = (y_1(t,a),..,y_n(t,a))^T$, $\mathbf{m}(t) = (m_1(t),..,m_n(t))^T$ as well as the matrix

$$\beta = \mathrm{d}iag\ (\beta_1,..,\beta_n)\,,\ \delta = \mathrm{d}iag\ (\delta_1,..,\delta_n)\,,\ \ E_n = (1,..,1)^T \in \mathbb{R}^n,$$
$$\mu_m = \mathrm{d}iag\ (\mu_{m,1},..,\mu_{m,n})\,,\ \rho(a) = \mathrm{d}iag\ (\rho_1(a),..,\rho_n(a))\,,$$

System (4.1)-(4.2) re-writes as

$$\begin{cases} \dfrac{dx(t)}{dt} = \Lambda - \mu_x x(t) - x(t)E_n^T\beta\mathbf{m}(t); \\ \partial_t\mathbf{y}(t,a) + \partial_a\mathbf{y}(t,a) = -\mu_x\mathbf{y}(t,a); \\ \mathbf{y}(t,0) = \beta x(t)\mathbf{m}(t); \\ \dfrac{d\mathbf{m}(t)}{dt} = \displaystyle\int_0^\infty \rho(a)\mathbf{y}(t,a)da - \mu_m\mathbf{m}(t) - \delta\beta x(t)\mathbf{m}(t); \end{cases} \tag{4.3}$$

supplemented together with initial data

$$\mathbf{y}(0,.) = \mathbf{y}_0(.) \in L^1\left(0,\infty;\mathbb{R}_+^n\right) \quad x(0) = x_0 \geq 0; \quad \mathbf{m}(0) = \mathbf{m}_0 \in \mathbb{R}_+^n; \tag{4.4}$$

and wherein we have set

$$\rho_j(a) = \rho_{y,j}(a)e^{-\int_0^a \mu_j(l)dl},\ \ j = 1,..,n,\ a \geq 0.$$

In (4.4) $\mathbb{R}_+^n$ denotes the positive orthant, namely $\mathbb{R}_+^n = \{(x_1,..,x_n)^T \in \mathbb{R}^n :\ \ x_i \geq 0,\ \forall i = 1,..,n\}$.

In what follow we shall discuss the asymptotic behaviour of System (4.3)-(4.4) and we will make use the following assumption.

Assumption 4.2.1. *We assume that, for each $j \in \{1,2,\cdots,n\}$ functions ρ_j belong to $L_+^\infty(0,\infty,\mathbb{R}_+)$ while $\Lambda > 0$, $\mu_x > 0$, $\mu_{m,j} > 0$, $\delta_j \in \{0,1\}$ and $\beta_j > 0$.*

As mentioned in the introduction we shall focus on the competitive exclusion principle generated by (4.3). Roughly speaking, to achieve such a goal we will provide an order to separate the different strains of the parasite. Hence let us introduce, for each strain, the quantity $\mathcal{T}_0^i$ defined by

$$\mathcal{T}_0^i = \frac{\beta_i\Lambda}{\mu_x\mu_{mi}}\left(\int_0^\infty \rho_i(a)l(a)da - \delta_i\right), \tag{4.5}$$

as well as

$$\mathcal{T}_0 = \max_{1\leq i\leq n} \mathcal{T}_0^i; \tag{4.6}$$

where function $l \equiv l(a)$ is defined by

$$l(a) = e^{-\mu_x a}. \tag{4.7}$$

As it will be seen below (see Theorem 4.2.1) the situation when $\mathcal{T}_0 \leq 1$ is rather simple because the infection asymptotically dies out. When $\mathcal{T}_0 > 1$ the situation is much more involved. We expect that System (4.3)-(4.4) exhibits the competition exclusion principle, that, roughly speaking, say that in presence of multiple strains only the strongest can asymptotically survive. The parameters $\{\mathcal{R}_0^i\}_{i=1,..,n}$ (see (4.5)) will be used to quantify the strength of the different strain-specific infection. We will now introduce some definitions. Let us first of all define the set of strains that can potentially survive $\mathcal{S}$ defined by

$$\mathcal{S} = \begin{cases} \{i \in \{1,..,n\} : \ \mathcal{T}_0^i > 1\} \ \text{if } \mathcal{T}_0 > 1 \\ \emptyset \ \text{if } \mathcal{T}_0 \leq 1. \end{cases} \tag{4.8}$$

On the set of index $\{1,..,n\}$ we define an order relation by

$$i \trianglelefteq j \ \Leftrightarrow \ \mathcal{T}_0^i \leq \mathcal{T}_0^j \ \text{ and } \ i \triangleleft j \ \Leftrightarrow \ \mathcal{T}_0^i < \mathcal{T}_0^j.$$

We would like to emphasize that when parameter δ_j are non-zero, the set of threshold $\{\mathcal{T}_0^i\}_{i=1,..,n}$ is different from the set of the different strain specific basic reproduction numbers. Indeed the strain $i-$specific basic reproduction number reads as (see Section 4.2.3 for the computation):

$$\mathcal{R}_0^i = 1 + \frac{\mu_{m,i}}{\mu_{m,i} + \delta_i \beta_i x_f} \left(\mathcal{T}_0^i - 1\right) \ \text{with } x_f = \frac{\Lambda}{\mu_x}. \tag{4.9}$$

Hence the above described ordered may be different from the one induced by the strain specific basic reproduction numbers.

We also denote by $\max^{\triangleleft}$ the maximum operator associated to the order $\trianglelefteq$. Note that in general the operator $\max^{\triangleleft}$ is multi-valued and is defined by

$$\max^{\triangleleft}\{i,j\} = \begin{cases} i \ \text{if } \mathcal{T}_0^i > \mathcal{T}_0^j, \\ j \ \text{if } \mathcal{T}_0^j > \mathcal{T}_0^i, \\ \{i,j\} \ \text{if } \mathcal{T}_0^i = \mathcal{T}_0^j. \end{cases}$$

A subset $\{i_1,..,i_p\} \subset \{1,..,n\} := \mathbb{N}_n$ is said to be *strictly ordered* if there exists a permutation σ of $\{1,..,p\}$ such that

$$i_{\sigma(1)} \triangleleft .. \triangleleft i_{\sigma(p)}.$$

Let us notice that on a strictly ordered set, the operator $\max^{\lhd}$ becomes a single-valued map. Let us also mention that for biological reason, since we aim to deal with competitive exclusion principle for our multi-strain model, it is relevant to assume that the different strain is distinguishable. Hence we shall assume in most parts of this work that, the species that can potentially survive are distinguishable, that is re-formulated by assuming the set $\{i \in \mathbb{N}_n : \ \mathcal{T}_0^i > 1\}$ is strictly ordered.

Before starting our main result let us introduce further notations that correspond to the stationary states of (4.3) (see Proposition 4.2.3): $x_f = \frac{\Lambda}{\mu}$ and for each $k \in \mathcal{S}$ (when $\mathcal{S} \neq \emptyset$) :

$$x_e^k = \frac{x_f}{\mathcal{T}_0^k}; \quad \mathbf{m}_e^k = \frac{\mu_x(\mathcal{T}_0^k - 1)}{\beta_k} (\delta_{i,k})_{i=1}^n ; \quad \mathbf{y}_e^k(a) = \beta_i x_e^k e^{-\mu_x a} \mathbf{m}_e^k, \tag{4.10}$$

wherein $\delta_{i,j}$ denotes the usual Kronecker symbol.

For technical reason in relation to some computations we shall assume some relation of the parameters. The set $\mathcal{S}$ (when $\mathcal{S} \neq \emptyset$) satisfies condition (Q) if

$$\left(\mathcal{T}_0^i - 1\right) \delta_i \beta_i x_f \leq \mathcal{R}_0^i \mu_{mi}, \ \forall i \in \mathcal{S}. \tag{4.11}$$

Let us first notice that the above condition is always satisfied when $\delta_i = 0$. When $\delta_i > 0$ then the above parameter condition can re-written in term of a limitation of the strain specific basic reproduction numbers (see (4.9)). Indeed, if one sets $\gamma_i = \frac{\delta_i \beta_i x_f}{\mu_{mi}}$ then condition (Q) re-writes as

$$\mathcal{R}_0^i \leq \max\left(1 + \frac{1}{1+2\gamma_i}; 1 + \frac{1+\sqrt{1+4\gamma_i}}{2\gamma_i}\right), \ \forall i \in \mathcal{S}.$$

Using the above notations the main result of this work reads as

Theorem 4.2.1. *Let Assumption 5.1.1 be satisfied. Assume that the set $\mathcal{S}$ is strictly ordered and satisfies the parameter condition (Q). Let $x_0 \geq 0$, $\mathbf{m}_0 \in \mathbb{R}_+^n$ and $\mathbf{y}_0 \in L^1\left(0, \infty; \mathbb{R}_+^n\right)$ be a given initial data and let us denote by $(x(t), \mathbf{m}(t), \mathbf{y}(t,.))$ the solution of (4.3)-(4.4). Then the following holds true:*

(i) If $\mathcal{J} := \mathcal{S} \cap \left\{k \in \{1, .., n\} : \ m_k + \int_0^\infty y_{0,k}(a)da > 0\right\} = \emptyset$ then

$$\lim_{t \to \infty} (x(t), \mathbf{m}(t), \mathbf{y}(t,.)) = \left(x_f, 0_{\mathbb{R}^n}, 0_{L^1(0,\infty;\mathbb{R}^n)}\right),$$

wherein the above convergence holds for the topology of $\mathbb{R} \times \mathbb{R}^n \times L^1(0, \infty; \mathbb{R}^n)$.

(ii) If $\mathcal{J} \neq \emptyset$ *then, setting* $i = \max^{\lhd} \mathcal{J}$ *and recalling* (4.10) *one has*

$$\lim_{t\to\infty} (x(t), \mathbf{m}(t), \mathbf{y}(t,.)) = \left(x_e^i, \mathbf{m}_e^i, \mathbf{y}_e^i(.)\right),$$

for the topology of $\mathbb{R} \times \mathbb{R}^n \times L^1(0,\infty;\mathbb{R}^n)$.

The first part of this result applies in particular when $\mathcal{S} = \emptyset$, namely $\mathcal{T}_0 \leq 1$. In that case all the strains asymptotically die out and the parasites cannot survive. Let us notice that the condition $\mathcal{T}_0 \leq 1$ can be re-written in term of basic reproduction $\mathcal{R}_0 := \max\{\mathcal{R}_0^i,\, i \in \mathbb{N}_n\}$ as $\mathcal{R}_0 \leq 1$. The second part of the above theorem says that when different strains are sufficiently strong to survive, then only the strongest present strain (with respect to the order $\trianglelefteq$) is surviving in the long term.

Remark 4.2.1. *The parameter condition* (Q) *seems to be only a technical condition that we cannot overcome. From numerical computations, the equilibrium associated to the strongest strain continue to be globally stable even if condition* (Q) *is violated.*

Table 4.1: Parameters values of model (4.1)

Parameters	Description	Value and Range	References
Λ	Production rate of RBC	1 RBC.h^{-1}	Assumed
β_1; β_2	Infection rate of uRBC	0.02/24 RBC ml^{-1} .h^{-1}	[2]
μ_x	Natural death rate of uRBC	0.00833/24 RBC .h^{-1}	[2]
μ_{m1}; μ_{m2}	Decay rates of malaria parasites	48/24	[101]
r_1; r_2	Merozoite mean rate produce by pRBC	16	[2]

Table 4.2: Initial values in model (4.1)

Variables	Description	Initial Values	References
$x(t)$	Population of uRBC	5×10^9 RBC.ml^{-1}	[2, 31, 101, 159]
$\omega_1(t,.)$; $\omega_2(t,.)$	Population of pRBC	0 RBC.ml^{-1}	[2, 31, 101, 159]
$m_1(t)$; $m_2(t)$	Population of malaria parasite	10^7 RBC.ml^{-1}	[2, 31, 101, 159]

We now provided some numerical simulations to illustrate the dynamics of System (4.1) in the case of two strains interactions ($n = 2$). They highlight the principle of competitive exclusion. The upper bound age of RBC infectivity is set to

$a_\dagger = 59.3$ hours ≈ 2.47 days [45]. Let us recall that when the meroziotes enter the RBC they grow and reproduce during the sequestration period. This period corresponding to the i-strain is denoted by $\tau_i \in [44; 52]$(hours) (see [45]). Following Su, Ruan and Wei in [196] we will consider that the age-specific exit rate of pRBC $\mu_i(a)$ for the i-strain takes the form

$$\mu_i(a) := \begin{cases} 0, & \text{if } a < \tau_i; \\ d_i(a), & \text{if } a \geq \tau_i, \end{cases}$$

together with $d_1 = d_2 \equiv 0.98$ while $\tau_1, \tau_2 \in \{48; 50\}$(hours). The other parameters of the model are described in Table 4.1.

Let us assume that the sequestration period for the production of free merozoites is $\tau_1 = 48$ hours for the strain 1 and $\tau_2 = 50$ hours for the strain 2. This means that pRBC with strain 2 release the new parasites two hours later than the pRBC infected by strain 1. The probability of pRBC to be still infected until age a approximately equals to 1 before two days of infection and exponentially decreases to zero after 48 hours for strain 1 and after 50 hours for strain 2 (see Figure 4.1c). The death rate of pRBC is illustrated by Figure 4.1a and the average number of parasites produced by pRBC after the sequestration period is represented in Figure 4.1b.

Using contact rate $\beta_1 = \beta_2 = 0.02/24$ Figure 4.2a represents the superimposition of the time evolution two strains alone (that is without interaction) while Figure 4.2b corresponds to the time evolution of competitive interactions between the two strains. Since the sequestration period for strain 1 is smaller then strain 1 becomes the strongest and it competitively suppresses strain 2. Let us also notice that the shape of these curves are qualitatively close to the experimental situations recently obtained by Wacker et al in [208]. Using these parameter sets, the basics reproduction rates for the system with strain 1 only (resp. strain 2 only) is computed as $R_0^1 = 5.75$ (resp. $R_0^2 = 4.74$); so that the basic reproduction rate for model (4.1) is $R_0 = 5.75$.

Let us finally emphasize that using the parameter set described in Tables 4.1 and 4.2, the weakest strain, namely, strain 2, is quickly suppressed after 20 days. This duration plays an important role on the transmission of gametocytes to mosquitoes. Note that such a conclusion has been reached without taking into account the interactions of the different strains during the liver stage of the disease. This could have an influence on the time needed to suppress the weakest strain during the blood stage and thus on the

spread of the different strains. This will be studied in a forthcoming work.

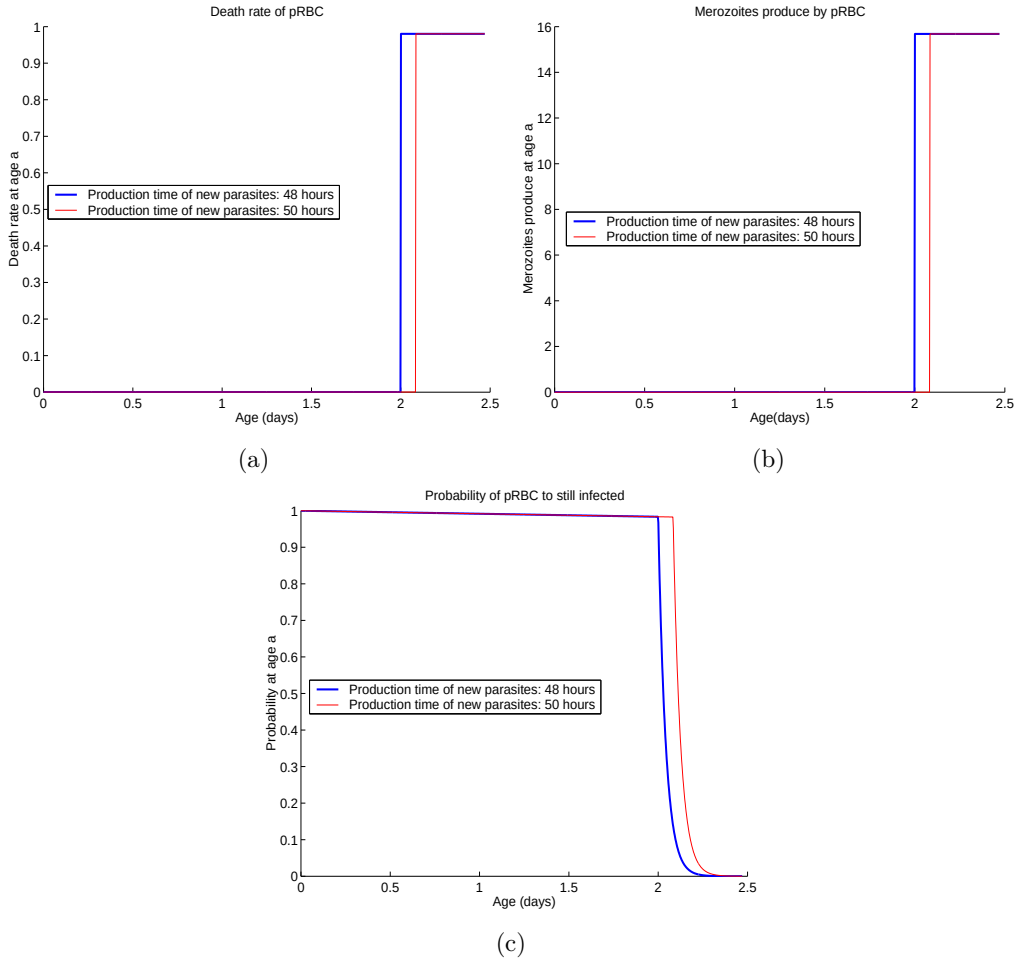
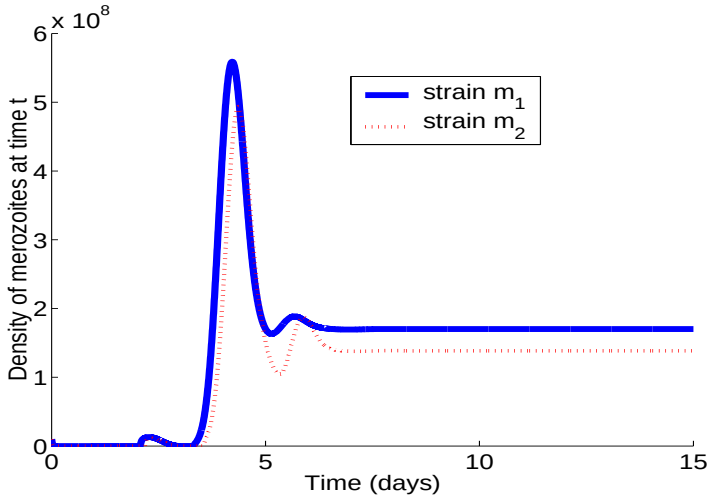
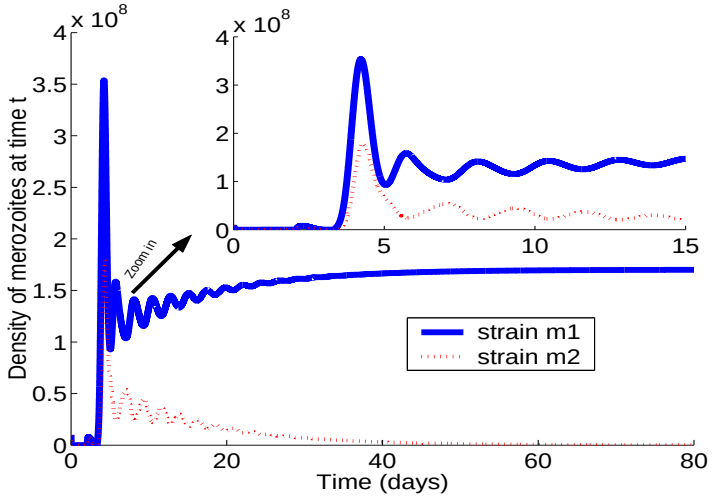


Figure 4.1: Parameters of the model (4.1) for variable sequestration period: exit rate of pRBC (Fig. 1 (a)); density of parasites produced by pRBC (Fig. 1 (b)) and the lifetime of pRBC (Fig. 1 (c)). pRBC by strain 1 (resp. by strain 2) release free merozoites after 48 hours (resp. 50 hours), that is $\tau_1 = 48$ (resp. $\tau_2 = 50$). All the other parameters are given by Table 4.1.



(a)



(b)

Figure 4.2: On the left hand-side superimposed time evolution of the density of merozoites for strains 1 and 2 alone; on the right hand-side competitive suppression of strain 2 when the two strains are mixed. However, with this parameters, the basics reproduction rates of the model only with strain 1 (resp. 2) is $R_0^1 = 4.79$ (resp. $R_0^2 = 3.95$). That is the basic reproduction rate for model (4.1) is $R_0 = 4.7975$. To highlight the competition of the two strains, initial value for the population of malaria parasites is assumed to be 10^7 (resp. 5×10^7) RBC.ml^{-1} for strain 1 (resp. 2). Other initial values in model (4.1) are given by Table 4.2.

4.2.2 Existence of semiflow and basic properties.

The aim of this section is to derive preliminary remarks on (4.3)-(4.4). These results include the existence of the unique maximal semiflow bounded dissipative associated to this system and the steady states of system (4.3)-(4.4).

Existence of semiflow.

In this section we shall deal with (4.3)-(4.4) using an integrated semigroup approach. This approach has been introduced by Thieme in [200] in the context of age-structured equations. We also refer to [123, 140, 144, 145, 58] and [201, 203] (see also the references cited therein).

Let us introduce the Banach space $\widehat{X} := \mathbb{R}^n \times L^1(0,\infty;\mathbb{R}^n)$ as well as its positive cone $\widehat{X}_+ = \mathbb{R}^n_+ \times L^1(0,\infty;\mathbb{R}^n_+)$ and the linear operator $\widehat{A} : D(\widehat{A}) \subset \widehat{X} \to \widehat{X}$ defined by

$$D(\widehat{A}) = \{0_{\mathbb{R}^n}\} \times W^{1,1}(0,\infty;\mathbb{R}^n),\ \widehat{A}\begin{pmatrix} 0_{\mathbb{R}^n} \\ \varphi \end{pmatrix} = \begin{pmatrix} -\varphi(0) \\ -\varphi' - \mu_x \varphi \end{pmatrix}. \tag{4.12}$$

Next consider the Banach space X and its positive cone X_+ defined by

$$X = \mathbb{R} \times \mathbb{R}^n \times \widehat{X} \text{ and } X_+ = \mathbb{R}_+ \times \mathbb{R}^n_+ \times \widehat{X}_+,$$

endowed with the norm

$$\left|\left|(x,\alpha,0_{\mathbb{R}^n},\varphi)^T\right|\right|_X = |x| + \sum_{i=1}^n |\alpha_i| + \sum_{i=1}^n ||\varphi_i||_{L^1(0,\infty;\mathbb{R})},\ \ \forall\,(x,\alpha,0_{\mathbb{R}^n},\varphi)^T \in X.$$

We easily find that the space X_+ is a normal cone with respect to the following partial order:

$$\begin{pmatrix} x \\ \alpha \\ 0_{\mathbb{R}^n} \\ \varphi \end{pmatrix} \leq \begin{pmatrix} y \\ \beta \\ 0_{\mathbb{R}^n} \\ \psi \end{pmatrix} \Leftrightarrow \begin{pmatrix} x \\ \alpha \\ 0_{\mathbb{R}^n} \\ \varphi \end{pmatrix} - \begin{pmatrix} y \\ \beta \\ 0_{\mathbb{R}^n} \\ \psi \end{pmatrix} \in X_+.$$

Let $A : D(A) \subset X \to X$ be the linear operator defined by

$$D(A) = \mathbb{R} \times \mathbb{R}^n \times D\left(\widehat{A}\right),\ \ A = \mathrm{d}iag\ \left(-\mu_x, -\mu_m, \widehat{A}\right). \tag{4.13}$$

Note that the domain of operator A is not dense in X because of the identity

$$\overline{D(A)} = \mathbb{R} \times \mathbb{R}^n \times \{0_{\mathbb{R}^n}\} \times L^1(0,\infty;\mathbb{R}^n) \neq X.$$

Finally let us introduce the nonlinear map $F : \overline{D(A)} \to X$ defined by

$$F\begin{pmatrix} x \\ \mathbf{m} \\ 0_{\mathbb{R}^n} \\ \mathbf{y} \end{pmatrix} = \begin{pmatrix} \Lambda - xE_n^T\beta\mathbf{m} \\ \int_0^\infty \rho(a)\mathbf{y}(a)da - \delta\beta x\mathbf{m} \\ \beta x\mathbf{m} \\ 0_{L^1(0,\infty;\mathbb{R}^n)} \end{pmatrix}.$$

By identifying $u(t)$ together with $(x(t), \mathbf{m}(t), 0_{\mathbb{R}^n}, \mathbf{y}(t,.))^T$ and by setting $u_0 = (x_0, \mathbf{m}_0, 0_{\mathbb{R}^n}, \mathbf{y}_0(.))^T$, one obtains that System (4.3)-(4.4) re-writes as the following non-densely defined Cauchy problem:

$$\begin{cases} \dfrac{du(t)}{dt} &= Au(t) + F(u(t)) \; ; \quad t \geq 0 \\ u(0) &= u_0 \in \overline{D(A)} \cap X_+. \end{cases} \tag{4.14}$$

We first derive that the above abstract Cauchy problem generates a unique globally defined and positive semiflow. Let us set $X_0 = \overline{D(A)}$ and $X_{0+} = X_0 \cap X_+$. Before the main result of this section, let us introduce the following lemmas and proposition.

Lemma 4.2.1. *Let Assumption 5.1.1 be satisfied. The nonlinear map $F : X_0 \to X$ is lipschitzian on bounded subset of X_0.*

Proof. Let $c > 0$ and $\overline{B(0,c)} = \left\{(x, \alpha, 0_{\mathbb{R}^n}, \varphi)^T \in X_0 : \left|\left|(x, \alpha, 0_{\mathbb{R}^n}, \varphi)^T\right|\right|_X \leq c\right\}$. Let $u := (x, \alpha, 0_{\mathbb{R}^n}, \varphi)^T$, $\tilde{u} := (\tilde{x}, \tilde{\alpha}, 0_{\mathbb{R}^n}, \tilde{\varphi})^T \in \overline{B(0,c)}$, then

$$F\begin{pmatrix} x \\ \alpha \\ 0_{\mathbb{R}^n} \\ \varphi \end{pmatrix} - F\begin{pmatrix} \tilde{x} \\ \tilde{\alpha} \\ 0_{\mathbb{R}^n} \\ \tilde{\varphi} \end{pmatrix} = \begin{pmatrix} -xE_n^T\beta\alpha + \tilde{x}E_n^T\beta\tilde{\alpha} \\ \int_0^\infty \rho(a)\varphi(a)da - \delta\beta x\varphi - \int_0^\infty \rho(a)\tilde{\varphi}(a)da + \delta\beta\tilde{x}\tilde{\varphi} \\ \beta x\varphi - \beta\tilde{x}\tilde{\varphi} \\ 0_{L^1(0,\infty;\mathbb{R}^n)} \end{pmatrix}.$$

Since the nonlinear functions $\mathbb{R} \times \mathbb{R}^n \ni (x, \alpha) \mapsto xE_n^T\beta\alpha \in \mathbb{R}$ and $\mathbb{R} \times \mathbb{R}^n \ni (x, \alpha) \mapsto \beta x\alpha \in \mathbb{R}^n$ are class C^1, we can find two positive constants $C_1(c, \beta)$ and $C_2(c, \beta)$ such that

$$||\beta x\alpha - \beta\tilde{x}\tilde{\alpha}|| \leq C_2(c,\beta)\left(|x - \tilde{x}| + \sum_{j=1}^n |\alpha_j - \tilde{\alpha}_j|\right),$$

and

$$\left|xE_n^T\beta\alpha - \tilde{x}E_n^T\beta\tilde{\alpha}\right| \leq C_1(c,\beta)\left(|x - \tilde{x}| + \sum_{j=1}^n |\alpha_j - \tilde{\alpha}_j|\right).$$

Therefore,

$$||Fu - F\tilde{u}||_X \leq \max\{C_1(c,\beta) + ||\rho||_\infty + (\delta+1)C_2(c,\beta)\}\,||u-\tilde{u}||_X.$$

□

Proposition 4.2.1. *Let A_0 be the part of A in X_0, where A is the linear operator given by (5.3). Then A is a Hile-Yosida operator and A_0 is generator of C_0-semigroup $\{T_{A_0}(t)\}_{t\geq 0}$ on the Banach space X_0.*

Proof. Let $\left(\tilde{x},\tilde{\alpha},\tilde{\psi},\tilde{\varphi}\right)^T \in X$ and $\lambda > 0$. Equation

$$(\lambda I - A)\,(x,\alpha,0_{\mathbb{R}^n},\varphi)^T = \left(\tilde{x},\tilde{\alpha},\tilde{\psi},\tilde{\varphi}\right)^T, \text{ for } (x,\alpha,0_{\mathbb{R}^n},\varphi)^T \in D(A),$$

rewrites as the following problem:

$$\begin{cases} \varphi'(a) = -(\lambda+\mu_x)\varphi(a) + \tilde{\varphi}(a), \\ \varphi(0) = \tilde{\psi}, \\ (\lambda+\mu_m)\alpha = \tilde{\alpha}, \\ (\lambda+\mu_x)x = \tilde{x}, \end{cases}$$

which the unique solution is

$$\begin{cases} \varphi(a) = & e^{-(\lambda+\mu_x)a}\tilde{\psi} + \displaystyle\int_0^a e^{-(\lambda+\mu_x)(a-s)}\tilde{\varphi}(s)ds, \forall \lambda > 0, \\ \alpha = & \dfrac{\tilde{\alpha}}{\lambda+\mu_m}, \\ x = & \dfrac{\tilde{x}}{\lambda+\mu_x}. \end{cases}$$

We deduce that $(0,+\infty) \subseteq \rho(A)$ and

$$\left|\left|(\lambda I - A)^{-1}\left(\tilde{x},\tilde{\alpha},\tilde{\psi},\tilde{\varphi}\right)^T\right|\right|_X = \left|\left|(x,\alpha,0_{\mathbb{R}^n},\varphi)^T\right|\right|_X = ||\varphi||_{L^1} + \frac{|\tilde{\alpha}|}{\lambda+\mu_m} + \frac{|\tilde{x}|}{\lambda+\mu_x}.$$

Furthermore,

$$||\varphi||_{L^1} \leq \frac{1}{\lambda}\left(|\tilde{\psi}| + ||\tilde{\varphi}||_{L^1}\right),$$

from where

$$\left|\left|(\lambda I - A)^{-1}\right|\right|_{\mathcal{L}(X)} \leq \frac{1}{\lambda}, \quad \forall \lambda > 0.$$

Hence A is a Hile-Yosida operator and satisfied

$$\lim_{\lambda\to+\infty}(\lambda I - A)^{-1}u = 0, \forall u \in X.$$

We find that $\overline{D(A_0)} = X_0$, and

$$\left|\left|(\lambda I - A_0)^{-1}\right|\right|_{\mathcal{L}(X_0)} \leq \left|\left|(\lambda I - A)^{-1}\right|\right|_{\mathcal{L}(X)} \leq \frac{1}{\lambda}, \quad \forall \lambda > 0,$$

thus A_0 is generator of a C_0-semigroup. □

Lemma 4.2.2. *Let Assumption 5.1.1 be satisfied.*

1. For all $C > 0$, there exists $\lambda_C > 0$ such that

$$(F + \lambda_C I)(x, \mathbf{m}, 0_{\mathbb{R}^n}, \mathbf{y})^T \in X_+, \forall (x, \mathbf{m}, 0_{\mathbb{R}^n}, \mathbf{y})^T \in \overline{B(0, C)} \cap X_+.$$

2. $(\lambda I - A)^{-1} X_+ \subseteq X_+, \forall \lambda > 0$.

Proof.

1. Let $(x, \mathbf{m}, 0_{\mathbb{R}^n}, \mathbf{y})^T \in \overline{B(0, C)} \cap X_+$ and $\lambda > 0$. We have

$$(F + \lambda I)(x, \mathbf{m}, 0_{\mathbb{R}^n}, \mathbf{y})^T = \begin{pmatrix} \Lambda - x E_n^T \beta \mathbf{m} + \lambda x \\ \int_0^\infty \rho(a)\mathbf{y}(a)da - \delta\beta x \mathbf{m} + \lambda \mathbf{m} \\ \beta x \mathbf{m} \\ \lambda \mathbf{y}. \end{pmatrix}$$

Then taking $\lambda_C = C \sum_{j=1}^n \beta_j$, item 1. follows.

2. Writing

$$(\lambda I - A)^{-1} \left(\tilde{x}, \tilde{\mathbf{m}}, \tilde{\psi}, \tilde{\mathbf{y}}\right)^T = (x, \mathbf{m}, 0_{\mathbb{R}^n}, \mathbf{y})^T,$$

with

$$\begin{cases} \mathbf{y}(a) = & e^{-(\lambda+\mu_x)a}\tilde{\psi} + \int_0^a e^{-(\lambda+\mu_x)(a-s)}\tilde{\mathbf{y}}(s)ds, \forall \lambda > 0, \\ \mathbf{m} = & \dfrac{\tilde{\mathbf{m}}}{\lambda + \mu_m}, \\ x = & \dfrac{\tilde{x}}{\lambda + \mu_x}. \end{cases}$$

Then, we easily find that $(x, \mathbf{m}, 0_{\mathbb{R}^n}, \mathbf{y})^T \in X_+$ as soon as $\left(\tilde{x}, \tilde{\mathbf{m}}, \tilde{\psi}, \tilde{\mathbf{y}}\right)^T \in X_+$. □

The precise result of this section is the following:

Theorem 4.2.2. *Let Assumption 5.1.1 be satisfied. Then there exists a unique strongly continuous semiflow $\{U(t) : X_{0+} \to X_{0+}\}_{t \geq 0}$ such that for each $u_0 \in X_{0+}$, the map $u \in$*

$C([0,\infty):X_{0+})$ defined by $u=U(.)u_0$ is a mild solution of (4.14), namely it satisfies

$$\int_0^t u(s)ds \in D(A),\ \ \forall t\geq 0,$$
$$u(t)=u_0+A\int_0^t u(s)ds+\int_0^t F(u(s))ds\ ;\quad t\geqslant 0.$$

Furthermore $\{U(t)\}_{t\geq 0}$ satisfies the following properties:

(i) Let $U(t)u_0=(x(t),\mathbf{m}(t),0_{\mathbb{R}^n},\mathbf{y}(t,.))^T$, then the following Voletrra integral formulation holds true for $j\in\{1,2,\cdots,n\}$

$$y_j(t,a)=\begin{cases} y_{0,j}(a-t)e^{-\mu_x t} \text{ if } a\geq t \\ \beta_j x(t-a)m_j(t-a)e^{-\mu_x a} \text{ if } a<t \end{cases},$$

so that $x(t)$ and $\mathbf{m}(t)$ becomes the unique solution of the problem

$$\frac{dx(t)}{dt}=\Lambda-\mu_x x(t)-x(t)E_n^T\beta\mathbf{m}(t);$$
$$\frac{d\mathbf{m}(t)}{dt}=\Psi(x,\mathbf{m})(t)-\mu_m\mathbf{m}(t)-\delta\beta x(t)\mathbf{m}(t);$$

where $\Psi(x,\mathbf{m})(t)=(\Psi_1(x,\mathbf{m})(t);\cdots;\Psi_n(x,\mathbf{m})(t))^T$ and for $j\in\mathbb{N}_n$

$$\Psi_j(x,\mathbf{m})(t)=\int_0^t \rho_j(a)\beta_j x(t-a)m_j(t-a)e^{-\mu_x a}da+\int_t^\infty \rho_j(a)y_{0,j}(a-t)e^{-\mu_x t}da.$$

(ii) For each $u_0\in X_{0+}$ one has for all $t\geq 0$:

$$x(t)+\int_0^\infty E_n^T\mathbf{y}(t,a)da\leq x_0+||E_n^T\mathbf{y}_0||_{L^1}+\frac{\Lambda}{\mu_x},$$
$$E_n^T\mathbf{m}(t)\leq E_n^T\mathbf{m}_0+\frac{1}{\mu_m^{min}}\left(x_0+||E_n^T\mathbf{y}_0||_{L^1}+\frac{\Lambda}{\mu_x}\right)\|\rho\|_{max}.$$

wherein we have set $u_0=(x_0,\mathbf{m}_0,(0_{\mathbb{R}^n},\mathbf{y}_0))^T$; $U(t)u_0=(x(t),\mathbf{m}(t),(0_{\mathbb{R}^n},\mathbf{y}(t,.)))^T$; $\mu_m^{min}=\min\limits_{1\leqslant j\leqslant n}\mu_{m,j}$ and $\|\rho\|_{max}=\max\limits_{1\leqslant j\leqslant n}\|\rho_j\|_{L^\infty}$.

(iii) The semiflow $\{U(t)\}_{t\geq 0}$ is bounded dissipative and asymptotically smooth.

Proof. The proof of this result is rather standard. Indeed it is easy to check that the nonlinear map F is locally lipschitzian, the operator A satisfies the Hille-Yosida property (see Lemmas 4.2.1, 4.2.2 and Proposition 4.2.1). Then standard methodologies apply to provide the existence and uniqueness of mild solution for System (4.3)-(4.4). (see for instance [140, 144, 145, 201, 203]).

Next the Voletrra integral formulation is also standard in the context of age-structured equation and we refer to [108, 211] and the references cited therein for more details.

Estimates stated in (ii) directly follow from the system of equations. Indeed adding-up the x-equation together with the y_i-equation yields

$$\frac{d}{dt}\left(x(t)+\int_0^\infty E_n^T\mathbf{y}(t,a)da\right)=\Lambda-\mu_x\left(x(t)+\int_0^\infty E_n^T\mathbf{y}(t,a)da\right);$$

from where one deduces the first estimate of (ii) while the second estimate directly follows from the first one applied to the m_i-equations.

It remains to prove (iii) and let us notice that the bounded dissipativity of the semiflow $\{U(t)\}_{t\geq 0}$ is a direct consequence of (ii). To prove the asymptotically smoothness, let B be a forward invariant bounded subset of X_{0+}. According to the results in [192] it is sufficient to show that the semiflow is asymptotically compact on B.

Let us consider a sequence of solutions $\left\{u_p=(x^p;\mathbf{m}^p,0,\mathbf{y}^p)^T\right\}_{p\geq 0}$ that is equibounded in X_{0+} and let consider a sequence $\{t_p\}_{p\geq 0}$ such that $t_p\to+\infty$. Let us show that the sequence $\{u_p(t_p)\}_{p\geq 0}$ is relatively compact in X_{0+}. To do so, we consider the sequence of map $\{w_p(t)=u_p(t+t_p)\}_{p\geq 0}$. Since x_p and $\mathbf{m}_p$ are uniformly bounded in the Lipschitz norm, Arzela-Ascoli theorem implies that, possibly along a sub-sequence, one may assume that $x_p(t+t_p)\to\widehat{x}$ and $\mathbf{m}_p(t+t_p)\to\widehat{\mathbf{m}}(t)$ locally uniformly for $t\in\mathbb{R}$. It remains to deal with the sequence $\{\mathbf{y}^p(t_p,.)\}_{p\geq 0}$. Let us denote by $\widetilde{\mathbf{y}}_p(t,.)=\mathbf{y}_p(t+t_p,.)$. Using the Volterra integral formulation one gets

$$\widetilde{\mathbf{y}}_p(t,a)=\begin{cases}\mathbf{y}_0(a-t+t_p)e^{-\mu_x(t+t_p)}\text{ if }a\geq t+t_p,\\ \beta x_p(t-a+t_p)\mathbf{m}_p(t-a+t_p)e^{-\mu_x a}\text{ if }a<t+t_p.\end{cases}\tag{4.15}$$

Finally sine $\beta x_p(t-a+t_p)\mathbf{m}_p(t-a+t_p)e^{-\mu_x a}$ convergences as $p\to\infty$ towards some function $\xi(t,a)=\beta\widehat{x}(t-a)\widehat{\mathbf{m}}(t-a)e^{-\mu_x a}$ locally uniformly, one easily concludes that

$$\mathbf{y}_p(t_p,.)=\widetilde{\mathbf{y}}_p(0,.)\to\beta\widehat{x}(-.)\widehat{\mathbf{m}}(-.)e^{-\mu_x\cdot}\text{ in }L^1\left(0,\infty;\mathbb{R}^n\right).$$

The result follows. □

Basic properties.

Now in order to deal with sub-system, it will be also convenient to introduce for each $J\subset\mathbb{N}_n$ the close subspaces $X^J\subset X$ and $X_0^J\subset X_0$ defined by

$$X^J=\left\{(x,\mathbf{m},\alpha;\mathbf{y})^T\in X:\ m_i+\int_0^\infty y_i(a)da=0,\ \ \forall i\in J\right\}\text{ and }X_0^J=X^J\cap X_0.$$

We also introduce X_{0+}^J, the positive cone of X_0^J defined by

$$X_{0+}^J = X_0^J \cap X_{0+}.$$

If $J = \emptyset$ then $X^J = X$, $X_0^J = X_0$ and $X_{0+}^J = X_{0+}$. Recalling definition (5.3), note that $A(D(A) \cap X_0^J) \subset X^J$. In the sequel we shall denote by $A_J : D(A_J) \subset X^J \to X^J$ the linear Hile Yosida operator defined by

$$D(A_J) = D(A) \cap X_0^J, \;\; A_J x = Ax, \;\; \forall x \in D(A) \cap X_0^J. \tag{4.16}$$

For each $i \in \mathbb{N}_n$ we also consider

$$M_0^i = \left\{ (x, \mathbf{m}, \alpha; \mathbf{y})^T \in X_{0+} : \; m_i + \int_0^\infty y_i(a)da > 0 \right\}.$$

Then the following lemma holds true

Lemma 4.2.3. *For each $J \subset \mathbb{N}_n$ and each $i \in \mathbb{N}_n$, the subsets $X_{0+}^J \subset X_{0+}$ and M_0^i are both positively invariant under the semiflow $\{U(t)\}_{t\geq 0}$; in other words*

$$U(t)M_0^i \subset M_0^i \text{ and } U(t)X_{0+}^J \subset X_{0+}^J \;\; \forall t \geq 0.$$

Proof. To prove the above result, let $i \in \mathbb{N}_n$ be given. Let $u_0 := (x_0; \mathbf{m}_0; 0_{\mathbb{R}^n}; \mathbf{y}_0) \in M_0^i$ be given and let us denote for each $t \geq 0$, $U(t)u_0 := (x(t); \mathbf{m}(t); 0_{\mathbb{R}^n}, \mathbf{y}(t, .))^T$ the orbit passing through u_0. Let us set $p_i(t) = m_i(t) + \displaystyle\int_0^\infty y_i(t, a)da$. It comes that $p_i'(t) \geq -\max(\mu_x, \mu_{mi})p_i(0)$. That is

$$m_i(t) + \int_0^\infty y_i(t, a)da \geq e^{-\max(\mu_x, \mu_{mi})t} \left(m_{0i} + \int_0^\infty y_{0i}(a)da \right).$$

This complete the fact that $U(t)M_0^i \subset M_0^i$.

Now, let $u_0 \in \partial M_0^i$. Using the Volterra formulation we easily find that $m_i(t) = 0$ for all $t \geq 0$ and

$$\begin{aligned} \textstyle\int_0^\infty y_i(t, a)da &= \beta_1 \textstyle\int_0^t x(t-a)m_i(t-a)e^{-\mu_x a}da + e^{-\mu_x t}||y_{0i}||_{L^1} \\ &= 0. \end{aligned}$$

Therefore $U(t)\partial M_0^i \subset \partial M_0^i$ for all $t \geq 0$. This ends the proof of the lemma. □

Then coupling Theorem 4.2.2 together with the results of Hale [91, 92], Hale et al. [93] , one obtains the following proposition:

Proposition 4.2.2. *Let $J \subset \mathbb{N}_n$ be given. There exists a non-empty compact set $\mathcal{A}_J \subset X_{0+}^J$ such that*

(i) $\mathcal{A}_J$ is invariant under the semiflow $\left\{U_J(t) := U(t)|_{X_{0+}^J}\right\}_{t\geq 0}$ that is:

$$U_J(t)\mathcal{A}_J = \mathcal{A}_J, \forall t \geq 0.$$

(ii) The subset $\mathcal{A}_J$ attracts the bounded sets of X_{0+}^J under the semiflow U_J, namely, for any bounded set $\mathcal{B} \subset X_{0+}^J$,

$$\lim_{t\to+\infty} \delta_J\left(U_J(t)\mathcal{B}, \mathcal{A}_J\right) = 0,$$

wherein the semi-distance δ_J is defined by $\delta_J(\mathcal{A}, \mathcal{B}) = \sup_{x\in\mathcal{A}} \inf_{y\in\mathcal{B}} ||x-y||_{X^J}$.

4.2.3 Steady states and basic reproduction number

Steady states of the model

Next the following proposition describes the equilibria of the model.

Proposition 4.2.3. *Let Assumption 5.1.1 be satisfied. Assume furthermore that the set $\mathcal{S}$ is strictly ordered. Then System (4.3) (or semiflow $\{U(t)\}_{t\geq 0}$ provided by Theorem 4.2.2) has exactly $1 + card\,\mathcal{S}$ stationary states:*

(i) *The disease free equilibrium defined by*

$$u_0^* = \left(x_f; 0_{\mathbb{R}^n}; 0_{\mathbb{R}^n}, 0_{L_1(0,\infty;\mathbb{R}^n)}\right)^T \in X_{0+}^{\mathbb{N}_n}, \quad x_f = \frac{\Lambda}{\mu_x},$$

is an equilibrium of U and it is the only one when $\mathcal{S} = \emptyset$.

(ii) *When $\mathcal{S} \neq \emptyset$, in addition to the disease free equilibrium u_0^*, the semiflow U has exactly card $\mathcal{S}$ endemic stationary states defined for each $k \in \mathcal{S}$ by*

$$u_k^* = \left(x_e^k, \mathbf{m}_e^k, 0_{\mathbb{R}^n}, \mathbf{y}_e^k\right)^T \in X_{0+}^{\mathbb{N}_n\setminus\{k\}} \cap M_0^k,$$

wherein the above quantities are defined in (4.10).

Proof. An equilibrium $(x, \mathbf{m}, 0_n; \mathbf{y})^T \in X_{0+}$ of system (4.3) is the solution of the following system of equations

$$\begin{cases} \Lambda - \mu_x x - x\sum_{i=1}^n \beta_i m_i = 0; \\ \beta_j m_j x(K_j - \delta_j) - \mu_{mj} m_j = 0; \ \text{ for } j = 1, \ldots, n; \\ \mathbf{y}(a) = xl(a)\beta\mathbf{m}, \forall a \geq 0; \end{cases}$$

with

$$K_j = \int_0^\infty \rho_j(a) l(a) da; \quad \text{for } j = 1, \ldots, n. \tag{4.17}$$

It is easily find that the disease free equilibrium $\left(x_f; 0_{\mathbb{R}^n}; 0_{\mathbb{R}^n}, 0_{L_1(0,\infty;\mathbb{R}^n)}\right)^T$ is always a solution of the system wherein $x_f = \dfrac{\Lambda}{\mu_x}$. If $\mathcal{T}_0^i > 1$, then there exists an endemic equilibrium $(x_e^i; m_e^i; 0_{\mathbb{R}^n}; y_e^i(.)) \in X_{0+}$, corresponding to strain i, defined by

$$x_e^i = \frac{x_f}{\mathcal{T}_0^i}; \quad m_{ei}^i = \frac{\mu_x(\mathcal{T}_0^i - 1)}{\beta_i}; \quad y_{ei}^i(a) = \beta_i x_e^i m_{ei}^i l(a), \forall a \in [0, \infty);$$

while the values for the other indexes $j \neq i$ are $m_{ej}^i = 0$ and $y_{ej}^i = 0_{L^1(0,\infty,\mathbb{R})}$ and wherein the value of $\mathcal{T}_0^i$ is given by (4.5). □

Basic reproduction rate of the model

Here we follow the methodology of Diekmann and Heesterbeek [48, 51] and Inaba [116] (see also the references cited therein) to define the reproductive number as the number of secondary infections that one infectious individual would create over the duration of the infectious period, provided that everyone else is susceptible.

Let $b_j(t)$ be the density of newly produced $j-$ merozoites at time t. Then from (4.1) one has

$$b_j(t) = \int_0^\infty r(a)\mu_j(a) w_j(t,a) da. \tag{4.18}$$

In the early stage of the disease invasion process, the dynamics of the population can be described by the linearized equation at the disease-free steady state. The linearized system (4.1) at the disease-free equilibrium leads to the following equations:

$$\begin{cases} \dfrac{dx(t)}{dt} = -\mu_x x(t) - x_f \displaystyle\sum_{j=1}^{n} \beta_j m_j(t); \\ \dfrac{\partial \omega_j(t,a)}{\partial t} + \dfrac{\partial \omega_j(t,a)}{\partial a} = -(\mu_j(a) + \mu_x)\omega_j(t,a); \\ \dfrac{dm_j(t)}{dt} = \displaystyle\int_0^\infty \rho_{y,j}(a)\omega_j(t,a)da - \mu_{m,j} m_j(t) - \delta_j \beta_j x_f m_j(t); \\ \omega_j(t,0) = \beta_j x_f m_j(t); \quad j \in \{1, 2, \cdots, n\}. \end{cases} \tag{4.19}$$

Integrating the ω_j-equation of system (4.19) belong the characteristics, we obtain that

$$\omega_j(t,a) = \begin{cases} \omega_{0,j}(a-t) e^{-\int_{a-t}^a (\mu_x + \mu_j(s))ds} \text{ if } a \geq t, \\ \beta_j x(t-a) m_j(t-a) e^{-\int_0^a (\mu_x + \mu_j(s))ds} \text{ if } a < t. \end{cases}$$

Therefore, equation (4.18) gives that

$$b_j(t) = \beta_j x_f \int_0^t \rho_j(a) l(a) m_j(t-a) da + \int_t^\infty \rho_{y,j}(a) w_j(0,a) da.$$

On the other hand, it follows from the m_j component of the linearized system (4.19) that $\dot{m}_j(t) = b_j(t) - (\mu_{m,j} + \delta_j \beta_j x_f) m_j(t)$, that re-writes as

$$m_j(t) = \int_0^t e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(t-s)} b_j(s) ds + m_j(0) e^{-(\mu_{m,j}+\delta_j\beta_j x_f)t}.$$

As a consequence b_j satisfies the following renewal equation:

$$\begin{aligned} b_j(t) &= \beta_j x_f \int_0^t \left(\int_0^a e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(a-s)} \rho_j(s) l(s) ds \right) b_j(t-a) da \\ &\quad + \beta_j x_f m_j(0) \int_0^t \rho_j(a) l(a) e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(t-a)} da + \int_t^\infty r_j(a) \mu_j(a) w_j(0,a) da. \end{aligned}$$

Due to the above formulation, the $j-$strain specific basic reproduction number $\mathcal{R}_0^j$ is calculated as

$$\mathcal{R}_0^j = \beta_j x_f \int_0^\infty \left(\int_0^a e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(a-s)} \rho_j(s) l(s) ds \right) da;$$

that is

$$\mathcal{R}_0^j = \frac{\beta_j x_f}{\mu_{m,j} + \delta_j \beta_j x_f} \int_0^\infty \rho_j(a) l(a) da.$$

Now let us notice that $sgn\left(\mathcal{R}_0^j - 1\right) = sgn\left(\mathcal{T}_0^j - 1\right)$. Indeed it is easy to check that

$$\begin{aligned} \mathcal{R}_0^j - 1 &= \frac{\beta_j x_f}{\mu_{m,j} + \delta_j \beta_j x_f} \int_0^\infty \rho_j(a) l(a) da - 1, \\ &= \frac{\mu_{m,j}}{\mu_{m,j} + \delta_j \beta_j x_f} \left[\frac{\beta_j x_f}{\mu_{m,j}} \int_0^\infty \rho_j(a) l(a) da - \frac{\mu_{m,j} + \delta_j \beta_j x_f}{\mu_{m,j}} \right], \\ &= \frac{\mu_{m,j}}{\mu_{m,j} + \delta_j \beta_j x_f} \left[\frac{\beta_j x_f}{\mu_{m,j}} \left(\int_0^\infty \rho_j(a) l(a) da - \delta_j \right) - 1 \right], \\ &= \frac{\mu_{m,j}}{\mu_{m,j} + \delta_j \beta_j x_f} \left(\mathcal{T}_0^j - 1 \right). \end{aligned}$$

Moreover one can notice that when $\delta_j = 0$ then $\mathcal{R}_0^j = \mathcal{T}_0^j$.

4.2.4 Technical materials

In this subsection we establish some properties of the entire solutions of System (4.3). These properties will be useful later to derive the asymptotic behaviour of (4.3) especially when $\mathcal{S} \neq \emptyset$.

Our first result is concerned with spectral properties of the linearized semiflow $U_J := U|_{X_{0+}^J}$ for some given subset $J \subset \mathbb{N}_n$ at an given stationary point $u^* \in \partial M_0^J$. Let $u^* = (x^*, \mathbf{m}^*, 0_{\mathbb{R}^n}, \mathbf{y}^*)^T \in X_{0+}^J$ be a given stationary state of the semiflow U_J. The associated linearized equation at the point u^* reads as

$$\frac{du(t)}{dt} = (A_J + B_{u^*})u(t);$$

where A_J is the linear operator defined in (4.16) while $B_{u^*} \in \mathcal{L}\left(X_0^J, X^J\right)$ is the bounded linear operator defined by:

$$B_{u^*}\begin{pmatrix} x \\ \mathbf{m} \\ 0_{\mathbb{R}^n} \\ \mathbf{y} \end{pmatrix} = \begin{pmatrix} -x^* E_n^T \beta \mathbf{m} - x E_n^T \beta \mathbf{m}^* \\ \int_0^\infty \rho(a)\mathbf{y}(a)da - \delta\beta(x^*\mathbf{m} + x\mathbf{m}^*) \\ x^*\beta\mathbf{m} + x\beta\mathbf{m}^* \\ 0_{L^1(0,\infty,\mathbb{R}^n)} \end{pmatrix}$$

Lemma 4.2.4. *Let $J \subset \mathbb{N}_n$ be given. Let us set $\Omega = \{\lambda \in \mathbb{C} : \ Re\ (\lambda) > -\mu_x\}$. Then the spectrum $\sigma\left(A_J + B_{u^*}\right) \cap \Omega \neq \emptyset$ only consists in point spectrum and one has*

$$\sigma\left(A_J + B_{u^*}\right) \cap \Omega = \left\{\lambda \in \Omega : \ \Delta^J(\lambda, u^*) = 0\right\},$$

where function $\Delta^J(., u^*) : \Omega \to \mathbb{C}$ is defined by

$$\Delta^J(\lambda, u^*) = \prod_{i \in \mathbb{N}_n \setminus J} \chi_i(\lambda, x^*),$$

while for each $i \in \mathbb{N}_n$ and each $x \in \mathbb{R}$, function $\chi_i(., x) : \Omega \to \mathbb{C}$ is defined by

$$\chi_i(\lambda, x) = 1 - \frac{\beta_i x}{\lambda + \mu_{mi}}\left[\int_0^\infty \rho_i(a) e^{-(\lambda+\mu_x)a} da - \delta_i\right]. \tag{4.20}$$

Proof. Let $J \subset \mathbb{N}_n$ be given. Let us denote by A_{0J} the part of A_J in X_0^J. Then it is the infinitesimal generator of a C_0-semigroup on X_0^J denoted by $\{T_{A_{0J}}(t)\}_{t\geq 0}$. Let $(x, \mathbf{m}, 0_n; \mathbf{y})^T \in X_0^J$; following results in [142], we find that

$$T_{A_{0J}}(t)\begin{pmatrix} x \\ \mathbf{m} \\ 0_{\mathbb{R}^n} \\ \mathbf{y} \end{pmatrix} = \begin{cases} \left(e^{-\mu_x t}x, e^{-\mu_m t}\mathbf{m}, 0_{\mathbb{R}^n}, e^{-\mu_x t}\mathbf{y}(a-t)\right)^T, \forall a \geq t, \\ \left(e^{-\mu_x t}x, e^{-\mu_m t}\mathbf{m}, 0_{\mathbb{R}^n}, 0_{L^1(0,\infty,\mathbb{R}^n)}\right)^T, \forall a < t. \end{cases}$$

Then, for $t \geq a_0$ we have

$$\begin{aligned}\left|\left|T_{A_{0J}}(t-a_0)(x,\mathbf{m},0_n;\mathbf{y})^T\right|\right|_X &= e^{-\mu_x(t-a_0)}|x| + e^{-\mu_m(t-a_0)}|\mathbf{m}| + \int_{t-a_0}^{\infty} e^{-\mu_x(t-a_0)}\mathbf{y}(a-t+a_0)da,\\ &\leq e^{-\min(\mu_x,\mu_m)(t-a_0)}||(x,\mathbf{m},0_n;\mathbf{y})^T||_X, \quad \forall t \geq a_0.\end{aligned}$$

We deduce that

$$||T_{A_{0J}}(t-a_0)||_{\mathcal{L}(X)} \leq e^{-\min(\mu_x,\mu_m)(t-a_0)}, \forall\, t \geq a_0.$$

Next it is easy to check that the growth rate of this semigroup satisfies

$$\omega_0\left(A_{0J}\right) := \lim_{t\to+\infty} \frac{\ln\left(||T_{A_{0J}}(t)||_{\mathcal{L}(X)}\right)}{t} \leq -\min(\mu_x,\mu_m).$$

Then since operator B_{u^*} is compact, the results in [203, 57] apply and provided that the essential growth rate of $\left\{T_{(A_J+B_{u^*})_0}(t)\right\}_{t\geq 0}$, the C_0-semigroup generated by the part of $(A_J + B_{u^*})$ in X_0^J satisfies

$$\omega_{0,ess}\left((A_J+B_{u^*})_0\right) \leq \omega_{0,ess}\left(A_{0J}\right) < \omega_0\left(A_{0J}\right) \leq -\min(\mu_x,\mu_m).$$

Applying the result in [145] (see also [69] and [213]), the latter inequality ensures that $\Omega \cap \sigma\left(A_J + B_{u^*}\right) \neq \emptyset$ and it is only composed of point spectrum of $(A_J + B_{u^*})$.

It remains to derive the characteristic equation (we refer to [33, 136, 147] for more details on the subject). Let $\lambda \in \rho\left(A_J + B_{u^*}\right)$. We have

$$\begin{aligned}&(\lambda I - A_J - B_{u^*})(x,\mathbf{m},0_n;\mathbf{y})^T = (\tilde{x},\tilde{\mathbf{m}},\tilde{\psi};\tilde{\mathbf{y}})^T \qquad \Leftrightarrow\\ &(\lambda I - A_J)(x,\mathbf{m},0_n;\mathbf{y})^T - B_{u^*}(x,\mathbf{m},0_n;\mathbf{y})^T = (\tilde{x},\tilde{\mathbf{m}},\tilde{\psi};\tilde{\mathbf{y}})^T \quad ,\end{aligned}$$

fromwhere we have the following fixed point equation

$$(x,\mathbf{m},0_n;\mathbf{y})^T = (\lambda I - A_J)^{-1}(\tilde{x},\tilde{\mathbf{m}},\tilde{\psi};\tilde{\mathbf{y}})^T + (\lambda I - A_J)^{-1}B_{u^*}(x,\mathbf{m},0_n;\mathbf{y})^T. \qquad (4.21)$$

Since

$$(\lambda I - A_J)^{-1}(\tilde{x},\tilde{\mathbf{m}},\tilde{\psi};\tilde{\mathbf{y}})^T = \left(\frac{\tilde{x}}{\lambda+\mu_x}, \frac{\tilde{\mathbf{m}}}{\lambda+\mu_m}, 0_{\mathbb{R}^n}, e^{-(\lambda+\mu_x)\cdot}\tilde{\psi} + \int_0^{\cdot} e^{-(\lambda+\mu_x)(\cdot-s)}\tilde{\mathbf{y}}(s)ds\right)^T,$$

we find that

$$(\lambda I - A_J)^{-1}B_{u^*}(x,\mathbf{m},0_n;\mathbf{y})^T = \begin{pmatrix} \dfrac{-x^*E_n^T\beta\mathbf{m} - xE_n^T\beta\mathbf{m}^*}{\lambda+\mu_x} \\ \dfrac{\int_0^\infty \rho(a)\mathbf{y}(a)da - \delta\beta(x^*\mathbf{m} + x\mathbf{m}^*)}{\lambda+\mu_m} \\ 0_{\mathbb{R}^n} \\ e^{-(\lambda+\mu_x)\cdot}\left(x^*\beta\mathbf{m} + x\beta\mathbf{m}^*\right) \end{pmatrix}.$$

Therefore, equation (4.21) rewrites as

$$\left(1+\frac{E_n^T\beta\mathbf{m}^*}{\lambda+\mu_x}\right)x+\frac{x^*E_n^T\beta}{\lambda+\mu_x}\mathbf{m}=\frac{\tilde{x}}{\lambda+\mu_x}, \tag{4.22}$$

$$\frac{\delta\beta\mathbf{m}^*}{\lambda+\mu_m}x+\left(1+\frac{\delta\beta\mathbf{m}^*}{\lambda+\mu_m}\right)\mathbf{m}-\frac{\int_0^\infty\rho(a)\mathbf{y}(a)da}{\lambda+\mu_m}=\frac{\tilde{\mathbf{m}}}{\lambda+\mu_m}, \tag{4.23}$$

$$\mathbf{y}(.)-e^{-(\lambda+\mu_x).}\left(x^*\beta\mathbf{m}+x\beta\mathbf{m}^*\right)=e^{-(\lambda+\mu_x).}\tilde{\psi}+\int_0^{\cdot}e^{-(\lambda+\mu_x)(.-s)}\tilde{\mathbf{y}}(s)ds, \tag{4.24}$$

Substituting (4.24) into (4.23), it comes that we can isolate x, $\mathbf{m}$ (and then $(x,\mathbf{m},0_n;\mathbf{y})$) in system (4.22)-(4.23) if and only if

$$\Delta^J(\lambda,u^*)=\prod_{i\in\mathbb{N}_n\setminus J}\chi_i(\lambda,x^*)\neq 0,$$

wherein the function $\chi_i(.,x):\Omega\to\mathbb{C}$ is defined by (4.20). Therefore,

$$\sigma\left(A_J+B_{u^*}\right)\cap\Omega=\left\{\lambda\in\Omega:\ \Delta^J(\lambda,u^*)=0\right\}.$$

□

Our next result relies on properties of the entire solutions of System (4.3)

Lemma 4.2.5. *Let* $\left\{u(t)=(x(t),\mathbf{m}(t),0_{\mathbb{R}^n},\mathbf{y}(t,.))^T\right\}_{t\in\mathbb{R}}$ *be a given entire solution of the semiflow* U*. Then* x *satisfies*

$$\inf_{t\in\mathbb{R}}x(t)>0. \tag{4.25}$$

Furthermore the following properties holds true:

(i) If there exist $i\in\mathbb{N}_n$ *and* $t_0\in\mathbb{R}$ *such that* $u(t_0)\in M_0^i$ *then*

$$m_i(t)>0,\ \forall t\in\mathbb{R}\ \text{and}\ y_i(t,a)>0,\ \forall(t,a)\in\mathbb{R}\times[0,\infty).$$

(ii) Assume that $\mathcal{S}\neq\emptyset$ *and assume there exist* $i\in\mathcal{S}$ *and* $t_0\in\mathbb{R}$ *such that* $u(t_0)\in M_0^i$*. If* $u(t)\to u^*$ *as* $t\to\infty$ *where* u^* *is an equilibrium point of* U*. Then one has*

$$u^*\in\left\{u_j^*:\ i\trianglelefteq j\right\}.$$

(iii) For each $i\in\mathbb{N}_n$ *there exist a constant* $M_i>1$ *such that*

$$\frac{m_i^-(t)}{M_i}e^{-\mu_x a}\leq y_i(t,a)\leq M_ie^{-\mu_x a};\ \forall(t,a)\in\mathbb{R}\times[0,\infty),$$

wherein we have set $m_i^-(t)=\inf_{s\leq t}m_i(s)$.

Proof. Let us first notice that since u is an entire solution then

$$\mathbf{y}(\sigma, a) = \beta x(\sigma - a)\mathbf{m}(\sigma - a)e^{-\mu_x a} \ \ \forall (\sigma, a) \in \mathbb{R} \times [0, \infty). \tag{4.26}$$

This expression directly follows from the Volterra integral formulation in Theorem 4.2.2.

From the estimates provided in Theorem 4.2.2 and the x-equation there exists some constant $C > 0$ such that for each $s \in \mathbb{R}$ and $t \geq 0$ one has

$$x(s)e^{-Ct} + \Lambda \int_0^t e^{-C(t-l)}dl \leq x(t+s) \leq x(s) + \frac{\Lambda}{\mu_x}. \tag{4.27}$$

This implies that $\inf_{t\in\mathbb{R}} x(t) > 0$ and complete the proof of (4.25).

We now turn to the proof of (i). Let us argue by contradiction by assuming that there exists $t_1 \in \mathbb{R}$ such that $m_i(t_1) = 0$. Then from the m_i-equation we deduce that $m_i(t) = 0$ for all $t \leq t_1$. Next we infer from (4.26) that

$$\int_0^\infty y_i(t, a)da = 0, \ \ \forall t \leq t_1.$$

Hence $m_i(t) + \int_0^\infty y_i(t, a)da \equiv 0$, a contradiction with the existence of t_0. On the other hand, due to (4.27) and (4.25), if there exists $(t_1, a_1) \in \mathbb{R}\times[0, \infty)$ such that $y_i(t_1, a_1) = 0$ then $m_i(t_1 - a_1) = 0$ and the first part of the argument applies.

Let us now prove (ii). Let us first notice that since $m_i(t_0) + \int_0^\infty y_i(t_0, a)da > 0$, (i) implies that

$$m_i(t) > 0 \text{ for all } t \in \mathbb{R} \text{ and } y_i(t, a) > 0 \text{ for all } (t, a) \in \mathbb{R} \times [0, \infty).$$

Next consider the function $\Gamma_i(a) = \int_a^\infty \rho_i(s)e^{\mu_x(a-s)}ds$ and note that $\Gamma_i \in L^\infty(0, \infty, \mathbb{R})$ and satisfies $\Gamma_i'(a) - \mu_x\Gamma_i(a) + \rho_i(a) = 0$ *a.e.* $a \geq 0$. Let us introduce the functional

$$\Phi_i[u](t) = \int_0^\infty \Gamma_i(a)y_i(t, a)da + m_i(t),$$

that satisfies (recalling Definition (4.5))

$$\frac{d\Phi_i[u](t)}{dt} = \mu_{mi}m_i(t)\left[\mathcal{R}_0^i\frac{x(t)}{x_f} - 1\right], \ \ \forall t \in \mathbb{R}. \tag{4.28}$$

Using this computation we will obtain a contradiction by assuming that $u(t) \to u_j^*$ as $t \to \infty$ for some $j \lhd i$. Indeed for $j = 0$ then $u(t) \to u_0^*$ as $t \to \infty$ implies that $x(t) \to x_f$ as $t \to \infty$. Then since $\mathcal{R}_0^i > 1$ then function $t \mapsto \Phi_i[u](t)$ is not decreasing for t large enough. Hence there exists $t_0 \in \mathbb{R}$ such that $\Phi_i[u](t) \geq \Phi_i[u](t_0)$ for all $t \geq t_0$. Since

$\Phi_i[u](t_0) > 0$, this prevents the component (y_i, m_i) to converge to $(0, 0_{L^1})$ as $t \to \infty$. A contradiction with $u(t) \to u_0^*$.

The same argument holds for $j \in \mathcal{S}$ with $j \lhd i$. Indeed in such a case $x(t) \to x_e^j$ as $t \to \infty$ and since

$$\left[\mathcal{R}_0^i \frac{x_e^j}{x_f} - 1\right] = \frac{\mathcal{R}_0^i}{\mathcal{R}_0^j} - 1 > 0,$$

the same arguments apply. This completes the proof of (ii).

Finally note that (iii) directly follows from (4.25) and (4.26). This ends the proof of Lemma 4.2.5. □

Our next lemma is a computation result which will be used in the sequel to perform Lyapunov arguments.

Lemma 4.2.6. *Let us assume that the same assumptions of Lemma 4.2.5 are satisfied. Let $h : (0, \infty) \to [0, \infty)$ be the function defined by*

$$h(s) = s - 1 - \ln s. \tag{4.29}$$

Let us assume that there exists $i_0 \in \mathcal{S}$ such that

$$\liminf_{t \to -\infty} m_{i_0}(t) > 0. \tag{4.30}$$

Then for each $t \in \mathbb{R}$ one has

$$\left[\int_{.}^{\infty} \rho_{i_0}(s) l(s) ds\right] h\left(\frac{y_{i_0}(t, .)}{y_{ei_0}^{i_0}(.)}\right) \in L^1(0, \infty, \mathbb{R}). \tag{4.31}$$

Consider now the map $V_{i_0}[u] : \mathbb{R} \to [0, \infty)$ defined by

$$V_{i_0}[u](t) := V_x(t) + V_{y_{i_0}}(t) + V_{m_{i_0}}(t) + \sum_{j=1; j \neq i_0}^{p} \int_0^{\infty} f_j(a) y_j(t, a) da + \sum_{j=1; j \neq i_0}^{p} d_j m_j(t), \tag{4.32}$$

wherein we have set

$$V_x(t) = h\left(\frac{x(t)}{x_e^{i_0}}\right); \quad V_{y_{i_0}}(t) = \int_0^{\infty} \alpha_{i_0}(a)\, h\left(\frac{y_{i_0}(t, a)}{y_{ei_0}^{i_0}(a)}\right) da; \quad V_{m_{i_0}}(t) = d_{i_0}\, h\left(\frac{m_{i_0}(t)}{m_{ei_0}^{i_0}}\right)$$

and

$$d_{i_0} = \frac{\beta_{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}; \quad d_j = \frac{\beta_j}{\mu_{mj}}, \quad \text{with } j \neq i_0; \tag{4.33}$$

$$f_j(a) = \frac{\beta_j}{\mu_{mj}} \int_a^{\infty} \rho_j(s) e^{-\mu_x(s-a)} ds; \tag{4.34}$$

$$\alpha_{i_0}(a) = \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \int_a^\infty \rho_{i_0}(a) l(a) da. \tag{4.35}$$

Then function $t \mapsto V_{i_0}[u](t)$ is of the class C^1 on $\mathbb{R}$ and we have

$$\begin{aligned}\dot{V}_{i_0}[u](t) = &-\frac{\Theta_{i_0}}{x_e^{i_0} x(t)} \left(x(t) - x_e^{i_0}\right)^2 + \frac{x(t)}{x_e^{i_0}} \sum_{j=1; j\neq i_0}^{p} \left(\frac{\mathcal{R}_0^j}{\mathcal{R}_0^{i_0}} - 1\right) \beta_j m_j(t) \\ &- \int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \rho_{i_0}(a) l(a) \left[h\left(\frac{y_{i_0}(t,a) m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a) m_{i_0}(t)}\right) + h\left(\frac{m_{i_0}(t) y_{ei_0}^{i_0}(0)}{m_{ei_0}^1 y_{i_0}(t,0)}\right)\right] da;\end{aligned}$$

with

$$\Theta_{i_0} = \mu_x - \delta_{i_0} \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}.$$

Proof. Let us first remark that (4.31) follows from the estimate provided by Lemma 4.2.5 (*iii*) as well as (4.30). Indeed function $a \mapsto \int_a^\infty \rho_{i_0}(s) l(s) ds$ satisfies

$$\int_0^\infty a \int_a^\infty \rho_{i_0}(s) l(s) ds ds < \infty.$$

Next note that function $t \mapsto V_{i_0}[u](t)$ is also well defined for each $t \in \mathbb{R}$ because of (4.25), Lemma 4.2.5 (*i*) and finally because of $f_j \in L^\infty(0,\infty)$ (see Definition (4.34)).

It now remains to compute the derivation of $t \mapsto V_{i_0}[u](t)$ (that is obviously of the class C^1 on $\mathbb{R}$ since u is an entire solution).

Firstly one has

$$\begin{aligned}\dot{V}_x(t) = &\frac{\Lambda}{x_e^{i_0}} + \mu_x - \mu_x \frac{x(t)}{x_e^{i_0}} - \frac{\Lambda}{x(t)} - \beta_{i_0} m_{ei_0}^{i_0} \frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)} + \beta_{i_0} m_{i_0}(t) \\ &+ \left(1 - \frac{x(t)}{x_e^{i_0}}\right) \sum_{j=1; j\neq i_0}^{p} \beta_j m_j(t).\end{aligned} \tag{4.36}$$

Secondly one has

$$\begin{aligned}\dot{V}_{y_{i_0}}(t) &= \int_0^\infty \alpha_{i_0}(a)\, h'\left(\frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)}\right) \frac{1}{y_{ei_0}^{i_0}(a)} \frac{\partial y_{i_0}(t,a)}{\partial t} da; \\ &= \int_0^\infty \alpha_{i_0}(a) \frac{1}{y_{ei_0}^{i_0}(a)} h'\left(\frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)}\right) \left(-\frac{\partial y_{i_0}(t,a)}{\partial a} - \mu_x y_{i_0}(t,a)\right) da; \\ &= -\int_0^\infty \alpha_{i_0}(a) \frac{e^{-\mu_x a}}{y_{ei_0}^{i_0}(a)} h'\left(\frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)}\right) \frac{d}{da}\left(e^{\mu_x a} y_{i_0}(t,a)\right); \\ &= \alpha_{i_0}(0) h\left(\frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)}\right) + \int_0^\infty \alpha_{i_0}'(a) h\left(\frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)}\right) da.\end{aligned}$$

Moreover we infer from the definition of α_{i_0} (see (4.35))

$$\dot{V}_{y_{i_0}}(t) = \int_0^\infty \frac{\beta_1^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \rho_{i_0}(a) l(a) \left[h\left(\frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)} \right) - h\left(\frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)} \right) \right] da.$$

From where we deduce

$$\dot{V}_{y_{i_0}}(t) = \int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \rho_{i_0}(a) l(a) \left[\frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)} - \frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)} - \ln \frac{y_{i_0}(t,0)}{y_{ei_0}(0)} + \ln \frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)} \right] da. \tag{4.37}$$

Next one can also check that

$$\begin{aligned} \dot{V}_{m_{i_0}}(t) = & \int_0^\infty d_{i_0} \delta_{i_0} \beta_{i_0} x_e^{i_0} \rho_{i_0}(a) l(a) \frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)} da - \frac{d_{i_0} \mu_{mi_0}}{m_{ei_0}^{i_0}} m_{i_0}(t) \\ & - d_{i_0} \delta_{i_0} \beta_{i_0} x_e^{i_0} \frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)} - \frac{d_{i_0}}{m_{i_0}(t)} \int_0^\infty \rho_{i_0}(a) y_{i_0}(t,a) da \\ & + d_{i_0} \delta_{i_0} \beta_{i_0} x(t) + d_{i_0} \mu_{mi_0}. \end{aligned} \tag{4.38}$$

Using the fact that

$$\begin{aligned} \int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \rho_{i_0}(a) l(a) da - \beta_{i_0} m_{ei_0}^{i_0} - d_{i_0} \delta_{i_0} \beta_{i_0} x_e^{i_0} & \\ = \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} (K_{i_0} - \delta_{i_0}) - \beta_{i_0} m_{ei_0}^{i_0}; & \\ = \beta_{i_0} m_{ei_0}^{i_0} \frac{x_e^{i_0} \mathcal{R}_0^{i_0}}{x_f} - \beta_{i_0} m_{ei_0}^{i_0}; & \\ = \beta_{i_0} m_{ei_0}^{i_0} - \beta_{i_0} m_{ei_0}^{i_0} = 0, & \end{aligned}$$

we infer from (4.36)-(4.38) that

$$\begin{aligned} & \dot{V}_x(t) + \dot{V}_{y_{i_0}}(t) + \dot{V}_{m_{i_0}}(t) = \\ & \frac{\Lambda}{x_e^{i_0}} + \mu_x + d_{i_0} \mu_{mi_0} - 2 \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} K_{i_0} + (d_{i_0} \delta_{i_0} \beta_{i_0} x_e^{i_0} - \mu_x) \frac{x(t)}{x_e^{i_0}} \\ & + \left(\frac{K_{i_0} \beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} - \frac{\Lambda}{x_e^{i_0}} \right) \frac{x_e^{i_0}}{x(t)} + \left(1 - \frac{x(t)}{x_e^{i_0}} \right) \sum_{j=1; j \neq i_0}^{p} \beta_j m_j(t) \\ & - \int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \rho_{i_0}(a) l(a) \left[h\left(\frac{y_{i_0}(t,a) m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a) m_{i_0}(t)} \right) + h\left(\frac{m_{i_0}(t) y_{ei_0}^{i_0}(0)}{m_{ei_0}^{i_0} y_{i_0}(t,0)} \right) \right] da. \end{aligned}$$

Since EE_{i_0} is an equilibrium of system (4.3), that is to say that $\frac{\Lambda}{x_e^{i_0}} = \mu_x + \beta_{i_0} m_{ei_0}^{i_0}$ and

$K_{i_0}\beta_{i_0}x_e^{i_0} = \mu_{mi_0} + \delta_{i_0}\beta_{i_0}x_e^{i_0}$, one gets

$$\begin{aligned}
&\dot{V}_x(t) + \dot{V}_{y_{i_0}}(t) + \dot{V}_{m_{i_0}}(t) = \\
&-\frac{\Theta_{i_0}}{x_e^{i_0}x(t)}\left(x(t) - x_e^{i_0}\right)^2 + \left(1 - \frac{x(t)}{x_e^{i_0}}\right)\sum_{j=1;j\neq i_0}^{p}\beta_j m_j(t) \\
&-\int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}\rho_{i_0}(a)l(a)\left[h\left(\frac{y_{i_0}(t,a)m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a)m_{i_0}(t)}\right) + h\left(\frac{m_{i_0}(t)y_{ei_0}^{i_0}(0)}{m_{ei_0}^{i_0}y_{i_0}(t,0)}\right)\right]da,
\end{aligned}$$

with

$$\Theta_{i_0} = \mu_x - \delta_{i_0}\frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}.$$

Using the fact that $f_j'(a) - \mu_x f_j(a) + d_j\rho_j(a) = 0$ for all $a \in [0,\infty)$ and

$$\delta_j d_j + \frac{1}{x_f} - f_j(0) = \frac{1-\mathcal{R}_0^j}{x_f},$$

one has

$$\begin{aligned}
\dot{V}_{EE_{i_0}}(t) = &-\frac{\Theta_{i_0}}{x_e^{i_0}x(t)}\left(x(t) - x_e^{i_0}\right)^2 + \frac{x(t)}{x_e^{i_0}}\sum_{j=1;j\neq i_0}^{p}\left(\frac{\mathcal{R}_0^j}{\mathcal{R}_0^{i_0}} - 1\right)\beta_j m_j(t) \\
&-\int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}\rho_{i_0}(a)l(a)\left[h\left(\frac{y_{i_0}(t,a)m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a)m_{i_0}(t)}\right) + h\left(\frac{m_{i_0}(t)y_{ei_0}^{i_0}(0)}{m_{ei_0}^{1}y_{i_0}(t,0)}\right)\right]da.
\end{aligned}$$

This ends the proof of the lemma. □

4.2.5 Proof of Theorem 4.2.1 (i)

The aim of this section is to prove the first part of Theorem 4.2.1. By using all the above introduced definitions and notations, this result can be reformulated as follows:

Proposition 4.2.4. *Let Assumption 5.1.1 be satisfied. Then the following holds true:*

$$\lim_{t\to\infty} U_{\mathcal{S}}(t)x = u_0^*,$$

for each $x \in X_{0+}^{\mathcal{S}}$ and where $U_{\mathcal{S}}$ denotes the restriction semiflow U at $X_{0+}^{\mathcal{S}}$.

Remember that if $\mathcal{S} = \emptyset$, namely $\mathcal{R}_0 \leq 1$ then $X_{0+}^{\mathcal{S}} = X_{0+}$ and $U_{\mathcal{S}} \equiv U$. This remark means that when $\mathcal{R}_0 \leq 1$ then the disease free equilibrium is globally attractive.

The proof of this result relies on the construction of a suitable Lyapunov functional on the entire solution of $U_{\mathcal{S}}$.

Proof. Let us consider $\mathcal{A}_{\mathcal{S}} \subset X_{0+}^{\mathcal{S}}$ the global compact attractor of $U_{\mathcal{S}}$ provided by Proposition 4.2.2. Let $x \in \mathcal{A}_{\mathcal{S}}$ be given and let $\{u(t)\}_{t\in\mathbb{R}} \subset \mathcal{A}_{\mathcal{S}}$ be an entire solution of $U_{\mathcal{S}}$ such that $u(0) = x$. Recalling that from Lemma 4.2.5 (iii), $\inf_{t\in\mathbb{R}} x(t) > 0$, one may consider the functional V defined for each entire solutions by

$$V[u](t) = h\left(\frac{x}{x_f}\right) + \sum_{j=1}^{n}\int_0^\infty f_j(a)y_j(a)da + \sum_{j=1}^{n} d_j m_j,$$

where the positives constants d_j and the functions f_j are defined respectively by (4.33) and (4.34) while function h is given in (4.29).

Next using System (4.3) we obtain

$$\begin{aligned}
\frac{d\,V[u](t)}{dt} =& -\mu_x\frac{(x(t)-x_f)^2}{x(t)} - \sum_{j=1}^{n}(d_j\mu_{mj}-\beta_j)m_j(t)\\
&-\sum_{j=1}^{n}\left(d_j\delta_j+\frac{1}{x_f}\right)\beta_j x(t)m_j(t) + \sum_{j=1}^{n} d_j\int_0^\infty \rho_j(a)y_j(t,a)da\\
&-\sum_{j=1}^{n}\int_0^\infty f_j(a)(\partial_a y_j(t,a)+\mu_x y_j(t,a))da;\\
=& -\mu_x\frac{(x(t)-x_f)^2}{x(t)} - \sum_{j=1}^{n}(d_j\mu_{mj}-\beta_j)m_j(t)\\
&-\sum_{j=1}^{n}\left(\delta_j d_j+\frac{1}{x_f}\right)\beta_j x(t)m_j(t) + \sum_{j=1}^{n} d_j\int_0^\infty \rho_j(a)y_j(t,a)da\\
&-\sum_{j=1}^{n}\int_0^\infty f_j(a)e^{-\mu_x a}(\partial_a y_j(t,a)e^{\mu_x a}+\mu_x e^{\mu_x a}y_j(t,a))da.
\end{aligned}$$

Integrating by part the last integral of the previous equality and using the y_j-boundary condition of (4.3) yield to

$$\begin{aligned}
\frac{d\,V[u](t)}{dt} =& -\mu_x\frac{(x(t)-x_f)^2}{x(t)} - \sum_{j=1}^{n}\left(d_j\mu_{mj}-\beta_j\right)m_j(t)\\
&-\sum_{j=1}^{n}\left(\delta_j d_j+\frac{1}{x_f}-f_j(0)\right)\beta_j x(t)m_j(t)\\
&+\sum_{j=1}^{n}\int_0^\infty \left(f_j'(a)-\mu_x f_j(a)+d_j\rho_j(a)\right)y_j(t,a)da.
\end{aligned}$$

Finally since $f_j'(a)-\mu_x f_j(a)+d_j\rho_j(a) = 0$ for all $a\in[0,\infty)$ and

$$\delta_j d_j + \frac{1}{x_f} - f_j(0) = \frac{1-\mathcal{R}_0^j}{x_f},$$

by recalling that $\{u(t)\}_{t\in\mathbb{R}} \subset X_{0+}^{\mathcal{S}}$, one concludes that

$$\frac{d\,V[u](t)}{dt} = -\mu_x \frac{(x(t)-x_f)^2}{x(t)} - x(t)\sum_{j\in\mathbb{N}_n\setminus\mathcal{S}} \frac{1-\mathcal{R}_0^j}{x_f}\beta_j m_j(t). \tag{4.39}$$

Hence we infer from the definition of $\mathcal{S}$ that $t \mapsto V[u](t)$ is decreasing along the entire solutions of $U_{\mathcal{S}}$. To conclude our proof let $\{t_n\}_{n\geq 0}$ be a sequence tending to $-\infty$ as $n \to \infty$ and consider the sequence of map $u_n(t) = u(t+t_n)$. Note that one has $V[u_n](t) = V[u](t+t_n)$. Up to a subsequence one may assume that $u_n(t) \to \widehat{u}(t)$ as $n \to \infty$ locally uniformly for $t \in \mathbb{R}$ where $\{\widehat{u}(t)\}_{t\in\mathbb{R}} \subset \mathcal{A}_{\mathcal{S}}$ is an entire solution of $U_{\mathcal{S}}$. Since V is decreasing, one obtains that

$$V\left[\widehat{u}\right](t) \equiv \lim_{t\to-\infty} V[u](t) = \sup_{t\in\mathbb{R}} V[u](t).$$

By setting $\widehat{u} = (\widehat{x}, \widehat{\mathbf{m}}, 0, \widehat{\mathbf{y}})^T$, (4.39) yields to $\widehat{x}(t) \equiv x_f$ while the $x-$equation provides that $\widehat{\mathbf{m}}(t) \equiv 0$ so that $\widehat{\mathbf{y}}(t,.) \equiv 0$. Hence $V\left[\widehat{u}\right](t) \equiv 0$ and $0 \leq V[u](t) \leq 0$ for $t \in \mathbb{R}$ and $u(t) \equiv u_0^*$. This completes the proof of Proposition 4.2.4.

□

4.2.6 Proof of Theorem 4.2.1 (ii)

The aim of this section is to proof Theorem 4.2.1 (ii). For this reason, we will assume throughout this section that $\mathcal{S} \neq \emptyset$. The proof of this result will follow an induction argument. To be more specific we will study the behaviour of the semiflow $U_{\mathcal{S}\setminus J}$ for each subset $J \subset \mathcal{S}$ using $card\, J \in \{1, .., card\, \mathcal{S}\}$ as the induction parameter.

The precise result we will prove in the following:

Theorem 4.2.3. *Let us assume that the assumptions of Theorem 4.2.1 are satisfied. Assume that $\mathcal{S} \neq \emptyset$. Then for each $J \subset \mathcal{S}$ the semiflow $\left\{U_{\mathcal{S}\setminus J}(t)\right\}_{t\geq 0}$ satisfies for each $x \in X_{0+}^{\mathcal{S}\setminus J}$:*

(i) if $\mathcal{J}(x) := J \cap \{i \in \mathbb{N}_n :\ x \in M_0^i\} = \emptyset$ then $x \in X_{0+}^{\mathcal{S}}$ and

$$\lim_{t\to\infty} U_{\mathcal{S}\setminus J}(t)x = u_0^*.$$

(ii) If $\mathcal{J}(x) \neq \emptyset$ we set $i = \max^{\lhd} \mathcal{J}(x)$ and one has

$$\lim_{t\to\infty} U_{\mathcal{S}\setminus J}(t)x = u_i^*.$$

Let us first notice that point (i) in the above theorem is a direct consequence of Theorem 4.2.1 (i) (see Proposition 4.2.4). As a consequence, it is sufficient to prove (ii) and let us notice that Theorem 4.2.1 (ii) corresponds to Theorem 4.2.3 with $J = \mathcal{S}$. As mentioned above, the proof of this result relies on an induction argument on c$ard\ J$. In the sequel we shall investigate the case where c$ard\ J = 1$ and we will then show how such a property is inherited.

Case c$ard\ J = 1$**.**

Let $i \in \mathcal{S}$ be given. For notational simplicity we consider the set $Y_{0+} = X_{0+}^{\mathcal{S}\setminus\{i\}}$ and let us denote by $\left\{V(t) := U_{\mathcal{S}\setminus\{i\}}(t)\right\}_{t\geq 0}$. We also consider the sets

$$N_0 = Y_{0+} \cap M_0^i \text{ and } \partial N_0 = Y_{0+} \setminus N_0 = X_{0+}^{\mathcal{S}}.$$

Before constructing a suitable Lyapunov function to study the asymptotic behaviour of $V(t)x$ for some $x \in N_0$ let us first collect in the following lemma some properties of the semiflow $\{V(t)\}_{t\geq 0}$:

Lemma 4.2.7. *Under the assumption of Theorem 4.2.3, the semiflow $\{V(t)\}_{t\geq 0}$ satisfies the following properties:*

(i) It is bounded dissipative and asymptotically smooth; N_0 and ∂N_0 are both positively invariant under V.

(ii) For each $x \in \partial N_0$ one has $V(t)x \to u_0^*$.

(iii) The semiflow V is uniformly persistent with respect to the pair $(N_0, \partial N_0)$ in the sense that there exists $\varepsilon > 0$ such that for each $x \in N_0$:

$$\liminf_{t\to\infty} d\left(U(t)x; \partial N_0\right) \geq \varepsilon.$$

Proof. Note that (i) directly follows from Theorem 4.2.2 (ii), (iii) and Lemma 4.2.3 while (ii) directly follows from Theorem 4.2.3 (i). It remains to prove (iii). To do so we will apply Theorem 4.2 in [93]. Let us first notice that u_0^* is an unstable stationary state with respect to the semiflow V. Indeed as an application of Lemma 4.2.4 we know that the eigenvalues in Ω of the linearized semiflow V at u_0^* are given the resolution of the equation $\Delta^{\mathcal{S}\setminus\{i\}}(\lambda, u_0^*) = 0$. On the other hand these eigenvalues contain the roots of the equation $\chi_i(\lambda, u_0^*) = 0$ (see (4.20)). Note that function $\chi_i(., u_0^*)$ satisfies

$$\chi_i(0, u_0^*) = 1 - \mathcal{R}_0^i < 0 \text{ and } \lim_{\lambda\to\infty} \chi_i(\lambda, u_0^*) = 1,$$

that ensures the existence of a strictly positive eigenvalue. The instability of u_0^* with respect to V follows.

Applying Theorem 4.2 in [93] to complete the proof of Lemma 4.2.7 (iii) it is sufficient to show that $W^s(\{u_0^*\}) \bigcap N_0 = \emptyset$ wherein we have set $W^s(\{u\}) = \{v \in Y_{0+} : \lim_{t\to+\infty} V(t)v = u\}$. To prove this assertion, let us argue by contradiction by assuming that there exists $x \in W^s(\{u_0^*\}) \bigcap N_0$. Then using the same computations as in Lemma 4.2.5 (ii), since $\mathcal{R}_0^i > 1$ one obtains that the function

$$\Phi[V(t)x] := \int_0^\infty \tilde{\Gamma}_i(a) y_i(t,a)da + m_i(t) \text{ with } \tilde{\Gamma}_i(a) := \int_a^\infty \rho_i(s) e^{a-s} ds,$$

is increasing for t large enough. This prevents the function $(y_i(t,.), m_i(t))$ to converge to $(0_{L^1}, 0)$ and provides a contradiction together with the definition x. This completes the proof Lemma 4.2.7. □

As a consequence of Lemma 4.2.7 and Theorem 3.7 in [143](see also the monograph [193]) there exists $\mathcal{B}_0$ a compact subset of N_0 which is a global attractor for the semiflow $\{V(t)\}_{t\geq 0}$ in N_0. To complete the proof of Theorem 4.2.3 (ii) in the case $J = \{i\}$ it remains to prove that $\mathcal{B}_0 = \{u_i^*\}$. This will be achieved by constructing a suitable Lyapunov functional on $\mathcal{B}_0$. This idea has been used by Magal et al [147] and Thieme [202].

Let $\left\{u(t) = (x(t), \mathbf{m}(t), 0_{\mathbb{R}^n}, \mathbf{y}(t,.))^T\right\}_{t\in\mathbb{R}} \subset \mathcal{B}_0$ be a given entire solution of V. We claim that

Claim 4.2.1. *Function m_i satisfies* $\inf_{t\in\mathbb{R}} m_i(t) > 0$.

Before proving this claim let us complete the proof of Theorem 4.2.3 for $J = \{i\}$. Using Claim 5.2.1 and Lemma 4.2.6, one can consider the functional (see Lemma 4.2.6 for the notations)

$$V[u](t) = V_x(t) + V_{y_i}(t) + V_{m_i}(t) + \sum_{j=1;j\neq i}^n \int_0^\infty f_j(a) y_j(t,a) da + \sum_{j=1;j\neq i}^n d_j m_j(t).$$

Then one has by setting $\Theta_i = \mu_x - \delta_i \dfrac{\beta_i^2 x_e^i m_{ei}^i}{\mu_{mi}}$:

$$\begin{aligned}\dot{V}[u](t) = &- \frac{\Theta_i}{x_e^i x(t)} \left(x(t) - x_e^i\right)^2 + \frac{x(t)}{x_e^i} \sum_{j\in\mathbb{N}_n\setminus\mathcal{S}} \left(\frac{\mathcal{R}_0^j}{\mathcal{R}_0^i} - 1\right) \beta_j m_j(t) \\ &- \int_0^\infty \frac{\beta_i^2 x_e^i m_{ei}^i}{\mu_{mi}} \rho_i(a) l(a) \left[h\left(\frac{y_i(t,a) m_{ei}^i}{y_{ei}^i(a) m_i(t)}\right) + h\left(\frac{m_i(t) y_{ei}^i(0)}{m_{ei}^1 y_i(t,0)}\right)\right] da.\end{aligned}$$

Recalling condition (Q) one obtains that $\Theta_i \leq 0$ so that $t \mapsto V[u](t)$ is a bounded and decreasing map. Finally arguing similarly as the end of the proof of Theorem 4.2.1 (i) yields to $u(t) \equiv u_i^*$.

It now remains to prove Claim 5.2.1.

Proof of Claim 5.2.1. Let us argue by contradiction by assuming that $\inf_{t\in\mathbb{R}} m_i(t) = 0$. Note that due to Lemma 4.2.5 (i), one has $m_i(t) > 0$. Hence let us for instance assume that $\liminf_{t\to-\infty} m_i(t) = 0$. Consider a sequence $\{t_n\}_{n\geq 0}$ tending to $-\infty$ as $n \to \infty$ such that $m_i(t_n) \to 0$ as $n \to \infty$. Consider the sequence of maps $\{u_n(t) := u(t + t_n)\}_{n\geq 0}$. Then up to a subsequence, one may assume that $u_n(t) \to \widehat{u}(t)$ locally uniformly wherein $\widehat{u}$ is an entire solution of V such that $\widehat{m}_i(0) = 0$. Lemma 4.2.5 (i) ensures that $(\widehat{m}_i(t), \widehat{y}_i(t, .)) \equiv (0, 0_{L^1})$ This prevents $\widehat{u}$ to belong to N_0, a contradiction. A similar argument holds true if one deals with $\liminf_{t\to+\infty} m_i(t) = 0$. This completes the proof of Claim 5.2.1. □

Case c$ard\,\mathcal{S} \geq 2$ **and** $2 \leq$ **c**$ard\,J \leq$ **c**$ard\,\mathcal{S}$

In this section we assume that $card\,\mathcal{S} \geq 2$. Note that the proof of Theorem 4.2.3 (ii) follows from the above section when $card\,\mathcal{S} = 1$. Let $J \subset \mathcal{S}$ be a given subset such that $card\,J \geq 2$. Our induction hypothesis is concerned with the validity of Theorem 4.2.3 for each subset $J' \subset \mathcal{S}$ such that $card\,J' < card\,J$. Consider now the set $Y_{0+} = X_{0+}^{\mathcal{S}\setminus J}$ as well as the semiflow $V := U_{\mathcal{S}\setminus J}$ on Y_{0+}. Let us denote $i = \max^{\lhd}(J)$ and let us consider

$$N_0 = Y_{0+} \cap M_0^i \text{ and } \partial N_0 = Y_{0+} \setminus N_0.$$

Let us first notice that to prove Theorem 4.2.3 (ii) for J, it is sufficient to show that

$$\lim_{t\to\infty} V(t)x = u_i^*, \ \ \forall x \in N_0. \tag{4.40}$$

Indeed, if $x \in \partial N_0$ then $x \in X_{0+}^{\mathcal{S}\setminus J'}$ with $J' = J \setminus \{i\}$. Since $J' \subset \mathcal{S}$ and $card\,J' < card\,J$ then $V(t)x = U_{\mathcal{S}\setminus J'}(t)x$ and the asymptotic behaviour follows from the induction hypothesis.

The proof of this section is rather similar to the one provided in the preceding section. The only difference relies on the proof of the uniform persistence of the semiflow V with respect to the pair $(N_0, \partial N_0)$ because of the dynamics of the semiflow on the boundary

∂N_0. Hence to complete the proof of Theorem 4.2.3 (ii) for J we will only prove the following lemma. The details are left to the reader.

Lemma 4.2.8. *The semiflow V is uniformly persistent with respect to the pair $(N_0, \partial N_0)$.*

Proof. The proof of this result is an application of Theorem 4.2 in [93] with a non-trivial dynamics for the boundary semiflow. Let us denote by $J' = J \setminus \{i\}$. Then note that $V|_{\partial N_0} = U_{\mathcal{S}\setminus J'}$. According to Proposition 4.2.2 let us consider $\mathcal{A}_\partial := \mathcal{A}_{\mathcal{S}\setminus J'}$ the global attractor of the semiflow $V|_{\partial N_0}$. Note that according to the induction hypothesis the following holds true:

$$\bigcup_{x\in\mathcal{A}_\partial} \omega(x) = \{u_0^*\} \cup \bigcup_{j\in J'} \left\{u_j^*\right\}.$$

Here for each $x \in Y_{0+}$, $\omega(x)$ denotes the omega-limit set of the point x with respect to the semiflow V. The application of Theorem 4.2 in [93] relies on some properties of the set $\widehat{A}_\partial$ defined by

$$\widehat{A}_\partial = \{u_0^*\} \cup \bigcup_{j\in J'} \left\{u_j^*\right\}.$$

Let us first claim:

Claim 4.2.2. *For each $j \in J' \cup \{0\}$ the stationary point u_j^* is unstable with respect to the semiflow V.*

Proof of Claim 4.2.2. The proof of the above claim relies on Lemma 4.2.4. Let us notice that for each $j \in J' \cup \{0\}$, function $\chi_i(., u_j^*$ (see (4.20)) satisfies

$$\chi_i(0, u_j^*) = \begin{cases} 1 - \mathcal{R}_0^i \text{ if } j = 0, \\ 1 - \frac{\mathcal{R}_0^i}{\mathcal{R}_0^j} \text{ if } j \in J'. \end{cases}$$

Hence since $i = \max^\lhd J$, $\chi_i(0, u_j^*) < 0$ and since $\chi_i(\lambda, u_j^*) \to 1$ as $\lambda \to \infty$, for each $j \in J' \cup \{0\}$ function $\chi_i(., u_j^*)$ has a strictly positive root. The result follows. □

Then we claim that:

Claim 4.2.3. *For each $(j, k) \in J' \cup \{0\}$ then if $\{u(t)\}_{t\in\mathbb{R}}$ is a non-trivial (that non-constant) entire solution of V such that*

$$\lim_{t\to-\infty} u(t) = u_j^* \text{ and } \lim_{t\to\infty} u(t) = u_k^*,$$

then $j \lhd k$.

Proof of Claim 4.2.3. The proof of this claim relies on the application of Lemma 4.2.5 (ii) as well as Lyapunov like argument.

Let us first consider the case where $j \in J'$. Then applying Lemma 4.2.5 (ii) we know that $j \trianglelefteq k$. It is therefore sufficient to show that there is no homoclinic connection at u_j^*. Let us argue by contradiction by assuming that

$$\lim_{t\to\pm\infty} u(t) = u_j^*.$$

Then applying once again Lemma 4.2.5 (ii) we obtain that for each $k \in J'$ such that $k \rhd j$:

$$y_k(t,.) \equiv 0 \text{ and } m_k(t) \equiv 0, \ \ \forall k \in J' \rhd j.$$

Then consider the functional

$$V_j[u](t) = V_x(t) + V_{y_j}(t) + V_{m_j}(t) + \sum_{p=1;p\neq j}^{n} \int_0^\infty f_p(a) y_p(t,a) da + \sum_{p=1;p\neq j}^{n} d_p m_p(t).$$

Using similar arguments and computations (see Lemma 4.2.6) as the ones provided in the preceding section and using the fact that for each $k \in \mathcal{S} \setminus J'$ and each $k \in J'$ such that $k \rhd j$

$$y_k(t,.) \equiv 0 \text{ and } m_k(t) \equiv 0,$$

one obtains that $u(t) \equiv u_j^*$, a contradiction.

It remains to consider the case $j = 0$ and to show that there is no homoclinic connection at u_0^*. Let us argue by contradiction by assuming that

$$\lim_{t\to\pm\infty} u(t) = u_0^*.$$

Then let us notice that due to Lemma 4.2.5 (ii) one has

$$y_k(t,.) \equiv 0 \text{ and } m_k(t) \equiv 0, \ \ \forall k \in \mathcal{S}.$$

Then by considering the map

$$V_0[u](t) = h\left(\frac{x}{x_f}\right) + \sum_{j=1}^{n} \int_0^\infty f_j(a) y_j(a) da + \sum_{j=1}^{n} d_j m_j,$$

as well as computations and arguments similar to the proof of Proposition 4.2.4 one concludes that

$$u(t) \equiv u_0^*,$$

a contradiction that completes the proof of Claim 4.2.3. □

As a consequence of Claim 4.2.2 and Claim 4.2.3, the set $\widehat{A}_\partial$ is isolated and has an acyclic covering. Hence since the semiflow is bounded dissipative and asymptotically smooth, Theorem 4.2 in [93] applies and to complete the proof of Lemma 4.2.8, it is sufficient to show that $N_0 \cap W^s\left(\left\{u_j^*\right\}\right) = \emptyset$ for each $j \in J' \cup \{0\}$. Similarly to the proof in Section 4.2.6 this latter property directly follows from the functional

$$\Phi\left[V(t)x\right] := \int_0^\infty \Gamma_i(a) y_i(t,a) da + m_i(t) \text{ with } \Gamma_i(a) := \int_a^\infty \rho_i(s) e^{a-s} ds.$$

This completes the proof of Lemma 4.2.8. □

4.2.7 Future directions

The emergence and spread of antimalarial drug resistance poses a severe and increasing public health threat. The *P. falciparum* parasite is now resistant to all of the used antimalarial drugs, even to the latest artemisinin-based combination treatments. Knowledge about resistance mechanisms involved may allow the development of new drugs that minimize or circumvent drug resistance, may allow the identification of new targets for drug development and to identify molecular markers for malaria resistance surveillance. That is, a deeper understanding of the dynamic of multiple strain *P. falciparum* infection can improve the understanding of the role of parasite interactions in the spread of drug-resistant parasites, perhaps suggesting different treatment strategies. To this end, age-structured within host malaria models can also consider two mains inputs. The first is to provide a good dynamics of the host immune system. The second is to incorporate the dynamics of antimalarial drugs into the model.

4.2.8 Summary

In this section, we have examined an age-structured within-host model for multistrain malaria infection. This model incorporates n strains for the parasite. Using integrated semigroup theory, we provided a global analysis of this model. The rationale for including multi-strain can be multiple. One reason is to take into account biological reasons, e.g., consideration of morphological or age classes. The second is due to the recent study on this subject. Recently, it has been proved that a deeper understanding of the dynamic growth responses of multiple strain *P. falciparum* infections, with and without drug pressure, can improve the understanding of the role of parasite interactions in

the spread of drug resistant parasites, perhaps suggesting different treatment strategies [208].

This model has been conceived from malaria infection, since it is well grounded that malaria is a multi-strain infection. However other parasitic infections can be considered by this model, e.g., the model can be extended to the HIV infections [105].

The main finding of this section can be summarized along the following lines:

✓ To separate the different strains we associated for each strain the i-specific basic reproduction number $\mathcal{R}_0^i$ defined by (4.9). We then find that the basic reproduction number of the model is defined by $\mathcal{R}_0 = \max_{i=1,\dots,n} \mathcal{R}_0^i$.

✓ We also find that if $\mathcal{R}_0 \leq 1$, the model exhibits a unique disease-free steady state, while if $\mathcal{R}_0 > 1$ the model has exactly n_E disease-endemic steady states, wherein $n_E = \text{Card}\left\{i \in \{1,\dots,n\} : \mathcal{R}_0^i > 1\right\}$.

✓ We prove that if the basic reproduction number of the model satisfies $\mathcal{R}_0 \leq 1$, then the disease free equilibrium is globally asymptotically stable; i.e., the parasite is cleared from the host population.

✓ Our global stability result when $\mathcal{R}_0 > 1$ can be summarized as a competitive exclusion principle. If $\mathcal{R}_0 > 1$, if one strain has its individual threshold $\mathcal{R}_0^i$ strictly larger than the thresholds of the other strains and if a mild sufficient condition gives by (4.11) is satisfied, then there exists a global asymptotic stable endemic equilibrium. This equilibrium corresponds to the extinction of all strains, except the strain with the largest threshold (winning strain).

4.3 Mathematical modeling of anopheles mosquito dynamics population.

In this section, we examined an advection-reaction model for anopheles mosquito dynamics population with time dependent parameters. We introduce the threshold values $\mathcal{R}^\diamondsuit$, $\mathcal{R}_\diamondsuit$ and $\mathcal{R}_*$. Then, we find that, if $\mathcal{R}^\diamondsuit < 1$, the anopheles mosquito population dies out. On the other hand, if $\mathcal{R}_\diamondsuit > 1$ (resp. $\mathcal{R}_* > 1$) then anopheles mosquito uniformly weakly (resp. strongly) persists in the population.

4.3.1 Model formulation

For the mathematical description, we assume that there are two main stages in the development of mosquitoes: an aquatic and an adult stage. The aquatic stage gathers eggs, larvae and pupae. The adult stage can be divided into several compartments: immature females, feeding females, resting females, breeding females (or more precisely "egg laying females") and males. We assume that there is no sex differences in the aquatic stage and mosquitoes, after emergence, are distributed between the immature female compartment and the male compartment. Following [44], we consider that the number of emerging females and emerging males is equal; therefore the sex ratio of emerging adults, r, is set to $\frac{1}{2}$. We assume that a female mates only once with a male in her lifetime. After mating with males, we assume that immature females start their gonotrophic cycles [44] by entering the feeding female compartment. The gonotrophic cycle defined by Clements [36] starts with a blood meal and ends with the first laid egg. Then, after blood meals, they get into the resting compartment, allowing egg maturation. Afterward, the females pass into the breeding compartment seeking for a breeding site to deposit eggs. Once egg deposit is done, females start a new gonotrophic cycle. The eggs laid by the breeding females supply the aquatic stage. We consider only one compartment for the males. For the females, it is necessary to take into account four sub-compartments since their behavior is very different.

At time t, the density of the anopheles mosquito population is divided into five compartments as follows: A of the population in aquatic stage, M of male, Y of immature females, Q of questing females, U of breeding females and R of resting females.

The population in the aquatic stage is recruited at rate ΦU where Φ is the average amount of eggs laid per fertilized female per day. In the model, we use a density dependent death rate for the aquatic stage since anopheles larvae are density sensitive, which imply an additional density mortality rate. In [44], the size of the population is also restricted only in the aquatic stage but in a different way by an explicit carrying capacity beyond which no eggs are laid. The population in the aquatic stage is affected by the density independent mortality rate μ_1 and the carrying capacity of the aquatic site K_A. Population in the aquatic stage emerges at rate γ with $1-\gamma$ being the fraction of emerging male mosquitoes. After mating with males mosquitoes, immature females leave the breeding sites and arrive at the human habitat and then become questing females

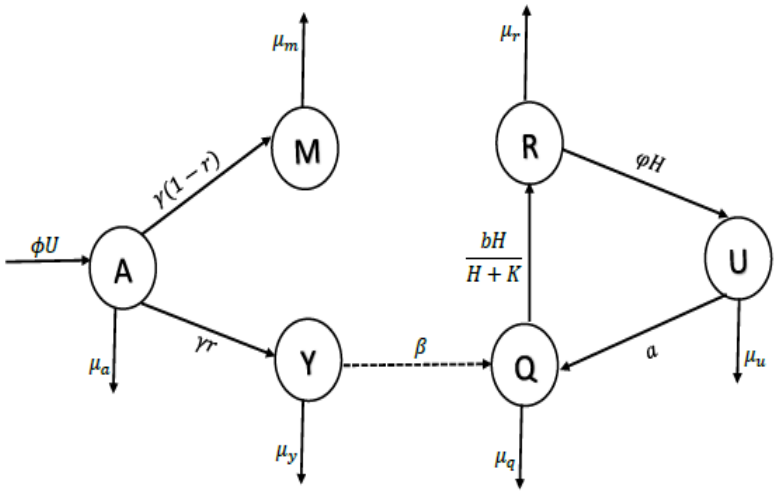
Q. We assume that immature females becomes questing females at rate βY with β the mating rate between immature females and males mosquitoes. At the human habitat, questing females interact with humans by mass action contact, during which contact they can either survive to reproduce or get killed. Once rest, questing females will begin to search blood meal and we assume that they are attracted to humans at rate $b\dfrac{H}{H+K}Q$ and enter the question class where $\dfrac{H}{H+K}Q$ models the proportion of questing females that prefers human blood as opposed to those that feed on other animals, K is a positive constant representing a constant alternative food source for the site and b is a positive constant. Questing females die at rate μ_q. Resting females becomes breeding females at rate φHQ where φ is the successful rate in taking a blood meal of questing females and H is a parameter representing the density of humans habitats. Resting females die at rate μ_r. After laying eggs, breeding females becomes questing females at rate a. The compartment of breeding females is affected by a mortality rate μ_u.

The structure of the model is depicted in Figure 4.3. The dashed arrow indicates the mating between males mosquito and immature females.

Using all biological explanations the mathematical model for anopheles mosquito population is the following system of ordinary differential equation:

$$\begin{cases} \dot{A} &= \phi U\left(1-\dfrac{A}{K_A}\right)-(\gamma+\mu_1)A, \\ \dot{Y} &= \gamma r A-\mu_y Y-\beta Y, \\ \dot{M} &= (1-r)\gamma A-\mu_m M, \\ \dot{R} &= \beta Y+b\dfrac{HQ}{H+K}-\varphi HR-\mu_r R, \\ \dot{U} &= \varphi HR-(a+\mu_u)U, \\ \dot{Q} &= aU-b\dfrac{HQ}{H+K}-\mu_q Q \end{cases} \tag{4.41}$$

Let us notice that model (4.41) is formulated and rigorously analyzed by Anguelov,



State Variable	Description
A	Aquatic stage
M	Male
Y	Immature females
Q	Questing females
U	Breeding females
R	Resting females

Figure 4.3: Anopheles mosquito flow chart. The dashed arrow indicates the mating between males mosquito and immature females. The above table summarize the state variable of the model. The description of parameters is also summarize in Tables 4.4 and 4.5.

Dumont and Lubuma in [6]. Setting

$$\begin{aligned}
\bar{A} &= K_A\left(1-\frac{1}{\mathcal{R}_0}\right),\\
\bar{Y} &= \frac{\gamma r}{\mu_Y+\beta}\bar{A}, \quad \bar{M} = \frac{(1-r)\gamma}{\mu_M}\bar{A}, \quad \bar{R} = \frac{\beta\gamma r}{D(\mu_Y+\beta)}\bar{A},\\
\bar{U} &= \frac{1}{a}\left(\frac{bH}{H+K}+\mu_q\right)\bar{R}, \quad \bar{Q} = \frac{a+\mu_U}{a\rho H}\left(\frac{bH}{H+K}+\mu_q\right)\bar{R},
\end{aligned} \tag{4.42}$$

wherein

$$\mathcal{R}_0 = \frac{\beta\gamma r\phi\left(\frac{bH}{H+K}+\mu_q\right)}{a(\gamma+\mu_1)(\mu_Y+\beta)D}, \tag{4.43}$$

and

$$D = \frac{a+\mu_U}{a\rho H}\left(\frac{bH}{H+K}+\mu_q\right) - \frac{bH}{H+K},$$

the essential properties of the model (4.41) as a dynamical system are summarized in the following theorem (see Theorem 7 in [6]).

Theorem 4.3.1. *The set of ODEs* (4.41) *defines a dissipative dynamical system on* $C_0 = \{x \in R_+^6 : x \geq \mathbf{0}\}$. *Moreover*

(i) If $\mathcal{R}_0 \leq 1$ *then the trivial equilibrium* $\mathbf{0}$ *is globally asymptotically stable on* C_0.

(ii) If $\mathcal{R}_0 > 1$ *then system has two equilibrium* $\mathbf{0}$ *and* $\bar{E} := (\bar{A}, \bar{M}, \bar{Y}, \bar{U}, \bar{Q}, \bar{R})^T$ *on* C_0 *where* $\bar{E}$ *is stable with basin of attraction* $C_0 \setminus \{x = (A, M, Y, U, Q, R) \in \mathbb{R}_+^6 : A = Y = U = Q = R = 0\}$ *and* $\mathbf{0}$ *is unstable with the nonnegative* M*-axis being a stable manifold.*

Now, let us formulate the spatial-temporal model with migration of the mosquito.

It is well known that the ecology of mosquito vectors and malaria parasites affect the incidence, seasonal transmission and geographical range of malaria [166]. According to Mordecai et al. [166] there is a relationships between temperature and the mosquito and parasite life-history traits that determine malaria risk. Therefore, we assume that the following parameters are time-dependent parameters: Eggs laid per adult female per day $\phi(.)$; mosquito adult mortality rate $\mu_y(.)$, $\mu_m(.)$, $\mu_r(.)$, $\mu_u(.)$, $\mu_q(.)$; Egg-to-adult survival probability $\mu_1(.)$; and larval development rate $\gamma(.)$. Then equations to describe the seasonal spatio-temporal dynamics of anopheles mosquito allowing migration are the following:

$$\begin{cases} \dfrac{\partial A(t,x)}{\partial t} = \phi(t)\left(1-\dfrac{A(t,x)}{K_A}\right)U(t,x) - (\gamma(t)+\mu_1(t))A(t,x), \\ \dfrac{\partial Y(t,x)}{\partial t} + \varepsilon_m \nabla Y(t,x) = \gamma(t) r A(t,x) - \mu_m(t)Y(t,x) - \beta Y(t,x), \\ \dfrac{\partial M(t,x)}{\partial t} + \varepsilon_m \nabla M(t,x) = (1-r)\gamma(t)A(t,x) - \mu_m(t)M(t,x), \\ \dfrac{\partial R(t,x)}{\partial t} + \varepsilon_m \nabla R(t,x) = \beta Y(t,x) + b\dfrac{HQ(t,x)}{H+K} - \varphi H R(t,x) - \mu_r(t)R(t,x), \\ \dfrac{\partial U(t,x)}{\partial t} + \varepsilon_m \nabla U(t,x) = \varphi H R(t,x) - (a+\mu_u(t))U(t,x), \\ \dfrac{\partial Q(t,x)}{\partial t} + \varepsilon_m \nabla Q(t,x) = aU(t,x) - b\dfrac{HQ(t,x)}{H+K} - \mu_q(t)Q(t,x), \end{cases} \tag{4.44}$$

System (4.44) is considered for $t \in \mathbb{R}_+$ in a domain Ω ($x = (x_1, x_2)^T \in \Omega \equiv [0, \omega_1) \times [0, \omega_2) \subset \mathbb{R}^2$), with initial and boundary conditions

$$\begin{cases} Y(t,x) = M(t,x) = Q(t,x) = U(t,x) = R(t,x) = 0 \ \ \forall (t,x) \in \mathbb{R}_+ \times \partial\Omega, \\ A(0,x) = A_0(x), \quad Y(0,x) = Y_0(x), \quad M(0,x) = M_0(x), \quad Q(0,x) = Q_0(x), \\ U(0,x) = U_0(x), \quad R(0,x) = R_0(x), \end{cases} \tag{4.45}$$

where $\nabla v(t,x) = \sum_{j=1}^{2} \dfrac{\partial v(t,x)}{\partial x_j}$ and ε_m is the migration coefficient of adult mosquito.

In order to deal with system (4.44)-(4.45) we first introduce the vector-valued $\mathbf{v}(t,.) = (A(t,.), M(t,.); Y(t,.); R(t,.); U(t,.); Q(t,.))^T$, $\varepsilon = (0, \varepsilon_m, \varepsilon_m, \varepsilon_m, \varepsilon_m, \varepsilon_m)^T$ and the usual scalar product $\langle ., . \rangle$ as well as the functional

$$F_1(t,\mathbf{v}) = \begin{pmatrix} -(\gamma(t)+\mu_1(t)+\frac{\phi(t)U}{K_A}) & 0 & 0 & 0 & \phi & 0 \\ (1-r)\gamma(t) & -\mu_m(t) & 0 & 0 & 0 & 0 \\ r\gamma(t) & 0 & -\mu_y(t)-\beta & 0 & 0 & 0 \\ 0 & 0 & \beta & -(\varphi H+\mu_r(t)) & 0 & \frac{bH}{H+K} \\ 0 & 0 & 0 & \varphi H & -(a+\mu_u(t)) & 0 \\ 0 & 0 & 0 & 0 & a & \frac{-bH}{H+K}-\mu_q(t) \end{pmatrix}; \tag{4.46}$$

system (4.44)-(4.45) rewrites as the following non-autonomous advection-reaction equation:

$$\begin{aligned} &\frac{\partial \mathbf{v}(t,x)}{\partial t} + diag(\varepsilon)\nabla \mathbf{v}(t,x) = F_1(t,\mathbf{v}(t,x))\mathbf{v}(t,x), \\ &\mathbf{v}(t,x) = 0, \ \ \forall (t,x) \in \mathbb{R}_+ \times \partial\Omega, \\ &\mathbf{v}(0,x) = \mathbf{v}_0(x) \in L^1(\Omega,\mathbb{R}^6_+), \end{aligned} \tag{4.47}$$

In what follows, we will make use of the following assumption.

Assumption 4.3.1. *We assume that, β, b, H, a, φ, r are nonnegative constants, $\varepsilon_m > 0$ while the functions $\phi(.)$, $\gamma(.)$, $\mu_1(.)$, $\mu_m(.)$, $\mu_y(.)$, $\mu_r(.)$, $\mu_u(.)$, $\mu_q(.)$ are ω-periodic and belong to $L^\infty(0,\infty,\mathbb{R}_+)$.*

4.3.2 Existence of positive solutions for seasonal model (4.44).

The aim of this section is to derive preliminary remarks on (4.47). These results include the existence of the unique maximal bounded semiflow associated to this system. We shall deal with the C_0-semigroup approach introduced by Pazy [180].

Let us introduce $X = L^1(\Omega,\mathbb{R}^6)$ as well as its positive cone $X_+ = L^1(\Omega,\mathbb{R}^6_+)$ and the linear operator $B : D(B) \subset X \to X$ defined by

$$\begin{aligned} &D(B) = \left\{ \mathbf{v} \in W^{1,1}(\Omega,\mathbb{R}^6_+) : \ \ \mathbf{v}(x) = 0, \ \ \forall x \in \partial\Omega \ \right\}, \\ &B(\mathbf{v}) = -diag(\varepsilon)\nabla \mathbf{v}. \end{aligned} \tag{4.48}$$

Finally, let us introduce the nonlinear map $F : [0,\omega) \times \overline{D(B)} \to X$ defined by

$$F(t,\mathbf{v}) = F_1(t,\mathbf{v})\mathbf{v}.$$

Following Pazy[180], we have the following results on the linear operator B.

Lemma 4.3.1. *Let Assumption 4.3.1 be satisfied.*

(i) The operator B is generator of a C_0-semigroup of linear bounded operators $\{T(t)\}_{t\geq 0}$ such that

$$T(t)\mathbf{v}(x) = \begin{cases} \mathbf{v}(x-t\varepsilon), & \text{if } (t, x-t\varepsilon) \in \mathbb{R}_+ \times \Omega \\ \mathbf{0}, & \text{if } (t, x-t\varepsilon) \in \mathbb{R}_+ \times \partial\Omega \end{cases}$$

(ii) The domain $D(B)$ of operator B is dense in X and B is a closed operator.

(iii) The nonlinear operator F defined from X to itself is continuous and locally Lipschitz.

Proof. The proof of this result is rather standard. Standard methodologies apply to provide item (i) (see Pazy 1983 [180]). Item (ii) is a direct consequence of the fact that the operator B is generator of a C_0-semigroup of linear bounded operators (see Corollary 2.5 in Pazy 1983 [180]). □

Setting $\psi(t) = \mathbf{v}(t, .)$; system (4.47) rewrites as the following densely defined Cauchy problem

$$\begin{cases} \dfrac{d\psi(t)}{dt} &= B\psi(t) + F(t, \psi(t)), \quad t \geq 0, \\ \psi(0) &= \psi_0 \in \overline{D(B)} = X; \end{cases} \tag{4.49}$$

Let us introduce the following lemma.

Lemma 4.3.2. *Let Assumption 4.3.1 be satisfied. The map $F : [0, \omega] \times X \to X$ is continuous and for each $\xi > 0$, there exists $K(\xi) > 0$ such that*

$$||F(t, \mathbf{v}_1) - F(t, \mathbf{v}_2)|| \leq K(\xi)||\mathbf{v}_1 - \mathbf{v}_2||,$$

whenever $\mathbf{v}_1, \mathbf{v}_2 \in X$ such that $||\mathbf{v}_1|| \leq \xi$, $||\mathbf{v}_2|| \leq \xi$.

Proof. Let $\xi > 0$ and $\mathbf{v}_1, \mathbf{v}_2 \in X$ such that $||\mathbf{v}_1|| \leq \xi$, $||\mathbf{v}_2|| \leq \xi$. We easily find that

$$||F(t, \mathbf{v}_1) - F(t, \mathbf{v}_2)|| \leq K(t, \xi)||\mathbf{v}_1 - \mathbf{v}_2||,$$

with

$$K(t, \xi) = \max\left(\phi(t) + \xi\frac{\phi(t)}{K_A} + \gamma(t) + \mu_1(t); r\gamma(t) + \mu_y(t) + \beta; (1-r)\gamma(t) + \mu_m(t); \right.$$
$$\left. \beta + \frac{bH}{H+K} + \rho H + \mu_r(t); \rho H + a + \mu_u(t); a + \frac{bH}{H+K} + \mu_q(t)\right).$$

Therefore Assumption 4.3.1 gives that $||F(t, \mathbf{v}_1) - F(t, \mathbf{v}_2)|| \leq ||K(., \xi)||_{L^\infty}.||\mathbf{v}_1 - \mathbf{v}_2||$.

□

In the following definition, τ is the *blow-up time* of maximal solutions of (4.49).

Definition 4.3.1. *Consider two maps* $\tau : [0,\omega) \times X \to (0,\omega]$ *and* $\mathcal{U} : D_\tau \to X$, *where* $D_\tau = \{(t,s,\mathbf{v}) \in [0,\omega)^2 \times X : s \leq t \leq s + \tau(s,\mathbf{v})\}$. *We say that* $\mathcal{U}$ *is a* maximal non-autonomous semiflow on X *if* U *satisfies the following properties:*

(i) $\tau(r,\mathcal{U}(r,s)\mathbf{v}) + r = \tau(s,\mathbf{v}) + s, \forall s \geq 0, \forall \mathbf{v} \in X, \forall r \in [s, s+\tau(s,\mathbf{v}))$.

(ii) $\mathcal{U}(s,s)\mathbf{v} = \mathbf{v}, \forall s \geq 0, \forall \mathbf{v} \in X$.

(iii) $\mathcal{U}(t,r)\mathcal{U}(r,s)\mathbf{v} = \mathcal{U}(t,s)\mathbf{v}, \forall s \geq 0, \forall \mathbf{v} \in X, \forall t,r \in [s, s+\tau(s,\mathbf{v}))$ *with* $t \geq r$.

(iv) If $\tau(s,\mathbf{v}) < +\infty$, *then* $\lim_{t \to (s+\tau(s,\mathbf{v}))^-} ||\mathcal{U}(t,s)\mathbf{v}|| = +\infty$.

Set $D = \{(t,s,\mathbf{v}) \in [0,\omega)^2 \times X : t \geq s\}$.

The main result of this subsection is the following theorem.

Theorem 4.3.2. *Let Assumption 4.3.1 be satisfied. Then there exist a map* $\tau[0,\omega) \times X \to (0,\omega]$ *and a maximal non-autonomous semiflow* $\mathcal{U} : D_\tau \to X$, *such that for each* $\mathbf{v} \in X_+$ *and each* $s \leq 0$, $\mathcal{U}(.,s)\mathbf{v} \in C([s, s+\tau(s,\mathbf{v})), X_+)$ *is a unique maximal solution of* (4.49). *Moreover,*

(i) D_τ *is open in* D *and the map* $(t,s,\mathbf{v}) \to \mathcal{U}(t,s)\mathbf{v}$ *is continuous from* D_τ *into* X.

(ii) Let $U(t,t_0)\mathbf{v}_0(.) = \mathbf{v}(t.,)$; *where* $\mathbf{v}(t,.) := (A(t,.), M(t,.); Y(t,.); R(t,.); U(t,.); Q(t,.))^T$ *solve* (4.44)-(4.45). *Assume that* $A_0(x) \leq K_A$ *for all* $x \in \overline{\Omega}$. *Then one has for all* $t \geq t_0 \geq 0$

$$\begin{aligned} &\int_\Omega A(t,x)dx \leq mes(\Omega)K_A; \\ &\int_\Omega \left(M(t,x) + Y(t,x) + R(t,x) + U(t,x) + Q(t,x)\right) dx \leq mes(\Omega)K_A \frac{\sup_{s\in[0,\omega]} \gamma(s)}{\inf_{s\in[0,\omega]} \mu(s)}; \end{aligned} \tag{4.50}$$

wherein $\mu(.) = \min\left(\mu_m(.), \mu_y(.), \mu_r(.), \mu_u(.), \mu_q(.)\right)$ *and* $mes(\Omega) = \omega_1\omega_2$.

Proof. The proof of this result is rather standard. Indeed it is easy to check that operator B satisfies the Hille-Yosida property (see the proof of Proposition 4.2.1). Then coupling Lemma 4.3.2 together with Theorem 4 in [146]; we obtain the existence of non-autonomous semiflow $\mathcal{U}$ satisfying item (i). It remains to check item (ii). Without lost of generality, we may assume that $t_0 = 0$. The A-equation of system (4.44) gives that

$$A(t,x) \leq \left(A_0(x) + \int_0^t \phi(s)U(s,x)e^{\int_0^s \frac{\phi(\eta)U(\eta,x)}{K_A}d\eta}ds\right) e^{-\int_0^t \frac{\phi(\eta)U(\eta,x)}{K_A}d\eta}; \forall x \in \Omega.$$

Since $A_0(.) \leq K_A$, we easily find that $A(t,.) \leq K_A$ for all $t \geq 0$. This ends the first estimate of (4.50). Now let us introduce the following quantity $\int_\Omega M(t,x)dx$. For convenience we still use

$$M(t) = \int_\Omega M(t,x)dx$$

and idem for the variables Y, Q, U and R. Therefore,

$$\begin{aligned} M'(t) &= \int_\Omega \partial_t M(t,x)dx, \\ &= -\varepsilon_m \int_\Omega \nabla M(t,x)dx + (1-r)\gamma(t)A(t) - \mu_m(t)M(t). \end{aligned}$$

Applying the divergence theorem, we find that

$$\int_\Omega \nabla M(t,x)dx = \int_{\partial\Omega} \langle M(t,x), \nu(x)\rangle \, d\sigma(x),$$

wherein $\nu(x)$ is the unit outward vector to Ω at $x \in \partial\Omega$. Since $M(t,x) = 0$ for all $x \in \partial\Omega$, then

$$M'(t) = (1-r)\gamma(t)A(t) - \mu_m(t)M(t).$$

Applying the same arguments to the variables Y, Q, U, R and using the first estimate of (4.50), it comes that

$$\frac{d}{dt}x(t) \leq mes(\Omega)K_A \sup_{s\in[0,\omega]} \gamma(s) - \inf_{s\in[0,\omega]} \mu(s)x(t), \forall t \geq 0,$$

with $x(t) = M(t)+Y(t)+R(t)+U(t)+Q(t)$. From where the second estimate of (4.50) follows and this end the proof of the theorem. □

The following result will be useful for the persistence results of the seasonal spatio-temporal model (4.44)-(4.45). We claim that

Claim 4.3.1. *$A(t,x) \leq K_A$, $Y(t,x) \leq \dfrac{rK_A||\gamma||_\infty}{\beta}$ and $R(t,x)+U(t,x)+Q(t,x) \leq \dfrac{rK_A||\gamma||_\infty}{\inf_{s\in[0,\omega]}\mu(s)}$ for all $(t,x) \in \mathbb{R}_+ \times \Omega$.*

Proof of Claim 4.3.1. Using the proof of item (ii) of theorem 4.3.2, we obtain that $A(t,x) \leq K_A$ for all $(t,x) \in \mathbb{R}_+ \times \Omega$. From the Y-equation of system (4.44)-(4.45) we find that

$$Y(t,x) = \int_0^t r\gamma(s)A(s, x+(s-t)\varepsilon_y)e^{-\int_s^t(\beta+\mu_y(\eta))d\eta}ds, \forall (t,x) \in \mathbb{R}_+ \times \Omega.$$

Therefore,

$$Y(t,x) \leq \frac{rK_A||\gamma||_\infty}{\beta}, \forall (t,x) \in \mathbb{R}_+ \times \Omega.$$

Adding up the Q, U and R equations of (4.44)-(4.45) we also find that

$$R(t,x)+U(t,x)+Q(t,x)\leq\int_0^t\beta Y(s,x+(s-t)\varepsilon)e^{-\int_s^t\mu(\eta)d\eta}ds,\forall(t,x)\in\mathbb{R}_+\times\Omega.$$

From where

$$R(t,x)+U(t,x)+Q(t,x)\leq\frac{rK_A||\gamma||_\infty}{\inf_{s\in[0,\omega]}\mu(s)},\forall(t,x)\in\mathbb{R}_+\times\Omega.$$

This ends the proof of the claim. □

Now let us introduce the following quantity $\int_\Omega A(t,x)dx$. For convenience we still use

$$A(t)=\int_\Omega A(t,x)dx$$

and idem for the variables Y, Q, U and R. From the $(R+U+Q)$-estimate of Claim 4.3.1 and the divergence theorem (see for instance the proof of Theorem 4.3.2) we easily find that

$$\begin{cases}\dfrac{dA(t)}{dt}=\phi(t)\displaystyle\int_\Omega\left(1-\frac{A(t,x)}{K_A}\right)U(t,x)dx-(\gamma(t)+\mu_1(t))A(t),\\[2ex]\dfrac{dY(t)}{dt}=\gamma(t)rA(t)-\mu_y(t)Y(t)-\beta Y(t),\\[2ex]\dfrac{dM(t)}{dt}=(1-r)\gamma(t)A(t)-\mu_m(t)M(t),\\[2ex]\dfrac{dR(t)}{dt}=\beta Y(t)+b\dfrac{HQ(t)}{H+K}-\varphi HR(t)-\mu_r(t)R(t),\\[2ex]\dfrac{dU(t)}{dt}=\varphi HR(t)-(a+\mu_u(t))U(t),\\[2ex]\dfrac{dQ(t)}{dt}=aU(t)-b\dfrac{HQ(t)}{H+K}-\mu_q(t)Q(t),\\A(0)=\displaystyle\int_\Omega A_0(x)dx;\\Y(0)=M(0)=Q(0)=U(0)=R(0)=0.\end{cases}\tag{4.51}$$

4.3.3 Mosquito extinction results for seasonal model (4.44).

Let us introduce the following notations:

$$\mathcal{A}_- = \begin{pmatrix} -\varphi H - \mu_{r\infty} & 0 & \frac{bH}{H+K} \\ \varphi H & -a - \mu_{u\infty} & 0 \\ 0 & a & -\frac{bH}{H+K} - \mu_{q\infty} \end{pmatrix},$$

wherein $\mu_{q\infty}$, $\mu_{u\infty}$ and $\mu_{r\infty}$ are the limits inferior of $\mu_r(t)$, $\mu_u(t)$ and $\mu_q(t)$ as $t \to +\infty$. Let

$$(\gamma(.) + \mu_1(.))_\Diamond = \liminf_{t\to\infty} \frac{1}{t} \int_0^t (\gamma(s) + \mu_1(s))ds,$$

$$\mathcal{R}^\Diamond = \frac{r\beta}{(\gamma(.) + \mu_1(.))_\Diamond} \times \limsup_{t\to\infty} \frac{1}{t} \int_0^t \phi(s) \int_0^s \gamma(\xi) e^{\int_0^\xi \phi(\eta)d\eta + \int_\xi^s (\gamma(\eta)+\mu_1(\eta))d\eta} \left(\int_\xi^s f_\infty(\sigma - t) e^{-\int_\xi^\sigma (\beta + \mu_y(\eta))d\eta} d\sigma \right) d\xi ds,$$

and

$$f_\infty(.) := \left\langle (0,1,0)^T; e^{.\mathcal{A}_-}(1,0,0)^T \right\rangle;$$

and where $\{e^{s\mathcal{A}_-}\}_s$ is the C_0-semigroup generate by the linear operator $\mathcal{A}_-$.

We have the extinction result of seasonal spatio-temporal model (4.44) as follows,

Theorem 4.3.3. *Let $\mathcal{R}^\Diamond < 1$. Then the anopheles mosquito population dies out, i.e., for every solution of (4.44)-(4.45) we have $A(t), Y(t), R(t), U(t), Q(t) \to 0$ as $t \to \infty$.*

Proof. From the Y-equation of (4.51) we have

$$Y(t) = \int_0^t r\gamma(s)A(s)e^{-\int_s^t (\beta+\mu_y(\eta))d\eta}. \tag{4.52}$$

The Q, U and R-equations of (4.51) give that

$$\frac{d}{dt}(R(t), U(t), Q(t))^T \leq \mathcal{A}_-(R(t), U(t), Q(t))^T + (\beta Y(t), 0, 0)^T,$$

that is

$$U(t) \leq \int_0^t \beta Y(s) f_\infty(s-t)ds. \tag{4.53}$$

Substituting (4.52) into (4.53) we find that

$$U(t) \leq \int_0^t r\beta\gamma(s)A(s) \left(\int_s^t f_\infty(\sigma - t) e^{-\int_s^\sigma (\beta+\mu_y(\eta))d\eta} d\sigma \right) ds. \tag{4.54}$$

The A-equation of (4.51) leads to

$$\frac{d}{dt} \ln A(t) \leq \phi(t) \frac{U(t)}{A(t)} - (\gamma(t) + \mu_1(t)). \tag{4.55}$$

Integrating (4.55), we have

$$\frac{1}{t}\ln\frac{A(t)}{A(0)} \leq \frac{1}{t}\int_0^t \phi(s)\frac{U(s)}{A(s)} - \frac{1}{t}\int_0^t (\gamma(s)+\mu_1(s))ds. \tag{4.56}$$

Using (4.54) we find that

$$\frac{U(s)}{A(s)} \leq \int_0^s r\beta\gamma(\xi)\frac{A(\xi)}{A(s)}\left(\int_\xi^s f_\infty(\sigma-t)e^{-\int_\xi^\sigma(\beta+\mu_y(\eta))d\eta}d\sigma\right)d\xi.$$

From the A-equation of system (4.51), we easily find that

$$A(0)e^{-\int_0^t(\gamma(\eta)+\mu_1(\eta))d\eta} \leq A(t) \leq A(0)e^{\int_0^t(\phi(\eta)-\gamma(\eta)-\mu_1(\eta))d\eta}; \quad \forall t\geq 0. \tag{4.57}$$

From where we find that

$$\frac{A(\xi)}{A(s)} \leq e^{\int_0^\xi\phi(\eta)d\eta+\int_\xi^s(\gamma(\eta)+\mu_1(\eta))d\eta}; \forall s\geq\xi\geq 0.$$

Hence, (4.56) gives

$$\begin{aligned}&\frac{1}{t}\ln\frac{A(t)}{A(0)} \leq \\ &r\beta\limsup_{t\to\infty}\frac{1}{t}\int_0^t\phi(s)\int_0^s\gamma(\xi)e^{\int_0^\xi\phi(\eta)d\eta+\int_\xi^s(\gamma(\eta)+\mu_1(\eta))d\eta}\left(\int_\xi^s f_\infty(\sigma-t)e^{-\int_\xi^\sigma(\beta+\mu_y(\eta))d\eta}d\sigma\right)d\xi ds \\ &-(\gamma(.)+\mu_1(.))_\Diamond,\end{aligned}$$

that is

$$\frac{1}{t}\ln\frac{A(t)}{A(0)} \leq (\gamma(.)+\mu_1(.))_\Diamond\left(\mathcal{R}^\Diamond-1\right).$$

Since $\mathcal{R}^\Diamond<1$, it comes that

$$A(t) \leq A(0)e^{(\gamma(.)+\mu_1(.))_\Diamond\left(\mathcal{R}^\Diamond-1\right)t} \to 0 \text{ as } t\to\infty.$$

The Y, Q, U and R-equations of (4.51) give that $Y(t), Q(t), U(t), R(t) \to 0$ as $t\to\infty$ □

4.3.4 Weak persistence results for seasonal model (4.44).

In order to obtain the weak persistence results of seasonal spatio-temporal model (4.44) we set:

$$\mathcal{A}^+ = \begin{pmatrix} -\varphi H-\mu_r^\infty & 0 & \frac{bH}{H+K} \\ \varphi H & -a-\mu_u^\infty & 0 \\ 0 & a & -\frac{bH}{H+K}-\mu_q^\infty \end{pmatrix},$$

where in μ_r^∞, μ_u^∞ and μ_q^∞ are the limits superior of $\mu_r(t)$, $\mu_u(t)$ and $\mu_q(t)$ as $t \to +\infty$. Let

$$(\gamma(.)+\mu_1(.))^\Diamond = \limsup_{t\to\infty} \frac{1}{t}\int_0^t (\gamma(s)+\mu_1(s))ds,$$

$$\mathcal{R}_\Diamond = \frac{r\beta}{(\gamma(.)+\mu_1(.))^\Diamond} \times \liminf_{t\to\infty} \frac{1}{t}\int_0^t \phi(s)\int_0^s \gamma(\xi)e^{-\int_0^\xi \phi(\eta)d\eta+\int_\xi^s(\gamma(\eta)+\mu_1(\eta))d\eta}\left(\int_\xi^s f^\infty(\sigma-t)e^{-\int_\xi^\sigma(\beta+\mu_y(\eta))d\eta}d\sigma\right)d\xi ds,$$

and

$$f^\infty(.) := \left\langle (0,1,0)^T; e^{.\mathcal{A}^+}(1,0,0)^T \right\rangle. \tag{4.58}$$

Theorem 4.3.4. *Let $\mathcal{R}_\Diamond > 1$. Then anopheles mosquito uniformly weakly persists in the population, in the sense that there exists some $\epsilon > 0$ such that*

$$\limsup_{t\to+\infty} A(t) > \epsilon$$

for all solutions $\mathcal{U}(t,0)\mathbf{v}_0 := (A(t,.), M(t,.); Y(t,.); R(t,.); U(t,.); Q(t,.))^T$, $t \geq 0$ of system (4.44)-(4.45).

Proof. Let us suppose that for every $\epsilon > 0$, there is some solution with $\limsup_{t\to+\infty} A(t) < \epsilon$. From the Y-equation of (4.51) we have

$$Y(t) = \int_0^t r\gamma(s)A(s)e^{-\int_s^t(\beta+\mu_y(\eta))d\eta}. \tag{4.59}$$

The Q, U and R-equations of (4.51) give that

$$\frac{d}{dt}(R(t),U(t),Q(t))^T \geq \mathcal{A}^+(R(t),U(t),Q(t))^T + (\beta Y(t),0,0)^T,$$

that is

$$U(t) = \int_0^t \beta Y(s)f^\infty(s-t)ds. \tag{4.60}$$

Substituting (4.59) into (4.60) we find that

$$U(t) = \int_0^t r\beta\gamma(s)A(s)\left(\int_s^t f^\infty(\sigma-t)e^{-\int_s^\sigma(\beta+\mu_y(\eta))d\eta}d\sigma\right)ds. \tag{4.61}$$

The A-equation of (4.51) leads to

$$\frac{d}{dt}\ln A(t) = \frac{\phi(t)}{A(t)}\int_\Omega \left(1-\frac{A(t,x)}{K_A}\right)U(t,x)dx - (\gamma(t)+\mu_1(t)). \tag{4.62}$$

Setting $A^\infty := \limsup_{t\to+\infty} A(t)$ and since $A^\infty < \epsilon$, then there exists $t_* > 0$ such that $A(t) < \epsilon$ for all $t > t_*$.

Integrating (4.62), we have for sufficiently large time t

$$\begin{aligned}\frac{1}{t-t_*}\ln\frac{A(t)}{A(t_*)} = & \frac{1}{t-t_*}\int_{t_*}^{t}\frac{\phi(s)}{A(s)}\int_{\Omega}\left(1-\frac{A(s,x)}{K_A}\right)U(s,x)dxds\\ & -\frac{1}{t-t_*}\int_{t_*}^{t}(\gamma(s)+\mu_1(s))ds.\end{aligned}$$

That is

$$\frac{1}{t-t_*}\ln\frac{A(t)}{A(t_*)} \geq \frac{1}{t-t_*}\int_{t_*}^{t}\phi(s)\left(\frac{U(s)}{A(s)}-\frac{U(s)}{K_A}\right)ds - \frac{1}{t-t_*}\int_{t_*}^{t}(\gamma(s)+\mu_1(s))ds. \tag{4.63}$$

Thus, using (4.61) and the fact that $A(t)<\epsilon$ for all $t>t_*$; we can find a non-negative function $c_0(.)$ such that $U(t)<\epsilon c_0(t)$ for all $t>t_*$. Therefore, (4.63) becomes

$$\frac{1}{t-t_*}\ln\frac{A(t)}{A(t_*)} \geq \frac{1}{t-t_*}\int_{t_*}^{t}\phi(s)\left(\frac{U(s)}{A(s)}-\frac{\epsilon c_0(s)}{K_A}\right)ds - \frac{1}{t-t_*}\int_{t_*}^{t}(\gamma(s)+\mu_1(s))ds. \tag{4.64}$$

Using (4.61) we find that

$$\frac{U(s)}{A(s)} = \int_0^s r\beta\gamma(\xi)\frac{A(\xi)}{A(s)}\left(\int_{\xi}^{s} f^{\infty}(\sigma-t)e^{-\int_{\xi}^{\sigma}(\beta+\mu_y(\eta))d\eta}d\sigma\right)d\xi.$$

Equation (4.57) leads to

$$\frac{A(\xi)}{A(s)} \geq e^{-\int_0^{\xi}\phi(\eta)d\eta+\int_{\xi}^{s}(\gamma(\eta)+\mu_1(\eta))d\eta}; \forall s\geq\xi\geq 0.$$

Hence, (4.64) becomes

$$\begin{aligned}&\frac{1}{t-t_*}\ln\frac{A(t)}{A(t_*)} \geq\\ &r\beta\frac{1}{t-t_*}\int_{t_*}^{t}\phi(s)\int_0^s\gamma(\xi)e^{-\int_0^{\xi}\phi(\eta)d\eta+\int_{\xi}^{s}(\gamma(\eta)+\mu_1(\eta))d\eta}\left(\int_{\xi}^{s}f^{\infty}(\sigma-t)e^{-\int_{\xi}^{\sigma}(\beta+\mu_y(\eta))d\eta}d\sigma\right)d\xi ds\\ &-\frac{\epsilon}{K_A}\frac{1}{t-t_*}\int_{t_*}^{t}\phi(s)c_0(s)ds - \frac{1}{t-t_*}\int_{t_*}^{t}(\gamma(s)+\mu_1(s))ds.\end{aligned}$$

For sufficiently large t we have

$$\begin{aligned}&\frac{1}{t-t_*}\ln\frac{A(t)}{A(t_*)} \geq\\ &r\beta\frac{1}{t-t_*}\int_{t_*}^{t}\phi(s)\int_0^s\gamma(\xi)e^{-\int_0^{\xi}\phi(\eta)d\eta+\int_{\xi}^{s}(\gamma(\eta)+\mu_1(\eta))d\eta}\left(\int_{\xi}^{s}f^{\infty}(\sigma-t)e^{-\int_{\xi}^{\sigma}(\beta+\mu_y(\eta))d\eta}d\sigma\right)d\xi ds\\ &-\frac{\epsilon}{K_A}(\phi(.)c_0(.))^{\Diamond} - (\gamma(.)+\mu_1(.))^{\Diamond}.\end{aligned}$$

Since $\mathcal{R}_{\Diamond}>1$,

$$\begin{aligned}&r\beta\liminf_{t\to\infty}\frac{1}{t}\int_0^t\phi(s)\int_0^s\gamma(\xi)e^{-\int_0^{\xi}\phi(\eta)d\eta+\int_{\xi}^{s}(\gamma(\eta)+\mu_1(\eta))d\eta}\left(\int_{\xi}^{s}f^{\infty}(\sigma-t)e^{-\int_{\xi}^{\sigma}(\beta+\mu_y(\eta))d\eta}d\sigma\right)d\xi ds\\ &-(\gamma(.)+\mu_1(.))^{\Diamond}>0.\end{aligned}$$

Hence

$$\frac{1}{t-t_*}\ln\frac{A(t)}{A(t_*)}\geq\tilde{\delta}$$

for large times t, with $\tilde{\delta}>0$ provided $\epsilon>0$ is chosen small enough. Thus

$$A(t)\geq A(t_*)e^{\tilde{\delta}(t-t_*)}$$

for sufficiently large t and $A(t)\to\infty$ as $t\to\infty$, a contradiction to the fact that A is bounded. □

4.3.5 Strong persistence results for seasonal model (4.44).

In order to formulate a strong persistence results, let

$$\bar{\mathcal{A}}^+=\begin{pmatrix}-\varphi H-\bar{\mu}_r^\infty & 0 & \frac{bH}{H+K}\\ \varphi H & -a-\bar{\mu}_u^\infty & 0\\ 0 & a & -\frac{bH}{H+K}-\bar{\mu}_q^\infty\end{pmatrix},$$

where in $\bar{\mu}_r^\infty$ is the limit superior of $\bar{\mu}_r(t)$, as $t\to+\infty$; and

$$\bar{\mu}_r(t)=\lim_{s\to\infty}\mu_r(s+t).$$

Similarly considerations hold for the variables $\bar{\mu}_u^\infty$ and $\bar{\mu}_q^\infty$.

Let

$$(\gamma(.)+\mu_1(.))^\star=\limsup_{s,t\to\infty}\frac{1}{t}\int_0^t(\gamma(s+r)+\mu_1(s+r))dr.$$

$$\mathcal{R}_\star=\frac{r\beta}{(\gamma(.)+\mu_1(.))^\star}\times$$
$$\liminf_{s,t\to\infty}\frac{1}{t}\int_0^t\phi(s+r)\int_0^r\gamma(s+\xi)e^{-\int_0^\xi\phi(s+\eta)d\eta+\int_\xi^r(\gamma(s+\eta)+\mu_1(s+\eta))d\eta}\times$$
$$\left(\int_\xi^r\bar{f}^\infty(\sigma-t)e^{-\int_\xi^\sigma(\beta+\mu_y(s+\eta))d\eta}d\sigma\right)d\xi dr.$$

$$\bar{f}^\infty(.)=\left\langle(0,1,0)^T;e^{.\bar{\mathcal{A}}^+}(1,0,0)^T\right\rangle.$$

Theorem 4.3.5. *Let $\mathcal{R}_\star>1$. Then anopheles mosquito uniformly strongly persists in the population, in the sense that there exists some $\epsilon>0$ such that*

$$\liminf_{t\to+\infty}A(t)>\epsilon$$

for all solutions $\mathcal{U}(t,0)\mathbf{v}_0:=(A(t,.),M(t,.);Y(t,.);R(t,.);U(t,.);Q(t,.))^T$, $t\geq0$ of system (4.44)-(4.45).

Proof. In order to get into framework of uniform persistence results introduce by Thieme [204], consider the space

$$X_0 = \left\{ \mathbf{v}(t,.) := (A(t,.), M(t,.); Y(t,.); R(t,.); U(t,.); Q(t,.)) \in X_+ : \int_\Omega A(t,x)dx > 0 \right\},$$

endowed with the standard metric. Further let

$$\rho_0 : \mathbf{v}(t,.) \in X \to [0,\infty) \ni \rho_0(\mathbf{v}(t,.)) := \int_\Omega A(t,x)dx$$

be a non-negative functional on X. Then the space X_0 rewrites as

$$X_0 = \{\mathbf{v}(t,.) \in X_+ : \rho_0(\mathbf{v}(t,.)) > 0\}.$$

We consider the function

$$\sigma_0 : D_\tau \to [0,\infty)$$

defined by

$$\sigma_0(t,s,u) = \rho_0(\mathcal{U}(t+s,s)u) := \int_\Omega A(t+s,x)dx,$$

where $\mathbf{v}(t,.) := (A(t,.), M(t,.); Y(t,.); R(t,.); U(t,.); Q(t,.))$ solve (4.44)-(4.45) and $\mathbf{v}(t,s) = u$.

According to Theorem 4.3.2 we have

$$\begin{aligned} &A^\infty \leq mes(\Omega)K_A; \\ &(M+Y+Q+U+R)^\infty \leq \frac{\sup\gamma}{\inf\mu}A^\infty; \end{aligned}$$

and the set

$$\Omega_0 = \left\{ (A,M;Y;R;U;Q) : A+M+Y+R+U+Q \leq \left(1+\frac{\sup\gamma}{\inf\mu}\right) mes(\Omega)K_A \right\}$$

is absorbing and forward invariant. A standard Gronwall argument implies that $\sigma_0(.,s,u)$ is continuous on $[0,\infty)$ uniformly in $u \in \Omega_0$, $s \geq 0$. Therefore the non-autonomous semi-flow $\mathcal{U}$ has the following **(CA)**-property:

(CA) There exists a subset Ω_0 in X with the following properties:

- For all $u \in X_0$, $s \geq 0$, we have $\mathcal{U}(t,s)u \to \Omega_0$, $t \to \infty$, that is Ω_0 absorbs $\mathcal{U}(.,s)u$.
- If (s_j) is a sequence of real numbers and (u_j) a sequence in X such that $s_j \to \infty$ and $u_j \to \Omega_0$ as $j \to \infty$ and, for some $\epsilon > 0$, $\rho_0(u_j) = \epsilon$ for all $j \in \mathbb{N}$, then the continuity of $\sigma(.,s_j)u_j$ is uniform in $j \in \mathbb{N}$, possibly after choosing a sub-sequence.

Now, for every $\epsilon > 0$, $t > 0$ we defined set $\Sigma(\epsilon)$ and $\Sigma(t,\epsilon)$ as follows (Ω_0 is the absorbing set in **(CA)**):

$$\begin{aligned}
\Sigma(t,\epsilon)\quad & \text{consists of continuous functions } \tilde{\sigma}_0 : [0,t] \to [0,\epsilon],\\
& \tilde{\sigma}_0(t) = 0 < \tilde{\sigma}_0(0) = \epsilon,\\
& \tilde{\sigma}_0(s) = \lim_{j\to\infty} \sigma_0(s, s_j)u_j \text{ uniformly in } s \in [0,t]\\
& \text{for sequences } (s_j) \subset [0,\infty), (u_j) \subset X \text{ with } s_j \to \infty, u_j \to \Omega_0, \text{ as } j \to \infty.\\
\Sigma(\epsilon)\quad & \text{consists of continuous functions } \tilde{\sigma}_0 : [0,\infty) \to (0,\epsilon],\\
& 0 < \tilde{\sigma}_0(0) = \epsilon,\\
& \tilde{\sigma}_0(s) = \lim_{j\to\infty} \sigma_0(s, s_j)u_j \text{ locally uniformly in } s \geq 0\\
& \text{for sequences } (s_j) \subset [0,\infty), (u_j) \subset X \text{ with } s_j \to \infty, u_j \to \Omega_0, \text{ as } j \to \infty.
\end{aligned} \tag{4.65}$$

The semiflow $\mathcal{U}$ is said to have property **(PS)** if the following holds:

(PS) If $\epsilon > 0$ is chosen sufficiently small, the sets $\Sigma(\epsilon)$ and $\Sigma(t,\epsilon)$ are empty for all $t \geq 0$.

Coupling Theorem 4.3.4 and the (CA)-property together with Theorem 2.3 in [204]; in order to check the uniformly strongly ρ_0-persistence of $\mathcal{U}$ it is sufficient to check property **(PS)**. Let us describe elements of $\Sigma(\epsilon)$ and $\Sigma(t,\epsilon)$ in (4.65) in terms of systems (4.51). To this end we consider sequences $s_j \to \infty$, $u_j \to \Omega_0$ in X, as $j \to \infty$. Let A_j, Y_j, R_j, U_j, Q_j be the solutions of

$$\begin{cases}
\dfrac{dA_j(t)}{dt} = \phi(t+s_j)\displaystyle\int_\Omega \left(1 - \frac{A_j(t,x)}{K_A}\right) U_j(t,x)dx - (\gamma(t+s_j) + \mu_1(t+s_j))A_j(t),\\[2ex]
\dfrac{dY_j(t)}{dt} = \gamma(t+s_j)rA_j(t) - \mu_y(t+s_j)Y_j(t) - \beta Y_j(t),\\[2ex]
\dfrac{dR_j(t)}{dt} = \beta Y_j(t) + b\dfrac{HQ_j(t)}{H+K} - \varphi H R_j(t) - \mu_r(t+s_j)R_j(t),\\[2ex]
\dfrac{dU_j(t)}{dt} = \varphi H R_j(t) - (a + \mu_u(t+s_j))U_j(t),\\[2ex]
\dfrac{dQ_j(t)}{dt} = aU_j(t) - b\dfrac{HQ_j(t)}{H+K} - \mu_q(t+s_j)Q_j(t),\\
(A_j(0), Y_j(0), R_j(0), U_j(0), Q_j(0)) = u_j.
\end{cases}$$

Since $L^1(0,\infty)$ is separable, the Alaoglu-Bourbaki theorem implies that, after choosing as sub-sequence, $\phi(t+s_j) \to \bar{\phi}(t)$, $\gamma(t+s_j) \to \bar{\gamma}(t)$, $\mu_1(t+s_j) \to \bar{\mu}_1(t)$, $\mu_y(t+s_j) \to \bar{\mu}_y(t)$,

$\mu_r(t+s_j) \to \bar{\mu}_r(t)$, $\mu_u(t+s_j) \to \bar{\mu}_u(t)$, $\mu_q(t+s_j) \to \bar{\mu}_q(t)$, as $j \to \infty$; where $\bar{\phi}$, $\bar{\gamma}$, $\bar{\mu}_1$, $\bar{\mu}_y$, $\bar{\mu}_r$, $\bar{\mu}_u$, $\bar{\mu}_q$ are elements of $L^\infty(0,\infty)$ and the convergence holds in the weak topology carried by $L^\infty(0,\infty)$ as dual space of $L^1(0,\infty)$.

The derivatives of A_j, Y_j, Q_j, U_j and R_j are bounded, uniformly in $j \in \mathbb{N}$. By Arzela-Ascoli theorem we have, after choosing a sub-sequence,

$$A_j(t) \to \bar{A}(t), \quad Y_j(t) \to \bar{Y}(t), \quad Q_j(t) \to \bar{Q}(t), \quad U_j(t) \to \bar{U}(t), \quad R_j(t) \to \bar{R}(t), \quad j \to \infty$$

locally uniformly in $t \geq 0$, where $\bar{A}$, $\bar{Y}$, $\bar{Q}$, $\bar{U}$ and $\bar{R}$ are bounded and absolutely continuous and satisfy

$$\begin{cases} \dfrac{d\bar{A}(t)}{dt} = \bar{\phi}(t)\displaystyle\int_\Omega \left(1 - \frac{\bar{A}(t,x)}{K_A}\right)\bar{U}(t,x)dx - (\bar{\gamma}(t) + \bar{\mu}_1(t))\bar{A}(t), \\ \dfrac{d\bar{Y}(t)}{dt} = \bar{\gamma}(t)r\bar{A}(t) - \bar{\mu}_y(t)\bar{Y}(t) - \beta\bar{Y}(t), \\ \dfrac{d\bar{R}(t)}{dt} = \beta\bar{Y}(t) + b\dfrac{H\bar{Q}(t)}{H+K} - \varphi H\bar{R}(t) - \bar{\mu}_r(t)\bar{R}(t), \\ \dfrac{d\bar{U}(t)}{dt} = \varphi H\bar{R}(t) - (a + \bar{\mu}_u(t))\bar{U}(t), \\ \dfrac{d\bar{Q}(t)}{dt} = a\bar{U}(t) - b\dfrac{H\bar{Q}(t)}{H+K} - \bar{\mu}_q(t)\bar{Q}(t), \\ (\bar{A}(0), \bar{Y}(0), \bar{R}(0), \bar{U}(0), \bar{Q}(0)) = u_0 \in \Omega_0. \end{cases} \tag{4.66}$$

Since $\bar{A}(0) = \epsilon > 0$, we first realize that

$$\bar{A}(t) \geq \bar{A}(0)e^{-\int_0^t(\bar{\gamma}(s)+\bar{\mu}_1(s))ds} > 0; \forall t \geq 0,$$

so $\Sigma(t,\epsilon)$ is empty.

The element of $\Sigma(\epsilon)$ in (4.65) can be identified as

$$\tilde{\sigma}(t) = \bar{A}(t),$$

where $\bar{A}$ satisfies (4.66) and $\bar{A}(0) > 0$, $\bar{A}(t) \leq \epsilon$ for all $t \geq 0$.

The same consideration as in the proof of Theorem 4.3.4 now implies that such an $\bar{A}$ cannot exist, if $\epsilon > 0$ is chosen small enough, provided that $\bar{\mathcal{R}}_\diamondsuit > 1$, where $\bar{\mathcal{R}}_\diamondsuit$ is the analogue of $\mathcal{R}_\diamondsuit$ in Theorem 4.3.4 with $\bar{\phi}$, $\bar{\gamma}$, $\bar{\mu}_1$, $\bar{\mu}_y$, $\bar{\mu}_r$, $\bar{\mu}_u$, $\bar{\mu}_q$ replacing ϕ, γ, μ_1, μ_y, μ_r,

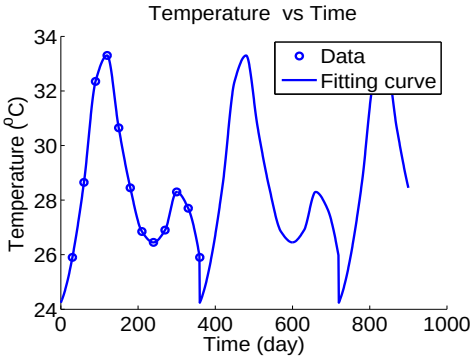
μ_u, μ_q. But, let us notice that

$$\begin{aligned}\bar{\phi}_{\diamondsuit} &= \liminf_{t\to\infty} \frac{1}{t}\int_0^t \bar{\phi}(r)dr = \liminf_{t\to\infty} \frac{1}{t}\int_0^t \lim_{j\to\infty} \phi(r+s_j)dr \\ &= \liminf_{t\to\infty} \frac{1}{t} \lim_{j\to\infty} \int_0^t \phi(r+s_j)dr \\ &\geq \liminf_{t\to\infty} \frac{1}{t} \liminf_{s\to\infty} \int_0^t \phi(r+s)dr \\ &\geq \liminf_{t,s\to\infty} \frac{1}{t}\int_0^t \phi(r+s)dr = \phi_\star.\end{aligned}$$

Similarly considerations holds for the other terms in $\bar{\mathcal{R}}_{\diamondsuit}$. Hence $\bar{\mathcal{R}}_{\diamondsuit} \geq \mathcal{R}_\star > 1$. This end the proof of the theorem. □

4.3.6 Numerical illustration

We now provide some numerical illustrations of the dynamics of the seasonal model (4.44). From the website of WMO (World Meteorological Organization) , we have obtained the monthly temperature of the town of Garoua (Cameroon) from 1971 to 2000. The real data and its fitted curve are shown in Figure 4.4.



Town of Garoua

Figure 4.4: The monthly temperature and its fitted curve.

In Table 4.5 we summarize parameters that are assumed to be constant in our model. This include the proportion of female to the whole population, r, the transition rates β, a, φ, the carrying capacity, K_A, the constant alternative of blood for vectors, K.

In Table 4.4, we present the temperature-varying parameters, according to [166], [44]. This include the average number of eggs laid per female per day, ϕ, the mortality rates for aquatic stage, for males, for immature females, for questing females, for breeding

females, for resting females, μ_1, μ_m, μ_y, μ_r, μ_u, μ_q, and the rate of emerging from the aquatic stage, γ.

The values of temperature-varying parameters, γ, is given in [44]. Since we consider continuous variations temperature, we interpolate the data parameter γ given in Table 4.3, using monotonic spline interpolation [73] (See Figure 4.5).

Now, according to Mordecai et al. 2012[166], let us describe how environmental temperature drives malaria transmission via its combined effects on the mosquito and parasite vital rates that determine transmission; namely the average number of eggs laid per female per day, ϕ, the mortality rates for aquatic stage, for males, for immature females, for questing females, for breeding females and for resting females, μ_1, μ_m, μ_y, μ_r, μ_u, μ_q. As all rate parameters in the temperature-dependent are expected to be unimodal with respect to temperature, they (Mordecai et al. [166]) fit quadratic and Brière functions (Briere et al. 1999 [21]) to each life-history parameter, as well as a linear function for comparison (Table 4.6). The Brière function is a left-skewed unimodal curve with three parameters, which represent the minimum temperature, maximum temperature and a rate constant (Briere et al. 1999 [21]). The unimodal functions are defined as Brière $[c(T_0 - T(t))(Tm - T(t))^{1/2}]$ and quadratic $[qT^2(t) + zT(t) + s]$, where $T(t)$ is temperature in degrees Celsius at time t and c, T_0 and T_m and q, z and s are fit parameters of each function respectively.

All time dependent parameters for model (4.44) are given by Table 4.6 and Fig. 4.5 and the other parameters are estimated by Table 4.5.

In Figure 4.7, we illustrate the distribution of mature females (questing, breeding and resting females) on a homogeneous landscape for different temperatures: 15^oC, 20^oC, 25^oC, 30^oC, 35^oC and 40^oC. With respect to each temperature, the lifetimes of mature females are respectively given by: 8.27, 12.79, 12.31, 7.67, 4.29 and 2.45 days.

Table 4.3: Values of temperature-varying parameter γ [44].

Unit	10^oC	15^oC	20^oC	25^oC	30^oC	35^oC	40^oC
day^{-1}	0	0.0236	0.0578	0.0671	0.0645	0.0515	0

γ=Rate of emerging from aquatic stage.

Ref.: Delatte et al. 2009 [44].

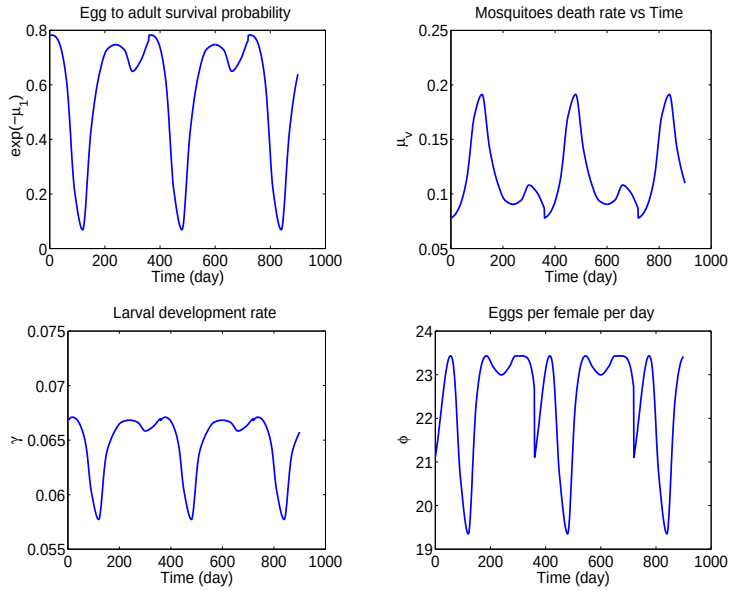


Figure 4.5: Time performance curves of mosquitoes traits for the town of Garoua. Quadratic fitting for egg-to-adult survival probability, mosquitoes death rate and for egg laid per adult female per day [166]. Rate of emerging from aquatic stage (larval development rate) is fitting using monotonic cubic spline interpolation [73].

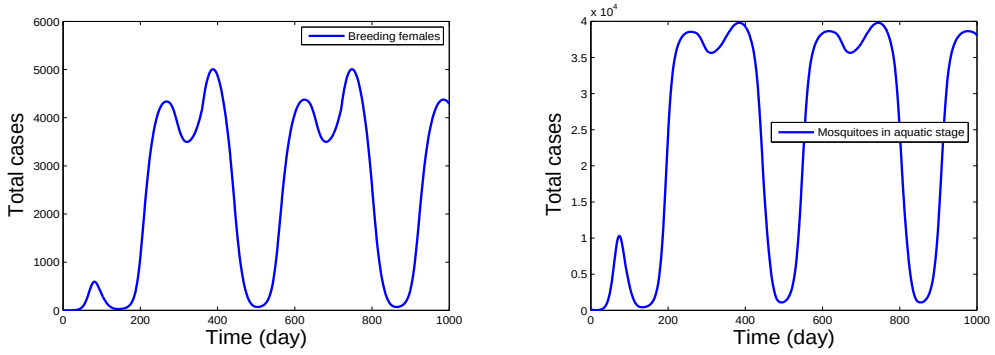


Figure 4.6: The long term behaviors of mosquitoes population in two stages using temperatures in the town of Garoua: Breeding females (left) and Aquatic stage (right). $b = 0.5$; $H = 100$; $K = 200$; $K_A = 5000$; $a = 0.3$, $\varphi = 0.8$. Other parameters are given by Tab. 4.5 and Tab. 4.6.

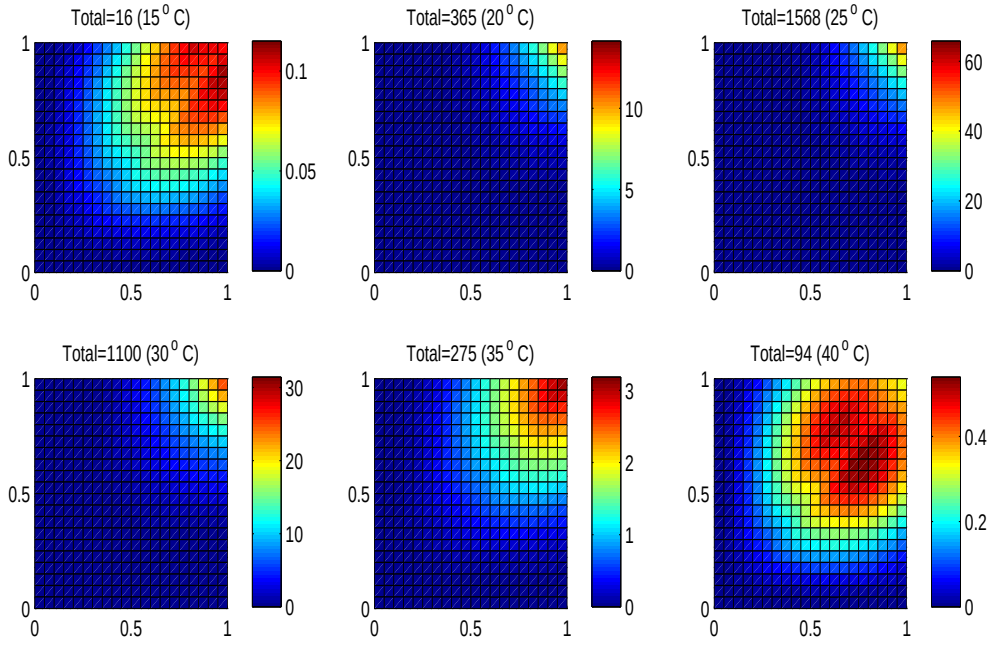


Figure 4.7: Distribution of mature females on a homogeneous landscape. $b = 0.5$; $H = 100$; $K = 200$; $K_A = 5000$; $a = 0.3$, $\varphi = 0.8$. Other parameters are given by Tab. 4.5 and Tab. 4.6.

Table 4.4: Temperature-varying parameters.

Parameter	Description	Ref.
ϕ	Number of eggs laid per female per day	[166]
μ_1	Mortality rate in aquatic stage	[166]
μ_m, μ_y, μ_r, μ_u, μ_q	Mortality rates of mosquitoes	[166], [44]
γ	Rate of emerging from aquatic stage	[44]

Ref.: Delatte et al. 2009 [44]; Mordecai et al. 2012 [166].

Table 4.5: Values of constant parameters.

Parameter	Description	Estimated value	Ref.
r	Ratio of emerging females	0.5	[44]
K_A	Carrying capacity	variable	
β	Mating rate between immature female and male	0.2 day^{-1}	[44]
φ	Probability of successfully taking a blood meal	variable	
H	Constant population density of humans	variable	
	at human habitat sites		
K	Constant alternative of blood for vectors	variable	
b	Rate at which vectors visits human habitat sites		
a	Rate at which resting females become breeding	variable	
ε_m	Adult mosquitoes speed of migration	0.1 $m\,s^{-1}$	[59], [127]

Ref.: Delatte et al. 2009 [44]; Dufourd et al. 2013 [59]; Lacroix et al. 2009 [127]

Table 4.6: The relationships between temperature and the mosquito and parasite life-history traits that determine malaria risk. Thermal performance curves were fitted to the data assuming Brière $[c(T_0-T(t))(Tm-T(t))^{1/2}]$, **B**, or Quadratic $[qT^2(t)+zT(t)+s]$, **Q**, functions; in which $T(t)$ is temperature (^oC) at time t. Standard deviations for the parameters are listed in parentheses alongside parameter values. (see Mordecai et al. 2012 [166] and references therein).

Parameters	Definition	Fit	Fit parameters (standard deviation)		
$e^{-\mu_y}$	Daily adult survival probability	**Q**	$q = -0.000828(0.0000519)$	$z = 0.0367(0.00239)$	$s = 0.522(0.0235)$
Mdr	Mosquito development rate	**B**	$c = 0.000111(0.00000954)$	$T_m = 34(0.000106)$	$T_0 = 14.7(0.831)$
pEA [pEA=$e^{-\mu_1}$]	Egg-to-adult survival probability	**Q**	$q = -0.00924(0.00123)$	$z = 0.453(0.0618)$	$s = -4.77(0.746)$
EFD	Egg laid per adult female per day	**Q**	$q = -0.153(0.0307)$	$z = 8.61(1.69)$	$s = -97.7(22.6)$
PDR	Parasite development rate	**B**	$c = 0.000111(0.0000161)$	$T_m = 34.4(0.000176)$	$T_0 = 14.7(1.48)$

4.3.7 Future directions

When mosquitoes are not submitted to stimuli, it is possible to assume that they move randomly in any direction [42]. This leads to a diffusion equation. For simplicity, let us describe a generic equation to model the spread of a mosquito population. So, let v represent the density of insects, then, one possible model is given by the following general advection-diffusion-reaction equation (see also [59]):

$$\begin{cases} \dfrac{\partial v(t,x)}{\partial t} = \nabla(D(t,x)v(t,x)) - \nabla((\nabla C(t,x) + W(t,x))v(t,x)) + g(t,x,v), \quad x \in \Omega, t > 0, \\ v(0,x) = v_0(x) \geq 0, \quad x \in \Omega, \\ (-D\nabla v(t,x) + W(t,x)v(t,x)) \cdot \eta_{in} = 0, \quad \forall x \in \partial\Omega_{in}, t > 0, \\ \nabla v(t,x) \cdot \eta_{out} = 0, \forall x \in \partial\Omega_{out}, t > 0, \end{cases} \tag{4.67}$$

where Ω is a bounded domain in $\mathbb{R}^n$ $(1 \leq n \leq 3)$ with a piecewise smooth boundary $\partial\Omega$. $D(t,x) \geq 0$ is the diffusion (dispersion) coefficient or the diffusivity and $v_0(.)$ is a continuous (or possibly discontinuous) function. Let $\partial\Omega_{in}$ and $\partial\Omega_{out}$ be partitions of the boundary $\partial\Omega$ where $\partial\Omega_{in}$ is the boundary at the inflow of mosquitoes in Ω and $\partial\Omega_{out}$ is the boundary at the outflow. η_{in} and η_{out} are respectively the unit outward normal to the boundaries Ω_{in} and Ω_{out}. We consider total flux Cauchy boundary conditions on $\partial\Omega_{in}$ [220], and Neumann boundary conditions on $\partial\Omega_{out}$.

Entomologists usually assume that there is no passive transportation of mosquito by the wind. Conversely, mosquitoes follow (or are looking for) odors and carbon dioxide (CO_2) carried by the wind [74], which gives a main direction of migration of mosquitoes; this is modeled by the term $\nabla(W(t,x)v(t,x))$. Indeed, it is well known that CO_2, in interaction with other components, acts as an attractant and induces a direct response to guide the mosquito towards the host. The breeding sites or the blood feeding sites attractions are modeled by the term $\nabla(\nabla C(t,x)v(t,x))$, where $\nabla C(t,x)$ represents the force of attraction towards favorable places. In C we take into account wind direction and strength to determine the area of attraction, which is commonly called *plume* by entomologists.

The reaction term $g(t,x,v)$ can be nonlinear, and represents death, birth, migration in the population. If one only focus on mosquito dispersal, we may consider a linear $g(t,x,v) = -A(x)v + b(t,x)$, where A would be the mean daily death rate, and b would

represent the birth rate in breeding sites.

Further works could be done from the mathematical and computational point of view with respect to model (4.67). For instance, the existence of a solution of the impulse parabolic system (4.67) could be considered, as well as the existence of a periodic equilibrium. Then, in order to take into account more precisely environmental and landscape parameters, High Performance Computing and more accurate numerical schemes should be considered or developed.

4.3.8 Summary

In section 4.3 we have examined an advection-reaction model for anopheles mosquito dynamics population. Knowledge of the population dynamics of the malaria vector is fundamental to the understanding of malaria epidemiology and the spread of insecticide resistance. Therefore, studies on the population structure of malaria vectors have important implications for the prediction and assessment of the effects of many vector control strategies. According to all malaria models, little has been done with regard to the studies on the population dynamics of malaria vectors.

The aim finding of section 4.3 can be summarized along the following lines:

✓ We first derive the model description. This includes the description of model parameters and the description of the state variables of the model (see Eq. (4.44)-(4.45)). This model takes into account seasonal transmission and the geographical range of malaria.

✓ Using the semigroup approach we first derive the existence of the unique bounded non-autonomous semiflow associated to the system (4.44)-(4.45).

✓ To find the behavior of the non-autonomous semiflow associated to the system (4.44)-(4.45), we introduce the threshold values $\mathcal{R}^{\diamondsuit}$, $\mathcal{R}_{\diamondsuit}$ and $\mathcal{R}_{*}$. Then, we find that, if $\mathcal{R}^{\diamondsuit} < 1$, the anopheles mosquito population dies out.

✓ We also derive persistence results for seasonal mosquito model (4.44)-(4.45). Namely, if $\mathcal{R}_{\diamondsuit} > 1$ (resp. $\mathcal{R}_{*} > 1$) then anopheles mosquito uniformly weakly (resp. strongly) persists in the population. Finally, we provide some illustrations of the dynamics of the seasonal model (4.44)-(4.45).

Chapter Five

Population Models Structured by Age: Hepatitis B and SIL models.

This chapter is organized in two sections and deals with two population models structured by age. The first section is concerned by a mathematical SIL (Susceptible-Infected-Lost of sight) model for the spread of a directly transmitted infectious disease in an age-structured population; taking into account the demographic process and the vertical transmission of the disease. There are important infective agents such as HBV (hepatitis B virus), HIV (human immunodeficiency virus) and HTLV (human T-cell leukemia virus) that can be vertically transmitted. The second section of the chapter is concerned by and age-structured model for the transmission of hepatitis B virus, with differential infectivity: symptomatic and asymptomatic infections.

5.1 Age-structured SIL model with demographics process and vertical transmission.

We consider a mathematical SIL model for the spread of a directly transmitted infectious disease in an age-structured population; taking into account the demographic process and the vertical transmission of the disease. First we establish the mathematical well-posedness of the time evolution problem by using the semigroup approach. Next we prove that the basic reproduction ratio R_0 is given as the spectral radius of a positive operator, and an endemic state exist if and only if the basic reproduction ratio R_0 is greater than unity, while the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$. We also show that the endemic steady states are forwardly bifurcated from the disease-free steady state when R_0 cross the unity. Finally we examine the conditions for the local stability of the endemic steady states.

5.1.1 Introduction

During the earliest centuries mankind faces ever more challenging environmental and public health problems, such as emergence of new diseases or the emergence of disease into new regions, and the resurgence diseases (tuberculosis, malaria HIV/AIDS, HBV). Mathematical models of populations incorporating age structure, or other structuring of individuals with continuously varing properties, have an extensive history.

The earliest models of age structured populations, due to Sharpe and Lotka in 1911 [194] and McKendrick in 1926 [154] established a foundation for a partial differential equations approach to modeling continuum age structure in an evolving population. At this early stage of development, the stabilization of age structure in models with linear mortality and fertility processes was recognized, although not rigorously established [138, 139]. Rigorous analysis of these linear models was accomplished later in 1941 by Feller [70], in 1963 by Bellman and Cooke [15], and others, using the methods of Volterra integral equations and Laplace transforms. Many applications of this theory have been developed in demography [37, 112, 125, 184], in biology [10, 12, 13, 38, 90, 207] and in epidemiology [25, 29, 71, 72, 102, 124, 56].

The increasingly complex mathematical issues involved in nonlinearities in age structured models led to the development of new technologies, and one of the most useful of these has been the method of semi-groups of linear and nonlinear operators in Banach spaces. Structured population models distinguish individual from another according to characteristics such as age, size, location, status and movement. The goal of structured population is to understand how these characteristics affect the dynamics of these models and thus the outcomes and consequence of the biological and epidemiological processes.

In this section we consider a mathematical S-I-L (Susceptibles-Infected-Lost of sight) model with demographics process, for the spread of a directly transmitted infectious disease in an age-structured population. By infected (I) we mean infectious taking a chemoprophylaxis in a care center. And by loss of sight (L), we mean infectious that begun their effective therapy in the hospital and never return to the hospital for the spuctrum examinations for many reasons such as long duration of treatment regimen, poverty, mentality, etc... The lost of sight class was previously consider in some papers as [20, 65].

In this section, the infective agent can be transmitted not only horizontally but also vertically from infected mothers to their newborns (perinatal transmission). There are important infective agents such as HBV (hepatitis B virus), HIV (human immunodeficiency virus) and HTLV (human T-cell leukemia virus) that can be vertically transmitted. Compared with the pure horizontal transmission case, so far we have not yet so many results for vertically diseases in structured populations. In Africa, the vertical transmission of the disease like HIV is in progression nowadays.

Worldwide, 1% of pregnant women are HIV-positive. However, sub-Saharan Africa where 95% of HIV positive women live carries the vast majority of this burden [198]. Without treatment, approximately 25%-50% of HIV-positive mothers will transmit the virus to their newborns during pregnancy, childbirth, or breastfeeding [17]. In 2007, over 2 million children worldwide were living with HIV/AIDS, with the overwhelming majority again in sub-Saharan Africa [198]. Approximately 400,000 infants contract HIV from their mother every year, which is about 15% of the total global HIV incidence [183, 218]. The rate of pediatric HIV infections in sub-Saharan Africa remains unacceptably high, with over 1,000 newborns infected with HIV per day [94].

Large simple trials which aim to study therapeutic interventions and epidemiological associations of human immunodeficiency virus (HIV) infection, including perinatal transmission, in Africa may have substantial rates of lost of sight. A better understanding of the characteristics and the impact of women and children lost of sight is needed. According to Ioannidis et al. [117], for the impact of lost of sight and vertical transmission cohort in Malawi, several predictors of lost of sight were identified in this large HIV perinatal cohort. Lost of sights can impact the observed transmission rate and the risk associations in different studies. They (Ioannidis et al.) also focus that the HIV infection status could not be determine for 36.9% of infant born to HIV-infected mothers; 6.7% with missing status because of various sample problems and 30.3% because they never returned to the clinic (Lost of sight).

Firstly, the epidemic system is formulated. Then, we will describe the semigroup approach to the time evolution problem of the abstract epidemic system. Next we consider the disease invasion process to calculate the basic reproduction ratio R_0, then, we prove that the disease-free steady state is locally asymptotically stable if $R_0 < 1$. Subsequently, we show that at least one endemic steady state exists if the basic

reproduction ratio R_0 is greater than unity. By introducing a bifurcation parameter, we show that the endemic steady state is forwardly bifurcated from the disease-free steady state when the basic reproduction ratio crosses unity. Finally, we consider the conditions for the local stability of the endemic steady states.

5.1.2 The model

In this section, we formulate a model for the spread of the disease in a host population. We consider a host population divided into three subpopulations; the susceptible class, the infective class (those who are infectious but taking a chemoprophylaxis) and the lost of sight class (those who are infectious but not on a chemoprophylaxis) denoted respectively by $S(t,a)$, $I(t,a)$ and $L(t,a)$ at time t and at specific age a. Let $\beta(.,.)$ be the contact rate between susceptible individuals and infectious individuals. Namely, $\beta(a,\sigma)$ is the transmission rate from the infectious individuals aged σ to the susceptible individuals aged a. All recruitment is into the susceptible class and occur at a specific rate $\Lambda(a)$. The rate of non-disease related death is $\mu(a)$. Infected and lost of sight have additional death rates due to the disease $d_1(a)$ and $d_2(a)$ respectively. The transmission of the disease occurs following adequate contacts between a susceptible and infectious or lost of sight. $r(a)$ denoted the proportion of individuals receiving an effective therapy in a care center and $\phi(a)$ the fraction of them who after begun their treatment will not return in the hospital for the examination. After some time, some of them can return in the hospital at specific rate $\gamma(a)$.

The basic system (age-structured SIL epidemic model) with vertical transmission can be formulated as follows by equation (5.1).

$$\begin{cases} \left(\dfrac{\partial}{\partial t}+\dfrac{\partial}{\partial a}\right)S(t,a) &= \Lambda(a)-(\lambda(t,a)+\mu(a))S(t,a), \\ \left(\dfrac{\partial}{\partial t}+\dfrac{\partial}{\partial a}\right)I(t,a) &= \lambda(t,a)S(t,a)-(\mu(a)+d_1(a) \\ & \quad +r(a)\phi(a))I(t,a)+\gamma(a)L(t,a), \\ \left(\dfrac{\partial}{\partial t}+\dfrac{\partial}{\partial a}\right)L(t,a) &= r(a)\phi(a)I(t,a)-(\mu(a)+d_2(a) \\ & \quad +\gamma(a))L(t,a). \end{cases} \tag{5.1}$$

For the boundary conditions of model (5.1), we consider that pregnant lost of sight women generally return to the clinic for the birth of they new born, therefore, we can

assume that there is not lost of sight new born (i.e. $L(t,0) = 0$). Due to the above consideration, the initial and boundary conditions of model (5.1) are given by:

$$\begin{cases} S(t,0) &= \int_0^{a^+} f(a)[S(t,a) + (1-p)(I(t,a) + L(t,a))]da, \\ I(t,0) &= p\int_0^{a^+} f(a)(I(t,a) + L(t,a))da, \\ L(t,0) &= 0, \\ S(0,a) &= \varphi_S(a); \quad a \in (0,a^+), \\ I(0,a) &= \varphi_I(a); \quad a \in (0,a^+), \\ L(0,a) &= \varphi_L(a); \quad a \in (0,a^+), \end{cases} \tag{5.2}$$

and where $f(a)$ is the age-specific fertility rate, p is the proportion of newborns produced from infected individuals who are vertically infected and $a^+ < \infty$ is the upper bound of age. The force of infection $\lambda(t,a)$ is given by

$$\lambda(t,a) = \int_0^{a^+} \beta(a,\sigma)(I(t,\sigma) + L(t,\sigma))d\sigma.$$

where $\beta(a,s)$ is the transmission rate between the susceptible individuals aged a and infectious or lost of sight individuals aged s. $a^+ < \infty$ is the upper bound of age.
Let us note that in the literature the transmission rate $\beta(a,\sigma)$ can take many forms: $\beta(a,\sigma) = \beta = constant$ (Dietz 1975 [54]; Greenhalgh 1987 [82]), $\beta(a,\sigma) = g(a)$ (Gripenberg 1983 [88]; Webb 1985 [211]), $\beta(a,\sigma) = g(a)h(\sigma)$ (Dietz and Schenzle 1985 [55]; Greenhalgh 1988 [83]; Castillo-Chavez and al. 1989 [29]).

In the following, we consider systems (5.1)-(5.2) under following assumption:

Assumption 5.1.1. *We assume that* $\beta \in L^\infty[(0,a^+,\mathbb{R}_+) \times (0,a^+,\mathbb{R}_+)]$ *and functions* f, d_1, d_2, γ, Λ, μ *belong to* $L^\infty(0,a^+,\mathbb{R}_+)$.

5.1.3 Existence of flow

The aim of this section is to derive premininary remarks on (5.1)-(5.2). These results include the existence of the unique maximal bounded semiflow associated to this system.

Abstract formulation

Let X be the space defined as $X := L^1(0,a^+,\mathbb{R}^3)$ with the norm $||\varphi||_X = \sum_{i=1}^{3} ||\varphi_i||_{L^1}$; where $\varphi = (\varphi_1,\varphi_2,\varphi_3)^T \in X$. Let us note X_+ the positive cone of X.

It is well known that $(X, ||.||_X)$ is a Banach space. Let $A : D(A) \subset X \to X$ be a operator defined by

$$A\varphi = -\varphi' - \mu\varphi, \tag{5.3}$$

with the domain

$$D(A) = \left\{ \varphi = (\varphi_1, \varphi_2, \varphi_3) \in W^{1,1}(0, a^+, \mathbb{R}^3) \text{ and } \begin{pmatrix} \varphi_1(0) \\ \varphi_2(0) \\ \varphi_3(0) \end{pmatrix} = \begin{pmatrix} \int_0^{a^+} f(a)[\varphi_1(a) + (1-p)(\varphi_2(a) + \varphi_3(a))]da \\ p\int_0^{a^+} f(a)(\varphi_2(a) + \varphi_3(a))da \\ 0 \end{pmatrix} \right\};$$

the function $F : \overline{D(A)} \to X$ defined by

$$F\begin{pmatrix} \varphi_1 \\ \varphi_2 \\ \varphi_3 \end{pmatrix} = \begin{pmatrix} \Lambda - \lambda[., \varphi]\varphi_1 \\ \lambda[., \varphi]\varphi_1 - (d_1 + r\phi)\varphi_2 + \gamma\varphi_3 \\ r\phi\varphi_2 - (d_2 + \gamma)\varphi_3 \end{pmatrix},$$

$\lambda[., \varphi] \in L^1(0, a^+, \mathbb{R})$ is a function such that

$$\lambda[a, \varphi] = \int_0^{a^+} \beta(a, \sigma)[\varphi_2(\sigma) + \varphi_3(\sigma)]d\sigma$$

and $W^{1,1}(0, a^+, \mathbb{R})$ is a usual Sobolev space.

Let us first derive the following lemma on operator A.

Lemma 5.1.1. *1. The operator A is generator of a C_0-semigroup of linear bounded operators $\{T(t)\}_{t\geq 0}$ such that*

$$T(t)\varphi(a) = \begin{cases} \varphi(a-t)e^{-\mu t} & if \quad a - t \geq 0 \\ C(t-a)e^{-\mu a} & if \quad a - t \leq 0 \end{cases} \quad for \ \ t \leq a^+$$

and $T(t)\varphi(a) = 0_{\mathbb{R}^3}$ for $t > a^+$; where $C(t) = (C_1(t), C_2(t), 0) \in \mathbb{R}^3$ is the unique solution of the following Volterra integral equation

$$C(t) = G(t) + \Phi(t, C),$$

with

$$G(t) = \left(\int_t^{a^+} f(s)(\varphi_1(s-t) + (1-p)\varphi_2(s-t) + \varphi_3(s-t))ds \ ; \ p\int_t^{a^+} f(s)\varphi_2(s-t)ds \ ; \ 0 \right),$$

$$\Phi(t, C) = \left(\int_0^t f(s)(C_1(t-s) + (1-p)C_2(t-s))ds \ ; \ p\int_0^t f(s)C_2(t-s)ds \ ; \ 0 \right).$$

2. The domain $D(A)$ of operator A is dense in X and A is a closed operator.

Proof. The proof of this result is rather standard. Standard methodologies apply to provide item 1 (see Pazy 1983 [180]). Item 2 is a direct consequence of the fact that the operator A is generator of a C_0-semigroup of linear bounded operators (see Corollary 2.5 in Pazy 1983 [180]). □

Therefore, one obtains that System (5.1)-(5.2) re-writes as the following densely defined Cauchy problem

$$\begin{cases} \dfrac{d\varphi(t)}{dt} &= A\varphi(t) + F(\varphi(t)), \\ \varphi(0) &= (\varphi_S, \varphi_I, \varphi_L)^T. \end{cases} \tag{5.4}$$

Existence and uniqueness of solutions

We set $X_0 := \overline{D(A)}$ and X_{0+} the positive cone of X_0. In general we can not solve (5.4) in this strong formulation, if $u_0 \in X_{0+} \setminus D(A)$. So, for arbitrary $\varphi_0 \in X_{0+}$, we solve it in the integrated form:

$$\varphi(t) = \varphi_0 + A\int_0^t \varphi(s)ds + \int_0^t F(\varphi(s))ds \,; t \geqslant 0. \tag{5.5}$$

A solution of (5.5) is called a *mild solution* of the initial value problem (5.4). So, in the following, we are looking for mild solution of abstract Cauchy-problem (5.4).

We can easily find that:

Lemma 5.1.2. *On Assumption 5.1.1, the nonlinear operator F from X to X is continuous and locally Lipschitz.*

Using Lemmas 5.1.1 and 5.1.2 the main results of this section reads as (see Theorem 1.4 in Pazy 1983[180]).

Theorem 5.1.1. *Let Assumption 5.1.1 be satisfied.*
If $\varphi_0 \in X_{0+} := L^1(0, a^+, \mathbb{R}^3_+)$. Then there exists a unique bounded continuous solution φ to the integrated problem (5.5) *defined on $[0, +\infty)$ with values in X_{0+}.*

5.1.4 Disease-Free Equilibrium (DFE)

The following proposition gives the characteristics of the disease-free equilibrium (DFE) of system (5.1)-(5.2).

Let us introduce $l(a) = exp\left(-\int_0^a \mu(s)ds\right)$ the average lifetime of individuals at age a.

Proposition 5.1.1. *Let* $\int_0^{a^+} f(a)l(a)da < 1$ *be satisfied. Then, system (5.1)-(5.2) has a unique Disease Free Equilibrium (DFE),* $\varphi_0 = (S_0, 0_{L^1}, 0_{L^1})$*, where* S_0 *is given by*

$$\begin{cases} S_0(0) = \dfrac{1}{1-\int_0^{a^+} f(a)l(a)da} \displaystyle\int_0^{a^+} f(a)l(a)\left(\int_0^a \frac{\Lambda(s)}{l(s)}ds\right)da, \\ S_0(a) = l(a)\left[S_0(0) + \displaystyle\int_0^a \frac{\Lambda(s)}{l(s)}ds\right] \ for\ 0 \le a \le a^+. \end{cases} \tag{5.6}$$

Proof. : φ is an equilibrium of problem (5.4) if and only if

$$\varphi \in D(A) \text{ and } A\varphi + F(\varphi) = 0_X. \tag{5.7}$$

For the DFE we have $\varphi_2 = \varphi_3 \equiv 0_{L^1}$. Hence $\lambda[a,\varphi] \equiv 0_{L^1}$. From where the result follows using straightforward computations. □

5.1.5 Endemic Equilibrium (EE)

φ is an endemic equilibrium of (5.4) if and only if (5.7) is satisfied. That is,

$$\begin{aligned}
\varphi_1(a) &= \varphi_1(0)l(a)\exp\left(-\int_0^a \lambda[\sigma,\varphi]d\sigma\right) \\
&\quad + \int_0^a \frac{l(a)}{l(s)}\exp\left(-\int_s^a \lambda[\sigma,\varphi]d\sigma\right)\Lambda(s)ds; && (5.8)\\
\varphi_2(a) &= \int_0^a \frac{l(a)\Gamma_1(a)}{l(s)\Gamma_1(s)}\exp\left(-\int_s^a r(\sigma)\phi(\sigma)d\sigma\right)\left[\gamma(s)\varphi_3(s) + \lambda[s,\varphi]\varphi_1(s)\right]ds \\
&\quad + \varphi_2(0)l(a)\Gamma_1(a)\exp\left(-\int_0^a r(\sigma)\phi(\sigma)d\sigma\right); && (5.9)\\
\varphi_3(a) &= \varphi_3(0)l(a)\Gamma_2(a)\exp\left(-\int_0^a \gamma(\sigma)d\sigma\right) \\
&\quad + \int_0^a \frac{l(a)\Gamma_2(a)}{l(s)\Gamma_2(s)}\exp\left(-\int_s^a \gamma(\sigma)d\sigma\right)r(s)\phi(s)\varphi_2(s)ds; && (5.10)\\
\varphi_1(0) &= \int_0^{a^+} f(a)[\varphi_1(a) + (1-p)(\varphi_2(a)+\varphi_3(a))]da; && (5.11)\\
\varphi_2(0) &= p\int_0^{a^+} f(a)(\varphi_2(a)+\varphi_3(a))da; && (5.12)\\
\varphi_3(0) &= 0. && (5.13)
\end{aligned}$$

where

$$\begin{aligned}
\Gamma_1(a) &= \exp\left(-\int_0^a (d_1(s) + r(s)\phi(s))ds\right); \\
\Gamma_2(a) &= \exp\left(-\int_0^a (d_2(s) + \gamma(s))ds\right).
\end{aligned}$$

Let us set $\lambda(s) = \lambda[s, \varphi]$ for $s \in [0, a^+)$. Equation (5.8) re-write as

$$\varphi_1(a) \;=\; \varphi_1(0)A_{11}(\lambda, a) + u_1(\lambda, a). \tag{5.14}$$

Equations (5.8) and (5.9) give

$$\varphi_2(a) \;=\; \varphi_1(0)A_{21}(\lambda, a) + \varphi_2(0)A_{22}(a) + u_2(\lambda, a). \tag{5.15}$$

Equations (5.10), (5.13) and (5.14) give

$$\varphi_3(a) \;=\; \varphi_1(0)A_{31}(\lambda, a) + \varphi_2(0)A_{32}(\lambda, a) + u_3(\lambda, a); \tag{5.16}$$

with

$$\begin{aligned}
&A_{11}(\lambda, a) = l(a) \exp\left(-\int_0^a \lambda(\sigma)d\sigma\right);\\
&A_{21}(\lambda, a) = \int_0^a \chi_{21}(a, s)\lambda(s) \exp\left(-\int_0^s \lambda(\sigma)d\sigma\right) ds;\\
&A_{22}(a) = l(a)\Gamma_1(a);\\
&A_{31}(\lambda, a) = \int_0^a \chi_{31}(a, s)\lambda(s) \exp\left(-\int_0^s \lambda(\sigma)d\sigma\right) ds;\\
&A_{32}(a) = l(a)\Gamma_2(a) \int_0^a \frac{\Gamma_1(s)}{\Gamma_2(s)} r(s)\phi(s)ds;\\
&u_1(\lambda, a) = \int_0^a \frac{l(a)}{l(s)}\Lambda(s) \exp\left(-\int_s^a \lambda(\sigma)d\sigma\right) ds;\\
&u_2(\lambda, a) = \int_0^a \frac{l(a)}{l(s)}\Lambda(s) \int_s^a \frac{\Gamma_1(a)}{\Gamma_1(\eta)}\lambda(\eta) \exp\left(-\int_s^\eta \lambda(\sigma)d\sigma\right) ds;\\
&u_3(\lambda, a) = \int_0^a \frac{l(a)\Gamma_2(a)}{l(s)\Gamma_2(s)} r(s)\phi(s)u_2(\lambda, s)ds\\
&+ \int_0^a \frac{l(a)\Gamma_1(a)}{l(s)\Gamma_1(s)} \exp\left(-\int_s^a r(\sigma)\phi(\sigma)d\sigma\right) \gamma(s)\varphi_3(s)ds;
\end{aligned}$$

and

$$\chi_{21}(a, s) = l(a)\frac{\Gamma_1(a)}{\Gamma_1(s)};\; \chi_{31}(a, s) = l(a) \int_s^a \frac{\Gamma_2(a)\Gamma_1(\eta)}{\Gamma_2(\eta)\Gamma_1(s)} r(\eta)\phi(\eta)d\eta.$$

From equations (5.11) and (5.12), we respectively deduce that

$$\begin{aligned}
&\left(1 - \int_0^{a^+} f(a)[A_{11}(\lambda, a) + (1-p)(A_{21}(\lambda, a) + A_{31}(\lambda, a))]da\right) \varphi_1(0)\\
&- (1-p)\varphi_2(0) \int_0^{a^+} f(a)[A_{22}(a) + A_{32}(a)]da = v_1(\lambda);
\end{aligned} \tag{5.17}$$

and

$$\begin{aligned} & p\varphi_1(0)\int_0^{a^+} f(a)[A_{21}(\lambda,a)+A_{31}(\lambda,a)]da \\ & +\varphi_2(0)\left(p\int_0^{a^+} f(a)[A_{22}(a)+A_{32}(a)]da-1\right)=-v_2(\lambda); \end{aligned} \tag{5.18}$$

where

$$\begin{aligned} v_1(\lambda) &= \int_0^{a^+} f(a)[u_1(\lambda,a)+(1-p)(u_2(\lambda,a)+u_3(\lambda,a))]da; \\ v_2(\lambda) &= p\int_0^{a^+} f(a)[u_2(\lambda,a)+u_3(\lambda,a)]da. \end{aligned}$$

Therefore, we find that $\varphi_1(0)=\dfrac{\Delta_1(\lambda)}{\Delta(\lambda)}$ and $\varphi_2(0)=\dfrac{\Delta_2(\lambda)}{\Delta(\lambda)}$; with

$$\begin{aligned} &\Delta(\lambda)=(1-p)p\int_0^{a^+} f(a)[A_{22}(a)+A_{32}(a)]da\times\int_0^{a^+} f(a)[A_{21}(\lambda,a)+A_{31}(\lambda,a)]da \\ &+\left(1-\int_0^{a^+} f(a)[A_{11}(\lambda,a)+(1-p)(A_{21}(\lambda,a)+A_{31}(\lambda,a))]da\right)\times \\ &\left(p\int_0^{a^+} f(a)[A_{22}(a)+A_{32}(a)]da-1\right); \\ &\Delta_1(\lambda)=v_1(\lambda)\left(p\int_0^{a^+} f(a)[A_{22}(a)+A_{32}(a)]da-1\right) \\ &-(1-p)v_2(\lambda)\int_0^{a^+} f(a)[A_{22}(a)+A_{32}(a)]da; \\ &\Delta_2(\lambda)=v_2(\lambda)\left(\int_0^{a^+} f(a)[A_{11}(\lambda,a)+(1-p)(A_{21}(\lambda,a)+A_{31}(\lambda,a))]da-1\right) \\ &-pv_1(\lambda)\int_0^{a^+} f(a)[A_{21}(\lambda,a)+A_{31}(\lambda,a)]da. \end{aligned}$$

Equations (5.15) and (5.16) give

$$\begin{cases} \varphi_2(a) &= \dfrac{\Delta_1(\lambda)}{\Delta(\lambda)}A_{21}(\lambda,a)+\dfrac{\Delta_2(\lambda)}{\Delta(\lambda)}A_{22}(a)+u_2(\lambda,a) \\ \varphi_3(a) &= \dfrac{\Delta_1(\lambda)}{\Delta(\lambda)}A_{31}(\lambda,a)+\dfrac{\Delta_2(\lambda)}{\Delta(\lambda)}A_{32}(a)+u_3(\lambda,a) \end{cases} \tag{5.19}$$

Since $\lambda(a)=\int_0^{a^+}\beta(a,s)(\varphi_2(s)+\varphi_3(s))ds$; then we have

$$\lambda(a)=H(\lambda)(a); \tag{5.20}$$

where H is the operator defined from $L^1(0,a^+,\mathbb{R})$ into itself by

$$\begin{aligned} H(\varphi)(a) &= \int_0^{a^+}\beta(a,s)\left[\frac{\Delta_1(\varphi)}{\Delta(\varphi)}(A_{21}(\varphi,s)+A_{31}(\varphi,s))+u_2(\varphi,s)+u_3(\varphi,s)\right. \\ &\left.+\frac{\Delta_2(\varphi)}{\Delta(\varphi)}(A_{22}(s)+A_{32}(s))\right]ds. \end{aligned} \tag{5.21}$$

Hence, system (5.1)-(5.2) have an endemic equilibrium if and only if the fixed point equation (5.20) has at least one positive solution.

Now let us introduce the following technical assumptions on the transmission rate β as in Inaba [114, 115, 113]:

Assumption 5.1.2. *1.* $\beta \in L^1_+(\mathbb{R}\times\mathbb{R})$ *such that* $\beta(a,s)=0$ *for all* $(a,s)\notin [o,a^+]\times[0,a^+]$.

2. $\lim\limits_{h\to 0}\int_{-\infty}^{+\infty}|\beta(a+h,\xi)-\beta(a,\xi)|da=0$ *for* $\xi\in\mathbb{R}$.

3. It exists a function ε *such that* $\varepsilon(s)>0$ *for* $s\in(0,a^+)$ *and* $\beta(a,s)\geqslant\varepsilon(s)$ *for all* $(a,s)\in(0,a^+)^2$.

On the above assumption, some properties of operator H are given by the following lemma.

Lemma 5.1.3. *Let Assumption 5.1.2 be satisfied.*

(i) H is a positive, continuous operator. There exist a closed, bounded and convex subset $D\subset L^1_+(0,a^+,\mathbb{R})$ *such that* $H(D)\subset D$.

(ii) Operator H has a Fréchet derivative H_0 *at the point* $\varphi\equiv 0$ *defined by* (5.22) *and* $H_0:=H'(0)$ *is a positive, compact and nonsupporting operator.*

Proof. (i) The positivity and the continuity of operator H are obvious. Let $\varphi\in L^1(0,a^+,\mathbb{R}_+)$, then

$$\begin{aligned}
&A_{21}(\varphi,a)\leq 1;\ A_{31}(\varphi,a)\leq\int_0^a\frac{l(a)\Gamma_2(a)}{l(s)\Gamma_2(s)}r(s)\phi(s)ds:=\tilde{A}_{31}(a);\\
&u_1(\varphi,a)\leq\int_0^a\frac{l(a)}{l(s)}\Lambda(s)ds;\ u_2(\varphi,a)\leq a||\Lambda||_\infty \text{ and}\\
&u_3(\varphi,a)\leq||\Lambda||_\infty\tilde{A}_{31}(a)+\sup_{s\in[0,a]}\gamma(s)||\varphi||_{L^1}.
\end{aligned}$$

Since $\frac{\Delta_1(\varphi)}{\Delta(\varphi)}=\varphi_1(0)$; $\frac{\Delta_2(\varphi)}{\Delta(\varphi)}=\varphi_2(0)$ and the flow of system (5.1)-(5.2) is bounded (Theorem 5.1.1), we can find $M_\Omega>0$ such that $|\varphi_1(0)|\leq M_\Omega$ and $|\varphi_2(0)|\leq M_\Omega$. Therefore, $||H(\varphi)||_{L^1}\leq M$; with

$$M=||\beta||_\infty\int_0^{a^+}\left[M_\Omega(1+A_{22}(s)+(\tilde{A}_{31}(s)+A_{32}(s))+\sup_{s\in[0,a]}\gamma(s))+||\Lambda||_\infty(\tilde{A}_{31}(s)+s)\right]ds.$$

Setting $D=\overline{B_+(0,M)}$ with $\overline{B_+(0,M)}:=\{\varphi\in L^1(0,a^+,\mathbb{R}_+):||\varphi||_{L^1}\leq M\}$. Hence $H(D)\subset D$. This end the proof of item (i).

(ii) We find that

$$H_0(\psi)(a) = \int_0^{a^+} \beta(a,s)\left[\frac{\Delta_1(0)}{\Delta(0)}(DA_{21}(0,s)(\psi) + DA_{31}(0,s)(\psi)) + Du_2(0,s)(\psi)\right.$$
$$\left.+Du_3(0,s)(\psi) + \frac{D\Delta_2(0)(\psi)}{\Delta(0)}(A_{22}(s) + A_{32}(s))\right] ds.$$

where Du denotes the derivative of the function u and

$$Du_2(0,a)(\psi) = \int_0^a \chi_2(a,s)\psi(s)ds; \quad Du_3(0,a)(\psi) = \int_0^a \chi_3(a,s)\psi(s)ds;$$
$$DA_{21}(0,a)(\psi) = \int_0^a \chi_{21}(a,s)\psi(s)ds; \quad DA_{31}(0,a)(\psi) = \int_0^a \chi_{31}(a,s)\psi(s)ds;$$
$$D\Delta_2(0)(\psi) = p\int_0^{a^+} \chi_4(a)\psi(a)da.$$

with

$$\chi_{21}(a,s) = \frac{l(a)\Gamma_1(a)}{l(s)\Gamma_1(s)}\exp\left(-\int_s^a r(\sigma)\phi(\sigma)d\sigma\right) l(s)$$
$$\chi_{31}(a,s) = \int_s^a \frac{l(a)\Gamma_2(a)}{l(\eta)\Gamma_2(\eta)} r(\eta)\phi(\eta)\chi_{21}(\eta,s)d\eta$$
$$\chi_2(a,s) = \chi_{21}(a,s)\int_0^s \frac{\Lambda(\eta)}{l(\eta)}d\eta; \quad \chi_3(a,s) = \chi_{31}(a,s)\int_0^s \frac{\Lambda(\eta)}{l(\eta)}d\eta;$$
$$\chi_4(a) = \left[\frac{S_0(a)}{l(a)}\int_0^{a^+} f(\sigma)l(\sigma)d\sigma - S_0(0)\right]\int_a^{a^+} f(s)\left[\chi_{21}(s,a) + \chi_{31}(s,a)\right] ds.$$

Hence, operator H_0 read as a kernel operator:

$$H_0(\psi)(a) = \int_0^{a^+} \chi(a,s)\psi(s)ds; \tag{5.22}$$

where the kernel $\chi(a,s)$ is defined by

$$\begin{aligned}\chi(a,s) &= \frac{S_0(s)}{l(s)}\int_s^{a^+} \beta(a,\eta)\left(\chi_{21}(\eta,s) + \chi_{31}(\eta,s)\right) d\eta \\ &\quad +\frac{p\chi_4(s)}{\Delta(0)}\int_0^{a^+} \beta(a,\sigma)(A_{22}(\sigma) + A_{32}(\sigma))d\sigma.\end{aligned} \tag{5.23}$$

The positivity of H_0 is obvious. Let us show the compactness of the operator H_0 on Assumption 5.1.2. Let $\psi \in L^1$ and $\epsilon > 0$. From Assumption 5.1.2; there exists $\rho = \rho(\epsilon) > 0$ such that, for $|h| < \rho$ we have $\int_0^{a^+} |\beta(a+h,\xi) - \beta(a,\xi)|da < \epsilon$. Is therefore $h \in \mathbb{R}$ such that $|h| < \rho$. $||\tau_h H_0(\psi) - H_0(\psi)||_{L^1} = \int_0^{a^+} |H_0(\psi)(a+h) - H_0(\psi)(a)|da$. It is easily checked that

$$|H_0(\psi)(a+h) - H_0(\psi)(a)| \leq ||\psi||_{L^1}\int_0^{a^+} |\beta(a+h,s) - \beta(a,s)|C_1(s)ds;$$

where

$$\begin{aligned} C_1(a) &= \left(||\Lambda||_\infty + \frac{\Delta_1(0)}{\Delta(0)}\right)\left(1 + \int_0^a \frac{l(a)\Gamma_2(a)}{l(s)\Gamma_2(s)} r(s)\phi(s)ds\right) \\ &\quad + \frac{||\Lambda||_\infty}{\Delta(0)}(A_{22}(a) + A_{32}(a)) \int_0^{a^+} f(a)\left(1 + \int_0^a \frac{l(a)\Gamma_2(a)}{l(s)\Gamma_2(s)} r(s)\phi(s)ds\right) da. \end{aligned}$$

Since $\left(|h| < \rho \Longrightarrow \int_0^{a^+} |\beta(a+h,s) - \beta(a,s)|da < \epsilon\right)$, it comes that

$$||\tau_h H_0(\psi) - H_0(\psi)||_{L^1} \leq \epsilon \left(\int_0^{a^+} C_1(a)da\right) ||\psi||_{L^1}.$$

Let $\mathbb{B}$ a bounded subset of L^1 such that $\psi \in \mathbb{B}$. Then

$$||\tau_h H_0(\psi) - H_0(\psi)||_{L^1} \leq \epsilon \left(\int_0^{a^+} C_1(a)da\right) \times \sup_{\varphi \in \mathbb{B}} \{||\varphi||_{L^1}\}.$$

Applying the Riesz-Fréchet-Kolmogorov theorem on $H_0(\mathbb{B})$ we conclude that $H_0(\mathbb{B})$ is relatively compact. From where H_0 si a compact operator.

Now, let us check that H_0 is a nonsupporting operator. We define the operator $F_0 \in (L^1(0, a^+, \mathbb{R}_+))^*$ (dual space of $L^1(0, a^+, \mathbb{R}_+)$) by

$$\langle F_0; \psi \rangle = \int_0^{a^+} \varepsilon(s)[Du_2(0,s)(\psi) + \delta(s)Du_3(0,s)]ds;$$

where ε is the positive function given by Assumption 5.1.2 and $\langle F_0; \psi \rangle$ is the value of $F_0 \in (L^1(0, a^+, \mathbb{R}_+))^*$ at $\psi \in L^1(0, a^+, \mathbb{R}_+)$. Then for $\psi \in L^1(0, a^+, \mathbb{R}_+)$ we have $H_0(\psi) \geq \langle F_0; \psi \rangle \cdot e$ (with $e = 1 \in L^1(0, a^+, \mathbb{R}_+)$). From where $H_0^{n+1}(\psi) \geq \langle F_0; \psi \rangle \langle F_0; e \rangle^n \cdot e \ \ \forall n \in \mathbb{N}$. Hence for all $n \in \mathbb{N}^*$; $F \in (L^1(0, a^+, \mathbb{R}_+))^* \setminus \{0\}$ and $\psi \in L^1(0, a^+, \mathbb{R}_+) \setminus \{0\}$ we have $\langle F; H_0^n(\psi) \rangle > 0$. Therefore, H_0 is a nonsupporting operator. □

The main results of this section reads as

Theorem 5.1.2. *Let Assumption 5.1.2 be satisfied. Let us note $R_0 = \rho(H_0)$ the spectral radius of operator H_0.*

1. *If $R_0 \leq 1$, system (5.1)-(5.2) has a unique DFE defined by* (5.6)*;*
2. *If $R_0 > 1$, in addition to the DFE, system (5.1)-(5.2) has at least one endemic equilibrium.*

Proof. The operator H always has $\lambda \equiv 0$ as fixed point. This corresponds to the permanent DFE for system (5.1)-(5.2). For the rest, we are looking for the positive fixed

point to the operator H. From Lemma 5.1.3 we know that there exists a closed, bounded and convex subset D of $L^1(0, a^+, \mathbb{R}_+)$ which is invariant by the operator H. Moreover, from Lemma 5.1.3, H has a Fréchet derivative H_0 at the point 0 and $H_0 = DH(0)$ is a compact and nonsupporting operator. Therefore, there exists a unique positive eigenvector ψ_0 corresponding to the eigenvalue $R_0 = \rho(H_0)$ of H_0. Using the same arguments as for the Krasnoselskii fixe point theorem [126], it comes that if $R_0 = \rho(H_0) > 1$, then the operator H has at least one positive fixed point $\lambda^* \in L^1(0, a^+, \mathbb{R}_+) \setminus \{0\}$, corresponding to the EE of system (5.1)-(5.2).

Let us suppose that $R_0 = \rho(H_0) \leq 1$. If the operator H has a positive fixe point $\lambda^* \in L^1(0, a^+, \mathbb{R}_+) \setminus \{0\}$ then $\lambda^* = H(\lambda^*)$. Let us notice that $H - H_0 \in L^1(0, a^+, \mathbb{R}_+) \setminus \{0\}$; hence $\lambda^* \leq H_0(\lambda^*)$. Let $F_0 \in (L^1(0, a^+, \mathbb{R}_+))^* \setminus \{0\}$ be the positive eigenfunctional corresponding to the eigenvalue $R_0 = \rho(H_0)$ of H_0 (Sawashima [190]). Therefore

$$\begin{aligned} 0 \leq \langle F_0; H_0(\lambda^*) - \lambda^* \rangle &= \langle F_0, ; H_0(\lambda^*) \rangle - \langle F_0; \lambda^* \rangle ; \\ &= \rho(H_0) \langle F_0; \lambda^* \rangle - \langle F_0; \lambda^* \rangle ; \\ &= (\rho(H_0) - 1) \langle F_0; \lambda^* \rangle . \end{aligned}$$

From where $(\rho(H_0) - 1) \langle F_0; \lambda^* \rangle \geq 0$. Since $\langle F_0; \lambda^* \rangle > 0$, it follows that $\rho(H_0) \geq 1$; which is a contradiction. □

5.1.6 Stability analysis for equilibrium

In order to investigate the local stability of the equilibrium solutions $(S^*(a); I^*(a); L^*(a))$ we rewrite (5.1)-(5.2) into the equation for small perturbations. Let

$$(S(t,a), I(t,a), L(t,a)) = (S^*(a), I^*(a), L^*(a)) + (x(t,a), y(t,a), z(t,a)).$$

Then from system (5.1) we have

$$\begin{aligned} \left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) x(t,a) &= -\lambda(t,a)(S^*(a) + x(t,a)) \\ &\quad -(\mu(a) + \lambda^*(a))x(t,a); \qquad (5.24) \\ \left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) y(t,a) &= \lambda(t,a)(x(t,a) + S^*(a)) + \lambda^*(a)x(t,a) \\ &\quad -(\mu(a) + d_1(a) + r(a)\phi(a))y(t,a); \qquad (5.25) \\ \left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) z(t,a) &= r(a)\phi(a)y(t,a) - (\mu(a) + d_2(a))z(t,a); \qquad (5.26) \end{aligned}$$

and from (5.2) we also have

$$\begin{cases} x(t,0) &= \int_0^{a^+} f(a)[x(t,a)+(1-p)(y(t,a)+z(t,a))]da; \\ y(t,0) &= p\int_0^{a^+} f(a)(y(t,a)+z(t,a))da; \\ z(t,0) &= 0; \end{cases} \tag{5.27}$$

with $\lambda(a,t)=\displaystyle\int_0^{a^+}\beta(a,s)(y(t,s)+z(t,s))ds$ and $\lambda^*(a)=\displaystyle\int_0^{a^+}\beta(a,s)(I^*(s)+L^*(s))ds$. Let us note $u(t)=(x(t),y(t),z(t))^T$. Then from equations (5.24), (5.25) and (5.26) we have

$$\frac{d}{dt}u(t) = Au(t)+G(u(t)); \tag{5.28}$$

where A is the operator defined by (5.3). The nonlinear term G is defined by

$$G(u)=\begin{pmatrix} -\mathcal{P}(u_2,u_3)(u_1+S^*)-(\lambda^*+\mu)u_1 \\ \mathcal{P}(u_2,u_3)(u_1+S^*)+\lambda^*u_1-(\mu+d_1+r\phi)u_2 \\ r\phi u_2-(\mu+d_2)u_3 \end{pmatrix};$$

and $\mathcal{P}$ is linear operator defined on $L^1\times L^1$ by

$$\mathcal{P}(u_2,u_3)(a)=\int_0^{a^+}\beta(a,s)(u_2(s)+u_3(s))ds. \tag{5.29}$$

The linearized equation of (5.28) around $u=0$ is given by

$$\frac{d}{dt}u(t) = (A+C)u(t); \tag{5.30}$$

where the linear operator C is the Fréchet derivative of $G(u)$ at $u=0$ and it is given by

$$C(u) = \begin{pmatrix} -\mathcal{P}(u_2,u_3)S^*-(\lambda^*+\mu)u_1 \\ \mathcal{P}(u_2,u_3)S^*+\lambda^*u_1-(\mu+d_1+r\phi)u_2 \\ r\phi u_2-(\mu+d_2)u_3 \end{pmatrix}$$

Now let us consider the resolvent equation for $\widehat{A}+C$:

$$(z-(A+C))\psi = \vartheta;\ \ \psi\in D(A),\ \ \vartheta\in X,\ \ z\in\mathbb{C}. \tag{5.31}$$

Applying the variation of constant formula to (5.79) we obtain the following equations:

$$\psi_1(a) = \Pi(a)l(a)e^{-za}\left[\psi_1(0)+\int_0^a(T_{11}(s)\vartheta_1(s)-T_{12}(s)\mathcal{P}(\psi_1,\psi_2)(s))ds\right]; \tag{5.32}$$

$$\psi_2(a) = \left[\psi_2(0)+\int_0^a\frac{e^{zs}}{\Gamma_1(s)l(s)}(\vartheta_2(s)+\lambda^*(s)\psi_1(s)+\mathcal{P}(\psi_1,\psi_2)(s)S^*(s))ds\right] \times\Gamma_1(a)l(a)e^{-za}; \tag{5.33}$$

$$\psi_3(a) = \Gamma_2(a)l(a)e^{-za}\left[\psi_3(0)+\int_0^a\frac{e^{zs}}{\Gamma_2(s)l(s)}(\vartheta_3(s)+r(s)\phi(s)\psi_2(s))ds\right]. \tag{5.34}$$

with $\Pi(a) = \exp\left(-\int_0^a \lambda^*(\sigma)d\sigma\right)$; $T_{11}(s) = \dfrac{e^{zs}}{\Pi(s)l(s)}$ and $T_{12}(s) = S^*(s)T_{11}(s)$.
Equations (5.32)-(5.33) and (5.35)-(5.34) respectively gives

$$\begin{aligned}\psi_2(a) &= \Gamma_1(a)l(a)e^{-za}\left[\psi_2(0) + T_{21}(a)\psi_1(0) + \int_0^a T_{23}(z,a,s)\mathcal{P}(\psi_1,\psi_2)(s))ds\right.\\ &\left. + \int_0^a T_{24}(z,a,s)\vartheta_1(s)ds + \int_0^a T_{25}(z,s)\vartheta_2(s)ds\right] \qquad (5.35)\end{aligned}$$

and

$$\begin{aligned}\psi_3(a) = \Gamma_2(a)l(a)e^{-za}&\left[T_{32}(a)\psi_2(0) + T_{31}(a)\psi_1(0) + \psi_3(0) + \int_0^a T_{33}(z,a,s)\mathcal{P}(\psi_1,\psi_2)(s))ds\right.\\ &\left. + \int_0^a T_{34}(z,a,s)\vartheta_1(s)ds + \int_0^a T_{35}(z,a,s)\vartheta_2(s)ds + \int_0^a T_{36}(z,a,s)\vartheta_3(s)ds\right]; \qquad (5.36)\end{aligned}$$

where

$$T_{21}(a) = \int_0^a \frac{\Pi(s)}{\Gamma_1(s)}\lambda^*(s)ds;\ \ T_{24}(z,a,s) = \frac{e^{zs}}{l(s)\Pi(s)}\int_s^a \frac{\Pi(\sigma)}{\Gamma_1(\sigma)}\lambda^*(\sigma)d\sigma,$$

$$T_{23}(z,a,s) = \frac{e^{zs}}{l(s)}S^*(s)\left(\frac{1}{\Gamma_1(s)} - \frac{1}{\Pi(s)}\int_s^a \frac{\Pi(\sigma)}{\Gamma_1(\sigma)}\lambda^*(\sigma)d\sigma\right),$$

$$T_{25}(z,s) = \frac{e^{zs}}{l(s)\Gamma_1(s)},\ \ T_{31}(a) = \int_0^a \frac{\Gamma_1(s)}{\Gamma_2(s)}r(s)\phi(s)T_{21}(s)ds,$$

$$T_{32}(a) = \int_0^a \frac{\Gamma_1(s)}{\Gamma_2(s)}r(s)\phi(s)ds,\ \ T_{36}(z,a) = \frac{e^{za}}{\Gamma_2(a)l(a)},$$

$$T_{33}(z,a,s) = \int_s^a \frac{\Gamma_1(\sigma)}{\Gamma_2(\sigma)}r(\sigma)\phi(\sigma)T_{23}(z,\sigma,s)d\sigma,$$

$$T_{34}(z,a,s) = \int_s^a \frac{\Gamma_1(\sigma)}{\Gamma_2(\sigma)}r(\sigma)\phi(\sigma)T_{24}(z,\sigma,s)d\sigma,$$

$$T_{35}(z,a,s) = T_{25}(z,s)\int_s^a \frac{\Gamma_1(\sigma)}{\Gamma_2(\sigma)}r(\sigma)\phi(\sigma)d\sigma.$$

Since $\psi \in D(A)$; it comes that

$$\psi_1(0) = \int_0^{a^+} f(a)[\psi_1(a) + (1-p)(\psi_2(a) + \psi_3(a))]da; \qquad (5.37)$$

$$\psi_2(0) = p\int_0^{a^+} f(a)(\psi_2(a) + \psi_3(a))da; \qquad (5.38)$$

$$\psi_3(0) = 0. \qquad (5.39)$$

Equations (5.36)-(5.39); (5.32)-(5.35)-(5.40)-(5.37) and (5.35)-(5.40)-(5.38) respectively lead to

$$\psi_3(a) = \Gamma_2(a)l(a)e^{-za}\left[T_{32}(a)\psi_2(0) + T_{31}(a)\psi_1(0) + + \int_0^a T_{33}(z,a,s)\mathcal{P}(\psi_1,\psi_2)(s))ds \right.$$
$$\left. + \int_0^a T_{34}(z,a,s)\vartheta_1(s)ds + \int_0^a T_{35}(z,a,s)\vartheta_2(s)ds + \int_0^a T_{36}(z,s)\vartheta_3(s)ds\right]; \tag{5.40}$$

$$(B_{11}(z)-1)\psi_1(0) + (1-p)B_{12}(z)\psi_2(0) + \int_0^{a^+} B_{13}(z,a)\mathcal{P}(\psi_1,\psi_2)(a)da$$
$$+ \int_0^{a^+} B_{14}(z,a)\vartheta_1(a)da + \int_0^{a^+} B_{15}(z,a)\vartheta_2(a)da + \int_0^{a^+} B_{16}(z,a)\vartheta_3(a)da = 0; \tag{5.41}$$

and

$$pB_{21}(z)\psi_1(0) + (pB_{22}(z)-1)\psi_2(0) + p\int_0^{a^+} B_{23}(z,a)\mathcal{P}(\psi_1,\psi_2)(a)da$$
$$+ p\int_0^{a^+} B_{24}(z,a)\vartheta_1(a)da + p\int_0^{a^+} B_{25}(z,a)\vartheta_2(a)da + p\int_0^{a^+} B_{26}(z,a)\vartheta_3(a)da = 0; \tag{5.42}$$

with

$$B_{11}(z) = \int_0^{a^+} f(a)l(a)e^{-za}\left[\Pi(a) + (1-p)(\Gamma_1(a)T_{21}(a) + \Gamma_2(a)T_{31}(a)\right]da;$$

$$B_{12}(z) = \int_0^{a^+} f(a)l(a)e^{-za}\left[\Gamma_1(a) + \Gamma_2(a)T_{32}(a)\right]da;$$

$$B_{13}(z,a) = \int_a^{a^+} f(s)l(s)e^{-zs}\left[-T_{12}(a)\Pi(s) + (1-p)(\Gamma_1(s)T_{23}(z,s,a) + \Gamma_2(s)T_{33}(z,s,a))\right]ds;$$

$$B_{14}(z,a) = \int_a^{a^+} f(s)l(s)e^{-zs}\left[T_{11}(a)\Pi(s) + (1-p)(\Gamma_1(s)T_{24}(z,s,a) + \Gamma_2(s)T_{34}(z,s,a))\right]ds;$$

$$B_{15}(z,a) = \int_a^{a^+} f(s)l(s)e^{-zs}\left[\Gamma_1(s)T_{25}(z,a) + (1-p)\Gamma_2(s)T_{35}(z,s,a)\right]ds;$$

$$B_{16}(z,a) = (1-p)\int_a^{a^+} f(s)l(s)e^{-zs}\Gamma_2(s)T_{36}(z,s)ds;$$

$$B_{21}(z) = \int_0^{a^+} f(a)l(a)e^{-za}[\Gamma_1(a)T_{21}(a) + \Gamma_2(a)T_{31}(a)]da;$$

$$B_{22}(z) = \int_0^{a^+} f(a)l(a)e^{-za}[\Gamma_1(a) + \Gamma_2(a)T_{32}(a)]da;$$

$$B_{23}(z,a) = \int_a^{a^+} f(s)l(s)e^{-zs}[\Gamma_1(s)T_{23}(z,s,a) + \Gamma_2(s)T_{33}(z,s,a)]ds;$$

$$B_{24}(z,a)=\int_a^{a^+} f(s)l(s)e^{-zs}[\Gamma_1(s)T_{24}(z,s,a)+\Gamma_2(s)T_{34}(z,s,a)]ds;$$

$$B_{25}(z,a)=T_{25}(z,a)\int_a^{a^+} f(s)l(s)e^{-zs}[\Gamma_1(s)T_{25}(z,a)+\Gamma_2(s)T_{35}(z,s,a)]ds;$$

$$B_{26}(z,a)=T_{36}(z,a)\int_a^{a^+} f(s)l(s)\Gamma_2(s)e^{-zs}ds.$$

System (5.41)-(5.42) is a linear system with respect to $\psi_1(0)$ and $\psi_2(0)$, hence

$$\begin{aligned}\psi_1(0) &= \int_0^{a^+} det_{11}(z,a)\mathcal{P}(\psi_1,\psi_2)(a)da+\int_0^{a^+} det_{12}(z,a)\vartheta_1(a)da+\\ &+\int_0^{a^+} det_{13}(z,a)\vartheta_2(a)da+\int_0^{a^+} det_{14}(z,a)\vartheta_3(a)da; \qquad (5.43)\\ \psi_2(0) &= \int_0^{a^+} det_{21}(z,a)\mathcal{P}(\psi_1,\psi_2)(a)da+\int_0^{a^+} det_{22}(z,a)\vartheta_1(a)da\\ &+\int_0^{a^+} det_{23}(z,a)\vartheta_2(a)da+\int_0^{a^+} det_{24}(z,a)\vartheta_3(a)da; \qquad (5.44)\end{aligned}$$

where

$$\begin{aligned}det_{11}(z,a)&=\frac{-1}{det}\left[(pB_{22}(z)-1)B_{13}(z,a)-p(1-p)B_{12}(z)B_{23}(z,a)\right];\\ det_{12}(z,a)&=\frac{-1}{det}\left[(pB_{22}(z)-1)B_{14}(z,a)-p(1-p)B_{12}(z)B_{24}(z,a)\right];\\ det_{13}(z,a)&=\frac{-1}{det}\left[(pB_{22}(z)-1)B_{15}(z,a)-p(1-p)B_{12}(z)B_{25}(z,a)\right];\\ det_{14}(z,a)&=\frac{-1}{det}\left[(pB_{22}(z)-1)B_{16}(z,a)-p(1-p)B_{12}(z)B_{26}(z,a)\right];\\ det_{21}(z,a)&=\frac{p}{det}\left[(B_{21}(z)B_{13}(z,a)-(B_{11}(z)-1)B_{23}(z,a)\right];\\ det_{22}(z,a)&=\frac{p}{det}\left[(B_{21}(z)B_{14}(z,a)-(B_{11}(z)-1)B_{24}(z,a)\right];\\ det_{23}(z,a)&=\frac{p}{det}\left[(B_{21}(z)B_{15}(z,a)-(B_{11}(z)-1)B_{25}(z,a)\right];\\ det_{24}(z,a)&=\frac{p}{det}\left[(B_{21}(z)B_{16}(z,a)-(B_{11}(z)-1)B_{26}(z,a)\right];\\ det&=(B_{11}(z)-1)(pB_{22}(z)-1)-p(1-p)B_{21}(z)B_{12}(z).\end{aligned}$$

From equations (5.29)-(5.35)-(5.40)-(5.43)-(5.44) it follows that

$$\mathcal{P}(\psi_2,\psi_3)(\eta)=(I-V_z)^{-1}\left[(U_z\vartheta_1)(\eta)+(W_z\vartheta_2)(\eta)+(Y_z\vartheta_3)(\eta)\right]; \qquad (5.45)$$

where V_z, U_z, W_z and Y_z are the Volterra operator define on $L^1(0,a^+,\mathbb{R})$ into itself by

$$\begin{aligned}(U_z\varphi)(a)&=\int_0^{a^+}\Theta_z(\eta,a)\varphi(a)da;\ \ (V_z\varphi)(a)=\int_0^{a^+}\chi_z(\eta,a)\varphi(a)da;\\ (Y_z\varphi)(a)&=\int_0^{a^+}E_z(\eta,a)\varphi(a)da;\ \ (W_z\varphi)(a)=\int_0^{a^+}K_z(\eta,a)\varphi(a)da;\end{aligned} \qquad (5.46)$$

where

$$\begin{aligned}
\chi_z(\eta,a) &= C_1^{te}(\eta)det_{11}(z,a) + C_2^{te}(\eta)det_{21}(z,a)\\
&+ \int_a^{a^+} \beta(\eta,s)l(s)e^{-zs}[\Gamma_1(s)T_{23}(z,s,a) + \Gamma_2(s)T_{33}(z,s,a)]ds;\\
\Theta_z(\eta,a) &= C_1^{te}(\eta)det_{12}(z,a) + C_2^{te}(\eta)det_{22}(z,a)\\
&+ \int_a^{a^+} \beta(\eta,s)l(s)e^{-zs}[\Gamma_1(s)T_{24}(z,s,a) + \Gamma_2(s)T_{34}(z,s,a)]ds;\\
K_z(\eta,a) &= C_1^{te}(\eta)det_{13}(z,a) + C_2^{te}(\eta)det_{23}(z,a)\\
&+ \int_a^{a^+} \beta(\eta,s)l(s)e^{-zs}[\Gamma_1(s)T_{25}(z,s,a) + \Gamma_2(s)T_{35}(z,s,a)]ds;
\end{aligned} \tag{5.47}$$

$$E_z(\eta,a) = C_1^{te}(\eta)det_{14}(z,a) + C_2^{te}(\eta)det_{24}(z,a) + \int_a^{a^+} \beta(\eta,s)l(s)e^{-zs}\Gamma_2(s)T_{36}(z,s,a)ds;$$

and

$$\begin{aligned}
C_1^{te}(\eta) &= \int_0^{a^+} \beta(\eta,a)l(a)e^{-za}[\Gamma_1(a)T_{21}(a) + \Gamma_2(a)T_{31}(a)]da;\\
C_2^{te}(\eta) &= \int_0^{a^+} \beta(\eta,a)l(a)e^{-za}[\Gamma_1(a) + \Gamma_2(a)T_{32}(a)]da;
\end{aligned}$$

Let us recall some definitions related to a C_0-semi-group $\{T(t)\}_{t\geqslant 0}$ on a Banach space with infinitesimal generator R. The *type* or the *growth bound* of the semi-group $\{T(t)\}_{t\geqslant 0}$ is the quantity:

$$\begin{aligned}
&\omega_0(R) :=\\
&\inf\{\alpha\in\mathbb{R}:\ \exists M\geq 1 \text{ such that } ||T(t)||\leq Me^{\alpha t}\ \forall t\geq 0\}\\
&= \lim_{t\to 0}\frac{\ln||T(t)||}{t}.
\end{aligned}$$

The *spectral bound* of the C_0-semi-group $\{T(t)\}_{t\geqslant 0}$ is the quantity:

$$s(R) \ := \ \sup\{R_e\lambda:\ \lambda\in\sigma_p(R)\},$$

where $\sigma_p(R)$ denote the point spectrum of R.

Wow, we conclude that

Lemma 5.1.4. *Recalling Assumptions 5.1.1 and 5.1.2. Then*

1. *The perturbated operator $A+C$ has a compact resolvent and*

$$\sigma(A+C)=\sigma_p(A+C)=\{z\in\mathbb{C}:\ 1\in\sigma_p(V_z)\};$$

where $\sigma(A)$ and $\sigma_p(A)$ denote the spectrum of A and the point spectrum of A respectively.

2. *Let $\{U(t)\}_{t\geq 0}$ be the C_0-semigroup generated by $A+C$. Then $\{U(t)\}$, $t\geq 0$ is eventually compact and*

$$\omega_0(A+C)=s(A+C).$$

Proof. 1) From equations (5.32), (5.43) and (5.46) we find that

$$\psi_1(a) \ = \ \Pi(a)l(a)e^{-za}\psi_1(0)+J_1(\vartheta_1)(a)+K_1(\vartheta_1,\vartheta_2)(a);$$

with

$$\begin{aligned} J_1(\vartheta_1)(a) &= \int_0^a \Pi(a)l(a)T_{11}(s)e^{-zs}\vartheta_1(s)ds;\\ K_1(\vartheta_1,\vartheta_2)(a) &= \int_0^a \Pi(a)l(a)T_{11}(s)S^*(s)e^{-zs}(I-V_z)^{-1}\\ &\quad [(U_z\vartheta_1)(s)+(W_z\vartheta_2)(s)+(Y_z\vartheta_3)(s)]ds. \end{aligned}$$

ψ_1 is a compact operator if and only if J_1 and K_1 are compact. Since J_1 is a Volterra operator with continue kernel, we deduce that J_1 is a compact operator on L^1. Using the same arguments as for the proof of the compactness of operator H_0 (Lemma 5.1.3), we can show that the operators U_z, W_z and Y_z are compact for all $z\in\mathbb{C}$. Let us set $\Sigma:=\{z\in\mathbb{C}:\ 1\in\sigma_p(V_z)\}$. Hence, if $z\in\mathbb{C}\setminus\Sigma$ then, K_1 is a compact operator from $L^1\times L^1$ to L^1. In the same way, we can show that $\psi_2(a)$ and $\psi_3(a)$ are represent by a compact operators. Therefore, the resolvent of $A+C$ is compact. From where $\sigma(A+C)=\sigma_p(A+C)$ (see Kato, p.187 [122]) i.e. $\mathbb{C}\setminus\Sigma\subset\rho(A+C)$ and $\rho(A+C)$ denotes the resolvent of $A+C$. In other words $\Sigma\supset\sigma(A+C)=\sigma_p(A+C)$. Since V_z is a compact operator, we know that $\sigma(V_z)\setminus\{0\}=\sigma_p(V_z)\setminus\{0\}$. If $z\in\Sigma$, then it exists $\psi_z\in L^1\setminus\{0\}$ such that $V_z\psi_z=\psi_z$. Let us set

$$\phi_1(a)=\Pi(a)l(a)e^{-za}\left[\int_0^{a^+} det_{11}(z,a)\psi_z(a)da-\int_0^a\frac{e^{za}}{\Pi(s)l(s)}\psi_z(s)ds\right];$$

$$\phi_2(a)=\Pi(a)l(a)e^{-za}\left[\int_0^{a^+} det_{21}(z,a)\psi_z(a)da-\int_0^a\frac{e^{za}}{\Gamma_1(s)l(s)}(\lambda^*(s)\phi_1(s)+S^*(s)\psi_z(s))ds\right];$$

$$\phi_3(a)=\Gamma_2(a)l(a)e^{-za}\int_0^a\frac{e^{za}}{\Gamma_2(s)l(s)}r(s)\phi(s)\psi_2(s)ds.$$

Then $(\phi_1, \phi_2, \phi_3)^T$ is an eigenvector of $A + C$ associated to the eigenvalue z. Hence, $z \in \sigma(A+C) = \sigma_p(A+C)$ i.e. $\Sigma \subset \sigma(A+C) = \sigma_p(A+C)$. This end the proof of item 1.

2) For $\psi \in X$, let us set

$$\begin{aligned} C_1\psi &= (-P(\psi_2,\psi_3)S^*, \mathcal{P}(\psi_2,\psi_3)S^*, 0)^T; \\ C_2\psi &= (-(\lambda^*+\mu)\psi_1, \lambda^*\psi_1 - (\mu+d_1+r\phi)\psi_2 r\phi\psi_2 - (\mu+d_2)\psi_3)^T; . \end{aligned}$$

Then $C = C_1 + C_2$. The operator $A+C_2$ generated a nilpotent C_0-semigroup $\{S_2(t)\}_{t\geq 0}$, from where $\{S_2(t)\}_{t\geq 0}$ is norm continuous. Using Assumptions 5.1.1 and 5.1.2, we find that C_1 is compact operator on X. From Theorem 1.30 of Nagel(1986) [168] it comes that C_1 is generator of a norm continuous C_0-semigroup $\{S_1(t)\}_{t\geq 0}$. Therefore, $S_1(t) + S_2(t)$ is a C_0-semigroup generated by $A+C$ and it is norm continuous (Spectral theorem P.87 Nagel [168]). □

Let us remark that if $\omega_0(A+C) < 0$, the equilibrium $u = 0$ of system (5.28) is locally asymptotically stable (linearized stability, Webb 1985[211]). Therefore, to study the stability of equilibrium states, we have to know the structure of the set $\Sigma := \{z \in \mathbb{C} : 1 \in \sigma_p(V_z)\}$. Since $||V_z||_{L^1} \to 0$ if $z \to +\infty$, $I - V_z$ is inversible for the large values of $R_e z$.

By theorem of Steinberg(1968)[197], the function $z \rightarrowtail (I - V_z)^{-1}$ is meromorphic in the complex domain, and hence the set Σ is a discrete set whose elements are poles of $(I - V_z)^{-1}$ of finite order.

In the following, we will use elements of positive operator theory.

For the positivity of operator V_z we make the following assumption

Assumption 5.1.3.

$$\int_0^{a^+} (d_1(\sigma) + r(\sigma)\phi(\sigma))d\sigma \leq \exp\left(-\int_0^{a^+} \lambda^*(\sigma)d\sigma\right); \tag{5.48}$$

where $\lambda^*(\sigma) = \int_0^{a^+} \beta(\sigma,\eta)(I^*(\eta) + L^*(\eta))d\eta$.

Lemma 5.1.5. *Let Assumption 5.1.3 be satisfied. Then*

1. *The operator V_z, $z \in \mathbb{R}$, is nonsupporting with respect to $L^1(0, a^+, \mathbb{R}_+)$ and*

$$\lim_{z\rightarrowtail -\infty} \rho(V_z) = +\infty \quad ; \quad \lim_{z\rightarrowtail +\infty} \rho(V_z) = 0.$$

2. There exists a unique $z_0 \in \mathbb{R} \cap \Sigma$ *such that*

$$\rho(V_{z_0}) = 1 \quad and \quad \begin{cases} z_0 > 0 \quad if \quad \rho(V_0) > 1, \\ z_0 = 0 \quad if \quad \rho(V_0) = 1, \\ z_0 < 0 \quad if \quad \rho(V_0) < 1. \end{cases}$$

3. $z_0 > \sup\{R_e z : \ z \in \Sigma \setminus \{z_0\}\}$.

Proof. 1) Let $z \in \mathbb{R}$. Unconditionally, V_z is a positive operator when $\lambda^*(a) \equiv 0$ (case of DFE). When $\lambda^*(a) > 0$, V_z is a positive operator once $\Gamma_1(s)T_{23}(z,a,s) + \Gamma_2(s)T_{33}(z,a,s) \geq 0$ for all $0 \leq a \leq s \leq a^+$. To have the previous inequality, it suffices that inequality (5.48) of Assumption 5.1.3 holds. We can checked that

$$V_z\psi \geq \langle f_z, \psi\rangle \cdot e; \tag{5.49}$$

where $\psi \in L^1(0, a^+, \mathbb{R}_+)$; $e \equiv 1 \in L^1(0, a^+, \mathbb{R}_+)$ and f_z is a positive linear functional defined by

$$< f_z, \psi > \ = \ m \int_0^{a^+} \int_a^{a^+} e^{-z(a-s)} \frac{l(s)}{l(a)} \left(\frac{1}{\Gamma_1(a)} - \frac{1}{\Pi(a)} \int_a^s \frac{\Pi(\sigma)}{\Gamma_1(\sigma)} \lambda^*(\sigma) d\sigma \right) dsda;$$

with $m = \inf_{(a,s)\in[0,a^+)^2} \beta(a,s)$. From (5.49), we show that $V_z^{n+1}\psi \geq \langle f_z, \psi\rangle \langle f_z, e\rangle^n \cdot e$ for all $n \in \mathbb{N}$. Since f_z is positive operator and $e \in L^1(0, a^+, \mathbb{R}_+)\setminus\{0\}$, we have $\langle F, V_z^n\psi\rangle > 0$ $\forall \psi \in (L^1(0, a^+, \mathbb{R}_+))^* \setminus \{0\}$ $\forall \psi \in L^1(0, a^+, \mathbb{R}_+) \setminus \{0\}$. That is V_z is nonsupporting.

Let F_z be the eigenfunctional of V_z that corresponds to the eigenvalue $\rho(V_z)$. Taking the duality pairing into inequality (5.49), we have

$$\rho(V_z) \langle F_z, \psi\rangle \ \geq \ \langle f_z, \psi\rangle \langle F_z, e\rangle .$$

Taking $\psi = e$ and since F_z is positive, it follows that $\rho(V_z) \geq \langle f_z, e\rangle \to +\infty$ when $z \to -\infty$. From where $\lim\limits_{z\mapsto-\infty} \rho(V_z) = +\infty$. since $||V_z||_{L^1} \to 0$ when $z \to +\infty$, we deduce that $\lim\limits_{z\mapsto+\infty} \rho(V_z) = 0$. This end the proof of item 1.

2) Let $h : \mathbb{R} \to \mathbb{C}$; $z \mapsto \rho(V_z)$. The kernel χ_z defined by (5.47) is strictly decreasing with respect to $z \in \mathbb{R}$. Let $z_1, z_2 \in \mathbb{R}$ such that $z_1 < z_2$, then $\chi_{z_1} < \chi_{z_2}$ that is $V_{z_1} > V_{z_2}$. Since V_{z_1} and V_{z_2} are compact and nonsupporting operators we deduce from Marek(1970) [150] that $\rho(V_{z_1}) > \rho(V_{z_2})$. Therefore, the function h is strictly decreasing. The limits of the function $h(z) = \rho(V_z)$ at $-\infty$ and $+\infty$ give that there exist a unique $z_0 \in \mathbb{R} \cap \Sigma$ such that $\rho(V_{z_0}) = 1$. If $\rho(V_0) > 1$ then $h(0) > h(z_0)$ i.e. $z_0 < 0$ (strictly

decreasing of h) and the other cases is show in the same way. This end the proof of item 2.

3)Let $z \in \Sigma$, then there exists $\psi_z \in L^1$ such that $V_z\psi_z = \psi_z$. Let $|\psi_z|$ be a function defined by $|\psi_z|(s) := |\psi_z(s)|$. The definition of V_z leads to

$$|\psi_z| = |V_z\psi_z| \leq V_{R_e z}|\psi_z|. \tag{5.50}$$

Let $F_{R_e z}$ be the positive eigenfunction associated to the eigenvalue $\rho(V_{R_e z})$ of $V_{R_e z}$. From (5.50) we deduce that $\langle F_{R_e z}, |\psi_z|\rangle \leq \langle F_{R_e z}, V_{R_e z}|\psi_z|\rangle = r(V_{R_e z})\langle F_{R_e z}, |\psi_z|\rangle$. The positivity of $F_{R_e z}$ implies that $r(V_{R_e z}) \geq 1$ that is $h(R_e z) \geq h(z_0)$ i.e. $z_0 \leq R_e z$. To end the proof, let us show that: if $z_0 = R_e z$ then $z = z_0$.
We know that $|\psi_z| \leq V_{R_e z}|\psi_z| = V_{z_0}|\psi_z|$. Let us suppose that $|\psi_z| < V_{z_0}|\psi_z|$; taking the pairing product with the dual function F_0 corresponding to the eigenvalue $\rho(V_{z_0}) = 1$, one has $\langle F_0, |\psi_z|\rangle > \langle F_0, |\psi_z|\rangle$, which is a contradiction. Hence $|\psi_z| = V_{z_0}|\psi_z|$. Therefore $|\psi_z| = c\psi_0$ where c is constant not equal to zero (Sawashima 1964 [190]) and ψ_0 is the eigenfunction corresponding to $\rho(V_{z_0}) = 1$. So $\psi_z(a) = c\psi_0(a)e^{i\alpha(a)}$ for a reel function α; moreover $|V_z\psi_z| = |\psi_z| = c\psi_0 = cV_{z_0}\psi_0$. Substituting $\psi_z(a) = c\psi_0(a)e^{i\alpha(a)}$ into the equality $|V_z\psi_z| = cV_{z_0}\psi_0$ one has

$$\begin{aligned}
&\int_0^{a^+}\int_a^{a^+} \beta(\eta,s)l(s)e^{-z_0(s-a)}[\Gamma_1(s)\tilde{T}_{23}(s,a) + \Gamma_2(s)\tilde{T}_{33}(s,a)]\psi_0(a)dsda = \\
&\left|\int_0^{a^+}\int_a^{a^+} \beta(\eta,s)l(s)e^{-(z_0+i(s-a)Imz)}[\Gamma_1(s)\tilde{T}_{23}(s,a) + \Gamma_2(s)\tilde{T}_{33}(s,a)]e^{i\alpha(a)}\psi_0(a)dsda\right|;
\end{aligned} \tag{5.51}$$

with

$$\begin{aligned}
\tilde{T}_{23}(a,s) &= \frac{S^*(s)}{l(s)}\left(\frac{1}{\Gamma_1(s)} - \frac{1}{\Pi(s)}\int_s^a \frac{\Pi(\sigma)}{\Gamma_1(\sigma)}\lambda^*(\sigma)d\sigma\right); \\
\tilde{T}_{33}(a,s) &= \int_s^a \frac{\Gamma_1(\sigma)}{\Gamma_2(\sigma)} r(\sigma)\phi(\sigma)\tilde{T}_{23}(a,\sigma)d\sigma.
\end{aligned}$$

Applying two times, Lemma 6.12 of Heijmans(1986) [97], to the relation (5.51) it comes that $(s-a)Imz + \alpha(a) = b$ for all $0 \leq a \leq s \leq a^+$ where b is a constant. From the equality $V_z\psi_z = \psi_z$ one has $e^{ib}V_{z_0}\psi_0 = \psi_0 e^{i\alpha(a)}$ i.e. $b = \alpha(a)$. From where $Imz = 0$, that is $z = z_0$. □

From the above result, we can state the threshold criterion as follows:

Proposition 5.1.2. *Recalling Assumption 5.1.3. Then equilibrium (S^*, I^*, L^*) is locally asymptotically stable if $\rho(V_0) < 1$ and unstable if $\rho(V_0) > 1$.*

Proof. From Lemma 5.1.5 (items 2. and 3.), we conclude that: $\sup\{R_e z;\ 1 \in \sigma_p(V_z)\} = z_0$. Hence $s(A+C) = \sup\{R_e z;\ 1 \in \sigma_p(V_z)\} < 0$ if $\rho(V_0) < 1$, and $s(A+C) = \sup\{R_e z;\ 1 \in \sigma_p(V_z)\} > 0$ if $\rho(V_0) > 1$. □

In the following, let us note V_0^0 the operator V_0 corresponding to the case $\lambda^*(\sigma) \equiv 0$ (DFE) and V_0^* the operator V_0 corresponding to the case $\lambda^*(\sigma) > 0$ (EE). It is easily checked that

$$\chi_0^0(a,s) \quad = \quad \chi(a,s); \tag{5.52}$$

where $\chi(a,s)$ is the kernel of the Volterra operator H_0 defined by (5.23).

Now, the main results for the local stability of our epidemic model reads as

Theorem 5.1.3. *Let Assumptions 5.1.1 and 5.1.2 be satisfied. Let $R_0 := \rho(H_0)$ be the spectral radius of the operator H_0 defined by (5.22). Then,*

1. *If $R_0 = \rho(H_0) < 1$ then, the unique equilibrium of (5.1)-(5.2) (DFE) is locally asymptotically stable.*
2. *If $R_0 = \rho(H_0) > 1$ then, the DFE is unstable.*
3. *If $R_0 = \rho(H_0) > 1$ then, in addition to the DFE system (5.1)-(5.2) has at least one endemic equilibrium (EE). Moreover, if $\rho(V_0^*) < 1$ and Assumption 5.1.3 holds, then the EE is locally asymptotically stable.*

Proof. For the DFE, one has $\lambda^*(\sigma) \equiv 0$. Hence, from (5.52) it comes that $\rho(H_0) = \rho(V_0^0) := \rho(V_0)$ (for $\lambda^* = 0$). From Prop. 5.1.2 we deduce that: if $\rho(H_0) = \rho(V_0) < 1$, the DFE is locally asymptotically stable; and unstable if $\rho(H_0) = \rho(V_0) > 1$. This end the proof of items 1. and 2.

The case of EE is a direct consequence of Prop. 5.1.2. □

Remark 5.1.1.

(♣) To emphasize the impact of vertical transmission on the spread of the disease, let us observe that the next generation operator H_0 can be rewrite as follows

$$H_0(\psi)(a) = \int_0^{a^+} \chi^{\diamondsuit}(a,s)\psi(s)ds + \int_0^{a^+} \chi_{\diamondsuit}(p,a,s)\psi(s)ds;$$

where the kernels $\chi^{\diamondsuit}(.,.)$ *and* $\chi_{\diamondsuit}(p,.,.)$ *are*

$$\begin{aligned}\chi^{\diamondsuit}(a,s) &= \frac{S_0(s)}{l(s)}\int_s^{a^+}\beta(a,\eta)\left(\chi_{21}(\eta,s)+\chi_{31}(\eta,s)\right)d\eta;\\ \chi_{\diamondsuit}(p,a,s) &= \frac{p\chi_4(s)}{\Delta(0)}\int_0^{a^+}\beta(a,\sigma)(A_{22}(\sigma)+A_{32}(\sigma))d\sigma.\end{aligned}$$

It is easy to see that when the proportion of infected newborns is zero ($p=0$)*, then the kernel* $\chi^{\diamondsuit}(0,.,.)\equiv 0$*. Therefore, the vertical transmission of the disease amplifies positively the spread of the disease.*

(♣♣) As a special case, we here briefly consider the proportionate mixing assumption, that is, the transmission rate β *can be written as* $\beta(a,s)=\beta_1(a)\beta_2(s)$ *(see Dietz and Schenzle [55]; Greenhalgh,1988 [83]). In this case, the basic reproductive number* $\mathcal{R}_0$ *is explicitly given by:*

$$R_0 := \rho(H_0) = \int_0^{a^+}\chi^{\diamondsuit}(s,s)ds + \int_0^{a^+}\chi_{\diamondsuit}(p,s,s)ds. \tag{5.53}$$

And the same conclusion follows as for item (♣). Thus the vertical transmission of the disease really has an impact on the dynamics and the spread of the disease into the host population. We also refer to Figures 5.2-5.4 for some illustrations of the state variables of system (5.1)-(5.2) when p *takes different values:* 0.02*;* 0.2 *and* 0.5*.*

5.1.7 Numerical analysis

In this section, we propose a numerical scheme for our model and gives some illustrations.

We adopt a finite differences scheme which is progressive of order 1 in time and regressive of order 1 in age. Our model has a structure of the following partial differential equation on the real axe:

$$\frac{\partial u}{\partial t}+\frac{\partial u}{\partial a}=f(t,a). \tag{5.54}$$

For equation (5.54), the numerical scheme is defined by:

$$\frac{u_i^{n+1}-u_i^n}{\Delta t}+\frac{u_i^n-u_{i-1}^n}{\Delta a}=f(t_n,a_i); \tag{5.55}$$

where i and n are the index of age and time discretization respectively; and $u_i^n := u(t_n,x_i)$.

We recall that, generally, all explicit numerical scheme is conditionally stable (Stricwerda[**?**]). To ensure the stability of the scheme (5.55) the necessary condition is the famous Courant-Friedrichs-Lewy (CFL) condition given as follow:

$$\frac{\Delta t}{\Delta a} \leqslant 1. \tag{5.56}$$

For a given age step discretization Δa, the restriction $\Delta t \leqslant \Delta a$ is necessary for the time step discretisation Δt.

We are able now to give the solution of the problem (5.1)-(5.2) on some time interval $[0, T]$ using the above numerical scheme.

The age-specific reproduction rate $f(a)$ is taken to be

$$f(a) = \begin{cases} \frac{1}{5}\sin^2\left(\frac{\pi(a-15)}{30}\right) \ if \ \ 15 \leq a \leq 45; \\ 0 \text{ if not.} \end{cases}$$

The fecundity function $f(.)$ is stated here in units of 1 / years for easier readability and assumes that from age 15 to 45 years a woman will generally give birth to three children, since $\int_0^{a^+} f(a)da = 3$, where $a^+ = 80$ is the largest age allowed for the simulation.

We also consider a low value of recruitment $\Lambda(.)$

$$\Lambda(a) = \begin{cases} \frac{1}{10}\sin^2\left(\frac{\pi(a-17)}{43}\right) \ if \ \ 17 \leq a \leq 60; \\ 0 \text{ if not.} \end{cases}$$

This recruitment assume that the total number of recruitment at time t is approximately equal two, that is $\int_0^{a^+} \Lambda(a) = 2.15$

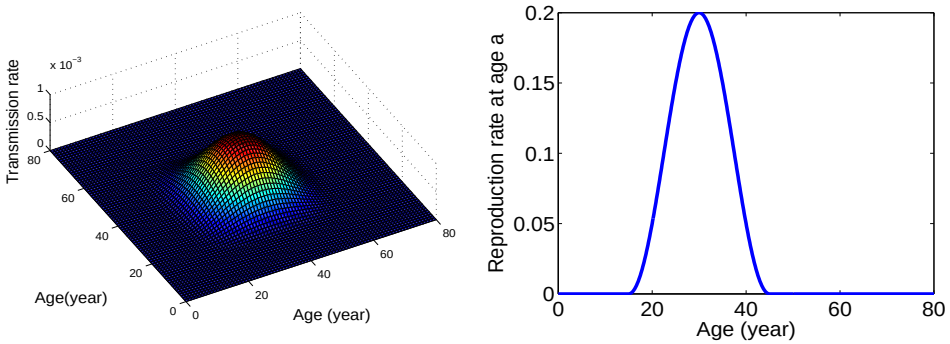
The transmission coefficient $\beta(.,.)$ is assume to be

$$\beta(a,s) = \begin{cases} \beta_0 \sin^2\left(\frac{\pi(a-14)}{46}\right)\sin^2\left(\frac{\pi(s-14)}{46}\right), \text{ if } a, s \in [14, 60]; \\ 0 \text{ if not.} \end{cases}$$

wherein the nonnegative constant β_0 (transmission constant) will be variable. Figure 5.1 illustrates the transmission coefficient β (for $\beta_0 = 10^{-3}$) and the fecundity function f. The other parameters of our system are arbitrarily chosen (see Table 5.1).

We provide numerical illustrations for different values of vertical transmission p: 0.02, 0.2 and 0.5

In Figure 5.2, the vertical transmission rate of the disease is fixed to be $p = 0.02$. We observe that infectious individuals (infected and lost of sight) are between 17 and 70 of



(a) (b)

Figure 5.1: (5.1a) Transmission coefficient $\beta(.,.)$ when the transmission constant $\beta_0 = 10^{-3}$. (5.1b) Fecundity function $f(.)$.

Table 5.1: Numerical values for the parameters of the model

Parameters	Description	Estimated value
β_0	Transmission constant	Variable
p	Vertical tranmission rate	Variable
μ	Natural death rate	0.0101/yr [1]
r	Rate of effective therapy	$1/yr$ [1]
ϕ	Rate at witch infectious become loss of sight	0.75/yr [1]
γ	Rate at witch lost of sight return to the hospital	0.02/yr [1]
d_1	Death rate of infectious	0.02/yr [1]
d_2	Death rate of lost of sight	0.2/yr [1]

Note: Source of estimates.

[1] Assumed.

age. The number of young infectious (namely infectious with age $a < 17$) is negligible, because the value of vertical transmission rate p is low.

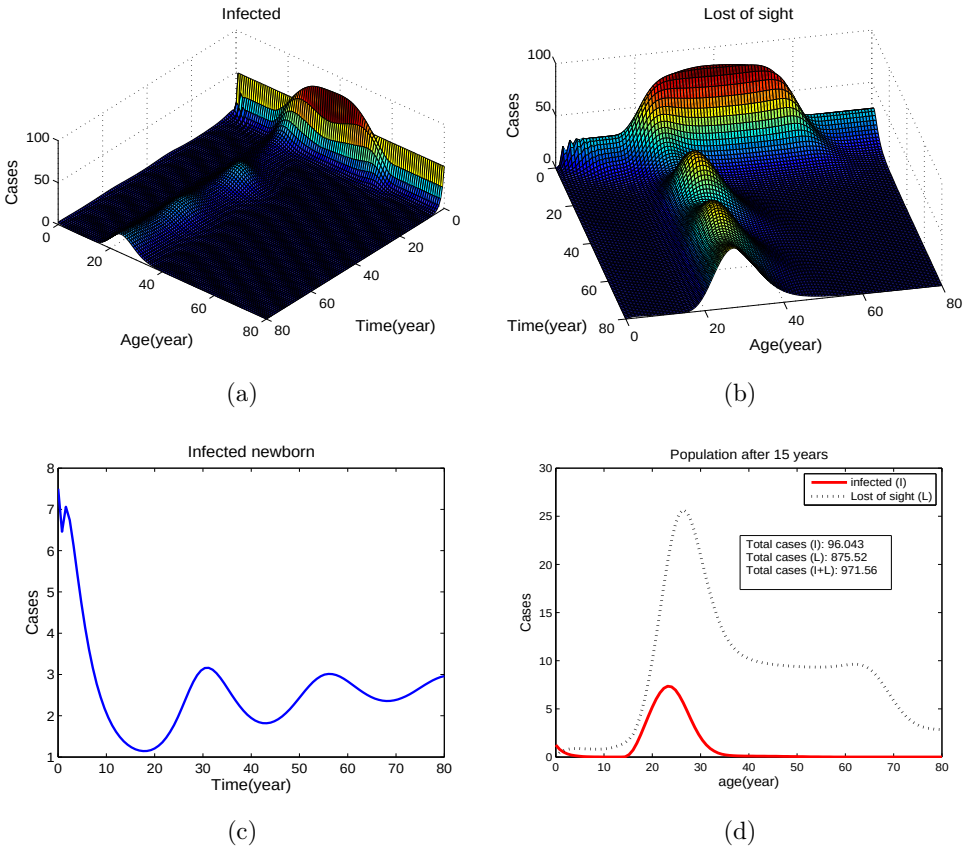
In figure 5.3, the vertical transmission rate of the disease is fixed to be $p = 0.2$. We observe that much of the infectious individuals (infected and lost of sight) are between 17 and 70 of age. Let us also observe that the number of infectious individuals with age between 17 and 70 is approximately the same than the number of infectious individuals with age between 17 and 70 when $p = 0.02$ (see Figs 5.2-5.3). But now, there are also infectious individuals with age $a < 17$ which was not the case when $p = 0.02$.

The same observation is given by Figure 5.4 where the vertical transmission rate of the disease is fixed to be $p = 0.5$. Hence Figures 5.2-5.4 emphasize that the vertical transmission of the disease really has an impact on the dynamics and the spread of the disease into the host population. See also Table 5.2 for the impact of the vertical transmission of the disease on the spread of the epidemic.

Table 5.2: Impact of the vertical transmission of the disease.

Vertical transmission rate (p)	Rate increase over the case when $p = 0$
$p = 0.02$	1.8%
$p = 0.2$	17.5%
$p = 0.5$	43.8%

Total cases (I+L) when $p = 0$: 954.85 cases. (i.e. when the vertical transmission of the disease is neglected in the host population.



(a) (b)

(c) (d)

Figure 5.2: The transmission constant and the vertical transmission rate are fixed to be $\beta_0 = 10^{-3}$ and $p = 0.02$. The other parameters are given by Table 5.1. (5.2a) Distribution of Infected individuals. (5.2b) Distribution of Lost of sight. (5.2c) Distribution of infected newborn. (5.2d) Distribution of Infected and Lost of sight individuals after 80 years of time observation.

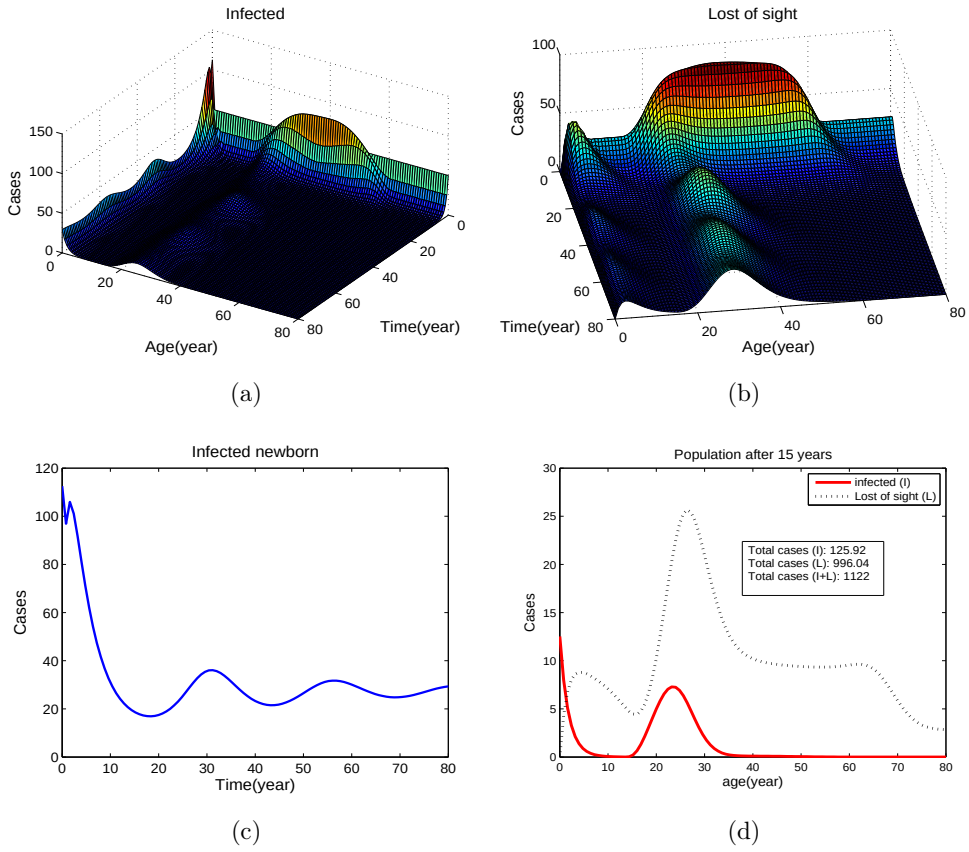


Figure 5.3: The transmission constant and the vertical transmission rate are fixed to be $\beta_0 = 10^{-3}$ and $p = 0.2$. The other parameters are given by Table 5.1. (5.3a) Distribution of Infected individuals. (5.3b) Distribution of Lost of sight. (5.3c) Distribution of infected newborn. (5.3d) Distribution of Infected and Lost of sight individuals after 80 years of time observation.

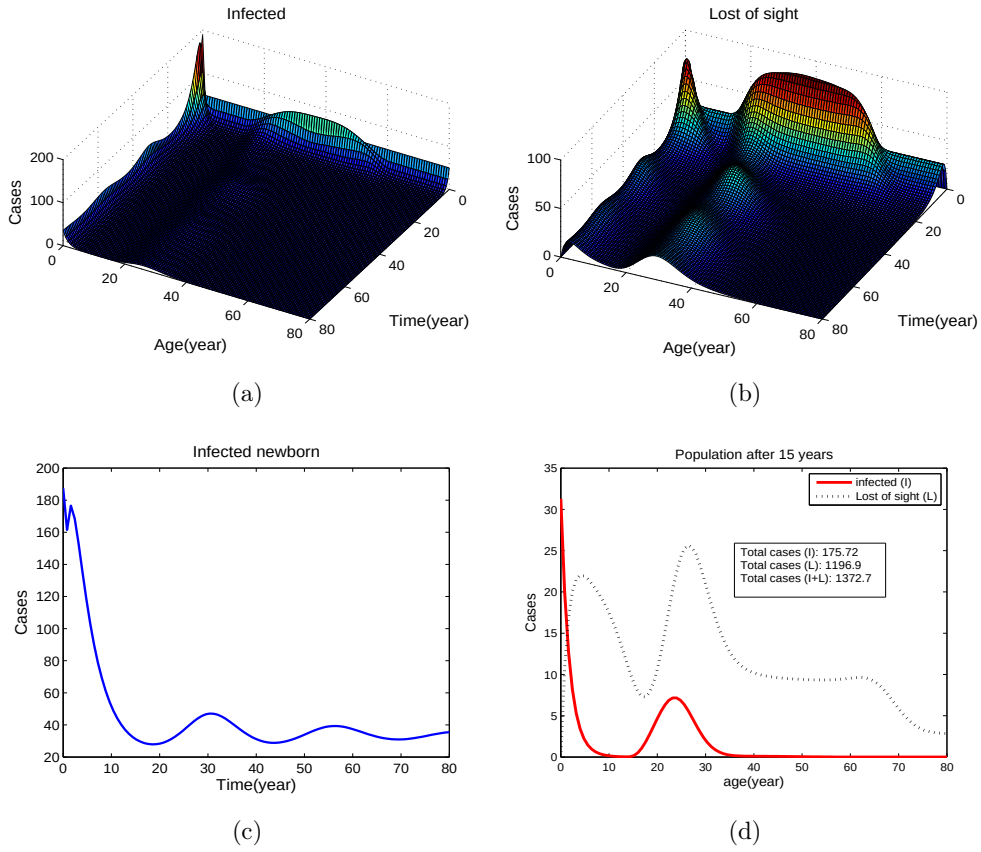


Figure 5.4: The transmission constant and the vertical transmission rate are fixed to be $\beta_0 = 10^{-3}$ and $p = 0.5$. The other parameters are given by Table 5.1. (5.4a) Distribution of Infected individuals. (5.4b) Distribution of Lost of sight. (5.4c) Distribution of infected newborn. (5.4d) Distribution of Infected and Lost of sight individuals after 80 years of time observation.

5.1.8 Future directions

In the absence of specific interventions the estimated rate of mother-to-child transmission ranges from 15% to 40%, the differences between populations being largely associated with the prevalence of breastfeeding [161]. Therefore, a SIL epidemic model that incorporates the control mechanism, representing the case finding effort and the prevention of mother-to-child transmission, could be considered.

The basic system (age-structured SIL epidemic model) with control can be formulated as follows:

$$\begin{cases} \left(\dfrac{\partial}{\partial t}+\dfrac{\partial}{\partial a}\right)S(t,a) &= \Lambda(a)-(\lambda(t,a)+\mu(a))S(t,a), \\ \left(\dfrac{\partial}{\partial t}+\dfrac{\partial}{\partial a}\right)I(t,a) &= \lambda(t,a)S(t,a)+\gamma(a)L(t,a)-(\mu(a)+d_1(a) \\ & \quad +r(a)\phi(a)(1-\pi_1(a)v_1(t,a)))I(t,a), \\ \left(\dfrac{\partial}{\partial t}+\dfrac{\partial}{\partial a}\right)L(t,a) &= r(a)\phi(a)(1-\pi_1(a)v_1(t,a))I(t,a) \\ & \quad -(\mu(a)+d_2(a)+\gamma(a))L(t,a), \end{cases} \tag{5.57}$$

with initial boundary conditions

$$\begin{cases} S(t,0) &= \int_0^{a^+} f(a)\left[s(t,a)+(1-p(1-\pi_2 v_2(t)))\left(I(t,a)+L(t,a)\right)\right]da, \\ I(t,0) &= p(1-\pi_2 v_2(t))\int_0^{a^+} f(a)(I(t,a)+L(t,a))da, \\ L(t,0) &= 0, \end{cases} \tag{5.58}$$

and wherein the state variables and the parameters are defined as previously.

In model (5.57)-(5.58), the functions $v_1(.,.)$ and $v_2(.)$ are control functions. The control $v_1(t,a)$ represents the effort that prevents an infectious individuals age a to become lost of sight at time t (case finding effort). The control $v_2(t)$ represents the effort that prevents the mother-to-child transmission at time t. The parameters π_i, $\pi_i \in (0,1)$, $i \in \{1,2\}$, measure the effectiveness of the controls. These parameters measure the efficacy of the control.

The optimal control problem is the following:

$$\begin{aligned} \text{minimize} \quad & \int_0^T \int_0^{a^+} \left[L(t,a)+p(1-\pi_2 v_2(t))f(a)(I(t,a)+L(t,a))+\frac{W_2(a)}{2}v_2^2(t,a)\right]dadt \\ & +\int_0^T \frac{W_1}{2}v_1^2(t)dt, \end{aligned} \tag{5.59}$$

subject to state system (5.57)-(5.58) and the control constrains

$$\begin{aligned} v_2 \in \Omega_2 := \; & \big\{ v(t,a) : 0 \leq v_{20} \leq v(t,a) \leq v_{21}, (t,a) \in [0,T] \times [0,a^+) \;\; a.e., \\ & v(t,a) \text{ mesurable on } [0,T] \times [0,a^+) \big\} \\ v_1 \in \Omega_1 := \; & \{ v(t) : 0 \leq v_{10} \leq v(t) \leq v_{11}, t \in [0,T] \;\; a.e., \\ & v(t) \text{ mesurable on } [0,T] \} \end{aligned} \tag{5.60}$$

where W_1 and W_2 are a measure of the relative cost of the interventions associated to the controls v_1, v_2, respectively.

5.1.9 Summary

In this section, we have considered a model for the spread of a directly transmitted infections disease in an age-structured population with demographics process. The disease can be transmitted not only horizontally but also vertically from infected mothers to their newborns. There are important infective agents such as HBV (hepatitis B virus), HIV (human immunodeficiency virus) and HTLV (human T-cell leukemia virus) that can be vertically transmitted. In Africa, the vertical transmission of the disease like HIV is in progression nowadays.

Worldwide, 1% of pregnant women are HIV-positive. However, sub-Saharan Africa where 95% of HIV positive women live carries the vast majority of this burden [198]. Without treatment, approximately 25%-50% of HIV-positive mothers will transmit the virus to their newborns during pregnancy, childbirth, or breastfeeding [17]. In 2007, over 2 million children worldwide were living with HIV/AIDS, with the overwhelming majority again in sub-Saharan Africa [198]. Approximately 400,000 infants contract HIV from their mother every year, which is about 15% of the total global HIV incidence [183, 217]. The rate of pediatric HIV infections in sub-Saharan Africa remains unacceptably high, with over 1,000 newborns infected with HIV per day [94].

The aim finding of this section can be summarized along the following lines:

✓ We formulated the dynamical system with boundary conditions, and then described the semigroup approach to the time evolution problem of the abstract epidemic system.

✓ Next we have calculated the basic reproduction ratio and proved that the model exhibits a unique disease-free steady state if $R_0 \leq 1$, and at least one endemic steady state exists if the basic reproduction ratio R_0 is greater than the unity.

✓ We prove that if the basic reproduction number of the model satisfies $R_0 < 1$, then the disease-free steady state is locally asymptotically stable, i.e., the disease died out from the host population.

✓ We have shown sufficient conditions which guarantee the local stability of the endemic steady state; that is the persistence of the disease in the host population. Roughly speaking, the endemic steady state is locally asymptotically stable if $R_0 > 1$ and if it corresponds to a very small force of infection.

✓ Finally, to highlight the impact of the vertical transmission of the disease into the host population, we provided some illustrations and discussion on the outcome of the state variables of the model when the vertical transmission rate p takes different values: 0.02, 0.2 and 0.5.

5.2 Age-structured model for the transmission of hepatitis B, with differential infectivity.

Hepatitis B virus (HBV) infection is endemic in many parts of the world. One of the characteristics of HBV transmission is the age structure of the host population and the vertical transmission of the disease (perinatal infection from carrier mothers). In this section, we propose an age-structured model for the transmission dynamics of HBV with differential infectivity: symptomatic infection and asymptomatic infection. The model is completely analyzed. We compute the basic reproduction number $\mathcal{R}_0$. We investigate the existence of equilibria and study their stability. We found that the model exhibits a forward bifurcation, that is, if $\mathcal{R}_0 \leq 1$, there exists a disease-free equilibrium which is globally asymptotically stable, while if $\mathcal{R}_0 > 1$, the disease-free equilibrium is unstable and there exists a unique endemic which is globally asymptotically stable. Numerical results are presented to illustrate analytical results. Through numerical simulation and sensitivity analysis, we found that a control strategy of HBV consist in a combination of immunization of newborns, immunization of susceptible individuals (at least young adults), and reduction of perinatal infection.

5.2.1 Introduction

According to CDC [30] and WHO [217], risk for chronic infection is inversely related to age at infection: approximately 90% of infected infants and 30% of infected children aged under 5 years become chronically infected, compared with 5% of adults. This difference in the evolution of infection introduces naturally differential susceptibility. Vaccination is recognized as the most efficient way of preventing hepatitis B. But the problem of imperfect vaccine introduce naturally differential susceptibility. Even if HBV vaccine is very efficient it does not offer 100% protection against infection. According to WHO, Hepatitis B vaccine is 95% effective in preventing HBV infection and its chronic consequences. Then vaccination also introduce individual with different susceptibility.

Many mathematical models have been proposed to investigate the transmission dynamics of HBV in various countries and regions in the world; covering many topics: sexual transmission of HBV which includes heterogeneous mixing with respect to age and sexual activity [5]; relation between the age at infection with HBV and the development of the carrier state [68]; HBV transmission in developing countries [158, 67, 215]; the long-term effectiveness of the vaccination [221]; determined the prevalence of infection [160]. Age-structured models have also been used to model the transmission dynamics of HBV by some researchers; see for instance Edmunds et al. [68], McLean and Blumberg [158], Zhao, Xu, and Lu[221], Zou, Ruan and Zhang[222].

Recently, Zou, Ruan and Zhang [223] have proposed a mathematical model for the transmission of HBV with susceptible, latently infected, acutely infectious, carrier, recovered, and immune following vaccination. They (Zou et al.) do not take into account age of the host population. However, outcome of the HBV infection is age dependent (Shepard et al. [195], Goldstein et al. [76], WHO [217], CDC [30]). This characteristic leads Zou et al. to extend they previous model to an age-structured model for the transmission of HBV (see Zou et al. [222]). To analyzed the model, due possible to his complexity, they ignored the perinatal infection of HBV (vertical transmission of the disease) and deaths directly related to HBV. These assumptions are not entirely realistic in many part of the world. In fact, HBV prevalence is highest in sub-Saharan Africa and East Asia. Most people in these regions become infected with the hepatitis B virus during birth (and childhood) with a high risk (90% at birth) of progressing to chronic infection (WHO [217] and CDC [30]). Moreover, about 600,000 people die every year

due to the acute or chronic consequences of hepatitis B (WHO [217]); that is deaths directly related to HBV should not be neglected.

In this section, we propose a 'simple' age-structured model for the transmission dynamics of HBV with differential infectivity: symptomatic HBV infection and asymptomatic HBV infection. The host population is divided into seven subclasses: susceptible and vaccinated population are stratified by age whereas latently infected progressing to the symptomatic infection, latently infected progressing to the asymptomatic infection , symptomatic HBV infectious, asymptomatic HBV infectious and recovered individuals are time dependent populations. The model also consider the perinatal infection of HBV and deaths directly related to HBV infection. The model we shall consider is an extension of the model proposed by Bonzi et al.[19] by taking into account a continuous age structure for the host population.

We first describe the mathematical model. Next, we prove the existence and stability of a disease-free equilibrium point, define the reproductive number, and describe the existence and stability of the endemic equilibrium point. Then, numerical simulation have been presented to illustrate theoretical results.

5.2.2 The model

We proposed an age-structured model to study the transmission dynamics of HBV with differential infectivity: symptomatic HBV infection and asymptomatic HBV infection. The model includes age-dependent process such as the force of infection and the probability of developing the chronicle infection, the susceptible population is stratified by age. We divide the total population into seven subclasses: susceptible individuals $S(t,a)$, immune individuals following vaccination $V(t,a)$ age a at time t, latently infected progressing to symptomatic HBV infectiousness $L_i(t)$, latently infected progressing to asymptomatic HBV infectiousness $L_c(t)$, symptomatic HBV infectiousness $I(t)$, asymptomatic HBV infectiousness $C(t)$ and recovered from HBV infection $R(t)$ at time t.

The age-structured model for the transmission of HVB is described by the following

system:

$$\begin{aligned}
&\frac{\partial S(t,a)}{\partial t}+\frac{\partial S(t,a)}{\partial a}=\psi V(t,a)-(\lambda(t,a)+\mu_1+p(a))S(t,a),\\
&\frac{\partial V(t,a)}{\partial t}+\frac{\partial V(t,a)}{\partial a}=p(a)S(t,a)-(\psi+\mu_1)V(t,a),\\
&\frac{dL_i(t)}{dt}=\int_0^{\omega}\alpha(a)\lambda(t,a)S(t,a)da-(\mu_1+\gamma)L_i(t),\\
&\frac{dL_c(t)}{dt}=\int_0^{\omega}(1-\alpha(a))\lambda(t,a)S(t,a)da+b\theta\nu C(t)-(\mu_1+\delta)L_c(t),\\
&\frac{dI(t)}{dt}=\gamma L_i(t)-(\gamma_1+\mu_1+\mu_I)I(t),\\
&\frac{dC(t)}{dt}=\delta L_c(t)-(\gamma_2+\mu_1+\mu_c)C(t),\\
&\frac{dR(t)}{dt}=\gamma_1 I(t)+\gamma_2 C(t)-\mu_1 R(t),
\end{aligned}\tag{5.61}$$

with the initial and boundary conditions

$$\begin{aligned}
&S(t,0)=\theta(\Lambda-b\nu C(t));\quad S(0,a)=S_0(a);\quad V(t,0)=(1-\theta)\Lambda;\quad V(0,a)=V_0(a),\\
&L_i(0)=L_{i0};\quad L_c(0)=L_{c0};\quad I(0)=I_0;\quad C(0)=C_0;\quad R(0)=R_0,
\end{aligned}\tag{5.62}$$

where $\lambda(t,a)$ is the force of infection defined by

$$\lambda(t,a)=\beta(a)\left(I(t)+C(t)\right),$$

ω is the upper bound of age of people in the model and Λ is the total number of births of the host population at time t (which is assumed to be constant).

The parameters of the model is describe in Table 5.3.

Table 5.3: Parameters description

Parameters	Description	Units
$p(a)$	successful vaccination rate of susceptible against HBV	/year
$\beta(a)$	probability that an infective individual will have contact with and successfully infect a susceptible individual of age a	/(human.year)
$\alpha(a)$	probability of susceptible age a to become latently infected (progressing to symptomatic infectiousness)	/year
μ_1	natural mortality rate	/year
μ_I, μ_C	HBV-related mortality rate	/year
γ	rate moving from latent to symptomatic infectiousness	/year
δ	rate moving from latent to asymptomatic infectiousness	/year
Λ	total number of births	human
b	equilibrium birth rate	/year
$1-\theta$	proportion of births with successful vaccination	/year
ψ	rate of waning vaccine-induced immunity	/year
γ_1	rate moving from symptomatic infectious to recovered	/year
γ_2	rate of moving from asymptomatic infectious to recovered	/year
ν	proportion of perinatally infected	/year

In order to deal with system (5.61) we first provide a parameter reduction by introducing the following unknown functions

$$s(t,a) = S(t,a)e^{\mu_1 a}, \quad v(t,a) = V(t,a)e^{\mu_1 a}.$$

Therefore, by introducing the vector-valued functions

$$\mathbf{u}(t) = (L_i(t), L_c(t), I(t), C(t))^T = (u_i)_{i=1,\cdots,4}^T; \quad \mathbf{y}(t,.) = (s(t,.), v(t,.))^T = (y_1, y_2)^T;$$

and $\mathbf{e}_1 = (1,0)$, $\mathbf{1}_n = (1,\ldots,1) \in \mathbb{R}^n$, $\mathbf{e} = (0,0,1,1)$; $F_4 = (0,0,\gamma_1,\gamma_2)$, as well as the

matrices

$$F_1(a)=\begin{pmatrix} -p(a) & \psi \\ p(a) & -\psi \end{pmatrix},\quad F_2(a)=\begin{pmatrix} 0 & 0 & \alpha(a) & \alpha(a) \\ 0 & 0 & 1-\alpha(a) & 1-\alpha(a) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$
$$F_3=\begin{pmatrix} -\gamma & 0 & 0 & 0 \\ 0 & -\delta & 0 & b\theta\nu \\ \gamma & 0 & -(\gamma_1+\mu_I) & 0 \\ 0 & \delta & 0 & -(\gamma_1+\mu_c) \end{pmatrix},\quad E_1=\begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}, \tag{5.63}$$

system (5.61) rewrites as

$$\begin{cases} \dfrac{\partial \mathbf{y}(t,a)}{\partial t}+\dfrac{\partial \mathbf{y}(t,a)}{\partial t}=-\beta(a)\langle \mathbf{e},\mathbf{u}(t)\rangle E_1.\mathbf{y}(t,a)+F_1(a)\mathbf{y}(t,a), \\ \dfrac{d}{dt}\mathbf{u}(t)=\displaystyle\int_0^{\omega} l(a)\beta(a)\langle \mathbf{e}_1,\mathbf{y}(t,a)\rangle F_2(a).\mathbf{u}(t)da+(F_3+diag(-\mu_1)).\mathbf{u}(t), \\ \dfrac{dR(t)}{dt}=\langle F_4,\mathbf{u}(t)\rangle-\mu_1 R(t), \end{cases} \tag{5.64}$$

wherein $\langle .,. \rangle$ is the usual scalar product.

System (5.64) supplemented together with boundary condition and initial data

$$\begin{cases} \mathbf{y}(t,0)=(\theta(\Lambda-b\nu u_4(t));(1-\theta)\Lambda)^T, \\ \mathbf{y}(0,.)=\mathbf{y}_0(.)\in L^1(0,\omega,\mathbb{R}^2),\quad \mathbf{u}(0)=\mathbf{u}_0\in\mathbb{R}^4,\quad R(0)=R_0. \end{cases} \tag{5.65}$$

The age-dependent parameter $l(a)$ into (5.64) is the survival function which is the proportion of individuals who survive to age a, and it is defined by

$$l(a):=e^{-\mu_1 a},\quad a\in[0,\omega).$$

In what follows we shall discuss the asymptotic behavior of system (5.64)-(5.65) and we will make use of the following assumptions.

Assumption 5.2.1. A1: *Recalling the description of parameters into Table 5.3; we assume that:* $\Lambda>0$*;* b*,* μ_1*,* μ_I*,* μ_C*,* γ*,* γ_1*,* γ_2*,* ψ*,* θ*,* ν*,* δ *are nonnegative constants,* $p(.)$ *is nonnegative function while* $\beta(.)$ $\mu(.)$ *and* $\alpha(.)$ *belong to* $L^{\infty}_{+}(0,\omega,\mathbb{R}_+)$*.*

A2: *As a technical assumption, we assume that the population of newborn carries born to carries is less than the natural mortality of the host population, that is* $b\nu<\mu_1$*.*

5.2.3 Existence of semiflow

The aim of this section is to derive preliminary remarks on (5.61)-(5.62). These results include the existence of the unique maximal bounded semiflow associated to this system. We shall deal with the integrated semigroup approach introduced by Thieme [200].

Let us introduce $\widehat{X} = \mathbb{R}^2 \times L^1(0,\omega,\mathbb{R}^2)$ as well as its positive cone $\widehat{X}_+ = \mathbb{R}^2_+ \times L^1(0,\omega,\mathbb{R}^2_+)$ and the linear operator $\widehat{A} : D(\widehat{A}) \subset \widehat{X} \to \widehat{X}$ defined by

$$D(\widehat{A}) = \{0_{\mathbb{R}^2}\} \times W^{1,1}(0,\omega,\mathbb{R}^2), \quad \widehat{A}\begin{pmatrix} 0_{\mathbb{R}^2} \\ \varphi \end{pmatrix} = \begin{pmatrix} -\varphi(0) \\ -\varphi' \end{pmatrix}. \tag{5.66}$$

Next consider the Banach space

$$X = \mathbb{R}^4 \times \mathbb{R} \times \widehat{X} \text{ and } X_+ = \mathbb{R}^4_+ \times \mathbb{R}_+ \times \widehat{X}_+$$

endowed with the usual product norm

$$\left|\left|(\mathbf{u},R,x,\mathbf{y})^T\right|\right| = \sum_{i=1}^{4}|u_i| + |R| + \sum_{i=1}^{2}|x_i| + \sum_{i=1}^{4}||y_i||_{L^1}; \quad \forall (\mathbf{u},R,x,\mathbf{y})^T \in X.$$

Let $A : D(A) \subset X \to X$ be the linear operator defined by

$$D(A) = \mathbb{R}^4 \times \mathbb{R} \times D(\widehat{A}), \quad A = diag\left(-\mu_1, \widehat{A}\right). \tag{5.67}$$

Note that the domain of operator A is not dense in X because of the identity

$$\overline{D(A)} = \mathbb{R}^5 \times \{0_{\mathbb{R}^2}\} \times L^1(0,\omega,\mathbb{R}^2) \neq X.$$

Finally, let us introduce the nonlinear map $F : \overline{D(A)} \to X$ defined by

$$F\left((\mathbf{u},R,0_{\mathbb{R}^2},\mathbf{y})^T\right) = \begin{pmatrix} \int_0^\omega l(a)\beta(a)\langle \mathbf{e}_1, \mathbf{y}(a)\rangle F_2(a)\mathbf{u}da + F_3\mathbf{u} \\ \langle F_4, \mathbf{u}\rangle - \mu_1 R \\ (\theta(\Lambda - b\nu u_4); (1-\theta)\Lambda; F_1(a)\mathbf{y} - \beta(a)\langle \mathbf{e}, \mathbf{u}\rangle E_1\mathbf{y})^T \end{pmatrix}^T.$$

By identifying $\varphi(t)$ together with $(\mathbf{u}(t), R(t), 0_{\mathbb{R}^2}, \mathbf{y}(t,.))^T$ and by setting

$$\varphi_0 = (\mathbf{u}_0, R_0, 0_{\mathbb{R}^2}, \mathbf{y}_0(.))^T,$$

one obtain that system (5.64)-(5.65) rewrites as the following nondensely defined Cauchy problem:

$$\begin{cases} \dfrac{d\varphi(t)}{dt} = A\varphi(t) + F(\varphi(t)), t \geq 0, \\ \varphi(0) = \varphi_0 \in \overline{D(A)} \cap X_+. \end{cases} \tag{5.68}$$

We first derive that the above abstract Cauchy problem generates a unique globally defined and positive semiflow. We set $X_0 = \overline{D(A)}$, $X_{0+} = X_0 \cap X_+$, $\mathcal{A} = \{\varphi \in X_{0+} : ||\varphi|| \leq \Lambda/\mu_1\}$ and the precise result is the following theorem.

Theorem 5.2.1. *Let Assumption 5.2.1 be satisfied. Then there exists a unique strongly continuous semiflow $\{U(t) : X_0 \to X_0\}_{t\geq 0}$ such that for each $\varphi_0 \in \mathcal{A}$, the map $\varphi \in \mathcal{C}([0,\omega), \mathcal{A})$ defined by $\varphi = U(.)\varphi_0$ is a mild solution of (5.68), namely, it satisfies*

$$\int_0^t \varphi(s)ds \in D(A) \quad \text{and} \quad \varphi(t) = \varphi_0 + A\int_0^t \varphi(s)ds + \int_0^t F(\varphi(s))ds; \forall t \geq 0.$$

Furthermore $\{U(t)\}_{t\geq 0}$ satisfies the following properties:

(i) *Let $U(t)\varphi_0 = (\mathbf{u}(t), R(t), 0_{\mathbb{R}^2}, \mathbf{y}(t,.))^T$; then the following Volterra integral formulation holds true:*

$$\mathbf{y}(t,a) = \begin{cases} \exp\left(\displaystyle\int_{a-t}^{a} (F_1(a) - \beta(a)\langle \mathbf{e}, \mathbf{u}(\sigma)\rangle E_1)\, d\sigma\right) \mathbf{y}_0(a-t); \ \text{if } a \geq t, \\ \exp\left(\displaystyle\int_{0}^{a} (F_1(\sigma) - \beta(\sigma)\langle \mathbf{e}, \mathbf{u}(t)\rangle E_1)\, d\sigma\right) \mathbf{y}(t-a,0); \ \text{if } a < t. \end{cases}$$

with $\mathbf{y}(t-a,0) = [\theta(\Lambda - b\nu u_4(t-a)); (1-\theta)\Lambda]^T$.

(ii) *For each $\varphi_0 \in \mathcal{A}$ one has for all $t \geq 0$*

$$\langle \mathbf{1}_4, \mathbf{u}(t)\rangle + R(t) + \int_0^{\omega} l(a)\langle \mathbf{1}_2, \mathbf{y}(t,a)\rangle da \leq \frac{\Lambda}{\mu_1}.$$

(iii) *The nonempty compact set $\mathcal{A}$ is invariant under the semiflow U, and the subset $\mathcal{A}$ attracts the bounded sets of X_{0+} under the semiflow U.*

Proof. The proof of this result is rather standard. Indeed it is easy to check that operator A satisfies the Hille-Yosida property. Then standard methodologies apply to provide the existence and uniqueness of a mild solution for system (5.64)-(5.65) (see, for instance, [144, 200, 113] and the proof of Theorem 4.2.2). Next the Volterra integral formulation is also standard in the context of age-structured equations and we refer to [110] and the references cited therein for more details. Estimates stated in (ii) directly follow from

the system of equations. Let us assume for a moment that $\mathbf{y}_0 \in W^{1,1}(0,\omega,\mathbb{R}^2)$; then adding up the equations of system (5.64) yields $\dot{v}(t) \leq \Lambda - \mu_1 v(t)$, that is

$$v(t) \leq \frac{\Lambda}{\mu_1} + e^{-\mu_1 t}\left(v(0) - \frac{\Lambda}{\mu_1}\right), \tag{5.69}$$

wherein $v(t) = \langle \mathbf{1}_4, \mathbf{u}(t)\rangle + R(t) + \displaystyle\int_0^\omega l(a)\langle \mathbf{1}_2, \mathbf{y}(t,a)\rangle da$. From where one deduces estimate (ii). Particularly, Assumption (item A2) gives that $S(t,0) = \theta(\Lambda - b\nu C(t)) > 0$ for all $t > 0$.

It remains to prove (iii) and this is a direct consequence of (5.69). □

5.2.4 The disease-free steady state and reproductive number

Existence of the disease-free steady state

A steady state $(\mathbf{u}, 0_{\mathbb{R}^2}, \mathbf{y}(a))$ of system (5.64)-(5.65) must satisfy the system of ordinary differential equations:

$$\begin{aligned}
&\frac{d\mathbf{y}(a)}{da} = -\beta(a)\langle \mathbf{e}, \mathbf{u}\rangle E_1.\mathbf{y}(a) + F_1(a)\mathbf{y}(a),\\
&\int_0^\omega l(a)\beta(a)\langle \mathbf{e}_1, \mathbf{y}(a)\rangle F_2(a).\mathbf{u}da + (F_3 + diag(-\mu_1)).\mathbf{u} = 0,\\
&\langle F_4, \mathbf{u}\rangle - \mu_1 R = 0,
\end{aligned} \tag{5.70}$$

with initial condition $\mathbf{y}(0) = (\theta(\Lambda - b\nu u_4); (1-\theta)\Lambda)^T$. Therefore, we obtain the disease-free steady state $\mathbf{E}^0 = (0_{\mathbb{R}^4}, 0, 0_{\mathbb{R}^2}, s^0(.), v^0(.))^T$, where

$$\begin{aligned}
s^0(a) &= \Lambda\left[\theta e^{-\int_0^a(\psi + p(\eta))d\eta} + \psi\int_0^a e^{-\int_\sigma^a(\psi+p(\eta))d\eta}d\sigma\right];\\
v^0(a) &= \Lambda - s^0(a).
\end{aligned}$$

Reproductive number.

We use the next generation operator approach as described by Diekmann-Heesterbeek-Metz [48] and Inaba [116] to define the reproductive number, $\mathcal{R}_0$, as the number of secondary infections that one infectious individual would create over the duration of the infectious period, provided that everyone else is susceptible.

In the early stage of the epidemic, the dynamics of the population can be described by the linearized equation at the disease-free steady state $\mathbf{E}^0$. Since the linearized equations

for infective population does not include other subpopulations, we can only consider the single equation for infective population as

$$\begin{aligned}&\frac{d}{dt}\mathbf{u}(t) = \int_0^{\omega} l(a)\beta(a)\langle \mathbf{e}_1, \mathbf{E}^0(a)\rangle F_2(a).\mathbf{u}(t)da + (F_3 + diag(-\mu_1)).\mathbf{u}(t),\\ &\mathbf{u}(0) \in \mathbb{R}^4.\end{aligned} \tag{5.71}$$

Equation (5.71) rewrites

$$\frac{d}{dt}\mathbf{u}(t) = \mathcal{F}\mathbf{u}(t) - \mathcal{V}\mathbf{u}(t), \quad \mathbf{u}(0) \in \mathbb{R}^4; \tag{5.72}$$

where the matrices $\mathcal{F}$ and $\mathcal{V}$ are respectively the rate of appearance of new infections in each class and the rate of transfer (into and out of) each class; and are defined by

$$\mathcal{F} = \begin{pmatrix} 0 & 0 & \mathcal{K}_i & \mathcal{K}_i \\ 0 & 0 & \mathcal{K}_c & \mathcal{K}_c + b\theta\nu \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} v_{11} & 0 & 0 & 0 \\ 0 & v_{22} & 0 & 0 \\ -\gamma & 0 & v_{33} & 0 \\ 0 & -\delta & 0 & v_{44} \end{pmatrix},$$

with

$$\mathcal{K}_i = \int_0^{\omega} \beta(a)\alpha(a)l(a)s^0(a)da, \quad \mathcal{K}_c = \int_0^{\omega} \beta(a)(1-\alpha(a))l(a)s^0(a)da,$$

and

$$\begin{aligned} v_{11} &= \mu_1 + \gamma; & v_{22} &= \mu_1 + \delta; \\ v_{33} &= \gamma_1 + \mu_I + \mu_1; & v_{44} &= \gamma_2 + \mu_c + \mu_1. \end{aligned} \tag{5.73}$$

Then the basic reproductive number is defined as the spectral radius of the next generation matrix $\mathcal{F}\mathcal{V}^{-1}$

$$\mathcal{R}_0 = \frac{1}{2}\left[\frac{\gamma\mathcal{K}_i}{v_{11}v_{33}} + \frac{\delta(\mathcal{K}_c + b\theta\nu)}{v_{22}v_{44}} + \left(\left(\frac{\gamma\mathcal{K}_i}{v_{11}v_{33}} + \frac{\delta(\mathcal{K}_c - b\theta\nu)}{v_{22}v_{44}}\right)^2 + \frac{4\delta^2 b\theta\nu\mathcal{K}_c}{v_{22}^2 v_{44}^2}\right)^{1/2}\right]. \tag{5.74}$$

Remark 5.2.1. *We can also follow van den Driessche and Watmough[206], we obtain that the basic reproduction number, defined as the expected number of secondary infections produced by an index case (Anderson and May [3]), is given by*

$$\widetilde{\mathcal{R}}_0 = \frac{\delta(\mathcal{K}_c + b\theta\nu)}{v_{22}v_{44}} + \frac{\gamma\mathcal{K}_i}{v_{11}v_{33}}. \tag{5.75}$$

In fact, simple calculation shows that $\mathcal{R}_0 < 1 (= 1, > 1)$ *is equivalent to* $\widetilde{\mathcal{R}}_0 < 1 (= 1, > 1)$.

Global stability of the disease-free steady state.

Theorem 5.2.2. *Under Assumption 5.2.1, the disease-free steady state* $\mathbf{E}^0$ *is globally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

Proof. Let us denote by A_0 the part of operator A in $\overline{D(A)}$. Then it is infinitesimal generator of a C_0-semigroup on $\overline{D(A)}$ denoted by $\{T_{A_0}(t)\}_{t\geq 0}$. Using the same arguments as in the proof of Lemma 4.2.4 we find that $\{T_{A_0}(t)\}_{t\geq 0}$ satisfies

$$||T_{A_0}(t)|| \leq \overline{M}e^{-\mu_1 t}, \quad \forall t \geq 0,$$

for some constant $\overline{M} > 0$. It follows that $\omega_{ess}(A_0)$, the essential growth of rate of $\{T_{A_0}(t)\}_{t\geq 0}$ is, $\leq -\mu_1$. Let $\left\{T_{(A_0+DF(\mathbf{E}^0))}(t)\right\}_{t\geq 0}$ be the linear C_0-semigroup generated by $(A + DF(\mathbf{E}^0))_0$ the part of $A + DF(\mathbf{E}^0) : D(A) \subset X \to X$ in $\overline{D(A)}$. Since $DF(\mathbf{E}^0)$ is a compact bounded linear operator, it follows that (Ref. [57] an references therein)

$$\omega_{ess}(A + DF(\mathbf{E}^0)) \leq -\mu_1.$$

Now, let us assume that $\mathcal{R}_0 > 1$. The linearized equation of system (5.64) at the disease-free steady state is given by (5.72). For $w = (w_i)_{i=1,\ldots,4} \in \mathbb{R}^4$ and $u = (u_i)_{i=1,\ldots,4} \in \mathbb{R}^4$; let us consider the resolvent equation:

$$(z - (\mathcal{F} - \mathcal{V}))\, w = u, \;\; z \in \mathbb{C} \text{ and } R_e(z) > -\mu_1. \tag{5.76}$$

then we have

$$(I - T(z))\, w = \left(\frac{u_i}{z + v_{ii}}\right)^T_{i=1,\ldots,4}; \tag{5.77}$$

where $T(z)$, $z \in \mathbb{C}$, is 4×4 matrix defined by:

$$T(z) = \begin{pmatrix} 0 & 0 & \frac{\mathcal{K}_i}{z+v_{11}} & \frac{\mathcal{K}_i}{z+v_{11}} \\ 0 & 0 & \frac{\mathcal{K}_c}{z+v_{22}} & \frac{\mathcal{K}_c+b\theta\nu}{z+v_{22}} \\ \frac{\gamma}{z+v_{33}} & 0 & 0 & 0 \\ 0 & \frac{\delta}{z+v_{44}} & 0 & 0 \end{pmatrix} \tag{5.78}$$

Let us observe that the basic reproduction ratio $\mathcal{R}_0$ is the spectral radius, denoted by $r\,(T(0))$, of the generation operator $T(0)$. (See Ref. [113] and references therein). Then, we claim that:

Claim 5.2.1. *There exists a unique* $z_0 > -v_{min} := -\min\left(v_{ii}\right)_{i=1,2,3,4}$ *such that* $r\left(T(z_0)\right) = 1$ *and*

$$\begin{cases} z_0 > 0 \text{ if } r\left(T(0)\right) > 1; \\ z_0 = 0 \text{ if } r\left(T(0)\right) = 1; \\ z_0 < 0 \text{ if } r\left(T(0)\right) < 1; \end{cases}$$

and it is the dominant characteristic root, as

$$z_0 > \sup\left\{R_e(z) : z \in \Sigma^0 \setminus \{z_0\}\right\};$$

where $\Sigma^0 := \{z \in \mathbb{C} : (I - T(z)) \text{ is not inversible}\}$ *is the spectrum of* $\mathcal{F} - \mathcal{V}$.

Proof. The positive operator $T(0)$ has the Perron-Frobenius properties, roughly speaking, $T(z)$ is irreducible and $r\left(T(z)\right)$ is decreasing for real $z \in (-v_{min}, +\infty)$. Moreover, $\lim_{z\to -v_{min}} r\left(T(z)\right) = +\infty$ and $\lim_{z\to+\infty} r\left(T(z)\right) = 0$; then the first half of the claim is the direct consequence of this monotonicity of $r\left(T(z)\right)$. Next we show the dominant property of z_0. For any $z \in \Sigma^0 \setminus \{z_0\}$, there is an vector ψ_z, such that $T(z)\psi_z = \psi_z$. Then we have $|\psi_z| = |T(z)\psi_z| \leq T(R_e z)|\psi_z|$. The eigenspace corresponding to the eigenvalue $r\left(T(R_e z)\right)$ is one-dimensional subspace of $\mathbb{R}^4$ spanned by a strictly positive functional $F_{R_e z}$. We obtain that

$$r\left(T(R_e z)\right)\left[F_{R_e z}, |\psi_z|\right] = \left[F_{R_e z}, T(R_e z)|\psi_z|\right] \geq \left[F_{R_e z}, |\psi_z|\right],$$

where we write the value of $F_{R_e z}$ at ψ_z as $[F_{R_e z}, \psi_z]$. Hence we have $r\left(T(R_e z)\right) \geq 1$ and $R_e z \leq z_0$ because $r\left(T(z)\right)$ is strictly deceasing for $z \in (-\mu_1, +\infty)$ and $r\left(T(R_e z_0)\right) = 1$. This end the proof of Claim 5.2.1. □

Therefore, the disease-free steady state is locally asymptotically stable if $\mathcal{R}_0 = r\left(T(0)\right) < 1$ and unstable if $\mathcal{R}_0 = r\left(T(0)\right) > 1$.

The second part of the proof deal with the global stability of the disease-free steady state. Let us consider $\mathcal{A} \subset X_{0+}$, the global attractor of U provided by Theorem 5.2.1. Let $(\mathbf{u}_0, R_0, 0_{\mathbb{R}^2}, \mathbf{y}_0) \in \mathcal{A}$ be given and let $\{\varphi(t) = (\mathbf{u}(t), R(t), 0_{\mathbb{R}^2}, \mathbf{y}(t, .))\}_{t\in\mathbb{R}}$ be the entire solution of U passing trough $(\mathbf{u}_0, R_0, 0_{\mathbb{R}^2}, \mathbf{y}_0)$. Since $s(0, .) \leq s^0(.)$ for all $(\mathbf{u}_0, R_0, 0_{\mathbb{R}^2}, \mathbf{y}_0) \in \mathcal{A}$, we deduce that $s(t, .) \leq s^0(.)$ for all $t \in \mathbb{R}$. One may consider the functional V defined for each entire solutions by

$$V\left[\varphi\right](t) = \mathbf{d}.\mathbf{u}(t),$$

where the positive constant vector $\mathbf{d} \in \mathbb{R}^4$ is defined by $d_1 = \frac{\gamma d_3}{\gamma+\mu_1}$, $d_2 = \frac{\delta d_4}{\mu_1+\delta}$, $d_3 = \frac{1}{2(\mu_1+\gamma_1+\mu_I)}$, and $d_4 = \frac{1}{2(\mu_c+\mu_1+\gamma_2)}$.

Next, using system (5.64) we obtain

$$\frac{dV[\varphi](t)}{dt} \leq (\mathcal{R}_0 - 1)\langle \mathbf{e}, \mathbf{u}(t)\rangle. \tag{5.79}$$

Hence we infer from the definition of X_{0+} that $t \mapsto V[\varphi](t)$ is decreasing along the entire solutions of U. To conlude our proof, let $\{t_n\}_{n\geq 0}$ be a sequence tending to $-\infty$ as $n \to +\infty$ and consider the sequence of map $\varphi_n(t) = \varphi(t + t_n)$. Note that one has $V[\varphi_n](t) = V[\varphi](t + t_n)$. Up to a subsequence one may assume that $\varphi_n(t) \to \widehat{\varphi}(t)$ as $n \to +\infty$ locally uniformly for $t \in \mathbb{R}$, where $\{\widehat{\varphi}(t)\}_{t\in\mathbb{R}} \subset \mathcal{A}$ is an entire solution of U. Since V is decreasing, one obtains that

$$V[\widehat{\varphi}](t) \equiv \lim_{t\to-\infty} V[\varphi](t) = \sup_{t\in\mathbb{R}} V[\varphi](t).$$

By setting $\widehat{\varphi} = (\widehat{\mathbf{u}}, \widehat{R}, 0_{\mathbb{R}^2}, \widehat{\mathbf{y}})$, equation (5.79) yields to $\widehat{\mathbf{u}}(t) \equiv 0$ while $\widehat{\mathbf{y}} \equiv (s^0(.), v^0(.))^T$. Hence $V[\widehat{\varphi}](t) \equiv 0$ and $0 \leq V[\varphi](t) \leq 0$ for $t \in \mathbb{R}$ and $\varphi(t) \equiv \mathbf{E}^0$. This end the proof of Theorem 5.2.2. □

Remark 5.2.2. *With respect to the result of Zou et al.[222], we do not ignore the proportion of perinatal infection to deal with the stability of the disease-free steady state of model* (5.64).

5.2.5 Disease-endemic steady states.

In this subsection, we discuss the existence and stability of the disease-endemic steady states. Endemic equilibrium points are steady-state solutions where the disease persists in the population. We use general bifurcation theory to prove the existence of at least one endemic equilibrium point for all $\mathcal{R}_0 > 1$. We have the following result.

Theorem 5.2.3. *Let Assumption 5.2.1 be satisfied and $\mathcal{R}_0 > 1$, then there is a unique positive disease-endemic steady state $\mathbf{E}^*(.) = (s^*(.), v^*(.), L_i^*, L_c^*, I^*, C^*, R^*)^T$ of system* (5.64)-(5.65).

Before giving the proof of Theorem 5.2.3, let us introduce the following useful result for the existence and uniqueness of a positive fixed point of a multi-variable function.

Theorem 5.2.4. *(Hethcote and Thieme [100], Theorem 2.1) Let $H(x)$ be a continuous, monotone non-decreasing, strictly sub linear, bounded function which maps the non-negative orthant $\mathbb{R}^n_+$ into itself. Let $H(0) = 0$ and $H'(0)$ exists and be irreducible. Then $H(x)$ does not have a non-trivial fixed point on the boundary of $\mathbb{R}^n_+$. Moreover, $H(x)$ has a positive fixed point iff the spectral radius $\rho(H'(0)) > 1$. If there is a positive fixed point, then it is unique.*

Proof of Theorem 5.2.3. The coordinates of $\mathbf{E}^*$ satisfied

$$\begin{aligned}
s(a) &= \theta(\Lambda - b\nu C)e^{-\int_0^a(\beta(\sigma)(I+C)+p(\sigma))d\sigma} \\
&\quad +\psi\int_0^a v(\eta)e^{-\int_\eta^a(\beta(\sigma)(I+C)+p(\sigma))d\sigma}d\eta, \qquad (5.80)\\
L_i &= \frac{I+C}{\mu_1+\gamma}\int_0^\omega \beta(a)\alpha(a)l(a)h(I,C,a)da,\\
L_c &= \frac{I+C}{\mu_1+\delta}\int_0^\omega \beta(a)(1-\alpha(a))l(a)h(I,C,a)da + \frac{b\theta\nu C}{\mu_1+\delta},\\
I &= \frac{\gamma(I+C)}{(\mu_1+\gamma)(\mu_1+\mu_I+\gamma_1)}\int_0^\omega \beta(a)\alpha(a)l(a)h(I,C,a)da, \qquad (5.81)\\
C &= \frac{\delta(I+C)}{(\mu_1+\delta)(\mu_1+\mu_c+\gamma_2)}\int_0^\omega \beta(a)(1-\alpha(a))l(a)h(I,C,a)da \\
&\quad +\frac{\delta b\theta\nu C}{(\mu_1+\delta)(\mu_1+\mu_c+\gamma_2)}, \qquad (5.82)\\
v(a) &= \Lambda(1-\theta)e^{-\psi a} + \int_0^a p(\eta)s(\eta)e^{-\psi(a-\eta)}d\eta,\\
R &= \frac{\gamma_1 I + \gamma_2 C}{\mu_1}.
\end{aligned}$$

wherein $h(I, C, a)$ is the right-hand side of (5.80).

Using equations (5.81) and (5.82) we have the following fixed point equation $H(I, C)^T = (I, C)^T$; where

$$H : (I,C) \in [0,M_0]\times[0,M_0] \subset \mathbb{R}^2 \to \mathbb{R}^2 \ni H(I,C)^T =$$
$$\begin{pmatrix} \frac{\gamma(I+C)}{(\mu_1+\gamma)(\mu_1+\mu_I+\gamma_1)}\int_0^\omega \beta(a)\alpha(a)l(a)h(I,C,a)da \\ \frac{\delta(I+C)}{(\mu_1+\delta)(\mu_1+\mu_c+\gamma_2)}\int_0^\omega \beta(a)(1-\alpha(a))l(a)h(I,C,a)da + \frac{\delta b\theta\nu C}{(\mu_1+\delta)(\mu_1+\mu_c+\gamma_2)} \end{pmatrix}, \qquad (5.83)$$

wherein M_0 is a positive constant provided by item (ii) of Theorem 5.2.1.

Thus the equilibrium points are fixed points of H given by

$$H(I,C)^T = (I,C)^T. \qquad (5.84)$$

The equation (5.84) implies that at the endemic steady state the infected population simply reproduce itself. Therefore we can call H the next generation operator at the endemic steady state. This fact will be used to show the stability of the endemic steady state in the next subsection.

We use (5.84) to prove existence and uniqueness of an endemic equilibrium point.

We easily find that $H(.,.)$ is continuous, bounded function. Since $h(0,0,.) = s^0(.)$ (the disease-free steady state) and H is infinitely differentiable, then the Jacobian at point $(0,0)$ is given by

$$H'(0,0) = \begin{pmatrix} \frac{\gamma \mathcal{K}_i}{(\mu_1+\gamma)(\mu_1+\mu_I+\gamma_1)} & \frac{\gamma \mathcal{K}_i}{(\mu_1+\gamma)(\mu_1+\mu_I+\gamma_1)} \\ \\ \frac{\delta \mathcal{K}_c}{(\mu_1+\delta)(\mu_1+\mu_c+\gamma_2)} & \frac{\delta(\mathcal{K}_c+b\theta\nu)}{(\mu_1+\delta)(\mu_1+\mu_c+\gamma_2)} \end{pmatrix}$$

Thus the function $H(I,C)$ is monotone non-decreasing and $H(0,0) = (0,0)$. Note that $\rho(H'(0,0)) = \mathcal{R}_0 > 1$. Thanks the graph theory, we claim that $H'(0,0)$ is irreducible because the associated graph of the matrix is strongly connected.

Let us now prove that H is strictly sub linear, i.e., $H(rI,rC) > rH(I,C)$, for any $(I,C) > 0$ and $r \in (0,1)$. For instance let us set $H(.,.) := (H_1(.,.); H_2(.,.))$, then

$$\frac{rH_1(I,C)}{H_1(rI,rC)} = \frac{r\int_0^\omega \beta(a)(1-\alpha(a))l(a)h(I,C,a)da}{\int_0^\omega \beta(a)(1-\alpha(a))l(a)h(rI,rC,a)da} \leq r < 1;$$

and the same argument gives that $\dfrac{rH_2(I,C)}{H_2(rI,rC)} < 1$. Then applying Theorem 5.2.4, the result follows. □

Remark 5.2.3. *As in Remark 5.2.2 and with respect to the result to result of Zou et al.[222] we do not ignore deaths directly related to HBV to deal with the existence of the disease-endemic steady state.*

The rest of this section deals with the stability of the endemic steady-state. The linearized system (5.64) at the endemic steady state $\mathbf{E}^* = (\mathbf{u}^*, R^*, \{0_{\mathbb{R}^2}\}, \mathbf{y}^*(.))$ can be written as

$$\frac{d\varphi(t)}{dt} = A\varphi(t) + F_e\varphi(t), \tag{5.85}$$

with $\varphi(t) = (\mathbf{u}(t), R, 0_{\mathbb{R}^2}, \mathbf{y}(t,.))^T$ and where the linear operator F_e is given by

$$F_e\left((\mathbf{u}(t), R(t), 0_{\mathbb{R}^2}, \mathbf{y}(t,.))^T\right) =$$

$$\begin{pmatrix} \int_0^\omega l(a)\beta(a)\langle \mathbf{e}_1, \mathbf{y}^*(a)\rangle F_2(a)\mathbf{u}(t)da + \int_0^\omega l(a)\beta(a)\langle \mathbf{e}_1, \mathbf{y}(t,a)\rangle F_2(a)\mathbf{u}^* da + F_3\mathbf{u}(t) \\ \langle F_4, \mathbf{u}(t)\rangle - \mu_1 R(t) \\ (-b\theta\nu u_4(t); 0; F_1(a)\mathbf{y}(t,a) - \beta(a)\langle \mathbf{e}, \mathbf{u}^*\rangle E_1\mathbf{y}(t,a) - \beta(a)\langle \mathbf{e}, \mathbf{u}(t)\rangle E_1\mathbf{y}^*(a)) \end{pmatrix}^T. \tag{5.86}$$

Since the linearized stability principle holds for the age-structured population system (5.64) (Ref. [211]), the endemic steady state is locally asymptotically stable if the trivial equilibrium $\varphi = 0$ of the linearized system (5.85) is locally asymptotically stable, while the endemic steady state is unstable if $\varphi = 0$ is unstable in (5.85).

In order to see the linearized stability by calculating the resolvent spectrum, let us consider the resolvent equation for the linearized operator:

$$(z - (A + F_e))\, w = u, \quad w \in D(A), \quad u \in X, \quad z \in \mathbb{C}.$$

Let $w = (\bar{s}(.), \bar{v}(.), \bar{L}_i, \bar{L}_c, \bar{C}, \bar{I}, \bar{R})$ and $u = (u_1(.), u_2(.), u_3, u_4, u_5, u_6, u_7)$. Then we have

$$\begin{aligned}
\bar{s}'(a) &= -(z + \beta(a)(I^* + C^*) + p(a))\bar{s}(a) + \psi\bar{v}(a) \\
&\quad -\beta(a)s^*(a)(\bar{I} + \bar{C}) + u_1(a), && (5.87)\\
\bar{v}'(a) &= -(z + \psi)\bar{v}(a) + p(a)\bar{s}(a) + u_2(a), \\
z\bar{L}_i &= (I^* + C^*)\int_0^\omega \alpha(a)l(a)\beta(a)\bar{s}(a)da && (5.88)\\
&\quad +(\bar{I} + \bar{C})\int_0^\omega \alpha(a)l(a)\beta(a)s^*(a)da - (\mu_1 + \gamma)\bar{L}_i + u_3, && (5.89)\\
z\bar{L}_c &= (I^* + C^*)\int_0^\omega (1 - \alpha(a))l(a)\beta(a)\bar{s}(a)da + b\theta\nu\bar{C} + u_4 \\
&\quad +(\bar{I} + \bar{C})\int_0^\omega (1 - \alpha(a))l(a)\beta(a)s^*(a)da - (\mu_1 + \delta)\bar{L}_c, && (5.90)\\
z\bar{I} &= \gamma\bar{L}_i - (\gamma_1 + \mu_1 + \mu_I)\bar{I} + u_5, && (5.91)\\
z\bar{C} &= \delta\bar{L}_c - (\gamma_2 + \mu_1 + \mu_c)\bar{C} + u_6, && (5.92)\\
z\bar{R} &= \gamma_1\bar{I} + \gamma_2\bar{C} - \mu_1\bar{R} + u_7, \\
&\quad \bar{s}(0) = -b\theta\nu\bar{C}; \quad \bar{v}(0) = 0. && (5.93)
\end{aligned}$$

Equations (5.88) and (5.87), coupling with (5.93), respectively gives

$$\bar{v}(a) = \int_0^a (p(\sigma) + u_2(\sigma))e^{-(z+\psi)}(a - \sigma)\bar{s}(\sigma)d\sigma,$$

and

$$\bar{s}(a) = -b\theta\nu\bar{C}e^{-\int_0^a (z+\beta(\eta)(I^*+C^*)+p(\eta))d\eta}$$
$$+\int_0^a [u_1(\sigma)+\psi\bar{v}(\sigma)-\beta(\sigma)s^*(\sigma)(\bar{I}+\bar{C})]e^{-\int_\sigma^a (z+\beta(\eta)(I^*+C^*)+p(\eta))d\eta}d\sigma.$$

Recalling (5.73); from (5.91) and (5.92) it comes that

$$\bar{L}_i = \frac{1}{\gamma}(z+v_{33}) - \frac{u_5}{\gamma}, \quad \bar{L}_c = \frac{1}{\delta}(z+v_{44}) - \frac{u_6}{\delta}. \tag{5.94}$$

Substituting (5.94) into system (5.89)-(5.90) we have

$$(I - B(z))(\bar{I},\bar{C})^T = (\chi_1,\chi_2)^T; \tag{5.95}$$

where $B(z)$, $z \in \mathbb{C}$ is 2×2 matrix defined by

$$B(z) = \begin{pmatrix} B_1(z) & B_1(z) \\ B_2(z) & B_2(z) + \dfrac{\delta b\theta\nu}{v_{22}v_{44}} \end{pmatrix}, \tag{5.96}$$

wherein

$$\begin{aligned} B_1(z) &= \frac{\gamma\int_0^\omega \alpha(a)l(a)\beta(a)s^*(a)da}{(z+v_{11})(z+v_{33})}; \\ B_2(z) &= \frac{\delta\int_0^\omega (1-\alpha(a))l(a)\beta(a)s^*(a)da}{(z+v_{22})(z+v_{44})}; \end{aligned}$$

and

$$\begin{aligned} \chi_1 &= \frac{\gamma(\bar{I}^*+\bar{C}^*)\int_0^\omega \alpha(a)l(a)\beta(a)s^*(a)da}{(z+v_{11})(z+v_{33})} + \frac{u_5}{z+v_{33}}; \\ \chi_2 &= \frac{\delta(\bar{I}^*+\bar{C}^*)\int_0^\omega (1-\alpha(a))l(a)\beta(a)s^*(a)da}{(z+v_{22})(z+v_{44})} + \frac{u_6}{z+v_{44}}. \end{aligned}$$

We can observe that $B(0) \leq H$, where H is the next generation operator at the endemic steady state. Since H is also irreducible, its spectral radius is the Frobenius eigenvalue corresponding to the unique positive eigenvector. If $\mathcal{R}_0 > 1$, H has a positive fixed point (see Theorem 5.2.3), that is $r(H) = 1$. Hence from Perron-Frobenius Theorem we obtain that $r(B(0)) < r(H) = 1$. Let Σ^* be the spectrum of $A + F_e$. By using the same argument as the proof of Claim 5.2.1, we know that the dominant characteristic root in Σ^* is given as the unique real root of equation $r(B(z)) = 1$, $z \in \mathbb{C}$, and it is less than zero if $r(B(0)) < 1$. Then it follows that the endemic steady state is locally asymptotically stable. Therefore, we obtain the following result on the stability of the disease-endemic steady state.

Theorem 5.2.5. *Let Assumption 5.2.1 be satisfied and $\mathcal{R}_0 > 1$, then the disease-endemic steady state $\mathbf{E}^*$ of system* (5.64) *is locally asymptotically stable.*

5.2.6 Numerical illustration

The model parameters.

Our numerical simulations are based on some main parameters used or derived in Zhao, Xu, and Lu[221]; Zou, Zhang and Ruan[222] for HBV infection.

We first have the transmission coefficient $\beta(a)$ given by

$$\beta(a) = \begin{cases} 0.13074116 - 0.01362531a + 0.00046463a^2 - 0.00000489a^3; \ 0 \leq a \leq 47.5, \\ \beta(47.5); \ a > 47.5 \end{cases} \tag{5.97}$$

The probability of susceptible age a to become latently infected (progressing to symptomatic infectiousness) is given by

$$\alpha(a) = 0.9153552 - 0.706004 \exp(-0.787711a), \tag{5.98}$$

thus $1 - \alpha(a)$ is the probability of susceptible age a to become latently infected (progressing to asymptomatic infectiousness). The remaining parameters are given in Table 5.6.

Using a constant p for $p(a)$, we simulate the behavior of the model. Fig. 5.5 illustrates the behavior of system for $p = 0.5$, $\theta = 0.1$, $\nu = 0.011$ such that $\mathcal{R}_0 = 0.8413 < 1$ ($\widetilde{\mathcal{R}}_0 = 0.8413 < 1$); that is the disease cannot persist. Secondly, we observe the behavior of the system for $p = 0.12$. In Figure 5.6, $\theta = 0.6$ such that $\mathcal{R}_0 = 2.3320 > 1$ ($\widetilde{\mathcal{R}}_0 = 2.3338 > 1$). This indicates that hepatitis B is endemic.

Sensitivity analysis of model parameters to $\widetilde{\mathcal{R}}_0$

We carried out the sensitivity analysis to determine the model robustness to parameter values. That is to help us know the parameters that have a hight impact on the reproduction number ($\mathcal{R}_0$); using the approach in(Chitnis et al. [32]).

Definition 5.2.1. *The normalized forward sensitivity index of basic reproduction number, $\widetilde{\mathcal{R}}_0$, that depends differentiably on a parameter, l, is defined as:*

$$\Upsilon_l^{\widetilde{\mathcal{R}}_0} := \frac{\partial \widetilde{\mathcal{R}}_0}{\partial l} \times \frac{l}{\widetilde{\mathcal{R}}_0}. \tag{5.99}$$

We therefore derive the sensitivity of the basic reproduction number $\widetilde{\mathcal{R}}_0$ to each of the following parameters: $p(.)$, $1 - \theta$ and $1 - \nu$ (see Table 5.6 for they description). As

for our numerical simulation, here we also assume that $p(.)$ is a constant parameter: $p(a) \equiv p = 90\%$ for all $a \in [0, \omega]$.

Recalling that

$$\widetilde{\mathcal{R}}_0 = \frac{\delta(\mathcal{K}_c(p) + b\theta\nu)}{v_{22}v_{44}} + \frac{\gamma\mathcal{K}_i(p)}{v_{11}v_{33}},$$

with

$$\mathcal{K}_i(p) = \int_0^\omega \beta(a)\alpha(a)l(a)s^0(p,a)da, \quad \mathcal{K}_c(p) = \int_0^\omega \beta(a)(1-\alpha(a))l(a)s^0(p,a)da,$$

and $s^0(p,a) \equiv s^0(a)$ (the disease-free steady state of the model) when $p(.)$ is assume to be the constant p. In this case, we easily find that

$$s^0(p,a) = \Lambda e^{-(p+\psi)a}\left(\theta - \frac{\psi}{\psi+p}\left(1 - e^{(p+\psi)a}\right)\right).$$

The detail sensitivity indices of $\widetilde{\mathcal{R}}_0$ resulting from the evaluation of parameters of the model are shown below:

$$\begin{aligned}
\Upsilon_p^{\widetilde{\mathcal{R}}_0} &= \left(\frac{\delta(K_c^0(p) + b\theta\nu)}{v_{22}v_{44}} + \frac{\gamma K_i^0(p)}{v_{11}v_{33}}\right)\frac{p}{\widetilde{\mathcal{R}}_0};\\
\Upsilon_{1-\theta}^{\widetilde{\mathcal{R}}_0} &= \frac{\delta b\nu}{v_{22}v_{44}} \times \frac{\theta - 1}{\widetilde{\mathcal{R}}_0};\\
\Upsilon_{1-\nu}^{\widetilde{\mathcal{R}}_0} &= \frac{\delta b\theta}{v_{22}v_{44}} \times \frac{\nu - 1}{\widetilde{\mathcal{R}}_0};
\end{aligned} \tag{5.100}$$

wherein

$$\mathcal{K}_i^0(p) = \int_0^\omega \beta(a)\alpha(a)l(a)\partial_p s^0(p,a)da, \quad \mathcal{K}_c^0(p) = \int_0^\omega \beta(a)(1-\alpha(a))l(a)\partial_p s^0(p,a)da.$$

The sensitivity index of basic reproduction number is summarize in Table 5.4.

Table 5.4 implies that increasing (resp. decreasing) the vaccination rate of susceptible, by 10%, decreases (resp. increases) the basic reproduction rate $\widetilde{\mathcal{R}}_0$ by 4.91%.

Increasing (resp. decreasing) the proportion of births with successful vaccination, $1-\theta$, by 10%, decreases (resp. increases) the basic reproduction rate $\widetilde{\mathcal{R}}_0$ by 0.34%.

Similarly, increasing (resp. decreasing) the proportion of births without perinatal infection, $1-\nu$, by 10%, decreases (resp. increases) the basic reproduction rate $\widetilde{\mathcal{R}}_0$ by 4.13%.

Actually, it is not easy to practice a mass vaccination to all the susceptible individuals: a specific age group of susceptible should be provided. Then, let us examine the impact of the mass group vaccination of susceptible (i.e. for a specific age group of susceptible

Table 5.4: Sensitivity index of model parameters to $\widetilde{\mathcal{R}}_0$

Parameter	Description	Sensitivity index
p	vaccination rate of susceptible	-0.4910
$1-\theta$	proportion of births with successful vaccination	-0.0341
$1-\nu$	proportion of births without perinatal infection	-0.4135

individuals) on the spread of the disease. To this end we consider two age groups: $0 \leq a \leq 5$ (years) and $a > 5$ (years). The vaccination rate of susceptible $p(a)$ is then define by:

$$p(a) = \begin{cases} p_1 \text{ per year; } 0 \leq a \leq 5 \text{ (years)}, \\ p_2 \text{ per year; } a > 5 \text{ (years)}, \end{cases} \tag{5.101}$$

wherein $p_j; (j = 1, 2)$ is the vaccination rate of susceptible for the specific age group.

Consider the same vaccination rate of susceptible for each age group, that is $p_j = 90\%; (j = 1, \ldots, 5)$ and $\theta = 0.6$ (the remaining parameters are given in Table 5.6), the sensitivity index of the vaccination rate of susceptible for the specific age group is summarize in Table 5.5. We observe that the much sensitive group is susceptible individuals with age between 0 and 5 years old (with respect to our set of parameters).

Let us simulate the impact of age group mass vaccination on the spread of the disease. For this end, consider $p_2 = 0$ (i.e. there is not vaccination on the group of susceptibles with more than 5 years old) and for different values of mass vaccination rate p_1 on the group age $[0, 5]$(years old). Figure 5.7 indicates that mass vaccination in infants (with less than 5 years old) can reduce the spread of the epidemic (specially the spread of the asymptotic infection of HBV). But, this is not enough to control the infection.

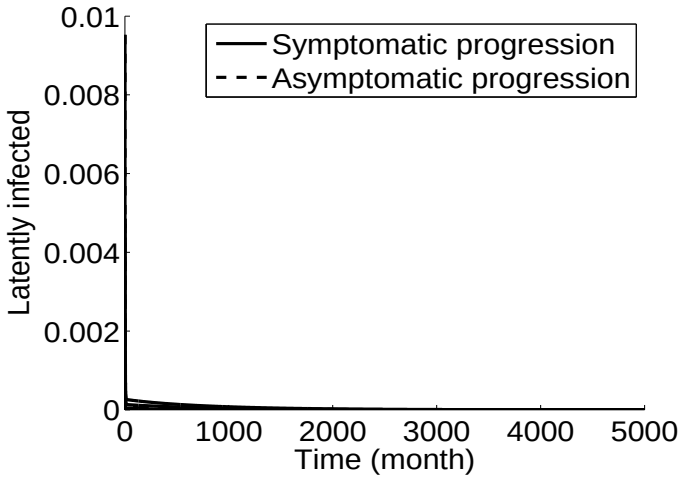
To find better control strategies for HBV infection, we would like to see what parameters can reduce the basic reproduction number $\mathcal{R}_0$ given by (5.74). From Fig. 5.8 we can see that $\mathcal{R}_0$ decreases if $1-\theta$ (immunization of newborns) increases, or ν (proportion of perinatally infected) decreases, or p (immunization of susceptible individuals) increases. Fig. 5.8(a) shows that combining immunization of susceptible individuals (at least young adults) and reduction of perinatal infection can reduce $\mathcal{R}_0$ to be less than 1. HBV could be eliminated even if $p = 0$ and $1-\nu$ is large enough (see Fig. 5.5). Fig. 5.8(b) also shows that combining immunization of newborns and reduction of perinatal infection is also an efficient intervention. HBV could be eliminated if both $1-\nu$ and $1-\theta$ are large enough. Fig. 5.8(c) shows that combining immunization of

Table 5.5: Sensitivity index of vaccination rate for the specific age group to $\widetilde{\mathcal{R}}_0$

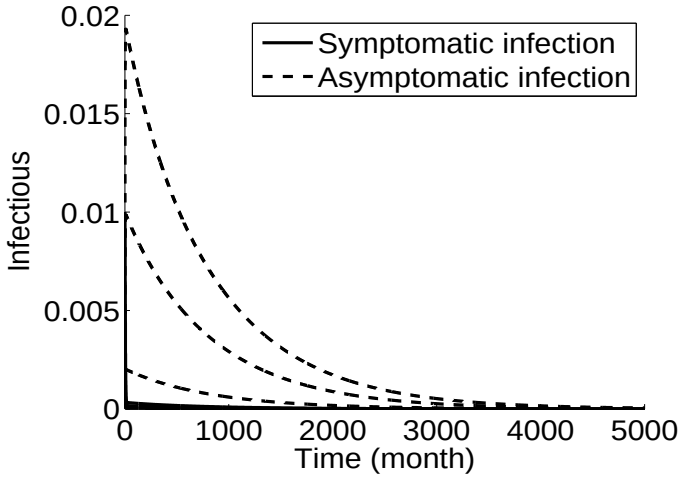
Two age groups case: $[0,5]$(years old) and $]5,\omega]$(years old)		
Parameter	Description	Sensitivity index
p_1	vaccination rate of susceptibles age a: $0 \leq a \leq 5(years)$	-0.4590
p_2	vaccination rate of susceptibles age a: $a > 5(years)$	-0.0772
$1-\theta$	proportion of births with successful vaccination	-0.0286
$1-\nu$	proportion of births without perinatal infection	-0.3473
Only one age group case: $[0,5]$(years old)		
Parameter	Description	Sensitivity index
p_1	vaccination rate of susceptibles age a: $0 \leq a \leq 5(years)$	-0.3347
$1-\theta$	proportion of births with successful vaccination	-0.0206
$1-\nu$	proportion of births without perinatal infection	-0.2500

both newborns and susceptible individuals can reduce $\mathcal{R}_0$ to be less than 1. HBV could be eliminated if both p and $1-\theta$ are large enough. If the transmission coefficient $\beta(.)$ is sufficiently small HBV could also be eliminated. However, it is difficult to control $\beta(.)$.

In the light of these results, we find that the control of the epidemic of hepatitis B virus pass through a reduction or even eradication of perinatal transmission of the disease (See Figs 5.8(a),(b),(c)). Therefore, although the proportion of perinatal transmission of the disease is low (as pointed in Zou et al.[222]), this factor should not be neglected in the transmission of HBV. A control strategy will be a combination of immunization of newborns, immunization of susceptible individuals (at least young adults), and reduction of perinatal infection.

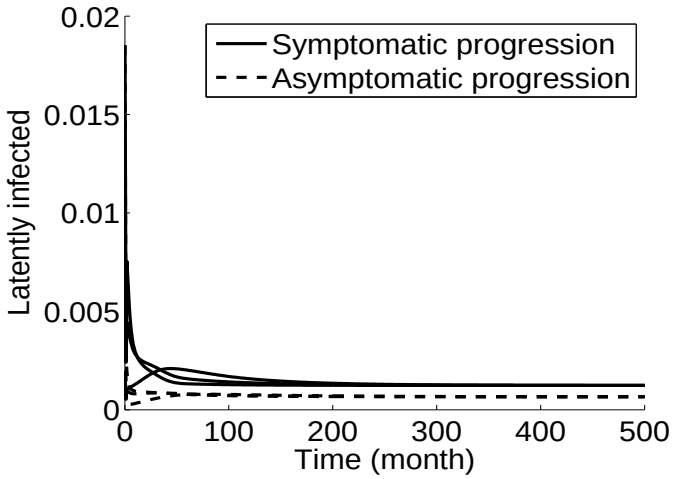


(a)

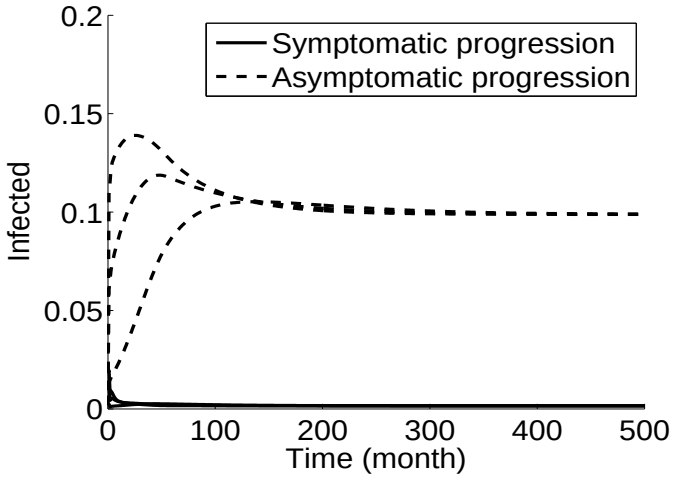


(b)

Figure 5.5: The behavior of system for $p = 0.5$, $\theta = 0.1$, $\nu = 0.011$ and $\mathcal{R}_0 = 0.8413$. All other parameters are given in Tab. 5.6 and Eqs. (5.97)-(5.98).

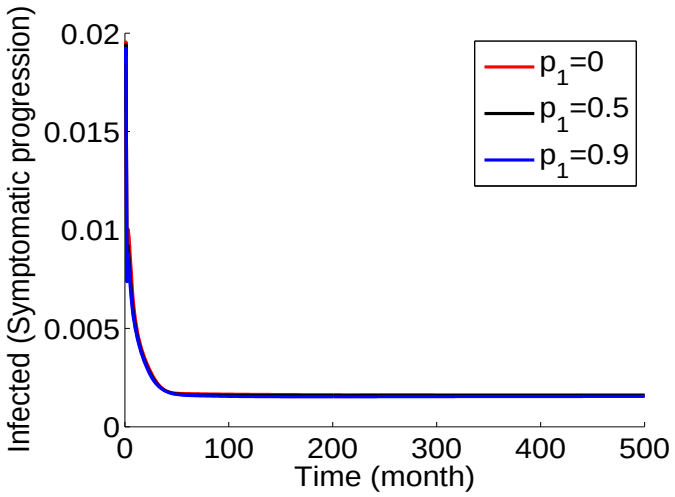


(a)

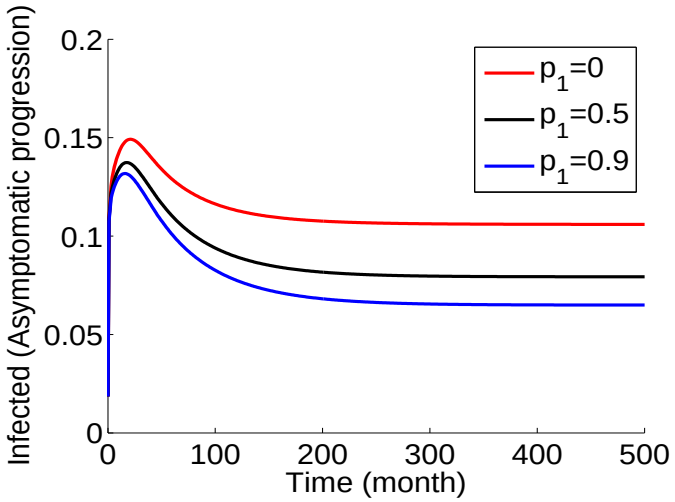


(b)

Figure 5.6: The behavior of system for $p = 0.12$, $\theta = 0.6$ and $\mathcal{R}_0 = 3.2707$. All other parameters are given in Tab. 5.6 and Eqs. (5.97)-(5.98).



(a)



(b)

Figure 5.7: Impact of the mass vaccination on the spread of the epidemic: $p_1 \in \{0, 0.5, 0.9\}$ for group $[0, 5]$(years old) and $p_2 = 0$ for group $]5, \omega]$(years old). $\theta = 0.6$ and all other parameters are given in Tab. 5.6 and Eqs. (5.97)-(5.98).

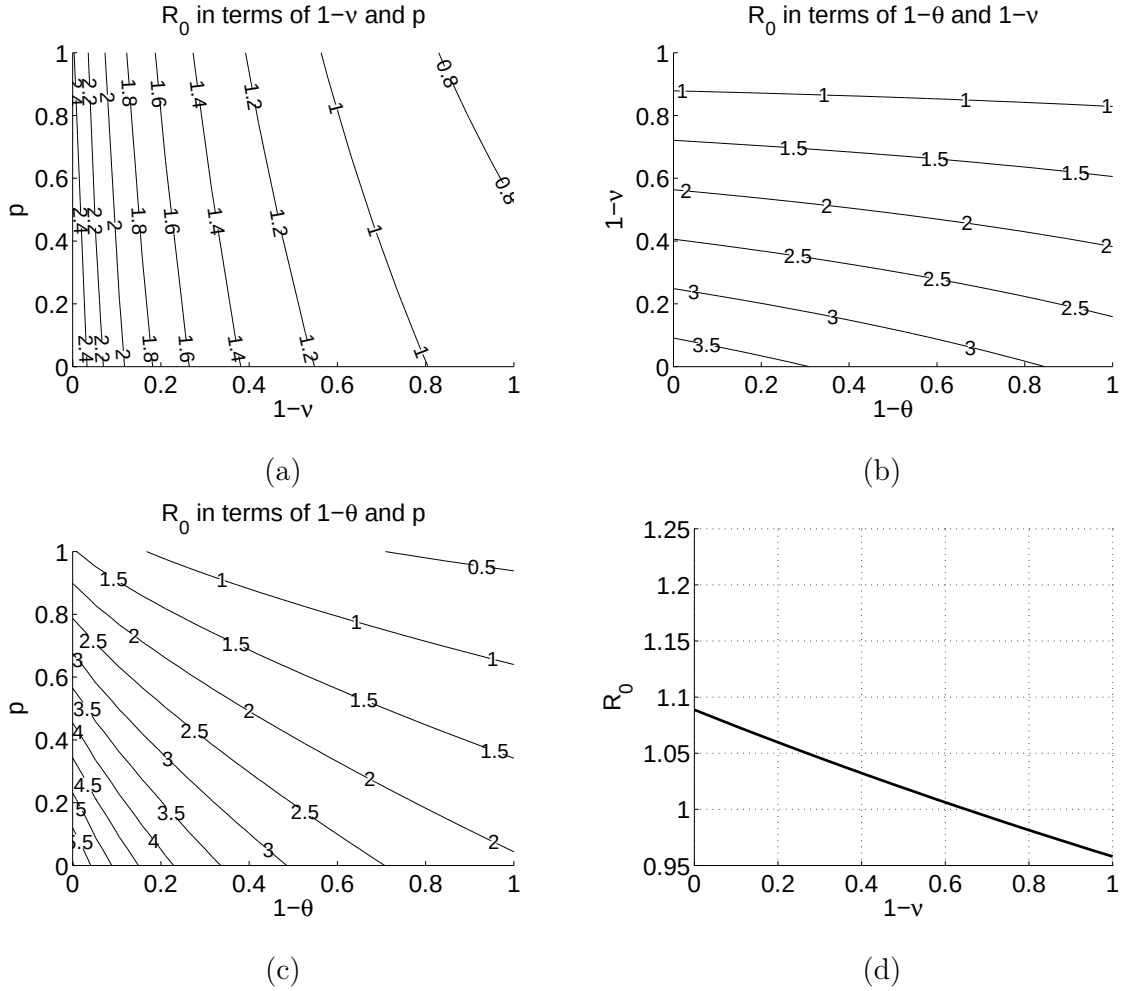


Figure 5.8: The graphs of the basic reproduction number $\mathcal{R}_0$ in terms of some parameters: (a) $\mathcal{R}_0$ in terms of $1-\nu$ and p. $1-\theta$ is fixed to be $1-\theta = 0.8$, (b) $\mathcal{R}_0$ in terms of $1-\theta$ and $1-\nu$. p is fixed to be $p = 0.5$, (c) $\mathcal{R}_0$ in terms of $1-\theta$ and p. $1-\nu$ is fixed to be $1-\nu = 0.89$, (d) $\mathcal{R}_0$ in terms of $1-\nu$. p and $1-\theta$ fixed to be $p = 0.45$ and $1-\theta = 0.87$. All other parameters are given in Tab. 5.6 and Eqs. (5.97)-(5.98).

5.2.7 Summary

In this section, we have examined an age-structured model for the transmission of Hepatitis B virus (HBV) with differential infectivity: symptomatic infection and asymptomatic infection. The rationale for including age-structured can be multiple. According to CDC and WHO, risk for chronic infection is inversely related to age at infection: approximately 90% of infected infants and 30% of infected children aged under 5 years

Table 5.6: Parameters values used in numerical simulation

Parameters	Description	Values	Ref.
$p(a)$	vaccination rate of susceptible	0 - 1	
μ_1	natural mortality rate	0.0132/yr	WHO[219]
μ_I, μ_C	HBV-related mortality rate	0.2%/yr	CDC[30]
γ	rate moving from latent infection to symptomatic infectiousness	6/yr	Edmunds et al.[67], CDC[30]
δ	rate moving from latent to asymptomatic infectiousness	6/yr	Edmunds et al.[67], CDC[30]
Λ	total number of births	variable	
b	equilibrium birth rate	0.0380/year	WHO[219]
$1-\theta$	proportion of births with successful vaccination	0 - 1	
ψ	rate of waning vaccine-induced immunity	0.1	Edmunds et al.[63]
γ_1	rate moving from symptomatic infectiousness to recovered	4.8/yr	Edmunds et al.[67], CDC[30]
γ_2	rate of moving from asymptomatic infectiousness to recovered	0.025/yr	Edmunds et al.[67], CDC[30]
ν	proportion of perinatally infected (from chronicle infectious mothers)	0.11	Edmunds et al.[67]

become chronically infected, compared with 5% of adults. Vaccination is recognized as the most efficient way of preventing hepatitis B. But the problem of imperfect vaccine introduce naturally differential susceptibility. Even if HBV vaccine is very efficient it does not offer 100% protection against infection. According to WHO, Hepatitis B vaccine is 95% effective in preventing HBV infection and its chronic consequences.

The main finding of this section can be summarized along the following lines:

✓ We discussed the existence and stability of the disease-free and disease-endemic equilibria of the model in terms of the basic reproduction number $\mathcal{R}_0$.

✓ We performed sensitivity analysis of the parameters with respect to the basic

reproduction number $\mathcal{R}_0$.

The analytical results and numerical simulations of the model suggest that :

✓ Mass vaccination in infants increases the average age of infection in unimmunized individuals and shifts the average age at infection to older age groups (Edmunds et al.[67]). This indicates that mass vaccination in infants might be not enough to control the infection and eradicate the virus (this is also supported by Zou et al.[222]).

✓ The control strategy consist in a combination of immunization of newborns, immunization of susceptible individuals (at least young adults), and reduction of perinatal infection.

Conclusion

This work deals with a recent within-host malaria infection model with multistrain for the parasites and a spatial modeling of anopheles mosquito dynamics population. In this work, we also consider population models of infectious disease structured by age. Namely, Hepatitis B virus (HBV) and Susceptible-Infected-Lost of sight (SIL) models.

The first section of the first true chapter of this work deals with an age-structured within-host model for multistrain malaria infection. This model incorporates n strains for the parasite. Using integrated semigroup theory, we provided a global analysis of this model. The rationale for including multi-strain can be multiple. One reason is to take into account biological reasons, e.g., consideration of morphological or age classes. The second is due to the recent study on this subject. Recently, it has been proved that a deeper understanding of the dynamic growth responses of multiple strain *P. falciparum* infections can improve the understanding of the role of parasite interactions in the spread of drug resistant parasites, perhaps suggesting different treatment strategies [208]. This model has been conceived from malaria infection, since it is well grounded that malaria is a multi-strain infection. However other parasitic infections can be considered by this model, e.g., the model can be extended to the HIV infections [105]. The main finding of this model is the following:

► To separate the different strains we associated for each strain the i-specific basic reproduction number $\mathcal{R}_0^i$. We then find that the basic reproduction number of the model is defined by $\mathcal{R}_0 = \max_{i=1,\dots,n} \mathcal{R}_0^i$.

► We also find that if $\mathcal{R}_0 \leq 1$, the model exhibits a unique disease-free steady state, while if $\mathcal{R}_0 > 1$ the model has exactly n_E disease-endemic steady states, wherein $n_E = \text{Card}\left\{i \in \{1,\dots,n\} : \mathcal{R}_0^i > 1\right\}$.

► We prove that if the basic reproduction number of the model satisfies $\mathcal{R}_0 \leq 1$, then the parasite is cleared from the host population. Our global stability result when $\mathcal{R}_0 > 1$ can be summarized as a competitive exclusion principle. If $\mathcal{R}_0 > 1$, then there exists

a global asymptotic stable endemic equilibrium. This equilibrium corresponds to the extinction of all strains, except the strain with the largest threshold (winning strain).

In the first true chapter of this work, we also consider an advection-reaction model for anopheles mosquito dynamics population. Knowledge of the population dynamics of the malaria vector is fundamental to the understanding of malaria epidemiology and the spread of insecticide resistance. Therefore, studies on the population structure of malaria vectors have important implications for the prediction and assessment of the effects of many vector control strategies. According to all malaria models, little has been done with regard to the studies on the population dynamics of malaria vectors. The aim finding of our analyzes can be summarized along as follows:

▶ The seasonal spatio-temporal model of anopheles mosquito is consider. This model takes into account seasonal transmission and the geographical range of malaria. Using the semigroup approach we derive the existence of the unique bounded non-autonomous semiflow associated to the seasonal spatio-temporal model.

▶ To find the behavior of the non-autonomous semiflow associated to the seasonal spatio-temporal model, we introduce three threshold values $\mathcal{R}^{\diamondsuit}$, $\mathcal{R}_{\diamondsuit}$ and $\mathcal{R}_{*}$.

▶ Then, we find that, if $\mathcal{R}^{\diamondsuit} < 1$, the anopheles mosquito population dies out.

▶ We also derive persistence results for the seasonal mosquito model. Namely, if $\mathcal{R}_{\diamondsuit} > 1$ (resp. $\mathcal{R}_{*} > 1$) then anopheles mosquito uniformly weakly (resp. strongly) persists in the population.

The second (and the last) true chapter of this work is organized in two sections and deals with two population models structured by age. The first section is concerned by a mathematical SIL (Susceptible-Infected-Lost of sight) model for the spread of a directly transmitted infectious disease. The second section of the chapter is concerned by and age-structured model for the transmission of hepatitis B virus, with differential infectivity: symptomatic infection and asymptomatic infection.

The first section considered a model for the spread of a directly transmitted infections disease in an age-structured population with demographics process, SIL-model. The disease can be transmitted not only horizontally but also vertically from infected mothers to their newborns. There are important infective agents such as HBV (hepatitis B virus), HIV (human immunodeficiency virus) and HTLV (human T-cell leukemia virus) that can be vertically transmitted. In Africa, the vertical transmission of the disease like HIV

is in progression nowadays. The aim finding of this section is summarized as follows:

► We formulated the dynamical system with boundary conditions, and then described the semigroup approach to the time evolution problem of the abstract epidemic system.

► Next we have calculated the basic reproduction ratio and proved that the SIL-model exhibits a unique disease-free steady state if $R_0 \leq 1$, and at least one endemic steady state exists if the basic reproduction ratio R_0 is greater than the unity.

► We prove that if the basic reproduction number of the SIL-model satisfies $R_0 < 1$, then the disease-free steady state is locally asymptotically stable, i.e., the disease died out from the host population.

► We have shown sufficient conditions which guarantee the local stability of the endemic steady state; that is the persistence of the disease in the host population. Roughly speaking, the endemic steady state is locally asymptotically stable if $R_0 > 1$ and if it corresponds to a very small force of infection.

► Finally, to highlight the impact of the vertical transmission of the disease into the host population, we provided some illustrations and discussion on the outcome of the state variables of the model when the vertical transmission rate p takes different values: 0.02, 0.2 and 0.5.

In the second section of the second true chapter of this work, we have examined an age-structured model for the transmission of Hepatitis B virus (HBV) with differential infectivity: symptomatic infection and asymptomatic infection. Vaccination is recognized as the most efficient way of preventing hepatitis B. But the problem of imperfect vaccine introduce naturally differential susceptibility. Even if HBV vaccine is very efficient it does not offer 100% protection against infection. According to WHO, Hepatitis B vaccine is 95% effective in preventing HBV infection and its chronic consequences. The main finding of this section can be summarized along the following lines:

► We discussed the existence and stability of the disease-free and disease-endemic equilibria of the model in terms of the basic reproduction number $\mathcal{R}_0$.

► We performed sensitivity analysis of the parameters with respect to the basic reproduction number $\mathcal{R}_0$.

► The analytical results and numerical simulations of the model suggest that, mass vaccination in infants increases the average age of infection in unimmunized individuals and shifts the average age at infection to older age groups (Edmunds et al.[67]). This

indicates that mass vaccination in infants might be not enough to control the infection and eradicate the virus (this is also supported by Zou et al.[222]).

► A optimal control strategy consist in a combination of immunization of newborns, immunization of susceptible individuals (at least young adults), and reduction of perinatal infection.

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ANNEXE

SIAM J. APPL. MATH.
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AN AGE-STRUCTURED WITHIN-HOST MODEL FOR MULTISTRAIN MALARIA INFECTIONS*

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Abstract. In this paper we propose an age-structured malaria within-host model taking into account multistrains interaction. We provide a global analysis of the model depending upon some threshold $\mathcal{T}_0$. When $\mathcal{T}_0 \leq 1$, then the disease-free equilibrium is globally asymptotically stable and the parasites are cleared. On the contrary, if $\mathcal{T}_0 > 1$, the model exhibits the competition exclusion principle. Roughly speaking, only the strongest strain, according to a suitable order, survives while the other strains go to extinction. Under some additional parameter conditions we prove that the endemic equilibrium corresponding to the strongest strain is globally asymptotically stable.

Key words. structured population, competitive exclusion principle, nonlinear dynamical systems, global stability, *Plasmodium falciparum*, intrahost model

AMS subject classifications. 35Q92, 34K20, 92D30

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1. Introduction.

In this paper we consider an age-structured system of equations modeling the blood stage of multistrain malaria infections. We more specifically focus upon human malaria caused by the protozoa *Plasmodium falciparum*, the most widespread within the tropics and particularly in Sub-Saharan Africa.

According to Read and Taylor [40] natural parasitic infections are often diverse, including multiple parasite species and/or distinct genotypes of the same species. Parasites of the Plasmodium genus are no exception. Human infections of multiple strains or species have been widely reported [6, 49] and it may be typical in highly endemic regions [27, 29].

Recently, using quantitative PCR methods, Wacker et al. [48] proved and quantified that the interactions between different strains of *P. falciparum* lead to the competitive suppression of the weakest one. This feature was already observed for *P. chabaudi*, the parasite responsible for rodent malaria (see [6] and the references therein). Such a competition has a strong influence on the spread of strains and thus on drug resistance. According to Wacker et al. [48], a deeper understanding of the dynamic of multiple strain *P. falciparum* infection can improve the understanding of the role of parasite interactions in the spread of drug-resistant parasites, perhaps suggesting different treatment strategies.

In this work we shall focus on the blood stage of the parasite where the aforementioned competitive suppression has been reported. Before going to the mathematical model, let us briefly review the features of malaria. The life cycle of malaria parasites inside the human body consists of two phases: an exoerythrocytic (the liver stage) and an erythrocytic phase (the blood stage). After an infective bite, a mosquito injects the pathogen in the so-called sporozoites form, which rapidly reaches the liver

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cells. An asymptomatic period follows during which parasites mature and multiply asexually within the liver cells, yielding to hepatic schizonts. Once hepatic schitzonts rupture, the parasitized cells release the so-called merozoites into the bloodstream, the starting point of the blood stage. During this phase, the merozoites enter uninfected red blood cells (uRBC) to undergo asexual multiplication. After a sequestration period of about 48 hours (for *P. falciparum*) the rupture of the parasitized red bood cells (pRBC) occurs releasing 8 to 32 free merozoites into the bloodstream ready to repeat the invasion scheme. The blood stage of the parasites is mainly responsible for the clinical symptoms of the infection. The rupture of pRBC causes clinical fever. Moreover *P. falciparum* infection is the most frequent acquired RBC disorder in the world (see Buffet et al. [3] and the references therein), that may also lead to severe symptoms such as anemia or cerebral malaria.

In this paper we consider an age-structured intrahost model for *P. falciparum* infection with n different strains for the parasites. The age structure will allow us to have a good description of the pRBC rupture and of the merozoites release phenomenon. These parameters play an important role in describing the strength of a strain and thus have important consequences on the spread of the infection. The model we shall consider is an extension of the model proposed by Iggidr et al. in [26] by taking into account a continuous age structure. It reads as

$$
\begin{cases}
\dfrac{dx(t)}{dt} = \Lambda - \mu_x x(t) - x(t)\displaystyle\sum_{j=1}^{n} \beta_j m_j(t), \\
\dfrac{\partial w_j(t,a)}{\partial t} + \dfrac{\partial w_j(t,a)}{\partial a} = -(\mu_j(a) + \mu_x) w_j(t,a), \\
\dfrac{dm_j(t)}{dt} = \displaystyle\int_0^\infty r_j(a)\mu_j(a) w_j(t,a) da - \mu_{m,j} m_j(t) - \delta_j \beta_j x(t) m_j(t), \\
w_j(t,0) = \beta_j x(t) m_j(t), \;\; j \in \{1, 2, \ldots, n\}.
\end{cases}
\tag{1.1}
$$

In (1.1), the RBC population is split into two classes: $x(t)$ denotes the concentration of uRBC at time t, while $w_j(t,a)$ denotes the age-specific concentration of pRBC at time t and parasitized since a time a by a specific j-strain. Finally $m_j(t)$ denotes the concentration of free specific j-merozoites in the blood stream. We briefly sketch the interpretation of the parameters arising in (1.1). Parameters μ_x, $\mu_{m,j}$, respectively, denote the natural death rates for uRBC and for free specific j-merozoites. Function $\mu_j(a)$ denotes the additional death rate of pRBC due to the j-parasites at age a and leading to the rupture. The rupture of pRBC at age a results in the release of an average number $r_j(a)$ of specific j-merozoites into the blood stream, so that pRBC infected by a specific j-strain then produce, at age a, j-merozoites with the rate $r_j(a)\mu_j(a)$. Together with this description, the quantity $\int_0^\infty r_j(a)\mu_j(a)w_j(t,a)da$ corresponds to the number of specific j-merozoites produced by pRBC at time t. Finally the parameter β_j describes the contact rate between uRBC and free specific j-merozoites while Λ denotes the recruitment rate of uRBC from the bone marrow. In the literature the parameter δ_j takes the values $\delta_j = 0$ when the loss of merozoites, when they enter an RBC, is ignored or takes the value $\delta_j = 1$ when this loss is not ignored. System (1.1) is supplemented together with initial data whose properties will be described below.

There have been numerous works on pathogen within-host dynamics describing *P. falciparum* infection. The pioneer work of Anderson [2], focused on describing parasitemia, has been further developed in several direction including, in particular,

immune response and oscillations [13, 20, 21, 22, 30, 38]. We also refer to the survey paper of Molineaux and Dietz [39] and the references therein. However all these works do not take into account an important characteristic of *P. falciparum* which is sequestration of merozoites within the pRBC and their ruptures. Such an issue has been considered using discrete age-structured systems of equations (see, for instance, [14, 15, 16, 37]) with a constant RBC population assumption. We finally refer to Iggidr et al. [26] for a mathematical study of a discrete age-structured model with varying RBC concentration. Note that in this latter work multistrain competitive interaction is also considered and the authors derived the so-called competitive exclusion principle. In another context, let us mention that the one-strain system (1.1) (namely, with $n = 1$) has been rigorously and recently studied by Huang, Liu, and Takeuchi [23] in the context of the HIV infection model (and with $\delta = 0$).

Here we will extend these results to (1.1) by proving that this problem exhibits the competitive exclusion principle. This work is organized as follows. In section 2, we describe the main results that will be proved in this work. Section 3 is devoted to deriving preliminary results and remarks that will be used to study the long-term behavior of the problem. Section 4 is concerned with the proof of the first part of Theorem 2.2 below that, roughly speaking, states that when some threshold (explicitly expressed using the parameters of the system) $\mathcal{T}_0 \leq 1$, then all the strains asymptotically die out and the parasites cannot survive. Finally, section 5 deals with the proof of the second part of Theorem 2.2, that, roughly speaking, says that when $\mathcal{T}_0 > 1$ and under some additional assumptions on the different strains, the competitive exclusion principle holds true, that is, only the strongest strain (using a suitable order) is asymptotically surviving.

2. Main results. In this section we will state the main results of this work. In order to deal with system (1.1) we first provide a parameter reduction by introducing the following unknown functions $y_j(t,a) = w_j(t,a)e^{\int_0^a \mu_j(l)dl}$. Therefore, by introducing the vector-valued functions $\mathbf{y}(t,a) = (y_1(t,a), \dots, y_n(t,a))^T$, $\mathbf{m}(t) = (m_1(t), \dots, m_n(t))^T$, as well as the matrices

$$\begin{aligned} \beta &= \text{diag } (\beta_1, \dots, \beta_n)\,,\ \delta = \text{diag } (\delta_1, \dots, \delta_n)\,,\ \ E_n = (1, \dots, 1)^T \in \mathbb{R}^n, \\ \mu_m &= \text{diag } (\mu_{m,1}, \dots, \mu_{m,n})\,,\ \rho(a) = \text{diag } (\rho_1(a), \dots, \rho_n(a))\,, \end{aligned}$$

system (1.1) rewrites as

$$\begin{cases} \dfrac{dx(t)}{dt} = \Lambda - \mu_x x(t) - x(t)E_n^T \beta \mathbf{m}(t), \\ \partial_t \mathbf{y}(t,a) + \partial_a \mathbf{y}(t,a) = -\mu_x \mathbf{y}(t,a), \\ \mathbf{y}(t,0) = \beta x(t)\mathbf{m}(t), \\ \dfrac{d\mathbf{m}(t)}{dt} = \displaystyle\int_0^\infty \rho(a)\mathbf{y}(t,a)da - \mu_m \mathbf{m}(t) - \delta\beta x(t)\mathbf{m}(t), \end{cases} \tag{2.1}$$

supplemented together with initial data

$$\mathbf{y}(0,.) = \mathbf{y}_0(.) \in L^1\left(0,\infty;\mathbb{R}^n_+\right),\ x(0) = x_0 \geq 0,\ \mathbf{m}(0) = \mathbf{m}_0 \in \mathbb{R}^n_+, \tag{2.2}$$

and where we have set $\rho_j(a) = r_j(a)\mu_j(a)e^{-\int_0^a \mu_j(l)dl}$ for $j = 1, \dots, n$. In (2.2), $\mathbb{R}^n_+$ denotes the positive orthant, namely, $\mathbb{R}^n_+ = \{(x_1, \dots, x_n)^T \in \mathbb{R}^n :\ x_i \geq 0\ \forall i = 1, \dots, n\}$.

In what follows we shall discuss the asymptotic behavior of system (2.1)–(2.2) and we will make use of the following assumption.

Assumption 2.1. *We assume that, for each* $j \in \{1, 2, \dots, n\}$, *functions* ρ_j *belong to* $L^\infty_+(0, \infty, \mathbb{R}_+)$ *while* $\Lambda > 0$, $\mu_x > 0$, $\mu_{m,j} > 0$, $\delta_j \in \{0, 1\}$, *and* $\beta_j > 0$.

As mentioned in the introduction we shall focus on the competitive exclusion principle generated by (2.1). Roughly speaking, to achieve such a goal we will provide an order to separate the different strains of the parasite. Hence let us introduce, for each strain, the quantity $\mathcal{T}_0^i$ defined by

$$\mathcal{T}_0^i = \frac{\beta_i \Lambda}{\mu_x \mu_{mi}} \left(\int_0^\infty \rho_i(a) l(a) da - \delta_i \right), \tag{2.3}$$

as well as $\mathcal{T}_0 = \max_{1 \le i \le n} \mathcal{T}_0^i$ and where function $l \equiv l(a)$ is defined by

$$l(a) = e^{-\mu_x a}. \tag{2.4}$$

As will be seen below (see Theorem 2.2) the situation when $\mathcal{T}_0 \le 1$ is rather simple because the infection asymptotically dies out. When $\mathcal{T}_0 > 1$ the situation is much more involved. We expect that system (2.1)–(2.2) exhibits the competition exclusion principle that, roughly speaking, says that in the presence of multiple strains only the strongest can asymptotically survive. The parameters $\{\mathcal{T}_0^i\}_{i=1,\dots,n}$ (see (2.3)) will be used to quantify the strength of the different strain-specific infections. We will now introduce some definitions. Let us first of all define the set of strains that can potentially survive as $\mathcal{S}$ defined by

$$\mathcal{S} = \begin{cases} \{ i \in \{1, \dots, n\} : \ \mathcal{T}_0^i > 1 \} & \text{if } \mathcal{T}_0 > 1, \\ \emptyset & \text{if } \mathcal{T}_0 \le 1. \end{cases} \tag{2.5}$$

On the set of index $\{1, \dots, n\}$ we define an order relation by

$$i \trianglelefteq j \ \Leftrightarrow \ \mathcal{T}_0^i \le \mathcal{T}_0^j \ \text{ and } \ i \triangleleft j \ \Leftrightarrow \ \mathcal{T}_0^i < \mathcal{T}_0^j.$$

We would like to emphasize that when the parameters δ_j are nonzero, the set of threshold $\{\mathcal{T}_0^i\}_{i=1,\dots,n}$ is different from the set of the different strain-specific basic reproduction numbers. Indeed the strain i–specific basic reproduction number reads as (see Appendix A for the computation)

$$\mathcal{R}_0^i = 1 + \frac{\mu_{m,i}}{\mu_{m,i} + \delta_i \beta_i x_f} \left(\mathcal{T}_0^i - 1 \right) \ \text{with } x_f = \frac{\Lambda}{\mu_x}. \tag{2.6}$$

Hence, when $\delta \neq 0$, the above described order may be different from the one induced by the strain-specific basic reproduction numbers.

We also denote by $\max^\triangleleft$ the maximum operator associated with the order $\trianglelefteq$. Note that in general the operator $\max^\triangleleft$ is multivalued and is defined by

$$\max{}^\triangleleft\{i, j\} = \begin{cases} i & \text{if } \mathcal{T}_0^i > \mathcal{T}_0^j, \\ j & \text{if } \mathcal{T}_0^j > \mathcal{T}_0^i, \\ \{i, j\} & \text{if } \mathcal{T}_0^i = \mathcal{T}_0^j. \end{cases}$$

A subset $\{i_1, \dots, i_p\} \subset \{1, \dots, n\} := \mathbb{N}_n$ is said to be *strictly ordered* if there exists a permutation σ of $\{1, \dots, p\}$ such that $i_{\sigma(1)} \triangleleft \cdots \triangleleft i_{\sigma(p)}$. Let us notice that on

a strictly ordered set, the operator $\max^{\lhd}$ becomes a single-valued map. Let us also mention that for biological reasons, since we aim to deal with the competitive exclusion principle for our multistrain model, it is relevant to assume that the different strain is distinguishable. Hence we shall assume in most parts of this work that the species that can potentially survive are distinguishable, that is, reformulated by assuming the set $\{i \in \mathbb{N}_n : \mathcal{T}_0^i > 1\}$ is strictly ordered.

Before stating our main result let us introduce further notations that correspond to the stationary states of (2.1) (see Proposition 3.4): $x_f = \frac{\Lambda}{\mu_x}$ and for each $k \in \mathcal{S}$ (when $\mathcal{S} \neq \emptyset$)

$$x_e^k = \frac{x_f}{\mathcal{T}_0^k}, \quad \mathbf{m}_e^k = \frac{\mu_x(\mathcal{T}_0^k - 1)}{\beta_k} (\delta_{i,k})_{i=1}^n, \quad \mathbf{y}_e^k(a) = \beta_i x_e^k e^{-\mu_x a} \mathbf{m}_e^k, \tag{2.7}$$

where $\delta_{i,j}$ denotes the usual Kronecker symbol.

For technical reasons in relation to some computations, we shall assume some relation between the parameters. The set $\mathcal{S}$ (when $\mathcal{S} \neq \emptyset$) satisfies condition (Q) if

$$\left(\mathcal{T}_0^i - 1\right) \delta_i \beta_i x_f \leq \mathcal{T}_0^i \mu_{mi} \ \forall i \in \mathcal{S}. \tag{2.8}$$

Let us first notice that the above condition is always satisfied when $\delta_i = 0$. When $\delta_i > 0$ the above parameter condition can be rewritten in terms of a limitation of the strain-specific basic reproduction numbers (see (2.6)). Indeed, if one sets $\gamma_i = \frac{\delta_i \beta_i x_f}{\mu_{mi}}$ then condition (Q) is rewriten as

$$\mathcal{R}_0^i \leq \max\left(1 + \frac{1}{1+2\gamma_i}; 1 + \frac{1+\sqrt{1+4\gamma_i}}{2\gamma_i}\right) \ \forall i \in \mathcal{S}.$$

Using the above notations the main result of this work is the following theorem.

THEOREM 2.2. *Let Assumption* 2.1 *be satisfied. Let* $x_0 \geq 0$, $\mathbf{m}_0 \in \mathbb{R}_+^n$, *and* $\mathbf{y}_0 \in L^1(0,\infty;\mathbb{R}_+^n)$ *be a given initial datum and let us denote by* $(x(t), \mathbf{m}(t), \mathbf{y}(t,.))$ *the solution of* (2.1)–(2.2). *Then the following hold true:*

(i) *If* $\mathcal{J} := \mathcal{S} \cap \{k \in \{1,\dots,n\} : m_{0,k} + \int_0^\infty y_{0,k}(a)da > 0\} = \emptyset$, *then*

$$\lim_{t\to\infty} (x(t), \mathbf{m}(t), \mathbf{y}(t,.)) = \left(x_f, 0_{\mathbb{R}^n}, 0_{L^1(0,\infty;\mathbb{R}^n)}\right),$$

wherein the above convergence holds for the topology of $\mathbb{R}\times\mathbb{R}^n\times L^1(0,\infty;\mathbb{R}^n)$.

(ii) *Let us assume that the set* $\mathcal{S}$ *is strictly ordered and satisfies the parameter condition* (Q). *If* $\mathcal{J} \neq \emptyset$, *then setting* $i = \max^{\lhd} \mathcal{J}$ *and recalling* (2.7) *one has*

$$\lim_{t\to\infty} (x(t), \mathbf{m}(t), \mathbf{y}(t,.)) = \left(x_e^i, \mathbf{m}_e^i, \mathbf{y}_e^i(.)\right)$$

for the topology of $\mathbb{R} \times \mathbb{R}^n \times L^1(0,\infty;\mathbb{R}^n)$.

The first part of this result applies in particular when $\mathcal{S} = \emptyset$, namely $\mathcal{T}_0 \leq 1$. In that case all the strains asymptotically die out and the parasites cannot persist. Let us notice that the condition $\mathcal{T}_0 \leq 1$ can be rewritten in terms of basic reproduction $\mathcal{R}_0 := \max\{\mathcal{R}_0^i,\, i \in \mathbb{N}_n\}$ as $\mathcal{R}_0 \leq 1$. The second part of the above theorem says that when different strains are sufficiently strong to survive, then only the strongest present strain (with respect to the order $\trianglelefteq$) survives in the long term.

Remark 2.3. The parameter condition (Q) seems to be only a technical condition that we cannot overcome. From numerical computations, the equilibrium associated

TABLE 2.1
Parameter set for (1.1).

Parameters	Description	Value and range	References
Λ	Production rate of RBC	1.73×10^6 cell·h^{-1}·ml^{-1}	[1]
β_1; β_2	Infection rate of uRBC	0.02/24 ml·cell^{-1}·h^{-1}	[1]
μ_x	Natural death rate of uRBC	0.00833/24 h^{-1}	[1]
μ_{m1}; μ_{m2}	Decay rates of malaria parasites	48/24 h^{-1}	[21]
r_1; r_2	Merozoite mean rate produced by pRBC	16	[1]

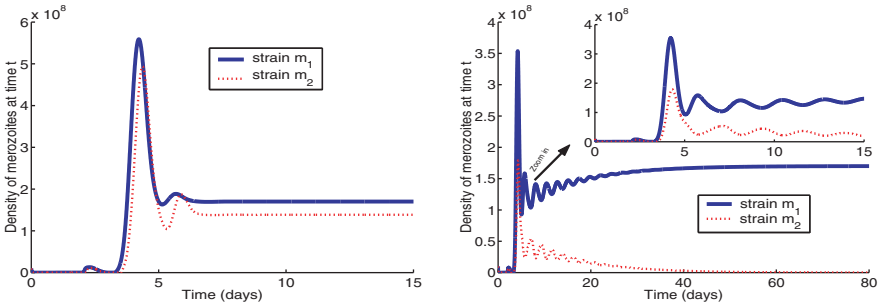

FIG. 1. *On the left-hand side, superimposed time evolution of the density of merozoites for strains* 1 *and* 2 *alone; on the right-hand side, competitive suppression of strain* 2 *when the two strains are mixed. Parameter set for* (1.1) *is described in Table* 2.1 *while initial distributions are given in Table* 2.2. *Here one has* $R_0^1 = 4.79$ *and* $R_0^2 = 3.95$.

TABLE 2.2
Initial values in model (1.1).

Variables	Description	Initial Values	References
$x(0)$	Population of uRBC	5×10^9 cell·ml^{-1}	[1, 4, 21, 37]
$w_1(0,.)$; $w_2(0,.)$	Population of pRBC	0 cell·ml^{-1}	[1, 4, 21, 37]
$m_1(0)$; $m_2(0)$	Malaria parasite	10^7 parasite·ml^{-1}	[1, 4, 21, 37]

with the strongest strain continue to be globally stable even if condition (Q) is violated.

We now provide some numerical simulations to illustrate the dynamics of system (1.1) in the case of two-strain interactions ($n = 2$) and using the parameter set described in Table 2.1. They highlight the principle of competitive exclusion. According to [7] the sequestration period for the i-strain satisfies $\tau_i \in [44; 52]$(hours). For numerical simulations we set $\tau_1 = 48$ and $\tau_2 = 50$ h while $\mu_i \equiv \mu_i(a)$ is set (following [43]) to

$$\mu_i(a) := 0 \text{ if } a < \tau_i \quad \text{and} \quad 0.98 \text{ if } a \geq \tau_i.$$

Using contact rate $\beta_1 = \beta_2 = 0.02/24$, Figure 1 (left) represents the superimposition of the time evolution of two strains alone, that is, without interaction while Figure 1 (right) corresponds to the time evolution of competitive interactions between the two strains. Since the sequestration period for strain 1 is smaller, strain 1 becomes the strongest and it competitively suppresses strain 2. Let us also notice that the shape of these curves are qualitatively close to the experimental situations recently obtained by Wacker et al. in [48]. Let us finally emphasize that using the parameter set described in Tables 2.1 and 2.2, the weakest strain, namely, strain 2, is quickly suppressed after

20 days. This duration plays an important role on the transmission of gametocytes to mosquitoes. Note that such a conclusion has been reached without taking into account the interactions of the different strains during the liver stage of the disease. This could have an influence on the time needed to suppress the weakest strain during the blood stage and thus on the spread of the different strains. This will be studied in a forthcoming work.

3. Preliminaries. The aim of this section is to derive preliminary remarks on (2.1)–(2.2). These results include the existence of the unique maximal bounded dissipative semiflow associated with this system. The second part of this section relies on technical material that will be used to prove our stability results.

3.1. Existence of semiflow and basic properties. In this section we shall deal with (2.1)–(2.2) using an integrated semigroup approach. This approach has been introduced by Thieme in [44] in the context of age-structured equations. We also refer to [11, 28, 32, 34, 35] and [45, 47] (see also the references cited therein).

Let us introduce the Banach space $\widehat{X} := \mathbb{R}^n \times L^1(0,\infty;\mathbb{R}^n)$ as well as its positive cone $\widehat{X}_+ = \mathbb{R}^n_+ \times L^1(0,\infty;\mathbb{R}^n_+)$ and the linear operator $\widehat{A} : D(\widehat{A}) \subset \widehat{X} \to \widehat{X}$ defined by

$$D(\widehat{A}) = \{0_{\mathbb{R}^n}\} \times W^{1,1}(0,\infty;\mathbb{R}^n),\ \widehat{A}\begin{pmatrix} 0_{\mathbb{R}^n} \\ \varphi \end{pmatrix} = \begin{pmatrix} -\varphi(0) \\ -\varphi' - \mu_x \varphi \end{pmatrix}. \tag{3.1}$$

Next consider the Banach space X and its positive cone X_+ defined by

$$X = \mathbb{R} \times \mathbb{R}^n \times \widehat{X} \text{ and } X_+ = \mathbb{R}_+ \times \mathbb{R}^n_+ \times \widehat{X}_+,$$

endowed with the usual product norm. Let $A : D(A) \subset X \to X$ be the linear operator defined by

$$D(A) = \mathbb{R} \times \mathbb{R}^n \times D\left(\widehat{A}\right),\ \ A = \text{diag}\ \left(-\mu_x, -\mu_m, \widehat{A}\right). \tag{3.2}$$

Note that the domain of operator A is not dense in X because of the identity

$$\overline{D(A)} = \mathbb{R} \times \mathbb{R}^n \times \{0_{\mathbb{R}^n}\} \times L^1(0,\infty;\mathbb{R}^n) \neq X.$$

Finally let us introduce the nonlinear map $F : \overline{D(A)} \to X$ defined by

$$F\left((x,\mathbf{m},0_{\mathbb{R}^n},\mathbf{y})^T\right) = \left(\Lambda - xE_n^T\beta\mathbf{m}, \int_0^\infty \rho(a)\mathbf{y}(a)da - \delta\beta x\mathbf{m}, \beta x\mathbf{m}, 0_{L^1(0,\infty;\mathbb{R}^n)}\right)^T.$$

By identifying $u(t)$ together with $(x(t),\mathbf{m}(t),0_{\mathbb{R}^n},\mathbf{y}(t,.))^T$ and by setting $u_0 = (x_0,\mathbf{m}_0, 0_{\mathbb{R}^n},\mathbf{y}_0(.))^T$, one obtains that system (2.1)–(2.2) rewrites as the following nondensely defined Cauchy problem:

$$\frac{du(t)}{dt} = Au(t) + F(u(t))\ t \geq 0 \text{ and } u(0) = u_0 \in \overline{D(A)} \cap X_+. \tag{3.3}$$

We first derive that the above abstract Cauchy problem generates a unique globally defined and positive semiflow. We set $X_0 = \overline{D(A)}$ and $X_{0+} = X_0 \cap X_+$ and the precise result is the following theorem.

THEOREM 3.1. *Let Assumption* 2.1 *be satisfied. Then there exists a unique strongly continuous semiflow* $\{U(t) : X_{0+} \to X_{0+}\}_{t\geq 0}$ *such that for each* $u_0 \in X_{0+}$,

the map $u \in C([0,\infty) : X_{0+})$ *defined by* $u = U(.)u_0$ *is a mild solution of* (3.3)*, namely, it satisfies*

$$\int_0^t u(s)ds \in D(A) \text{ and } u(t) = u_0 + A\int_0^t u(s)ds + \int_0^t F(u(s))ds \ \ \forall t \geqslant 0.$$

Furthermore $\{U(t)\}_{t\geq 0}$ *satisfies the following properties:*

(i) *Let* $U(t)u_0 = (x(t), \mathbf{m}(t), 0_{\mathbb{R}^n}, \mathbf{y}(t,.))^T$*; then the following Volterra integral formulation holds true:*

$$\mathbf{y}(t,a) = \begin{cases} \mathbf{y}_0(a-t)e^{-\mu_x t} & \text{if } a \geq t, \\ \beta x(t-a)\mathbf{m}(t-a)e^{-\mu_x a} & \text{if } a < t, \end{cases}$$

coupled with the $x(t)$ *and* $\mathbf{m}(t)$ *equations of* (2.1)*.*

(ii) *For each* $u_0 \in X_{0+}$ *one has for all* $t \geq 0$

$$x(t) + \int_0^\infty E_n^T \mathbf{y}(t,a)da \leq x_0 + ||E_n^T \mathbf{y}_0||_{L^1} + \frac{\Lambda}{\mu_x},$$
$$E_n^T \mathbf{m}(t) \leq E_n^T \mathbf{m}_0 + \frac{1}{\mu_m^{\min}} \left(x_0 + ||E_n^T \mathbf{y}_0||_{L^1} + \frac{\Lambda}{\mu_x} \right) \|\rho\|_{\max},$$

where we have set $\mu_m^{\min} = \min_{1\leqslant j\leqslant n} \mu_{m,j}$ *and* $\|\rho\|_{\max} = \max_{1\leqslant j\leqslant n} \|\rho_j\|_{L^\infty}$*.*

(iii) *The semiflow* $\{U(t)\}_{t\geq 0}$ *is bounded dissipative and asymptotically smooth.*

Proof. The proof of this result is rather standard. Indeed it is easy to check that operator A satisfies the Hille–Yosida property. Then standard methodologies apply to provide the existence and uniqueness of a mild solution for system (2.1)–(2.2) (see, for instance, [32, 34, 35, 45, 47]).

Next the Volterra integral formulation is also standard in the context of age-structured equations and we refer to [25, 50] and the references cited therein for more details.

Estimates stated in (ii) directly follow from the system of equations. Let us assume for a moment that $\mathbf{y}_0 \in W^{1,1}(0,\infty;\mathbb{R}^n)$; then adding up the x equation together with the y_i equations yields

$$\frac{d}{dt}\left(x(t) + \int_0^\infty E_n^T \mathbf{y}(t,a)da \right) = \Lambda - \mu_x \left(x(t) + \int_0^\infty E_n^T \mathbf{y}(t,a)da \right),$$

from where one deduces the first estimate of (ii) when $\mathbf{y}_0$ is smooth enough. Then a usual density argument coupled with the continuity of the semiflow with respect to the initial data yield the conclusion for $\mathbf{y}_0 \in L^1(0,\infty;\mathbb{R}^n_+)$. Then the second estimate directly follows from the first one applied to the m_i equations.

It remains to prove (iii) and let us notice that the bounded dissipativity of the semiflow $\{U(t)\}_{t\geq 0}$ is a direct consequence of (ii). To prove the asymptotic smoothness, let B be a forward invariant bounded subset of X_{0+}. According to the results in [41] it is sufficient to show that the semiflow is asymptotically compact on B.

Let us consider a sequence of solutions $\{u_p = (x^p; \mathbf{m}^p, 0, \mathbf{y}^p)^T\}_{p\geq 0}$ that is equi-bounded in X_{0+} and let us consider a sequence $\{t_p\}_{p\geq 0}$ such that $t_p \to +\infty$. Let us show that the sequence $\{u_p(t_p)\}_{p\geq 0}$ is relatively compact in X_{0+}. To do so, we consider the sequence of map $\{w_p(t) = u_p(t+t_p)\}_{p\geq 0}$. Since x_p and $\mathbf{m}_p$ are uniformly bounded in the Lipschitz norm, the Arzela–Ascoli theorem implies that, possibly along a subsequence, one may assume that $x_p(t+t_p) \to \widehat{x}$ and $\mathbf{m}_p(t+t_p) \to \widehat{\mathbf{m}}(t)$ locally

uniformly for $t \in \mathbb{R}$. It remains to deal with the sequence $\{\mathbf{y}^p(t_p,.)\}_{p\geq 0}$. Let us denote $\widetilde{\mathbf{y}}_p(t,.) = \mathbf{y}_p(t+t_p,.)$. Using the Volterra integral formulation one gets

$$\widetilde{\mathbf{y}}_p(t,a) = \begin{cases} \mathbf{y}_0(a-t+t_p)e^{-\mu_x(t+t_p)} & \text{if } a \geq t+t_p, \\ \beta x_p(t-a+t_p)\mathbf{m}_p(t-a+t_p)e^{-\mu_x a} & \text{if } a < t+t_p. \end{cases} \tag{3.4}$$

Finally since $\beta x_p(t-a+t_p)\mathbf{m}_p(t-a+t_p)e^{-\mu_x a}$ converges as $p \to \infty$ towards some function $\xi(t,a) = \beta\widehat{x}(t-a)\widehat{\mathbf{m}}(t-a)e^{-\mu_x a}$ locally uniformly, one easily concludes that

$$\mathbf{y}_p(t_p,.) = \widetilde{\mathbf{y}}_p(0,.) \to \beta\widehat{x}(-.)\widehat{\mathbf{m}}(-.)e^{-\mu_x \cdot} \text{ in } L^1(0,\infty;\mathbb{R}^n).$$

The result follows. □

Now in order to deal with the subsystem, it will be also convenient to introduce for each $J \subset \mathbb{N}_n$ the closed subspaces $X^J \subset X$ and $X_0^J \subset X_0$ defined by

$$X^J = \left\{(x,\mathbf{m},\alpha;\mathbf{y})^T \in X :\ m_i + \int_0^\infty y_i(a)da = 0 \ \ \forall i \in J\right\} \text{ and } X_0^J = X^J \cap X_0.$$

We also introduce X_{0+}^J, the positive cone of X_0^J defined by $X_{0+}^J = X_0^J \cap X_{0+}$. If $J = \emptyset$, then $X^J = X$, $X_0^J = X_0$, and $X_{0+}^J = X_{0+}$. Recalling definition (3.2), note that $A(D(A)\cap X_0^J) \subset X^J$. In the sequel we shall denote by $A_J : D(A_J) \subset X^J \to X^J$ the linear Hille–Yosida operator defined by

$$D(A_J) = D(A) \cap X_0^J, \quad A_J x = Ax \ \ \forall x \in D(A)\cap X_0^J. \tag{3.5}$$

For each $i \in \mathbb{N}_n$ we also consider

$$M_0^i = \left\{(x,\mathbf{m},\alpha;\mathbf{y})^T \in X_{0+} :\ m_i + \int_0^\infty y_i(a)da > 0\right\}.$$

Then the following lemma holds true.

LEMMA 3.2. *For each $J \subset \mathbb{N}_n$ and each $i \in \mathbb{N}_n$, the subsets $X_{0+}^J \subset X_{0+}$ and M_0^i are both positively invariant under the semiflow $\{U(t)\}_{t\geq 0}$; in other words,*

$$U(t)M_0^i \subset M_0^i \text{ and } U(t)X_{0+}^J \subset X_{0+}^J \ \ \forall t \geq 0.$$

Proof. To prove the above result, let $i \in \mathbb{N}_n$ be given. Let $u_0 := (x_0;\mathbf{m}_0;0_{\mathbb{R}^n};\mathbf{y}_0) \in M_0^i$ be given and let us denote for each $t \geq 0$, $U(t)u_0 := (x(t);\mathbf{m}(t);0_{\mathbb{R}^n},\mathbf{y}(t,.))^T$, the orbit passing through u_0. Let us set $p_i(t) = m_i(t) + \int_0^\infty y_i(t,a)da$. It follows that $p_i'(t) \geq -\max(\mu_x,\mu_{mi})p_i(0)$. That is

$$m_i(t) + \int_0^\infty y_i(t,a)da \geq e^{-\max(\mu_x,\mu_{mi})t}\left(m_{0i} + \int_0^\infty y_{0i}(a)da\right).$$

This completes the fact that $U(t)M_0^i \subset M_0^i$.

Now, let $u_0 \in \partial M_0^i$. Using the Volterra formulation we easily find that $m_i(t) = 0$ for all $t \geq 0$ and

$$\int_0^\infty y_i(t,a)da = \beta_1 \int_0^t x(t-a)m_i(t-a)e^{-\mu_x a}da + e^{-\mu_x t}||y_{0i}||_{L^1} = 0.$$

Therefore $U(t)\partial M_0^i \subset \partial M_0^i$ for all $t \geq 0$. This ends the proof of the lemma. □

Then coupling Theorem 3.1 together with the results of Hale [17, 18] and Hale and Waltman [19], one obtains the following proposition.

PROPOSITION 3.3. *Let $J \subset \mathbb{N}_n$ be given. There exists a nonempty compact set $\mathcal{A}_J \subset X_{0+}^J$ such that*

(i) *$\mathcal{A}_J$ is invariant under the semiflow $\{U_J(t) := U(t)|_{X^J_{0+}}\}_{t\geq 0}$;*

(ii) *the subset $\mathcal{A}_J$ attracts the bounded sets of X^J_{0+} under the semiflow U_J.*

Next, the following proposition describes the equilibria of the model.

PROPOSITION 3.4. *Let Assumption* 2.1 *be satisfied. Assume furthermore that the set $\mathcal{S}$ is strictly ordered. Then system* (2.1) *(or semiflow $\{U(t)\}_{t\geq 0}$ provided by Theorem* 3.1*) has exactly $1 + \operatorname{card}\mathcal{S}$ stationary states.*

(i) *The disease-free equilibrium defined by*

$$u_0^* = \left(x_f; 0_{\mathbb{R}^n}; 0_{\mathbb{R}^n}, 0_{L_1(0,\infty;\mathbb{R}^n)}\right)^T \in X^{\mathbb{N}_n}_{0+}, \;\; x_f = \frac{\Lambda}{\mu_x},$$

is an equilibrium of U and it is the only one when $\mathcal{S} = \emptyset$.

(ii) *When $\mathcal{S} \neq \emptyset$ the semiflow U has exactly* card $\mathcal{S}$ *endemic stationary states defined for each $k \in \mathcal{S}$ by*

$$u_k^* = \left(x_e^k, \mathbf{m}_e^k, 0_{\mathbb{R}^n}, \mathbf{y}_e^k\right)^T \in X^{\mathbb{N}_n\setminus\{k\}}_{0+} \cap M_0^k,$$

where the above quantities are defined in (2.7).

The proof of this result follows from straightforward algebra. The details are left to the reader.

3.2. Technical materials. In this subsection we establish some properties of the entire solutions of system (2.1). These properties will be useful later to derive the asymptotic behavior of (2.1) especially when $\mathcal{S} \neq \emptyset$.

Our first result is concerned with spectral properties of the linearized semiflow $U_J := U|_{X^J_{0+}}$ for some given subset $J \subset \mathbb{N}_n$ at a given stationary point $u^* \in \partial M_0^J$. Let $u^* = (x^*, \mathbf{m}^*, 0_{\mathbb{R}^n}, \mathbf{y}^*)^T \in X^J_{0+}$ be a given stationary state of the semiflow U_J. The associated linearized equation at the point u^* reads as

$$\frac{du(t)}{dt} = (A_J + B_{u^*})u(t),$$

where A_J is the linear operator defined in (3.5) while $B_{u^*} \in \mathcal{L}(X_0^J, X^J)$ is the bounded linear operator defined by:

$$B_{u^*}\begin{pmatrix} x \\ \mathbf{m} \\ 0_{\mathbb{R}^n} \\ \mathbf{y} \end{pmatrix} = \begin{pmatrix} -x^* E_n^T \beta \mathbf{m} - x E_n^T \beta \mathbf{m}^* \\ \int_0^\infty \rho(a)\mathbf{y}(a)da - \delta\beta(x^*\mathbf{m} + x\mathbf{m}^*) \\ x^*\beta\mathbf{m} + x\beta\mathbf{m}^* \\ 0_{L^1(0,\infty,\mathbb{R}^n)} \end{pmatrix}.$$

LEMMA 3.5. *Let $J \subset \mathbb{N}_n$ be given. Let us set $\Omega = \{\lambda \in \mathbb{C} : \text{ Re } (\lambda) > -\mu_x\}$. Then the spectrum $\sigma(A_J + B_{u^*}) \cap \Omega$ only consists of a point spectrum and one has*

$$\sigma\left(A_J + B_{u^*}\right) \cap \Omega = \left\{\lambda \in \Omega : \; \Delta^J(\lambda, u^*) = 0\right\},$$

where the function $\Delta^J(., u^*) : \Omega \to \mathbb{C}$ is defined by

$$\Delta^J(\lambda, u^*) = \prod_{i\in\mathbb{N}_n\setminus J} \chi_i(\lambda, x^*),$$

while for each $i \in \mathbb{N}_n$ and each $x \in \mathbb{R}$, the function $\chi_i(., x) : \Omega \to \mathbb{C}$ is defined by

$$\chi_i(\lambda, x) = 1 - \frac{\beta_i x}{\lambda + \mu_{mi}}\left[\int_0^\infty \rho_i(a)e^{-(\lambda+\mu_x)a}da - \delta_i\right]. \tag{3.6}$$

Proof. Let $J \subset \mathbb{N}_n$ be given. Let us denote by A_{0J} the part of A_J in X_0^J. Then it is the infinitesimal generator of a C_0-semigroup on X_0^J denoted by $\{T_{A_{0J}}(t)\}_{t\geq 0}$. Next it is easy to check that the essential growth rate of this semigroup satisfies $\omega_{0,ess}(A_{0J}) \leq -\mu_x$. Then since operator B_{u^*} is compact, the results in [10, 47] apply and ensure that the essential growth rate of $\{T_{(A_J+B_{u^*})_0}(t)\}_{t\geq 0}$, the C_0-semigroup generated by the part of $(A_J + B_{u^*})$ in X_0^J satisfies $\omega_{0,ess}((A_J + B_{u^*})_0) \leq -\mu_x$. Applying the result in [35] (see also [12] and [51]), the latter inequality ensures that $\Omega \cap \sigma(A_J + B_{u^*})$ is only composed of a point spectrum of $(A_J + B_{u^*})$.

It remains to derive the characteristic equation. However this part is also standard and we refer, for instance, to [5, 31, 36]. □

Our next result relies on properties of the entire solutions of system (2.1).

LEMMA 3.6. *Let $\{u(t) = (x(t), \mathbf{m}(t), 0_{\mathbb{R}^n}, \mathbf{y}(t,.))^T\}_{t\in\mathbb{R}}$ be a given entire solution of the semiflow U. Then x satisfies*

$$\inf_{t\in\mathbb{R}} x(t) > 0. \tag{3.7}$$

Furthermore the following properties hold true:

(i) *If there exist $i \in \mathbb{N}_n$ and $t_0 \in \mathbb{R}$ such that $u(t_0) \in M_0^i$, then $m_i(t) > 0$ $\forall t \in \mathbb{R}$ and $y_i(t,a) > 0$ for any $(t,a) \in \mathbb{R} \times [0,\infty)$.*

(ii) *Assume that $\mathcal{S} \neq \emptyset$ and assume there exist $i \in \mathcal{S}$ and $t_0 \in \mathbb{R}$ such that $u(t_0) \in M_0^i$. If $u(t) \to u^*$ as $t \to \infty$, where u^* is an equilibrium point of U, then one has $u^* \in \{u_j^* : i \trianglelefteq j\}$.*

(iii) *For each $i \in \mathbb{N}_n$ there exists a constant $M_i > 1$ such that*

$$\frac{m_i^-(t)}{M_i} e^{-\mu_x a} \leq y_i(t,a) \leq M_i e^{-\mu_x a} \ \forall (t,a) \in \mathbb{R} \times [0,\infty),$$

where we have set $m_i^-(t) = \inf_{s\leq t} m_i(s)$.

Proof. Let us first notice that since u is an entire solution then

$$\mathbf{y}(\sigma, a) = \beta x(\sigma - a)\mathbf{m}(\sigma - a)e^{-\mu_x a} \ \ \forall (\sigma, a) \in \mathbb{R} \times [0,\infty). \tag{3.8}$$

This expression directly follows from the Volterra integral formulation in Theorem 3.1.

From the estimates provided in Theorem 3.1 and the x equation there exists some constant $C > 0$ such that for each $s \in \mathbb{R}$ and $t \geq 0$ one has

$$x(s)e^{-Ct} + \Lambda \int_0^t e^{-C(t-l)} dl \leq x(t+s) \leq x(s) + \frac{\Lambda}{\mu_x}. \tag{3.9}$$

This implies that $\inf_{t\in\mathbb{R}} x(t) > 0$ and completes the proof of (3.7).

We now turn to the proof of (i). Let us argue by contradiction by assuming that there exists $t_1 \in \mathbb{R}$ such that $m_i(t_1) = 0$. Then from the m_i equation we deduce that $m_i(t) = 0$ for all $t \leq t_1$. Next we infer from (3.8) that $\int_0^\infty y_i(t,a)da = 0$ for any $t \leq t_1$. Hence $m_i(t) + \int_0^\infty y_i(t,a)da \equiv 0$, a contradiction with the existence of t_0. On the other hand, due to (3.9) and (3.7), if there exists $(t_1, a_1) \in \mathbb{R} \times [0,\infty)$ such that $y_i(t_1, a_1) = 0$, then $m_i(t_1 - a_1) = 0$ and the first part of the argument applies.

Let us now prove (ii). Let us first notice that since $m_i(t_0) + \int_0^\infty y_i(t_0, a)da > 0$, (i) implies that $m_i(t) > 0$ for all $t \in \mathbb{R}$ and $y_i(t,a) > 0$ for all $(t,a) \in \mathbb{R} \times [0,\infty)$. Next consider the function $\Gamma_i(a) = \int_a^\infty \rho_i(s)e^{\mu_x(a-s)}ds$ and note that $\Gamma_i \in L^\infty(0,\infty,\mathbb{R})$ and satisfies $\Gamma_i'(a) - \mu_x\Gamma_i(a) + \rho_i(a) = 0$ *a.e.* $a \geq 0$. Let us introduce the functional

$$\Phi_i[u](t) = \int_0^\infty \Gamma_i(a)y_i(t,a)da + m_i(t)$$

that satisfies (recalling definition (2.3))

$$\frac{d\Phi_i[u](t)}{dt} = \mu_{mi} m_i(t) \left[\mathcal{T}_0^i \frac{x(t)}{x_f} - 1 \right] \quad \forall t \in \mathbb{R}. \tag{3.10}$$

Using this computation we will obtain a contradiction by assuming that $u(t) \to u_j^*$ as $t \to \infty$ for some $j \lhd i$. Indeed for $j = 0$, $u(t) \to u_0^*$ as $t \to \infty$ implies that $x(t) \to x_f$ as $t \to \infty$. Then since $\mathcal{T}_0^i > 1$ function $t \mapsto \Phi_i[u](t)$ is not decreasing for t large enough. Hence there exists $t_0 \in \mathbb{R}$ such that $\Phi_i[u](t) \geq \Phi_i[u](t_0)$ for all $t \geq t_0$. Since $\Phi_i[u](t_0) > 0$, this prevents the component (y_i, m_i) from converging to $(0, 0_{L^1})$ as $t \to \infty$. A contradiction with $u(t) \to u_0^*$.

The same argument holds for $j \in \mathcal{S}$ with $j \lhd i$. Indeed in such a case $x(t) \to x_e^j$ as $t \to \infty$ and since

$$\left[\mathcal{T}_0^i \frac{x_e^j}{x_f} - 1 \right] = \frac{\mathcal{T}_0^i}{\mathcal{T}_0^j} - 1 > 0,$$

the same arguments apply. This completes the proof of (ii).

Finally note that (iii) directly follows from (3.7) and (3.8). This ends the proof of Lemma 3.6. □

Our next lemma is a computational result that will be used in what follows to perform Lyapunov arguments.

LEMMA 3.7. *Let us assume that the same assumptions of Lemma* 3.6 *are satisfied. Let* $h : (0, \infty) \to [0, \infty)$ *be the function defined by*

$$h(s) = s - 1 - \ln s. \tag{3.11}$$

Let us assume that there exists $i_0 \in \mathcal{S}$ *such that*

$$\liminf_{t \to -\infty} m_{i_0}(t) > 0. \tag{3.12}$$

Then

(i) *for each* $t \in \mathbb{R}$ *one has*

$$\left[\int_{\cdot}^{\infty} \rho_{i_0}(s) l(s) ds \right] h\left(\frac{y_{i_0}(t, .)}{y_{ei_0}^{i_0}(.)} \right) \in L^1(0, \infty, \mathbb{R}). \tag{3.13}$$

(ii) *Consider now the map* $V_{i_0}[u] : \mathbb{R} \to [0, \infty)$ *defined by*

$$V_{i_0}[u](t) := W_{i_0}(t) + \sum_{j=1; j \neq i_0}^{p} \int_0^{\infty} f_j(a) y_j(t, a) da + \sum_{j=1; j \neq i_0}^{p} d_j m_j(t), \tag{3.14}$$

where we have set $W_{i_0}(t) = V_x(t) + V_{y_{i_0}}(t) + V_{m_{i_0}}(t)$ *and*

$$V_x(t) = h\left(\frac{x(t)}{x_e^{i_0}} \right), \quad V_{y_{i_0}}(t) = \int_0^{\infty} \alpha_{i_0}(a)\, h\left(\frac{y_{i_0}(t, a)}{y_{ei_0}^{i_0}(a)} \right) da, \quad V_{m_{i_0}}(t) = d_{i_0}\, h\left(\frac{m_{i_0}(t)}{m_{ei_0}^{i_0}} \right),$$

and

$$d_{i_0} = \frac{\beta_{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}, \quad d_j = \frac{\beta_j}{\mu_{mj}} \quad \text{with } j \neq i_0, \tag{3.15}$$

$$f_j(a) = \frac{\beta_j}{\mu_{mj}} \int_a^{\infty} \rho_j(s) e^{-\mu_x(s-a)} ds, \text{ and } \alpha_{i_0}(a) = \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \int_a^{\infty} \rho_{i_0}(a) l(a) da. \tag{3.16}$$

Then function $t \mapsto V_{i_0}[u](t)$ is of the class C^1 on $\mathbb{R}$ and we have

$$\dot{V}_{i_0}[u](t) = -\frac{\Theta_{i_0}}{x_e^{i_0} x(t)} \left(x(t) - x_e^{i_0}\right)^2 + \frac{x(t)}{x_e^{i_0}} \sum_{j=1; j\neq i_0}^{p} \left(\frac{\mathcal{T}_0^j}{\mathcal{T}_0^{i_0}} - 1\right) \beta_j m_j(t)$$
$$- \int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \rho_{i_0}(a) l(a) \left[h\left(\frac{y_{i_0}(t,a) m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a) m_{i_0}(t)} \right) + h\left(\frac{m_{i_0}(t) y_{ei_0}^{i_0}(0)}{m_{ei_0}^1 y_{i_0}(t,0)} \right) \right] da$$

with

$$\Theta_{i_0} = \mu_x - \delta_{i_0} \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}. \tag{3.17}$$

Proof. (i) Let us first remark that (3.13) follows from the estimate provided by Lemma 3.6(iii) as well as (3.12). Indeed function $a \mapsto \int_a^\infty \rho_{i_0}(s) l(s) ds$ satisfies

$$\int_0^\infty a \int_a^\infty \rho_{i_0}(s) l(s) ds ds < \infty.$$

(ii) Next note that function $t \mapsto V_{i_0}[u](t)$ is also well defined for each $t \in \mathbb{R}$ because of (3.7), Lemma 3.6(i), and finally because of $f_j \in L^\infty(0,\infty)$ (see definition (3.16)).

It now remains to compute the derivation of $t \mapsto V_{i_0}[u](t)$ (that is obviously of the class C^1 on $\mathbb{R}$ since u is an entire solution).
First one has

$$\begin{aligned} \dot{V}_x(t) = {} & \frac{\Lambda}{x_e^{i_0}} + \mu_x - \mu_x \frac{x(t)}{x_e^{i_0}} - \frac{\Lambda}{x(t)} - \beta_{i_0} m_{ei_0}^{i_0} \frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)} + \beta_{i_0} m_{i_0}(t) \\ & + \left(1 - \frac{x(t)}{x_e^{i_0}}\right) \sum_{j=1; j\neq i_0}^{p} \beta_j m_j(t). \end{aligned} \tag{3.18}$$

Second using the y_{i_0} equation and integration by parts, simple algebra leads to

$$\dot{V}_{y_{i_0}}(t) = \alpha_{i_0}(0) h\left(\frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)} \right) + \int_0^\infty \alpha_{i_0}'(a) h\left(\frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)} \right) da.$$

Moreover we infer from the definition of α_{i_0} (see (3.16))

$$\dot{V}_{y_{i_0}}(t) = \int_0^\infty \frac{\beta_1^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \rho_{i_0}(a) l(a) \left[h\left(\frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)} \right) - h\left(\frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)} \right) \right] da. \tag{3.19}$$

Next one can also check that

$$\begin{aligned} \dot{V}_{m_{i_0}}(t) = {} & \int_0^\infty d_{i_0} \delta_{i_0} \beta_{i_0} x_e^{i_0} \rho_{i_0}(a) l(a) \frac{y_{i_0}(t,a)}{y_{ei_0}^{i_0}(a)} da - \frac{d_{i_0} \mu_{mi_0}}{m_{ei_0}^{i_0}} m_{i_0}(t) \\ & - d_{i_0} \delta_{i_0} \beta_{i_0} x_e^{i_0} \frac{y_{i_0}(t,0)}{y_{ei_0}^{i_0}(0)} - \frac{d_{i_0}}{m_{i_0}(t)} \int_0^\infty \rho_{i_0}(a) y_{i_0}(t,a) da \\ & + d_{i_0} \delta_{i_0} \beta_{i_0} x(t) + d_{i_0} \mu_{mi_0}. \end{aligned} \tag{3.20}$$

Using the fact that

$$\int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} \rho_{i_0}(a) l(a) da - \beta_{i_0} m_{ei_0}^{i_0} - d_{i_0} \delta_{i_0} \beta_{i_0} x_e^{i_0} = 0,$$

we infer from (3.18)–(3.20) that

$$\begin{aligned}\dot{W}_{i_0}(t) =&\frac{\Lambda}{x_e^{i_0}} + \mu_x + d_{i_0}\mu_{mi_0} - 2\frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} K_{i_0} + (d_{i_0}\delta_{i_0}\beta_{i_0}x_e^{i_0} - \mu_x)\frac{x(t)}{x_e^{i_0}}\\ &+ \left(\frac{K_{i_0}\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}} - \frac{\Lambda}{x_e^{i_0}}\right)\frac{x_e^{i_0}}{x(t)} + \left(1 - \frac{x(t)}{x_e^{i_0}}\right)\sum_{j=1;j\neq i_0}^{p}\beta_j m_j(t)\\ &- \int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}\rho_{i_0}(a)l(a)\left[h\left(\frac{y_{i_0}(t,a)m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a)m_{i_0}(t)}\right) + h\left(\frac{m_{i_0}(t)y_{ei_0}^{i_0}(0)}{m_{ei_0}^{i_0}y_{i_0}(t,0)}\right)\right]da.\end{aligned}$$

Since EE_{i_0} is an equilibrium of system (2.1) one gets

$$\begin{aligned}\dot{W}_{i_0}(t) =& -\frac{\Theta_{i_0}}{x_e^{i_0}x(t)}\left(x(t) - x_e^{i_0}\right)^2 + \left(1 - \frac{x(t)}{x_e^{i_0}}\right)\sum_{j=1;j\neq i_0}^{p}\beta_j m_j(t)\\ &- \int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}\rho_{i_0}(a)l(a)\left[h\left(\frac{y_{i_0}(t,a)m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a)m_{i_0}(t)}\right) + h\left(\frac{m_{i_0}(t)y_{ei_0}^{i_0}(0)}{m_{ei_0}^{i_0}y_{i_0}(t,0)}\right)\right]da,\end{aligned}$$

with Θ_{i_0} defined in (3.17). Using the fact that $f_j'(a) - \mu_x f_j(a) + d_j\rho_j(a) = 0$ for all $a \geq 0$ and $\delta_j d_j + \frac{1}{x_f} - f_j(0) = \frac{1-\mathcal{T}_0^j}{x_f}$, one has

$$\begin{aligned}\dot{V}_{i_0}[u](t) =& -\frac{\Theta_{i_0}}{x_e^{i_0}x(t)}\left(x(t) - x_e^{i_0}\right)^2 + \frac{x(t)}{x_e^{i_0}}\sum_{j=1;j\neq i_0}^{p}\left(\frac{\mathcal{T}_0^j}{\mathcal{T}_0^{i_0}} - 1\right)\beta_j m_j(t)\\ &- \int_0^\infty \frac{\beta_{i_0}^2 x_e^{i_0} m_{ei_0}^{i_0}}{\mu_{mi_0}}\rho_{i_0}(a)l(a)\left[h\left(\frac{y_{i_0}(t,a)m_{ei_0}^{i_0}}{y_{ei_0}^{i_0}(a)m_{i_0}(t)}\right) + h\left(\frac{m_{i_0}(t)y_{ei_0}^{i_0}(0)}{m_{ei_0}^{1}y_{i_0}(t,0)}\right)\right]da.\end{aligned}$$

This ends the proof of the lemma. □

4. Proof of Theorem 2.2(i). The aim of this section is to prove the first part of Theorem 2.2. By using all the above introduced definitions and notations, this result can be reformulated as follows.

PROPOSITION 4.1. *Let Assumption* 2.1 *be satisfied. Then the following holds true:*

$$\lim_{t\to\infty} U_{\mathcal{S}}(t)x = u_0^*$$

for each $x \in X_{0+}^{\mathcal{S}}$ *and where* $U_{\mathcal{S}}$ *denotes the restriction semiflow* U *at* $X_{0+}^{\mathcal{S}}$.

Remember that if $\mathcal{S} = \emptyset$, namely, $\mathcal{T}_0 \leq 1$, then $X_{0+}^{\mathcal{S}} = X_{0+}$ and $U_{\mathcal{S}} \equiv U$. This remark means that when $\mathcal{T}_0 \leq 1$ the disease-free equilibrium is globally attractive.

The proof of this result relies on the construction of a suitable Lyapunov functional on the entire solution of $U_{\mathcal{S}}$.

Proof. Let us consider $\mathcal{A}_{\mathcal{S}} \subset X_{0+}^{\mathcal{S}}$, the global compact attractor of $U_{\mathcal{S}}$ provided by Proposition 3.3. Let $x \in \mathcal{A}_{\mathcal{S}}$ be given and let $\{u(t)\}_{t\in\mathbb{R}} \subset \mathcal{A}_{\mathcal{S}}$ be an entire solution of $U_{\mathcal{S}}$ such that $u(0) = x$. Recalling that from Lemma 3.6(iii), $\inf_{t\in\mathbb{R}} x(t) > 0$, one may consider the functional V defined for each entire solutions by

$$V[u](t) = h\left(\frac{x}{x_f}\right) + \sum_{j=1}^{n}\int_0^\infty f_j(a)y_j(a)da + \sum_{j=1}^{n} d_j m_j,$$

where the positive constants d_j and the functions f_j are defined, respectively, by (3.15) and (3.16) while function h is given in (3.11).

Next, using system (2.1) we obtain

$$\begin{aligned}\frac{d\,V[u](t)}{dt} &= -\mu_x\frac{(x(t)-x_f)^2}{x(t)} - \sum_{j=1}^{n}(d_j\mu_{mj}-\beta_j)m_j(t)\\ &\quad - \sum_{j=1}^{n}\left(\delta_j d_j + \frac{1}{x_f}\right)\beta_j x(t)m_j(t) + \sum_{j=1}^{n} d_j\int_0^\infty \rho_j(a)y_j(t,a)da\\ &\quad - \sum_{j=1}^{n}\int_0^\infty f_j(a)e^{-\mu_x a}(\partial_a y_j(t,a)e^{\mu_x a} + \mu_x e^{\mu_x a}y_j(t,a))da.\end{aligned}$$

Integrating by parts the last integral of the previous equality, using the y_j boundary condition of (2.1) together with $f_j'(a) - \mu_x f_j(a) + d_j\rho_j(a) = 0$ for all $a \geq 0$, one obtains, recalling $\{u(t)\}_{t\in\mathbb{R}} \subset X_{0+}^{\mathcal{S}}$, that

$$\frac{d\,V[u](t)}{dt} = -\mu_x\frac{(x(t)-x_f)^2}{x(t)} - x(t)\sum_{j\in\mathbb{N}_n\setminus\mathcal{S}}\frac{1-\mathcal{T}_0^j}{x_f}\beta_j m_j(t). \tag{4.1}$$

Hence we infer from the definition of $\mathcal{S}$ that $t \mapsto V[u](t)$ is decreasing along the entire solutions of $U_{\mathcal{S}}$. To conclude our proof, let $\{t_n\}_{n\geq 0}$ be an increasing sequence tending to $-\infty$ as $n \to \infty$ and consider the sequence of map $u_n(t) = u(t+t_n)$. Note that one has $V[u_n](t) = V[u](t+t_n)$. Up to a subsequence one may assume that $u_n(t) \to \widehat{u}(t)$ as $n \to \infty$ locally uniformly for $t \in \mathbb{R}$, where $\{\widehat{u}(t)\}_{t\in\mathbb{R}} \subset \mathcal{A}_{\mathcal{S}}$ is an entire solution of $U_{\mathcal{S}}$. Since V is decreasing, one obtains that

$$V\left[\widehat{u}\right](t) \equiv \lim_{t\to-\infty} V[u](t) = \sup_{t\in\mathbb{R}} V[u](t).$$

By setting $\widehat{u} = (\widehat{x}, \widehat{\mathbf{m}}, 0, \widehat{\mathbf{y}})^T$, (4.1) yields to $\widehat{x}(t) \equiv x_f$ while the x equation provides that $\widehat{\mathbf{m}}(t) \equiv 0$ so that $\widehat{\mathbf{y}}(t,.) \equiv 0$. Hence $V[\widehat{u}](t) \equiv 0$ and $0 \leq V[u](t) \leq 0$ for $t \in \mathbb{R}$ and $u(t) \equiv u_0^*$. This completes the proof of Proposition 4.1. □

5. Proof of Theorem 2.2(ii). The aim of this section is to prove Theorem 2.2(ii). For this reason, we will assume throughout this section that $\mathcal{S} \neq \emptyset$. The proof of this result will follow an induction argument. To be more specific we will study the behavior of the semiflow $U_{\mathcal{S}\setminus J}$ for each subset $J \subset \mathcal{S}$ using card $J \in \{1, \ldots, \text{card}\,\mathcal{S}\}$ as the induction parameter.

The precise result we will prove is the following.

THEOREM 5.1. *Let us assume that the assumptions of Theorem* 2.2 *are satisfied. Assume that* $\mathcal{S} \neq \emptyset$. *Then for each* $J \subset \mathcal{S}$ *the semiflow* $\{U_{\mathcal{S}\setminus J}(t)\}_{t\geq 0}$ *satisfies, for each* $x \in X_{0+}^{\mathcal{S}\setminus J}$,

(i) *if* $\mathcal{J}(x) := J \cap \{i \in \mathbb{N}_n : x \in M_0^i\} = \emptyset$, *then* $x \in X_{0+}^{\mathcal{S}}$ *and*

$$\lim_{t\to\infty} U_{\mathcal{S}\setminus J}(t)x = u_0^*;$$

(ii) *if* $\mathcal{J}(x) \neq \emptyset$ *we set* $i = \max^{\lhd}\mathcal{J}(x)$ *and one has*

$$\lim_{t\to\infty} U_{\mathcal{S}\setminus J}(t)x = u_i^*.$$

Let us first notice that point (i) in the above theorem is a direct consequence of Theorem 2.2(i) (see Proposition 4.1). As a consequence, it is sufficient to prove (ii) and let us notice that Theorem 2.2(ii) corresponds to Theorem 5.1 with $J = \mathcal{S}$. As mentioned above, the proof of this result relies on an induction argument on card J. In what follows we shall investigate the case where card $J = 1$ and we will then show how such a property is inherited.

5.1. Case card $J = 1$. Let $i \in \mathcal{S}$ be given. For notational simplicity we consider the set $Y_{0+} = X_{0+}^{\mathcal{S}\setminus\{i\}}$ and let us denote $\{V(t) := U_{\mathcal{S}\setminus\{i\}}(t)\}_{t\geq 0}$. We also consider the sets

$$N_0 = Y_{0+} \cap M_0^i \text{ and } \partial N_0 = Y_{0+} \setminus N_0 = X_{0+}^{\mathcal{S}}.$$

Before constructing a suitable Lyapunov function to study the asymptotic behavior of $V(t)x$ for some $x \in N_0$ let us first collect in the following lemma some properties of the semiflow $\{V(t)\}_{t\geq 0}$.

LEMMA 5.2. *Under the assumption of Theorem* 5.1, *the semiflow* $\{V(t)\}_{t\geq 0}$ *satisfies the following properties:*

(i) *It is bounded dissipative and asymptotically smooth;* N_0 *and* ∂N_0 *are both positively invariant under* V.
(ii) *For each* $x \in \partial N_0$ *one has* $V(t)x \to u_0^*$.
(iii) *The semiflow* V *is uniformly persistent with respect to the pair* $(N_0, \partial N_0)$ *in the sense that there exists* $\varepsilon > 0$ *such that, for each* $x \in N_0$,

$$\liminf_{t\to\infty} d\left(U(t)x; \partial N_0\right) \geq \varepsilon.$$

Proof. Note that (i) directly follows from Theorem 3.1(ii), (iii) and Lemma 3.2 while (ii) directly follows from Theorem 5.1(i). It remains to prove (iii). To do so we will apply Theorem 4.2 in [19]. Let us first notice that u_0^* is an unstable stationary state with respect to the semiflow V. Indeed as an application of Lemma 3.5 we know that the eigenvalues in Ω of the linearized semiflow V at u_0^* are given the resolution of the equation $\Delta^{\mathcal{S}\setminus\{i\}}(\lambda, u_0^*) = 0$. On the other hand these eigenvalues contain the roots of the equation $\chi_i(\lambda, u_0^*) = 0$ (see (3.6)). Note that function $\chi_i(., u_0^*)$ satisfies

$$\chi_i(0, u_0^*) = 1 - \mathcal{T}_0^i < 0 \text{ and } \lim_{\lambda\to\infty} \chi_i(\lambda, u_0^*) = 1$$

that ensures the existence of a strictly positive eigenvalue. The instability of u_0^* with respect to V follows.

Applying Theorem 4.2 in [19] to complete the proof of Lemma 5.2(iii), it is sufficient to show that $W^s(\{u_0^*\}) \bigcap N_0 = \emptyset$ where we have set $W^s(\{u\}) = \{v \in Y_{0+} : \lim_{t\to+\infty} V(t)v = u\}$. To prove this assertion, let us argue by contradiction by assuming that there exists $x \in W^s(\{u_0^*\}) \bigcap N_0$. Then using the same computations as in Lemma 3.6(ii), since $\mathcal{T}_0^i > 1$ one obtains that the function

$$\Phi\left[V(t)x\right] := \int_0^\infty \Gamma_i(a) y_i(t,a) da + m_i(t) \text{ with } \Gamma_i(a) := \int_a^\infty \rho_i(s) e^{a-s} ds$$

is increasing for t large enough. This prevents the function $(y_i(t,.), m_i(t))$ from converging to $(0_{L^1}, 0)$ and provides a contradiction together with the definition x. This completes the proof of Lemma 5.2. □

As a consequence of Lemma 5.2 and Theorem 3.7 in [33] (see also the monograph [42]), there exists $\mathcal{B}_0$, a compact subset of N_0, which is a global attractor for the

semiflow $\{V(t)\}_{t\geq 0}$ in N_0. To complete the proof of Theorem 5.1(ii) in the case $J=\{i\}$ it remains to prove that $\mathcal{B}_0=\{u_i^*\}$. This will be achieved by constructing a suitable Lyapunov functional on $\mathcal{B}_0$. This idea has been used by Magal, McCluskey, and Webb [36] and Thieme [46].

Let $\{u(t)=(x(t),\mathbf{m}(t),0_{\mathbb{R}^n},\mathbf{y}(t,.))^T\}_{t\in\mathbb{R}}\subset\mathcal{B}_0$ be a given entire solution of V. We make the following claim.

CLAIM 5.3. *Function m_i satisfies $\inf_{t\in\mathbb{R}} m_i(t)>0$.*

Before proving this claim let us complete the proof of Theorem 5.1 for $J=\{i\}$. Using Claim 5.3 and Lemma 3.7, one can consider the functional $V_i[u]$ defined in Lemma 3.7. Defining Θ_i as in (3.17) one has

$$\dot{V}_i[u](t)=-\frac{\Theta_i}{x_e^i x(t)}\left(x(t)-x_e^i\right)^2+\frac{x(t)}{x_e^i}\sum_{j\in\mathbb{N}_n\setminus\mathcal{S}}\left(\frac{\mathcal{T}_0^j}{\mathcal{T}_0^i}-1\right)\beta_j m_j(t)$$
$$-\int_0^\infty\frac{\beta_i^2 x_e^i m_{ei}^i}{\mu_{mi}}\rho_i(a)l(a)\left[h\left(\frac{y_i(t,a)m_{ei}^i}{y_{ei}^i(a)m_i(t)}\right)+h\left(\frac{m_i(t)y_{ei}^i(0)}{m_{ei}^1 y_i(t,0)}\right)\right]da.$$

Recalling condition (Q) one obtains that $\Theta_i\geq 0$ so that $t\mapsto V[u](t)$ is a bounded and decreasing map. Finally arguing similarly as the end of the proof of Theorem 2.2(i) yields $u(t)\equiv u_i^*$.

It now remains to prove Claim 5.3.

Proof of Claim 5.3. Let us argue by contradiction by assuming that $\inf_{t\in\mathbb{R}} m_i(t)=0$. Note that due to Lemma 3.6(i), one has $m_i(t)>0$. Hence let us for instance assume that $\liminf_{t\to-\infty} m_i(t)=0$. Consider a sequence $\{t_n\}_{n\geq 0}$ tending to $-\infty$ as $n\to\infty$ such that $m_i(t_n)\to 0$ as $n\to\infty$. Consider the sequence of maps $\{u_n(t):=u(t+t_n)\}_{n\geq 0}$. Then up to a subsequence, one may assume that $u_n(t)\to\widehat{u}(t)$ locally uniformly where $\widehat{u}$ is an entire solution of V such that $\widehat{m}_i(0)=0$. Lemma 3.6(i) ensures that $(\widehat{m}_i(t),\widehat{y}_i(t,.))\equiv(0,0_{L^1})$ This prevents $\widehat{u}$ from belonging to N_0, a contradiction. A similar argument holds true if one deals with $\liminf_{t\to+\infty} m_i(t)=0$. This completes the proof of Claim 5.3. □

5.2. Case card $\mathcal{S}\geq 2$ and $2\leq$ card $J\leq$ card $\mathcal{S}$. In this section we assume that card $\mathcal{S}\geq 2$. Note that the proof of Theorem 5.1(ii) follows from the above section when card $\mathcal{S}=1$. Let $J\subset\mathcal{S}$ be a given subset such that card $J\geq 2$. Our induction hypothesis is concerned with the validity of Theorem 5.1 for each subset $J'\subset\mathcal{S}$ such that card $J'<$ card J. Consider now the set $Y_{0+}=X_{0+}^{\mathcal{S}\setminus J}$ as well as the semiflow $V:=U_{\mathcal{S}\setminus J}$ on Y_{0+}. Let us denote $i=\max^{\lhd}(J)$ and let us consider

$$N_0=Y_{0+}\cap M_0^i \text{ and } \partial N_0=Y_{0+}\setminus N_0.$$

Let us first notice that to prove Theorem 5.1(ii) for J, it is sufficient to show that

$$\lim_{t\to\infty} V(t)x=u_i^*\ \ \forall x\in N_0. \tag{5.1}$$

Indeed, if $x\in\partial N_0$, then $x\in X_{0+}^{\mathcal{S}\setminus J'}$ with $J'=J\setminus\{i\}$. Since $J'\subset\mathcal{S}$ and card $J'<$ card J, then $V(t)x=U_{\mathcal{S}\setminus J'}(t)x$ and the asymptotic behavior follows from the induction hypothesis.

The proof of this section is rather similar to the one provided in the preceding section. The only difference relies on the proof of the uniform persistence of the semiflow V with respect to the pair $(N_0,\partial N_0)$ because of the dynamics of the semiflow

on the boundary ∂N_0. Hence to complete the proof of Theorem 5.1(ii) for J we will only prove the following lemma. The details are left to the reader.

LEMMA 5.4. *The semiflow V is uniformly persistent with respect to the pair $(N_0, \partial N_0)$.*

Proof. The proof of this result is an application of Theorem 4.2 in [19] with a nontrivial dynamics for the boundary semiflow. Let us denote $J' = J \setminus \{i\}$. Then note that $V|_{\partial N_0} = U_{\mathcal{S}\setminus J'}$. According to Proposition 3.3 let us consider $\mathcal{A}_\partial := \mathcal{A}_{\mathcal{S}\setminus J'}$, the global attractor of the semiflow $V|_{\partial N_0}$. Note that according to the induction hypothesis the following holds true:

$$\bigcup_{x\in\mathcal{A}_\partial} \omega(x) = \{u_0^*\} \cup \bigcup_{j\in J'} \{u_j^*\}.$$

Here for each $x \in Y_{0+}$, $\omega(x)$ denotes the omega-limit set of the point x with respect to the semiflow V. The application of Theorem 4.2 in [19] relies on some properties of the set $\widehat{A}_\partial$ defined by

$$\widehat{A}_\partial = \{u_0^*\} \cup \bigcup_{j\in J'} \{u_j^*\}.$$

Let us first claim the following.

CLAIM 5.5. *For each $j \in J' \cup \{0\}$ the stationary point u_j^* is unstable with respect to the semiflow V.*

Proof of Claim 5.5. The proof of the above claim relies on Lemma 3.5. Let us notice that for each $j \in J' \cup \{0\}$, function $\chi_i(., u_j^*)$ (see (3.6)) satisfies

$$\chi_i(0, u_j^*) = \begin{cases} 1 - \mathcal{T}_0^i & \text{if } j = 0, \\ 1 - \frac{\mathcal{T}_0^i}{\mathcal{T}_0^j} & \text{if } j \in J'. \end{cases}$$

Hence since $i = \max^\lhd J$, $\chi_i(0, u_j^*) < 0$, and since $\chi_i(\lambda, u_j^*) \to 1$ as $\lambda \to \infty$, for each $j \in J' \cup \{0\}$, function $\chi_i(., u_j^*)$ has a strictly positive root. The result follows. ∎

Then we claim the following.

CLAIM 5.6. *For each $(j, k) \in J' \cup \{0\}$, if $\{u(t)\}_{t\in\mathbb{R}}$ is a nontrivial (that is nonconstant) entire solution of V such that*

$$\lim_{t\to-\infty} u(t) = u_j^* \text{ and } \lim_{t\to\infty} u(t) = u_k^*,$$

then $j \lhd k$.

Proof of Claim 5.6. The proof of this claim relies on the application of Lemma 3.6(ii) as well as a Lyapunov-functional-like argument.

Let us first consider the case where $j \in J'$. Then applying Lemma 3.6(ii) we know that $j \trianglelefteq k$. It is therefore sufficient to show that there is no homoclinic connection at u_j^*. Let us argue by contradiction by assuming that

$$\lim_{t\to\pm\infty} u(t) = u_j^*.$$

Then applying once again Lemma 3.6(ii) we obtain that for each $k \in J'$ such that $k \rhd j$,

$$y_k(t, .) \equiv 0 \text{ and } m_k(t) \equiv 0 \ \ \forall k \in J' \rhd j.$$

Then consider the functional

$$V_j[u](t) = V_x(t) + V_{y_j}(t) + V_{m_j}(t) + \sum_{p=1;p\neq j}^{n} \int_0^\infty f_p(a) y_p(t,a) da + \sum_{p=1;p\neq j}^{n} d_p m_p(t).$$

Using similar arguments and computations (see Lemma 3.7) as the ones provided in the preceding section and using the fact that, for each $k \in \mathcal{S} \setminus J'$ and each $k \in J'$ such that $k \rhd j$,

$$y_k(t,.) \equiv 0 \text{ and } m_k(t) \equiv 0,$$

one obtains that $u(t) \equiv u_j^*$, a contradiction.

It remains to consider the case $j = 0$ and to show that there is no homoclinic connection at u_0^*. Let us argue by contradiction by assuming that

$$\lim_{t\to\pm\infty} u(t) = u_0^*.$$

Then let us notice that due to Lemma 3.6(ii) one has

$$y_k(t,.) \equiv 0 \text{ and } m_k(t) \equiv 0, \ \ \forall k \in \mathcal{S}.$$

Then by considering the map

$$V_0[u](t) = h\left(\frac{x}{x_f}\right) + \sum_{j=1}^{n} \int_0^\infty f_j(a) y_j(a) da + \sum_{j=1}^{n} d_j m_j,$$

as well as computations and arguments similar to the proof of Proposition 4.1, one concludes that

$$u(t) \equiv u_0^*,$$

a contradiction that completes the proof of Claim 5.6. □

As a consequence of Claims 5.5 and 5.6, the set $\widehat{A}_\partial$ is isolated and has an acyclic covering. Hence since the semiflow is bounded dissipative and asymptotically smooth, Theorem 4.2 in [19] applies and to complete the proof of Lemma 5.4, it is sufficient to show that $N_0 \cap W^s(\{u_j^*\}) = \emptyset$ for each $j \in J' \cup \{0\}$. Similarly to the proof in section 5.1 this latter property directly follows from the functional

$$\Phi\left[V(t)x\right] := \int_0^\infty \Gamma_i(a) y_i(t,a) da + m_i(t) \text{ with } \Gamma_i(a) := \int_a^\infty \rho_i(s) e^{a-s} ds.$$

This completes the proof of Lemma 5.4. □

Appendix A. Basic reproduction rate of system (1.1). Here we follow the methodology of Diekmann and co-workers [8, 9] and Inaba [24] (see also the references cited therein). Let $b_j(t)$ be the density of newly produced j-merozoites at time t. Then from (1.1) one has

$$b_j(t) = \int_0^\infty r(a)\mu_j(a) w_j(t,a) da.$$

Since w_j is given by the resolution of the linearized system (1.1) at the disease-free equilibrium (DFE), the Volterra formulation of the transport equation yields

$$b_j(t) = \beta_j x_f \int_0^t \rho_j(a) l(a) m_j(t-a) da + \int_t^\infty \rho_{y,j}(a) w_j(0,a) da.$$

On the other hand, it follows from the m_j component of the linearized system (1.1) at the DFE that

$$\dot{m}_j(t) = b_j(t) - (\mu_{m,j} + \delta_j \beta_j x_f) m_j(t),$$

that rewrites as

$$m_j(t) = \int_0^t e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(t-s)} b_j(s) ds + m_j(0) e^{-(\mu_{m,j}+\delta_j\beta_j x_f)t}.$$

As a consequence b_j satisfies the following renewal equation:

$$\begin{aligned} b_j(t) = \beta_j x_f \int_0^t \left(\int_0^a e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(a-s)} \rho_j(s) l(s) ds \right) b_j(t-a) da \\ + \beta_j x_f m_j(0) \int_0^t \rho_j(a) l(a) e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(t-a)} da + \int_t^\infty r_j(a) \mu_j(a) w_j(0,a) da. \end{aligned}$$

Due to the above formulation, the j-strain specific basic reproduction number $\mathcal{R}_0^j$ is calculated as

$$\mathcal{R}_0^j = \beta_j x_f \int_0^\infty \left(\int_0^a e^{-(\mu_{m,j}+\delta_j\beta_j x_f)(a-s)} \rho_j(s) l(s) ds \right) da;$$

that is,

$$\mathcal{R}_0^j = \frac{\beta_j x_f}{\mu_{m,j} + \delta_j \beta_j x_f} \int_0^\infty \rho_j(a) l(a) da.$$

Now let us notice that $\operatorname{sgn}(\mathcal{R}_0^j - 1) = \operatorname{sgn}(\mathcal{T}_0^j - 1)$. Indeed it is easy to check that

$$\mathcal{R}_0^j - 1 = \frac{\mu_{m,j}}{\mu_{m,j} + \delta_j \beta_j x_f} \left(\mathcal{T}_0^j - 1 \right).$$

Moreover one can notice that when $\delta_j = 0$, $\mathcal{R}_0^j = \mathcal{T}_0^j$.

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Analysis of an Age-structured SIL model

with demographics process and vertical transmission

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ABSTRACT. We consider a mathematical SIL model for the spread of a directly transmitted infectious disease in an age-structured population; taking into account the demographic process and the vertical transmission of the disease. First we establish the mathematical well-posedness of the time evolution problem by using the semigroup approach. Next we prove that the basic reproduction ratio R_0 is given as the spectral radius of a positive operator, and an endemic state exist if and only if the basic reproduction ratio R_0 is greater than unity, while the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$. We also show that the endemic steady states are forwardly bifurcated from the disease-free steady state when R_0 cross the unity. Finally we examine the conditions for the local stability of the endemic steady states.

RÉSUMÉ. Nous considérons ici un modèle mathématique SIL de transmission directe de la maladie dans une population hôte structurée en âge; prenant en compte les processus démographiques et la transmission verticale de la maladie. Premièrement, nous étudions le caractère bien posé du problème par la théorie des semi-groupes. Ensuite, nous montrons que le taux de reproduction de base R_0 est le rayon spectral d'un opérateur positif; et un équilibre endémique existe si et seulement si R_0 est supérieur à l'unité, tandis que l'équilibre sans maladie est localement asymptotiquement stable si $R_0 < 1$. Nous établissons aussi l'existence d'une bifurcation de l'équilibre sans maladie quand R_0 passe par l'unité. Enfin, nous donnons des conditions nécessaires pour la stabilité locale de l'équilibre endémique.

KEYWORDS : Age-structured model, Semigroup, Basic reproduction ratio, Stability.

MOTS-CLÉS : Modèle structuré en âge, Semigroup, Taux de reproduction de base, Stabilité.

1. Introduction

During the earliest centuries mankind faces ever more challenging environmental and public health problems, such as emergence of new diseases or the emergence of disease into new regions, and the resurgence diseases (tuberculosis, malaria HIV/AIDS, HBV). Mathematical models of populations incorporating age structure, or other structuring of individuals with continuously varing properties, have an extensive history.

The earliest models of age structured populations, due to Sharpe and Lotka in 1911 [37] and McKendrick in 1926 [39] established a foundation for a partial differential equations approach to modeling continuum age structure in an evolving population. At this early stage of development, the stabilization of age structure in models with linear mortality and fertility processes was recognized, although not rigorously established [35, 36]. Rigorous analysis of these linear models was accomplished later in 1941 by Feller [16], in 1963 by Bellman and Cooke [4], and others, using the methods of Volterra integral equations and Laplace transforms. Many applications of this theory have been developed in demography [9, 27, 33, 43], in biology [1, 2, 3, 10, 24, 48] and in epidemiology [7, 8, 17, 18, 22, 32, 13, 12].

The increasingly complex mathematical issues involved in nonlinearities in age structured models led to the development of new technologies, and one of the most useful of these has been the method of semi-groups of linear and nonlinear operators in Banach spaces. Structured population models distinguish individual from another according to characteristics such as age, size, location, status and movement. The goal of structured population is to understand how these characteristics affect the dynamics of these models and thus the outcomes and consequence of the biological and epidemiological processes.

In this paper we consider a mathematical S-I-L (Susceptibles-Infected-Lost of sight) model with demographics process, for the spread of a directly transmitted infectious disease in an age-structured population. By infected (I) we mean infectious taking a chemoprophylaxis in a care center. And by loss of sight (L), we mean infectious that begun their effective therapy in the hospital and never return to the hospital for the spuctrum examinations for many reasons such as long duration of treatment regimen, poverty, mentality, etc... The lost of sight class was previously consider in some papers as [6, 15].

In this paper, the infective agent can be transmitted not only horizontally but also vertically from infected mothers to their newborns (perinatal transmission). There are important infective agents such as HBV (hepatitis B virus), HIV (human immunodeficiency virus) and HTLV (human T-cell leukemia virus) that can be vertically transmitted. Compared with the pure horizontal transmission case, so far we have not yet so many results for vertically diseases in structured populations. In Africa, the vertical transmission of the disease like HIV is in progression nowadays.

Worldwide, 1% of pregnant women are HIV-positive. However, sub-Saharan Africa where 95% of HIV positive women live carries the vast majority of this burden [46]. Without treatment, approximately 25%-50% of HIV-positive mothers will transmit the virus to their newborns during pregnancy, childbirth, or breastfeeding [5]. In 2007, over 2 million children worldwide were living with HIV/AIDS, with the overwhelming majority again in sub-Saharan Africa [46]. Approximately 400,000 infants contract HIV from their mother every year, which is about 15% of the total global HIV incidence [41, 50]. The

rate of pediatric HIV infections in sub-Saharan Africa remains unacceptably high, with over 1,000 newborns infected with HIV per day [25].

Large simple trials which aim to study therapeutic interventions and epidemiological associations of human immunodeficiency virus (HIV) infection, including perinatal transmission, in Africa may have substantial rates of lost of sight. A better understanding of the characteristics and the impact of women and children lost of sight is needed. According to Ioannidis et al. [30], for the impact of lost of sight and vertical transmission cohort in Malawi, several predictors of lost of sight were identified in this large HIV perinatal cohort. Lost of sights can impact the observed transmission rate and the risk associations in different studies. They (Ioannidis et al.) also focus that the HIV infection status could not be determine for 36.9% of infant born to HIV-infected mothers; 6.7% with missing status because of various sample problems and 30.3% because they never returned to the clinic (Lost of sight).

Firstly, the epidemic system is formulated. Then, we will describe the semigroup approach to the time evolution problem of the abstract epidemic system. Next we consider the disease invasion process to calculate the basic reproduction ratio R_0, then, we prove that the disease-free steady state is locally asymptotically stable if $R_0 < 1$. Subsequently, we show that at least one endemic steady state exists if the basic reproduction ratio R_0 is greater than unity. By introducing a bifurcation parameter, we show that the endemic steady state is forwardly bifurcated from the disease-free steady state when the basic reproduction ratio crosses unity. Finally, we consider the conditions for the local stability of the endemic steady states.

2. The model

In this section, we formulate a model for the spread of the disease in a host population. We consider a host population divided into three subpopulations; the susceptible class, the infective class (those who are infectious but taking a chemoprophylaxis) and the lost of sight class (those who are infectious but not on a chemoprophylaxis) denoted respectively by $S(t,a)$, $I(t,a)$ and $L(t,a)$ at time t and at specific age a. Let $\beta(.,.)$ be the contact rate between susceptible individuals and infectious individuals. Namely, $\beta(a,\sigma)$ is the transmission rate from the infectious individuals aged σ to the susceptible individuals aged a. All recruitment is into the susceptible class and occur at a specific rate $\Lambda(a)$. The rate of non-disease related death is $\mu(a)$. Infected and lost of sight have additional death rates due to the disease $d_1(a)$ and $d_2(a)$ respectively. The transmission of the disease occurs following adequate contacts between a susceptible and infectious or lost of sight. $r(a)$ denoted the proportion of individuals receiving an effective therapy in a care center and $\phi(a)$ the fraction of them who after begun their treatment will not return in the hospital for the examination. After some time, some of them can return in the hospital at specific rate $\gamma(a)$.

The basic system (age-structured SIL epidemic model) with vertical transmission can be formulated as follows by equation (1).

$$\begin{cases} \left(\dfrac{\partial}{\partial t}+\dfrac{\partial}{\partial a}\right)S(t,a) &= \Lambda(a)-(\lambda(t,a)+\mu(a))S(t,a), \\ \left(\dfrac{\partial}{\partial t}+\dfrac{\partial}{\partial a}\right)I(t,a) &= \lambda(t,a)S(t,a)-(\mu(a)+d_1(a) \\ & \quad +r(a)\phi(a))I(t,a)+\gamma(a)L(t,a), \\ \left(\dfrac{\partial}{\partial t}+\dfrac{\partial}{\partial a}\right)L(t,a) &= r(a)\phi(a)I(t,a)-(\mu(a)+d_2(a) \\ & \quad +\gamma(a))L(t,a). \end{cases} \tag{1}$$

For the boundary conditions of model (1), we consider that pregnant lost of sight women generally return to the clinic for the birth of they new born, therefore, we can assume that there is not lost of sight new born (i.e. $L(t,0)=0$). Due to the above consideration, the initial boundary conditions of model (1) is given by:

$$\begin{cases} S(t,0) &= \int_0^{a^+} f(a)[S(t,a)+(1-p)(I(t,a)+L(t,a))]da, \\ I(t,0) &= p\int_0^{a^+} f(a)(I(t,a)+L(t,a))da, \\ L(t,0) &= 0, \\ S(0,a) &= \varphi_S(a);\ \ a\in(0,a^+), \\ I(0,a) &= \varphi_I(a);\ \ a\in(0,a^+), \\ L(0,a) &= \varphi_L(a);\ \ a\in(0,a^+), \end{cases} \tag{2}$$

and where $f(a)$ is the age-specific fertility rate, p is the proportion of newborns produced from infected individuals who are vertically infected and $a^+<\infty$ is the upper bound of age. The force of infection $\lambda(t,a)$ is given by

$$\lambda(t,a)=\int_0^{a^+}\beta(a,\sigma)(I(t,\sigma)+L(t,\sigma))d\sigma.$$

where $\beta(a,s)$ is the transmission rate between the susceptible individuals aged a and infectious or lost of sight individuals aged s. $a^+<\infty$ is the upper bound of age.
Let us note that in the literature the transmission rate $\beta(a,\sigma)$ can take many forms: $\beta(a,\sigma)=\beta=constant$ (Dietz 1975 [11]; Greenhalgh 1987 [19]), $\beta(a,\sigma)=g(a)$ (Gripenberg 1983 [20]; Webb 1985 [49]), $\beta(a,\sigma)=g(a)h(\sigma)$ (Dietz and Schenzle 1985 [14]; Greenhalgh 1988 [23]; Castillo-Chavez and al. 1989 [8]).

In the following, we consider systems (1)-(2) under following assumption:

Assumption 1. *We assume that* $\beta\in L^\infty[(0,a^+,\mathbb{R}_+)\times(0,a^+,\mathbb{R}_+)]$ *and functions* $f,\ d_1,\ d_2,\ \gamma,\ \Lambda,\ \mu$ *belong to* $L^\infty(0,a^+,\mathbb{R}_+)$.

3. Existence of flow

The aim of this section is to derive preminirary remarks on (1)-(2). These results include the existence of the unique maximal bounded semiflow associated to this system.

3.1. Abstract formulation

Let X be the space defined as

$$X := L^1(0, a^+, \mathbb{R}^3)$$

with the norm

$$||\varphi||_X = \sum_{i=1}^{3} ||\varphi_i||_{L^1};$$

where $\varphi = (\varphi_1, \varphi_2, \varphi_3)^T \in X$. Let us note X_+ the positive cone of X.
It is well known that $(X, ||.||_X)$ is a Banach space. Let $A : D(A) \subset X \to X$ be a operator defined by

$$A\varphi = -\varphi' - \mu\varphi, \tag{3}$$

with the domain

$$D(A) = \left\{ \varphi = (\varphi_1, \varphi_2, \varphi_3) \in W^{1,1}(0, a^+, \mathbb{R}^3) \; and \; \begin{pmatrix} \varphi_1(0) \\ \varphi_2(0) \\ \varphi_3(0) \end{pmatrix} = \begin{pmatrix} \int_0^{a^+} f(a)[\varphi_1(a) + (1-p)(\varphi_2(a) + \varphi_3(a))]da \\ p\int_0^{a^+} f(a)(\varphi_2(a) + \varphi_3(a))da \\ 0 \end{pmatrix} \right\};$$

the function $F : \overline{D(A)} \to X$ defined by

$$F\begin{pmatrix} \varphi_1 \\ \varphi_2 \\ \varphi_3 \end{pmatrix} = \begin{pmatrix} \Lambda - \lambda[., \varphi]\varphi_1 \\ \lambda[., \varphi]\varphi_1 - (d_1 + r\phi)\varphi_2 + \gamma\varphi_3 \\ r\phi\varphi_2 - (d_2 + \gamma)\varphi_3 \end{pmatrix},$$

$\lambda[., \varphi] \in L^1(0, a^+, \mathbb{R})$ is a function such that

$$\lambda[a, \varphi] = \int_0^{a^+} \beta(a, \sigma)[\varphi_2(\sigma) + \varphi_3(\sigma)]d\sigma$$

and $W^{1,1}(0, a^+, \mathbb{R})$ is a usual Sobolev space.

Let us first derive the following lemma on operator A.

Lemma 1. *1) The operator A is generator of a C_0-semigroup of linear bounded operators $\{T(t)\}_{t\geq 0}$ such that*

$$T(t)\varphi(a) = \begin{cases} \varphi(a-t) & if \quad a - t \geq 0 \\ C(t-a) & if \quad a - t \leq 0 \end{cases} \qquad for \;\; t \leq a^+$$

and $T(t)\varphi(a) = 0_{\mathbb{R}^3}$ for $t > a^+$; where $C(t) = (C_1(t), C_2(t), 0) \in \mathbb{R}^3$ is the unique solution of the following Volterra integral equation

$$C(t) = G(t) + \Phi(t, C),$$

with

$$G(t) = \left(\int_t^{a^+} f(s)(\varphi_1(s-t) + (1-p)\varphi_2(s-t) + \varphi_3(s-t))ds \; ; \; p\int_t^{a^+} f(s)\varphi_2(s-t)ds \; ; \; 0 \right),$$

$$\Phi(t, C) = \left(\int_0^{t} f(s)(C_1(t-s) + (1-p)C_2(t-s))ds \; ; \; p\int_0^{t} f(s)C_2(t-s)ds \; ; \; 0 \right).$$

2) The domain $D(A)$ of operator A is dense in X and A is a closed operator.

Proof. The proof of this result is rather standard. Standard methodologies apply to provide item 1 (see Pazy 1983 [40]). Item 2 is a direct consequence of the fact that the operator A is generator of a C_0-semigroup of linear bounded operators (see Corollary 2.5 in Pazy 1983 [40]). □

Therefore, one obtains that System (1)-(2) re-writes as the following densely defined Cauchy problem

$$\left\{ \begin{array}{rcl} \dfrac{d\varphi(t)}{dt} & = & A\varphi(t) + F(\varphi(t)), \\ \varphi(0) & = & (\varphi_S, \varphi_I, \varphi_L)^T. \end{array} \right. \tag{4}$$

3.2. Existence and uniqueness of solutions

We set $X_0 := \overline{D(A)}$ and X_{0+} the positive cone of X_0. In general we can not solve (4) in this strong formulation, if $u_0 \in X_{0+} \setminus D(A)$. So, for arbitrary $\varphi_0 \in X_{0+}$, we solve it in the integrated form:

$$\varphi(t) \quad = \quad \varphi_0 + A\int_0^t \varphi(s)ds + \int_0^t F(\varphi(s))ds \; ; t \geqslant 0. \tag{5}$$

A solution of (5) is called a *mild solution* of the initial value problem (4). So, in the following, we are looking for mild solution of abstract Cauchy-problem (4).

We can easily find that:

Lemma 2. *On Assumption 1, the nonlinear operator F from X to X is continuous and locally Lipschitz.*

Using Lemmas 1 and 2 the main results of this section reads as (see Theorem 1.4 in Pazy 1983[40]).

Theorem 1. *Recalling Assumption 1 and let Lemmas 1 and 2 be satisfied. If $\varphi_0 \in X_{0+} := L^1(0, a^+, \mathbb{R}^3_+)$. Then there exists a unique bounded continuous solution φ to the integrated problem (5) defined on $[0, +\infty)$ with values in X_{0+}.*

4. Equilibria

4.1. Disease-Free Equilibrium (DFE)

The following proposition gives the characteristics of the disease-free equilibrium (DFE) of system (1)-(2).

Let us introduce $l(a) = exp\left(-\int_0^a \mu(s)ds\right)$ the average lifetime of individuals at age a.

Proposition 1. *Let* $\int_0^{a^+} f(a)l(a)da < 1$ *be satisfied. Then, system (1)-(2) has a unique Disease Free Equilibrium (DFE),* $\varphi_0 = (S_0, 0_{L^1}, 0_{L^1})$*, where* S_0 *is given by*

$$\begin{cases} S_0(0) = \dfrac{1}{1 - \int_0^{a^+} f(a)l(a)da} \displaystyle\int_0^{a^+} f(a)l(a) \left(\int_0^a \frac{\Lambda(s)}{l(s)} ds \right) da, \\ S_0(a) = l(a) \left[S_0(0) + \displaystyle\int_0^a \frac{\Lambda(s)}{l(s)} ds \right] \quad for\ 0 \le a \le a^+. \end{cases} \tag{6}$$

Proof. : φ is an equilibrium of problem (4) if and only if

$$\varphi \in D(A) \text{ and } A\varphi + F(\varphi) = 0_X. \tag{7}$$

For the DFE we have $\varphi_2 = \varphi_3 \equiv 0_{L^1}$. Hence $\lambda[a, \varphi] \equiv 0_{L^1}$. From where the result follows using straightforward computations. □

4.2. Endemic equilibrium (EE)

φ is an endemic equilibrium of (4) if and only if (7) is satisfied. That is,

$$\begin{aligned} \varphi_1(a) &= \varphi_1(0)l(a) \exp\left(- \int_0^a \lambda[\sigma, \varphi] d\sigma \right) \\ &\quad + \int_0^a \frac{l(a)}{l(s)} \exp\left(- \int_s^a \lambda[\sigma, \varphi] d\sigma \right) \Lambda(s) ds; \end{aligned} \tag{8}$$

$$\begin{aligned} \varphi_2(a) &= \int_0^a \frac{l(a)\Gamma_1(a)}{l(s)\Gamma_1(s)} \exp\left(- \int_s^a r(\sigma)\phi(\sigma) d\sigma \right) \left[\gamma(s)\varphi_3(s) + \lambda[s, \varphi]\varphi_1(s) \right] ds \\ &\quad + \varphi_2(0)l(a)\Gamma_1(a) \exp\left(- \int_0^a r(\sigma)\phi(\sigma) d\sigma \right); \end{aligned} \tag{9}$$

$$\begin{aligned} \varphi_3(a) &= \varphi_3(0)l(a)\Gamma_2(a) \exp\left(- \int_0^a \gamma(\sigma) d\sigma \right) \\ &\quad + \int_0^a \frac{l(a)\Gamma_2(a)}{l(s)\Gamma_2(s)} \exp\left(- \int_s^a \gamma(\sigma) d\sigma \right) r(s)\phi(s)\varphi_2(s) ds; \end{aligned} \tag{10}$$

$$\varphi_1(0) = \int_0^{a^+} f(a)[\varphi_1(a) + (1-p)(\varphi_2(a) + \varphi_3(a))] da; \tag{11}$$

$$\varphi_2(0) = p \int_0^{a^+} f(a)(\varphi_2(a) + \varphi_3(a)) da; \tag{12}$$

$$\varphi_3(0) = 0. \tag{13}$$

where

$$\begin{aligned} \Gamma_1(a) &= \exp\left(- \textstyle\int_0^a (d_1(s) + r(s)\phi(s)) ds \right); \\ \Gamma_2(a) &= \exp\left(- \textstyle\int_0^a (d_2(s) + \gamma(s)) ds \right). \end{aligned}$$

Let us set $\lambda(s) = \lambda[s, \varphi]$ for $s \in [0, a^+)$. Equation (8) re-write as

$$\varphi_1(a) = \varphi_1(0)A_{11}(\lambda, a) + u_1(\lambda, a). \tag{14}$$

Equations (8) and (9) give

$$\varphi_2(a) \quad = \quad \varphi_1(0)A_{21}(\lambda,a) + \varphi_2(0)A_{22}(a) + u_2(\lambda,a). \tag{15}$$

Equations (10), (13) and (14) give

$$\varphi_3(a) \quad = \quad \varphi_1(0)A_{31}(\lambda,a) + \varphi_2(0)A_{32}(\lambda,a) + u_3(\lambda,a); \tag{16}$$

with

$$A_{11}(\lambda,a) = l(a)\exp\left(-\int_0^a \lambda(\sigma)d\sigma\right);$$

$$A_{21}(\lambda,a) = \int_0^a \chi_{21}(a,s)\lambda(s)\exp\left(-\int_0^s \lambda(\sigma)d\sigma\right)ds;$$

$$A_{22}(a) = l(a)\Gamma_1(a);$$

$$A_{31}(\lambda,a) = \int_0^a \chi_{31}(a,s)\lambda(s)\exp\left(-\int_0^s \lambda(\sigma)d\sigma\right)ds;$$

$$A_{32}(a) = l(a)\Gamma_2(a)\int_0^a \frac{\Gamma_1(s)}{\Gamma_2(s)}r(s)\phi(s)ds;$$

$$u_1(\lambda,a) = \int_0^a \frac{l(a)}{l(s)}\Lambda(s)\exp\left(-\int_s^a \lambda(\sigma)d\sigma\right)ds;$$

$$u_2(\lambda,a) = \int_0^a \frac{l(a)}{l(s)}\Lambda(s)\int_s^a \frac{\Gamma_1(a)}{\Gamma_1(\eta)}\lambda(\eta)\exp\left(-\int_s^\eta \lambda(\sigma)d\sigma\right)ds;$$

$$u_3(\lambda,a) = \int_0^a \frac{l(a)\Gamma_2(a)}{l(s)\Gamma_2(s)}r(s)\phi(s)u_2(\lambda,s)ds$$

$$+\int_0^a \frac{l(a)\Gamma_1(a)}{l(s)\Gamma_1(s)}\exp\left(-\int_s^a r(\sigma)\phi(\sigma)d\sigma\right)\gamma(s)\varphi_3(s)ds;$$

and

$$\chi_{21}(a,s) = l(a)\frac{\Gamma_1(a)}{\Gamma_1(s)};\ \chi_{31}(a,s) = l(a)\int_s^a \frac{\Gamma_2(a)\Gamma_1(\eta)}{\Gamma_2(\eta)\Gamma_1(s)}r(\eta)\phi(\eta)d\eta.$$

From equations (11) and (12), we respectively deduce that

$$\begin{aligned}&\left(1-\int_0^{a^+} f(a)[A_{11}(\lambda,a)+(1-p)(A_{21}(\lambda,a)+A_{31}(\lambda,a))]da\right)\varphi_1(0)\\ &-(1-p)\varphi_2(0)\int_0^{a^+} f(a)[A_{22}(a)+A_{32}(a)]da = v_1(\lambda);\end{aligned} \tag{17}$$

and

$$\begin{aligned}&p\varphi_1(0)\int_0^{a^+} f(a)[A_{21}(\lambda,a)+A_{31}(\lambda,a)]da\\ &+\varphi_2(0)\left(p\int_0^{a^+} f(a)[A_{22}(a)+A_{32}(a)]da-1\right) = -v_2(\lambda);\end{aligned} \tag{18}$$

where

$$\begin{aligned} v_1(\lambda) &= \int_0^{a^+} f(a)[u_1(\lambda,a)+(1-p)(u_2(\lambda,a)+u_3(\lambda,a))]da; \\ v_2(\lambda) &= p\int_0^{a^+} f(a)[u_2(\lambda,a)+u_3(\lambda,a)]da. \end{aligned}$$

Therefore, we find that $\varphi_1(0)=\dfrac{\Delta_1(\lambda)}{\Delta(\lambda)}$ and $\varphi_2(0)=\dfrac{\Delta_2(\lambda)}{\Delta(\lambda)}$; with

$$\begin{aligned} &\Delta(\lambda)=(1-p)p\int_0^{a^+} f(a)[A_{22}(a)+A_{32}(a)]da\times\int_0^{a^+} f(a)[A_{21}(\lambda,a)+A_{31}(\lambda,a)]da \\ &+\left(1-\int_0^{a^+} f(a)[A_{11}(\lambda,a)+(1-p)(A_{21}(\lambda,a)+A_{31}(\lambda,a))]da\right)\times \\ &\left(p\int_0^{a^+} f(a)[A_{22}(a)+A_{32}(a)]da-1\right); \\ &\Delta_1(\lambda)=v_1(\lambda)\left(p\int_0^{a^+} f(a)[A_{22}(a)+A_{32}(a)]da-1\right) \\ &-(1-p)v_2(\lambda)\int_0^{a^+} f(a)[A_{22}(a)+A_{32}(a)]da; \\ &\Delta_2(\lambda)=v_2(\lambda)\left(\int_0^{a^+} f(a)[A_{11}(\lambda,a)+(1-p)(A_{21}(\lambda,a)+A_{31}(\lambda,a))]da-1\right) \\ &-pv_1(\lambda)\int_0^{a^+} f(a)[A_{21}(\lambda,a)+A_{31}(\lambda,a)]da. \end{aligned}$$

Equations (15) and (16) give

$$\left\{\begin{array}{rcl} \varphi_2(a) &=& \dfrac{\Delta_1(\lambda)}{\Delta(\lambda)}A_{21}(\lambda,a)+\dfrac{\Delta_2(\lambda)}{\Delta(\lambda)}A_{22}(a)+u_2(\lambda,a) \\ \varphi_3(a) &=& \dfrac{\Delta_1(\lambda)}{\Delta(\lambda)}A_{31}(\lambda,a)+\dfrac{\Delta_2(\lambda)}{\Delta(\lambda)}A_{32}(a)+u_3(\lambda,a) \end{array}\right. \tag{19}$$

Since $\lambda(a)=\int_0^{a^+}\beta(a,s)(\varphi_2(s)+\varphi_3(s))ds$; then we have

$$\lambda(a)=H(\lambda)(a); \tag{20}$$

where H is the operator defined from $L^1(0,a^+,\mathbb{R})$ into itself by

$$\begin{aligned} H(\varphi)(a) &= \int_0^{a^+}\beta(a,s)\left[\frac{\Delta_1(\varphi)}{\Delta(\varphi)}(A_{21}(\varphi,s)+A_{31}(\varphi,s))+u_2(\varphi,s)+u_3(\varphi,s)\right. \\ &\left.+\frac{\Delta_2(\varphi)}{\Delta(\varphi)}(A_{22}(s)+A_{32}(s))\right]ds. \end{aligned} \tag{21}$$

Hence, system (1)-(2) have an endemic equilibrium if and only if the fixed point equation (20) has at least one positive solution.

Now let us introduce the following technical assumptions on the transmission rate β as in Inaba [26, 28, 29]:

Assumption 2. *1)* $\beta \in L^1_+(\mathbb{R}\times\mathbb{R})$ *such that* $\beta(a,s)=0$ *for all* $(a,s)\notin [o,a^+]\times[0,a^+]$.

2) $\lim\limits_{h\to 0}\int_{-\infty}^{+\infty}|\beta(a+h,\xi)-\beta(a,\xi)|da=0$ *for* $\xi\in\mathbb{R}$.

3) It exists a function ε *such that* $\varepsilon(s)>0$ *for* $s\in(0,a^+)$ *and* $\beta(a,s)\geqslant\varepsilon(s)$ *for all* $(a,s)\in(0,a^+)^2$.

On the above assumption, some properties of operator H are given by the following lemma.

Lemma 3. *Let Assumption 2 be satisfied.*

(i) H *is a positive, continu operator. There exist a closed, bounded and convex subset* $D\subset L^1_+(0,a^+,\mathbb{R})$ *such that* $H(D)\subset D$.

(ii) Operator H *has a Fréchet derivative* H_0 *at the point* $\varphi\equiv 0$ *defined by* (22) *and* $H_0:=H'(0)$ *is a positive, compact and nonsupporting operator.*

Proof. (i) The positivity and the continuity of operator H are obvious. Let $\varphi\in L^1(0,a^+,\mathbb{R}_+)$, then

$$A_{21}(\varphi,a)\leq 1;\ A_{31}(\varphi,a)\leq\int_0^a\frac{l(a)\Gamma_2(a)}{l(s)\Gamma_2(s)}r(s)\phi(s)ds:=\tilde{A}_{31}(a);$$

$$u_1(\varphi,a)\leq\int_0^a\frac{l(a)}{l(s)}\Lambda(s)ds;\ u_2(\varphi,a)\leq a||\Lambda||_\infty \text{ and}$$

$$u_3(\varphi,a)\leq||\Lambda||_\infty\tilde{A}_{31}(a)+\sup_{s\in[0,a]}\gamma(s)||\varphi||_{L^1}.$$

Since $\frac{\Delta_1(\varphi)}{\Delta(\varphi)}=\varphi_1(0)$; $\frac{\Delta_2(\varphi)}{\Delta(\varphi)}=\varphi_2(0)$ and the flow of system (1)-(2) is bounded (Theorem 1), we can find $M_\Omega>0$ such that $|\varphi_1(0)|\leq M_\Omega$ and $|\varphi_2(0)|\leq M_\Omega$. Therefore, $||H(\varphi)||_{L^1}\leq M$; with

$$M=||\beta||_\infty\int_0^{a^+}\left[M_\Omega(1+A_{22}(s)+(\tilde{A}_{31}(s)+A_{32}(s))+\sup_{s\in[0,a]}\gamma(s))+||\Lambda||_\infty(\tilde{A}_{31}(s)+s)\right]ds.$$

Setting $D=\overline{B_+(0,M)}$ with $\overline{B_+(0,M)}:=\{\varphi\in L^1(0,a^+,\mathbb{R}_+):||\varphi||_{L^1}\leq M\}$. Hence $H(D)\subset D$. This end the proof of item (i).

(ii) We find that

$$H_0(\psi)(a)=\int_0^{a^+}\beta(a,s)\left[\frac{\Delta_1(0)}{\Delta(0)}(DA_{21}(0,s)(\psi)+DA_{31}(0,s)(\psi))+Du_2(0,s)(\psi)\right.$$

$$\left.+Du_3(0,s)(\psi)+\frac{D\Delta_2(0)(\psi)}{\Delta(0)}(A_{22}(s)+A_{32}(s))\right]ds.$$

where Du denotes the derivative of the function u and

$$Du_2(0,a)(\psi) = \int_0^a \chi_2(a,s)\psi(s)ds; \quad Du_3(0,a)(\psi) = \int_0^a \chi_3(a,s)\psi(s)ds;$$

$$DA_{21}(0,a)(\psi) = \int_0^a \chi_{21}(a,s)\psi(s)ds; \quad DA_{31}(0,a)(\psi) = \int_0^a \chi_{31}(a,s)\psi(s)ds;$$

$$D\Delta_2(0)(\psi) = p\int_0^{a^+} \chi_4(a)\psi(a)da.$$

with

$$\chi_{21}(a,s) = \frac{l(a)\Gamma_1(a)}{l(s)\Gamma_1(s)}\exp\left(-\int_s^a r(\sigma)\phi(\sigma)d\sigma\right) l(s)$$

$$\chi_{31}(a,s) = \int_s^a \frac{l(a)\Gamma_2(a)}{l(\eta)\Gamma_2(\eta)} r(\eta)\phi(\eta)\chi_{21}(\eta,s)d\eta$$

$$\chi_2(a,s) = \chi_{21}(a,s)\int_0^s \frac{\Lambda(\eta)}{l(\eta)}d\eta; \quad \chi_3(a,s) = \chi_{31}(a,s)\int_0^s \frac{\Lambda(\eta)}{l(\eta)}d\eta;$$

$$\chi_4(a) = \left[\frac{S_0(a)}{l(a)}\int_0^{a^+} f(\sigma)l(\sigma)d\sigma - S_0(0)\right]\int_a^{a^+} f(s)\left[\chi_{21}(s,a) + \chi_{31}(s,a)\right]ds.$$

Hence, operator H_0 read as a kernel operator:

$$H_0(\psi)(a) = \int_0^{a^+} \chi(a,s)\psi(s)ds; \tag{22}$$

where the kernel $\chi(a,s)$ is defined by

$$\begin{aligned}\chi(a,s) &= \frac{S_0(s)}{l(s)}\int_s^{a^+} \beta(a,\eta)\left(\chi_{21}(\eta,s) + \chi_{31}(\eta,s)\right)d\eta \\ &\quad + \frac{p\chi_4(s)}{\Delta(0)}\int_0^{a^+} \beta(a,\sigma)(A_{22}(\sigma) + A_{32}(\sigma))d\sigma.\end{aligned} \tag{23}$$

The positivity of H_0 is obvious. Let us show the compactness of the operator H_0 on Assumption 2. Let $\psi \in L^1$ and $\epsilon > 0$. From Assumption 2; there exists $\rho = \rho(\epsilon) > 0$ such that, for $|h| < \rho$ we have $\int_0^{a^+} |\beta(a+h,\xi) - \beta(a,\xi)|da < \epsilon$. Is therefore $h \in \mathbb{R}$ such that $|h| < \rho$. $||\tau_h H_0(\psi) - H_0(\psi)||_{L^1} = \int_0^{a^+} |H_0(\psi)(a+h) - H_0(\psi)(a)|da$. It is easily checked that

$$|H_0(\psi)(a+h) - H_0(\psi)(a)| \leq ||\psi||_{L^1}\int_0^{a^+} |\beta(a+h,s) - \beta(a,s)|C_1(s)ds;$$

where

$$\begin{aligned}C_1(a) &= \left(||\Lambda||_\infty + \frac{\Delta_1(0)}{\Delta(0)}\right)\left(1 + \int_0^a \frac{l(a)\Gamma_2(a)}{l(s)\Gamma_2(s)} r(s)\phi(s)ds\right) \\ &\quad + \frac{||\Lambda||_\infty}{\Delta(0)}(A_{22}(a) + A_{32}(a))\int_0^{a^+} f(a)\left(1 + \int_0^a \frac{l(a)\Gamma_2(a)}{l(s)\Gamma_2(s)} r(s)\phi(s)ds\right)da.\end{aligned}$$

Since $\left(|h| < \rho \Longrightarrow \int_0^{a^+} |\beta(a+h,s) - \beta(a,s)|da < \epsilon\right)$, it comes that

$$||\tau_h H_0(\psi) - H_0(\psi)||_{L^1} \quad \leq \quad \epsilon \left(\int_0^{a^+} C_1(a)da\right) ||\psi||_{L^1}.$$

Let $\mathbb{B}$ a bounded subset of L^1 such that $\psi \in \mathbb{B}$. Then

$$||\tau_h H_0(\psi) - H_0(\psi)||_{L^1} \quad \leq \quad \epsilon \left(\int_0^{a^+} C_1(a)da\right) \times \sup_{\varphi \in \mathbb{B}} \{||\varphi||_{L^1}\}.$$

Applying the Riesz-Fréchet-Kolmogorov theorem on $H_0(\mathbb{B})$ we conclude that $H_0(\mathbb{B})$ is relatively compact. From where H_0 si a compact operator.
Now, let us check that H_0 is a nonsupporting operator. We define the operator $F_0 \in (L^1(0,a^+,\mathbb{R}_+))^*$ (dual space of $L^1(0,a^+,\mathbb{R}_+)$) by

$$\langle F_0; \psi \rangle \quad = \quad \int_0^{a^+} \varepsilon(s)[Du_2(0,s)(\psi) + \delta(s)Du_3(0,s)]ds;$$

where ε is the positive function given by Assumption 2 and $\langle F_0; \psi \rangle$ is the value of $F_0 \in (L^1(0,a^+,\mathbb{R}_+))^*$ at $\psi \in L^1(0,a^+,\mathbb{R}_+)$. Then for $\psi \in L^1(0,a^+,\mathbb{R}_+)$ we have $H_0(\psi) \geq \langle F_0; \psi \rangle \cdot e$ (with $e = 1 \in L^1(0,a^+,\mathbb{R}_+)$). From where $H_0^{n+1}(\psi) \geq \langle F_0; \psi \rangle \langle F_0; e \rangle^n \cdot e \ \ \forall n \in \mathbb{N}$. Hence for all $n \in \mathbb{N}^*$; $F \in (L^1(0,a^+,\mathbb{R}_+))^* \setminus \{0\}$ and $\psi \in L^1(0,a^+,\mathbb{R}_+) \setminus \{0\}$ we have $\langle F; H_0^n(\psi) \rangle > 0$. Therefore, H_0 is a nonsupporting operator. □

The main results of this section reads as

Theorem 2. *Let Assumption 2 be satisfied. Let us note $R_0 = \rho(H_0)$ the spectral radius of operator H_0.*

1) If $R_0 \leq 1$, system (1)-(2) has a unique DFE defined by (6);

2) If $R_0 > 1$, in addition to the DFE, system (1)-(2) has at least one endemic equilibrium.

Proof. The operator H always has $\lambda \equiv 0$ as fixed point. This corresponds to the permanent DFE for system (1)-(2). For the rest, we are looking for the positive fixed point to the operator H. From Lemma 3 we know that there exists a closed, bounded and convex subset D of $L^1(0,a^+,\mathbb{R}_+)$ which is invariant by the operator H. Moreover, from Lemma 3, H has a Fréchet derivative H_0 at the point 0 and $H_0 = DH(0)$ is a compact and nonsupporting operator. Therefore, there exists a unique positive eigenvector ψ_0 corresponding to the eigenvalue $R_0 = \rho(H_0)$ of H_0. Using the same arguments as for the Krasnoselskii fixe point theorem [34], it comes that if $R_0 = \rho(H_0) > 1$, then the operator H has at least one positive fixed point $\lambda^* \in L^1(0,a^+,\mathbb{R}_+) \setminus \{0\}$, corresponding to the EE of system (1)-(2).

Let us suppose that $R_0 = \rho(H_0) \leq 1$. If the operator H has a positive fixe point $\lambda^* \in L^1(0,a^+,\mathbb{R}_+) \setminus \{0\}$ then $\lambda^* = H(\lambda^*)$. Let us notice that $H - H_0 \in L^1(0,a^+,\mathbb{R}_+) \setminus \{0\}$; hence $\lambda^* \leq H_0(\lambda^*)$. Let $F_0 \in (L^1(0,a^+,\mathbb{R}_+))^* \setminus \{0\}$ be the positive eigenfunctional corresponding to the eigenvalue $R_0 = \rho(H_0)$ of H_0 (Sawashima [44]). Therefore

$$\begin{aligned} 0 \leq \langle F_0; H_0(\lambda^*) - \lambda^* \rangle \quad &= \quad \langle F_0, ; H_0(\lambda^*) \rangle - \langle F_0; \lambda^* \rangle ; \\ &= \quad \rho(H_0) \langle F_0; \lambda^* \rangle - \langle F_0; \lambda^* \rangle ; \\ &= \quad (\rho(H_0) - 1) \langle F_0; \lambda^* \rangle . \end{aligned}$$

From where $(\rho(H_0)-1)\langle F_0;\lambda^*\rangle \geq 0$. Since $\langle F_0;\lambda^*\rangle > 0$, it follows that $\rho(H_0) \geq 1$; which is a contradiction. □

5. Stability analysis for equilibrium

In order to investigate the local stability of the equilibrium solutions $(S^*(a);I^*(a);L^*(a))$ we rewrite (1)-(2) into the equation for small perturbations. Let

$$(S(t,a),I(t,a),L(t,a)) = (S^*(a),I^*(a),L^*(a)) + (x(t,a),y(t,a),z(t,a)).$$

Then from system (1) we have

$$\begin{aligned}
\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)x(t,a) &= -\lambda(t,a)(S^*(a)+x(t,a)) \\
&\quad -(\mu(a)+\lambda^*(a))x(t,a); \qquad (24)\\
\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)y(t,a) &= \lambda(t,a)(x(t,a)+S^*(a))+\lambda^*(a)x(t,a) \\
&\quad -(\mu(a)+d_1(a)+r(a)\phi(a))y(t,a); \qquad (25)\\
\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)z(t,a) &= r(a)\phi(a)y(t,a)-(\mu(a)+d_2(a))z(t,a); \qquad (26)
\end{aligned}$$

and from (2) we also have

$$\left\{\begin{array}{rcl} x(t,0) &=& \int_0^{a^+} f(a)[x(t,a)+(1-p)(y(t,a)+z(t,a))]da; \\ y(t,0) &=& p\int_0^{a^+} f(a)(y(t,a)+z(t,a))da; \\ z(t,0) &=& 0; \end{array}\right. \qquad (27)$$

with $\lambda(a,t) = \displaystyle\int_0^{a^+}\beta(a,s)(y(t,s)+z(t,s))ds$ and $\lambda^*(a) = \displaystyle\int_0^{a^+}\beta(a,s)(I^*(s)+L^*(s))ds$.

Let us note $u(t)=(x(t),y(t),z(t))^T$. Then from equations (24), (25) and (26) we have

$$\frac{d}{dt}u(t) = Au(t)+G(u(t)); \qquad (28)$$

where A is the operator defined by (3). The nonlinear term G is defined by

$$G(u) = \begin{pmatrix} -\mathcal{P}(u_2,u_3)(u_1+S^*)-(\lambda^*+\mu)u_1 \\ \mathcal{P}(u_2,u_3)(u_1+S^*)+\lambda^*u_1-(\mu+d_1+r\phi)u_2 \\ r\phi u_2-(\mu+d_2)u_3 \end{pmatrix};$$

and $\mathcal{P}$ is linear operator defined on $L^1\times L^1$ by

$$\mathcal{P}(u_2,u_3)(a) = \int_0^{a^+}\beta(a,s)(u_2(s)+u_3(s))ds. \qquad (29)$$

The linearized equation of (28) around $u = 0$ is given by

$$\frac{d}{dt}u(t) \quad = \quad (A + C)u(t); \tag{30}$$

where the linear operator C is the Fréchet derivative of $G(u)$ at $u = 0$ and it is given by

$$C(u) \quad = \quad \begin{pmatrix} -\mathcal{P}(u_2, u_3)S^* - (\lambda^* + \mu)u_1 \\ \mathcal{P}(u_2, u_3)S^* + \lambda^* u_1 - (\mu + d_1 + r\phi)u_2 \\ r\phi u_2 - (\mu + d_2)u_3 \end{pmatrix}$$

Now let us consider the resolvent equation for $\widehat{A} + C$:

$$(z - (A + C))\psi \quad = \quad \vartheta; \;\; \psi \in D(A), \;\; \vartheta \in X, \;\; z \in \mathbb{C}. \tag{31}$$

Applying the variation of constant formula to (31) we obtain the following equations:

$$\psi_1(a) \quad = \quad \Pi(a)l(a)e^{-za}\left[\psi_1(0) + \int_0^a (T_{11}(s)\vartheta_1(s) - T_{12}(s)\mathcal{P}(\psi_1, \psi_2)(s))ds\right] \tag{32}$$

$$\psi_2(a) \quad = \quad \left[\psi_2(0) + \int_0^a \frac{e^{zs}}{\Gamma_1(s)l(s)}(\vartheta_2(s) + \lambda^*(s)\psi_1(s) + \mathcal{P}(\psi_1, \psi_2)(s)S^*(s))ds\right]$$
$$\times\Gamma_1(a)l(a)e^{-za}; \tag{33}$$

$$\psi_3(a) \quad = \quad \Gamma_2(a)l(a)e^{-za}\left[\psi_3(0) + \int_0^a \frac{e^{zs}}{\Gamma_2(s)l(s)}(\vartheta_3(s) + r(s)\phi(s)\psi_2(s))ds\right]. \tag{34}$$

with $\Pi(a) = \exp\left(-\int_0^a \lambda^*(\sigma)d\sigma\right)$; $T_{11}(s) = \dfrac{e^{zs}}{\Pi(s)l(s)}$ and $T_{12}(s) = S^*(s)T_{11}(s)$.
Equations (32)-(33) and (35)-(34) respectively gives

$$\psi_2(a) \quad = \quad \Gamma_1(a)l(a)e^{-za}\left[\psi_2(0) + T_{21}(a)\psi_1(0) + \int_0^a T_{23}(z, a, s)\mathcal{P}(\psi_1, \psi_2)(s))ds\right.$$
$$\left. + \int_0^a T_{24}(z, a, s)\vartheta_1(s)ds + \int_0^a T_{25}(z, s)\vartheta_2(s)ds\right] \tag{35}$$

and

$$\psi_3(a) = \Gamma_2(a)l(a)e^{-za}\left[T_{32}(a)\psi_2(0) + T_{31}(a)\psi_1(0) + \psi_3(0) + \int_0^a T_{33}(z, a, s)\mathcal{P}(\psi_1, \psi_2)(s))ds\right.$$
$$\left. + \int_0^a T_{34}(z, a, s)\vartheta_1(s)ds + \int_0^a T_{35}(z, a, s)\vartheta_2(s)ds + \int_0^a T_{36}(z, a, s)\vartheta_3(s)ds\right]; \tag{36}$$

where

$$T_{21}(a) = \int_0^a \frac{\Pi(s)}{\Gamma_1(s)}\lambda^*(s)ds; \;\; T_{24}(z, a, s) = \frac{e^{zs}}{l(s)\Pi(s)}\int_s^a \frac{\Pi(\sigma)}{\Gamma_1(\sigma)}\lambda^*(\sigma)d\sigma,$$

$$T_{23}(z, a, s) = \frac{e^{zs}}{l(s)}S^*(s)\left(\frac{1}{\Gamma_1(s)} - \frac{1}{\Pi(s)}\int_s^a \frac{\Pi(\sigma)}{\Gamma_1(\sigma)}\lambda^*(\sigma)d\sigma\right),$$

$$T_{25}(z,s)=\frac{e^{zs}}{l(s)\Gamma_1(s)},\ \ T_{31}(a)=\int_0^a\frac{\Gamma_1(s)}{\Gamma_2(s)}r(s)\phi(s)T_{21}(s)ds,$$
$$T_{32}(a)=\int_0^a\frac{\Gamma_1(s)}{\Gamma_2(s)}r(s)\phi(s)ds,\ \ T_{36}(z,a)=\frac{e^{za}}{\Gamma_2(a)l(a)},$$
$$T_{33}(z,a,s)=\int_s^a\frac{\Gamma_1(\sigma)}{\Gamma_2(\sigma)}r(\sigma)\phi(\sigma)T_{23}(z,\sigma,s)d\sigma,$$
$$T_{34}(z,a,s)=\int_s^a\frac{\Gamma_1(\sigma)}{\Gamma_2(\sigma)}r(\sigma)\phi(\sigma)T_{24}(z,\sigma,s)d\sigma,$$
$$T_{35}(z,a,s)=T_{25}(z,s)\int_s^a\frac{\Gamma_1(\sigma)}{\Gamma_2(\sigma)}r(\sigma)\phi(\sigma)d\sigma.$$

Since $\psi\in D(A)$; it comes that

$$\psi_1(0) = \int_0^{a^+} f(a)[\psi_1(a)+(1-p)(\psi_2(a)+\psi_3(a))]da; \tag{37}$$
$$\psi_2(0) = p\int_0^{a^+} f(a)(\psi_2(a)+\psi_3(a))da; \tag{38}$$
$$\psi_3(0) = 0. \tag{39}$$

Equations (36)-(39); (32)-(35)-(40)-(37) and (35)-(40)-(38) respectively lead to

$$\psi_3(a)=\Gamma_2(a)l(a)e^{-za}\left[T_{32}(a)\psi_2(0)+T_{31}(a)\psi_1(0)++\int_0^a T_{33}(z,a,s)\mathcal{P}(\psi_1,\psi_2)(s))ds\right.$$
$$\left.+\int_0^a T_{34}(z,a,s)\vartheta_1(s)ds+\int_0^a T_{35}(z,a,s)\vartheta_2(s)ds+\int_0^a T_{36}(z,s)\vartheta_3(s)ds\right]; \tag{40}$$

$$(B_{11}(z)-1)\psi_1(0)+(1-p)B_{12}(z)\psi_2(0)+\int_0^{a^+}B_{13}(z,a)\mathcal{P}(\psi_1,\psi_2)(a)da$$
$$+\int_0^{a^+}B_{14}(z,a)\vartheta_1(a)da+\int_0^{a^+}B_{15}(z,a)\vartheta_2(a)da+\int_0^{a^+}B_{16}(z,a)\vartheta_3(a)da=0; \tag{41}$$

and

$$pB_{21}(z)\psi_1(0)+(pB_{22}(z)-1)\psi_2(0)+p\int_0^{a^+}B_{23}(z,a)\mathcal{P}(\psi_1,\psi_2)(a)da$$
$$+p\int_0^{a^+}B_{24}(z,a)\vartheta_1(a)da+p\int_0^{a^+}B_{25}(z,a)\vartheta_2(a)da+p\int_0^{a^+}B_{26}(z,a)\vartheta_3(a)da=0; \tag{42}$$

with

$$B_{11}(z)=\int_0^{a^+}f(a)l(a)e^{-za}\left[\Pi(a)+(1-p)(\Gamma_1(a)T_{21}(a)+\Gamma_2(a)T_{31}(a)\right]da;$$

$$B_{12}(z) = \int_0^{a^+} f(a)l(a)e^{-za}\left[\Gamma_1(a) + \Gamma_2(a)T_{32}(a)\right]da;$$

$$B_{13}(z,a) = \int_a^{a^+} f(s)l(s)e^{-zs}\left[-T_{12}(a)\Pi(s) + (1-p)(\Gamma_1(s)T_{23}(z,s,a) + \Gamma_2(s)T_{33}(z,s,a))\right]ds;$$

$$B_{14}(z,a) = \int_a^{a^+} f(s)l(s)e^{-zs}\left[T_{11}(a)\Pi(s) + (1-p)(\Gamma_1(s)T_{24}(z,s,a) + \Gamma_2(s)T_{34}(z,s,a))\right]ds;$$

$$B_{15}(z,a) = \int_a^{a^+} f(s)l(s)e^{-zs}\left[\Gamma_1(s)T_{25}(z,a) + (1-p)\Gamma_2(s)T_{35}(z,s,a)\right]ds;$$

$$B_{16}(z,a) = (1-p)\int_a^{a^+} f(s)l(s)e^{-zs}\Gamma_2(s)T_{36}(z,s)ds;$$

$$B_{21}(z) = \int_0^{a^+} f(a)l(a)e^{-za}[\Gamma_1(a)T_{21}(a) + \Gamma_2(a)T_{31}(a)]da;$$

$$B_{22}(z) = \int_0^{a^+} f(a)l(a)e^{-za}[\Gamma_1(a) + \Gamma_2(a)T_{32}(a)]da;$$

$$B_{23}(z,a) = \int_a^{a^+} f(s)l(s)e^{-zs}[\Gamma_1(s)T_{23}(z,s,a) + \Gamma_2(s)T_{33}(z,s,a)]ds;$$

$$B_{24}(z,a) = \int_a^{a^+} f(s)l(s)e^{-zs}[\Gamma_1(s)T_{24}(z,s,a) + \Gamma_2(s)T_{34}(z,s,a)]ds;$$

$$B_{25}(z,a) = T_{25}(z,a)\int_a^{a^+} f(s)l(s)e^{-zs}[\Gamma_1(s)T_{25}(z,a) + \Gamma_2(s)T_{35}(z,s,a)]ds;$$

$$B_{26}(z,a) = T_{36}(z,a)\int_a^{a^+} f(s)l(s)\Gamma_2(s)e^{-zs}ds.$$

System (41)-(42) is a linear system with respect to $\psi_1(0)$ and $\psi_2(0)$, hence

$$\begin{aligned}\psi_1(0) &= \int_0^{a^+} det_{11}(z,a)\mathcal{P}(\psi_1,\psi_2)(a)da + \int_0^{a^+} det_{12}(z,a)\vartheta_1(a)da + \\ &+ \int_0^{a^+} det_{13}(z,a)\vartheta_2(a)da + \int_0^{a^+} det_{14}(z,a)\vartheta_3(a)da; \qquad (43)\\ \psi_2(0) &= \int_0^{a^+} det_{21}(z,a)\mathcal{P}(\psi_1,\psi_2)(a)da + \int_0^{a^+} det_{22}(z,a)\vartheta_1(a)da \\ &+ \int_0^{a^+} det_{23}(z,a)\vartheta_2(a)da + \int_0^{a^+} det_{24}(z,a)\vartheta_3(a)da; \qquad (44)\end{aligned}$$

where

$$det_{11}(z,a) = \frac{-1}{det}\left[(pB_{22}(z)-1)B_{13}(z,a) - p(1-p)B_{12}(z)B_{23}(z,a)\right];$$

$$det_{12}(z,a) = \frac{-1}{det}\left[(pB_{22}(z)-1)B_{14}(z,a) - p(1-p)B_{12}(z)B_{24}(z,a)\right];$$

$$det_{13}(z,a) = \frac{-1}{det}\left[(pB_{22}(z)-1)B_{15}(z,a) - p(1-p)B_{12}(z)B_{25}(z,a)\right];$$

$$det_{14}(z,a) = \frac{-1}{det}\left[(pB_{22}(z)-1)B_{16}(z,a) - p(1-p)B_{12}(z)B_{26}(z,a)\right];$$

$$det_{21}(z,a) = \frac{p}{det}\left[(B_{21}(z)B_{13}(z,a) - (B_{11}(z)-1)B_{23}(z,a)\right];$$

$$det_{22}(z,a) = \frac{p}{det}\left[(B_{21}(z)B_{14}(z,a) - (B_{11}(z)-1)B_{24}(z,a)\right];$$

$$det_{23}(z,a) = \frac{p}{det}\left[(B_{21}(z)B_{15}(z,a) - (B_{11}(z)-1)B_{25}(z,a)\right];$$

$$det_{24}(z,a) = \frac{p}{det}\left[(B_{21}(z)B_{16}(z,a) - (B_{11}(z)-1)B_{26}(z,a)\right];$$

$$det = (B_{11}(z)-1)(pB_{22}(z)-1) - p(1-p)B_{21}(z)B_{12}(z).$$

From equations (29)-(35)-(40)-(43)-(44) it follows that

$$\mathcal{P}(\psi_2,\psi_3)(\eta) = (I-V_z)^{-1}\left[(U_z\vartheta_1)(\eta) + (W_z\vartheta_2)(\eta) + (Y_z\vartheta_3)(\eta)\right]; \tag{45}$$

where V_z, U_z, W_z and Y_z are the Volterra operator define on $L^1(0,a^+,\mathbb{R})$ into itself by

$$\begin{aligned}(U_z\varphi)(a) &= \int_0^{a^+} \Theta_z(\eta,a)\varphi(a)da;\ \ (V_z\varphi)(a) = \int_0^{a^+} \chi_z(\eta,a)\varphi(a)da;\\ (Y_z\varphi)(a) &= \int_0^{a^+} E_z(\eta,a)\varphi(a)da;\ \ (W_z\varphi)(a) = \int_0^{a^+} K_z(\eta,a)\varphi(a)da;\end{aligned} \tag{46}$$

where

$$\begin{aligned}\chi_z(\eta,a) &= C_1^{te}(\eta)det_{11}(z,a) + C_2^{te}(\eta)det_{21}(z,a)\\ &+ \int_a^{a^+} \beta(\eta,s)l(s)e^{-zs}[\Gamma_1(s)T_{23}(z,s,a) + \Gamma_2(s)T_{33}(z,s,a)]ds;\end{aligned} \tag{47}$$

$$\begin{aligned}\Theta_z(\eta,a) &= C_1^{te}(\eta)det_{12}(z,a) + C_2^{te}(\eta)det_{22}(z,a)\\ &+ \int_a^{a^+} \beta(\eta,s)l(s)e^{-zs}[\Gamma_1(s)T_{24}(z,s,a) + \Gamma_2(s)T_{34}(z,s,a)]ds;\end{aligned}$$

$$\begin{aligned}K_z(\eta,a) &= C_1^{te}(\eta)det_{13}(z,a) + C_2^{te}(\eta)det_{23}(z,a)\\ &+ \int_a^{a^+} \beta(\eta,s)l(s)e^{-zs}[\Gamma_1(s)T_{25}(z,s,a) + \Gamma_2(s)T_{35}(z,s,a)]ds;\end{aligned}$$

$$E_z(\eta,a) = C_1^{te}(\eta)det_{14}(z,a) + C_2^{te}(\eta)det_{24}(z,a) + \int_a^{a^+} \beta(\eta,s)l(s)e^{-zs}\Gamma_2(s)T_{36}(z,s,a)ds;$$

and

$$\begin{aligned} C_1^{te}(\eta) &= \int_0^{a^+} \beta(\eta,a) l(a) e^{-za} [\Gamma_1(a) T_{21}(a) + \Gamma_2(a) T_{31}(a)] da; \\ C_2^{te}(\eta) &= \int_0^{a^+} \beta(\eta,a) l(a) e^{-za} [\Gamma_1(a) + \Gamma_2(a) T_{32}(a)] da; \end{aligned}$$

Let us recall some definitions related to a C_0-semi-group $\{T(t)\}_{t\geqslant 0}$ on a Banach space with infinitesimal generator R. The *type* or the *growth bound* of the semi-group $\{T(t)\}_{t\geqslant 0}$ is the quantity:

$$\begin{aligned} &\omega_0(R) := \\ &\inf\{\alpha \in \mathbb{R} :\ \exists M \geq 1 \text{ such that } ||T(t)|| \leq M e^{\alpha t}\ \forall t \geq 0\} \\ &= \lim_{t\to 0} \frac{\ln ||T(t)||}{t}. \end{aligned}$$

The *spectral bound* of the C_0-semi-group $\{T(t)\}_{t\geqslant 0}$ is the quantity:

$$s(R) := \sup\{R_e\lambda :\ \lambda \in \sigma_p(R)\},$$

where $\sigma_p(R)$ denote the point spectrum of R.

Wow, we conclude that

Lemma 4. *Recalling Assumptions 1 and 2. Then*

1) The perturbated operator $A + C$ has a compact resolvent and

$$\sigma(A + C) = \sigma_p(A + C) = \{z \in \mathbb{C} :\ 1 \in \sigma_p(V_z)\};$$

where $\sigma(A)$ and $\sigma_p(A)$ denote the spectrum of A and the point spectrum of A respectively.

2) Let $\{U(t)\}_{t\geq 0}$ be the C_0-semigroup generated by $A + C$. Then $\{U(t)\}$, $t \geq 0$ is eventually compact and

$$\omega_0(A + C) = s(A + C).$$

Proof. 1) From equations (32), (43) and (46) we find that

$$\psi_1(a) = \Pi(a) l(a) e^{-za} \psi_1(0) + J_1(\vartheta_1)(a) + K_1(\vartheta_1, \vartheta_2)(a);$$

with

$$\begin{aligned} J_1(\vartheta_1)(a) &= \int_0^a \Pi(a) l(a) T_{11}(s) e^{-zs} \vartheta_1(s) ds; \\ K_1(\vartheta_1, \vartheta_2)(a) &= \int_0^a \Pi(a) l(a) T_{11}(s) S^*(s) e^{-zs} (I - V_z)^{-1} \\ &\quad [(U_z\vartheta_1)(s) + (W_z\vartheta_2)(s) + (Y_z\vartheta_3)(s)] ds. \end{aligned}$$

ψ_1 is a compact operator if and only if J_1 and K_1 are compact. Since J_1 is a Volterra operator with continue kernel, we deduce that J_1 is a compact operator on L^1. Using the same arguments as for the proof of the compactness of operator H_0 (Lemma 3), we can

show that the operators U_z, W_z and Y_z are compact for all $z \in \mathbb{C}$. Let us set $\Sigma := \{z \in \mathbb{C} : \ 1 \in \sigma_p(V_z)\}$. Hence, if $z \in \mathbb{C}\setminus\Sigma$ then, K_1 is a compact operator from $L^1 \times L^1$ to L^1. In the same way, we can show that $\psi_2(a)$ and $\psi_3(a)$ are represent by a compact operators. Therefore, the resolvent of $A+C$ is compact. From where $\sigma(A+C) = \sigma_p(A+C)$ (see Kato, p.187 [31]) i.e. $\mathbb{C}\setminus\Sigma \subset \rho(A+C)$ and $\rho(A+C)$ denotes the resolvent of $A+C$. In other words $\Sigma \supset \sigma(A+C) = \sigma_p(A+C)$. Since V_z is a compact operator, we know that $\sigma(V_z)\setminus\{0\} = \sigma_p(V_z)\setminus\{0\}$. If $z \in \Sigma$, then it exists $\psi_z \in L^1 \setminus \{0\}$ such that $V_z\psi_z = \psi_z$. Let us set

$$\phi_1(a) = \Pi(a)l(a)e^{-za}\left[\int_0^{a^+} det_{11}(z,a)\psi_z(a)da - \int_0^a \frac{e^{za}}{\Pi(s)l(s)}\psi_z(s)ds\right];$$

$$\phi_2(a) = \Pi(a)l(a)e^{-za}\left[\int_0^{a^+} det_{21}(z,a)\psi_z(a)da - \int_0^a \frac{e^{za}}{\Gamma_1(s)l(s)}(\lambda^*(s)\phi_1(s) + S^*(s)\psi_z(s))ds\right];$$

$$\phi_3(a) = \Gamma_2(a)l(a)e^{-za}\int_0^a \frac{e^{za}}{\Gamma_2(s)l(s)}r(s)\phi(s)\psi_2(s)ds.$$

Then $(\phi_1,\phi_2,\phi_3)^T$ is an eigenvector of $A+C$ associated to the eigenvalue z. Hence, $z \in \sigma(A+C) = \sigma_p(A+C)$ i.e. $\Sigma \subset \sigma(A+C) = \sigma_p(A+C)$. This end the proof of item 1.

2) For $\psi \in X$, let us set

$$\begin{aligned} C_1\psi &= (-P(\psi_2,\psi_3)S^*, \mathcal{P}(\psi_2,\psi_3)S^*, 0)^T; \\ C_2\psi &= (-(\lambda^*+\mu)\psi_1, \lambda^*\psi_1 - (\mu+d_1+r\phi)\psi_2 r\phi\psi_2 - (\mu+d_2)\psi_3)^T;. \end{aligned}$$

Then $C = C_1+C_2$. The operator $A+C_2$ generated a nilpotent C_0-semigroup $\{S_2(t)\}_{t\geq 0}$, from where $\{S_2(t)\}_{t\geq 0}$ is norm continuous. Using Assumptions 1 and 2, we find that C_1 is compact operator on X. From Theorem 1.30 of Nagel(1986) [42] it comes that C_1 is generator of a norm continuous C_0-semigroup $\{S_1(t)\}_{t\geq 0}$. Therefore, $S_1(t)+S_2(t)$ is a C_0-semigroup generated by $A+C$ and it is norm continuous (Spectral theorem P.87 Nagel [42]). □

Let us remark that if $\omega_0(A+C) < 0$, the equilibrium $u = 0$ of system (28) is locally asymptotically stable (linearized stability, Webb 1985[49]). Therefore, to study the stability of equilibrium states, we have to know the structure of the set $\Sigma := \{z \in \mathbb{C} : 1 \in \sigma_p(V_z)\}$. Since $||V_z||_{L^1} \to 0$ if $z \to +\infty$, $I - V_z$ is inversible for the large values of $R_e z$.
By theorem of Steinberg(1968)[47], the function $z \rightarrowtail (I-V_z)^{-1}$ is meromorphic in the complex domain, and hence the set Σ is a discrete set whose elements are poles of $(I-V_z)^{-1}$ of finite order.

In the following, we will use elements of positive operator theory.

For the positivity of operator V_z we make the following assumption

Assumption 3.

$$\int_0^{a^+}(d_1(\sigma)+r(\sigma)\phi(\sigma))d\sigma \quad \leq \quad \exp\left(-\int_0^{a^+}\lambda^*(\sigma)d\sigma\right); \tag{48}$$

where $\lambda^*(\sigma) = \int_0^{a^+}\beta(\sigma,\eta)(I^*(\eta)+L^*(\eta))d\eta$.

Lemma 5. *Let Assumption 3 be satisfied. Then*

1) The operator V_z, $z \in \mathbb{R}$, is nonsupporting with respect to $L^1(0, a^+, \mathbb{R}_+)$ and

$$\lim_{z \rightarrowtail -\infty} \rho(V_z) = +\infty \quad ; \quad \lim_{z \rightarrowtail +\infty} \rho(V_z) = 0.$$

2) There exists a unique $z_0 \in \mathbb{R} \cap \Sigma$ such that

$$\rho(V_{z_0}) = 1 \quad and \quad \begin{cases} z_0 > 0 & if \quad \rho(V_0) > 1, \\ z_0 = 0 & if \quad \rho(V_0) = 1, \\ z_0 < 0 & if \quad \rho(V_0) < 1. \end{cases}$$

3) $z_0 > \sup\{R_e z : \ z \in \Sigma \setminus \{z_0\}\}$.

Proof. 1) Let $z \in \mathbb{R}$. Unconditionally, V_z is a positive operator when $\lambda^*(a) \equiv 0$ (case of DFE). When $\lambda^*(a) > 0$, V_z is a positive operator once $\Gamma_1(s)T_{23}(z, a, s) + \Gamma_2(s)T_{33}(z, a, s) \geq 0$ for all $0 \leq a \leq s \leq a^+$. To have the previous inequality, it suffices that inequality (48) of Assumption 3 holds. We can checked that

$$V_z\psi \geq \langle f_z, \psi \rangle \cdot e; \tag{49}$$

where $\psi \in L^1(0, a^+, \mathbb{R}_+)$; $e \equiv 1 \in L^1(0, a^+, \mathbb{R}_+)$ and f_z is a positive linear functional defined by

$$< f_z, \psi > \quad = \quad m \int_0^{a^+} \int_a^{a^+} e^{-z(a-s)} \frac{l(s)}{l(a)} \left(\frac{1}{\Gamma_1(a)} - \frac{1}{\Pi(a)} \int_a^s \frac{\Pi(\sigma)}{\Gamma_1(\sigma)} \lambda^*(\sigma) d\sigma \right) dsda;$$

with $m = \inf_{(a,s) \in [0,a^+)^2} \beta(a, s)$. From (49), we show that $V_z^{n+1}\psi \geq \langle f_z, \psi \rangle \langle f_z, e \rangle^n \cdot e$ for all $n \in \mathbb{N}$. Since f_z is positive operator and $e \in L^1(0, a^+, \mathbb{R}_+) \setminus \{0\}$, we have $\langle F, V_z^n \psi \rangle > 0 \ \forall \psi \in (L^1(0, a^+, \mathbb{R}_+))^* \setminus \{0\} \ \forall \psi \in L^1(0, a^+, \mathbb{R}_+) \setminus \{0\}$. That is V_z is nonsupporting.

Let F_z be the eigenfunctional of V_z that corresponds to the eigenvalue $\rho(V_z)$. Taking the duality pairing into inequality (49), we have

$$\rho(V_z) \langle F_z, \psi \rangle \quad \geq \quad \langle f_z, \psi \rangle \langle F_z, e \rangle .$$

Taking $\psi = e$ and since F_z is positive, it follows that $\rho(V_z) \geq \langle f_z, e \rangle \rightarrow +\infty$ when $z \rightarrow -\infty$. From where $\lim_{z \rightarrowtail -\infty} \rho(V_z) = +\infty$. since $||V_z||_{L^1} \rightarrow 0$ when $z \rightarrow +\infty$, we deduce that $\lim_{z \rightarrowtail +\infty} \rho(V_z) = 0$. This end the proof of item 1.

2) Let $h : \mathbb{R} \rightarrow \mathbb{C}$; $z \mapsto \rho(V_z)$. The kernel χ_z defined by (47) is strictly decreasing with respect to $z \in \mathbb{R}$. Let $z_1, z_2 \in \mathbb{R}$ such that $z_1 < z_2$, then $\chi_{z_1} < \chi_{z_2}$ that is $V_{z_1} > V_{z_2}$. Since V_{z_1} and V_{z_2} are compact and nonsupporting operators we deduce from Marek(1970) [38] that $\rho(V_{z_1}) > \rho(V_{z_2})$. Therefore, the function h is strictly decreasing. The limits of the function $h(z) = \rho(V_z)$ at $-\infty$ and $+\infty$ give that there exist a unique $z_0 \in \mathbb{R} \cap \Sigma$ such that $\rho(V_{z_0}) = 1$. If $\rho(V_0) > 1$ then $h(0) > h(z_0)$ i.e. $z_0 < 0$ (strictly decreasing of h) and the other cases is show in the same way. This end the proof of item 2.

3)Let $z \in \Sigma$, then there exists $\psi_z \in L^1$ such that $V_z\psi_z = \psi_z$. Let $|\psi_z|$ be a function defined by $|\psi_z|(s) := |\psi_z(s)|$. The definition of V_z leads to

$$|\psi_z| = |V_z\psi_z| \leq V_{R_e z}|\psi_z|. \tag{50}$$

Let $F_{R_e z}$ be the positive eigenfunction associated to the eigenvalue $\rho(V_{R_e z})$ of $V_{R_e z}$. From (50) we deduce that $\langle F_{R_e z}, |\psi_z| \rangle \leq \langle F_{R_e z}, V_{R_e z}|\psi_z| \rangle = r(V_{R_e z}) \langle F_{R_e z}, |\psi_z| \rangle$. The positivity of $F_{R_e z}$ implies that $r(V_{R_e z}) \geq 1$ that is $h(R_e z) \geq h(z_0)$ i.e. $z_0 \leq R_e z$. To end the proof, let us show that: if $z_0 = R_e z$ then $z = z_0$.
We know that $|\psi_z| \leq V_{R_e z}|\psi_z| = V_{z_0}|\psi_z|$. Let us suppose that $|\psi_z| < V_{z_0}|\psi_z|$; taking the pairing product with the dual function F_0 corresponding to the eigenvalue $\rho(V_{z_0}) = 1$, one has $\langle F_0, |\psi_z| \rangle > \langle F_0, |\psi_z| \rangle$, which is a contradiction. Hence $|\psi_z| = V_{z_0}|\psi_z|$. Therefore $|\psi_z| = c\psi_0$ where c is constant not equal to zero (Sawashima 1964 [44]) and ψ_0 is the eigenfunction corresponding to $\rho(V_{z_0}) = 1$. So $\psi_z(a) = c\psi_0(a)e^{i\alpha(a)}$ for a reel function α; moreover $|V_z\psi_z| = |\psi_z| = c\psi_0 = cV_{z_0}\psi_0$. Substituting $\psi_z(a) = c\psi_0(a)e^{i\alpha(a)}$ into the equality $|V_z\psi_z| = cV_{z_0}\psi_0$ one has

$$\int_0^{a^+}\int_a^{a^+} \beta(\eta,s)l(s)e^{-z_0(s-a)}[\Gamma_1(s)\tilde{T}_{23}(s,a) + \Gamma_2(s)\tilde{T}_{33}(s,a)]\psi_0(a)dsda =$$
$$\left|\int_0^{a^+}\int_a^{a^+} \beta(\eta,s)l(s)e^{-(z_0+i(s-a)Imz)}[\Gamma_1(s)\tilde{T}_{23}(s,a) + \Gamma_2(s)\tilde{T}_{33}(s,a)]e^{i\alpha(a)}\psi_0(a)dsda\right|; \tag{51}$$

with

$$\begin{aligned}\tilde{T}_{23}(a,s) &= \frac{S^*(s)}{l(s)}\left(\frac{1}{\Gamma_1(s)} - \frac{1}{\Pi(s)}\int_s^a \frac{\Pi(\sigma)}{\Gamma_1(\sigma)}\lambda^*(\sigma)d\sigma\right);\\ \tilde{T}_{33}(a,s) &= \int_s^a \frac{\Gamma_1(\sigma)}{\Gamma_2(\sigma)} r(\sigma)\phi(\sigma)\tilde{T}_{23}(a,\sigma)d\sigma.\end{aligned}$$

Applying two times, Lemma 6.12 of Heijmans(1986) [21], to the relation (51) it comes that $(s-a)Imz + \alpha(a) = b$ for all $0 \leq a \leq s \leq a^+$ where b is a constant. From the equality $V_z\psi_z = \psi_z$ one has $e^{ib}V_{z_0}\psi_0 = \psi_0 e^{i\alpha(a)}$ i.e. $b = \alpha(a)$. From where $Imz = 0$, that is $z = z_0$. □

From the above result, we can state the threshold criterion as follows:

Proposition 2. *Recalling Assumption 3. Then equilibrium (S^*, I^*, L^*) is locally asymptotically stable if $\rho(V_0) < 1$ and unstable if $\rho(V_0) > 1$.*

Proof. From Lemma 5 (items 2. and 3.), we conclude that: $\sup\{R_e z;\ 1 \in \sigma_p(V_z)\} = z_0$. Hence $s(A+C) = \sup\{R_e z;\ 1 \in \sigma_p(V_z)\} < 0$ if $\rho(V_0) < 1$, and $s(A+C) = \sup\{R_e z;\ 1 \in \sigma_p(V_z)\} > 0$ if $\rho(V_0) > 1$. □

In the following, let us note V_0^0 the operator V_0 corresponding to the case $\lambda^*(\sigma) \equiv 0$ (DFE) and V_0^* the operator V_0 corresponding to the case $\lambda^*(\sigma) > 0$ (EE). It is easily checked that

$$\chi_0^0(a,s) = \chi(a,s); \tag{52}$$

where $\chi(a,s)$ is the kernel of the Volterra operator H_0 defined by (23).

Now, the main results for the local stability of our epidemic model reads as

Theorem 3. *Let Assumptions 1 and 2 be satisfied. Let $R_0 := \rho(H_0)$ be the spectral radius of the operator H_0 defined by (22). Then,*

1) If $R_0 = \rho(H_0) < 1$ then, the unique equilibrium of (1)-(2) (DFE) is locally asymptotically stable.

2) If $R_0 = \rho(H_0) > 1$ then, the DFE is unstable.

3) If $R_0 = \rho(H_0) > 1$ then, in addition to the DFE system (1)-(2) has at least one endemic equilibrium (EE). Moreover, if $\rho(V_0^*) < 1$ and Assumption 3 holds, then the EE is locally asymptotically stable.

Proof. For the DFE, one has $\lambda^*(\sigma) \equiv 0$. Hence, from (52) it comes that $\rho(H_0) = \rho(V_0^0) := \rho(V_0)$ (for $\lambda^* = 0$). From Prop. 2 we deduce that: if $\rho(H_0) = \rho(V_0) < 1$, the DFE is locally asymptotically stable; and unstable if $\rho(H_0) = \rho(V_0) > 1$. This end the proof of items 1. and 2.
The case of EE is a direct consequence of Prop. 2. □

Remark 1.

(♣) To emphasize the impact of vertical transmission on the spread of the disease, let us observe that the next generation operator H_0 can be rewrite as follows

$$H_0(\psi)(a) = \int_0^{a^+} \chi^{\diamondsuit}(a,s)\psi(s)ds + \int_0^{a^+} \chi_{\diamondsuit}(p,a,s)\psi(s)ds;$$

where the kernels $\chi^{\diamondsuit}(.,.)$ and $\chi_{\diamondsuit}(p,.,.)$ are

$$\begin{aligned} \chi^{\diamondsuit}(a,s) &= \frac{S_0(s)}{l(s)} \int_s^{a^+} \beta(a,\eta)\left(\chi_{21}(\eta,s) + \chi_{31}(\eta,s)\right) d\eta; \\ \chi_{\diamondsuit}(p,a,s) &= \frac{p\chi_4(s)}{\Delta(0)} \int_0^{a^+} \beta(a,\sigma)(A_{22}(\sigma) + A_{32}(\sigma))d\sigma. \end{aligned}$$

It is easy to see that when the proportion of infected newborns is zero ($p = 0$), then the kernel $\chi^{\diamondsuit}(0,.,.) \equiv 0$. Therefore, the vertical transmission of the disease amplifies positively the spread of the disease.

(♣♣) As a special case, we here briefly consider the proportionate mixing assumption, that is, the transmission rate β can be written as $\beta(a,s) = \beta_1(a)\beta_2(s)$ (see Dietz and Schenzle [14]; Greenhalgh,1988 [23]). In this case, the basic reproductive number $\mathcal{R}_0$ is explicitly given by:

$$R_0 := \rho(H_0) = \int_0^{a^+} \chi^{\diamondsuit}(s,s)ds + \int_0^{a^+} \chi_{\diamondsuit}(p,s,s)ds. \tag{53}$$

And the same conclusion follows as for item (♣). Thus the vertical transmission of the disease really has an impact on the dynamics and the spread of the disease into the host population. We also refer to Figures 2-4 for some illustrations of the state variables of system (1)-(2) when p takes different values: 0.02; 0.2 and 0.5.

6. Numerical analysis

In this section, we propose a numerical scheme for our model and gives some illustrations.

We adopt a finite differences scheme which is progressive of order 1 in time and regressive of order 1 in age. Our model has a structure of the following partial differential equation on the real axe:

$$\frac{\partial u}{\partial t} + \frac{\partial u}{\partial a} = f(t,a). \tag{54}$$

For equation (54), the numerical scheme is defined by:

$$\frac{u_i^{n+1} - u_i^n}{\Delta t} + \frac{u_i^n - u_{i-1}^n}{\Delta a} = f(t_n, a_i); \tag{55}$$

where i and n are the index of age and time discretization respectively; and $u_i^n := u(t_n, x_i)$.

We recall that, generally, all explicit numerical scheme is conditionally stable (Stricwerda[45]). To ensure the stability of the scheme (55) the necessary condition is the famous Courant-Friedrichs-Lewy (CFL) condition given as follow:

$$\frac{\Delta t}{\Delta a} \leqslant 1. \tag{56}$$

For a given age step discretization Δa, the restriction $\Delta t \leqslant \Delta a$ is necessary for the time step discretisation Δt.

We are able now to give the solution of the problem (1)-(2) on some time interval $[0, T]$ using the above numerical scheme.

The age-specific reproduction rate $f(a)$ is taken to be

$$f(a) = \begin{cases} \frac{1}{5}\sin^2\left(\frac{\pi(a-15)}{30}\right) \ if \ \ 15 \leq a \leq 45; \\ 0 \text{ if not.} \end{cases}$$

The fecundity function $f(.)$ is stated here in units of 1 / years for easier readability and assumes that from age 15 to 45 years a woman will generally give birth to three children, since $\int_0^{a^+} f(a)da = 3$, where $a^+ = 80$ is the largest age allowed for the simulation.

We also consider a low value of recruitment $\Lambda(.)$

$$\Lambda(a) = \begin{cases} \frac{1}{10}\sin^2\left(\frac{\pi(a-17)}{43}\right) \ if \ \ 17 \leq a \leq 60; \\ 0 \text{ if not.} \end{cases}$$

This recruitment assume that the total number of recruitment at time t is approximately equal two, that is $\int_0^{a^+} \Lambda(a) = 2.15$

The transmission coefficient $\beta(.,.)$ is assume to be

$$\beta(a,s) = \begin{cases} \beta_0 \sin^2\left(\frac{\pi(a-14)}{46}\right)\sin^2\left(\frac{\pi(s-14)}{46}\right), \text{ if } a, s \in [14, 60]; \\ 0 \text{ if not.} \end{cases}$$

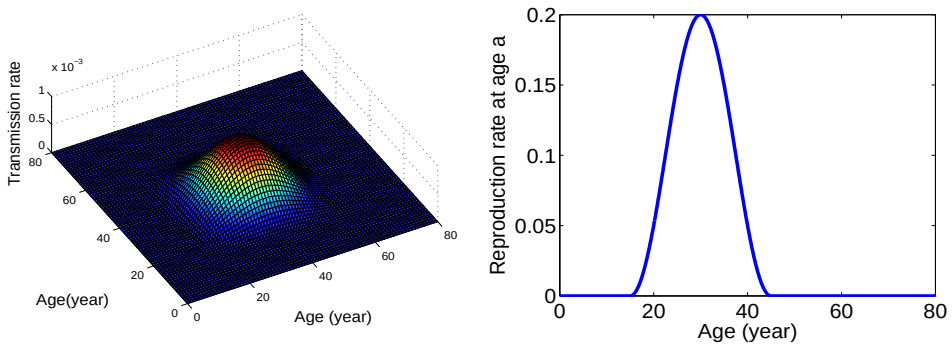

Figure 1: (1a) Transmission coefficient $\beta(.,.)$ when the transmission constant $\beta_0 = 10^{-3}$. (1b) Fecundity function $f(.)$.

Table 1: Numerical values for the parameters of the model

Parameters	Description	Estimated value
β_0	Transmission constant	Variable
p	Vertical tranmission rate	Variable
μ	Natural death rate	0.0101/yr [1]
r	Rate of effective therapy	$1/yr$ [1]
ϕ	Rate at witch infectious become loss of sight	0.75/yr [1]
γ	Rate at witch lost of sight return to the hospital	0.02/yr [1]
d_1	Death rate of infectious	0.02/yr [1]
d_2	Death rate of lost of sight	0.2/yr [1]

Note: Source of estimates.
[1] Assumed.

wherein the nonnegative constant β_0 (transmission constant) will be variable. Figure 1 illustrates the transmission coefficient β (for $\beta_0 = 10^{-3}$) and the fecundity function f. The other parameters of our system are arbitrarily chosen (see Table 1).

We provide numerical illustrations for different values of vertical transmission p: 0.02, 0.2 and 0.5

In Figure 2, the vertical transmission rate of the disease is fixed to be $p = 0.02$. We observe that infectious individuals (infected and lost of sight) are between 17 and 70 of age. The number of young infectious (namely infectious with age $a < 17$) is negligible, because the value of vertical transmission rate p is low.

In figure 3, the vertical transmission rate of the disease is fixed to be $p = 0.2$. We observe that much of the infectious individuals (infected and lost of sight) are between

17 and 70 of age. Let us also observe that the number of infectious individuals with age between 17 and 70 is approximately the same than the number of infectious individuals with age between 17 and 70 when $p = 0.02$ (see Figs 2-3). But now, there are also infectious individuals with age $a < 17$ which was not the case when $p = 0.02$.

The same observation is given by Figure 4 where the vertical transmission rate of the disease is fixed to be $p = 0.5$. Hence Figures 2-4 emphasize that the vertical transmission of the disease really has an impact on the dynamics and the spread of the disease into the host population. See also Table 2 for the impact of the vertical transmission of the disease on the spread of the epidemic.

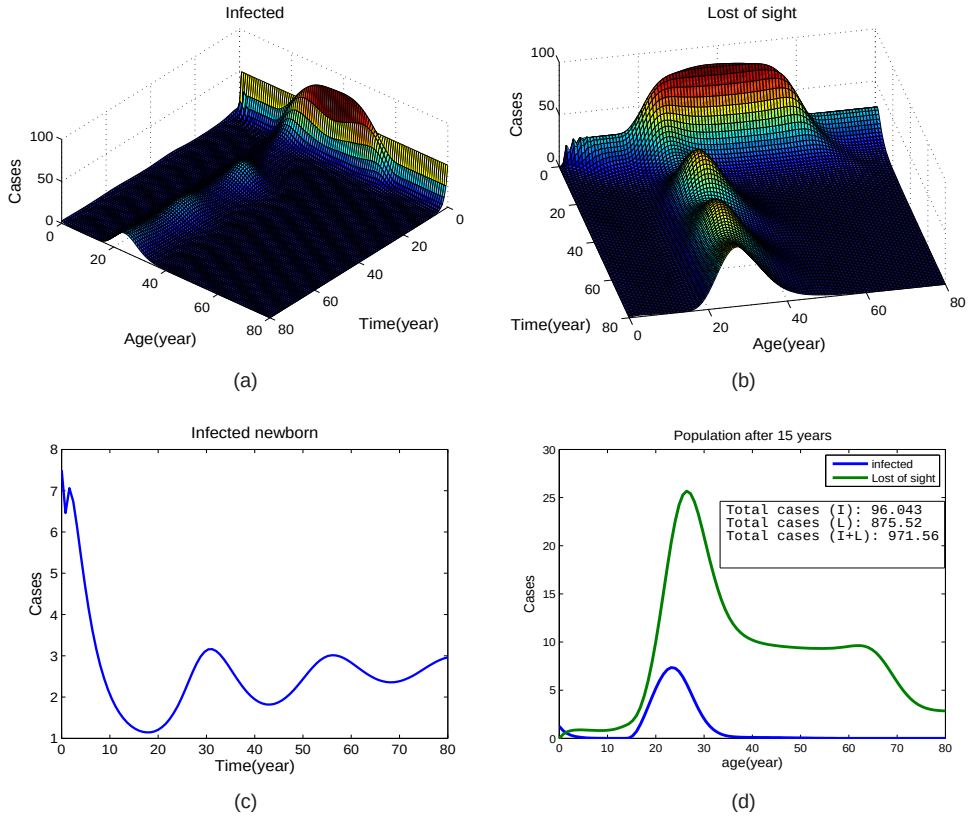

Figure 2: The transmission constant and the vertical transmission rate are fixed to be $\beta_0 = 10^{-3}$ and $p = 0.02$. The other parameters are given by Table 1. (2a) Distribution of Infected individuals. (2b) Distribution of Lost of sight. (2c) Distribution of infected newborn. (2d) Distribution of Infected and Lost of sight individuals after 80 years of time observation.

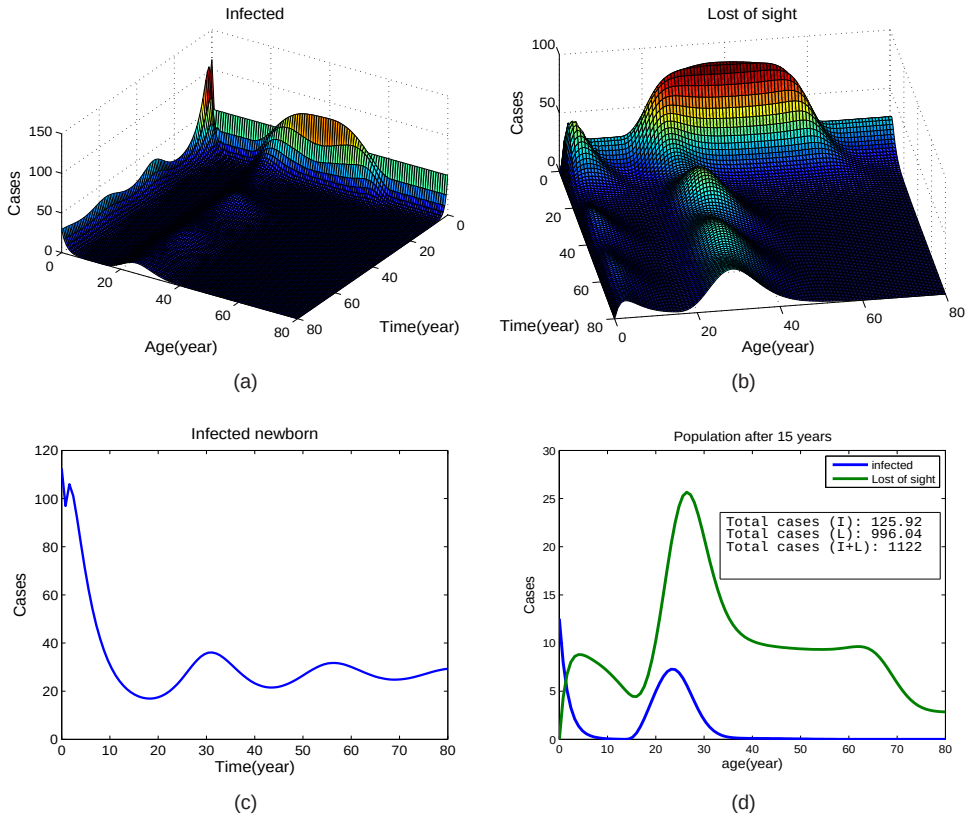

Figure 3: The transmission constant and the vertical transmission rate are fixed to be $\beta_0 = 10^{-3}$ and $p = 0.2$. The other parameters are given by Table 1. (3a) Distribution of Infected individuals. (3b) Distribution of Lost of sight. (3c) Distribution of infected newborn. (3d) Distribution of Infected and Lost of sight individuals after 80 years of time observation.

Table 2: Impact of the vertical transmission of the disease.

Vertical transmission rate (p)	Rate increase over the case when $p = 0$
$p = 0.02$	1.8%
$p = 0.2$	17.5%
$p = 0.5$	43.8%

Total cases (I+L) when $p = 0$: 954.85 cases. (i.e. when the vertical transmission of the disease is neglected in the host population.

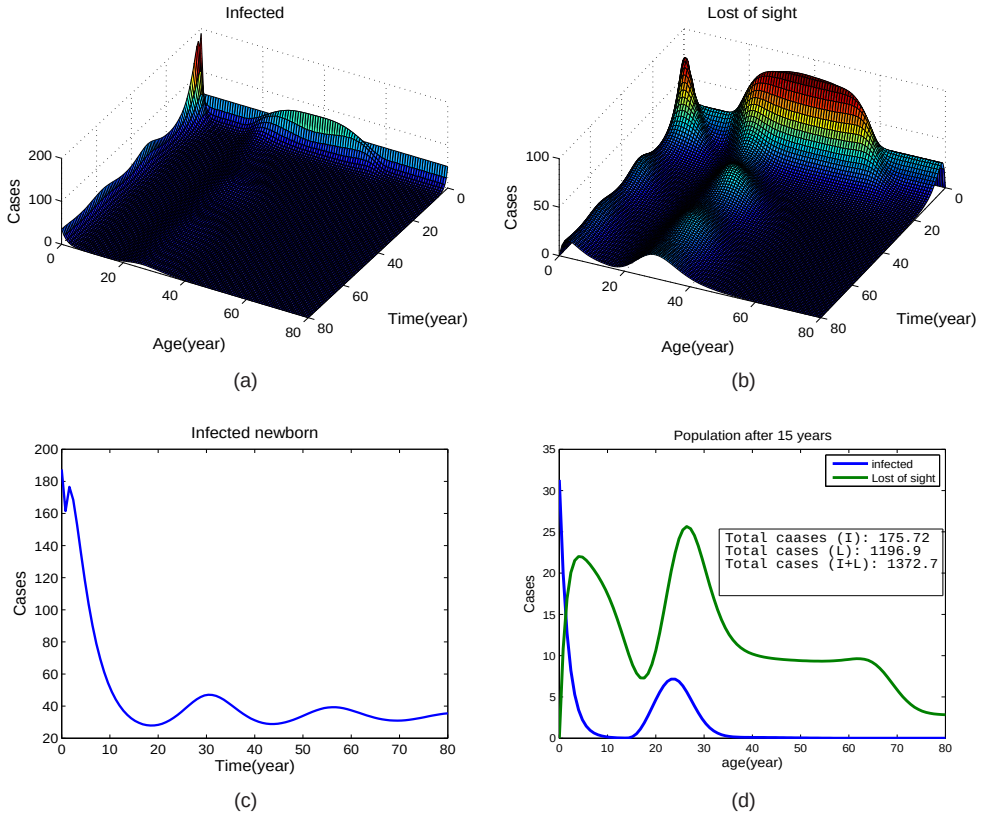

Figure 4: The transmission constant and the vertical transmission rate are fixed to be $\beta_0 = 10^{-3}$ and $p = 0.5$. The other parameters are given by Table 1. (4a) Distribution of Infected individuals. (4b) Distribution of Lost of sight. (4c) Distribution of infected newborn. (4d) Distribution of Infected and Lost of sight individuals after 80 years of time observation.

7. Conclusion

In this paper, we consider a mathematical model for the spread of a directly transmitted infections disease in an age-structured population with demographics process. The disease can be transmitted not only horizontally but also vertically from adult individuals to their children. The dynamical system is formulated with boundary conditions.

We have described the semigroup approach to the time evolution problem of the abstract epidemic system. Next we have calculated the basic reproduction ratio and proved that the disease-free steady state is locally asymptotically stable if $R_0 < 1$, and at least one endemic steady state exists if the basic reproduction ratio R_0 is greater than the unity. Moreover, we have shown that the endemic steady state is forwardly bifurcating from the disease-free steady state at $R_0 = 1$. Finally we have shown sufficient conditions which guarantee the local stability of the endemic steady state. Roughly speaking, the endemic

steady state is locally asymptotically stable if it corresponds to a very small force of infection.

However the global stability of the model still an interesting open problem. Moreover, biologically appropriate assumptions for the unique existence of an endemic steady state is also not yet know.

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OPTIMAL CONTROL FOR AN AGE-STRUCTURED MODEL FOR THE TRANSMISSION OF HEPATITIS B

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Abstract One of the characteristics of HBV transmission is the age structure of the host population and the vertical transmission of the disease. That is the infection is transmitted directly from infected mother to an embryo, fetus, or baby during pregnancy or childbirth (the perinatal infection). We formulated an age-structured model for the transmission dynamics of HBV with differential infectivity: symptomatic and asymptomatic infections. The model without intervention strategies is completely analyzed. We compute the basic reproduction number which determines the outcome of the disease. We also compute equilibria and study their stability. The sensitivity analysis of the initial model parameters is performed (to determine the impact of control-related parameters on outbreak severity). Using optimal control theory, we determine the cots-effective balance of three interventions methods which minimizes HBV-related deaths as well as the costs associated with intervention.

Keywords HBV · Age structure · Nonlinear dynamical system · Stability · Optimal control

Mathematics Subject Classification (2000) 35Q92 · 49J20 · 35B35 · 92D30

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1 Introduction

Hepatitis B virus (HBV) infection is widespread in many parts of the world, especially in Africa, Southeast Asia, the Middle East, South and Western Pacific islands, the interior Amazon River basin, and certain parts of the Caribbean (Centers for Disease Control and Prevention (CDC [7])). By the estimation of the World Health Organization (WHO [38]), about 2 billion people have been infected with HBV. An estimate of 600,000 persons die each year due to the acute or chronic consequences of the virus (WHO [38]).

Hepatitis B is transmitted through body fluids like blood, semen, and vaginal secretions. One of the most important factors influencing the probability of developing of HBV is age. Acute HBV infection causes chronic (long-term) infection in 30-90% of persons infected as infants or young children and in less than 5% of adolescents and adults (Shepard et al. [34], Goldstein et al. [22]). A person suffering from a HBV infection can progress to a symptomatic infection or to an asymptomatic infection. (McMahon et al. [31]).

According to CDC [7] and WHO [38], risk for chronic infection is inversely related to age at infection: approximately 90% of infected infants and 30% of infected children aged under 5 years become chronically infected, compared with 5% of adults. This difference in the evolution of infection introduces naturally differential susceptibility.

Many mathematical models have been proposed to investigate the transmission dynamics of HBV in various countries and regions in the world; covering many topics: sexual transmission of HBV which includes heterogeneous mixing with respect to age and sexual activity [2]; relation between the age at infection with HBV and the development of the carrier state [12]; HBV transmission in developing countries [30, 13, 40]; the long-term effectiveness of the vaccination [41]; determined the prevalence of infection [32]. Age-structured models have also been used to model the transmission dynamics of HBV by some researchers (see for instance Edmunds et al. [12], McLean and Blumberg [30], Zhao, Xu, and Lu [41], Zou, Ruan and Zhang [42, 43]).

Mathematical models can provide a powerful tool for investigating the dynamics and control of infectious diseases. Optimal control theory provides a valuable tool to begin to assess the trade-offs between vaccination and treatment strategies. Optimal control is a mathematical technique derived from the calculus of variations. Anyhow we can give suggestions to the public health authorities about the effects of a particular control policy with respect to others, and in this context the analysis and simulation of mathematical models may become a powerful tool in the hands of the above authorities. Several HBV intervention options (called controls) do exist. Individual with HBV infection require a special treatment to overcome the infection. As for preventive measures, vaccination strategies can be consider to reduce the size of the epidemic. There have been numerous works on optimal control of the epidemics (see for example Emvudu et al. [16, 15], Bowong [6], Neilan et al. [33] and references cited therein). In the context of optimal control of age-structured populations Anita [3] consider optimal harvesting in single equation case. Da Prato et al.[8] treated boundary control involving the birth rate for a Lotka-McKendrick equation. Barbu et al. [4] also examined a boundary control problem with an application to an

epidemic model. For work involving optimal control of interacting species see Fister et al. [21] and references cited therein. For the existence of an optimal control of age-structured dynamics, see Ekerland variational principle [17]. Reader may also consult Feichtinger et al. [20] for the necessary optimality conditions.

This paper builds on the existing works mentioned above and fills the gaps observed in these works. In view of the usefulness and the current investigation on the spread of HBV within a population and taking into account a continuous age structure, the perinatal infection of HBV and death directly related to HBV infection, we propose an age-structured model for the transmission dynamics of HBV with differential infectivity: symptomatic and asymptomatic HBV infections. We do an in-depth optimal control for an age-structure HBV dynamics which to the author knowledge has not been addressed in the literature.

The rest of the paper is organized as follows. In Section 2, we formulate the model without optimal intervention strategies and present the mathematical analysis of the model. More precisely, we formulate the model, show the existence of semi flow, compute the basic reproduction number, compute and study the stability of steady states (free and endemic) and perform the sensitivity analysis of the initial model parameters to determine the impact of control-related parameters on outbreak severity. In Section 3, we introduce three intervention strategies: vaccination effort of young susceptible individuals, the effort to prevent perinatal infection and the treatment of people with HBV symptomatic infection. Using optimal control theory (see [20,4,21] and refs. cited therein) and numerical simulations, we determine the cots-effective balance of three interventions methods which minimizes HBV-related deaths as well as the costs associated with intervention. Finally, we access the effectiveness of balancing multiple intervention methods (or vaccination of young adults) relative to the two other optimal strategies of one intervention method alone (treatment of symptomatic infections or prevention of perinatal infections). Conclusion and discussions end the paper in Section 4.

2 Model formulation and mathematical analysis

2.1 The model

Herein, we propose an age-structured model to study the transmission dynamics of HBV with differential infectivity: symptomatic and asymptomatic HBV infections. We divide the total population into seven sub classes: the proportion of susceptible to infection $S(t,a)$, those immune following vaccination $V(t,a)$, latently infected progressing to symptomatic HBV infections $L_i(t)$, latently infected progressing to asymptomatic HBV infections $L_c(t)$, symptomatic HBV infections $I(t)$, asymptomatic HBV infections $C(t)$ and recovered from HBV infections with protective immunity $R(t)$.

First of all, let us answer the following question: *why consider an age-structured for susceptible and immune classes?* It is well know that symptomatic and asymptomatic HBV infections are age-dependent. Indeed, the probability to progress to symptomatic infection at age *a* is given by [41]:

$$\alpha(a) = 0.9153552 - 0.706004e^{-0.787711a}. \quad (1)$$

Hence, we find that risk of asymptomatic HBV infection is inversely related to age at infection (see Fig. 1).

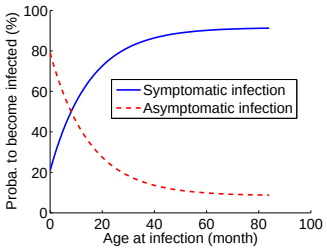

Fig. 1: Probability to move to symptomatic infection at age a.

We now briefly describe the model. We define the force of infection by $\lambda(t,a) := \beta(a)(I(t) + \tau C(t))$ as the product of transmission rate, $\beta(a)$, and the number of infectious individuals at time t. τ is the reduced transmission rate. Then infected individuals move to the exposed class in two groups at rates $\alpha(a)\lambda(t,a)S(t,a)$ and $(1-\alpha(a))\lambda(t,a)S(t,a)$ for symptomatic and asymptomatic infections respectively. That is $\int_0^\omega \alpha(a)\lambda(t,a)S(t,a)da$ and $\int_0^\omega (1-\alpha(a))\lambda(t,a)S(t,a)da$ are the number of infected individuals progressing to symptomatic and asymptomatic infections respectively at time t; wherein ω is the upper bound of age of people in the model. Susceptible individuals are immune by vaccination at rate $p(a)$ and the immunity to HBV is assumed to wane at rate ψ. Rates moving from latent infection classes to infectious classes are γ and δ for symptomatic and asymptomatic infections respectively. For symptomatic and asymptomatic classes, μ_I and μ_C are HBV-related death rates, γ_1 and γ_2 are rates of recovery from HBV. $\mu(a)$ and μ_1 are the natural mortality rates of the host population. Now, let us describe the dynamics of the newborns. We define the proportion of newborns with successful vaccination by $(1-\theta)b$ as the product of proportion of birth with successful vaccination $1-\theta$ and the equilibrium birth rate b. Among the proportion of newborns without successful vaccination θb, some of them will be infected by their carrier mother at rate ν and would move to an asymptomatic infection. That is $b\theta(1-\nu C(t))$ is the proportion of susceptible newborns at time t, and $b\theta\nu C(t)$ is the proportion of newborns with perinatal infection at time t.

Table 1: Parameters values used in numerical simulation

Parameters	Description	Values	Ref.
$p(a)$	vaccination rate of susceptible	0 - 1	
μ_1	natural mortality rate	0.0132/yr	WHO[39]
μ_I, μ_C	HBV-related mortality rate	0.2%/yr	CDC[7]
τ	Reduced transmission rate	0.16	Edmunds et al.[13]
γ	rate moving from latent infection to symptomatic infectiousness	6/yr	Edmunds et al.[13], CDC[7]
δ	rate moving from latent to asymptomatic infectiousness	6/yr	Edmunds et al.[13], CDC[7]
b	equilibrium birth rate	0.0380/year	WHO[39]
$1-\theta$	proportion of births with successful vaccination	0 - 1	
ψ	rate of waning vaccine-induced immunity	0.1	Edmunds et al.[14]
γ_1	rate moving from symptomatic infectiousness to recovered	4.8/yr	Edmunds et al.[13], CDC[7]
γ_2	rate of moving from asymptomatic infectiousness to recovered	0.025/yr	Edmunds et al.[13], CDC[7]
ν	proportion of perinatally infected (from chronicle infectious mothers)	0.11	Edmunds et al.[13]

Then, age-structured model for the transmission of HBV is described by the following system:

$$\begin{aligned}
&\frac{\partial S(t,a)}{\partial t}+\frac{\partial S(t,a)}{\partial a}=\psi V(t,a)-(\lambda(t,a)+\mu_1+p(a))S(t,a),\\
&\frac{\partial V(t,a)}{\partial t}+\frac{\partial V(t,a)}{\partial a}=p(a)S(t,a)-(\psi+\mu_1)V(t,a),\\
&\frac{dL_i(t)}{dt}=\int_0^{\omega}\alpha(a)\lambda(t,a)S(t,a)da-(\mu_1+\gamma)L_i(t),\\
&\frac{dL_c(t)}{dt}=\int_0^{\omega}(1-\alpha(a))\lambda(t,a)S(t,a)da+b\theta\nu C(t)-(\mu_1+\delta)L_c(t),\\
&\frac{dI(t)}{dt}=\gamma L_i(t)-(\gamma_1+\mu_1+\mu_I)I(t),\\
&\frac{dC(t)}{dt}=\delta L_c(t)-(\gamma_2+\mu_1+\mu_c)C(t),\\
&\frac{dR(t)}{dt}=\gamma_1 I(t)+\gamma_2 C(t)-\mu_1 R(t),
\end{aligned}\tag{2}$$

with the initial and boundary conditions

$$\begin{aligned}
&S(t,0)=\theta b(1-\nu C(t));\quad S(0,a)=S_0(a);\quad V(t,0)=(1-\theta)b;\quad V(0,a)=V_0(a),\\
&L_i(0)=L_{i0};\quad L_c(0)=L_{c0};\quad I(0)=I_0;\quad C(0)=C_0;\quad R(0)=R_0.
\end{aligned}\tag{3}$$

The model parameters are described in Table 1.

In order to deal with system (2) we first provide a parameter reduction by introducing the following unknown functions $s(t,a)=S(t,a)e^{\mu_1 a}$, $v(t,a)=V(t,a)e^{\mu_1 a}$. Therefore, by introducing the vector-valued functions $\mathbf{u}(t)=(L_i(t),L_c(t),I(t),C(t))^T=(u_i)_{i=1,\cdots,4}^T$; $\mathbf{y}(t,.)=(s(t,.),v(t,.))^T=(y_1,y_2)^T$; $\mathbf{e}_1=(1,0)$, $\mathbf{1}_n=(1,\ldots,1)\in\mathbb{R}^n$,

$\mathbf{e} = (0,0,1,1)$ and the usual scalar product $\langle .,. \rangle$ as well as the matrices

$$
\begin{aligned}
&F_1(a) = \begin{pmatrix} -p(a) & \psi \\ p(a) & -\psi \end{pmatrix},\ F_2(a) = \begin{pmatrix} 0 & 0 & \alpha(a) & \tau\alpha(a) \\ 0 & 0 & 1-\alpha(a) & \tau(1-\alpha(a)) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \\
&F_3 = \begin{pmatrix} -\gamma & 0 & 0 & 0 \\ 0 & -\delta & 0 & b\theta\nu \\ \gamma & 0 & -(\gamma_1+\mu_I) & 0 \\ 0 & \delta & 0 & -(\gamma_1+\mu_c) \end{pmatrix},\ E_1 = \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}, \\
&F_4 = (0,0,\gamma_1,\gamma_2),
\end{aligned} \tag{4}
$$

system (2) rewrites as

$$
\begin{cases}
\dfrac{\partial \mathbf{y}(t,a)}{\partial t} + \dfrac{\partial \mathbf{y}(t,a)}{\partial t} = -\beta(a)\langle \mathbf{e}, \mathbf{u}(t)\rangle E_1.\mathbf{y}(t,a) + F_1(a)\mathbf{y}(t,a), \\
\dfrac{d}{dt}\mathbf{u}(t) = \displaystyle\int_0^{\omega} l(a)\beta(a)\langle \mathbf{e}_1, \mathbf{y}(t,a)\rangle F_2(a).\mathbf{u}(t)da + (F_3 + diag(-\mu_1)).\mathbf{u}(t), \\
\dfrac{dR(t)}{dt} = \langle F_4, \mathbf{u}(t)\rangle - \mu_1 R(t),
\end{cases} \tag{5}
$$

supplemented together with boundary condition and initial data

$$
\begin{cases}
\mathbf{y}(t,0) = (\theta b(1-\nu u_4(t)); (1-\theta)b)^T, \\
\mathbf{y}(0,.) = \mathbf{y}_0(.) \in L^1(0,\omega,\mathbb{R}^2), \quad \mathbf{u}(0) = \mathbf{u}_0 \in \mathbb{R}^4, \quad R(0) = R_0,
\end{cases} \tag{6}
$$

wherein $l(a) := e^{-\mu_1 a}$ is the survival function which is the proportion of individuals who survive to age a.

In what follows, we shall discuss the asymptotic behavior of system (5)-(6) and we will make use of the following assumptions.

Assumption 1 *We assume that: b, μ_1, μ_I, μ_C, γ, γ_1, γ_2, ψ, θ, ν, δ are nonnegative constants, $p(.)$ is nonnegative function while $\beta(.)$ $\mu(.)$ and $\alpha(.)$ belong to $L^{\infty}_{+}(0,\omega,\mathbb{R}_+)$.*

2.2 Existence of semiflow

We shall deal with the integrated semigroup approach introduced by Thieme [35]. We also refer to Djidjou et al. [9] (see also references therein).

Let us introduce $\widehat{X} = \mathbb{R}^2 \times L^1(0,\omega,\mathbb{R}^2)$ as well as its positive cone $\widehat{X}_+ = \mathbb{R}^2 \times L^1(0,\omega,\mathbb{R}^2_+)$ and the linear operator $\widehat{A} : D(\widehat{A}) \subset \widehat{X} \to \widehat{X}$ defined by

$$
D(\widehat{A}) = \{0_{\mathbb{R}^2}\} \times W^{1,1}(0,\omega,\mathbb{R}^2), \quad \widehat{A}\begin{pmatrix} 0_{\mathbb{R}^2} \\ \varphi \end{pmatrix} = \begin{pmatrix} -\varphi(0) \\ -\varphi' \end{pmatrix}. \tag{7}
$$

Next consider the Banach space $X = \mathbb{R}^4 \times \mathbb{R} \times \widehat{X}$ and $X_+ = \mathbb{R}^4_+ \times \mathbb{R}_+ \times \widehat{X}_+$ endowed with the usual product norm $||.||$. Let $A : D(A) \subset X \to X$ be the linear operator defined by

$$
D(A) = \mathbb{R}^4 \times \mathbb{R} \times D(\widehat{A}), \quad A = diag\left(-\mu_1, \widehat{A}\right). \tag{8}
$$

Note that the domain of operator A is not dense in X because of the identity

$$\overline{D(A)} = \mathbb{R}^5 \times \{0_{\mathbb{R}^2}\} \times L^1(0,\omega,\mathbb{R}^2) \neq X.$$

Finally, let us introduce the nonlinear map $F : \overline{D(A)} \to X$ defined by

$$F\left((\mathbf{u},R,0_{\mathbb{R}^2},\mathbf{y})^T\right) = \begin{pmatrix} \int_0^\omega l(a)\beta(a)\langle \mathbf{e}_1,\mathbf{y}(a)\rangle F_2(a)\mathbf{u}da + F_3\mathbf{u} \\ \langle F_4,\mathbf{u}\rangle - \mu_1 R \\ (\theta b(1-\nu u_4);(1-\theta)b;F_1(a)\mathbf{y} - \beta(a)\langle \mathbf{e},\mathbf{u}\rangle E_1\mathbf{y}) \end{pmatrix}^T.$$

By identifying $\varphi(t)$ together with $(\mathbf{u}(t),R(t),0_{\mathbb{R}^2},\mathbf{y}(t,.))^T$ and by setting $\varphi_0 = (\mathbf{u}_0,R_0,0_{\mathbb{R}^2},\mathbf{y}_0(.))^T$, one obtains that system (5)-(6) rewrites as the following non-densely defined Cauchy problem:

$$\frac{d\varphi(t)}{dt} = A\varphi(t) + F(\varphi(t)), t \geq 0 \quad \text{and} \quad \varphi(0) = \varphi_0 \in \overline{D(A)} \cap X_+. \tag{9}$$

We set $X_0 = \overline{D(A)}$, $X_{0+} = X_0 \cap X_+$, $\mathscr{A} = \{\varphi \in X_{0+} : ||\varphi|| \leq b/\mu_1\}$ and the precise result is the following theorem.

Theorem 2 *Let Assumption 1 be satisfied. Then there exists a unique strongly continuous semiflow $\{U(t) : X_0 \to X_0\}_{t\geq 0}$ such that for each $\varphi_0 \in \mathscr{A}$, the map $\varphi \in \mathscr{C}([0,\omega),\mathscr{A})$ defined by $\varphi = U(.)\varphi_0$ is a mild solution of* (9)*, namely, it satisfies $\int_0^t \varphi(s)ds \in D(A)$ and $\varphi(t) = \varphi_0 + A\int_0^t \varphi(s)ds + \int_0^t F(\varphi(s))ds; \forall t \geq 0$. Furthermore $\{U(t)\}_{t\geq 0}$ satisfies the following properties:*

(i) Let $U(t)\varphi_0 = (\mathbf{u}(t),R(t),0_{\mathbb{R}^2},\mathbf{y}(t,.))^T$; then the following Volterra integral formulation holds true:

$$\mathbf{y}(t,a) = \begin{cases} e^{\int_{a-t}^a (F_1(a) - \beta(a)\langle \mathbf{e},\mathbf{u}(\sigma)\rangle E_1)d\sigma}\mathbf{y}_0(a-t); \text{ if } a \geq t, \\ e^{\int_0^a (F_1(\sigma) - \beta(\sigma)\langle \mathbf{e},\mathbf{u}(t)\rangle E_1)d\sigma}\mathbf{y}(t-a,0); \text{ if } a < t. \end{cases}$$

with $\mathbf{y}(t-a,0) = [\theta b(1-\nu u_4(t-a));(1-\theta)b]^T$.

(ii) For each $\varphi_0 \in \mathscr{A}$ one has for all $t \geq 0$

$$\langle \mathbf{1}_4,\mathbf{u}(t)\rangle + R(t) + \int_0^\omega l(a)\langle \mathbf{1}_2,\mathbf{y}(t,a)\rangle da \leq \frac{b}{\mu_1}.$$

(iii) The nonempty compact set $\mathscr{A}$ is invariant under the semiflow U, and the subset $\mathscr{A}$ attracts the bounded sets of X_{0+} under the semiflow U.

Proof The proof of this result is rather standard. Indeed it is easy to check that operator A satisfies the Hille-Yosida property. Then standard methodologies apply to provide the existence and uniqueness of a mild solution for system (5)-(6) (see, for instance, Refs. [28,35,26,9]). Next the Volterra integral formulation is also standard in the context of age-structured equations and we refer to Ref. [25] and the references cited therein for more details. Estimates stated in (ii) directly follow from the system

of equations. Let us assume for a moment that $\mathbf{y}_0 \in W^{1,1}(0,\omega,\mathbb{R}^2)$; then adding up the equations of system (5) yields $\dot{v}(t) \leq b - \mu_1 v(t)$, that is

$$v(t) \leq \frac{b}{\mu_1} + e^{-\mu_1 t}\left(v(0) - \frac{b}{\mu_1}\right), \tag{10}$$

wherein $v(t) = \langle \mathbf{1}_4, \mathbf{u}(t)\rangle + R(t) + \int_0^\omega l(a)\langle \mathbf{1}_2, \mathbf{y}(t,a)\rangle da$. From where one deduces estimate (ii). It remains to prove (iii) and this is a direct consequence of (10).

2.3 Mathematical analysis

2.3.1 The disease-free steady state and reproductive number

The disease-free steady state is $\mathbf{E}^0 = \left(0_{\mathbb{R}^4}, 0, 0_{\mathbb{R}^2}, s^0(.), v^0(.)\right)^T$, where

$$s^0(a) = b\left[\theta e^{-\int_0^a (\psi + p(\eta))d\eta} + \psi \int_0^a e^{-\int_\sigma^a (\psi+p(\eta))d\eta} d\sigma\right]; v^0(a) = b - s^0(a).$$

For the computation of the basic reproduction number, we use the next generation operator approach as described by Diekmann-Heesterbeek-Metz[10], Inaba[27] and Djidjou-Ducrot[9] to define the basic reproduction number, $\mathscr{R}_0$, as the number of secondary infections that one infectious individual would create over the duration of the infectious period, provided that everyone else is susceptible.

In the early stage of the epidemic, the dynamics of the population can be described by the linearized equation at the disease-free steady state $\mathbf{E}^0$. Since the linearized equations for infective population does not include other subpopulations, we find that

$$\mathscr{R}_0 = \frac{1}{2}\left[\frac{\gamma\mathscr{K}_i}{v_{11}v_{33}} + \frac{\delta(\mathscr{K}_c + b\theta v)}{v_{22}v_{44}} + \left(\left(\frac{\gamma\mathscr{K}_i}{v_{11}v_{33}} + \frac{\delta(\mathscr{K}_c - b\theta v)}{v_{22}v_{44}}\right)^2 + \frac{4\delta^2 b\theta v.\mathscr{K}_c}{v_{22}^2 v_{44}^2}\right)^{1/2}\right], \tag{11}$$

wherein $\mathscr{K}_i = \int_0^\omega \beta(a)\alpha(a)l(a)s^0(a)da$, $\mathscr{K}_c = \tau\int_0^\omega \beta(a)(1-\alpha(a))l(a)s^0(a)da$, $v_{11} = \mu_1 + \gamma$; $v_{22} = \mu_1 + \delta$; $v_{33} = \gamma_1 + \mu_I + \mu_1$; and $v_{44} = \gamma_2 + \mu_c + \mu_1$.

Remark 1

1. We can also follow van den Driessche and Watmough[36], we obtain that the basic reproduction number, defined as the expected number of secondary infections produced by an index case (Anderson and May[1]), is given by

$$\widetilde{\mathscr{R}}_0 = \frac{\delta(\mathscr{K}_c + b\theta v)}{v_{22}v_{44}} + \frac{\gamma\mathscr{K}_i}{v_{11}v_{33}}. \tag{12}$$

In fact, simple calculation shows that $\mathscr{R}_0 < 1 (= 1, > 1)$ is equivalent to $\widetilde{\mathscr{R}}_0 < 1 (= 1, > 1)$.

2. Actually, it's more easier to interpret the term $\widetilde{\mathscr{R}}_0$ than the term $\mathscr{R}_0$. In fact, according to (12), we can observe that the first fraction in the sum is the number of secondary infections induced by asymptomatic infections and the other is the number of secondary infections induced by symptomatic infections.

2.3.2 Global stability of the disease-free steady state.

We have the following result about the global stability of the disease-free steady state.

Theorem 3 *Under Assumption 1, the disease-free steady state* $\mathbf{E}^0$ *is globally asymptotically stable if* $\mathscr{R}_0 < 1$ *and unstable if* $\mathscr{R}_0 > 1$.

Proof Since $\left\{T_{A_0}(t)\right\}_{t\geq 0}$ the semigroup generated by A_0 the part of A in $\overline{D(A)}$ satisfies $\left|\left|T_{A_0}(t)\right|\right| \leq \overline{M}e^{-\mu_1 t}, \quad \forall t \geq 0$, for some constant $\overline{M} > 0$. It follows that $\omega_{ess}(A_0)$, the essential growth of rate of $\left\{T_{A_0}(t)\right\}_{t\geq 0}$ is, $\leq -\mu_1$. Let $\left\{T_{\left(A_0+DF(\mathbf{E}^0)\right)}(t)\right\}_{t\geq 0}$ be the linear C_0-semigroup generated by $\left(A+DF(\mathbf{E}^0)\right)_0$ the part of $A+DF(\mathbf{E}^0)$: $D(A) \subset X \to X$ in $\overline{D(A)}$. Since $DF(\mathbf{E}^0)$ is a compact bounded linear operator, it follows that (Ref. [11] an references therein) $\omega_{ess}(A+DF(\mathbf{E}^0)) \leq -\mu_1$.

Now, let us assume that $\mathscr{R}_0 > 1$. Let $w = (w_i)_{i=1,\ldots,4} \in \mathbb{R}^4$, $u = (u_i)_{i=1,\ldots,4} \in \mathbb{R}^4$ and using the linearized equation of system (5) at the disease-free steady state, let us consider the resolvent equation:

$$(zI - \mathscr{V})\, w = u, \;\; z \in \mathbb{C} \text{ and } R_e(z) > -\mu_1. \tag{13}$$

with

$$\mathscr{V} = \begin{pmatrix} -\nu_{11} & 0 & \mathscr{K}_i & \mathscr{K}_i \\ 0 & -\nu_{22} & \mathscr{K}_c & \mathscr{K}_c + b\theta\nu \\ \gamma & 0 & -\nu_{33} & 0 \\ 0 & \delta & 0 & -\nu_{44} \end{pmatrix}.$$

Then, one has

$$(I - T(z))\, w = \left(\frac{u_i}{z+\nu_{ii}}\right)^T_{i=1,\ldots,4}; \tag{14}$$

where $T(z)$, $z \in \mathbb{C}$, is 4×4 matrix defined by:

$$T(z) = \begin{pmatrix} 0 & 0 & \frac{\mathscr{K}_i}{z+\nu_{11}} & \frac{\mathscr{K}_i}{z+\nu_{11}} \\ 0 & 0 & \frac{\mathscr{K}_c}{z+\nu_{22}} & \frac{\mathscr{K}_c+b\theta\nu}{z+\nu_{22}} \\ \frac{\gamma}{z+\nu_{33}} & 0 & 0 & 0 \\ 0 & \frac{\delta}{z+\nu_{44}} & 0 & 0 \end{pmatrix} \tag{15}$$

Let us observe that the basic reproduction ratio $\mathscr{R}_0$ is the spectral radius, denoted by $r(T(0))$, of the generation operator $T(0)$. (See Ref. [26] and references therein). Then, we claim that (see Appendix A for the proof):

Claim There exists a unique $z_0 > -\nu_{min} := -\min(\nu_{ii})_{i=1,2,3,4}$ such that $r(T(z_0)) = 1$ and $z_0 > 0$ if $r(T(0)) > 1$; $z_0 = 0$ if $r(T(0)) = 1$; $z_0 < 0$ if $r(T(0)) < 1$, and it is the dominant characteristic root, as

$$z_0 > \sup\left\{R_e(z) : z \in \Sigma^0 \setminus \{z_0\}\right\};$$

where $\Sigma^0 := \{z \in \mathbb{C} : (I - T(z)) \text{ is not inversible}\}$ is the spectrum of $\mathscr{V}$.

Therefore, the disease-free steady state is locally asymptotically stable if $\mathscr{R}_0 = r(T(0)) < 1$ and unstable if $\mathscr{R}_0 = r(T(0)) > 1$.

The second part of the proof deals with the global stability of the disease-free steady state. Let us consider $\mathscr{A} \subset X_{0+}$, the global attractor of U provided by Theorem 2. Let $(\mathbf{u}_0, R_0, 0_{\mathbb{R}^2}, \mathbf{y}_0) \in \mathscr{A}$ be given and let $\{\varphi(t) = (\mathbf{u}(t), R(t), 0_{\mathbb{R}^2}, \mathbf{y}(t,.))\}_{t\in\mathbb{R}}$ be the entire solution of U passing trough $(\mathbf{u}_0, R_0, 0_{\mathbb{R}^2}, \mathbf{y}_0)$. Since $s(0,.) \leq s^0(.)$ for all $(\mathbf{u}_0, R_0, 0_{\mathbb{R}^2}, \mathbf{y}_0) \in \mathscr{A}$, we deduce that $s(t,.) \leq s^0(.)$ for all $t \in \mathbb{R}$. One may consider the functional V defined for each entire solutions by $V[\varphi](t) = \mathbf{d}.\mathbf{u}(t)$, where the positive constant vector $\mathbf{d} \in \mathbb{R}^4$ is defined by $d_1 = \frac{\gamma d_3}{\gamma+\mu_1}$, $d_2 = \frac{\delta d_4}{\mu_1+\delta}$, $d_3 = \frac{1}{2(\mu_1+\gamma_1+\mu_I)}$, and $d_4 = \frac{1}{2(\mu_c+\mu_1+\gamma_2)}$.

Next, using system (5) we obtain

$$\frac{dV[\varphi](t)}{dt} \leq (\mathscr{R}_0 - 1)\langle \mathbf{e}, \mathbf{u}(t)\rangle. \tag{16}$$

Hence, we infer from the definition of X_{0+} that $t \mapsto V[\varphi](t)$ is decreasing along the entire solutions of U. To conclude our proof, let $\{t_n\}_{n\geq 0}$ be an increasing sequence tending to $-\infty$ as $n \to +\infty$ and consider the sequence of map $\varphi_n(t) = \varphi(t+t_n)$. Note that one has $V[\varphi_n](t) = V[\varphi](t+t_n)$. Up to a subsequence one may assume that $\varphi_n(t) \to \widehat{\varphi}(t)$ as $n \to +\infty$ locally uniformly for $t \in \mathbb{R}$, where $\{\widehat{\varphi}(t)\}_{t\in\mathbb{R}} \subset \mathscr{A}$ is an entire solution of U. Since V is decreasing, one obtains that $V[\widehat{\varphi}](t) \equiv \lim_{t\to-\infty} V[\varphi](t) = \sup_{t\in\mathbb{R}} V[\varphi](t)$.

By setting $\widehat{\varphi} = (\widehat{\mathbf{u}}, \widehat{R}, 0_{\mathbb{R}^2}, \widehat{\mathbf{y}})$, (16) yields to $\widehat{\mathbf{u}}(t) \equiv 0$ while $\widehat{\mathbf{y}} \equiv (s^0(.), v^0(.))^T$. Hence $V[\widehat{\varphi}](t) \equiv 0$ and $0 \leq V[\varphi](t) \leq 0$ for $t \in \mathbb{R}$ and $\varphi(t) \equiv \mathbf{E}^0$. This end the proof of Theorem 3.

2.3.3 Disease-endemic steady states.

The existence and uniqueness of the disease-endemic steady is stated in Theorem 4 and proved in Appendix B.

Theorem 4 *Let Assumption 1 be satisfied and $\mathscr{R}_0 > 1$, then there is a unique disease-endemic steady state $\mathbf{E}^*$ of system* (5)-(6).

Now, we investigate the stability of the unique endemic steady-state. The linearized system (5) at the endemic steady state $\mathbf{E}^* = (\mathbf{u}^*, R^*, \{0_{\mathbb{R}^2}\}, \mathbf{y}^*(.))$ can be written as

$$\frac{d\varphi(t)}{dt} = A\varphi(t) + F_e\varphi(t), \tag{17}$$

with $\varphi(t) = (\mathbf{u}(t), R, 0_{\mathbb{R}^2}, \mathbf{y}(t,.))^T$ and where the linear operator F_e is given by

$$F_e\left((\mathbf{u}(t), R(t), 0_{\mathbb{R}^2}, \mathbf{y}(t,.))^T\right) = \begin{pmatrix} \int_0^\omega l(a)\beta(a)\langle \mathbf{e}_1, \mathbf{y}^*(a)\rangle F_2(a)\mathbf{u}(t)da + \int_0^\omega l(a)\beta(a)\langle \mathbf{e}_1, \mathbf{y}(t,a)\rangle F_2(a)\mathbf{u}^* da + F_3\mathbf{u}(t) \\ \langle F_4, \mathbf{u}(t)\rangle - \mu_1 R(t) \\ (-b\theta v u_4(t); 0; F_1(a)\mathbf{y}(t,a) - \beta(a)\langle \mathbf{e}, \mathbf{u}^*\rangle E_1\mathbf{y}(t,a) - \beta(a)\langle \mathbf{e}, \mathbf{u}(t)\rangle E_1\mathbf{y}^*(a)) \end{pmatrix}^T. \tag{18}$$

Since the linearized stability principle holds for the age-structured population system (5) (Ref. [37]), the endemic steady state is locally asymptotically stable if the trivial equilibrium $\varphi = 0$ of the linearized system (17) is locally asymptotically stable, while the endemic steady state is unstable if $\varphi = 0$ is unstable in (17).

In order to see the linearized stability by calculating the resolvent spectrum, let us consider the resolvent equation for the linearized operator:

$$(zI - (A+F_e))\,w = u, \quad w \in D(A), \quad u \in X, \quad z \in \mathbb{C}.$$

Let $w = (\bar{s}(.), \bar{v}(.), \bar{L}_i, \bar{L}_c, \bar{C}, \bar{I}, \bar{R})$ and $u = (u_1(.), u_2(.), u_3, u_4, u_5, u_6, u_7)$. Then we have

$$\begin{aligned}
\vec{\bar{s}}(a) &= -(z+\beta(a)(I^*+\tau C^*)+p(a))\bar{s}(a) + \psi\bar{v}(a) \\
&\quad -\beta(a)s^*(a)(\bar{I}+\tau\bar{C}) + u_1(a), \qquad (19)\\
\vec{\bar{v}}(a) &= -(z+\psi)\bar{v}(a) + p(a)\bar{s}(a) + u_2(a),\\
z\bar{L}_i &= (I^*+\tau C^*)\int_0^\omega \alpha(a)l(a)\beta(a)\bar{s}(a)da \qquad (20)\\
&\quad +(\bar{I}+\tau\bar{C})\int_0^\omega \alpha(a)l(a)\beta(a)s^*(a)da - (\mu_1+\gamma)\bar{L}_i + u_3, \qquad (21)
\end{aligned}$$

$$\begin{aligned}
z\bar{L}_c &= (I^*+\tau C^*)\int_0^\omega (1-\alpha(a))l(a)\beta(a)\bar{s}(a)da + b\theta\nu\bar{C} + u_4\\
&\quad +(\bar{I}+\tau\bar{C})\int_0^\omega (1-\alpha(a))l(a)\beta(a)s^*(a)da - (\mu_1+\delta)\bar{L}_c, \qquad (22)\\
z\bar{I} &= \gamma\bar{L}_i - (\gamma_1+\mu_1+\mu_I)\bar{I} + u_5, \qquad (23)\\
z\bar{C} &= \delta\bar{L}_c - (\gamma_2+\mu_1+\mu_c)\bar{C} + u_6, \qquad (24)\\
z\bar{R} &= \gamma_1\bar{I} + \gamma_2\bar{C} - \mu_1\bar{R} + u_7,\\
&\quad \bar{s}(0) = -b\theta\nu\bar{C}; \quad \bar{v}(0) = 0. \qquad (25)
\end{aligned}$$

Equations (20) and (19), coupling with (25), respectively give

$$\bar{v}(a) = \int_0^a (p(\sigma)+u_2(\sigma))e^{-(z+\psi)}(a-\sigma)\bar{s}(\sigma)d\sigma,$$

and

$$\begin{aligned}
&\bar{s}(a) = -b\theta\nu\bar{C}e^{-\int_0^a (z+\beta(\eta)(I^*+\tau C^*)+p(\eta))d\eta}\\
&+\int_0^a [u_1(\sigma)+\psi\bar{v}(\sigma)-\beta(\sigma)s^*(\sigma)(\bar{I}+\tau\bar{C})]e^{-\int_\sigma^a (z+\beta(\eta)(I^*+\tau C^*)+p(\eta))d\eta}d\sigma.
\end{aligned}$$

From (23) and (24) it comes that

$$\bar{L}_i = \tfrac{1}{\gamma}(z+\nu_{33}) - \tfrac{u_5}{\gamma}, \quad \bar{L}_c = \tfrac{1}{\delta}(z+\nu_{44}) - \tfrac{u_6}{\delta}. \qquad (26)$$

Substituting (26) into system (21)-(22) we have

$$(I - B(z))(\bar{I},\bar{C})^T = (\chi_1,\chi_2)^T; \qquad (27)$$

where $B(z)$, $z \in \mathbb{C}$ is 2×2 matrix defined by

$$B(z) = \begin{pmatrix} B_1(z) & B_1(z) \\ B_2(z) & B_2(z) + \frac{\delta b\theta\nu}{\nu_{22}\nu_{44}} \end{pmatrix}, \qquad (28)$$

wherein $B_1(z) = \frac{\gamma \int_0^\omega \alpha(a) l(a) \beta(a) s^*(a) da}{(z+v_{11})(z+v_{33})}$; $B_2(z) = \frac{\delta \int_0^\omega (1-\alpha(a)) l(a) \beta(a) s^*(a) da}{(z+v_{22})(z+v_{44})}$; and

$$\chi_1 = \frac{\gamma(I^* + \tau C^*) \int_0^\omega \alpha(a) l(a) \beta(a) s^*(a) da}{(z+v_{11})(z+v_{33})} + \frac{u_5}{z+v_{33}};$$
$$\chi_2 = \frac{\delta(I^* + \tau C^*) \int_0^\omega (1-\alpha(a)) l(a) \beta(a) s^*(a) da}{(z+v_{22})(z+v_{44})} + \frac{u_6}{z+v_{44}}.$$

We can observe that $B(0) \leq H$, where H is the next generation operator at the endemic steady state given by (48). Since H is also irreducible, its spectral radius is the Frobenius eigenvalue corresponding to the unique positive eigenvector. If $\mathscr{R}_0 > 1$, H has a positive fixed point (see Theorem 4), that is $r(H) = 1$. Hence from Perron-Frobenius Theorem we obtain that $r(B(0)) < r(H) = 1$. Let Σ^* be the spectrum of $A + F_e$. By using the same argument as the proof of Claim 2.3.2, we know that the dominant characteristic root in Σ^* is given as the unique real root of $r(B(z)) = 1$ and it is less than zero if $r(B(0)) < 1$. Then it follows that the endemic steady state is locally asymptotically stable. Therefore, we obtain the following result on the stability of the disease-endemic steady state.

Theorem 5 *Let Assumption 1 be satisfied and $\mathscr{R}_0 > 1$, then the disease-endemic steady state $\mathbf{E}^*$ of system* (5) *is stable.*

2.3.4 Numerical illustrations

Numerical simulations are based on some main parameters used or derived in Zhao, Xu, and Lu[41]; Zou, Zhang and Ruan[42] for HBV infection.

We first have the transmission coefficient $\beta(a)$ given by

$$\beta(a) = \begin{cases} 0.13074116 - 0.01362531a + 0.00046463a^2 - 0.00000489a^3; \ 0 \leq a \leq 47.5, \\ \beta(47.5); \ a > 47.5 \end{cases} \tag{29}$$

The remaining parameters are given by (30) and Table 1.

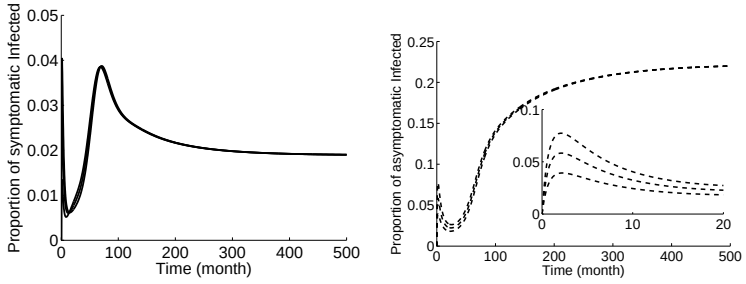

Fig. 2: The behavior of system for $p = 0.12$, $\theta = 0.6$ and $\mathscr{R}_0 = 1.4796$. All other parameters are given in Tab. 1 and Eqs. (29)-(1).

Using a constant p for $p(a)$ (vaccination rate at age a), we simulate the behavior of the model.

We observe the behavior of the system for $p = 0.12$. In Figure 2, $\theta = 0.6$ such that $\mathscr{R}_0 = 1.7499 > 1$ ($\widetilde{\mathscr{R}}_0 = 1.7522 > 1$). This indicates that hepatitis B is endemic in the host population.

2.3.5 Sensitivity analysis

We carried out the sensitivity analysis to determine the model robustness to parameter values. That is to help us know the parameters that are most influential in determining disease dynamics. A Latin Hypercute Sampling (LHS) scheme (Marino et al. [29]; Blower et al. [5]) samples 1000 values for each input parameter using a uniform distribution over the range of biologically realistic values, listed in Table 2 with descriptions and references given in Table 1. Using the system of differential equations that describe (2) and a time period of 500 months, 1000 model simulations are performed by randomly pairing sampled values for all LHS parameters. Four outcome measures are calculated for each run: the maximum and total size of the symptomatic and asymptomatic infected population over the model's time span. Partial Rank Correlation Coefficients (PRCC) and corresponding p-values are computed. An output is assumed sensitive to an input if the corresponding PRCC is less than -0.50 or greater than $+0.50$, and the corresponding p-value is less than 5%.

To examine the impact of the mass group vaccination of susceptible (i.e. for a specific age group of susceptible individuals) on the spread of the disease, we consider two age groups: $0 \leq a \leq 5$ (years) and $a > 5$ (years). The vaccination rate of susceptible $p(a)$ is then defined by:

$$p(a) = \begin{cases} p_1 \text{ per year; } 0 \leq a \leq 5 \text{ (years)}, \\ 0 \text{ per year; } a > 5 \text{ (years)}, \end{cases} \tag{30}$$

wherein p_1 is the vaccination rate of susceptible for the specific age group.

The sensitivity results suggest that maximum monthly symptomatic and asymptomatic infections and the total size of symptomatic infection outcome measures are sensitive to changes in the parameters p_1, μ_I, μ_C, γ, δ, θ, ν, γ_1 and γ_2.

The sensitivity results suggest that the control of the epidemic of hepatitis B virus pass through a combination of immunization of newborns, immunization of susceptible individuals (at least young adults), and reduction of perinatal infection. Therefore, although the proportion of perinatal transmission of the disease is low, this factor should not be neglected in the transmission of HBV. HBV could also be eliminated if the transmission coefficient $\beta(.)$ is sufficiently small. However, it is difficult to control $\beta(.)$.

3 Optimal intervention strategies

3.1 Extended model with intervention methods

Several HBV treatment and intervention options do exists. The treatment of HBV asymptomatic infections is not considered here against any financial trade-off. On the

Table 2: Sensitivity analysis of the model without controls

LHS-PRCC sensitivity analysis					
Parameter	Parameter ranges		PRCC values[1]		
	Min	Max	Maximum symptomatic infection	Maximum asymptomatic infection	Total size of of all infected classes
p_1	0.001	0.99	-0.87*	-0.70*	-0.83*
μ_I	0.001	0.05	-0.87*	-0.69*	-0.82*
μ_C	0.001	0.05	-0.86*	-0.68*	-0.82*
γ	0.001	0.99	-0.86*	-0.68*	-0.81*
δ	0.01	0.8	-0.86*	-0.67*	-0.82*
θ	0.001	0.5	-0.86*	-0.67*	-0.83*
ν	0.001	0.3	-0.86*	-0.68*	-0.83*
γ_1	0.01	0.3	-0.87*	-0.70*	-0.84*
γ_2	0.01	0.05	-0.87*	-0.70*	-0.84*

[1]Asterisks indicate the corresponding p-values which represent the significance of a nonzero PRCC: * denotes a p-value bellow 0.001

other hand, individual with HBV symptomatic infections require a special treatment to overcome the infection. As for preventive measures, two vaccination strategies can be consider: the immunization of young adults (at least susceptible with the age less than 5 years old) and the reduction of perinatal infection. Those interventions are also supported by the sensitivity analysis.

Three interventions strategies, called controls, are include into our initial model. Controls are represented as functions of time and assigned reasonable upper and lower bounds. First, vaccination effort moves susceptible individuals age a to immune class at rate $h_1(t,a)$ at time t. Second, the effort to prevent perinatal infection is at rate $h_2(t)$ at time t (i.e. the screening of pregnant women for a potential asymptomatic HBV during each pregnancy). Third, $h_3(t)$ is the proportion of people with HBV symptomatic infection who receive treatment at time t. Those receiving a treatment are assume to have an increased rate of recovery ($\tilde{\gamma}_1 > \gamma_1$) and a decreased rate of death due to HBV ($\tilde{\mu}_I < \mu_I$).

Using the same parameter and class names as model (2) and Table 1, the system describing our model with controls is:

$$
\begin{aligned}
&\frac{\partial S(t,a)}{\partial t}+\frac{\partial S(t,a)}{\partial a}=\psi V(t,a)-(\lambda(t,a)+\mu_1+p(a)(1+h_1(t,a))S(t,a),\\
&\frac{\partial V(t,a)}{\partial t}+\frac{\partial V(t,a)}{\partial a}=p(a)(1+h_1(t,a))S(t,a)-(\psi+\mu_1)V(t,a),\\
&\frac{dL_i(t)}{dt}=(I(t)+\tau C(t))q_1(t)-(\mu_1+\gamma)L_i(t),\\
&\frac{dL_c(t)}{dt}=(I(t)+\tau C(t))q_2(t)+b\theta\nu(1-h_2(t))(1-h_1(t,0))C(t)-(\mu_1+\delta)L_c(t),\\
&\frac{dI(t)}{dt}=\gamma L_i(t)-\mu_1 I(t)-(\gamma_1+\mu_I)(1-h_3(t))I(t)-(\tilde{\gamma}_1+\tilde{\mu}_I)h_3(t)I(t),\\
&\frac{dC(t)}{dt}=\delta L_c(t)-(\gamma_2+\mu_1+\mu_c)C(t),\\
&\frac{dR(t)}{dt}=\gamma_1(1-h_3(t))I(t)+\tilde{\gamma}_1 h_3(t)I(t)+\gamma_2 C(t)-\mu_1 R(t),\\
&S(t,0)=\theta(1-h_1(t,0))b(1-\nu(1-h_2(t))C(t));\quad V(t,0)=(1-\theta(1-h_1(t,0)))b,
\end{aligned}
\tag{31}
$$

with $q_1(t)=\int_0^\omega \alpha(a)\beta(a)S(t,a)da$ and $q_2(t)=\int_0^\omega(1-\alpha(a))\beta(a)S(t,a)da$.

Setting $\mathbf{y}(t,.)=(V(t,.);S(t.,))^T$ and $\mathbf{x}(t)=(L_i(t),I(t),L_c(t),C(t))^T$ system (31) becomes

$$
\begin{cases}
(\partial_t+\partial_a)\mathbf{y}(t,a)=\mathbf{f}(t,a,y(t,a),h_1(t,a)):=\mathbf{f}(t,a),\\
\dot{\mathbf{x}}(t)=\mathbf{g}(t,x(t),q_y(t),h_2(t),h_3(t)):=\mathbf{g}(t),\\
\mathbf{y}(t,0)=\varphi(t);\quad \mathbf{y}(0,.)=\mathbf{y}^0(.):=(V(0,.);S(0.,))^T,\\
\mathbf{x}(0)=\mathbf{x}^0:=(L_i(0),I(0),L_c(0),C(0))^T,
\end{cases}
\tag{32}
$$

wherein $q(t)=(q_1(t),q_2(t))^T$ and $\varphi(t)=[(1-\theta(1-h_1(t,0)))b,\theta(1-h_1(t,0))b(1-\nu(1-h_2(t))C(t))]$. Moreover, $\mathbf{f}(t,a)$ is given by the right-hand side of (31) for the (V,S)-compartment; $\mathbf{g}(t):=(g_i(t))_{i=1,\dots,4}^T$ with g_1, g_2, g_3 and g_4 given by the the right-hand side of (31) for the L_i, I, L_c and C-compartment respectively.

3.2 Optimal control problem

A successful scheme is one which reduces HBV-related deaths with a minimal cost. We assume that the control scheme is optimal if it minimizes the objective functional

$$
\mathbf{J}(h_1,h_2,h_3)=\int_0^{T_f} L_0(t,\mathbf{x},h_2,h_3)dt+\int_0^{T_f}\int_0^\omega L(t,a,\mathbf{y},h_1)dadt,
\tag{33}
$$

with

$$
\begin{aligned}
L_0(t,\mathbf{x},h_2,h_3)=&B[\tilde{\mu}_I h_3(t)I(t)+(1-h_3(t))\mu_I I(t)+\mu_C C(t)]+B_3 h_3(t)I(t)\\
&+\lambda_3 h_3^2(t)+B_2 h_2(t)C(t)+\lambda_2 h_2^2(t),\\
L(t,a,\mathbf{y},h_1)=&B_1(a)h_1(t,a)(S(t,a)+L_i(t)+L_c(t)+C(t))+\lambda_1(a)h_1^2(t,a),
\end{aligned}
$$

and where B, B_1, B_2, B_3, λ_1, λ_2, λ_3 are balancing coefficients transforming the integral into cost expended over a finite period of T_f months (See Tab. 3). The first sum in the first integral, multiply by B, is the cost of death due to HBV and the remaining expressions (for both integrals) are costs for implementation for the three controls. Quadratic expressions of the controls are included to indicate non-linear costs potentially arising at high treatment levels. The term $(L_i + L_c + C)$ in the cost function is due to the fact that individuals in C and the two latent classes probably would be vaccinating without any effect on them, but those vaccinations would cost.

Table 3: Cost coefficients in objective functional

Parameter	Value
B	2000 USD per human death
B_1	50 USD per vaccinated individual
B_2	195 USD per perinatal infection prevention
B_3	800 USD per month of treatment
λ_1	10 USD per (vaccination rate)^2
λ_2	10 USD per (perinatal infection prevention rate)^2
λ_3	10 USD per (proportion of I treated)^2

The problem now is to find (h_1^*, h_2^*, h_3^*) satisfying

$$\mathbf{J}(h_1^*, h_2^*, h_3^*) = \min_{\mathscr{U}} \mathbf{J}(h_1, h_2, h_3), \tag{34}$$

on the control set

$$\mathscr{U} = \{((h_1, h_2, h_3)) \in L^\infty(\mathscr{Q}) : 0 \leq h_1(.,a) \leq h_{1max}(a); 0 \leq h_2(.) \leq h_{2max}; 0 \leq h_3(.) \leq h_{3max}\},$$

where $\mathscr{Q} := \big[(0,T_f) \times (0,\omega)\big] \times \big(0,T_f\big) \times \big(0,T_f\big)$; h_{2max}, h_{3max} are given positive constants and $h_{1max}(.)$ is given measurable positive function.

3.3 The necessary optimality condition

To deal with necessary optimality condition, we will make use of the results in Feichtinger et al. [20] and references cited therein. We introduce the following adjoint functions $(\lambda_V(t,a), \lambda_S(t,a))$; $(\lambda_{L_i}(t), \lambda_I(t), \lambda_{L_c}(t), \lambda_C(t))$, considered as row-vector functions (while $\mathbf{y}$, $\mathbf{x}$ are column-vectors). We also define the following functional

$$H_0(t, h_2, h_3) = L_0(t, \mathbf{x}, h_2, h_3) + g_1(t)\lambda_{L_i}(t) + g_2(t)\lambda_I(t) + g_3(t)\lambda_{L_c}(t) + g_4(t)\lambda_C(t). \tag{35}$$

Below $\triangle_z$ denotes differentiation with respect to the variable z. Introducing the following distributed Hamiltonian (see [20])

$$H(t, a, h_1, h_2, h_3) = H_0(t, h_2, h_3) + L(t, a, h_1) + \xi(t,a) \cdot \mathbf{f}(t,a), \tag{36}$$

we find that the adjoint system is given by

$$\begin{cases} -(\partial_t+\partial_a)\xi(t,a) = \triangle_{\mathbf{y}} L(t,a) + \xi(t,a)\cdot\triangle_{\mathbf{y}}\mathbf{f}(t,a), \\ \xi(T_f,a)=0; \quad \xi(t,\omega)=0, \\ -\dot{\lambda}_{L_i} = \frac{\partial H_0}{\partial_{L_i}}; \quad -\dot{\lambda}_I = \frac{\partial H_0}{\partial_I}; \quad -\dot{\lambda}_{L_c} = \frac{\partial H_0}{\partial_{L_c}}; \quad -\dot{\lambda}_C = \frac{\partial H_0}{\partial_C}, \\ \lambda_{L_i}(T_f) = \lambda_I(T_f) = \lambda_{L_c}(T_f) = \lambda_C(T_f) = 0, \end{cases}$$

that is

$$\begin{cases} -(\partial_t+\partial_a)\lambda_V = -(\psi+\mu_1)\lambda_V + \psi\lambda_S, \\ -(\partial_t+\partial_a)\lambda_S = p(a)(1+h_1(t,a))\lambda_V - (\lambda(t,a)+\mu_1+p(a)(1+h_1(t,a)))\lambda_S \\ \qquad\qquad +B_1(a)h_1(t,a), \\ -\dot{\lambda}_{L_i} = -(\mu_1+\gamma)\lambda_{L_i} + \gamma\lambda_I, \\ -\dot{\lambda}_I = B\tilde{\mu}_I h_3(t) + B(1-h_3(t))\mu_I + B_3 h_3(t) + q_1(t)\lambda_{L_i} \\ \qquad\qquad -(\mu_1+(1-h_3(t))(\gamma_1+\mu_I)\lambda_I + h_3(t)(\tilde{\gamma}_1+\tilde{\mu}_I))\lambda_I + q_2(t)\lambda_{L_c}, \\ -\dot{\lambda}_{L_c} = -(\mu_1+\delta)\lambda_{L_c} + \delta\lambda_C, \\ -\dot{\lambda}_C = B\mu_C + B_2 h_2(t) + q_1(t)\lambda_{L_i} + (q_2(t)+(1-h_2(t))b\theta\nu)\lambda_{L_c} \\ \qquad\qquad -(\gamma_2+\mu_1+\mu_C)\lambda_C, \end{cases} \tag{37}$$

with the boundary conditions

$$\begin{cases} \lambda_V(T_f,a) = \lambda_S(T_f,a) = 0; \lambda_V(t,\omega) = \lambda_S(t,\omega) = 0, \\ \lambda_{L_i}(T_f) = \lambda_I(T_f) = \lambda_{L_c}(T_f) = \lambda_C(T_f) = 0. \end{cases} \tag{38}$$

Note that the final time boundary conditions (transversality conditions) are zero since there is no dependence on the states at the final time in the objective functional.

Furthermore, if (h_1^*, h_2^*, h_3^*) in $\mathscr{U}$ is an optimal control minimizing (33), then it is characterized by

$$\begin{aligned} h_1^*(t,a) &= \max\left(0, \min\left(\hat{h}_1(t,a), h_{1max}(a)\right)\right), \\ h_2^*(t) &= \max\left(0, \min\left(\hat{h}_2(t), h_{2max}\right)\right), \\ h_3^*(t) &= \max\left(0, \min\left(\hat{h}_3(t), h_{3max}\right)\right) \end{aligned} \tag{39}$$

wherein

$$\hat{h}_1(t,a) = \frac{p(a)(\lambda_S(t,a)-\lambda_V(t,a))S(t,a) - B_1(a)(S(t,a)+L_i(t)+L_c(t)+C(t))}{2\lambda_1(a)},$$

$$\hat{h}_2(t) = \frac{b\theta\nu(1-h_1(t,0))C(t)\lambda_{L_c}(t) - B_2C(t)}{2\lambda_2},$$

$$\hat{h}_3(t) = \frac{(\tilde{\gamma}_1+\tilde{\mu}_I-\gamma_1-\mu_I)I(t)\lambda_I(t) - B(\tilde{\mu}_I-\mu_I)I(t) - B_3I(t)}{2\lambda_3}.$$

The control characterization h_1^* comes from $\frac{\partial H}{\partial h_1} = 0$ whenever $0 < h_1^*(t,a) < h_{1max}(a)$ and taking bounds into account, and similarly for the controls h_2 and h_3.

The state system of differential equations and the adjoint system of differential equations together with the control characterization above form the optimality system

to be solved numerically. Since the state equations have initial conditions and the adjoint equations have final time conditions, we cannot solve the optimality system directly by only sweeping forward in time. Thus, an iterative algorithm, "forward-backward sweep method", is used (see Emvudu et al. [15,16] and Lenhart et al. [23]).

3.4 Existence of an optimal control

We first give some useful notations for this section. Given a control vector $h := (h_1, h_2, h_3) \in \mathscr{U}$, the corresponding state variables is denotes by w^h and the corresponding adjoint variables by λ^h. We also define the mapping $\mathscr{L} : L^1(\mathscr{Q}_1) \times L^1(\mathscr{Q}_2) \times L^1(\mathscr{Q}_2) \to L^\infty(\mathscr{Q}_1) \times L^\infty(\mathscr{Q}_2) \times L^\infty(\mathscr{Q}_2)$ by $\mathscr{L}(H_1, H_2, H_3) = (\mathscr{L}_1 H_1, \mathscr{L}_2 H_2, \mathscr{L}_2 H_3)$ with

$$\mathscr{L}_i H_i = \begin{cases} 0, & \text{if } H_i < 0, \\ H_i, & \text{if } 0 \le H_i < h_{imax}, \ i = 1,2,3, \\ h_{imax}, & \text{if } H_i \ge h_{imax}, \end{cases}$$

and $\mathscr{Q}_1 = (0, T_f) \times (0, \omega)$; $\mathscr{Q}_2 = (0, T_f)$.

Denoting by $\mathscr{X} := \mathscr{Q}_1^2 \times \mathscr{Q}_2^4$, we also define the norm $||\cdot||_{L^1(\mathscr{X})}$ as follows: for $(y,x) := (y_i, x_j)_{i=1,2; j=1,\cdots,4} \in \mathscr{X}$,

$$||(y,x)||_{L^1(\mathscr{X})} = \int_{\mathscr{Q}_1} (|y_1| + |y_2|)(t,a) da dt + \sum_{j=1}^{4} \int_{\mathscr{Q}_2} |x_j|(t) dt,$$

In the same way, ce define the norms $||\cdot||_{L^\infty(\mathscr{X})}$, $||\cdot||_{L^1(\mathscr{Q})}$, $||\cdot||_{L^\infty(\mathscr{Q})}$, $||\cdot||_{L^1(\mathscr{Q}_i)}$ and $||\cdot||_{L^\infty(\mathscr{Q}_i)}$ $(i = 1,2)$.

We embed our optimal problem in the space $L^1(\mathscr{Q})$ by defining the following functional

$$\mathscr{J}(h) = \begin{cases} \mathbf{J}(h), & \text{if } h \in \mathscr{U}, \\ +\infty, & \text{if } h \notin \mathscr{U}. \end{cases} \tag{40}$$

To prove the existence of the optimal control, let us introduce the following lemma.

Lemma 6 *Let T_f be sufficiently small.*
1. The map $h \in \mathscr{U} \to w^h \in L^1(\mathscr{X})$ is Lipschitz in the following ways:

$$||w^h - w^v||_{L^1(\mathscr{X})} \le T_f C_1 ||h - v||_{L^1(\mathscr{Q})},$$
$$||w^h - w^v||_{L^\infty(\mathscr{X})} \le T_f C_2 ||h - v||_{L^\infty(\mathscr{Q})},$$

for all $h, v \in \mathscr{U}$.
2. For $h \in \mathscr{U}$, the adjoint system (37) *has a weak solution λ^h in $L^\infty(\mathscr{X})$ such that*

$$||\lambda^h - \lambda^v||_{L^\infty(\mathscr{X})} \le T_f C_3 ||h - v||_{L^\infty(\mathscr{Q})},$$

for all $h, v \in \mathscr{U}$.
3. The functional $\mathscr{J}(h)$ is upper semicontinuous with respect to $L^1(\mathscr{Q})$ convergence.

Proof See C.

It seen easily that the functional $\mathscr{J} : \mathscr{Q} \to (-\infty, \infty]$ is lower semi-continuous with respect to strong L^1 convergence not with respect to weak L^1 convergence. Thus, in general it does not attain its infimum on $\mathscr{Q}$. Thus we have to circumvent this situation by using the Ekerland variational principle (see [17]): for $\varepsilon > 0$, there exists h_ε in $L^1(\mathscr{Q})$ such that

$$\mathscr{J}(h_\varepsilon) \leq \inf_{h \in \mathscr{U}} \mathscr{J}(h) + \varepsilon, \tag{41}$$

$$\mathscr{J}(h_\varepsilon) = \min_{h \in \mathscr{U}} \left\{ \mathscr{J}(h) + \sqrt{\varepsilon} ||h_\varepsilon - h||_{L^1(\mathscr{Q})} \right\}. \tag{42}$$

Note that, by (42), the perturbed functional

$$\mathscr{J}_\varepsilon(h) = \mathscr{J}(h) + \sqrt{\varepsilon} ||h_\varepsilon - h||_{L^1(\mathscr{Q})}$$

attains its infimum at h_ε. By the same argument as in Section 3.3, and using the projection map $\mathscr{L}$ on $\mathscr{U}$, we find that

Lemma 7 *If h_ε is an optimal control minimizing the functional $\mathscr{J}_\varepsilon(h)$, then*

$$h_\varepsilon = \mathscr{L}\left(\hat{h}_1(w^{h_\varepsilon}, \lambda^{h_\varepsilon}) + \frac{\sqrt{\varepsilon}\pi_1^\varepsilon}{2\lambda_1}, \hat{h}_2(w^{h_\varepsilon}, \lambda^{h_\varepsilon}) + \frac{\sqrt{\varepsilon}\pi_2^\varepsilon}{2\lambda_2}, \hat{h}_3(w^{h_\varepsilon}, \lambda^{h_\varepsilon}) + \frac{\sqrt{\varepsilon}\pi_3^\varepsilon}{2\lambda_3} \right),$$

where $\pi_1^\varepsilon \in L^\infty(\mathscr{Q}_1)$; $\pi_2^\varepsilon, \pi_3^\varepsilon \in L^\infty(\mathscr{Q}_2)$, with $|\pi_1^\varepsilon(\cdot,\cdot)| \leq 1$, $|\pi_i^\varepsilon(\cdot)| \leq 1 (i = 2,3)$, and

$$\hat{h}_1(w^{h_\varepsilon}, \lambda^{h_\varepsilon}) = \frac{p(\lambda_S^{h_\varepsilon} - \lambda_V^{h_\varepsilon})S^{h_\varepsilon} - B_1(S^{h_\varepsilon} + L_i^{h_\varepsilon} + L_c^{h_\varepsilon} + C^{h_\varepsilon})}{2\lambda_1},$$

$$\hat{h}_2(w^{h_\varepsilon}, \lambda^{h_\varepsilon}) = \frac{b\theta v(1 - \hat{h}_1(w^{h_\varepsilon}, \lambda^{h_\varepsilon})(\cdot, 0))C^{h_\varepsilon}\lambda_{L_c}^{h_\varepsilon} - B_2 C^{h_\varepsilon}}{2\lambda_2},$$

$$\hat{h}_3(w^{h_\varepsilon}, \lambda^{h_\varepsilon}) = \frac{(\tilde{\gamma}1 + \tilde{\mu}_I - \gamma_1 - \mu_I)I^{h_\varepsilon}\lambda_I^{h_\varepsilon} - B(\tilde{\mu}_I - \mu_I)I^{h_\varepsilon} - B_3 I^{h_\varepsilon}}{2\lambda_3}.$$

We are now ready to prove the existence and uniqueness of an optimal controller. Namely, we have the following theorem.

Theorem 8 *Assume that the balancing coefficient λ_1 is constant parameter ($\lambda_1(a) \equiv \lambda_1$). If $\frac{T_f}{2}(1/\lambda_1 + 1/\lambda_2 + 1/\lambda_3)$ is sufficiently small, there exists one and only one optimal controller h^* in $\mathscr{U}$ minimizing $\mathscr{J}(h)$.*

Proof Let us start with the uniqueness. Define $\mathscr{F} : \mathscr{U} \to \mathscr{U}$ by

$$\mathscr{F}(h) = \mathscr{L}\left(\hat{h}_1(w^h, \lambda^h), \hat{h}_2(w^h, \lambda^h), \hat{h}_3(w^h, \lambda^h) \right),$$

wherein w^h and λ^h are state and adjoint solutions corresponding to h. Using the Lipschitz properties of w^h and λ^h (see Lemma 6), for $h, v \in \mathscr{U}$, we find that

$$\begin{aligned} ||\mathscr{L}_1(h_1) - \mathscr{L}_1(v_1)||_{L^\infty(\mathscr{Q}_1)} &= \left|\left| \tfrac{p(\lambda_S^h - \lambda_V^h)S^h - B_1(S^h + L_i^h + L_c^h + C^h)}{2\lambda_1} - \tfrac{p(\lambda_S^v - \lambda_V^v)S^v - B_1(S^v + L_i^v + L_c^v + C^v)}{2\lambda_1} \right|\right|_{L^\infty(\mathscr{Q}_1)} \\ &\leq \tfrac{T_f C_8}{2\lambda_1} ||h - v||_{L^\infty(\mathscr{Q})}. \end{aligned}$$

By the same argument, we also find that

$$||\mathscr{L}_i(h_i)-\mathscr{L}_i(v_i)||_{L^\infty(\mathscr{Q}_2)} \leq \tfrac{T_f C_{7+i}}{2\lambda_i}||h-v||_{L^\infty(\mathscr{Q})}, \quad i=2,3.$$

Therefore,

$$||\mathscr{F}(h)-\mathscr{F}(v)||_{L^\infty(\mathscr{Q})} \leq T_f C_{11}||h-v||_{L^\infty(\mathscr{Q})}\sum_{i=1}^{3}\frac{1}{2\lambda_i}, \tag{43}$$

where the constant C_{11} depends on the L^∞ bounds on the state and adjoint solutions and Lipschitz constants. If $\frac{T_f}{2}(1/\lambda_1+1/\lambda_2+1/\lambda_3)<1$, then the map $\mathscr{F}$ has a unique fixed point h^*.

To prove that this fixed point is an optimal controller, we used the approximate minimizers h_ε from Ekerland variational principle. From Lemma 7 and the contraction property of $\mathscr{F}$, we have

$$\begin{aligned}
&\left|\left|\mathscr{F}(h_\varepsilon)-\mathscr{L}\left(\hat{h}_1(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\frac{\sqrt{\varepsilon}\pi_1^\varepsilon}{2\lambda_1},\hat{h}_2(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\frac{\sqrt{\varepsilon}\pi_2^\varepsilon}{2\lambda_2},\hat{h}_3(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\frac{\sqrt{\varepsilon}\pi_3^\varepsilon}{2\lambda_3}\right)\right|\right|_{L^\infty(\mathscr{Q})}=\\
&\left|\left|\mathscr{L}\left(\hat{h}_1(w^{h_\varepsilon},\lambda^{h_\varepsilon}),\hat{h}_2(w^{h_\varepsilon},\lambda^{h_\varepsilon}),\hat{h}_3(w^{h_\varepsilon},\lambda^{h_\varepsilon})\right)-\right.\\
&\left.\mathscr{L}\left(\hat{h}_1(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\frac{\sqrt{\varepsilon}\pi_1^\varepsilon}{2\lambda_1},\hat{h}_2(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\frac{\sqrt{\varepsilon}\pi_2^\varepsilon}{2\lambda_2},\hat{h}_3(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\frac{\sqrt{\varepsilon}\pi_3^\varepsilon}{2\lambda_3}\right)\right|\right|_{L^\infty(\mathscr{Q})}\\
&\leq\left|\left|\frac{\sqrt{\varepsilon}\pi_1^\varepsilon}{2\lambda_1}\right|\right|_{L^\infty(\mathscr{Q}_1)}+\sum_{i=2}^{3}\left|\left|\frac{\sqrt{\varepsilon}\pi_i^\varepsilon}{2\lambda_i}\right|\right|_{L^\infty(\mathscr{Q}_2)}\leq\sqrt{\varepsilon}\sum_{i=1}^{3}\frac{1}{2\lambda_i}.
\end{aligned}\tag{44}$$

Consequently, from (43)-(44), we have

$$\begin{aligned}
&||h^*-h_\varepsilon||_{L^\infty(\mathscr{Q})}=\\
&\left|\left|\mathscr{F}(h^*)-\mathscr{L}\left(\hat{h}_1(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\tfrac{\sqrt{\varepsilon}\pi_1^\varepsilon}{2\lambda_1},\hat{h}_2(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\tfrac{\sqrt{\varepsilon}\pi_2^\varepsilon}{2\lambda_2},\hat{h}_3(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\tfrac{\sqrt{\varepsilon}\pi_3^\varepsilon}{2\lambda_3}\right)\right|\right|_{L^\infty(\mathscr{Q})}\leq\\
&||\mathscr{F}(h^*)-\mathscr{F}(h_\varepsilon)||_{L^\infty(\mathscr{Q})}\\
&+\left|\left|\mathscr{F}(h_\varepsilon)-\mathscr{L}\left(\hat{h}_1(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\tfrac{\sqrt{\varepsilon}\pi_1^\varepsilon}{2\lambda_1},\hat{h}_2(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\tfrac{\sqrt{\varepsilon}\pi_2^\varepsilon}{2\lambda_2},\hat{h}_3(w^{h_\varepsilon},\lambda^{h_\varepsilon})+\tfrac{\sqrt{\varepsilon}\pi_3^\varepsilon}{2\lambda_3}\right)\right|\right|_{L^\infty(\mathscr{Q})}\\
&\leq T_f C_{11}||h^*-h_\varepsilon||_{L^\infty(\mathscr{Q})}\textstyle\sum_{i=1}^{3}\frac{1}{2\lambda_i}+\sqrt{\varepsilon}\sum_{i=1}^{3}\frac{1}{2\lambda_i}.
\end{aligned}$$

Since $T_f\sum_{i=1}^{3}\frac{1}{2\lambda_i}$ is sufficiently small, it comes

$$||h^*-h_\varepsilon||_{L^\infty(\mathscr{Q})}\leq\sqrt{\varepsilon}\left[1-T_f C_{11}\sum_{i=1}^{3}\frac{1}{2\lambda_i}\right]^{-1}\sum_{i=1}^{3}\frac{1}{2\lambda_i},$$

thus $h_\varepsilon\to h^*$ in $L^\infty(\mathscr{Q})$ and by (41) (as $\varepsilon\to 0$)

$$\mathscr{J}(h^*)=\inf_{h\in\mathscr{U}}\mathscr{J}(h).$$

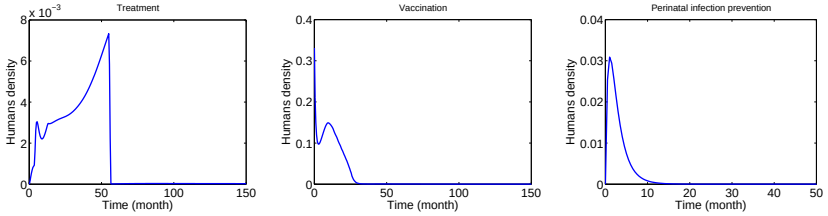

Fig. 3: Optimal balance of multiple controls. Using the three controls, the proportions of people receiving treatment and people being vaccinated are shown in the first two frames, while the proportion of immune newborns from perinatal infection is shown in the third frame. See Table 4 for the costs of different strategies.

3.5 Numerical simulations

Cost coefficients are fixed within the objective functional (33) and the optimal schedule of the three controls over $T_f = 130$ months is simulated.

As Figure 3 illustrates, optimal results provide clearly different strategies for relative application of immunization of newborns from perinatal infection, vaccination of young adults and treatment of infected individuals. The optimal control schemes shows that vaccinating at maximum rates initially is optimal in preventing deaths regardless of the population's ratio of asymptomatic to symptomatic infections (see proportion of people being vaccinated, Fig. 3). Vaccination of young adults can greatly reduce the total number of infected individuals and is crucial to apply during the first few months of the disease detection. Even in the absence of the other controls (treatment of symptomatic infection and immunization of newborns from perinatal infection), immediate vaccination of young adults remains a cost-effective method of minimizing death by preventing severe infections.

Optimal three-part intervention strategies provide considerable reductions in the severity of the projected outbreaks (see Fig. 4). HBV death is reduced by 81.9% during the outbreak period. Significant reduction of greater than 55% (resp. 13%) is also achieved in peak number of symptomatic (resp. asymptomatic) infections.

Let us notice that the optimal control problem can be formulated to find the optimal strategy of each intervention method when used alone. Assuming only one of the three controls is feasible, we set the remaining two controls to identically zero in the system (31) and in the objective functional (33). Using parameters value in Tab. 1 and cost coefficients in Tab. 3, the optimal schedule of each intervention method is determined numerically. In the absence of vaccination of young adults and immunization of newborns from perinatal infection, the optimal quantity of treatment nearly triples due to an increased number on symptomatic infections. Fig. 5 displays the corresponding asymptomatic and symptomatic infected populations resulting from each of the optimal single intervention strategies as well as those corresponding to the optimal strategy balancing all three controls.

In optimal schedule of treatment alone reduces the number of deaths by 5.5% (cost 991.3 USD). The optimal applications of vaccination of young adults alone

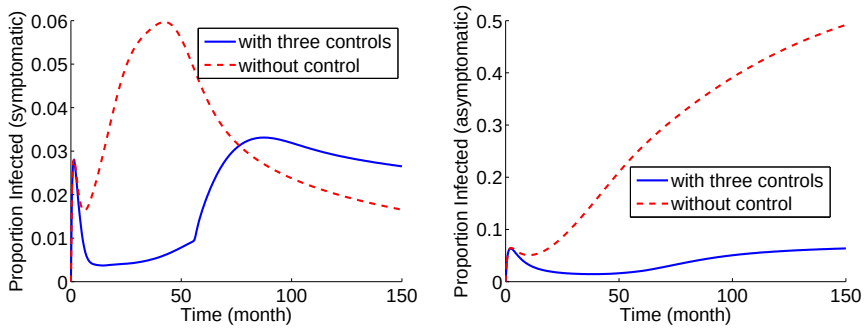

Fig. 4: Dynamics of two infected classes (symptomatic and asymptomatic). Dotted curves correspond to outbreak dynamics without controls. Solid curves indicates the alleviated outbreak dynamics with multiple controls strategy. Solid curves indicate a considerable reduction in the size of the infectious classes.

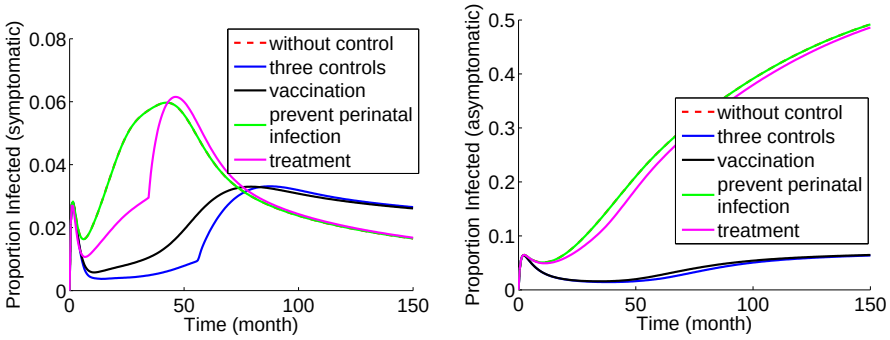

Fig. 5: Dynamics of two infected classes (symptomatic and asymptomatic) of one control and multiple controls. Comparing the optimal strategies for each single control, the strategy comprise of only vaccination of young adults is most effective in reducing the size of both infected classes during the outbreak while also reducing the death toll. In the absence of the other two controls, prevention of perinatal infections does little to reduce the size of the epidemic for both infected classes. The treatment of symptomatic infections is effective in decreasing the size of symptomatic infected classes. According to our model, the optimal strategy balancing the three controls is close to the strategy comprise of only vaccination of young adults. (Color figure online).

and immunization of newborns from perinatal infection alone reduce the number of deaths by 79.8% (cost 3.7617×10^5 USD) and 0.02% (cost 428.6 USD), respectively. The prevention of perinatal infection (only) has no effect on the outbreack of the disease. The optimal strategy balancing of three controls (or vaccination of young adults) is considerably more effective in reducing both HBV-related death and total infections than the treatment of symptomatic infections. But the strategy of three controls (or vaccination) is approximately 386 times much expensive than the treatment of symptomatic infections (but 15 times more effective in reducing both HBV-related death and total infections than the treatment only).

Table 4: Costs of intervention strategies.

Intervention:	Prevent perinatal infection	Treatment of symptomatic infection	Vaccination of young adults	Three intervention strategies
Costs (USD):	428.6	991.3	3.7617×10^5	3.8335×10^5

4 Conclusion and Discussions

Hepatitis B virus (HBV) infection is endemic in many parts of the world. One of the characteristics of HBV transmission is the age structure of the host population and the vertical transmission of the disease (perinatal infection from carrier mothers).

In this paper, we proposed an age-structured model for the transmission dynamics of HBV with differential infectivity: symptomatic and asymptomatic infections. We discussed the existence and stability of the disease-free and disease-endemic equilibria of the model in terms of the basic reproduction number and performed sensitivity analysis of the parameters. Then, we consider three intervention options (called controls): vaccination of young adults, prevention of HBV perinatal infections and treatment of symptomatic HBV infections. The analytical results and numerical simulations of the model suggest that a optimal control strategy is a combination of immunization of young adults (at least susceptible with the age less than 5 years old) and treatment of HBV symptomatic infections.

We also observe that mass vaccination in infants increases the average age of infection in unimmunized individuals and shifts the average age at infection to older age groups (see Fig. 6). This indicates that mass vaccination in infants might be not enough to control the infection and eradicate the virus (this is also supported by Zou et al.[42]). Different immunization programs can be evaluated by considering the prevalence of carriers after the implementation of immunization.

A Proof of Claim 2.3.2

The positive operator $T(0)$ has the Perron-Frobenius properties, roughly speaking, $T(z)$ is irreducible and $r(T(z))$ is decreasing for real $z\in(-v_{min},+\infty)$. Moreover, $\lim_{z\to-v_{min}} r(T(z))=+\infty$ and $\lim_{z\to+\infty} r(T(z))=$

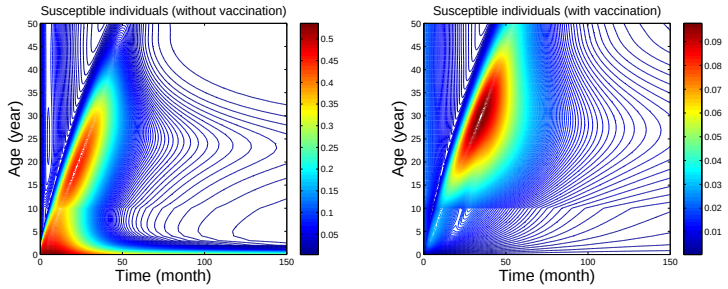

Fig. 6: Dynamics of susceptible individuals without any control and with vaccination strategy only. Mass vaccination in infants (with maximum of 5 years old) increases the average age of infection in unimmunized individuals (Color figure online).

0; then the first half of the proposition is the direct consequence of this monotonicity of $r(T(z))$. Next we show the dominant property of z_0. For any $z \in \Sigma^0 \setminus \{z_0\}$, there is an vector ψ_z, such that $T(z)\psi_z = \psi_z$. Then we have $|\psi_z| = |T(z)\psi_z| \leq T(R_e z)|\psi_z|$. The eigenspace corresponding to the eigenvalue $r(T(R_e z))$ is one-dimensional subspace of $\mathbb{R}^4$ spanned by a strictly positive functional $F_{R_e z}$. We obtain that

$$r(T(R_e z))[F_{R_e z}, |\psi_z|] = [F_{R_e z}, T(R_e z)|\psi_z|] \geq [F_{R_e z}, |\psi_z|],$$

where we write the value of $F_{R_e z}$ at ψ_z as $[F_{R_e z}, \psi_z]$. Hence we have $r(T(R_e z)) \geq 1$ and $R_e z \leq z_0$ because $r(T(z))$ is strictly deceasing for $z \in (-\mu_1, +\infty)$ and $r(T(R_e z_0)) = 1$. This end the proof of Claim 2.3.2.

B Proof of Theorem 4

The coordinates of $\mathbf{E}^*$ satisfied

$$\begin{aligned}
s(a) &= \theta b(1-\nu C)e^{-\int_0^a (\beta(\sigma)(I+\tau C)+p(\sigma))d\sigma} \\
&\quad + \psi \int_0^a \nu(\eta) e^{-\int_\eta^a (\beta(\sigma)(I+\tau C)+p(\sigma))d\sigma} d\eta, \qquad (45) \\
L_i &= \frac{I+\tau C}{\mu_1+\gamma} \int_0^\omega \beta(a)\alpha(a) l(a) h(I,C,a) da, \\
L_c &= \frac{I+\tau C}{\mu_1+\delta} \int_0^\omega \beta(a)(1-\alpha(a)) l(a) h(I,C,a) da + \frac{b\theta\nu C}{\mu_1+\delta}, \\
I &= \frac{\gamma(I+\tau C)}{(\mu_1+\gamma)(\mu_1+\mu_I+\gamma_1)} \int_0^\omega \beta(a)\alpha(a) l(a) h(I,C,a) da, \qquad (46) \\
C &= \frac{\delta(I+\tau C)}{(\mu_1+\delta)(\mu_1+\mu_c+\gamma_2)} \int_0^\omega \beta(a)(1-\alpha(a)) l(a) h(I,C,a) da \\
&\quad + \frac{\delta b\theta\nu C}{(\mu_1+\delta)(\mu_1+\mu_c+\gamma_2)}, \qquad (47) \\
\nu(a) &= b(1-\theta)e^{-\psi a} + \int_0^a p(\eta) s(\eta) e^{-\psi(a-\eta)} d\eta, \\
R &= \frac{\gamma_1 I + \gamma_2 C}{\mu_1}.
\end{aligned}$$

wherein $h(I,C,a)$ is the right-hand side of (45).

Using equations (46) and (47) we have the following fixed point equation $H(I,C)^T = (I,C)^T$; where $H(I,C)^T = \big(H_1(I,C), H_2(I,C)\big)^T$ and $H_1(I,C)$; $H_2(I,C)$ are respectively the right-hand side of equations (46) and (47).

Thus the equilibrium points are fixed points of H given by

$$H(I,C)^T = (I,C)^T. \tag{48}$$

The equation (48) implies that at the endemic steady state the infected population simply reproduce itself. Therefore we can call H the next generation operator at the endemic steady state. This fact is used to show the stability of the endemic steady state in Section 2.3.3.

We use (48) to prove existence and uniqueness of an endemic equilibrium point. Then we use a theorem for the existence and uniqueness of a positive fixed point of a multi-variable function (see Hethcote and Thieme [24], Theorem 2.1).

In fact $H(I,C)$ is continuous, bounded function. Since $h(0,0,.) = s^0(.)$ (the disease-free steady state) and H infinitely differentiable, then the Jacobian at point $(0,0)$ is given by

$$H'(0,0) = \begin{pmatrix} \frac{\gamma \mathscr{K}_i}{(\mu_1+\gamma)(\mu_1+\mu_I+\gamma_1)} & \frac{\gamma \mathscr{K}_i}{(\mu_1+\gamma)(\mu_1+\mu_I+\gamma_1)} \\ \\ \frac{\delta \mathscr{K}_c}{(\mu_1+\delta)(\mu_1+\mu_c+\gamma_2)} & \frac{\delta(\mathscr{K}_c+b\theta v)}{(\mu_1+\delta)(\mu_1+\mu_c+\gamma_2)} \end{pmatrix}$$

Thus the function $H(I,C)$ is monotone non-decreasing and $H(0,0) = (0,0)$. Note that $\rho(H'(0,0)) = \mathscr{R}_0 > 1$. Thanks the graph theory, we claim that $H'(0,0)$ is irreducible because the associated graph of the matrix is strongly connected.

Let us now prove that H is strictly sub linear, i.e., $H(rI,rC) > rH(I,C)$, for any $(I,C) > 0$ and $r \in (0,1)$. For instance

$$\frac{rH_1(I,C)}{H_1(rI,rC)} = \frac{r\int_0^\omega \beta(a)(1-\alpha(a))l(a)h(I,C,a)da}{\int_0^\omega \beta(a)(1-\alpha(a))l(a)h(rI,rC,a)da} \leq r < 1;$$

and the same argument gives that $\frac{rH_2(I,C)}{H_2(rI,rC)} < 1$. In this way we end the proof of Theorem 4.

C Proof of Lemma 6

1. Let us set $w^h := (S^h, V^h, L_i^h, I^h, L_c^h, C^h)$ and the same for w^v. Using the Volterra integral formulation and system (31), we find that

$$||S^h - S^v||_{L^1(\mathscr{Q}_1)} + ||V^h - V^v||_{L^1(\mathscr{Q}_1)} \leq T_f C_4(||w^h - w^v||_{L^1(\mathscr{X})} + ||h - v||_{L^1(\mathscr{Q})} + ||h_1(.,0) - v_1(.,0)||_{L^1(\mathscr{Q}_2)}).$$

We also find that

$$||(L_i^h, I^h, L_c^h, C^h) - (L_i^v, I^v, L_c^v, C^v)||_{L^1(\mathscr{Q}_2)} \leq T_f C_5(||w^h - w^v||_{L^1(\mathscr{X})} + ||h - v||_{L^1(\mathscr{Q})} + ||h_1(.,0) - v_1(.,0)||_{L^1(\mathscr{Q}_2)}).$$

Then, for T_f sufficiently small,

$$||w^h - w^v||_{L^1(\mathscr{X})} \leq T_f C_1 ||h - v||_{L^1(\mathscr{Q})}.$$

The same arguments can be apply for the second estimate of item 1. and for item 2. It remains to check item 3.

3. We suppose that $h_n := (h_{1n}, h_{2n}, h_{3n}) \to h := (h_1, h_2, h_3)$ in $L^1(\mathscr{Q}$. Possibly along a subsequence (using the same notation), $h_n^2 \to h^2$ a.e. on $\mathscr{Q}$ by (see [18], p.21). By Lebesgue's dominated convergence theorem, it comes $\lim_{n\to\infty} ||h_n^2||_{L^1(\mathscr{Q})} = ||h^2||_{L^1(\mathscr{Q})}$. We have the similar arguments for $||v^2||_{L^1(\mathscr{Q})}$. These handle the convergence of the squared terms in our functional.

Next, we illustrate the convergence of one term in the functional,

$$\begin{aligned} ||B_1(h_{1n}S^{h_n} - h_1 S^h)||_{L^1(\mathscr{Q}_1)} &\leq ||B_1||_\infty \tfrac{b}{\mu_1} ||h_n - h||_{L^1(\mathscr{Q})} + ||B_1||_\infty ||h_{1max}||_\infty ||w^{h_n} - w^h||_{L^1(\mathscr{X})} \\ &\leq C_6(T_f)||h_n - h||_{L^1(\mathscr{Q})}. \end{aligned}$$

Therefore,

$$|\mathscr{J}(h_n) - \mathscr{J}(h)| \leq C_7(T_f)||h_n - h||_{L^1(\mathscr{Q})}.$$

Hence we have the lower semi-continuity, $\mathscr{J}(h) \leq \liminf_{n\to\infty} \mathscr{J}(h_n)$.

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Optimal control using state-dependent Riccati equation of lost of sight in a tuberculosis model

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Abstract This paper deals with the problem of optimal control for the transmission dynamics of tuberculosis (TB). A TB model which considers the existence of a new class (mainly in the African context) is considered: the lost of sight individuals. Based on the model formulated and studied in Tewa and Bowong (Commun Nonlinear Sci Numer Simul 14:4010–4021, 2009), the TB control is formulated and solved as an optimal control theory problem using state-dependent Riccati equation. This control strategy indicates how the control of the class of lost of sight can considerably influence the basic reproduction ratio so as to reduce their number. Numerical results illustrate the performance of the optimization strategy.

Keywords Nonlinear dynamical systems · Tuberculosis models · Basic reproduction ratio · Optimal control · Lost of sight

Mathematics Subject Classification 92D25 · 49K15 · 34D23 · 92D30 · 49J15

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1 Introduction

Tuberculosis (TB) is a disease caused by infection with Mycobacterium tuberculosis, which most frequently affects the lungs (pulmonary TB). At present, about 95 % of the estimated 8 million new cases of TB occurring each year are in developing countries, where 80 % occur among people between the ages of 15 and 59 Dye et al. (1999). In Sub-Saharan Africa, TB is the leading cause of mortality, and in developing countries it accounts for an estimated 2 million deaths which accounts for a quarter of avoidable adult deaths Raviglione et al. (1997). TB was assumed to be on its way out in developed countries until the number of TB cases began to increase in the 1980s. With this return, we face the paradox of a well-known bacteria, fully treatable with efficient and affordable drugs according to internationally recommended guidelines, which yet causes increasing human suffering and death. As the world is experiencing the devastating effect of HIV/AIDS epidemic, it is now necessary to ask why we have so far failed to control TB and define the limits of the global TB control programs Raviglione (2002). Currently, half of the people living with HIV are TB co-infected and three quarters of all dually infected people live in Sub-Saharan Africa. In Cameroon for example, it is estimated that in the absence of effective epidemiology statistics, there are 100 new cases for 100,000 habitants per year Bercion and Kuaban (1998). As it is the case in many subsaharian African countries, the fight against tuberculosis (TB) in Cameroon is difficult due to the interaction with the Human Immunodeficiency Virus (HIV) Global Tuberculosis Control (2005) and particularly with the poor socio-economic conditions. We note that, the statistic studies Boulahbal and Chaulet (2004) prove that many infectious patients do not take their treatment until the end due to a brief relief or a long time for complete treatment. Otherwise, some of those individuals can transmit the disease without presenting any symptom. In this work, we call them lost of sight individuals. In Cameroon, for example, for a national program of fight against TB , there is about 10 % of infectious individuals who do not end their treatment and become lost of sight individuals. Lost of sight individuals are very dangerous for human health, because they are able to transmit the disease very quickly and discreetly.

In the literature, there are many TB mathematical models Feng and Castillo-Chavez (1998), Blower et al. (1996), Bowong et al. (2010). The study of these models has an impact in the control process of the disease. Most of those models are SEIR-models; for those models, one supposes that the population is subdivided into four epidemiological classes: susceptible individuals, latently infected individuals (those who are infected but not infectious yet), infectious and the recovered or cured individuals. The particularity of those type of models is that, the rate at which susceptible individuals become latently infected or infectious is a function of infectious individuals number in a population at that time. The class of loss of sight individuals class (L) has already been taken into account by some authors Tewa and Bowong (2009), Bowong et al. (2010). Tewa and Bowong (2009) studied an SEIL-tuberculosis model in which they took into account the low and fast progression of susceptibles to latently infected and infectious classes, respectively. This model also takes into account infectious individuals on chemoprophylaxis, and they introduce a constant rate to become cured individuals. In (2010), Bowong deals with the problem of optimal control for the transmission dynamics of tuberculosis for an SEI-tuberculosis model using state-dependent Riccati equations. The feedback control is proved to be capable to reduce the number of individuals with active TB.

This paper considers the optimal control problem of the dynamic transmission of tuberculosis. We present a SEIL-tuberculosis model [based on the model presented in Tewa and Bowong (2009)] that incorporates the control mechanism, representing the case finding efforts. This is incorporated by adding a control term so that the rate at which infectious

individuals become lost of sight individuals will be reduced. Our model also presents the essential biological and epidemiological features of the disease such as exogenous reinfection and chemoprophylaxis of latently infected individuals. The model is shown to exhibit the phenomenon of backward bifurcation, where a stable disease-free equilibrium coexists with one or more stable endemic equilibria when the associated basic reproduction number is less than unity. Comparing to existing results Bowong (2010), our work differs from these studies in that we completely analyse a SEIL-tuberculosis model that incorporates the control mechanism and we address the question of controlling the disease, our policy based on decreasing the number of people going to the class of lost of sight individuals. We first formulate a mathematical model taking into account our control mechanism. Then, we perfect a mathematical analysis of the controlled model where we compute the basic reproduction ratio of the controlled system. We then define a cost function so that we could deduce the optimal control function. A huge part of this work is to compute the solutions numerically and then draw a conclusion about the efficiency of the control. Numerical simulation shows that the proposed optimal algorithm permits the reduction of the number of lost of sight individuals accounting the control effort.

2 The model

We consider a population of N people. We assume that latently infected individuals (inactive TB) have a variable (typically long) latency period. At any given time, an individual is in one of the following four states: susceptible, latently infected (i.e., exposed to TB but are not infectious yet), infectious (i.e., have active TB but are in a care center) and lost of sight (i.e., have active TB but are not in a care center). We will denote these states by S, E, I and L. Every recruitment is into the susceptible class, and occurs at a constant rate Λ. The transmission of tuberculosis occurs following an adequate contact between a susceptible individual and an infectious individual or between a susceptible individual and a lost of sight who is still infectious. On an adequate contact with infectious or lost of sight, a susceptible individual becomes infected but not infectious yet. This individual remains in the latently infected class for some latent period. Since we do not know if lost of sight individuals are recovered, died or are still infectious, we assume that a fraction δ of them is still infectious and can transmit disease to susceptible. We use the standard mass balance incidence expressions βSI and $\beta\delta SL$ to indicate the successful transmission of tuberculosis due to nonlinear contact dynamics in the population. After receiving an effective therapy, individuals leave the infectious class I to the latently infected class E at the rate r_2. We assume that chemoprophylaxis of latently infected individuals reduce their reactivation at a constant rate r_1. Another assumption is that among the fraction $1 - r_2$ of infectious who did not recover, some of them who had begun their treatment would not return to the hospital for the examination of sputum at a constant rate ϕ and enter the class of lost of sight L. After some times, some of them will continue to suffer from the disease and will return to the hospital at a constant rate γ. The constant rate for non-disease related death is μ, thus $1/\mu$ is the average lifetime. Infectious and lost to follow-up have additional death rates due to TB-induce mortality with constant rates d_1 and d_2, 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 TB, an individual will remain so for unless reactivation occurs. To account for treatment, we define $r_1 E$ as the fraction of infected individuals receiving effective chemoprophylaxis. We assume that chemoprophylaxis of latently infected individuals E reduces their reactivation at rate r_1. Thus, a fraction $(1 - r_1)E$ of infected indi-

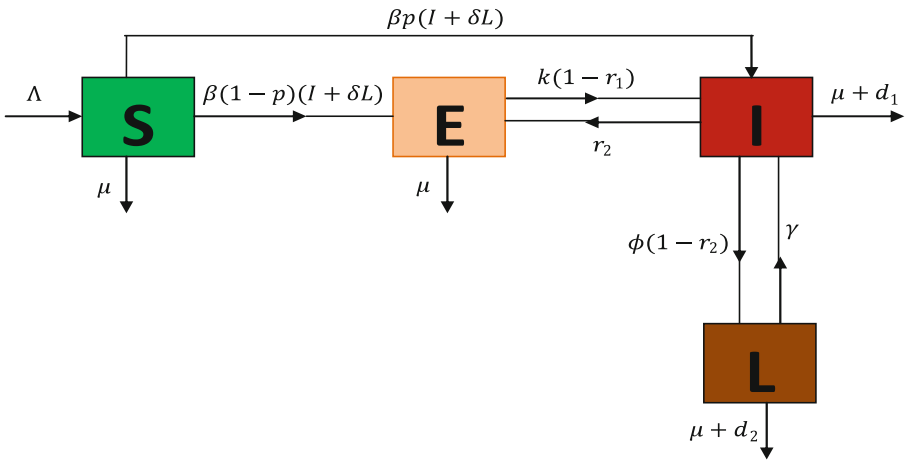

Fig. 1 Flow diagram of the model without control

viduals who does not receive chemoprophylaxis becomes infectious with a rate k, so that $1/k$ is the average latent period. Thus, individuals leave the class E to I at the rate $k(1-r_1)$.

Thus, the corresponding transfer diagram is given by Fig. 1 [see Tewa and Bowong (2009)].

We have $N = S + E + I + L$ individuals.

The above scheme leads to the following differential system:

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

2.1 The control and its policy

The aim of the control is to decrease the total number of the lost of sight patients during a period of time t_f. The strategy of control we adopt consists of introducing one control parameter $v(t)$ representing the effort made to take the infectious patients in a health center in charge systematically.

Having introduced the functions $v(t)$, we obtain the following compartmental model.

The Fig. 2 leads us to the following differential system:

$$\begin{cases} \dot{S} = \Lambda - \mu S - \beta(I+\delta L)S; \\ \dot{E} = \beta(1-p)(I+\delta L)S + r_2 I - [\mu + k(1-r_1)]E; \\ \dot{I} = \beta p(I+\delta L)S + k(1-r_1)E + \gamma L \\ \qquad -[r_2 + \mu + d_1 + \Phi(1-v)(1-r_2)]I; \\ \dot{L} = \Phi(1-v)(1-r_2)I - (\gamma + \mu + d_2)L. \end{cases} \tag{1}$$

with initial conditions $(S(0); E(0); I(0); L(0)) \in \mathbb{R}^4_+$.

Remark 2.1 The functions $v(t)$ are assumed to be integrable in the sense of Lebesgue, bounded with $(0 \leq v(t) \leq 1)$. When the control functions are near to 1, the control is very strict.

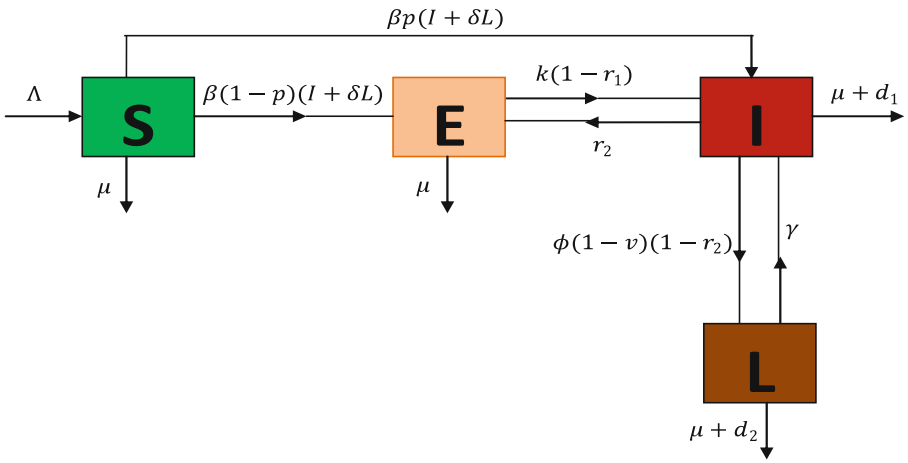

Fig. 2 Flow diagram of the model with control

3 Mathematical analysis of the model with control

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

$$\begin{cases} \dot{S} = \varphi(S) - S\langle \eta, Y\rangle; \\ \dot{Y} = S\langle \eta, Y\rangle B + A(t)Y. \end{cases} \tag{2}$$

where S is a state representing the compartment of susceptible individuals, $Y = (E, I, L)^{\mathrm{T}}$is the vector representing the state compartment of different infected individuals (latently infected individuals, infectious, lost of sight individuals). $\varphi(S) = \Lambda - \mu S$ is a function that depends on $S \in \mathbb{R}_+$, $\eta = (0, \beta, \beta\delta)^{\mathrm{T}}$, $B = (1-p, p, 0)$ and $\langle , \rangle$ is the usual scalar product in $\mathbb{R}^3$ and A is a Metzler Berman and Plemmons (1994) 3×3 non-constant matrix defined as

$$A(t) = \begin{bmatrix} -A_1 & r_2 & 0 \\ k(1-r_1) & -A_2 & \gamma \\ 0 & \phi(1-v(t))(1-r_2) & -A_3 \end{bmatrix};$$

where

$$\begin{aligned} A_1 &= \mu + k(1-r_1), \\ A_2 &= r_2 + \mu - d_1 + \phi(1-v(t))(1-r_2), \\ A_3 &= \gamma + \mu + d_2. \end{aligned}$$

Remark 3.1 The dynamic of the susceptibles is asymptotically stable. In other words, for the system

$$\dot{S} = \varphi(S);$$

there exists a unique equilibrium $S_0 = \frac{\Lambda}{\mu}$ such that

$$\begin{aligned} \varphi(S) &> 0 \quad \text{for } 0 < S < S_0, \\ \varphi(S) &< 0 \quad \text{for } S_0 < S. \end{aligned} \tag{3}$$

3.1 Positive invariance of the non-negative orthant

We have the following result:

Proposition 3.2 *The non-negative orthant* $\mathbb{R}^4_+$ *is positively invariant for the system* (2).

Proof The system (2) can be written as

$$\begin{cases} \dot{S} = \varphi(S) - S\langle \eta, Y\rangle, \\ \dot{Y} = (SB\eta^{\mathrm{T}} + A(t))Y. \end{cases} \tag{4}$$

The first equation of system (4) implies that

$$KS(t) = KS_0 \mathrm{e}^{-K(t-t_0)} + \Lambda(1 - \mathrm{e}^{-K(t-t_0)}),$$

for $t \geq t_0$; where $K = \mu + \beta(I + \delta L)$. For $I \geq 0$; $L \geq 0$ and $S_0 \geq 0$ it comes that $S(t) \geq 0 \ \ \forall t \geq t_0$. As consequence, $\mathbb{R}_+$ is invariant for the system $\dot{S} = \varphi(S) - S\langle \eta, Y\rangle$. Since $S \geq 0$, the matrix $(SB\eta^{\mathrm{T}} + A(t))$ is a Metzler matrix. And it is well known that linear Metzler matrices let invariant the non-negative orthant. This proves the positive invariance of the non-negative orthant $\mathbb{R}^4_+$ for the system (2) □

3.2 Boundedness of trajectories

Adding all equations of model (2), one has

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

Thus, one can deduce that

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

Integrating the previous inequality we obtain

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

Therefore,

$$\lim_{t \to +\infty} N(t) \leq S_0.$$

It is straightforward to prove that for $\epsilon > 0$ the simplex

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

is a compact invariant set for the system (2) and that this set is absorbing. So, we limit our study to this simplex.

3.3 Basic reproduction ratio

The basic reproduction ratio is the average number of secondary cases produced by a single infective individual which is introduced into an entirely susceptible population. We are going to compute the basic reproduction ratio of the system with control, and then deduce the basic reproduction ratio of the system without control.

Proposition 3.3 *The basic reproduction ratio* $R_0(v)$ *of system* (1), *with the control function* v, *is given by*

$$R_0(v) = \frac{\beta S_0}{R_{03}(v)}(R_{01} + \delta R_{02}(v)); \tag{5}$$

where

$$\begin{aligned} R_{0,1} &= (\mu + d_2 + \gamma)(p\mu + k(1 - r_1)), \\ R_{0,2}(v) &= \phi(1 - v)(1 - r_2)(\mu + k(1 - r_1)), \\ R_{03}(v) &= r_2\mu(\mu + d_2) + (\mu + k(1 - r_1))[\gamma(\mu + d_1) \\ &\quad + (\mu + d_2)(\mu + d_1 + \phi(1 - v)(1 - r_2))]. \end{aligned}$$

Proof The system (2) has an evident equilibrium $(S_0, 0, 0, 0)$ where there is no disease. This equilibrium is the disease free equilibrium (DFE). We calculate the basic reproduction ratio, $R_0(v)$, using the Van Den Driesseche and Watmough next generation approach Driessche (2002) and the techniques reported in Refs. Luenberger (1979), Diekmann et al. (1990). In order to compute the basic reproduction ratio, it is important to distinguish new infections from all other class transitions in the population. The infected classes are I, E and L. We can write system (2) as

$$\dot{x} = \mathcal{F}(x) - \mathcal{V}(x) = \mathcal{F}(x) - (\mathcal{V}^+(x) - \mathcal{V}^-(x)) \tag{6}$$

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

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

and

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

The Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$ at the disease free equilibrium DFE can be partitioned as

$$D\mathcal{F}(\mathrm{DFE}) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad D\mathcal{V}(\mathrm{DFE}) = \begin{bmatrix} V & 0 \\ 0 & 0 \end{bmatrix}$$

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

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

and

$$V = \begin{pmatrix} A_1 & -r_2 & 0 \\ -k(1 - r_1) & A_2 & -\gamma \\ 0 & -\phi(1 - v)(1 - r_2) & A_3 \end{pmatrix}.$$

The basic reproduction ratio is defined, following Van den Driessche and Watmough Driessche (2002), as the spectral radius of the next generation matrix, FV^{-1}. □

From $R_0(v)$, we deduce $R_0(0)$ (basic reproduction ratio of the system without control) by taking $v \equiv (0, 0)$. We are going to compare $R_0(v)$ and $R_0(0)$.

Let us assume that

H1 : $(\mu + d_2)(\mu + \gamma + r_2) \leq \delta[(\mu + d_1)(\mu + d_2 + \gamma) + r_2\mu(\mu + d_1 + \gamma)]$

Assumption **H1** can be interpreted as: *The number of secondary cases generated by an individual in infection state I is less than or equal to the number of secondary cases generated by an individual in infection state L.*

Proposition 3.4 *We have $R_0(v) \leq R_0(0)$ (i.e., the basic reproduction ratio of the system with control is less than or equal to the one without control) if and only if assumption **H1** is satisfied.*

Proof It is easily checked that

$$R_0(v) - R_0(0) = \frac{\beta S_0[p\mu - k(1-r_1)]\phi(1-r_2)v}{[\mu + k(1-r_1)]R_{0,2}(0)R_{0,2}(v)}[(\mu+d_2)(\mu+\gamma+r_2) \\ -\delta[(\mu+d_1)(\mu+\gamma+d_2)+r_2\mu(\mu+\gamma+d_1)]]$$

This ends the proof. □

3.4 Equilibria

The equilibrium (S, Y) on system (2) can be obtained by setting the right hand side of all the equations in model (2) equal to zero, that is,

$$\begin{cases} \varphi(S) - S\langle \eta, Y\rangle = 0; \\ S\langle \eta, Y\rangle B + A(t)Y = 0. \end{cases} \tag{7}$$

From the second equation of (7), one has $Y = S(-A^{-1}(t))\langle \eta, Y\rangle B$. And replacing in $\langle \eta, Y\rangle$ yields

$$\langle \eta, Y\rangle = S\langle \eta, (-A^{-1}(t))B\rangle\langle \eta, Y\rangle. \tag{8}$$

The case $\langle \eta, Y\rangle = 0$ implies $\varphi(S) = 0$ and $A(t)Y = 0$. Since A is non-singular, this gives the disease free equilibrium $P^0 = (S_0, 0, 0, 0)$.
The case $\langle \eta, Y\rangle \neq 0$ implies $S^* = \frac{S_0}{R_0(v)}$. From (7), we have $Y^* = (E^*, I^*, L^*)^{\mathrm{T}} = (-A^{-1}(t)B\varphi(S^*)$.
After calculations, we obtained that with $R_0(v) > 1$, the model (2) has a unique endemic equilibrium $P^*(v) = (S^*(v), E^*(v), I^*(v), L^*(v))$ which is in the non-negative orthant $\mathbb{R}^4_+$ given by

$$\begin{aligned} S^*(v) &= \frac{S_0}{R_0(v)}; \\ E^*(v) &= \frac{Q_1\Lambda}{R_{0,2}(v)}\left(1 - \frac{1}{R_0(v)}\right); \\ I^*(v) &= \frac{Q_2\Lambda}{R_{0,2}(v)}\left(1 - \frac{1}{R_0(v)}\right); \\ L^*(v) &= \frac{Q_3(v)\Lambda}{R_{0,2}(v)}\left(1 - \frac{1}{R_0(v)}\right); \end{aligned} \tag{9}$$

where

$$\begin{aligned} Q_1 &= r_2 p(\gamma + \mu + d_2) + (r_2 + \mu + d_1)(1-p)\gamma \\ &\quad + (1-p)(\mu + d_2)[r_2 + \mu + d_1 + \phi(1-r_2)]; \\ Q_2 &= (1-p)k(1-r_1)(\mu + d_2) + (1-p)\gamma k(1-r_1) \\ &\quad + p(\gamma_1 + \mu + d_2)[\mu + k(1-r_1)]; \\ Q_3(v) &= \phi(1-v)k(1-r_1) + \phi(1-v)\mu p. \end{aligned}$$

Lemma 3.5 Tewa and Bowong (2009) *When* $R_0(v) > 1$, *model* (2) *has a unique endemic equilibrium defined by* (9).

Remark 3.6 Without control, it is shown in Tewa and Bowong (2009) that

- If $R_0(0) \leq 1$, the disease free equilibrium P^0 is globally asymptotically stable on the non-negative orthant $\mathbb{R}^+_4$. This means that, the disease naturally dies out in the host population.
- If $R_0(0) > 1$, then the positive endemic equilibrium $P^*(0)$ of model (2) is globally asymptotically stable on the set Ω_ϵ.

4 Optimal control

The classical epidemiological requirement of making R_0 less than unity is not longer sufficient, although necessary, for effectively controlling the spread of TB in a community.

4.1 Definition of the cost function

The system (2) can be represented by the following nonlinear structure, having state-dependent coefficients:

$$\dot{X} = \Gamma + D_1(X)X + B_1 v(t); \tag{10}$$

where $X = (S, E, I, L)^{\mathrm{T}}$; $\Gamma = (\Lambda, 0, 0, 0)^{\mathrm{T}}$; $B_1 = [0, 0, \phi(1-r_2), -\phi(1-r_2))^{\mathrm{T}}$ and

$$D_1(X) = \begin{bmatrix} -\mu - \beta(I + \delta L) & 0 & 0 & 0 \\ \beta(1-p)(I + \delta L) & -\mu - k(1-r_1) & r_2 & 0 \\ \beta(I + \delta L) & k(1-r_1) & -\mu - d_1 - \phi(1-r_1) & \gamma \\ 0 & 0 & \phi(1-r_2) & -\mu - d_2 - \gamma \end{bmatrix}.$$

Remark 4.1 The factorization of state system (2) to the form (10) is not unique, specially for the term $D_1(X)X$. The controllability issue of such technique is fully discussed in Cloutier et al. (1996).

Proposition 4.2 *The system* (10) *can be written as*

$$\dot{Y} = D_2(Y)Y + B_2 v(t); \tag{11}$$

where $Y = (X, 1)^{\mathrm{T}}$ *and* $B_2 = [B_1, 0]^{\mathrm{T}}$ *are* $\mathbb{R}^5$ *vectors.* $D_2 = \begin{bmatrix} D_1(X) & \Gamma \\ 0 & 0 \end{bmatrix}$ *is a* 5×5 *state-dependent matrix.*

Proof It is easy to prove this proposition as follows: the system (10) is equivalent to the following state-dependent system

$$\begin{pmatrix} \dot{X} \\ 1 \end{pmatrix} = \begin{bmatrix} D_1(X) & \Gamma \\ 0 & 0 \end{bmatrix} \begin{pmatrix} X \\ 1 \end{pmatrix} + \begin{pmatrix} B_1 \\ 0 \end{pmatrix} v$$

□

Let λ be the cost associated to the control $v(t)$; $t \in [0, t_f]$. λ represents the necessary means to realize the control defined by v. Our cost function is the following:

$$J(v) = \frac{1}{2} \int_0^{t_f} [L(t)^2 + \lambda v(t)^2] \, \mathrm{d}t.$$

The cost function is defined having in mind that, we are going to penalize the number of lost of sight individuals. This justifies the presence of the term L. The functional J can be rewritten as

$$J(v) = \int_0^{t_f} [||Y(t)||_W^2 + ||v(t)||_V^2] \, \mathrm{d}t; \tag{12}$$

where $||Y(t)||_W^2 = Y(t)^{\mathrm{T}} W(t) Y(t)$; $||v(t)||_V^2 = v(t)^{\mathrm{T}} V(t) v(t)$; $V(t) = \frac{\lambda}{2}$ and

$$W(t) = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1/2 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \text{ is a } 5 \times 5 \text{ matrix.}$$

The matrices W and V are the ponderosity matrices.

Remark 4.3 The matrix W is positive, but not necessarily definite. The matrix V is positive definite. For example, if $W \equiv 0$ the cost function is always minimal for $v = 0$.

The problem now is to find v^* satisfying

$$J(v^*) = \min_{\Omega} J(v) \tag{13}$$

Where Ω is the control set defined by

$$\Omega = \{v \in L^2(0, t_f) : v \, measurable, 0 \leq v(t) \leq 1, t \in [0, t_f]\}. \tag{14}$$

4.2 Existence of an optimal control

The existence of the optimal control can be obtained using a result in Refs. Fleming and Rishel (1975), Hattaf and Yousfi (2011).

Theorem 4.4 *There exists an optimal control v^* such that*

$$J(v^*) = \min_{\Omega} J(v).$$

Proof To use an existence result in Fleming and Rishel (1975), we must check the following properties:

(a) The set of controls and corresponding state variables is non-empty;
(b) The control set Ω defined by (14) is convex and closed;
(c) The right hand side of the state system (1) is bounded by a linear function in the state and control variables;
(d) The integrand of the objective functional (12) is concave on Ω;
(e) There exist constants $c_1, c_2 > 0$, and $c_3 > 1$ such that the integrand $\mathcal{L}(L, v)$ of the objective functional satisfies

$$\mathcal{L}(L(t), v(t)) \geq c_2 + c_1 |v(t)|^{c_3},$$

for all $t \in [0, t_f]$.

In order to verify these conditions, we use a result by Hattaf and Yousfi (2011) to give the existence of solutions of system (1), which gives condition (a). The control set Ω is convex and closed by definition, which gives condition (b). Since our state system is linear in v, in the sense that system (1) can be represented by Eq. (10): $\dot{X} = \Gamma + D_1(X)X + B_1 v(t)$. Then the right hand side of system (1) satisfies condition (c). The integrand of the objective functional (12) is defined by $\mathcal{L}(L, v) = \frac{1}{2}(L^2 + \lambda v^2)$, with $v \in \Omega$. The second-order Fréchet derivative of $\mathcal{L}$ is positive on Ω, then $\mathcal{L}$ is concave on Ω. It is easily checked that

$$\mathcal{L}(L(t), v(t)) \geq \frac{1}{2}(L(t)^2 + \lambda v(t)^2).$$

This ends the proof. □

4.3 Resolution of the optimal problem

The theorem below gives the form of the optimized functional.

Theorem 4.5 Bowong (2010), Willard and Randal (2002), Rafikov and Balthazar (2008) *The feedback control*

$$v(t) = -V(t)^{-1} B_2(t)^{\mathrm{T}} F(t) Y(t), \tag{15}$$

minimizes the functional (12), *where the positive definite matrix* $F(t)$ *is evaluated through the solution of the matrix formulation of the Riccati differential equation* Brogan (1991)*:*

$$\begin{cases} \dot{F} = -W - D_2^{\mathrm{T}}(Y)F - F D_2(Y) + F B_2 V^{-1} B_2^{\mathrm{T}} F; \\ F(t_f) = 0. \end{cases} \tag{16}$$

Proof Let us consider the feedback control (15) with matrix F defined by (16), minimizing the functional

$$J_1(v) = \int_0^{t_f} [C(Y) + ||v(t)||_V^2] \, \mathrm{d}t; \tag{17}$$

where the function $C(Y)$ needs to be determined. According to the Dynamic Programming rules Wyse et al. (2007), one knows that if the minimum of functional J_1 exists and if V_L is a smooth function of the initial conditions, then it satisfies the following Hamilton–Jacobi–Bellman equation

$$\frac{\mathrm{d}V_L}{\mathrm{d}t} + C(Y) + ||v(t)||_V^2 = 0.$$

Considering a Lyapunov functional

$$V_L(Y) = Y^{\mathrm{T}} F(t) Y, \tag{18}$$

where $F(t)$ is a symmetric positive definite matrix which satisfies the differential Riccati equation (16). The time derivative of the function $V_L(Y)$, evaluated in the optimal state-trajectory with control given by (15), is

$$\begin{aligned} \dot{V}_L(Y) &= \dot{Y}^{\mathrm{T}} F(t) Y + Y^{\mathrm{T}} \dot{F}(t) Y + Y^{\mathrm{T}} F(t) \dot{Y}, \\ &= Y^{\mathrm{T}} [D_2^{\mathrm{T}} F(t) + \dot{F}(t) + F(t) D_2] Y + v^{\mathrm{T}} B_2^{\mathrm{T}} F(t) Y + Y^{\mathrm{T}} F(t) B_2 v, \\ &= Y^{\mathrm{T}} [\dot{F}(t) + D_2^{\mathrm{T}} F(t) + F(t) D_2 - 2F(t) B_2 V^{-1} B_2^{\mathrm{T}} F(t)] Y, \end{aligned} \tag{19}$$

and

$$\begin{aligned} ||v(t)||_V^2 &= v(t)^{\mathrm{T}} V v(t), \\ &= Y^{\mathrm{T}} F(t) B_2 V^{-1} B_2^{\mathrm{T}} F(t) Y. \end{aligned} \tag{20}$$

Substituting $\dot{V}_L$ and $||v(t)||_V^2$ into the Hamilton–Jacobi–Bellman equation (17) yields

$$Y^{\mathrm{T}} [\dot{F}(t) + D_2^{\mathrm{T}} F(t) + F(t) D_2 - F(t) B_2 V^{-1} B_2^{\mathrm{T}} F(t)] Y + C(Y) = 0. \tag{21}$$

Taking into account the fact that $F(t)$ satisfies the differential Riccati equation (16), the equation (21) becomes

$$-Y^{\mathrm{T}} W Y + C(Y) = 0;$$

i.e.,

$$C(Y) = ||Y(t)||_W^2.$$

We can conclude that, the control function (15) minimizes the functional

$$J_1(v) = \int_0^{t_f} [||Y(t)||_W^2 + ||v(t)||_V^2] \, \mathrm{d}t.$$

Note that for the positive function $C(y)$ and positive definite matrix V, the time derivative of the function (18), evaluated in the optimal trajectory of system (11), is given by

$$\dot{V}(Y) = -||Y||_W^2 - ||v(t)||_V^2;$$

and it is negative definite. Thus, the function (18) is a Lyapunov function, and the controlled system (11) is asymptotically stable. □

Remark 4.6 As we are finding our optimal control v^* into Ω, it comes from theorem (4.5) that

$$v^*(t) = \min\{\max\{a;\ -V(t)^{-1} B_2(t)^{\mathrm{T}} F(t) Y(t)\};\ b\} \text{ for all } t \in [0, t_f]$$

where $a, b \in [0, 1]$. We can also note that, this choice of v^* in the set Ω is not unique.

4.4 Determination of the control function

In this section, we are going to show step by step, how to determine the optimal functions numerically.

Remark 4.7 The main difficulty here for the optimal control is that we have initial condition for system (11) and final condition for the associated Riccati differential equation (16).

To overcome this difficulty, we proceed as follows:

Step 1 We choose a control function $v(t) \equiv v^c(t)$ in the set Ω. However, this choice is not a random process, it depends on the strategy we need to adopt. For example, in this paper, we adopt a strategy which is very strict at the beginning of the control. We choose

$$u_1^c(t) = b \quad \forall t \in [0, t_f].$$

Step 2 Then, with this choice of the control function $v^c(t)$, we determine the solution $(S(t), E(t), I(t), L(t))$ of the Cauchy problem associated to system (2).

Step 3 The knowledge of $v(t) \equiv v^c(t)$ and $(S(t), E(t), I(t), L(t))$ allows us to determine the solution $F(t)$ of the state-dependent Riccati equation defined by system (16). This leads us to the control functions defined in (15) by $v^* := -V(t)^{-1} B_2(t)^{\mathrm{T}} F(t) Y(t)$.

Step 4 On one hand, we have the chosen control function v^c, and on the other hand, we have the control function v^*. We take a convex combination of those functions as follows:

$$v(t) = \left(1 - \frac{t}{t_f}\right) v^c(t) + \frac{t}{t_f} v^*(t)$$

for $t \in [0, t_f]$.

Step 5 This process is repeated (Steps 2, 3 and 4), and iterations are stopped when the values at the unknown iteration are very closed to the ones at the present iteration.

5 Numerical simulations

We are going to study an optimal strategy of our TB model and the basic reproduction ratio $R_0(u)$ and $R_0(0)$ with control and without control numerically.
We will illustrate that the optimal control strategies depend on the parameters ϕ and β, which denote respectively the rate of progression from infectious to lost of sight and the rate of the disease transmission. The values of parameters are given by Table 1.
We solve the state equation (2) with the chosen functions $v^c(t$ using the Runge–Kutta forward scheme of order 4. Then, we solve the state-dependent Riccati equation (16) using the backward Runge–Kutta scheme of order 4. We deduce v^* from system (15).
For those simulations, we take $t_f = 5$ years as control period.

Figure 3: The transmission coefficient $\beta = 0.002$ is chosen to assure that the reproduction ratio R_0 without control is less than 1. The rate at which infectious become lost of sight $\phi = 0.0022$ is chosen here small enough to show that the control of lost of sight individuals would not really be necessary (Fig. 3a).

Figure 3b: the average basic reproduction ratio is about 0.1344 without control and about 0.1330 with the control of lost of sight individuals. Both of the previous reproduction ratio are approximately equal, this is due to the fact that our control is not rigorous enough.

Table 1 Table of parameter values National Institute of Statistics (2007), WHO (2004), CNPFAT (2001)

Parameters	Description	Estimated values	Source
Λ	Recruitment rate of susceptible individuals	2 $(\text{year})^{-1}$	National Institute of Statistics (2007)
β	Transmission coefficient	variable	Assumed
μ	Natural death rate	0.019896 $(\text{year})^{-1}$	National Institute of Statistics (2007)
d_1	Death rate of the infectious	0.02272 $(\text{year})^{-1}$	CNPFAT (2001)
d_2	Death rate for the lost of sight	0.20 $(\text{year})^{-1}$	CNPFAT (2001)
δ	Fraction of lost of sight that is till infectious	1 $(\text{year})^{-1}$	Assumed
ϕ	Rate at which infectious become lost of sight	variable	Assumed
p	Proportion of newly infected individuals that have fast progression to the infectious class	0.3 $(\text{year})^{-1}$	CNPFAT (2001)
r_1	Rate of effective chemoprophylaxis of individuals	0 $(\text{year})^{-1}$	CNPFAT (2001)
r_2	Rate of effective chemoprophylaxis of infectious individuals	0.8182 $(\text{year})^{-1}$	CNPFAT (2001)
γ	Rate at which the lost of sight return to the hospital to continue the treatment	0.01 $(\text{year})^{-1}$	Assumed
k	Rate of progression from latently infected to infectious	0.005 $(\text{year})^{-1}$	WHO (2004)

Figure 3f: for $L(0) = 40$, the average number during $t_f = 5$ years of lost of sight is about 24.1143 individuals without control. This average number is approximately the same with control (24.1230), because the rate at which infectious become lost of sight $\phi = 0.0022$ is chosen here very small.

The Figs. 3c, d and e respectively represent the time evolution of susceptibles $S(t)$, latently infected $E(t)$ and infectious $I(t)$.

Figure 4: We take the transmission rate $\beta = 0.003$ to assure that the reproduction ratio R_0 without control is less than 1. The rate at which infectious become lost of sight ϕ is assumed here to be $\phi = 0.1$.

Figure 4a: The associated control function v is strict during the two first years.

Figure 4b: The average basic reproduction ratio is about 0.2286 without control of lost of sight individuals and about 0.2167 with the control.

Figure 4f: for $L(0) = 40$, the average number during $t_f = 5$ years of lost of sight is about 28.0065 individuals without control and about 24.5704 with the control of lost of sight individuals. In a period of five years of control ($t_f = 5$) , we succeed in keeping about 10 % of infectious individuals in a care center with the control strategy.

The Figs. 4c, d and e respectively represent the time evolution of susceptibles $S(t)$, latently infected $E(t)$ and infectious $I(t)$.

Figure 5: here, the transmission rate of the disease is $\beta = 0.02$, and the rate at which individuals become lost of sight is $\phi = 0.5$.

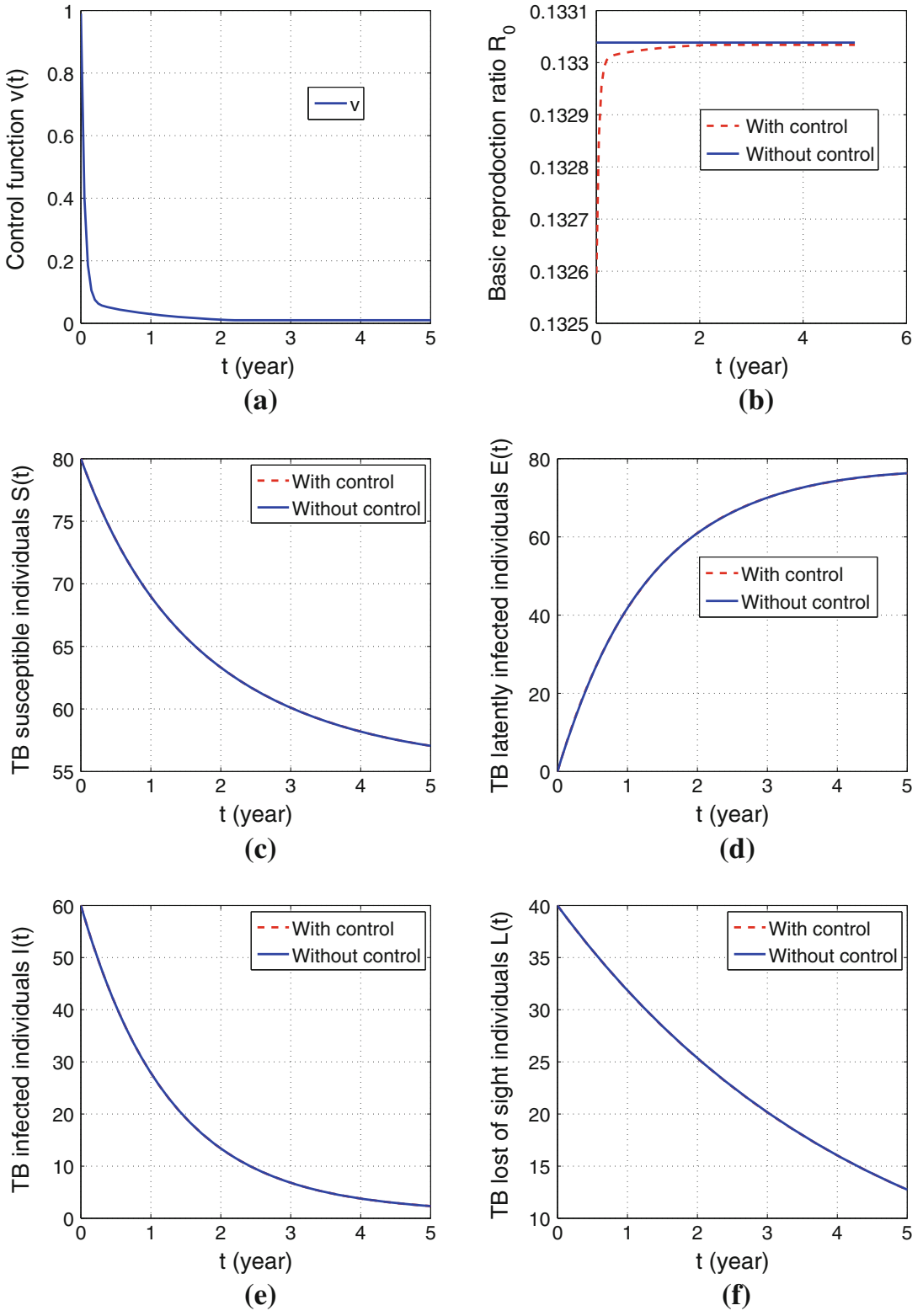

Fig. 3 The influence of the control with $\beta = 0.002$ and $\phi = 0.0022$. All the other parameter values are as in Table 1

Figure 5a: for the chosen value of the rate at which individuals become lost of sight (ϕ), the associated control function v is strict for the third first years of the control period.

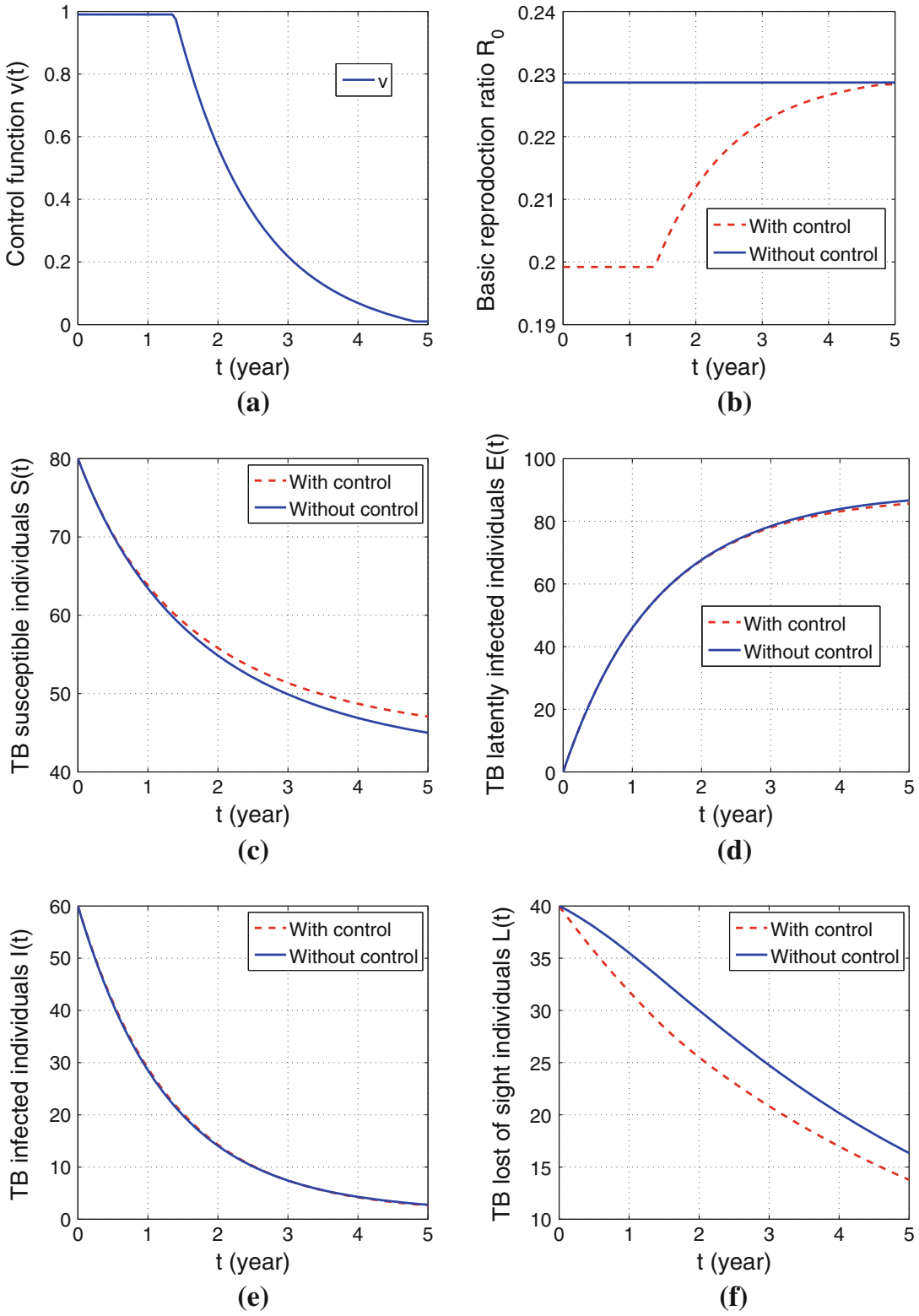

Fig. 4 The influence of the control with $\beta = 0.003$ and $\phi = 0.1$. All the other parameter values are as in Table 1

Figure 5b: the average basic reproduction ratio is about 0.2226 without control of the lost of sight individuals and about 0.1584 with the control.
Figure 5f: for $L(0) = 40$, the average number during the five years of control period of the

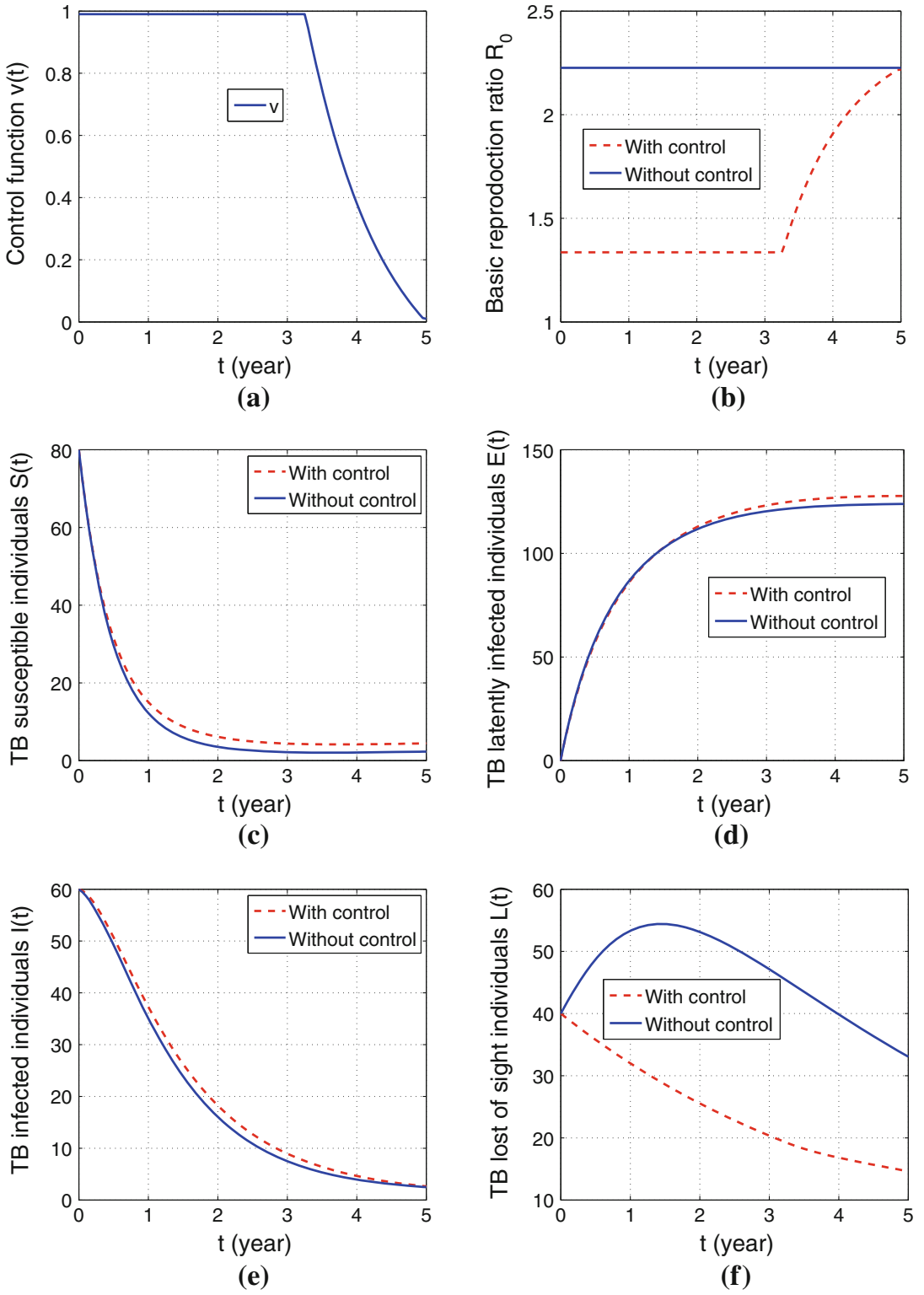

Fig. 5 The influence of the control with $\beta = 0.02$ and $\phi = 0.5$. All the other parameter values are as in Table 1

lost of sight is about 42.3987 individuals without the control of the lost of sight individuals and about 24.5510 with the control. In a period of five years ($t_f = 5$) of control, we succeed in keeping about 42% of infectious individuals in a care center.

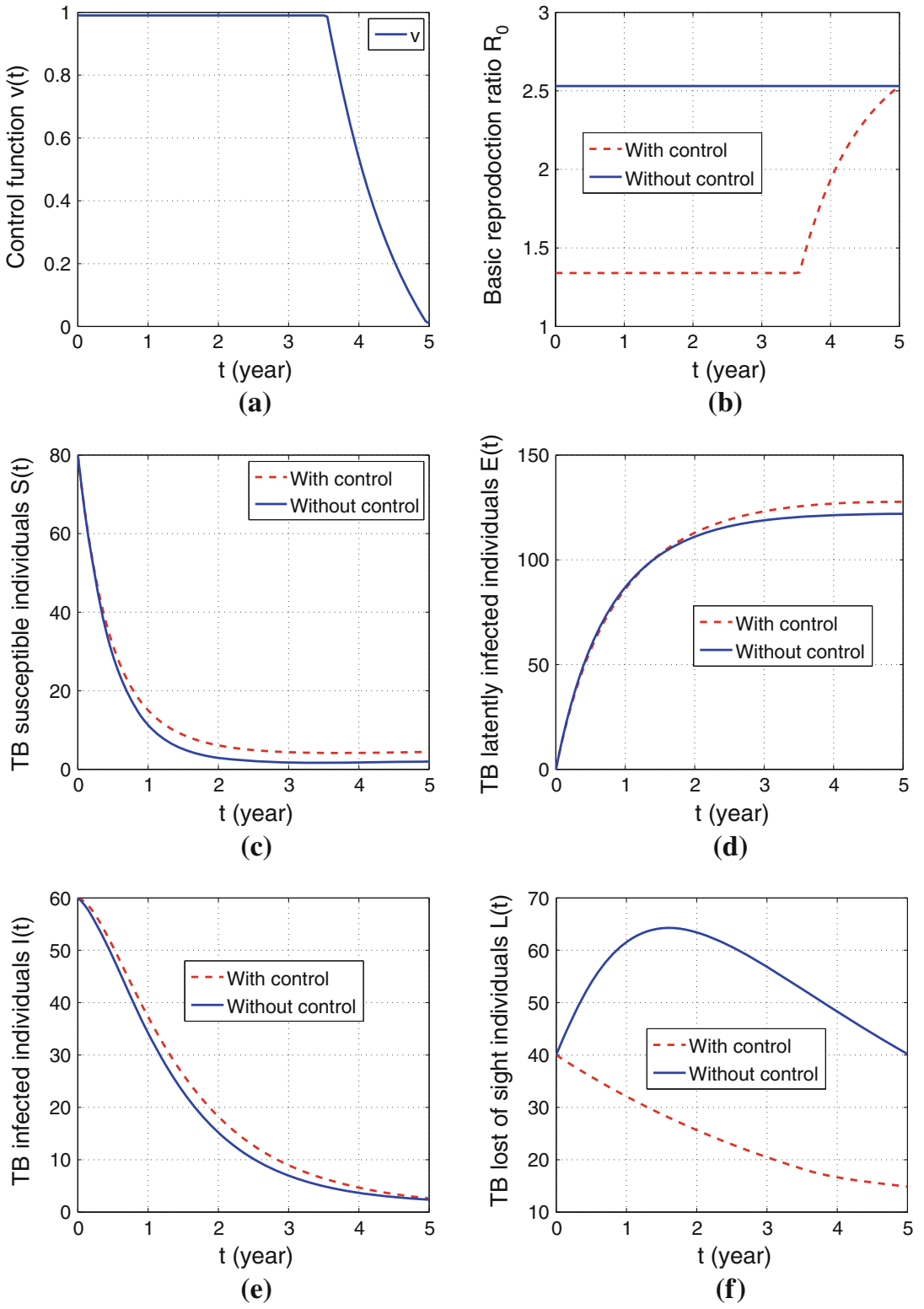

Fig. 6 The influence of the control with $\beta = 0.02$ and $\phi = 0.7$. All the other parameter values are as in Table 1

The Figs. 5c, d and e respectively represent the time evolution of susceptibles $S(t)$, latently infected $E(t)$ and infectious $I(t)$.

Figure 6: for this simulation, the transmission rate of the disease is $\beta = 0.02$ and the rate at which individuals become lost of sight is $\phi = 0.7$.

Figure 6a: for the chosen value of the rate at which individuals become lost of sight (ϕ), the associated control function v is strict for the third and the half first years of the control period.
Figure 6b: the average basic reproduction ratio is about 2.5307 without the control of the lost of sight individuals and about 1.5776 with the control.
Figure 5f: for $L(0) = 40$, the average number during the 5 years of the control period of the lost of sight is about 55.1286 individuals without the control of the lost of sight individuals and about 24.6178 with the control. In a period of five years ($t_f = 5$) of control, we succeed in keeping about 55 % of infectious individuals in a care center.
The Figs. 6c, d and e respectively represent the time evolution of susceptibles $S(t)$, latently infected $E(t)$ and infectious $I(t)$.

6 Conclusion

This has considered the problem of optimal control of the transmission dynamic of TB. A model considering a new class has been investigated and analyzed. An optimal control strategy has been presented and the results show how important it is to control the lost of sight class which is very crucial to the study of the disease. Numerical simulations have been given to illustrate the effectiveness and efficiency of the proposed control scheme. In Africa, it is very important to keep infectious individuals in a care center in order to complete their treatment and avoid the quick transmission of the disease. Our control strategy helps to do so, though other control strategies could be investigated.

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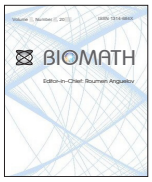

Predator-Prey Model with Prey Harvesting, Holling Response Function of Type III and SIS Disease

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***Abstract*—The populations of prey and predator interact with prey harvesting. When there is no predator, the logistic equation models the behavior of the preys. For interactions between preys and predators, we use the generalized Holling response function of type III. This function which models the consumption of preys by predators is such that the predation rate of predators increases when the preys are few and decreases when they reach their satiety. Our main goal is to analyze the influence of a SIS infectious disease in the community. The epidemiological SIS model with simple mass incidence is chosen, where only susceptibles and infectious are counted. We assume firstly that the disease spreads only among the prey population and secondly that it spreads only among the predator population. There are many bifurcations as: Hopf bifurcation, transcritical bifurcation and saddle-node bifurcation. The results indicate that either the disease dies out or persists and then, at least one population can disappear because of infection. For some particular choices of the parameters however, there exists endemic equilibria in which both populations survive. Numerical simulations on MATLAB and SCILAB are used to illustrate our results.**

***Keywords*-Predator; Prey; Infectious disease; Response function; Bifurcation; Global Stability**

I. INTRODUCTION

There are many epidemiological or ecological models [6], [7], [8], [9], [10], [11], [5] in the literature and also many models which encompass the two fields [3], [4], [8], [9], [10], [11], [12]. Dynamic models for infectious diseases are mostly based on compartment structures that were initially proposed by Kermack and McKendrick (1927,1932) and developed later by many other researchers.

The main questions regarding population dynamics concern the effects of infectious diseases in regulating natural populations, decreasing their population sizes, reducing their natural fluctuations, or causing destabilizations of equilibria into oscillations of the population states. With the Holling function response of type III, it is well known that the predators increase their searching activity when the prey density increases.

Generally, if x denotes the density of prey population, the Holling function of type I is $\phi_1(x) = r\,x$ where r is the intrinsic growth rate of preys. The Holling function of type II is $\phi_2(x) = \dfrac{B\,\omega_0\,x}{1 + B\,\omega_1\,x}$, where ω_0 and ω_1 denote respectively the time taking by a predator to search and

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capture preys, B is the predation rate per unit of time. In the models considered in this work, the Holling function of type III is used for interactions between predators and preys : $\phi_3(x) = \dfrac{m\,x^2}{a\,x^2+b\,x+1}$ [2], where m and a are positive constants, b is an arbitrary constant. This function models the consumption of preys by predators. It is well known that with this function, the predation rate of predators increases when the preys are few and decreases when they reach their satiety (a predator increases his searching activity when the prey density increases). The functions ϕ_1, ϕ_2 and ϕ_3 are respectively also referred to as Lotka-Volterra, Michaelis-Menten and sigmoidal response functions. Generally, there are more macroparasitic infections which can affect only preys, only predators or both preys and predators. Our goal in this paper is to analyze the influence of a SIS infectious disease which spreads only in one of the two populations. The models considered and analyzed here are different from all the models in the literature. Moreover, we use numerical simulations on MATLAB and SCILAB to illustrate our results.

II. The Model Formulation

The model (s1) is obtained from the classic Lotka-Volterra model with simple mass action when the disease spreads only inside the prey population. In this model, the infected preys do not reproduce and there is no disease related mortality. The model (s2) is obtained when the disease spreads only inside the predator population. These models are respectively

$$\begin{cases} \dot{x} = \tilde{r}\left(1-\dfrac{x}{\tilde{k}}\right)x - \dfrac{\tilde{m}x^2y}{\tilde{a}x^2+\tilde{b}x+1} - \tilde{\lambda}x\,z \\ \qquad +\tilde{\gamma}z - \tilde{h}_1, \\ \dot{z} = \tilde{\lambda}x\,z - \tilde{\gamma}z - \dfrac{\tilde{m}_1z^2y}{\tilde{a}z^2+\tilde{b}z+1}, \qquad (s1) \\ \dot{y} = \dfrac{\tilde{c}\tilde{m}x^2y}{\tilde{a}x^2+\tilde{b}x+1} - \dfrac{\tilde{m}_2z^2y}{\tilde{a}z^2+\tilde{b}z+1} - \tilde{d}y, \\ x\geq 0,\ z\geq 0,\ y\geq 0, \end{cases}$$

$$\begin{cases} \dot{x} = \tilde{r}\left(1-\dfrac{x}{\tilde{k}}\right)x - \dfrac{\tilde{m}x^2y}{\tilde{a}x^2+\tilde{b}x+1} - \dfrac{\tilde{\eta}_1x^2\omega}{\tilde{a}x^2+\tilde{b}x+1} \\ \qquad -\tilde{h}_1, \\ \dot{y} = \dfrac{\tilde{c}\tilde{m}x^2y}{\tilde{a}x^2+\tilde{b}x+1} - \tilde{d}\,y - \tilde{\delta}\,y\,\omega + \tilde{\mu}\,\omega, \qquad (s2) \\ \dot{\omega} = \dfrac{\tilde{e}\tilde{m}x^2\omega}{\tilde{a}x^2+\tilde{b}x+1} + \tilde{\delta}y\omega - (\tilde{\mu}+\tilde{d})\omega, \\ x\geq 0,\ y\geq 0,\ \omega\geq 0. \end{cases}$$

where the variables z and ω denotes respectively the infected preys and infected predators, $\tilde{r}$ denotes the intrinsic growth rate of preys, $\tilde{d}$ is the natural death rate of predators, $\tilde{k}$ is the capacity of environment to support the growth of preys, $\tilde{h}_1$ is the rate of preys's harvesting, $\tilde{\gamma}$ and $\tilde{\mu}$ are the recover rates of infected preys and infected predators respectively, $\tilde{\lambda}$ is the adequate contact rate between susceptible preys and infected preys while $\tilde{\delta}$ is the adequate contact rate between susceptible predators and infected predators. We also assume that infected predators still can catch preys at a different rate $\tilde{\eta}_1$ than sound ones. The parameter $\tilde{\eta}_1$ can be thought to be less than $\tilde{m}$, if the disease affects the ability in hunting of the predators or larger than $\tilde{m}$, if we want to emphasize that the interactions with infected predators cause the preys to die for the disease even if they are not caught. $\tilde{a}$ and $\tilde{b}$ are positive constants. $\tilde{m}>0$ and $\tilde{m_1}>0$ denote the adequate predation rate between predators and preys. $\tilde{c}$ and $\tilde{e}$ denote the conversion coefficients. $\tilde{m_2}$ can be negative (conversion of prey's biomass into predator's biomass) or positive (bad effect of the infected preys for the predator population due to disease).

Trough the linear transformation and time scaling $(X,Z,Y,W,T) = \left(\dfrac{x}{\tilde{k}}, \dfrac{z}{\tilde{k}}, \dfrac{y}{\tilde{c}\tilde{k}}, \dfrac{\omega}{\tilde{e}\tilde{k}}, \tilde{c}\tilde{m}\tilde{k}^2t\right)$, the following simplified systems are obtained from (s1) and (s2),

$$\begin{cases} \dot{x} = \rho x(1-x) - p(x)\,y - \lambda\,x\,z + \gamma\,z - h_1, \\ \dot{z} = \lambda\,x\,z - \gamma\,z - m_1\,p(z)\,y, \\ \dot{y} = p(x)\,y - m_2\,p(z)\,y - d\,y, \\ x\geq 0; y\geq 0; z\geq 0, \end{cases} \qquad (1)$$

$$\begin{cases} \dot{x} = \rho x(1-x) - p(x)\,y - \eta_1\,p(x)\,\omega - h_1, \\ \dot{y} = p(x)y - dy - \delta\,y\,\omega + \mu\,\omega, \\ \dot{\omega} = e\,p(x)\omega + \delta_1\,y\,\omega - \mu_1\,\omega, \\ x\geq 0; y\geq 0; \omega\geq 0, \end{cases} \qquad (2)$$

where the parameters are defined as follow

$$\begin{aligned} &\rho = \frac{\tilde{r}}{\tilde{c}\tilde{m}\tilde{k}^2}, \eta_1 = \frac{\tilde{\eta}_1\tilde{e}}{\tilde{c}\tilde{m}}, \eta_2 = \frac{\tilde{\eta}_2\tilde{e}}{\tilde{c}\tilde{m}}, h_1 = \frac{\tilde{h_1}}{\tilde{c}\tilde{m}\tilde{k}^3}, \lambda = \frac{\tilde{\lambda}}{\tilde{c}\tilde{m}\tilde{k}}, \\ &\gamma = \frac{\tilde{\gamma}}{\tilde{c}\tilde{m}\tilde{k}^2}, m_1 = \frac{\tilde{m}_1}{\tilde{m}}, m_2 = \frac{\tilde{m}_2}{\tilde{c}\tilde{m}}, m_3 = \frac{\tilde{m}_3}{\tilde{c}\tilde{m}}, d = \frac{d}{\tilde{c}\tilde{m}\tilde{k}^2}, \\ &\delta = \frac{\delta\tilde{e}}{\tilde{c}\tilde{m}\tilde{k}}, \mu = \frac{\tilde{\mu}\tilde{e}}{\tilde{c}^2\tilde{m}\tilde{k}^2}, e = \frac{\tilde{e}}{\tilde{c}}, \delta_1 = \frac{\tilde{\delta}}{\tilde{m}\tilde{k}}, \mu_1 = \frac{\tilde{\mu}+d}{\tilde{c}\tilde{m}\tilde{k}^2}, \\ &a = \tilde{a}\tilde{k}^2, b = \tilde{b}\tilde{k}, p(x) = \frac{x^2}{a\,x^2+b\,x+1}. \end{aligned} \qquad (3)$$

Systems (1) and System (2) are new and different from all the models in the literature. These models without disease give us the same system which has been analyzed without disease in [1].

III. RESULTS

A. Results for the Model (1) with Disease only in Prey Population

Let us set $u_1(x) = \dfrac{\rho x(1-x) - h_1}{(1+m)p(x) - md}$, $R_0 = \dfrac{m_2(p(\eta)-d)u_1^2(\eta)}{a(p(\eta)-d)^2u_1^2(\eta) + b(\lambda\eta-\gamma)(p(\eta)-d)u_1(\eta) + (\lambda\eta-\gamma)^2}$ the basic reproduction number, and

$$x_1 = \frac{1-\sqrt{1-4\frac{h_1}{\rho}}}{2},\ x_2 = \frac{1+\sqrt{1-4\frac{h_1}{\rho}}}{2}, \qquad (4)$$
$$x_z = \frac{\gamma}{\lambda}, x_0 = \frac{1}{2}, z_0 \in \mathbb{R}_+^*,$$

the expressions of the positive real values x_0, x_1, x_2, x_z.

Theorem 1: The equilibrium points of System (1), according to the values of the parameters, are given as follow :

- When $h_1 > \dfrac{\rho}{4}$, then there is no equilibrium point.
- When $h_1 = \dfrac{\rho}{4}$, then the unique equilibrium is $B_0(x_0, 0, 0)$ which is a double point if $d \neq \dfrac{1}{a+2b+4}$ and triple point if $d = \dfrac{1}{a+2b+4}$.
- When $h_1 < \dfrac{\rho}{4}$ and $a\,d \geq 1$, then the equilibria are $B_1(x_1, 0, 0)$ and $B_2(x_2; 0; 0)$.
- When $h_1 < \dfrac{\rho}{4}$; $a\,d < 1$ and $x_3 = x_1$, then $B_1(x_1, 0, 0)$ is a double point and $B_2(x_2, 0, 0)$ exists.
- When $h_1 < \dfrac{\rho}{4}$; $a\,d < 1$ and $x_3 = x_2$, then $B_1(x_1, 0, 0)$ is simple and $B_2(x_2, 0, 0)$ is a double point.
- When $h_1 < \dfrac{\rho}{4}$; $a\,d < 1$ and $x_3 \in]x_1; x_2[$, then $B_1(x_1, 0, 0)$; $B_2(x_2, 0, 0)$ and $B_3(x_3, 0, y_3)$ exist, where $y_3 = \dfrac{\rho x_3(1-x_3) - h_1}{d} > 0$.
- When $h_1 < \dfrac{\rho}{4}$; $a\,d < 1$ and $x_3 \in [0; x_1[\cup]x_2; +\infty[$, then $B_1(x_1, 0, 0)$ and $B_2(x_2, 0, 0)$ exist.
- When $h_1 < \dfrac{\rho}{4}$; $ad < 1$; $x_4 \in]\eta; x_2[$, $x_2 > \max\left(x_3; \dfrac{\gamma}{\lambda}\right)$ and $R_0 > 1$, then $B_1(x_1, 0, 0)$; $B_2(x_2, 0, 0)$ and $B_4(x_4, z_4, y_4)$ exist, where $x_4 > 0$, $z_4 > 0$ and $y_4 > 0$.

Proof : These equilibria are obtained by setting the right hand side of (1) equals to zero. For $y = 0$ one has equation $\rho x^2 - \rho x + h_1 = 0$. Then we have B_0, B_1 and B_2. For $z = 0$, one has $p(x) = d \iff (1 - a\,d)x^2 - b\,dx - d = 0$. We deduce x_3 and then B_3. The condition for existence of B_4 is $p(z) = \dfrac{1}{m_2}(p(x) - d) > 0$ ie $p(x) - d > 0 \iff a\,d < 1$ and $x \in]x_3, +\infty[$.

Concerning the stability of these equilibria, the following theorem hold.

Theorem 2: Let's consider System (1).

- The equilibria B_0 and B_1 are always unstable.
- The equilibrium B_2 is stable if one of the following conditions is satisfied : $h_1 < \dfrac{\rho}{4}$, $\dfrac{\gamma}{\lambda} \geq x_2$ and $p(x_2) \leq d$, or $h_1 < \dfrac{\rho}{4}$, $\dfrac{\gamma}{\lambda} < x_2$, $p(x_2) = d$ and $p''(x_2) \leq 0$.
- The equilibrium B_3 is stable if one of the following conditions is satisfied. $h_1 < \dfrac{\rho}{4}$, $ad < 1$, $x_3 \in]x_1; x_2[$ and $x_3 = \dfrac{\gamma}{\lambda}$, or $h_1 < \dfrac{\rho}{4}$, $ad < 1$, $x_3 \in]x_1; x_2[$, $x_3 < \dfrac{\gamma}{\lambda}$ and $d > \dfrac{1}{a+2b+4}$, or $h_1 < \dfrac{\rho}{4}$, $ad < 1$, $x_3 \in]x_1; x_2[$, $x_3 < \dfrac{\gamma}{\lambda}$, $d < \dfrac{1}{a+2b+4}$ and $\chi_0(x_3) < 0$, where $\chi_0(x_3)$ is the eigenvalue of x_3.
- The equilibrium point $B_4(x_4, z_4, y_4)$ is asymptotically stable if and only if the following conditions hold : $a_2 < 0$; $a_2a_1 + a_0 > 0$ and $a_1a_0 > 0$, where

$$\begin{cases} a_2 = \rho(1-2x_4) - p'(x_4)y_4 - \lambda z_4 \\ \qquad +\lambda x_4 - \gamma - m_1p'(z_4)y_4, \\ a_1 = -\left[\rho(1-2x_4) - p'(x_4)y_4 - \lambda z_4\right] \times \\ \quad [\lambda x_4 - \gamma - m_1p'(z_4)y_4] \\ \quad -\lambda m_1p(z_4)y_4 - p(x_4)p'(x_4)y_4, \\ a_0 = -\left[\rho(1-2x_4) - p'(x_4)y_4 - \lambda z_4\right] \times \\ [\lambda x_4 - \gamma - m_1p'(z_4)y_4] + \lambda m_2p(x_4)p'(z_4)y_4z_4 \\ +p'(x_4)y_4m_1p(z_4)(\lambda x_4 - \gamma) \\ +p(x_4)p'(x_4)y_4(\lambda x_4 - \gamma - m_1p'(z_4)y_4). \end{cases} \qquad (5)$$

Proof : The eigenvalues of the jacobian matrix $J(B_0)$ are $\chi_1 = 0$; $\chi_2 = \lambda x_0 - \gamma$ and $\chi_3 = p(x_0) - d$.

a) If $\dfrac{\gamma}{\lambda} < \dfrac{1}{2}$ or $d < \dfrac{1}{a+2b+4} = p(x_0)$, then $\chi_2 > 0$ or $\chi_3 > 0$ and B_0 is unstable.

b) If $\dfrac{\gamma}{\lambda} > \dfrac{1}{2}$ and $d = \dfrac{1}{a+2b+4} = p(x_0)$, then $\chi_2 < 0$ and $\chi_3 = 0$. Hence, the stability of B_0 is given by the center manifold theorem. The translation $(u_1, u_2, u_3) = (x - x_0, z, y)$ brings the singular point B_0 to the origin. In the neighborhood of the origin and, since $h_1 = \dfrac{\rho}{4}$, System (1) has a new form. The Jacobian matrix $J(B_0)$ is not diagonalizable and the passage matrix to the Jordan's basis is

$P = \begin{pmatrix} -1 & 0 & 1 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}$. By the transformation $(v_1, v_2, v_3)^T = P^{-1}(u_1, u_2, u_3)^T$, the system becomes:

$$\begin{cases} \dot{v}_1 = v_2 + p'(x_0)(v_1v_3 - v_3^2) \\ +\frac{p''(x_0)}{2}(v_1^2 + v_3^2 - 2v_1v_3)v_2 \\ +\frac{m_1p''(0)}{2}v_2v_3^2 + O(|(v_1, v_2, v_3)|^4), \\ \dot{v}_2 = v_3 + p'(x_0)(v_1v_3 - v_3^2) \\ +\frac{p''(x_0)}{2}(v_1^2 + v_3^2 - 2v_1v_3)v_2 \\ -\frac{m_2p''(0)}{2}v_2v_3^2 + O(|(v_1, v_2, v_3)|^4), \\ \dot{v}_3 = \chi_2 v_3 - \lambda(v_1v_3 - v_3^2) + \frac{m_1p''(0)}{2}v_2v_3^2 \\ +O(|(v_1, v_2, v_3)|^4). \end{cases} \quad (6)$$

We can now find that the center manifold is given by $W^c = \{v_3 = 0\}$. Therefore, the system (6) is topologically equivalent, around the origin, to the following system:

$$\begin{cases} \dot{v}_1 = v_2 + \frac{p''(x_0)}{2}v_1^2v_2 + O(|(v_1, v_2)|^4), \\ \dot{v}_2 = O(|(v_1, v_2)|^4), \\ \dot{v}_3 = O(|(v_1, v_2)|^4). \end{cases}$$

Then, the singular point B_0 is unstable.

c) If $\frac{\gamma}{\lambda} = \frac{1}{2}$ and $d = \frac{1}{a+2b+4} = p(x_0)$, then $\chi_2 = 0$ and $\chi_3 = 0$. Applying the center manifold theory as previously, B_0 is unstable.

d) If $\frac{\gamma}{\lambda} = \frac{1}{2}$ and $d > \frac{1}{a+2b+4} = p(x_0)$, we have $\chi_2 = 0$ and $\chi_3 < 0$. Applying the center manifold theory as previously, B_0 is unstable.

The stability of B_1 is obtained with jacobian matrix. The stability of B_2 is obtained using the center manifold theorem. Taking into account the fact that $p(x_3) = d$, one find that the characteristic polynomial of the linearized system around the singular point B_3 is

$$\begin{aligned} Q(\chi) &= (\chi - \lambda x_3 + \gamma)\left[-\chi^2 + (\rho(1-2x_3) - p'(x_3)y_3)\chi\right] \\ &\quad -d(\chi - \lambda x_3 + \gamma)p'(x_3)y_3. \end{aligned}$$

The discriminant of $Q(\chi)$ is

$$\Delta_3(h_1) = \left(\rho(1-2x_3) - p'(x_3)y_3\right)^2 - 4dp'(x_3)y_3. \quad (7)$$

a) If $x_3 > \frac{\gamma}{\lambda}$, then the eigenvalue $\chi_1 = \lambda x_3 - \gamma > 0$. Hence, B_3 is unstable.

b) If $x_3 < \frac{\gamma}{\lambda}$, then $\chi_1 < 0$.

b1) When $\Delta_3(h_1) = 0$ the Jacobian matrix at B_3 has a double eigenvalue

$$\chi_0(x_3) := \frac{\rho(1-2x_3) - p'(x_3)y_3}{2}. \quad (8)$$

• If $d \geq \frac{1}{a+2b+4}$, then $x_3 > \frac{1}{2}$. From where $\chi_0(h_1) < 0$. Therefore, the singular point B_3 is stable.

• If $d < \frac{1}{a+2b+4}$, then: When $\chi_0(h_1) < 0$ (resp. $\chi_0(h_1) > 0$) the singular point B_3 is stable (resp. unstable).

b2) When $\Delta_3 > 0$ the eigenvalues of the Jacobian matrix at B_3 are $\chi_1 < 0$, $\chi_2 = \chi_0(h_1) - \frac{\sqrt{\Delta_3}}{2}$ and $\chi_3 = \chi_0(h_1) + \frac{\sqrt{\Delta_3}}{2}$. We have, $\chi_2\chi_3 = dp'(h_1)y_3 > 0$ and $\chi_2 + \chi_3 = \chi_0(h_1)$, where $\chi_0(h_1)$ is defined by (8).

- If $d \geq \frac{1}{a+2b+4}$, then the singular point B_3 is stable.
- If $d < \frac{1}{a+2b+4}$, then: When $\chi_0(h_1) < 0$ (resp. $\chi_0(h_1) > 0$) the singular point B_3 is stable (resp. unstable).

b3) If $\Delta_3 < 0$, then the eigenvalues of the Jacobian matrix at B_3 are $\chi_1 < 0$, $\chi_2 = \chi_0(h_1) - i\frac{\sqrt{-\Delta_3}}{2}$ and $\chi_3 = \chi_0(h_1) + i\frac{\sqrt{-\Delta_3}}{2}$, where $\chi_0(h_1)$ is defined by (8). If $d \geq \frac{1}{a+2b+4}$, then the singular point B_3 is stable. If $d < \frac{1}{a+2b+4}$ and $\chi_0(h_1) < 0$ then, the singular point B_3 is stable. If $d < \frac{1}{a+2b+4}$ and $\chi_0(h_1) > 0$ then, the singular point is unstable. If $d < \frac{1}{a+2b+4}$ and $\chi_0(h_1) = 0$ then, the real central and stable spaces are respectively defined by $E^c = \langle(1,0,0);(0,0,1)\rangle$ and $E^s = \left\langle(1, -1 - \frac{dp'(x_3)y_3}{\chi_1^2}, \frac{p'(x_3)y_3}{\chi_1})\right\rangle$. Then applying the center manifold theorem it comes that the singular point B_3 is unstable.

The stability of B_4 is obtained using the Routh-Hurwitz conditions.

B. Results for the Model (2) with Disease only inside Predator Population

Let us set $u_2(x) = \frac{e}{\delta}\left[\frac{\mu_1}{e} - p(x)\right]$ and $v_2(x) = \frac{(p(x)-d)u_2(x)}{e\left[\frac{d}{e} - p(x)\right]}$. Let x_5 the eventual positive root of equation $p(x_5) = \frac{d}{e}$ and the function $g_2(x) = \rho x(1-x) - h_1 - p(x)u_2(x) - \eta_1 p(x)v_2(x)$.

Hypothesis 1 : The attack of non-infected predators is more important than the one of the infected predators i.e. $e = \frac{\tilde{e}}{\tilde{c}} \leq 1$.

Theorem 3: The equilibria of System (2), where x_0; x_1 and x_2 are given by (4), according to the values of the parameters, are given as follow.

- When $h_1 > \frac{\rho}{4}$, then there is no equilibrium point.
- When $h_1 = \frac{\rho}{4}$, then $C_0(x_0;0;0)$ is a double point if $d \neq \frac{1}{a+2b+4}$ and triple point if $d = \frac{1}{a+2b+4}$.
- When $h_1 < \frac{\rho}{4}$ and $a\,d \geq 1$, then $C_1(x_1;0;0)$ and $C_2(x_2;0;0)$ exist.
- When $h_1 < \frac{\rho}{4}$; $a\,d < 1$ and $x_3 = x_1$, then $C_1(x_1;0;0)$ is a double point and $C_2(x_2;0;0)$ exists.
- When $h_1 < \frac{\rho}{4}$; $a\,d < 1$ and $x_3 = x_2$, then $C_1(x_1;0;0)$ exists and $C_2(x_2;0;0)$ is a double point.
- When $h_1 < \frac{\rho}{4}$; $a\,d < 1$ and $x_3 \in]x_1;x_2[$, then the equilibria are $C_1(x_1;0;0)$; $C_2(x_2;0;0)$ and $C_3(x_3;y_3;0)$, where $y_3 = \frac{\rho x_3(1-x_3) - h_1}{d} > 0$.
- When $h_1 < \frac{\rho}{4}$; $a\,d < 1$ and $x_3 \in [0;x_1[\cup]x_2;+\infty[$, then the equilibria are $C_1(x_1;0;0)$ and $C_2(x_2;0;0)$.
- When $h_1 < \frac{\rho}{4}$; $a\,d < 1$; $\frac{a\,d}{e} \geq 1$, $x_6 \in]x_1;x_2[\cap]x_3;+\infty[$; $x_2 > x_3$ or $h_1 < \frac{\rho}{4}$; $\frac{a\,d}{e} < 1$, $x_6 \in]x_1;x_2[\cap]x_3;x_5[$; $x_2 > x_3$; $x_1 < x_5$, then the equilibria are $C_1(x_1;0;0)$; $C_2(x_2;0;0)$ and $C_4(x_6;y_6;\omega_6)$, $y_6 = u_2(x_6)$ and $\omega_6 = v_2(x_6)$.

Proof : The equilibria C_0, C_1, C_2 and C_3 are obtained in the same way as in theorem 1, setting the right hand side of the system equals to zero. Equilibrium C_4 exists when the previous conditions are satisfied.

Concerning the Stability analysis of these equilibria, the following theorem holds.

Theorem 4: Let's consider the System (2) and suppose that Hypothesis 1 holds.

- The equilibria C_0 and C_1 are always unstable.
- The equilibrium C_2 is stable if $h_1 < \frac{\rho}{4}$ and $p(x_2) < d$.
- The equilibrium C_3 is stable if and only if one of these conditions is satisfied : $h_1 < \frac{\rho}{4}$, $ad < 1$, $x_3 \in]x_1;x_2[$ and $y_3 = \frac{e}{\delta_1}\left(\frac{\mu_1}{e} - d\right)$ or $h_1 < \frac{\rho}{4}$, $ad < 1$, $x_3 \in]x_1;x_2[$, $y_3 < \frac{e}{\delta_1}\left(\frac{\mu_1}{e} - d\right)$, $d > p(x_0)$, or $h_1 < \frac{\rho}{4}$, $ad < 1$, $x_3 \in]x_1;x_2[$, $y_3 < \frac{e}{\delta_1}\left(\frac{\mu_1}{e} - d\right)$, $d < p(x_0)$, $\xi_0(x_3) < 0$.
- The singular point $C_4(x_6, y_6, \omega_6)$ is asymptotically stable if and only if the following conditions are satisfied : $b_2 < 0$; $b_2 b_1 + b_0 > 0$ and $b_1 b_0 > 0$, where

$$\begin{cases} b_2 = \rho(1-2x_6) - p'(x_6)(y_6 + \eta_1\omega_6) \\ \quad +p(x_6) - d - \delta\omega_6; \\ b_1 = -\left(\rho(1-2x_6) - p'(x_6)(y_6+\eta_1\omega_6)\right)\times \\ \quad (p(x_6) - d - \delta\omega_6) + \delta_1\omega_6(\mu - \delta y_6) \\ \quad -p(x_6)p'(x_6)y_6 - e\eta_1 p(x_6)p'(x_6)\omega_6; \\ \\ b_0 = ep(x_6)p'(x_6)\omega_6\left[\delta y_6 - \mu + \eta_1(p(x_6) - d - \delta\omega_6)\right] \\ -\delta_1\eta_1 p(x_6)p'(x_6)y_6\omega_6 \\ -\delta_1\omega_6(\mu - \delta y_6)\left(\rho(1-2x_6) - p'(x_6)(y_6+\eta_1\omega_6)\right). \end{cases} \quad (9)$$

Proof : The stability of C_0 is deduce as for B_0 in theorem 2. The jacobian matrix always has a positive eigenvalue. Then, C_1 is unstable. We obtain the stability of C_2 and C_3 applying the same arguments as for B_2 and B_3 in theorem 2. The stability of C_4 is obtained using the Routh-Hurwitz conditions.

IV. Hopf Bifurcation

Let us introduce the following parameters

$$h_{10} = \frac{\rho x_3}{bx_3 + 2}\left[2ax_3^3 + (b-a)x_3^2 + 1\right], \quad (10)$$

and

$$\Pi = \frac{1}{16}\left[p^{(2)}(x_3) + p^{(3)}(x_3)\right] - \frac{(p'(x_3))^2}{4\sqrt{-\Delta_3(h_{10})}}. \quad (11)$$

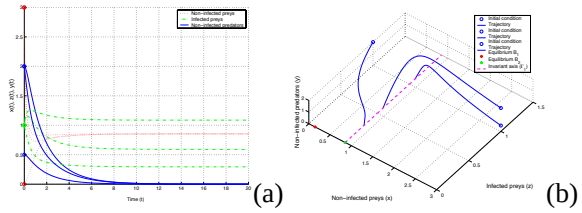
Recalling (4), the flow of System (1) and System (2) respectively undergo a supercritical Hopf bifurcation around h_{10} given by the following result

Theorem 5: (Hopf bifurcation) Let $h_1 < \frac{\rho}{4}$; $ad < 1$; $x_3 \in]x_1, \min\left(\frac{1}{2}, \frac{\gamma}{\lambda}\right)[$. Thanks to Hypothesis 1. Then, a unique stable curve of periodic solution bifurcates from the singular points B_3 and C_3 into the regions $h_1 > h_{10}$ if $\Pi < 0$ or $h_1 < h_{10}$ if $\Pi > 0$. The singular points B_3 and C_3 are stable for $h_1 < h_{10}$ and unstable for

$h_1 \geq h_{10}$. This correspond to supercritical stable Hopf bifurcation.

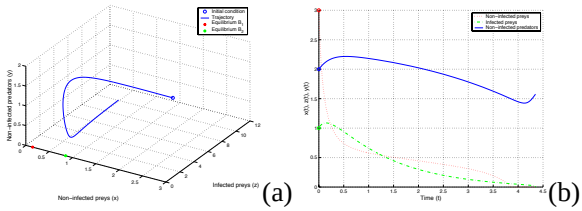
Proof : The proof can be obtained as in [13].

V. Numerical Simulations



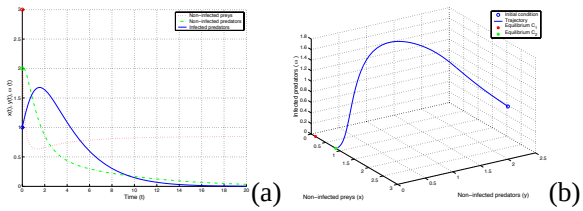
(a) (b)

Fig. 1. Phase portraits of System (1) for $h_1 < \frac{\rho}{4}$; $\frac{\gamma}{\lambda} = x_2$ and $p(x_2) < d$. B_1 and B_2 are unstable. The axis $x = \frac{\gamma}{\lambda}$ is stable.



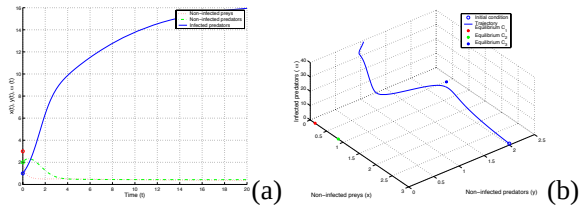
(a) (b)

Fig. 2. Phase portraits of System (1). The case (a) corresponds to $h_1 < \frac{\rho}{4}$; $\frac{\gamma}{\lambda} < x_2$ and $p(x_2) < d$. The case (b) corresponds to $h_1 = \frac{\rho}{4}$; $\frac{\gamma}{\lambda} > 1/2$ and $d = \frac{1}{a+2b+4}$. Unstability of B_1 and B_2.



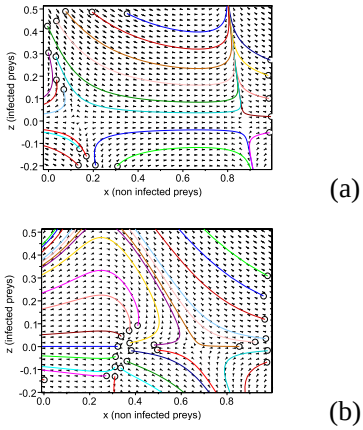
(a) (b)

Fig. 3. Phase portraits of System (2) for $h_1 < \frac{\rho}{4}$ and $d > p(x_2)$. Stability of C_2.



(a) (b)

Fig. 4. Phase portraits of System (2) for $h_1 < \frac{\rho}{4}$ and $d < p(x_2)$. Unstability of C_1, C_2 and C_3.



(a) (b)

Fig. 5. Phase portraits of System (1). The case (a) corresponds to $h_1 < \rho\frac{\gamma}{\lambda}\left(1-\frac{\gamma}{\lambda}\right)$. The case (b) corresponds to $h_1 > \rho\frac{\gamma}{\lambda}\left(1-\frac{\gamma}{\lambda}\right)$ and $\frac{\gamma}{\lambda} < \frac{1}{2}$. Illustration of saddle-node bifurcation phenomenon.

VI. Conclusion

Our goal was to analyze the modifications on a predator prey model (generalized Gause model) with prey harvesting and Holling response type III : $\frac{m\,x^2}{a\,x^2+b\,x+1}$, to account for a disease spreading among one of the two species. The simple epidemiological model SIS has been chosen, where only susceptibles and infectives are counted. The results indicate that either the disease dies out, leaving only neutral cycles of generalized Gause model, or one species disappears and all individuals in the other one eventually become infected. For some particular choices of the parameters however, endemic equilibria in which both populations survive seem to arise.

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