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► **To cite this version:**

Martin L Mann-Manyombe, Abdoulaye Mendy, Ousmane Seydi, Ramsès Djidjou-Demasse. Linking within-and between-host scales for understanding the evolutionary dynamics of quantitative antimicrobial resistance. *Journal of Mathematical Biology*, 2023, 10.1007/s00285-023-02008-1 . hal-03911294v2

**HAL Id: hal-03911294**

**<https://hal.science/hal-03911294v2>**

Submitted on 27 Oct 2023

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# Linking within- and between-host scales for understanding the evolutionary dynamics of quantitative antimicrobial resistance

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## Abstract

Understanding both the epidemiological and evolutionary dynamics of antimicrobial resistance is a major public health concern. In this paper, we propose a nested model, explicitly linking the within- and between-host scales, in which the level of resistance of the bacterial population is viewed as a continuous quantitative trait. The within-host dynamics is based on integro-differential equations structured by the resistance level, while the between-host scale is additionally structured by the time since infection. This model simultaneously captures the dynamics of the bacteria population, the evolutionary transient dynamics which lead to the emergence of resistance, and the epidemic dynamics of the host population. Moreover, we precisely analyze the model proposed by particularly performing the uniform persistence and global asymptotic results. Finally, we discuss the impact of the treatment rate of the host population in controlling both the epidemic outbreak and the average level of resistance, either if the within-host scale therapy is a success or failure. We also explore how transitions between infected populations (treated and untreated) can impact the average level of resistance, particularly in a scenario where the treatment is successful at the within-host scale.

**Key words.** Antimicrobial resistance; Evolutionary dynamics; Nested models; Non-linear dynamical system.

## 1 Introduction

Antimicrobial resistance (AMR) is one of the major challenges we face in the modern area [27]. An antimicrobial substance is a chemical agent interacting with the physiology of a bacterial cell. The antimicrobial activity on a given bacterium's ( $\mathcal{S}$ ) is an increasing function of its concentration in the medium ( $\mathcal{C}$ ), such that  $\mathcal{S}(0) = 0$  and  $\mathcal{S}(\mathcal{C}) \rightarrow \mathcal{S}_{\text{sat}}$  as  $\mathcal{C} \rightarrow \mathcal{C}_{\text{sat}}$ , where  $\mathcal{S}_{\text{sat}}$  and  $\mathcal{C}_{\text{sat}}$  are saturating constants. This intuitive approach implies that there exists  $\mathcal{C}^*$  in  $(0, \mathcal{C}_{\text{sat}})$  such that  $\mathcal{S}(\mathcal{C}^*)$  is equal to the intrinsic rate of increase and reverses the growth of a bacterial population. Such a threshold concentration at which a bacterial population does not grow (at least in *in vitro*) is called the Minimum Inhibitory Concentration (MIC). The level of resistance to a given antimicrobial is then a continuous trait by nature referred to as antimicrobial quantitative resistance (qAMR), at least at the population level, and qAMR is key to better understanding the evolutionary dynamics of AMR [16]. Here, we introduce a quantitative descriptor  $x \in \mathbb{R}$  – a label of the bacterial strain with resistance level  $x$  – describing the level of resistance. Most of the modelling approaches devoted to AMR tackling the case of qualitative (or “binary”) resistance are generally based on the dynamical interaction between two parasite strains resulting in a discrete and finite formulation of MICs [5]. This analysis ignores the evolutionary short-term transient dynamics which lead to the emergence of resistance (*eg.*, [10, 11, 14, 26, 28, 36, 39]).

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Here, we proposed a nested (or embedded) model explicitly linking the within- and between-host evolutionary dynamics. Such a nested structure is particularly important because, over the past few decades, it is clear that ecological and evolutionary dynamics are influenced by processes operating across scales [18]. Very few studies considered the continuous nature of AMR in the context of this work (*eg.*, [16]), and few studies have implemented a nested model in this context so far (*eg.*, [4, 37]). The bacterial population is assumed to be phenotypically (and genetically) diverse through the level of antimicrobial resistance  $x$ . This quantitative trait affects different components of the bacterial population life cycle, such as growth and death rates. In addition to those effects on the death and birth rates, bacterial population resistance level also mitigates the antimicrobial efficiency with respect to that population. From a theoretical point of view, properties of the within-host model proposed here are based on previous analytical quantitative genetics results developed in [7, 15].

An integro-differential equation is used to model the within-host dynamics of the bacterial population. Such a within model formulation is previously proposed in [16]. Each host individual is classified as either a treated host, labeled as  $T$ , or an untreated host, labeled as  $U$ . The model tracks the dynamics of a bacterial population within a treated host ( $b^T$ ) or an untreated host ( $b^U$ ). At time  $\tau$ , the bacteria density with resistance level  $y \in \mathbb{R}$  within a treated and untreated host is quantified by  $b_i^T(\tau, y)$  and  $b_i^U(\tau, y)$  respectively. The subscript "i" (with  $i \in \mathcal{I} = \{1, 2, \dots, n\}$ ) represents an individual immune system and then allows taking into account the immune system heterogeneity in the host population. A bacteria with resistance level  $y$  generate offspring with resistance level  $x$  at a per-capita rate  $J(x-y)p(y)b_i^\vartheta(\tau, y)$ , where  $p(y)$  is the bacterial intrinsic growth rate, and  $J(x-y)$  is the probability for a bacterial population with resistance level  $y$  to mutate towards a level  $x$  during the reproduction process. Therefore, the total number of bacteria produced at time  $\tau$  with a resistance level  $x$  is quantified by  $(1 + \int_{\mathbb{R}} b_i^\vartheta(\tau, x)dx)^{-\kappa} \int_{\mathbb{R}} J(x-y)p(y)b_i^\vartheta(\tau, y)dy$ , where  $\kappa$  is a positive parameter. The parameter  $\kappa > 0$  is introduced to impose the bacterial population homeostasis. The within-host model reads as

$$\begin{cases} \partial_\tau b_i^\vartheta(\tau, x) = \frac{1}{(1 + B_i^\vartheta(\tau))^\kappa} \int_{\mathbb{R}} J(x-y)p(y)b_i^\vartheta(\tau, y)dy - \xi_i^\vartheta(x)b_i^\vartheta(\tau, x), \\ b_i^\vartheta(0, \cdot) = b_0(\cdot), \end{cases} \quad (1.1)$$

where  $B_i^\vartheta(\tau) = \int_{\mathbb{R}} b_i^\vartheta(\tau, x)dx$ , is the total bacteria load. The term  $\xi_i^\vartheta$  accounts for the individual clearance of bacterial cells with resistance level  $x$ , either by the immune system ( $\mu_i$ ) or by the efficiency of antimicrobial pressure ( $k$ ). Thus,  $\xi_i^U(x) = \mu_i(x)$ , for untreated host, and  $\xi_i^T(x) = \mu_i(x) + k(x)$ , for treated host. Here, it is assumed that bacteria are subject to a biocidal antimicrobial pressure, *ie.* killing and not diminishing the birth rate of bacteria. Note that, the within-host model (1.1) allows to follow evolutionary parameters such as the average level of resistance for treated ( $\bar{x}_i^T(\tau)$ ) and untreated ( $\bar{x}_i^U(\tau)$ ) individuals  $\tau$ -time post infection given by

$$\bar{x}_i^\vartheta(\tau) = \int_{\mathbb{R}} x \frac{b_i^\vartheta(\tau, x)}{B_i^\vartheta(\tau)} dx, \quad \vartheta \in \{T, U\}.$$

At the between-host scale, the host population is subdivided into three states. At any time  $t$ , an individual –with the immune system's response level  $i \in \mathcal{I}$ – can be susceptible to the infection  $S_i(t)$  or infected  $I_i^\vartheta(t, \tau, \bar{x}_i^\vartheta(\tau))$ ,  $\vartheta = \{T, U\}$ . The variables  $\tau$  and  $\bar{x}_i^\vartheta(\tau)$  respectively represent the time post-infection and the average resistance level of the infected host. It is important to clearly understand the meaning of infected individuals  $I_i^\vartheta(t, \tau, \bar{x}_i^\vartheta(\tau))$ . Indeed, each infected individuals is potentially infected with multiple bacteria strains with variable frequencies and resistance levels. Therefore,  $\bar{x}_i^\vartheta(\tau)$  represent the individual resistance level quantified by the within-host dynamics through the above formula. However, for simplicity, and without loss of generality, we will note  $I_i^\vartheta(t, \tau, \bar{x}_i^\vartheta(\tau)) \equiv I_i^\vartheta(t, \tau)$  for  $\vartheta \in \{T, U\}$  and  $i \in \mathcal{I}$ .

Individual transmission and loss rates at the between-host scale,  $\tau$ -time since infection,  $\beta_i^\vartheta(\tau)$  and  $\alpha_i^\vartheta(\tau)$ , are linked to the within-host dynamics at time  $\tau$ . As an example, these parameters can be

represented as Holling functions of type II (or similarly the Beddington-DeAngelis functional response) such that, for all  $\vartheta \in \{T, U\}$ ,

$$\beta_i^\vartheta(\tau) = \frac{\beta_0 B_i^\vartheta(\tau)}{r_0 + B_i^\vartheta(\tau)} \quad \text{and} \quad \alpha_i^\vartheta(\tau) = \frac{\alpha_0 B_i^\vartheta(\tau)}{r_0 + B_i^\vartheta(\tau)} + \gamma^\vartheta(\tau), \quad (1.2)$$

where  $\beta_0$  and  $\alpha_0$  are scaling constants, and  $r_0$  is the half-saturation constant for the total bacterial load  $B_i^\vartheta$ . Note that, for the loss rate of infected individuals  $\alpha_i^\vartheta$ , the term  $\alpha_0 B_i^\vartheta / (r_0 + B_i^\vartheta)$  represents the loss due to the disease induced mortality while  $\gamma^\vartheta$  is the loss due to recovery. We can assume that the function  $\gamma^\vartheta$  is of the form

$$\gamma_i^\vartheta(\tau) = \begin{cases} 0, & \text{if } B_i^\vartheta(\tau) > B_{min}, \\ 1, & \text{if } B_i^\vartheta(\tau) \leq B_{min}, \end{cases} \quad (1.3)$$

where  $B_{min}$  is the threshold below which the infection becomes undetectable such that the infected individuals is considered as recovered.

The force of infection induced by infected individuals at time  $t$  is then given by

$$\lambda(t) = \sum_{i \in \mathcal{I}} \int_0^\infty [\beta_i^T(\tau) I_i^T(t, \tau) + \beta_i^U(\tau) I_i^U(t, \tau)] d\tau.$$

The nested model proposed here then makes it possible to simultaneously track the epidemiological dynamics of the host population as well as evolutionary quantities such as the average level of resistance at both the within- and between-host scales. Such an approach is original and to our knowledge, no study has considered nested models for the evolutionary dynamics of AMR, viewed as a continuous quantitative trait.

The dynamics of newly infected individuals (*i.e.*  $\tau = 0$ ) in each group (treated or untreated) is thus defined by (for  $\vartheta \in \{T, U\}$ )

$$I_i^\vartheta(t, \tau = 0) = q_i^\vartheta \lambda(t) S_i(t), \quad (1.4)$$

where  $q_i^T \in (0, 1)$  is the treatment rate in the host population and  $q_i^U = 1 - q_i^T$ . During their infection, treated individuals can stop the treatment at rate  $\omega_U^T(\tau)$ , and untreated infections can join the treated group at rate  $\omega_T^U(\tau)$ . The loss rate of infected individuals  $\tau$ -time post infection occurs at rate  $\alpha_i^\vartheta(\tau)$ . Susceptible individuals are recruited at a constant rate  $\Lambda_i$  and the natural death rate of the host population is  $\mu_h$ . The between-host model then reads

$$\begin{cases} \dot{S}_i(t) = \Lambda_i - S_i(t)\lambda(t) - \mu_h S_i(t), \\ (\partial_t + \partial_\tau) I_i^T(t, \tau) = -(\alpha_i^T(\tau) + \omega_U^T(\tau) + \mu_h) I_i^T(t, \tau) + \omega_T^U(\tau) I_i^U(t, \tau), \\ (\partial_t + \partial_\tau) I_i^U(t, \tau) = -(\alpha_i^U(\tau) + \omega_T^U(\tau) + \mu_h) I_i^U(t, \tau) + \omega_U^T(\tau) I_i^T(t, \tau), \\ S_i(0) = S_{i,0}, \quad I_i^\vartheta(0, \tau) = I_{i,0}^\vartheta(\tau). \end{cases} \quad (1.5)$$

Finally, the nested within-host (1.1) and between-host model (1.4)-(1.5) are summarised by Figure 1. The main variables and parameters are listed in Table 1. We emphasize that the dynamical properties (that we will recall later) of within-host model (1.1) are precisely analyzed in [16]. Therefore, our main objective here is devoted to the analysis of the nested model (1.1)-(1.5).

The rest of this work is organized as follows. In Section 2, we state the main results of the nested model that are obtained in this work. These include the existence of the globally defined non-negative semiflow and the existence of the unique positive equilibrium for the within-host model, and global threshold analysis results for the between-host model. The model's typical dynamics are provided in Section 3. This includes the within- and between-host models parameterization and the characterization of the evolutionary parameters such as the average levels of resistance. In Section 4, we delve into the effects of various parameters on the equilibrium structure of the host population, along with addressing the parameterization issue within nested models. Section 5 focuses on providing preliminary results.

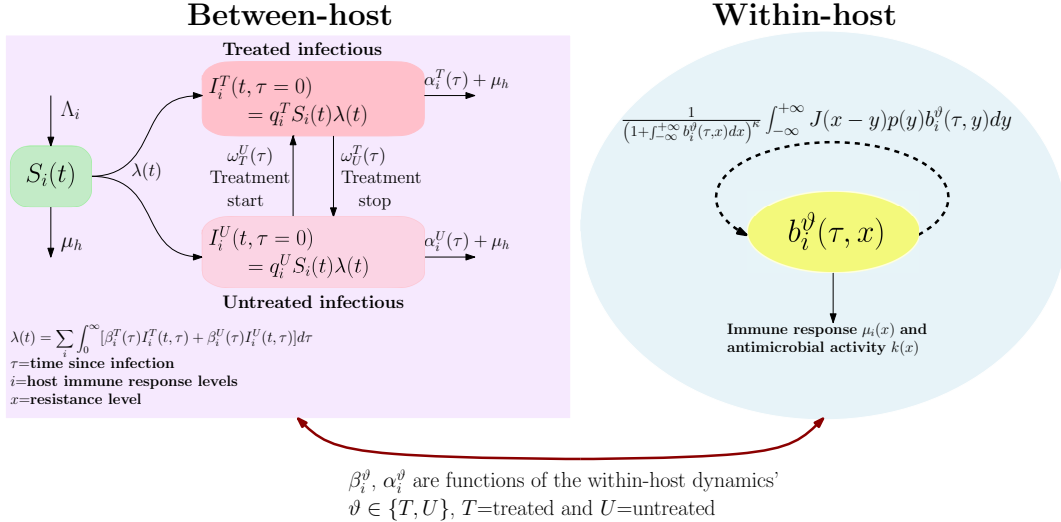


Figure 1: Flow diagram of the nested model. **Within-host model:** The number of bacteria produced at time  $\tau$  with resistance level  $x$  is  $\frac{1}{(1 + \int_{-\infty}^{+\infty} b_i^\vartheta(\tau, x) dx)^\kappa} \int_{-\infty}^{+\infty} J(x-y) p(y) b_i^\vartheta(\tau, y) dy$ , where  $J(x-y)$  is the probability for a bacterial with resistance level  $y \in \mathbb{R}$  to mutate towards a level  $x \in \mathbb{R}$  and  $p(y)$  is the bacterial intrinsic growth rate. Bacterial cells with resistance level  $x$ , within an individual with immune system level  $i$  are cleared either by the immune system at rate  $\mu_i(x)$  or by the antimicrobial efficiency at rate  $k(x)$ . **Between-host model:** Susceptible individuals are recruited at a constant rate  $\Lambda_i$ .  $I_i^T(t, \tau)$  and  $I_i^U(t, \tau)$  are respectively treated and untreated infected individuals at time  $t$ , which are infected since time  $\tau$ . The force of infection in the whole population at time  $t$  is  $\lambda(t) = \sum_{i \in \mathcal{I}} \int_0^\infty [\beta_i^T(\tau) I_i^T(t, \tau) + \beta_i^U(\tau) I_i^U(t, \tau)] d\tau$ , with  $\beta_i^\vartheta(\tau)$  the disease transmission rate of an infected individual  $\tau$ -time post infection. At the time  $t$ , new infections occur at rate  $\lambda(t) S_i(t)$ , and are either treated with a probability  $q_i^T$  or untreated with a probability  $q_i^U = 1 - q_i^T$ . The natural death rate of individuals is  $\mu_h$ . If infected since time  $\tau$ , the loss rate is  $\alpha_i^\vartheta(\tau)$ . Untreated individuals, and infected since time  $\tau$  start the treatment at rate  $\omega_T^U(\tau)$  while treated individuals stop the treatment at rate  $\omega_T^T(\tau)$ .

Specifically, it addresses the existence and uniqueness of solutions, derivation of the basic reproduction number, and the existence of a unique endemic equilibrium for System (1.4)-(1.5). Finally, Section 6 is devoted to the proof of the global asymptotic results.

## 2 Main results

This section is devoted to the main results of the nested model (1.1)-(1.5). Such results include the existence of the unique maximal bounded semiflow, and a precise description of the unique positive equilibrium of Model (1.4)-(1.5). By providing global stability results, we will also conduct a precise threshold analysis of the between-host model (1.4)-(1.5).

First of all, for biological feasibility of the nested model (1.1)-(1.5), we make use of the following assumptions. More precisely, the within-host model (1.1) is formulated based on the following assumption

**Assumption 2.1** 1. Functions  $\mu_i, k, \xi_i^\vartheta$ , and  $p$  are always positive on  $\mathbb{R}$ , with  $\vartheta \in \{T, U\}$ . Furthermore,  $p$  is a bounded function on  $\mathbb{R}$  and  $\kappa > 0$ . Finally, the function  $\frac{p}{\xi_i^\vartheta}$  is continuous on  $\mathbb{R}$  and satisfies  $\frac{p}{\xi_i^\vartheta} > 0$  and  $\lim_{|x| \rightarrow \infty} \frac{p}{\xi_i^\vartheta}(x) = 0$ .

2. The mutation kernel  $J$  is bounded and integrable on  $\mathbb{R}^+$ , positive almost everywhere, and satisfies  $\int_{\mathbb{R}^+} J(x) dx > 0$ ,  $J(-x) = J(x)$ , for all  $x$ .

Table 1: Within- and between-host model variables and parameters

<b>Notations</b>	
$t$	Time
$\tau$	Time since infection (infection age)
$x$	Resistance level
$i$	host immune response level
Model state variables	
<b>Within-host</b>	
$b_i^T(\tau, x)$	Bacteria density with resistance level $x$ at time $\tau$ in a treated host.
$b_i^U(\tau, x)$	Bacteria density with resistance level $x$ at time $\tau$ in an untreated host.
<b>Between-host</b>	
$S_i(t)$	Susceptible humans at time $t$
$I_i^T(t, \tau)$	Treated infected humans, infected since time $\tau$
$I_i^U(t, \tau)$	Untreated infected humans, infected since time $\tau$
Model parameters	
<b>Within-host</b>	
$\kappa$	Limitation on bacterial growth factor
$J(x - y)$	Mutation probability from resistance level $x$ to $y$ per cell division
$p(x)$	Intrinsic growth rate of bacterial population with resistance level $x$
$k(x)$	Killing rate of bacterial population with resistance level $x$ due to drug
$\mu_i(x)$	Individual clearance rate of the bacterial cell with resistance level $x$ due to the immune response
$\xi_i^U(x) = \mu_i(x)$	Bacteria clearance rate with resistance level $x$ in untreated hosts
$\xi_i^T(x) = k(x) + \mu_i(x)$	Bacteria clearance rate with resistance level $x$ in treated hosts due to the immune response and drug
<b>Between-host</b>	
$\beta_i^\vartheta(\tau), \vartheta \in \{T, U\}$	Transmission rate of infected individuals
$\alpha_i^\vartheta(\tau), \vartheta \in \{T, U\}$	Loss rate of infected individuals
$\omega_U^T(\tau)$	Rate of treatment cessation
$\omega_T^U(\tau)$	Rate of treatment start
$q_i^T$	Proportion of treated hosts
$q_i^U = 1 - q_i^T$	Proportion of untreated hosts
$\Lambda_i$	Recruitment rate of susceptibles
$\mu_h$	Human natural death rate

3. The mutation kernel  $J$  decays rather rapidly towards infinity in the sense that  $J(x) = O\left(\frac{1}{|x|^\infty}\right)$  as  $|x| \rightarrow \infty$ . In other words,  $\lim_{|x| \rightarrow \infty} |x|^n J(x) = 0$ , for all  $n \in \mathbb{N}$ .

Furthermore, the between-host model's parameters satisfy the following assumption.

- Assumption 2.2**
1. Recruitment rate  $\Lambda_i$  ( $i \in \mathcal{I}$ ) and natural death rate  $\mu_h$  are positive constants.
  2. The treatment rates  $q_i^\vartheta$  ( $i \in \mathcal{I}$ ,  $\vartheta \in \{T, U\}$ ) are positive constants.
  3. The rates  $\omega_T^T, \omega_T^U$  belongs to  $L^\infty(\mathbb{R}_+)$ , with respective essential upper bounds  $\bar{\omega}_T^T, \bar{\omega}_T^U$  and positive essential lower bounds  $\underline{\omega}_T^T, \underline{\omega}_T^U$ .
  4. Parameters  $\beta_i^\vartheta$  and  $\alpha_i^\vartheta$  ( $i \in \mathcal{I}$ ,  $\vartheta \in \{T, U\}$ ) are such that  $\beta_i^\vartheta, \alpha_i^\vartheta \in L^\infty(\mathbb{R}_+)$ .
  5. The transmission rates  $\beta_i^\vartheta(\cdot)$ ,s are Lipschitz continuous almost everywhere on  $\mathbb{R}_+$ .

## 2.1 Summary key findings on the within-host dynamics

The dynamical properties of the within-host model (1.1) have been precisely investigated in [16]. The first result of Model (1.1) is about the existence of the unique maximal bounded semiflow. Such a result reads as,

**Theorem 2.3** *Let Assumption 2.1 be satisfied. Let  $b_{i0}^\vartheta \in L_+^1$ . Then,*

1. There exists a unique global solution  $v(\cdot, b_{i0}^\vartheta) : [0, \infty) \rightarrow L_+^1(\mathbb{R})$  of (1.1) with  $v(0, b_{i0}^\vartheta) = b_{i0}^\vartheta$  and  $v(\tau, b_{i0}^\vartheta) = b_i^\vartheta(\tau, \cdot)$  for all  $\tau > 0$ .
2. The semi-flow defined by  $\{v(\tau, b_{i0}^\vartheta)\}_\tau$  is bounded dissipative and asymptotically smooth, and hence, its admits a global attractor in  $L_+^1(\mathbb{R})$ .
3. The semi-flow  $\{v(\tau, b_{i0}^\vartheta)\}_\tau$  is such that for any  $b_{i0}^\vartheta \in L_+^1(\mathbb{R}) \setminus \{0\}$ ,  $b_i^\vartheta(\tau, x) > 0$ , for all  $\tau > 0$ ,  $x \in \mathbb{R}$ .

The basic reproduction number  $\mathcal{N}_{i0}^\vartheta$  – defined as the expected number of bacteria arising from one bacterium in a bacteria-free environment– of the bacteria population with resistance level  $x$ , within an individual with immune system level  $i$ , is calculated as

$$\mathcal{N}_{i0}^\vartheta(x) = \frac{p(x)}{\xi_i^\vartheta(x)}, \text{ for } \vartheta \in \{U, T\}. \quad (2.1)$$

Next, a non-trivial equilibrium of Model (1.1) is strongly related to the principal eigenpair of the below linear integral operator  $H_i^\vartheta$  defined on  $L^p(\mathbb{R})$  (for any  $p \geq 1$ ), by

$$H_i^\vartheta[v_i^\vartheta](x) = \sqrt{\mathcal{N}_{i0}^\vartheta(x)} \int_{\mathbb{R}} J(x-y) \sqrt{\mathcal{N}_{i0}^\vartheta(y)} v_i^\vartheta(y) dy. \quad (2.2)$$

We then have the following result.

**Theorem 2.4** *Let  $r(H_i^\vartheta)$ , the spectral radius of the operator  $H_i^\vartheta$ , and  $\phi > 0$  the associated eigenfunction normalized such that  $\|\phi\|_{L^1} = 1$ .*

1. When  $r(H_i^\vartheta) \leq 1$ , the bacteria-free equilibrium  $F_{i0}^\vartheta$  is the unique equilibrium of Model (1.1).

2. When  $r(H_i^\vartheta) > 1$ , in addition to  $F_{i0}^\vartheta$ , Model (1.1) has a unique equilibrium  $\bar{F}_i^\vartheta > 0$  such that

$$\bar{F}_i^\vartheta(x) = \left( \frac{(r(H_i^\vartheta))^{\frac{1}{\kappa}} - 1}{\int_{\mathbb{R}} \frac{\phi}{\sqrt{p} \xi_i^\vartheta} dy} \right) \frac{\phi(x)}{\sqrt{p(x) \xi_i^\vartheta(x)}}. \quad (2.3)$$

Furthermore, the semi-flow  $\{v(\tau, b_{i0}^\vartheta)\}_\tau$  is uniformly persistent, that is, there exists a constant  $\eta$  such that for any  $b_{i0}^\vartheta \in L_+^1(\mathbb{R}) \setminus \{0\}$ , the unique solution  $v(\tau, b_{i0}^\vartheta) = b_i^\vartheta(\tau, \cdot)$  of Model (1.1) with initial data  $b_{i0}^\vartheta$  satisfies  $\liminf_{\tau \rightarrow \infty} \|b_i^\vartheta(\tau, \cdot)\|_{L^1} > \eta$ .

3. The bacteria-free equilibrium  $F_{i0}^\vartheta$  of Model (1.1) is asymptotically stable if  $r(H_i^\vartheta) < 1$  and unstable if  $r(H_i^\vartheta) > 1$ .

4. When  $r(H_i^\vartheta) < 1$ , the bacteria-free equilibrium  $F_{i0}^\vartheta$  is globally asymptotically stable in  $L_+^1(\mathbb{R})$ , that is, for any solution  $b_i^\vartheta(\tau, \cdot)$  with initial  $b_{i0}^\vartheta \in L_+^1(\mathbb{R}) \setminus \{0\}$ , we have  $b_i^\vartheta(\tau, \cdot) \rightarrow 0$  in  $L_+^1(\mathbb{R})$ , as  $\tau \rightarrow \infty$ .

We recall that the within-host model (1.1) is precisely analyzed in [16]. We then refer to Appendices F-I in [16] for the detailed proof of Theorem 2.3 and 2.4. Note that the linear operator  $H_i^\vartheta$  naturally emerges when characterizing the positive equilibrium of the within-host model (1.1) [16].

Furthermore, the estimate (2.3) gives that the endemic equilibrium  $\bar{F}_i^\vartheta$  of the within-host model (1.1) basically relied to the principal eigenfunction of the linear operator  $H_i^\vartheta$  for any given probability kernel  $J$  satisfying Assumption 2.1. However, the profile of the endemic equilibrium  $\bar{F}_i^\vartheta$  with respect to  $x \in \mathbb{R}$  can be precisely described when the mutation kernel  $J$  depends on a small positive parameter (let say  $\varepsilon \ll 1$ ) with the scaling form

$$J_\varepsilon(x) = \varepsilon^{-1} J(\varepsilon^{-1}x), \quad (2.4)$$

where  $\varepsilon > 0$  represents the mutation variance in the phenotypic space. More precisely, when  $\varepsilon > 0$  is small, then the endemic equilibrium  $\bar{F}_i^\vartheta$  concentrates on the set  $\mathcal{S}_i^\vartheta$  defined by

$$\mathcal{S}_i^\vartheta = \left\{ x \in \mathbb{R} : \mathcal{N}_{i0}^\vartheta(x) = \|\mathcal{N}_{i0}^\vartheta\|_\infty \right\}.$$

The set  $\mathcal{S}_i^\vartheta$  is referred to as the set of Evolutionary Attractors (or dominant strains) of the within-host model in the classical adaptive dynamics theory (eg., [20, 35]). Furthermore, when the function  $\mathcal{N}_{i0}^\vartheta$  is at least of class  $\mathcal{C}^1$ , with a finite number of maximum, it is shown in [15] that these dominant strains coincide with the set  $\mathcal{S}_i^\vartheta$ . Denoting by  $H_{i,\varepsilon}^\vartheta$ , the operator  $H_i^\vartheta$  –by replacing the kernel  $J$  by  $J_\varepsilon$ – by results in [15] (Theorem 2.2), the spectral radius  $r(H_{i,\varepsilon}^\vartheta)$  of  $H_{i,\varepsilon}^\vartheta$  satisfied, for  $\varepsilon$  sufficiently small

$$r(H_{i,\varepsilon}^\vartheta) = \left( \mathcal{N}_{i0}^\vartheta(x^*) \right)^2 + \mathcal{O}(\varepsilon), \quad \text{for all } x^* \in \mathcal{S}_i^\vartheta.$$

By the above estimate,  $\text{sign} \left[ r(H_{i,\varepsilon}^\vartheta) - 1 \right] = \text{sign} \left[ \mathcal{N}_{i0}^\vartheta(x^*) - 1 \right]$ , for all  $x^* \in \mathcal{S}_i^\vartheta$  and  $\varepsilon$  sufficiently small.

Furthermore, if  $\varepsilon \ll 1$ ,  $\mathcal{S}_i^\vartheta = \{x_i^*\}$  and  $\mathcal{N}_{i0}^\vartheta(x_i^*) > 1$ , then the unique positive stationary state  $\bar{F}_i^\vartheta \equiv \bar{F}_{i,\varepsilon}^\vartheta$ , given by (2.3), of the within-host model (1.1) is concentrated around the evolutionary attractor  $x_i^*$  in the space of resistance level  $\mathbb{R}$ . In other words,  $x_i^*$  is the average bacterial resistance level at the within-host scale equilibrium and we have  $\lim_{\varepsilon \rightarrow 0} \int_{\mathbb{R}} u(x) \bar{F}_{i,\varepsilon}^\vartheta(x) dx = u(x_i^*)$  for any continuous function  $u \in \mathcal{C}(\mathbb{R})$ . We refer to Theorem 2.3 in [15] for such a concentration phenomenon.

## 2.2 Key findings of the nested within- and between-host dynamics

At the between-host scale, by setting  $\mathbf{S}(t) = (S_i(t))_{i \in \mathcal{I}}$ ,  $\mathbf{I}_i(t, \tau) = (I_i^T(t, \tau), I_i^U(t, \tau))$ ,  $\mathbf{I}(t, \tau) = (\mathbf{I}_i(t, \tau))_{i \in \mathcal{I}}$ ,  $\boldsymbol{\alpha}_i(\tau) = \text{diag}(\alpha_i^T(\tau), \alpha_i^U(\tau))$ ,  $\boldsymbol{\beta}_i(\tau) = (\beta_i^T(\tau), \beta_i^U(\tau))$ ,  $\mathbf{q}_i = (q_i^T, q_i^U)$ ,  $\boldsymbol{\omega}(\tau) = \begin{pmatrix} 0 & \omega_T^U(\tau) \\ \omega_U^T(\tau) & 0 \end{pmatrix}$ , and



$e = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}$ , System (1.4)-(1.5) rewrites into the following compact form,

$$\begin{cases} \dot{\mathbf{S}}(t) = \mathbf{\Lambda} - \mathbf{S}(t)\lambda(t) - \mu_h \mathbf{S}(t), \\ \mathbf{I}(t, \tau = 0) = \lambda(t) \text{diag}(\mathbf{S}(t)) \mathbf{q}, \\ (\partial_t + \partial_\tau) \mathbf{I}(t, \tau) = (-\text{diag}(\mathbf{\Phi}(\tau)) + \text{diag}(\boldsymbol{\omega}(\tau))) \mathbf{I}(t, \tau), \end{cases} \quad (2.5)$$

where  $\lambda(t) = \sum_i \int_0^\infty \langle \boldsymbol{\beta}_i(\tau), \mathbf{I}_i(t, \tau) \rangle d\tau$ ,  $\mathbf{\Lambda} = (\Lambda_i)_{i \in \mathcal{I}}$ ,  $\mathbf{q} = (\mathbf{q}_i)_{i \in \mathcal{I}}$ ,  $\mathbf{\Phi}(\tau) = (\Phi_i(\tau))_{i \in \mathcal{I}}$ , with  $\Phi_i(\tau) = e\boldsymbol{\omega}(\tau) + \boldsymbol{\alpha}_i(\tau) + \mu_h$ .

Using the next-generation operator approach (eg., [12, 25]), the basic reproduction number  $\mathcal{R}_0^i$  of the whole infected individuals of group  $i$ , is given by

$$\mathcal{R}_0^i = \frac{\Lambda_i}{\mu_h} \sum_{k \in \mathcal{I}} \int_0^\infty \langle \boldsymbol{\beta}_k(\tau), \mathbf{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle d\tau = \frac{\Lambda_i}{\mu_h} \sum_{k \in \mathcal{I}} \chi_k,$$

where

$$\chi_k = \int_0^\infty \langle \boldsymbol{\beta}_k(\tau), \mathbf{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle d\tau,$$

and where  $\mathbf{\Pi}_i(\tau_2, \tau_1)$ ,  $0 \leq \tau_1 \leq \tau_2 < \infty$ , is the evolutionary system generated by the linear operator  $[-\mathbf{\Phi}_i(\tau) + \boldsymbol{\omega}(\tau)]$ ; see Remark 2.5 for some details on  $\mathbf{\Pi}_i$ . Moreover, the basic reproduction number  $\mathcal{R}_0$  at the whole between-host scale is such that

$$\mathcal{R}_0 = \sum_{i \in \mathcal{I}} \frac{\Lambda_i}{\mu_h} \chi_i = \sum_{i \in \mathcal{I}} \underbrace{\frac{\chi_i}{\sum_{k \in \mathcal{I}} \chi_k}}_{\substack{\text{Overall relative infectiousness} \\ \text{of individuals of group } i.}} \times \mathcal{R}_0^i. \quad (2.6)$$

We refer to Section 5.2 for details of the computation of  $\mathcal{R}_0^{i,s}$  and  $\mathcal{R}_0$ .

Note that the parameter  $\chi_k$  quantifies the overall infectiousness of the whole infected individuals of group  $k \in \mathcal{I}$ . A more explicit expression of the infectiousness  $\chi_k$  is difficult to obtain in general. However, one can go further steps in some particular configurations of the treatment status transition rates  $\boldsymbol{\omega}(\tau)$ . Indeed, assume that we can find  $\tau_0 > 0$  and  $\tau_1 > 0$  such that

$$\boldsymbol{\omega}_T^U(\tau) = \begin{cases} 0, & \text{for } \tau < \tau_0, \\ \bar{\omega}_1, & \text{for } \tau_0 < \tau < \tau_0 + \tau_1, \end{cases} \quad \text{and} \quad \boldsymbol{\omega}_U^T(\tau) = 0, \quad \text{for } \tau < \tau_0 + \tau_1. \quad (2.7)$$

In the above scenario, the regimen  $(0, \tau_0)$ -post infection may corresponds to the initial phase where each infections, either treated or untreated, remain to their initial treatment status. The second regimen  $(\tau_0, \tau_0 + \tau_1)$ -post infection may corresponds to the phase during which previously untreated infections becomes treated while treated infections remain to their initial status. In such a configuration, we have (see Section 5.2 for details)

$$\chi_k = q_k^T \chi_k^T + q_k^U \chi_k^U + \mathcal{O}\left(e^{-c_k(\tau_0 + \tau_1)}\right),$$

with  $c_k = \mu_h + \inf_\tau \alpha_k^U(\tau) + \inf_\tau \alpha_k^T(\tau)$ ,

$$\begin{aligned} \chi_k^T &= \int_0^{\tau_0 + \tau_1} \beta_k^T(\tau) \Gamma_0^{k,T}(\tau) d\tau + \Gamma_0^{k,T}(\tau_0) \bar{\omega}_1 \int_{\tau_0}^{\tau_0 + \tau_1} \beta_k^T(\tau) \int_{\tau_0}^\tau \frac{\Gamma_1^{k,T}(\tau)}{\Gamma_1^{k,T}(\eta)} \Gamma_1^{k,U}(\eta) d\eta d\tau, \\ \chi_k^U &= \int_0^{\tau_0} \beta_k^U(\tau) \Gamma_0^{k,U}(\tau) d\tau + \Gamma_0^{k,U}(\tau_0) \int_{\tau_0}^{\tau_0 + \tau_1} \beta_k^U(\tau) \frac{\Gamma_1^{k,U}(\tau)}{\Gamma_1^{k,U}(\tau_0)} d\tau, \end{aligned}$$

and

$$\begin{aligned}\Gamma_0^{k,\vartheta}(\tau) &= e^{-\mu_h\tau} e^{-\int_0^\tau \alpha_k^\vartheta(\sigma) d\sigma}, \quad \vartheta \in \{T, U\}, \\ \Gamma_1^{k,U}(\tau) &= e^{-(\bar{\omega}_1 + \mu_h)\tau} e^{-\int_0^\tau \alpha_k^U(\sigma) d\sigma}, \quad \Gamma_1^{k,T}(\tau) = e^{-\mu_h\tau} e^{-\int_0^\tau \alpha_k^T(\sigma) d\sigma}.\end{aligned}$$

Note that parameters  $\Gamma_0^{k,\vartheta}$ 's and  $\Gamma_1^{k,\vartheta}$ 's are survival probabilities during phases  $(0, \tau_0)$  and  $(\tau_0, \tau_0 + \tau_1)$ -post infection of infected individuals of group  $k \in \mathcal{I}$ , treated ( $\vartheta = T$ ) or untreated ( $\vartheta = U$ ).

**Remark 2.5** Let  $\mathbf{\Pi}_i(\tau_2, \tau_1)$ ,  $0 \leq \tau_1 \leq \tau_2 < \infty$ , the evolutionary system generated by the linear operator  $\mathbf{A}_i(\tau) := -\mathbf{\Phi}_i(\tau) + \boldsymbol{\omega}(\tau)$ . It means that  $\mathbf{\Pi}_i$  is generated from the following evolutionary system

$$(\partial_t + \partial_\tau) I_i(t, \tau) = \mathbf{A}_i(\tau) I_i(t, \tau). \quad (2.8)$$

If, for example, the linear operator  $\mathbf{A}_i$  is diagonal, we have

$$I_i(t, \tau) = \begin{cases} e^{\int_0^\tau \mathbf{A}_i(\eta) d\eta} I_i(t - \tau, 0) = \mathbf{\Pi}_i(\tau, 0) I_i(t - \tau, 0); & t > \tau \\ e^{\int_{\tau-t}^\tau \mathbf{A}_i(\eta) d\eta} I_i(0, \tau - t) = \mathbf{\Pi}_i(\tau, \tau - t) I_i(0, \tau - t); & t < \tau. \end{cases}$$

In such a configuration we explicitly have  $\mathbf{\Pi}_i(\tau_2, \tau_1) = e^{\int_{\tau_1}^{\tau_2} \mathbf{A}_i(\eta) d\eta}$ . However, obtaining an explicit expression for  $\mathbf{\Pi}_i$  may not always be straightforward or possible in general. A naive approach would be to solve problem (2.8) as above, but it is well known that such an exponent formula does not give a solution to the problem at hand.

In addition to the disease-free equilibrium –the DFE–  $\mathbf{E}^0 = (\mathbf{S}^0, \mathbf{0}_{L^1((0,\infty), \mathbb{R}^{2n})})$ , with  $\mathbf{S}^0 = (\Lambda_i / \mu_h)_{i \in \mathcal{I}}$ , which is always an equilibrium of Model (1.4)-(1.5), this model also exhibits an endemic equilibrium given by the following result

**Theorem 2.6** Let Assumptions 2.1 and 2.2 hold. If  $\mathcal{R}_0 > 1$ , then system (1.4)-(1.5) has a unique endemic equilibrium  $\mathbf{E}^* = (\mathbf{S}^*, \mathbf{I}^*(\tau))$ , such that  $\forall i \in \mathcal{I}$ ,

$$S_i^* = \frac{S_i^0}{\mathcal{R}_0} \quad \text{and} \quad \mathbf{I}_i^*(\tau) = \lambda^* S_i^* \mathbf{\Pi}_i(\tau, 0) \mathbf{q}_i,$$

where  $\lambda^* = \mu_h(\mathcal{R}_0 - 1)$ .

Therefore, the threshold dynamics of Model (1.4)-(1.5) is summarized as follows

**Theorem 2.7** Let Assumptions 2.1 and 2.2 hold. Then,

- (i) If  $\mathcal{R}_0 \leq 1$  or  $\sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau), \mathbf{I}_{i0}(\tau) \rangle d\tau = 0$ , then the disease-free equilibrium  $\mathbf{E}^0 = (\mathbf{S}^0, \mathbf{0}_{L^1((0,\infty), \mathbb{R}^{2n})})^t$  of system (1.4)-(1.5) is globally asymptotically stable in the sens that

$$\lim_{t \rightarrow \infty} (S_i(t), I_i^T(t, \cdot), I_i^U(t, \cdot))_{i \in \mathcal{I}} = \mathbf{E}^0,$$

where the above convergence holds for the topology of  $\mathbb{R}^n \times L^1((0, \infty), \mathbb{R}^{2n})$ .

- (ii) If  $\mathcal{R}_0 > 1$  and  $\sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau), \mathbf{I}_{i0}(\tau) \rangle d\tau > 0$ , then the endemic equilibrium  $\mathbf{E}^*$  of system (1.4)-(1.5) is globally asymptotically stable, that is,

$$\lim_{t \rightarrow \infty} (S_i(t), I_i^T(t, \cdot), I_i^U(t, \cdot))_{i \in \mathcal{I}} = \mathbf{E}^*,$$

for the topology of  $\mathbb{R}^n \times L^1((0, \infty), \mathbb{R}^{2n})$ .

### 3 Numerical illustrations

Here, we present a series of numerical simulations employing semi-explicit finite difference numerical schemes. We refer to [13] for an example of a code repository within the context of the model proposed here. We illustrate an example of typical dynamics that can be simulated by the nested model (1.1)-(1.5). The model simultaneously captures the outbreak dynamics as well as the evolutionary dynamics of the average resistance level within the host population. The within-host model parameters are basically the same as in [16]. Intuitively there exist two threshold levels, assumed here 0 and 1 (called reference "sensitive" and "resistant" strains) such that, a strain with resistance level  $x$  can be classically referred to as "sensitive", "intermediate", or "resistant" depending on whether  $x < 0$ ,  $0 < x < 1$ , or  $x > 1$ . For sake of simplicity, we assume that the host population is homogeneous in terms of immune system level, *i.e.*,  $\text{card}(\mathcal{I}) = 1$ . For all illustrative scenarios, we will have  $\mathcal{R}_0 > 1$  such that the disease is persistent at the between-host scale (Theorem 2.7). The probability density function at the within-host scale ( $J \equiv J_\varepsilon$ ) is assumed of type (2.4). Specifically, we define  $J_\varepsilon$  as a Gaussian distribution  $J_\varepsilon(x) = \frac{1}{\varepsilon\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{x}{\varepsilon}\right)^2}$ , where  $\varepsilon > 0$  represents a small parameter that signifies the mutation variance within the phenotypic space.

**Within-host parameterization.** The antimicrobial killing rate function  $k(\cdot)$  is a decreasing function with respect to the resistance level  $x$  such that,  $k(x) = k_0 \left(\frac{k_1}{k_0}\right)^x$ , where  $k_0$  and  $k_1$  are the antimicrobial activity undergone by the reference sensitive and resistant strains. Moreover, knowing  $p_0$  and  $p_1$ , respectively the intrinsic growth rate of reference strains 0 and 1, a suitable expression for function of  $p$  is  $p(x) = p_m \left[1 + \left(\frac{p_m - p_0}{p_0}\right) \left(\frac{p_0}{p_1} \cdot \frac{p_m - p_1}{p_m - p_0}\right)^x\right]^{-1}$ , where  $p_m$  is the upper bound of the intrinsic growth rate  $p$  and  $0 < p_1 < p_0 < p_m$ . The qualitative behaviour of functions  $k$  and  $p$  can be found in ([16], Figure 2). We assume that the clearance rate of the bacteria cell due to the immune response,  $\mu(\cdot)$ , is a constant function given by  $\mu(x) = \mu$ . Furthermore, the average fitness cost-benefit ratio of resistance within a bacterial population can be expressed as  $c_b = \frac{\log(\Delta)}{\log(1+\delta)}$ . Here,  $\Delta = \frac{(p_m - p_1)/p_1}{(p_m - p_0)/p_0} > 1$  quantifies the relative cost of resistance, while  $\delta = \frac{k_0 - k_1}{k_1} > 0$  measures the fitness advantage of the reference resistant strain (see [16] for details).

**Between-host parameterization.** Parameters  $\beta_i^\vartheta$  and  $\alpha_i^\vartheta$  are defined using Holling type functional responses introduced by (1.2). For all simulations, the threshold  $B_{min}$ , introduced by (1.3), below which the infection becomes undetectable such that the infected individuals is considered as recovered is fixed as  $B_{min} = 10^{-3}B_0$ , with  $B_0 = B(0)$  the initial total bacteria load. The total bacteria load ( $B_i^\vartheta(\tau)$ ) and the recovery probability ( $1 - \exp(-\int_0^\tau \gamma_i^\vartheta(s)ds)$ ),  $\tau$ -time post infection, are illustrated in Figure 2.

Furthermore, an untreated infected individual joins the treated compartment when her total bacteria load is above a threshold  $(1 + \theta)B_0$ , with  $\theta \geq 0$ . Therefore, the influx rate from untreated to treated is assumed to be a function with respect to time  $\tau$  and is defined as follows

$$\omega_T^U(\tau) = \begin{cases} 0, & \text{if } B^U(\tau) \leq (1 + \theta)B_0, \\ 1, & \text{if } B^U(\tau) > (1 + \theta)B_0. \end{cases} \quad (3.1)$$

Similarly, we assume that an infected individual under treatment can drop down such a treatment when the bacteria load reach the same range as before the treatment. Therefore, the influx rate from treated to untreated is given by

$$\omega_U^T(\tau) = \begin{cases} 0, & \text{if } B^T(\tau) \leq B_0, \\ 1, & \text{if } B^T(\tau) > B_0. \end{cases} \quad (3.2)$$

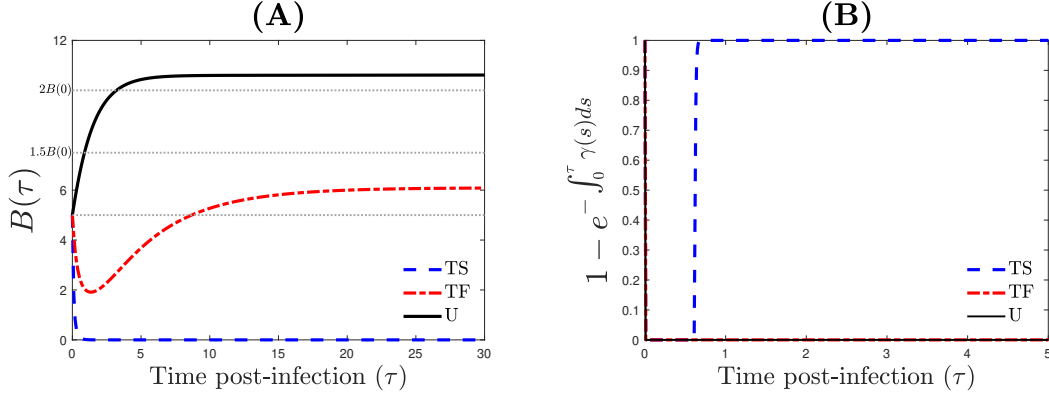


Figure 2: Illustration of the within- and between-host parameterization of infected individuals, either untreated –U, under treatment failure –TF, or under treatment with success –TS. (A) The total bacteria load  $B^\vartheta(\tau)$ . (B) The recovery probability  $1 - \exp(-\int_0^\tau \gamma^\vartheta(s)ds)$ .

**Initial conditions and model outputs.** The initial bacterial population  $b_0^\vartheta(x)$  is assumed to be composed by a sensitive bacterial population with average resistance level  $x = 0$ . Hence, we set  $b_0^\vartheta(x) = m_0 \times \mathcal{N}(0, \sigma_0, x)$ , where  $\mathcal{N}(0, \sigma_0, x)$  stands for the normalized density function of the Gaussian distribution at  $x$  with mean 0 and variance  $\sigma_0^2$ . This means that the initial bacterial population is mostly composed of the reference "sensitive" strain. At the between-host scale, the initial condition of the epidemiological model is taken such that the susceptible population starts close to its disease-free equilibrium. More precisely, assuming an initial infection prevalence denoted as  $P_{\text{rev}} = 10\%$ , we derive the initial susceptible population as  $S_0 = (1 - P_{\text{rev}}) \frac{\Lambda}{\mu_h}$ , along with the initial distribution of infectives which consists of  $I_0^T(\tau) = 0$  and  $I_0^U(\tau) = P_{\text{rev}} \frac{\Lambda}{\mu_h} \times L(\tau)$  for all  $\tau \geq 0$ . Here,  $L(\tau) = 10 \ln(10) \times 10^{-10\tau}$ , and it is important to note that  $L$  symbolizes the arbitrary initial distribution of individuals who have been infected since time  $\tau$ . This distribution is scaled so that  $\int_{\mathbb{R}} L(\tau) d\tau = 1$ .

The average level of resistance at within-host scale ( $\eta(t)$ ) of the host population at time  $t$  is such that

$$\eta(t) = \int_0^\infty \left( \bar{x}^T(\tau) \frac{I^T(t, \tau)}{I(t)} + \bar{x}^U(\tau) \frac{I^U(t, \tau)}{I(t)} \right) d\tau,$$

where  $\bar{x}^\vartheta, s$  are the individual average level of resistance and  $I(t) = \int_0^\infty (I^T(t, \tau) + I^U(t, \tau)) d\tau$ .

**Simulated scenarios.** Two simulated scenarios are considered, the first when the treatment is successful at the within-host level, and the second when the treatment failed at the within-host level. For all our simulated scenarios, the infection is assumed here to be always successful for untreated individuals, *ie.*, the immune system alone is no more enough to control the infection such that  $\max_{x \in \mathbb{R}} \mathcal{N}_0^U(x) > 1$ , leading to the bacterial persistence for untreated infections.

Our first scenario is for the case where the treatment is successful at the within-host level, *ie.*, the basic reproduction number of treated individuals  $\mathcal{N}_0^T$  is such that  $\max_{x \in \mathbb{R}} \mathcal{N}_0^T(x) < 1$  (Figure 3C). In such a situation, the bacterial load is under control in the relatively short term for treated individuals (Figure 3A), while it remains persistent for untreated individuals (Figure 3B). At the between-host scale, the treatment rate have a strong effect on the epidemic outbreak (Figure 3F,G,H). More precisely, increasing the treatment rate  $q^T$  in the host population strongly reduce the overall epidemic size (Figure 3F,G,H), with  $\mathcal{R}_0 = 4.7815, 2.6750$  and  $0.5685$ , respectively. Furthermore, the average resistance level in the host population rapidly reach an equilibrium for which the level of resistance is moderately high compared to the initial resistance level of the host population (Figure 3E).

In the second scenario, the treatment is assumed unsuccessful at the within-host level, *ie.*, the basic reproduction number of treated individuals  $\mathcal{N}_0^T$  is such that  $\max_{x \in \mathbb{R}} \mathcal{N}_0^T(x) > 1$  (Figure 4C). In such a

situation, the bacterial load remains persistent for both treated and untreated infections (Figure 4A,B). Indeed, while we can observe an apparent decreasing of the bacteria load for some period of time for treated infections (Figure 4A), at the end, we have the re-emergence of the bacteria population at within-host scale. Such a transient dynamics is explain by the fact that the initiation of treatment modifies the fitness landscape by shifting the maximum point of the within-host basic reproduction number  $\mathcal{N}_0^T$  to the point  $x = x^* > 0$  (Figure 4C). In contrast to the treatment success scenario (Figure 3), increasing the treatment rate  $q^T$  in the host population have marginal effect in controlling the epidemic outbreak (Figure 4F,G,H). In fact, with  $q^T = 0.1, 0.5$  and  $0.9$ , the outbreak remains persistent with  $\mathcal{R}_0 = 10.9451, 9.5855$  and  $8.2259$ , respectively. Significantly, it is worth noting that although the average resistance level in the host population continues to rise with the treatment rate  $q^T$  at equilibrium (Figure 4E), there is a substantial increase in the range of resistance levels compared to the initial resistance level. This stands in contrast to the treatment success scenario (Figure 3E), where the range of resistance levels remained relatively low. Additionally, in the treatment success scenario (Figure 3E), the average resistance level in the host population quickly reaches equilibrium. However, in the treatment failure scenario (Figure 4E), there is a comparatively longer transient period before the average resistance level in the host population reaches equilibrium. Overall, during the transient regimen, there is an initial subsequent increase in the average level of resistance to significantly higher levels, followed by a small decrease (Figure 4E). This behavior is mostly attributed to the alteration of the fitness landscape caused by the treatment (Figure 4C).

## 4 Discussion

**Optimizing the treatment rate in the host population is key to controlling both the epidemic outbreak and the average level of resistance.** Increasing the treatment rate in the host population contributes to reducing the epidemic size at the between-host scale, although the effect is quite marginal in the treatment failure scenario at the within-host scale (Figures 3F,G,H and 4F,G,H). This can be primarily attributed to the fact that, even in cases of treatment failure, the within-host infection remains controlled for a certain period (Figure 4A). However, the subsequent phase is characterized by an increase in bacterial population density (Figure 4A). Conversely, raising the treatment rate within the host population leads to an elevation in the average resistance level of that population, regardless of the treatment scenario at the within-host scale (Figures 3E and 4E). However, this increase in the average resistance level is particularly pronounced in the case of treatment failure (Figure 4E), in comparison to the case of treatment success (Figure 3E). In the case of treatment success, the resistance level remains highly similar to that of the initial bacterial population. Consequently, depending on the treatment regimen implemented within the host population, it becomes essential and intriguing to determine an optimal treatment rate to effectively manage both the outbreak and the average level of antimicrobial resistance.

**The delay for treating infections can impact the epidemic outbreak as well as average level of resistance.** Assume the scenario where the treatment is successful at the within-host scale (Figure 3A) and at least 50% of infected individuals are under treatment ( $q^T \geq 0.5$ ). Two configurations are introduced. In the first configuration, untreated individuals begin treatment at a rate  $\omega_T^U$  (defined by (3.1)) when their total bacterial load reaches a threshold value of  $1.5 \times B_0$ , *ie.*,  $\theta = 0.5$ . In the second configuration, untreated individuals start treatment at a rate  $\omega_T^U$  when their total bacterial load reaches a threshold value of  $2 \times B_0$ , *ie.*,  $\theta = 1$ . The case of  $\theta = 0.5$  indicates a situation where the delay before initiating the treatment is very short. On the other hand, in the case of  $\theta = 1$ , the delay before starting the treatment is relatively more significant (Figure 2A). In general, the average resistance level in the host population decreases as the delay before initiating treatment increases (Figure 5A, B). One possible explanation is that untreated infected individuals do not significantly contribute to the increase in the average resistance level within the host population. Nevertheless, although early treatment effectively

controls the epidemic outbreak for both moderate and high treatment rates (Figure 5C,D) –with  $\mathcal{R}_0 = 0.3922$  and  $0.1120$ , respectively– delaying the treatment of infected individuals leads to an epidemic that is out of control, except in cases where the treatment rate is exceptionally high (Figure 5E,F) –with  $\mathcal{R}_0 = 2.6750$  and  $0.5685$ , respectively.

**Nested models parameterization issue.** Explicitly connecting the within- to and between-host scales are crucial to gain a more realistic picture aiming to integrate into the same modelling framework the epidemic dynamics and the evolutionary dynamics of antimicrobial resistance. However, such an approach requires making assumptions about the parameters at the within-host scale that are equally unknown as the parameters at the between-host scale and hence leading to uncertainty about the appropriate parametrization [41]. Such uncertainty is amplified by our approach where the level of resistance is considered a continuous quantitative trait, compared to the classical qualitative (or "binary") approaches [16].

**Time-scale separation hypothesis.** Within the context of nesting within- and between-host scales, for the modelling of the epidemiology and evolution of pathogens, some studies assumed that the epidemiological and evolutionary time scales are distinct, *ie.*, the within-host dynamic is fast relative to the between-host dynamic such that the within-host model remains at equilibrium, *eg.* [1, 2, 6, 9, 21, 44]. Although such an assumption on the within-host equilibrium dynamic' might be appropriate for chronic infections, it leads to a population-scale model that does not explicitly account for the individual time-dependent infectiousness dynamics [24]. Furthermore, our illustrative examples (Figures 3,4) strongly highlight the infectiousness' time-dependency of infected individuals and show that the between-host dynamic is not necessarily faster compared to the within-host dynamic.

## 5 Preliminaries and technical materials

We will go through details on the proof of our main results, namely Theorem 2.7. We will first discuss the existence of a positive global solution of the nested model. Next, we will give details on the derivation of the basic reproduction number of System (1.4)-(1.5) for individuals with an immune system of level  $i$ . We will also derive the existence of a unique endemic equilibrium of System (1.4)-(1.5) when  $\mathcal{R}_0 > 1$ , as well as the long-term persistence of the epidemic in such a case.

### 5.1 Existence of the semiflow

We establish the existence of a positive global solution of the system (2.5). We first formulate system (2.5) in an abstract Cauchy problem. For that, we introduce the Banach space  $\mathcal{X} = \mathbb{R}^n \times \mathbb{R}^{2n} \times L^1((0, \infty), \mathbb{R}^{2n})$ , endowed with the usual product norm  $\|\cdot\|_{\mathcal{X}}$  as well as its positive cone  $\mathcal{X}_+$ . Let  $A : D(A) \subset \mathcal{X} \rightarrow \mathcal{X}$  be the linear operator defined by  $D(A) = \mathbb{R}^n \times \{\mathbf{0}_{\mathbb{R}^{2n}}\} \times W^{1,1}((0, \infty), \mathbb{R}^{2n})$  and

$$A(\mathbf{S}, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{I}) = \left( -\mu_h \mathbf{S}, -\mathbf{I}(0), -\partial_\tau \mathbf{I} + (-\text{diag}(\Phi(\tau)) + \text{diag}(\omega(\tau))) \mathbf{I} \right). \quad (5.1)$$

Let us introduce the non-linear map  $F : \overline{D(A)} \rightarrow \mathcal{X}$  defined by

$$F(\mathbf{S}, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{I}) = (\mathbf{A} - \mathbf{S}(t)\lambda(t), \lambda(t) \text{diag}(\mathbf{S}(t)) \mathbf{q}, \text{diag}(\omega(\cdot))\mathbf{I}).$$

By identifying  $\varphi(t)$  together with  $(\mathbf{S}(t), \mathbf{0}_{L^1}, \mathbf{I}(t, \cdot))^t$  and by setting  $\varphi_0 = (\mathbf{S}_0, \mathbf{0}_{L^1}, \mathbf{I}_0(\cdot))^t$  the associated initial condition, System (2.5) becomes

$$\begin{cases} \frac{d\varphi(t)}{dt} = A\varphi(t) + F(\varphi(t)), \\ \varphi(0) = \varphi_0. \end{cases} \quad (5.2)$$

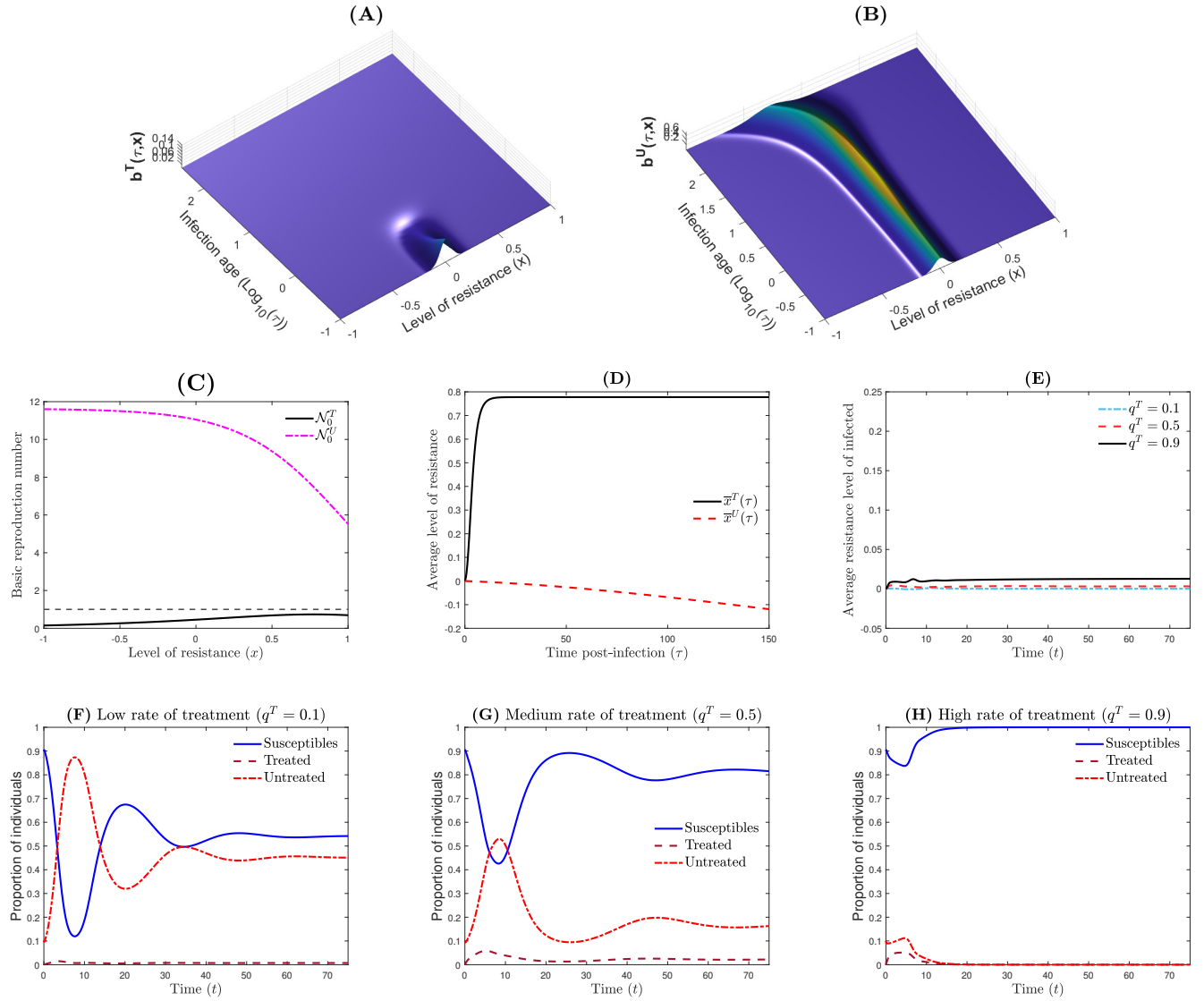


Figure 3: Dynamics of the nested model when the therapeutic treatment is successful. **(A,B)** The bacterial population (treated and untreated) with respect to time  $\tau$  and resistance level  $x$ . **(C)** The basic reproduction numbers at the within-host level  $\mathcal{N}_0^T(x)$  and  $\mathcal{N}_0^U(x)$ , with and without drug respectively. **(D)** The average resistance level  $\bar{x}^\vartheta(\tau)$ ,  $\vartheta \in \{T, U\}$  of the infected host. **(E)** The average resistance level  $\eta(t)$  of the host population. **(F,G,H)** The between-host dynamics with respect to the treatment rate where  $\mathcal{R}_0 = 4.7815, 2.6750$  and  $0.5685$ , respectively. Parameter values are  $(\sigma_0, m_0, k_0, p_1/p_0, k_1/k_0, \mu) = (0.05, 0.05, 20, 0.5, 0.3, 0.8598)$  and  $\Lambda = 5e4$ ,  $\mu_h = 5.2675e - 2$ ,  $\beta_0 = 1.2e - 3$ ,  $\alpha_0 = 7.5e - 2$ ,  $\theta = 1$ ,  $r_0 = 9e3$ .

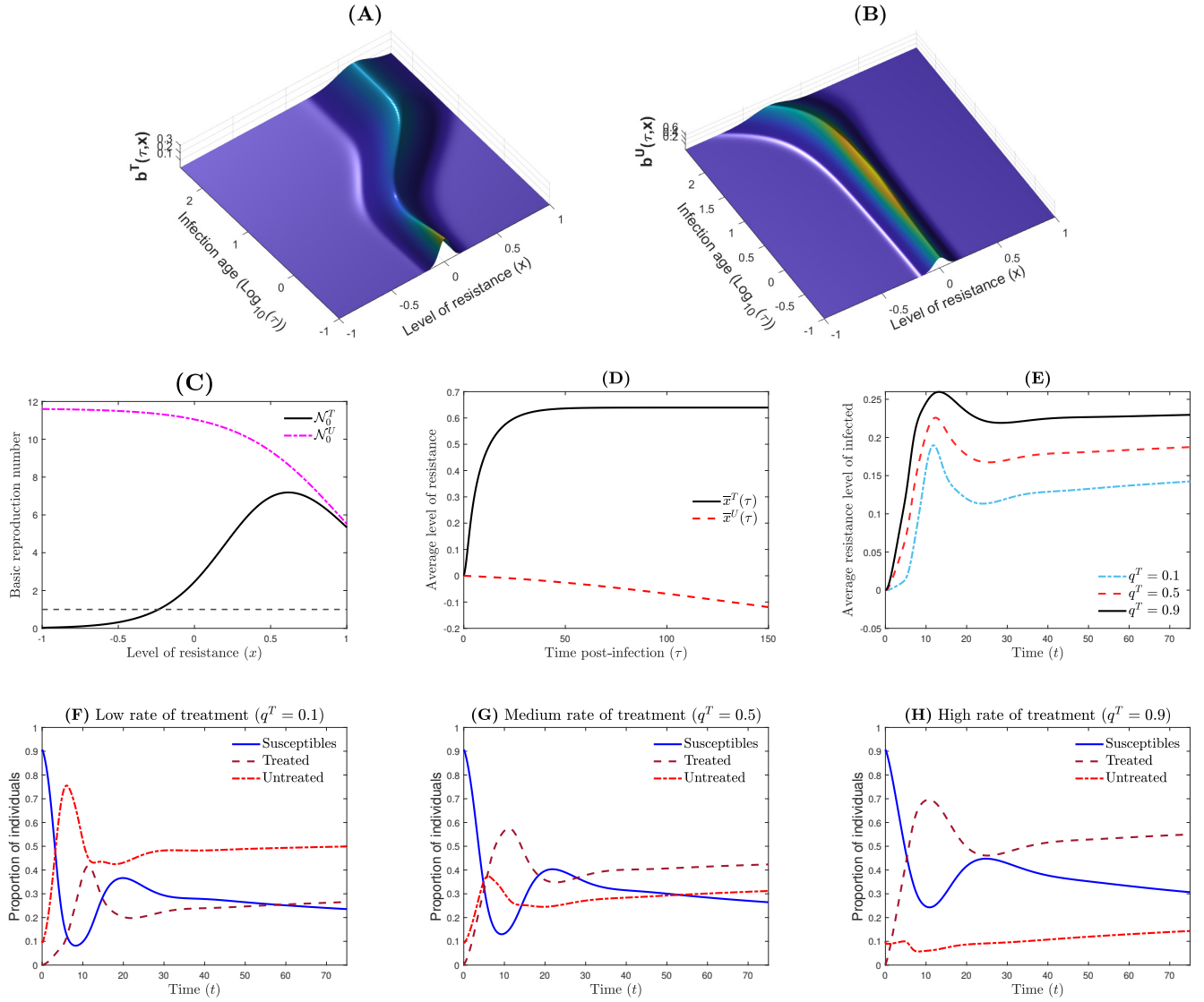


Figure 4: Dynamics of the nested model when the therapeutic treatment failed. **(A,B)** The bacterial population (treated and untreated) with respect to time  $\tau$  and resistance level  $x$ . **(C)** The basic reproduction numbers at the within-host level  $\mathcal{N}_0^T(x)$  and  $\mathcal{N}_0^U(x)$ , with and without drug respectively. **(D)** The average resistance level  $\bar{x}^\vartheta(\tau)$ ,  $\vartheta \in \{T, U\}$  of the infected host. **(E)** The average resistance level  $\eta$  of the host population. **(F,G,H)** The between-host dynamics with respect to the treatment rate where  $\mathcal{R}_0 = 10.9451$ ,  $9.5855$  and  $8.2259$ , respectively. Parameter values are  $(\sigma_0, m_0, k_0, p_1/p_0, k_1/k_0, \mu) = (0.05, 0.05, 3, 0.5, 0.01, 0.8598)$  and  $\Lambda = 5e4$ ,  $\mu_h = 5.2675e-2$ ,  $\beta_0 = 1.2e-3$ ,  $\alpha_0 = 7.5e-2$ ,  $\theta = 1$ ,  $r_0 = 9e3$ .



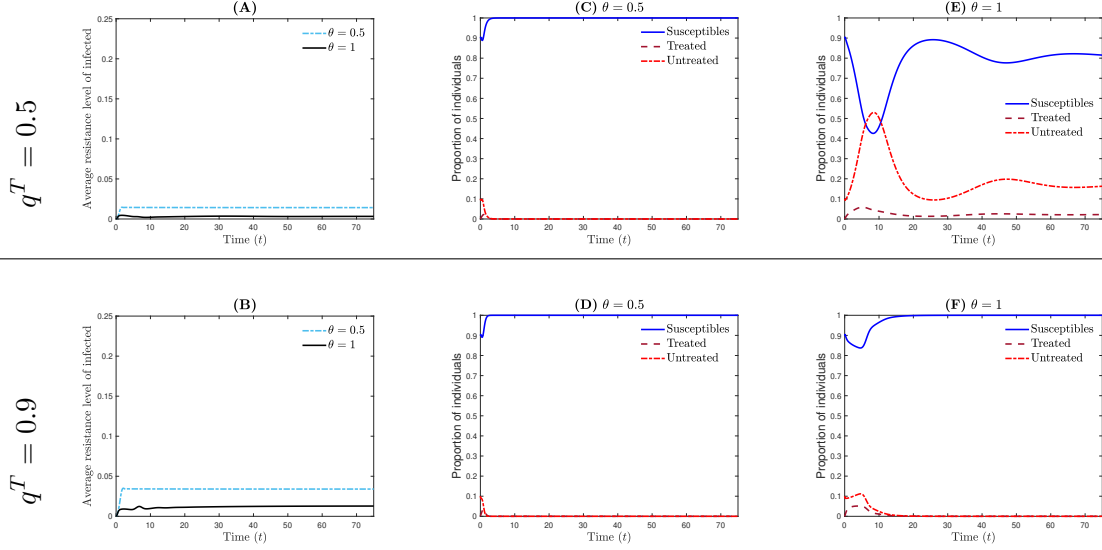


Figure 5: The effect of delay for treating infections on the epidemic outbreak and the average level of resistance when the therapeutic treatment is successful. **Line 1.** The treatment rate  $q^T = 0.5$ . **(A)** The average resistance level  $\eta$  of the host population for  $\theta \in \{0.5, 1\}$ . **(C,E)** The between-host dynamics for  $\theta = 0.5$  and  $1$ , where  $\mathcal{R}_0 = 0.3922$  and  $2.6750$  respectively. **Line 2.** As in line 1 for  $q^T = 0.9$  where  $\mathcal{R}_0 = 0.1120$  and  $0.5685$  respectively. Other parameter values are  $(\sigma_0, m_0, k_0, p_1/p_0, k_1/k_0, \mu) = (0.05, 0.05, 20, 0.5, 0.3, 0.8598)$  and  $\Lambda = 5e4$ ,  $\mu_h = 5.2675e - 2$ ,  $\beta_0 = 1.2e - 3$ ,  $\alpha_0 = 7.5e - 2$ ,  $r_0 = 9e3$ .

By setting  $\mathcal{X}_0 = D(A)$  and  $\mathcal{X}_{0+} = \mathcal{X}_0 \cap \mathcal{X}_+$ , the positivity and boundedness of the solutions of System (2.5) are provided by the following result.

**Theorem 5.1** *There exists a unique strongly continuous semiflow  $\{\Psi(t, \cdot) : \mathcal{X}_0 \rightarrow \mathcal{X}_0\}_{t \geq 0}$  such that, for each  $\varphi_0 \in \mathcal{X}_{0+}$ , the map  $\varphi \in \mathcal{C}([0, \infty), \mathcal{X}_{0+})$  defined by  $\varphi = \Psi(\cdot, \varphi_0)$  is a mild solution of (5.2). That is,  $\int_0^t \varphi(s) ds \in D(A)$  and  $\varphi(t) = \varphi_0 + A \int_0^t \varphi(s) ds + \int_0^t F(\varphi(s)) ds$  for all  $t \geq 0$ . Moreover,  $\{\Psi(t, \cdot)\}_t$  satisfies the following properties:*

1. Let  $\Psi(t, \varphi_0) = (S(t), \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{I}(t, \cdot))^t$ , then the following Volterra formulation holds true for all  $i \in \mathcal{I}$

$$\mathbf{I}_i(t, \tau) = \begin{cases} \mathbf{\Pi}_i(\tau, \tau - t) \mathbf{I}_{i0}(\tau - t), & \text{if } t \leq \tau, \\ \lambda(t - \tau) S_i(t - \tau) \mathbf{\Pi}_i(\tau, 0) \mathbf{q}_i, & \text{if } t > \tau, \end{cases} \quad (5.3)$$

coupled with the  $S_i(t)$  equation of (2.5), and where  $\mathbf{\Pi}_i(\tau_2, \tau_1)$ ,  $0 \leq \tau_1 \leq \tau_2 < \infty$ , is the evolutionary system generated by the linear operator  $[-\Phi_i(\tau) + \omega(\tau)]$ .

2. For all  $\varphi_0 \in \mathcal{X}_{0+}$ , and for all  $t \geq 0$ , one has

$$\sum_{i \in \mathcal{I}} \left( S_i(t) + \int_0^\infty (I_i^T(t, \tau) + I_i^U(t, \tau)) d\tau \right) \leq \max \left\{ \frac{\bar{\Lambda}}{\mu_h}, N_0 \right\}, \quad (5.4)$$

where  $\bar{\Lambda} = \sum_{i \in \mathcal{I}} \Lambda_i$  and  $N_0 = \sum_{i \in \mathcal{I}} \left( S_{i0} + \int_0^\infty (I_{i0}^T(\tau) + I_{i0}^U(\tau)) d\tau \right)$ . Furthermore, the subset of the phase space

$$\left\{ (S, \mathbf{I}) \in \mathbb{R}^n \times L^1((0, \infty), \mathbb{R}^{2n}) \mid \sum_{i \in \mathcal{I}} \left( S_i(t) + \int_0^\infty (I_i^T(t, \tau) + I_i^U(t, \tau)) d\tau \right) \leq \frac{\bar{\Lambda}}{\mu_h} \right\},$$

is positively invariant and attracts all nonnegative solutions.

3. The semiflow  $\{\Psi(t, \cdot)\}_t$  generated by (2.5) is bounded dissipative, that is, there exists a bounded set  $\mathcal{B} \subset \mathcal{X}_0$  such that for any bounded set  $U \subset \mathcal{X}_0$ , we can find  $\sigma = \sigma(U, \mathcal{B}) \geq 0$  such that  $\Psi(t, U) \subset \mathcal{B}$  for  $t \geq \sigma$ .

*Proof.* It is easy to check that the operator  $A$  is a Hille-Yosida operator. Then standard results apply to provide the existence and uniqueness of a mild solution to (2.5) (we refer to [31, 40] for more details). The Volterra formulation is also standard and we refer to [29, 43] for more details.

The  $S_i$  equation of (2.5) gives  $\dot{S}_i(t) \leq \Lambda_i - \mu_h S_i(t)$ , that is

$$S_i(t) \leq \max \left\{ \frac{\Lambda_i}{\mu_h}, S_{i0} \right\}.$$

Next, for estimate (5.4), let  $\varphi_0 \in \mathcal{X}_{0+}$ , then adding up the  $S_i$ ,s equation together with the  $I_i^T$ ,s and  $I_i^U$ ,s equations of (1.5) yields for all  $i \in \mathcal{I}$

$$\frac{d}{dt} \left( S_i(t) + \int_{\mathbb{R}} \int_0^\infty (I_i^T(t, \tau) + I_i^U(t, \tau)) d\tau \right) \leq \Lambda_i - \mu_h S_i(t) - \mu_h \int_{\mathbb{R}} \int_0^\infty (I_i^T(t, \tau) + I_i^U(t, \tau)) d\tau.$$

It comes

$$\limsup_{t \rightarrow \infty} \sum_{i \in \mathcal{I}} \left( S_i(t) + \int_{\mathbb{R}} \int_0^\infty (I_i^T(t, \tau) + I_i^U(t, \tau)) d\tau \right) \leq \frac{\bar{\Lambda}}{\mu_h},$$

with  $\bar{\Lambda} = \sum_{i \in \mathcal{I}} \Lambda_i$ . From where one deduces estimate (5.4) and which ends item 2. of the theorem.

The bounded dissipativity of the semiflow  $\{\Psi(t, \cdot)\}_t$  is a direct consequence of estimate 2.  $\blacksquare$

The following result is straightforward.

**Lemma 5.2** *Let  $0 \leq \tau_1 \leq \tau_2 < \infty$ . By setting  $\mathbf{\Pi}_i(\tau_2, \tau_1) = \left( \mathbf{\Pi}_{i,j}^k(\tau_2, \tau_1) \right)_{k,j}$ , with  $k, j \in \{T, U\}$ , we have*

$$\gamma_0 e^{-(\mu_h + \alpha_0)(\tau_2 - \tau_1)} \leq \mathbf{\Pi}_{i,j}^k(\tau_2, \tau_1) \leq \gamma_1 e^{-\mu_h(\tau_2 - \tau_1)}, \quad (5.5)$$

where  $\gamma_0, \gamma_1 > 0$  and  $\alpha_0 = \max_i(\sup \alpha_i^T, \sup \alpha_i^U)$ .

*Proof.* Let  $0 \leq \tau_1 \leq \tau_2 < \infty$ . Note that, for all  $\tau \geq 0$ , we have  $-\omega_1 \leq \omega_U^T(\tau) \leq \omega_1$  and  $-\omega_2 \leq \omega_T^U(\tau) \leq \omega_2$ , with  $\omega_i > 0$ . Then, for all  $\tau \geq 0$ ,

$$\begin{pmatrix} -\omega_1 - \alpha_0 - \mu_h & \omega_2 \\ \omega_1 & -\omega_2 - \alpha_0 - \mu_h \end{pmatrix} \leq -\Phi_i(\tau) + \omega(\tau) \leq \begin{pmatrix} -\omega_1 - \mu_h & \omega_2 \\ \omega_1 & -\omega_2 - \mu_h \end{pmatrix}.$$

Therefore,

$$e^{-(\mu_h + \alpha_0)(\tau_2 - \tau_1)} \mathbf{\Gamma}(\tau_2, \tau_1) \leq \mathbf{\Pi}_i(\tau_2, \tau_1) \leq e^{-\mu_h(\tau_2 - \tau_1)} \mathbf{\Gamma}(\tau_2, \tau_1),$$

where

$$\mathbf{\Gamma}(\tau_2, \tau_1) = \begin{pmatrix} \frac{\omega_1 e^{-(\tau_2 - \tau_1)(\omega_1 + \omega_2)} + \omega_2}{\omega_1 + \omega_2} & \frac{\omega_2}{\omega_1 + \omega_2} \left( 1 - e^{-(\tau_2 - \tau_1)(\omega_1 + \omega_2)} \right) \\ \frac{\omega_1}{\omega_1 + \omega_2} \left( 1 - e^{-(\tau_2 - \tau_1)(\omega_1 + \omega_2)} \right) & \frac{\omega_2 e^{-(\tau_2 - \tau_1)(\omega_1 + \omega_1)} + \omega_2}{\omega_1 + \omega_2} \end{pmatrix}.$$

Note that

$$\underline{\mathbf{\Gamma}} \leq \mathbf{\Gamma}(\tau_2, \tau_1) \leq \bar{\mathbf{\Gamma}}, \quad \text{where} \quad \bar{\mathbf{\Gamma}} = \begin{pmatrix} 1 & \frac{\omega_2}{\omega_1 + \omega_2} \\ \frac{\omega_1}{\omega_1 + \omega_2} & 1 \end{pmatrix} \quad \text{and} \quad \underline{\mathbf{\Gamma}} = \begin{pmatrix} \frac{\omega_2}{\omega_1 + \omega_2} & 0 \\ 0 & \frac{\omega_1}{\omega_1 + \omega_2} \end{pmatrix}.$$

Thus,

$$e^{-(\mu_h + \alpha_0)(\tau_2 - \tau_1)} \underline{\mathbf{\Gamma}} \leq \mathbf{\Pi}_i(\tau_2, \tau_1) \leq e^{-\mu_h(\tau_2 - \tau_1)} \bar{\mathbf{\Gamma}},$$

from where inequality (5.5) follows, and this ends the proof of the lemma.  $\blacksquare$

## 5.2 The basic reproduction number

In the absence of infection, that is  $\mathbf{I}(t, \tau) = \mathbf{0}_{L^1((0, \infty), \mathbb{R}^{2n})}$ , the system (2.5) has a disease-free equilibrium (DFE) given by  $\mathbf{E}^0 = (\mathbf{S}^0, \mathbf{0}_{L^1((0, \infty), \mathbb{R}^{2n})})$ , with  $\mathbf{S}^0 = (\Lambda_i / \mu_h)_{i \in \mathcal{I}}$ . Let  $\Theta_i(t)$  be the number of new infections in the host population of group  $i$  at time  $t$ . Then in an initially infection-free population, by (2.5), we have

$$\Theta_i(t) = \lambda(t) S_i^0 = \left( \sum_{k \in \mathcal{I}} \int_0^\infty \langle \beta_k(\tau), \mathbf{I}_k(t, \tau) \rangle d\tau \right) S_i^0,$$

where  $\langle \cdot; \cdot \rangle$  is the usual scalar product.

Linearizing the Volterra formulation (5.3) at the DFE, it comes

$$\mathbf{I}_k(t, \tau) = \begin{cases} \mathbf{\Pi}_k(\tau, \tau - t) \mathbf{I}_{k0}(\tau - t), & \text{if } t \leq \tau, \\ \lambda(t - \tau) S_k^0 \mathbf{\Pi}_k(\tau, 0) \mathbf{q}_k, & \text{if } t > \tau. \end{cases}$$

From where,

$$\begin{aligned} \Theta_i(t) &= S_i^0 \sum_{k \in \mathcal{I}} \int_0^t \lambda(t - \tau) S_k^0 \langle \beta_k(\tau), \mathbf{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle d\tau + f_i(t), \quad \forall t \geq 0, \\ &= S_i^0 \sum_{k \in \mathcal{I}} \int_0^t \langle \beta_k(\tau), \mathbf{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle \Theta_k(t - \tau) d\tau + f_i(t), \quad \forall t \geq 0, \end{aligned}$$

where  $f_i(t)$  is the number of new infections produced by the initial population. Therefore, the basic reproduction number  $\mathcal{R}_0^i$  of individuals of group  $i$  is calculated as

$$\mathcal{R}_0^i = S_i^0 \sum_{k \in \mathcal{I}} \int_0^\infty \langle \beta_k(\tau), \mathbf{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle d\tau = S_i^0 \sum_{k \in \mathcal{I}} \chi_k,$$

with

$$\chi_k = \int_0^\infty \langle \beta_k(\tau), \mathbf{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle d\tau.$$

The term  $\chi_k(\tau) = \langle \beta_k(\tau), \mathbf{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle$  quantifies the infectiousness at  $\tau$ -time post infection of the whole infected individuals of group  $k \in \mathcal{I}$ .

Next, let  $\Theta(t) = (\Theta_i(t))_{i \in \mathcal{I}}$ , the number of new infections in all groups at time  $t$  and,  $f(t) = (f_i(t))_{i \in \mathcal{I}}$  the number of new infections produced by the initial population. We have

$$\begin{aligned} \Theta(t) &= \left( S_i^0 \sum_{k \in \mathcal{I}} \int_0^t \chi_k(\tau) \Theta_k(t - \tau) d\tau \right)_{i \in \mathcal{I}} + f(t) \\ &= \left( \int_0^t (S_i^0 \chi_k(\tau))_{i, k \in \mathcal{I}} \Theta(t - \tau) d\tau \right) + f(t), \quad \forall t > 0, \end{aligned}$$

Due to the above formulation, the basic reproduction number  $\mathcal{R}_0$  of all individuals is calculated as the spectral radius of the matrix  $(a_{i,k})_{i, k \in \mathcal{I}}$ , where

$$a_{i,k} = S_i^0 \int_0^\infty \chi_k(\tau) d\tau = S_i^0 \chi_k.$$

Some calculations give

$$\mathcal{R}_0 = \sum_{k \in \mathcal{I}} S_k^0 \int_0^\infty \chi_k(\tau) d\tau = \sum_{k \in \mathcal{I}} S_k^0 \chi_k.$$

A more explicit expression of the infectiousness  $\chi_k$  is difficult to obtain in general. However, one can go further steps in some particular configurations of the treatment status transition rates  $\omega(\tau) = \begin{pmatrix} 0 & \omega_U^T(\tau) \\ \omega_U^T(\tau) & 0 \end{pmatrix}$ . Indeed, assume that (2.7) holds. In such a configuration, we have

$$\mathbf{\Pi}_k(\tau, 0) = \begin{cases} \mathbf{\Pi}_{k0}(\tau, 0), & \text{if } 0 < \tau < \tau_0, \\ \mathbf{\Pi}_{k0}(\tau_0, 0)\mathbf{\Pi}_{k1}(\tau, \tau_0), & \text{if } \tau_0 < \tau < \tau_0 + \tau_1, \\ \mathcal{O}(e^{-c_k\tau}), & \text{if } \tau > \tau_0 + \tau_1, \end{cases}$$

with  $c_k = \mu_h + \inf_{\tau} \alpha_k^U(\tau) + \inf_{\tau} \alpha_k^T(\tau)$ , and

$$\begin{aligned} \mathbf{\Pi}_{k0}(\tau, 0) &= e^{-\mu_h\tau} \text{diag} \left( e^{-\int_0^\tau \alpha_k^T(\sigma) d\sigma}, e^{-\int_0^\tau \alpha_k^U(\sigma) d\sigma} \right), \\ \mathbf{\Pi}_{k1}(\tau, 0) &= \text{diag} \left( \bar{\omega}_1 \int_0^\tau e^{-\mu_h(\tau-\eta)} e^{-\int_\eta^\tau \alpha_k^T(\sigma) d\sigma} e^{-(\bar{\omega}_1 + \mu_h)\eta} e^{-\int_0^\eta \alpha_k^U(\sigma) d\sigma} d\eta, e^{-(\bar{\omega}_1 + \mu_h)\tau} e^{-\int_0^\tau \alpha_k^U(\sigma) d\sigma} \right). \end{aligned}$$

From where, by setting

$$\begin{aligned} \Gamma_0^{k,\vartheta}(\tau) &= e^{-\mu_h\tau} e^{-\int_0^\tau \alpha_k^\vartheta(\sigma) d\sigma}, \quad \vartheta \in \{T, U\}, \\ \Gamma_1^{k,U}(\tau) &= e^{-(\bar{\omega}_1 + \mu_h)\tau} e^{-\int_0^\tau \alpha_k^U(\sigma) d\sigma}, \\ \Gamma_1^{k,T}(\tau) &= e^{-\mu_h\tau} e^{-\int_0^\tau \alpha_k^T(\sigma) d\sigma}, \end{aligned}$$

it comes

$$\chi_k = q_k^T \chi_k^T + q_k^U \chi_k^U + \mathcal{O}\left(e^{-c_k(\tau_0 + \tau_1)}\right),$$

where

$$\begin{aligned} \chi_k^T &= \int_0^{\tau_0 + \tau_1} \beta_k^T(\tau) \Gamma_0^{k,T}(\tau) d\tau + \Gamma_0^{k,T}(\tau_0) \bar{\omega}_1 \int_{\tau_0}^{\tau_0 + \tau_1} \beta_k^T(\tau) \int_{\tau_0}^\tau \frac{\Gamma_1^{k,T}(\tau)}{\Gamma_1^{k,T}(\eta)} \Gamma_1^{k,U}(\eta) d\eta d\tau, \\ \chi_k^U &= \int_0^{\tau_0} \beta_k^U(\tau) \Gamma_0^{k,U}(\tau) d\tau + \Gamma_0^{k,U}(\tau_0) \int_{\tau_0}^{\tau_0 + \tau_1} \beta_k^U(\tau) \frac{\Gamma_1^{k,U}(\tau)}{\Gamma_1^{k,U}(\tau_0)} d\tau. \end{aligned}$$

### 5.3 Proof of Theorem 2.6

The equilibrium of system (2.5) is obtained by solving the following system for all  $i \in \mathcal{I}$

$$\begin{cases} 0 = \Lambda_i - S_i^* \lambda^* - \mu_h S_i^*, \\ \mathbf{I}_i^*(\tau = 0) = \lambda^* S_i^* \mathbf{q}_i, \\ \partial_\tau \mathbf{I}_i^*(\tau) = (-e\omega(\tau) - \alpha_i(\tau) - \mu_h + \omega(\tau)) \mathbf{I}_i^*(\tau), \end{cases} \quad (5.6)$$

where

$$\lambda^* = \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau), \mathbf{I}_i^*(\tau) \rangle d\tau. \quad (5.7)$$

Solving (5.6) for  $S_i^*$  and  $\mathbf{I}_i^*$  yields

$$S_i^* = \frac{\Lambda_i}{\mu_h + \lambda^*} \quad \text{and} \quad \mathbf{I}_i^*(\tau) = \lambda^* S_i^* \mathbf{\Pi}_i(\tau, 0) \mathbf{q}_i. \quad (5.8)$$

Replacing (5.8) in (5.7) leads to  $(1 + \mu_h^{-1} \lambda^*) \lambda^* = \mathcal{R}_0 \lambda^*$  and since  $\lambda^* > 0$ , we have  $\lambda^* = \mu_h(\mathcal{R}_0 - 1)$ .

It follows that system (2.5) has a unique positive endemic equilibrium when  $\mathcal{R}_0 > 1$ , such that  $\forall i \in \mathcal{I}$ ,

$$S_i^* = \frac{S_i^0}{\mathcal{R}_0} \quad \text{and} \quad \mathbf{I}_i^*(\tau) = \lambda^* S_i^* \mathbf{\Pi}_i(\tau, 0) \mathbf{q}_i,$$

where  $\lambda^* = \mu_h(\mathcal{R}_0 - 1)$ .

## 5.4 Technical materials

Before proceed to the proof Theorem 2.7, we introduce some technical materials including the existence of a global compact attractor for the solution semiflow of Model (2.5), the spectral properties of the linearized semiflow of Model (2.5) at any given equilibrium, and the uniform persistence of Model (2.5) when  $\mathcal{R}_0 > 1$ .

### 5.4.1 Global compact attractor

To derive the global properties of the solution dynamics, it is necessary to show that the semiflow generated by system (2.5) has a global compact attractor. Denote by

$$\mathcal{Y} = \mathbb{R}^n \times L^1((0, \infty), \mathbb{R}^{2n}) \quad \text{and} \quad \mathcal{Y}_+ = \mathbb{R}_+^n \times L_+^1((0, \infty), \mathbb{R}^{2n}),$$

and endow the set  $\mathcal{Y}$  with the norm

$$\|(\mathbf{S}, \mathbf{I}(\cdot))\| = \sum_{i \in \mathcal{I}} \left( |S_i| + \int_0^\infty (|I_i^T(t, \tau)| + |I_i^U(t, \tau)|) d\tau \right).$$

For any initial condition  $\varphi_0 \in \mathcal{Y}$ , the solution semiflow of system (2.5) in  $\mathcal{Y}_+$  is denoted by  $\Psi^*(t, \varphi_0) = (\mathbf{S}(t), \mathbf{I}(t, \cdot))^t$ . From the Volterra formulation (5.3), we rewrite system (2.5) as follows for all  $i \in \mathcal{I}$  :

$$\dot{S}_i(t) = \Lambda_i - S_i(t)\lambda(t) - \mu_h S_i(t),$$

$$I_i^T(t, \tau) = \begin{cases} \Pi_{i,T}^T(\tau, \tau - t) I_{i0}^T(\tau - t) + \Pi_{i,U}^T(\tau, \tau - t) I_{i0}^U(\tau - t), & \text{if } t \leq \tau, \\ \Pi_{i,T}^T(\tau, 0)\lambda(t - \tau) S_i(t - \tau), & \text{if } t > \tau, \end{cases} \quad (5.9)$$

$$I_i^U(t, \tau) = \begin{cases} \Pi_{i,T}^U(\tau, \tau - t) I_{i0}^T(\tau - t) + \Pi_{i,U}^U(\tau, \tau - t) I_{i0}^U(\tau - t), & \text{if } t \leq \tau, \\ \Pi_{i,U}^U(\tau, 0)\lambda(t - \tau) S_i(t - \tau), & \text{if } t > \tau, \end{cases} \quad (5.10)$$

where

$$\Pi_i^T(\tau, 0) = \Pi_{i,T}^T(\tau, 0)q_i^T + \Pi_{i,U}^T(\tau, 0)q_i^U \quad \text{and} \quad \Pi_i^U(\tau, 0) = \Pi_{i,T}^U(\tau, 0)q_i^T + \Pi_{i,U}^U(\tau, 0)q_i^U.$$

We need to prove the following claim.

**Claim 5.3** *Let Assumption 2.2 be satisfied. Then, function  $\lambda(\cdot)$  is Lipschitz continuous on  $\mathbb{R}_+$ .*

*Proof of Claim 5.3.* Let  $C_0 \geq \max \left\{ \frac{\bar{\Lambda}}{\mu_h}, \|\varphi_0\| \right\}$ ,  $\|\beta_i\|_\infty = \max \left\{ \|\beta_i^T\|_\infty, \|\beta_i^U\|_\infty \right\}$  and  $\|\beta\|_\infty = \max_{i \in \mathcal{I}} \|\beta_i\|_\infty$ . Then,  $|\lambda(t)| \leq C_0 \|\beta\|_\infty$ . Let  $t > 0$  and  $h > 0$ . It comes that

$$\begin{aligned} \lambda(t+h) - \lambda(t) &= \sum_{i \in \mathcal{I}} \int_0^h \langle \beta_i(\tau), \mathbf{I}_i(t+h, \tau) \rangle d\tau + \sum_{i \in \mathcal{I}} \int_h^\infty \langle \beta_i(\tau), \mathbf{I}_i(t+h, \tau) \rangle d\tau - \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau), \mathbf{I}_i(t, \tau) \rangle d\tau \\ &= \sum_{i \in \mathcal{I}} \int_0^h \langle \beta_i(\tau), \Pi_i(\tau, 0) \mathbf{I}_i(t+h-\tau, 0) \rangle d\tau + \sum_{i \in \mathcal{I}} \int_h^\infty \langle \beta_i(\tau), \mathbf{I}_i(t+h, \tau) \rangle d\tau \\ &\quad - \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau), \mathbf{I}_i(t, \tau) \rangle d\tau \\ &\leq C_0^2 \|\beta\|_\infty^2 h + \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau+h), \mathbf{I}_i(t+h, \tau+h) \rangle d\tau - \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau), \mathbf{I}_i(t, \tau) \rangle d\tau. \end{aligned}$$

Recalling (5.3) and combining the integrals, we obtain

$$\begin{aligned}
\lambda(t+h) - \lambda(t) &\leq C_0^2 \|\beta\|_\infty^2 h + \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau+h), (\mathbf{\Pi}_i(\tau+h, \tau) - \mathbb{I}) \mathbf{I}_i(t, \tau) \rangle d\tau \\
&\quad + \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau+h) - \beta_i(\tau), \mathbf{I}_i(t, \tau) \rangle d\tau \\
&\leq C_0^2 \|\beta\|_\infty^2 h + \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau+h), (\gamma_1 e^{-\mu_h h} - 1) \mathbf{I}_i(t, \tau) \rangle d\tau \\
&\quad + \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau+h) - \beta_i(\tau), \mathbf{I}_i(t, \tau) \rangle d\tau.
\end{aligned}$$

We have  $|\gamma_1 e^{-\mu_h h} - 1| \leq |e^{-\mu_h h} - 1| \leq \mu_h h$ . Using the Lipschitzianity of  $\beta_i^\vartheta$ , we find a positive constant  $C_\beta$  such that

$$|\lambda(t+h) - \lambda(t)| \leq C_0^2 \|\beta\|_\infty^2 h + C_0 \|\beta\|_\infty \mu_h h + C_\beta C_0 h \leq C_\lambda h,$$

where  $C_\lambda = C_0^2 \|\beta\|_\infty^2 + C_0 \|\beta\|_\infty \mu_h + C_\beta C_0$ .  $\blacksquare$

Next, we will show that system (2.5) has a global attractor. By using the similar method as in [8, 34], we can state the following result.

**Lemma 5.4** *There exists  $\mathcal{A}_0$ , a compact subset of  $\mathcal{Y}_+$ , which is a global attractor for the solution semiflow of system (2.5). Moreover,  $\mathcal{A}_0$  is invariant under the solution semiflow, that is*

$$\Psi^*(t, \varphi_0) \subseteq \mathcal{A}_0, \quad \text{for every } \varphi_0 \in \mathcal{A}_0, \quad \forall t \geq 0.$$

*Proof.* We show that  $\Psi^*$  satisfies the assumptions of Lemma 3.2.3 and Theorem 3.4.6 in [22]. To this end, we split the solution semiflow into two parts. For any initial condition  $\varphi_0 \in \mathcal{Y}_+$ , we let  $\Psi^*(t, \varphi_0) = \widehat{\Psi}^*(t, \varphi_0) + \widetilde{\Psi}^*(t, \varphi_0)$ , where

$$\widehat{\Psi}^*(t, \varphi_0) = \begin{cases} (\mathbf{0}_{\mathbb{R}^n}, \mathbf{0}_{L^1}), & t > \tau, \\ (\mathbf{0}_{\mathbb{R}^n}, \mathbf{I}(t, \tau)), & t \leq \tau, \end{cases} \quad \text{and} \quad \widetilde{\Psi}^*(t, \varphi_0) = \begin{cases} (\mathbf{S}(t), \mathbf{I}(t, \tau)), & t > \tau, \\ (\mathbf{S}(t), \mathbf{0}_{L^1}), & t \leq \tau. \end{cases}$$

In such a way, we need to prove the following claim :

**Claim 5.5** (1)  $\widehat{\Psi}^*(t, \varphi_0) \rightarrow 0$  as  $t \rightarrow \infty$  for every  $\varphi_0$  in  $\mathcal{Y}$ .

(2) For a fixed  $t$  and any bounded set  $B$  in  $\mathcal{Y}$ , the set  $\{\widetilde{\Psi}^*(t, \varphi_0) : \varphi_0 \in B\}$  is precompact.

*Proof of Claim 5.5.* Now, we show that the first claim holds.

From (5.9) and Lemma 5.2, we have

$$\begin{aligned}
\|\widehat{\Psi}^*(t, \varphi_0)\| &= \sum_{i \in \mathcal{I}} \int_0^\infty (|I_i^T(t, \tau)| + |I_i^U(t, \tau)|) d\tau \\
&= \sum_{i \in \mathcal{I}} \int_0^\infty [\Pi_{i,T}^T(\tau, \tau-t) + \Pi_{i,T}^U(\tau, \tau-t)] I_{i0}^T(\tau-t) d\tau \\
&\quad + \sum_{i \in \mathcal{I}} \int_{\mathbb{R}} \int_0^\infty [\Pi_{i,U}^T(\tau, \tau-t) + \Pi_{i,U}^U(\tau, \tau-t)] I_{i0}^U(\tau-t) d\tau \\
&\leq 2\gamma_1 e^{-\mu_h t} \|\varphi_0\|,
\end{aligned}$$

Note that for any bounded  $\varphi_0$ ,  $2\gamma_1 e^{-\mu_h t} \|\varphi_0\| \rightarrow 0$  as  $t \rightarrow \infty$ . This completes the first claim.

To show that the second claim holds, let  $B \subset \mathcal{Y}$  be a bounded subset such that  $\Psi^*(t, \cdot)B \subset B$ . Choose  $C_0 > 0$  such that  $\|\varphi_0\| \leq C_0$  for all  $\varphi_0 \in B$ . From Theorem 5.1 Item 2,  $\cup_{\varphi_0 \in B} \{\mathbf{S}(t)\}$  is bounded in  $\mathbb{R}^n$  and then is precompact in  $\mathbb{R}^n$ . Hence, to show the compactness, it suffices to show that the set  $\tilde{\Psi}^*(t, \varphi_0)B$  is precompact for

$$\tilde{\mathbf{I}}(t, \tau) = \begin{cases} \mathbf{I}(t, \tau), & t > \tau, \\ \mathbf{0}_{L^1}, & t \leq \tau. \end{cases} \quad (5.11)$$

By Frechet-Kolmogorov theorem (see Theorem B.2 in [38]), it is sufficient to verify the following conditions :

- (i)  $\sup_{\varphi_0 \in B} \sum_{i \in \mathcal{I}} \int_0^\infty \left( \tilde{I}_i^T(t, \tau) + \tilde{I}_i^U(t, \tau) \right) d\tau < \infty$ ,
- (ii)  $\lim_{h \rightarrow \infty} \sum_{i \in \mathcal{I}} \int_h^\infty \left( |\tilde{I}_i^T(t, \tau)| + |\tilde{I}_i^U(t, \tau)| \right) d\tau = 0$  uniformly with respect to  $\varphi_0 \in B$ .
- (iii)  $\lim_{h \rightarrow 0} \sum_{i \in \mathcal{I}} \int_0^\infty \left( |\tilde{I}_i^T(t, \tau) - \tilde{I}_i^T(t, \tau + h)| + |\tilde{I}_i^U(t, \tau) - \tilde{I}_i^U(t, \tau + h)| \right) d\tau = 0$  uniformly with respect to  $\varphi_0 \in B$ .
- (iv)  $\lim_{h \rightarrow 0} \sum_{i \in \mathcal{I}} \int_0^h \left( |\tilde{I}_i^T(t, \tau)| + |\tilde{I}_i^U(t, \tau)| \right) d\tau = 0$  uniformly with respect to  $\varphi_0 \in B$ .

By (5.11) we have for all  $i \in \mathcal{I}$

$$\tilde{\mathbf{I}}_i(t, \tau) = \begin{cases} \lambda(t - \tau) S_i(t - \tau) \mathbf{\Pi}_i(\tau, 0) \mathbf{q}_i, & t > \tau, \\ \mathbf{0}_{L^1}, & t \leq \tau. \end{cases}$$

It follows that above conditions (i), (ii) and (iv) are satisfied.

Now, we show that condition (iii) holds. We have for  $i \in \mathcal{I}$  and  $h \leq t$ ,

$$\begin{aligned} & \int_0^\infty |\tilde{I}_i^T(t, \tau) - \tilde{I}_i^T(t, \tau + h)| d\tau \\ &= \int_0^{t-h} \left| \mathbf{\Pi}_i^T(\tau, 0) \lambda(t - \tau) S_i(t - \tau) - \mathbf{\Pi}_i^T(\tau + h, 0) \lambda(t - \tau - h) S_i(t - \tau - h) \right| d\tau \\ & \quad + \int_{t-h}^t \left| \mathbf{\Pi}_i^T(\tau, 0) \lambda(t - \tau) S_i(t - \tau) \right| d\tau \\ &:= C_1(t, h) + C_2(t, h). \end{aligned}$$

By Lemma 5.2, and the boundedness of the semiflow, we can find a positive constant  $C_0$  such that

$$C_2(t, h) = \int_{t-h}^t \left| \mathbf{\Pi}_i^T(\tau, 0) \lambda(t - \tau) S_i(t - \tau) \right| d\tau \leq C_0^2 \|\beta\|_\infty \gamma_1 h \rightarrow 0 \quad \text{as } h \rightarrow 0. \quad (5.12)$$

Again by Lemma 5.2, we have

$$\begin{aligned}
C_1(t, h) &\leq \int_0^{t-h} \Pi_i^T(\tau, 0) S_i(t - \tau) \left| \lambda(t - \tau) - \lambda(t - \tau - h) \right| d\tau \\
&\quad + \int_0^{t-h} \lambda(t - \tau - h) \left| \Pi_i^T(\tau, 0) S_i(t - \tau) - \Pi_i^T(\tau + h, 0) S_i(t - \tau - h) \right| d\tau \\
&\leq \int_0^{t-h} \Pi_i^T(\tau, 0) S_i(t - \tau) \left| \lambda(t - \tau) - \lambda(t - \tau - h) \right| d\tau \\
&\quad + \int_0^{t-h} \lambda(t - \tau - h) S_i(t - \tau) \left| \Pi_i^T(\tau, 0) - \Pi_i^T(\tau + h, 0) \right| d\tau \\
&\quad + \int_0^{t-h} \lambda(t - \tau - h) \Pi_i^T(\tau + h, 0) \left| S_i(t - \tau) - S_i(t - \tau - h) \right| d\tau \\
&\leq C_0^2 \|\beta\|_\infty \int_0^\infty \left| \Pi_i^T(\tau, 0) - \Pi_i^T(\tau + h, 0) \right| d\tau + \gamma_1 C_0 \int_0^{t-h} e^{-\mu_h \tau} \left| \lambda(t - \tau) - \lambda(t - \tau - h) \right| d\tau \\
&\quad + \gamma_1 C_0 \|\beta\|_\infty \int_0^{t-h} e^{-\mu_h \tau} \left| S_i(t - \tau) - S_i(t - \tau - h) \right| d\tau \\
&\leq C_0^2 \|\beta\|_\infty \left| \partial_\tau \Pi_i^T(\tau, 0) \right| |h| + \left( \gamma_1 C_0 C_\lambda + \gamma_1 C_0 C_{S_i} \|\beta\|_\infty \right) h \int_0^{t-h} e^{-\mu_h \tau} d\tau \\
&\leq C_0^2 \|\beta\|_\infty \left| \partial_\tau \Pi_i^T(\tau, 0) \right| |h| + \frac{\gamma_1 C_0}{\mu_h} \left( C_\lambda + C_{S_i} \|\beta\|_\infty \right) h \rightarrow 0 \quad \text{as } h \rightarrow 0,
\end{aligned} \tag{5.13}$$

with  $C_{S_i} = \Lambda_i + C_{i0}(C_0 \|\beta\|_\infty + \mu_h)$ . By (5.12) and (5.13) one concludes that the criterion (iii) holds, and then the second claim holds.  $\blacksquare$

This completes the proof of the lemma.  $\blacksquare$

#### 5.4.2 Spectral properties of the linearized semiflow

The next result is concerned with spectral properties of the linearized semiflow  $\Psi$  of Model (2.5) at a given equilibrium point  $\tilde{\varphi} \in \mathcal{X}_{0+}$ . The associated linearized system (2.5) at the point  $\tilde{\varphi}$  reads as

$$\frac{d\varphi(t)}{dt} = (A + G[\tilde{\varphi}])\varphi(t),$$

where  $A$  is the linear operator defined in (5.1) while  $G[\tilde{\varphi}] \in \mathcal{L}(\mathcal{X}_0, \mathcal{X})$  is the bounded linear operator defined by :

$$G[\tilde{\varphi}]\varphi = \begin{pmatrix} -\mathbf{S}\tilde{\lambda} - \tilde{\mathbf{S}}\lambda \\ \tilde{\lambda} \text{diag}(\mathbf{S}) \mathbf{q} + \lambda \text{diag}(\tilde{\mathbf{S}}) \mathbf{q} \\ \mathbf{0}_{L^1((0, \infty), \mathbb{R}^{2n})} \end{pmatrix},$$

where  $\tilde{\lambda} = \sum_i \int_0^\infty \langle \beta_i(\tau), \tilde{\mathbf{I}}_i(\tau) \rangle d\tau$  and  $\lambda = \sum_i \int_0^\infty \langle \beta_i(\tau), \mathbf{I}_i(\tau) \rangle d\tau$ . We then have the following lemma.

**Lemma 5.6** *Let us set  $\Omega = \{\nu \in \mathbb{C} : \text{Re}(\nu) > -\mu_h\}$ . Then, the spectrum  $\sigma(A + G[\tilde{\varphi}]) \cap \Omega \neq \emptyset$  only consists of the point spectrum and one has*

$$\sigma(A + G[\tilde{\varphi}]) \cap \Omega = \{\nu \in \Omega : \Delta(\nu, \tilde{\varphi}) = 0\},$$

where function  $\Delta(\cdot, \tilde{\varphi}) : \Omega \rightarrow \mathbb{C}$  is defined by

$$\Delta(\nu, \tilde{\varphi}) = 1 - \mathcal{R}_\nu[\tilde{\varphi}] + \frac{\mathcal{R}_\nu[\tilde{\varphi}] \tilde{\lambda}}{\nu + \mu_h + \tilde{\lambda}}, \tag{5.14}$$

with  $\mathcal{R}_\nu[\tilde{\varphi}] = \sum_{i \in \mathcal{I}} \tilde{S}_i \int_0^\infty \langle \beta_i(\tau), \mathbf{\Pi}_i(\tau, 0) \mathbf{q}_i \rangle e^{-\nu \tau} d\tau$ .



*Proof.*

Let us denote by  $A_0 : D(A_0) \subset \mathcal{X}_0 \rightarrow \mathcal{X}_0$  the part of  $A$  in  $\mathcal{X}_0 = D(A)$ , which is defined by

$$A_0\varphi = A\varphi, \quad \forall \varphi \in D(A_0) = \{\varphi \in D(A) : A\varphi \in D(A)\}.$$

Then, it is the infinitesimal generator of a  $C_0$ -semigroup on  $\mathcal{X}_0$  denoted by  $\{T_{A_0}(t)\}_{t \geq 0}$ . Let  $\varphi = (\mathbf{S}, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{I}(\cdot))^t$ . We find that

$$T_{A_0}(t)\varphi(\tau) = \begin{cases} \left( e^{-\mu_h t} \mathbf{S}, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{\Pi}(\tau, \tau - t) \mathbf{I}(\tau - t) \right)^t, & \forall t \leq \tau, \\ \left( e^{-\mu_h t} \mathbf{S}, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{0}_{L^1((0, \infty), \mathbb{R}^{2n})} \right)^t, & \forall t > \tau. \end{cases}$$

Then, for  $t \geq \tau_0$ , we have  $\|T_{A_0}(t - \tau_0)\varphi\|_{\mathcal{X}} \leq e^{-\mu_h(t - \tau_0)}\|\varphi\|_{\mathcal{X}}, \forall t \geq \tau_0$ . We deduce that the growth rate  $\omega_0(A_0) = \lim_{t \rightarrow +\infty} \frac{\ln(\|T_{A_0}(t)\|_{\mathcal{L}(\mathcal{X})})}{t}$  of this semigroup satisfies  $\omega_0(A_0) \leq -\mu_h$ . Since operator  $G_i[\tilde{\varphi}]$  is compact, the results in [3] or [17] apply and provided that the essential growth rate of  $\left\{ T_{(A+G[\tilde{\varphi}])_0}(t) \right\}_{t \geq 0}$  - the  $C_0$ -semigroup generated by the part of  $(A + G[\tilde{\varphi}])$  in  $\mathcal{X}_0$  satisfies

$$\omega_{0,ess}((A + G[\tilde{\varphi}])_0) \leq \omega_{0,ess}(A_0) < \omega_0(A_0) \leq -\mu_h.$$

By results in [19, 42], the latter inequality ensures that  $\Omega \cap \sigma(A + G[\tilde{\varphi}]) \neq \emptyset$ , and it is only composed of point spectrum of  $(A + G[\tilde{\varphi}])$ .

It remains to derive the characteristic equation. Let  $\nu \in \rho(A + G[\tilde{\varphi}])$ , where  $\rho(\cdot)$  stands for the resolvent. For  $\hat{\varphi} = (\hat{\mathbf{S}}, \hat{\mathbf{u}}, \hat{\mathbf{I}}(\cdot))^t \in \mathcal{X}$  and  $\varphi = (\mathbf{S}, \mathbf{0}_{L^1}, \mathbf{I}(\cdot))^t \in D(A)$ , we have  $(\nu I - A - G[\tilde{\varphi}])\varphi = \hat{\varphi}$ , that is  $(\nu I - A)\varphi - G[\tilde{\varphi}]\varphi = \hat{\varphi}$ , and from where

$$\varphi = (\nu I - A)^{-1}\hat{\varphi} + (\nu I - A)^{-1}G[\tilde{\varphi}]\varphi. \quad (5.15)$$

Since

$$(\nu I - A)^{-1}\hat{\varphi} = \left( \left( \frac{\hat{S}_i}{\nu + \mu_h} \right)_{i \in \mathcal{I}}, \mathbf{0}_{\mathbb{R}^{2n}}, \left( e^{-\nu \cdot} \mathbf{\Pi}_i(\cdot, 0) \hat{\mathbf{u}}_i + \int_0^\cdot \mathbf{\Pi}_i(\cdot, s) \hat{\mathbf{I}}_i(s) e^{-\nu(\cdot-s)} ds \right)_{i \in \mathcal{I}} \right)^t,$$

we find that

$$(\nu I - A)^{-1}G[\tilde{\varphi}]\varphi = \begin{pmatrix} \left( \frac{-S_i \tilde{\lambda} - \tilde{S}_i \lambda}{\nu + \mu_h} \right)_{i \in \mathcal{I}} \\ \mathbf{0}_{\mathbb{R}^{2n}} \\ \left( e^{-\nu \cdot} \mathbf{\Pi}_i(\cdot, 0) (S_i \tilde{\lambda} \mathbf{q}_i + \tilde{S}_i \lambda \mathbf{q}_i) \right)_{i \in \mathcal{I}} \end{pmatrix}.$$

Thus, for all  $i \in \mathcal{I}$ , equality (5.15) rewrites as

$$\begin{aligned} & \left( 1 + \frac{\tilde{\lambda}}{\nu + \mu_h} \right) S_i + \frac{\tilde{S}_i \lambda}{\nu + \mu_h} = \frac{\hat{S}_i}{\nu + \mu_h}, \\ & \begin{cases} S_i = \frac{\hat{S}_i}{\nu + \mu_h + \tilde{\lambda}} - \frac{\tilde{S}_i \lambda}{\nu + \mu_h + \tilde{\lambda}} \\ \mathbf{I}_i(\tau) = e^{-\nu \tau} \mathbf{\Pi}_i(\tau, 0) (S_i \tilde{\lambda} \mathbf{q}_i + \tilde{S}_i \lambda \mathbf{q}_i) + e^{-\nu \tau} \mathbf{\Pi}_i(\tau, 0) \hat{\mathbf{u}}_i + \int_0^\tau \mathbf{\Pi}_i(\tau, s) \hat{\mathbf{I}}_i(s) e^{-\nu(\tau-s)} ds. \end{cases} \end{aligned} \quad (5.16)$$

Substituting (5.16) into expression for  $\lambda$ , it comes

$$\left(1 - \mathcal{R}_\nu[\tilde{\varphi}] + \frac{\mathcal{R}_\nu[\tilde{\varphi}] \tilde{\lambda}}{\nu + \mu_h + \tilde{\lambda}}\right) \lambda = \frac{\mathcal{R}_\nu[\tilde{\varphi}] \tilde{\lambda}}{\nu + \mu_h + \tilde{\lambda}} + \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau), \hat{\mathbf{y}}_i(\tau) \rangle d\tau, \quad (5.17)$$

where  $\mathcal{R}_\nu[\tilde{\varphi}] = \sum_{i \in \mathcal{I}} \tilde{S}_i \int_0^\infty \langle \beta_i(\tau), \mathbf{\Pi}_i(\tau, 0) \mathbf{q}_i \rangle e^{-\nu\tau} d\tau$  and  $\hat{\mathbf{y}}_i(\tau) = e^{-\nu\tau} \mathbf{\Pi}_i(\tau, 0) \hat{\mathbf{u}}_i + \int_0^\tau \mathbf{\Pi}_i(\tau, s) \hat{\mathbf{I}}_i(s) e^{-\nu(\tau-s)} ds$ .

Therefore, we can isolate  $\lambda$  in system (5.17) if and only if  $\Delta(\nu, \tilde{\varphi}) = 1 - \mathcal{R}_\nu[\tilde{\varphi}] + \frac{\mathcal{R}_\nu[\tilde{\varphi}] \tilde{\lambda}}{\nu + \mu_h + \tilde{\lambda}} \neq 0$ .  $\blacksquare$

## 5.5 Uniform persistence

Our next technical material concerns the uniform persistence of Model (2.5) when  $\mathcal{R}_0 > 1$  by using the method developed in Theorem 5.2 in [38]. For the invariant sets of uniform persistence, we introduce

$$\mathcal{M} = \mathbb{R}^n \times \{\mathbf{0}_{\mathbb{R}^{2n}}\} \times \mathcal{M}_I, \quad \text{and} \quad \partial\mathcal{M} = \mathcal{X}_{0+} \setminus \mathcal{M},$$

where

$$\mathcal{M}_I = \left\{ \mathbf{I} \in L^1_+((0, \infty), \mathbb{R}^{2n}) : \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau), \mathbf{I}_i(\tau) \rangle d\tau > 0 \right\}.$$

For the unique solution  $\varphi = (\mathbf{S}, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{I})$  of system (2.5) associated to the initial condition  $\varphi_0 = (\mathbf{S}_0, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{I}_0(\cdot)) \in \mathcal{M}$ , we define  $\Psi(t, \varphi_0) = (\mathbf{S}(t), \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{I}(t, \cdot))$  the semiflow of Model (2.5) passing through  $\varphi_0$ . Next, we first claim that

**Claim 5.7** *The subsets  $\mathcal{M}$  and  $\partial\mathcal{M}$  are positively invariant with respect to the semiflow  $\Psi(t, \cdot)$  generated by system (2.5). Furthermore,  $\lim_{t \rightarrow \infty} \Psi(t, \varphi_0) = (\mathbf{S}^0, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{0}_{L^1_+((0, \infty), \mathbb{R}^{2n})})^T$  for each  $\varphi_0 \in \partial\mathcal{M}$ .*

*Proof of Claim 5.7.* Let  $\varphi_0 = (\mathbf{S}_0, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{I}_0(\cdot))^T \in \mathcal{M}$  be given and  $\Psi(t, \varphi_0) = (\mathbf{S}, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{I}(t, \cdot))^T$ , the orbit passing through  $\varphi_0$ . Since  $\varphi_0 \in \mathcal{M}$ , then  $\lambda(0) > 0$ . Through a direct calculation, we have

$$\begin{aligned} \partial_t \lambda(t) &= \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau), \partial_t \mathbf{I}_i(t, \tau) \rangle d\tau, \\ &\geq -(\alpha_0 + \omega_0 + \mu_h) \lambda(t), \end{aligned}$$

where  $\alpha_0 = \max_{i \in \mathcal{I}} \{\sup \alpha_i^T, \sup \alpha_i^U\}$  and  $\omega_0 = \max\{\bar{\omega}_T^U, \bar{\omega}_U^T\}$ . Thus, one obtains that

$$\lambda(t) \geq e^{-(\alpha_0 + \omega_0 + \mu_h)t} \lambda(0) > 0,$$

for  $t \geq 0$ . This complete the fact that  $\mathcal{M}$  is positively invariant.

Now, let  $\varphi_0 \in \partial\mathcal{M}$ . Since for all  $i \in \mathcal{I}$ ,  $S_i(t) \leq S_i^0$  as  $t$  is large enough, the comparison principle implies that

$$\mathbf{I}_i(t, \tau) \leq \tilde{\mathbf{I}}_i(t, \tau), \quad \forall i \in \mathcal{I}, \quad (5.18)$$

where  $\tilde{\mathbf{I}}_i(t, \tau)$  is the solution of the following system

$$\begin{cases} \tilde{\mathbf{I}}_i(t, \tau = 0) = \tilde{\lambda}(t) S_i^0 \mathbf{q}_i, \\ \tilde{\mathbf{I}}_i(0, \tau) = \mathbf{I}_{i0}(\tau), \\ (\partial_t + \partial_\tau) \tilde{\mathbf{I}}_i(t, \tau) = (-e\omega(\tau) - \alpha_i(\tau) - \mu_h + \omega(\tau)) \tilde{\mathbf{I}}_i(t, \tau). \end{cases} \quad (5.19)$$

By the Volterra formulation, we have from (5.19) that

$$\tilde{\mathbf{I}}_i(t, \tau) = \begin{cases} \mathbf{\Pi}_i(\tau, \tau - t) \mathbf{I}_{i0}(\tau - t), & \text{if } t \leq \tau, \\ \mathbf{\Pi}_i(\tau, 0) \mathbf{q}_i S_i^0 \tilde{\lambda}(t - \tau), & \text{if } t > \tau, \end{cases}$$

where  $\tilde{\lambda}(t)$  satisfies

$$\begin{aligned}\tilde{\lambda}(t) &= \sum_{k \in \mathcal{I}} S_k^0 \int_0^t \langle \boldsymbol{\beta}_k(\tau), \boldsymbol{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle \tilde{\lambda}(t - \tau) d\tau \\ &\quad + \sum_{k \in \mathcal{I}} \int_t^\infty \langle \boldsymbol{\beta}_k(\tau), \boldsymbol{\Pi}_k(\tau, \tau - t) \mathbf{I}_{k0}(\tau - t) \rangle d\tau.\end{aligned}$$

The initial condition with  $\sum_{k \in \mathcal{I}} \int_0^\infty \langle \boldsymbol{\beta}_k(\tau), \mathbf{I}_{k0}(\tau) \rangle d\tau = 0$ , leads to

$$\tilde{\lambda}(t) = \sum_{k \in \mathcal{I}} S_k^0 \int_0^t \langle \boldsymbol{\beta}_k(\tau), \boldsymbol{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle \tilde{\lambda}(t - \tau) d\tau.$$

Since  $\tilde{\lambda}(0) = 0$ , we have  $\tilde{\lambda}(t) = 0$  for all  $t \geq 0$ , and then  $\tilde{\mathbf{I}}_i(t, \cdot) = 0$  for all  $i \in \mathcal{I}$  and  $t \geq 0$ . The comparison in (5.18) implies that  $\mathbf{I}_i(t, \cdot) = 0$  for all  $i \in \mathcal{I}$  and  $t \geq 0$  and then  $\partial\mathcal{M}$  is positively invariant under the semiflow  $\boldsymbol{\Psi}(t, \cdot)$ . In addition, it is clear for the solution remaining in  $\partial\mathcal{M}$ , we have for all  $i \in \mathcal{I}$ ,  $S_i \rightarrow S_i^0$ . Hence,  $\lim_{t \rightarrow \infty} \boldsymbol{\Psi}(t, \boldsymbol{\varphi}_0) = (\mathbf{S}^0, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{0}_{L^1_+((0, \infty), \mathbb{R}^{2n})})^T$  for each  $\boldsymbol{\varphi}_0 \in \partial\mathcal{M}$ . This ends the proof of Claim 5.7. ■

Finally, we end this technical material section by establishing the uniform persistence of system (2.5).

**Theorem 5.8** *The semiflow  $\{\boldsymbol{\Psi}(t, \cdot)\}_{t \geq 0}$  generated by system (2.5) is uniformly persistent in  $\mathcal{M}$  with respect to  $(\mathcal{M}, \partial\mathcal{M})$ , that is, there exists a constant  $\eta > 0$  such that for each  $\boldsymbol{\varphi}_0 \in \mathcal{M}$ ,*

$$\liminf_{t \rightarrow \infty} \mathbf{S}(t) \geq \eta,$$

and

$$\liminf_{t \rightarrow \infty} \|\mathbf{I}(t, \cdot)\|_{L^1_+} \geq \eta \quad \text{whenever } \mathcal{R}_0 > 1.$$

Furthermore, there exists compact global attractor  $\mathcal{A}_1$  in  $\mathcal{M}$  for the semiflow  $\{\boldsymbol{\Psi}(t, \cdot)\}_{t \geq 0}$ .

*Proof.* In the following, we will prove that  $W^S(\{\mathbf{E}^0\}) \cap \mathcal{M} = \emptyset$ , where

$$W^S(\{\mathbf{E}^0\}) = \{\boldsymbol{\varphi}_0 \in \mathcal{X}_{0+} : \lim_{t \rightarrow +\infty} \boldsymbol{\Psi}(t, \boldsymbol{\varphi}_0) = \mathbf{E}^0\}.$$

Since from Claim 5.7 the disease-free equilibrium  $\mathbf{E}^0$  is globally asymptotically stable in  $\partial\mathcal{M}$ , we need only to study the behavior of the solution starting in  $\mathcal{M}$  in some neighborhood of  $\mathbf{E}^0$ . To this end, it is sufficient to show that there exists  $\sigma > 0$  satisfying for each  $\boldsymbol{\varphi} \in \{\mathbf{v} \in \mathcal{M} : \|\mathbf{E}^0 - \mathbf{v}\| \leq \sigma\}$  there exists  $t_0 \geq 0$  such that  $\|\boldsymbol{\Psi}(t, \boldsymbol{\varphi}_0) - \mathbf{E}^0\| > \sigma$ .

By the way of contradiction, suppose that for each integer  $n \geq 0$  there exists a  $\boldsymbol{\varphi}_0^n = (\mathbf{S}_0^n, \mathbf{0}_{L^1}, \mathbf{I}_0^n) \in \{\mathbf{v} \in \mathcal{M} : \|\mathbf{E}^0 - \mathbf{v}\| \leq \sigma\}$  such that

$$\|\mathbf{E}^0 - \boldsymbol{\Psi}(t, \boldsymbol{\varphi}_0^n)\| \leq \frac{1}{n+1}, \quad \forall t \geq 0.$$

Denote  $\boldsymbol{\Psi}(t, \boldsymbol{\varphi}_0^n) = (\mathbf{S}^n(t), \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{I}^n(t, \cdot))$ , then for all  $t \geq 0$  we have

$$|\mathbf{S}^n(t) - \mathbf{S}^0| \leq \frac{1}{n+1}, \quad \forall t \geq 0. \tag{5.20}$$

It follows that for all  $i$ , we have  $S_i^n(t) \geq S_i^0 - \frac{1}{n+1}$  for all  $t \geq 0$ . Consider the following system

$$\begin{cases} (\partial_t + \partial_\tau) \mathbf{I}^n(t, \tau) = (-\text{diag}(\boldsymbol{\Phi}(\tau)) + \text{diag}(\boldsymbol{\omega}(\tau))) \mathbf{I}^n(t, \tau), \\ \mathbf{I}^n(t, 0) = \lambda^n(t) \text{diag}(\mathbf{S}^n(t)) \mathbf{q}, \\ \mathbf{S}^n(0) = \mathbf{S}_0^n, \quad \mathbf{I}^n(0, \cdot) = \mathbf{I}_0^n(\cdot), \quad (\mathbf{S}_0^n, \mathbf{I}_0^n) \in \mathcal{M}, \end{cases}$$

where  $\lambda^n(t) = \sum_{i \in \mathcal{I}} \int_0^t \langle \beta_i(\tau), \mathbf{I}_i^n(t, \tau) \rangle d\tau$ ,  $\mathbf{S}_0^n = (\mathbf{S}_{i0}^n)_{i \in \mathcal{I}}$  and  $\mathbf{I}_0^n(\cdot) = (\mathbf{I}_{i0}^n(\cdot))_{i \in \mathcal{I}}$ . By the comparison principle, we have

$$\mathbf{I}^n(t, \cdot) \geq \tilde{\mathbf{I}}^n(t, \cdot), \quad (5.21)$$

where  $\tilde{\mathbf{I}}^n(t, \cdot)$  is the solution of the following auxiliary system

$$\begin{cases} (\partial_t + \partial_\tau) \tilde{\mathbf{I}}^n(t, \tau) = (-\text{diag}(\Phi(\tau)) + \text{diag}(\omega(\tau))) \tilde{\mathbf{I}}^n(t, \tau), \\ \tilde{\mathbf{I}}^n(t, 0) = \tilde{\lambda}^n(t) \text{diag} \left( \mathbf{S}^0 - \frac{1}{n+1} I \right) \mathbf{q}, \\ \tilde{\mathbf{I}}^n(0, \cdot) = \mathbf{I}_0^n(\cdot), \end{cases}$$

which gives for all  $i$ ,

$$\begin{cases} (\partial_t + \partial_\tau) \tilde{\mathbf{I}}_i^n(t, \tau) = (-\Phi_i(\tau) + \omega(\tau)) \tilde{\mathbf{I}}_i^n(t, \tau), \\ \tilde{\mathbf{I}}_i^n(t, 0) = \tilde{\lambda}^n(t) \left( \mathbf{S}_i^0 - \frac{1}{n+1} \right) \mathbf{q}_i, \\ \tilde{\mathbf{I}}_i^n(0, \cdot) = \mathbf{I}_{i0}^n(\cdot). \end{cases} \quad (5.22)$$

For ease of notation, let us rewrite the system (5.22) as the following form :

$$\frac{d\tilde{\mathbf{v}}_i^n(t)}{dt} = \left( \tilde{A}_i^n + \tilde{\mathcal{L}}_i^n \right) \tilde{\mathbf{v}}_i^n(t), \quad \forall t \geq 0, \quad (5.23)$$

$\tilde{\mathbf{v}}_i^n(0) \in \overline{D(\tilde{A}_i^n)}$ , the closure of  $D(\tilde{A}_i^n) = \{\mathbf{0}_{\mathbb{R}^2}\} \times W^{1,1}((0, \infty), \mathbb{R}^2)$ , where  $\tilde{\mathbf{v}}_i^n(t) = (\mathbf{0}_{\mathbb{R}^2}, \tilde{\mathbf{I}}_i^n(t, \cdot))^t$  and the operators  $\tilde{A}_i^n$  and  $\tilde{\mathcal{L}}_i^n$  are defined as

$$\tilde{A}_i^n(\mathbf{0}_{\mathbb{R}^2}, \tilde{\mathbf{I}}_i^n) = \left( -\tilde{\mathbf{I}}_i^n(0), -\partial_\tau \tilde{\mathbf{I}}_i^n + (-\Phi_i(\tau) + \omega(\tau)) \tilde{\mathbf{I}}_i^n \right)$$

and

$$\tilde{\mathcal{L}}_i^n(\mathbf{0}_{\mathbb{R}^2}, \tilde{\mathbf{I}}_i^n) = \left( \tilde{\lambda}^n(t) \left( \mathbf{S}_i^0 - \frac{1}{n+1} \right) \mathbf{q}_i, \mathbf{0}_{L^1((0, \infty), \mathbb{R}^2)} \right).$$

Similarly to the proof of Lemma 5.6, we can derive the characteristic equation  $\Delta(\nu_n) = 0$  for system (5.22), where

$$\Delta(\nu_n) = 1 - \sum_{i \in \mathcal{I}} \left( \mathbf{S}_i^0 - \frac{1}{n+1} \right) \int_0^\infty \langle \beta_i(\tau), \mathbf{\Pi}_i(\tau, 0) \mathbf{q}_i \rangle e^{-\nu_n \tau} d\tau.$$

Since  $\mathcal{R}_0 > 1$ , there exists  $n_0 > 0$  large enough such that for  $n \geq n_0$ ,

$$\mathcal{R}_0^n = \sum_{i \in \mathcal{I}} \left( \mathbf{S}_i^0 - \frac{1}{n+1} \right) \int_0^\infty \langle \beta_i(\tau), \mathbf{\Pi}_i(\tau, 0) \mathbf{q}_i \rangle d\tau > 1.$$

The largest eigenvalue  $\nu_n^*$  of system (5.23) satisfies the characteristic equation  $\Delta(\nu_n) = 0$ . Furthermore,  $\mathcal{R}_0^n > 1$  implies the existence of a dominant eigenvalue  $\nu_n^* > 0$  such that  $\Delta(\nu_n^*) = 0$ . Therefore,  $\nu_n^* > 0$  is a simple dominant eigenvalue of  $(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)$ . From Lemma 5.6, we have shown that  $\omega_{0,ess}(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n) \leq -\mu_h$  and since the semigroup  $\left\{ T_{(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)}(t) \right\}_{t \geq 0}$  is irreducible, it follows from Corollary 4.6.8 in [32] that  $\left\{ T_{(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)}(t) \right\}_{t \geq 0}$  has asynchronous exponential growth with intrinsic growth constant  $\nu_n^* \in \mathbb{R}$ . Therefore, using Theorem 3.9 in [30], we have

$$T_{(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)_0}(t) \tilde{\Pi}_{\nu_n^*} = \tilde{\Pi}_{\nu_n^*} T_{(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)_0}(t) = e^{\nu_n^* t} \tilde{\Pi}_{\nu_n^*}, \quad \forall t \geq 0,$$

and there exist constants  $\varepsilon_0 > 0$  and  $\eta_0 > 0$  such that

$$\|T_{(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)_0}(t)(I - \tilde{\Pi}_{\nu_n^*})\| \leq \eta_0 e^{(\nu_n^* - \varepsilon_0)t} \|(I - \tilde{\Pi}_{\nu_n^*})\|, \quad \forall t \geq 0,$$

where  $\tilde{\Pi}_{\nu_n^*}$  is the projector on the generalized eigenspace associated with the largest eigenvalue  $\nu_n^* > 0$ . We deduce that

$$\tilde{\Pi}_{\nu_n^*} \tilde{v}_i^n(t) = e^{\nu_n^* t} \tilde{\Pi}_{\nu_n^*} \tilde{v}_{i0}^n.$$

Since  $\nu_n^* > 0$ , it follows that  $\lim_{t \rightarrow \infty} \|\tilde{\Pi}_{\nu_n^*} \tilde{v}_i^n(t)\|_{L^1} = +\infty$ . Therefore,  $\lim_{t \rightarrow \infty} \|\tilde{\mathbf{I}}_i^n(t, \cdot)\|_{L^1} = +\infty$  and from (5.21), we have  $\lim_{t \rightarrow \infty} \|\mathbf{I}_i^n(t, \cdot)\|_{L^1} = +\infty$ , which is a contradiction to the boundedness of the solution. Thus,  $W^S(\{\mathbf{E}^0\}) \cap \mathcal{M} = \emptyset$  and we derive from Theorem 4.2 in [23] that the semiflow  $\{\Psi(t, \cdot)\}_{t \geq 0}$  is uniform persistent with respect to the pair  $(\mathcal{M}, \partial\mathcal{M})$ . Moreover, by Theorem 3.7 in [33], there exists a compact global attractor  $\mathcal{A}_1 \subset \mathcal{M}$  for the semiflow  $\{\Psi(t, \cdot)\}_{t \geq 0}$ .  $\blacksquare$

## 6 Proof of Theorem 2.7

The proof of Theorem 2.7 is decomposed into two parts. The first part is devoted to the global stability of the disease-free equilibrium, while the second part is devoted to the global stability of the endemic equilibrium.

### 6.1 Proof of Theorem 2.7 (i): global stability of the disease-free equilibrium

When the initial condition of System (2.5) satisfies  $\varphi_0 \in \partial\mathcal{M}$ , i.e.,  $\sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau), \mathbf{I}_{i0}(\tau) \rangle d\tau = 0$ , by Claim 5.7, it comes that the semiflow  $\Psi(t, \varphi_0)$  generated by system (2.5) is such that  $\lim_{t \rightarrow \infty} \Psi(t, \varphi_0) = (\mathbf{S}^0, \mathbf{0}_{\mathbb{R}^{2n}}, \mathbf{0}_{L^1_+((0, \infty), \mathbb{R}^{2n})})$ . It then remain to prove the global stability of the disease-free equilibrium when  $\mathcal{R}_0 \leq 1$ .

**Theorem 6.1** *If  $\mathcal{R}_0 \leq 1$  then, the disease-free equilibrium  $\mathbf{E}^0 = (\mathbf{S}^0, \mathbf{0}_{L^1_+((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n})})$  of system (2.5) is globally asymptotically stable.*

*Proof.* By Theorem 5.8, we introduce the following well defined Lyapunov functional  $V(t) = V_1(t) + V_2(t)$ , with

$$V_1(t) = \sum_{k \in \mathcal{I}} \left( S_k - S_k^0 - S_k^0 \ln \frac{S_k}{S_k^0} \right) \quad \text{and} \quad V_2(t) = \sum_{k \in \mathcal{I}} \int_0^\infty (c_k^T(\tau) I_k^T(t, \tau) + c_k^U(\tau) I_k^U(t, \tau)) d\tau,$$

where  $\mathbf{c}_k(\tau) = (c_k^T(\tau), c_k^U(\tau))^T$  is a vector of positive constants such that

$$\mathbf{c}_k(\tau) = \bar{S}^0 \int_\tau^\infty {}^t \mathbf{\Pi}_k(\sigma, \tau) \boldsymbol{\beta}_k(\sigma) d\sigma, \quad (6.1)$$

with  $\bar{S}^0 = \sum_{k \in \mathcal{I}} S_k^0$  and  $\mathbf{c}_k(\tau) \rightarrow 0$  as  $\tau \rightarrow \infty$ . From (6.1), we have

$$\begin{cases} \bar{S}^0 \beta_k^T(\tau) + \partial_\tau c_k^T(\tau) - \gamma_k^T(\tau) c_k^T(\tau) + \omega_U^T(\tau) c_k^U(\tau) = 0, \\ \bar{S}^0 \beta_k^U(\tau) + \partial_\tau c_k^U(\tau) - \gamma_k^U(\tau) c_k^U(\tau) + \omega_T^U(\tau) c_k^T(\tau) = 0, \end{cases} \quad (6.2)$$

with

$$\gamma_k^T(\tau) = \alpha_k^T(\tau) + \omega_U^T(\tau) + \mu_h \quad \text{and} \quad \gamma_k^U(\tau) = \alpha_k^U(\tau) + \omega_T^U(\tau) + \mu_h.$$

Differentiating  $V_1(t)$  and using  $\Lambda_k = \mu_h S_k^0$ , we have

$$\begin{aligned}
\frac{dV_1(t)}{dt} &= \sum_{k \in \mathcal{I}} \left(1 - \frac{S_k^0}{S_k}\right) (\Lambda_k - S_k(t)\lambda(t) - \mu_h S_k(t)) \\
&= \sum_{k \in \mathcal{I}} \Lambda_k \left(2 - \frac{S_k^0}{S_k} - \frac{S_k}{S_k^0}\right) + \sum_{k \in \mathcal{I}} (\lambda(t)S_k^0 - \lambda(t)S_k) \\
&= \sum_{k \in \mathcal{I}} \Lambda_k \left(2 - \frac{S_k^0}{S_k} - \frac{S_k}{S_k^0}\right) - \sum_{k \in \mathcal{I}} \lambda(t)S_k \\
&\quad + \sum_{k \in \mathcal{I}} \bar{S}^0 \int_0^\infty \left(\beta_k^T(\tau)I_k^T(t, \tau) + \beta_k^U(\tau)I_k^U(t, \tau)\right) d\tau.
\end{aligned}$$

Differentiating  $V_2(t)$ , we have

$$\begin{aligned}
\frac{dV_2(t)}{dt} &= \sum_{k \in \mathcal{I}} \int_0^\infty \left(c_k^T(\tau) \frac{\partial}{\partial t} I_k^T(t, \tau) + c_k^U(\tau) \frac{\partial}{\partial t} I_k^U(t, \tau)\right) d\tau \\
&= - \sum_{k \in \mathcal{I}} \int_0^\infty c_k^T(\tau) \left(\frac{\partial}{\partial \tau} I_k^T(t, \tau) + \gamma_k^T(\tau)I_k^T(t, \tau) - \omega_T^U(\tau)I_k^U(t, \tau)\right) d\tau \\
&\quad - \sum_{k \in \mathcal{I}} \int_0^\infty c_k^U(\tau) \left(\frac{\partial}{\partial \tau} I_k^U(t, \tau) + \gamma_k^U(\tau)I_k^U(t, \tau) - \omega_T^T(\tau)I_k^T(t, \tau)\right) d\tau.
\end{aligned}$$

By integrating by parts, we have

$$\sum_{k \in \mathcal{I}} \int_0^\infty c_k^T(\tau) \frac{\partial}{\partial \tau} I_k^T(t, \tau) d\tau = - \sum_{k \in \mathcal{I}} c_k^T(0)I_k^T(t, 0) - \sum_{k \in \mathcal{I}} \int_0^\infty \partial_\tau c_k^T(\tau) I_k^T(t, \tau) d\tau$$

and

$$\sum_{k \in \mathcal{I}} \int_0^\infty c_k^U(\tau) \frac{\partial}{\partial \tau} I_k^U(t, \tau) d\tau = - \sum_{k \in \mathcal{I}} c_k^U(0)I_k^U(t, 0) - \sum_{k \in \mathcal{I}} \int_0^\infty \partial_\tau c_k^U(\tau) I_k^U(t, \tau) d\tau.$$

Replacing these expressions in  $\frac{dV_2(t)}{dt}$  and using the fact that  $I_k^T(t, 0) = q_k^T \lambda(t) S_k(t)$  and  $I_k^U(t, 0) = q_k^U \lambda(t) S_k(t)$ , we have

$$\begin{aligned}
\frac{dV_2(t)}{dt} &= \sum_{k \in \mathcal{I}} \lambda(t) S_k \left(c_k^T(0)q_k^T + c_k^U(0)q_k^U\right) + \sum_{k \in \mathcal{I}} \int_0^\infty \left(\partial_\tau c_k^T(\tau) - \gamma_k^T(\tau)c_k^T(\tau) + \omega_T^U(\tau)c_k^U(\tau)\right) I_k^T(t, \tau) d\tau \\
&\quad + \sum_{k \in \mathcal{I}} \int_0^\infty \left(\partial_\tau c_k^U(\tau) - \gamma_k^U(\tau)c_k^U(\tau) + \omega_T^T(\tau)c_k^T(\tau)\right) I_k^U(t, \tau) d\tau.
\end{aligned}$$

Finally, combining  $\frac{dV_1(t)}{dt}$  and  $\frac{dV_2(t)}{dt}$ , gathering some terms and using (6.2), it follows that

$$\begin{aligned}
\frac{dV(t)}{dt} &= \sum_{k \in \mathcal{I}} \Lambda_k \left(2 - \frac{S_k^0}{S_k} - \frac{S_k}{S_k^0}\right) + \sum_{k \in \mathcal{I}} \lambda(t) S_k \left(c_k^T(0)q_k^T + c_k^U(0)q_k^U - 1\right) \\
&\quad + \sum_{k \in \mathcal{I}} \int_0^\infty \left(\bar{S}^0 \beta_k^T(\tau) + \partial_\tau c_k^T(\tau) - \gamma_k^T(\tau)c_k^T(\tau) + \omega_T^U(\tau)c_k^U(\tau)\right) I_k^T(t, \tau) d\tau \\
&\quad + \sum_{k \in \mathcal{I}} \int_0^\infty \left(\bar{S}^0 \beta_k^U(\tau) + \partial_\tau c_k^U(\tau) - \gamma_k^U(\tau)c_k^U(\tau) + \omega_T^T(\tau)c_k^T(\tau)\right) I_k^U(t, \tau) d\tau \\
&= \sum_{k \in \mathcal{I}} \Lambda_k \left(2 - \frac{S_k^0}{S_k} - \frac{S_k}{S_k^0}\right) + \sum_{k \in \mathcal{I}} \lambda(t) S_k \left(\langle \mathbf{c}_k(0), \mathbf{q}_k \rangle - 1\right).
\end{aligned}$$

Using (6.1), we have

$$\begin{aligned} \sum_{k \in \mathcal{I}} S_k^0 \langle \mathbf{c}_k(0), \mathbf{q}_k \rangle &= \bar{S}^0 \sum_{k \in \mathcal{I}} S_k^0 \int_0^\infty \langle \beta_k(\tau), \mathbf{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle d\tau = \bar{S}^0 \mathcal{R}_0 \\ &= \sum_{k \in \mathcal{I}} S_k^0 \mathcal{R}_0 \leq \sum_{k \in \mathcal{I}} S_k^0, \quad \text{since } \mathcal{R}_0 \leq 1. \end{aligned}$$

That implies that for all  $k$ ,  $\langle \mathbf{c}_k(0), \mathbf{q}_k \rangle \leq 1$ , when  $\mathcal{R}_0 \leq 1$ . Therefore, we have  $\frac{dV(t)}{dt} \leq 0$  when  $\mathcal{R}_0 \leq 1$ . The strict equality holds only if  $S_k(t) = S_k^0$  hold simultaneously with either  $\mathcal{R}_0 = 1$  or  $\mathbf{I}_k(t, 0) = 0$ . It is easy to verify that largest invariant set in  $\{\frac{dV}{dt} = 0\}$  is the singleton  $\{\mathbf{E}^0\}$ . Thus, all solutions of system (2.5) converge to the disease-free equilibrium  $\mathbf{E}^0$ . Hence,  $\mathbf{E}^0$  is globally asymptotically stable when  $\mathcal{R}_0 \leq 1$ . ■

## 6.2 Proof of Theorem 2.7 (ii): global stability of the endemic equilibrium

**Theorem 6.2** *Assume  $\mathcal{R}_0 > 1$ , then the endemic equilibrium  $\mathbf{E}^* = (\mathbf{S}^*, \mathbf{I}^*)^t$  of system (2.5) is globally asymptotically stable in  $\mathcal{Y}_+$ .*

*Proof.* By Theorem 5.8, we introduce the following well defined Lyapunov functional  $L(t) = L_1(t) + L_2(t) + L_3(t)$ , where

$$\begin{aligned} L_1(t) &= \sum_{k \in \mathcal{I}} S_k^* h\left(\frac{S_k}{S_k^*}\right), \\ L_2(t) &= \sum_{k \in \mathcal{I}} \int_0^\infty d_k^T(\tau) I_k^{T*}(\tau) h\left(\frac{I_k^T(t, \tau)}{I_k^{T*}(\tau)}\right) d\tau \quad \text{and} \quad L_3(t) = \sum_{k \in \mathcal{I}} \int_0^\infty d_k^U(\tau) I_k^{U*}(\tau) h\left(\frac{I_k^U(t, \tau)}{I_k^{U*}(\tau)}\right) d\tau, \end{aligned}$$

with  $h$  the function defined by  $h(z) = z - 1 - \ln z$  ( $z \in \mathbb{R}_+$ ), and  $\mathbf{d}_k(\tau) = (d_k^T(\tau), d_k^U(\tau))^T$  a vector of positive constants given by

$$\mathbf{d}_k(\tau) = \bar{S}^* \int_\tau^\infty {}^t \mathbf{\Pi}_k(\sigma, \tau) \beta_k(\sigma) d\sigma, \quad (6.3)$$

where  $\bar{S}^* = \sum_{k \in \mathcal{I}} S_k^*$  and  $\mathbf{d}_k(\tau) \rightarrow 0$  as  $\tau \rightarrow \infty$ . From (6.3), we have

$$\partial_\tau \mathbf{d}_k(\tau) - \left( - {}^t \mathbf{e} \omega(\tau) - \alpha_k(\tau) - \mu_h + \omega(\tau) \right) \mathbf{d}_k(\tau) = -\bar{S}^* \beta_k(\tau). \quad (6.4)$$

By using the property of function  $h$ , we find that the function  $L(t)$  is nonnegative with its global minimum point  $\mathbf{E}^*$ .

**Step 1 :** Differentiating  $L_1(t)$  along the solution of system (1.5) and using  $\Lambda_k = S_k^* \lambda^* + \mu_h S_k^*$ , we obtain

$$\begin{aligned} \frac{dL_1(t)}{dt} &= \sum_{k \in \mathcal{I}} \left( 1 - \frac{S_k}{S_k^*} \right) (\Lambda_k - S_k(t) \lambda(t) - \mu_h S_k(t)) \\ &= \sum_{k \in \mathcal{I}} \mu_h S_k^* \left( 2 - \frac{S_k}{S_k^*} - \frac{S_k}{S_k^*} \right) + \sum_{k \in \mathcal{I}} \lambda^* S_k^* \left( 1 + \frac{\lambda(t)}{\lambda^*} - \frac{\lambda(t) S_k}{\lambda^* S_k^*} - \frac{S_k}{S_k^*} \right) \\ &= \sum_{k \in \mathcal{I}} \mu_h S_k^* \left( 2 - \frac{S_k}{S_k^*} - \frac{S_k}{S_k^*} \right) + \sum_{k \in \mathcal{I}} \lambda^* S_k^* \left[ h\left(\frac{\lambda(t)}{\lambda^*}\right) - h\left(\frac{S_k}{S_k^*}\right) - h\left(\frac{\lambda(t) S_k(t)}{\lambda^* S_k^*}\right) \right]. \end{aligned}$$

**Step 2 :** Note that

$$\partial_\tau I_k^{T*}(\tau) = -\gamma_k^T(\tau) I_k^{T*}(\tau) + \omega_T^U(\tau) I_k^{U*}(\tau) \quad \text{and} \quad \partial_\tau I_k^{U*}(\tau) = -\gamma_k^U(\tau) I_k^{U*}(\tau) + \omega_U^T(\tau) I_k^{T*}(\tau). \quad (6.5)$$

Using (6.5), we have

$$\left(1 - \frac{I_k^{T^*}(\tau)}{I_k^T(t, \tau)}\right) \frac{\partial}{\partial \tau} I_k^T(t, \tau) = I_k^{T^*}(\tau) \frac{\partial}{\partial \tau} h\left(\frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)}\right) - \left(1 - \frac{I_k^{T^*}(\tau)}{I_k^T(t, \tau)}\right) \left(\gamma_k^T(\tau) - \omega_T^U(\tau) \frac{I_k^{U^*}(\tau)}{I_k^{T^*}(\tau)}\right) I_k^T(t, \tau). \quad (6.6)$$

Differentiating  $L_2(t)$  and, using (6.6) and integration by parts, we obtain

$$\begin{aligned} \frac{dL_2(t)}{dt} &= - \sum_{k \in \mathcal{I}} \int_0^\infty d_k^T(\tau) \left(1 - \frac{I_k^{T^*}(\tau)}{I_k^T(t, \tau)}\right) \left(\frac{\partial}{\partial \tau} I_k^T(t, \tau) + \gamma_k^T(\tau) I_k^T(t, \tau) - \omega_T^U(\tau) I_k^U(t, \tau)\right) d\tau \\ &= - \sum_{k \in \mathcal{I}} \int_0^\infty d_k^T(\tau) \left[ I_k^{T^*}(\tau) \frac{\partial}{\partial \tau} h\left(\frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)}\right) - \omega_T^U(\tau) I_k^{U^*}(\tau) - \omega_T^U(\tau) I_k^U(t, \tau) \right. \\ &\quad \left. + \omega_T^U(\tau, x) I_k^{U^*}(\tau) \frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)} + \omega_T^U(\tau) I_k^{T^*}(\tau) \frac{I_k^U(t, \tau)}{I_k^T(t, \tau)} \right] d\tau \\ &= - \sum_{k \in \mathcal{I}} d_k^T(\tau) I_k^{T^*}(\tau) h\left(\frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)}\right) \Big|_{\tau=0}^{\tau=\infty} \\ &\quad + \sum_{k \in \mathcal{I}} \int_0^\infty d_k^T(\tau) \omega_T^U(\tau) I_k^{U^*}(\tau) \left[1 + \frac{I_k^U(t, \tau)}{I_k^{U^*}(\tau)} - \frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)} - \frac{I_k^{T^*}(\tau) I_k^U(t, \tau)}{I_k^T(t, \tau) I_k^{U^*}(\tau)}\right] d\tau \\ &\quad + \sum_{k \in \mathcal{I}} \int_0^\infty h\left(\frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)}\right) \left(I_k^{T^*}(\tau) \partial_\tau d_k^T(\tau) + d_k^T(\tau) \partial_\tau I_k^{T^*}(\tau)\right) d\tau \\ &= \sum_{k \in \mathcal{I}} d_k^T(0) I_k^{T^*}(0) h\left(\frac{I_k^T(t, 0)}{I_k^{T^*}(0)}\right) \\ &\quad + \sum_{k \in \mathcal{I}} \int_0^\infty d_k^T(\tau) \omega_T^U(\tau) I_k^{U^*}(\tau) \left[1 + \frac{I_k^U(t, \tau)}{I_k^{U^*}(\tau)} - \frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)} - \frac{I_k^{T^*}(\tau) I_k^U(t, \tau)}{I_k^T(t, \tau) I_k^{U^*}(\tau)}\right] d\tau \\ &\quad + \sum_{k \in \mathcal{I}} \int_0^\infty h\left(\frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)}\right) \left(I_k^{T^*}(\tau) \partial_\tau d_k^T(\tau) + d_k^T(\tau) \partial_\tau I_k^{T^*}(\tau)\right) d\tau. \end{aligned}$$

Since  $I_k^{T^*}(0) = q_k^T \lambda^* S_k^*$  and  $I_k^T(t, 0) = q_k^T \lambda(t) S_k(t)$ , then we have

$$\begin{aligned} \frac{dL_2(t)}{dt} &= \sum_{k \in \mathcal{I}} \lambda^* S_k^* d_k^T(0) q_k^T h\left(\frac{\lambda(t) S_k(t)}{\lambda^* S_k^*}\right) \\ &\quad + \sum_{k \in \mathcal{I}} \int_0^\infty d_k^T(\tau) \omega_T^U(\tau) I_k^{U^*}(\tau) \left[1 + \frac{I_k^U(t, \tau)}{I_k^{U^*}(\tau)} - \frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)} - \frac{I_k^{T^*}(\tau) I_k^U(t, \tau)}{I_k^T(t, \tau) I_k^{U^*}(\tau)}\right] d\tau \\ &\quad + \int_{\mathbb{R}} \sum_{k \in \mathcal{I}} \int_0^\infty h\left(\frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)}\right) \left(I_k^{T^*}(\tau) \partial_\tau d_k^T(\tau) + d_k^T(\tau) \partial_\tau I_k^{T^*}(\tau)\right) d\tau. \end{aligned}$$

By a similarly manner, the derivative of  $L_3(t)$  gives

$$\begin{aligned} \frac{dL_3(t)}{dt} &= \sum_{k \in \mathcal{I}} \lambda^* S_k^* d_k^U(0) q_k^U h\left(\frac{\lambda(t) S_k(t)}{\lambda^* S_k^*}\right) \\ &\quad + \sum_{k \in \mathcal{I}} \int_0^\infty d_k^U(\tau) \omega_U^T(\tau) I_k^{T^*}(\tau) \left[1 + \frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)} - \frac{I_k^U(t, \tau)}{I_k^{U^*}(\tau)} - \frac{I_k^{U^*}(\tau) I_k^T(t, \tau)}{I_k^U(t, \tau) I_k^{T^*}(\tau)}\right] d\tau \\ &\quad + \sum_{k \in \mathcal{I}} \int_0^\infty h\left(\frac{I_k^U(t, \tau)}{I_k^{U^*}(\tau)}\right) \left(I_k^{U^*}(\tau) \partial_\tau d_k^U(\tau) + d_k^U(\tau) \partial_\tau I_k^{U^*}(\tau)\right) d\tau. \end{aligned}$$



**Step 3:** Finally, combining  $\frac{dL_1(t)}{dt}$ ,  $\frac{dL_2(t)}{dt}$  and  $\frac{dL_3(t)}{dt}$ , we obtain

$$\begin{aligned}
\frac{dL(t)}{dt} &= \sum_{k \in \mathcal{I}} \mu_h S_k^* \left( 2 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*} \right) + \sum_{k \in \mathcal{I}} \lambda^* S_k^* \left[ h \left( \frac{\lambda(t)}{\lambda^*} \right) - h \left( \frac{S_k^*}{S_k} \right) - h \left( \frac{\lambda(t) S_k(t)}{\lambda^* S_k^*} \right) \right] \\
&+ \sum_{k \in \mathcal{I}} \lambda^* S_k^* \langle \mathbf{d}_k(0), \mathbf{q}_k \rangle h \left( \frac{\lambda(t) S_k(t)}{\lambda^* S_k^*} \right) \\
&+ \sum_{k \in \mathcal{I}} \int_0^\infty h \left( \frac{I_k^T(t, \tau)}{I_k^{T*}(\tau)} \right) \left( I_k^{T*}(\tau) \partial_\tau d_k^T(\tau) + d_k^T(\tau) \partial_\tau I_k^{T*}(\tau) \right) d\tau \\
&+ \sum_{k \in \mathcal{I}} \int_0^\infty h \left( \frac{I_k^U(t, \tau)}{I_k^{U*}(\tau)} \right) \left( I_k^{U*}(\tau) \partial_\tau d_k^U(\tau) + d_k^U(\tau) \partial_\tau I_k^{U*}(\tau) \right) d\tau \\
&+ \sum_{k \in \mathcal{I}} \int_0^\infty d_k^T(\tau) \omega_T^U(\tau) I_k^{U*}(\tau) \left[ 1 + \frac{I_k^U(t, \tau)}{I_k^{U*}(\tau)} - \frac{I_k^T(t, \tau)}{I_k^{T*}(\tau)} - \frac{I_k^{T*}(\tau) I_k^U(t, \tau)}{I_k^T(t, \tau) I_k^{U*}(\tau)} \right] d\tau \\
&+ \sum_{k \in \mathcal{I}} \int_0^\infty d_k^U(\tau) \omega_U^T(\tau) I_k^{T*}(\tau) \left[ 1 + \frac{I_k^T(t, \tau)}{I_k^{T*}(\tau)} - \frac{I_k^U(t, \tau)}{I_k^{U*}(\tau)} - \frac{I_k^{U*}(\tau) I_k^T(t, \tau)}{I_k^U(t, \tau) I_k^{T*}(\tau)} \right] d\tau.
\end{aligned}$$

We observe that  $d_k^T(\tau)$  and  $d_k^U(\tau)$  satisfy

$$d_k^U(\tau) \omega_T^U(\tau) I_k^{T*}(\tau) = d_k^T(\tau) \omega_U^T(\tau) I_k^{U*}(\tau). \quad (6.7)$$

By using (6.7), (6.5), and (6.4), we obtain

$$\partial_\tau d_k^\vartheta(\tau) I_k^{\vartheta*}(\tau) + d_k^\vartheta(\tau) \partial_\tau I_k^{\vartheta*}(\tau) = -\bar{S}^* \beta_k^\vartheta(\tau) I_k^{\vartheta*}(\tau), \quad \vartheta = \{T, U\}. \quad (6.8)$$

Moreover, by using (5.7) and (5.8), we have

$$\lambda^* = \lambda^* \sum_{k \in \mathcal{I}} S_k^* \int_0^\infty \langle \beta_k(\tau), \mathbf{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle d\tau. \quad (6.9)$$

Thus, using (6.3) and (6.9), it can be verified that

$$\sum_{k \in \mathcal{I}} \lambda^* S_k^* \langle \mathbf{d}_k(0), \mathbf{q}_k \rangle = \lambda^* \bar{S}^* \sum_{k \in \mathcal{I}} S_k^* \int_0^\infty \langle \beta_k(\tau), \mathbf{\Pi}_k(\tau, 0) \mathbf{q}_k \rangle d\tau = \lambda^* \bar{S}^* = \sum_{k \in \mathcal{I}} \lambda^* S_k^*, \quad (6.10)$$

which implies that for all  $k$ ,  $\langle \mathbf{d}_k(0), \mathbf{q}_k \rangle = d_k^T(0) q_k^T + d_k^U(0) q_k^U = 1$ . In addition, note that

$$\sum_{k \in \mathcal{I}} \lambda^* S_k^* h \left( \frac{\lambda(t)}{\lambda^*} \right) = \sum_{k \in \mathcal{I}} \int_0^\infty \bar{S}^* \left( \beta_k^T(\tau) I_k^{T*}(\tau) + \beta_k^U(\tau) I_k^{U*}(\tau) \right) h \left( \frac{\lambda(t)}{\lambda^*} \right) d\tau. \quad (6.11)$$

Replacing (6.7), (6.8), (6.10) and (6.11) in  $\frac{dL(t)}{dt}$  and gathering some terms, we obtain

$$\begin{aligned}
\frac{dL(t)}{dt} &= \sum_{k \in \mathcal{I}} \mu_h S_k^* \left( 2 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*} \right) - \sum_{k \in \mathcal{I}} \lambda^* S_k^* h \left( \frac{S_k^*}{S_k} \right) \\
&+ \sum_{k \in \mathcal{I}} \int_0^\infty \bar{S}^* \beta_k^T(\tau) I_k^{T*}(\tau) \left[ h \left( \frac{\lambda(t)}{\lambda^*} \right) - h \left( \frac{I_k^T(t, \tau)}{I_k^{T*}(\tau)} \right) \right] d\tau \\
&+ \sum_{k \in \mathcal{I}} \int_0^\infty \bar{S}^* \beta_k^U(\tau) I_k^{U*}(\tau) \left[ h \left( \frac{\lambda(t)}{\lambda^*} \right) - h \left( \frac{I_k^U(t, \tau)}{I_k^{U*}(\tau)} \right) \right] d\tau \\
&+ \sum_{k \in \mathcal{I}} \int_0^\infty d_k^T(\tau) \omega_T^U(\tau) I_k^{U*}(\tau) \left( 2 - \frac{I_k^{T*}(\tau) I_k^U(t, \tau)}{I_k^T(t, \tau) I_k^{U*}(\tau)} - \frac{I_k^{U*}(\tau) I_k^T(t, \tau)}{I_k^U(t, \tau) I_k^{T*}(\tau)} \right) d\tau.
\end{aligned}$$

Note that

$$h\left(\frac{\lambda(t)}{\lambda^*}\right) - h\left(\frac{I_k^\vartheta(t, \tau)}{I_k^{\vartheta^*}(\tau)}\right) = -h\left(\frac{I_k^\vartheta(t, \tau)\lambda^*}{I_k^{\vartheta^*}(\tau)\lambda(t)}\right) + \left(\frac{\lambda(t)}{\lambda^*} - 1\right) \left(1 - \frac{I_k^\vartheta(t, \tau)\lambda^*}{I_k^{\vartheta^*}(\tau)\lambda(t)}\right), \quad \vartheta = \{T, U\}.$$

Hence, we have

$$\begin{aligned} \frac{dL(t)}{dt} &= \sum_{k \in \mathcal{I}} \mu_h S_k^* \left(2 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*}\right) - \sum_{k \in \mathcal{I}} \int_0^\infty \bar{S}^* \beta_k^T(\tau) I_k^{T^*}(\tau) h\left(\frac{I_k^T(t, \tau)\lambda^*}{I_k^{T^*}(\tau)\lambda(t)}\right) d\tau \\ &\quad - \sum_{k \in \mathcal{I}} \lambda^* S_k^* h\left(\frac{S_k^*}{S_k}\right) - \sum_{k \in \mathcal{I}} \int_0^\infty \bar{S}^* \beta_k^U(\tau) I_k^{U^*}(\tau) h\left(\frac{I_k^U(t, \tau)\lambda^*}{I_k^{U^*}(\tau)\lambda(t)}\right) d\tau \\ &\quad + \sum_{k \in \mathcal{I}} \int_0^\infty d_k^T(\tau) \omega_T^U(\tau) I_k^{U^*}(\tau) \left(2 - \frac{I_k^{T^*}(\tau)}{I_k^T(t, \tau)} \frac{I_k^U(t, \tau)}{I_k^{U^*}(\tau)} - \frac{I_k^{U^*}(\tau)}{I_k^U(t, \tau)} \frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)}\right) d\tau \\ &\quad + \left(\frac{\lambda(t)}{\lambda^*} - 1\right) \sum_{k \in \mathcal{I}} \int_0^\infty \left[ \bar{S}^* \beta_k^T(\tau) I_k^{T^*}(\tau) \left(1 - \frac{I_k^T(t, \tau)\lambda^*}{I_k^{T^*}(\tau)\lambda(t)}\right) \right. \\ &\quad \left. + \bar{S}^* \beta_k^U(\tau) I_k^{U^*}(\tau) \left(1 - \frac{I_k^U(t, \tau)\lambda^*}{I_k^{U^*}(\tau)\lambda(t)}\right) \right] d\tau. \end{aligned}$$

Note that

$$\sum_{k \in \mathcal{I}} \int_0^\infty \left[ \bar{S}^* \beta_k^T(\tau) I_k^{T^*}(\tau) \left(1 - \frac{I_k^T(t, \tau)\lambda^*}{I_k^{T^*}(\tau)\lambda(t)}\right) + \bar{S}^* \beta_k^U(\tau) I_k^{U^*}(\tau) \left(1 - \frac{I_k^U(t, \tau)\lambda^*}{I_k^{U^*}(\tau)\lambda(t)}\right) \right] d\tau = 0.$$

Finally, we have

$$\begin{aligned} \frac{dL(t)}{dt} &= \sum_{k \in \mathcal{I}} \mu_h S_k^* \left(2 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*}\right) - \sum_{k \in \mathcal{I}} \int_0^\infty \bar{S}^* \beta_k^T(\tau) I_k^{T^*}(\tau) h\left(\frac{I_k^T(t, \tau)\lambda^*}{I_k^{T^*}(\tau)\lambda(t)}\right) d\tau \\ &\quad - \sum_{k \in \mathcal{I}} \lambda^* S_k^* h\left(\frac{S_k^*}{S_k}\right) - \sum_{k \in \mathcal{I}} \int_0^\infty \bar{S}^* \beta_k^U(\tau) I_k^{U^*}(\tau) h\left(\frac{I_k^U(t, \tau)\lambda^*}{I_k^{U^*}(\tau)\lambda(t)}\right) d\tau \\ &\quad + \sum_{k \in \mathcal{I}} \int_0^\infty d_k^T(\tau) \omega_T^U(\tau) I_k^{U^*}(\tau) \left(2 - \frac{I_k^{T^*}(\tau)}{I_k^T(t, \tau)} \frac{I_k^U(t, \tau)}{I_k^{U^*}(\tau)} - \frac{I_k^{U^*}(\tau)}{I_k^U(t, \tau)} \frac{I_k^T(t, \tau)}{I_k^{T^*}(\tau)}\right) d\tau. \end{aligned}$$

Thus,  $\frac{dL(t)}{dt} \leq 0$  with equality if and only if  $S_k(t) = S_k^*$ ,  $I_k^T(t, \tau) = I_k^{T^*}(\tau)$  and  $I_k^U(t, \tau) = I_k^{U^*}(\tau)$ . Then, it can be verified that largest invariant set in  $\{\frac{dL}{dt} = 0\}$  is the singleton  $\{\mathbf{E}^*\}$ . It follows that the compact global attractor  $\mathcal{A}_0$ , stated by Lemma 5.4, is such that  $\mathcal{A}_0 = \{\mathbf{E}^*\}$ . Therefore, the endemic equilibrium  $\mathbf{E}^*$  is globally asymptotically stable in  $\mathcal{Y}_+$  when  $\mathcal{R}_0 > 1$ .  $\blacksquare$

## Acknowledgements

This work was supported by the ANR (<https://anr.fr/en/>) grant QUASAR (grant agreement ANR-21-CE45-0004). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## Conflict of interest disclosure

The authors of this article declare that they have no financial conflict of interest with the content of this article.

## References

- [1] A. E. S. Almcera, V. K. Nguyen, and E. A. Hernandez-Vargas. Multiscale model within-host and between-host for viral infectious diseases. *Journal of Mathematical Biology*, 77(4):1035–1057, Oct. 2018.
- [2] J.-B. André and S. Gandon. Vaccination, within-host dynamics, and virulence evolution. *Evolution; International Journal of Organic Evolution*, 60(1):13–23, Jan. 2006.
- [3] O. Arino, D. Axelrod, M. Kimmel, V. Capasso, W. Fitzgibbon, P. Jagers, D. Kirschner, C. Mode, B. Novak, R. Sachs, W. Stephan, A. Swierniak, H. Thieme, and A. Boussouar. Advances in Mathematical Population Dynamics ? Molecules, Cells and Man. In *Advances in Mathematical Population Dynamics ? Molecules, Cells and Man*, volume Volume 6 of *Series in Mathematical Biology and Medicine*, pages 1–910. WORLD SCIENTIFIC, Feb. 1998.
- [4] R. E. Beardmore, R. Peña-Miller, F. Gori, and J. Iredell. Antibiotic Cycling and Antibiotic Mixing: Which One Best Mitigates Antibiotic Resistance? *Molecular Biology and Evolution*, 34(4):802–817, Apr. 2017.
- [5] F. Blanquart. Evolutionary epidemiology models to predict the dynamics of antibiotic resistance. *Evolutionary Applications*, 12(3):365–383, Mar. 2019.
- [6] B. Boldin and O. Diekmann. Superinfections can induce evolutionarily stable coexistence of pathogens. *Journal of Mathematical Biology*, 56(5):635–672, May 2008.
- [7] J.-B. Burie, R. Djidjou-Demasse, and A. Ducrot. Asymptotic and transient behaviour for a nonlocal problem arising in population genetics. *European Journal of Applied Mathematics*, 31(1):84–110, Feb. 2020.
- [8] C.-Y. Cheng, Y. Dong, and Y. Takeuchi. An age-structured virus model with two routes of infection in heterogeneous environments. *Nonlinear Analysis: Real World Applications*, 39:464–491, Feb. 2018.
- [9] D. Coombs, M. A. Gilchrist, and C. L. Ball. Evaluating the importance of within- and between-host selection pressures on the evolution of chronic pathogens. *Theoretical Population Biology*, 72(4):576–591, Dec. 2007.
- [10] E. M. C. D’Agata, M. Dupont-Rouzeyrol, P. Magal, D. Olivier, and S. Ruan. The Impact of Different Antibiotic Regimens on the Emergence of Antimicrobial-Resistant Bacteria. *PLOS ONE*, 3(12):e4036, Dec. 2008.
- [11] T. Day and A. F. Read. Does High-Dose Antimicrobial Chemotherapy Prevent the Evolution of Resistance? *PLOS Computational Biology*, 12(1):e1004689, Jan. 2016.
- [12] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz. On the definition and the computation of the basic reproduction ratio  $R_0$  in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology*, 28(4):365–382, June 1990.
- [13] R. Djidjou-Demasse. Antimicrobial-Quantitative-Resistance-v1.0. Zenodo, Sept. 2021.
- [14] R. Djidjou-Demasse, S. Alizon, and M. T. Sofonea. Within-host bacterial growth dynamics with both mutation and horizontal gene transfer. *Journal of Mathematical Biology*, 82(3):16, Feb. 2021.
- [15] R. Djidjou-Demasse, A. Ducrot, and F. Fabre. Steady state concentration for a phenotypic structured problem modeling the evolutionary epidemiology of spore producing pathogens. *Mathematical Models and Methods in Applied Sciences*, 27(02):385–426, Feb. 2017.

- [16] R. Djidjou-Demasse, M. T. Sofonea, M. Choisy, and S. Alizon. Within-host evolutionary dynamics of antimicrobial quantitative resistance. *Mathematical Modelling of Natural Phenomena*, June 2023.
- [17] A. Ducrot, Z. Liu, and P. Magal. Essential growth rate for bounded linear perturbation of non-densely defined Cauchy problems. *Journal of Mathematical Analysis and Applications*, 341(1):501–518, May 2008.
- [18] B. D. Elderd, N. Mideo, and M. A. Duffy. Looking across Scales in Disease Ecology and Evolution. *The American Naturalist*, 199(1):51–58, Jan. 2022.
- [19] K.-J. Engel and R. Nagel. One-parameter semigroups for linear evolution equations. *Semigroup Forum*, 63(2):278–280, June 2001.
- [20] S. A. H. Geritz, J. A. J. Metz, É. Kisdi, and G. Meszéna. Dynamics of Adaptation and Evolutionary Branching. *Physical Review Letters*, 78(10):2024–2027, Mar. 1997.
- [21] M. A. Gilchrist and D. Coombs. Evolution of virulence: Interdependence, constraints, and selection using nested models. *Theoretical Population Biology*, 69(2):145–153, Mar. 2006.
- [22] J. K. Hale. *Asymptotic Behavior of Dissipative Systems*. American Mathematical Soc., Jan. 2010.
- [23] J. K. Hale and P. Waltman. Persistence in Infinite-Dimensional Systems. *SIAM Journal on Mathematical Analysis*, 20(2):388–395, Mar. 1989.
- [24] W. S. Hart, P. K. Maini, C. A. Yates, and R. N. Thompson. A theoretical framework for transitioning from patient-level to population-scale epidemiological dynamics: Influenza A as a case study. *Journal of The Royal Society Interface*, 17(166):20200230, May 2020.
- [25] H. Inaba. On a new perspective of the basic reproduction number in heterogeneous environments. *Journal of Mathematical Biology*, 65(2):309–348, Aug. 2012.
- [26] T. B. Kepler and A. S. Perelson. Drug concentration heterogeneity facilitates the evolution of drug resistance. *Proceedings of the National Academy of Sciences of the United States of America*, 95(20):11514–11519, Sept. 1998.
- [27] D. G. J. Larsson and C.-F. Flach. Antibiotic resistance in the environment. *Nature Reviews Microbiology*, 20(5):257–269, May 2022.
- [28] M. Lipsitch and B. R. Levin. The population dynamics of antimicrobial chemotherapy. *Antimicrobial Agents and Chemotherapy*, 41(2):363–373, Feb. 1997.
- [29] I. M. Mathematical Theory of Age-Structured Population Dynamics. *Giardini Editori e Stampatori in Pisa*, 1995.
- [30] P. Magal and C. McCluskey. Two-Group Infection Age Model Including an Application to Nosocomial Infection. *SIAM Journal on Applied Mathematics*, 73(2):1058–1095, Jan. 2013.
- [31] P. Magal and S. Ruan. On semilinear Cauchy problems with non-dense domain. *Advances in Differential Equations*, 14(11-12):1041–1084, 2009.
- [32] P. Magal and S. Ruan. *Theory and Applications of Abstract Semilinear Cauchy Problems*, volume 201 of *Applied Mathematical Sciences*. Springer International Publishing, Cham, 2018.
- [33] P. Magal and X.-Q. Zhao. Global Attractors and Steady States for Uniformly Persistent Dynamical Systems. *SIAM Journal on Mathematical Analysis*, 37(1):251–275, Jan. 2005.

- [34] M. Martcheva and H. R. Thieme. Progression age enhanced backward bifurcation in an epidemic model with super-infection. *Journal of Mathematical Biology*, 46(5):385–424, May 2003.
- [35] J. A. J. Metz, S. A. H. Geritz, G. Meszina, F. J. A. Jacobs, and J. S. van Heerwaarden. Adaptive dynamics: A geometrical study of the consequences of nearly faithful reproduction. North-Holland, Amsterdam, 1996.
- [36] A. S. Millan, R. Peña-Miller, M. Toll-Riera, Z. V. Halbert, A. R. McLean, B. S. Cooper, and R. C. MacLean. Positive selection and compensatory adaptation interact to stabilize non-transmissible plasmids. *Nature Communications*, 5(1):5208, Oct. 2014.
- [37] M. Shen, Y. Xiao, L. Rong, and G. Zhuang. Global dynamics and cost-effectiveness analysis of HIV pre-exposure prophylaxis and structured treatment interruptions based on a multi-scale model. *Applied Mathematical Modelling*, 75:162–200, Nov. 2019.
- [38] H. L. Smith and H. R. Thieme. *Dynamical Systems and Population Persistence*. American Mathematical Soc., 2011.
- [39] S. J. Tazzyman and S. Bonhoeffer. Plasmids and Evolutionary Rescue by Drug Resistance. *Evolution*, 68(7):2066–2078, 2014.
- [40] H. R. Thieme. Global stability of the endemic equilibrium in infinite dimension: Lyapunov functions and positive operators. *Journal of Differential Equations*, 250(9):3772–3801, May 2011.
- [41] H. Uecker and S. Bonhoeffer. Antibiotic treatment protocols revisited: The challenges of a conclusive assessment by mathematical modelling. *Journal of the Royal Society, Interface*, 18(181):20210308, Aug. 2021.
- [42] G. F. Webb. An operator-theoretic formulation of asynchronous exponential growth. *Transactions of the American Mathematical Society*, 303(2):751–763, 1987.
- [43] G. F. Webb and WEBB. *Theory of Nonlinear Age-Dependent Population Dynamics*. CRC Press, Jan. 1985.
- [44] K. S. Xue and J. D. Bloom. Linking influenza virus evolution within and between human hosts. *Virus Evolution*, 6(1):veaa010, Jan. 2020.