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ASYMPTOTIC BEHAVIOR IN NOSOCOMIAL EPIDEMIC MODELS WITH ANTIBIOTIC RESISTANCE

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Abstract. We study a model of an antibiotic resistance in a hospital setting. The model connects two population levels - bacteria and patients. The bacteria population is divided into non-resistant and resistant strains. The bacterial strains satisfy ordinary differential equations describing the recombination and reversion processes producing the two strains within each infected individual. The patient population is divided into susceptibles, infectives infected with the non-resistant bacterial strain, and infectives infected with the resistant bacterial stain. The infective classes satisfy partial differential equations for the infection age densities of the two classes. We establish conditions for the existence of three possible equilibria for this model: (1) extinction of both infective classes, (2) extinction of the resistant infectives and endemicity of the non-resistant infectives, and (3) endemicity of both infective classes. We investigate the asymptotic behavior of the solutions of the model with respect to these equilibria.

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1. Introduction

The amplification in hospital settings of bacteria strains resistant to antibiotics is an increasingly serious public health problem. Such nosocomial epidemics occur when patients are exposed to resistant bacteria strains during antibiotic therapy. In [37] we formulated a two-level population model to quantify key elements in such epidemics. At the bacteria level both strains are generated by patients infected with these strains. At the patient level susceptible patients are infected by infected patients at rates proportional to the total bacteria load of each strain present in the hospital. The main objective of this model is to understand how the resistant strain becomes endemic in the hospital and what measures are effective in preventing this from happening.

In this paper we continue the analysis of the model in [37], which is formulated as follows: Let $S(t)$ be the number of susceptible patients in the hospital at time t and let $I_N(t)$ $(I_R(t))$ be the number of patients infected by bacteria non-resistant (resistant) to antibiotics at time t. In order to determine the contribution of each infected patient to the total bacterial load in the hospital, we track each one according to their infection age. For a patient infected with only non-resistant bacteria let $V_F(a)$ represent the population level of bacteria present at infection age a. $V_F(a)$ satisfies the logistic growth equation

$$\frac{dV_F(a)}{da} = V_F(a)\Big(\beta_F - \frac{V_F(a)}{\kappa_F}\Big), \quad a \geq 0, \quad V_F(0) = V_{F_0}, \tag{1.1}$$

where V_{F_0} is the number of bacteria inoculated at the time of acquisition $(a = 0)$, $\beta_F > 0$ is the proliferation rate of bacteria in the individual ($\log 2/\beta_F$ is the doubling time of the bacteria without limitation of carrying capacity), and $\beta_F\kappa_F$ is the carrying capacity (the maximal sustainable bacteria population in an infected patient).

For a patient infected with resistant bacteria both strains are generated through proliferation by cell division, recombination of plasmid bearing (resistant) and plasmid free (non-resistant), and reversion of plasmid bearing to plasmid free. Let $V^-(a)$ and $V^+(a)$ denote the population levels of plasmid free and plasmid bearing bacteria at infection age a, respectively, in an individual infected with both resistant and non-resistant bacteria. We assume $V^-(a)$ and $V^+(a)$ satisfy

$$\begin{cases} \dfrac{dV^-(a)}{da} = \Big(-\tau\dfrac{V^+(a)}{V^-(a)+V^+(a)} + \beta_- - \dfrac{V^-(a)+V^+(a)}{\kappa_F}\Big)V^-(a) + \gamma V^+(a), \\ \dfrac{dV^+(a)}{da} = \Big(\tau\dfrac{V^-(a)}{V^-(a)+V^+(a)} + \beta_+ - \dfrac{V^-(a)+V^+(a)}{\kappa_F} - \gamma\Big)V^+(a), \end{cases} \tag{1.2}$$

where $V^{+}(0) = V_0^{+} > 0$ and $V^{-}(0) = V_0^{-} > 0$ are the number of bacteria inoculated at acquisition, β_- and β_+ are the proliferation rates of plasmid free and plasmid bearing strains, respectively, τ is the reversion rate of plasmid bearing to plasmid free, and γ is the recombination rate of plasmid free and plasmid bearing to plasmid bearing. In [37] we analyzed system (1.2) and showed the following: If $\sigma = \tau - \gamma + \beta_+ - \beta_- < 0$, then $\lim_{a\to\infty} V^-(a) = \beta_-\kappa_F$ and $\lim_{a\to\infty} V^+(a) = 0$. If $\sigma = \tau - \gamma + \beta_+ - \beta_- > 0$, then

$$\lim_{a\to\infty} V^-(a) = \frac{\gamma\kappa_F(\sigma\beta_+ + \gamma\beta_-)}{(\gamma+\sigma)^2}, \quad \lim_{a\to\infty} V^+(a) = \frac{\sigma\kappa_F(\sigma\beta_+ + \gamma\beta_-)}{(\gamma+\sigma)^2}.$$

The solutions of equations (1.2) thus provide the total bacterial load of both strains in terms of the infection age status of all infected patients present in the hospital.

At the patient level let $i_N(t,a)$ ($i_R(t,a)$) be the infection age density of individuals infected by bacteria non-resistant (resistant) to antibiotics at time t and infection age a. Thus,

$$I_N(t) = \int_0^{+\infty} i_N(t,a)da, \ I_R(t) = \int_0^{+\infty} i_R(t,a)da, \ t \geq 0.$$

The bacteria level and patient level of the model are coupled in the system

$$\begin{cases} \frac{dS(t)}{dt} = \lambda - \nu S(t) - \eta\left[\Phi_F(i_N(t)) + \Phi_{V^-+V^+}(i_R(t))\right] S(t), \\ (\partial_t + \partial_a)\, i_N(t,a) = -(\nu + \nu_N(a)) i_N(t,a), \ a \in (0,+\infty), \\ (\partial_t + \partial_a)\, i_R(t,a) = -(\nu + \nu_R(a)) i_R(t,a), \ a \in (0,+\infty), \\ i_N(t,0) = \eta\left[\Phi_F(i_N(t)) + \Phi_{V^-}(i_R(t))\right] S(t), \\ i_R(t,0) = \eta \Phi_{V^+}(i_R(t)) S(t), \\ (S(0), i_N(0,a), i_R(0,a)) = (S_0, \varphi_N(a), \varphi_R(a)), \end{cases} \tag{1.3}$$

where $S_0 \in [0,+\infty)$, $\varphi_N(a), \varphi_R(a) \in L^1_+(0,+\infty)$, $i_N(t) = i_N(t,\cdot), i_R(t) = i_R(t,\cdot) \in L^1(0,+\infty)$, $\lambda > 0$ corresponds to the patient admission rate, $\eta > 0$ corresponds to the exposure of patients to bacteria, $\nu > 0$ is the exit rate from the hospital of susceptible patients, $\nu_N, \nu_R \in L^\infty(0,+\infty)$ correspond to patient lengths of stay in the hospital, and

$$\Phi_\chi(\psi) = \int_0^{+\infty} \chi(a)\psi(a)da, \ \ \forall \psi \in L^1(0,+\infty), \ \ \forall \chi \in L^\infty(0,+\infty).$$

In [37] the equilibrium solutions for (1.3) are analyzed and conditions are established on parameters for the existence of nontrivial equilibria for the two classes of infected patient populations (we recall these conditions here in Section 3.3). The goal of this work is to investigate the asymptotic behavior of the solutions of (1.3) with respect to these equilibria, specifically the uniform persistence of individuals infected by resistant bacteria. Persistence means that there exists $\varepsilon > 0$, such that for all initial values $(S_0, \varphi_N, \varphi_R) \in [0,+\infty) \times L^1_+(0,+\infty) \times L^1_+(0,+\infty)$, with $\varphi_R \neq 0$,

$$\liminf_{t\to+\infty} \|i_R(t)\| \geq \varepsilon.$$

The first abstract results concerning persistence are due to Butler *et al.* [4] and Butler and Waltman [5]. These results have been developed for discrete and continuous time systems, see Freedman *et al.* [11], Freedman and So [12], Hale and Waltman [15], Hirsch *et al.* [19], Hofbauer and So [20], Thieme [30, 31], Yang and Ruan [38], Zhao [39], and others. To study this question here we shall apply the results in Hale and Waltman [15].

In Section 2, we recall the notions and results that we shall use in this article. In Section 3 we develop preliminary results. We first give conditions to guarantee the existence of a global attractor. Then we compute the equilibria and investigate the non-uniform persistence of individuals infected by resistant bacteria. In Section 4, we consider the system

$$\begin{cases} \frac{dS(t)}{dt} = \lambda - \nu S(t) - \eta\Phi_F(i_N(t))S(t), \\ (\partial_t + \partial_a)\, i_N(t,a) = -(\nu + \nu_N(a)) i_N(t,a),\ a \in (0,+\infty), \\ i_N(t,0) = \eta\Phi_F(i_N(t))S(t), \\ (S(0), i_N(0,a)) = (S_0, \varphi_N(a)) \in [0,+\infty) \times L^1_+(0,+\infty). \end{cases} \tag{1.4}$$

In order to apply the uniform persistence theorem in Hale and Waltman [15], we need to prove the global asymptotic stability of the endemic equilibrium of system (1.4). Although system (1.4) has been investigated by Thieme and Castillo-Chavez [33, 34], the global asymptotic stability of the endemic equilibrium has not been studied. Here we use the following transformation to prove the global asymptotic stability of the endemic equilibrium. Consider a bounded complete orbit of system (1.4). Set $x(t) = \eta\Phi_F(i_N(t)),\ \forall t \in \mathbb{R}$. We derive the delay integral equation

$$x(t) = \lambda \int_0^{+\infty} e^{-\nu s} J_{\beta,x_t}(s)ds, \ \ \forall t \in \mathbb{R}, \tag{1.5}$$

where $J_{\beta,x_t}(s)$ is the solution of the ordinary differential equation

$$\begin{cases} \dfrac{dJ_{\beta,x_t}(s)}{ds} = x(t-s)\left(\beta(s) - J_{\beta,x_t}(s)\right), \ \ \forall s \geq 0, \\ J_{\beta,x_t}(0) = 0 \end{cases}$$

with

$$\beta(a) = \eta V_F(a) \exp(-\int_0^a \nu_N(s)ds),$$

for all $a \geq 0$ and $x_t \in C\left((-\infty, 0], \mathbb{R}\right)$, $x_t(-s) = x(t-s)$, for all $s \geq 0$. When β is constant (1.5) becomes

$$x(t) = \lambda \int_0^{+\infty} e^{-\nu s}\beta(0)\left[1 - e^{-\int_0^s x(t-r)dr}\right] ds, \quad \forall t \in \mathbb{R},$$

and we obtain an integral equation similar to the one considered by Brauer [2, 3]. In this case, we obtain a monotone dynamical system and the global asymptotic stability of the endemic equilibrium follows. More generally, when $s \to \beta(s)$ is non-decreasing, (1.5) generates a monotone dynamical system (see Lemmas 4.7 and 4.8). We also refer to Zhou *et al.* [40] for a global stability result for a population that is structured in both age and the age of infection. The main assumption made in [40] is that

$$\beta(a) = \beta(0)e^{-\gamma a}, \quad \forall a \geq 0, \text{ for some } \gamma \geq 0. \tag{1.6}$$

In this case, if we set $I(t) = \Phi_{\frac{V_F}{V_F(0)}}(i_N(t))$ (and assume $V_F \in W^{1,\infty}(0, +\infty, \mathbb{R})$), then we obtain

$$\begin{cases} \frac{dS(t)}{dt} = \lambda - \nu S(t) - \eta V_F(0) I(t) S(t), \\ \frac{dI(t)}{dt} = \eta V_F(0) I(t) S(t) - (\nu + \gamma) I(t). \end{cases} \tag{1.7}$$

The global asymptotic stability of the endemic equilibrium of system (1.7) is investigated by Hethcote in [16, 17] (a general survey of epidemic models is provided by Hethcote in [18]).

In Section 4, we prove the global asymptotic stability of the endemic equilibrium of (1.4) by assuming that

$$\beta(a) \geq e^{-\nu(a-s)}\beta(s), \quad \forall a \geq s \geq 0.$$

This condition includes a relatively large class of situations, compared with the particular choice made in (1.6). In Section 5, we conclude the paper by applying the result of Hale and Waltman [15] to obtain the persistence results for the bacterial infection model. The paper ends with a brief discussion in Section 6.

2. Attractors and Uniform Persistence

We first introduce some notation and definitions in infinite-dimensional dynamical systems (see Hale [13, 14], Sell and You [28], and Raugel [27]).

Let (M, d) be a complete metric space with metric d. Suppose that $\{U(t)\}_{t \geq 0}$ is a continuous semigroup on M; that is,

(i) $U(0) = \text{Id}$;

(ii) $U(t+s) = U(t)U(s)$, $\forall t, s \geq 0$;

(iii) $(t, x) \to U(t)x$ is continuous from $[0, +\infty) \times M$ to M.

Let A be a subset of M and B a subset of $M \setminus A$. We say that A *is ejective in* B *for* $\{U(t)\}_{t\geq 0}$ if there exists an $\varepsilon > 0$ such that for all $x \in B$ with $d(x, A) := \inf_{y\in A} d(x, y) \leq \varepsilon$, there exists a $t^* = t^*(x, \varepsilon) > 0$ such that

$$d(U(t^*)x, A) \geq \varepsilon.$$

We say that A *is ejective for* $\{U(t)\}_{t\geq 0}$ if A is ejective in $M \setminus A$ for $\{U(t)\}_{t\geq 0}$.

We say that A is *positively invariant* (respectively: *invariant*) by $\{U(t)\}_{t\geq 0}$ if $U(t)A \subset A$, for all $t \geq 0$ (respectively: $U(t)A = A$, for all $t \geq 0$). We say that A *attracts* a subset $C \subset M$ for $\{U(t)\}_{t\geq 0}$ if

$$\delta(U(t)C, A) \to 0 \text{ as } t \to +\infty,$$

where δ is the semi-distance $\delta(B, A) = \sup_{x\in B} d(x, A)$.

$\{U(t)\}_{t\geq 0}$ is said to be *point dissipative* if there exists a bounded subset M which attracts the points of M for $\{U(t)\}_{t\geq 0}$. $\{U(t)\}_{t\geq 0}$ is said to be *asymptotically smooth* if for each non-empty closed bounded subset $B \subset M$, which is positively invariant by $\{U(t)\}_{t\geq 0}$, there exists a compact subset $C \subset M$ which attracts B for $\{U(t)\}_{t\geq 0}$.

Assumption 2.1. Let M_0 be an open subset of M and $\partial M_0 = M \setminus M_0$. Assume that

$$U(t)\partial M_0 \subset \partial M_0 \text{ and } U(t)M_0 \subset M_0, \ \ \forall t \geq 0.$$

We say that $\{U(t)\}_{t\geq 0}$ is *uniformly persistent with respect to* $(M_0, \partial M_0)$ if there exists an $\varepsilon > 0$ such that

$$\liminf_{t\to+\infty} d(U(t)x, \partial M_0) \geq \varepsilon, \ \ \forall x \in M_0.$$

Denote by $\gamma^+(x) = \{U(t)x\}_{t\geq 0}$ the *positive orbit through* $x \in M$. If $\gamma^+(x)$ is relatively compact, denote by

$$\omega(x) := \bigcap_{t\geq 0} \overline{\bigcup_{s\geq t} \{U(s)x\}}$$

the omega-limit set of x.

We say that $\gamma(x) = \{u(t)\}_{t\in\mathbb{R}}$ is *a complete orbit through* $x \in M$ *in* $A \subset M$ if $u(0) = x$, $u(t+s) = U(t)u(s)$, $\forall t \geq 0$, $\forall s \in \mathbb{R}$ and $u(t) \in A$, $\forall t \in \mathbb{R}$. If $\gamma(x)$ is a relatively compact complete orbit through $x \in M$, denote

$$\alpha_\gamma(x) = \bigcap_{t\leq 0} \overline{\bigcup_{s\leq t} \{u(s)\}}.$$

A subset $A \subset M$ is said to be *isolated in* M for $\{U(t)\}_{t\geq 0}$ if it is the maximal invariant set in some neighborhood of A in M.

Let A and B be two subsets of ∂M_0. A is said to be *chained* to B in ∂M_0, written $A \underset{\partial M_0}{\rightarrow} B$, if there exists a relatively compact complete orbit $\gamma(x) \subset \partial M_0$ through some $x \notin A \cup B$ such that $\omega(x) \subset B$ and $\alpha_\gamma(x) \subset A$. A finite sequence $\{C_1, ..., C_k\}$ of invariant sets is called a *chain* in ∂M_0 if $C_1 \underset{\partial M_0}{\rightarrow} C_2 \underset{\partial M_0}{\rightarrow} ... \underset{\partial M_0}{\rightarrow} C_k$. The chain is called a *cycle* if $C_k = C_1$. A collection $\{C_1, C_2, ..., C_k\}$ of pairwise disjoint, compact, and invariant subsets of ∂M_0 is called an *acyclic covering* of $\Omega(\partial M_0) = \bigcup_{x \in \partial M_0} \omega(x)$ if C_i is isolated in ∂M_0, $\Omega(\partial M_0) \subset \bigcup_{i=1,...,k} C_i$, and no subset of C_i's forms a cycle in ∂M_0.

The following theorem is due to Hale and Waltman [15] (see Theorem 4.2).

Theorem 2.2. *Let Assumption* 2.1 *be satisfied. Assume in addition that*

(i) $\{U(t)\}_{t \geq 0}$ *is asymptotically smooth;*
(ii) $\{U(t)\}_{t \geq 0}$ *is point dissipative;*
(iii) $\Omega(\partial M_0)$ *has an acyclic covering* $\{C_1, C_2, ..., C_k\}$ *in* ∂M_0 *for* $\{U(t)\}_{t \geq 0}$*;*
(iv) *For each* $i = 1, ..., k$*,* C_i *is isolated in* M *for* $\{U(t)\}_{t \geq 0}$.

Then $\{U(t)\}_{t \geq 0}$ *is uniformly persistent if and only if for each* $C_i \in \{C_1, C_2, ..., C_k\}$,

$$W^s(C_i) \cap M_0 = \emptyset,$$

where $W^s(B) = \{x \in M : \omega(x) \neq \emptyset, \omega(x) \subset B\}$ *for each subset* $B \subset M$.

Remark 2.3. The statement is not exactly the same as in Hale and Waltman [15]. Under conditions (i) and (ii) there exists a compact subset which attracts the point of M. So we can apply the same arguments as in Hale and Waltman [15] and the result follows.

A nonempty, compact and invariant set $A \subset M$ is said to be an *attractor for* $\{U(t)\}_{t \geq 0}$ if A attracts one of its neighborhoods; a *global attractor for* $\{U(t)\}_{t \geq 0}$ if A is an attractor that attracts every point in M; a *strong global attractor for* $\{U(t)\}_{t \geq 0}$ if A attracts every bounded subset of M.

The following theorem is due to Hale [13, 14] (see [25] for a proof).

Theorem 2.4. *Assume that* $\{U(t)\}_{t \geq 0}$ *is asymptotically smooth, point dissipative, and for each compact subset* $C \subset M$, $\cup_{t \geq 0} \{U(t)C\}$ *is bounded. Then* $\{U(t)\}_{t \geq 0}$ *has a global attractor* $A \subset M$*. Moreover, if for each bounded set* $B \subset M$, $\cup_{t \geq 0} \{U(t)B\}$ *is bounded, then* A *is a strong global attractor.*

From now on, we denote by $\{U_0(t)\}_{t \geq 0}$ the restriction of $\{U(t)\}_{t \geq 0}$ to M_0. The following theorem is due to Magal and Zhao [25].

Theorem 2.5. *Let Assumption* 2.1 *be satisfied. Assume that* $\{U(t)\}_{t\geq 0}$ *is asymptotically smooth and uniformly persistent with respect to* $(M_0, \partial M_0)$ *and has a global attractor* $A \subset M$. *Then* $\{U_0(t)\}_{t\geq 0}$ *has a global attractor* $A_0 \subset M_0$.

Remark 2.6. If A_0 is a global attractor for $\{U_0(t)\}_{t\geq 0}$, then A_0 is stable and attracts the compact sets of M_0 for $\{U_0(t)\}_{t\geq 0}$.

3. Preliminary Results

Set $\gamma_N = \eta V_F,\ \gamma_{NR} = \eta V^-,\ \gamma_R = \eta V^+$. Consider

$$\begin{cases} \dfrac{dS(t)}{dt} = \lambda - \nu S(t) - \left[\Phi_{\gamma_N}(i_N(t)) + \Phi_{\gamma_{NR}+\gamma_R}(i_R(t))\right] S(t), \\ (\partial_t + \partial_a)\, i_N(t,a) = -\left(\nu + \nu_N(a)\right) i_N(t,a),\ a \in (0,+\infty), \\ (\partial_t + \partial_a)\, i_R(t,a) = -\left(\nu + \nu_R(a)\right) i_R(t,a),\ a \in (0,+\infty), \\ i_N(t,0) = \left[\Phi_{\gamma_N}(i_N(t)) + \Phi_{\gamma_{NR}}(i_R(t))\right] S(t), \\ i_R(t,0) = \Phi_{\gamma_R}(i_R(t)) S(t), \\ (S(0), i_N(0,a), i_R(0,a)) = (S_0, \varphi_N(a), \varphi_R(a)), \end{cases} \tag{3.1}$$

where $S_0 \in [0,+\infty), \varphi_N(a), \varphi_R(a) \in L^1_+(0,+\infty)$. Denote $C_{B,U}([0,+\infty),\mathbb{R})$ to be the set of bounded and uniformly continuous mappings from $[0,+\infty)$ to $\mathbb{R}$.

Assumption 3.1. Suppose that

(a) $\lambda, \nu \in (0,+\infty)$;
(b) $\nu_N, \nu_R \in L^\infty_+(0,+\infty)$;
(c) $\gamma_N, \gamma_{NR}, \gamma_R \in C_{B,U}([0,+\infty),\mathbb{R}) \cap C_+([0,+\infty),\mathbb{R})$ and for each $a \geq 0$, there exist two constants $s, r \geq a$ such that $\gamma_N(s) > 0,\ \gamma_R(r) > 0$.

At this point one may use a Volterra formulation of the problem (see Webb [35] and Iannelli [21]) or equivalently an integrated semigroup formulation of the problem (see Thieme [29]). For convenience, we start with the integrated semigroup formulation. We will also consider a Volterra formulation of the problem (see system (3.4)).

3.1. **Integrated Semigroup Formulation.** Set

$$X = \mathbb{R} \times Y^2,\ \ X_+ = [0,+\infty) \times Y_+^2,\ \ X_0 = \mathbb{R} \times Y_0^2,\ \ X_{+0} = X_0 \cap X_+$$

with

$$Y = \mathbb{R} \times L^1(0,+\infty),\ Y_+ = [0,+\infty) \times L^1_+(0,+\infty),\ Y_0 = \{0\} \times L^1(0,+\infty).$$

Let $D(A) = \mathbb{R} \times Z^2$ with $Z = \{0_\mathbb{R}\} \times W^{1,1}(0,+\infty)$. For each $x = (S, 0_\mathbb{R}, i_N, 0_\mathbb{R}, i_R) \in X_0$, Define $A : D(A) \subset X_0 \subset X \to X$ and $F : X_0 \to X$ by

$$Ax = \begin{pmatrix} -\nu S \\ -i_N(0) \\ -\dfrac{di_N(\cdot)}{da} - (\nu + \nu_N(\cdot))\, i_N(\cdot) \\ -i_R(0) \\ -\dfrac{di_R(\cdot)}{da} - (\nu + \nu_R(\cdot))\, i_R(\cdot) \end{pmatrix} \text{ if } x \in D(A),$$

and

$$F(x) = \begin{pmatrix} \lambda - S\left[\Phi_{\gamma_N}(i_N) + \Phi_{\gamma_{NR}+\gamma_R}(i_R)\right] \\ S\left[\Phi_{\gamma_N}(i_N) + \Phi_{\gamma_{NR}}(i_R)\right] \\ 0_{L^1} \\ S\Phi_{\gamma_R}(i_R) \\ 0_{L^1} \end{pmatrix}.$$

Rewrite problem (3.1) as an abstract Cauchy problem

$$\frac{du_x(t)}{dt} = Au_x(t) + F(u_x(t)),\ t \geq 0,\ \ u_x(0) = x \in X_{0+}. \tag{3.2}$$

It is well known that A is a Hille-Yosida operator. More precisely, we have $(-\nu, +\infty) \subset \rho(A)$ and for each $\lambda > -\nu$,

$$\left\|(\lambda - A)^{-1}\right\|_{\mathcal{L}(X,X)} \leq \frac{1}{\lambda + \nu}.$$

Denote $\{\mathcal{S}(t)\}_{t\geq 0}$ to be the integrated semigroup generated by A (see Arendt, *et al*. [1]). Also denote by $\{T_0(t)\}_{t\geq 0}$ the strongly continuous semigroup of bounded linear operators generated by A_0, the part of A in X_0; that is,

$$A_0 x = Ax,\ \forall x \in D(A_0) = \{x \in D(A) : Ax \in X_0\}.$$

We have for all $t \geq 0,\ x = (S, 0_{\mathbb{R}}, i_N, 0_{\mathbb{R}}, i_R) \in X_0$, that

$$T_0(t)x = \begin{pmatrix} e^{-\nu t} S \\ 0_{\mathbb{R}} \\ T_{0N}(t) i_N \\ 0_{\mathbb{R}} \\ T_{0R}(t) i_R \end{pmatrix},$$

where for $K = N, R$,

$$T_{0K}(t)(\varphi)(a) = \begin{cases} \exp\left(-\int_{a-t}^{a} (\nu + \nu_K(l))\, dl\right) \varphi(a-t) & \text{if } a \geq t \\ 0 \quad \text{if } a \leq t. \end{cases}$$

Denote for $T > 0$ and $f \in L^1((0,T), X)$,

$$(\mathcal{S} * f)(t) = \int_0^t \mathcal{S}(t-s)f(s)ds, \ \ \forall t \in [0,T].$$

Then we know that (see Kellermann and Hieber [22]) $(\mathcal{S}*f)(\cdot) \in C^1([0,T],X) \cap C^0([0,T],D(A))$. Denote

$$(\mathcal{S} \diamond f)(t) = \frac{d}{dt}(\mathcal{S} * f)(t), \ \ \forall t \in [0,T].$$

Using the results in Webb [35] or in Magal [23], we have the following theorem.

Theorem 3.2. *Let Assumption* 3.1 *be satisfied.*

(i) *For each $x \in X_{0+}$, there exists $U(\cdot)x \in C([0,+\infty), X_0)$ which is a unique solution of the equation*

$$U(t)x = x + A\int_0^t U(s)xds + \int_0^t F(U(s)x)\,ds, \ \ \forall t \geq 0, \ \ \forall x \in X_{0+}$$

or equivalently of the equation

$$U(t)x = T_0(t)x + (\mathcal{S} \diamond F(U(.)x))(t), \ \ \forall t \geq 0, \ \ \forall x \in X_{0+}.$$

(ii) *$U(t)x \in X_{0+}, \ \forall t \geq 0$, and*

$$\|U(t)x\| \leq e^{-\nu t}\|x\| + \int_0^t e^{-\nu(t-s)}\lambda ds, \ \ \forall t \geq 0, \ \ \forall x \in X_{0+}. \tag{3.3}$$

(iii) *$\{U(t)\}_{t\geq 0}$ defines a strongly continuous semigroup of continuous nonlinear operators from X_{0+} into itself. Moreover, the map $(t,x) \to U(t)x$ is continuous from $[0,+\infty) \times X_{0+}$ to X_{0+}.*

(iv) *Denote $D((A+F)_0) = \{x \in D(A) : (A+F)(x) \in X_0\}$. Then $X_{0+} \cap D((A+F)_0)$ is dense in X_{0+} and for all $x \in X_{0+} \cap D((A+F)_0)$, $t \to U(t)x$ is a classical solution of* (3.2); *that is, $U(\cdot)x \in C^1([0,+\infty), X) \cap C^0([0,+\infty), D(A))$ and*

$$\frac{dU(t)x}{dt} = AU(t)x + F(U(t)x), \ \ \forall t \geq 0.$$

For all $x = (S, 0_{\mathbb{R}}, i_N, 0_{\mathbb{R}}, i_R) \in X_0$, define $P_S : X_0 \to \mathbb{R}$, $P_N, P_R : X_0 \to L^1(0,+\infty)$ by

$$P_S(x) = S, \ P_N(x) = i_N, \ P_R(x) = i_R$$

Set

$$M_R = X_{0+}, \qquad M_{R0} = \{x \in M_R : P_R x \neq 0\}, \qquad \partial M_{R0} = M_R \setminus M_{R0},$$
$$M_N = \partial M_{R0}, \qquad M_{N0} = \{x \in M_N : P_N x \neq 0\}, \qquad \partial M_{N0} = M_N \setminus M_{N0},$$

$M_S = \partial M_{N0}$.

Lemma 3.3. *Let Assumption* 3.1 *be satisfied. Then we have for all* $t \geq 0$ *that*

$$U(t)M_{K0} \subset M_{K0}, \;\; U(t)\partial M_{K0} \subset \partial M_{K0}, \;\; K = N, R.$$

Denote for each $t \geq 0$,

$$U_R(t) = U(t), \; U_N(t) = U(t)\mid_{M_N}, \; U_{N0}(t) = U(t)\mid_{M_{N0}}, \; U_S(t) = U(t)\mid_{M_S}.$$

Lemma 3.4. *Let Assumption* 3.1 *be satisfied. Then we have the following*

(i) $\|T_0(t)\| \leq e^{-\nu t}$, *for all* $t \geq 0$.

(ii) *For each bounded set* $B \subset X_{0+}$ *and each* $T > 0$,

$$\{(\mathcal{S} \diamond F(U(.)x))(t) : x \in B, t \in [0, T]\}$$

has a compact closure.

(iii) *For each bounded set* $B \subset X_{0+}$,

$$\alpha(U(t)B) \leq e^{-\nu t}\alpha(B), \;\; \forall t \geq 0,$$

where α *is the Kuratovski measure of non-compactness* (*see Martin* [26]).

Proof. (i) is immediate. (ii) is a consequence of the fact that $\gamma_N, \gamma_{NR}, \gamma_R \in C_{B,U}([0, +\infty), \mathbb{R})$, and Theorem 5.7 in Magal and Thieme [24] applied with $\tau^* = 0$ and $\widehat{X} = X_0$. (iii) is a consequence of (i) and (ii). □

Theorem 3.5. *Let Assumption* 3.1 *be satisfied. Then for each* $K = R, N, S$, $\{U_K(t)\}_{t\geq 0}$ *has a strong global attractor* $A_K \subset M_K$.

Proof. The result is a direct consequence of the inequality (3.3), Lemma 3.4 (iii), and Theorem 3.4.2 in Hale [13]. □

3.2. Volterra Formulation.

Set

$$l_K(a) = \exp\Big(- \int_0^a (\nu + \nu_K(s))\, ds\Big), \;\; \forall a \geq 0, \;\; \forall K = N, R.$$

For all $t, t_0 \in [0, +\infty)$ with $t \geq t_0$, we have

$$\left\{ \begin{array}{l} \dfrac{dS(t)}{dt} = \lambda - \nu S(t) - [B_N(t) + B_R(t)]\, S(t), \\ i_K(t,a) = \left\{ \begin{array}{ll} \dfrac{l_K(a)}{l_K(a-t)}\varphi_K(a-t) & \text{if } a \geq t, \\ l_K(a)S(t-a)B_K(t-a) & \text{if } a \leq t, \end{array} \right. \quad \text{for } K = N, R, \end{array} \right. \tag{3.4}$$

where $B_N(t) = \Phi_{\gamma_N}(P_N U(t)x) + \Phi_{\gamma_{NR}}(P_R U(t)x)$ and $B_R(t) = \Phi_{\gamma_R}(P_R U(t)x)$ are solutions of the following system of Volterra equations:

$$\begin{aligned} B_N(t) =& f_N(t) + f_{NR}(t) + \int_0^t \gamma_N(a) l_N(a) S(t-a) B_N(t-a) da \\ &+ \int_0^t \gamma_{NR}(a) l_R(a) S(t-a) B_R(t-a) da \\ B_R(t) =& f_R(t) + \int_0^t \gamma_R(a) l_R(a) S(t-a) B_R(t-a) da \end{aligned}$$

with

$$\begin{aligned} f_N(t) &= \Phi_{\gamma_N}(T_{0N}(t)\varphi_N) = \int_t^{+\infty} \gamma_N(a) \frac{l_N(a)}{l_N(a-t)} \varphi_N(a-t) da, \\ f_{NR}(t) &= \Phi_{\gamma_{NR}}(T_{0R}(t)\varphi_R) = \int_t^{+\infty} \gamma_{NR}(a) \frac{l_R(a)}{l_R(a-t)} \varphi_R(a-t) da, \\ f_R(t) &= \Phi_{\gamma_R}(T_{0R}(t)\varphi_R) = \int_t^{+\infty} \gamma_R(a) \frac{l_R(a)}{l_R(a-t)} \varphi_R(a-t) da. \end{aligned}$$

Using the above Volterra formulation, we deduce

Lemma 3.6. *Let Assumption* 3.1 *be satisfied. Then*

$$S(t) = P_S U(t)x > 0, \quad \forall t > 0, \quad \forall x \in M_R.$$

Moreover, for $K = N, R$, we have:

(i) *For all $x \in M_K$ with $P_K x \neq 0$, there exists a $t_1 = t_1(K, P_K x) \geq 0$ such that*

$$\Phi_{\gamma_K}(P_K U(t)x) > 0, \quad \forall t \geq t_1.$$

(ii) *There exists a $t_2 = t_2(K) \geq 0$ such that for any $x \in M_K$ with $\Phi_{\gamma_K}(P_K x) > 0$,*

$$\Phi_{\gamma_K}(P_K U(t)x) > 0, \quad \forall t \geq t_2.$$

Proof. To prove this lemma we use Assumption 3.1 (c) and the fact that for $K = N, R, \ t \geq 0$,

$$\begin{aligned} \Phi_{\gamma_K}(P_K U(t)x) &= \Phi_{\gamma_K}(T_{0K}(t)\varphi_K) + \int_0^t \gamma_K(a) l_K(a) S(t-a) B_K(t-a) da \\ &\geq \Phi_{\gamma_K}(T_{0K}(t)\varphi_K) + \int_0^t \gamma_K(a) l_K(a) S(t-a) \Phi_{\gamma_K}(P_K U(t-a)x) da, \end{aligned}$$

where $\varphi_K = P_K x$. The result then follows. □

3.3. **Equilibria.** Denote by

$$\overline{S}_K := (\Phi_{\gamma_K}(l_K))^{-1},\ K = R, N.$$

We find the equilibria in M_S, M_{NO} and M_{RO}, respectively.

(1) *Equilibrium in* M_S : The unique equilibrium in M_S is given by

$$\overline{x}_S = \left(\frac{\lambda}{\nu}, 0_{\mathbb{R}}, 0_{L^1}, 0_{\mathbb{R}}, 0_{L^1}\right).$$

(2) *Equilibrium in* M_{N0} : There exists an equilibrium $\overline{x}_N \in M_{N0}$ if and only if $\lambda/\nu > \overline{S}_N$. Moreover, in this case we have

$$\overline{x}_N = \left(\overline{S}_N, 0_{\mathbb{R}}, (\lambda - \nu\overline{S}_N)l_N, 0_{\mathbb{R}}, 0_{L^1}\right) \in M_N.$$

(3) *Equilibrium in* M_{R0} : There exists an equilibrium $\overline{x}_R \in M_{R0}$ if and only if either i) $\lambda/\nu > \overline{S}_R$ and $\overline{S}_N > \overline{S}_R$; or ii)$\lambda/\nu > \overline{S}_R$, $\overline{S}_N = \overline{S}_R$, and $\gamma_{RN} = 0$. Moreover, in this case we have

$$\overline{x}_R = \left(\overline{S}_R, 0_{\mathbb{R}}, C_N l_N, 0_{\mathbb{R}}, C_R l_R\right)$$

where C_N and C_R are solutions of the following system

$$C_N + C_R = \lambda - \nu\overline{S}_R,$$
$$C_N\left(\overline{S}_N - \overline{S}_R\right) = C_R\overline{S}_N\overline{S}_R\Phi_{\gamma_{RN}}(l_R).$$

Remark 3.7. When $\overline{S}_N = \overline{S}_R$ and $\gamma_{RN} = 0$, we obtain an infinite number of equilibria. In particular, we find $\overline{x}_R$ as close to ∂M_{R0} as we want. Moreover, when $\overline{S}_N = \overline{S}_R$ and $\gamma_{RN} \neq 0$, there is no equilibrium in M_{R0}.

3.4. **Non-uniform Persistence in** M_{R0}**.** We now investigate extinction properties and start with the following lemma.

Lemma 3.8. *Let Assumption* 3.1 *be satisfied. Then we have the following:*

(i) $A_S = \{\overline{x}_S\}$;
(ii) *for all* $x \in A_R$, $P_S x \leq \lambda/\nu$.

Denote

$$\Gamma_K(a) = \Phi_{\gamma_K}(l_K)^{-1}\int_a^{+\infty} e^{-\int_a^s(\nu+\nu_K(l))dl}\gamma_K(s)ds,\ \ \forall a \geq 0,\ \ \forall K = N, R.$$

Then, we have for $K = N, R$ that

$$\begin{cases} \Gamma_K'(a) = (\nu + \nu_K(a))\,\Gamma_K(a) - \Phi_{\gamma_K}(l_K)^{-1}\gamma_K(a) & \text{for a.e. } a \geq 0, \\ \Gamma_K(0) = 1. \end{cases}$$

One can see that under Assumption 3.1 (c), we have $\Gamma_K(a) > 0$, for all $a \geq 0$, $K = N, R$.

Lemma 3.9. *Let Assumption* 3.1 *be satisfied. Then for* $K = N, R$ *and each* $x \in M_K$, *we have*

$$\frac{d\Phi_{\Gamma_K}(i_K(t))}{dt} = \left(S(t) - \overline{S}_K\right)\Phi_{\gamma_K}(i_K(t)), \ \ \forall t \geq 0,$$

where $S(t) = P_S U(t)x$ *and* $i_R(t) = P_R U(t)x$, *for all* $t \geq 0$.

Proof. The proof is straightforward. □

Proposition 3.10. *Let Assumption* 3.1 *be satisfied. We have the following:*

(i) *If* $\lambda/\nu \leq \overline{S}_N$, *then* $A_N = A_S = \{\overline{x}_S\}$. *In particular, for each* $x \in M_N$,

$$U(t)x \to \overline{x}_S \quad \text{as } t \to +\infty$$

and $\{\overline{x}_S\}$ *is stable for* $\{U_N(t)\}_{t\geq 0}$.

(ii) *If* $\lambda/\nu \leq \overline{S}_R$, *then* $A_R = A_N$. *In particular, for each* $x \in M_R$,

$$P_R U(t)x \to 0 \quad \text{as } t \to +\infty.$$

Proof. We only prove (ii); the proof of (i) is similar. Assume that $\frac{\lambda}{\nu}\Phi_{\gamma_R}(l_R) \leq 1 \Leftrightarrow \frac{\lambda}{\nu} \leq \overline{S}_R$ and $A_R \neq A_N$. Then $A_R \cap M_{R0} \neq \emptyset$. Let $x \in A_R \cap M_{R0}$. Then we can find $\gamma(x) = \{u(t)\}_{t\in\mathbb{R}}$, a complete orbit through x in $A_R \cap M_{R0}$. Denote $S(t) = P_S u(t), i_R(t) = P_R u(t)$, for all $t \in \mathbb{R}$. Then, it follows from Lemma 3.9 that

$$\frac{d\Phi_{\Gamma_R}(i_R(t))}{dt} = \left(S(t) - \overline{S}_R\right)\Phi_{\gamma_R}(i_R(t)), \ \ \forall t \in \mathbb{R}.$$

By Lemma 3.8 (ii), we have $S(t) \leq \frac{\lambda}{\nu}$, for all $t \in \mathbb{R}$. So $t \to \Phi_{\Gamma_R}(i_R(t))$ is non-increasing. Since $\Gamma_R(a) > 0$, for all $a \geq 0$, it follows that $\Phi_{\Gamma_R}(i_R(0)) > 0$. We know that $\alpha_\gamma(x)$ is a compact subset and $U(t)\alpha_\gamma(x) = \alpha_\gamma(x)$, for all $t \geq 0$. Moreover, there exists a $C \geq \Phi_{\Gamma_R}(i_R(0)) > 0$ such that

$$\Phi_{\Gamma_R}(P_R y) = C, \ \ \forall y \in \alpha_\gamma(x).$$

Let $y \in \alpha_\gamma(x)$ be fixed. Denote for $t \geq 0$,

$$S_y(t) = P_S U(t)y, \quad i_{Ry}(t) = P_R U(t)y, \ \ i_{Ry}(t) = P_R U(t)y.$$

We have for $t \geq 0$ that

$$\frac{dS_y(t)}{dt} = \lambda - \left[\nu + \Phi_{\gamma_N}(i_{Ny}(t)) + \Phi_{\gamma_{NR}+\gamma_R}(i_{Ry}(t))\right] S_y(t)$$

and

$$\frac{d\Phi_{\Gamma_R}(i_{Ry}(t))}{dt} = \left(S_y(t) - \overline{S}_R\right)\Phi_{\gamma_R}(i_{Ry}(t)).$$

Since $\Phi_{\Gamma_R}(P_R y) = C > 0$, it follows that $P_R y \neq 0$. Lemma 3.6 (i) implies that there exists a $t_1 > 0$ such that

$$\Phi_{\gamma_R}(i_{Ry}(t)) > 0, \;\; \forall t \geq t_1.$$

Since $\frac{d\Phi_{\Gamma_R}(i_{Ry}(t))}{dt} = 0$, we deduce that $S_y(t) = \overline{S}_R, \forall t \geq t_1$. Thus, for all $t \geq t_1$,

$$0 = \lambda - [\nu + \Phi_{\gamma_N}(i_{Ny}(t)) + \Phi_{\gamma_{NR}+\gamma_R}(i_{Ry}(t))]\, \overline{S}_R.$$

This implies that

$$0 < \Phi_{\gamma_R}(i_{Ry}(t))\overline{S}_R \leq \lambda - \nu\overline{S}_R \leq 0, \;\; \forall t \geq t_1,$$

which is impossible. So $A_R \cap M_{R0} = \emptyset$ and $A_R = A_N$. □

Proposition 3.11. *Let Assumption* 3.1 *be satisfied. We have the following:*

(i) *If $\lambda/\nu > \overline{S}_N$, then $\overline{x}_N$ is locally asymptotically stable in M_N for $\{U_N(t)\}_{t\geq 0}$.*

(ii) *If $\lambda/\nu > \overline{S}_R > \overline{S}_N$, then $\overline{x}_N$ is locally asymptotically stable in M_R for $\{U_R(t)\}_{t\geq 0}$. In particular, there exists an $\varepsilon > 0$ such that for each $x \in M_{R0}$ with $\|x - \overline{x}_N\| \leq \varepsilon$,*

$$U_R(t)x \to \overline{x}_N \;\; \text{as } t \to +\infty.$$

Proof. We can use Theorem 4.2 of Thieme [29], Propositions 2.1, 2.2 and 2.4 in Webb [36] to reduce the problem to the study of a characteristic equation. Then the results in Thieme and Castillo-Chavez [34] apply to the characteristic equation and the conclusion follows. □

4. The System Restricted to M_N

In this section, we investigate the global asymptotic behavior of the system restricted to M_N; that is, we consider the system

$$\begin{cases} \dfrac{dS(t)}{dt} = \lambda - \nu S(t) - \Phi_{\gamma_N}(i_N(t))S(t), \\ (\partial_t + \partial_a)\, i_N = -\left(\nu + \nu_N(a)\right) i_N(t,a), \;\; a \in (0, +\infty)\,, \\ i_N(t,0) = \Phi_{\gamma_N}(i_N(t))S(t), \\ (S(0), i_N(0,a)) = (S_0, \varphi_N(a)) \in [0, +\infty) \times L^1_+\left(0, +\infty\right). \end{cases}$$

We first make the following assumption.

Assumption 4.1. Assume that

(a) $\lambda, \nu \in (0, +\infty)\,.$

(b) $\nu_N \in L^\infty_+\left(0, +\infty\right).$

(c) $\gamma_N \in C_{B,U}([0,+\infty),\mathbb{R}) \cap C_+([0,+\infty),\mathbb{R})$ and for each $a \geq 0$ there exists $s \geq a$ such that

$$\gamma_N(s) > 0.$$

We have proved in Proposition 3.10 that $\overline{x}_S$ is globally asymptotically stable when $\lambda/\nu \leq \overline{S}_N$. So it remains to consider the case $\lambda/\nu > \overline{S}_N$.

Lemma 4.2. *Let Assumption* 4.1 *be satisfied. If* $\lambda/\nu > \overline{S}_N$ *then* $\overline{x}_S$ *is ejective in* M_{N0} *for* $\{U_N(t)\}_{t\geq 0}$.

Proof. Let $\delta > 0$ and $\varepsilon \in (0, \lambda/\nu)$ satisfy $(\lambda/\nu - \varepsilon)\int_0^\delta \gamma_N(a)l_N(a)da > 1$. Let $x = (S_0, 0_\mathbb{R}, \varphi_N, 0_\mathbb{R}, 0_{L^1}) \in M_{N0}$ with $\|x - \overline{x}_S\| \leq \varepsilon$. Assume that

$$\|U(t)x - \overline{x}_S\| \leq \varepsilon, \ \ \forall t \geq 0. \tag{4.1}$$

Denote $S(t) = P_S U(t)$ and $i_N(t) = P_N U(t)x$, for all $t \geq 0$. From (4.1), it follows that

$$S(t) \geq \frac{\lambda}{\nu} - \varepsilon, \ \ \forall t \geq 0.$$

Moreover, if we denote $B_N(t) = \Phi_{\gamma_N}(i_N(t))$, for all $t \geq 0$, then

$$B_N(t) = f_n(t) + \int_0^t \gamma_N(a)l_N(a)S(t-a)B_N(t-a)da, \ \ \forall t \geq 0$$

with

$$f_n(t) = \int_t^{+\infty} \gamma_N(a)\frac{l_N(a)}{l_N(a-t)}\varphi_N(a-t)da, \ \ \forall t \geq 0.$$

Thus, for $t \geq \delta$, we have

$$B_N(t) \geq \left(\frac{\lambda}{\nu} - \varepsilon\right)\int_0^\delta \gamma_N(a)l_N(a)B_N(t-a)da. \tag{4.2}$$

By Lemma 3.6 (i), there exists $t_1 \geq 0$ such that $B_N(t) > 0$, for all $t \geq t_1$. Hence, there exists $\eta > 0$ such that $B_N(t) \geq \eta$, for all $t \in [2t_1, 2t_1 + \delta]$. Set

$$\widehat{t} = \sup\{t \geq 2t_1 + \delta : B_N(l) \geq \eta, \ \forall l \in [2t_1 + \delta, t]\}.$$

Assume that $\widehat{t} < +\infty$. Then

$$\begin{aligned} B_N(\widehat{t}) &\geq \left(\frac{\lambda}{\nu} - \varepsilon\right)\int_0^\delta \gamma_N(a)l_N(a)B_N(t-a)da \\ &\geq \left(\frac{\lambda}{\nu} - \varepsilon\right)\int_0^\delta \gamma_N(a)l_N(a)da\eta. \end{aligned}$$

Thus, $B_N(\widehat{t}) > \eta$. By the continuity of $t \to B_N(t)$, it follows that there exists an $\widehat{\varepsilon} > 0$ such that $B_N(t) \geq \eta$, for all $t \in \left[\widehat{t}, \widehat{t} + \widehat{\varepsilon}\right]$, which contradicts the definition of $\widehat{t}$. Therefore, $B_N(t) \geq \eta$, for all $t \geq 2t_1$. Denote $B^* = \liminf_{t\to+\infty} B_N(t) \geq \eta > 0$. Using (4.2), it follows that $B^* \geq B^* (\lambda/\nu - \varepsilon) \int_0^\delta \gamma_N(a) l_N(a) da$, which is impossible. □

Proposition 4.3. *Let Assumption* 4.1 *be satisfied. If* $\lambda/\nu > \overline{S}_N$, *then there exists a global attractor* $A_{N0} \subset M_{N0}$ *for* $\{U_{N0}(t)\}_{t\geq 0}$. *Moreover, there exists an* $\varepsilon > 0$ *such that*

$$\Phi_{\gamma_N}(P_N x) \geq \varepsilon, \quad \forall x \in A_{N0}.$$

Proof. Using Theorem 4.2 in [15], we know that $\{U_N(t)\}_{t\geq 0}$ is uniformly persistent with respect to $(M_{N0}, \partial M_{N0})$. So there exists a global attractor $A_{N0} \subset M_{N0}$ for $\{U_{N0}(t)\}_{t\geq 0}$.

We claim that $\Phi_{\gamma_N}(P_N x) > 0$, for all $x \in A_{N0}$. Let $x \in A_{N0}$. Since $U_{N0}(t)A_{N0} = A_{N0}$, for all $t \geq 0$, we can find a complete orbit $\{u(t)\}_{t\in\mathbb{R}}$ through x in A_{N0}. Set $S(t) = P_S u(t)$ and $i_N(t) = P_N u(t)$, for all $t \in \mathbb{R}$. Then $S(t) > 0$, for all $t \in \mathbb{R}$ and for $t \geq 0, r \in \mathbb{R}$, we have

$$\begin{aligned}\int_0^{+\infty} i_N(t+r)(a)da &= \int_t^{+\infty} \frac{l_N(a)}{l_N(a-t)} i_N(r)(a-t) \\ &\quad + \int_0^t l_N(a) S(t-a+r) \Phi_{\gamma_N}(i_N(t-a+r))da.\end{aligned}$$

Setting $\widehat{t} = t + r$, it follows that for $t \geq r$,

$$\begin{aligned}\int_0^{+\infty} i_N(t)(a)da &= \int_{t-r}^{+\infty} \frac{l_N(a)}{l_N(a-(t-r))} i_N(r)(a-(t-r)) \\ &\quad + \int_0^{t-r} l_N(a) S(t-a) \Phi_{\gamma_N}(i_N(t-a))da\end{aligned}$$

and for $t \geq r$,

$$\left| \int_{t-r}^{+\infty} \frac{l_N(a)}{l_N(a-(t-r))} i_N(r)(a-(t-r)) \right| \leq e^{-\nu(t-r)} \left\| i_N(r) \right\|_{L^1(0,+\infty)}.$$

Since $u(t) \in A_{N0}$ and A_{N0} is compact, it follows that (as $r \to -\infty$) for $t \in \mathbb{R}$,

$$\int_0^{+\infty} i_N(t)(a)da = \int_0^{+\infty} l_N(a) S(t-a) \Phi_{\gamma_N}(i_N(t-a))da.$$

By construction, we have

$$\int_0^{+\infty} i_N(t)(a)da > 0, \quad \forall t \in \mathbb{R},$$

it follows that for all $t \in \mathbb{R}$, there exists a $\widehat{t} \leq t$ such that $\Phi_{\gamma_N}(i_N(\widehat{t})) > 0$. Lemma 3.6 (ii) implies that there exists $t_2 \geq 0$ such that for all $y \in M_R$ with $\Phi_{\gamma_N}(P_N y) > 0$, we have $\Phi_{\gamma_N}(P_N U(t)y) > 0$, for all $t \geq t_2$. Let $\widehat{t} \in [t_2, +\infty)$ be such that $\Phi_{\gamma_N}(i_N(-\widehat{t})) = \Phi_{\gamma_N}(P_N u(-\widehat{t})) > 0$. Then we have $\Phi_{\gamma_N}(P_N u(-\widehat{t})) > 0$ and $\widehat{t} \geq t_2$, so $\Phi_{\gamma_N}(P_N x) = \Phi_{\gamma_N}(P_N U(\widehat{t})u(-\widehat{t})) > 0$. We conclude that $\Phi_{\gamma_N}(P_N x) > 0$, for all $x \in A_{N0}$. Since A_{N0} is compact, it follows that there exists an $\varepsilon > 0$ such that $\Phi_{\gamma_N}(P_N x) \geq \varepsilon$, for all $x \in A_{N0}$. □

We are now interested in the global asymptotic stability of $\overline{x}_N$ in M_{N0}. This is equivalent to showing that $A_{N0} = \{\overline{x}_N\}$. Define

$$\beta(a) = \gamma_N(a) \exp(-\int_0^a \nu_N(s)ds), \quad \forall a \geq 0.$$

Under Assumption 4.1 we have $\beta \in C_{B,U}([0,+\infty), \mathbb{R}) \cap C_+([0,+\infty), \mathbb{R})$. We make another assumption.

Assumption 4.4. Assume that β satisfies the following:

(d) $\beta(a) \geq e^{-\nu(a-s)}\beta(s), \forall a \geq s \geq 0$.

(e) Either 1) $\beta(0) > 0$ or 2) $\beta(0) = 0$, and there exists $s_0 > 0$ such that $\beta(s_0) > 0$ and $\beta\mid_{[0,s_0]}$ is non-decreasing.

In order to state and prove the main theorem of this section, we need several lemmas. Set

$$\overline{x} := \lambda \int_0^{+\infty} e^{-\nu s}\beta(s)ds - \nu, \; x_- := \inf_{x \in A_{N0}} \Phi_{\gamma_N}(P_N x), \; x_+ := \sup_{x \in A_{N0}} \Phi_{\gamma_N}(P_N x).$$

By Proposition 4.3 we know that $x_- > 0$.

Lemma 4.5. *Let Assumption* 4.1 *be satisfied. Let $x \in A_{N0}$ and $\{u(t)\}_{t\in\mathbb{R}}$ be a complete orbit through x in A_{N0}. Denote*

$$x(t) = \Phi_{\gamma_N}(P_N u(t)), \quad \forall t \in \mathbb{R}.$$

If $\lambda/\nu > \overline{S}_N$, then

$$0 < x_- \leq x(t) \leq x_+, \quad \forall t \in \mathbb{R}$$

and x satisfies the scalar neutral delay equation

$$x(t) = \lambda \int_0^{+\infty} e^{-\nu s} J_{\beta,x_t}(s)ds, \quad \forall t \in \mathbb{R}, \tag{4.3}$$

where for each $t \in \mathbb{R}$, $x_t \in C((-\infty,0], \mathbb{R})$ is defined by

$$x_t(-s) = x(t-s), \quad \forall s \geq 0 \tag{4.4}$$

and $J_{\beta,x_t}(s)$ is the unique solution of the ordinary differential equation

$$\begin{cases} \dfrac{dJ_{\beta,x_t}(s)}{ds} = x\,(t-s)\,(\beta(s) - J_{\beta,x_t}(s))\,, \quad \forall s \geq 0, \\ J_{x_t}(0) = 0. \end{cases} \tag{4.5}$$

Proof. For $t \in \mathbb{R}$, set

$$S(t) = P_S u(t), \quad i_N(t) = P_N u(t), \quad x(t) = \Phi_{\gamma_N}(P_N u(t)).$$

Then

$$\frac{dS(t)}{dt} = \lambda - [\nu + x(t)]\, S(t), \;\; \forall t \in \mathbb{R}.$$

So for $t \geq r \geq 0$,

$$S(t) = e^{-\int_r^t (\nu + x(l))dl} S(r) + \lambda \int_r^t e^{-\int_s^t (\nu + x(l))dl} ds.$$

Since $t \to S(t)$ is bounded, when $r \to -\infty$ we have

$$S(t) = \lambda \int_{-\infty}^t e^{-\int_s^t (\nu + x(l))dl} ds, \;\; \forall t \in \mathbb{R}.$$

Moreover, for all $t \geq r$,

$$\int_0^{+\infty} \gamma_N(a) i_N(t)(a) da = \int_{t-r}^{+\infty} \gamma_N(a) \frac{l_N(a)}{l_N(a-(t-r))} i_N(r)(a-(t-r)) + \int_0^{t-r} \gamma_N(a) l_N(a) S(t-a) \Phi_{\gamma_N}(i_N(t-a)) da.$$

Since $t \to i_N(t)$ is bounded and $\beta(a)e^{-\nu a} = \gamma_N(a) l_N(a)$, when $r \to -\infty$ we obtain

$$x(t) = \int_0^{+\infty} \gamma_N(a) l_N(a) S(t-a) x(t-a) da, \;\; \forall t \in \mathbb{R}.$$

Thus, for all $t \in \mathbb{R}$,

$$\begin{aligned} x(t) &= \lambda \int_0^{+\infty} \beta(a) e^{-\nu a} \int_{-\infty}^{t-a} e^{-\int_s^{t-a} (\nu + x(l))dl} ds\, x(t-a) da \\ &= \lambda \int_{-\infty}^{t} \beta(t-a) e^{-\nu(t-a)} \int_{-\infty}^{a} e^{-\int_s^{a} (\nu + x(l))dl} ds\, x(a) da \\ &= \lambda \int_{-\infty}^{t} \int_s^t \beta(t-a) e^{-\nu(t-a)} e^{-\int_s^{a} (\nu + x(l))dl} x(a) da ds \\ &= \lambda \int_{-\infty}^{t} e^{-\nu(t-s)} \int_s^t \beta(t-a) e^{-\int_s^{a} x(l)dl} x(a) da ds \end{aligned}$$

$$\begin{aligned}
&= \lambda \int_0^{+\infty} e^{-\nu s} \int_{t-s}^{t} \beta(t-a) e^{-\int_{t-s}^{a} x(l)dl} x(a) da ds \\
&= \lambda \int_0^{+\infty} e^{-\nu s} \int_0^{s} \beta(a) e^{-\int_{t-s}^{t-a} x(l)dl} x(t-a) da ds \\
&= \lambda \int_0^{+\infty} e^{-\nu s} \int_0^{s} \beta(a) e^{-\int_a^{s} x(t-l)dl} x(t-a) da ds.
\end{aligned}$$

It follows that

$$x(t) = \lambda \int_0^{+\infty} e^{-\nu s} J_{x_t}(s) ds, \ \ \forall t \in \mathbb{R},$$

where

$$J_{\beta,x_t}(s) = \int_0^{s} \beta(a) e^{-\int_a^{s} x(t-l)dl} x(t-a) da, \ \ \forall t \in \mathbb{R}.$$

This competes the proof of the lemma. □

For all $\varphi \in C((-\infty,0], \mathbb{R}_+)$ and $\widehat{\beta} \in L^\infty([0,+\infty), \mathbb{R})$, denote

$$J_{\widehat{\beta},\varphi}(s) = \int_0^{s} \widehat{\beta}(a) e^{-\int_a^{s} \varphi(-l)dl} \varphi(-a) da, \ \ \forall s \geq 0.$$

Then the mapping $s \to J_{\widehat{\beta},\varphi}(s)$ is differentiable almost everywhere and

$$\begin{cases} \dfrac{dJ_{\widehat{\beta},\varphi}(s)}{ds} = x(t-s)\left(\widehat{\beta}(s) - J_{\widehat{\beta},\varphi}(s)\right) \text{ for a.e. } s \geq 0, \\ J_{\widehat{\beta},\varphi}(0) = 0. \end{cases}$$

Lemma 4.6. *Let* $\beta_1, \beta_2 \in L^\infty([0,+\infty), \mathbb{R})$ *and* $\varphi \in C((-\infty,0], \mathbb{R}_+)$. *Then for all* $s \geq 0$,

$$|J_{\beta_1,\varphi}(s)| \leq \|\beta_1\|_{L^\infty(0,+\infty)}, \quad |J_{\beta_1,\varphi}(s) - J_{\beta_2,\varphi}(s)| \leq \|\beta_1 - \beta_2\|_{L^\infty(0,s)}.$$

Proof. The proof is straightforward. □

Lemma 4.7. *Let* $b > a \geq 0$, $\widehat{\beta} \in C([a,b], \mathbb{R})$ *and* $\varphi \in C([-b,-a], \mathbb{R})$. *Consider*

$$\begin{cases} \dfrac{dx(s)}{ds} = \varphi(-s)\left(\widehat{\beta}(s) - x(s)\right), \ \ \forall s \geq a, \\ x(a) = x_a \in \mathbb{R}. \end{cases}$$

Then we have the following:

(i) *If* $x_a \leq \widehat{\beta}(a)$ *and* $\widehat{\beta}$ *is non-decreasing on* $[a,b]$, *then* $x(s) \leq \widehat{\beta}(s)$, $\forall s \in [a,b]$.

(ii) *If* $x_a \geq \widehat{\beta}(a)$ *and* $\widehat{\beta}$ *is non-increasing on* $[a,b]$, *then* $x(s) \geq \widehat{\beta}(s)$, $\forall s \in [a,b]$.

Proof. The proof for the case $\widehat{\beta} \in C^1([a,b],\mathbb{R})$ is immediate. For the continuous case, we approximate $\widehat{\beta}$ by $\beta^n(s) = \frac{1}{n}\int_s^{s+1/n}\overline{\beta}(l)dl$, where $\overline{\beta}(s) = \widehat{\beta}(s)$ if $s \in [a,b]$, and $\overline{\beta}(s) = \widehat{\beta}(b)$ if $s \geq b$. The result then follows. □

Lemma 4.8. *Let $b > a \geq 0$, $\widehat{\beta} \in C([a,b],\mathbb{R})$ and $\varphi_1, \varphi_2 \in C([-b,-a],\mathbb{R})$. Consider for $j = 1,2$*

$$\begin{cases} \dfrac{dx_j(s)}{ds} = \varphi_j(-s)\left(\widehat{\beta}(s) - x_j(s)\right), \ \forall s \in [a,b], \\ x_j(a) = x_{j,a} \in \mathbb{R}. \end{cases}$$

Then we have the following:

(i) *If $(x_{1,a} - x_{2,a}) \geq 0$ and $(\varphi_1(-l) - \varphi_2(-l))\left(\widehat{\beta}(l) - x_1(l)\right) \geq 0$, $\forall s \in [a,b]$, then $x_1(s) \geq x_2(s), \forall s \in [a,b]$.*

(ii) *If $(x_{1,a} - x_{2,a}) \leq 0$ and $(\varphi_1(-l) - \varphi_2(-l))\left(\widehat{\beta}(l) - x_1(l)\right) \leq 0$, $\forall s \in [a,b]$, then $x_1(s) \leq x_2(s)$, $\forall s \in [a,b]$.*

Proof. We have for all $s \in [a,b]$ that

$$\begin{aligned} &\frac{d[x_1(s) - x_2(s)]}{ds} \\ &= (\varphi_1(-s) - \varphi_2(-s))\left(\widehat{\beta}(s) - x_1(s)\right) - \varphi_2(-s)(x_1(s) - x_2(s)). \end{aligned}$$

The result follows. □

Lemma 4.9. *Assume that β satisfies Assumption 4.4(e). Then we have the following:*

(i) *$\exists s^* = s^*(x_+) > 0$ such that $\forall \varphi \in C((-\infty,0],\mathbb{R})$ with $0 \leq \varphi(-s) \leq x_+$, $\forall s \geq 0$, we have $\beta(s) \geq J_{\beta,\varphi}(s)$, $\forall s \in [0,s^*]$.*

(ii) *$\exists \delta = \delta(x_+,x_-) > 0$ such that $\forall \varphi \in C((-\infty,0],\mathbb{R})$ with $0 < x_- \leq \varphi(-s) \leq x_+, \forall s \geq 0$, we have $\int_0^{s^*} e^{-\nu s} J_{\beta,\varphi}(s)ds \geq \delta$.*

Proof. The proof follows from Lemmas 4.7 and 4.8. □

Lemma 4.10. *Let Assumptions 4.1 and 4.4 be satisfied. Assume that $\lambda/\nu > \overline{S}_N$. Then*

(i) $\int_0^{+\infty} e^{-\nu s} J_{\beta,\gamma}(s)ds \frac{\gamma}{\nu+\gamma}\int_0^{+\infty} e^{-\nu s}\beta(s)ds, \ \forall \gamma \geq 0.$

(ii) *For all $\varphi \in C_+((-\infty,0],\mathbb{R})$,*

$$\begin{aligned} &\left|\lambda \int_0^{+\infty} e^{-\nu s}\left[J_{\beta,\varphi}(s) - J_{\beta,\overline{x}}(s)\right]ds\right| \\ &\leq \frac{\int_0^{+\infty} e^{-\nu s}\left|\beta(s) - J_{\beta,\varphi}(s)\right|ds}{\int_0^{+\infty} e^{-\nu s}\beta(s)ds}\sup_{s\geq 0}\left|\varphi(-s) - \overline{x}\right|. \end{aligned}$$

Proof. Let $\gamma \geq 0$. Then (i) follows from the fact that

$$\lambda \int_0^{+\infty} e^{-\nu s} J_{\beta,\gamma}(s) ds = \lambda \int_0^{+\infty} \int_l^{+\infty} e^{-\nu s} e^{-(s-l)\gamma} \gamma\beta(l) ds dl.$$

To prove (ii), notice that for all $s \geq 0$,

$$\frac{d\left(J_{\beta,\varphi} - J_{\beta,\overline{x}}\right)(s)}{ds} = \left(\varphi(-s) - \overline{x}\right)\left(\beta(s) - J_{\beta,\varphi}(s)\right) - \overline{x}\left(J_{\beta,\varphi} - J_{\beta,\overline{x}}\right)(s),$$

so

$$\left(J_{\beta,\varphi} - J_{\beta,\overline{x}}\right)(s) = \int_0^s e^{-\overline{x}(s-l)} \left(\varphi(-l) - \overline{x}\right)\left(\beta(l) - J_{\beta,\varphi}(l)\right) dl.$$

Thus, we have

$$\begin{aligned} &\lambda \int_0^{+\infty} e^{-\nu s} \left(J_{\beta,\varphi} - J_{\beta,\overline{x}}\right)(s) ds \\ &= \lambda \int_0^{+\infty} e^{-\nu s} \int_0^s e^{-\overline{x}(s-l)} \left(\varphi(-l) - \overline{x}\right)\left(\beta(l) - J_{\beta,\varphi}(l)\right) dl ds \\ &= \frac{\lambda}{\nu + \overline{x}} \int_0^{+\infty} e^{-\nu l} \left(\varphi(-l) - \overline{x}\right)\left(\beta(l) - J_{\beta,\varphi}(l)\right) dl. \end{aligned}$$

The conclusion (ii) then follows. □

We are now in the position to state and prove the main result of this section.

Theorem 4.11. *Let Assumptions* 4.1 *and* 4.4 *be satisfied. If* $\lambda/\nu > \overline{S}_N$, *then* $A_{N0} = \{\overline{x}_N\}$. *In particular, for all* $x \in M_{N0}$,

$$U(t)x \to \overline{x}_N \quad \text{as } t \to +\infty$$

and $\{\overline{x}_N\}$ *is stable.*

Proof. It is sufficient to show that $x_- = x_+ = \overline{x}$ since this implies that $\Phi_{\gamma_N}(P_N x) = \overline{x}$, for all $x \in A_{N0}$. Let $x \in A_{N0}$. Then there exists a complete solution orbit $\{u(t)\}_{t\in\mathbb{R}}$ through x in A_{N0}. Setting $S(t) = P_S u(t)$, for all $t \in \mathbb{R}$, we have

$$\frac{dS(t)}{dt} = \lambda - \left[\nu + \overline{x}\right] S(t), \quad \forall t \in \mathbb{R}.$$

Since $t \to S(t)$ on $\mathbb{R}$, we must have $S(0) = \overline{S}_N = \lambda/(\nu + \overline{x})$ and the result follows. So it remains to show that $x_- = x_+ = \overline{x}$. Using Lemmas 4.5 and 4.10, it is sufficient to show that

$$\sup_{\substack{\varphi \in C((-\infty,0],\mathbb{R}) \\ x_- \leq \varphi \leq x_+}} \frac{\int_0^{+\infty} e^{-\nu s} \left|\beta(s) - J_{\beta,\varphi}(s)\right| ds}{\int_0^{+\infty} e^{-\nu s} \beta(s) ds} < 1.$$

We need to show that there exists$\varepsilon > 0$ such that for all $\varphi \in C_+((-\infty, 0], \mathbb{R})$ with $x_- \leq \varphi \leq x_+$,

$$\int_0^{+\infty} e^{-\nu s} |\beta(s) - J_{\beta,\varphi}(s)| \, ds \leq \int_0^{+\infty} e^{-\nu s} \beta(s) ds - \varepsilon.$$

By Lemma 4.9, there exist $s^* > 0$ and $\delta > 0$ such that for all $\varphi \in C_+((-\infty, 0], \mathbb{R})$ with $x_- \leq \varphi \leq x_+$, we have $\beta(s) - J_{\beta,\varphi}(s) \geq 0$, for all $s \in [0, s^*]$ and

$$\int_0^{s(x_+)} e^{-\nu s} J_\varphi(s) ds \geq \delta > 0.$$

Taking $\varepsilon = \delta/2$, it is sufficient to verify that for all $\varphi \in C_+((-\infty, 0], \mathbb{R})$ with $x_- \leq \varphi \leq x_+$,

$$\int_{s^*}^{+\infty} e^{-\nu s} |\beta(s) - J_{\beta,\varphi}(s)| \, ds \leq \int_{s^*}^{+\infty} e^{-\nu s} \beta(s) ds + \frac{\delta}{2}.$$

By Lemma 4.6, we have $J_{\beta,\varphi}(s) \leq \sup_{s \geq 0} \beta(s)$. Let $\widehat{s} > s^*$ be such that

$$\sup_{s \geq 0} \beta(s) \int_{\widehat{s}}^{+\infty} e^{-\nu s} ds \leq \frac{\delta}{8}.$$

Then we need to show that for all $\varphi \in C_+((-\infty, 0], \mathbb{R})$ with $x_- \leq \varphi \leq x_+$,

$$\int_{s^*}^{\widehat{s}} e^{-\nu s} |\beta(s) - J_{\beta,\varphi}(s)| \, ds \leq \int_{s^*}^{\widehat{s}} e^{-\nu s} \beta(s) ds + \frac{\delta}{4}.$$

For $n \geq 0$ and $i = 0, ..., n$, set $s_i^n = \frac{i}{n} \widehat{s}$ and

$$\beta^n(s) = \sum_{i=0}^{n-1} \beta(s_i^n) e^{-\nu\left(s - s_i^n\right)} 1_{\left[s_i^n, s_{i+1}^n\right)}(s), \quad \forall s \in [0, \widehat{s}].$$

It follows from Assumption 4.4 (d) that $\beta^n(s) \geq e^{-\nu(a-s)} \beta^n(a)$, for all $s, a \in [0, \widehat{s}]$ with $s \geq a$ and

$$\sup_{s \in [0, \widehat{s}]} |\beta(s) - \beta^n(s)| \to 0 \text{ as } n \to +\infty.$$

If we denote

$$J_{\beta^n,\varphi}(s) = \int_0^s \beta^n(a) e^{-\int_a^s \varphi(-l) dl} \varphi(-a) da, \quad \forall s \in [0, \widehat{s}],$$

then there exists $n_0 \geq 0$ such that for all $n \geq n_0$ and all $\varphi \in C_+((-\infty, 0], \mathbb{R})$ with $x_- \leq \varphi \leq x_+$, we have

$$\Big| \int_{s^*}^{\widehat{s}} e^{-\nu s} \left[|\beta(s) - J_{\beta,\varphi}(s)| - |\beta^n(s) - J_{\beta^n,\varphi}(s)| \right] ds \Big| \leq \frac{\delta}{16},$$

$$\left| \int_{s^*}^{\widehat{s}} e^{-\nu s} \left[\beta(s) - \beta^n(s) \right] ds \right| \leq \frac{\delta}{16}.$$

It is now sufficient to show that for all $n \geq n_0 > 0$, $\varphi \in C_+\left((-\infty, 0], \mathbb{R} \right)$ with $x_- \leq \varphi \leq x_+$, we have

$$\int_{s^*}^{\widehat{s}} e^{-\nu s} \left| \beta^n(s) - J_{\beta^n,\varphi}(s) \right| ds \leq \int_{s^*}^{\widehat{s}} e^{-\nu s} \beta^n(s) ds + \frac{\delta}{8}.$$

Let $n \geq n_0$ and $\varphi \in C_+\left((-\infty, 0], \mathbb{R} \right)$ with $x_- \leq \varphi \leq x_+$ be fixed. Denote

$$I_- = \left\{ s \in [s^*, \widehat{s}] : \beta^n(s) - J_{\beta^n,\varphi}(s) < 0 \right\}.$$

We need to show that

$$\int_{I_-} e^{-\nu s} \left[J_{\beta^n,\varphi}(s) - \beta^n(s) \right] ds \leq \int_{I_-} e^{-\nu s} \beta^n(s) ds + \frac{\delta}{8}.$$

Using the special form of β^n and Lemma 4.7, we deduce that there exists $\{a_1, ..., a_k\}$ and $\{b_1, ..., b_k\}$ with $a_p < b_p < a_{p+1}$, for all $p = 1, .., k-1$, and $a_k < b_k$, such that

$$I_- = \cup_{p=1,...,k} \left(a_p, b_p \right).$$

Moreover, since

$$J'_{\beta^n,\varphi}(s) = \varphi(-s) \left(\beta^n(s) - J_{\beta^n,\varphi}(s) \right) < 0 \text{ for a.e. } s \in \left(a_p, b_p \right),$$

we obtain that

$$J_{\beta^n,\varphi}(s) \leq J_{\beta^n,\varphi}(a_p) \leq \beta^n(a_p), \ \ \forall s \in \left(a_p, b_p \right).$$

Finally it needs to be shown that for all $p = 1, ..., k$,

$$\int_{a_p}^{b_p} e^{-\nu s} \beta^n(a_p) ds \leq 2 \int_{a_p}^{b_p} e^{-\nu s} \beta^n(s) ds.$$

Since $\beta^n(s) \geq e^{-\nu(s-a_p)} \beta^n(a_p)$, for all $s \in \left(a_p, b_p \right)$, the inequality follows. This completes the proof of the theorem. □

5. Uniform Persistence in M_{R0}

To establish the persistence results, we need the following lemma which can be proven with an argument similar to the proof of Lemma 4.2.

Lemma 5.1. *Let Assumption* 3.1 *be satisfied. Then we have the following:*

(i) *If $\lambda/\nu > \overline{S}_R$, then $\overline{x}_S$ is ejective in M_{R0}.*
(ii) *If $\lambda/\nu > \overline{S}_N > \overline{S}_R$, then $\overline{x}_N$ is ejective in M_{R0}.*

Theorem 5.2. *Let Assumption* 3.1 *be satisfied. Assume that $\lambda/\nu \leq \overline{S}_N$. Then $\{\overline{x}_S\}$ is a global attractor for $\{U_N(t)\}_{t \geq 0}$. Moreover, we have the following alternative:*

(i) *If* $\lambda/\nu \leq \overline{S}_R$*, then* $\lim_{t\to+\infty} \|P_R U(t)x\| = 0$*, for all* $x \in M_{R0}$.
(ii) *If* $\lambda/\nu > \overline{S}_R$*, then there exists* $\varepsilon > 0$ *such that for all* $x \in M_{R0}$*,*

$$\liminf_{t\to+\infty} \|P_R U(t)x\| \geq \varepsilon.$$

Proof. It remains to prove (ii). But (ii) is a consequence of Theorem 4.2 in Hale and Waltman [15] applied with $\Omega(\partial M_{R0}) = \{\overline{x}_S\}$. Using Proposition 3.10 (i) and Lemma 5.1 (i), the result follows. □

Theorem 5.3. *Let Assumptions* 3.1 *and 4.4 be satisfied. Assume that* $\lambda/\nu > \overline{S}_N$*. Then we have the following:*

(i) *If* $\lambda/\nu \leq \overline{S}_R$*, then* $\lim_{t\to+\infty} \|P_R U(t)x\| = 0$*, for all* $x \in M_{R0}$.
(ii) *If* $\lambda/\nu > \overline{S}_R > \overline{S}_N$*, then there exists* $\varepsilon > 0$ *such that for all* $x \in M_{R0}$ *with* $\|x - \overline{x}_N\| \leq \varepsilon$*,*

$$U(t)x \to \overline{x}_N \quad as \quad t \to +\infty.$$

In particular, $\lim_{t\to+\infty} \|P_R U(t)x\| = 0$.
(iii) *If* $\overline{S}_N > \overline{S}_R$*, then there exists* $\varepsilon > 0$ *such that for all* $x \in M_{R0}$*,*

$$\liminf_{t\to+\infty} \|P_R U(t)x\| \geq \varepsilon.$$

Proof. It remains to prove (iii). But it is a consequence of Theorem 2.2 applied with $\Omega(\partial M_{R0}) = \{\overline{x}_S\} \cup \{\overline{x}_N\}$. The result now follows from Theorem 4.11 and Lemma 5.1. This completes the proof of the theorem. □

6. SUMMARY

For an epidemic in a hospital setting total bacteria load present in the hospital is an important determinant of infection rates. The bacterial load of separate antibiotic non-resistant and resistant strains is dependent on the number of patients infected with each of these strains, their stage of infection, and their use of antibiotics. A natural way to track the stage of infection in individuals is infection age, and many researchers have investigated age structure in epidemic models (Diekmann *et al.* [8], Dietz and Schenzle [9], Thieme [32], Thieme and Castillo-Chavez [33, 34], Brauer [2], Castillo-Chavez and Huang [6], Feng *et al.* [10], Zhou *et al.* [40]). In the model we analyze here the two population levels of bacteria and patients are connected in a system of differential equations for the two classes of bacteria (non-resistant and resistant) and the three classes of patients (susceptibles, infectives infected by the non-resistant strain, and infectives infected by the resistant strain). In another work [37] we study equilibria of this model and provide conditions on the parameters to distinguish the mutually exclusive cases: (1) neither infective class has a positive equilibrium, (2) the non-resistant infective class has a positive equilibrium, but the resistant class does not, and (3) both infective classes have a positive equilibrium. In our study here we have used results in Hale and Waltman [15] to investigate the behavior of the solutions of the model with respect to these cases in terms of the model parameters. Specifically, we proved that in case (1) both infective classes extinguish (Proposition 3.10 and Theorem 5.2 (i)), in case (2) the non-resistant infective class becomes endemic and the resistant infective class extinguishes (Theorem 4.11 and Theorem 5.3 (i), (ii)), and in case (3) the resistant infective class persists uniformly (Theorem 5.2 (ii) and Theorem 5.3 (iii)).

The distinction between these three cases is determined by the model parameters as follows: Let

$$T_{V_F} = \int_0^{+\infty} V_F(a)\exp[-\int_0^a (\nu + \nu_N(s))ds]da = \frac{1}{\eta \overline{S}_N},$$
$$T_{V^+} = \int_0^{+\infty} V^+(a)\exp[-\int_0^a (\nu + \nu_R(s))ds]da = \frac{1}{\eta \overline{S}_R},$$
$$T_{V^-} = \int_0^{+\infty} V^-(a)\exp[-\int_0^a (\nu + \nu_R(s))ds]da.$$

Then T_F is the total non-resistant bacterial load produced by a patient infected with only the non-resistant bacteria during their hospital stay, and T_{V^-} (T_{V^+}) is the total non-resistant (resistant) bacterial load produced by a patient infected with the resistant bacteria during their hospital stay. In [37] it is shown that case (1) corresponds to $T_F < \frac{\nu}{\eta\lambda}$ and $T_{V^+} < \frac{\nu}{\eta\lambda}$, case (2) corresponds to $T_F > \frac{\nu}{\eta\lambda}$ and $T_{V^+} < T_F$, and case (3) corresponds to $T_{V^+} > \frac{\nu}{\eta\lambda}$ and $T_F < T_{V^+}$.

Since these cases are distinguished by simple conditions on the parameters at the bacteria level (cell doubling times, recombination rates, reversion rates), and at the patient level (hospital admission rates, exposure of susceptibles to total bacterial load, antibiotic therapy schedules, hospital lengths of stay), it is possible to evaluate control measures which can alter the epidemic outcomes. The impact of control measures such as isolation of patients infected with resistant strains, restricted use of antibiotics, and reduced or extended hospital stays, is discussed in terms of the model parameters in [37].

References

[1] W. Arendt, C.J.K. Batty, M. Hieber, and F. Neubrander, "Vector-Valued Laplace Transforms and Cauchy Problems," Birkhäuser, Basel, 2001.

[2] F. Brauer, *Infection Disease models with chronological age structure and epidemiological age structure,* in "Mathematical Approaches for Emerging and Reemerging Diseases: Models, Methods, and Theory," eds. by C. Castillo-Chavez, S. Blower, D. Kirschner, P. van den Driessche and A.A. Yakubu, Springer-Verlag, 2001, pp. 241–243.

[3] F. Brauer, *A model for an SI disease in age-structured population,* Discr. Contin. Dynam. Sys. - Ser. B, 2 (2002), 257–264.

[4] G.J. Butler, H.I. Freedman, and P. Waltman, *Uniform persistent systems,* Proc. Amer. Math. Soc., 96 (1986), 425–430.

[5] G.J. Butler and P. Waltman, *Persistence in dynamical systems,* J. Differential Equations, 63 (1986), 255–263.

[6] C. Castillo-Chavez and W. Huang, *Age-structured core group model and its impact on STD dynamics,* in "Mathematical Approaches for Emerging and Reemerging Diseases: Models, Methods, and Theory," eds. by C. Castillo-Chavez, S. Blower, D. Kirschner, P. van den Driessche and A. A. Yakubu, Springer-Verlag, 2001, pp. 261–273.

[7] E. D'Agata, M.A. Horn, and G.F. Webb, *The impact of persistent gastrointestinal colonization on the transmission dynamics of vancomycin-resistant Enterococci*, J. Infect. Dis., 185 (2002), 766–773.

[8] O. Diekmann, J.A.P. Heesterbeek, and J.A.J. Mets, *On the definition and the computation of basic reproductive ratio R_0 in models for infectious diseases in heterogeneous population,* J. Math. Biol., 28 (1990), 365–382.

[9] K. Dietz and D. Schenzle, *Proportinate mixing models for age-dependent infection transmission,* J. Math. Biol., 22 (1985), 117–120.

[10] Z. Feng, W. Huang, and C. Castillo-Chavez, *On the role of variable latent periods in mathematical models for tuberculosis,* J. Dynam. Differential Equations, 13 (2001), 425–452.

[11] H.I. Freedman, S. Ruan, and M. Tang, *Uniform persistence and flows near a closed positive invariant set,* J. Dynam. Differential Equations, 6 (1994), 583–600.

[12] H.I. Freedman and J.W H. So, *Persistence in discrete semi-dynamical systems,* SIAM J. Math. Anal., 20 (1989), 930–932.

[13] J.K. Hale, "Asymptotic Behavior of Dissipative Systems," Mathematical Surveys and Monographs 25, Amer. Math. Soc., Providence, 1988.

[14] J.K. Hale, *Dissipation and attractors,* International Conference on Differential Equations (Berlin, 1999), Eds. Fiedler, Groeger and Sprekels, World Scientific, (2000).

[15] J.K. Hale and P. Waltman, *Persistence in finite dimensional systems,* SIAM J. Math. Anal., 20 (1989), 388–395.

[16] H.W. Hethcote, *Qualitative analyses of communicable disease models,* Math. Biosci., 28 (1976), 335–356.

[17] H.W. Hethcote, *Three basic epidemiological models,* in "Applied Mathematical Ecology," eds. by L. Gross, T. G. Hallam and S. A. Levin, Springer-Verlag, Berlin, 1989, pp. 119–144.

[18] H.W. Hethcote, *The mathematics of infectious diseases,* SIAM Rev., 42 (2000), 599–653.

[19] M. W. Hirsch, H. L. Smith, and X.-Q. Zhao, *Chain transitivity, attractivity and strong repellors for semidynamical systems,* J. Dynam. Differential Equations, 13 (2001), 107–131.

[20] J. Hofbauer and J.W.H. So, *Uniform persistence and repellors for maps,* Proc. Amer. Math. Soc., 107 (1989), 1137–1142.

[21] M. Iannelli, "Mathematical Theory of Age-structured Population Dynamic," Giadini Editori e stampatori, Pisa, 1994.
[22] H. Kellermann and M. Hieber, *Integrated semigroups,* J. Funct. Anal., 84 (1989), 160–180.
[23] P. Magal, *Compact attractors for time periodic age-structured population models,* Electronic J. Differential Equations, 2001 (2001), No. 65, 1–35.
[24] P. Magal and H.R. Thieme, *Eventual compactness for a semiflow generated by an age-structured models,* Comm. Pure Appl. Anal., 3 (2004), 695–727.
[25] P. Magal and X-Q. Zhao, *Global attractors and steady states for uniformly persistent dynamical systems,* SIAM J. Math. Anal., 37 (2005), 251–275.
[26] R.H. Martin, "Nonlinear Operators and Differential Equations in Banach spaces," John Wiley & Sons, 1976.
[27] G. Raugel, "Global Attractors in Partial Differential Equations, Handbook of Dynamical Systems," Vol. 2, 885-982, North-Holland, Amsterdam, (2002).
[28] G.R. Sell and Y. You, "Dynamics of Evolutionary Equations," Springer-Verlag, New York, 2002.
[29] H.R. Thieme, *Semiflows Generated by Lipschitz perturbations of non-densely defined operators,* Diff. Int. Eqns., 3 (1990), 1035–1066.
[30] H R. Thieme, *Persistence under relaxed point-dissipativity (with application to an endemic model),* SIAM J. Math. Anal., 24 (1993), 407–435.
[31] H.R. Thieme, *Uniform persistence and permanence for non-autonomous semiflows in population biology,* Math. Biosci., 166 (2000), 173–201.
[32] H.R. Thieme, "Mathematics in Population Biology," Princeton University Press, Princeton, 2003.
[33] H.R. Thieme and C. Castillo-Chavez, *On the role of variable infectivity in the dynamics of the human immunodeficiency virus epidemic,* in "Mathematical and Statistical Approaches to AIDS Epidemiology," ed. by C. Castillo-Chavez, Lecture Notes in Biomath. 83, Springer-Verlag, Berlin, 1989, pp. 157–176.
[34] H.R. Thieme and C. Castillo-Chavez, *How may infection-age-dependent infectivity affect the dynamics of HIV/AIDS*? SIAM. J. Appl. Math., 53 (1993), 1447–1479.
[35] G.F. Webb, "Theory of Nonlinear Age-Dependent Population Dynamics,' Marcel Dekker, New York, 1985.
[36] G.F. Webb, *An operator-theoretic exponential growth in differential equations,* Trans. Amer. Math. Soc., 303 (1987), 751–763.
[37] G.F. Webb, E. D'Agata, P. Magal and S. Ruan, *A model of antibiotic resistant bacterial epidemics in hospitals,* Proc. Natl. Acad. Sci. USA, 102 (2005), 13343–13348.
[38] F. Yang and S. Ruan, *A generalization of the Butler-McGehee lemma and its applications in persistence theory,* Diff. Int. Eqns, 9 (1996), 1321–1330.
[39] X.Q. Zhao, *Uniform persistence and periodic coexistence states in infinite-dimensional periodic semiflows with applications,* Can. Appl. Math. Quart, 3 (1995), 473–495.
[40] Y. Zhou, B. Song, and Z. Ma, *The global stability analysis for an SIS model with age and infection age structures,* in "Mathematical Approaches for Emerging and Reemerging Diseases: Models, Methods, and Theory," eds. by C. Castillo-Chavez, S. Blower, D. Kirschner, P. van den Driessche and A. A. Yakubu, Springer-Verlag, New York, 2001, pp. 313–335.