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Global Stability of a Viral Infection Model with Defectively Infected Cells and Latent Age*

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Abstract The authors propose and analyze a viral infection model with defectively infected cells and age of the latently infected cells. The existence of steady states is determined by the basic reproduction number of virus. With the Lyapunov's direct method, they establish a threshold dynamics of the model with the basic reproduction number of virus as the threshold parameter. To achieve it, a novel procedure is proposed. Its novelties are two-folded. On one hand, the coefficients involved in the specific forms of the used Lyapunov functionals for the two feasible steady states are determined by the same set of inequalities. On the other hand, for the infection steady state, a new approach is proposed to check whether the derivative of the Lyapunov functional candidate along solutions is negative (semi-)definite or not. This procedure not only simplifies the analysis but also exhibits the relationship between the two Lyapunov functionals for the two feasible steady states. Moreover, the procedure is expected to be applicable for other similar models.

Keywords Viral infection model, Basic reproduction number, Equilibrium, Global stability, Lyapunov direct method, Age structure
2000 MR Subject Classification 34D20, 35B40, 92D60, 92D40

1 Introduction

Dynamic models of viral infection have played an important role in understanding the interaction between viruses and host cells. The basic model of viral dynamics was proposed by Nowak and Bangham in 1996 (see [27]). The model is described by a system of ordinary differential equations (ODEs for short) to study the evolution of the densities of uninfected cells, infected cells and free viruses. Since then, the model has become very popular among theorists and experimentalists (see, for example, [3, 28, 31] and references therein). Based on this model, many viral dynamic models have been developed (see, for example, [3, 5–8, 13, 19, 31] and references therein).

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In 1996, Kirschner and Webb [17] were the first to introduce the age of cellular infection (i.e., the time that has elapsed since the cell was infected by a virus (HIV) particle) to an HIV infection model, where the change of the densities of infected cells is described by a partial differential equation due to the consideration of infection age. Besides the existence of steady states, they also used numerical simulations for some quantitative analyses of the dynamics. Until 2004, corresponding to the basic model of viral dynamics in [27], a basic age-structured model of viral infection was proposed and investigated by Nelson et al. [26]. It is easy to see that the model in [26] is a generalization of that in [27] and the generalized form is also regarded as the basic model of viral dynamics with age structure later on. Its global stability was completely analyzed by Huang et al.in 2012 (see [6]). Since then, a number of viral dynamic models with age structures based on it have been built and investigated (see [9–10, 12, 33, 37]).

During viral infection and replication within cells, due to viral variation, effect of immune system, treatment and other factors, some infected cells could contain defective viral genomes. These infected cells produce defective proviruses that will not produce any offspring viruses (see [11, 20, 25]). To study this phenomenon, Nowak and May [28] proposed a model, where the infected cells are divided into three subclasses, longer lived latently infected cells that produce only a few free viruses in a long time, actively infected cells that produce large quantities of free viruses in a short time, and defectively infected cells that contain mutated virus genomes and cannot produce new virion. The model is described by a system of ODEs and is a generalization of the basic model in [27]. The global stability of the model was recently obtained in 2022 (see [21]). Based on the characteristics of the latently infected cells and motivated by the works [10, 17, 26, 33], in this paper, we extend the model in [28] by incorporating age of latently infected cells (i.e., the time elapsed since the cell is infected and stays in the latent stage). The proposed model generalizes the one in [26]. Our aim here is to investigate its global stability.

Global stability of viral dynamic models is important to understand the mechanism of viral infection and is very useful in predicting the outcome of treatment. So far, the Lyapunov's direct method is still the most efficient way of proving global stability, although it is often difficult to find an appropriate Lyapunov function/functional for a model. However, for some ODE models, there have been some systematic approaches to determine whether the derivative of a Lyapunov candidate along solutions is negative (semi-)definite or not (see, for example [14–15, 22–23]). Usually, it is easy to find a suitable Lyapunov function/functional for proving the global stability of the infection-free equilibrium (i.e., the boundary equilibrium). But for proving the global stability of the infection equilibrium (i.e., the positive equilibrium), it needs some necessary techniques and experience to do so.

Recently, given the type of a Lyapunov function, a novel method with certain universality was proposed to determine simultaneously the concrete forms of the function to prove the global stability of the two feasible equilibria of an ODE model (see [21]). More precisely, when both the Lyapunov function candidate for the infection equilibrium and its derivative along solutions of the model can be expressed as a linear combination of $g(u) = u - 1 - \ln u$ (i.e., Volterra-type function), the positive coefficients of the Lyapunov function can be found by solving a set of linear algebraic inequalities. Moreover, the Lyapunov function for the infection-free equilibrium can also be determined by solving almost the same set of inequalities.

For the global stability of models with age structures, the Lyapunov functional candidates are more difficult to construct. In 2010, Magal et al. [24] proved the global stability of the endemic equilibrium for an SI epidemic model with infection age by applying a Lyapunov functional involving the integral of the Volterra-type function. Since then, functions of this form have been successfully used to investigate the global stability of many viral dynamic models and epidemic models (see [1, 16, 30, 32, 38–39] and references therein). For the Volterra-type Lyapunov functionals in the aforementioned literature, the coefficients are usually given directly without any indication of how they are chosen. To make some contribution in this direction, in this paper, we generalize the idea in [21].

The organization of this paper is as follows. In the next section, we formulate the model and provide some preliminary results. Then in Section 3, we investigate the existence of feasible steady states, which is determined by the basic reproduction number. The main result on the global stability of the infection-free and infection steady states is established in Section 4 by using the approach of Lyapunov functionals. The paper ends with a brief discussion on the idea of proving global stability.

2 Formulation of the Model

Our model is based on the one in [28]. First, taking into account the structure of the viral infection model with defectively infected cells and considering the stage characteristics of the infected cells during their development, we propose the following modified model of (4.8) in [28],

$$\begin{cases} \dfrac{\mathrm{d}x}{\mathrm{d}t} = \lambda - \mu x - \beta x v, \\ \dfrac{\mathrm{d}y_1}{\mathrm{d}t} = p_1 \beta x v - (\delta_1 + \gamma + \gamma_0) y_1, \\ \dfrac{\mathrm{d}y_2}{\mathrm{d}t} = p_2 \beta x v + \gamma y_1 - (\delta_2 + \gamma_0') y_2, \\ \dfrac{\mathrm{d}y_3}{\mathrm{d}t} = p_3 \beta x v + \gamma_0 y_1 + \gamma_0' y_2 - \delta_3 y_3, \\ \dfrac{\mathrm{d}v}{\mathrm{d}t} = k_1 y_1 + k_2 y_2 - c v, \end{cases} \tag{2.1}$$

where $x = x(t)$, $y_1 = y_1(t)$ $y_2 = y_2(t)$, $y_3 = y_3(t)$, and $v = v(t)$ represent the numbers of uninfected cells, latently infected cells, actively infected cells, defectively infected cells and free viruses at time t, respectively. Here it is assumed that both latently and actively infected cells may develop into defectively infected cells. Moreover, the latently infected cells can also produce virion. In (2.1), uninfected cells are recruited at a constant rate λ, die at rate μx and are infected with a rate $\beta x v$. The parameter p_i $(i = 1, 2, 3)$ with $\sum\limits_{i=1}^{3} p_i = 1$ denotes the probability that upon infection a cell will become an infected cell of type y_i, $\delta_i y_i$ $(i = 1, 2, 3)$ is the death rate of the associated infected cells, γy_1 is the transfer rate of latently infected cells to actively infected ones, $k_1 y_1$ and $k_2 y_2$ are the rates at which latently and actively infected cells

produce free viruses, respectively. $\gamma_0 y_1$ and $\gamma_0' y_2$ are the rates at which the latently and actively infected cells develop into the defectively infected cells, respectively. Free virus is cleared at a rate cv.

Model (2.1) includes many existing ones as special cases. For example, the case where $p_2 = p_3 = k_1 = \gamma_0 = \gamma_0' = 0$ is studied by Korobeinikov [18], the case where $p_3 = k_1 = \gamma_0 = \gamma_0' = 0$ and $p_1 = 1 - \alpha$, $p_2 = \alpha$ with $\alpha \in (0, 1)$ is studied by Korobeinikov [19] and Elaiw [4], the case where $p_3 = \gamma = \gamma_0 = \gamma_0' = 0$ and $p_1 = 1 - \alpha$, $p_2 = \alpha$ with $\alpha \in (0, 1)$ is investigated by Korobeinkov [18], and the case where $\gamma_0 = \gamma_0' = 0$ is analyzed by Nowak and May [28] and Li et al. [21]. The global stability of (2.1) can be analyzed completely by similar arguments as those in [21].

In model (2.1), all the parameters are constant, which imply that transformations among infected cells do not depend on the times they stay in the corresponding states. However, for the case where latently infected cells have a long incubation period, it is feasible to assume that the transformation of latent cells into active cells and defective cells, and the release of free viruses from the latent cells all depend on the latent age (the time elapsed since an uninfected cell becomes latently infected). For example, in the transmission of HIV, Zika and many others, the infectivities of infected cells vary with respect to the time since infected. Therefore, introduction of the latent age provides greater flexibility in modeling the transformation of the latently infected cells since it allows the relevant parameters to depend on the lifetime of the cells. Denote the coefficients of death rate, releasing rate of free viruses, transfer rates to actively and defectively infected cells of latently infected cells at age a as $\delta_1(a)$, $k_1(a)$, $\gamma(a)$ and $\gamma_0(a)$, respectively. Here $\delta_1(a)$, $k_1(a)$, $\gamma(a)$, $\gamma_0(a) \in L^1_+(0, \infty)$, the set of all integrable functions from $(0, \infty)$ into $\mathbb{R}_+ = [0, \infty)$. Then, following the mechanism of viral infection for model (2.1) and including the age of the latently infected cells by letting $y_1(t, a)$ be the density of latently infected cells at age a, we have the following viral infection model,

$$\begin{cases} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - \mu x(t) - \beta x(t) v(t), \\ \dfrac{\partial y_1(t,a)}{\partial t} + \dfrac{\partial y_1(t,a)}{\partial a} = -[\delta_1(a) + \gamma(a) + \gamma_0(a)] y_1(t,a), \\ \dfrac{\mathrm{d}y_2(t)}{\mathrm{d}t} = p_2 \beta x(t) v(t) + \displaystyle\int_0^\infty \gamma(a) y_1(t,a) \mathrm{d}a - (\delta_2 + \gamma_0') y_2(t), \\ \dfrac{\mathrm{d}y_3(t)}{\mathrm{d}t} = p_3 \beta x(t) v(t) + \displaystyle\int_0^\infty \gamma_0(a) y_1(t,a) \mathrm{d}a + \gamma_0' y_2(t) - \delta_3 y_3(t), \\ \dfrac{\mathrm{d}v(t)}{\mathrm{d}t} = \displaystyle\int_0^\infty k_1(a) y_1(t,a) \mathrm{d}a + k_2 y_2(t) - c v(t) \end{cases} \tag{2.2}$$

with the boundary condition

$$y_1(t, 0) = p_1 \beta x(t) v(t). \tag{2.3}$$

Obviously, model (2.2) with boundary condition (2.3) extends the model in [26]. Note that $y_3(t)$ is decoupled from the other equations in model (2.2). Thus we only need to focus on

$$\begin{cases} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - \mu x(t) - \beta x(t)v(t), \\ \dfrac{\partial y_1(t,a)}{\partial t} + \dfrac{\partial y_1(t,a)}{\partial a} = -\sigma(a)y_1(t,a), \\ \dfrac{\mathrm{d}y_2(t)}{\mathrm{d}t} = p_2\beta x(t)v(t) + \displaystyle\int_0^\infty \gamma(a)y_1(t,a)\mathrm{d}a - \delta y_2(t), \\ \dfrac{\mathrm{d}v(t)}{\mathrm{d}t} = \displaystyle\int_0^\infty k_1(a)y_1(t,a)\mathrm{d}a + k_2y_2(t) - cv(t), \end{cases} \tag{2.4}$$

where $\sigma(a) = \delta_1(a) + \gamma(a) + \gamma_0(a)$ and $\delta = \delta_2 + \gamma_0'$. We impose the boundary condition (2.3) and the initial condition

$$(x(0), y_1(0,a), y_2(0), v(0)) = (x^{(0)}, y_1^{(0)}(a), y_2^{(0)}, v^{(0)}) \in \mathbb{X} \triangleq \mathbb{R}_+ \times L^1_+(0,\infty) \times \mathbb{R}_+ \times \mathbb{R}_+$$

on model (2.4). Note that $\mathbb{X}$ is a positive cone of the Bach space $\mathbb{R} \times L^1(0,\infty) \times \mathbb{R} \times \mathbb{R}$ equipped with the product norm. In the sequel, we also assume that there exists $\sigma_0 > 0$ such that

$$\delta_1(a) + \gamma_0(a) \geq \sigma_0 \quad \text{for } a \in \mathbb{R}_+.$$

Integrating the PDE in (2.4) along the characteristics and incorporating the boundary condition (2.3) gives

$$y_1(t,a) = \begin{cases} \phi(a)p_1\beta x(t-a)v(t-a), & \text{if } t > a, \\ \dfrac{\phi(a)}{\phi(a-t)}y_1(0,a-t), & \text{if } t \leq a, \end{cases}$$

where $\phi(a) = \exp\big(-\int_0^a \sigma(s)\mathrm{d}s\big)$. Then the equivalent integral formulation of (2.4) is the following systems of integro-differential equations:

$$\begin{cases} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - \mu x(t) - \beta x(t)v(t), \\ y_1(t,a) = \phi(a)p_1\beta x(t-a)v(t-a)\mathbf{1}_{\{t>a\}} + \frac{\phi(a)}{\phi(a-t)}y_1(0,a-t)\mathbf{1}_{\{a\geq t\}}, \\ \dfrac{\mathrm{d}y_2(t)}{\mathrm{d}t} = p_2\beta x(t)v(t) + \displaystyle\int_0^\infty \gamma(a)y_1(t,a)\mathrm{d}a - \delta y_2(t), \\ \dfrac{\mathrm{d}v(t)}{\mathrm{d}t} = \displaystyle\int_0^\infty k_1(a)y_1(t,a)\mathrm{d}a + k_2y_2(t) - cv(t). \end{cases}$$

Here $\mathbf{1}_{\{t>a\}}(t,a) = 1$ if $t > a$ and 0 otherwise. $\mathbf{1}_{\{a\geq t\}}$ is defined similarly. With a minor modification of the proof of [2, Theorem 2.1], we can show that (2.4) with (2.3) has a unique (local) solution in $\mathbb{R} \times L^1(0,\infty) \times \mathbb{R} \times \mathbb{R}$. Then, arguing similarly as in the proof of [2, Lemma 2.2], we can show that the solution remains nonnegative. Moreover, choose $K > 0$ large enough

such that $\sigma_0 - \frac{\|k_1\|_\infty}{K} > 0$ and $\delta - \frac{k_2}{K} > 0$. Then, on the interval of maximal existence $[0, t_f)$, we have

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}\Big(x(t) + \int_0^\infty y_1(t,a)\mathrm{d}a + y_2(t) + \frac{v(t)}{K}\Big)\\
&= \lambda - \mu x(t) - \beta x(t)v(t) + \int_0^\infty \Big[-\frac{\partial y_1(t,a)}{\partial a} - \sigma(a)y_1(t,a)\Big]\mathrm{d}a\\
&\quad + p_2\beta x(t)v(t) + \int_0^\infty \gamma_1(a)y_1(t,a)\mathrm{d}a - \delta y_2(t)\\
&\quad + \frac{1}{K}\Big[\int_0^\infty k_1(a)y_1(t,a)\mathrm{d}a + k_2y_2(t) - cv(t)\Big]\\
&= \lambda - \mu x(t) - \beta x(t)v(t) - y_1(t,0) + y_1(t,\infty) - \int_0^\infty \sigma(a)y_1(t,a)\mathrm{d}a\\
&\quad + p_2\beta x(t)v(t) + \int_0^\infty \gamma_1(a)y_1(t,a)\mathrm{d}a - \delta y_2(t)\\
&\quad + \frac{1}{K}\Big[\int_0^\infty k_1(a)y_1(t,a)\mathrm{d}a + k_2y_2(t) - cv(t)\Big]\\
&\le \lambda - \mu x(t) - \Big(\sigma_0 - \frac{\|k_1\|_\infty}{K}\Big)\|y_1(t,\cdot)\| - \Big(\delta - \frac{k_2}{K}\Big)y_2 - \frac{c}{K}v(t)\\
&\le \lambda - M\Big(x(t) + \int_0^\infty y_1(t,a)\mathrm{d}a + y_2(t) + \frac{v(t)}{K}\Big),
\end{aligned}$$

where $M = \min\big\{\mu, \sigma_0 - \frac{\|k_1\|_\infty}{K}, \delta - \frac{k_2}{K}, c\big\}$. It follows that

$$\begin{aligned}
&x(t) + \int_0^\infty y_1(t,a)\mathrm{d}a + y_2(t) + \frac{v(t)}{K}\\
&\le \mathrm{e}^{-Mt}\Big(x(0) + \int_0^\infty y_1(0,a)\mathrm{d}a + y_2(0) + \frac{v(0)}{K}\Big) + \frac{\lambda}{M}(1 - \mathrm{e}^{-Mt})
\end{aligned} \tag{2.5}$$

for $t \in [0, t_f)$. This means that the solution is bounded and hence the solution exists globally. Moreover, it follows from (2.5) that

$$\limsup_{t\to\infty}\Big(x(t) + \int_0^\infty y_1(t,a)\mathrm{d}a + y_2(t) + \frac{v(t)}{K}\Big) \le \frac{\lambda}{M},$$

which means that solutions are globally bounded.

3 The Basic Reproduction Number and Steady States

For convenience, we define Ψ_1, $\Psi_2 : \mathbb{R}_+ \to \mathbb{R}_+$ by

$$\Psi_1(a) = \int_0^a \gamma(\theta)\mathrm{e}^{-\int_0^\theta \sigma(\tau)\mathrm{d}\tau}\mathrm{d}\theta, \quad \Psi_2(a) = \int_0^a k_1(\theta)\mathrm{e}^{-\int_0^\theta \sigma(\tau)\mathrm{d}\tau}\mathrm{d}\theta \quad \text{for } a \in \mathbb{R}_+.$$

Denote

$$R_0 = \frac{\beta\lambda}{c\mu}\Big[p_1\Psi_2(\infty) + \frac{k_2}{\delta}(p_1\Psi_1(\infty) + p_2)\Big].$$

In fact, in the absence of viral infection, the steady state of uninfected cells is $x_0 = \frac{\lambda}{\mu}$. When a viral particle is introduced into the host without infection, during its lifespan $\frac{1}{c}$, it

will infect $\frac{\beta x_0}{c}$ uninfected cells. Among them, a proportion of p_1 enters the latently infected subpopulation and a proportion of p_2 becomes actively infected. Note that $\mathrm{e}^{-\int_0^a \sigma(\tau)\mathrm{d}\tau}$ is the probability for a latently infected cell being still latent after a time units. On the one hand, $\Psi_2(\infty)$ is the burst size[1] of a latently infected cell. Thus a total of $\frac{p_1\beta x_0}{c}\Psi_2(\infty)$ viral particles will be produced by the $\frac{p_1\beta x_0}{c}$ latently infected cells. On the other hand, $\Psi_1(\infty)$ represents the proportion of latently infected cells leaving the latent stage and then entering the active stage. Then there is a total of $\frac{\beta x_0}{c}(p_1\Psi_1(\infty)+p_2)$ actively infected cells. They will produce a total of $\frac{\beta x_0}{c}[p_1\Psi_1(\infty)+p_2]\frac{k_2}{\delta}$ viral particles since the burst size of an actively infected cell is $\frac{k_2}{\delta}$. Therefore, if a viral particle is introduced into a population of wholly uninfected cells, a total of R_0 viral particle will be produced during its lifespan. This means that R_0 is the basic reproduction number of virus for system (2.4) with (2.3).

The following main result of this section tells us that the steady states are determined by R_0.

Theorem 3.1 (i) *If $R_0 \le 1$, then system* (2.4) *with* (2.3) *only has the infection-free steady state $P_0(x_0, 0, 0, 0)$, where $x_0 = \frac{\lambda}{\mu}$.*

(ii) *If $R_0 > 1$, then besides P_0, system* (2.4) *with* (2.3) *also has a unique infection steady state $P^*(x^*, y_1^*(a), y_2^*, v^*)$, where*

$$x^* = \frac{x_0}{R_0},$$

$$v^* = \frac{\mu}{\beta}(R_0 - 1),$$

$$y_1^*(a) = p_1\beta x^* v^* \mathrm{e}^{-\int_0^a \sigma(\theta)}\mathrm{d}\theta$$

for

$$a \in \mathbb{R}_+,$$

$$y_2^* = \frac{\beta x^* v^*}{\delta}(p_1\Psi_1(\infty) + p_2).$$

Proof Clearly, a steady state $P(x, y_1(a), y_2, v)$ of (2.4) with (2.3) satisfies

$$\begin{cases} 0 = \lambda - \mu x - \beta x v, \\ \dfrac{\mathrm{d}y_1}{\mathrm{d}a} = -\sigma(a)y_1(a), \\ 0 = p_2\beta x v + \displaystyle\int_0^\infty \gamma(a)y_1(a)\mathrm{d}a - \delta y_2, \\ 0 = \displaystyle\int_0^\infty k_1(a)y_1(a)\mathrm{d}a + k_2 y_2 - cv, \\ y_1(0) = p_1\beta x v. \end{cases} \tag{3.1}$$

[1]The burst size is the total number of viral particles produced by an infected cell in its lifespan (see [26]).

It follows from the second and the last equations of (3.1) that

$$y_1(a) = p_1\beta x v \mathrm{e}^{-\int_0^a \sigma(\theta)\mathrm{d}\theta}. \tag{3.2}$$

If $v = 0$, then $x = x_0$ and $y_1(a) \equiv 0$. These combined with the third equation of (3.1) produce $y_2 = 0$. So there is always the infection-free steady state P_0. Now we assume that $v > 0$. Substituting (3.2) into the third equation gives

$$y_2 = \frac{\beta x v}{\delta}(p_1\Psi_1(\infty) + p_2). \tag{3.3}$$

As $v > 0$, substituting (3.2)–(3.3) into the fourth equation of (3.1) yields $x = \frac{x_0}{R_0}$. This, together with the first equation of (3.1), implies that $v = \frac{\mu}{\beta}(R_0 - 1)$, which is possible only when $R_0 > 1$. This completes the proof.

4 A Threshold Dynamics

In this section, we study the global dynamics of system (2.4) with the boundary condition (2.3), which is a threshold dynamics characterized by the basic reproduction number of virus, R_0. The technique used is the LaSalle's invariance principle. For the statement on strongly continuous nonlinear semigroups, we refer to Webb [36, Proposition 4.6] for example.

We start with a result on the existence of solutions to a system of algebraic inequalities. The result not only plays an important role in determining the suitable specific form of Lyapunov functionals but also is applicable to other similar models.

Lemma 4.1 *Suppose that ρ satisfies*

$$0 < \rho \le \frac{c\delta}{\beta\{k_2[p_1\Psi_1(\infty) + p_2] + \delta p_1\Psi_2(\infty)\}}, \tag{4.1}$$

where β, μ, c, p_1, p_2, $\sigma(a)$, δ, $k_1(a)$, k_2 and $\gamma(a)$ are given parameters in (2.4) *with* (2.3). *Then the following system of inequalities*

$$\begin{cases} n_2 c \ge \beta\rho, \\ n_1\delta \ge n_2 k_2, \\ n_1[p_1\Psi_1(\infty) + p_2] + n_2 p_1\Psi_2(\infty) \le 1 \end{cases} \tag{4.2}$$

has positive solutions (n_1, n_2).

Proof It is easy to check that the system

$$\begin{cases} n_1\delta = n_2 k_2, \\ n_1[p_1\Psi_1(\infty) + p_2] + n_2 p_1\Psi_2(\infty) = 1 \end{cases}$$

has a unique solution

$$\begin{aligned} n_1 = n_1^* &\triangleq \frac{k_2}{k_2[p_1\Psi_1(\infty)+p_2]+\delta p_1\Psi_2(\infty)}, \\ n_2 = n_2^* &\triangleq \frac{\delta}{k_2[p_1\Psi_1(\infty)+p_2]+\delta p_1\Psi_2(\infty)}, \end{aligned} \tag{4.3}$$

which is positive. Also it follows from (4.1) that $\frac{\beta\rho}{c} \le n_2^*$. Then we can easily see that the solutions to (4.2) are the set D^* in the n_1-n_2 plane (see Figure 1), where

$$D^* = \Big\{(n_1, n_2) : \frac{n_2k_2}{\delta} \le n_1 \le \frac{1-n_2p_1\Psi_2(\infty)}{p_1\Psi_1(\infty)+p_2}, \frac{\beta\rho}{c} \le n_2 \le n_2^*\Big\}.$$

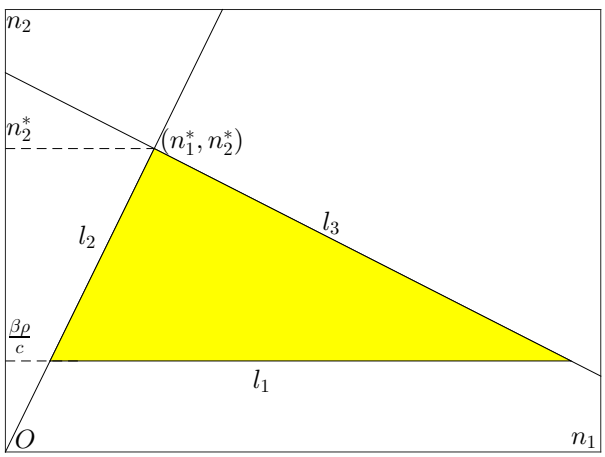

Figure 1 The solution set of (4.2), where the straight lines l_1, l_2, and l_3 correspond to $n_2c = \beta\rho$, $n_1\delta = n_2k_2$ and $n_1[p_1\Psi_1(\infty)+p_2]+n_2p_1\Psi_2(\infty) = 1$, respectively.

This completes the proof.

Remark 4.1 (i) From the proof of Lemma 4.1, we see that (4.2) only has a unique solution (n_1^*, n_2^*) if $\rho = \frac{c\delta}{\beta\{k_2[p_1\Psi_1(\infty)+p_2]+\delta p_1\Psi_2(\infty)\}}$.

(ii) Let (n_1, n_2) be a positive solution of (4.2), then $n_1\Psi_1(\infty)+n_2\Psi_2(\infty) \le \frac{1-n_1p_2}{p_1}$. Choose $n(0) \in \big[n_1\Psi_1(\infty)+n_2\Psi_2(\infty), \frac{1-n_1p_2}{p_1}\big]$ and define

$$n(a) = \mathrm{e}^{\int_0^a \sigma(\tau)\mathrm{d}\tau}\{n(0)-[n_1\Psi_1(a)+n_2\Psi_2(a)]\} \quad \text{for } a \in \mathbb{R}_+. \tag{4.4}$$

Since $\Psi_i(a) \le \Psi_i(\infty)$ for $a \in \mathbb{R}_+$ and $i = 1, 2$, we know that $n(0)-[n_1\Psi_1(a)+n_2\Psi_2(a)] \ge 0$. We also know that $n(a)$ is bounded as $\sigma(a) \in L_+^1(0,\infty)$. Moreover, n is differentiable and

$$\frac{\mathrm{d}n(a)}{\mathrm{d}a} - n(a)\sigma(a) + [n_1\gamma(a)+n_2k_1(a)] = 0.$$

In the construction of Lyapunov functionals, we need some qualitative properties on solutions of (2.4) with (2.3). Since every solution is nonnegative, it is not difficult to show that $x(t) > 0$ for $t > 0$. Moreover, denote

$$\mathbb{X}_0 = \{(x, y_1, y_2, v) \in \mathbb{X} : v > 0\}$$

and define $\rho : \mathbb{X} \to \mathbb{R}_+$ by $\rho((x, y_1(\cdot), y_2, v)) = v$ for $(x, y_1(\cdot), y_2, v) \in \mathbb{X}$. Then, applying [34, Theorem 5.2], one can obtain the following results: If $R_0 > 1$, then (2.4) with (2.3) has a global compact attractor $\mathcal{A}$ in $\mathbb{X}_0$ and its solution semi-flow is uniformly ρ-persistent, that is, there exists an $\varepsilon > 0$ such that

$$\liminf_{t\to\infty} v(t) > \varepsilon$$

for every solution $(x(t), y_1(t, a), y_2(t), v(t))$ of (2.4) with (2.3) and initial conditions in $\mathbb{X}_0$. As a result, one can show that there exists $\xi > 0$ such that $x(t)$, $y_1(t, 0)$, $y_2(t)$, $v(t) \geq \xi$ for all $t \in \mathbb{R}$, where $(x(t), y_1(t, a), y_2(t), v(t))$ is any total-trajectory in $\mathcal{A}$. Their proofs are quite standard for age-structured epidemic models and hence we omit the details here. Interested readers refer to [35, 38], for example.

Now we are ready to state and prove the main result of this paper.

Theorem 4.1 (i) *If $R_0 \leq 1$, then the infection-free steady state P_0 of* (2.4) *with* (2.3) *is globally asymptotically stable in $\mathbb{X}$.*

(ii) *If $R_0 > 1$, then the infection steady state P^* is globally asymptotically stable in $\mathbb{X}_0$.*

Proof (i) Suppose $R_0 \leq 1$. We consider a functional of the form

$$L_1 = x_0 g\Big(\frac{x}{x_0}\Big) + \int_0^\infty n(a) y_1(t, a)\mathrm{d}a + n_1 y_2 + n_2 v,$$

where $g(u) = u - 1 - \ln u$ for $u > 0$ is the Volterra-type function mentioned before, $n(a)$ is a positive continuous function for $a \geq 0$ to be determined, n_1 and n_2 are positive numbers to be specified. L_1 can be regarded as well-defined since $x(t) > 0$ for $t > 0$ for each solution of (2.4) with (2.3).

First, it follows from the second equation of (2.4) that

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty n(a) y_1(t, a)\mathrm{d}a = -\int_0^\infty n(a)\Big[\sigma(a) y_1(t, a) + \frac{\partial y_1(t, a)}{\partial a}\Big]\mathrm{d}a.$$

Then applying integration by parts to $\int_0^\infty n(a)\frac{\partial y_1(t,a)}{\partial a}\mathrm{d}a$ yields

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty n(a) y_1(t, a)\mathrm{d}a = &-\int_0^\infty n(a)\sigma(a) y_1(t, a)\mathrm{d}a \\ &+ n(0) y_1(t, 0) - [n(a) y_1(t, a)]|_{a=\infty} + \int_0^\infty y_1(t, a)\frac{\mathrm{d}n(a)}{\mathrm{d}a}\mathrm{d}a\end{aligned}$$

$$= -\int_0^\infty n(a)\sigma(a)y_1(t,a)\mathrm{d}a$$
$$+ n(0)p_1\beta x(t)v(t) - [n(a)y_1(t,a)]|_{a=\infty} + \int_0^\infty y_1(t,a)\frac{\mathrm{d}n(a)}{\mathrm{d}a}\mathrm{d}a,$$

where the boundary condition (2.3) has been used.

Next, noting $\lambda = \mu x_0$, we see that the derivative of L_1 with respect to t along solutions of (2.4) is given by

$$\begin{aligned}
\frac{\mathrm{d}L_1}{\mathrm{d}t}\Big|_{(2.4)} &= -\frac{\mu(x-x_0)^2}{x} - \beta(x-x_0)v - \int_0^\infty n(a)\sigma(a)y_1(t,a)\mathrm{d}a \\
&\quad + n(0)p_1\beta xv - [n(a)y_1(t,a)]|_{a=\infty} + \int_0^\infty y_1(t,a)\frac{\mathrm{d}n(a)}{\mathrm{d}a}\mathrm{d}a \\
&\quad + n_1\Big[p_2\beta xv + \int_0^\infty \gamma(a)y_1(t,a)\mathrm{d}a - \delta y_2\Big] \\
&\quad + n_2\Big[\int_0^\infty k_1(a)y_1(t,a)\mathrm{d}a + k_2y_2 - cv\Big] \\
&= -\frac{\mu(x-x_0)^2}{x} - [n(a)y_1(t,a)]|_{a=\infty} \\
&\quad - \beta xv[1 - n(0)p_1 - n_1p_2] - v(n_2c - \beta x_0) - y_2(n_1\delta - n_2k_2) \\
&\quad - \int_0^\infty y_1(t,a)\Big[n(a)\sigma(a) - n_1\gamma(a) - n_2k_1(a) - \frac{\mathrm{d}n(a)}{\mathrm{d}a}\Big]\mathrm{d}a \\
&\le -\frac{\mu(x-x_0)^2}{x} - \beta xv[1 - n(0)p_1 - n_1p_2] - v(n_2c - \beta x_0) - y_2(n_1\delta - n_2k_2) \\
&\quad - \int_0^\infty y_1(t,a)\Big[n(a)\sigma(a) - n_1\gamma(a) - n_2k_1(a) - \frac{\mathrm{d}n(a)}{\mathrm{d}a}\Big]\mathrm{d}a,
\end{aligned}$$

where $[n(a)y_1(t,a)]|_{a=\infty} \ge 0$ was used.

Since $R_0 \le 1$ implies that $x_0 \le \frac{c\delta}{\beta\{k_2[p_1\Psi_1(\infty)+p_2]+\delta p_1\Psi_2(\infty)\}}$, it follows from Lemma 4.1 with $\rho = x_0$ that (4.2) has a positive solution (n_1, n_2). Let $n(a)$ be defined by (4.4) with $n(0) = n_1\Psi_1(\infty) + n_2\Psi_2(\infty)$. With these choices of n_1, n_2, and $n(a)$, we then have

$$\frac{\mathrm{d}L_1}{\mathrm{d}t}\Big|_{(2.4)} \le -\frac{\mu(x-x_0)^2}{x}.$$

Moreover, $\frac{\mathrm{d}L_1}{\mathrm{d}t}\big|_{(2.4)} = 0$ if $x(t) = x_0$. Let $(x(t), y_1(t,a), y_2(t), v(t))$ be a solution in the largest invariant set of $\big\{\frac{\mathrm{d}L_1}{\mathrm{d}t}|_{(2.4)} = 0\big\}$. Then $x(t) \equiv x_0$. This, together with the first equation of (2.4), implies that $v(t) \equiv 0$. This, combined with the fourth equation of (2.4) and nonnegativity of solutions, gives us $y_1(t,a) \equiv 0 = y_2(t)$. Thus when $R_0 \le 1$, the largest invariant set of (2.4) in $\big\{\frac{\mathrm{d}L_1}{\mathrm{d}t}\big|_{(2.4)} = 0\big\}$ is the singleton $\{P_0\}$. Therefore, by LaSalle invariance principle, P_0 is globally stable in $\mathbb{X}$ when $R_0 \le 1$.

(ii) Now we assume that $R_0 > 1$. First it is routine to show that P^* is locally asymptotically stable. As a result, it suffices to show that P^* is attractive in $\mathcal{A}$. Let $(x(t), y_1(t,a), y_2(t), v(t))$ be a total trajectory in $\mathcal{A}$.

First consider a function of the form

$$L_{21} = x^* g\Big(\frac{x}{x^*}\Big) + n_1 y_2^* g\Big(\frac{y_2}{y_2^*}\Big) + n_2 v^* g\Big(\frac{v}{v^*}\Big),$$

where n_1 and n_2 are positive numbers to be specified. L_{21} is well defined from the discussion before the statement of the theorem. Straightforward calculation gives the derivative of L_{21} with respect to t along solutions of (2.4),

$$\begin{aligned}\frac{\mathrm{d}L_{21}}{\mathrm{d}t}\Big|_{(2.4)} &= \Big(1-\frac{x^*}{x}\Big)(\lambda-\mu x-\beta x v)\\ &\quad + n_1\Big(1-\frac{y_2^*}{y_2}\Big)\Big[p_2\beta x v + \int_0^\infty \gamma(t,a)y_1(t,a)\mathrm{d}a - \delta y_2\Big]\\ &\quad + n_2\Big(1-\frac{v^*}{v}\Big)\Big[\int_0^\infty k_1(a)y_1(t,a)\mathrm{d}a + k_2 y_2 - cv\Big].\end{aligned}$$

For the simplicity of notation, denote

$$u(t)=\frac{x(t)}{x^*},\quad w_1(t,a)=\frac{y_1(t,a)}{y_1^*(a)},\quad w_2(t)=\frac{y_2(t)}{y_2^*},\quad z(t)=\frac{v(t)}{v^*}. \tag{4.5}$$

Then $\frac{\mathrm{d}L_{21}}{\mathrm{d}t}\big|_{(2.4)}$ can be reexpressed as

$$\frac{\mathrm{d}L_{21}}{\mathrm{d}t}\Big|_{(2.4)} = C_0^* - \overline{H}_1(t) - \int_0^\infty \overline{H}_1^*(t,a)\mathrm{d}a,$$

where

$$\begin{aligned}C_0^* &= \lambda+\mu x^* + n_1\delta y_2^* + n_2 c v^*,\\ \overline{H}_1(t) &= \mu x^* u + \frac{\lambda}{u} + \beta x^* v^*(1-n_1p_2)uz + (n_2c-\beta x^*)v^* z\\ &\quad + (n_1\delta - n_2k_2)y_2^* w_2 + n_1p_2\beta x^* v^*\frac{uz}{w_2} + n_2k_2y_2^*\frac{w_2}{z},\\ \overline{H}_1^*(t,a) &= n_1\gamma(a)y_1^*(a)\Big[\frac{w_1(t,a)}{w_2} - w_1(t,a)\Big] + n_2k_1(a)y_1^*(a)\Big[\frac{w_1(t,a)}{z(t)} - w_1(t,a)\Big].\end{aligned}$$

To express $\frac{\mathrm{d}L_{21}}{\mathrm{d}t}\big|_{(2.4)}$ as an integral, we choose an arbitrary continuous function $r(a)$ satisfying $\int_0^\infty r(a)\mathrm{d}a = 1$. Then

$$\frac{\mathrm{d}L_{21}}{\mathrm{d}t}\Big|_{(2.4)} = \int_0^\infty [r(a)C_0^* - h_1(t,a)]\mathrm{d}a,$$

where

$$\begin{aligned}h_1(t,a) &= r(a)\Big[\mu x^* u + \frac{\lambda}{u} + \beta x^* v^*(1-n_1p_2)uz + (n_2c-\beta x^*)v^* z\Big]\\ &\quad + r(a)\Big[(n_1\delta - n_2k_2)y_2^* w_2 + n_1p_2\beta x^* v^*\frac{uz}{w_2} + n_2k_2y_2^*\frac{w_2}{z}\Big]\\ &\quad + n_1\gamma(a)y_1^*(a)\frac{w_1(t,a)}{w_2} + n_2k_1(a)y_1^*(a)\frac{w_1(t,a)}{z(t)}\\ &\quad - [n_1\gamma(a)+n_2k_1(a)]y_1^*(a)w_1(t,a).\end{aligned}$$

Further, corresponding to the function $h_1(t,a)$, we define a function $h_1^*(t,a)$ as

$$\begin{aligned}h_1^*(t,a) &= r(a)\Big[\mu x^*\ln u+\lambda\ln\Big(\frac{1}{u}\Big)+\beta x^*v^*(1-n_1p_2)\ln(uz)+(n_2c-\beta x^*)v^*\ln z\Big]\\&\quad+r(a)\Big[(n_1\delta-n_2k_2)y_2^*\ln w_2+n_1p_2\beta x^*v^*\ln\Big(\frac{uz}{w_2}\Big)+n_2k_2y_2^*\ln\Big(\frac{w_2}{z}\Big)\Big]\\&\quad+n_1\gamma(a)y_1^*(a)\ln\Big(\frac{w_1(t,a)}{w_2}\Big)+n_2k_1(a)y_1^*(a)\ln\Big(\frac{w_1(t,a)}{z(t)}\Big)\\&\quad-[n_1\gamma(a)+n_2k_1(a)]y_1^*(a)\ln w_1(t,a).\end{aligned}$$

With a straightforward calculation, one can reduce $h_1^*(t,a)$ to

$$\begin{aligned}h_1^*(t,a) &= r(a)(\mu x^*+\beta x^*v^*-\lambda)\ln u\\&\quad+n_2[r(a)(cv^*-k_2y_2^*)-k_1(a)y_1^*(a)]\ln z\\&\quad+n_1[r(a)(\delta y_2^*-p_2\beta x^*v^*)-\gamma(a)y_1^*(a)]\ln w_2(t).\end{aligned}\tag{4.6}$$

With the help of (3.1), we see $\int_0^\infty h_1^*(t,a)\mathrm{d}a=0$ since $\int_0^\infty r(a)\mathrm{d}a{=}1$. Moreover, it is easy to verify that $r(a)C_0^*$ equals exactly the sum of the coefficients of all the logarithmic functions in $h_1^*(t,a)$, which is expressed by (4.6). Therefore, we can rewrite $\frac{\mathrm{d}L_{21}}{\mathrm{d}t}\big|_{(2.4)}$ as

$$\frac{\mathrm{d}L_{21}}{\mathrm{d}t}\Big|_{(2.4)}=\int_0^\infty[r(a)C_0^*-h_1(t,a)+h_1^*(t,a)]\mathrm{d}a=-\int_0^\infty H_1(t,a)\mathrm{d}a,$$

where

$$\begin{aligned}H_1(t,a) &= r(a)\Big[\mu x^*g(u)+\lambda g\Big(\frac{1}{u}\Big)+\beta x^*v^*(1-n_1p_2)g(uz)+(n_2c-\beta x^*)v^*g(z)\Big]\\&\quad+r(a)\Big[(n_1\delta-n_2k_2)y_2^*g(w_2)+n_1p_2\beta x^*v^*g\Big(\frac{uz}{w_2}\Big)+n_2k_2y_2^*g\Big(\frac{w_2}{z}\Big)\Big]\\&\quad+n_1\gamma(a)y_1^*(a)g\Big(\frac{w_1(t,a)}{w_2}\Big)+n_2k_1(a)y_1^*(a)g\Big(\frac{w_1(t,a)}{z(t)}\Big)\\&\quad-[n_1\gamma(a)+n_2k_1(a)]y_1^*(a)g(w_1(t,a)).\end{aligned}$$

Next, we define a functional

$$L_{22}=\int_0^\infty n(a)y_1^*(a)g\Big(\frac{y_1(t,a)}{y_1^*(a)}\Big)\mathrm{d}a,$$

where $n(a)$ is an undetermined nonnegative differentiable function. The derivative of L_{22} along solutions of (2.4) is

$$\begin{aligned}\frac{\mathrm{d}L_{22}}{\mathrm{d}t}\Big|_{(2.4)} &= \int_0^\infty n(a)\Big[1-\frac{y_1^*(a)}{y_1(t,a)}\Big]\frac{\partial y_1(t,a)}{\partial t}\mathrm{d}a\\&=-\int_0^\infty n(a)\Big[1-\frac{y_1^*(a)}{y_1(t,a)}\Big]\Big[\frac{\partial y_1(t,a)}{\partial a}+\sigma(a)y_1(t,a)\Big]\mathrm{d}a.\end{aligned}$$

Noting $\sigma(a)=-\frac{\mathrm{d}y_1^*(a)}{\mathrm{d}a}\cdot\frac{1}{y_1^*(a)}$, we have

$$\frac{\mathrm{d}L_{22}}{\mathrm{d}t}\Big|_{(2.4)}=-\int_0^\infty n(a)\Big[1-\frac{y_1^*(a)}{y_1(t,a)}\Big]\Big[\frac{\partial y_1(t,a)}{\partial a}-\frac{dy_1^*(a)}{\mathrm{d}a}\cdot\frac{y_1(t,a)}{y_1^*(a)}\Big]\mathrm{d}a$$

$$= -\int_0^\infty n(a)y_1^*(a)\Big[1-\frac{y_1^*(a)}{y_1(t,a)}\Big]\frac{\partial}{\partial a}\Big(\frac{y_1(t,a)}{y_1^*(a)}\Big)\mathrm{d}a$$
$$= -\int_0^\infty n(a)y_1^*(a)\frac{\partial}{\partial a}g\Big(\frac{y_1(t,a)}{y_1^*(a)}\Big)\mathrm{d}a.$$

Using integration by parts yields

$$\begin{aligned}\frac{\mathrm{d}L_{22}}{\mathrm{d}t}\Big|_{(2.4)} &= n(0)y_1^*(0)g\Big(\frac{y_1(t,0)}{y_1^*(0)}\Big) - \Big[n(a)y_1^*(a)g\Big(\frac{y_1(t,a)}{y_1^*(a)}\Big)\Big]\Big|_{a=\infty}\\ &\quad + \int_0^\infty \frac{\mathrm{d}[n(a)y_1^*(a)]}{\mathrm{d}a}g\Big(\frac{y_1(t,a)}{y_1^*(a)}\Big)\mathrm{d}a\\ &= n(0)y_1^*(0)g\Big(\frac{x(t)v(t)}{x^*v^*}\Big) - \Big[n(a)y_1^*(a)g\Big(\frac{y_1(t,a)}{y_1^*(a)}\Big)\Big]\Big|_{a=\infty}\\ &\quad + \int_0^\infty \frac{\mathrm{d}[n(a)y_1^*(a)]}{\mathrm{d}a}g\Big(\frac{y_1(t,a)}{y_1^*(a)}\Big)\mathrm{d}a,\end{aligned}$$

where we have used $y_1(t,0) = p_1\beta x(t)v(t)$ and $y_1^*(0) = p_1\beta x^*v^*$. With the notation in (4.5) and the function $r(a)$ chosen before, we have

$$\begin{aligned}\frac{\mathrm{d}L_{22}}{\mathrm{d}t}\Big|_{(2.4)} &= n(0)y_1^*(0)g(u(t)z(t)) - [n(a)y_1^*(a)g(w_1(t,a))]|_{a=\infty}\\ &\quad + \int_0^\infty \frac{\mathrm{d}[n(a)y_1^*(a)]}{\mathrm{d}a}g(w_1(t,a))\mathrm{d}a\\ &\le -\int_0^\infty H_2(t,a)\mathrm{d}a,\end{aligned}$$

where

$$H_2(t,a) = -r(a)n(0)y_1^*(0)g(u(t)z(t)) - \frac{\mathrm{d}[n(a)y_1^*(a)]}{\mathrm{d}a}g(w_1(t,a)).$$

Here we have used $n(a)y_1^*(a)g(w_1(t,a)) \ge 0$ and $\int_0^\infty r(a)\mathrm{d}a = 1$.

Now, let

$$L_2 = L_{21} + L_{22}.$$

Then we have

$$\frac{\mathrm{d}L_2}{\mathrm{d}t}\Big|_{(2.4)} \le -\int_0^\infty H(t,a)\mathrm{d}a,$$

where

$$\begin{aligned}H(t,a) = r(a)\Big\{&\mu x^*g(u) + \lambda g\Big(\frac{1}{u}\Big) + n_1p_2\beta x^*v^*g\Big(\frac{uz}{w_2}\Big)\\ &+ (n_2c - \beta x^*)v^*g(z) + (n_1\delta - n_2k_2)y_2^*g(w_2)\\ &+[\beta x^*v^*(1-n_1p_2) - n(0)y_1^*(0)]g(uz) + n_2k_2y_2^*g\Big(\frac{w_2}{z}\Big)\Big\}\\ &+ n_1\gamma(a)y_1^*(a)g\Big(\frac{w_1(t,a)}{w_2}\Big) + n_2k_1(a)y_1^*(a)g\Big(\frac{w_1(t,a)}{z(t)}\Big)\\ &- \Big\{[n_1\gamma(a) + n_2k_1(a)]y_1^*(a) + \frac{\mathrm{d}[n(a)y_1^*(a)]}{\mathrm{d}a}\Big\}g(w_1(t,a))\end{aligned}$$

$$
\begin{aligned}
&= r(a)\Big\{\mu x^* g(u) + \lambda g\Big(\frac{1}{u}\Big) + n_1 p_2 \beta x^* v^* g\Big(\frac{uz}{w_2}\Big) \\
&\quad + (n_2 c - \beta x^*) v^* g(z) + (n_1\delta - n_2 k_2) y_2^* g(w_2) \\
&\quad + [\beta x^* v^*(1 - n_1 p_2) - p_1 n(0)] g(uz) + n_2 k_2 y_2^* g\Big(\frac{w_2}{z}\Big)\Big\} \\
&\quad + n_1\gamma(a) y_1^*(a) g\Big(\frac{w_1(t,a)}{w_2}\Big) + n_2 k_1(a) y_1^*(a) g\Big(\frac{w_1(t,a)}{z(t)}\Big) \\
&\quad - \Big\{\frac{\mathrm{d}n(a)}{\mathrm{d}a} - n(a)\sigma(a) + [n_1\gamma(a) + n_2 k_1(a)]\Big\} y_1^*(a) g(w_1(t,a)).
\end{aligned}
$$

Here we have used the fact that $y_1^*(a) = p_1\beta x^* v^* \mathrm{e}^{-\int_0^a \sigma(\theta)\mathrm{d}\theta}$ (see (3.2)). Recall that $x^* = \frac{x_0}{R_0} = \frac{c\delta}{\beta\{k_2[p_1\Psi_1(\infty)+p_2]+\delta p_1\Psi_2(\infty)\}}$. Thus by Lemma 4.1 and Remark 4.1, system (4.2) with $\rho = x^*$ has a unique positive solution (n_1^*, n_2^*) shown in (4.3). Let $n_1 = n_1^*$, $n_2 = n_2^*$ and $n(a)$ be defined by (4.4) with $n(0) = n_1\Psi_1(\infty) + n_2\Psi_2(\infty)$. Then with these choices, we have

$$
\begin{aligned}
H(t,a) &= r(a)\Big\{\mu x^* g(u) + \lambda g\Big(\frac{1}{u}\Big) + n_1 p_2 \beta x^* v^* g\Big(\frac{uz}{w_2}\Big) + n_2 k_2 y_2^* g\Big(\frac{w_2}{z}\Big)\Big\} \\
&\quad + n_1\gamma(a) y_1^*(a) g\Big(\frac{w_1(t,a)}{w_2}\Big) + n_2 k_1(a) y_1^*(a) g\Big(\frac{w_1(t,a)}{z(t)}\Big) \\
&\geq 0.
\end{aligned}
$$

Hence $\frac{\mathrm{d}L_2}{\mathrm{d}t}\big|_{(2.4)} \leq 0$ and the equality holds only if $u(t) = 1$ and $w_1(t,a) = w_2(t) = z(t)$, or equivalenty, $\frac{x(t)}{x^*} = 1$ and $\frac{y_1(t,a)}{y_1^*(a)} = \frac{y_2(t)}{y_2^*} = \frac{v(t)}{v^*}$. It follows from the first equation of (2.4) that $x(t) = x^*$ implies $v(t) = v^*$ and thus $y_1(t,a) = y_1^*(a)$ and $y_2(t) = y_2^*$ from $\frac{y_1(t,a)}{y_1^*(a)} = \frac{y_2(t)}{y_2^*} = \frac{v(t)}{v^*} = 1$. This means that the largest invariant set of (2.4) in $\big\{\frac{\mathrm{d}L_2}{\mathrm{d}t}\big|_{(2.4)} = 0\big\}$ is the singleton $\{P^*\}$. Therefore, by LaSalle invariance principle, P^* is globally attractive in $\mathcal{A}$. This completes the proof.

5 Conclusion and Discussion

In this paper, based on the characteristics of viral infection with latent stage, we first proposed an ODE model of viral infection with defectively infected cells and stage structure, which includes some models in the literature as special cases. The global stability of the ODE model can be obtained by using the similar method as that in [21]. Then, according to differentiability of the latently infected cells and the development of all infected cells, we incorporated the age of the latently infected cells into the ODE model, which is described by a hyperbolic partial differential equation and ODEs. This model is a generalization of both the one without age structure in [28] and the one without latent stage but with age structure in [26]. We have shown that the global stability is determined completely by the basic reproduction number of virus, R_0. That is, the infection-free steady state is globally stable when $R_0 \leq 1$ while the infection steady state is globally stable when $R_0 > 1$.

The global stability of the model was established by the Lyapunov's direct method. With respect to the construction of the suitable Lyapunov functionals, the commonly used Voterra-type function is used. Usually, it is easy to determine an appropriate Lyapunov functional for the infection-free steady state. However, it is difficult to find that for the infection steady state. In this work, we first guess a form of suitable Lyapunov functional. Then we applied a rigorous way to determine the coefficients and hence the concrete Lyapunov functionals. The analysis indicates that the coefficients of Lyapunov functionals for both infection-free steady state and infection steady state satisfy the same set of inequalities. This reveals a connection of the suitable Lyapunov functionals for both the steady states.

Regarding the proof of global stability of the infection steady state, two points are worthy to be pointed out on proving the negative (semi-)definiteness of the derivative of the Lyapunov functional along solutions. First, we express the derivative as an integral form $\int_0^\infty H(t,a)\mathrm{d}a$ by means of an auxiliary function $r(a)$ satisfying $\int_0^\infty r(a)\mathrm{d}a = 1$. Next, we reexpress the integrand $H(t,a)$ in a specific form, $-\sum_{i=1}^{K} b_i(a)g_i(u(t,a))$, that is, a linear combination of some functions of form $g(u) = u - 1 - \ln u$ for $u > 0$. Since $g(u) \geq 0$ and $g(u) = 0$ if and only if $u = 1$, the conditions $b_i(a) \geq 0$ $(i = 1, 2, \cdots, K)$ ensure the negative (semi-)definiteness of $H(t,a)$. Lemma 4.1 guarantees that these conditions can be satisfied. In the literature, to determine the negative (semi-)definiteness of the derivative of the Lyapunov functionals, some ones rearrange the derivative in a given form according to the geometric mean and arithmetic mean inequality (see [21]). This requires certain skill and experience. In some cases, it may not work. Our approach here avoids these complex processes and is much simpler. The approach has some kind of universality and can be applied to some other similar epidemic models, too.

Declarations

Conflicts of interest The authors declare no conflicts of interest.

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