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An analytical approach to determining the coefficients in Lyapunov direct method: with application to an age-structured epidemiological model

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Abstract

Lyapunov direct method has been employed as a powerful tool to show the global stability of an equilibrium in differential equations. One widely cited Lyapunov function for population growth models takes the form $L(t) = \sum_{i=1}^{n} c_i L_i(t)$ with $L_i(t) = x_i(t) - x_i^* - x_i^* \ln(x_i(t)/x_i^*)$ if $x_i^* > 0$ or $L_i(t) = x_i(t)$ if $x_i^* = 0$, a combination of functions involving different state variables $x_i(t)$ of the model system with $(x_1^*, x_2^*, \ldots, x_n^*)$ being an equilibrium. However, two challenges hinder the efficient applications of Lyapunov direct method: (a) determining the coefficients c_i; and (b) rearranging the time derivative $L'(t)$ along the trajectories of the system to show it is negative (semi-)definite. This study is to propose an easy-to-follow analytical approach to tackle these two challenges, which will be illustrated through an application to an epidemiological model with vaccination age. Furthermore, the Lyapunov functional for the endemic equilibrium can be reformulated to investigate the global stability for the disease-free equilibrium and a family of Lyapunov functionals can be proposed for the same purpose. It is expected that the approach can be further applied to other age-structured models and be extended to analyze more complicated models with other heterogeneous factors.

Keywords: Lyapunov functional; determination of coefficients; global stability; age-structured model

Highlights:

1 Propose an analytical approach to determine the coefficients of the suitable Lyapunov functionals for population models with age structure.

2 Show the negative (semi-)definiteness of the derivative of the Lyapunov functionals by expressing it as a specific form.

3 The Lyapunov functional for the endemic equilibrium can be reformulated to investigate the global stability for the disease-free equilibrium.

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4 The approach extends the applications of the Lyapunov direct method to age-structured models.

5 Illustrate the existence of a family of Lyapunov functionals.

1. Introduction

Epidemiological models have played a very important role in predicting and controlling the spread of infectious diseases [2]. The Coronavirus Disease 2019 (COVID-19) pandemic has placed epidemic modeling at the forefront of policy making [3]. For many epidemiological models, the basic reproduction number $\mathcal{R}_0$, which is defined as the expected number of secondary cases produced by a typical infectious individual during its whole period of infectiousness in a completely susceptible population (see [2, 5, 24]), serves as a threshold parameter to indicate the possibilities of disease outbreak: outbreak will happen when $\mathcal{R}_0 > 1$ and there is no disease outbreak when $\mathcal{R}_0 \leq 1$. For a transmission process described by models of dynamic systems, this result can be gained through showing the global stability of the disease-free equilibrium (when $\mathcal{R}_0 \leq 1$) and the endemic equilibrium in the interior of the feasible region (when $\mathcal{R}_0 > 1$). However, there is no universal method to establish the global stability results for dynamic systems, in particular, when the dimension of the phase space is high or infinite.

Lyapunov function (functional) method has been widely cited as a powerful tool to establish the global stability of equilibria and the method has been extensively used to various types of differential equations including: ordinary differential equations [8, 11], delay differential equations [9, 17], age-structured models [21, 22], reaction-diffusion systems without time delay [7] or with delays [25], impulsive differential systems [23], and fractional order differential systems [1]. In population growth models [8, 17], a widely used Lyapunov function to establish the global stability of an equilibrium $(x_1^*, x_2^*, \dots, x_n^*)$ takes the form

$$L(t) = \sum_{i=1}^{n} c_i L_i(t)$$

a linear combination of similar terms $L_i(t)$ with $L_i(t) = x_i(t) - x_i^* - x_i^* \ln(x_i(t)/x_i^*)$ (if $x_i^* > 0$) and $L_i(t) = x_i(t)$ (if $x_i^* = 0$). However, two challenges are involved: (i) to determine the constant coefficients c_i; and (ii) to appropriately rearrange the time derivative $L'(t)$ along the trajectories of the system to show its negative (semi-)definiteness. These two aspects are closed interrelated. One efficient approach to tackle these challenges is based on graph theory [8, 17], which allows one to find global Lyapunov functions for large-scale coupled systems from systems of individual group or vertex. However, the function/functional is given mainly by experiences while no specific approach has been developed to determine the coefficients and to verify the negative (semi-)definiteness of the derivative of the Lyapunov function/functional along solutions. To address this problem, an algebraic approach has been proposed in [14, 16] to choose appropriate coefficients c_i and automatically establish the negative (semi-)definiteness of $L'(t)$, and this approach has been successfully employed to some epidemic models in the form of ordinary differential systems. However, as far as we know, there are no corresponding results on other types of differential equation models.

The main purpose of the current study is to extend the approach in [14, 16] to models with age structures, so that the construction of the suitable Lyapunov functionals and the proof of the negative (semi-)definiteness of its derivative follows a novel procedure, instead of depending on the experiences of investigators. The theoretical approach proposed here will be illustrated through an epidemiological model with vaccination age, which is a system consisting of a hyperbolic partial differential equation (PDE) coupled with several ordinary differential equations. The main contribution is extending the Lyapunov functional method from the following perspectives: (i) Lyapunov functionals with different set of coefficients c_i can be constructed to show the global stability of a particular equilibrium; (ii) the arranged forms are also non-unique for the given Lyapunov functional to show the negative (semi-)definiteness of its derivative; and (iii) the Lyapunov functional for the endemic equilibrium can be modified for the boundary equilibrium.

The paper is organized as follows. The next section proposes an epidemiological model with vaccination age and demonstrates some theoretic results on the model. Section 3 establishes global stability of equilibria by means of Lyapunov direct method, which presents the main contributions of the current study. Numerical simulations are performed in Section 4 to illustrate the validity of the theoretic methods and show the non-uniqueness of valid Lyapunov functionals. Finally, a brief conclusion and discussion is stated in the last section.

2. The epidemiological model and basic properties

In this section, we first formulate an epidemiological model with vaccination age, and then provide some basic results including the well-posednes of the model, the basic reproduction number, as well as existence and local stability of equilibria.

2.1. Formulation of the epidemiological model

The vaccine-induced immunity is waning and a vaccinated individual may lose immune protection after a period since vaccination. From compartmental modeling point of view for disease transmission, a vaccinated individual may return to susceptible class after a period of time. However, the duration of vaccine-based immunity may vary among individuals, giving rise to a distribution for the duration of immunity. To appropriately incorporate the distribution of sojourn time (duration of immunity) in the vaccinated compartment, an age-structured modeling framework with partial differential equations or a Lotka integral form can be employed with a suitable sojourn function [20]. In this manuscript, we couple a susceptible-exposed-infectious (SEI) compartmental model with an additional vaccinated class of individuals structured by vaccination ages, which allows us to describe the waning immunity of vaccinated individuals with heterogeneous immunity durations. In particular, we introduce a state variable, the vaccination age $a \geq 0$, for a vaccinated individual, and this individual may be protected by the vaccine (stay in the immune class) or lose immune protection (move to the susceptible compartment), and the probability is given by the sojourn function $P(a)$. Please note that the function $P(a)$ is non-increasing and $P(0) = 1$. Assume that $v(t, a)$ is the population density of vaccinated individuals with immune protection at time t and vaccination age a. Then the rate of change $\varepsilon(a)$ for $v(t, a)$ from the immune class to the susceptible class is given by the related probability density function for the probability function $P(a)$. Assume that susceptible individuals get vaccinated at a constant rate, that is, the density of vaccinated population with vaccination age zero can be given by $v(t,0) = pS(t)$, that is, p is the effective vaccination rate for susceptible population. Considering the vaccination and loss of immunity, we can extend the SEI model into the following one with the new variable $v(t,a)$:

$$\begin{cases} \frac{dS(t)}{dt} = A - (\mu + p)S(t) - \beta S(t)I(t) + \int_0^\infty \varepsilon(a)v(t,a)da, \\ \frac{\partial v(t,a)}{\partial t} + \frac{\partial v(t,a)}{\partial a} = -[\mu + \varepsilon(a)]v(t,a), \\ \frac{dE(t)}{dt} = \beta S(t)I(t) - (\mu + \gamma)E(t), \\ \frac{dI(t)}{dt} = \gamma E(t) - \mu_0 I(t), \\ v(t,0) = pS(t) \end{cases} \tag{2.1}$$

with the initial condition

$$S(0) = S_s > 0, v(0,a) = v_s(a) \in L^1_+(\mathbb{R}_+, \mathbb{R}_+), E(0) = E_s \geq 0, I(0) = I_s \geq 0, \tag{2.2}$$

where $\mathbb{R}_+ = [0, \infty)$ and

$$L^1_+(\mathbb{R}_+, \mathbb{R}_+) = \left\{ f : \mathbb{R}_+ \to \mathbb{R} | f(x) \geq 0 \text{ for } x \in \mathbb{R}_+ \text{ and } \int_0^\infty f(x)da < \infty \right\}.$$

In this model, $S(t)$, $E(t)$, $I(t)$ represent the numbers of the susceptible, latent, and infectious individuals at time t, respectively. Other model parameters are: A is the recruitment rate of susceptibles; μ is the per capita natural death rate; β is the effective transmission rate of the infection; $\frac{1}{\gamma}$ is the mean latency period; $\mu_0(\geq \mu)$ is the per capita removal rate for infectious compartment variable $I(t)$, accounting for the natural and disease-induced death and recovery from the disease.

Before performing analytical arguments to the model, we would like to address a remark on the model formulation. The vaccination age has been introduced as a widely used idea to account for the waning of immunity [10, 15, 18]. However, the waning of immunity is a more complicated process than that described in model (2.1). For example, a vaccinated individual may increase susceptibility to infection during immunity waning process, and individuals whose susceptibility, infectiousness, and symptoms all vary with vaccination age [4]. However, to impose minimal assumptions, the model in this study uses a simple on-off switch of immune protection.

Using the theory of age-structured dynamical systems introduced in [27], one can show that system (2.1) with the initial condition (2.2) has a unique solution. The boundedness and the asymptotic smoothness of its solutions can also be obtained by similar arguments as those in [28]. Moreover, it is easy to show that solutions of system (2.1) through non-negative initial values exist on $[0, \infty)$ and remain nonnegative for all $t \geq 0$. For any initial value $(S(0), v(0,a), E(0), I(0))$ from the feasible region $\mathbb{X} = \mathbb{R}_+ \times L^1_+ \times \mathbb{R}_+ \times \mathbb{R}_+$, the solution $(S(t), v(t,a), E(t), I(t))$ for the Cauchy problem defined by model (2.1) is nonnegative. Moreover, $S(t) > 0$ for $t > 0$. Furthermore, it can be shown that $v(t,a) > 0$ for $t > 0$ by the explicit solution $v(t,a)$ through the characteristic line method as in Lemma 3.3.

2.2. Equilibria and the basic reproduction number

In this subsection, we first establish the existence of feasible equilibria of (2.1), and then explain these results in terms of the basic reproduction number.

Assume that $\left(\bar{S}, \bar{v}(a), \bar{E}, \bar{I}\right)$ is a feasible equilibrium for system (2.1). Then it must satisfy the following equalities:

$$\begin{cases} A - (\mu + p)S - \beta SI + \int_0^\infty \varepsilon(a)v(a)da = 0, \\ \frac{dv(a)}{da} = -[\mu + \varepsilon(a)]v(a), \\ \beta SI - (\mu + \gamma)E = 0, \\ \gamma E - \mu_0 I = 0, \\ v(0) = pS. \end{cases} \tag{2.3}$$

Obviously, the disease-free steady state $P_0 = (S_0, v_0(a), 0, 0)$ is an equilibrium with S_0 and $v_0(a)$ satisfying

$$\begin{cases} A - (\mu + p)S_0 + \int_0^\infty \varepsilon(a)v_0(a)da = 0, \\ \frac{dv_0(a)}{da} = -[\mu + \varepsilon(a)]v(a), \\ v_0(0) = pS_0. \end{cases} \tag{2.4}$$

Solving this system obtains

$$S_0 = \frac{A}{\mu + p(1-\theta)} \text{ and } v_0(a) = pS_0 e^{-\int_0^a [\mu + \varepsilon(\eta)]d\eta}$$

where

$$\theta = \int_0^\infty \varepsilon(a)e^{-\int_0^a [\mu+\varepsilon(\xi)]d\xi}da < \int_0^\infty \varepsilon(a)e^{-\int_0^a \varepsilon(\eta)d\eta}da = 1 - e^{-\int_0^\infty \varepsilon(\eta)d\eta} < 1. \tag{2.5}$$

Now we are searching for possible endemic equilibria $P^* = (S^*, v^*(a), E^*, I^*)$ where $E^* > 0$ or $I^* > 0$. In this case, the third and the fourth equations of (2.3) imply $S^* = \frac{\mu_0(\mu+\gamma)}{\beta\gamma}$. Hence,

$$v(a) = pS^* e^{-\int_0^a [\mu+\varepsilon(\xi)]d\xi} = p\frac{\mu_0(\mu+\gamma)}{\beta\gamma}e^{-\int_0^a [\mu+\varepsilon(\xi)]d\xi}$$

and

$$\int_0^\infty \varepsilon(a)v^*(a)da = p\theta S^* = p\frac{\mu_0(\mu+\gamma)}{\beta\gamma}\theta.$$

The first equation of (2.3) becomes

$$I^* = \frac{A - [\mu + p(1-\theta)]S^*}{\beta S^*} = \frac{\mu + p(1-\theta)}{\beta}\left\{\frac{A\gamma\beta}{[\mu + p(1-\theta)]\mu_0(\mu+\gamma)} - 1\right\}.$$

Introducing the basic reproduction number $\mathcal{R}_0 = \dfrac{\beta\gamma S_0}{\mu_0(\mu+\gamma)} = \dfrac{A\gamma\beta}{[\mu + p(1-\theta)]\mu_0(\mu+\gamma)}$ with formulation details given later, system (2.1) has a unique endemic equilibrium $P^*(S^*, v^*(a), E^*, I^*)$

when $\mathcal{R}_0 > 1$, where

$$S^* = \frac{\mu_0(\mu+\gamma)}{\beta\gamma}, v^*(a) = pS^* e^{-\int_0^a [\mu+\varepsilon(\xi)]d\xi}, E^* = \frac{\mu_0}{\gamma} I^*, I^* = \frac{\mu + p(1-\theta)}{\beta} (\mathcal{R}_0 - 1). \quad (2.6)$$

Therefore, we have the following statement on the existence of the equilibria of (2.1).

Proposition 2.1. *System* (2.1) *always admits a disease-free equilibrium* $P_0(S_0, v_0(a), 0, 0)$. *When* $\mathcal{R}_0 > 1$, *there is another unique endemic equilibrium* $P^*(S^*, v^*(a), E^*, I^*)$ *given by* (2.6).

To derive the basic reproduction number, which estimates the expected number of cases generated by one typical case in a population where all individuals are susceptible to the infection, we consider the population full of susceptibles and vaccinated individuals, that is, near the disease-free equilibrium P_0 given in Proposition 2.1. Then we have the following linear system near the equilibrium for infected compartments:

$$\begin{cases} \frac{dE(t)}{dt} = \beta S_0 I(t) - (\mu+\gamma)E(t), \\ \frac{dI(t)}{dt} = \gamma E(t) - \mu_0 I(t). \end{cases}$$

This system takes the form of an ordinary differential equations and the next generation matrix method [24] gives the basic reproduction number

$$\mathcal{R}_0 = \frac{\beta\gamma S_0}{\mu_0(\mu+\gamma)} = \frac{A\gamma\beta}{[\mu + p(1-\theta)]\mu_0(\mu+\gamma)}.$$

The disease-free equilibrium P_0 and the basic reproduction number $\mathcal{R}_0$ can be interpreted from an epidemiological perspective. With a per-capita leaving rate $\mu + \varepsilon(a)$ of the vaccinated individuals with vaccination age a, an exponential survival probability is assumed and $e^{-\int_0^a [\mu+\varepsilon(\xi)]d\xi}$ describes the probability of the vaccinated individuals with vaccination age a staying in the vaccinated compartment. As $\varepsilon(a)$ is the rate at which vaccinated individuals move from the immune class to the susceptible class, therefore, θ defined in (2.5) measures the proportion of the vaccinated individuals which become susceptible. On the other hand, $\frac{p}{\mu+p}$ and $\frac{\mu}{\mu+p}$ represent the fractions of susceptible individuals which are vaccinated and not vaccinated, respectively. Thus, $\delta = \frac{p\theta}{\mu+p}$ can be interpreted as the fraction of susceptible individuals which lose immunity after vaccination and become susceptible again. In the absence of vaccination and infection, the number of individuals remains at the equilibrium $\frac{A}{\mu}$. Then the number of unvaccinated and susceptible individuals at the equilibrium is $\frac{A}{\mu} \cdot \frac{\mu}{\mu+p}$. According to the meaning of δ, there are $\frac{A}{\mu} \cdot \frac{\mu}{\mu+p} \cdot \delta$ vaccinated individuals receiving first dose and lose immunity; $\frac{A}{\mu} \cdot \frac{\mu}{\mu+p} \cdot \delta^2$ vaccinated individuals receiving second dose and lose immunity; and $\frac{A}{\mu} \cdot \frac{\mu}{\mu+p} \cdot \delta^k$ vaccinated individuals receiving k-th dose and lost immunity. Therefore, the total susceptible individuals should be $S_0 = \frac{A}{\mu} \cdot \frac{\mu}{\mu+p} \cdot \sum_{k=0}^{\infty} \delta^k = \frac{A}{\mu+p(1-\theta)}$, which gives rise to the equilibrium for susceptible compartment at the disease-free equilibrium. In the presence of infection, the rate at which the susceptible individuals in the completely susceptible population are infected by a typical infectious individual is βS_0. Partial of these individuals, with fraction $\frac{\gamma}{\mu+\gamma}$, may survive through the latency period and become infectious, with mean infectious period $\frac{1}{\mu_0}$. The product of these three terms gives the basic reproduction number $\mathcal{R}_0 = \beta S_0 \cdot \frac{\gamma}{\mu+\gamma} \cdot \frac{1}{\mu_0}$.

By linearizing the system at the equilibrium and studying the corresponding eigenvalue problem, as performed in [19, 21, 26], we can establish the local stability properties of the equilibria in the next proposition. Since the main focus of the current study is on Lyapunov functional formulation, we omit the details on local stability analysis here.

Proposition 2.2. *The disease-free equilibrium $P_0(S_0, v_0(a), 0, 0)$ is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$. When $\mathcal{R}_0 > 1$, the unique endemic equilibrium $P^*(S^*, v^*(a), E^*, I^*)$ is locally asymptotically stable.*

Moreover, denote

$$\mathbb{X}_0 = \{(S, v(\cdot), E, I) \in \mathbb{X} : I > 0\}$$

and define $\rho : \mathbb{X} \to \mathbb{R}_+$ by $\rho((S, v(\cdot), E, I)) = I$ for $(S, v(\cdot), E, I) \in \mathbb{X}$. If $\mathcal{R}_0 > 1$, then (2.1) has a global compact attractor $\mathcal{A}$ in $\mathbb{X}_0$ and its solution semi-flow is uniformly ρ-persistent [30], that is, for every solution $(S(t), v(t, a), E(t), I(t))$ of (2.1) in $\mathbb{X}_0$, there exists a $\delta > 0$ such that

$$\liminf_{t\to\infty} I(t) > \delta.$$

One can further show that there exists $\xi > 0$ such that

$$\liminf_{t\to\infty} \min\{S(t), v(t, 0), E(t), I(t)\} \geq \xi.$$

The proofs are quite standard for epidemiological models with age structures (see for example [21, 26, 28, 29]) and hence we omit the details here.

3. Global stability

This section is devoted to establishing the global stability of the equilibria of system (2.1) with (2.2) by using Lyapunov direct method. In particular, we are going to establish the following statement:

Theorem 3.1. *For system (2.1), the disease-free equilibrium P_0 is globally stable when $\mathcal{R}_0 \leq 1$, while the endemic equilibrium P^* is globally stable if exists.*

Before presenting the proof details in subsections 3.2 and 3.3, some preliminaries will be stated in subsection 3.1. Distinct from existing studies with Lyapunov direct method, we will first show the global stability of the endemic equilibrium with a Lyapunov functional $L_1(t)$, while the Lyapunov functional for the boundary equilibrium $L_2(t)$ can be reformulated through $L_1(t)$.

3.1. Preliminary

Introduce the function

$$g(u) = u - 1 - \ln u, \;\; u > 0$$

which will be used to construct the Lyapunov functional. It is easy to see that $g(u)$ is strictly decreasing when $u \in (0, 1]$ and strictly increasing when $u \in [1, \infty)$. Furthermore, $g(1) = 0$ is the global minimum value of $g(u)$ for $u > 0$, that is $g(u) \geq 0$. Since $g(u) = u - 1 - \ln(u) \geq 0$ for all $u > 0$, we have

$$n - \sum_{i=1}^{n} a_i + \ln\left(\Pi_{i=1}^{n} a_i\right) = -\sum_{i=1}^{n} g(a_i) \leq 0, \quad a_i > 0.$$

The following observation holds and will play a pivotal role in determining the coefficients in Lyapunov functions.

Lemma 3.2. *For $a_i > 0$ $(i = 1, 2, \cdots, n)$, the inequality $n - \sum_{i=1}^{n} a_i + \ln\left(\Pi_{i=1}^{n} a_i\right) \leq 0$ holds, and the equality holds if and only if $a_1 = a_2 = \cdots a_n = 1$.*

When $n = 1$, this Lemma is equivalent to the statement that $-g(u) \leq 0$. When $n = 2$, it implies that $2 - a_1 - a_2 + \ln(a_1 a_2) \leq 0$.

We next illustrate two observations in terms of inequalities.

Lemma 3.3. *Assume $\rho(a)$ is nonnegative and belongs to $L_+^\infty[0,\infty)$. Moreover, there exists $\delta > 0$ such that $\rho(a) \geq \delta$ for almost every $a \geq 0$. Suppose $w(t,a)$ is the solution of the following partial differential equation*

$$\frac{\partial w(t,a)}{\partial t} + \frac{\partial w(t,a)}{\partial a} = -\rho(a) w(t,a), \ t \geq 0, \ a \geq 0, \tag{3.1}$$

with the boundary condition $w(t,0) = \phi(t) \in L_{+0}^1[0,\infty)$ and the initial condition $w(0,a) = \psi(a) \in L_{+0}^1[0,\infty)$, where $L_{+0}^1[0,\infty) = \left\{ f | f(x) > 0 \text{ for } x \in \mathbb{R}_+ \text{ and } \int_0^\infty f(x)dx < \infty \right\}$. Then, for any $q(a) \in L_{+0}^1[0,\infty)$ and any endemic equilibrium $w^*(a)$ of (3.1), we have the following inequality

$$\frac{d}{dt}\left[\int_0^\infty q(a) w^*(a) g\left(\frac{w(t,a)}{w^*(a)}\right) da\right] \leq q(0) w^*(0) g\left(\frac{w(t,0)}{w^*(0)}\right) + \int_0^\infty \frac{d[q(a)w^*(a)]}{da} g\left(\frac{w(t,a)}{w^*(a)}\right) da. \tag{3.2}$$

Proof. Firstly, integrating (3.1) with the corresponding conditions along its characteristic line

$$t - a = \text{constant}$$

yields the following expression,

$$w(t,a) = \begin{cases} \phi(t-a) e^{-\int_0^a \rho(\xi) d\xi}, & 0 < a \leq t; \\ \psi(a-t) e^{-\int_{a-t}^a \rho(\xi) d\xi}, & a > t > 0. \end{cases}$$

Then, from $\phi(t), \psi(a) \in L_{+0}^1[0,\infty)$ it follows that $w(t,a) > 0$ for $t > 0$ and $a > 0$. Furthermore, the corresponding equilibrium $w^*(a)$ (if exists) must be positive. Moreover, the integrals $\int_0^\infty q(a) w^*(a) g\left(\frac{w(t,a)}{w^*(a)}\right) da$ and $\int_0^\infty \frac{d[q(a)w^*(a)]}{da} g\left(\frac{w(t,a)}{w^*(a)}\right) da$ exist, and $\lim\limits_{a\to\infty} q(a) w^*(a) = 0$.

A straightforward calculation gives

$$
\begin{aligned}
& \frac{d}{dt}\left[\int_0^\infty q(a)w^*(a)g\left(\frac{w(t,a)}{w^*(a)}\right)da\right] \\
= \; & \int_0^\infty q(a)w^*(a)\frac{\partial}{\partial t}g\left(\frac{w(t,a)}{w^*(a)}\right)da \\
= \; & \int_0^\infty q(a)w^*(a)\left[1-\frac{w^*(a)}{w(t,a)}\right]\frac{\partial}{\partial t}\left(\frac{w(t,a)}{w^*(a)}\right)da \\
= \; & \int_0^\infty q(a)w^*(a)\left[1-\frac{w^*(a)}{w(t,a)}\right]\frac{1}{w^*(a)}\frac{\partial w(t,a)}{\partial t}da.
\end{aligned}
$$

Applying (3.1) to the last equation yields

$$
\begin{aligned}
& \frac{d}{dt}\left[\int_0^\infty q(a)w^*(a)g\left(\frac{w(t,a)}{w^*(a)}\right)da\right] \\
= \; & -\int_0^\infty q(a)w^*(a)\left[1-\frac{w^*(a)}{w(t,a)}\right]\frac{1}{w^*(a)}\left\{\rho(a)w(t,a)+\frac{\partial w(t,a)}{\partial a}\right\}da.
\end{aligned}
$$

Since $w = w^*(a)$ is an equilibrium of (3.1), the identity $\rho(a) = -\frac{1}{w^*(a)}\frac{dw^*(a)}{da}$ holds. Thus

$$
\begin{aligned}
& \frac{d}{dt}\left[\int_0^\infty q(a)w^*(a)g\left(\frac{w(t,a)}{w^*(a)}\right)da\right] \\
= \; & -\int_0^\infty q(a)w^*(a)\left[1-\frac{w^*(a)}{w(t,a)}\right]\frac{1}{w^*(a)}\left\{-\frac{dw^*(a)}{da}\frac{w(t,a)}{w^*(a)}+\frac{\partial w(t,a)}{\partial a}\right\}da \\
= \; & -\int_0^\infty q(a)w^*(a)\left[1-\frac{w^*(a)}{w(t,a)}\right]\frac{\partial}{\partial a}\left(\frac{w(t,a)}{w^*(a)}\right)da \\
= \; & -\int_0^\infty q(a)w^*(a)\frac{\partial}{\partial a}g\left(\frac{w(t,a)}{w^*(a)}\right)da.
\end{aligned}
$$

Further, integration by parts obtains

$$
\begin{aligned}
& \frac{d}{dt}\left[\int_0^\infty q(a)w^*(a)g\left(\frac{w(t,a)}{w^*(a)}\right)da\right] \\
= \; & q(0)w^*(0)g\left(\frac{w(t,0)}{w^*(0)}\right)-\left\{q(a)w^*(a)g\left(\frac{w(t,a)}{w^*(a)}\right)\right\}\Bigg|_{a=\infty}+\int_0^\infty\frac{d[q(a)w^*(a)]}{da}g\left(\frac{w(t,a)}{w^*(a)}\right)da.
\end{aligned}
$$

Since $g(u) \geq 0$ for $u > 0$, the non-negativity of $q(a)$ and $w^*(a)$ implies that

$$
\left\{q(a)w^*(a)g\left(\frac{w(t,a)}{w^*(a)}\right)\right\}\Bigg|_{a=\infty} \geq 0.
$$

Thus the inequality (3.2) holds, which completes the proof. $\square$

The integral form $\int_0^\infty q(a)w^*(a)g\left(\frac{w(t,a)}{w^*(a)}\right)da$ in Lemma 3.3 has been involved in many studies of Lyapunov functionals for age-structured models, where $q(a)$ is a function to be determined similar to the coefficient of the Lyapunov function for the ordinary differential equation systems. The inequality (3.2) establishes a general property of solutions for linear age-structured models. However, in the general computation process, it is required to write the right-hand side of (3.2) as an integral of a full term. Interesting, it is valid based on the following observation.

Lemma 3.4. *For $w^*(a)$ and $q(a)$ given in Lemma 3.3, there is $r(a) \in L_+^\infty[0,\infty)$ such that*

$$\frac{d}{dt}\int_0^\infty q(a)w^*(a)g\left(\frac{w(t,a)}{w^*(a)}\right)da \le \int_0^\infty r(a)q(0)w^*(0)\left\{\frac{w(t,0)}{w^*(0)} - \frac{w(t,a)}{w^*(a)} + \ln\left[\frac{w^*(0)}{w(t,0)}\cdot\frac{w(t,a)}{w^*(a)}\right]\right\}da. \tag{3.3}$$

Proof. In fact, for given $q(a)$ and $w^*(a)$, introduce $r(a)$ which satisfies the following equation

$$\frac{d\left[q(a)w^*(a)\right]}{da} = -r(a)q(0)w^*(0), \tag{3.4}$$

that is,

$$r(a) = -\frac{1}{q(0)w^*(0)}\frac{d\left[q(a)w^*(a)\right]}{da}.$$

It is easy to verify $\int_0^\infty r(a)da = 1$ since $\lim_{a\to\infty} q(a)w^*(a) = 0$. Solving the differential equation (3.4) gets

$$q(a) = \frac{q(0)w^*(0)}{w^*(a)}\left[1 - \int_0^a r(\xi)d\xi\right] = \frac{q(0)w^*(0)}{w^*(a)}\int_a^\infty r(\xi)d\xi.$$

Since the equilibrium $w^*(a)$ satisfies $\frac{dw^*(a)}{da} = -\rho(a)w^*(a)$, we have $w^*(a) = w^*(0)e^{-\int_0^a \rho(\xi)d\xi}$. Hence $q(a)$ can be expressed in terms of $r(a)$ as

$$q(a) = q(0)e^{\int_0^a \rho(\xi)d\xi}\int_a^\infty r(\xi)d\xi. \tag{3.5}$$

Then (3.2) can be reformulated into

$$\begin{aligned}
\frac{d}{dt}\int_0^\infty q(a)w^*(a)g\left(\frac{w(t,a)}{w^*(a)}\right)da &\le \int_0^\infty \left[r(a)q(0)w^*(0)g\left(\frac{w(t,0)}{w^*(0)}\right) + \frac{d[q(a)w^*(a)]}{da}g\left(\frac{w(t,a)}{w^*(a)}\right)\right]da \\
&= \int_0^\infty \left[r(a)q(0)w^*(0)g\left(\frac{w(t,0)}{w^*(0)}\right) - r(a)q(0)w^*(0)g\left(\frac{w(t,a)}{w^*(a)}\right)\right]da \\
&= \int_0^\infty r(a)q(0)w^*(0)\left\{\frac{w(t,0)}{w^*(0)} - \frac{w(t,a)}{w^*(a)} + \ln\left[\frac{w^*(0)}{w(t,0)}\cdot\frac{w(t,a)}{w^*(a)}\right]\right\}da.
\end{aligned}$$

This completes the proof of Lemma 3.4. □

The differential inequality (3.3) will be used in the subsequent proof for global stability of the disease-free and the endemic equilibria. The main methodology of applying Lypunov functional method is strongly motivated by a previous study [13] on discussing the global stability of ordinary differential equation systems. At the end of this subsection, we revisit these procedures in [13] for readers' easy reference when analyzing an autonomous system of ordinary differential equations,

$$\frac{dx}{dt} = f(x), \tag{3.6}$$

where $x = (x_1, x_2, \ldots, x_n)^T$ and $f(x) = (f_1(x), f_2(x), \ldots, f_n(x))^T$ with the superscript T representing the transpose. For a Lyapunov function candidate $L(x) = L(x_1, x_2, \ldots, x_n)$, the derivative of L along solutions of (3.6) can be rearranged into the following form

$$\left.\frac{dL}{dt}\right|_{(3.6)} = C - \sum_{k=1}^{K} c_k h_k(x),$$

where C is a constant term, K is the number of non-constant terms h_k in $L'|_{(3.6)}$, and h_k satisfies $h_k(x) > 0$ for $x \in \mathbb{R}^n_{+0}$ with $h_k(x) = 1$ at $x = P^*$ ($k = 1, 2, \ldots, K$). For the linear combination term $\sum_{k=1}^{K} c_k h_k$ in $L'|_{(3.6)}$, the authors in [13] introduced a corresponding function $G^* = \sum_{k=1}^{K} c_k \ln h_k$. The Lyapunov function, in particular, the coefficients, can be determined from satisfying

(a) $G^* = 0$;

(b) For each $k \in \{1, 2, , \ldots, K\}$, c_k is nonnegative; and

(c) $C = \sum_{k=1}^{K} c_k$.

In this case, $L'|_{(3.6)}$ can be reformulated into

$$\left.\frac{dL}{dt}\right|_{(3.6)} = C - \sum_{k=1}^{K} c_k h_k(x) = \sum_{k=1}^{K} c_k - \sum_{k=1}^{K} c_k h_k(x) + \sum_{k=1}^{K} c_k \ln h_k = -\sum_{k=1}^{K} c_k g(h_k) \leq 0.$$

3.2. Proof of global stability of the endemic equilibrium P^*

Define a functional

$$\begin{aligned} L_1(t) &= \Phi_1(S(t), v(t,\cdot), E(t), I(t)) \\ &= S^* g\left(\tfrac{S(t)}{S^*}\right) + \int_0^\infty c_1(a) v^*(a) g\left(\tfrac{v(t,a)}{v^*(a)}\right) da + c_2 E^* g\left(\tfrac{E(t)}{E^*}\right) + c_3 I^* g\left(\tfrac{I(t)}{I^*}\right), \end{aligned} \tag{3.7}$$

where $c_1(a)$, c_2 and c_3 are to be specified later. Then applying (3.3) to the derivative of L_1 with respect to t along solutions of (2.1) gives

$$\begin{aligned} \left.\tfrac{dL_1}{dt}\right|_{(2.1)} \leq \; & \left(1 - \tfrac{S^*}{S(t)}\right)\left[A - (\mu + p)S(t) - \beta S(t) I(t) + \int_0^\infty \varepsilon(a) v(t,a) da\right] \\ & + \int_0^\infty r(a) c_1(0) v^*(0) \left[\tfrac{v(t,0)}{v^*(0)} - \tfrac{v(t,a)}{v^*(a)} + \ln\left(\tfrac{v^*(0)}{v(t,0)} \cdot \tfrac{v(t,a)}{v^*(a)}\right)\right] da \\ & + c_2 \left(1 - \tfrac{E^*}{E(t)}\right)[\beta S(t) I(t) - (\mu + \gamma) E] + n\left(1 - \tfrac{I^*}{I(t)}\right)(\gamma E(t) - \mu_0 I(t)), \end{aligned}$$

where $r(a)$ and $c_1(a)$ satisfy (3.4). Substituting $v(t, 0) = pS(t)$ and $v^*(0) = pS^*$ into $L_1'|_{(2.1)}$ gives

$$\begin{aligned} \left.\tfrac{dL_1}{dt}\right|_{(2.1)} \leq \; & \left(1 - \tfrac{S^*}{S(t)}\right)\left[A - (\mu + p)S(t) - \beta S(t) I(t) + \int_0^\infty \varepsilon(a) v(t,a) da\right] \\ & + \int_0^\infty r(a) c_1(0) p S^* \left[\tfrac{S}{S^*} - \tfrac{v(t,a)}{v^*(a)} + \ln\left(\tfrac{S^*}{S} \cdot \tfrac{v(t,a)}{v^*(a)}\right)\right] da \\ & + c_2 \left(1 - \tfrac{E^*}{E(t)}\right)[\beta S(t) I(t) - (\mu + \gamma) E(t)] + n\left(1 - \tfrac{I^*}{I(t)}\right)(\gamma E(t) - \mu_0 I(t)). \end{aligned}$$

Denote $x(t) = \frac{S(t)}{S^*}$, $u(t,a) = \frac{v(t,a)}{v^*(a)}$, $y(t) = \frac{E(t)}{E^*}$, and $z(t) = \frac{I(t)}{I^*}$ for notational simplicity, and use $\int_0^\infty r(a)da = 1$, we have

$$\begin{aligned}
&\frac{dL_1}{dt}\Big|_{(2.1)}\\
\leq\ & \left(1-\frac{1}{x(t)}\right)\left[A-(\mu+p)S^*x(t)-\beta S^*I^*x(t)z(t)+\int_0^\infty \varepsilon(a)v^*(a)u(t,a)da\right]\\
&+\int_0^\infty r(a)c_1(0)pS^*\left[x(t)-u(t,a)+\ln\left(\frac{u(t,a)}{x(t)}\right)\right]da\\
&+c_2\beta S^*I^*\left(1-\frac{1}{y(t)}\right)(x(t)z(t)-y(t))+c_3\gamma E^*\left(1-\frac{1}{z(t)}\right)(y(t)-z(t))\\
=\ & \left(1-\frac{1}{x(t)}\right)\left[A-(\mu+p)S^*x(t)-\beta S^*I^*x(t)z(t)+\int_0^\infty \varepsilon(a)v^*(a)u(t,a)da\right]\times\int_0^\infty r(a)da\\
&+\int_0^\infty r(a)c_1(0)pS^*\left[x(t)-u(t,a)+\ln\left(\frac{u(t,a)}{x(t)}\right)\right]da\\
&+\left[m\beta S^*I^*\left(1-\frac{1}{y(t)}\right)(x(t)z(t)-y(t))+c_3\gamma E^*\left(1-\frac{1}{z(t)}\right)(y(t)-z(t))\right]\times\int_0^\infty r(a)da\\
=\ & \int_0^\infty H_1(t,a)da,
\end{aligned}$$

where

$$\begin{aligned}
H_1(t,a)=\ & r(a)\left(1-\frac{1}{x(t)}\right)[A-(\mu+p)S^*x(t)-\beta S^*I^*x(t)z(t)]\\
&+\varepsilon(a)v^*(a)\left(1-\frac{1}{x(t)}\right)u+r(a)c_1(0)pS^*\left[x(t)-u(t,a)+\ln\left(\frac{u(t,a)}{x(t)}\right)\right]\\
&+r(a)c_2\beta S^*I^*\left(1-\frac{1}{y(t)}\right)(x(t)z(t)-y(t))\\
&+r(a)c_3\gamma E^*\left(1-\frac{1}{z(t)}\right)(y(t)-z(t)).
\end{aligned}$$

To determine $r(a), c_1(0), c_2$ and c_3 such that $\int_0^\infty H_1(t,a) \leq 0$, we introduce two non-negative numbers to be determined, k_1 and k_2, satisfying $k_1 + k_2 = 1$, and rewrite $H_1(t,a)$ into $H_1(t,a) = H_1^*(t,a) + H_1^{**}(t,a)$, where

$$H_1^*(t,a)=r(a)c_1(0)pS^*\left[k_1\left(1-\frac{u(t,a)}{x(t)}+\ln\frac{u(t,a)}{x(t)}\right)+k_2\left(2-\frac{1}{x(t)}-u(t,a)+\ln\frac{u(t,a)}{x(t)}\right)\right]$$

and

$$\begin{aligned}
&H_1^{**}(t,a)\\
=&r(a)\left(1-\frac{1}{x(t)}\right)[A-(\mu+p)S^*x(t)-\beta S^*I^*x(t)z(t)]+\varepsilon(a)v^*(a)\left(1-\frac{1}{x(t)}\right)u(t,a)\\
&+r(a)m\beta S^*I^*\left(1-\frac{1}{y(t)}\right)(x(t)z(t)-y(t))+r(a)c_3\gamma E^*\left(1-\frac{1}{z(t)}\right)(y(t)-z(t))\\
&+r(a)c_1(0)pS^*\left[x(t)-u(t,a)+k_1\left(\frac{u(t,a)}{x(t)}-1\right)+k_2\left(\frac{1}{x(t)}+u(t,a)-2\right)\right].
\end{aligned}$$

Obviously, $H_1^*(t,a) \leq 0$ by Lemma 3.2. Now we are in the position to find suitable $r(a)$, $c_1(0)$, c_2, c_3, and k_1 with $k_2 = 1 - k_1$ such that $\int_0^\infty H_1^{**}(t,a)da \leq 0$. Rearrange $H_1^{**}(t,a)$ as the form $H_1^{**}(t,a) = C^* - \tilde{H}_1^{**}(t,a)$, where

$$C^* = r(a)\left[A + (\mu+p)S^* + c_2\beta S^* I^* + c_3\gamma E^* - c_1(0)pS^*(1+k_2)\right]$$

and

$$\begin{aligned}\tilde{H}_1^{**}(t,a) = \ & r(a)[\mu+p-c_1(0)p]S^* x(t) + r(a)\left[A - c_1(0)pS^*k_2\right]\tfrac{1}{x(t)} \\ & + \left[\varepsilon(a)v^*(a) - r(a)c_1(0)pS^*k_1\right]\tfrac{u(t,a)}{x(t)} \\ & + \left[r(a)c_1(0)pS^*k_1 - \varepsilon(a)v^*(a)\right]u(t,a) \\ & + r(a)\left[c_2\beta S^* I^* \tfrac{x(t)z(t)}{y(t)} + c_3\gamma E^* \tfrac{y(t)}{z(t)} + (c_3\gamma E^* - \beta S^* I^*)z(t)\right] \\ & + r(a)\left[\beta S^* I^*(1-c_2)x(t)z(t) + (c_2\beta S^* I^* - c_3\gamma E^*)y(t)\right].\end{aligned}$$

Applying the approach proposed in [13] and formulated in section 3.1, define a function corresponding to the function $\tilde{H}_1^{**}(t,a)$ as

$$\begin{aligned}\hat{H}_1^{**}(t,a) = \ & r(a)[\mu+p-c_1(0)p]S^* \ln x(t) + r(a)\left[A - c_1(0)pS^*k_2\right]\ln\left(\tfrac{1}{x(t)}\right) \\ & + \left[\varepsilon(a)v^*(a) - r(a)c_1(0)pS^*k_1\right]\ln\left(\tfrac{u(t,a)}{x(t)}\right) \\ & + \left[r(a)c_1(0)pS^*k_1 - \varepsilon(a)v^*(a)\right]\ln u(t,a) \\ & + r(a)\left[c_2\beta S^* I^* \ln\left(\tfrac{x(t)z(t)}{y(t)}\right) + c_3\gamma E^* \ln\left(\tfrac{y(t)}{z(t)}\right) + (c_3\gamma E^* - \beta S^* I^*)\ln z(t)\right] \\ & + r(a)\left[\beta S^* I^*(1-c_2)\ln\left(x(t)z(t)\right) + (c_2\beta S^* I^* - c_3\gamma E^*)\ln y(t)\right].\end{aligned}$$

Straightforward calculation shows

$$\hat{H}_1^{**}(t,a) = \left\{r(a)\left[(\mu+p)S^* + \beta S^* I^* - A\right] - \varepsilon(a)v^*(a)\right\}\ln x(t).$$

Then $\int_0^\infty r(a)da = 1$ and the first equation of (2.3) imply that $\int_0^\infty H_1^{**}(t,a)da = 0$. It is easy to verify that C^* is equal to the sum of all the coefficients of $\hat{H}_1^{**}(t,a)$. Thus it follows that

$$\int_0^\infty H_1^{**}(t,a)da = \int_0^\infty \left[C^* - \tilde{H}_1^{**}(t,a) + \hat{H}_1^{**}(t,a)\right]da = -\int_0^\infty \bar{H}_1^{**}(t,a)da,$$

where

$$\begin{aligned}\bar{H}_1^{**}(t,a) = \ & r(a)[\mu+p-c_1(0)p]S^* g\left(x(t)\right) + r(a)\left[A - c_1(0)pS^*k_2\right]g\left(\tfrac{1}{x(t)}\right) \\ & + \left[\varepsilon(a)v^*(a) - r(a)c_1(0)pS^*k_1\right]g\left(\tfrac{u(t,a)}{x(t)}\right) \\ & + \left[r(a)c_1(0)pS^*k_1 - \varepsilon(a)v^*(a)\right]g\left(u(t,a)\right) \\ & + r(a)\left[c_2\beta S^* I^* g\left(\tfrac{x(t)z(t)}{y(t)}\right) + c_3\gamma E^* g\left(\tfrac{y(t)}{z(t)}\right) + (c_3\gamma E^* - \beta S^* I^*)g\left(z(t)\right)\right] \\ & + r(a)\left[\beta S^* I^*(1-c_2)g\left(x(t)z(t)\right) + (c_2\beta S^* I^* - c_3\gamma E^*)g(y(t))\right].\end{aligned}$$

From the property of function $g(u) = u - 1 - \ln u$ for $u > 0$, $\bar{H}_1^{**}(t,a) \geq 0$ when the inequality system of $r(a), k_1 (= 1 - k_2), c_1(0), c_2$ and c_3,

$$\begin{cases} \mu + p \geq c_1(0)p, \\ A \geq c_1(0)pS^* k_2, \\ \varepsilon(a)v^*(a) \geq r(a)c_1(0)pS^* k_1, \\ r(a)c_1(0)pS^* k_1 \geq \varepsilon(a)v^*(a), \\ c_3\gamma E^* \geq \beta S^* I^*, \\ 1 \geq c_2, \\ c_2 \beta S^* I^* \geq c_3 \gamma E^* \end{cases} \tag{3.8}$$

has positive solutions.

From the last three inequalities of (3.8) it is easy to obtain that $c_2 = 1$ and $c_3 = \frac{\beta S^* I^*}{\gamma E^*} \left(= \frac{\mu+\gamma}{\gamma}\right)$. From the third and the fourth inequalities of (3.8) it follows that $\varepsilon(a)v^*(a) = r(a)c_1(0)pS^* k_1$. It implies that $k_1 \neq 0$ and that

$$r(a) = \frac{\varepsilon(a)v^*(a)}{c_1(0)pS^* k_1} = \frac{\varepsilon(a)e^{-\int_0^a [\mu+\varepsilon(\xi)]d\xi}}{c_1(0)k_1}.$$

Further, applying it into (3.5) yields

$$c_1(a) = \frac{e^{\int_0^a [\mu+\varepsilon(\xi)]d\xi}}{k_1} \int_a^\infty \varepsilon(\xi) e^{-\int_0^\xi [\mu+\varepsilon(\eta)]d\eta}. \tag{3.9}$$

Then $c_1(0) = \frac{\theta}{k_1}$. It implies that

$$r(a) = \frac{\varepsilon(a)e^{-\int_0^a [\mu+\varepsilon(\xi)]d\xi}}{\theta}. \tag{3.10}$$

Substituting $c_1(0) = \frac{\theta}{k_1}$ into the first inequality of (3.8) gives $k_1 \geq \frac{\theta p}{\mu+p} \triangleq k_1^*$. Substituting $c_1(0) = \frac{\theta}{k_1}$ and $k_2 = 1 - k_1$ into the second inequality of (3.8) yields $k_1 \geq \frac{\theta p S^*}{A+\theta p S^*} \triangleq k_1^{**}$. Notice that $\int_0^\infty \varepsilon(a)v^*(a)da = p\theta S^*$. Then the first equation of (2.3) becomes $A + \theta p S^* - (\mu+p)S^* = \beta S^* I^*$. Therefore,

$$k_1^* - k_1^{**} = \frac{\theta p[A + \theta p S^* - (\mu + p)S^*]}{(\mu + p)(A + \theta p S^*)} = \frac{\theta p \beta S^* I^*}{(\mu + p)(A + \theta p S^*)} > 0.$$

Thus, from the first two inequalities of (3.8) and $k_1 + k_2 = 1$ for $k_1,\ k_2 \geq 0$ it follows that $\frac{\theta p}{\mu+p} \leq k_1 \leq 1$. Therefore, when $c_2 = 1$, $c_3 = \frac{\mu+\gamma}{\gamma}$, and $c_1(a)$ is determined by (3.9) with

$\frac{\theta p}{\mu+p} \leq k_1 \leq 1$, the Lyapunov functional L_1 is well-defined. Furthermore,

$$
\begin{aligned}
\frac{dL_1}{dt}\Big|_{(2.1)} \leq\ & \int_0^\infty \left[H_1^*(t,a) + H_1^{**}(t,a)\right] da \\
=\ & -\int_0^\infty r(a)\frac{\theta p S^*}{k_1}\left[k_1 g\left(\frac{u(t,a)}{x(t)}\right) + k_2 g\left(\frac{1}{x(t)}\right) + k_2 g(u(t,a))\right] da \\
& -\left(\mu + p - \frac{\theta p}{k_1}\right) S^* g\left(x(t)\right) - \left(A + \theta p S^* - \frac{\theta p S^*}{k_1}\right) g\left(\frac{1}{x(t)}\right) \\
& - c_2 \beta S^* I^* g\left(\frac{x(t)z(t)}{y(t)}\right) - c_3 \gamma E^* g\left(\frac{y(t)}{z(t)}\right) \\
=\ & -\int_0^\infty r(a)\frac{\theta p S^*}{k_1}\left[k_1 g\left(\frac{u(t,a)}{x(t)}\right) + k_2 g(u(t,a))\right] da - \left(\mu + p - \frac{\theta p}{k_1}\right) S^* g\left(x(t)\right) \\
& - A g\left(\frac{1}{x(t)}\right) - c_2 \beta S^* I^* g\left(\frac{x(t)z(t)}{y(t)}\right) - c_3 \gamma E^* g\left(\frac{y(t)}{z(t)}\right).
\end{aligned}
$$

The property of function $g(u)$ shows that $L_1'|_{(2.1)} \leq 0$ since $H_1(t,a) \leq 0$ and $L_1'|_{(2.1)} = 0$ if and only if $x(t) = 1$, $u(t,a) = 1$, and $y(t) = z(t)$, that is,

$$
S(t) = S^*, \qquad v(t,a) = v^*(a), \qquad \frac{E(t)}{E^*} = \frac{I(t)}{I^*}.
$$

Note that substituting $S(t) = S^*$ and $v(t,a) = v^*(a)$ into the first equation of system (2.1) gives $I(t) = I^*$. Furthermore, from the last equation of (2.1) it follows that $E(t) = E^*$. Then the largest invariant set of (2.1) with (2.2) on $L_1'|_{(2.1)} = 0$ is the singleton $\{P^*\}$. Therefore, LaSalle Invariance Principle [12] implies that the endemic equilibrium P^* is globally stable.

At this point, we have proved the global stability of the endemic equilibrium P^* according to a predetermined procedure which is the extension of the approach proposed in [13]. In the following, we highlight several novel aspects in the proof process.

Remark 3.5. *The inequality $\frac{\theta p}{\mu+p} \leq k_1 \leq 1$ provides the range of admissible k_1 values, indicating that the choices of coefficient k_1 are not unique (which will be shown in simulations in Section 4). Correspondingly, $c_1(0) = \frac{\theta}{k_1}$ is not unique, either. That is, the candidate $c_1(a)$ in the Lyapunov functional L_1 is not unique.*

On the other hand, k_1 is introduced since function $H_1^*(t,a)$ is defined. The purpose of defining this function is to find all the combinations including the logarithmic term which are negative (semi-)definite. To be more specific, corresponding to the logarithmic term $\ln\frac{u(t,a)}{x(t)}$ in $H_1(t,a)$, find all combinations of the terms in the derivative $L_1'|_{(2.1)}$ which includes $\frac{u(t,a)}{x(t)}$, and then split $\ln\frac{u(t,a)}{x(t)}$ according to the number of the found combinations. Thus, Lemma 3.2 can be used. Again, the negative (semi-)definiteness of the other terms of the derivative is shown by applying the approach proposed in [13] and introduced in Section 3.1.

Furthermore, for the coefficients of the suitable Lyapunov functional L_1, $c_1(a)$ is determined by (3.9), $c_2 = 1$, and $c_3 = \frac{\mu+\gamma}{\gamma}$. They are all independent of the values of the equilibrium of (2.1).

3.3. Proof of the global stability of the disease-free equilibrium P_0

To prove the global stability of the disease-free equilibrium $P_0(S_0, v_0(a), 0, 0)$, the Lyapunov functional candidate usually shares the following form

$$\begin{aligned} L_0(t) &= \Phi_0(S(t), v(t,\cdot), E(t), I(t)) \\ &= S_0 g\left(\frac{S(t)}{S_0}\right) + \int_0^\infty c_1(a) v_0(a) g\left(\frac{v(t,a)}{v_0(a)}\right) da + c_2 E(t) + c_3 I(t). \end{aligned}$$

It remains to determine the coefficients $c_1(a)$, c_2, and c_3, which usually are given directly based on experience. This approach based on experience is very challenging and difficult to navigate for most models.

Here we are going to use a fundamentally distinct approach to determine the coefficients, which is based on the Lyapunov functional L_1 in (3.7) used for the endemic equilibrium P^*. This novel approach is based on the following observations:

(i) The two-variable function $V(u, u^*) = u^* g\left(\frac{u}{u^*}\right) = u - u^* - u^* \ln \frac{u}{u^*}$ with $u, u^* > 0$ satisfies $\lim\limits_{u^* \to 0^+} V(u, u^*) = u$ for any $u > 0$;

(ii) The endemic equilibrium $(S^*, v^*(a), E^*, I^*)$ approaches the disease-free equilibrium $P_0(S_0, v_0(a), 0, 0)$ when $\mathcal{R}_0 \to 1^+$, that is, $\lim_{\mathcal{R}_0 \to 1^+} P^* = P_0$;

(iii) The coefficients $c_1(a)$, c_2, and c_3 in the Lyapunov functional L_1 in (3.7), which are given by

$$c_1(a) = \frac{e^{\int_0^a [\mu+\varepsilon(\xi)] d\xi}}{k_1} \int_a^\infty \varepsilon(\xi) e^{-\int_0^\xi [\mu+\varepsilon(\eta)] d\eta} d\xi \ (\text{with } \frac{\theta p}{\mu + p} \le k_1 \le 1), \ c_2 = 1, \ c_3 = \frac{\mu+\gamma}{\gamma},$$

are independent of the values of the equilibrium.

These observations prompt us to ask the following natural question: Whether the Lyapunov functional L_1 in (3.7) for verifying the global stability of the endemic equilibrium is still applicable to discuss the global stability of the disease-free equilibrium $P_0(S_0, v_0(a), 0, 0)$. The answer is a definite "yes". In what follows, we will present the details to show the feasibility of $L_0(t)$ as a suitable Lyapunov functional.

According to (3.3), the derivative of L_0 with respect to t along solutions of (2.1) becomes

$$\begin{aligned} \frac{dL_0}{dt}\Big|_{(2.1)} \le \ & \left(1 - \frac{S_0}{S(t)}\right) \left[A - (\mu+p)S(t) - \beta S(t) I(t) + \int_0^\infty \varepsilon(a) v(t,a) da\right] \\ & + \int_0^\infty r(a) c_1(0) v_0(0) \left[\frac{v(t,0)}{v_0(0)} - \frac{v(t,a)}{v_0(a)} + \ln\left(\frac{v_0(0)}{v(t,0)} \cdot \frac{v(t,a)}{v_0(a)}\right)\right] da \\ & + c_2[\beta S(t) I(t) - (\mu+\gamma) E(t)] + c_3(\gamma E(t) - \mu_0 I(t)), \end{aligned}$$

where $r(a) = \frac{\varepsilon(a) e^{-\int_0^a [\mu+\varepsilon(\xi)] d\xi}}{\theta}$ defined by (3.10). Since $v(t, 0) = pS(t)$ and $v_0(0) = pS_0$, the previous inequality reduces to

$$\begin{aligned} \frac{dL_0}{dt}\Big|_{(2.1)} \le \ & \left(1 - \frac{S_0}{S(t)}\right) \left[A - (\mu+p)S(t) - \beta S(t) I(t) + \int_0^\infty \varepsilon(a) v(t,a) da\right] \\ & + \int_0^\infty r(a) c_1(0) p S_0 \left[\frac{S(t)}{S_0} - \frac{v(t,a)}{v_0(a)} + \ln\left(\frac{S_0}{S(t)} \cdot \frac{v(t,a)}{v_0(a)}\right)\right] da \\ & + c_2[\beta S(t) I(t) - (\mu+\gamma) E(t)] + c_3(\gamma E(t) - \mu_0 I(t)). \end{aligned}$$

Introducing $x(t) = \frac{S(t)}{S_0}$ and $u(t,a) = \frac{v(t,a)}{v_0(a)}$ for notational simplicity, and substituting $c_2 = 1$ and $c_3 = \frac{\mu+\gamma}{\gamma}$ into the last inequality yields

$$\begin{aligned}\frac{dL_0}{dt}\Big|_{(2.1)} \leq \;& \left(1 - \tfrac{1}{x(t)}\right)\left[A - (\mu+p)S_0x(t) - \beta S_0 x(t)I(t) + \int_0^\infty \varepsilon(a)v_0(a)u(t,a)da\right] \\ & + \int_0^\infty r(a)c_1(0)pS_0\left[x(t) - u(t,a) + \ln\tfrac{u(t,a)}{x(t)}\right]da \\ & + c_2[\beta S_0x(t)I(t) - (\mu+\gamma)E(t)] + c_3(\gamma E(t) - \mu_0 I(t)) \\ = \;& \int_0^\infty H_0(t,a)da + \tfrac{\mu_0(\mu+\gamma)}{\gamma}(\mathcal{R}_0 - 1)I(t),\end{aligned} \tag{3.11}$$

where

$$\begin{aligned}H_0(t,a) =& r(a)\left(1-\frac{1}{x(t)}\right)[A-(\mu+p)S_0x(t)] + \varepsilon(a)v_0(a)\left(1-\frac{1}{x(t)}\right)u(t,a) \\ & + r(a)c_1(0)pS_0\left[x(t) - u(t,a) + \ln\frac{u(t,a)}{x(t)}\right].\end{aligned}$$

Similar to proving that $\int_0^\infty H_1(t,a)da \leq 0$ in the previous subsection, we also introduce two non-negative numbers, k_1 and k_2, satisfying $k_1 + k_2 = 1$, and then rewrite $H_0(t,a)$ as $H_0(t,a) = H_0^*(t,a) + H_0^{**}(t,a)$, where

$$H_0^*(t,a) = r(a)c_1(0)pS_0\left[k_1\left(1 - \frac{u(t,a)}{x(t)} + \ln\frac{u(t,a)}{x(t)}\right) + k_2\left(2 - \frac{1}{x(t)} - u(t,a) + \ln\frac{u(t,a)}{x(t)}\right)\right]$$

and

$$\begin{aligned}H_0^{**}(t,a) = \;& r(a)\left(1-\tfrac{1}{x(t)}\right)[A-(\mu+p)S_0x(t)] + \varepsilon(a)v_0(a)\left(1-\tfrac{1}{x(t)}\right)u(t,a) \\ & + r(a)c_1(0)pS_0\left[x(t) - u(t,a) - k_1\left(1 - \tfrac{u(t,a)}{x(t)}\right) - k_2\left(2 - \tfrac{1}{x(t)} - u(t,a)\right)\right].\end{aligned}$$

It is easy to know from Lemma 3.2 that

$$1 - \frac{u(t,a)}{x(t)} + \ln\frac{u(t,a)}{x(t)} \leq 0 \text{ and } 2 - \frac{1}{x(t)} - u(t,a) + \ln\frac{u(t,a)}{x(t)} \leq 0.$$

Therefore, $H_0^*(t,a) \leq 0$. Furthermore, $H_0^{**}(t,a)$ can be expressed as

$$\begin{aligned}H_0^{**}(t,a) = \;& C_0^* - r(a)[(\mu+p) - c_1(0)p]S_0x(t) - r(a)\left[A - c_1(0)pk_2S_0\right]\tfrac{1}{x(t)} \\ & - [r(a)c_1(0)pS_0k_1 - \varepsilon(a)v_0(a)]u(t,a) - [\varepsilon(a)v_0(a) - r(a)c_1(0)pS_0k_1]\tfrac{u(t,a)}{x(t)},\end{aligned}$$

where $k_1 + k_2 = 1$ and $C_0^* = r(a)\left[A + (\mu+p)S_0 - c_1(0)pS_0(1+k_2)\right]$ have been used.

In the following, we apply the approach proposed in [13] to discuss the negative (semi-)definiteness of $\int_0^\infty H_0^{**}(t,a)da$. Corresponding to the part of $H_0^{**}(t,a)$ except for C_0^*, define a function

$$\begin{aligned}\bar{H}_0^{**}(t,a) = \;& r(a)[(\mu+p)-c_1(0)p]S_0\ln x(t) + r(a)\left[A - c_1(0)pk_2S_0\right]\ln\tfrac{1}{x(t)}\\ & +[r(a)c_1(0)pS_0k_1 - \varepsilon(a)v_0(a)]\ln u(t,a)\\ & +\left[\varepsilon(a)v_0(a) - r(a)c_1(0)pS_0k_1\right]\ln\tfrac{u(t,a)}{x(t)}.\end{aligned}$$

Direct calculation shows $\bar{H}_0^{**}(t,a) = -\left\{r(a)[A-(\mu+p)S_0] + \varepsilon(a)v_0(a)\right\}\ln x(t)$. Since

$$\int_0^\infty r(a)da = 1 \text{ and } A-(\mu+p)S_0 + \int_0^\infty \varepsilon(a)v_0(a)da = 0$$

from the first equation of (2.4), we have

$$\int_0^\infty \bar{H}_0^{**}(t,a)da = -\left[A-(\mu+p)S_0+\int_0^\infty \varepsilon(a)v_0(a)da\right]\ln x(t) = 0.$$

Note that C_0^* is equal to the sum of the coefficients of $\bar{H}_0^{**}(t,a)$. Then

$$\begin{aligned}\textstyle\int_0^\infty H_0^{**}(t,a)da = \;& \textstyle\int_0^\infty[H_0^{**}(t,a)+\bar{H}_0^{**}(t,a)]da\\ = \;& -[(\mu+p)-c_1(0)p]S_0g(x(t)) - [A-c_1(0)pk_2S_0]\,g\left(\tfrac{1}{x(t)}\right)\\ & -\textstyle\int_0^\infty[r(a)c_1(0)pS_0k_1-\varepsilon(a)v_0(a)]g(u(t,a))da\\ & -\textstyle\int_0^\infty\left[\varepsilon(a)v_0(a)-r(a)c_1(0)pS_0k_1\right]g\left(\tfrac{u(t,a)}{x(t)}\right)da.\end{aligned}$$

Since $c_1(0)=\frac{\theta}{k_1}$, $r(a)=\frac{\varepsilon(a)e^{-\int_0^a[\mu+\varepsilon(\xi)]d\xi}}{\theta}$ and $v_0(a)=pS_0e^{-\int_0^a[\mu+\varepsilon(\xi)]d\xi}$, it follows that

$$\begin{aligned}\textstyle\int_0^\infty H_0^{**}(t,a)da = \;& -\left[(\mu+p)-\tfrac{\theta p}{k_1}\right]S_0g(x(t)) - \left(A-\tfrac{\theta pk_2S_0}{k_1}\right)g\left(\tfrac{1}{x(t)}\right)\\ = \;& -\left[(\mu+p)-\tfrac{\theta p}{k_1}\right]S_0\left[g(x(t))+g\left(\tfrac{1}{x(t)}\right)\right]\\ = \;& -\left[(\mu+p)-\tfrac{\theta p}{k_1}\right]S_0\left[2-x(t)-\tfrac{1}{x(t)}\right],\end{aligned}$$

where $A=[\mu+p(1-\theta)]S_0$ and $k_2=1-k_1$ were used.

Summarizing the above arguments, (3.11) implies that

$$\begin{aligned}\tfrac{dL_0}{dt}\Big|_{(2.1)} \le \;& \textstyle\int_0^\infty r(a)c_1(0)pS_0\left[k_1\left(1-\tfrac{u(t,a)}{x(t)}+\ln\tfrac{u(t,a)}{x(t)}\right)+k_2\left(2-\tfrac{1}{x(t)}-u(t,a)+\ln\tfrac{u(t,a)}{x(t)}\right)\right]da\\ & -\left[(\mu+p)-\tfrac{\theta p}{k_1}\right]S_0\left[2-x(t)-\tfrac{1}{x(t)}\right]+\tfrac{\mu_0(\mu+\gamma)}{\gamma}(\mathcal{R}_0-1)I(t).\end{aligned}$$

Since $\frac{\theta p}{\mu+p}\le k_1\le 1$ and $k_2=1-k_1$, $L_0'|_{(2.1)}$ is negative (semi-)definite with respect to $(S_0, v_0(a), 0, 0)$ when $\mathcal{R}_0\le 1$. It is easy to verify that the largest invariant set of (2.1) with (2.2) on $L_0'|_{(2.1)}=0$ is the singleton $\{P_0\}$. Therefore, P_0 is globally stable in the feasible region for $\mathcal{R}_0\le 1$ by LaSalle Invariance Principle [12].

4. Numerical simulation

This section presents some numerical simulations to validate the above-obtained theoretical results. In particular, existence of multiple Lyapunov functionals will be presented. For illustration purpose, we take parameter values as follows: $A = 100$, $\mu = 0.1$, $\beta = 10^{-3}$, $\gamma = 0.3$, $\mu_0 = 0.2$. There have been some existing studies to fit the waning immunity rate from clinical trial immunogenicity data, including [6]. As illustrations, we take $\varepsilon(a)$ to represent the probability density function based on Weibull distributions

$$\begin{aligned}\varepsilon(a) &= f(a;\eta_2,\eta_1,\eta_3)\\ &= \begin{cases} (\eta_1/\eta_2) * ((a-\eta_3)/\eta_2)^{\eta_1-1} * \exp(-(a-\eta_3)/\eta_2)^{\eta_1} * \exp(0.2a), & a \geq \eta_3\\ 0, & a < \eta_3\end{cases}\end{aligned}$$

with $\eta_1 = 5$, $\eta_2 = 6.824$ and $\eta_3 = 3$. Here η_1, η_2, and η_3 are shape, scale, and location parameters, respectively. The solutions for different vaccination rates are illustrated in Figure 1. In particular, Figure 1 (a) shows that the disease can spread with low vaccination rates ($p = 0$, 0.1, 0.2 and 0.3) while the disease can be controlled through the vaccination program with a higher rate ($p = 0.4$), where $\mathcal{R}_0 = 3.75$, 2.17, 1.52, 1.17, and 0.95 corresponding to $p = 0$, 0.1, 0.2, 0.3, and 0.4, respectively. Vaccination programs play a positive role in reducing the disease transmission risk. Furthermore, Figure 1 (b) illustrates the global stability of the endemic equilibrium and the disease-free equilibrium when $\mathcal{R}_0 > 1$ and $\mathcal{R}_0 \leq 1$, respectively.

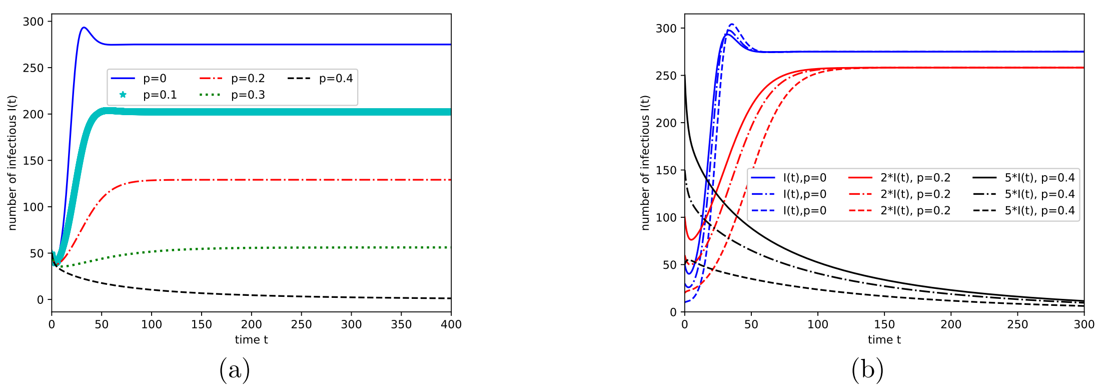
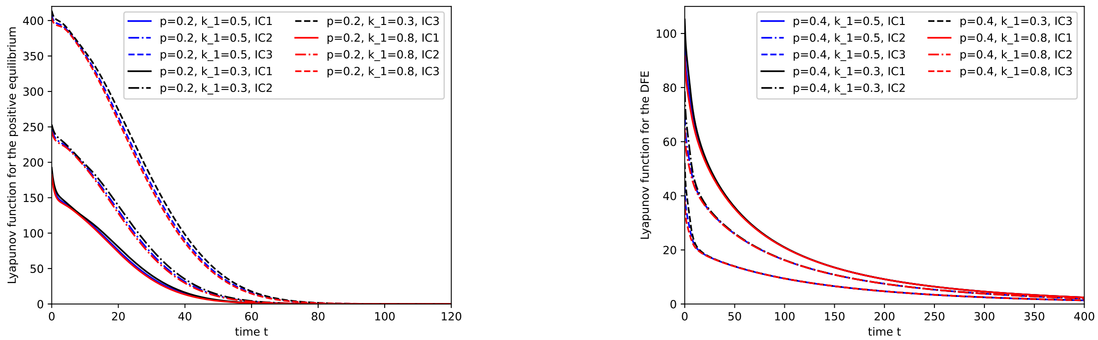


Figure 1: The solution profiles when different values of vaccination rates p are taken. (a) The corresponding basic reproduction numbers are 3.75, 2.17, 1.52, 1.17, and 0.95 for increasing values p; (b) The solutions from different initial values when p is set as 0, 0.2 and 0.4 respectively.

To show the existence of different valid Lyapunov functionals, we have performed numerical simulations in Figure 2. As a matter of fact, k_1 is allowed to take any value between $\frac{\theta p}{\mu+p}$ and 1. On the other hand, $\frac{\theta p}{\mu+p} = 0.182$ and 0.218 when $p = 0.2$ and 0.4, respectively. In Figure 2, $k_1 = 0.3$, 0.5, and 0.8 are taken. It is easy to see that for three different initial values marked in Figure 2 by IC1, IC2, and IC3, the Lyapunov functionals are always decreasing and approaching zero. These curves show that three different Lyapunov functionals are permitted to be taken to prove the global stability of an equilibrium.



(a) (b)

Figure 2: The different choices of Lyapunov functionals to show the global stability of endemic equilibrium (a) and disease-free equilibrium (b). Different k_1 values are allowed to be chosen in Lyapunov functionals, and ICi ($i = 1, 2, 3$) represent different initial conditions.

5. Conclusion and discussion

Lyapunov functions (functionals) have been widely employed to show the global behavior of dynamic systems. One type of well-used Lyapunov functions for an equilibrium $(x_1^*, x_2^*, \dots, x_n^*)$ takes the form of $L(t) = \sum_{i=1}^{n} c_i L_i(t)$, a linear combination of $L_i(t)$ with $L_i(t) = x_i(t) - x_i^* - x_i^* \ln(x_i(t)/x_i^*)$ (if $x_i^* > 0$) and $L_i(t) = x_i(t)$ (if $x_i^* = 0$). Usually, the coefficients c_i are given in the Lyapunov function based on the experiences of investigators and no analytical arguments can be followed to determine them. Furthermore, it becomes challenging sometimes to rearrange the terms in $L'(t)$ to show the (semi-)definite negativeness of $L'(t)$. These two challenges pose the main motivation of the current study, which is devoted to proposing an easy-to-follow theoretical method to determine the coefficients c_i and rearrange the terms in an appropriate manner to easily verify the (semi-)definite negativeness.

The theoretical approach is illustrated with applications to an epidemiological model with age-structured variable $v(t, a)$, where age measures the time elapsed since vaccination to characterize the loss of the immunity of vaccinated individuals. The global stability of an equilibrium for this model is argued through the Lyapunov direct method: The disease-free equilibrium is globally stable when $\mathcal{R}_0 \leq 1$ while the endemic equilibrium is globally stable when $\mathcal{R}_0 > 1$. However, since the age variable is involved in $v(t, a)$, the Lyapunov functional candidate includes a term $\int_0^\infty c(a)[v^*(a) - v(t, a) + v^*(a)\ln(\frac{v(t,a)}{v^*(a)})]da$, with a coefficient function $c(a)$ to be determined. To employ the Lyapunov direct method, three key steps are involved: (i) express the derivative with an integral form by introducing an auxiliary function $r(a)$ satisfying $\int_0^\infty r(a)da = 1$; (ii) arrange the integrand into two parts; (iii) determine the associated coefficients of the Lyapunov functional by solving the inequalities to guarantee that the derivative is negative (semi-)definite.

The analytical arguments give a feasible region for admissible c_i, instead of a singleton, which shows that the coefficients in Lyapunov functional are not unique. In other words, different Lyapunov functionals can be constructed to prove the global stability of the same equilibrium. Furthermore, we show that the Lyapunov functional for the endemic equilibrium can be easily revised, while keeping the coefficients unchanged, to show the global stability of the disease-free equilibrium. Please note that existing studies [8, 17] propose methodologies to determine coefficients of Lyapunov functions/functionals for multi-group models or coupled systems of differential equations on networks, given that the Lyapunov function/functional is known for a single group or a node in the network. The current study is to determine coefficients for the Lyapunov functional for a system describing the dynamics for a single group or for a node of the network. It is appealing to adopt the current study to coupled systems by employing existing results in [8, 17]. It is expected that the approach can be further applied to other age-structured models and be extended to analyze more complicated models with other heterogeneous factors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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