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An age-structured model for coupling within-host and between-host dynamics in environmentally-driven infectious diseases

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ABSTRACT

In this paper, an age-structured epidemic model for coupling within-host and between-host dynamics in environmentally-driven infectious diseases is investigated. The model is described by a mixed system of ordinary and partial differential equations which is constituted by the within-host viral infectious fast time ordinary system and the between-host disease transmission slow time age-structured system. The isolated fast system has been investigated in previous literatures, and the main results are introduced. For the isolated slow system, the basic reproduction number $R_0$, the positivity and ultimate boundedness of solutions are obtained, the existence of equilibria, the local stability of equilibria, and the global stability of disease-free equilibrium are established. We see that when $R_0 \leq 1$ the system only has the disease-free equilibrium which is globally asymptotically stable, and when $R_0 > 1$ the system has a unique endemic equilibrium which is local asymptotically stable. With regard to the coupled slow system, the basic reproduction number $R_0$, the positivity and boundedness of solutions and the existence of equilibria are firstly obtained. Particularly, the coupled slow system can exist two positive equilibria when $R_0 < 1$ and a unique endemic equilibrium when $R_0 > 1$. When $R_0 < 1$ the disease-free equilibrium is local asymptotically stable, and when $R_0 > 1$ and additional condition is satisfied the unique endemic equilibrium is local asymptotically stable. When there exist two positive equilibria, under an additional condition the local asymptotic stability of a positive equilibrium and the instability of other positive equilibrium also are established. The numerical examples show that the additional condition may be removed. The research shows that the coupled slow age-structured system has more complex dynamical behavior than the corresponding isolated slow system.

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1. Introduction

There are many viral infectious diseases in the world, such as viral influenza, Japanese encephalitis, measles, infant paralysis, viral hepatitis, rabies, AIDS, Ebola, SARS, Novel coronavirus pneumonia caused by 2019-nCov, and so on. These diseases not only damage the health and happiness of individuals and families, but also have a great impact on society and the country. Hence, further research in virus area appears to be very critical and necessary, which present leading treatments and control measures for diseases.

The previous researches have done a lot on the virus model, and obtained some good results. See, for example, Feng et al. [1,2], Cen et al. [3], Feng et al. [4], Wen et al. [5], Mideo et al. [6], Coombs et al. [7], Gilchrist and Coombs [8], Korobeinikov [9], Hattaf et al. [10], Gilchrist and Sasaki [11], Tian and Liu [12], Wang et al. [13], O’Malley [14], Fenichel [15] and the references cited therein. There are also many stochastic environment models in the last 2–3 years, we just list [17–19]. Some compartmental models [1–5] have been established to better understand coupled within-host and between-host infectious diseases through environment compartment. These articles show that couple the disease dynamics at two levels can generate new insights. In [3,4], the authors proposed a coupled cell pathogen model and epidemic model. At the cellular level, within-host dynamics takes the usual form of cell-virus or cell-parasite interactions, at the population level consists of an SI system for the host and environmental pollution concentration $E$. By studying, the authors draw a new conclusion that the sharp threshold condition of classical epidemiological model threshold imposed by $R_0$ no longer holds. The model in [1] is the extension of the models in [3,4] by including a disease-induced death rate for the hosts. Furthermore, according to Gilchrist and Coombs [8], the authors studied the evolution of virulence. Particu-
larly, based on the assumptions about the dependence of between-host variables, they illustrated the possible occurrence of a conflict between natural selection at the individual and population levels. Similarly, the model in [1] still have multiple attractors when reproduction number $R_0 < 1$ due to a backward bifurcation.

It’s not hard to find models [1–15] are based on the assumption that individuals in each class are homogeneous. For example, infected individuals have the same infectivity and by-product mortality during their period of infection. This assumption is reasonable when modeling infectious diseases such as influenza and sexually transmitted diseases. However, infectivity experiments on HIV/AIDS epidemic recognized the importance of variable infectivity in the transmission dynamics of infectious diseases in [16]. Furthermore, researchers proposed stage-structured models described by ordinary differential equations (ODEs). To be more realistic and reasonable, we introduce continuous infection age, which also increased the difficulty of research. In recent years, many papers have studied age-structured model, we just list [20–32].

So far, works on coupled within-host and between-host dynamics with infection age are very rare. In [29], the authors proposed an infection-age structured HIV-1 model linking within-host and between-host by introducing viral load-dependent transmission rate and different transmission rates at different ages of infection are discussed. This makes us want to extend the model in [1] by introducing age-dependent mortality due to infection at the population level. There are two time scales in our model, one is the dynamic evolution time in the host $s$, the other is the dynamic evolution time between the hosts $t$. Usually, the dynamic time at the cellular level is much faster than that at the population level. That is to say, $s$ is a faster time variable, $t$ is a slower time variable (see [1–5]). The concepts of fast time and slow time were introduced in [31–35] early. Our main purpose of this paper is to explore the potential effect of within-host dynamics on the between-host transmission dynamics in environmentally-driven infectious diseases.

We construct the following nested model with two time scales and infection age:

\[
\begin{align*}
\frac{dT}{dt} &= \Lambda_c - kVT - mt, \\
\frac{dT}{dt} &= kVT - (m + d)T^*, \\
\frac{dV}{dt} &= g(E(t)) + pT^* - cV.
\end{align*}
\]

(1)

\[
\begin{align*}
\frac{dS}{dt} &= \Lambda_h - \beta ES - \mu S, \\
\frac{di(t, a)}{dt} &= \frac{di(t, a)}{da}, \\
\frac{di(t, a)}{dt} &= \theta IV(s)(1 - E) - \gamma E, \\
I(0, 0) &= \beta ES, \\
I &= \int_0^{\infty} i(t, a)da.
\end{align*}
\]

(2)

where $S = S(t)$ represents the number of susceptible at time $t$; $E = E(t)$ represents the level of environment contamination at time $t (0 \leq E(t) \leq 1)$; $T = T(s)$, $T^* = T^*(s)$ and $V = V(s)$ denote the densities of healthy cells and infected cells, and the parasite load related to the degree of environment contamination at time $s$, respectively. The parameters in systems (1) and (2) have the following meanings: $\Lambda_c$ is the recruitment rate of cells which free from infection, $k$ is the infection rate of cells, $m$ represents the natural mortality of infected cells, $d$ denotes the infection-induced mortality rate of infected cells, $p$ is the parasite production rate by an infected cell, $c$ is the clearance rate of parasites within-host, $\Lambda_h$ is the recruitment rate of hosts, $\beta$ is the infection rate of hosts in a contaminative environment, $\mu$ denotes the natural death rate of hosts, $\alpha(a)$ is the disease-induced mortality rate of hosts at age $a$, $\gamma$ is the clearance rate of virus in environment. As we know, the level of environmental pollution can be related to the number of infected individuals and the within-host virus concentrations with the form $\theta IV$. Meanwhile, the virus-contaminated environment generates an increase on within-host virus concentrations is given by $g(E)$.

The article is arranged as follows. In Section 2, we introduce some main results of the isolated fast system (3). In Section 3, the isolated slow system (6) is discussed. The basic reproduction number $R_0$ and some criteria on the positivity, boundedness, existence and local asymptotic stability of equilibria are stated and proved. Furthermore, we obtain global asymptotic stability of disease-free equilibrium. In Section 4, the coupled slow system (25) is discussed. We obtain basic reproduction number $R_0$, positivity and boundedness of solutions, and the existence of equilibria. Particularly, it is show that the number of equilibria depends on the magnitude of basic reproduction number and the sign of $H_M$, and the system can have two positive equilibria when $R_0 < 1$. The local asymptotic stability of equilibrium stated and proved under the certain conditions and the instability of other positive equilibrium also is established. In Section 5, the numerical examples are presented to illustrate the main conclusions obtained in Section 4. Finally, in Section 6, we give a conclusion.

2. Analysis of isolated fast system

In fast time system (1), we assume that the environmental virus concentration $E(t)$ is a constant $E$ and $0 \leq E \leq 1$, where $E = 0$ means there is no virus in the environment, $E > 0$ represents there has virus in the environment, and $E = 1$ indicates that the virus in the environment reaches its maximum. Thus, fast time system (1) becomes into an isolated within-host virus infection system

\[
\begin{align*}
\frac{dT}{dt} &= \Lambda_c - kVT - mt, \\
\frac{dT}{dt} &= kVT - (m + d)T^*, \\
\frac{dV}{dt} &= g(E) + pT^* - cV.
\end{align*}
\]

(3)

We introduce the following assumption for function $g(E)$:

1. $g(0) = 0$, $g(E) \geq 0$, $g'(E) > 0$ and $g''(E) < 0$.

2. From the biological background of system (3), we assume that any solution $(T(s), T^*(s), V(s))$ of system (3) satisfies the following initial conditions

\[
T(0) > 0, \quad T^*(0) > 0, \quad V(0) > 0.
\]

(4)

The fast time system (3) has been investigated in [1–4], and in [5] for a discrete analog of system (3). The complete dynamical properties of system (3) have been established. Here, we summarize these results in the following.

Firstly, with regard to the positivity and boundedness of the solutions and the existence of equilibria for system (3) we have the following results.

**Lemma 1.** The solution $(T(s), T^*(s), V(s))$ of system (3) with initial conditions (4) is positive for all $s \geq 0$ and ultimately bounded. Furthermore, $\lim_{s \to \infty} T(s) \leq T_0$, $\lim_{s \to \infty} T^*(s) \leq T^*_0$, $\lim_{s \to \infty} V(s) \leq \frac{\sup_{s \geq 0} V(s)}{g(\Lambda_c)}$, where $g = \max_{E \geq 1} [g(E)]$.

The within-host reproduction number is defined as follows

\[
R_0 = \frac{k\beta T_0}{\Lambda_c}, \quad \text{where} \quad T_0 = \frac{\Lambda_c}{\mu}.
\]

We rewrite $R_0 = \frac{k\beta T_0}{\Lambda_c}$. Here we see that $k$ indicates the probability that the virus will come into contact with healthy cells in the host and infect them, $\frac{1}{\gamma}$ is the survival time of the virus, $\frac{p}{\Lambda_c}$ represents the amount of virus released by within-host infected cells during their survival period, $T_0$ is the number of healthy cells at the beginning of the infection. Therefore, $R_0$ represents the number of cases in which an infected cell infects healthy cells in their survival time at the early stages of infection.
Lemma 2. Let $E = 0$, then system (3) always has infection-free equilibrium $U_0 = (T_0, 0, 0)$, and when $R_w > 1$, system (3) has a unique infectious equilibrium $U_1 = (T_1, T^*_1, V_1)$, where $T_1 = \frac{c_m (m + d)}{\mu_p}$, $T^*_1 = \frac{c_m (R_w - 1)}{\mu_p}$, $V_1 = \frac{p_m k_0}{m (m + d)} \left( 1 - \frac{1}{R_w} \right)$.

Lemma 3. Let $E > 0$, then system (3) always has a unique positive equilibrium $U_2 = (\hat{T}(E), \hat{T}^*(E), \hat{V}(E))$, where

$$
\hat{T}(E) = \frac{1}{2} \left( u - \sqrt{u^2 - 4v} \right), \quad \hat{T}^*(E) = \frac{m}{m + d} (T_0 - \hat{T}(E)),
$$

$$
\hat{V}(E) = \frac{1}{c} \left[ g(E) + \frac{mp}{m + d} (T_0 - \hat{T}(E)) \right],
$$

$$
u = \frac{g(E) (m + d)}{pm} + T_0 \left( 1 + \frac{1}{R_w} \right), \quad v = \frac{T_2}{R_w}.
$$

Furthermore,

$$\lim_{E \to 0} U_2(\hat{T}(E), \hat{T}^*(E), \hat{V}(E)) = \begin{cases} U_0(T_0, 0, 0), & \text{if } R_w \leq 1, \\ U_1(T_1, T^*_1, V_1), & \text{if } R_w > 1. \end{cases}$$

On the global asymptotic stability of the infection-free equilibrium and infectious equilibrium of system (3), the following theorems are established.

Theorem 1. Let $E = 0$ in system (3).

(a) If $R_w \leq 1$, then infection-free equilibrium $U_0$ is globally asymptotically stable.

(b) If $R_w > 1$, then infectious equilibrium $U_1$ is globally asymptotically stable.

Theorem 2. Let $E > 0$ in system (3), then infectious equilibrium $U_2$ is globally asymptotically stable.

Theorem 2 indicates that when there is always virus in the environment and the environmental virus directly affects the virus infection in the host, it will directly increase the amount of virus in the host, then the virus infection always exists in the host. Meanwhile, healthy cells, infected cells and the virus eventually stabilize at a positive equilibrium $(\hat{T}(E), \hat{T}^*(E), \hat{V}(E))$ in the host which related to the environment contamination level $E$.

Moreover, Lemma 3 shows that as the virus in the environment is gradually cleared, that is, $E \to 0$, the amount of virus and infected cells in the host will be gradually removed when the basic reproduction number $R_w \leq 1$; when $R_w > 1$, even if the virus in the environment is gradually removed, the virus and the infected cells in the host will eventually still stabilize at a positive balance $V_1$ and $T^*_1$. So as time goes on, the virus in the host will be excreted by the host and enter the environment after a period of time, thereby increasing the amount of virus in the environment. When the amount of virus in the environment reaches a certain level, it will infect other healthy hosts in the environment, so that the virus begins to spread among the population (that is, between the hosts). Then, infectious disease is prevalent among hosts caused by the virus and it’s epidemic regular pattern expressed by the age-structured SIE model (2).

3. Analysis of isolated slow system

We consider that the virus in the environment does not affect the virus infection in the host, that is, we have $g(E) \equiv 0$ in the fast time system (1). When the basic reproduction number $R_w \leq 1$, the amount of virus in the infected person will eventually be cleared and the disease caused by the virus will eventually be eliminated without an epidemic. Therefore, in the following discussion, we always assume the basic reproduction number $R_w > 1$. It is obvious that the dynamics of the fast system of virus infection in the host is much faster than that of the slow system of disease transmission between the hosts, so that we can assume that the state of the fast system has reached its limit equilibrium state without further changes in the state of the slow system. Namely, when $R_w > 1$, we have $(T(s), T^*(s), V(s)) \equiv (T^*_1, V_1)$. We emphasize that this equilibrium state $V_1$ doesn’t depend on the amount of virus in the environment $E$. Furthermore, we assume that the amount of virus excreted into the environment by the infected person is $\theta V_1 (1 - E)$. Thus, system (3) becomes into an isolated between-host disease transmission system

$$
\begin{align*}
\frac{dx}{dt} & = \lambda h - \beta c E - \mu S, \\
\frac{d\hat{a}}{dt} & = \beta c E - \alpha(a) \hat{a}, \\
\frac{d\hat{v}}{dt} & = \mu S - \mu \hat{v} - \gamma E, \\
\end{align*}
$$

(6)

We introduce the following assumptions.

$$(H_2)$$ Function $\alpha(a)$ is nonnegative and Lipschitz continuous for all $a \geq 0$ with Lipschitz constants $M_\alpha$, and belongs to $L^1_{\mu}(0, \infty)$ with essential upper bound $\tilde{a}$.

$$(H_3)$$ There is a maximum age of infection $\tilde{a} > 0$, such that $\int_{\tilde{a}}^\infty i(t, a) \, da = 0$.

3.1. Positivity and boundedness

We take the phase space of system (6) by $X = \mathbb{R}^1 \times \mathbb{R}^1_{\mu}(0, \infty) \times \mathbb{R}^1_{\mu}$ with the norm $\| (x_1, x_2, x_3) \|_X = |x_1| + |x_2| + |x_3(a)| \, da + |x_3|$ for any $(x_1, x_2, x_3) \in X$. From the biological background of system (6), we assume that the initial value for any solution of system (6) is defined by $X_0 := (S_0, \hat{a}_0, \hat{E}(0)) \in X$ satisfying the following conditions

$$S(0) > 0, \quad \hat{a}(0) \geq 0, \quad 0 \leq \hat{E}(0) \leq 1.$$

(7)

It follows from the standard theory of differential equation, we can obtain that system (6) has a unique solution $\Phi(t, X_0) = (S(t), i(t, \cdot), E(t))$ satisfying the initial condition $\Phi(0, X_0) = X_0$.

On the positivity and ultimate boundedness of solutions for system (6), we have the following results.

Lemma 4. The solution $\Phi(t, X_0)$ of system (6) with initial value (7) is nonnegative for all $t > 0$ and ultimately bounded. Particularly, we have $\limsup_{t \to \infty} S(t) + \int_0^\infty i(t, a) \, da \leq \frac{\lambda h}{\mu_0}$ and $0 \leq E(t) \leq 1$ for all $t \geq 0$.

Proof. The nonnegativity of solutions can be proved by using the similar method given [23], and we hence omit the proof. Now, we prove the ultimate boundedness of solutions. Let $N(t) = S(t) + \int_0^\infty i(t, a) \, da$, then

$$\frac{dN(t)}{dt} = \frac{\partial S(t)}{\partial t} + \int_0^\infty \frac{\partial i(t, a)}{\partial t} \, da = \lambda h - \beta E S - \mu S - \int_0^\infty \frac{\partial i(t, a)}{\partial t} \, da - \int_0^\infty (\mu + \alpha(a)) i(t, a) \, da = \lambda h - \mu S - \int_0^\infty (\mu + \alpha(a)) i(t, a) \, da \leq -\lambda h.$$

Therefore, we have $\limsup_{t \to \infty} S(t) \leq \frac{\lambda h}{\mu_0}$ and $\Phi(t, X_0)$. Particularly, when $N(0) \leq \frac{\lambda h}{\mu_0}$ we also have $\Phi(t) \leq \frac{\lambda h}{\mu_0}$ for all $t \geq 0$.

Now, we prove $0 \leq E(t) \leq 1$ for all $t \geq 0$. In fact, we only need to show that $E(t) \leq 1$ is established. If not, then there exists $t_1 > 0$ satisfying $E(t_1) = 1$ and $E(t) \leq 1$ for all $t \in [0, t_1]$. Thus, $E'(t_1) \geq 0$. From the third equation of system (6), we have
\[ E'(t_1) = \theta I(t_1) V_1(t_1) (1 - E(t_1)) - \gamma E(t_1) = -\gamma E(t_1) < 0, \quad \text{where} \quad I(t_1) = \int_{0}^{\infty} i(t_1, \alpha) \, da. \]

This leads to a reproduction. Hence, \( 0 \leq E(t) \leq 1 \) for all \( t \geq 0 \). This shows that \( \Phi(t, X_0) \) is ultimately bounded. This completes the proof. \( \square \)

**Remark 1.** From Lemma 4 we can further obtain that solution \( \Phi(t, X_0) \) of system (6) is defined for all \( t > 0 \). Therefore, the continuous semi-flow \( \Phi : \mathbb{R}_+ \times \mathbb{X} \to \mathbb{X} \) defined by system (6) takes the following form
\[
\Phi(t, X_0) = (S(t), \int(t, -), E(t)), \quad t \geq 0, \quad X_0 \in \mathbb{X}. \tag{8}
\]

### 3.2. Equilibrium and basic reproduction number

Clearly, system (6) always has a disease-free equilibrium \( W_0 = (S_0, 0, 0) \), where \( S_0 = \frac{\lambda}{\mu} \). We define the between-host reproduction number as follows:
\[
R_0 = \frac{\beta \theta V_1 I_0(1 - \bar{E})}{\gamma (\mu + \alpha(\pi) da),}
\]
where \( \pi(\alpha) = e^{-\int_{0}^{\infty} (\mu + \alpha(\pi) da) \, ds} \) is the probability for an individual becomes an infected person after a period of time \( a \). We rewrite \( R_0 = \bar{\beta} \cdot \frac{\int_{0}^{\infty} \theta V_1(1 - \bar{E}) \, da}{\gamma (\mu + \alpha(\pi) da) \cdot S_0} \). Here we see that \( \bar{\beta} \) represents the probability for the virus in the environment contacts the healthy person and makes them infected, \( \frac{1}{\gamma} \) is the survival time of the virus in the environment, \( \theta V_1(1 - \bar{E}) \, da \) is the amount of an infected person discharging virus into the environment and \( S_0 \) is the number of healthy people in the environment at the beginning of the epidemic. Therefore, \( R_0 \) indicates the number of infected cases in which an infected person infects susceptible in their survival time at the early stages of infection.

If system (6) has an endemic equilibrium \( W_1(S, \int(\alpha), \bar{E}) \), then it must satisfy the following equations:
\[
\begin{align*}
\Lambda_h - \bar{\beta} \bar{S} \bar{E} - \mu \bar{S} &= 0, \\
\frac{d\theta V_1}{da} &= \frac{-\mu + \alpha(\pi)}{\gamma} \int_{0}^{\infty} \theta V_1(1 - \bar{E}) \, da = 0,
\end{align*}
\tag{9}
\]

It follows from the first equation of (9) that
\[
\bar{S} = \frac{\mu S_0 - \bar{I}(0)}{\mu}. \tag{10}
\]

Integrating the second equation of (9) from 0 to \( a \) one can get
\[
\bar{I}(a) = \bar{I}(0) \pi(\alpha). \quad \text{We obtain from the third equation of (9) that}
\]
\[
\bar{E} = \frac{\theta V_1}{\gamma} \int_{0}^{\infty} \bar{I}(a) \, da. \tag{11}
\]

On substituting (10) and (11) into the fourth equation of (9), we have
\[
\bar{I}(a) = \frac{\beta \theta V_1(1 - \bar{E})}{(\mu + \alpha(\pi) da) \bar{E}} \int_{0}^{\infty} \pi(\alpha) \, da = \frac{1}{\mu} (\theta V_1(1 - \bar{E}) \int_{0}^{\infty} \bar{I}(a) \, da - \gamma \bar{E}). \tag{12}
\]

Therefore, \( \bar{I}(0) = \frac{\beta \theta V_1(1 - \bar{E})}{\gamma} \int_{0}^{\infty} \pi(\alpha) \, da = \frac{\mu S_0}{\mu + \beta \theta V_1(1 - \bar{E}) \, da} \). Hence, if \( R_0 > 1 \), then system (6) has an endemic equilibrium \( W_1(\bar{S}, \bar{I}(\alpha), \bar{E}) \), where \( \bar{S} = S_0 - \frac{\gamma}{(\mu + \beta \theta V_1(1 - \bar{E}) \, da)}, \bar{I}(\alpha) = \frac{\mu S_0}{(\mu + \beta \theta V_1(1 - \bar{E}) \, da)}, \bar{E} = \frac{\theta V_1}{\mu \gamma (\mu + \beta \theta V_1(1 - \bar{E}) \, da)} \).

**Lemma 5.** If \( R_0 \leq 1 \), system (6) has only a disease-free equilibrium \( W_0 \); if \( R_0 > 1 \), besides \( W_0 \), system (6) has a unique endemic equilibrium \( W_1 \).

### 3.3. Stability of the disease-free equilibrium

We first consider the local stability of disease free equilibrium \( W_0(S_0, 0, 0) \). Linearizing system (6) at equilibrium \( W_0 \) we have
\[
\begin{align*}
\frac{dx(t)}{dt} &= -\mu x(t) - \beta S z(t), \\
\frac{dy(t)}{dt}(t) + \frac{\gamma y(t)}{a} &= -\mu (a(\pi) + \alpha(\pi)) y(t), \\
\frac{dz(t)}{dt} &= -\gamma z(t) + \theta V_1 \int_{0}^{\infty} y(t, a) \, da.
\end{align*}
\tag{13}
\]

Let \( x(t) = y(t) = 1 \), \( y(t, a) = \eta(t, a) e^{\lambda t}, z(t) = z(t) e^{\lambda t} \), we obtain the following eigenvalue problem:
\[
\begin{align*}
(\lambda + \mu) z(t) &= -\beta S z(t), \\
\frac{dy(t)}{dt}(t) + \frac{\gamma y(t)}{a} &= -\mu (a + \alpha(\pi)) y(t), \\
\frac{dz(t)}{dt} &= -\gamma z(t) + \theta V_1 \int_{0}^{\infty} y(t, a) \, da.
\end{align*}
\tag{14}
\]

Integrating the second equation of (14) from 0 to \( a \) we can obtain
\[
y(t) = \frac{\gamma y(t)}{a} e^{\lambda t} - \int_{0}^{a} e^{\lambda t} (\lambda + \mu + \alpha(\pi)) \, da = \frac{\gamma y(t)}{a} e^{\lambda t} - \int_{0}^{a} e^{\lambda t} (\lambda + \mu + \alpha(\pi)) \, da.
\tag{15}
\]

It follows from the fourth equation of (14) that
\[
\lambda = \frac{y(t)}{y(t)} - \frac{\gamma y(t)}{a} e^{\lambda t} - \int_{0}^{a} e^{\lambda t} (\lambda + \mu + \alpha(\pi)) \, da.
\tag{16}
\]

Substituting (15) and (16) into the third equation of (14) yields
\[
\frac{dy(t)}{dt}(t) + \frac{\gamma y(t)}{a} = -\mu (a + \alpha(\pi)) y(t).
\tag{17}
\]

Let us denote the left hand of (17) by \( f(\lambda) \). Obviously, \( f(0) = \frac{\beta S \theta V_1(1 - \bar{E})}{\gamma} - \int_{0}^{\infty} e^{\lambda t} (\lambda + \mu + \alpha(\pi)) \, da = R_0(0), \lim_{\lambda \to -\infty} f(\lambda) = 0, \lim_{\lambda \to \infty} f(\lambda) = 0. \) Therefore, \( f(\lambda) \) is a decreasing function. If \( R_0 > 1 \), due to the continuity and differentiability of \( f(\lambda) \), there has a unique positive root. Accordingly, equilibrium \( W_0 \) is unstable when \( R_0 > 1 \).

We now claim that if \( R_0 < 1 \), equilibrium \( W_0 \) is locally asymptotically stable. If not, Eq. (17) has at least one root \( \lambda_1 = a_1 + b_1 i \) satisfying \( a_1 \) is positive thus \( f(\lambda_1) = 0 \). In this case, one has \( f(\lambda_1) \) produces a contradiction. Hence, if \( R_0 < 1 \), all roots of characteristic equation have negative real parts. Accordingly, equilibrium \( W_0 \) is locally asymptotically stable if \( R_0 < 1 \). Therefore, we get the following conclusion.

**Theorem 3.** For system (6), if \( R_0 < 1 \), then disease-free equilibrium \( W_0 \) is locally asymptotically stable; if \( R_0 > 1 \), then \( W_0 \) is unstable.

Now, we give a result on the global asymptotic stability of disease-free equilibrium \( W_0 \) of system (6).

**Theorem 4.** For system (6), if \( R_0 \leq 1 \), then disease-free equilibrium \( W_0 \) is globally asymptotically stable.

The proof of Theorem 4 is given in Appendix A.

### 3.4. Stability of the endemic equilibrium

We are now in a position to study the local stability of endemic equilibrium \( W_1(\bar{S}, \bar{I}(\alpha), \bar{E}) \) of system (6). Linearizing system (6) at
endemic equilibrium \( W_1 \) we have
\[
\begin{align*}
\frac{dx_2(t)}{dt} &= - (\mu + \beta E)x_2(t) - \beta S z_2(t), \\
\frac{dy_2(t,a)}{dt} + \frac{dy_1(t,a)}{dt} &= - (\mu + \alpha(a))y_2(t, a), \\
\frac{dz_2(t)}{dt} &= \theta V_1 (1 - \hat{E}) \int_0^\infty y_2(t, a) da - (\theta V_1 \int_0^\infty \hat{t}(a) da + \gamma) z_2(t), \\
y_2(t, 0) &= \beta \hat{E} x_2(t) + \beta \hat{S} z_2(t).
\end{align*}
\] (18)

Let \( x_2(t) = x_2(t)e^{\lambda t} \), \( y_2(t, a) = y_2(t,a)e^{\lambda t} \), \( z_1(t) = z_2(t)e^{\lambda t} \), we obtain the following eigenvalue problem:
\[
\begin{align*}
(\lambda + \mu + \beta \hat{E})x_2(t) &= - \beta \hat{S} z_2(t), \\
\frac{dy_2(t,a)}{dt} &= - (\lambda + \mu + \alpha(a))y_2(t, a), \\
(\lambda + \theta V_1 \int_0^\infty \hat{t}(a) da + \gamma) z_2(t) &= \theta V_1 (1 - \hat{E}) \int_0^\infty y_2(t, a) da, \\
y_2(t, 0) &= \beta \hat{E} x_2(t) + \beta \hat{S} z_2(t).
\end{align*}
\] (19)

If \( \lambda = - \mu - \beta \hat{E} \) or \( \lambda = - \theta V_1 \int_0^\infty \hat{t}(a) da - \gamma \), then \( \lambda \) is a root which has negative real part, if \( \lambda \neq - \theta V_1 \int_0^\infty \hat{t}(a) da - \gamma \) and \( \lambda \neq - \mu - \beta \hat{E} \), then \( y_2(t, 0) \neq 0 \). It follows from the first equation of (19) that
\[
x_2(t) = - \beta \hat{S} z_2(t). \] (20)

Integrating the second equation of (19) from 0 to \( a \) we can obtain
\[
y_2(t, a) = y_2(t, 0)e^{-\int_0^a (\lambda + \mu + \alpha(s)) ds}. \] (21)

From the third equation of (19) one can get
\[
2z_2(t) = \frac{\theta V_1 (1 - \hat{E}) \int_0^\infty y_2(t, a) da}{\lambda + \theta V_1 \int_0^\infty \hat{t}(a) da + \gamma}. \] (22)

Substituting (20) and (22) into the fourth of (19) and combined with (21), we obtain the characteristic equation of system (6) at equilibrium \( W_1 \) of the form
\[
f_1(\lambda) = 1, \] (23)

where
\[
f_1(\lambda) = \frac{\beta \hat{S}(\lambda + \mu) \theta V_1 \int_0^\infty e^{-\int_0^a (\lambda + \mu + \alpha(s)) ds} da }{ (\lambda + \mu + \beta \hat{E})(\lambda + \gamma + \theta V_1 \int_0^\infty \hat{t}(a) da + \gamma) } \] (24)

We claim that all roots of Eq. (23) have negative real parts. Otherwise, Eq. (23) has at least one root \( \lambda_2 = \alpha_2 + i \beta_2 \) satisfying \( \alpha_2 \geq 0 \). In this case, we have \( |f_1(\lambda_2)| \leq \frac{\theta V_1 \int_0^\infty \hat{t}(a) da}{\mu \theta V_1 \int_0^\infty \hat{t}(a) da + \gamma} \leq 1 \). This produces a contradiction. Hence, all roots of the characteristic Eq. (23) have nonnegative real parts when \( R_{00} > 1 \). That is, equilibrium \( W_1 \) is locally asymptotically stable when \( R_{00} > 1 \). In conclusion, we have the following result.

**Theorem 5.** For system (6), then endemic equilibrium \( W_1 \) is locally asymptotically stable when \( R_{00} > 1 \).

**Remark 2.** When \( R_{00} > 1 \), whether endemic equilibrium \( W_1 \) of system (6) is also globally asymptotically stable is still an important open problem.

**Remark 3.** From the discussions in this section, we see that the isolated slow system (6) has the well dynamical properties. Here, we establish the almost complete conclusions. That is, when \( R_{00} \leq 1 \) the disease-free equilibrium is globally asymptotically stable, and when \( R_{00} > 1 \) the endemic equilibrium \( W_1 \) is locally asymptotically stable. But, unfortunately, we do not get the global asymptotic stability of \( W_1 \) when \( R_{00} > 1 \).

From Theorems 3–6 we can obtain that the transmission and prevalence of diseases caused by virus infection of isolated between-host slow system is completely determined by the basic reproduction number \( R_{00} \). When \( R_{00} \leq 1 \), even if viral infection continues in the host, but the epidemic eventually dies out among the hosts; when \( R_{00} > 1 \), infectious diseases will spread and prevail between the hosts, and eventually become an endemic disease.

**4. The analysis for coupled slow system**

When the virus in the environment has an effect on the virus infection in the host, we assume that this effect causes the amount of virus in the host to increase, and use the function \( g(E) \) to express this increase. In this way, the dynamic change of the virus in the host will satisfy the equation \( \frac{dv}{dt} = g(E) + pT^+ - CV \). When \( E > 0 \), due to the dynamics of the fast system of virus infection in the host is much faster than that of the slow system of disease transmission between the hosts, we can assume that the state of the fast system has reached its equilibrium state without further changes in the state of the slow system. Namely, we have \( (T(s), V(s), V(s)) \equiv (T(E), T^*(E), V(E)) \). Thus, we can let \( V(s) = \hat{V}(E) \) in system (2), and further have the following coupled slow system:
\[
\begin{align*}
\frac{dt}{ds} &= \Lambda_0 - \beta \hat{ES} - \mu S, \\
\frac{dU(t,a)}{ds} + \frac{dU(t,a)}{ds} &= - (\mu + \alpha(a))i(t, a). \\
\frac{dE}{ds} &= \theta V_1 (1 - \hat{E}) \int_0^\infty y_2(t, a) da - (\theta V_1 \int_0^\infty \hat{t}(a) da + \gamma) (\hat{E} x_2(t) + \hat{S} z_2(t)), \\
i(t, 0) &= \beta \hat{E} x_2(t) + \beta \hat{S} z_2(t).
\end{align*}
\] (25)

In Section 2, we obtain that for any \( E \geq 0 \) the solution \((T(s), V(s))\) of isolated fast system (3) has \( \lim_{t \to \infty} (T(s), V(s)) = \{(U_0(T_0, 0, 0), 0), \text{ if } E = 0, R_{00} \leq 1; U_1(T_1, T_1^*, V_1), \text{ if } E = 0, R_{00} > 1\} \). We denote \( \hat{U}(E) = U_2(T(E), T^*(E), \hat{V}(E)), \text{ if } E > 0. \)

\( \hat{T}(E), \hat{T}^*(E), \hat{V}(E) \) \( \) is unique solution \( \Phi(t, X_0) \) of \( (S(t), i(t, t), E(t)) \) satisfying the initial condition \( \Phi(0, X_0) = X_0 \).

Firstly, on the positivity and boundedness of solutions for system (25), we have the following results which is similar to isolated slow system (6).

**Lemma 6.** The solution \( \Phi(t, X_0) \) of system (25) with initial value \( X_0 \) is positive for all \( t \geq 0 \) and ultimately bounded. Particularly, we also have \( \lim_{t \to \infty} \hat{U}(E) = \lim_{t \to \infty} (T(s), V(s)) \) and \( \lim_{t \to \infty} i(t, a) da \)

Similarly, to isolated slow system (6), the phase space of system (25) is taken by \( X = \mathbb{R}_+^3 \times \mathbb{R}_+^5 \), and the initial condition of any solution of system (25) is defined by \( X_0 = (S(0), i(0, \cdot), E(0)) \) with \( S(0) > 0, i(0, \cdot) \geq 0 \) and \( 0 \leq E(0) \leq 1 \).

It is clear that system (25) has a unique solution \( \Phi(t, X_0) \) satisfying the initial condition \( \Phi(0, X_0) = X_0 \).

We give the between-host reproduction number for system (25) when \( R_{00} > 1 \) as follows: \( R_{00} = \frac{\delta \theta V_1 \int_0^\infty \hat{t}(a) da}{\hat{E} \mu \int_0^\infty \hat{t}(a) da - \gamma} \). Rewriting \( R_{00} = \beta + \frac{1}{\gamma} \theta V_1 \int_0^\infty \hat{t}(a) da \). At this time we can see that \( \beta \) indicates the probability of virus in the environment contacting healthy people and causing them to be infected, \( \frac{1}{\gamma} \) is the survival time of the virus in the environment, \( \theta \hat{V}(0, \int_0^\infty \hat{t}(a) da) \) is the amount of virus that an infected person discharges into the environment when the amount of virus in the environment \( E = 0 \) at time.
the beginning of the infectious disease, and \( S_0 \) is the number of healthy person at the beginning of the infectious disease. Therefore, \( R_b \) represents the number of infected cases in which an infected person infects susceptible in their survival time at the early stages of infection when the virus in the environment has an impact on the within-host virus infection.

According to the expression of \( V(0) \), we see that \( R_b < 0 \) when \( R_m < 1 \), \( R_b = 0 \) when \( R_m = 1 \) and \( R_b > 0 \) when \( R_m > 1 \). Furthermore, if \( R_b \geq 1 \) then we definitely get \( R_m > 1 \).

4.1. Existence of equilibrium

Firstly, system (25) always has a disease-free equilibrium \( W_0(S_0, 0, 0) \) with \( S_0 = \frac{1}{\beta} \). Let \( \tilde{W}(\tilde{S}, \tilde{i}(a), \tilde{E}) \) denote a positive equilibrium of system (25). We denote \( R_j = \frac{\beta \mu S_0 \pi(a) \alpha}{\gamma} \), \( \tilde{i}(a) \). Obviously, \( R_b = R_j \tilde{V}(0) \). Then \( \tilde{W}(\tilde{S}, \tilde{i}(a), \tilde{E}) \) must satisfy the following equations:

\[
\begin{align*}
\dot{\tilde{S}} &= \mu S_0 - \beta \tilde{S} \tilde{E} - \mu \tilde{S}, \\
\dot{\tilde{i}}(a) &= -((\mu + \alpha(a)) \tilde{i}(a)), \\
\dot{\tilde{E}} &= (1 - \tilde{E}) - \gamma \tilde{E} = 0, \\
\tilde{i}(0) &= \beta \tilde{E} \tilde{S}.
\end{align*}
\]

It follows from the first equation of (27) that

\[
\tilde{S} = \frac{\mu S_0}{\beta \tilde{E} + \mu} - \frac{\tilde{i}(0)}{\mu}.
\]

Integrating the second equation of (27) from 0 to \( a \) one can get

\[
\tilde{i}(a) = \tilde{i}(0) \pi(a).
\]

It follows from the third equation of (27) that

\[
\dot{\tilde{V}}(\tilde{E}) \tilde{i} - (\dot{\tilde{V}}(\tilde{E})) \tilde{i} + \gamma \tilde{E} = 0, \\
\tilde{E} = \frac{\dot{\tilde{V}}(\tilde{E}) \tilde{i}}{\gamma}.
\]

Obviously, \( 0 < \tilde{E} < 1 \). Substituting (28) and (30) into the fourth equation of (27) and combining with (29), we can obtain

\[
\begin{align*}
\beta \mu S_0 \tilde{V}(\tilde{E}) & \left(1 - \tilde{E}\right) \frac{\pi(a) \alpha}{\gamma} = 1. \\
\end{align*}
\]

4.2. Stability of equilibrium

Theorem 6. (i) If \( R_b < 1 \), then disease-free equilibrium \( W_0 \) is locally asymptotically stable.

(ii) If \( R_b > 1 \), then \( W_0 \) is unstable.

The proof of Theorem 6 is given in Appendix B.

Theorem 6 shows that when the basic reproduction number \( R_b < 1 \), because the coupled slow system may have two positive equilibrium at this time, the infectious disease will be extinct only when the number of infected individuals is relatively small. When this number is relatively larger, the transmission dynamics of disease will be complicated in the between-host, and there may even be new disease outbreaks.

Theorem 7. If \( R_b < 1 \) and \( H_m > 0 \), then positive equilibrium \( \hat{W}_1 \) is unstable.

The proof of Theorem 7 is given in Appendix C.

Theorem 8. If \( R_b < 1 \), \( H_m > 0 \), and \( \frac{\gamma}{\mu + \beta \tilde{E}} < 1 \), then positive equilibrium \( \hat{W}_2 \) is locally asymptotically stable.

The proof of Theorem 8 is given in Appendix D.
Theorem 9. If $R_0 > 1$ and $\frac{\gamma}{\mu + \beta E_2} \leq 1$, then endemic equilibrium $W_2$ is locally asymptotically stable.

Proof. From (40), we can obtain the characteristic equation of system (25) at equilibrium $W_0$ can be established as follows:

$$f_3(\lambda) = \frac{\beta S_0}{\gamma} \left( e^{-\beta e^{\gamma S_0} \gamma} e^{\gamma S_0} + e^{-\beta e^{\gamma S_0} \gamma} e^{\gamma S_0} \right) = 0.$$ 

This is completely similar to the proof method of Theorem 8 (See Appendix D), we can easily get that equilibrium $W_2$ is locally asymptotically stable when $\frac{\gamma}{\mu + \beta E_2} \leq 1$. This completes the proof. □

Theorem 9 indicates that when the coupled slow system has only one endemic equilibrium, as long as the condition $\frac{\gamma}{\mu + \beta E_2} \leq 1$ is satisfied, the infectious disease will be long-term popular in the coupled slow system, and it will become into an endemic disease. The condition $\frac{\gamma}{\mu + \beta E_2} \leq 1$ is a purely mathematical condition, it is only used in the mathematical argument of Theorem 9.

Remark 5. Comparing with Theorem 5 for the isolated slow system, we here have an interesting open problem. That is, whether endemic equilibrium $W_2$ of system (25) also is locally asymptotically stable only when $R_0 > 1$.

Remark 6. From discussions in this section, we see that the coupled slow system (25) has the complex dynamical behaviors. Particularly, there exists the backward bifurcation. That is, when $R_0 < 1$ and is close to 1, then system (25) has two positive equilibria $W_1$ and $W_2$, and from Theorems 7 and 8 we get that $W_1$ is unstable, and $W_2$ is locally asymptotically stable.

5. Numerical examples

In this section, we give some numerical examples to verify the theoretical results obtained in Theorems 6–9. For the convenience of numerical simulations, we take the function $g(E) = wE$ in the following examples, where $w$ is a positive constant.

Example 1. In systems (1) and (2), we choose the parameters $\Lambda_{10} = 10, \beta = 0.04, \mu = 0.04, \gamma = 0.015, \theta = 1.5 \times 10^{-8}$, $\Lambda_{20} = 8500, k = 1.5 \times 10^{-6}$, $m = 0.15, d = 0.15, p = 900, c = 50, w = 4 \times 10^5$ and $\alpha = 0.045$.

By calculation we obtain $R_0 = 0.7514 < 1$. The numerical simulations given in Fig. 1 (a)–(c) show that the disease-free equilibrium $W_0(S_0, 0, 0)$ is locally asymptotically stable for system (25), where $S_0 = 250$. The initial value $(S(0), i_0(a), E(0))$ in Fig. 1 (a) are chosen by $(850, 10 \exp(-0.09(a-1)) + 7/5 \exp(-0.05(a-1))^2, 5, 0.85),(300, 10 \exp(-0.09(a-1)) + 7/5 \exp(-0.05(a-1))^2, 15, 0.35)$ and $(900, 10 \exp(-0.09(a-1)) + 7/5 \exp(-0.05(a-1))^2, 20, 0.2)$, respectively. Thus, the conclusion obtained in Theorem 6 is verified by the numerical example. Example 2. Here we verify Theorems 7 and 8. We will give the following two cases to show that the condition $\frac{\gamma}{\mu + \beta E_2} < 1$ may be a purely mathematical condition, which is only used in the mathematical argument of Theorem 8.

Case (i). We take the parameters in systems (1) and (2) $\Lambda_{10} = 4, \beta = 0.025, \mu = 0.04, \gamma = 0.015, \theta = 1.5 \times 10^{-8}$, $\Lambda_{20} = 6000, k = 1.5 \times 10^{-6}$, $m = 0.3, d = 0.15, p = 955, c = 60, w = 4 \times 10^5$ and $\alpha = 0.045$.

By calculation, we obtain $R_0 = 0.784 < 1$. The numerical simulations given in Fig. 2 (a)–(c) show that the positive equilibrium $W_2(S_1, i_2(a), E_2)$ is locally asymptotically stable, and the positive equilibrium $W_1(S_1, i_1(a), E_1)$ is unstable. The initial value $(S(0), i_0(a), E(0))$ in Fig. 2 are chosen by $(100, 10 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 0.2), (50.7 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 0.45)$ and $(150.8 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 0.35)$, respectively. In addition, the diagram of function $H(E)$ with $E \in [0, 1]$ is also given in Fig. 2 (d).

Case (ii). We take the parameters in systems (1) and (2) $\Lambda_{10} = 4, \beta = 0.039, \mu = 0.04, \gamma = 0.15, \theta = 1.5 \times 10^{-8}$, $\Lambda_{20} = 6000, k = 1.5 \times 10^{-6}$, $m = 0.3, d = 0.15, p = 955, c = 60, w = 4 \times 10^5$ and $\alpha = 0.045$.

By calculation, we obtain $R_0 = 0.9682 < 1$. The numerical simulations given in Fig. 2 (a)–(c) show that the positive equilibrium $W_2(S_1, i_2(a), E_2)$ is locally asymptotically stable, and the positive equilibrium $W_1(S_1, i_1(a), E_1)$ is unstable. The initial value $(S(0), i_0(a), E(0))$ in Fig. 2 are chosen by $(150, 10 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 0.2), (50.7 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 0.45)$ and $(150.8 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 0.35)$, respectively. In addition, the diagram of function $H(E)$ with $E \in [0, 1]$ is also given in Fig. 2 (d).

Example 3. Now, we verify Theorem 9. We will give the following two cases to show that the condition $\frac{\gamma}{\mu + \beta E_2} < 1$ is a purely mathematical condition, which is used in the mathematical argument of Theorem 9.

Case (i). The parameters are chosen in systems (1) and (2) $\Lambda_{10} = 6, \beta = 0.04, \mu = 0.04, \gamma = 0.015, \theta = 7.5 \times 10^{-8}$, $\Lambda_{20} = 8500, k = 1.5 \times 10^{-6}$, $m = 0.3, d = 0.15, p = 900, c = 50, w = 4 \times 10^5$ and $\alpha = 0.045$.

By calculation, we obtain $R_0 = 76.976 > 1$, and system (25) has a unique endemic equilibrium $W_2(S_2, i_2(a), E_2)$, where $S_2 = 76.028$. The numerical simulations given in Fig. 4 (a)–(c) show that the endemic equilibrium $W_2(S_2, i_2(a), E_2)$ is locally asymptotically stable. The initial value $(S(0), i_0(a), E(0))$ in Fig. 4 are chosen by $(500, 10 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 0.29), (366, 10 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 3.08)$ and $(50, 10 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 0.33)$, respectively. In addition, the diagram of function $H(E)$ with $E \in [0, 1]$ is also given in Fig. 4 (d).

Case (ii). We choose the parameters in systems (1) and (2) $\Lambda_{10} = 40, \beta = 0.04, \mu = 0.04, \gamma = 0.15, \theta = 6.5 \times 10^{-8}$, $\Lambda_{20} = 8500, k = 3.5 \times 10^{-7}$, $m = 0.15, d = 0.15, p = 900, c = 50, w = 4 \times 10^5$ and $\alpha = 0.045$.

By calculation, we obtain $R_0 = 25.868 > 1$. The numerical simulations given in Fig. 5 (a)–(c) show that the endemic equilibrium $W_2(S_2, i_2(a), E_2)$ is still locally asymptotically stable. The initial value $(S(0), i_0(a), E(0))$ in Fig. 5 are chosen by $(850, 10 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 0.26), (100, 10 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 5.58)$ and $(150, 10 \exp(-0.09(a-1)) + 0.7 \sin \sin(0.05(a-1))^2, 10.33)$, respectively. In addition, the diagram of function $H(E)$ with $E \in [0, 1]$ is also given in Fig. 5 (d).
6. Conclusion

In this paper we propose an age-structured epidemic model for coupling within-host and between-host dynamics in environmentally-driven infectious diseases. The model is described by a mixed system of ordinary and partial differential equations which is divided into a fast time system of ordinary differential equations and a slow time age-structured system by using the idea of perturbation theory.

For isolated fast system (3), The dynamical behavior has been investigated in [1–5]. We only list the main results in this paper.

For isolated slow system (6), we firstly obtain the positivity and ultimately boundedness of solutions, the basic reproduction number \( R_{00} \) and the existence of equilibrium. Next, as main results, the local and global stability of equilibrium by using the linearization method and Lyapunov functions, respectively. We obtain that the disease-free equilibrium is globally asymptotically stable if \( R_{00} \leq 1 \), and the endemic equilibrium is locally asymptotically stable if \( R_{00} > 1 \). However, an open problem is to establish the concrete criterion for the global stability of the endemic equilibrium.

For coupled slow system (25), we firstly obtain the existence of positive equilibrium with the help of basic reproduction number \( R_b \) and \( H_M \). Particularly, we get that system (6) can have two positive equilibria \( \hat{W}_1(S_1, I_1(a), E_1) \) and \( \hat{W}_2(S_2, I_2(a), E_2) \) with \( E_1 < E_2 \) when \( R_b < 1 \) and \( H_M > 0 \), and a unique endemic equilibrium \( \hat{W}_3 \) when \( R_b > 1 \). This shows that system (6) can undergo a backward bifurcation at \( R_b = 1 \). We further establish a series of criteria for the local stability of disease-free equilibrium and positive equilibrium. That is, the disease-free equilibrium is locally asymptotically stable if \( R_b < 1 \), the positive equilibrium \( \hat{W}_1 \) is unstable when \( R_b < 1 \) and \( H_M > 0 \), the endemic equilibrium \( \hat{W}_3 \) is locally asymptotically stable if \( R_b < 1, H_M > 0 \) and \( \frac{\gamma}{\mu + \beta E_1} \leq 1 \), and the unique endemic equilibrium \( \hat{W}_3 \) is locally asymptotically stable if \( R_b > 1 \) and \( \frac{\gamma}{\mu + \beta E_1} \leq 1 \). In general, we just want the local stability of the equilibrium of system (25) to be only related to the basic reproduction number \( R_b \). Therefore, an open problem arises whether we can obtain the local asymptotic stability of the equilibria if there is no condition \( \frac{\gamma}{\mu + \beta E_1} \leq 1 \). The numerical examples given in Section 5 show that the condition \( \frac{\gamma}{\mu + \beta E_1} \leq 1 \) may be removed. Furthermore, we also do not obtain the global asymptotic stability of the endemic equilibrium \( \hat{W}_3 \), because the construction of the Lyapunov function can be very challenging.

There are some interesting and important problems which can be further investigated. In this paper we do not investigate the persistence of disease. For isolated slow system (6) and coupled slow system (25), when basic reproduction numbers \( R_{00} > 1 \) and \( R_b > 1 \), whether we also can obtain the uniform persistence of disease. In addition, in view of the important role of nonlinear incidence rate in epidemic models, whether the main conclusions established in this paper also can be extended to the model with nonlinear incidence. These problems are very challenging and will be solved in the future.

Author Statement

The main idea of this paper was proposed by Zhidong Teng. Jingjing Lu prepared the manuscript initially and performed all
the steps of the proofs in this research. Yingke Li performed the numerical examples. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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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Appendix A. Proof of Theorem 4

Proof. We denote \( G(x) = x - 1 - \ln x \). Define a Lyapunov function \( V_1(t) = S_0 G \left( \frac{S(t)}{S_0} \right) + \int_0^t F(a) \| t \| (a) \, da + qE(t) \). Calculating the derivative with time \( t \), we have

\[
\frac{dV_1(t)}{dt} = (1 - \frac{S_0}{S(t)}) [\Lambda_h - \beta E(t) S(t) - \mu S(t)] + \int_0^\infty F(a) \frac{\partial \| t \| (a)}{\partial t} \, da + q[\partial V(t) (1 - E(t)) - \gamma E(t)]
\]

\[
= (1 - \frac{S_0}{S(t)}) [\mu S(t) - \beta E(t) S(t)] - \beta E(t) S(t) + \beta E(t) S_0
\]

\[- \int_0^\infty [F(a) - (\mu + \alpha(a)) F(a) \| t \| (a) \, da + F(0) i(t, 0) + q\partial V(t) - q\partial V(t) E(t) - q\gamma E(t) \].

Choose \( F(a) = \frac{\beta S_0 V}{\gamma} e^{-\frac{\beta S_0 V}{\gamma}} \theta(\mu + \alpha(a), a) \, da \), \( q = \frac{\beta S_0}{\gamma} \). A direct calculation shows that \( F'(a) = -\frac{\beta S_0 V}{\gamma} + (\mu + \alpha(a)) F(a), F(0) = \frac{\beta S_0 V}{\gamma} \theta(0, a) \, da = R_{60} \lim_{a \to \infty} F(a) = 0 \). Therefore, \( \frac{dV_1(t)}{dt} = -\mu S(t) - \beta E(t) S(t) - \frac{\beta S_0 V}{\gamma} i(t, 0) \). Clearly, if \( R_{60} \leq 1 \), \( V_1'(t) \leq 0 \) holds and \( V_1'(t) = 0 \) implies that \( S(t) = S_0, i(t, a) = 0, E(t) = 0 \). Hence, the largest invariant subset of \( V_1(t) = 0 \) is the single \( W_1 = (S_0, 0, 0) \). Therefore, the global asymptotic stability of \( W_1 \) follows from LaSalle’s invariance principle. This completes the proof. □

Appendix B. Proof of Theorem 6

Proof. Linearizing system (25) at equilibrium \( W_0 \) we have

\[
\begin{align*}
\frac{dx_3(t)}{dt} &= -\mu x_3(t) - \beta_0 z_3(t), \\
\frac{dy_3(t)}{dt} + \frac{\partial y_3(t, a)}{\partial a} &= -\mu y_3(t) - \beta_0 y_3(t, a), \\
\frac{dz_3(t)}{dt} &= -\gamma z_3(t) + \theta V(0) \int_0^\infty y_3(t, a) \, da, \\
y_3(t, 0) &= \beta_0 z_3(t).
\end{align*}
\]
Let $x_3(t) = x_{31}e^{\lambda t}$, $y_3(t, a) = y_{31}(a)e^{\lambda t}$, $z_3(t) = z_{31}e^{\lambda t}$, we obtain the following eigenvalue problem:

$$
\begin{align*}
(\lambda + \mu) x_{31} &= -\beta S_0 z_{31}, \\
\frac{dy_{31}(a)}{da} &= -(\lambda + \mu + \alpha(a)) y_{31}(a), \\
(\lambda + \gamma) z_{31} &= \theta \tilde{V}(0) \int_{0}^{\infty} y_{31}(a) da, \\
y_{31}(0) &= \beta S_0 z_{31}.
\end{align*}
$$

If $\lambda = -\gamma$ or $\lambda = -\mu$, then $\lambda$ is a root which has negative real part. If $\lambda \neq -\gamma$ and $\lambda \neq -\mu$, then $y_{31}(0) \neq 0$. Integrating the second equation of (33) from 0 to $a$ we can obtain

$$
y_{31}(a) = y_{31}(0)e^{-\int_{0}^{a}(\lambda + \mu + \alpha(s)) ds}. \quad (34)
$$

It follows from the third equation of (33) that

$$
z_{31} = \frac{\theta \tilde{V}(0) \int_{0}^{\infty} y_{31}(a) da}{\lambda + \gamma}. \quad (35)
$$

Substituting (34) and (35) into the fourth equation of (33) yields the characteristic equation of the slow system at $W_0$:

$$
f_2(\lambda) = \frac{\beta \theta \tilde{V}(0) S_0 \int_{0}^{\infty} e^{-\int_{0}^{a}(\lambda + \mu + \alpha(s)) ds} da}{\lambda + \gamma} = 1, \quad (36)
$$

Obviously, $f_2(0) = \frac{\beta \theta \tilde{V}(0) S_0 \int_{0}^{\infty} \pi(a) da}{\lambda + \gamma} = \lim_{\lambda \to \infty} f_2(\lambda) = 0$. $f_2(\lambda) < 0$. Therefore, $f_2(\lambda)$ is a decreasing function. If $R_0 > 1$, due to the continuity and differentiability of $f_2(\lambda)$, there has a unique positive root. Accordingly, equilibrium $W_0$ is unstable when $R_0 > 1$. Assume that equilibrium $W_0$ is unstable when $R_0 < 1$. then Eq. (36) has at least one root $\lambda_3 = a_3 + ib_3$ satisfying $a_3 > 0$ thus $f_2(\lambda_3) = 1$. In this case, one has $|f_2(\lambda_3)| < \beta \theta \tilde{V}(0) S_0 \int_{0}^{\infty} e^{-\int_{0}^{a}(\lambda + \mu + \alpha(s)) ds} da = f(a_3) = R_0 < 1$. This leads to a contradiction. Therefore, equilibrium $W_0$ is locally asymptotically stable when $R_0 < 1$. This completes the proof. ∎

### Appendix C. Proof of Theorem 7

**Proof.** Let $\tilde{W}(\tilde{S}, \tilde{t}(a), \tilde{E})$ be any positive equilibrium of system (25). Linearizing the system (25) at equilibrium $\tilde{W}$ we have

$$
\begin{align*}
\frac{dx_4(t)}{dt} &= -(\mu + \beta \tilde{E}) x_4(t) - \beta \tilde{S} z_4(t), \\
\frac{dy_4(t,a)}{dt} &= -(\lambda + \alpha(a)) y_4(t,a), \\
\frac{dz_4(t)}{dt} &= \theta \int_{0}^{\infty} y_4(t,a) da \tilde{V}(\tilde{E})(1 - \tilde{E}) \\
&+ \theta \int_{0}^{\infty} \tilde{V}(\tilde{E})(1 - \tilde{E}) - \tilde{V}(\tilde{E}) z_4(t) - \gamma z_4(t), \\
y_{41}(0) &= \beta \tilde{E} z_4(t) + \beta \tilde{S} z_4(t).
\end{align*}
$$

Let $x_4(t) = x_{41}e^{\lambda t}$, $y_4(t, a) = y_{41}(a)e^{\lambda t}$, $z_4(t) = z_{41}e^{\lambda t}$, we obtain the following eigenvalue problem:

$$
\begin{align*}
(\lambda + \mu + \beta \tilde{E}) x_{41} &= -\beta \tilde{S} z_{41}, \\
\frac{dy_{41}(a)}{da} &= -(\lambda + \mu + \alpha(a)) y_{41}(a), \\
(\lambda + \gamma - \theta \int_{0}^{\infty} \tilde{V}(\tilde{E})(1 - \tilde{E}) - \tilde{V}(\tilde{E}) z_{41}) &= \theta \int_{0}^{\infty} y_{41}(a) da \tilde{V}(\tilde{E})(1 - \tilde{E}) \\
y_{41}(0) &= \beta \tilde{E} z_{41} + \beta \tilde{S} z_{41}.
\end{align*}
$$
Let the function $Q(E) = F(E) - E F'(E)$. Clearly, $Q'(E) = -E F''(E) = -E H''(E) > 0$. Thus, the following equation can be founded:

$$Q(E) > Q(0) = F(0) = \frac{m_{\beta_0}}{\theta} > 0, \quad 0 \leq E \leq 1.$$  \(\gamma - \theta F(\hat{V}(\hat{E})(1 - \hat{E}) - \hat{V}(\hat{E})) = \frac{E \hat{F}(E) - E \theta \hat{F}'(E)}{\hat{F}(E)} = \frac{\gamma \hat{Q}(E)}{\hat{F}(E)}.$$

Hence, we can rewrite the form of (38) as follows:

$$\begin{align*}
\begin{cases}
(\lambda + \mu + \beta \hat{E}) y_{41} = -\beta \hat{S} z_{41}, \\
\frac{d y_{41}(a)}{d a} = - (\lambda + \mu + \alpha(a)) y_{41}(a), \\
(\lambda + \frac{\beta \hat{E}}{\hat{F}(E)}) z_{41} = \theta \int_0^\infty y_{41}(a) da \hat{V}(\hat{E})(1 - \hat{E}) \\
y_{41}(0) = \beta \hat{E} x_{41} + \beta \hat{S} z_{41}.
\end{cases}
\end{align*}$$  \(\tag{39}\)

If $\lambda = -(\mu + \beta \hat{E})$ or $\lambda = -\frac{\gamma \hat{Q}(E)}{\hat{F}(E)}$, then $\lambda$ is a root which has negative real part. If $\lambda \neq -(\mu + \beta \hat{E})$ and $\lambda \neq -\frac{\gamma \hat{Q}(E)}{\hat{F}(E)}$, then $y_{41}(0) \neq 0$. We can get following equation from the first equation of (39) $x_{41} = -\frac{\beta \hat{S} z_{41}}{\lambda + \mu + \beta \hat{E}}$. Integrating the second equation of (39) from 0 to $a$ we can obtain $y_{41}(a) = y_{41}(0) e^{-\frac{\beta \hat{E}}{\hat{F}(E)} (\lambda + \mu + \alpha(a)) da}$. It follows from the third equation of (39) that $z_{41} = \frac{\theta \int_0^\infty y_{41}(a) da}{\lambda + \frac{\beta \hat{E}}{\hat{F}(E)}}$. Hence, the characteristic equation of system (25) at equilibrium $\hat{W}_1$ can be established as follows:

$$f_1(\lambda) = \frac{\beta \hat{S} (\lambda + \mu) \hat{V}(\hat{E})(1 - \hat{E}) \int_0^\infty e^{-\frac{\beta \hat{E}}{\hat{F}(E)} (\lambda + \mu + \alpha(s)) s} da}{\lambda + \frac{\beta \hat{E}}{\hat{F}(E)}} = 1.$$  \(\tag{40}\)

Now, we consider equilibrium $\hat{W}_1 (\hat{S}_1, \hat{I}_1(a), \hat{E}_1)$. Based on the definition and properties of $F(E)$, $G(E)$ and $Q(E)$, we have the following results: $Q(\hat{E}_1) = F(\hat{E}_1) - \hat{E}_1 F'(\hat{E}_1) < G(\hat{E}_1) - \hat{E}_1 G'(\hat{E}_1) = -\frac{1}{\theta_{11}}$. Hence, we have $f_3(0) = \frac{\beta \hat{S} \hat{V}(\hat{E}_1)(1 - \hat{E}_1) \int_0^\infty e^{-\frac{\beta \hat{E}}{\hat{F}(E)} (\lambda + \mu + \alpha(s)) s} da}{\lambda + \frac{\beta \hat{E}}{\hat{F}(E)}} = 1.$

At present, we obtain the inequality $f_3(0) > 1$, according to the expression of $f_3(\lambda)$, we also acquire $\lim_{\lambda \to \infty} f_3(\lambda) = 0$. Consequently, the characteristic equation of system (25) at equilibrium $\hat{W}_1$ at least has a unique positive part thanks to the continuity of $f_3(\lambda)$. In other words, equilibrium $\hat{W}_1$ is unstable. This completes the proof.  \(\Box\)

\section*{Appendix D. Proof of Theorem 8}

\textbf{Proof.} From (40), we can obtain the characteristic equation of system (25) at equilibrium $\hat{W}_2$ can be established as follows:

$$f_4(\lambda) = \frac{\beta \hat{S} (\lambda + \mu + \beta \hat{E}) \hat{V}(\hat{E}_2)(1 - \hat{E}_2) \int_0^\infty e^{-\frac{\beta \hat{E}}{\hat{F}(E)} (\lambda + \mu + \alpha(s)) s} da}{\lambda + \frac{\beta \hat{E}}{\hat{F}(E)}} = 1.$$  \(\tag{41}\)

Rewriting the characteristic equation with the following form:

$$\beta \hat{S} \hat{V}(\hat{E}_2)(1 - \hat{E}_2) \int_0^\infty e^{-\frac{\beta \hat{E}}{\hat{F}(E)} (\lambda + \mu + \alpha(s)) s} da = \frac{(\lambda + \mu + \beta \hat{E})^2}{\lambda + \mu + \beta \hat{E}}.$$  \(\tag{42}\)

Assume that equilibrium $\hat{W}_2$ is unstable when $R_0 < 1$, $H_M > 0$ and $\frac{\gamma \hat{Q}(E)}{\hat{F}(E)} \leq 1$. then the characteristic equation has at least one root $\lambda_4 = a_4 + i b_4$ satisfying $a_4 > 0$. In this case, we introduce some notations as follows:
LHS = $\beta S_0 \theta \dot{V}(\hat{E}_2) (1 - \hat{E}_2) \int_0^\infty e^{-\int_0^s (\lambda + \mu + \alpha(s))ds} ds a$.

RHS = $\frac{(\lambda + \mu + \beta \hat{E}_2) \int_0^\infty e^{-\int_0^s (\lambda + \mu + \alpha(s))ds} ds}{\lambda + \mu}$.

The characteristic root $\lambda_4$ is substituted into the LHS and RHS, we can get following result:

$LHS = \beta S_0 \theta \dot{V}(\hat{E}_2) (1 - \hat{E}_2) \int_0^\infty e^{-\int_0^s (\lambda + \mu + \alpha(s))ds} e^{-\alpha a}$

$\times [\cos(ab) - i \sin(ab)] da.$

$RHS = \left[ (a_4 + \mu + \beta \hat{E}_2) (a_4 + \mu) + b_2^2 a_2 \hat{E}_2 \right]^{a + \mu + b_4}.$

Thus, $Re(LHS) = \beta S_0 \theta \dot{V}(\hat{E}_2) (1 - \hat{E}_2) \int_0^\infty e^{-\int_0^s (\lambda + \mu + \alpha(s))ds} \cos(ab) da$.

From (31), we have $Re(LHS) \leq \gamma.$

$Re(RHS) = \left[ (a_4 + \mu + \beta \hat{E}_2) (a_4 + \mu) + b_2^2 a_2 \hat{E}_2 \right]^{a + \mu + b_4}.$

From the definition of $H(E)$ and $\hat{E}_2$ is the zero of $H(E)$, we further have $F(\hat{E}_2) = G(\hat{E}_2) = \frac{\beta \hat{E}_2}{\mu + \beta \hat{E}_2}$.

From $H'(E) < 0$ for all $0 < E \leq 1$, we get $H'(E)$ is a strictly monotone decreasing function in $[0,1].$ We assume $H_M = H(E^*), 0 < E^* < 1, \text{ then } 0 < E^* < \hat{E}_2 < 1$ and $H'(E^*) = 0$. Hence, $H'(\hat{E}_2) = F'(\hat{E}_2) = G'(\hat{E}_2) < 0.$ Namely, $F'(\hat{E}_2) < G'(\hat{E}_2).$ Based on the $\hat{E}_2$ is the zero of $H(E)$ and $H(E) = F(E) - G(E)$, we have $F(\hat{E}_2) = G(\hat{E}_2).$ Furthermore, $Q(\hat{E}_2) = F(\hat{E}_2) - \hat{E}_2 G(\hat{E}_2)$.

Hence, we have $Q(\hat{E}_2) > \frac{1}{\mu + \beta \hat{E}_2}.$

Thus, $Re(RHS) = \left[ (a_4 + \mu + \beta \hat{E}_2) (a_4 + \mu) + b_2^2 a_2 \hat{E}_2 \right]^{a + \mu + b_4}$.

When $\frac{\gamma}{\mu + \beta \hat{E}_2} = 1$, we directly have $Re(RHS) = a_4 + \mu + \beta \hat{E}_2 = \gamma$, which leads to a contradiction.

Let $\frac{\gamma}{\mu + \beta \hat{E}_2} \neq 1$. Define a function $f(x, y) = \frac{\beta \hat{E}_2 (x + \mu) (x + \mu + y^2) + \beta \hat{E}_2 y^2}{(x + \mu)^2 + y^2}$, where $(x, y) \in \mathbb{R}^2_+.$ We now calculate the minimum $f_{\text{min}}$ of $f(x, y)$ in $\mathbb{R}^2_+$. Calculating the partial derivative of $f(x, y)$ with respect to $x$ and $y$, by deducing in detail we can obtain

$$\frac{\partial f(x, y)}{\partial x} = \frac{\beta \hat{E}_2 (x + \mu) (x + \mu + y^2) - 2 \beta \hat{E}_2 \mu (1 - \frac{\gamma}{\mu + \beta \hat{E}_2}) x}{(x + \mu)^2 + y^2},$$

$$\frac{\partial f(x, y)}{\partial y} = \frac{2 \beta \hat{E}_2 \mu (1 - \frac{\gamma}{\mu + \beta \hat{E}_2}) x + 2 \beta \hat{E}_2 \mu^2 (1 - \frac{\gamma}{\mu + \beta \hat{E}_2}) y}{(x + \mu)^2 + y^2}.$$
We further have $\frac{\partial f(x, y)}{\partial x} = 0 \Leftrightarrow (x + \mu)y^2 - y^2 = 0$, $\frac{\partial f(x, y)}{\partial y} = 0 \Leftrightarrow (x + \mu)y = 0$. This shows that $f(x, y)$ has only a stationary point $(-\mu, 0)$ in $\mathbb{R}^2$, and this stationary point is not in the first quadrant. Thus, the minimum of $f(x, y)$ in $\mathbb{R}^2_+$ is reached at the boundary $\partial \mathbb{R}^2_+$. When $\frac{\gamma \mu}{\mu + \beta E_2} < 1$, we easily obtain that $\frac{\partial f(x, y)}{\partial y} > 0$ if $y = 0$
and $\frac{\partial f(x, y)}{\partial y} > 0$ if $x = 0$. Hence, we have $f_m = f(0, 0) = \frac{\beta E_2 \gamma \mu^2}{\mu^2 + \beta E_2} = \frac{\gamma \beta E_2}{\mu + \beta E_2}$. Furthermore,

$$\Re(\text{RHS}) > a_4 + \frac{\gamma \mu}{\mu + \beta E_2} + \frac{\beta E_2 (a_4 + \mu)(a_4 + \gamma \mu \frac{\beta E_2}{\mu + \beta E_2})}{(a_4 + \mu)^2 + (\gamma \mu)^2 + \beta E_2^2}$$

$$\geq \frac{\gamma \mu}{\mu + \beta E_2} + \frac{\beta E_2^2}{\mu + \beta E_2} = \gamma$$

is a contradiction. This completes the proof. □

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