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Global analysis of an environmental disease transmission model linking within-host and between-host dynamics

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Abstract

In this paper, a multi-scale mathematical model for environmentally transmitted diseases is proposed which couples the pathogen-immune interaction inside the human body with the disease transmission at the population level. The model is based on the nested approach that incorporates the infection-age-structured immunological dynamics into an epidemiological system structured by the chronological time, the infection age and the vaccination age. We conduct detailed analysis for both the within-host and between-host disease dynamics. Particularly, we derive the basic reproduction number R_0 for the between-host model and prove the uniform persistence of the system. Furthermore, using carefully constructed Lyapunov functions, we establish threshold-type results regarding the global dynamics of the between-host system: the disease-free equilibrium is globally asymptotically stable when $R_0 < 1$, and the endemic equilibrium is globally asymptotically stable when $R_0 > 1$. We explore the connection between the within-host and between-host dynamics through both mathematical analysis and numerical simulation. We show that the pathogen load and immune strength at the individual level contribute to the disease transmission and spread at the population level. We also find that, although the between-host transmission risk correlates positively with the within-host pathogen load, there is no simple monotonic relationship between the disease prevalence and the individual pathogen load.

MSC:

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Keywords

multi-scale modeling; cholera; uniform persistence; global stability

1. Introduction

Environmentally transmitted diseases, such as cholera, leptospirosis, toxoplasmosis, amebiasis, and typhoid fever, remain a significant public health burden at present. One of the

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well-known environmentally transmitted diseases is cholera, a severe waterborne infection caused by the bacterium *Vibrio cholerae*, which can spread rapidly through contaminated water and food. Frequent cholera outbreaks in recent years have led to serious threat to human health. According to the World Health Organization (WHO) [1], there were about 100,000 cases and more than 4,000 deaths in the Zimbabwe cholera outbreak during 2008–2009. Between 2010 and 2012, Haiti had more than 530,000 cholera cases and 7,000 related deaths. In 2017, there were 1,227,391 cholera cases and 5,654 deaths reported throughout the world [2]. Cholera is currently listed by WHO as one of the infectious diseases requiring priority prevention and intervention.

In order to better understand the disease mechanisms and to design more effective control strategies, many scholars [3–13] have been using mathematical models to study environmentally transmitted infections, cholera in particular. For example, Codeço [4] in 2001 proposed a compartmental cholera model by explicitly incorporating the environmental bacterial concentration into a standard SIR (susceptible-infected-recovered) formulation. Hartley et al. [5] in 2006 added a hyperinfectious state of the pathogens to Codeço's model and emphasized that freshly shed vibrios can have an infectivity hundreds of times higher than that of the environmental vibrios. Tien and Earn [10] considered both the direct and indirect transmission routes of waterborne infections in 2011. Wang and Liao [11] in 2012 developed a model with the incidence and bacterial dynamics represented by general functions. Shuai et al. [9] published a model of cholera transmission among human hosts with infection age in 2012. Lin, Xu and Tian [6,7] further investigated cholera transmission dynamics with the infection age of infectious individuals and the biological age of the pathogen in the environment and saturation-based incidence. These modeling studies are concerned with the epidemiology of the diseases and do not take into account the immunological dynamics.

Traditionally, immunology and epidemiology are regarded as two independent fields when modeling infectious diseases. For example, a viral dynamics model typically only considers the process of viral infection within the human body (see, e.g., [14,15]), while an epidemiological model is normally concerned with the disease transmission and spread at the population level. In such an epidemiological model, it is typically assumed that all infected persons are identical and have a uniform and constant pathogen load. This assumption is largely unrealistic as human individuals differ by age, gender, health conditions, and susceptibility and immunity levels [16], which would lead to varied pathogen loads and immune responses among different individuals. In fact, for many infectious diseases, the higher pathogen load inside the human body, the more serious damage to the immune system, and the greater ability of the disease to spread from person to person, and in turn, the higher possibility of between-host infection [18]. This process involves the coupled immuno-epidemiological dynamics. Martcheva et al. [19] summarized the importance of constructing immuno-epidemiological models: (1) Changes in immune dynamics can impact key factors associated with the spread of a disease, such as the incidence and the basic reproduction number; (2) The biological understanding of disease progression is more comprehensive and accurate based on data from both the population and individual levels; (3) For infectious diseases, such as dengue fever, the severity depends on

the strength of the antibody immune response; (4) The establishment and analysis of coupled models can further reveal the influence of the pathogen evolution on epidemic development.

In 2002, Gilchrist and Sasaki [20] introduced a nested model that links the virus infection inside the human body and the disease transmission among human hosts. Since then, many studies have integrated the within-host pathogen dynamics with the between-host transmission of infectious diseases. Particularly, Feng et al. [18,21] proposed a coupled ordinary differential equation (ODE) model to analyze the transmission of toxoplasma gondii, and found that even if the basic reproductive number of the epidemiological sub-model is lower than unity, the disease can still be transmitted between the hosts. Kostova et al. [22] embedded a host immune response model into an infectious disease network model, and found that even though the immune response clears every isolated virus infection in the body, the disease continues to spread among human individuals.

The nested modeling approach has been used in recent years to analyze the dynamics of *HIV*, *HBV*, *HCV* and many other chronic diseases as well as bacterial infections, and has generated many new results [19,23–27]. On the other hand, there have been relatively few studies on the coupled immuno-epidemiological modeling of cholera and other environmentally transmitted bacterial infections [12]. A possible reason is the complexity of the disease mechanism involved in the bacterial-immune interaction within the human body and the multiple transmission pathways among human hosts. Consequently, several fundamental questions regarding such bacterial infections remain unanswered at present; for example, how does the within-host bacterial dynamics affect the population-level reproduction number and prevalence, and what are the evolutionary and co-evolutionary consequences of the within-host pathogen dynamics?

In this paper, our aim is to investigate the immuno-epidemiological dynamics for environmentally transmitted bacterial infections, cholera in particular, and address the above questions by constructing and analyzing a nested disease model. At the within-host level, our immunological model describes the interaction between the bacterial growth and the host immune response inside the human body. At the between-host level, our epidemiological model represents multiple transmission pathways that include both the environment-to-human and human-to-human transmission routes, and is structured by the infection age and vaccination age. We then couple the two systems through the age-since-infection structure and through the use of between-host parameters that explicitly depend on the within-host pathogen load and immune strength.

The remainder of this paper is organized as follows. In Section 2, we present the details of our mathematical model. In Section 3, we analyze the Local dynamics of equilibria for the within-host and between-host systems. In particular, we obtain an explicit formula for the between-host basic reproduction number. In Section 4, by applying the persistence theory for infinite-dimensional systems, we show that the disease is uniformly persistent if the basic reproduction number is higher than unity. In Section 5, we study the global dynamics of our model and establish the global asymptotic stability properties for the disease-free equilibrium and the endemic equilibrium. We present numerical results, by Haiti cholera

outbreak data in 2010 to verify and fit our analytical predictions in Section 6, and conclude our paper with some discussion in Section 7.

2. Model formulation

We consider an environmentally transmitted bacterial infection. We first construct a dynamical system for the disease transmission among the human hosts. Let $S(t)$ denote the number of susceptible individuals at time t , $i(\tau, t)$ denote the density of infected individuals with infection age τ at time t , and $v(a, t)$ denote the density of the vaccinated individuals with vaccination age a at time t . Meanwhile, we let $B(t)$ represent the concentration of the pathogenic bacteria in the contaminated environment at time t . We assume that susceptible individuals are recruited at a constant rate Λ . These susceptible people become infected through two transmission routes: the indirect, environment-to-human transmission with a constant rate β_e , and the direct, human-to-human transmission with an infection-age-dependent rate $\beta_h(\tau)$. Meanwhile, susceptible individuals are vaccinated at a rate Ψ . Let $I(t) = \int_0^{+\infty} i(a, t) da$, and $V(t) = \int_0^{+\infty} v(a, t) da$ respectively, represent the total number of the infected and vaccinated individuals at time t . Infected individuals have an age-dependent, disease-induced death rate $\rho(\tau)$ and a recovery rate $\gamma_1(\tau)$. Vaccinated individuals have an immunity loss rate $\gamma_2(a)$ depending on the vaccination age a . In addition, all human individuals have a natural death rate μ_h . We also assume that the growth of the environmental bacterial concentration $B(t)$ is due to the shedding from the infected hosts, with an age-dependent shedding rate $\xi(\tau)$. Furthermore, the environmental bacteria have a natural removal rate δ .

Based on these assumptions, the between-host disease transmission dynamics are described by the following equations.

$$\begin{aligned} \frac{dS(t)}{dt} &= \Lambda - \mu_h S(t) - S(t) \int_0^\infty \beta_h(\tau) i(\tau, t) d\tau - \beta_e S(t) B(t) - \Psi S(t) + \int_0^\infty \gamma_2(a) \\ &\quad v(a, t) da, \\ \frac{\partial i(\tau, t)}{\partial \tau} + \frac{\partial i(\tau, t)}{\partial t} &= -(\mu_h + \gamma_1(\tau) + \rho(\tau)) i(\tau, t), \\ \frac{\partial v(a, t)}{\partial a} + \frac{\partial v(a, t)}{\partial t} &= -(\mu_h + \gamma_2(a)) v(a, t), \\ i(0, t) &= S(t) \int_0^\infty \beta_h(\tau) i(\tau, t) d\tau + \beta_e S(t) B(t), \\ v(0, t) &= \Psi S(t). \end{aligned} \quad (2.1)$$

Next, we consider the within-host pathogen dynamics. In general, such pathogenic bacteria can proliferate rapidly after entering the human body and release a large amount of exotoxin, causing damage to the human host. Meanwhile, the immune system of the human body would respond to the bacterial invasion and attempt to clear the pathogen. We let $P(\tau)$ denote the within-host concentration of the pathogenic bacteria, and $M(\tau)$ the concentration of host immune cells, at infection age τ . We assume that the growth of the bacteria inside the human body follows a logistic model with an intrinsic growth rate r_P and a capacity K . The bacteria are killed by the immune cells with a clearance rate d_P . Meanwhile, the immune cells are

stimulated by the invading pathogen at a rate b_M , become inactive at a rate d_M after interacting with the pathogen, and go through natural death at a rate μ_M .

Hence, the following dynamical system, structured by the age of infection, describes the interaction between the pathogenic bacteria and immune cells inside the human body.

$$\begin{aligned}\frac{dP(\tau)}{d\tau} &= r_P P(\tau) \left(1 - \frac{P(\tau)}{K}\right) - d_P M(\tau) P(\tau), \\ \frac{dM(\tau)}{d\tau} &= b_M P(\tau) - d_M M(\tau) P(\tau) - \mu_M M(\tau).\end{aligned}\quad (2.2)$$

A flowchart illustrating our between-host and within-host nested disease model is shown in Figure 1. We now connect the two systems (2.1) and (2.2) through the age-dependent parameters $\beta_h(\tau)$, $\gamma_1(\tau)$, $\rho(\tau)$ and $\xi(\tau)$.

First, $\beta_h(\tau)$ is the direct transmission rate between susceptible and infected individuals and it depends on the level of the pathogen within the infected host individual. We assume that

$$\beta_h(\tau) = \frac{\beta_1 P(\tau)}{P(\tau) + k_1},$$

where β_1 is the direct contact rate and k_1 is the half-saturating constant for the bacteria. Biologically, this representation implies that the transmission rate $\beta_h(\tau)$ would increase monotonically with the within-host pathogen load $P(\tau)$, but the increase of $\beta_h(\tau)$ would be slower than linear when $P(\tau)$ is high; i.e., following a saturating fashion.

Second, $\gamma_1(\tau)$ represents the recovery rate of infected persons. We assume that it is proportional to the strength of the host immune response, characterized by $M(\tau)$, while inversely proportional to the pathogen load $P(\tau)$ (subject to saturation). We thus have

$$\gamma_1(\tau) = \frac{c_1 M(\tau)}{P(\tau) + k_1},$$

where c_1 is a correlation constant.

Next, $\rho(\tau)$ is the death rate caused by the disease, and we assume that it depends on the within-host pathogen load in a similar manner as $\beta_h(\tau)$ does:

$$\rho(\tau) = \frac{\rho P(\tau)}{P(\tau) + k_1},$$

where ρ is a scaling constant.

In addition, the host shedding rate $\xi(\tau)$ is assumed to take the form

$$\xi(\tau) = \xi_1 P(\tau),$$

where ξ_1 is a proportional constant.

We provide the following initial conditions to the coupled system (2.1) and (2.2):

$$S(0) = S_0, \quad i(\tau, 0) = i_0(\tau), \quad v(a, 0) = v_0(a), \quad B(0) = B_0, \quad P(0) = P_0, \quad M(0) = M_0.$$

For biological feasibility, we make the following assumption regarding the model parameters.

Assumption 2.1. The parameters and functions in system (2.1) satisfy the following conditions

1. All the parameters are positive;
2. The functions $\beta_H(\tau)$, $\rho(\tau)$, $\xi(\tau)$, $\gamma_1(\tau)$, $\gamma_2(a) \in L^\infty(0, \infty)$ are uniformly continuous and bounded.
3. The function $i_0(\tau)$, $v_0(a)$ is non-negative and integrable in $L^\infty(0, \infty)$.

Let $X_0 = R_+ \times L_+^1(0, \infty) \times L_+^1(0, \infty) \times R_+$. By using the semigroup theory and the methods in [16,17], we can show that system (2.1) is well-posed in the positive cone X_0 provided that Assumption 2.1 holds. Thus, we can define a solution semiflow

$$\Phi: (t, S_0, i_0(\cdot), v_0(\cdot), B_0) = (S(t), i(a, t), v(a, t), B(t)),$$

$$R_+ \times L_+^1 \times L_+^1 \times R_+ \rightarrow R_+ \times L_+^1 \times L_+^1 \times R_+$$

for $t \in R_+$ and $(S_0, i_0(\cdot), v_0(\cdot), B_0) \in R_+ \times L_+^1 \times L_+^1 \times R_+$.

Let $N(t) = S(t) + I(t) + V(t)$. It follows from (2.1) that

$$\frac{dN(t)}{dt} \leq \Lambda - \mu_h N(t),$$

which implies that $\limsup_{t \rightarrow \infty} N(t) \leq \frac{\Lambda}{\mu_h}$ and $\limsup_{t \rightarrow \infty} B(t) \leq \frac{\Lambda \int_0^\infty \xi(\tau) d\tau}{\mu_h \delta} \stackrel{\text{def}}{=} \tilde{\delta}$. Let

$$\Omega = \left\{ (S(t), i(\tau, t), v(a, t), B(t)) \in X_0 : S(t) + I(t) + V(t) \leq \frac{\Lambda}{\mu_h}, B(t) \leq \tilde{\delta} \right\}.$$

It is straightforward to show that Ω is positively invariant and attracts all positive solutions in system (2.1). In what follows, we restrict our attention to solutions of (2.1) with the initial conditions and Assumption 2.1.

3. Equilibrium analysis

We first conduct an equilibrium analysis of the within-host dynamics. Let (P^*, M^*) denote an equilibrium of system (2.2). we have

$$\begin{aligned} r_P P^* \left(1 - \frac{P^*}{K}\right) - d_P M^* P^* &= 0, \\ b_M P^* - d_M P^* M^* - \mu_M M^* &= 0. \end{aligned} \quad (3.1)$$

From the second equation above, we obtain

$$M^* = \frac{b_M P^*}{d_M P^* + \mu_M}. \quad (3.2)$$

Substituting (3.2) into the first equation of (3.1), we find either $P^* = 0$, or

$$\frac{r_P d_M P^{*2}}{K} + \left(\frac{r_P \mu_M}{K} + b_M d_P - r_P d_M\right) P^* - r_P \mu_M = 0.$$

The above quadratic equation yields a unique positive root

$$P^* = \frac{\sqrt{\left(\frac{\mu_M}{K} - d_M + \frac{b_M d_P}{r_P}\right)^2 + \frac{4d_M \mu_M}{K}} - \left(\frac{\mu_M}{K} - d_M + \frac{b_M d_P}{r_P}\right)}{\frac{2d_M}{K}}. \quad (3.3)$$

Hence, system (2.2) has two equilibria: one is the trivial equilibrium $e^0 = (0, 0)$, and the other is the positive equilibrium $e^* = (P^*, M^*)$ with P^* given in (3.3) and M^* given in (3.2).

Note that

$$\Omega_0 = \left\{ (P, M) \in \mathbb{R}_+^2 : P \leq K, M \leq \frac{b_M}{\mu_M} K \right\}$$

is a biologically feasible domain for system (2.2) and one can choose $\phi(P, M) = \frac{1}{P}$ such that

$$\operatorname{div}(\phi \dot{P}, \phi \dot{M}) = \frac{\partial(\phi \dot{P})}{\partial P} + \frac{\partial(\phi \dot{M})}{\partial M} = -\frac{r_P}{K} - d_M - \frac{\mu_M}{P} < 0$$

in $\mathbb{R}_+^2$. Hence, system (2.2) has no non-constant periodic solution in $\mathbb{R}_+^2$ based on the Bendixson-Dulac theorem. Thereby for any initial point $x_0 = (P_0, M_0) \in \Omega_0$, the semi-orbit $\Gamma^+(x_0)$ either converges to e^0 or converges to e^* . Obviously, if $P_0 = 0$, $\Gamma^+(x_0)$ will converge to e^0 . However, for $P_0 > 0$, if $\Gamma^+(x_0)$ converges to e^0 , then

$$\dot{P} = P(\tau) \left(r_P - \frac{r_P P(\tau)}{K} - d_P M(\tau) \right) > 0,$$

for sufficient large τ , which is a contradiction. Consequently, ε^0 attracts all points on the set $\{(P, M) \in \Gamma_0 : P = 0\}$ and ε^* attracts all points on the set $\{(P, M) \in \Gamma_0 : P > 0\}$.

In addition, one can easily obtain

$$\frac{\partial P^*}{\partial r_P} = \frac{K b_M d_P}{2 d_M r_P^2} \left(1 - \frac{\frac{\mu_M}{K} - d_M + \frac{b_M d_P}{r_P}}{\sqrt{\left(\frac{\mu_M}{K} - d_M + \frac{b_M d_P}{r_P}\right)^2 + \frac{4 d_M \mu_M}{K}}} \right) > 0 \quad (3.4)$$

from (3.3) and, by (3.2),

$$\frac{\partial M^*}{\partial r_P} = \frac{\partial M^*}{\partial P^*} \frac{\partial P^*}{\partial r_P} = \frac{b_M \mu_M}{(d_M P^* + \mu_M)^2} \frac{\partial P^*}{\partial r_P} > 0. \quad (3.5)$$

Hence, the pathogen load and the immune strength at the positive steady state will both increase with the bacterial growth rate, r_P .

Next, we study the equilibrium of the between-host system (2.1). Here we first introduce the following notations

$$\pi_1(\tau) = e^{-\int_0^\tau \theta(\sigma) d\sigma} \text{ with } \theta(\tau) = \mu_h + \gamma_1(\tau) + \rho(\tau).$$

Obviously, system (2.1) has a disease-free equilibrium $E^0 = (S^0, 0, v^0(a), 0)$, where

$$S^0 = \frac{\Lambda}{\mu_h + \Psi - \Psi D(0)}, \quad v^0(a) = \Psi S^0 \pi_2(a),$$

with

$$\pi_2(a) = e^{-\mu_h a - \int_0^a \gamma_2(s) ds}, \quad D(0) = \int_0^\infty \gamma_2(s) \pi_2(s) ds.$$

The endemic equilibrium of system (2.1) satisfies the following equations

$$\begin{aligned} \Lambda - \mu_h S^* - S^* \int_0^\infty \beta_h(\tau) i^*(\tau) d\tau - \beta_e S^* B^* - \Psi S^* + \int_0^\infty \gamma_2(a) v^*(a) da &= 0, \\ \frac{di^*(\tau)}{d\tau} &= -(\mu_h + \gamma_1(\tau) + \rho(\tau)) i^*(\tau), \quad i^*(0) = S^* \int_0^\infty \beta_h(\tau) i^*(\tau) d\tau + \beta_e S^* B^*, \\ \frac{dv^*(a)}{da} &= -(\mu_h + \gamma_2(a)) v^*(a), \quad v^*(0) = \Psi S^*, \\ \int_0^\infty \xi(\tau) i^*(\tau) d\tau - \delta B^* &= 0, \end{aligned} \quad (3.6)$$

From (3.6), we obtain

$$i^*(\tau) = i^*(0)e^{-\mu_1\tau - \int_0^\tau (\gamma_1(\sigma) + \rho(\sigma))d\sigma} = i^*(0)e^{-\int_0^\tau \theta(\sigma)d\sigma} = i^*(0)\pi_1(\tau),$$

$$B^* = \frac{1}{\delta} \int_0^\infty \xi(\tau)i^*(\tau)d\tau = \frac{1}{\delta} \int_0^\infty \xi(\tau)i^*(0)\pi_1(\tau)d\tau,$$

$$v^*(a) = v^*(0)\pi_2(a) = \Psi S^*\pi_2(a).$$

Substitute into $i^*(0) = S^* \int_0^\infty \beta_h(\tau)i^*(\tau)d\tau + \beta_e S^* B^*$ to obtain

$$\begin{aligned} i^*(0) &= S^* \int_0^\infty \beta_h(\tau)i^*(\tau)d\tau + \beta_e S^* B^*, \\ &= S^* \int_0^\infty \beta_h(\tau)i^*(0)\pi_1(\tau)d\tau + S^* \frac{\beta_e}{\delta} \int_0^\infty \xi(\tau)i^*(0)\pi_1(\tau)d\tau. \end{aligned}$$

Dividing $i^*(0)$ from both sides of this equation, we have

$$S^* = \frac{1}{\int_0^\infty \beta_h(\tau)\pi_1(\tau)d\tau + \frac{\beta_e}{\delta} \int_0^\infty \xi(\tau)\pi_1(\tau)d\tau}. \quad (3.7)$$

Let

$$R_0 = S^0 \int_0^\infty \beta_h(\tau)\pi_1(\tau)d\tau + S^0 \frac{\beta_e}{\delta} \int_0^\infty \xi(\tau)\pi_1(\tau)d\tau. \quad (3.8)$$

Using the first equation of system (3.6), we can rewrite $i^*(0)$ as

$$\begin{aligned} i^*(0) &= \Lambda - \mu_h S^* - \Psi S^* + \Psi S^* D(0), \\ &= \Lambda - (\mu_h + \Psi - \Psi D(0))S^*, \\ &= \Lambda \left(1 - \frac{1}{R_0}\right). \end{aligned}$$

Thus, R_0 can be regarded as the basic reproduction number [28] in system (2.1). Clearly, R_0 is shaped by both the between-host and within-host factors; in particular, the between-host basic reproduction number depends on the within-host pathogen load and immune strength.

Using the expression (3.7) and (3.8), we obtain

$$S^* = \frac{S^0}{R_0}.$$

Therefore, the positive endemic equilibrium of the system (2.1) is given by

$$E^* = \left(\frac{S^0}{R_0}, A \left(1 - \frac{1}{R_0} \right) \pi_1(\tau), \frac{1}{\delta} \int_0^\infty \xi(\tau) i^*(0) \pi_1(\tau) d\tau, \Psi S^* \pi_2(a) \right)$$

and it exists if and only if $R_0 > 1$.

In the remaining part of this section, we shall investigate the local stability of the equilibria in system (2.1). We establish the following results

Theorem 3.1. (i) *The disease-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$ and it is unstable if $R_0 > 1$. (ii) If $R_0 > 1$, then the endemic equilibrium E^* is locally asymptotically stable.*

Proof. Linearizing system (2.1) around an equilibrium $(S^*, I^*(\tau), v^*(a), B^*)$. Here by applying the approach similar to [29] (see Appendix B in [29]), we can show that the linear stability of the system (2.1) can be determined by the eigenvalues of its linearized system. We introduce the following notations for the perturbations $S(t) = x(t) + S^*$, $I(\tau, t) = y(\tau, t) + I^*(\tau)$, $v(a, t) = z(a, t) + v^*$, $B(t) = w(t) + B^*$. We obtain a perturbation linear system and consider the eigenvalue problem for the linear system. For simplicity, we denote the time-independent perturbations corresponding to an eigenvalue λ using the same letters. Thus, we have the following eigenvalue problem

$$\begin{aligned} & \left(\lambda + \mu_h + \int_0^\infty \beta_h(\tau) i^*(\tau) d\tau + \beta B^* + \Psi \right) x = - S^* \int_0^\infty \beta_h(\tau) y(\tau) d\tau - \beta_e S^* w \\ & + \int_0^\infty \gamma_2(a) z(a) da, \\ & \frac{dy(\tau)}{d\tau} = - (\lambda + \theta(a)) y(\tau), \quad y(0) = x \left(\int_0^\infty \beta_h(\tau) i^*(\tau) d\tau + \beta_e B^* \right) + S^* \int_0^\infty \beta_h(\tau) \\ & y(\tau) d\tau + \beta_e S^* w, \\ & \frac{dz(a)}{da} = - (\lambda + \mu_h + \gamma_2(a)) z(a), \quad z(0) = \Psi x, \\ & (\lambda + \delta) w = \int_0^\infty \xi y(a) da. \end{aligned} \quad (3.9)$$

Now we first discuss the local stability of the disease-free equilibrium $(S^0, 0, v^0(a), 0)$. Solving the differential equation (3.9), we obtain the expressions of w , $y(\tau)$ and $z(a)$. Substituting for w , $y(\tau)$ and $z(a)$ in the equation for x , expressing x in terms of $y(0)$, and replacing $y(0)$ in the equation for $y(0)$, we obtain the following characteristic equation of $\mathcal{G}(\lambda) = 1$, where

$$\mathcal{G}(\lambda) = S^0 \int_0^\infty \beta_h(\tau) \pi_1(\tau) e^{-\lambda \tau} d\tau + S^0 \frac{\beta_e}{\lambda + \delta} \int_0^\infty \xi(\tau) \pi_2(\tau) e^{-\lambda \tau} d\tau. \quad (3.10)$$

Assume that λ has the real part $\operatorname{Re} \lambda < 0$. For such λ , we have

$$|\mathcal{G}(\lambda)| \leq |\mathcal{G}(\operatorname{Re} \lambda)| \leq \mathcal{G}(0) < 1.$$

Hence, the equations $\mathcal{G}(\lambda) = 1$ does not have a solution with nonnegative real part and the disease-free equilibrium $(S^0, 0, \nu^0(a), 0)$ is locally asymptotically stable.

Now we turn to the local stability of the endemic equilibrium E^* . Similarly, by direct computation, we obtain the following characteristic equation for λ : $\mathcal{H}(\lambda) = 1$, where

$$\begin{aligned} \mathcal{H}(\lambda) = & \frac{(\lambda + \mu_h + \Psi(1 - D(0))S^*}{\lambda + \mu_h + \int_0^\infty \beta_h(\tau)i^*(\tau)d\tau + \beta_e B^* + \Psi(1 - D(0))} \\ & \times \left(\int_0^\infty \beta_h(\tau)\pi_1(\tau)e^{-\lambda\tau}d\tau + \frac{\beta_e}{\lambda + \delta} \int_0^\infty \xi(\tau)\pi_2(\tau)e^{-\lambda\tau}d\tau \right). \end{aligned} \quad (3.11)$$

It is assumed that λ in Eq. (3.11) with the real part satisfies $\operatorname{Re} \lambda < 0$. Notice that $\int_0^\infty \beta_h(\tau)i^*(\tau)d\tau + \beta_e B^* > 0$. Thus, we have

$$\left| \frac{\lambda + \mu_h + \Psi(1 - D(0))}{\lambda + \mu_h + \int_0^\infty \beta_h(\tau)i^*(\tau)d\tau + \beta_e B^* + \Psi(1 - D(0))} \right| < 1.$$

Hence, for λ with the real part satisfies $\operatorname{Re} \lambda < 0$, we have

$$\begin{aligned} |\mathcal{H}(\lambda)| & \leq \left| \frac{\lambda + \mu_h + \Psi(1 - D(0))}{\lambda + \mu_h + \int_0^\infty \beta_h(\tau)i^*(\tau)d\tau + \beta_e B^* + \Psi(1 - D(0))} \right| \\ & \times \left| \left(\int_0^\infty \beta_h(\tau)\pi_1(\tau)e^{-\lambda\tau}d\tau + \frac{\beta_e}{\lambda + \delta} \int_0^\infty \xi(\tau)\pi_2(\tau)e^{-\lambda\tau}d\tau \right) \right| \\ & \leq S^* \left(\int_0^\infty \beta_h(\tau)\pi_1(\tau)e^{-\operatorname{Re} \lambda \tau}d\tau + \frac{\beta_e}{\operatorname{Re} \lambda + \delta} \int_0^\infty \xi(\tau)\pi_2(\tau)e^{-\operatorname{Re} \lambda \tau}d\tau \right) \\ & \leq \frac{S^0}{R_0} \left(\int_0^\infty \beta_h(\tau)\pi_1(\tau)d\tau + \frac{\beta_e}{\delta} \int_0^\infty \xi(\tau)\pi_2(\tau)d\tau \right) = 1. \end{aligned}$$

Hence, the equations $\mathcal{H}(\lambda) = 1$ does not have a solution with nonnegative real part $\operatorname{Re} \lambda \geq 0$ and the endemic equilibrium E^* is locally asymptotically stable. $\square$

4. Disease persistence

In this section, we shall investigate disease persistence in system (2.1) by using the theory and methods developed in [29,30].

Let $\tilde{I}(t) = \tilde{I}(0, t)$. Integrating the second equation of the system (2.1) along the characteristic line $t - \tau$, we have

$$i(\tau, t) = \begin{cases} \hat{i}(t - \tau)\pi_1(\tau), & t \geq \tau \geq 0, \\ i_0(\tau - t) \frac{\pi_1(\tau)}{\pi_1(\tau - t)}, & \tau \geq t \geq 0. \end{cases} \quad (4.1)$$

Similarly, integrating the vaccinated individuals equation in system (2.1) along the characteristic lines, we have

$$v(a, t) = \begin{cases} \psi S(t-a)\pi_2(a), & t > a, \\ v_0(a-t)\frac{\pi_2(a)}{\pi_2(a-t)}, & t < a. \end{cases} \quad (4.2)$$

Thus, the boundary condition of system (2.1) can be rewritten as the following,

$$\begin{aligned} \hat{i}(t) = & \beta_e S(t)B(t) + S(t) \left(\int_0^t \beta_h(\tau)\pi_1(\tau)\hat{i}(t-\tau)d\tau + \int_t^\infty \beta_h(\tau)i_0(\tau-t) \right. \\ & \left. \frac{\pi_1(\tau)}{\pi_1(\tau-t)}d\tau \right). \end{aligned} \quad (4.3)$$

Now we prove the uniformly weakly persistence for system (2.1).

Proposition 4.1. *If $R_0 > 1$, for all initial conditions that belong to X_0 in system (2.1), there exists a positive number ε such that*

$$\limsup_{t \rightarrow \infty} \int_0^\infty \beta_h(\tau)i(\tau, t)d\tau + \beta_e B(t) \geq \varepsilon.$$

Proof. By way of contradiction, assume that for all initial conditions that belong to X_0 , there exists an $\varepsilon > 0$ such that $(S(t), i(\cdot, t), v(\cdot, t), B(t)) \in X_0$ in system (2.1) with $\limsup_{t \rightarrow \infty} \int_0^\infty \beta_h(\tau)i(\tau, t)d\tau + \beta_e B(t) \leq \frac{\varepsilon}{2}$. Thus, there exists $t_0 \in R_+$ such that $\limsup_{t \rightarrow \infty} \int_0^\infty \beta_h(\tau)i(\tau, t)d\tau + \beta_e B(t) \leq \varepsilon$ for $t \geq t_0$. Without loss of generality, it is assumed that $\limsup_{t \rightarrow \infty} \int_0^\infty \beta_h(\tau)i(\tau, t)d\tau + \beta_e B(t) \leq \varepsilon$ for $t \geq 0$. Furthermore, from the first equation of system (2.1), choosing a sequence $\{t_n\}$ such that $t_n \rightarrow \infty$, and using the expression (4.2), we have

$$\frac{dS(t_n)}{dt} \geq \Lambda - \mu_h S(t_n) - \varepsilon S(t_n) - \Psi S(t_n) + \int_0^{t_n} \gamma_2(a)\Psi S(t_n-a)\pi_2(a)da. \quad (4.4)$$

Using Fluctuation Lemma [31], as $n \rightarrow \infty$, $S(t_n) \rightarrow \inf_{t \rightarrow \infty} S(t)$, and $\frac{dS(t_n)}{dt} \rightarrow 0$, we obtain

$$\limsup_{t \rightarrow \infty} S(t) \geq \liminf_{t \rightarrow \infty} S(t) \geq \frac{\Lambda}{\mu_h + \varepsilon + \Psi(1 - D(0))}.$$

Using the inequality above, we can obtain from equation (4.3) that

$$\hat{i}(t) \geq \frac{\Lambda}{\mu_h + \varepsilon + \Psi(1 - D(0))} \left(\beta_e B(t) + \int_0^\infty \beta_h(\tau)\pi_1(\tau)i(\tau, t)d\tau \right).$$

Now, we apply expression (4.1) to obtain the following system of inequalities in $\hat{i}(t)$ and $B(t)$

$$\begin{aligned}\hat{i}(t) &\geq \frac{\Lambda}{\mu_h + \varepsilon + \Psi(1 - D(0))} \left(\beta_e B(t) + \int_0^t \beta_h(\tau) \pi_1(\tau) \hat{i}(t - \tau) d\tau \right) \\ \frac{dB(t)}{dt} &\geq \int_0^t \xi(\tau) \hat{i}(t - \tau) d\tau - \delta B(t).\end{aligned}\quad (4.5)$$

Taking Laplace transform in both sides of (4.5). Since all functions above are bounded, their Laplace transforms exist for $\lambda > 0$. We denote by $\mathcal{L}(\hat{i})$ the Laplace transform of $\hat{i}(t)$ and by $\mathcal{L}(B)$ the Laplace transform of $B(t)$. Thus, we have

$$\begin{aligned}\mathcal{L}(\hat{i}) &\geq \frac{\Lambda}{\mu_h + \varepsilon + \Psi(1 - D(0))} \left(\beta_e \mathcal{L}(B) + \mathcal{L}(\hat{i}) \int_0^\infty \beta_h(\tau) \pi_1(\tau) d\tau \right) \\ \lambda \mathcal{L}(B) - B(0) &\geq \mathcal{L}(\hat{i}) \int_0^\infty \xi(\tau) d\tau - \delta \mathcal{L}(B).\end{aligned}\quad (4.6)$$

In Eq. (4.6), eliminating $\mathcal{L}(B)$, we obtain

$$\begin{aligned}-\frac{\Lambda}{\mu_h + \varepsilon + \Psi(1 - D(0))} \frac{\beta_e}{\lambda + \delta} B(0) &\geq \left[\frac{\Lambda}{\mu_h + \varepsilon + \Psi(1 - D(0))} \left(\frac{\beta_e}{\lambda + \delta} \int_0^\infty \xi(\tau) d\tau \right. \right. \\ &\quad \left. \left. + \int_0^\infty \beta_h(\tau) \pi_1(\tau) d\tau - 1 \right) \mathcal{L}(\hat{i}) \right].\end{aligned}\quad (4.7)$$

The above inequality (4.7) should hold for the given $\varepsilon \approx 0$ and for any $\lambda > 0$. But it is impossible since for $\varepsilon \approx 0$ and $\lambda \approx 0$, the coefficient in front of $\mathcal{L}(\hat{i})$ on the right-hand side is positive for $R_0 > 1$, while the term on the left-hand side is negative. This is a contradiction from the assumption that

$$\limsup_{t \rightarrow \infty} \int_0^\infty \beta_h(\tau) i(\tau, t) d\tau + \beta_e B(t) < \varepsilon.$$

Therefore, there exist $\varepsilon > 0$ such that for any initial condition in X_0 , we have

$$\limsup_{t \rightarrow \infty} \int_0^\infty \beta_h(\tau) i(\tau, t) d\tau + \beta_e B(t) \geq \varepsilon.$$

It remains to be seen that each of the components is bounded below. The inequality (4.5) implies that $\limsup_{t \rightarrow \infty} \hat{i}(t) \geq \frac{\Lambda \varepsilon}{\mu_h + \varepsilon + \Psi(1 - D(0))}$. Hence, using the expression (4.1), we have

$$\limsup_{t \rightarrow \infty} \int_0^\infty \xi(\tau) i(\tau, t) d\tau \geq \frac{\Lambda \varepsilon}{\mu_h + \varepsilon + \Psi(1 - D(0))} \int_0^\infty \xi(\tau) \pi_1(\tau) d\tau$$

In addition, the differential equation for $B(t)$ can be rewritten in the following form

$$\frac{dB(t)}{dt} \geq \frac{\Lambda \varepsilon}{\mu_h + \varepsilon + \Psi(1 - D(0))} \int_0^t \xi(\tau) \pi_1(\tau) d\tau - \delta B(t).$$

Similarly, using Fluctuation Lemma [31], we can obtain $B^\infty \geq \frac{\Lambda \varepsilon}{\delta(\mu_h + \varepsilon + \Psi(1 - D(0)))}$. Using the expression (4.2), we have

$$\int_0^\infty \xi(\tau) v(a, t) da = \int_0^t \gamma_2(a) \Psi S(t-a) \pi_2(a) da + \int_t^\infty v_0(a-t) \frac{\pi_2(a)}{\pi_2(a-t)} da.$$

Taking limit inferior on both sides of the above, we have

$$\limsup_{t \rightarrow \infty} \int_0^\infty \xi(\tau) v(a, t) da \geq \Psi \liminf_{t \rightarrow \infty} S(t) \int_0^\infty \gamma_2(a) \pi_2(a) da.$$

This completes the proof. $\square$

Proposition 4.2. *If $R_0 > 1$, then there exists a compact subset M_0 of X_0 , which is the global attractor for the solution semiflow of system (2.1). Moreover, A is invariant under the solution semiflow Φ , that is $\Phi(t, x_0) \in M_0$, for every $x_0 \in M_0$, $\forall t \geq 0$.*

Proof. To establish this result, we will apply Lemma 3.1.3 and Theorem 3.4.6 in [32]. These methods and techniques have been recently employed in [29]. To do so, we split the solution semiflow into two components. For any initial condition $x_0 \in X_0$, we let $\Phi(t, x_0) = \hat{\Phi}(t, x_0) + \tilde{\Phi}(t, x_0)$. In such a way, we need to prove the following claim:

1. $\hat{\Phi}(t, x_0) \rightarrow 0$ as $t \rightarrow \infty$ for every $x_0 \in X_0$;
2. For a fixed t and any bounded set M_0 in X_0 , the set $\{\Phi(t, x_0) : x_0 \in M_0\}$ is precompact.

Note that the two components of the semiflow in system (2.1) are, respectively, defined as follows:

$$\begin{aligned} \hat{\Phi}(t, S_0, i_0(\cdot), v_0(\cdot), B_0) &= (0, \hat{i}(\cdot, t), \hat{v}(\cdot, t), 0), \\ \tilde{\Phi}(t, S_0, i_0(\cdot), v_0(\cdot), B_0) &= (\tilde{S}(t), \tilde{i}(\cdot, t), \tilde{v}(\cdot, t), \tilde{B}(t)), \end{aligned} \quad (4.8)$$

where

$$\hat{i}(\tau, t) = \begin{cases} 0, & \text{for } 0 \leq \tau \leq t, \\ \hat{i}_0(\tau-t) \frac{\pi_1(\tau)}{\pi_1(\tau-t)}, & \text{for } t < \tau, \end{cases} \quad (4.9)$$

and

$$\tilde{i}(\tau, t) = \begin{cases} \hat{i}(t - \tau)\pi_1(\tau), & \text{for } 0 \leq \tau \leq t, \\ 0 & \text{for } t < \tau. \end{cases} \quad (4.10)$$

$$\hat{v}(a, t) = \begin{cases} 0, & \text{for } 0 \leq a \leq t, \\ v_0(a - t)\frac{\pi_2(a)}{\pi_2(a - t)}, & \text{for } t < a, \end{cases} \quad (4.11)$$

and

$$\tilde{v}(a, t) = \begin{cases} \Psi S(t - a)\pi_2(\tau), & \text{for } 0 \leq a \leq t, \\ 0 & \text{for } t < a. \end{cases} \quad (4.12)$$

Now we show that the first claim above holds. In fact, it is easy to know that $\hat{i}$, $\hat{v}$, $\tilde{i}$, and $\tilde{v}$ are nonnegative. It follows from (4.9) and (4.11) that

$$\begin{aligned} \|\hat{\Phi}(t, x_0)\|_{X_0} &= \|\hat{i}(t, \cdot)\|_{L^1} + \|\hat{v}(t, \cdot)\|_{L^1} \\ &= \int_t^\infty \hat{i}_0(\tau - t)\frac{\pi_1(\tau)}{\pi_1(\tau - t)}d\tau + \int_t^\infty v_0(a - t)\frac{\pi_2(a)}{\pi_2(a - t)}da \\ &= \int_0^\infty \hat{i}_0(\tau)\frac{\pi_1(\tau + t)}{\pi_1(\tau)}d\tau + \int_0^\infty v_0(a)\frac{\pi_2(a + t)}{\pi_2(a)}da \\ &\leq e^{-\mu h t}(\|\hat{i}_0\|_{L^1} + \|v_0\|_{L^1}) \rightarrow 0 \quad \text{as } t \rightarrow \infty. \end{aligned} \quad (4.13)$$

Next we need to prove the second claim. By our previous the defined set $\Omega \subset X_0$, it is easy to obtain that the family $\{\tilde{\Phi}(t, x_0) : x_0 \in X_0, t - \text{fixed}\} \in X_0$ is bounded. To show the compactness, we need to show the remaining conditions, which are done by using the Fréchet-Kolmogorov theorem to show the compactness in $L^1(0, \infty)$ (see [33]).

Since $\int_0^\infty \tilde{i}(\tau, t)d\tau + \int_0^\infty \tilde{v}(a, t)da = 0$, the third condition is trivial in Fréchet-Kolmogorov theorem. Now we only need to show the following relations hold

$$\lim_{h \rightarrow 0+} \int_0^\infty |\tilde{i}(\tau + h, t) - \tilde{i}(\tau, t)|d\tau = 0, \quad \text{uniformly in some bounded set } \Omega_0 \subset X_0;$$

$$\lim_{h \rightarrow 0+} \int_0^\infty |\tilde{v}(a + h, t) - \tilde{v}(a, t)|da = 0, \quad \text{uniformly in some bounded set } \Omega_0 \subset X_0.$$

In fact, notice that

$$\tilde{i}(\tau, t) = \begin{cases} \hat{i}(t - \tau)\pi_1(\tau), & \text{for } 0 \leq \tau \leq t, \\ 0 & \text{for } t < \tau, \end{cases} \quad (4.14)$$

where

$$\hat{i}(t) = \beta_e S(t)B(t) + S(t) \int_0^t \beta_h(\tau)\pi_1(\tau)\hat{i}(t-\tau)d\tau. \quad (4.15)$$

From the previous analysis, we know that $S(t)$, $B(t)$ are bounded. Thus, $\hat{i}(t)$ is bounded for any $x_0 \in X_0$. From Eq. (4.15), it can obtain that $\hat{i}(t)$ satisfies the following inequality

$$\hat{i}(t) \leq c_1 \int_0^t \hat{i}(t-\tau)d\tau + c_0,$$

where c_0, c_1 are some constants that depend on the bounded of the parameters and the bounds of solution in system. By using Gronwall inequality, we obtain that $\hat{i}(t) \leq c_0 e^{c_1 t}$. By differentiate (4.15), we have

$$\begin{aligned} \frac{d\hat{i}(t)}{dt} &= \beta_e S'(t)B(t) + \beta_e S(t)B'(t) + S'(t) \int_0^t \beta_h(\tau)\pi_1(\tau)\hat{i}(t-\tau)d\tau \\ &+ S(t) \int_0^t \beta_h(\tau)\pi_1(\tau)\hat{i}'(t-\tau)d\tau + S(t)\beta_h(t)\pi_1(t)\hat{i}(0) \end{aligned} \quad (4.16)$$

Similarly, $\frac{d\hat{i}(t)}{dt}$ satisfies the following inequality

$$|\frac{d\hat{i}(t)}{dt}| \leq c_2 \int_0^t |\hat{i}(t-\tau)|d\tau + c_3,$$

where c_2, c_3 are some constants. By Gronwall inequality, we have $|\frac{d\hat{i}(t)}{dt}| \leq c_3 e^{c_2 t}$. To estimate the bound of $\frac{\partial \tilde{i}}{\partial \tau}$, differentiating (4.14) with respect to τ and using comparison principle, we obtain

$$|\frac{\partial \tilde{i}(\tau, t)}{\partial \tau}| \leq \begin{cases} |\hat{i}'(t-\tau)\pi_1(\tau) + \hat{i}(t-\tau)\pi_1'(\tau)|, & \text{for } 0 \leq \tau \leq t, \\ 0 & \text{for } t < \tau, \end{cases} \quad (4.17)$$

By the above analysis, we have

$$\|\partial_\tau \tilde{i}(\tau, t)\|_{L^1} \leq c_3 e^{c_2 t} \int_0^\infty \pi_1(\tau)d\tau + c_0 e^{c_1 t}(\mu_h + \tilde{c}) \int_0^\infty \pi_1(\tau)d\tau < C,$$

where $\tilde{c}$ is constant, which depends on the bounds of parameters in system.

Notice that

$$\int_0^\infty |\tilde{i}(\tau + h, t) - \tilde{i}(\tau, t)| d\tau \leq \|\partial_\tau \tilde{i}(\tau, t)\|_L^1 |h| \leq C|h|.$$

Obviously, this integral can be arbitrary small uniformly in the family of functions. Similarly, since $S(t)$, $\pi_2(a)$ are bounded and using Eq. (4.13), we can show that the integral

$$\int_0^\infty |\tilde{v}(a + h, t) - \tilde{v}(a, t)| da \leq \|\partial_a \tilde{v}(\tau, t)\|_L^1 |h| \leq \hat{C}|h|$$

can be also made arbitrarily small uniformly in the family of functions. This conclusion is also proved by the methods in [34]. Hence, three conditions in Fréchet-Kolmogorov theorem [33] are satisfied. We can determine that the family is compact. This completes the proof. $\square$

By Proposition 4.1 and Proposition 4.2, and using Theorem 2.6 in [35] (similar techniques have been recently employed in [29]), we immediately obtain the following result

Theorem 4.3. *If $R_0 > 1$, then there exists a constant $0 < \eta < 1$ (independent of initial conditions), such that any solution $(S(t), i(\tau, t), v(a, t), B(t))$ of (2.1) with $(S_0, i_0(\cdot), v_0(\cdot), B(0)) \in X_0$ satisfies*

$$\liminf_{t \rightarrow +\infty} \int_0^\infty \beta_h(\tau) i(\tau, t) d\tau + \beta_e B(t) > \eta.$$

5. Global stability

Now we are ready to conduct a deeper investigation into our model and resolve the global dynamics of the equilibria in system (2.1). Inspired by recent work of Magal et al [36], McCluskey [37], Shuai and van den Driessche [38], Yang et al [39] and Cai et al [26], we construct a suitable Lyapunov functional to establish the global stability of each equilibrium in system (2.1). We establish the following global stability result

Theorem 5.1.

1. *If $R_0 < 1$, then the disease-free equilibrium E^0 of system (2.1) is globally asymptotically stable;*
2. *If $R_0 > 1$, then E^0 is unstable, and the endemic equilibrium E^* of system (2.1) is globally asymptotically stable.*

Proof. We first prove the global stability of the disease-free equilibrium E^0 . To that end, with $g(x) = x - 1 - \ln x$, we construct the following Lyapunov functions $L(t) = L_1(t) + L_2(t) + L_3(t) + L_4(t)$, where

$$L_1(t) = S^0 g\left(\frac{S(t)}{S^0}\right), \quad L_2(t) = \int_0^\infty p(\tau) \frac{i(\tau, t)}{\pi_1(\tau)} d\tau, \quad L_3(t) = \int_0^\infty q(a) g\left(\frac{v(a, t)}{v^0(a)}\right) da, \quad L_4(t) = \frac{\beta_e S^0 B(t)}{\delta},$$

where,

$$\begin{aligned} p(\tau) &= S^0 \int_{\tau}^{\infty} \beta_h(\sigma) \pi_1(\sigma) d\sigma + S^0 \frac{\beta_e}{\delta} \int_{\tau}^{\infty} \xi(\sigma) \pi_1(\sigma) d\sigma, \\ q(a) &= \int_a^{\infty} \gamma_2(s) v^0(s) ds. \end{aligned} \quad (5.1)$$

Differentiating $L_1(t)$, we obtain

$$\begin{aligned} \frac{dL_1(t)}{dt} &= \left(1 - \frac{S^0}{S(t)} \right) \left((\mu_h + \Psi) S^0 - \int_0^{\infty} \gamma_2(a) v^0(a) da - \mu_h S(t) - S(t) \int_0^{\infty} \beta_h(\tau) i(\tau, t) d\tau \right. \\ &\quad \left. - \beta_e S(t) B(t) - \Psi S(t) + \int_0^{\infty} \gamma_2(a) v(a, t) da \right) \end{aligned}$$

Using $(\mu_h + \Psi) S^0 = \Lambda + \int_0^{\infty} \gamma_2(a) v^0(a) da$, we have

$$\begin{aligned} \frac{dL_1(t)}{dt} &= \Lambda \left(2 - \frac{S^0}{S(t)} - \frac{S(t)}{S^0} \right) + \left(-\frac{S(t)}{S^0} + 1 + \ln \frac{S(t)}{S^0} \right) \int_0^{\infty} \gamma_2(a) v^0(a) da - S(t) \\ &\quad \int_0^{\infty} \beta_h(\tau) i(\tau, t) d\tau \\ &\quad + S^0 \int_0^{\infty} \beta_h(\tau) i(\tau, t) d\tau - \beta_e S(t) B(t) + \beta_e S^0 B(t) + \int_0^{\infty} \gamma_2(a) v^0(a) \\ &\quad \left(\frac{v(a, t)}{v^0(a)} - \ln \frac{S(t)}{S^0} - \frac{S^0 v(a, t)}{S(t) v^0(a)} \right) da. \end{aligned} \quad (5.2)$$

Before differentiating $L_2(t)$, we rewrite it as the following form

$$\begin{aligned} L_2(t) &= \int_0^t p(\tau) \frac{i(\tau, t)}{\pi_1(\tau)} d\tau + \int_t^{\infty} p(\tau) \frac{i(\tau, t)}{\pi_1(\tau)} d\tau \\ &= \int_0^t p(t - \tau) \hat{i}(\tau) d\tau + \int_0^{\infty} p(t + \tau) \frac{i_0(\tau)}{\pi_1(\tau)} d\tau. \end{aligned} \quad (5.3)$$

Differentiating Eq. (5.3), we have

$$\frac{dL_2(t)}{dt} = p(0) \hat{i}(t) + \int_0^t p'(\tau) \hat{i}(t - \tau) d\tau + \int_t^{\infty} p'(\tau) \frac{i_0(\tau - t)}{\pi_1(\tau - t)} d\tau.$$

From (5.1), we obtain

$$\begin{aligned} p(0) &= \int_{\tau}^{\infty} \beta_h(\sigma) \pi_1(\sigma) d\sigma + S^0 \frac{\beta_e}{\delta} \int_{\tau}^{\infty} \xi(\sigma) \pi_1(\sigma) d\sigma, \\ p'(\tau) &= -S^0 \left(\beta_h(\tau) + \frac{\beta_e}{\delta} \xi(\tau) \right) \pi_1(\tau). \end{aligned}$$

Thus, we have

$$\frac{dL_2(t)}{dt} = \int_0^\infty S^0 \left(\beta_h(\tau) + \frac{\beta_e}{\delta} \xi(\tau) \right) \pi_1(\tau) d\tau i(0, t) - \int_0^\infty S^0 \left(\beta_h(\tau) + \frac{\beta_e}{\delta} \xi(\tau) \right) i(\tau, t) d\tau. \quad (5.4)$$

Calculating the derivative of $L_3(t)$ with respect to t along system (2.1), we obtain

$$\begin{aligned} \frac{dL_3(t)}{dt} &= \int_0^\infty q(a) \left(1 - \frac{v^0(a)}{v(a, t)} \right) \frac{1}{v^0(a)} \frac{\partial v(a, t)}{\partial t} da \\ &= - \int_0^\infty q(a) \left(\frac{v(a, t)}{v^0(a)} - 1 \right) \left(\frac{v_a(a, t)}{v(a, t)} + \mu_h + \gamma_2(a) \right) da. \end{aligned}$$

By direct computation, we have

$$\frac{\partial}{\partial a} g \left(\frac{v(a, t)}{v^0(a)} \right) = \left(\frac{v(a, t)}{v^0(a)} - 1 \right) \left(\frac{v_a(a, t)}{v(a, t)} + \mu_h + \gamma_2(a) \right),$$

where $v_a(a, t)$ denotes $\frac{\partial v(a, t)}{\partial a}$. Thus, we have

$$\frac{dL_3(t)}{dt} = - \int_0^\infty q(a) \frac{\partial}{\partial a} g \left(\frac{v(a, t)}{v^0(a)} \right) da.$$

By using integration by parts, we have

$$\begin{aligned} \frac{dL_3(t)}{dt} Y &= - q(a) g \left(\frac{v(a, t)}{v^0(a)} \right) \Big|_{a=0}^{\infty} + \int_0^\infty q'(a) g \left(\frac{v(a, t)}{v^0(a)} \right) da \\ &= q(0) g \left(\frac{v(0, t)}{v^0(0)} \right) - \int_0^\infty \gamma_2(a) v^0(a) g \left(\frac{v(a, t)}{v^0(a)} \right) da. \end{aligned}$$

By substituting the following equalities

$$q(0) = \int_0^\infty \gamma_2(a) v^0(a) da, \quad q'(a) = -\gamma_2(a) v^0(a), \quad v(0, t) = \Psi S(t), \quad v^0(0) = \Psi S^0,$$

we have

$$\begin{aligned} \frac{dL_3(t)}{dt} &= \int_0^\infty \gamma_2(a) v^0(a) g \left(\frac{S(t)}{S^0} \right) da - \int_0^\infty \gamma_2(a) v^0(a) g \left(\frac{v(a, t)}{v^0(a)} \right) da \\ &= \int_0^\infty \gamma_2(a) v^0(a) g \left(\frac{S(t)}{S^0} \right) da + \int_0^\infty \gamma_2(a) v^0(a) \left(-\frac{v(a, t)}{v^0(a)} + 1 + \ln \frac{S^0 v(a, t)}{S(t) v^0(a)} + \ln \frac{S(t)}{S^0} \right) da. \end{aligned} \quad (5.5)$$

Let $L(t) = L_1(t) + L_2(t) + L_3(t) + L_4(t)$. Differentiating $L(t)$, combining (5.2), (5.4) and (5.5), and removing all terms that cancel out, we obtain

$$\begin{aligned}
\frac{dL(t)}{dt} &= \Lambda \left(2 - \frac{S^0}{S(t)} - \frac{S(t)}{S^0} \right) - S(t) \int_0^\infty \beta_h(\tau) i(\tau, t) d\tau - \beta_e S(t) B(t) \\
&\quad + \int_0^\infty S^0 \left(\beta_h(\tau) + \frac{\beta_e}{\delta} \xi(\tau) \right) \pi_1(\tau) d\tau i(0, t) - \int_0^\infty \gamma_2(a) v^0(a) g \left(\frac{S^0 v(a, t)}{S(t) v^0(a)} \right) da \\
&= \Lambda \left(2 - \frac{S^0}{S(t)} - \frac{S(t)}{S^0} \right) + (R_0 - 1) i(0, t) - \int_0^\infty \gamma_2(a) v^0(a) g \left(\frac{S^0 v(a, t)}{S(t) v^0(a)} \right) da.
\end{aligned}$$

Therefore, when $R_0 < 1$, we have $\frac{dL(t)}{dt} \leq 0$ in the region Ω . The strict equality holds only if $S(t) = S^0$ and $v(\tau, t) = v^0(\tau)$ hold simultaneously with either $R_0 = 1$ or $i(0, t) = 0$. It is easy to verify that the disease-free equilibrium E^0 is the unique invariant set of system (2.1). By Lyapunov-LaSalle invariance principle, if $R_0 < 1$, then E^0 is globally asymptotically stable.

Now, we shall investigate the global stability of the endemic equilibrium $E^*(S^*, i^*(\tau), v^*(a), B^*)$. we define the following Lyapunov functional $W(t) = W_s(t) + W_v(t) + W_i(t) + W_b(t)$, where

$$W_s(t) = S^* g \left(\frac{S(t)}{S^*} \right), \quad W_i(t) = \int_0^\infty p(\tau) g \left(\frac{i(\tau, t)}{i^*(\tau)} \right) d\tau,$$

$$W_v(t) = \int_0^\infty q(a) g \left(\frac{v(a, t)}{v^*(a)} \right) da, \quad W_b(t) = \frac{\beta_e S^0}{\delta} g \left(\frac{B(t)}{B^*} \right),$$

where,

$$\begin{aligned}
p(\tau) &= S^* \int_\tau^\infty \beta_h(\sigma) \pi_1(\sigma) d\sigma + S^* \frac{\beta_e}{\delta} \int_\tau^\infty \xi(\sigma) \pi_1(\sigma) d\sigma, \\
q(a) &= \int_a^\infty \gamma_2(s) \pi_2(s) ds.
\end{aligned} \tag{5.6}$$

Differentiating $W_s(t)$ along the solution of system (2.1), we obtain

$$\begin{aligned}
\frac{dW_s(t)}{dt} &= \left(1 - \frac{S^*}{S(t)} \right) \left((\mu_h + \Psi) S^* + S^* \int_0^\infty \beta_h(\tau) i^*(\tau) d\tau + \beta_e S^* B^* - \int_0^\infty \gamma_2(a) v^*(a) da \right. \\
&\quad \left. - \mu_h S(t) - S(t) \int_0^\infty \beta_h(\tau) i(\tau, t) d\tau - \beta_e S(t) B(t) - \Psi S(t) + \int_0^\infty \gamma_2(a) v(a, t) da \right) \\
&= \left(\mu_h + \Psi(1 - D(0)) S^* \left(2 - \frac{S^*}{S(t)} - \frac{S(t)}{S^*} \right) + \left(-\frac{S(t)}{S^*} + 1 + \ln \frac{S(t)}{S^*} \right) \int_0^\infty \gamma_2(a) v^*(a) da \right. \\
&\quad \left. + \int_0^\infty \beta_h(\tau) S^* i^*(\tau) \left(1 - \frac{S^*}{S(t)} - \frac{S(t) i(\tau, t)}{S^* i^*(\tau)} + \frac{i(\tau, t)}{i^*(\tau)} \right) d\tau + \beta_e S^* B^* \left(1 - \frac{S^*}{S(t)} \right. \right. \\
&\quad \left. \left. - \frac{S(t) B(t)}{S^* B^*} + \frac{B(t)}{B^*} \right) + \int_0^\infty \gamma_2(a) v^*(a) \left(\frac{v(a, t)}{v^*(a)} - \ln \frac{S(t)}{S^*} - \frac{S^* v(a, t)}{S(t) v^*(a)} \right) da \right).
\end{aligned} \tag{5.7}$$

Differentiating $W_v(t)$, similar to the calculation process on $L_3(t)$ in (5.5), we obtain

$$\begin{aligned} \frac{dW_v(t)}{dt} &= \int_0^\infty \gamma_2(a) v^*(a) \left(\frac{S(t)}{S^*} - 1 - \ln \frac{S(t)}{S^*} \right) da \\ &+ \int_0^\infty \gamma_2(a) v^*(a) \left(-\frac{v(a, t)}{v^*(a)} + 1 + \ln \frac{S^* v(a, t)}{S(t) v^*(a)} + \ln \frac{S(t)}{S^*} \right) da. \end{aligned} \quad (5.8)$$

Before differentiating $W_\lambda(t)$, we rewrite it by using the representation of $\hat{i}(\tau, t)$.

$$\begin{aligned} W_i(t) &= \int_0^\infty p(\tau) g\left(\frac{i(\tau, t)}{i^*(\tau)}\right) d\tau = \int_0^\infty p(\tau) g\left(\frac{\hat{i}(t-\tau)}{\hat{i}^*(0)}\right) d\tau \\ &= \int_{-\infty}^t p(t-\tau) g\left(\frac{\hat{i}(\tau)}{\hat{i}^*(0)}\right) d\tau. \end{aligned} \quad (5.9)$$

Differentiating $W_\lambda(t)$, from (5.9), we have

$$\begin{aligned} \frac{dW_i(t)}{dt} &= p(0) g\left(\frac{\hat{i}(t)}{\hat{i}^*(0)}\right) + \int_{-\infty}^t p'(t-\tau) g\left(\frac{\hat{i}(\tau)}{\hat{i}^*(0)}\right) d\tau \\ &= p(0) g\left(\frac{\hat{i}(t)}{\hat{i}^*(0)}\right) + i^*(0) \int_0^\infty p'(t-\tau) g\left(\frac{i(\tau, t)}{i^*(\tau)}\right) d\tau \\ &= \int_0^\infty \left(\beta_h(\tau) + \frac{\beta_e}{\delta} \xi(\tau) \right) S^* i^*(\tau) \left(g\left(\frac{i(0, t)}{i^*(0)}\right) - g\left(\frac{i(\tau, t)}{i^*(\tau)}\right) \right) d\tau \\ &= \int_0^\infty \left(\beta_h(\tau) + \frac{\beta_e}{\delta} \xi(\tau) \right) S^* i^*(\tau) \left(\frac{i(0, t)}{i^*(0)} - \frac{i(\tau, t)}{i^*(\tau)} \right) - \ln \frac{i(0, t)}{i^*(0)} + \ln \frac{i(\tau, t)}{i^*(\tau)} d\tau. \end{aligned} \quad (5.10)$$

Differentiating $W_b(t)$, we obtain

$$\begin{aligned} \frac{dW_b(t)}{dt} &= \frac{\beta_e S^*}{\delta} \left(1 - \frac{B^*}{B(t)} \right) \left(\int_0^\infty \xi(\tau) i(\tau, t) d\tau - \delta B(t) \right) \\ &= \frac{\beta_e S^*}{\delta} \left(1 - \frac{B^*}{B(t)} \right) \left(\int_0^\infty \xi(\tau) (i(\tau, t) - i^*(\tau)) d\tau - \delta (B(t) - B^*) \right) \\ &= \frac{\beta_e S^*}{\delta} \int_0^\infty \xi(\tau) i^*(\tau) \left(\frac{i(\tau, t)}{i^*(\tau)} - 1 - \frac{B^* i(\tau, t)}{B(t) i^*(\tau)} + \frac{B^*}{B(t)} \right) d\tau + \beta_e S^* B^* \left(2 - \frac{B(t)}{B^*} - \frac{B^*}{B(t)} \right) \end{aligned} \quad (5.11)$$

Let $W(t) = W_s(t) + W_v(t) + W_\lambda(t) + W_b(t)$. Add together with (5.7), (5.8), (5.10) and (5.11).

Notice that

$$\begin{aligned} &\int_0^\infty \left(\beta_h(\tau) + \frac{\beta_e}{\delta} \xi(\tau) \right) S^* i^*(\tau) \frac{i(0, t)}{i^*(0)} d\tau - \left(\int_0^\infty \beta_h(\tau) S(t) i(\tau, t) d\tau + \beta_e S(t) B(t) \right) \\ &= 0. \end{aligned} \quad (5.12)$$

We obtain

$$\begin{aligned}
\frac{dW(t)}{dt} = & \left(\mu_h + \Psi(1 - D(0))S^* \left(2 - \frac{S^*}{S(t)} - \frac{S(t)}{S^*} \right) + \beta_e S^* B^* \left(1 - \frac{S^*}{S(t)} \right) \right. \\
& + \int_0^\infty \beta_h(\tau) S^* i^*(\tau) \left(1 - \frac{S^*}{S(t)} + \ln \frac{i(\tau, t)}{i^*(\tau)} - \ln \frac{i(0, t)}{i^*(0)} \right) d\tau \\
& + \frac{\beta_e S^*}{\delta} \int_0^\infty \xi(\tau) i^*(\tau) \left(\ln \frac{i(\tau, t)}{i^*(\tau)} - \ln \frac{i(0, t)}{i^*(0)} - 1 - \frac{B^* i(\tau, t)}{B(t) i^*(\tau)} \right) d\tau + 2\beta_e S^* B^* \\
& \left. + \int_0^\infty \gamma_2(a) v^*(a) \left(1 + \ln \frac{S^* v(a, t)}{S(t) v^*(a)} - \frac{S^* v(a, t)}{S(t) v^*(a)} \right) da \right). \quad (5.13)
\end{aligned}$$

From (5.12), it is easy to obtain that

$$\int_0^\infty \left(\beta_h(\tau) S^* i^*(\tau) \left(1 - \frac{S(t) i(0, t) i^*(0)}{S^* i^*(\tau) i^*(0)} \right) d\tau + \beta_e S^* B^* \left(1 - \frac{S(t) B(t) i^*(0)}{S^* B^* i(0, t)} \right) \right) = 0. \quad (5.14)$$

Adding (5.16) to (5.15), we obtain

$$\begin{aligned}
\frac{dW(t)}{dt} = & \left(\mu_h + \Psi(1 - D(0))S^* \left(2 - \frac{S^*}{S(t)} - \frac{S(t)}{S^*} \right) \right. \\
& + \beta_e S^* B^* \left(2 - \frac{S^*}{S(t)} - \frac{S(t) B(t) i^*(0)}{S^* B^* i(0, t)} \right) \\
& + \int_0^\infty \beta_h(\tau) S^* i^*(\tau) \left(2 - \frac{S^*}{S(t)} + \ln \frac{i(\tau, t)}{i^*(\tau)} - \ln \frac{i(0, t)}{i^*(0)} - \frac{S(t) i(0, t) i^*(0)}{S^* I^*(\tau) i^*(0)} \right) d\tau \\
& + \frac{\beta_e S^*}{\delta} \int_0^\infty \xi(\tau) i^*(\tau) \left(\ln \frac{i(\tau, t)}{i^*(\tau)} - \ln \frac{i(0, t)}{i^*(0)} - 1 - \frac{B^* i(\tau, t)}{B(t) i^*(\tau)} \right) d\tau + 2\beta_e S^* B^* \\
& \left. + \int_0^\infty \gamma_2(a) v^*(a) \left(1 + \ln \frac{S^* v(a, t)}{S(t) v^*(a)} - \frac{S^* v(a, t)}{S(t) v^*(a)} \right) da \right). \quad (5.15)
\end{aligned}$$

(5.15) can be re-arranged as

$$\begin{aligned}
\frac{dW(t)}{dt} = & \left(\mu_h + \Psi(1 - D(0))S^* \left(2 - \frac{S^*}{S(t)} - \frac{S(t)}{S^*} \right) \right. \\
& + \beta_e S^* B^* \left(2 - \frac{S^*}{S(t)} - \frac{S(t) B(t) i^*(0)}{S^* B^* i(0, t)} \right) \\
& + \int_0^\infty \beta_h(\tau) S^* i^*(\tau) \left(2 - \frac{S^*}{S(t)} + \ln \frac{i(\tau, t)}{i^*(\tau)} - \ln \frac{i(0, t)}{i^*(0)} - \frac{S(t) i(0, t) i^*(0)}{S^* I^*(\tau) i^*(0)} \right) d\tau \\
& - \frac{\beta_e S^*}{\delta} \int_0^\infty \xi(\tau) i^*(\tau) \ln \frac{i(0, t)}{i^*(0)} d\tau - \frac{\beta_e S^*}{\delta} \int_0^\infty \xi(\tau) i^*(\tau) d\tau + 2\beta_e S^* B^* \\
& + \frac{\beta_e S^*}{\delta} \int_0^\infty \xi(\tau) i^*(\tau) \left(1 + \ln \frac{i(\tau, t)}{i^*(\tau)} - \frac{B^* i(\tau, t)}{B(t) i^*(\tau)} + \ln \frac{B^*}{B(t)} - \ln \frac{B^*}{B(t)} - 1 \right) d\tau \\
& \left. + \int_0^\infty \gamma_2(a) v^*(a) \left(1 + \ln \frac{S^* v(a, t)}{S(t) v^*(a)} - \frac{S^* v(a, t)}{S(t) v^*(a)} \right) da \right). \quad (5.16)
\end{aligned}$$

Thus, we have

$$\begin{aligned} \frac{dW(t)}{dt} = & \left(\mu_h + \Psi(1 - D(0))S^* \left(2 - \frac{S^*}{S(t)} - \frac{S(t)}{S^*} \right) + \beta_e S^* B^* \left(g\left(\frac{S^*}{S(t)}\right) + g\left(\frac{S(t)B(t)i^*(0)}{S^* B^* i(0, t)}\right) \right) \right. \\ & - \int_0^\infty \beta_h(\tau) S^* i^*(\tau) \left(g\left(\frac{S^*}{S(t)}\right) + g\left(\frac{S(t)i(0, t)i^*(0)}{S^* I^*(\tau)i^*(0)}\right) \right) d\tau \\ & \left. - \frac{\beta_e S^*}{\delta} \int_0^\infty \xi(\tau) i^*(\tau) g\left(\frac{B^* i(\tau, t)}{B(t) i^*(\tau)}\right) d\tau - \int_0^\infty \gamma_2(a) v^*(a) g\left(\frac{S^* v(a, t)}{S(t) v^*(a)}\right) da \right). \end{aligned}$$

Thus $\frac{dW(t)}{dt} \leq 0$ with equality if and only if

$$S(t) = S^*, i(0, t) = i^*(0), v(a, t) = v^*(a), B(t) = B^*.$$

It is easy to show that $\{E^*\}$ is the maximal compact invariant set of the set with $\frac{dW(t)}{dt} = 0$.

By LaSalle invariance principle we obtain that the endemic equilibrium E^* of system (2.1) is globally stable for $R_0 > 1$. $\square$

6. Numerical results

We now conduct numerical simulation to our coupled between-host/within-host model and compare our numerical results with the analytical findings. To that end, we focus on cholera as a significant example of those environmentally transmitted bacterial infections. We list the values of the epidemiological parameters in Table 1, and the values of the immunological parameters in Table 2.

We first examine the within-host dynamics. Figure 2 illustrates a typical scenario for the time evolution of the concentrations of the pathogenic bacteria (i.e., *Vibrio cholerae*) and the immune cells; both converge to a steady state represented by the positive equilibrium (P^* , M^*), as predicted by our equilibrium analysis in Section 3. Meanwhile, we have also calculated the survival probability [20] of an infected individual based on the within-host dynamics. The survival probability $\sigma(\tau)$ satisfies

$$\frac{d\sigma(\tau)}{d\tau} = -\rho(\tau)\sigma(\tau) = -\frac{\rho P(\tau)\sigma(\tau)}{P(\tau) + k_1}, \quad \sigma(0) = 1.$$

Thus we have

$$\sigma(\tau) = e^{-\rho \int_0^\tau \frac{P(s)}{P(s) + k_1} ds}.$$

A numerical simulation result for σ versus the infection age τ is shown in Figure 2. As can be naturally expected, the survival probability $\sigma(\tau)$ decreases monotonically with τ . The decreasing rate of σ depends on the disease induced death rate, which in turn depends on the pathogen load.

On the other hand, the between-host dynamics are characterized by the value of the basic reproduction number R_0 which is shaped by both the between-host and within-host quantities. Figure 3 shows that when $R_0 < 1$, the total number of infected individuals, $I(t)$,

converges to the disease-free equilibrium with $I_0 = 0$; when $R_0 > 1$, in contrast, $I(t)$ converges to the endemic-equilibrium with $I^* > 0$. Compared with Figure 2, we see that the between-host dynamics, from the initiation to the stabilization at the steady state, take place on a much slower time scale than the within-host dynamics do. Figure 4 displays a phase portrait for each of the two scenarios shown in Figure 3. We observe that when $R_0 < 1$, the infection curves $B(t)$ vs. $I(t)$ starting from different initial conditions all converge to the disease-free equilibrium with $B_0 = I_0 = 0$, demonstrating the global asymptotical stability of the disease-free equilibrium. When $R_0 > 1$, all the curves $S(t)$ vs. $I(t)$ converge to the positive endemic equilibrium with $S^* > 0$ and $I^* > 0$, demonstrating the global asymptotical stability of the endemic equilibrium. These results are consistent with the conclusion in Theorem 5.1.

To further quantify the connection between the within-host dynamics at the individual level and the disease transmission at the population level, we examine the relationship between the intrinsic bacterial growth rate and two between-host measurements: the basic reproduction number R_0 and the disease prevalence (or, infection level) at the endemic state I^* . The intrinsic bacterial growth rate, r_P , is a critical parameter in shaping the within-host dynamics. As shown in equation (3.4), the pathogen load P^* increases monotonically with r_P . Figure 5 shows that the basic reproduction number R_0 of the between-host system also increases with respect to r_P , indicating that the disease transmission risk at the population level positively correlates with the pathogen load at the individual level and that a lower transmission risk could result from a reduction of the individual pathogen load. On the other hand, the disease prevalence at the endemic state I^* is not related to the within-host pathogen load in a simple monotone manner. As shown in Figure 5, the value of I^* first increases with r_P , reaching a peak, and then decreases afterwards. An observation is that we may be able to reduce the infection level at the endemic state by controlling the individual bacterial growth rate through medical treatment, provided that we can push the value of r_P to a small neighborhood of 0 where a positive correlation exists between I^* and r_P .

Next, we conduct a more realistic simulation to demonstrate the real-world application of our modeling framework. We consider the Haiti cholera epidemic during 2010 – 2011, which is regarded as one of the largest cholera outbreaks in the last few decades, as a practical case study. Weekly reported data for this epidemic can be found in [44], for example. Vaccination was not implemented during the Haiti cholera outbreak due to limited vaccine availability, complex logistical and operational challenges, and various socioeconomic factors, but the issue has since been under intensive discussion [45]. The aim of our study here is to apply our mathematical model to the Haiti cholera outbreak and to quantify the potential impact of a vaccination campaign in reducing the epidemic burden.

To this end, we first remove the vaccinated compartment, v , from the system (2.1), assuming that no individuals receive vaccination. We then use this model to fit the reported data for a period of about 100 days starting from October 22, 2010 [44]. We conduct data fitting for the two transmission parameters β_1 (the direct contact rate) and β_e (the indirect transmission rate), which are two key parameters in our model and which tend to vary from place to place [46]. Other parameter values are fixed, and we employ the standard least squares method for the fitting. Figure 6 shows our data fitting results in terms of the cumulative infected cases. The normalized mean square error for the data fitting is 0.00393, and the 95% confidence

intervals for the parameters β_1 and β_e are $(0.474 \times 10^{-9}, 1.660 \times 10^{-9})$ and $(0, 5.90 \times 10^{-10})$, respectively.

Based on the parameter values from data fitting, we then apply the full model (2.1) and study the impact of vaccination. Figure 7 (left) displays the comparison between the two scenarios, with and without vaccination, in terms of the infection level $I(t)$. We clearly observe that the deployment of vaccination can not only significantly reduce the peak value of the infection (from about 2.4×10^4 to 1.4×10^4) but also shorten the duration of the epidemic. Meanwhile, Figure 7 (right) shows the comparison of the cumulative cases with and without vaccination. At the end of this time period, the cumulative cases have been reduced from 3.2×10^5 to 1.1×10^5 , which represents a 65% reduction. Simple calculation shows that in this modeling scenario, approximately 32% of the total population have received vaccination during the time period. Interestingly, the authors in [47] also conducted a hypothetical study on the vaccination strategy for Haiti cholera outbreak and reported that with enough vaccine for 30% of the population in Haiti, it would reduce the total cases by 55%, a result similar to our model predictions.

7. Conclusion and discussion

In this paper, we have presented a multi-scale mathematical model based on the nested modeling approach to investigate the dynamics of environmentally transmitted bacterial infections. Our model links the between-host disease transmission and the within-host immunological dynamics. The between-host system includes the dual (human-to-human and environment-to-human) transmission routes and is structured by the infection age and vaccination age. The within-host system describes the interaction between the pathogenic bacteria and the host immune cells. The two systems are connected through the infection age and through the use of between-host parameters that explicitly depend on the within-host pathogen load and immune strength.

We have conducted a detailed analysis for the proposed nested model. We find that the within-host system has two equilibria: a trivial equilibrium which is always unstable, and a non-trivial (or, positive) equilibrium which is globally asymptotically stable provided that the initial bacterial concentration is non-zero. The pathogen load and immunity level at the non-trivial steady state both depend on, and positively correlates with, the intrinsic bacterial growth rate. Meanwhile, we have focused our attention on the study of the dynamical properties of the between-host system using the basic reproduction number R_0 derived from our equilibrium analysis. We establish the uniform persistence of the system for $R_0 > 1$. Moreover, through rigorous global dynamical analysis, we find that when $R_0 < 1$, there is a unique disease-free equilibrium that is globally asymptotically stable; when $R_0 > 1$, the disease-free equilibrium becomes unstable, and there is a unique endemic equilibrium that is globally asymptotically stable. In this sense, the between-host system exhibits regular threshold dynamics, characterized by a forward transcritical bifurcation. Note, however, that the within-host variables are incorporated into our between-host system and play a significant role in shaping the dynamical behavior at the population level. Particularly, the basic reproduction number R_0 is determined by both the between-host and within-host factors. Therefore, our analysis provides important quantification for the disease

transmission risk and epidemic development, in the context of coupled between-host and within-host dynamics, and could provide more meaningful guidelines for disease control and management, compared to previously published models based solely on the between-host disease dynamics.

We have further explored the connection between the within-host and between-host infection dynamics by numerically examining the relationship between R_0 and the within-host bacterial growth rate r_P . We find that R_0 is monotonically increasing as r_P increases, indicating that a larger bacterial growth rate inside the human body leads to a higher cholera infection risk at the population level. Since the pathogen load also increases with r_P , this establishes a positive correlation between the within-host pathogen load and the between-host transmission risk. On the other hand, we find that the disease prevalence at the endemic state does not have a simple monotonic relationship with the within-host bacterial growth (and the pathogen load). This observation, in terms of our environmental disease transmission model, indicates an intriguing connection between the long-term disease dynamics at the population level (characterized by the endemic state) and the short-term pathogen dynamics at the individual host level. Such non-monotone relationship between disease prevalence and within-host variables has also been observed in modeling studies of other types of diseases (see, e.g., [48]).

Our coupled between-host/within-host model, like most other models based on the nested approach, specifies a one-way connection by nesting the within-host dynamics into the between-host system. On the other hand, the between-host disease transmission and spread do not have any impact on the within-host system. For many environmentally transmitted diseases, this is not very realistic. For example, experiment studies [49] show that the within-host dynamics of cholera could be far more complex than described by our pathogen-immune interaction model (2.2) and the environmental vibrio concentration (one of the between-host variables) could directly affect the within-host pathogen evolution. We hope to improve our modeling framework in future efforts and establish a two-way coupling between the within-host and between-host systems, to strengthen the connection between the two systems and to better understand the multi-scale dynamics of cholera and other environmentally transmitted bacterial infections.

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Fig. 1.
A flowchart for the nested disease model.

Fig. 2.

The left figure shows that the concentrations of the pathogenic bacteria and immune cells inside the human body approach the positive equilibrium ε^* when the initial value $P(0)$ is positive. The right figure shows that the individual survival probability decreases with the infection age.

Fig. 3.

The figure on the left shows that the number of infected individuals approaches 0 when $R_0 < 1$. The figure on the right shows that the number of infected individuals persists and eventually stabilizes at a positive level when $R_0 > 1$.

Fig. 4. Phase portraits of B vs. I for $R_0 < 1$ (left figure) and S vs. I for $R_0 > 1$ (right figure).

Fig. 5.

The left figure shows that R_0 increases with r_P . The right figure shows that the endemic prevalence level I^* first and then decreases as r_P grows.

Fig. 6.

Data fitting for Haiti cholera outbreak in a period of about 100 days. The circles denote the reported cumulative cases, and the curve represents the numerical simulation result.

Fig. 7.

Comparison of the two scenarios, with and without vaccination, for Haiti cholera outbreak in a 200-day period starting from October 22, 2010. The left figure compares the infection level $I(t)$, and the right figure compares the cumulative cases.

Table 1

Between-host parameters

Parameter	Interpretation	Value	Reference
Λ	recruitment rate	762.9 day^{-1}	[40]
β_1	direct contact rate	$1.067 \times 10^{-9} \text{ day}^{-1}$	data fitting
c_1	correlation constant of recovery rate	1.3 day^{-1}	estimate
μ_h	natural death rate	$7.629 \times 10^{-5} \text{ day}^{-1}$	[40]
δ	clearance rate of <i>Vibrio cholerae</i>	$1/30 \text{ day}^{-1}$	[41]
ψ	vaccination rate	10^{-4} day^{-1}	estimate
β_e	indirect transmission rate	$4.277 \times 10^{-14} \text{ day}^{-1}$	data fitting
ξ_1	proportional constant of shedding rate	0.005 day^{-1}	estimate
ρ	scaling constant of $\rho(\tau)$	0.02 day^{-1}	estimate

Table 2

Within-host parameters

Parameter	Interpretation	Value	Reference
k_1	half-saturation constant	10^4 cell	[42]
r_p	intrinsic growth rate of <i>Vibrio cholerae</i>	0.5 day^{-1}	variable
b_M	stimulation rate of immune cells	0.25 day^{-1}	estimate
d_p	clearance rate of <i>Vibrio cholerae</i>	$5 \times 10^{-4} \text{ day}^{-1}$	estimate
d_m	inactivation rate of immune cells	10^{-4} day^{-1}	estimate
μ_m	death rate of immune cell	0.15 day^{-1}	[43]
K	maximum capacity of cells	10^6 cell	[12]