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An immuno-epidemiological model with threshold delay: a study of the effects of multiple exposures to a pathogen

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Abstract An immuno-epidemiological model of pathogen transmission is developed. This model incorporates two main features: (i) the epidemiological model includes within-host pathogen dynamics for an infectious disease, (ii) the susceptible individuals to the infection experience a series of exposures via the pathogen before becoming infectious. It is shown that this model leads naturally to a system of differential delay equations of the threshold type and that these equations can be transformed, in a biologically natural way, to differential equations with state-dependent delay. An interesting dynamical behavior of the model is the bistability phenomena, when the basic reproductive ratio R_0 is less than unity, which raises many new challenges to effective infection control.

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1 Introduction

Epidemiological and in-host models have been separately developed and studied for
many diseases (i.e. Anderson and May 1991; Brauer et al. 2008; Brauer 1990; Brauer
and Castillo-Chavez 2001; Castillo-Chavez et al. 2002; Diekmann and Heesterbeek
2000; Hethcote 2000; Ma et al. 2009; Nowak and May 2001; Thieme 2003). However,
there is evidence that for many diseases important relationships exist between what
is happening in the host and what is occurring at the population level (i.e. André
and Gandon 2006; Dushoff 1996; Gilchrist and Sasaki 2002; Heffernan and Keeling
2009; Hellriegel 2001; Hoppensteadt and Waltman 1971; Martcheva and Sergei 2006;
Waltman 1974). Indeed, immune system and pathogen dynamics cannot be understood
in isolation, since in-host processes interact in many ways with the environment of
the host (Pradeu and Carosella 2006). Despite this, few conceptual frameworks have
been presented which directly link both the between- and in-host populations (André
and Gandon 2006; Dushoff 1996; Gilchrist and Sasaki 2002; Heffernan and Keeling
2009; Hoppensteadt and Waltman 1971; Martcheva and Sergei 2006; Waltman 1974).
Furthermore, in many studies the in-host dynamics are characterized by quite severe
simplifying assumptions. In particular, in-host competitive processes are assumed
to be instantaneous with respect to epidemiological timescales. In reality, in-host
competition between different viral particles can occur at timescales comparable to
those in epidemiology.

In this paper, we present an immuno-epidemiological model which incorporates
pathogen progression to infection in an epidemiological model. The relationship
between the population and in-host dynamics leads to an age-structured epidemio-
logical model with a varying boundary. Importantly, the model structure enables the
study of the effects of multiple exposures to a pathogen on an individual, and how this
is reflected at the population level. Mathematical models have been widely used to
investigate the impact of a single-exposure on infectious diseases (see, for example,
Anderson and May 1991; Brauer 1990; Cooke and Van Den Driessche 1996). Some
previous studies within the fields of Biology and Medicine have shown that there is
an inverse relationship between the dose size at exposure and the length of the latent
phase of infection for some infectious diseases (see, for example Fine 2003; Hollinger
et al. 1991; Hughes et al. 2002; Spekreijse et al. 2011). Recently, there has been an
interest in studying the effects of mulitple exposure to a pathogen on the latent or
exposed stages of infection (Cowling et al. 2013). The model presented here presents
a first mathematical study of this issue.

Our immuno-epidemiological model takes the form of a age-structured system
of differential equations with moving boundary coupled with an algebraic equation.
Using the characteristic method, this model is simplified and reduced to a system of
differential equations with so-called threshold-type delay.

Threshold delay equations (TDEs) arise naturally in compartmental models for which the time spent in a particular compartment is not constant, but rather is determined by the requirement that a fixed threshold quantity of an entity is accumulated during the time in residence in that compartment. This class of equations has attracted a lot of attention in recent years (i.e. Kuang and Smith 1992; Smith and Kuang 1992; Walther 2009 and references therein), and started earlier in the 1960s (Cooke 1967). In 1988, Gatica and Waltman (1988) studied the existence of solutions, and uniqueness and continuous dependence on initial conditions for some general TDEs arising from biological problems. Gatica and Waltman (1982, 1988) derived TDEs directly in models of the immune response. These studies were motivated by the threshold integral equation models derived by Hoppensteadt and Waltman (1971); Waltman (1974) in the modelling of epidemics, apparently first used by Cooke (1967) in an epidemiological setting. In these epidemiological models, a susceptible individual that is first exposed to a pathogen at time $t - T$ will become infectious at time t provided the individual accumulates a sufficient dose of infection, usually modeled by some function of the infective population, during the time from $t - T$ to t.

TDEs can be difficult to analyze. To overcome this difficulty a Global Implicit Function Theorem (GIFT) (Ichiraku 1985) can be used to further simplify a TDE system to a state-dependent delay system of differential equations. The linearization of state-dependent delay equations has been rigorously studied by Walther (2003). For a complete review on state-dependent delay differential equations we refer the readers to Hartung et al. (2006).

Our analysis shows that the incorporation of the pathogen dynamics into an epidemiological model provides insights into possible mechanisms for multiple stable states when the basic reproductive ratio (or basic reproduction number) R_0 is less than unity. In most epidemic models, a disease will be eradicated from a population if $R_0 < 1$, and persists if $R_0 > 1$ (Brauer and Castillo-Chavez 2001; Diekmann and Heesterbeek 2000; Hellriege et al. 1990; Hethcote 2000). However, in some cases $R_0 < 1$ is not sufficient to completely remove a disease (see, for example, Van den Driessche and Watmough 2002; Qesmi et al. 2010, 2011). In this case, the stable disease-free state competes with a stable endemic state. Such a scenario, known as the bistable phenomenon, has been explored in many epidemic models, in particular, in vaccination models with imperfect vaccines (Alexander and Moghadas 2004) and models containing different classes for susceptibles or infectives (Hadeler and Van den Driessche 1997; Qesmi et al. 2010, 2011). However, to the best of our knowledge, there is no study to date that has highlighted backward bifurcation or bistable phenomenon for models with threshold-delay and/or state-dependent delay.

The article is organized as follows. Section 2 is devoted to the formulation of the model, that originally takes the form of an age-structured system of differential equations coupled with an algebraic equation. This system is then reduced to a system of differential equations with threshold delay in Sect. 3. Using a GIFT, in Sect. 4, we transform the system with threshold delay to a state-dependent delay system of differential equations. Properties of the resulting system, such as positivity and existence of steady states, are established in Sect. 5. We then focus on the stability of the disease-free equilibrium and prove a sufficient condition for its global stability in Sect. 6. We perform the analysis of transcritical bifurcation as well as backward bifurcation in

Sect. 7. Discussion and conclusions are given in Sect. 8. All the proofs of the obtained results are presented in the Appendix.

2 Model development

2.1 In-host modeling

We are interested in the early stages of infection immediately after exposure to a pathogen. We will assume that an individual is exposed to an infectious quantum , c, which is the unit of pathogen load needed to produce an infection. Therefore, we will assume that the infectious pathogen load will grow, overcoming the non-specific immune response. We also assume that during the early stages of infection the specific immune response is absent since it has not yet been activated by the non-specific innate immune system. Therefore, we can model the pathogen load after exposure as an increasing function.

$$\dot{V} = rV.$$

In the early stages of infection we consider an individual to be in the exposed class. When the pathogen load has increased to a level A we then consider the individual to be infectious. During the exposed period it is possible for an individual to incur consecutive exposures to the pathogen. We assume that the repeated exposures increase the pathogen load in-host. Hence the pathogen load must also be tracked by an age of infection, a, since the first exposure of an uninfected individual, and the number of repeated exposures during the exposed period. Furthermore, since transmission occurs from infected individuals, the pathogen load due to an exposure will depend on the infected population. Using the conservation law of mass, the dynamics of the pathogen load, denoted by $V(t, a)$, during the exposure stage $(V(t, a) < A)$ is governed by the equation

$$\frac{\partial V}{\partial t} + \frac{\partial V}{\partial a} = rV(t, a) + F(I(t)),$$

subject to the boundary condition describing the pathogen load introduced in the body of the exposed per each contact:

$$V(t, 0) = c.$$

Here, $F(I(t))$ includes additive pathogen load in the exposed individual due to multiple exposures to infectious individuals, $I(t)$. Furthermore, we suppose that, after the infectious level A has been achieved, repeated exposure has no effect on increasing the pathogen load of the host since a new exposure of pathogen load will be small compared to the total load already residing in the host. Thus, it is reasonable to assume a saturation effect for an exposed individual. To reflect this, we incorporate the additive pathogen load due to multiple exposures using the following Holling functional response type 2 (see Michaelis and Menten 1913).

$$F(I(t)) = \frac{bcI(t)}{kI(t) + 1},$$

where b is the number of effective contacts between an exposed and infectious individuals, c is the pathogen load introduced in the body of the exposed per each contact, and k is an adjustable parameter which measures how soon saturation occurs. Note that, during the exposed and infectious periods of infection, pathogen load generally rises to high levels (Wodarz 2006). Note that $rA > bc/k$ must be true here, since a pathogen load introduced in the body must be smaller than the threshold A and the growth of the pathogen rV must dominate over F(I(t)). In what follows, we will assume that $k > \frac{b}{r}$.

Here, we state some properties of the pathogen load which will be used in the next sections.

Lemma 1 *There exists a unique positive function* $\tau : [0, \infty) \to [0, \infty)$, *such that*

1. $V(t, \tau(t)) = A$ for all $t \geq 0$;
2. $V(t, a) \leq A$ is equivalent to $0 \leq a \leq \tau(t)$;
3. the map $t \mapsto t - \tau(t)$ is increasing and τ is bounded;
4. $\Psi(\tau(t), I_t) = 0$ where Ψ is a function, defined on $R^+ \times C$ by,

$$\Psi(s, \phi) = ce^{rs} + \int_{-s}^{0} e^{-ru} F(\phi(u)) du - A \tag{1}$$

and, for each $t \geq 0$, I_t is the history function of the infectious population defined, on $[-\max_{s \in [0, \infty]}(\tau(s)), 0]$, by

$$I_t(\theta) = I(t + \theta).$$

Remark 2 Note that, since A is the pathogen load needed for an exposed individual to become infectious, it is assumed that the pathogen load per contact $c < A$.

2.2 Between-host modeling

The compartmental model diagram is shown in Fig. 1 and illustrates how a pathogen can spread in a population. The mathematical model considers a population that is divided into susceptible (S), exposed (E) and infectious (I) individuals. Susceptible individuals enter the population at rate π and, once infected through contact with infectious individuals β, become exposed. Exposed individuals become infectious (able to transmit the infection) when the internal pathogen load exceeds the threshold value A, or equivalently, when the age since exposure is greater than $\tau(t)$. Susceptible individuals die with rate d, exposed individuals of age a since exposure die with rate $\delta(a)$, and infectious individuals die or recover with rate μ. The model is given by the

Fig. 1 Immuno-epidemiological diagram of early infection. An exposed individual becomes infectious when pathogen load $V > A$. Multiple exposures can reduce the time taken to become infectious

following system of algebraic-partial differential equations

$$
\begin{cases}
\dot{S}(t) = \pi - \beta S(t)I(t) - dS(t) \\
\frac{\partial E}{\partial t} + \frac{\partial E}{\partial a} = -\delta(a)E(t,a), & \text{if } t \geq 0 \text{ and } 0 \leq a \leq \tau(t), \\
\dot{I}(t) = E(t,\tau(t)) - \mu I(t) \\
\Psi(\tau(t), I_t) = 0
\end{cases}
\tag{2}
$$

subject to the following boundary condition

$$
E(t,0) = \beta S(t)I(t).
$$

3 Reducing the partial differential to a threshold-delay system

The system of equations (2) may be transformed to a system of threshold delay equations (Gatica and Waltman 1982; Mahaffy et al. 1998; Metz and Diekmann 1986). The solution $E(t,a)$ of the second equation of system (2) subject to the following boundary condition

$$
E(t,0) = \beta S(t)I(t)
$$

is given, for $t > 0$ and $a > 0$, by

$$
E(t,a) = \begin{cases}
\beta e^{-\int_0^a \delta(s)ds} S(t-a)I(t-a) & \text{if } t > a, \\
e^{-\int_0^a \delta(s)ds} e^{-\int_0^{a-t} \delta(s)ds} E(0,a) & \text{if } t \leq a.
\end{cases}
\tag{3}
$$

Let $E(t) = \int_0^{\tau(t)} E(t, a)da$ be the total population of the exposed individuals. Let τ_∞ be the maximal delay $(\tau_\infty = \max_{s \geq 0}(\tau(s)))$. Using (3), the $I-$class becomes, for $t \geq \tau_\infty$,

$$I'(t) = \beta e^{-\int_0^{\tau(t)} \delta(s)ds} S(t - \tau(t))I(t - \tau(t)) - \mu I(t).$$

However, $E(t)$ is explicitly given, for $t \geq \tau(t)$, by

$$E(t) = \beta \int\limits_0^{\tau(t)} e^{-\int_0^\theta \delta(s)ds} S(t - \theta)I(t - \theta)d\theta.$$

Thus, we omit the E-equation and, furthermore, the system (2) will be reduced, for $t \geq \tau_\infty$, to a threshold-delay (TDE) system

$$\begin{cases} S'(t) = \pi - \beta S(t)I(t) - dS(t), \\ I'(t) = \beta e^{-\int_0^{\tau(t)} \delta(s)ds} S(t - \tau(t))I(t - \tau(t)) - \mu I(t), \\ \Psi(\tau(t), I_t) = 0. \end{cases} \tag{4}$$

4 Reducing the threshold-delay to state-dependent delay system

The system (4) consists of a threshold-delay system of differential equations coupled in a complicated manner. It is difficult to conduct analysis on such systems (Alt 1979; Kuang and Smith 1992; Smith and Kuang 1992; Walther 2009) [see also Sect. 2.5 of the survey (Hartung et al. 2006)]. To overcome this difficulty we use a GIFT and show that the TDE system (4) can be reduced to a system of differential equations with state-dependent delay.

Denote by C the space of continuous functions defined on $[-\tau_\infty, 0]$. Let a function $h : C \to R$. The function h is said to be decreasing if, for $\phi, \psi \in C, \phi(\theta) \leq \psi(\theta)$ implies that $h(\phi) \geq h(\psi)$. We have the following Lemma.

Lemma 3 *There exists a unique and continuously differentiable map* $\sigma : C \to R^+$ *such that* $\Psi(\sigma(\phi), \phi) = 0$ *for any* $\phi \in C$. *Furthermore, the function* σ *is decreasing and satisfies*

$$\sigma(0) = \frac{1}{r} \ln\left(\frac{A}{c}\right). \tag{5}$$

Thus, the threshold-delay system (4) is equivalent to the state-dependent delay differential system given, for $t \geq \tau_\infty$, by

$$\begin{cases} S'(t) = \pi - \beta S(t)I(t) - dS(t), \\ I'(t) = \beta e^{-\int_0^{\sigma(I_t)} \delta(s)ds} S(t - \sigma(I_t))I(t - \sigma(I_t)) - \mu I(t), \end{cases} \tag{6}$$

where $\sigma : C \rightarrow R^+$ is a decreasing and continuously differentiable map which satisfies

$$\Psi(\sigma(\phi), \phi) = 0 \text{ for any } \phi \in C \text{ and } \sigma(0) = \frac{1}{r} \ln\left(\frac{A}{c}\right).$$

Thus, by making a change of variables $x(t) = S(t + \sigma(0))$ and $y(t) = I(t + \sigma(0))$, system (6) can be written as a state-dependent delay differential system, for $t \geq 0$,

$$\begin{cases} x'(t) = \pi - \beta x(t)y(t) - dx(t), \\ y'(t) = \beta e^{-\int_0^{\sigma(y_t)} \delta(s)ds} x(t - \sigma(y_t))y(t - \sigma(y_t)) - \mu y(t). \end{cases} \tag{7}$$

Existence and uniqueness of solutions of (7) cannot be easily deduced. Equation (7) can be written as

$$X'(t) = g(X_t), \qquad \text{for } t \geq 0, \tag{8}$$

where X_t is defined by $X_t(\theta) = X(t + \theta)$ for $\theta \in [-\sigma(0), 0]$, and the function $g : C \times C \rightarrow R^2$ is given, for $\phi, \psi \in C$, the space of continuous functions on $[-\sigma(0), 0]$, by

$$g(\phi, \psi) = \begin{pmatrix} \pi - \beta\phi(0)\psi(0) - d\phi(0), \\ \beta e^{-\int_0^{\sigma(\psi)} \delta(s)ds} \phi(-\sigma(\psi))\psi(-\sigma(\psi)) - \mu\psi(0) \end{pmatrix}.$$

Since $\sigma(\phi)$ is continuously differentiable on C, then g is also continuously differentiable on $C \times C$. Therefore, existence and uniqueness of a solution of (7) is defined on $[0, +\infty)$ for an initial condition belonging to C^1, and the space of continuously differentiable function on $[-\sigma(0), 0]$ follows from Mallet-Paret et al. (1994) and Walther (2003). One may note that it is not reasonable to expect a well-posed state-dependent delay differential problem by searching for solutions in C (see Walther 2003).

5 Properties of the model and existence of steady states

In this section, we focus on some properties of (7) including positivity and the existence of steady states. In the following it is assumed the existence and uniqueness of solutions of (7) hold for $t \in [-\sigma(0), +\infty)$.

Proposition 4 *For all nonnegative initial conditions, the unique solution $(x(t), y(t))$ of (7) is nonnegative and bounded.*

The model (7) has a disease-free equilibrium (DFE) given by,

$$\mathcal{E}_f = (\overline{x}, 0) = \left(\frac{\pi}{d}, 0\right),$$

in which there is no infection. This result is straightforward and can be obtained, for instance, using a method similar to the one presented in Adimy et al. (2010). It can

also be obtained using the same proof for SIR models with constant delay since σ is a bounded function.

We now focus on the existence of endemic states of (7).

Proposition 5 *Assume that, for all y positive,*

$$e^{-\int_0^{\sigma(y)} \delta(s)ds} < \frac{\beta y + d}{d} e^{-\int_0^{\sigma(0)} \delta(s)ds}. \tag{9}$$

Then, system (7) has:

(i) *at least one endemic equilibrium if $\frac{\beta\pi e^{-\int_0^{\sigma(0)} \delta(s)ds}}{\mu d} > 1$;*

(ii) *no endemic equilibrium if $\frac{\beta\pi e^{-\int_0^{\sigma(0)} \delta(s)ds}}{\mu d} \leq 1$.*

However, if (9) does not hold, then system (7) has:

(iii) *at least one endemic equilibrium if $\frac{\beta\pi e^{-\int_0^{\sigma(0)} \delta(s)ds}}{\mu d} \geq 1$;*

(iv) *at least two endemic equilibria if $R_c < \frac{\beta\pi e^{-\int_0^{\sigma(0)} \delta(s)ds}}{\mu d} < 1$, where R_c is a given positive constant;*

(v) *at least one endemic equilibrium if $R_c = \frac{\beta\pi e^{-\int_0^{\sigma(0)} \delta(s)ds}}{\mu d}$,*

(vi) *no endemic equilibrium if $\frac{\beta\pi e^{-\int_0^{\sigma(0)} \delta(s)ds}}{\mu d} < R_c$.*

Moreover, all the endemic equilibria, $\mathcal{E}^* = (x^*, y^*)$, satisfy

$$\beta\pi e^{-\int_0^{\sigma(y^*)} \delta(s)ds} = \mu(\beta y^* + d) \ and \ x^* = \frac{\pi}{\beta y^* + d}. \tag{10}$$

Remark 6 Let $\bar{x} = \frac{\pi}{d}$ and R_0 be the following positive number

$$R_0 = \frac{\beta\bar{x} e^{-\int_0^{\sigma(0)} \delta(s)ds}}{\mu}. \tag{11}$$

The quantity R_0 is called the basic reproductive ratio (or basic reproduction number), and is defined as the number of secondary infections produced by a single infective in a totally susceptible population. Here, R_0 is determined by the number of exposed individuals that an infectious individual produces, on average, $\frac{\beta\bar{x}}{\mu}$ during their average lifespan ($\frac{1}{\mu}$), and the survival probability $e^{-\int_0^{\sigma(0)} \delta(s)ds}$ into the infectious state. Generally, the quantity R_0 determines whether a given disease may spread ($R_0 > 1$), or die out ($R_0 < 1$) in a population. For a review on R_0 see Heffernan et al. (2005).

6 Asymptotic stability of the trivial steady state

In the next theorem, we give a sufficient condition for the disease-free steady state of (7), when it is unique, to be globally asymptotically stable. Let α be the positive real value given by $\alpha = e^{\int_{\sigma^*}^{\sigma(0)} \delta(s)ds}$ such that $\sigma^* = \inf_{\phi \in C} \sigma(\phi) \geq 0$.

Theorem 7 *Assume that*

$$\alpha R_0 < 1. \tag{12}$$

Then, the disease-free equilibrium of (7) is globally asymptotically stable.

Next, we analyze the local asymptotic stability of the disease-free equilibrium of system (7), $\mathcal{E}_f = (\overline{x}, 0)$, by studying the sign of the real parts of eigenvalues of the associated characteristic equation (see Hartung et al. 2006; Walther 2003 for more details about linearization and stability of state-dependent delay differential equations).

Linearizing system (7) at an equilibrium $(x^e, y^e) \in (R^+)^2$ gives the following linear system

$$\begin{cases} x'(t) = -\beta x(t) y^e - \beta y(t) x^e - dx(t), \\ y'(t) = \beta e^{-\int_0^{\sigma(y^e)} \delta(s)ds} y^e \left(x(t - \sigma(y^e)) - \delta(\sigma(y^e)) \sigma'(y^e) y(t) x^e \right) \\ \qquad + \beta e^{-\int_0^{\sigma(y^e)} \delta(s)ds} x^e y(t - \sigma(y^e)) - \mu y(t). \end{cases}$$

Substituting the Anstaz $\mathcal{E}_0 e^{\lambda t}$, where $\mathcal{E}_0 = (x_0, y_0)$, leads to

$$\begin{cases} \lambda e^{\lambda t} x_0 = -\beta e^{\lambda t} x_0 y^e - \beta e^{\lambda t} y_0 x^e - d e^{\lambda t} x_0, \\ \lambda e^{\lambda t} y_0 = \beta e^{-\int_0^{\sigma(y^e)} \delta(s)ds} y^e \left(e^{\lambda(t-\sigma(y^e))} x_0 - \delta(\sigma(y^e)) \sigma'(y^e) e^{\lambda t} y_0 x^e \right) \\ \qquad + \beta x^e e^{-\int_0^{\sigma(y^e)} \delta(s)ds} e^{\lambda(t-\sigma(y^e))} y_0 - \mu e^{\lambda t} y_0. \end{cases}$$

Without loss of generality, we may assume $y_0 = 1$. Eliminating $e^{\lambda t}$, we obtain $x_0 = -\frac{\beta x_e}{\lambda + d + \beta y^e}$ where λ is a root of the characteristic functions

$$\begin{aligned} \Delta(\lambda) = &\; \lambda + \mu - \beta x^e e^{-\int_0^{\sigma(y^e)} \delta(s)ds} e^{-\lambda \sigma(y^e)} \\ &+ \beta e^{-\int_0^{\sigma(y^e)} \delta(s)ds} y^e \left(e^{-\lambda \sigma(y^e)} \frac{\beta x_e}{\lambda + d + \beta y^e} + \delta(\sigma(y^e)) \sigma'(y^e) x^e \right). \end{aligned} \tag{13}$$

We easily obtain the following theorem.

Theorem 8 *The DFE $\mathcal{E}_f = (\overline{x}, 0)$ of (7) is unstable when $R_0 > 1$, and locally asymptotically stable when $R_0 < 1$.*

7 Bifurcation analysis

7.1 Transcritical bifurcation

This section is devoted to the local asymptotic stability analysis of the positive steady state $\mathcal{E}^*$ of (7). We are going to investigate the sign of real parts of eigenvalues of (13) to obtain the existence of a transcritical bifurcation. Throughout this section, we assume the function σ is given by $\sigma(\phi) = \nu \tilde{\sigma}(\phi)$, where ν is a positive parameter and $\tilde{\sigma} : C^+ \to R^+$ is a positive, decreasing, bounded and differentiable function.

Equation (7) reads

$$
\begin{cases}
x'(t) = \pi - \beta x(t) y(t) - d x(t), \\
y'(t) = \beta e^{-\int_0^{v\tilde{\sigma}(y_t)} \delta(s)ds} x(t - v\tilde{\sigma}(y_t)) y_t(t - v\tilde{\sigma}(y_t))) - \mu y(t).
\end{cases} \tag{14}
$$

Moreover, we assume conditions (9) and $R_0 > 1$ hold, to ensure the existence of the positive steady state $\mathcal{E}^*$ of (7). We will study the behaviour of solutions around the positive steady state $\mathcal{E}^* \equiv (x^*, y^*)$ when the parameter v changes and condition (9) holds true.

One can see that $R_0 \leq 1$ is equivalent to $v \geq v_0$ where v_0 is a positive value given by

$$
v_0 = \varrho^{-1} \left(\log \left(\frac{\mu d}{\beta \pi} \right) \right) \text{ and } \varrho(v) = \int_0^{v\tilde{\sigma}(0)} \delta(s)ds.
$$

This describes the fact that exposure duration cannot be too long for system (14) to exhibit a steady state other than the disease-free equilibrium. In other words, a long period of exposure will render the endemic equilibria unachievable.

The positive steady state $\mathcal{E}^* \equiv (x^*, y^*)$ depends on the parameter $v \in [0, v_0)$ and y^* is given implicitly by

$$
\beta \pi e^{-\int_0^{v\tilde{\sigma}(y^*(v))} \delta(s)ds} = \mu(\beta y^*(v) + d), \qquad v \in [0, v_0). \tag{15}
$$

Hence, by the Implicit Functions Theorem, y^* is a decreasing continuously differentiable function of v. Taking v as a real parameter, our purpose is to prove the existence of the transcritical bifurcation of (14).

From (13), the characteristic equation associated with $\mathcal{E}^*(v)$ is written as

$$
\begin{aligned}
\Delta(\lambda, v) = {} & \lambda + \mu + v\overline{\alpha}(v)\tilde{\sigma}'(y^*(v))e^{-\int_0^{v\tilde{\sigma}(y^*(v))} \delta(s)ds} \\
& + \overline{\beta}(v, \lambda) e^{-\int_0^{v\tilde{\sigma}(y^*(v))} \delta(s)ds} e^{-\lambda v\tilde{\sigma}(y^*(v))},
\end{aligned} \tag{16}
$$

where

$$
\overline{\alpha}(v) = \beta y^*(v) x^*(v) \delta(v\tilde{\sigma}(y^*(v))) \quad \text{and} \quad \overline{\beta}(v, \lambda) = \beta x^*(v) \left(\frac{\beta y^*(v)}{\lambda + d + \beta y^*(v)} - 1 \right).
$$

The next result states the existence of a transcritical bifurcation of the positive steady state when $v = v_0$. The proof is given in Appendix E.

Theorem 9 *Assume that condition (9) holds. When $v = v_0$, the positive steady state undergoes a transcritical bifurcation, that is for $v < v_0$, v close to v_0, the positive steady state is locally asymptotically stable, whereas, the trivial steady state is unstable, and for $v > v_0$ the DFE is locally asymptotically stable of (14).*

7.2 Backward bifurcation

When condition (9) does not hold, the case (iv) of Proposition (5) indicates the existence of at least two endemic equilibria, $\mathcal{E}_m = (x_m, y_m)$ and $\mathcal{E}_M = (x_M, y_M)$. Therefore, a backward bifurcation may occur for values of R_0 such that $R_c < R_0 < 1$ (where the locally-asymptotically stable DFE co-exists with a locally-asymptotically endemic equilibrium).

The two equilibria, denoted $\mathcal{E}_m = (x_m, y_m)$ and $\mathcal{E}_M = (x_M, y_M)$, that we will choose are those for which, y_m and y_M are the first two solutions of equation $\chi(y) = \mu$ given by (19) with $\chi'(y_m) > 0$ and $\chi'(y_M) < 0$. Thus,

$$\beta + \nu\delta(\nu\tilde{\sigma}(y_m(\nu)))\tilde{\sigma}'(y_m(\nu))\,(d + \beta y_m(\nu)) < 0,$$
$$\beta + \nu\delta(\nu\tilde{\sigma}(y_M(\nu)))\tilde{\sigma}'(y_M(\nu))\,(d + \beta y_M(\mu)) > 0. \tag{17}$$

We state and prove the following theorem. The proof is given in Appendix F.

Theorem 10 *Assume that condition (9) does not hold. When $\nu = \nu_0$, the system (14) undergoes a backward bifurcation. That is, for $\nu < \nu_0$, ν close to ν_0, there is only one positive steady state which is locally asymptotically stable whereas the trivial steady state is unstable; and for $\nu \geq \nu_0$, ν close to ν_0, the DFE together with an endemic equilibrium are locally asymptotically stable whereas a second positive steady state exists and is unstable.*

Remark 11 Note that in the case of no additive exposure, i.e, $b = 0$, system (7) is a system of constant-delay differential equations. Moreover, no backward bifurcation occurs. Indeed, in the absence of additive exposure, condition (9) holds true for all parameters of system (7). Generally, there is a positive threshold b_1^* above which the backward bifurcation appears and another positive threshold b_2^* below which the backward bifurcation disappears. To prove this, we need to emphasize the dependence of the delay function σ by the number of contacts during the exposure period, b. Namely, $\sigma(b, y) = \sigma(y)$ for $b \geq 0$ and $y \geq 0$. Note that, for any $b \geq 0$ and $y \geq 0$,

$$\sigma(b, 0) = \sigma(0, y) = \sigma(0, 0) = \frac{1}{r}\ln\left(\frac{A}{c}\right).$$

Consider the function $\hat{\chi}$ given, for $b \geq 0$ and $y \geq 0$, by

$$\hat{\chi}(b, y) = \frac{\beta\pi e^{-\int_0^{\sigma(b,y)}\delta(s)ds}}{\beta y + d}.$$

Note that $\hat{\chi}$ has the same values as the function χ defined in (19) for each b and y. When $b = 0$, this function will be given by

$$\hat{\chi}(0, y) := \frac{\beta\pi e^{-\int_0^{\sigma(0,0)}\delta(s)ds}}{\beta y + d}$$

and satisfies $\hat\chi(0, y) < \hat\chi(0, 0)$ for all $y \geq 0$ and $\hat\chi(b, 0) = \hat\chi(0, 0)$ for all $y \geq 0$. Furthermore, χ is increasing by means of $b > 0$. Using the equation $\Psi(\sigma(b, z), z) = 0$ for $z \in R$, where Ψ is the function given in (1), the derivative of the function $\sigma(b, .)$ is given by

$$\sigma_z'(b, z) = -\frac{bc}{(1 + kz)^2} \frac{\int_{-\sigma(b,z)}^{0} e^{-ru}\,du}{rce^{r\sigma(b,z)} + \frac{bcz}{1+kz}\left(e^{r\sigma(b,z))} - 1\right)}.$$

In particular, we have

$$\sigma_z'(0, z) = 0, \quad \sigma_z'(b, 0) = -b\frac{\int_{-\sigma(0,0)}^{0} e^{-ru}\,du}{re^{r\sigma(0,0)}} \quad \text{and} \quad \lim_{b\to\infty} \sigma_z'(b, 0) = -\infty.$$

On the other hand, $\hat\chi(b, .)$ is differentiable and its derivative, for each $b \geq 0$, is given by

$$\hat\chi_y{'}(b, y) = \beta\pi e^{-\int_0^{\sigma(b,y)} \delta(s)ds} \frac{-\sigma_z'(b, y)\delta(\sigma(b, y))\,(\beta y + d) - \beta}{(\beta y + d)^2}.$$

Thus, $\hat\chi_y{'}(0, 0) = -\pi e^{-\int_0^{\sigma(0,0)} \delta(s)ds} \frac{\beta^2}{d^2} < 0$ and $\lim_{b\to\infty} \hat\chi_y{'}(b, 0) = +\infty$. Furthermore, for each $b \geq 0$, $\hat\chi_y{'}(., 0)$ is an increasing function. Hence, since $\hat\chi'(., 0)$ is continuous function on R^+, there exists a unique $b_1^* > 0$ such that $\hat\chi_y{'}(b_1^*, 0) = 0$, $\hat\chi_y{'}(b, 0) < 0$ for $b \in [0, b_1^*[$ and $\hat\chi'(b, 0) > 0$ for $b > b_1^*$. In particular, for each $b > b_1^*$, there exists $y^* > 0$ close to zero and satisfies $\chi(b, y^*) > \chi(b, 0)$. This means that the backward bifurcation appears for all $b > b_1^*$ (see the proof of Proposition 5).

On the other hand, for $y > 0$,

$$\hat\chi_y{'}(0, y) = -e^{-\int_0^{\sigma(0,0)} \delta(s)ds} \frac{\beta^2\pi}{(\beta y + d)^2} < 0.$$

Thus, there exists $b_2^* > 0$ such that, for $b < b_2^*$, $\chi(b, y) < \chi(b, 0)$ for all $y > 0$. Finally, the backward bifurcation disappears for all $b < b_2^*$

8 Discussion

In this paper, we have proposed an immuno-epidemiological model with threshold delay to understand the effect of the duration of latency and how this is affected by multiple exposures to a pathogen. We find that, when the basic reproductive ratio $R_0 < 1$, the model has a locally-asymptotically stable DFE, however, to eradicate an infectious disease, it may not be sufficient to reduce R_0 below unity. For example, a small increase in the transmission rate, (β), causes a large increase in the number of disease cases. A subsequent small decrease in the transmission rate does not lead to the sudden disappearance of the endemic disease. Decreasing the number of exposures, b,

has the effect of eradicating the disease (see Remark 11). Another eradication factor is the exposure duration (ν) which cannot be too long for system (14) to exhibit a steady state other than the eradication of infection.

In the case of the forward transcritical bifurcation ($\nu \in [0, \nu_0)$), long exposed periods (ν) lead to the eradication of infection. This is meaningful since, from Eq. (5), a long exposed period to reach the threshold A needs either a small amount of the pathogen load introduced to the body (c), or a low internal growth production rate (r) of the pathogen. However, large amounts of the pathogen load introduced to the body during the exposed period (ν) lead to a shorter time for the exposed individual to become infectious.

In the case of bistability, the asymptotic behavior of the proportion of infectives depends on the initial conditions. Here, a large initial number of infectives can cause a large endemic equilibrium to arise rather suddenly even if other parameters, such as β and $\sigma(0)$, reduce $R_0 < 1$. To eradicate the infectious disease here, R_0 must be further reduced.

Our work has several limitations. There is clearly still room to strengthen condition (9) and to find more relevant biological interpretations of our results. Of particular importance, our results need to be extended to specifically incorporate vaccination events. Besides incorporating vaccination, work is needed to account for a transmission rate that depends on the pathogen load of an infectious individuals or on the duration of exposure.

Future infectious disease research would benefit by striving to not only continue to understand the properties of an invading pathogen, or the body's response to infections, but how these properties jointly affect the propagation of an infection throughout a population. These initial results offer a refinement to current immuno-epidemiological modelling methodology, and reinforce how coupling principles of pathogen dynamics and immunology in-host with epidemiology can provide insight into a multi-scaled description of an infection.

Overall, these results constitute an important step towards articulating an integrated, more refined epidemiological theory of the reciprocal influences between host-pathogen interactions, epidemiological mixing, and disease spread.

Appendix A: Proof of Lemma 1

Proof Let t be a fixed positive real value. Since $V(t, .)$ is an increasing function for $a \geq 0$ such that $V(t, a) \leq A$, then there exist a unique $\tau(t) \geq 0$ which is the first instant such that $V(t, \tau(t)) = A$. Furthermore, $V(t, a) \leq A$ is equivalent to $0 \leq a \leq \tau(t)$. Now, differentiating both sides of the equation $V(t, \tau(t)) = A$ with respect to t, we obtain

$$\frac{\partial}{\partial a} V(t, \tau(t)) \frac{d}{dt} (t - \tau(t)) = rV(t, \tau(t)) + F(I(t)).$$

Thus, since $V(t, a)$ is increasing for $a \leq \tau(t)$ and the right hand side of the above equation is positive, the function $t - \tau(t)$ is increasing for $t \geq 0$. Using the characteristic method (See, Webb 1985), we obtain, for $a \leq \tau(t)$ and $0 \leq a \leq t$,

$$V(t, a) = ce^{ra} + \int_{-a}^{0} e^{-ru} F(I(t + u)) du.$$

Thus, $V(t, \tau(t)) = A$ leads to

$$ce^{r\tau(t)} + \int_{-\tau(t)}^{0} e^{-ru} F(I(t + u)) du = A.$$

Furthermore, τ is bounded on $[0, \infty[$ and, for $t \in [0, \infty[$,

$$\tau(t) \leq \frac{1}{r} \ln\left(\frac{A}{c}\right).$$

$\square$

Appendix B: Proof of Lemma 3

Proof To prove this Lemma, we will use a global implicit function theorem (GIFT) in Ichiraku (1985, Theorem 3) (See Appendix 1). In what follows, we will prove conditions 1–3 of this theorem:

1) Let $\phi \in C$. We need to solve the equation $\Psi(s, \phi) = 0$ for $s > 0$. This last equation can be written as

$$\int_{-s}^{0} e^{ru} F(\phi(u)) du + ce^{rs} - A = 0.$$

Remember that $c < A$. Thus, $\Delta(0, \phi) = c - A < 0$. Moreover, since $\Psi(s, \phi) > ce^{rs} - A$, $\lim_{s \to \infty} \Psi(s, \phi) = \infty$. Hence, there exists $s_0 > 0$ such that $\Psi(s_0, \phi) = 0$. On the other hand, the derivative $D_s \Psi(s, \phi)$ is given by

$$D_s \Psi(s, \phi) = rce^{rs} + e^{rs} F(\phi(-s)) - F(\phi(0)).$$

However, since $k > \frac{b}{r}$, we have,

$$\max_{x \geq 0}(F(x)) = \frac{bc}{k} < rce^{rs}, \quad \text{for all } s > 0.$$

Thus, $D_s \Psi(s, \phi) > 0$ for all $s > 0$ and $\Psi(., \phi)$ is increasing. Consequently, there exists unique $s_0 > 0$ such that $\Psi(s_0, \phi) = 0$.

2) The second partial derivative $D_\phi \Delta(s, \phi)$ is given by

$$D_\phi \Delta(s, \phi) = \int\limits_{-s}^{0} e^{-ru} DF(\phi(u))du$$

for $s \geq 0$ and $\phi \in C$. This map is invertible since F is an increasing function.

3) Let $(s_i, \phi_i)_{i \geq 1}$ be a sequence of vectors in $R^+ \times C$ such that $\Psi(s_i, \phi_i) = 0$ and the sequence ϕ_i converge to ϕ in C as i tends to infinity. Thus, for $i \geq 1$,

$$\int\limits_{-s_i}^{0} e^{-ru} F(\phi(u))du = -ce^{rs} + A > 0$$

and, consequently,

$$ce^{rs_i} < A.$$

This implies that the sequence s_i is bounded and, thus, there xists a subsequence of s_i which converges to a point in R^+.

Finally, using the GIFT theorem in Ichiraku (1985, Theorem 3), there exists a unique and continuous map $\sigma : C \rightarrow R^+$ such that $\Psi(\sigma(\phi), \phi) = 0$ for any $\phi \in C$. The function σ is given, for $\phi \in C$, by

$$\int\limits_{-\sigma(\phi)}^{0} e^{-ru} F(\phi(u))du = -ce^{r\sigma(\phi)} + A.$$

Thus, since $F(0) = 0$, $e^{r\sigma(0)} = \frac{A}{c}$. Consequently,

$$\sigma(0) = \frac{1}{r} \ln\left(\frac{A}{c}\right) > 0.$$

Using the global function theorem, for Banach spaces, in Dieudonné et al. (1960, chp. 6, pp. 270), we conclude that the map σ s continuously differentiable and satisfy, for all $\psi \in C$,

$$\sigma'(\phi)\psi = -\frac{D_\phi \Psi(\sigma(\phi), \phi)\psi}{D_s \Psi(\sigma(\phi), \phi)} = -\frac{\int_{-\sigma(\phi)}^{0} e^{-ru} DF(\phi(u))\psi(u)du}{ce^{r\sigma(\phi)} + e^{r\sigma(\phi)} F(\phi(-\sigma(\phi))) - F(\phi(0))} \tag{18}$$

for $\phi \in C$. Since $D_\phi \Psi(\sigma(\phi), \phi)$ and $D_\phi \Psi(\sigma(\phi), \phi)$ are positive for all $\phi \in C$, the function $\sigma(.)$ is decreasing. This achieves the proof of the Lemma. □

Appendix C: Proof of Proposition 5

Proof Define, for $y \geq 0$, the function

$$\chi(y) := \frac{\beta \pi e^{-\int_0^{\sigma(y)} \delta(s)ds}}{\beta y + d}. \tag{19}$$

Note that any nontrivial equilibrium $\mathcal{E}^* = (x^*, y^*)$ atisfy $\chi(y^*) = \mu$. We have

$$\chi(0) = \frac{\beta \pi e^{-\int_0^{\sigma(0)} \delta(s)ds}}{d} \qquad \text{and} \qquad \lim_{y \to +\infty} \chi(y) = 0.$$

Moreover, condition (9) is equivalent to $\chi(z) < \chi(0)$ for all z positive. Hence, the existence and number of positive equilibria depends on the sign of $\chi(0) - \mu$. This prove all the assertions of the proposition. $\qquad \square$

Appendix D: Proof of Theorem 7

Proof Let $\alpha \in R$ be given by $\alpha = e^{\int_{\sigma^*}^{\sigma(0)} \delta(s)ds}$ such that $\sigma^* = \inf_{\phi \in C} \sigma(\phi) \geq 0$. Assume that $\alpha R_0 < 1$, then for ϵ small enough

$$\alpha \left(\frac{\pi}{d} + \epsilon\right) \beta e^{-\int_0^{\sigma(0)} \delta(s)ds} < \mu. \tag{20}$$

Furthermore we already have

$$\limsup_{t \to \infty} x(t) \leq \frac{\pi}{d}.$$

Then for $\epsilon > 0$, there is $T_1 > 0$ such that $x(t) \leq \frac{\pi}{d} + \epsilon$. Thus, for $t \geq T_1 + \sigma(0)$

$$\dot{y}(t) \leq -\mu y(t) + \beta e^{-\int_0^{\sigma(y_t)} \delta(s)ds} y_t \left(\frac{\pi}{d} + \epsilon\right) y(t - \sigma(y_t)) \tag{21}$$

$$\leq -\mu y(t) + \beta \left(\frac{\pi}{d} + \epsilon\right) e^{-\int_0^{\sigma^*} \delta(s)ds} y(t - \sigma(y_t))$$

$$\leq -\mu y(t) + \alpha \beta \left(\frac{\pi}{d} + \epsilon\right) e^{-\int_0^{\sigma(0)} \delta(s)ds} y(t - \sigma(y_t))$$

Now, consider the linear scalar equation

$$\dot{y}(t) = -\mu y(t) + \alpha \beta \left(\frac{\pi}{d} + \epsilon\right) e^{-\int_0^{\sigma(0)} \delta(s)ds} y(t - \sigma(0)). \tag{22}$$

We claim that the trivial equilibrium $y = 0$ of Eq. (22) is globally asymptotically stable (GAS). Indeed, Eq. (22) is linear and its characteristic equation around the

trivial equilibrium $y = 0$ is given by

$$\Delta(\lambda) = \lambda + \mu - \alpha\beta \left(\frac{\pi}{d} + \epsilon \right) e^{- \int_0^{\sigma(0)} \delta(s)ds} e^{-\lambda\sigma(0)} = 0.$$

Let $\lambda = a + ib$ a root of $\Delta(\lambda)$ with $a \geq 0$. Then $| e^{-\lambda\sigma(0)} | \leq 1$. Therefore, from the above characteristic equation and (20),

$$\begin{aligned} | \lambda + \mu | &= \alpha\beta \left(\frac{\pi}{d} + \epsilon \right) e^{- \int_0^{\sigma(0)} \delta(s)ds} | e^{-\lambda\sigma(0)} | \\ &\leq \alpha\beta \left(\frac{\pi}{d} + \epsilon \right) e^{- \int_0^{\sigma(0)} \delta(s)ds} \\ &< \mu. \end{aligned}$$

However, since $a \geq 0$, $| \lambda + \mu | \geq \mu$ hold true. This is a contradiction and, therefore, every root of the equation $\Delta(\lambda) = 0$ has negative real part and the trivial equilibrium $y = 0$ of the linear equation (22) is locally asymptotically stable. It follows directly that $y = 0$ of this equation is also GAS.

On the other hand, from Lemma (3), and (18), σ is continuously differentiable and its derivative σ' is bounded on C. Thus, using Theorem 2.4 of Gyori and Hartung (2007) paper, we deduce that the trivial equilibrium of equation

$$\dot{y}(t) = -\mu y(t) + \alpha\beta \left(\frac{\pi}{d} + \epsilon \right) e^{- \int_0^{\sigma(0)} \delta(s)ds} y(t - \sigma(y_t))$$

is GAS. Let $(x(t), y(t))$ be a solution of Eq. (7) with positive initial condition. It follows, by comparison, that $y(t)$ converges to 0 as t tends to ∞. Furthermore, integrating the first equation in (7) and taking the limit, we obtain $\lim_{t\to\infty} x(t) = \frac{\pi}{d}$. The proof of Theorem 7 is complete. □

Appendix E: Proof of Theorem 8

Proof The characteristic equation (13), when $y^e = 0$ and $x^e = \overline{x}$, is given by

$$\Delta(\lambda) = \lambda + \mu - \beta\overline{x}e^{- \int_0^{\sigma(0)} \delta(s)ds} e^{-\lambda\sigma(0)} = 0. \tag{23}$$

Thus,

$$\begin{aligned} \Delta(0) &= -\beta\overline{x}e^{- \int_0^{\sigma(0)} \delta(s)ds} + \alpha = \mu \left(1 - \frac{\beta\overline{x}}{\mu} e^{- \int_0^{\sigma(0)} \delta(s)ds} \right), \\ &= \mu (1 - R_0) \end{aligned}$$

and $\lim_{\lambda\to\infty} \Delta(\lambda) = +\infty$. When $R_0 > 1$ holds, then $\Delta(0) < 0$, so there exists $\lambda_0 > 0$ such that $\Delta(\lambda_0) = 0$. This proves the instability of the trivial steady state.

Conversely, assume that $R_0 < 1$. Let $\lambda = a + ib$ a root of $\Delta(\lambda)$ with $a \geq 0$. Then $| e^{-\lambda \sigma(0)} | \leq 1$. Therefore, from (23),

$$
\begin{aligned}
| \lambda + \mu | &= \beta \overline{x} e^{- \int_0^{\sigma(0)} \delta(s) ds} | e^{-\lambda \sigma(0)} | \\
&\leq \beta \overline{x} e^{- \int_0^{\sigma(0)} \delta(s) ds} \\
&= R_0 \mu < \mu.
\end{aligned}
$$

However, since $a \geq 0$, $| \lambda + \mu | \geq \mu$ hold true. This is a contradiction and, therefore, every root of the equation $\Delta(\lambda) = 0$ has negative real part and the DFE $\mathcal{E}_f$ is locally asymptotically stable. $\qquad \square$

Appendix E: Proof of Theorem 9

Proof The stability and uniqueness of the DFE follows from Theorems 7 and 8. We investigate local asymptotic stability of $\mathcal{E}^*(\nu)$ in a neighborhood of ν_0. We have

$$
\Delta(0, \nu) = \mu - \beta x^*(\nu) e^{- \int_0^{\nu \tilde{\sigma}(y^*(\nu))} \delta(s) ds} + Q(\nu),
$$

where

$$
\begin{aligned}
Q(\nu) &= \beta e^{- \int_0^{\nu \tilde{\sigma}(y(\nu))} \delta(s) ds} \frac{\beta x^*(\nu) y^*(\nu)}{d + \beta y^*(\nu)} \\
&\quad + \nu \beta y^*(\nu) x^*(\nu) e^{- \int_0^{\nu \tilde{\sigma}(y^*(\nu))} \delta(s) ds} \delta(\nu \tilde{\sigma}(y^*(\nu))) \tilde{\sigma}'(y^*(\nu)) \\
&= \beta e^{- \int_0^{\nu \tilde{\sigma}(y^*(\nu))} \delta(s) ds} x^*(\nu) y^*(\nu) \left(\frac{\beta}{d + \beta y^*(\nu)} + \nu \delta(\nu \tilde{\sigma}(y^*(\nu))) \tilde{\sigma}'(y^*(\nu)) \right).
\end{aligned}
$$

However, $\frac{\beta}{d + \beta y^*(\nu)} + \nu \delta(\nu \tilde{\sigma}(y^*(\nu))) \tilde{\sigma}'(y^*(\nu)) > 0$. Therefore, $Q(\nu) > 0$. On the other hand, from (15),

$$
\mu - \beta x^*(\nu) e^{- \int_0^{\nu \tilde{\sigma}(y^*(\nu))} \delta(s) ds} = \mu - \frac{\beta e^{- \int_0^{\nu \tilde{\sigma}(y^*(\nu))} \delta(s) ds}}{d + \beta y^*(\nu)} = 0.
$$

Thus, $\Delta(0, \nu) > 0$, which prove that $\lambda = 0$ is not a root of $\Delta(\lambda, \nu) = 0$ for ν close to $\overline{\nu}$.

Therefore, $\Delta(\lambda, \nu) = 0$ is equivalent to

$$
\lambda + \mu + \beta x_M(\nu) e^{- \int_0^{\nu \tilde{\sigma}(y_M(\nu))} \delta(s) ds} e^{-\lambda \nu \tilde{\sigma}(y^*(\nu))} = Q_1 + Q_2, \tag{24}
$$

where

$$
Q_1 = \frac{\beta y^*(\nu)}{\lambda + d + \beta y^*(\nu)} \beta x^*(\nu) e^{- \int_0^{\nu \tilde{\sigma}(y^*(\nu))} \delta(s) ds} e^{-\lambda \nu \tilde{\sigma}(y^*(\nu))}
$$

and

$$Q_2 = \nu\beta x^*(\nu)\delta(\nu\tilde{\sigma}(y^*(\nu)))y^*(\nu)\tilde{\sigma}'(y^*(\nu))e^{-\int_0^{\nu\tilde{\sigma}(y^*(\nu))}\delta(s)ds}.$$

Now, let $\lambda = a + ib$ be a root of $\Delta(\lambda, \nu)$ with $a \geq 0$. Then $\lambda \neq 0$ and $\mid e^{-\lambda\nu\tilde{\sigma}(y^*(\nu))} \mid \leq 1$. Thus

$$\mid Q_1 + Q_2 \mid = \beta x^*(\nu)e^{-\int_0^{\nu\tilde{\sigma}(y^*(\nu))}\delta(s)ds}\mid \frac{\beta y^*(\nu)}{\lambda + d + \beta y^*(\nu)}e^{-\lambda\nu\tilde{\sigma}(y^*(\nu))}$$

$$+\nu y^*(\nu)\delta(\nu\tilde{\sigma}(y^*(\nu)))\tilde{\sigma}'(y^*(\nu)) \mid$$

$$\leq \beta x^*(\nu)y^*(\nu)e^{-\int_0^{\nu\tilde{\sigma}(y^*(\nu))}\delta(s)ds}\mid \frac{\beta}{d + \beta y^*(\nu)} + \nu\delta(\nu\tilde{\sigma}(y^*(\nu)))\tilde{\sigma}'(y^*(\nu)) \mid.$$

However

$$\frac{\beta}{d + \beta y^*(\nu)} + \delta(\nu\tilde{\sigma}(y^*(\nu)))\nu\tilde{\sigma}'(y^*(\nu)) > 0$$

and $\tilde{\sigma}'(y^*(\nu)) < 0$. Thus,

$$\mid Q_1 + Q_2 \mid \leq \beta x^*(\nu)e^{-\int_0^{\nu\tilde{\sigma}(y^*(\nu))}\delta(s)ds}\left(\frac{\beta}{d + \beta y^*(\nu)} + \delta(\nu\tilde{\sigma}(y^*(\nu)))\nu\tilde{\sigma}'(y^*(\nu))\right)y^*(\nu)$$

$$\leq \beta x^*(\nu)e^{-\int_0^{\mu\tilde{\sigma}(y^*(\nu))}\delta(s)ds}.$$

Moreover, $\mu = \beta x^*(\nu)e^{-\int_0^{\nu\tilde{\sigma}(y^*(\nu))}\delta(s)ds}$ and $\mid \lambda + \mu \mid > \mu$. Thus,

$$\beta x^*(\nu)e^{-\int_0^{\nu\tilde{\sigma}(y^*(\nu))}\delta(s)ds}\mid 1 + e^{-\lambda\nu\tilde{\sigma}(y^*(\nu))} \mid$$

$$\leq \mid \mu + \beta x^*(\nu)e^{-\int_0^{\nu\tilde{\sigma}(y^*(\nu))}\delta(s)ds}e^{-\lambda\nu\tilde{\sigma}(y^*(\nu))} \mid$$

$$\leq \mid \lambda + \mu + \beta p\gamma x^*(\nu)e^{-\int_0^{\nu\tilde{\sigma}(y^*(\nu))}\delta(s)ds}e^{-\lambda\nu\tilde{\sigma}(y^*(\nu))} \mid$$

$$= \mid Q_1 + Q_2 \mid$$

$$\leq \beta x^*(\nu)e^{-\int_0^{\nu\tilde{\sigma}(y^*(\nu))}\delta(s)ds}.$$

Consequently,

$$\mid 1 + e^{-\lambda\nu\tilde{\sigma}(y^*(\mu))} \mid \leq 1,$$

which is false since $\lambda = 0$ is not a root of $\Delta(\lambda, \nu)$. Therefore, every root has negative real part and the local asymptotic stability of the positive steady state immediately follows □

Appendix F: Proof of Theorem 10

Proof We will prove that the equilibrium $\mathcal{E}_M(\nu) = (x_M(\nu), y_M(\nu))$ is locally asymptotically stable and $\mathcal{E}_m(\nu) = (x_m(\nu), y_m(\nu))$ is unstable when $R_0 < 1$ or equivalently

$\nu > \nu_0$. First of all, we prove that $\lambda = 0$ is not a root of $\Delta(\lambda, \nu) = 0$ for ν close to $\overline{\nu}$. Using the above definition of $\overline{\alpha}(\nu)$ and $\overline{\beta}(\nu, 0)$,

$$\Delta(0, \nu) = \mu - \beta x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s) ds} + Q(\nu),$$

where

$$Q(\nu) = \beta e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s) ds} \frac{\beta x_M(\nu) y_M(\nu)}{d + \beta y_M(\nu)}$$

$$+ \nu\beta y_M(\nu) x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s) ds} \delta(\nu\tilde{\sigma}(y_M(\nu))) \tilde{\sigma}'(y_M(\nu))$$

$$= \beta e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s) ds} x_M(\nu) y_M(\nu) \left(\frac{\beta}{d + \beta y_M(\nu)} + \nu\delta(\nu\tilde{\sigma}(y_M(\nu))) \tilde{\sigma}'(y_M(\nu)) \right).$$

However, from (17), $\frac{\beta}{d + \beta y_M(\nu)} + \nu\delta(\nu\tilde{\sigma}(y_M(\nu))) \tilde{\sigma}'(y_M(\nu)) > 0$. Therefore, $Q(\nu) > 0$. On the other hand, from (15),

$$\mu - \beta x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s) ds} = \mu - \frac{\pi\beta e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s) ds}}{d + \beta y_M(\nu)} = 0.$$

Thus, $\Delta(0, \nu) > 0$, which prove that $\lambda = 0$ is not a root of $\Delta(\lambda, \nu) = 0$ for ν close to ν_0,

Therefore, $\Delta(\lambda, \nu) = 0$ is equivalent to

$$\lambda + \mu + \beta x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s) ds} e^{-\lambda\nu\tilde{\sigma}(y_M(\nu))} = Q_1 + Q_2, \qquad (25)$$

where

$$Q_1 = \frac{\beta y_M(\nu)}{\lambda + d + \beta y_M(\nu)} \beta x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s) ds} e^{-\lambda\nu\tilde{\sigma}(y_M(\nu))}$$

and

$$Q_2 = \nu\beta x_M(\nu) \delta(\nu\tilde{\sigma}(y_M(\nu))) y_M(\nu) \tilde{\sigma}'(y_M(\nu)) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s) ds}.$$

Now, let $\lambda = a + ib$ be a root of $\Delta(\lambda, \nu)$ with $a \geq 0$. Then $\lambda \neq 0$ and $| e^{-\lambda\nu\tilde{\sigma}(z_M(\nu))} | \leq 1$. Thus,

$$| Q_1 + Q_2 | = \beta x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s) ds} | \frac{\beta y_M(\nu)}{\lambda + d + \beta y_M(\nu)} e^{-\lambda\nu\tilde{\sigma}(y_M(\nu))}$$

$$+ \nu y_M(\nu) \delta(\nu\tilde{\sigma}(y_M(\nu))) |$$

$$\leq \beta x_M(\nu) y_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s) ds} | \frac{\beta}{d + \beta y_M(\nu)}$$

$$+ \delta(\nu\tilde{\sigma}(y_M(\nu))) \nu\tilde{\sigma}'(y_M(\nu)) | .$$

However $\frac{\beta}{d+\beta y_M(\nu)} + \delta(\nu\tilde{\sigma}(y_M(\nu)))\nu\tilde{\sigma}'(y_M(\nu)) > 0$ and $\tilde{\sigma}'(y_M(\nu)) < 0$. Thus,

$$| Q_1 + Q_2 | \le \beta x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s)ds} \left(\frac{\beta}{d + \beta y_M(\nu)} + \delta(\nu\tilde{\sigma}(y_M(\nu)))\nu\tilde{\sigma}'(y_M(\nu)) \right) y_M(\nu)$$

$$\le \beta x_M(\nu) e^{-\int_0^{\mu\tilde{\sigma}(y_M(\nu))} \delta(s)ds}.$$

Moreover, $\mu = \beta x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s)ds}$ and $| \lambda + \mu | > \mu$. Thus,

$$\beta x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s)ds} | 1 + e^{-\lambda\nu\tilde{\sigma}(y_M(\nu))} |$$
$$\le | \mu + \beta x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s)ds} e^{-\lambda\nu\tilde{\sigma}(y_M(\nu))} |$$
$$\le | \lambda + \mu + \beta x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s)ds} e^{-\lambda\nu\tilde{\sigma}(y_M(\nu))} |$$
$$= | Q_1 + Q_2 |$$
$$\le \beta x_M(\nu) e^{-\int_0^{\nu\tilde{\sigma}(y_M(\nu))} \delta(s)ds}.$$

Consequently,

$$| 1 + e^{-\lambda\nu\tilde{\sigma}(y_M(\mu))} | \le 1,$$

which is false since $\lambda = 0$ is not a root of $\Delta(\lambda, \nu)$. Therefore, every root has negative real part and the endemic equilibrium $\mathcal{E}_M$ is locally asymptotically stable.

The characterstic equation associated to $\mathcal{E}_m(\nu) = (x_m(\nu), y_m(\nu))$ satisfies

$$\Delta(0, \nu) = \beta e^{-\int_0^{\nu\tilde{\sigma}(y_m(\nu))} \delta(s)ds} x_m(\nu) y_m(\nu) \left(\frac{\beta}{d + \beta y_m(\nu)} + \nu\delta(\nu\tilde{\sigma}(y_m(\nu)))\tilde{\sigma}'(y_m(\nu)) \right).$$

However, from (17), $\frac{\beta}{d+\beta y_m(\nu)} + \nu\delta(\nu\tilde{\sigma} y_m(\nu)))\tilde{\sigma}'(y_m(\nu)) < 0$. Therefore, $\Delta(0, \nu) < 0$. Thus, there exists $\lambda^* > 0$ such that $\Delta(\lambda^*, \nu) = 0$. This concludes the proof of the theorem. $\square$

References

Alt W (1979) Periodic solutions of some autonomous differential equations with variable time delay. Lecture notes in mathematics, vol 730. Springer-Verlag, New York, Berlin, pp 16–31

Adimy M, Crauste F, Hbid M, Qesmi R (2010) Stability and hopf bifurcation for a cell population model withstate-dependent delay. SIAM J Appl Math 70(5):1611–1633

Alexander M, Moghadas S (2004) Periodicity in an epidemicmodelwith a generalized non-linearincidence. Math Biosci 189(1):75–96

André J, Gandon S (2006) Vaccination, within-host dynamics, and virulence evolution. Evolution 60(1):13–23

Anderson RM, May RM (1991) Infectious diseases of humans: dynamics and control. Oxford University Press, Oxford

Brauer F (1990) Models for the spread of universally fatal diseases. J Math Biol 28(4):451–462

Brauer F, Castillo-Chavez C (2001) Mathematical models in population biology and epidemiology, vol 40. Springer-Verlag, Berlin-Heidelberg-New York

Brauer F, Van den Driessche P, Wu J (2008) Mathematical epidemiology. Lecture notes in mathematical epidemiology, vol 1945. Springer Verlag, New York

Castillo-Chavez C, Blower S, Van den Driessche P, Kirschner D, Yakubu AA (eds) (2002) Mathematical approaches for emerging and reemerging infectious diseases: models, methods and theory. Springer-verlag, Berlin- Heidelberg-New York

Cooke K (1967) Functional-differential equations; some models and perturbation problems. Differential equations and dynamical systems. Academic Press, New York, pp 167–183

Cooke K, Van Den Driessche P (1996) Analysis of an seirs epidemicmodel with two delays. J Mathe Biol 35(2):240–260

Cowling B, Ip D, Fang V, Suntarattiwong P, Olsen S, Levy J, Uyeki T, Leung G, Peiris J, Chotpitayasunondh T, Nishiura H, Simmerman J (2013) Aerosol transmission is an important model of influenza a virus spread. Nat Commun 4(2013/06/04/online).

Diekmann O, Heesterbeek JAP (2000) Mathematical epidemiology of infectious diseases: model building, analysis and interpretation. Wiley series in mathematical and computational biology. John Wiley and Sons, ltd., Chichester.

Diekmann O, Heesterbeek J, Metz J (1990) On the definition and the computation of the basic reproduction ratio r 0 in models for infectious diseases in heterogeneous populations. J Math Biol 28(4):365–382

Dieudonné J, Dieudonné J, Mathematician F, Dieudonné J (1960) Foundations of modern analysis, vol 286. Academic press, New York

Dushoff J (1996) Incorporating mmunological ideas in epidemiological models. J Theor Biol 180(3):181–187

Fine PE (2003) The interval betweensuccessive cases of an infectious disease. Am J Epidemiol 158(11):1039–1047

Gatica J, Waltman P (1982) A threshold model of antigen antibody dynamics with fading memory. Nonlinear Phenom Math Sci, 425–439.

Gatica J, Waltman P (1988) A system of functional differential equations modeling threshold phenomena. Appl Anal 28(1):39–50

Gilchrist M, Sasaki A (2002) Modeling host-parasite coevolution: a nested approach based onmechanistic models. J Theor Biol 218(3):289–308

Gyori I, Hartung F (2007) Exponential stability of a state-dependent delay system. Discret Contin Dyn Syst 18(4):773

Hadeler K, Van den Driessche P (1997) Backward bifurcation in epidemic control. Math Biosci 146(1):15–35

Hartung F, Krisztin T, Walther H, Wu J (2006) Functional differential equationswith state-dependent delays: theoryand applications. Handb Differ Equ Ordinary Differ Equ 3:435–545

Hellriegel B (2001) Immunoepidemiology-bridging the gap between immunology and epidemiology. Trends Parasitol 17(2):102–106

Hethcote H (2000) The mathematicsof infectious diseases. SIAM Review 42(4):599–653

Heffernan J, Keeling M (2009) Implications of vaccination and waning immunity. Proc Royal Soc B Biol Sci 276(1664):2071–2080

Heffernan J, Smith R, Wahl L (2005) Perspectives on the basic reproductive ratio. J Royal Soc Interface 2(4):281–293

Hoppensteadt F, Waltman P (1971) A problem in the theory ofepidemics, ii. Mathe Biosci 12(1):133–145

Hollinger F, Robinson W, Purcell R, Gerin J, Ticehurst J (1991) Viral Hepatitis, 2nd edn. Raven Press, New York

Hughes G, Kitching R, Woolhouse M (2002) Dose-dependent responses ofsheep inoculated intranasally with a type o foot-and-mouth diseasevirus. J Comp Pathol 127(1):22–29. doi:10.1053/jcpa.2002.0560.http://www.sciencedirect.com/science/article/pii/S0021997502905608

Ichiraku S (1985) Anote on global implicit function theorems. Circuits and systems. IEEE Trans 32(5):503–505

Kuang Y, Smith H (1992) Slowly oscillating periodic solutions of autonomous state-dependent delay equations. Nonlinear Anal TMA 19(9):855–872

Martcheva M, Sergei S (2006) An epidemic model structured by hostimmunity. J Biol Syst 14(02):185–203

Mallet-Paret J, Nussbaum R, Paraskevopoulos P (1994) Periodic solutions to functional differential equations with multiple state-dependent time lags. Topological methods in nonlinear analysis. J Juliusz Schauder Center 3:101–162

Mahaffy J, Bélair J, Mackey M (1998) Hematopoietic model with moving boundary condition and statedependent delay: applications in erythropoiesis. J Theor Biol 190(2):135–146

Ma Z, Zhou Y, Wu J (2009) Modeling and dynamics of infectious diseases. Series in contemporary applied mathematics CAM, vol 11. Higher Education Press, Beijing.

Metz JAJ, Diekmann O (1986) The dynamics of physiologically structured populations. Springer-Verlag, Berlin

Michaelis L, Menten M (1913) Die kinetik der invertinwirkung. Biochem z 49(333–369):352

Nowak M, May R (2001) Virus dynamics: mathematical principles of immunology and virology.Oxford University Press, USA.

Pradeu T, Carosella E (2006) The self model and the conception of biological identity in immunology. Biol Philos 21(2):235–252

Qesmi R, Wu J, Wu J, Heffernan J (2010) Influence of backward bifurcation in a model of hepatitis b and cviruses. Math Biosci 224(2):118–125

Qesmi R, ElSaadany S, Heffernan J, Wu J (2011) A hepatitis b and c virus model with age since infection that exhibits backward bifurcation. SIAM J Appl Math 71(4):1509–1530

Smith H, Kuang Y (1992) Periodic solutions of differential delay equations with threshold-type delays. ContempMath 129:153–176

Spekreijse D, Bouma A, Stegeman J, Koch G, de Jong M (2011) The effect of inoculation dose of a highly pathogenic avian influenza virus strain H5N1 on the infectiousness of chickens. Vet Microbiol 147(12):59–66. doi:10.1016/j.vetmic.2010.06.012. http://www.sciencedirect.com/science/article/pii/S0378113510003147

Thieme H (2003) Mathematics in population biology. Princeton University Press, Princeton

Van den Driessche P, Watmough J (2002) Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math Biosci 180(1):29–48

Waltman P (1974) Deterministic threshold models in the theory of epidemics. Springer, Verlag

Walther H (2003) The solution manifold and¡i¿ c¡/i¿¡ sup¿ 1¡/sup¿ -smoothness for differentialequations with state-dependent delay. J Differ Equ 195(1):46–65

Walther H (2009) Algebraic-delay differential systems, state-dependent delay, and temporal order ofreactions. J Dyn Differ Equ 21(1):195–232

Webb G (1985) Theory of nonlinear age-dependent population dynamics. Marcel Dekker, New York

Wodarz D (2006) Killer cell dynamics: mathematical and computational approaches to immunology. Series: interdisciplinary applied mathematics. Springer-Verlag, New York.