CANADIAN APPLIED
MATHEMATICS QUARTERLY
Volume 19, Number 3, Fall 2011

GLOBAL DYNAMICS OF A DISEASE MODEL INCLUDING LATENCY WITH DISTRIBUTED DELAYS

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ABSTRACT. An infectious disease model with two distributed delays is proposed to incorporate both the latency of the infection in a vector and the latent period in an infected host. The basic reproduction number $\mathcal{R}_0$ is defined and shown to give a sharp threshold. Specifically, if $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium is globally asymptotically stable and the disease dies out; whereas if $\mathcal{R}_0 > 1$, then a Lyapunov functional is used to prove that the endemic equilibrium is globally asymptotically stable, thus the disease persists at an endemic level. This model includes and extends several delay models in the literature.

1 Introduction Disease models study the transmission dynamics of infectious diseases in the host population. The infectious agents can be viruses, bacteria, or parasites. Normally a certain amount of pathogen is required to break down the natural defence (immune) system of a host; the pathogen also takes a certain time to develop inside a host. As a result, after the initial infection, a host can stay in a latent period before becoming infectious. Such a latency in disease transmission is modelled by introducing a new compartment into a mathematical model, called a latent or exposed compartment. The resulting model is normally an ordinary differential equation system, in which the latent period is assumed to be exponentially distributed; see, for example, [**16, 18**]. If the latent period is assumed to satisfy a general distribution, then a delay and/or integro-differential system is formed; see, for example, [**26, 28**].

Some infectious diseases, such as malaria, dengue, West Nile virus and Lyme disease, are transmitted indirectly to the host population by

AMS subject classification: 34K20, 92D30.
Keywords: Disease model, latency, distributed delay, global stability, Lyapunov functional.

vectors (e.g., mosquitos or ticks). The vector population is infected by an infectious host and then can transmit the disease to a susceptible host. These vector-borne diseases are modelled by taking both host and vector population into account; see, for example, [**4, 6, 24**] and [**1,** Chapter 14]. An alternative way is to use delay differential equations approximating the interplay between the vector and the pathogen. For example, the latent delay in a vector can be used to describe the time needed before the pathogen develops sufficiently in the vector to pass the infection to a susceptible host [**3**].

The recent papers [**11, 12**] have separately included these two kinds of latent delays (in the host and in the vector) in different models and provided nice comparisons between them. In this paper, we propose a general disease model to simultaneously incorporate both latent delays. The model is formulated in Section 2 and can be used to model transmission and spread of vector-borne or water-borne diseases. The basic reproduction number $\mathcal{R}_0$ is defined in Section 3, and proved in Sections 3 and 4 to determine a sharp threshold. Specifically, if $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium is globally asymptotically stable and the disease dies out; whereas if $\mathcal{R}_0 > 1$, then there exists a unique endemic equilibrium that is globally asymptotically stable, thus the disease persists at a positive level. Section 5 contains discussion of our results showing specifically how they include and extend some previous results for directly and indirectly transmitted disease models.

2 Model formulation Let $S(t), E(t), I(t)$ and $R(t)$ be the number of individuals in the susceptible, exposed (latent), infectious and recovered class, respectively, with the total population $N(t) = S(t) + E(t) + I(t) + R(t)$. Assume that $A > 0$ represents the constant recruitment, $m > 0$ represents the natural mortality rate, and $\alpha \geq 0$ represents the mortality rate due to the disease. The rate of change of $N(t)$ is

$$N'(t) = A - mN(t) - \alpha I(t). \tag{2.1}$$

Let $\gamma > 0$ be the recovery rate, then the rate of change of $R(t)$ is

$$R'(t) = \gamma I(t) - mR(t). \tag{2.2}$$

Susceptible individuals can be infected directly, or indirectly by infectious individuals via either vectors for vector-borne diseases or contaminated water for water-borne diseases. To account for latency in the

vector, the disease transmission at time t is assumed to take the form

$$\int_0^\infty f(S(t), I(t-r))\, k(r)\, dr. \tag{2.3}$$

Here, f is a general incidence function, that is assumed to be sufficiently smooth and $f(S,I) \geq 0, f(S,0) = f(0,I) = 0$ for all $S, I \geq 0$. In the literature, function f takes different forms, such as mass action incidence $f(S,I) = \lambda SI$ and saturating incidence $f(S,I) = \lambda S \frac{I}{B+I}$, where B is a positive constant. The kernel function k is assumed to be nonnegative and integrable with

$$K = \int_0^\infty k(r)\, dr > 0.$$

For vector-borne diseases, function $k(r)$ represents the vector infection rate due to the presence of infectious hosts times the fraction of the vector population surviving to time r, which is the time taken for the vector to become infectious after infection from the host. For water-borne diseases, $k(r)$ represents the pathogen shedding rate of infectious hosts times the fraction of pathogen surviving in the environment that was shed from infectious individuals r time units ago. For both cases, it is biologically reasonable to assume the time r is finite, which is a special case of (2.3); however, we keep the infinite interval in our study to incorporate possible reservoirs in the environment/vector where pathogen was shed a long time ago. For directly transmitted diseases, $k(r)$ is a Dirac function, $k(r) = \delta(r)$, thus the disease transmission term (2.3) becomes $f(S(t), I(t))$.

Using the general transmission term (2.3), the rate of change of $S(t)$ is written as

$$S'(t) = A - \int_0^\infty f(S(t), I(t-r))\, k(r)\, dr - mS(t). \tag{2.4}$$

To account for latency in the host, let $P(t)$ denote the probability (without taking death into account) that an exposed individual still remains in the exposed class t time units after entering the exposed class. It is assumed that $P : [0,\infty) \to [0,1]$ is nonincreasing, piecewise continuous with possibly finitely many jumps and satisfies $P(0+) = 1$, $\lim_{t\to\infty} P(t) = 0$ with $\int_0^\infty P(u)du$ positive and finite. The proportion of exposed individuals can be expressed by the integral

$$E(t) = \int_0^t e^{-m(t-u)}\, P(t-u) \int_0^\infty f(S(u), I(u-r))\, k(r)\, dr\, du. \tag{2.5}$$

Differentiating (2.5) gives

$$
\begin{aligned}
E'(t) &= \int_0^\infty f(S(t), I(t-r))\, k(r)\, dr - mE(t) \\
&\quad + \int_0^t e^{-m(t-u)}\, d_t P(t-u) \\
&\quad \times \int_0^\infty f(S(u), I(u-r))\, k(r)\, dr\, du \\
&= \int_0^\infty f(S(t), I(t-r))\, k(r)\, dr - mE(t) \\
&\quad + \int_0^t e^{-mu}\, d_u P(u) \\
&\quad \times \int_0^\infty f(S(t-u), I(t-u-r))\, k(r)\, dr\, du.
\end{aligned} \tag{2.6}
$$

Since $P(t)$ is possibly not differentiable and has finitely many jumps, the integral in (2.6) is interpreted in the sense of Riemann-Stieltjes.

Substituting (2.1), (2.2), (2.4) and (2.6) into $I'(t) = N'(t) - S'(t) - E'(t) - R'(t)$ leads to

$$
\begin{aligned}
I'(t) &= -\int_0^t e^{-mu}\, d_u P(u) \\
&\quad \times \int_0^\infty f(S(t-u), I(t-u-r)) k(r)\, dr\, du - (m+\alpha+\gamma) I(t).
\end{aligned} \tag{2.7}
$$

Notice that $E(t)$ and $R(t)$ do not appear in (2.4) and (2.7). Hence we can study the reduced system of $S(t)$ and $I(t)$ first and then (2.5) or (2.6), and (2.2) determine the behaviors of $E(t)$ and $R(t)$. In the rest of the paper, we study the delay integro-differential equation system consisting of (2.4) & (2.7), and its limiting system [**23**] for the endemic equilibrium. The limiting system is

$$
\begin{aligned}
S'(t) &= A - \int_0^\infty f(S(t), I(t-r))\, k(r)\, dr - mS(t), \\
I'(t) &= -\int_0^\infty e^{-mu}\, d_u P(u) \int_0^\infty f(S(t-u), I(t-u-r)) \\
&\quad \times k(r)\, dr\, du - (m+\alpha+\gamma) I(t).
\end{aligned} \tag{2.8}
$$

To the best of our knowledge, model (2.2), (2.4), (2.6), (2.7) is the first disease model in the literature that simultaneously incorporates both distributed delays for the latency of the infection in a vector and the latent period in an infected host.

Our model includes as special cases many earlier SEIR models in the literature, such as the standard ordinary differential equation (ODE) model [**13, 14, 16, 18**], the delay model with latency in a vector [**3, 11, 12, 19, 20, 21, 22**], the model with host latent delay [**26**] and the delay model incorporating age-structure and varying infectivity [**25**]. For example, when k is assumed to be a Dirac function, say $k(r) = \delta(r - \tau)$, the discrete time lag τ represents a constant latency of the infection in the vector population. If further letting $\tau \to 0$, then the indirect disease transmission can be treated as direct transmission, thus our model can also be used to model directly transmitted diseases. The probability function P can also take different special forms; for example, $P(t) = e^{-\epsilon t}$ with mean host latent period $1/\epsilon$. In this case, when the disease is transmitted directly (i.e., $k(r) = \delta(r)$), our model becomes the standard ODE SEIR model [**13, 14, 16, 18**]. Similarly, when choosing different functions for f, k and P, our model contains various delay models cited above; see Section 5 for further discussion.

Since both systems (2.4) & (2.7) and (2.8) include infinite delays, a suitable phase space is needed (see, for example, [**2**] and references therein). Assume that there exists a positive number λ such that $\int_0^\infty k(r)e^{\lambda r}\,dr < \infty$. Define the following Banach space of fading memory type [**2**]

$$\mathcal{C} = \Big\{\phi \in C((-\infty, 0], \mathbb{R}) : \phi(s)e^{\lambda s} \text{ is uniformly continuous on } (-\infty, 0], \text{ and } \sup_{s\le 0} |\phi(s)|e^{\lambda s} < \infty\Big\},$$

with the norm $\|\phi\| = \sup_{s\le 0} |\phi(s)|e^{\lambda s}$. For $\psi \in C(\mathbb{R}, \mathbb{R})$ and $t > 0$, let $\psi_t \in \mathcal{C}$ be such that $\psi_t(s) = \psi(t + s)$, $s \in (-\infty, 0]$. Consider both systems (2.4) & (2.7) and (2.8) in the phase space

$$X = \mathcal{C} \times \mathcal{C}. \tag{2.9}$$

Let $\phi, \psi \in \mathcal{C}$ such that $\phi(s) \ge 0$, $\psi(s) \ge 0$ for all $s \in (-\infty, 0]$. For any solution (S_t, I_t) of systems (2.4) & (2.7) and (2.8) with initial conditions (ϕ, ψ), the standard theory of functional differential equations [**10**] implies that $S_t, I_t \in \mathcal{C}$ for all $t > 0$. It can be verified that the set

$$\Gamma = \Big\{ (S(\cdot), I(\cdot)) \in X : \, S(s) \geq 0, I(s) \geq 0, \\ s \in (-\infty, 0], S(0) + I(0) \leq \frac{A}{m} \Big\}$$

is positively invariant for each of the systems (2.4) & (2.7) and (2.8). It follows that if $S(0) + I(0) \leq \frac{A}{m}$, then $S(t) + I(t) \leq \frac{A}{m}$ for all $t > 0$. The set Γ is commonly called the feasible region, in which we study the disease dynamics.

3 Basic reproduction number and the disease-free equilibrium Both systems (2.4) & (2.7) and (2.8) always have a disease-free equilibrium (DFE) $P_0 = (S_0, 0)$ with $S_0 = A/m$. In this section, we study the global stability of P_0.

Assume that

$$0 < \lim_{I \to 0^+} \frac{f(S, I)}{I} =: C(S) \leq +\infty, \quad \forall\, 0 < S \leq S_0.$$

Let $c = C(S_0)$. If the incidence function f is differentiable, then $c = \frac{\partial f}{\partial I}(S_0, 0)$. Let

$$Q = - \lim_{t \to \infty} \int_0^t e^{-mu} d_u P(u)\, du, \tag{3.1}$$

and it can be verified that $0 < Q < 1$. Define the basic reproduction number as

$$\mathcal{R}_0 = \frac{cQK}{m + \alpha + \gamma}. \tag{3.2}$$

Here, $1/(m + \alpha + \gamma)$ is the average time hosts stay in the infectious compartment taking death into account, c is the disease transmission rate in a totally susceptible host population, Q is the probability of hosts surviving the latent stage, and K is the disease transmission of vector to host times the average time vectors stay infectious. We refer readers to [**1, 5, 29**] for more discussion about $\mathcal{R}_0$.

The following theorem shows that the basic reproduction number $\mathcal{R}_0$ determines the stability of the DFE P_0. The proofs of Theorem 3.1 and Theorem 4.2 in Section 4 utilize global Lyapunov functions that are used in [**13, 14**] and global Lyapunov functionals that are motivated by the work in [**20, 21, 22**].

Theorem 3.1. *Suppose that the incidence function satisfies*

$$f(S,I) \le C(S)I < cI \quad \textit{for all} \quad 0 \le S < S_0,\ I > 0. \tag{3.3}$$

For both systems (2.4) & (2.7) *and* (2.8)*, if* $\mathcal{R}_0 \le 1$*, then the disease-free equilibrium* P_0 *is globally asymptotically stable in* Γ*; if* $\mathcal{R}_0 > 1$*, then* P_0 *is unstable.*

Proof. For the system (2.4) & (2.7), consider a Lyapunov functional $L = L_1 + L_2 + L_3$ with

$$L_1 = I + Q\int_{S(t)}^{S_0}\left(\lim_{x\to 0^+}\frac{f(S_0,x)}{f(\xi,x)} - 1\right)d\xi,$$

$$L_2 = \int_0^t Q(u)\int_0^\infty f(S(t-u), I(t-u-r))k(r)\,dr\,du,$$

and

$$L_3 = \frac{m+\alpha+\gamma}{K}\int_0^\infty I(t-u)\int_u^\infty k(r)\,dr\,du.$$

Here, constant Q is defined in (3.1) and function $Q(r)$ is defined as follows

$$Q(r) = -\int_r^\infty e^{-mu} d_u P(u)\,du. \tag{3.4}$$

Notice that $Q = Q(0)$. It is easy to see that $L_2 \ge 0, L_3 \ge 0$, and that $L_1 \ge 0$ in Γ under the assumption (3.3). Thus, $L \ge 0$ and $L = 0$ if and only if $S = S_0$ and $I(r) = 0$ for all $r \le t$. Differentiating L_1, L_2 and L_3 along the system (2.4) & (2.7) and using integration by parts for L_2' and L_3' give

$$\begin{aligned} L_1' &= I' + QS'\left(1 - \lim_{x\to 0^+}\frac{f(S_0,x)}{f(S(t),x)}\right) \\ &= -\int_0^t e^{-mu}\,d_u P(u) \\ &\quad\times \int_0^\infty f(S(t-u), I(t-u-r))\,k(r)\,dr\,du \end{aligned} \tag{3.5}$$

$$
\begin{aligned}
&- (m+\alpha+\gamma)I(t) \\
&+ Q\bigg(A - \int_0^\infty f(S(t), I(t-r))\, k(r)\, dr - A\frac{S(t)}{S_0}\bigg) \\
&\cdot \bigg(1 - \lim_{x\to 0^+} \frac{f(S_0,x)}{f(S(t),x)}\bigg) \\
&= -\int_0^t e^{-mu}\, d_u P(u) \\
&\times \int_0^\infty f(S(t-u), I(t-u-r))\, k(r)\, dr\, du \\
&- (m+\alpha+\gamma)I(t) \\
&+ QA\bigg(1 - \frac{S(t)}{S_0}\bigg)\bigg(1 - \lim_{x\to 0^+} \frac{f(S_0,x)}{f(S(t),x)}\bigg) \\
&- Q\bigg(1 - \lim_{x\to 0^+} \frac{f(S_0,x)}{f(S(t),x)}\bigg) \int_0^\infty f(S(t), I(t-r))\, k(r)\, dr \\
&\le -\int_0^t e^{-mu}\, d_u P(u) \int_0^\infty f(S(t-u), I(t-u-r)) \\
&\times k(r)\, dr\, du - (m+\alpha+\gamma)I(t) \\
&- Q\bigg(1 - \lim_{x\to 0^+} \frac{f(S_0,x)}{f(S(t),x)}\bigg) \int_0^\infty f(S(t), I(t-r)) k(r)\, dr,
\end{aligned}
$$

$$
\begin{aligned}
L_2' &= Q(t) \int_0^\infty f(S(0), I(-r))\, k(r)\, dr \\
&\quad + \int_0^t Q(u) \frac{\partial}{\partial t}\bigg(\int_0^\infty f(S(t-u), I(t-u-r))\, k(r)\, dr\bigg)\, du \\
&= Q(t) \int_0^\infty f(S(0), I(-r))\, k(r)\, dr + \int_0^t Q(u)\,(-1) \\
&\quad \times \frac{\partial}{\partial u}\bigg(\int_0^\infty f(S(t-u), I(t-u-r))\, k(r)\, dr\bigg)\, du \\
&= Q(t) \int_0^\infty f(S(0), I(-r))\, k(r)\, dr \\
&\quad - \bigg[Q(u) \int_0^\infty f(S(t-u), I(t-u-r))\, k(r)\, dr\bigg]_{u=0}^{t}
\end{aligned} \tag{3.6}
$$

$$+\int_0^t \frac{dQ(u)}{du}\int_0^\infty f(S(t-u),I(t-u-r))\,k(r)\,dr\,du$$
$$=Q\int_0^\infty f(S(t),I(t-r))\,k(r)\,dr+\int_0^t e^{-mu}d_uP(u)$$
$$\times\int_0^\infty f(S(t-u),I(t-u-r))\,k(r)\,dr\,du$$

and

$$L_3'=\frac{m+\alpha+\gamma}{K}\int_0^\infty \frac{\partial}{\partial t}\Big(I(t-u)\Big)\int_u^\infty k(r)\,dr\,du \tag{3.7}$$
$$=\frac{m+\alpha+\gamma}{K}\int_0^\infty (-1)\frac{\partial}{\partial u}\Big(I(t-u)\Big)\int_u^\infty k(r)\,dr\,du$$
$$=-\frac{m+\alpha+\gamma}{K}\Big[I(t-u)\int_u^\infty k(r)\,dr\Big]_{u=0}^\infty$$
$$-\frac{m+\alpha+\gamma}{K}\int_0^\infty I(t-u)k(u)\,du$$
$$=(m+\alpha+\gamma)I(t)-\frac{m+\alpha+\gamma}{K}\int_0^\infty I(t-u)k(u)\,du.$$

Hence, adding (3.5), (3.6) and (3.7) and using (3.3), it follows that

(3.8)
$$L'=L_1'+L_2'+L_3'$$
$$\le\int_0^\infty\Big(\lim_{x\to0^+}\frac{Qf(S(t),I(t-r))f(S_0,x)}{f(S(t),x)}$$
$$-\frac{m+\alpha+\gamma}{K}I(t-r)\Big)\,k(r)\,dr$$
$$\le\int_0^\infty\Big(\lim_{x\to0^+}\frac{QI(t-r)f(S_0,x)}{x}-\frac{m+\alpha+\gamma}{K}I(t-r)\Big)\,k(r)\,dr$$
$$=\int_0^\infty\Big((\mathcal{R}_0-1)\frac{m+\alpha+\gamma}{K}I(t-r)\Big)\,k(r)\,dr\le0\qquad\text{if }\mathcal{R}_0\le1.$$

It can be verified that the largest invariant set where $L'=0$ is the singleton $\{P_0\}$. Using the LaSalle-Lyapunov Theorem (see [**15,** Theorem

3.4.7] or [**9,** Theorem 5.3.1]), it follows that the DFE P_0 attracts all solutions of system (2.4) & (2.7) whose initial conditions are in Γ. Furthermore, the Lyapunov functional L can be used to show that P_0 is locally stable using the same proof as that for Corollary 5.3.1 in [**9**]; see also Lemma A.1 in [**26**]. Therefore, P_0 is globally asymptotically stable in Γ.

If $\mathcal{R}_0 > 1$ and $I \neq 0$, it follows that

$$(\mathcal{R}_0 - 1)(m + \alpha + \gamma)I(t) > 0. \tag{3.9}$$

Inequality (3.9) and continuity imply that $L' > 0$ in a small enough neighbourhood of P_0 in the interior of Γ, denoted by $\overset{\circ}{\Gamma}$. Therefore, P_0 is unstable when $\mathcal{R}_0 > 1$.

For the limiting system (2.8), a similar Lyapunov functional as L (i.e., changing the upper limit of the outer integral in L_1 to infinity) can be used to prove the global stability of the DFE. We omit the detailed proof since most of the derivations are similar as those for the system (2.4) & (2.7), which we have shown above. □

Remark 1. It can be easily verified that assumption (3.3) holds for mass action incidence, or if the incidence function $f(S, I)$ is (i) monotone increasing in S and I and (ii) concave down in I. The latter condition (ii) can be replaced by $f(S, I)/I$ is monotone decreasing in I. Hence, Theorem 3.1 holds for different incidence functions that are commonly used in the literature, such as $f(S, I) = \lambda S^q I^p$, $f(S, I) = \lambda S^q \frac{I^p}{B+I^p}$ with constants p, q, λ, B positive and $p \leq 1$, or $f(S, I) = \lambda \frac{SI}{S+I}$.

Remark 2. When the incidence function takes the form $f(S, I) = \lambda S^q I^p$ or $f(S, I) = \lambda S^q \frac{I^p}{B+I^p}$ with constants $p > 1$ and $q, \lambda, B > 0$, assumption (3.3) fails; in fact, when $p > 1$, the disease-free equilibrium P_0 is always locally stable but the global dynamics can be very complicated; see, for example, [**18**].

4 Global stability of the endemic equilibrium In this section we study the dynamical behavior when the basic reproduction number $\mathcal{R}_0 > 1$. In particular, we prove the existence, uniqueness and global stability of an endemic equilibrium for the limiting system (2.8) and show all solutions of (2.4) & (2.7) approach the endemic equilibrium of (2.8) as time tends to infinity.

The endemic equilibrium $(S^*, I^*),\ S^*, I^* > 0$ of system (2.8) satisfies

$$\begin{aligned} A - Kf(S^*, I^*) - mS^* &= 0, \\ QKf(S^*, I^*) - (m + \alpha + \gamma)I^* &= 0, \end{aligned} \tag{4.1}$$

which are also the equilibrium equations for the ordinary differential equation system

$$\begin{aligned} S' &= A - Kf(S, I) - mS, \\ I' &= Kf(S, I) - \frac{m + \alpha + \gamma}{Q} I. \end{aligned} \tag{4.2}$$

Notice that the basic reproduction number for (4.2) has the same expression as the basic reproduction number for (2.8), i.e., as defined in (3.2). It has been shown in the literature (see, for example, [**17,** Section 7]) that there exists at least one endemic equilibrium for (4.2) if $\mathcal{R}_0 > 1$, where $\mathcal{R}_0$ is defined in (3.2). Therefore, we have the following lemma about the existence of the endemic equilibrium for (2.8).

Lemma 4.1. *If $\mathcal{R}_0 > 1$, then there exists at least one endemic equilibrium $P^* = (S^*, I^*) \in \overset{\circ}{\Gamma}$ for the limiting system* (2.8).

The uniqueness and global stability of P^* is established in the following theorem.

Theorem 4.2. *Assume that there exists a function $\Phi : (0, S_0] \to \mathbb{R}_+$ such that*

$$(S - S^*)(\Phi(S) - \Phi(S^*)) > 0, \qquad 0 < S \le S_0, S \ne S^*, \tag{4.3}$$

and

$$\left(\frac{f(S, I)\Phi(S^*)}{f(S^*, I^*)\Phi(S)} - 1\right)\left(1 - \frac{f(S^*, I^*)\Phi(S)I}{f(S, I)\Phi(S^*)I^*}\right) \le 0, \qquad 0 < S \le S_0,\ I > 0. \tag{4.4}$$

If $\mathcal{R}_0 > 1$, then the endemic equilibrium P^* of the limiting system (2.8) *is unique and globally asymptotically stable in $\overset{\circ}{\Gamma}$; furthermore, all solutions of the system* (2.4) & (2.7) *starting in $\overset{\circ}{\Gamma}$ approach the endemic equilibrium P^* of* (2.8).

Proof. Define a nonnegative function $\Theta : (0,\infty) \to [0,\infty)$, $\Theta(x) = x - 1 - \ln x$ with $\Theta(x) = 0$ iff $x = 1$. Consider a Lyapunov functional $V = V_1 + V_2 + V_3$, where

$$V_1 = Q\int_{S^*}^{S} \frac{\Phi(\xi) - \Phi(S^*)}{\Phi(\xi)}\, d\xi + I^*\Theta\left(\frac{I}{I^*}\right),$$
$$V_2 = \int_0^\infty Q(u)\int_0^\infty f(S^*, I^*)\Theta\left(\frac{f(S(t-u), I(t-u-r))}{f(S^*, I^*)}\right)k(r)\, dr\, du,$$

and

$$V_3 = Q\int_0^\infty f(S^*, I^*)\Theta\left(\frac{I(t-u)}{I^*}\right)\int_u^\infty k(r)\, dr\, du.$$

Here, constant Q and function $Q(r)$ are defined in (3.1) and (3.4), respectively, and $Q(0) = Q$. From the definitions, $V_2 \geq 0$, $V_3 \geq 0$, and under assumption (4.3) it follows that $V_1 \geq 0$. Differentiating V_1 along the solution of (2.8), and using the equilibrium equations (4.1) and assumption (4.3) give

$$\begin{aligned}
V_1' &= QS'\left(1 - \frac{\Phi(S^*)}{\Phi(S(t))}\right) + I'\left(1 - \frac{I^*}{I(t)}\right) \\
&= Q\Bigg(Kf(S^*, I^*) + mS^* \\
&\quad - \int_0^\infty f(S(t), I(t-r))\, k(r)\, dr - mS(t)\Bigg) \\
&\quad \times \left(1 - \frac{\Phi(S^*)}{\Phi(S(t))}\right) - \Bigg(\int_0^\infty e^{-mu}\, d_u P(u) \\
&\quad \times \int_0^\infty f(S(t-u), I(t-u-r))\, k(r)\, dr\, du \\
&\quad + QKf(S^*, I^*)\frac{I(t)}{I^*}\Bigg)\left(1 - \frac{I^*}{I(t)}\right) \\
&= Q\left(Kf(S^*, I^*) - \int_0^\infty f(S(t), I(t-r))\, k(r)\, dr\right) \\
&\quad \times \left(1 - \frac{\Phi(S^*)}{\Phi(S(t))}\right) + Qm(S^* - S(t))\left(1 - \frac{\Phi(S^*)}{\Phi(S(t))}\right)
\end{aligned} \tag{4.5}$$

$$
\begin{aligned}
&- QKf(S^*, I^*)\frac{I(t)}{I^*} + QKf(S^*, I^*) \\
&- \left(1 - \frac{I^*}{I(t)}\right) \int_0^\infty e^{-mu}\, d_u P(u) \\
&\times \int_0^\infty f(S(t-u), I(t-u-r))\, k(r)\, dr\, du \\
&\leq 2QKf(S^*, I^*) - QKf(S^*, I^*)\frac{\Phi(S^*)}{\Phi(S)} - QKf(S^*, I^*)\frac{I(t)}{I^*} \\
&- Q\left(1 - \frac{\Phi(S^*)}{\Phi(S(t))}\right) \int_0^\infty f(S(t), I(t-r))\, k(r)\, dr \\
&- \left(1 - \frac{I^*}{I(t)}\right) \int_0^\infty e^{-mu}\, d_u P(u) \\
&\times \int_0^\infty f(S(t-u), I(t-u-r))\, k(r)\, dr\, du.
\end{aligned}
$$

Differentiating V_2 and V_3 along the solution of (2.8) and using integration by parts give

(4.6)

$$
\begin{aligned}
V_2' &= \int_0^\infty Q(u)\, \frac{\partial}{\partial t}\Big[\int_0^\infty f(S^*, I^*) \\
&\quad \times \Theta\left(\frac{f(S(t-u), I(t-u-r))}{f(S^*, I^*)}\right) k(r)\, dr\Big]\, du \\
&= \int_0^\infty Q(u)\, (-1)\, \frac{\partial}{\partial u}\Big[\int_0^\infty f(S^*, I^*) \\
&\quad \times \Theta\left(\frac{f(S(t-u), I(t-u-r))}{f(S^*, I^*)}\right) k(r)\, dr\Big]\, du \\
&= -\Big[Q(u) \int_0^\infty f(S^*, I^*)\, \Theta\left(\frac{f(S(t-u), I(t-u-r))}{f(S^*, I^*)}\right) k(r)\, dr\Big]_{u=0}^\infty \\
&\quad + \int_0^\infty \frac{dQ(u)}{du} \int_0^\infty f(S^*, I^*)\, \Theta\left(\frac{f(S(t-u), I(t-u-r))}{f(S^*, I^*)}\right) k(r)\, dr\, du \\
&= Q \int_0^\infty f(S^*, I^*)\, \Theta\left(\frac{f(S(t), I(t-r))}{f(S^*, I^*)}\right) k(r)\, dr \\
&\quad + \int_0^\infty e^{-mu} d_u P(u) \int_0^\infty f(S^*, I^*)
\end{aligned}
$$

$$\times \Theta\left(\frac{f(S(t-u),I(t-u-r))}{f(S^*,I^*)}\right) k(r)\,dr\,du$$

and

$$\begin{aligned}
V_3' &= Q\int_0^\infty f(S^*,I^*)\,\frac{\partial}{\partial t}\Theta\left(\frac{I(t-u)}{I^*}\right)\int_u^\infty k(r)\,dr\,du \\
&= Q\int_0^\infty f(S^*,I^*)\,(-1)\,\frac{\partial}{\partial u}\Theta\left(\frac{I(t-u)}{I^*}\right)\int_u^\infty k(r)\,dr\,du \\
&= -\left[Qf(S^*,I^*)\Theta\left(\frac{I(t-u)}{I^*}\right)\int_u^\infty k(r)\,dr\right]_{u=0}^\infty \\
&\qquad + Q\int_0^\infty f(S^*,I^*)\,\Theta\left(\frac{I(t-u)}{I^*}\right)\frac{d}{du}\left(\int_u^\infty k(r)\,dr\right)du \\
&= QKf(S^*,I^*)\Theta\left(\frac{I(t)}{I^*}\right) \\
&\qquad - Q\int_0^\infty f(S^*,I^*)\Theta\left(\frac{I(t-u)}{I^*}\right)k(u)\,du.
\end{aligned} \tag{4.7}$$

Adding (4.5), (4.6) and (4.7) together yields

$$\begin{aligned}
V' &= \int_0^\infty e^{-mu}(-d_uP(u))\int_0^\infty f(S^*,I^*)k(r) \\
&\qquad \times\left[2-\frac{\Phi(S^*)}{\Phi(S(t))}-\frac{I(t-r)}{I^*}+\frac{\Phi(S^*)f(S(t),I(t-r))}{\phi(S(t))f(S^*,I^*)}\right. \\
&\qquad -\frac{I^*f(S(t-u),I(t-u-r))}{I(t)f(S^*,I^*)} \\
&\qquad \left.+\ln\frac{I(t-r)f(S(t-u),I(t-u-r))}{I(t)f(S(t),I(t-r))}\right]dr\,du \\
&= \int_0^\infty e^{-mu}(-d_uP(u))\int_0^\infty f(S^*,I^*)k(r) \\
&\qquad \times\left[-\Theta\left(\frac{\Phi(S^*)}{\Phi(S(t))}\right)-\Theta\left(\frac{I^*f(S(t-u),I(t-u-r))}{I(t)f(S^*,I^*)}\right)\right. \\
&\qquad -\Theta\left(\frac{\Phi(S(t))f(S^*,I^*)I(t-r)}{\Phi(S^*)f(S(t),I(t-r))I^*}\right) \\
&\qquad \left.\times\left(\frac{\Phi(S^*)f(S(t),I(t-r))}{\Phi(S(t))f(S^*,I^*)}-1\right)\right.
\end{aligned}$$

$$\times \left(1 - \frac{\Phi(S(t))f(S^*, I^*)I(t-r)}{\Phi(S^*)f(S(t), I(t-r))I^*}\right)\Bigg] dr\, du$$
$$\leq 0.$$

The last inequality holds since $\Theta(x) \geq 0$ and assumption (4.4) holds. It can be verified that the largest invariant set where $V' = 0$ is the singleton $\{P^*\}$, thus the endemic equilibrium P^* of (2.8) is globally asymptotically stable in $\overset{\circ}{\Gamma}$, using the same argument as in the proof of Theorem 3.1. An immediate consequence of Theorem 7.2 in [**23**] is that P^* attracts all solutions of (2.4) & (2.7) starting in $\overset{\circ}{\Gamma}$. □

One common choice for the function Φ in Theorem 4.2 is $\Phi(S) = f(S, I^*)$. In this situation, inequalities (4.3) and (4.4) become

$$(S - S^*)(f(S, I^*) - f(S^*, I^*)) > 0, \qquad 0 < S \leq S_0,\, S \neq S^*$$

and

$$\left(\frac{f(S,I)}{f(S,I^*)} - 1\right)\left(1 - \frac{f(S,I^*)I}{f(S,I)I^*}\right) \leq 0, \quad 0 < S \leq S_0,\, I > 0.$$

If the incidence function $f(S, I)$ is mass action, or monotone increasing in S, I and concave down in I, then both the above inequalities are satisfied. Hence Theorem 4.2 holds for the incidence functions discussed in Remark 1. In particular, if the incidence function is assumed to be mass action or saturating incidence, then there exists a unique endemic equilibrium provided $\mathcal{R}_0 > 1$ and the endemic equilibrium is globally asymptotically stable. However, there are incidence functions, such as those in Remark 2, for which the result of Theorem 4.2 fails, multiple endemic equilibria may exist and periodic solutions may occur due to Hopf bifurcation; see, for example, [**18**].

5 Discussion The model (2.2), (2.4), (2.6), (2.7) and its limiting system (2.8) proposed here are general compartment SEIR models for infectious diseases that include both the latency of the infection in a vector and the latent period in an infected host. General nonlinear incidence and general kernel functions for both distributed latent delays are incorporated, thus including and extending several earlier delay models in the literature; see Table 1 for detailed discussion. In Table 1 note that τ is a constant latent period in the vector, and ω is a constant

latent period in the host. Our global stability results, Theorems 3.1 and 4.2, show that $\mathcal{R}_0$ acts as a sharp threshold, with disease dying out if $\mathcal{R}_0 \leq 1$, or becoming endemic if $\mathcal{R}_0 > 1$. In special cases they reduce to previous results in the references given in Table 1. The Lyapunov functionals constructed in the proofs of Theorems 3.1 and 4.2 contain as special cases (up to a constant) those in [**8, 11, 20, 21, 22**], but are different from those used in [**3, 12, 26**].

$f(S,I)$	$k(t)$	$P(t)$	reference
$\lambda\frac{SI}{S+I}$	$\delta(t)$ †	$H_\omega(t)$ ‡	Gourley *et al.* [**7,** Eq. (10)]
			Guo and Cai [**8,** Eq. (3)]
$F(S)G(I)$	$\delta(t)$	$H_\omega(t)$	Huang *et al.* [**12,** Eq. (15)]
$f(S,I)$	$\delta(t)$	$H_\omega(t)$	Huang and Takeuchi [**11,** Eq. (17)]
λSI	$\delta(t)$	$P(t)$	Shuai and van den Driessche [**26,** Eq. (2.6)]
λSI	$\delta(t-\tau)$	$H_0(t)$ ♯	Ma *et al.* [**19,** Eq. (1.1)]
			McCluskey [**21,** Eq. (5.1)]
$F(S)G(I)$	$\delta(t-\tau)$	$H_0(t)$	Huang *et al.* [**12,** Eq. (1)]
$f(S,I)$	$\delta(t-\tau)$	$H_0(t)$	Huang and Takeuchi [**11,** Eq. (1)]
λSI	$k(t)$	$H_0(t)$	Beretta and Takeuchi [**3,** Eq. (5)]
			Röst and Wu [**25,** Eqs. (2)-(3)] §
			McCluskey [**20,** Eq. (3)] §
λSI	$k(t)$ ¶	$H_0(t)$	McCluskey [**21,** Eq. (2.1)]
$f(S,I)$	$k(t)$ ¶	$H_0(t)$	McCluskey [**22,** Eq. (1)]

† A Dirac function ‡ A step function $H_\omega(t) = 1$ for all $0 \leq t \leq \omega$ and $H_\omega(t) = 0$ otherwise ♯ A step function $H_0(0) = 1$ and $H_0(t) = 0$ otherwise § After replacing variable E by I in the reference ¶ With compact support

TABLE 1: Special cases of model (2.2), (2.4), (2.6), (2.7)

For water-borne diseases, let $f(S,I) = \lambda SI$ (mass action), $k(t) = \frac{\beta}{\lambda}\delta(t)+\xi e^{-\eta t}$ (giving direct and indirect transmission) and $P(t) = H_0(t)$, then our model becomes

$$\begin{aligned} S'(t) &= A - \beta S(t)I(t) - \int_0^\infty \lambda S(t)I(t-r)\xi e^{-\eta r}\,dr - mS(t), \\ I'(t) &= \beta S(t)I(t) + \int_0^\infty \lambda S(t)I(t-r)\xi e^{-\eta r}\,dr - (m+\alpha+\gamma)I(t). \end{aligned} \tag{5.1}$$

Let $W(t) = \int_0^\infty I(t-r)\xi e^{-\eta r}\,dr = \int_{-\infty}^t I(u)\xi e^{-\eta(t-u)}\,du$ denote the number of pathogen in the contaminated water. Differentiating $W(t)$ and rewriting (5.1) lead to the following ODE system

$$\begin{aligned} S' &= A - \beta SI - \lambda SW - mS, \\ I' &= \beta SI + \lambda SW - (m+\alpha+\gamma)I, \\ W' &= \xi I - \eta W, \end{aligned} \tag{5.2}$$

which has previously been proposed in [**27**] to include both direct human-to-human transmission and indirect transmission via contaminated water for water-borne diseases such as cholera. Our Theorems 3.1 and 4.2 contain and extend the global stability results in [**27**].

Our model can serve as a general framework for modeling the spread and transmission of infectious diseases, such as vector-borne diseases (e.g., malaria, dengue, West Nile virus and Lyme disease) or water-borne diseases (e.g., cholera). Various heterogeneous structures such as heterogeneous spatial distribution of host and/or vector populations, heterogeneous susceptibility among host age groups, multiple infection stages in the host population, and multiple host and/or vector populations can be incorporated. The resulting models, customarily called multi-patch, multi-group or multi-stage models, may be useful for understanding the spatial spread of diseases and identifying optimal control interventions for diseases with latency in the host and/or in the vector.

Acknowledgments This research was supported in part by grants from the Natural Science and Engineering Research Council of Canada (NSERC) and from the Mprime project "Transmission Dynamics and Spatial Spread of Infectious Diseases: Modelling, Prediction and Control." Z. Shuai acknowledges the support of an NSERC Postdoctoral Fellowship, and partial funding to attend the 5th Geoffrey J. Butler Memorial Conference on Differential Equations and Population Biology at the University of Alberta in Edmonton, July 25–30, 2011.

REFERENCES

1. R. M. Anderson and R. M. May, *Infectious Diseases of Humans: Dynamics and Control,* Oxford University Press, Oxford, 1991.

2. F. V. Atkinson and J. R. Haddock, *On determining phase spaces for functional differential equations,* Funkcial. Ekvac. **31** (1988), 331–347.
3. E. Beretta and Y. Takeuchi, *Global stability of an SIR epidemic model with time delays,* J. Math. Biol. **33** (1995), 250–260.
4. C. Bowman, A. B. Gumel, P. van den Driessche, J. Wu and H. Zhu, *A mathematical model for assessing control strategies against West Nile virus,* Bull. Math. Biol. **67** (2005), 1107–1133.
5. O. Diekmann, J. A. P. Heesterbeek and J. A. J. Metz, *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** (1990), 365-382.
6. Z. Feng and J. X. Velasco-Hernández, *Competitive exclusion in a vector-host model for the dengue fever,* J. Math. Biol. **35** (1997), 523–544.
7. S. A. Gourley, Y. Kuang and J. D. Nagy, *Dynamics of a delay differential equation model of hepatitis B virus infection*, J. Biol. Dyn. **2** (2008), 140–153.
8. B.-Z. Guo and L.-M. Cai, *A note for the global stability of a delay differential equation of hepatitis B virus infection,* Math. Biosci. Eng. **8** (2011), 689–694.
9. J. K. Hale and S. M. V. Lunel, *Introduction to Functional Differential Equations,* Appl. Math. Sci., vol. 99, Springer, New York, 1993.
10. Y. Hino, S. Murakami and T. Naito, *Functional Differential Equations with Infinite Delay,* Lecture Notes in Math., vol. 1473, Springer, Berlin, 1991.
11. G. Huang and Y. Takeuchi, *Global analysis on delay epidemiological dynamic models with nonlinear incidence*, J. Math. Biol. **63** (2011), 125–139.
12. G. Huang, Y. Takeuchi, W. Ma and D. Wei, *Global stability for delay SIR and SEIR epidemic models with nonlinear incidence rate,* Bull. Math. Biol. **72** (2010), 1192–1207.
13. A. Korobeinikov, *Global properties of infectious disease models with nonlinear incidence,* Bull. Math. Biol. **69** (2007), 1871-1886.
14. A. Korobeinikov and P. K. Maini, *A Lyapunov function and global properties for SIR and SEIR epidemiological models with nonlinear incidence,* Math. Biosci. Eng. **1** (2004), 57-60.
15. J. P. LaSalle, *The Stability of Dynamical Systems,* Reg. Conf. Ser. Appl. Math., SIAM, Philadelphia, 1976.
16. M. Y. Li and J. S. Muldowney, *Global stability for the SEIR model in epidemiology,* Math. Biosci. **125** (1995), 155-164.
17. M. Y. Li and Z. Shuai, *Global-stability problems for coupled systems of differential equations on networks*, J. Differential Equations **248** (2010), 1–20.
18. W.-M. Liu, H. W. Hethcote and S. A. Levin, *Dynamical behavior of epidemiological models with nonlinear incidence rates,* J. Math. Biol. **25** (1987), 359–380.
19. W. Ma, M. Song and Y. Takeuchi, *Global stability of an SIR epidemic model with time delay,* Appl. Math. Lett. **17** (2004), 1141–1145.
20. C. C. McCluskey, *Global stability for an SEIR epidemiological model with varying infectivity and infinity delay*, Math. Biosci. Eng. **6** (2009), 603-610.
21. C. C. McCluskey, *Complete global stability for an SIR epidemic model with delay-distributed or discrete,* Nonlinear Anal. Real World Appl. **11** (2010), 55–59.
22. C. C. McCluskey, *Global stability of an SIR epidemic model with delay and general nonlinear incidence*, Math. Biosci. Eng. **7** (2010), 837–850.
23. R. K. Miller, *Nonlinear Volterra Integral Equations*, Benjamin, Menlo Park, California, 1971.
24. R. Rosá and A. Pugliese, *Effects of tick population dynamics and host densities on the persistence of tick-borne infections*, Math. Biosci. **208** (2007), 216–240.
25. G. Röst and J. Wu, *SEIR epidemiological model with varying infectivity and infinite delay,* Math. Biosci. Eng. **5** (2008), 389–402.

26. Z. Shuai and P. van den Driessche, *Impact of heterogeneity on the dynamics of an SEIR epidemic model*, Math. Biosci. Eng. **9** (2012), 393–411.
27. J. H. Tien and D. J. D. Earn, *Multiple transmission pathways and disease dynamics in a waterborne pathogen model*, Bull. Math. Biol. **72** (2010), 1506-1533.
28. P. van den Driessche, L. Wang and X. Zou, *Modeling diseases with latency and relapse*, Math. Biosci. Eng. **4** (2007), 205-219.
29. P. van den Driessche and J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission,* Math. Biosci. **180** (2002), 29-48.

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