

GLOBAL DYNAMICS OF A COUPLED EPIDEMIC MODEL

HONGYING SHU

Department of Mathematics, Tongji University
Shanghai 200092, China

XIANG-SHENG WANG*

Department of Mathematics, University of Louisiana at Lafayette
Lafayette, LA 70503, USA

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ABSTRACT. In this paper, we propose a novel epidemic model coupling direct and indirect transmission of disease and study the global dynamic of the model system. Despite the nonlinearity and complexity of the system, the basic reproduction number exhibits a nice linear property: it is simply the sum of two basic reproduction numbers for direct and indirect disease transmissions respectively. We further demonstrate that the local and global dynamics of the system are related to the basic reproduction number. The new model has the advantage that it generalizes or connects to various disease models on HIV, Zika virus, avian influenza, H1N1 and so on.

1. Introduction. We propose and study the following three-dimensional disease model system:

$$x'(t) = b - \frac{\beta_1 x(t)y(t)}{x(t) + y(t)} - \beta_2 x(t)z(t) - \mu x(t), \quad (1)$$

$$y'(t) = \frac{\beta_1 x(t)y(t)}{x(t) + y(t)} + \beta_2 x(t)z(t) - \gamma y(t), \quad (2)$$

$$z'(t) = py(t) - \delta z(t), \quad (3)$$

where x and y denote the susceptible and infected population sizes, respectively. The constants μ and γ are death rates of these two groups, and b is a constant birth rate. The disease could transmit directly via a standard incidence function $\beta_1 xy/(x+y)$ and indirectly via a mass-action infection term $\beta_2 xz$, where z accounts for the vector of the indirect transmission. We assume in the third equation that the growth of disease vector is proportional to the number of infected individuals, and its decay rate is a constant δ . The units of parameters $\beta_1, \mu, \gamma, p, \delta$ are the same as the reciprocal of time unit, but the unit for b is the unit of β_1 multiplied by the

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* Corresponding author.

population size/density unit, while the unit of β_2 is the unit of β_1 divided by the population size/density unit.

If $\beta_1 = 0$ (namely, there is no direct transmission), the above system (1-3) reduces to the classical HIV model [17], where x, y, z represent the densities of target cells, infected cells and virus, respectively. It is well-known that the global dynamics of this reduced system is fully determined by the basic reproduction number [5, 21]

$$R_0^i := \frac{b\beta_2 p}{\mu\gamma\delta}. \quad (4)$$

To be more specific, if $R_0^i \leq 1$, then the infection-free equilibrium is globally asymptotically stable; if $R_0^i > 1$, then there exists a unique positive equilibrium which is globally asymptotically stable. Here, the superscript i means indirect disease transmission.

On the other hand, if the indirect transmission is ignored (i.e., $\beta_2 = 0$), then the equation (3) can be decoupled from the original system, and the remaining system (1-2) is the same as the Kermack-McKendrick epidemic model [8] with standard incidence function, while the infected class is assumed to be removed from the social activity after being recovered/quarantined; see [22]. The basic reproduction number for the reduced direct-transmission-only model is given by [5, 21]

$$R_0^d := \frac{\beta_1}{\gamma}, \quad (5)$$

where the superscript d corresponds to the direct disease transmission. A similar dichotomy result holds: if $R_0^d \leq 1$, then the disease-free equilibrium is globally asymptotically stable; if $R_0^d > 1$, then there exists a unique positive equilibrium which is globally asymptotically stable. For global stability analysis on epidemic models with more general direct transmission rates, we refer to [9, 10, 15] and references therein.

The proposed system (1-3) is motivated by the observations of cell-to-cell transmission of HIV [20] and human-to-human transmission of Zika virus [7]. It is of both biological and mathematical interests to study a disease model that couples direct transmission with indirect transmission. The coupled virus models with both transmissions being assumed to be mass-actions have been studied in [13, 14, 18], where the basic reproduction number for the coupled system is simply the sum of two basic reproduction numbers for the subsystems with only direct or indirect disease transmissions respectively. Similar results were also obtained for cholera models [19], pathogen models [2, 3] and treatment models [24]. The coupled model proposed in [1] incorporated two virions with sensitive and resistant strains, respectively, and the basic reproduction number for the full system is the maximum of two basic reproduction numbers of viral strains. However, the basic reproduction number corresponds to each viral strain is still the sum of two basic reproduction numbers for the direct and indirect transmissions when both transmission functions are chosen as mass-actions. One nature question is whether this linear property of basic reproduction number of nonlinear coupled systems is universal, regardless of the choices of nonlinear incidence functions. In our system (1-3), we assume that the contact probability between a susceptible individual and an infected individual is decreasing as total population of two groups is increasing [4, 11], which leads to a standard incidence function for the direct disease transmission. On the other hand, the contact probability between a susceptible individual and a disease vector is assumed to be a constant, so the indirect disease transmission is characterized by

a mass-action incidence (or bilinear function). Biologically, we may still define the basic reproduction number of this coupled system as the sum of R_0^i and R_0^d :

$$R_0 := \frac{b\beta_2 p}{\mu\gamma\delta} + \frac{\beta_1}{\gamma}. \tag{6}$$

We intend to explore the relation of local and global dynamics for the model system with the basic reproduction number.

2. Main results. We first establish the nonnegativeness and boundedness of the solutions to the system (1-3) with given nonnegative initial conditions.

Proposition 1. *If the initial values are nonnegative, then the solutions of the system (1-3) are nonnegative for all $t \geq 0$ and ultimately bounded as $t \rightarrow \infty$.*

Proof. Note from (1) that $x'(t_0) > 0$ whenever $x(t_0) = 0$ for some $t = t_0$. This implies that $x(t) > 0$ for all $t > 0$ if $x(0) \geq 0$. Now, we claim $y(t)$ and $z(t)$ are nonnegative for all $t \geq 0$. If not, then there exists a $t_0 \geq 0$ such that $y(t) \geq 0$ and $z(t) \geq 0$ for all $t \leq t_0$ and either $y(t)$ or $z(t)$ becomes negative right after t_0 . On one hand, if $y(t) < 0$ for t close to the right of t_0 , then $y(t_0) = 0$ and $y'(t_0) < 0$. However, we obtain from (2) that $y'(t_0) = \beta_2 x(t_0) z(t_0) \geq 0$, a contradiction. On the other hand, if $z(t) < 0$ for t close to the right of t_0 , then $z(t_0) = 0$ and $z'(t_0) < 0$. However, we obtain from (3) that $z'(t_0) = p y(t_0) \geq 0$, a contradiction. Therefore, neither $y(t)$ nor $z(t)$ could be negative for any $t \geq 0$.

Next, we show that the solutions are ultimately bounded as $t \rightarrow \infty$. Adding equations (1) and (2) gives

$$x'(t) + y'(t) = b - \mu x(t) - \gamma y(t) \leq b - \min(\mu, \gamma)[x(t) + y(t)].$$

Thus, we have $\limsup_{t \rightarrow \infty} [x(t) + y(t)] \leq b / \min(\mu, \gamma)$. Especially, $x(t)$ and $y(t)$ are ultimately bounded as $t \rightarrow \infty$. It is then easily seen from (3) that $z(t)$ is also ultimately bounded as $t \rightarrow \infty$. \square

Now, we consider the equilibria which satisfy the following algebraic system:

$$0 = b - \frac{\beta_1 xy}{x + y} - \beta_2 xz - \mu x, \tag{7}$$

$$0 = \frac{\beta_1 xy}{x + y} + \beta_2 xz - \gamma y, \tag{8}$$

$$0 = py - \delta z, \tag{9}$$

It is readily seen that there is a disease-free equilibrium $(x_0, 0, 0)$ with $x_0 = b/\mu$. Now, we are looking for the endemic equilibrium and assume $y \neq 0$. Eliminating the variables y and z from equations (7)-(9) gives $z = py/\delta$, $y = (b - \mu x)/\gamma$ and

$$p\beta_2(\gamma - \mu)x^2 + (bp\beta_2 + \beta_1\gamma\delta + \gamma\delta\mu - \gamma^2\delta)x - b\gamma\delta = 0. \tag{10}$$

Recall that γ and μ denote the death rates of infected and susceptible individuals, respectively. Biologically, it is nature to assume that $\gamma \geq \mu$. In this case, we always have a unique positive solution $x = x^*$ to the above equation, where

$$x^* = \begin{cases} b\gamma\delta / (bp\beta_2 + \beta_1\gamma\delta), & \gamma = \mu; \\ \frac{-(bp\beta_2 + \beta_1\gamma\delta + \gamma\delta\mu - \gamma^2\delta) + \sqrt{(bp\beta_2 + \beta_1\gamma\delta + \gamma\delta\mu - \gamma^2\delta)^2 + 4b\gamma\delta p\beta_2(\gamma - \mu)}}{2p\beta_2(\gamma - \mu)}, & \gamma > \mu. \end{cases} \tag{11}$$

We further have $y = y^*$ and $z = z^*$, where

$$y^* = \frac{b - \mu x^*}{\gamma}, \quad z^* = \frac{(b - \mu x^*)p}{\gamma\delta}. \tag{12}$$

To make $y^* > 0$ and $z^* > 0$, we need $x^* < b/\mu$, which, by a simple calculation, is equivalent with $R_0 > 1$, where R_0 is defined in (6). The equivalence is obvious when $\gamma = \mu$. When $\gamma > \mu$, we rewrite $x^* < b/\mu$ as

$$\frac{-B + \sqrt{B^2 + 4AC}}{2A} < \frac{b}{\mu}$$

where $A = p\beta_2(\gamma - \mu) > 0$, $B = bp\beta_2 + \beta_1\gamma\delta + \gamma\delta\mu - \gamma^2\delta$ and $C = b\gamma\delta > 0$. Isolating the square root and squaring both sides gives $B + 2Ab/\mu > 0$ and

$$B^2 + 4AC < B^2 + \frac{4BAb}{\mu} + \frac{4A^2b^2}{\mu^2}.$$

Simplifying the last inequality yields $C\mu^2 < Bb\mu + Ab^2$. We make use of the expressions of A, B, C and rewrite the inequality as

$$b\gamma\delta\mu^2 < b\mu(bp\beta_2 + \beta_1\gamma\delta + \gamma\delta\mu - \gamma^2\delta) + b^2p\beta_2(\gamma - \mu).$$

By expanding and canceling, we obtain $\gamma\delta\mu < bp\beta_2 + \beta_1\delta\mu$, which is the same as $R_0 > 1$. Furthermore, coupling $R_0 > 1$ and $\gamma > \mu$ implies $B + 2Ab/\mu > 0$. Thus, we obtain that the endemic equilibrium exists if and only if $R_0 > 1$. Next, we will establish the local stability theory of disease-free and endemic equilibria.

Theorem 2.1. *If $R_0 \leq 1$, then the disease-free equilibrium is locally asymptotically stable. If $R_0 > 1$, then the disease-free equilibrium is unstable. If further, $\gamma \geq \mu$, then there exists a unique endemic equilibrium and it is locally asymptotically stable.*

Proof. We calculate the Jacobian matrix of the system (1-3) about the disease-free equilibrium $(x_0, 0, 0)$ and endemic equilibrium (x^*, y^*, z^*) , respectively. At the disease-free equilibrium, we have

$$J_0 = \begin{pmatrix} -\mu & -\beta_1 & -\beta_2x_0 \\ 0 & \beta_1 - \gamma & \beta_2x_0 \\ 0 & p & -\delta \end{pmatrix}. \tag{13}$$

The three eigenvalues of the Jacobian matrix are calculated as $-\mu$ and $(Tr \pm \sqrt{Tr^2 - 4Det})/2$, where Tr and Det denote the trace and determinant of the sub-matrix

$$\begin{pmatrix} \beta_1 - \gamma & \beta_2x_0 \\ p & -\delta \end{pmatrix}.$$

That is, $Tr = \beta_1 - \gamma - \delta$ and $Det = \delta(\gamma - \beta_1) - \beta_2x_0p$. Recall that $x_0 = b/\mu$ and $R_0 = (bp\beta_2)/(\mu\gamma\delta) + \beta_1/\gamma$. If $R_0 < 1$, we have $Tr < 0$ and $Det > 0$, and thus all three eigenvalues have negative real parts, which implies that the disease-free equilibrium is locally asymptotically stable. On the other hand, if $R_0 > 1$, then $Det < 0$, which implies that at least one of the three eigenvalues (i.e., $(Tr - \sqrt{Tr^2 - 4Det})/2$) is real and positive. Consequently, the disease-free equilibrium is unstable.

For the critical case $R_0 = 1$, the Jacobian matrix J_0 has two negative real eigenvalue $-\mu$ and $\beta_1 - \gamma - \delta$, and one zero eigenvalue. We introduce the matrix of eigenvectors

$$P = \begin{pmatrix} -\frac{\delta\gamma}{\mu} & \frac{(\beta_1 - \delta)\beta_2x_0}{\beta_1 - \gamma - \delta + \mu} & 1 \\ \delta & -\beta_2x_0 & 0 \\ p & \delta & 0 \end{pmatrix}$$

such that $J_0P = P\Lambda$, where Λ is the diagonal matrix $\text{diag}\{0, \beta_1 - \gamma - \delta, -\mu\}$. We make the linear transformation $(u, v, w)^T = P^{-1}(x - x_0, y, z)^T$, where

$$P^{-1} = \begin{pmatrix} 0 & \frac{\delta}{\delta^2 + p\beta_2x_0} & \frac{\beta_2x_0}{\delta^2 + p\beta_2x_0} \\ 0 & \frac{-p}{\delta^2 + p\beta_2x_0} & \frac{\delta}{\delta^2 + p\beta_2x_0} \\ 1 & \frac{\beta_2\mu - \delta\gamma}{\mu(\beta_1 - \beta - \delta + \mu)} & \frac{(\beta - \mu)\beta_2x_0}{\mu(\beta_1 - \beta - \delta + \mu)} \end{pmatrix}.$$

The Jacobian matrix for the differential equations of (u, v, w) about the zero equilibrium is exactly Λ . To analyze the local asymptotic stability of this zero equilibrium, we need to calculate the restricted dynamical system on the center manifold for u sufficiently small and $v = O(u^2)$, $w = O(u^2)$; see [23, Ch. 2]. Note that $u = (\delta y + \beta_2x_0z)/(\delta^2 + p\beta_2x_0)$. We obtain from equations (2-3) that

$$(\delta^2 + p\beta_2x_0)u'(t) = \delta\beta_2(x - x_0)z - \frac{\delta\beta_1y^2}{x + y}.$$

Next, we make use of $x - x_0 = -(\delta\gamma/\mu)u + O(u^2)$, $y = \delta u + O(u^2)$ and $z = pu + O(u^2)$ to obtain

$$(\delta^2 + p\beta_2x_0)u'(t) = -(\delta^2\gamma p\beta_2/\mu + \delta^2\beta_1/x_0)u^2 + O(u^3).$$

Since the above restricted system is stable about $u = 0$, the original system (2-3) is stable about the disease-free equilibrium $(x_0, 0, 0)$.

Finally, we investigate the Jacobian matrix at the endemic equilibrium:

$$J^* = \begin{pmatrix} -\frac{\beta_1(y^*)^2}{(x^* + y^*)^2} - \beta_2z^* - \mu & -\frac{\beta_1(x^*)^2}{(x^* + y^*)^2} & -\beta_2x^* \\ \frac{\beta_1(y^*)^2}{(x^* + y^*)^2} + \beta_2z^* & \frac{\beta_1(x^*)^2}{(x^* + y^*)^2} - \gamma & \beta_2x^* \\ 0 & p & -\delta \end{pmatrix}. \tag{14}$$

The corresponding characteristic equation is $\lambda^3 + c_2\lambda^2 + c_1\lambda + c_0 = 0$, where

$$\begin{aligned} c_2 &= \frac{\beta_1(y^* - x^*)}{x^* + y^*} + \beta_2z^* + \mu + \gamma + \delta; \\ c_1 &= \frac{(\gamma + \delta)\beta_1(y^*)^2}{(x^* + y^*)^2} - \frac{(\delta + \mu)\beta_1(x^*)^2}{(x^* + y^*)^2} + (\gamma + \delta)\beta_2z^* - p\beta_2x^* + \delta\mu + \mu\gamma + \delta\gamma; \\ c_0 &= \frac{\gamma\delta\beta_1(y^*)^2}{(x^* + y^*)^2} - \frac{\delta\mu\beta_1(x^*)^2}{(x^* + y^*)^2} + \gamma\delta\beta_2z^* + \delta\mu\gamma - \mu p\beta_2x^*. \end{aligned}$$

Since the endemic equilibrium (x^*, y^*, z^*) satisfies the system (2-3), we can rewrite the above expressions as

$$\begin{aligned} c_2 &= \frac{b}{x^*} + \frac{\beta_2x^*z^*}{y^*} + \delta; \\ c_1 &= \frac{\delta b}{x^*} + \frac{\mu\beta_2x^*z^*}{y^*} + \frac{\mu\beta_1x^*y^*}{(x^* + y^*)^2} + \frac{\gamma\beta_1(y^*)^2}{(x^* + y^*)^2} + \gamma\beta_2z^*; \\ c_0 &= \frac{\delta\mu\beta_1x^*y^*}{(x^* + y^*)^2} + \frac{\delta\gamma\beta_1(y^*)^2}{(x^* + y^*)^2} + \delta\gamma\beta_2z^*. \end{aligned}$$

Especially, $c_2 > 0$, $c_1 > 0$, $c_0 > 0$, and $c_2c_1 > c_0$. By Routh-Hurwitz criterion, it follows that all eigenvalues of J^* have negative real parts, which implies the local asymptotic stability of endemic equilibrium. \square

Now, we are ready to establish the global dynamics of the system (1-3).

Theorem 2.2. *If $R_0 \leq 1$, then the disease-free equilibrium of system (1-3) with nonnegative initial conditions is globally asymptotically stable; namely, as $t \rightarrow \infty$, we have $(x(t), y(t), z(t)) \rightarrow (x_0, 0, 0)$.*

Proof. We consider two different cases: (1) $x(t) > x_0$ for all $t \geq 0$; (2) $x(t_0) \leq x_0$ for some $t_0 > 0$.

For the first case, we observe from (1) that $x'(t) \leq b - \mu x(t) < 0$, which implies that $x(t)$ is strictly decreasing and has a lower bound x_0 . Thus, there exists $x_1 \geq x_0$ such that $x(t) \rightarrow x_1$ as $t \rightarrow \infty$. We claim $x_1 = x_0$. If not, it then follows from the monotonicity of $x(t)$ and (1) that $x'(t) \leq b - \mu x_1 < 0$. Consequently, $x(t) \leq x(0)e^{(b-\mu x_1)t} \rightarrow 0$ as $t \rightarrow \infty$, a contradiction. Hence, the function $x(t)$ decreases to x_0 as t increases to infinity. We add the equations (1) and (2) to obtain $(x + y)' = b - \mu x - \gamma y < 0$, which implies that $x(t) + y(t)$ is also strictly decreasing with a lower bound x_0 . Hence, $y(t)$ has a limit, denoted by $y_1 \geq 0$, as $t \rightarrow \infty$. If $y_0 > 0$, then there exists $t_1 \geq 0$ such that $y(t) > y_0/2$ for all $t \geq t_1$. But, $(x + y)' < -\gamma y_0/2$ and $x(t) + y(t) < [x(t_1) + y(t_1)]e^{-\gamma y_0(t-t_1)/2} \rightarrow 0$ as $t \rightarrow \infty$, a contradiction. So, $y_0 = 0$. Similarly, we could show that $z(t) \rightarrow 0$ as $t \rightarrow \infty$, noting from (1-3) that $(x + y + \gamma z/p)' = b - \mu x - \gamma \delta z/p$.

For the second case, we could assume without loss of generality that $t_0 = 0$ and $x(0) \leq x_0$. We claim that $x(t) \leq x_0$ for all $t \geq 0$. If not, then there exists $t_1 \geq 0$ such that $x(t) \leq x_0$ for all $t \leq t_1$, $x(t_1) = x_0$, and $x'(t_1) > 0$. However, it follows from (1) that $x'(t_1) \leq b - \mu x(t_1) = 0$, a contradiction. Now, we define $u(t) := y(t) + \beta x_0 z(t)/\delta$ and obtain from (2) and (3) that

$$u' = -\frac{\beta_1 y^2}{x + y} + \left(\beta_1 + \frac{p\beta_2 x_0}{\delta} - \gamma \right) y + \beta_2(x - x_0)z.$$

Since $R_0 \leq 1$ and $x \leq x_0$, we have $u' \leq 0$. Since $u \geq 0$, we have $u(t) \rightarrow u_1$ as $t \rightarrow \infty$ for some $u_1 \geq 0$. We claim $u_1 = 0$. If not, we substitute $y = u - \beta x_0 z/\delta$ into equation (3) and find $z' = pu - (p\beta x_0/\delta + \delta)z$, which, together with the limit of $u(t)$, implies that $z \rightarrow z_1$ as $t \rightarrow \infty$, where $z_1 = pu_1/(p\beta x_0/\delta + \delta) > 0$. Furthermore, $y \rightarrow y_1$ as $t \rightarrow \infty$, where $y_1 = u_1 - \beta x_0 z_1/\delta = \delta u_1/(p\beta x_0/\delta + \delta) > 0$. Especially, there exists $t_2 \geq 0$ such that $y(t) > y_1/2$ for all $t \geq t_2$. However, since $u' \leq -\beta_1 y < -\beta_1 y_1/2$, we have $u(t) < u(t_2)e^{-\beta_1 y_1(t-t_2)/2} \rightarrow 0$ as $t \rightarrow \infty$, a contradiction. Therefore, we have shown that $u_1 = 0$, which implies that $y(t) \rightarrow 0$ and $z(t) \rightarrow 0$ as $t \rightarrow \infty$. Finally, we set $v(t) := x(t) + y(t)$ and add the equations (1) and (2) to obtain $v' = b - \mu v + (\mu - \gamma)y$, which, together with the limit of $y(t)$, implies $v \rightarrow x_0$ as $t \rightarrow \infty$. This proves the global asymptotic stability of disease-free equilibrium $(x_0, 0, 0)$. □

The next main result states the global asymptotic stability of endemic equilibrium.

Theorem 2.3. *If the initial values are nonnegative and either $y(0) > 0$ or $z(0) > 0$, then the solutions are positive for all $t > 0$. If further, $R_0 > 1$ and either $\gamma = \mu$ or $\gamma > \mu \geq \beta_1/4$ is satisfied, then the unique endemic equilibrium is globally asymptotically stable; namely, $(x(t), y(t), z(t)) \rightarrow (x^*, y^*, z^*)$ as $t \rightarrow \infty$.*

Proof. We assume that the initial conditions are nonnegative and either $y(0) > 0$ or $z(0) > 0$. It is readily seen from (1) that $x(t) > 0$ for all $t > 0$. If both $y(0)$ and $z(0)$ are positive, then $y(t)$ and $z(t)$ are positive for any small $t > 0$. If $y(0) > 0$ and $z(0) = 0$, then it follows from (3) that $z'(0) = py(0) > 0$, which implies positiveness

of $z(t)$ for sufficiently small $t > 0$. If $y(0) = 0$ and $z(0) > 0$, then it follows from (2) that $e^{\gamma t}y(t) \geq \int_0^t \beta_2 x(s)z(s)ds > 0$ for any small $t > 0$. Therefore, we have shown the positiveness of $y(t)$ and $z(t)$ right after the initial time. Now, we claim that both $y(t)$ and $z(t)$ are positive for all $t > 0$. Assume the contrary that the positiveness fails for the first time at $t = t_1 > 0$, which means that $y(t) > 0$ and $z(t) > 0$ for all $0 < t < t_1$, and either $y(t_1) = 0$ or $z(t_1) = 0$. If $y(t_1) = 0$, then $y'(t_1) < 0$, but from (2) we have $y'(t_1) = \beta_2 x(t_1)z(t_1) \geq 0$, a contradiction; if $z(t_1) = 0$, then $z'(t_1) < 0$, but from (3) we have $z'(t_1) = py(t_1) \geq 0$, a contradiction again. Hence, $y(t) > 0$ and $z(t) > 0$ for all $t > 0$.

Now, we assume $R_0 > 1$ and $\gamma \geq \mu$, then the endemic equilibrium (x^*, y^*, z^*) exists and it is unique. We consider the following three cases respectively.

(C1) $\beta_1(y^* - x^*)^2 \leq 4\mu x^*(x^* + y^*)$;

(C2) $y^* - x^* \geq 0$;

(C3) $0 \leq x^* - y^* \leq [2\mu x^* + 2\mu\gamma(x^* + y^*)/\beta_1]/(\mu + \gamma)$ and

$$\mu\gamma^2(x^* + y^*)^2 + \beta_1(x^* + y^*)[\gamma(\mu + \gamma)y^* - \mu(\gamma - \mu)x^*] + \beta_1^2 y^*[\gamma y^* - (\gamma - \mu)x^*] \geq 0.$$

We will prove global asymptotic stability of endemic equilibrium for each of the above three cases by constructing difference Lyapunov functions.

Case I. $\beta_1(y^* - x^*)^2 \leq 4\mu x^*(x^* + y^*)$. We construct the Lyapunov function

$$V_1(x, y, z) := x - x^* \ln x + y - y^* \ln y + \frac{\beta_2 x^* z^*}{py^*}(z - z^* \ln z) - K_1, \tag{15}$$

where K_1 is a constant such that $V_1(x^*, y^*, z^*) = 0$. Taking the derivative of V_1 along the solution of system (1-3), we obtain

$$\begin{aligned} \frac{dV_1}{dt} &= \left(1 - \frac{x^*}{x}\right) \left(b - \frac{\beta_1 xy}{x+y} - \beta_2 xz - \mu x\right) + (y - y^*) \left(\frac{\beta_1 x}{x+y} + \frac{\beta_2 xz}{y} - \gamma\right) \\ &\quad + \frac{\beta_2 x^* z^*}{py^*}(z - z^*) \left(\frac{py}{z} - \delta\right). \end{aligned}$$

Recall that the endemic equilibrium satisfies the following equations:

$$\begin{aligned} b &= \frac{\beta_1 x^* y^*}{x^* + y^*} + \beta_2 x^* z^* + \mu x^*, \\ \gamma &= \frac{\beta_1 x^*}{x^* + y^*} + \frac{\beta_2 x^* z^*}{y^*}, \\ \delta &= \frac{py^*}{z^*}. \end{aligned}$$

We then have

$$\begin{aligned} \frac{dV_1}{dt} &= -\frac{\mu(x - x^*)^2}{x} - \frac{\beta_1 y^*(x - x^*)^2}{x(x^* + y^*)} + \frac{\beta_1(x - x^*)[y^*(x - x^*) - x^*(y - y^*)]}{(x + y)(x^* + y^*)} \\ &\quad + \beta_2 x^* z^* \left(1 - \frac{x^*}{x} - \frac{xz}{x^* z^*} + \frac{z}{z^*}\right) + \frac{\beta_1(y - y^*)[y^*(x - x^*) - x^*(y - y^*)]}{(x + y)(x^* + y^*)} \\ &\quad + \beta_2 x^* z^* \left(1 - \frac{y}{y^*} - \frac{xy^* z}{x^* y z^*} + \frac{xz}{x^* z^*}\right) + \beta_2 x^* z^* \left(1 - \frac{z}{z^*} - \frac{yz^*}{y^* z} + \frac{y}{y^*}\right). \end{aligned}$$

By using $x \leq x + y$, we obtain

$$\frac{dV_1}{dt} \leq -\frac{\mu(x^* + y^*)(x - x^*)^2}{(x + y)(x^* + y^*)} - \frac{\beta_1 y^*(x - x^*)^2}{(x + y)(x^* + y^*)}$$

$$\begin{aligned}
& + \frac{\beta_1[y^*(x-x^*)^2 + (y^*-x^*)(x-x^*)(y-y^*) - x^*(y-y^*)^2]}{(x+y)(x^*+y^*)} \\
& + \beta_2 x^* z^* \left(3 - \frac{x^*}{x} - \frac{xy^*z}{x^*yz^*} - \frac{yz^*}{y^*z} \right).
\end{aligned}$$

Since $3 - a - b - c \leq 0$ for any positive a, b, c such that $abc = 1$, it follows that

$$\frac{dV_1}{dt} \leq \frac{-\beta_1 \left[\frac{\mu(x^*+y^*)}{\beta_1} (x-x^*)^2 - (y^*-x^*)(x-x^*)(y-y^*) + x^*(y-y^*)^2 \right]}{(x+y)(x^*+y^*)} \leq 0$$

if $\beta_1(y^*-x^*)^2 \leq 4\mu x^*(x^*+y^*)$. The largest invariant set on which $V_1'(t) = 0$ is a singleton (x^*, y^*, z^*) . We obtain from Lyapunov-LaSalle invariance principle [12, p. 30] that the endemic equilibrium is globally asymptotically stable.

Case II. $y^* - x^* \geq 0$. We use V_1 defined in (15) to construct the Lyapunov function:

$$V_2 := V_1 + \frac{\beta_1(y^* - x^*)}{(\mu + \gamma)(x^* + y^*)} [x + y - (x^* + y^*) \ln(x + y)] - K_2, \quad (16)$$

where K_2 is a constant such that $V_2(x^*, y^*, z^*) = 0$. Taking derivative along the solution of system (1-3), we obtain

$$\begin{aligned}
\frac{dV_2}{dt} \leq & \frac{-\beta_1 \left[\frac{\mu(x^*+y^*)}{\beta_1} (x-x^*)^2 - (y^*-x^*)(x-x^*)(y-y^*) + x^*(y-y^*)^2 \right]}{(x+y)(x^*+y^*)} \\
& - \frac{\beta_1(y^* - x^*)[(x-x^*) + (y-y^*)][\mu(x-x^*) + \gamma(y-y^*)]}{(\mu + \gamma)(x^* + y^*)(x + y)},
\end{aligned}$$

where we have used the equations $(x+y)' = b - \mu x - \gamma y$ and $b = \mu x^* + \gamma y^*$. Note that the coefficients of $(x-x^*)(y-y^*)$ in the numerator cancel out with each other. It then follows that

$$\frac{dV_2}{dt} \leq \frac{-\beta_1 \left\{ \left[\frac{\mu(x^*+y^*)}{\beta_1} + \frac{\mu(y^*-x^*)}{\mu+\gamma} \right] (x-x^*)^2 + \left[x^* + \frac{\gamma(y^*-x^*)}{\mu+\gamma} \right] (y-y^*)^2 \right\}}{(x+y)(x^*+y^*)} \leq 0.$$

The largest invariant set on which $V_2'(t) = 0$ is a singleton (x^*, y^*, z^*) . We obtain from Lyapunov-LaSalle invariance principle [12, p. 30] that the endemic equilibrium is globally asymptotically stable.

Case III. $0 \leq x^* - y^* \leq [2\mu x^* + 2\mu\gamma(x^* + y^*)/\beta_1]/(\mu + \gamma)$ and

$$\mu\gamma^2(x^* + y^*)^2 + \beta_1(x^* + y^*)[\gamma(\mu + \gamma)y^* - \mu(\gamma - \mu)x^*] + \beta_1^2 y^*[\gamma y^* - (\gamma - \mu)x^*] \geq 0.$$

We use V_1 defined in (15) to construct the Lyapunov function:

$$V_3 := V_1 + \frac{\lambda\beta_1}{x^* + y^*} [x + y - (x^* + y^*) \ln(x + y)] - K_3, \quad (17)$$

where

$$\lambda := \frac{2\mu x^* + 2\mu\gamma(x^* + y^*)/\beta_1 - (x^* - y^*)(\mu + \gamma)}{(\mu - \gamma)^2},$$

and K_3 is a constant such that $V_3(x^*, y^*, z^*) = 0$. Taking the derivative along the solution of system (1-3), we obtain

$$\frac{dV_3}{dt} = \frac{-\beta_1 \left\{ \left[\frac{\mu(x^*+y^*)}{\beta_1} + \lambda\mu \right] X^2 + [x^* - y^* + \lambda(\mu + \gamma)]XY + (x^* + \lambda\gamma)Y^2 \right\}}{(x+y)(x^*+y^*)},$$

where $X := x - x^*$ and $Y := y - y^*$. To prove $V_3' \leq 0$, it is sufficient to show that

$$[x^* - y^* + \lambda(\mu + \gamma)]^2 \leq 4 \left[\frac{\mu(x^* + y^*)}{\beta_1} + \lambda\mu \right] (x^* + \lambda\gamma),$$

which is equivalent with

$$(\mu - \gamma)^2 \lambda^2 + 2 \left[(x^* - y^*)(\mu + \gamma) - 2\mu x^* - \frac{2\mu\gamma(x^* + y^*)}{\beta_1} \right] \lambda + (x^* - y^*)^2 - \frac{4\mu x^*(x^* + y^*)}{\beta_1} \leq 0.$$

From the choice of λ , we can rewrite the above inequality as

$$\frac{[2\mu x^* + \frac{2\mu\gamma(x^* + y^*)}{\beta_1} - (x^* - y^*)(\mu + \gamma)]^2}{(\mu - \gamma)^2} + (x^* - y^*)^2 - \frac{4\mu x^*(x^* + y^*)}{\beta_1} \leq 0.$$

A simple calculation shows that the above inequality is the same as

$$\mu\gamma^2(x^* + y^*)^2 + \beta_1(x^* + y^*)[\gamma(\mu + \gamma)y^* - \mu(\gamma - \mu)x^*] + \beta_1^2 y^*[\gamma y^* - (\gamma - \mu)x^*] \geq 0.$$

Thus, $V_3' \leq 0$ if the above inequality is satisfied. Again, the largest invariant set on which $V_3'(t) = 0$ is a singleton (x^*, y^*, z^*) . We have the global asymptotic stability of endemic equilibrium from Lyapunov-LaSalle invariance principle [12, p. 30].

Finally, we note that if $\gamma = \mu$, then either (C2) or (C3) should be satisfied; namely, either $y^* - x^* \geq 0$ or

$$0 \leq x^* - y^* \leq x^* = \frac{2\mu x^*}{\mu + \gamma} \leq \frac{2\mu x^* + 2\mu\gamma(x^* + y^*)/\beta_1}{\mu + \gamma}.$$

On the other hand, if $\gamma > \mu \geq \beta_1/4$, then (C1) and (C2) include all possible parameter values. Assume the contrary, then there exist some parameter values such that $x^* > y^*$ and $\beta_1(x^* - y^*)^2 > 4\mu x^*(x^* + y^*)$. Since $\mu \geq \beta_1/4$, we have $(x^* - y^*)^2 > x^*(x^* + y^*)$. But $0 < x^* - y^* < x^* < x^* + y^*$ and thus $(x^* - y^*)^2 < x^*(x^* + y^*)$, a contradiction. This concludes the proof. \square

3. Discussion. In this paper, we propose a simple epidemic model coupling both direct and indirect transmission mechanisms of infectious diseases. This model has potential applications in the study of various diseases. For example, it generalizes the HIV model where x, y, z correspond to uninfected cells, infected cells and virus, respectively. In the study of Zika virus, we let x, y, z be the uninfected individuals, infected individuals, and infected mosquitoes, respectively. When we apply our model to analyze the epidemic waves of H1N1 and seasonal influenzas, x and y still denote uninfected and infected individuals, respectively, while z stands for the contaminated environment such as classrooms, buses, theaters, or other public places. We could also use our model to study the cross transmission of avian influenza among migratory birds and domestic poultry, where x, y, z denote the uninfected migratory birds, infected migratory birds, and infected domestic poultry, respectively.

We would like to mention that the transmission mechanisms within and without groups may not be the same, so we assume standard incidence function for within group transmission (such as bird-to-bird transmission, or person-to-person transmission) and mass action function for transmission among different groups (such as poultry-to-bird transmission, or mosquito-to-person transmission). One may argue

that there should be poultry-to-poultry transmission and bird-to-poultry transmission, so that equation (3) would have been written as

$$z'(t) = \frac{\beta_3 w(t) z(t)}{w(t) + z(t)} + \beta_4 w(t) y(t) - \sigma z(t),$$

where $w(t)$ is the population of uninfected poultry. However, for simplicity, we could assume that this quantity is a large constant $w(t) \equiv W$ with respect to the infected poultry $z(t)$. Therefore, the above equation can be approximated by (3) with $p = \beta_4 W$ and $\delta = \sigma - \beta_3$. A similar argument works for mosquito-borne disease models where x, y, z, w correspond to the uninfected individuals, infected individuals, infected mosquitoes, and uninfected mosquitoes, respectively. When the dynamical system on mosquito population is much faster than the disease transmission system, the population of uninfected mosquitoes reaches its ecological equilibrium $w(t) \equiv W$ very quickly and thus its variation is negligible in the slow system. For simplicity, we further assume that the ratio of infected mosquitoes over uninfected mosquitoes is relatively small. These assumptions help us to obtain a reduced equation for the infected mosquitoes: $z'(t) = py(t) - \delta z(t)$. Nevertheless, a more realistic and more general model incorporating with the changes on the uninfected mosquitoes should be studied and we leave it as a future work.

It is noted that the basic reproduction number of the coupled system is simply the sum of the basic reproduction numbers for the two reduced systems with only direct or indirect disease transmission, respectively. This means that, in the study of infectious disease (Zika virus, for instance) with multiple transmission mechanics, it is dangerous to ignore either direct or indirect transmission because that would underestimate the seriousness of the disease: it is possible that both R_0^d and R_0^i are less than one, but their sum exceeds the critical value one. To create a suitable policy for disease control, one should not only reduce the possibility of direct transmission, but also avoid indirect disease transmission (such as closing schools to reduce vector transmission channels of H1N1 and other pandemic influenzas [6]).

Due to the difference between direct and indirect transmission mechanisms, it becomes more difficult to analyze the model system than the one in [13] where both transmissions were chosen as mass action functions. As seen in the proof of our main theorems, the most challenging part is the construction of a suitable Lyapunov function which could nicely balance the two different nonlinear transmissions. Note that we introduce some technical conditions to prove global asymptotic stability of endemic equilibrium; see (C1)-(C3) in the proof of Theorem 2.3. From numerical simulations one could still observe global asymptotic stability of endemic equilibrium even though these technical assumptions are violated. It remains an open problem to prove global asymptotic stability of endemic equilibrium whenever it exists. Another future project would be the extension of our results to the more general situation when disease transmission delay and multi-group [16] are taken into consideration.

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E-mail address: hshu@tongji.edu.cn

E-mail address: xswang@louisiana.edu