



Coinfection dynamics of two diseases in a single host population



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ABSTRACT

A susceptible-infectious-susceptible (SIS) epidemic model that describes the coinfection and cotransmission of two infectious diseases spreading through a single population is studied. The host population consists of two subclasses: susceptible and infectious, and the infectious individuals are further divided into three subgroups: those infected by the first agent/pathogen, the second agent/pathogen, and both. The basic reproduction numbers for all cases are derived which completely determine the global stability of the system if the presence of one agent/pathogen does not affect the transmission of the other. When the constraint on the transmissibility of the dually infected hosts is removed, we introduce the invasion reproduction number, compare it with two other types of reproduction number and show the uniform persistence of both diseases under certain conditions. Numerical simulations suggest that the system can display much richer dynamics such as backward bifurcation, bistability and Hopf bifurcation.

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1. Introduction

Different infectious agents may infect or colonize a host at the same time [21]. Many examples can be found, these involving HIV [30,37] (for example, HIV and TB [19], HIV and Hepatitis B [12,26], HIV and Hepatitis C [23], and HIV and malaria [2]), as well as some not involving HIV (for example, Hepatitis B and C coinfection [11], gonorrhea and Chlamydia [13], and herpes simplex viruses 1 and 2 [41,59]). Moreover, simultaneous infection may occur with multiple strains or serotypes of the same organism, as is the case for influenza [20,49], human papilloma virus [9], and HIV [55,63,22], for just three of many examples. However, simultaneous colonization or infection may occur even when there appears to be little or no interaction between the two agents, as in the case of infection by ocular strains of chlamydia and nasopharyngeal colo-

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nization by pneumococcus [24]. The dynamics of coinfection is important in this case, because antimicrobials used to treat one infection may affect the other (e.g., [51,24]).

A variety of mathematical models for coinfections with multiple specific diseases, such as HIV/TB [43, 48,6,47], HIV/gonorrhoea [40], HIV/malaria [1,39], malaria and meningitis [29], general diseases [5,7,35,28], and microparasites (viruses, bacteria, protozoa, fungi) [54,10,3,4,61], have been developed and analyzed in the past few years. Ferguson et al. [16] and Kawaguchi et al. [27] presented models to describe the coinfection of two serotypes of dengue virus in a human community. With respect to the interaction between nonspecific agents or pathogens, Blyuss and Kyrychko [7] studied a two-disease SIS model with equal transmission efficiency for both susceptible and singly infected individuals; Allen et al. [5] studied an SI model for a single host population with two viral infections, in which one is vertically transmitted and the other is horizontally transmitted; Zhang et al. [60] proposed an ODEs coinfection model with two strains of parasites and two host types to study the influence of heterogeneities in parasite virulence and host life history on the persistence and spread of parasite strains; Martcheva and Pilyugin [35] considered an epidemic model of two diseases: a primary disease and a secondary disease, structured by time since infection structure (for the primary disease); in the monograph of Keeling and Rohani [28], the interaction of two pathogens spreading through a host population was discussed in four cases: complete cross-immunity, no cross-immunity, enhanced susceptibility and partial cross-immunity. Among these models either the uninfected hosts cannot become infected with both diseases/strains directly [38,35,28,10], or there is no recovery and an infection is lifelong [54,5,4], or both [60,3].

In this paper, we develop and analyze a simple model of multiple infections; this model includes the possibility that the two agents are simultaneously transmitted, thereby inaugurating a dual infection. It exhibits aspects of *Chlamydia trachomatis* and pneumococcus, though we do not restrict the analysis to this setting (see [31,46] for examples of cotransmission in vector-borne disease ecology and human case reports, respectively). Our model will also include the possibility that an individual who is currently infected with one agent will become dually infected as a result of an exposure to the second agent. In this paper, the condition of being simultaneously infected by multiple agents will be referred to simply as *coinfection*. Our model is similar to the model of Blyuss and Kyrychko [7] where the disease induced mortality is included, the doubly infected hosts recover from both diseases simultaneously and strong restrictions on transmission parameters are required, and to the models for coinfection by different species in Tanaka and Feldman [54] and Alizon [4] where disease-induced mortality may occur, but no recovery is possible (and the forces of infection follow a different rule).

We will assess a two-disease SIS model with no immunity or cross-immunity. For simplicity, we will refer to the first and second disease, recognizing that the model applies equally well to colonization or to subclinical infections. In Section 3, we carry out a complete global stability analysis of the model for the case where the force of infection of one disease is not affected by the presence of the other (i.e., no interaction between two infections). In Section 4, when the two infections interact with each other, we calculate the invasion reproduction numbers and obtain their epidemiologically meaningful lower and upper bounds, and show that the interaction outcome could be extinction of one or both diseases or persistence of both diseases. In Section 5, four numerical examples are provided to support the existence of competitive exclusion, backward bifurcation, bistability and Hopf bifurcation, respectively.

2. The model

We propose a simple SIS epidemic model with two infectious agents (or strains of the same agent) spreading through one host species. Let $S(t)$, $I_1(t)$, $I_2(t)$ and $I_{12}(t)$ be the fractions of the population infected with no infectious agent, the first agent, the second agent and both agents at time t , respectively. A susceptible individual who contacts coinfecting persons can be infected with either one or both disease agents as a result of a single contact. Using ocular strains of *Chlamydia trachomatis* and nasopharyngeal

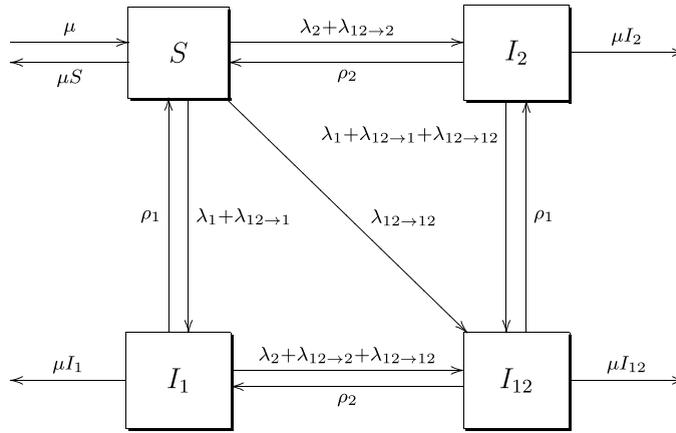


Fig. 1. Flowchart of a two-disease coinfection model. S , I_1 , I_2 and I_{12} represent the fractions of population infected with no infectious agent, the first agent, the second agent and both agents, respectively.

pneumococcus as an example, transmission of either or both organisms could occur as a result of a single contact. This process is illustrated in Fig. 1. The model is then described by a system of four ordinary differential equations as follows:

$$\begin{aligned}
 \frac{dS}{dt} &= \mu - (\lambda_1 + \lambda_2 + \lambda_{12\rightarrow 1} + \lambda_{12\rightarrow 12} + \lambda_{12\rightarrow 2})S + (\rho_1 I_1 + \rho_2 I_2) - \mu S, \\
 \frac{dI_1}{dt} &= (\lambda_1 + \lambda_{12\rightarrow 1})S - (\lambda_2 + \lambda_{12\rightarrow 2} + \lambda_{12\rightarrow 12})I_1 + (\rho_2 I_{12} - \rho_1 I_1) - \mu I_1, \\
 \frac{dI_2}{dt} &= (\lambda_2 + \lambda_{12\rightarrow 2})S - (\lambda_1 + \lambda_{12\rightarrow 1} + \lambda_{12\rightarrow 12})I_2 + (\rho_1 I_{12} - \rho_2 I_2) - \mu I_2, \\
 \frac{dI_{12}}{dt} &= \lambda_{12\rightarrow 12}S + (\lambda_2 + \lambda_{12\rightarrow 2} + \lambda_{12\rightarrow 12})I_1 + (\lambda_1 + \lambda_{12\rightarrow 1} + \lambda_{12\rightarrow 12})I_2 \\
 &\quad - (\rho_1 + \rho_2)I_{12} - \mu I_{12}, \quad 1 = S + I_1 + I_2 + I_{12},
 \end{aligned} \tag{2.1}$$

where the forces of infection are proportional to disease prevalence, i.e.,

$$\lambda_1 = \beta_1 I_1, \quad \lambda_2 = \beta_2 I_2, \quad \lambda_{12\rightarrow 12} = \beta_{12} I_{12}, \quad \lambda_{12\rightarrow 1} = \beta_{10} I_{12}, \quad \lambda_{12\rightarrow 2} = \beta_{02} I_{12}.$$

Parameters ρ_1 and ρ_2 represent the recovery rate of the first and second diseases, respectively. The disease induced death rate is ignored. We assume that the natural birth and death rates are balanced and equal to μ , so that the total population size is constant. All parameters are assumed to be positive, except that $\beta_{12} \geq 0$. As stated earlier, the possibility of simultaneous transmission from a single contact with a dually infected individual, which we model according to the assumption $\beta_{12} > 0$. An underlying assumption in the model is that individuals in all disease states have the same contact rate; we do not assume that individuals have fewer contacts if they are infected. The rates/probabilities of transmission of the model in Blyuss and Kyrychko [7] satisfy $\beta_{12} + \beta_{10} = \beta_1, \beta_{12} + \beta_{02} = \beta_2, \beta_{12} = \beta_1 \beta_2$, which is a special case of ours.

Following the method and notations of van den Driessche and Watmough [58] and Diekmann et al. [14, 15], we have

$$F = \begin{pmatrix} \beta_1 & 0 & \beta_{10} \\ 0 & \beta_2 & \beta_{02} \\ 0 & 0 & \beta_{12} \end{pmatrix} \text{ and } V = \begin{pmatrix} \rho_1 + \mu & 0 & -\rho_2 \\ 0 & \rho_2 + \mu & -\rho_1 \\ 0 & 0 & \rho_1 + \rho_2 + \mu \end{pmatrix}.$$

The basic reproduction number associated with the model (2.1) is defined as the spectral radius of the next generation matrix FV^{-1} , i.e., $\mathcal{R}_0 = \max\{\mathcal{R}_{10}, \mathcal{R}_{20}, \mathcal{R}_{30}\}$, where

$$\mathcal{R}_{10} = \frac{\beta_1}{\rho_1 + \mu}, \quad \mathcal{R}_{20} = \frac{\beta_2}{\rho_2 + \mu}, \quad \mathcal{R}_{30} = \frac{\beta_{12}}{\rho_1 + \rho_2 + \mu}.$$

Let $\Omega = \{(S, I_1, I_2, I_{12}) \in \mathbb{R}_+^4 : S + I_1 + I_2 + I_{12} = 1\}$. Clearly, the set Ω is positively invariant for system (2.1), so we will always set initial values within Ω . It is immediate that system (2.1) has up to three boundary equilibria as follows.

Proposition 2.1. *For system (2.1), we have*

- (i) *the disease-free equilibrium $E_0 = (1, 0, 0, 0)$ always exists;*
- (ii) *the equilibrium with the presence of only the first disease $E_1 = (1/\mathcal{R}_{10}, 1 - 1/\mathcal{R}_{10}, 0, 0)$ exists if and only if $\mathcal{R}_{10} > 1$;*
- (iii) *the equilibrium with the presence of only the second disease $E_2 = (1/\mathcal{R}_{20}, 0, 1 - 1/\mathcal{R}_{20}, 0)$ exists if and only if $\mathcal{R}_{20} > 1$.*

3. Noninteracting transmission

We begin with the simpler case where the presence of each disease does not affect the transmission of the other; throughout this section, we assume that a doubly infected individual has the same total infectivity as a singly infected person, which translates to

$$\beta_{12} + \beta_{10} = \beta_1 \text{ and } \beta_{12} + \beta_{02} = \beta_2. \quad (\text{H})$$

Under the assumption (H), the persistence and extinction of one disease, and the total fraction of people infected by that disease, are not affected by the presence of the other disease. The ability of a disease to invade an uninfected population is completely determined by its own basic reproduction number.

Theorem 3.1. *Let $\Omega_0 = \{E_0\}$, $\Omega_1 = \{(S, I_1, 0, 0) \in \Omega : I_1 > 0\}$ and $\Omega_2 = \{(S, 0, I_2, 0) \in \Omega : I_2 > 0\}$. For system (2.1) under assumption (H), we have*

- (1) *if $\mathcal{R}_0 \leq 1$ then the disease-free equilibrium E_0 is globally asymptotically stable in Ω ;*
- (2) *if $\mathcal{R}_{10} > 1 \geq \mathcal{R}_{20}$ (or $\mathcal{R}_{20} > 1 \geq \mathcal{R}_{10}$), then E_1 (or E_2) is globally asymptotically stable in $\Omega \setminus (\Omega_0 \cup \Omega_2)$ (or $\Omega \setminus (\Omega_0 \cup \Omega_1)$) where $\Omega_0 \cup \Omega_2$ (or $(\Omega_0 \cup \Omega_1)$) is the attractor of E_0 ;*
- (3) *if $\mathcal{R}_{10} > 1$ and $\mathcal{R}_{20} > 1$, then there exists a unique coexistence equilibrium, denoted by $E_{12} = (S^*, I_1^*, I_2^*, I_{12}^*)$, which is globally asymptotically stable in*

$$\Omega \setminus (\Omega_0 \cup \Omega_1 \cup \Omega_2) = \{(S, I_1, I_2, I_{12}) \in \Omega : I_{12} > 0 \text{ or } I_1 I_2 > 0\}.$$

Here Ω_0 , Ω_1 and Ω_2 are the attractor of E_0 , E_1 and E_2 , respectively.

Proof. The summations of the second and fourth equations of (2.1) and the third and fourth equations of (2.1) give

$$\frac{d(I_1 + I_{12})}{dt} = -(\rho_1 + \mu - \beta_1(S + I_2))(I_1 + I_{12})$$

and

$$\frac{d(I_2 + I_{12})}{dt} = -(\rho_2 + \mu - \beta_2(S + I_1))(I_2 + I_{12}),$$

respectively. It follows from $S + I_1 + I_2 + I_{12} = 1$ that the above two logistic equations satisfy

$$I_1(t) + I_{12}(t) \rightarrow \max \left\{ 0, 1 - \frac{1}{\mathcal{R}_{10}} \right\} \text{ and } I_2(t) + I_{12}(t) \rightarrow \max \left\{ 0, 1 - \frac{1}{\mathcal{R}_{20}} \right\} \text{ as } t \rightarrow \infty,$$

respectively, if both diseases present initially. If, for example, $\mathcal{R}_{10} \leq 1$, then $I_1(t) + I_{12}(t) \rightarrow 0$ which implies $\lim_{t \rightarrow \infty} I_1(t) = \lim_{t \rightarrow \infty} I_{12}(t) = 0$. Thus, the first two arguments are established.

Now we assume that $\mathcal{R}_{10} \geq \mathcal{R}_{20} > 1$ and the symmetric case $\mathcal{R}_{20} \geq \mathcal{R}_{10} > 1$ can be proved similarly. If $E_{12} = (S^*, I_1^*, I_2^*, I_{12}^*)$ exists, then it must satisfy

$$I_1^* = \frac{1}{\mathcal{R}_{20}} - S^*, \quad I_2^* = \frac{1}{\mathcal{R}_{10}} - S^* \text{ and } I_{12}^* = S^* + 1 - \frac{1}{\mathcal{R}_{10}} - \frac{1}{\mathcal{R}_{20}} \tag{3.1}$$

and substituting them into the first equation of (2.1) yields

$$\frac{dS^*}{dt} = \beta_{12}(S^*)^2 - \left(\left(\frac{1}{\mathcal{R}_{10}} + \frac{1}{\mathcal{R}_{20}} - 1 \right) \beta_{12} + (\beta_1 + \beta_2) - \mu \right) S^* + \frac{\rho_1}{\mathcal{R}_{20}} + \frac{\rho_2}{\mathcal{R}_{10}} + \mu = 0. \tag{3.2}$$

Meanwhile, solving I_{12}^* in terms of S^* from the first equation of (2.1) gives

$$I_{12}^* = \frac{\beta_1 \left(\frac{1}{\mathcal{R}_{10}} - S^* \right) I_1^* + \beta_2 \left(\frac{1}{\mathcal{R}_{20}} - S^* \right) I_2^*}{(\beta_{10} + \beta_{02} + \beta_{12}) S^* - \mu} = \frac{(\beta_1 + \beta_2) \left(\frac{1}{\mathcal{R}_{10}} - S^* \right) \left(\frac{1}{\mathcal{R}_{20}} - S^* \right)}{(\beta_1 + \beta_2 - \beta_{12}) S^* - \mu} \geq \frac{I_1^* I_2^*}{S^*}.$$

Claim 1: If $\beta_{12} = 0$, then $S^* = \left(\frac{\rho_1}{\mathcal{R}_{20}} + \frac{\rho_2}{\mathcal{R}_{10}} + \mu \right) / (\beta_1 + \beta_2 - \mu)$ and there exists a unique endemic equilibrium

$$E_{12} = \frac{1}{\beta_1 + \beta_2 - \mu} \left(\frac{\rho_1}{\mathcal{R}_{20}} + \frac{\rho_2}{\mathcal{R}_{10}} + \mu, \left(1 - \frac{1}{\mathcal{R}_{10}} \right) \left(\frac{\beta_1 + \beta_2}{\mathcal{R}_{20}} - \mu \right), \right. \\ \left. \left(1 - \frac{1}{\mathcal{R}_{20}} \right) \left(\frac{\beta_1 + \beta_2}{\mathcal{R}_{10}} - \mu \right), \left(1 - \frac{1}{\mathcal{R}_{10}} \right) \left(1 - \frac{1}{\mathcal{R}_{20}} \right) (\beta_1 + \beta_2) \right).$$

If $\beta_{12} > 0$, then (3.2) has two roots, labeled by S_1^* and S_2^* , satisfying $0 < \Re S_1^* \leq \Re S_2^*$. Here $\Re(z)$ is the real part of a complex number z . Dividing both sides of (3.2) by β_{12} yields

$$F(S^*) \equiv (S^*)^2 - (v_1 + v_2 - 1 + g - h) S^* + g v_1 v_2 + (1 - v_1 - v_2) h = 0,$$

where $v_1 = \frac{1}{\mathcal{R}_{10}}, v_2 = \frac{1}{\mathcal{R}_{20}}, g = \frac{\beta_1 + \beta_2}{\beta_{12}}$ and $h = \frac{\mu}{\beta_{12}}$. Clearly, $v_1 \leq v_2 < 1, g > 2$ and $g > 2h$.

Claim 2: $0 < S_1^* < v_1 \leq v_2 < 1 < S_2^*$. It follows from $F(0) = S_1^* S_2^* > 0$ and

$$F(v_1) = v_1^2 - (v_1 + v_2 - 1 + g - h) v_1 + g v_1 v_2 + (1 - v_1 - v_2) h \\ = -(v_2 - 1 + g - g v_2) v_1 + (1 - v_2) h = (1 - v_2) (h - v_1 (g - 1)) \\ = (1 - v_2) \left(\frac{\mu}{\beta_{12}} - \frac{\rho_1 + \mu}{\beta_1} \left(\frac{\beta_1 + \beta_2}{\beta_{12}} - 1 \right) \right) \\ = (1 - v_2) \left(\frac{\mu}{\beta_{12}} - \frac{\rho_1 + \mu}{\beta_{12}} - \frac{\rho_1 + \mu}{\beta_1} \left(\frac{\beta_2}{\beta_{12}} - 1 \right) \right) < 0$$

that both S_1^* and S_2^* are positive real numbers and $S_1^* < v_1$. In addition,

$$\begin{aligned}
 S_2^* &= v_1 + v_2 - 1 + g - h - S_1^* > v_2 - 1 + g - h \\
 &= \frac{\rho_2 + \mu}{\beta_2} - 1 + \frac{\beta_1 + \beta_2}{\beta_{12}} - \frac{\mu}{\beta_{12}} \geq \left(\frac{\mu}{\beta_2} - 1 + \frac{\beta_2}{\beta_{12}} - \frac{\mu}{\beta_{12}} \right) + \frac{\beta_1}{\beta_{12}} \\
 &= \left(\frac{\beta_2}{\beta_{12}} - 1 \right) \left(1 - \frac{\mu}{\beta_2} \right) + \frac{\beta_1}{\beta_{12}} > \frac{\beta_1}{\beta_{12}} > 1.
 \end{aligned}$$

When $S^* = S_1^*$, the positivities of I_1^* and I_2^* follow from $S_1^* < v_1 \leq v_2$ and $I_{12}^* > 0$ is equivalent to $S_1^* > \mu/(\beta_1 + \beta_2 - \beta_{12}) = h/(g - 1) \in (0, 1)$, which is guaranteed by

$$F\left(\frac{h}{g-1}\right) = \frac{g(h - (g-1)v_1)(h - (g-1)v_2)}{(g-1)^2} > 0 = F(S_1^*) \text{ and } h < (g-1)v_1 \leq (g-1)v_2.$$

Consequently, if $\mathcal{R}_{10} > 1$ and $\mathcal{R}_{20} > 1$, then (2.1) has a unique endemic equilibrium

$$E_{12} = (S^*, I_1^*, I_2^*, I_{12}^*) = \left(S^*, \frac{1}{\mathcal{R}_{20}} - S^*, \frac{1}{\mathcal{R}_{10}} - S^*, S^* + 1 - \frac{1}{\mathcal{R}_{10}} - \frac{1}{\mathcal{R}_{20}} \right),$$

where $S^* \in (0, 1)$ is the unique feasible solution to (3.2).

The spectrum of the Jacobian matrix of system (2.1) at E_{12} is

$$\{-\mu, -\beta_1 + \rho_1 + \mu, -\beta_2 + \rho_2 + \mu, -\beta_1 - \beta_2 + \mu + \beta_{12} - \beta_{12}(I_1^* + I_2^*)\},$$

which means the endemic equilibrium is locally asymptotically stable. It follows from the result on asymptotically autonomous differential equations [56] that E_{12} is globally attractive. Hence the endemic equilibrium is globally asymptotically stable when it exists. □

Remark 3.2. When coinfection is impossible, the competitive exclusion principle holds and the disease with a larger reproduction number must exclude the other [8]. Thus coinfection is a mechanism for the coexistence of multiple agents or pathogens [35].

Remark 3.3. It follows from $S^* + (v_1 - S^*) + (v_2 - S^*) + (v_1 - S^*)(v_2 - S^*)/S^* \leq 1$ and (3.1) that $\min\{v_1, v_2\} > S^* \geq v_1 v_2$, $I_1^* \leq (1 - v_1)v_2$, $I_2^* \leq (1 - v_2)v_1$, and $I_{12}^* \geq (1 - v_1)(1 - v_2)$. Both the uninfected population and the coinfecting population are increasing in the cotransmission rate. Indeed, differentiating $F(S^*) = 0$ with respect to β_{12} gives

$$\begin{aligned}
 \frac{\partial S^*}{\partial \beta_{12}} &= \frac{g v_1 v_2 + (1 - v_1 - v_2)h - (g - h)S^*}{(2S^* - (v_1 + v_2 + g - 1 - h))\beta_{12}} = \frac{(S^*)^2 - (v_1 + v_2 - 1)S^*}{((v_1 - S^*) + (v_2 - S^*) + (g - 1 - h))\beta_{12}} \\
 &> \frac{(v_1 v_2 - (v_1 + v_2 - 1))S^* \beta_{12}^{-1}}{(v_1 - S^*) + (v_2 - S^*) + (g - 1 - h)} = \frac{(1 - v_1)(1 - v_2)S^* \beta_{12}^{-1}}{(v_1 - S^*) + (v_2 - S^*) + (g - 1 - h)} > 0,
 \end{aligned}$$

and $I_{12}^* = S^* + 1 - v_1 - v_2$ implies that $\frac{\partial I_{12}^*}{\partial \beta_{12}} = \frac{\partial S^*}{\partial \beta_{12}} > 0$.

In the setting of multiple diseases, we may treat the entire population (mass treatment, $\rho_i \rightarrow \rho_i + \theta$ for any i), or only a fraction of people infected by a specific disease (targeted treatment, $\rho_i \rightarrow \rho_i + \theta_i$ for some i). Under both treatment strategies, it is shown that for model (2.1) with the restriction (H) the uninfected population is always increased by choosing a higher treatment rate; this differs from the two-disease model we studied in [17].

Corollary 3.4. For system (2.1) under assumption (H), the fraction of susceptible, S^* , is always increasing in the mass treatment rate θ (or targeted treatment rate θ_i).

Proof. If $\beta_{12} = 0$, then under the mass treatment and targeted treatment we have

$$\frac{\partial S^*}{\partial \theta} = \frac{(\beta_1 + \beta_2)(\rho_1 + \rho_2 + 2\theta + \mu)}{\beta_1\beta_2(\beta_1 + \beta_2 - \mu)} \quad \text{and} \quad \frac{\partial S^*}{\partial \theta_i} = \frac{\beta_i(\rho_j + \mu) + \beta_j\rho_j}{\beta_1\beta_2(\beta_1 + \beta_2 - \mu)}, \quad i \neq j, \quad i, j = 1, 2,$$

respectively. Now assume that $\beta_{12} > 0$ and $v_1 \geq v_2$, it follows from the differentiation of $F(S^*) = 0$ with respect to targeted treatment rate θ_i or mass treatment rate θ that

$$\frac{\partial S^*}{\partial \theta_i} = \frac{(S^* - gv_j + h)\beta_i^{-1}}{2S^* - (v_1 + v_2 + g - 1 - h)} = \frac{((v_j - S^*) + (v_j(g - 1) - h))\beta_i^{-1}}{(v_1 - S^*) + (v_2 - S^*) + (g - 1 - h)} > 0$$

and

$$\begin{aligned} \frac{\partial S^*}{\partial \theta} &= \frac{S^* - g(\rho_1 + \theta + \mu + \rho_2 + \theta + \mu)/(\beta_1 + \beta_2) + h}{2S^* - (v_1 + v_2 + g - 1 - h)} \cdot \left(\frac{1}{\beta_1} + \frac{1}{\beta_2}\right) \\ &> \frac{S^* - gv_1 + h}{2S^* - (v_1 + v_2 + g - 1 - h)} \cdot \left(\frac{1}{\beta_1} + \frac{1}{\beta_2}\right) > 0. \end{aligned}$$

The last inequality holds because of $S^* - gv_1 + h < 0$ and $2S^* - (v_1 + v_2 + g - 1 - h) < 0$. \square

4. Interacting transmission

In the rest of the paper, we remove the requirement (H), namely, $\beta_{12} + \beta_{10} \neq \beta_1$ or $\beta_{12} + \beta_{02} \neq \beta_2$. Biologically, this means that a dually-infected individual may transmit each agent either more or less efficiently than a person infected with each agent singly. Three possible scenarios are listed as follows:

- (1) Mutual enhancement: $\beta_{12} + \beta_{10} > \beta_1$ and $\beta_{12} + \beta_{02} > \beta_2$;
- (2) Enhancement and inhibition: $\beta_{12} + \beta_{10} > \beta_1$ and $\beta_{12} + \beta_{02} < \beta_2$, or $\beta_{12} + \beta_{10} < \beta_1$ and $\beta_{12} + \beta_{02} > \beta_2$;
- (3) Mutual inhibition: $\beta_{12} + \beta_{10} < \beta_1$ and $\beta_{12} + \beta_{02} < \beta_2$.

The dynamics are simple equilibrium if the double infection has mild impact on the transmission of one of the two infections. The following proof utilizes the theory of monotone dynamical systems [52], simplifying the proof of Theorem 3.1.

Proposition 4.1. *Assume that dual infection has no impact on the transmission of the first disease, i.e., $\beta_{12} + \beta_{10} = \beta_1$. For system (2.1), every orbit with initial value in Ω converges to an equilibrium.*

Proof. The assumption $\beta_{12} + \beta_{10} = \beta_1$ implies that $I_1(t) + I_{12}(t) \rightarrow \max\{0, 1 - 1/\mathcal{R}_{10}\}$ as $t \rightarrow \infty$ for $I_1(0) + I_{12}(0) > 0$. If $\mathcal{R}_{10} \leq 1$, then either E_0 or E_2 is globally stable. If $\mathcal{R}_{10} > 1$, then $I_1(t) + I_{12}(t) \rightarrow 1 - 1/\mathcal{R}_{10}$ and $S(t) + I_2(t) \rightarrow 1/\mathcal{R}_{10}$ as $t \rightarrow \infty$. Thus, the 4-dimensional system (2.1) can be reduced to a 2-dimensional system in I_1 and I_2 . Denote the Jacobian matrix of this two-dimensional system by $J_2 = (a_{ij})_{2 \times 2}$, where

$$a_{12} = -(\beta_1 - \beta_{12})(1 - 1/\mathcal{R}_{10}) - (\beta_2 + \beta_{12})I_1 < 0 \quad \text{and} \quad a_{21} = -\rho_1 - (1/\mathcal{R}_{10} - I_2)\beta_{02} < 0.$$

Thus, the reduced 2-dimensional system is competitive. By Theorem 3.2.2 in Smith [52], every orbit converges to an equilibrium. \square

The stability analysis for system (2.1) now becomes more complicated, and we need to introduce a new threshold parameter—the invasion reproduction number, which is used to measure the ability of one disease

to invade an equilibrium of the other disease [42,35,60]. We now assume that the equilibrium E_1 exists, or equivalently, $\mathcal{R}_{10} > 1$. Using the next generation matrix method [14,15,58], the vectors for the rate of the appearance of new infections by disease two and the rate of transfer of individuals are, respectively,

$$\begin{aligned} \mathcal{F}_2(I_2, I_{12}) &= \begin{pmatrix} (\lambda_2 + \lambda_{12 \rightarrow 2})\bar{S} \\ \lambda_{12 \rightarrow 12}\bar{S} + \lambda_2\bar{I}_1 + (\lambda_{12 \rightarrow 2} + \lambda_{12 \rightarrow 12})\bar{I}_1 \end{pmatrix}, \\ \mathcal{V}_2(I_2, I_{12}) &= \begin{pmatrix} (\lambda_1 + \lambda_{12 \rightarrow 1} + \lambda_{12 \rightarrow 12})\bar{I}_2 - (\rho_1\bar{I}_{12} - \rho_2\bar{I}_2) + \mu\bar{I}_2 \\ -\lambda_1\bar{I}_2 - (\lambda_{12 \rightarrow 1} + \lambda_{12 \rightarrow 12})\bar{I}_2 + (\rho_1 + \rho_2)\bar{I}_{12} + \mu\bar{I}_{12} \end{pmatrix}, \end{aligned}$$

where $(\bar{S}, \bar{I}_1) = (1/\mathcal{R}_{10}, 1 - 1/\mathcal{R}_{10})$. The derivatives of \mathcal{F}_2 and \mathcal{V}_2 at $(I_2, I_{12}) = (0, 0)$ are, respectively,

$$\begin{aligned} F_2 &= D\mathcal{F}_2(0, 0) = \begin{pmatrix} \beta_2\bar{S} & \beta_{02}\bar{S} \\ \beta_2\bar{I}_1 & \beta_{12}\bar{S} + (\beta_{12} + \beta_{02})\bar{I}_1 \end{pmatrix}, \\ V_2 &= D\mathcal{V}_2(0, 0) = \begin{pmatrix} \beta_1\bar{I}_1 + \rho_2 + \mu & -\rho_1 \\ -\beta_1\bar{I}_1 & \rho_1 + \rho_2 + \mu \end{pmatrix}. \end{aligned}$$

The characteristic polynomial of the matrix $F_2V_2^{-1}$ is $A_2\lambda^2 + A_1\lambda + A_0 = 0$, where

$$\begin{aligned} A_2 &= (\beta_1 + \rho_2)(\rho_2 + \mu), A_0 = \beta_2\beta_{12}(\rho_1 + \mu)/\beta_1, \\ A_1 &= -(\beta_2\bar{S}(\rho_1 + \rho_2 + \mu) + \beta_{02}\bar{S}\beta_1\bar{I}_1 + \beta_2\bar{I}_1\rho_1 + (\beta_{12}\bar{S} + (\beta_{12} + \beta_{02})\bar{I}_1)(\beta_1\bar{I}_1 + \rho_2 + \mu)) \\ &= -(\beta_{12} + \beta_{02})\beta_1 + ((\beta_{12} + \beta_{02})(\rho_1 - \rho_2) - \beta_2\rho_1) + (\beta_{02} - \beta_2)(\rho_1 + \mu)(\rho_2 + \mu)/\beta_1 < 0. \end{aligned}$$

The invasion reproduction number of disease 2, denoted by \mathcal{R}_2^1 , is given by the spectral radius of the non-negative matrix $F_2V_2^{-1}$, i.e.,

$$\mathcal{R}_2^1 = \rho(F_2V_2^{-1}) = \frac{-A_1 + \sqrt{A_1^2 - 4A_0A_2}}{2A_2} > 0.$$

It follows from $A_0 > 0$ that the characteristic equation has two positive roots as $\beta_{12} > 0$. If $\beta_{12} = 0$ then $A_0 = 0$ and $\mathcal{R}_2^1 = -A_1/A_2$.

Similarly, we can derive a formula for the invasion reproduction number of disease 1, denoted by \mathcal{R}_1^2 . By Theorem 2 in van den Driessche and Watmough [58], disease 1 can invade disease 2 if $\mathcal{R}_1^2 > 1$ and disease 2 can invade disease 1 if $\mathcal{R}_2^1 > 1$ (see Appendix A for a direct proof).

Proposition 4.2. *For system (2.1), when the equilibrium E_1 exists (i.e., $\mathcal{R}_{10} > 1$), it is locally asymptotically stable if $\mathcal{R}_2^1 < 1$ and unstable if $\mathcal{R}_2^1 > 1$. Symmetrically, the equilibrium E_2 is locally asymptotically stable if $\mathcal{R}_1^2 < 1$ and unstable if $\mathcal{R}_1^2 > 1$.*

Define $\tilde{\mathcal{R}}_{20} = (\beta_{12} + \beta_{02})/(\rho_2 + \mu)$; this quantity, analogous to a basic reproduction number, is the number of cases of disease 2 resulting from the introduction of a dually infected person into a wholly susceptible population. We can establish the lower and upper bounds for the invasion reproduction number \mathcal{R}_2^1 .

Proposition 4.3. *Assume that E_1 exists, or equivalently, $\mathcal{R}_{10} > 1$. Then the following statements are valid:*

- (i) $\tilde{\mathcal{R}}_{20} < \mathcal{R}_2^1 < \mathcal{R}_{20}$ if and only if $\beta_2 > \beta_{12} + \beta_{02}$;
- (ii) $\tilde{\mathcal{R}}_{20} > \mathcal{R}_2^1 > \mathcal{R}_{20}$ if and only if $\beta_2 < \beta_{12} + \beta_{02}$;
- (iii) $\tilde{\mathcal{R}}_{20} = \mathcal{R}_2^1 = \mathcal{R}_{20}$ if and only if $\beta_2 = \beta_{12} + \beta_{02}$.

Proof. $\mathcal{R}_{20} - \mathcal{R}_2^1$ has the same sign as $\beta_2 - \beta_{12} - \beta_{02}$. In fact, we can rewrite $\mathcal{R}_{20} < \mathcal{R}_2^1$ as

$$\frac{\beta_2}{\rho_2 + \mu} < \frac{-A_1 + \sqrt{A_1^2 - 4A_0A_2}}{2A_2} \Leftrightarrow 2\beta_2A_2 + (\rho_2 + \mu)A_1 < (\rho_2 + \mu)\sqrt{A_1^2 - 4A_0A_2}.$$

If $G \equiv 2\beta_2A_2 + (\rho_2 + \mu)A_1 \geq 0$, then $\mathcal{R}_{20} < \mathcal{R}_2^1$ is equivalent to

$$\begin{aligned} &4\beta_2^2A_2^2 + 4\beta_2(\rho_2 + \mu)A_1A_2 + (\rho_2 + \mu)^2A_1^2 < (\rho_2 + \mu)^2A_1^2 - 4(\rho_2 + \mu)^2A_0A_2 \\ \Leftrightarrow &4A_2(A_2\beta_2^2 + A_1\beta_2(\rho_2 + \mu) + A_0(\rho_2 + \mu)^2) < 0 \\ \Leftrightarrow &\beta_2(\beta_2 - \beta_{12} - \beta_{02})(\beta_1 - \rho_1 - \mu)(\rho_2 + \mu)(\beta_1 + \rho_2 + \mu) < 0 \Leftrightarrow \beta_2 < \beta_{12} + \beta_{02}. \end{aligned}$$

If $G < 0$, then $G = (\rho_2 + \mu)(G_0 + (\beta_2 - \beta_{12} - \beta_{02})G_1)$ where

$$\begin{aligned} G_0 &= [\beta_1\beta_{02}(\beta_1 + \rho_2) + \beta_{12}(\beta_1(\beta_1 + \rho_2) - (\rho_1 + \mu)(\rho_2 + \mu))]/\beta_1, \\ G_1 &= 2(\beta_1 + \rho_2) - \rho_1 - (\rho_1 + \mu)(\rho_2 + \mu)/\beta_1. \end{aligned}$$

Note that $G_0 > 0$ and $G_1 > 0$ when $\mathcal{R}_{10} > 1$. If $\beta_2 \geq \beta_{12} + \beta_{02}$ then $G > 0$, a contradiction.

On the other hand, $\tilde{\mathcal{R}}_{20} < \mathcal{R}_2^1$ is equivalent to

$$\begin{aligned} &A_2(\beta_{12} + \beta_{02})^2 + A_1(\beta_{12} + \beta_{02})(\rho_2 + \mu) + A_0(\rho_2 + \mu)^2 < 0 \\ \Leftrightarrow &(\beta_{12} + \beta_{02} - \beta_2)(\rho_2 + \mu)(\mu^2\beta_{02} + \mu\beta_{02}(\rho_1 + \rho_2) + \rho_1(\beta_1(\beta_{12} + \beta_{02}) + \beta_{02}\rho_2)) < 0 \\ \Leftrightarrow &\beta_{12} + \beta_{02} < \beta_2. \end{aligned}$$

This completes the proof. \square

Therefore, it is possible that $\mathcal{R}_{20} < 1 < \mathcal{R}_2^1$ as $\beta_2 < \beta_{12} + \beta_{02}$. Moreover, we will show that the second disease may be able to invade in the presence of the first disease even if it cannot persist alone. That is, the presence of the first disease promotes persistence of the second disease. Similar to the model in Martcheva and Pilyugin [35], we can obtain the following result about the consequence of competition.

Proposition 4.4. *For system (2.1), if $\tilde{\mathcal{R}}_{10} \leq 1$ or $\tilde{\mathcal{R}}_{20} \leq 1$ and $\mathcal{R}_{10} \leq 1$, $\mathcal{R}_{20} \leq 1$, then both diseases go extinct and the disease-free equilibrium is globally stable; if $\max\{\mathcal{R}_{10}, \tilde{\mathcal{R}}_{10}\} \leq 1$ (or $\max\{\mathcal{R}_{20}, \tilde{\mathcal{R}}_{20}\} \leq 1$) then disease 1 (or 2) goes extinct; if $\min\{\mathcal{R}_{10}, \tilde{\mathcal{R}}_{10}\} > 1$ (or $\min\{\mathcal{R}_{20}, \tilde{\mathcal{R}}_{20}\} > 1$) then disease 1 (or 2) persists.*

Proof. It follows from the second and fourth equations of system (2.1) that

$$\frac{d(I_1 + I_{12})}{dt} = -(\rho_1 + \mu)(I_1 + I_{12}) + (\beta_{12}I_{12} + \beta_{10}I_{12} + \beta_1I_1)(S + I_2)$$

and hence

$$\begin{aligned} \frac{d(I_1 + I_{12})}{dt} &\leq (\max\{\beta_{12} + \beta_{10}, \beta_1\} - (\rho_1 + \mu))(I_1 + I_{12}) - \max\{\beta_{12} + \beta_{10}, \beta_1\}(I_1 + I_{12})^2, \\ \frac{d(I_1 + I_{12})}{dt} &\geq (\min\{\beta_{12} + \beta_{10}, \beta_1\} - (\rho_1 + \mu))(I_1 + I_{12}) - \min\{\beta_{12} + \beta_{10}, \beta_1\}(I_1 + I_{12})^2. \end{aligned}$$

By a simple comparison principle [53], we get

$$\limsup_{t \rightarrow \infty} (I_1 + I_{12}) \leq \max \left\{ 1 - \frac{\rho_1 + \mu}{\max\{\beta_1, \beta_{12} + \beta_{10}\}}, 0 \right\},$$

$$\liminf_{t \rightarrow \infty} (I_1 + I_{12}) \geq \max \left\{ 1 - \frac{\rho_1 + \mu}{\min\{\beta_1, \beta_{12} + \beta_{10}\}}, 0 \right\}$$

if $I_1(0) + I_{12}(0) > 0$. \square

Remark 4.5. A necessary condition for the existence of a coexistence equilibrium $E^* = (S^*, I_1^*, I_2^*, I_{12}^*)$ is that $\max\{\mathcal{R}_{i0}, \tilde{\mathcal{R}}_{i0}\} > 1$ for $i = 1, 2$. When E^* exists, it satisfies

$$1 - \frac{\rho_1 + \mu}{\min\{\beta_1, \beta_{12} + \beta_{10}\}} \leq I_1^* + I_{12}^* \leq 1 - \frac{\rho_1 + \mu}{\max\{\beta_1, \beta_{12} + \beta_{10}\}},$$

$$1 - \frac{\rho_2 + \mu}{\min\{\beta_2, \beta_{12} + \beta_{02}\}} \leq I_2^* + I_{12}^* \leq 1 - \frac{\rho_2 + \mu}{\max\{\beta_2, \beta_{12} + \beta_{02}\}}.$$

The above result indicates that the two diseases coexist whenever $\min\{\mathcal{R}_{i0}, \tilde{\mathcal{R}}_{i0}\} > 1, i = 1, 2$. By a similar argument to that of Theorem 2.5 in Gao and Ruan [18], we will show that it remains true under a weaker condition: $\min\{\mathcal{R}_{i0}, \mathcal{R}_i^j\} > 1, i \neq j, i, j = 1, 2$.

Theorem 4.6. For model (2.1), if

$$\mathcal{R}_{10} > 1, \mathcal{R}_{20} > 1, \mathcal{R}_1^2 > 1 \text{ and } \mathcal{R}_2^1 > 1, \quad (4.1)$$

then (2.1) admits at least one coexistence equilibrium and both diseases are uniformly persistent, i.e., there is a constant $\kappa > 0$ such that each solution $\phi_t(\mathbf{x}_0) \equiv (S(t), I_1(t), I_2(t), I_{12}(t))$ of system (2.1) with $\mathbf{x}_0 \equiv (S(0), I_1(0), I_2(0), I_{12}(0)) \in \Omega_0 \equiv \{(S, I_1, I_2, I_{12}) \in \Omega : I_1 I_2 > 0 \text{ or } I_{12} > 0\}$ satisfies

$$\liminf_{t \rightarrow \infty} I_1(t) > \kappa, \quad \liminf_{t \rightarrow \infty} I_2(t) > \kappa \text{ and } \liminf_{t \rightarrow \infty} I_{12}(t) > \kappa.$$

Proof. Denote $\partial\Omega_0 = \Omega \setminus \Omega_0 = \{(S, I_1, I_2, I_{12}) \in \Omega : I_1 = 0 \text{ or } I_2 = 0, I_{12} = 0\}$. It is sufficient to show that system (2.1) is uniformly persistent with respect to $(\Omega_0, \partial\Omega_0)$. Obviously, $\partial\Omega_0$ is relatively closed in Ω . It is clear that Ω and Ω_0 are positively invariant and system (2.1) is point dissipative.

Let $M_\partial = \{\mathbf{x}_0 \in \partial\Omega_0 : \phi_t(\mathbf{x}_0) \in \partial\Omega_0 \text{ for } t \geq 0\}$. Therefore, $M_\partial = \partial\Omega_0$. The boundary equilibria E_0, E_1 and E_2 are in M_∂ . Let $W^s(E_i)$ be the stable manifold of E_i for $i = 0, 1, 2$. We will show that $W^s(E_i) \cap \Omega_0 = \emptyset$ whenever (4.1) holds.

Define

$$\mathcal{R}_1^\varepsilon = \frac{(1 - \varepsilon)\beta_1}{(\beta_2 + \beta_{12} + \beta_{02})\varepsilon + \rho_1 + \mu}.$$

It follows from $\mathcal{R}_{10} > 1$ that there is an $\varepsilon_0 > 0$ such that $\mathcal{R}_1^\varepsilon > 1$ for $\varepsilon \in [0, \varepsilon_0]$. Select η_0 small enough such that

$$S(0) \geq 1 - \varepsilon_0 \quad \text{for } \|\mathbf{x}_0 - E_0\| \leq \eta_0.$$

We claim that $\limsup_{t \rightarrow \infty} \|\phi_t(\mathbf{x}_0) - E_0\| > \eta_0$ for $\mathbf{x}_0 \in \Omega_0$, where $\|\cdot\|$ is the Euclidean norm. Supposing not, then by translation, we have $\|\phi_t(\mathbf{x}_0) - E_0\| \leq \eta_0$ for all $t \geq 0$ and hence

$$\begin{aligned} \frac{dI_1}{dt} &\geq \beta_1(1 - \varepsilon_0)I_1 - (\beta_2 + \beta_{12} + \beta_{02})\varepsilon_0 I_1 - \rho_1 I_1 - \mu I_1 \\ &= (\beta_1(1 - \varepsilon_0) - (\beta_2 + \beta_{12} + \beta_{02})\varepsilon_0 - \rho_1 - \mu)I_1. \end{aligned}$$

By a comparison theorem, $I_1(t) \rightarrow \infty$ as $t \rightarrow \infty$; the contradiction establishes the result.

To show $W^s(E_1) \cap \Omega_0 = \emptyset$, we define

$$\Delta = \begin{pmatrix} \beta_2 + \beta_1 + 2\beta_{12} + 2\beta_{10} & \beta_{02} \\ \beta_1 + \beta_2 & 2\beta_{12} + \beta_{02} \end{pmatrix} \text{ and } M_\varepsilon = F_2 - V_2 - \varepsilon\Delta.$$

Since $s(F_2 - V_2) > 0$ if and only if $\mathcal{R}_2^1 > 1$, there is an $\varepsilon_1 > 0$ such that $s(M_\varepsilon) > 0$ for $\varepsilon \in [0, \varepsilon_1]$. Recall that $(\bar{S}, \bar{I}_1) = (1/\mathcal{R}_{10}, 1 - 1/\mathcal{R}_{10})$. Choose η_1 small enough such that

$$\bar{S} - \varepsilon_1 \leq S(0) \leq \bar{S} + \varepsilon_1 \text{ and } \bar{I}_1 - \varepsilon_1 \leq I_1(0) \leq \bar{I}_1 + \varepsilon_1 \text{ for } \|\mathbf{x}_0 - E_1\| \leq \eta_1.$$

We claim that $\limsup_{t \rightarrow \infty} \|\phi_t(\mathbf{x}_0) - E_1\| > \eta_1$ for $\mathbf{x}_0 \in \Omega_0$. Supposing not, then again by translation, we have $\|\phi_t(\mathbf{x}_0) - E_1\| \leq \eta_1$ for all $t \geq 0$ and hence

$$\begin{aligned} \frac{dI_2}{dt} &\geq (\beta_2 I_2 + \beta_{02} I_{12})(\bar{S} - \varepsilon_1) - (\beta_1(\bar{I}_1 + \varepsilon_1) + (\beta_{12} + \beta_{10})2\varepsilon_1)I_2 + (\rho_1 I_{12} - \rho_2 I_2) - \mu I_2, \\ \frac{dI_{12}}{dt} &\geq \beta_{12} I_{12}(\bar{S} - \varepsilon_1) + (\beta_1 + \beta_2)(\bar{I}_1 - \varepsilon_1)I_2 + (\beta_{12} + \beta_{02})I_{12}(\bar{I}_1 - \varepsilon_1) - (\rho_1 + \rho_2 + \mu)I_{12}. \end{aligned}$$

Notice that M_{ε_1} has a positive eigenvalue $s(M_{\varepsilon_1})$ associated to a positive eigenvector. It follows from a comparison theorem that $I_2(t) \rightarrow \infty$ and $I_{12}(t) \rightarrow \infty$ as $t \rightarrow \infty$, a contradiction.

Since $W^s(E_0) = \{E_0\}$, $W^s(E_1) = \{(S, I_1, I_2, I_{12}) \in \Omega : I_1 > 0, I_2 = I_{12} = 0\}$, $W^s(E_2) = \{(S, I_1, I_2, I_{12}) \in \Omega : I_2 > 0, I_1 = I_{12} = 0\}$ and $M_\partial = W^s(E_0) \cup W^s(E_1) \cup W^s(E_2)$, $\{E_0\}$, $\{E_1\}$ and $\{E_2\}$ are isolated invariant sets and acyclic in M_∂ . By Theorem 4.6 in Thieme [57], system (2.1) is uniformly persistent with respect to $(\Omega_0, \partial\Omega_0)$. Moreover, by Theorem 2.4 in Zhao [62], we know that system (2.1) has an equilibrium $E^* = (S^*, I_1^*, I_2^*, I_{12}^*) \in \Omega_0$. It is easy to check that E^* is a positive equilibrium of system (2.1). \square

Remark 4.7. Similarly, we can show the uniform persistence of both diseases and the existence of a coexistence equilibrium under the assumption $\mathcal{R}_{10} > 1$ and $\mathcal{R}_{20} < 1 < \mathcal{R}_2^1$, or $\mathcal{R}_{20} > 1$ and $\mathcal{R}_{10} < 1 < \mathcal{R}_1^1$. In this case, one disease goes extinct in the absence of the other and the presence of the other disease mediates the coexistence. Control strategies toward a reduction of both infections are favored.

A more detailed classification for the transmission dynamics of the coinfection model (2.1) based on its basic reproduction numbers and invasion reproduction numbers [35] is beyond the scope of current paper. For example, we are particularly interested in the local/global stability of the coexistence equilibrium under conditions in Theorem 4.6, but numerical examples in the next section show that an unstable coexistence equilibrium could present in case of backward bifurcation, bistability or a Hopf bifurcation. This suggests that it is hard to use the well-known Routh–Hurwitz criterion to determine the local stability of the coexistence equilibrium.

5. Numerical simulations

In this section, we illustrate, by numerical examples, possible phenomena the model of coinfection may exhibit.

Example 5.1 (Competitive exclusion). Two diseases cannot coexist even if each one can persist independently. Parameter values: $\beta_1 = 1.05, \beta_2 = 2.5, \rho_1 = 1, \rho_2 = 0.8, \mu = 0.02, \beta_{12} = 0.05, \beta_{10} = 0.2, \beta_{02} = 2$. The respective basic reproduction numbers are $\mathcal{R}_{10} = 1.0294 > 1$ and $\mathcal{R}_{20} = 3.0488 > 1$. Fig. 2 shows that the first disease goes extinct while the second persists. It provides a theoretically plausible treatment strategy for some pathogens: suppose that $1 < \mathcal{R}_{10} < \mathcal{R}_{20}$, $\beta_{12} + \beta_{10} < \beta_1$ and $\beta_{12} + \beta_{02} < \beta_2$; there is an effective

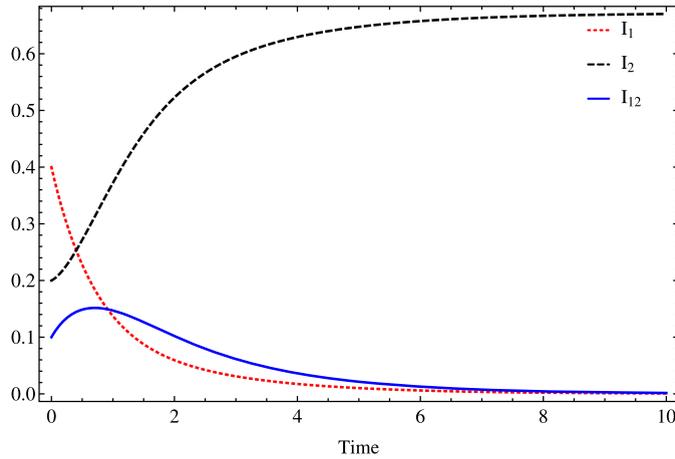


Fig. 2. Numerical solution of system (2.1) with initial condition $(S(0), I_1(0), I_2(0), I_{12}(0)) = (0.3, 0.4, 0.2, 0.1)$. Dotted red line: I_1 ; dashed black line: I_2 ; solid blue line: I_{12} . Two infections cannot coexist even if each one can survive independently. (Color appears in the web version of this article.)

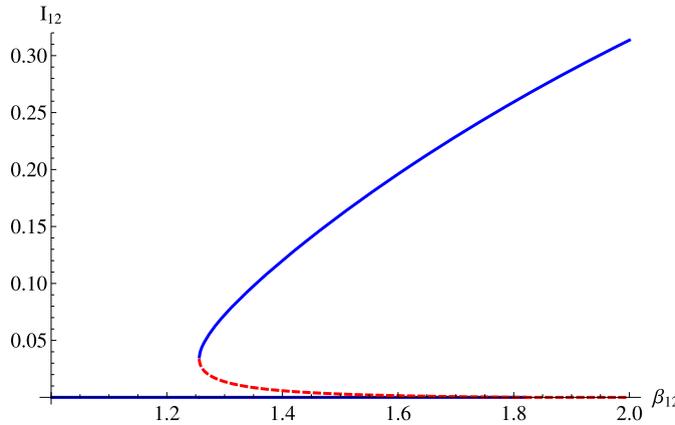


Fig. 3. Backward bifurcation arising from the change of β_{12} . Solid blue line—stable, dashed red line—unstable. Two diseases can coexist even if each one dies out independently. (Color appears in the web version of this article.)

way to treat pathogen 2, but not for pathogen 1. Here, one could in principle introduce pathogen 2 to eradicate pathogen 1.

Moreover, consider a scenario in which $\beta_1 = 2.9, \beta_2 = 3, \rho_1 = \rho_2 = \mu = 1, \beta_{12} = 0.5, \beta_{10} = 2, \beta_{02} = 0.1$; we have $\mathcal{R}_{10} = 1.45, \mathcal{R}_{20} = 1.5, \mathcal{R}_1^2 = 1.3612$ and $\mathcal{R}_2^1 = 0.9860$. Thus, E_1 is locally stable but E_2 is unstable and there is no coexistence equilibrium. Interestingly, in this case the competitive exclusion principle still holds, but the disease with a higher reproduction number dies out while the other one persists (in contrast with [8]).

Example 5.2 (Backward bifurcation). Assume that $\mathcal{R}_{10} < 1$ and $\mathcal{R}_{20} < 1$. If $\beta_{12} + \beta_{10} > \beta_1$ and $\beta_{12} + \beta_{02} > \beta_2$, then it is possible that both diseases become persistent. Parameter values: $\beta_1 = 0.9, \beta_2 = 0.7, \rho_1 = 1, \rho_2 = 0.8, \mu = 0.02, \beta_{10} = \beta_{02} = 0.6$. A bifurcation diagram for model (2.1) shows that the endemic equilibrium value of I_{12} with respect to β_{12} is presented in Fig. 3. In this setting, there is one stable coexistence equilibrium and one unstable coexistence equilibrium for $\beta_{12} \in (1.256, 1.82)$. Biologically, this means that a small perturbation in model parameters or initial conditions may lead to a large difference in the dynamic behavior of the disease. The occurrence of backward bifurcation precludes, in general, the global stability of the disease-free equilibrium as $\mathcal{R}_0 < 1$. Note that backward bifurcation still exists even if there is no cotransmission ($\beta_{12} = 0$).

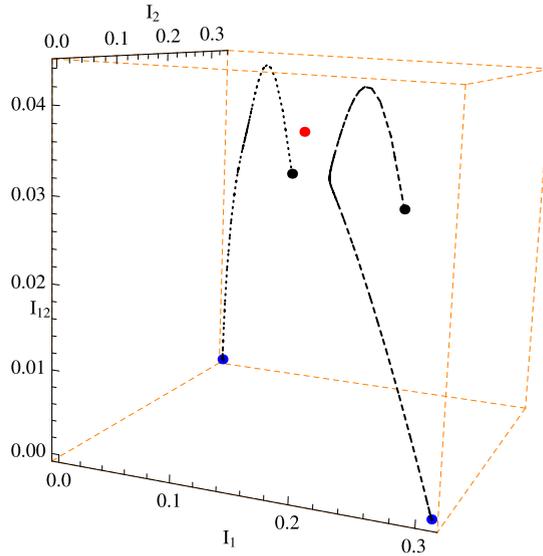


Fig. 4. Numerical solutions of system (2.1) with initial conditions: (0.62, 0.25, 0.1, 0.03) and (0.62, 0.1, 0.25, 0.03) (black dots). Bistability: the two boundary equilibria $E_1 = (20/29, 9/29, 0, 0)$ and $E_2 = (2/3, 0, 1/3, 0)$ (blue dots) are locally stable, and the coexistence equilibrium $E^* \approx (0.701, 0.165, 0.096, 0.038)$ (red dot) is unstable. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Example 5.3 (Bistability ($\mathcal{R}_{10} > 1, \mathcal{R}_{20} > 1, \mathcal{R}_1^2 < 1$ and $\mathcal{R}_2^1 < 1$)). The two boundary equilibria E_1 and E_2 are locally stable, while the coexistence equilibrium E^* is unstable. Parameter setting: $\beta_1 = 2.9, \beta_2 = 3, \rho_1 = \rho_2 = \mu = 1, \beta_{12} = 0.5, \beta_{10} = 0.3, \beta_{02} = 0.05$. Direct calculations yield the basic reproduction numbers $\mathcal{R}_{10} = 1.45, \mathcal{R}_{20} = 1.5$ and the invasion reproduction numbers $\mathcal{R}_1^2 = 0.9714, \mathcal{R}_2^1 = 0.9747$. A bistability phenomenon is observed in Fig. 4. The disease outcome depends on initial conditions and there exists a smooth surface separating the feasible region into two domains.

The occurrence of bistability also implies that the infection with a higher reproduction number is not necessarily the winner, so to speak, of the competition. In addition, there is no bistability phenomenon when the mortality rate μ is small enough (see Appendix B for a proof). Namely, if $\mathcal{R}_{20} > \max\{\mathcal{R}_{10}, 1\}$, then the second disease always persists as $\mu \rightarrow 0$.

Example 5.4 (Hopf bifurcation). The model can exhibit non-equilibrium dynamical behavior—periodic oscillations under certain conditions. Set $\beta_1 = 5, \beta_2 = 0.2, \rho_1 = \rho_2 = 0, \mu = 1, \beta_{12} = 0.805, \beta_{10} = 0$ and $\beta_{02} \in [70, 100]$. It follows from $\mathcal{R}_{10} = 5 > 1 > \mathcal{R}_{20} = 0.2$ and $\mathcal{R}_2^1 \gg 1$ that both diseases are uniformly persistent and there is a coexistence equilibrium (see Remark 4.7). The Jacobian matrix at the coexistence equilibrium has a pair of complex eigenvalues with negative real parts as $\beta_{02} \in [70, 84.74)$, a pair of purely imaginary eigenvalues as $\beta_{02} \approx 84.74$, and a pair of complex eigenvalues with positive real parts as $\beta_{02} \in (84.74, 100]$. Therefore, the coexistence equilibrium loses its stability and a Hopf bifurcation appears (see Fig. 5). For sufficiently small but nonzero ρ_1, ρ_2 and β_{10} , the system still has a Hopf bifurcation.

6. Discussion

In this paper, we proposed a simple two-disease SIS coinfection model featuring simultaneous transmission of infection due to contacts with dually infected individuals, as well as superinfection leading to dual infection. In our model, there are four epidemiological classes: susceptible to both diseases, susceptible to disease 2 but infectious for disease 1, susceptible to disease 1 but infectious for disease 2, and infectious for both diseases. It is a simplified version of the two-disease three-strain model in Gao et al. [17] in which the first disease exhibits both drug sensitive and resistant strains. The cotransmission dynamics of two diseases

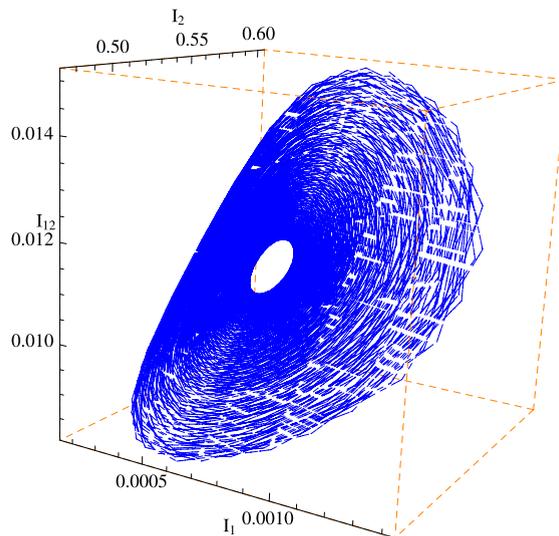


Fig. 5. Hopf bifurcation—two diseases coexist in an oscillatory mode.

modeled as a SIS process is of interest as a simplified model of, for instance, ocular chlamydia [33,32,34] and respiratory pneumococcal colonization [36]. In hyperendemic trachoma regions, both organisms are common and both are affected by trachoma control programs [24].

We considered the case for which the transmission of the first disease is completely unaffected by the presence of the second; that is, when coinfecting people transmit infection to the same degree as singly infected people, disease dynamics are completely determined by the basic reproduction numbers of each. The two diseases coexist at an endemic level as long as they can persist independently. However, if the assumption does not hold, then we calculated the invasion reproduction number to measure the ability of one disease to invade the other at its steady state. The relation between the basic reproduction number and the invasion reproduction number was investigated, and sufficient conditions for the persistence of both diseases were obtained. Using numerical methods, more complicated dynamics including backward bifurcation, bistability and Hopf bifurcation were found. The disease with smaller reproduction number may be able to invade and competitively exclude the other disease even if there is no coexistence steady state. It is noteworthy that some of these dynamical behaviors have been observed in previous studies based on different models [7,35,60,61]. Our study provides further theoretical results on the stability and persistence in a model of coinfection. The results throughout this paper for one disease also holds for the other due to the symmetry of the model. Note that some of our analytical results are applicable to models of coinfection by different parasites (e.g. [54,4,3]) where there is no recovery ($\rho_1 = \rho_2 = 0$).

It is well known that, for a simple SIS epidemic model, the disease goes extinct if the basic reproduction number is less than unity and persists at a unique endemic equilibrium otherwise. Our analysis shows that the disease dynamics become more complicated in the presence of a second disease. For instance, the presence of coinfection could mediate coexistence despite that fact that one or both diseases could not survive independently. Different types of interaction in dually infected hosts can yield different outcomes. These findings emphasize the importance of understanding the interactions among pathogens and developing a multi-disease approach in the treatment of coinfecting patients.

A complete classification of the model studied here is not yet available. For example, we would like to know how to rigorously prove the existence of Hopf bifurcations and whether a Hopf bifurcation is impossible for small death rate. It will be interesting to analyze our model from the perspective of evolutionary epidemiology [45,10,3,4]. The current model may be extended to other natural history models, such as the SEIR assumption, or include three or more agents/strains [61]. There may be partial cross-immunity or enhanced susceptibility to either of the two infections [28]. Coinfecting patients may have more serious illness

and take a longer time to recover. In general, treatment of one infection in a doubly infected person may affect the other infection directly or indirectly (e.g. [50,25,44,51]). We will leave these for future consideration.

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Appendix A. The equivalence between $s(F_2 - V_2) < 0$ and $\mathcal{R}_2^1 < 1$

As we know, the boundary equilibrium E_1 is locally asymptotically stable if and only if all eigenvalues of the Jacobian matrix $F_2 - V_2$ have negative real parts. This is also equivalent to $\mathcal{R}_2^1 < 1$ by Theorem 2 in van den Driessche and Watmough [58]. Here we provide a direct proof. For simplicity, we consider two matrices

$$F_2 = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \text{ and } V_2 = \begin{pmatrix} h & -i \\ -j & k \end{pmatrix}$$

satisfying $a, b, c, d, h, i, j, k \geq 0$ and $hk - ij > 0$. The characteristic polynomial of the matrix $F_2 - V_2$ is

$$\lambda^2 + (h - a + k - d)\lambda + (h - a)(k - d) - (b + i)(c + j) = 0.$$

By the Routh–Hurwitz criterion, the spectral bound $s(F_2 - V_2) < 0$ if and only if

$$h - a + k - d > 0, \tag{A.1a}$$

$$(h - a)(k - d) - (b + i)(c + j) > 0. \tag{A.1b}$$

Meanwhile, the characteristic polynomial of the matrix $F_2V_2^{-1}$ is $A_2\lambda^2 + A_1\lambda + A_0 = 0$, where

$$A_2 = hk - ij > 0, A_1 = -(ak + bj + ci + dh), A_0 = ad - bc.$$

Then $\mathcal{R}_2^1 = \rho(F_2V_2^{-1}) < 1$ if and only if

$$2A_2 + A_1 = 2(hk - ij) - (ak + bj + ci + dh) > 0, \tag{A.2a}$$

$$A_2 + A_1 + A_0 = (hk - ij) + (ad - bc) - (ak + bj + ci + dh) > 0. \tag{A.2b}$$

Note that (A.1b) is the same as (A.2b). It suffices to show that (A.1) implies (A.2a) and (A.2) implies (A.1a), respectively.

It follows from (A.1) that $h > a$ and $k > d$. Thus

$$\begin{aligned} 2A_2 + A_1 &= hk + (h - a + a)(k - d + d) - 2ij - (ak + bj + ci + dh) \\ &= hk + (h - a)(k - d) + (h - a)d + a(k - d) + ad - 2ij - (ak + bj + ci + dh) \\ &> hk + (b + i)(c + j) + (h - a)d + a(k - d) + ad - 2ij - (hk - ij) - (ad - bc) \\ &= bj + ci + (h - a)d + a(k - d) \geq 0. \end{aligned}$$

On the other hand, suppose that $h - a + k - d \leq 0$, then (A.1b) or (A.2b) implies that $h < a$ and $k < d$. We obtain

$$2A_2 + A_1 < 2(hk - ij) - (hk + bj + ci + kh) = -2ij - bj - ci \leq 0,$$

a contradiction. The proof is complete.

Appendix B. The nonexistence of bistability for small μ

If $\mathcal{R}_{20} > \max\{\mathcal{R}_{10}, 1\}$, then the second disease always persists for sufficiently small μ . We only need to show the instability of the equilibrium E_1 when it exists. In fact, E_1 is locally asymptotically stable if and only if $s(F_2 - V_2) < 0$. The characteristic equation of $F_2 - V_2$ is $\beta_1\lambda^2 + C_1(\beta_1)\lambda + C_0(\beta_1) = 0$, where

$$C_1(\beta_1) = \beta_1^2 + \beta_1(2\rho_2 + \mu - \beta_{12} - \beta_{02}) - (\beta_2 - \beta_{02})(\rho_1 + \mu) \text{ and } C_0(\beta_1) = a_2\beta_1^2 + a_1\beta_1 + a_0.$$

Here $a_2 = \rho_2 + \mu - \beta_{12} - \beta_{02}$, $a_1 = -\beta_2\rho_1 + (\beta_{12} + \beta_{02})(\rho_1 - \rho_2) + \mu\rho_2 + \rho_2^2$, and $a_0 = -(\rho_1 + \mu)(\beta_2(\rho_2 + \mu - \beta_{12}) - \beta_{02}(\rho_2 + \mu))$.

Thus, by the Routh–Hurwitz stability criterion, E_1 is locally stable if $C_1 > 0$ and $C_0 > 0$. In particular, if $\beta_{12} = 0$ then E_1 is locally stable if $C_0 > 0$ (by Appendix A). For the instability of the equilibrium E_1 , It suffices to show that $C_0 < 0$ in case of $\mathcal{R}_{10} > 1$ and $\beta_{12} + \beta_{02} < \rho_2 + \mu$ by Remark 4.5. This follows from $a_2 > 0$, $a_0 < 0$, $\beta_1 < (\rho_1 + \mu)\mathcal{R}_{20}$ and

$$\begin{aligned} C_0((\rho_1 + \mu)\mathcal{R}_{20}) &= (\rho_2 + \mu)^{-2}(\rho_1 + \mu)(\beta_2 - \rho_2 - \mu) \\ &\quad \times (\beta_2\mu(\rho_2 + \mu - \beta_{12} - \beta_{02}) - \beta_2\rho_1(\beta_{12} + \beta_{02}) - \beta_{02}(\rho_2 + \mu)^2) < 0 \end{aligned}$$

for small enough $\mu > 0$.

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