An environmentally-driven two-strain mutualistic coinfection model with coupling transmission in vivo and vitro and humoral immunity

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Abstract: In this paper, a coupling transmission epidemic model with mutualistic two-strain of virus in body and vitro of host is proposed, in which humoral immune response only works for strain 1 due to immunity evasion of mutation. For the within-host subsystem, the global stability of all feasible equilibria with and without environmental influence are discussed. For the between-host subsystem, the basic reproduction number R_0 is obtained. When $R_0 < 1$, the disease-free equilibrium is local stable, while the endemic equilibrium is local stable and the disease is uniformly persistent if $R_0 > 1$. Meanwhile, backward bifurcation would occur when there exists immune response within host. Finally, numerical examples are provided to illustrate obtained conclusions, by which we find that the mutualism between two strains during co-infection leads to a more persistent disease than single strain, even the basic reproduction number is small than 1 in each single strain.

Keywords: Mutualistic two-strain; Immune response; Coupled model; Local and global stability; Backward bifurcation.

MSC Classification: 34D20, 34D23, 92B05, 92D30

1 Introduction

It is well known that most serious epidemics have huge impacts on the human health, social and national stability, e.g., AIDS, Cholera, SARS, Ebola, COVID-19, etc [1–5]. In the past decades, a lot of significant epidemic models were established to study the transmission dynamics of such diseases, which primary focuses consist of the stability of equilibrium (or periodic solution), persistence (or extinction) of disease, the computation of basic reproduction number, bifurcation and chaos, etc [6–8].

Usually, the transmission of infectious diseases could be divided into two processes, i.e., within-host pathogen invasion and between-host disease transmission [9]. For the former, the pathogen grows, spreads or is eliminated in the body of host, while in the latter, the susceptible individuals are infected by close contact with infected individuals or environmental pathogen

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[10]. Recently, a large number of epidemic models either within-host or between-host have been studied separately [11, 12]. However, more evidence suggests that the dynamics of various scales are not isolated, but connected to each other [13, 14], and many various coupled models linking the transmission or mortality rates between-host and the viral load within-host have been considered [15–18].

For many environmentally-driven infectious diseases, the contamination status of pathogen plays a major role in disease transmission such as Toxoplasma [9], norovirus [19], airborne diseases [20, 21], etc. Feng et al. [9, 22] proposed the following coupling model of Toxoplasma in vivo and vitro of host with environmental contamination,

$$\begin{cases} \dot{X}(s) = \lambda - kZX - dX, \\ \dot{Y}(s) = kZX - (\delta + d)Y, \\ \dot{Z}(s) = pY - cZ + g(E), \end{cases} \tag{1}$$

$$\begin{cases} \dot{S}(t) = \Lambda - \beta ES - \mu S, \\ \dot{I}(t) = \beta ES - (\mu + \alpha)I, \\ \dot{E}(t) = \xi ZI(1 - E) - aE, \end{cases} \tag{2}$$

where $X(s)$, $Y(s)$ represent the concentrates of healthy cells, productively infected cells at time s, respectively. $Z(s)$ is the parasite load at time s. The parameters λ, k, d and δ represent the recruitment rate, infection rate, natural mortality rate and infection-induced mortality rate of cells, respectively. p and c are the production rate and clearance rate of parasite, respectively. $S(t)$, $I(t)$ and $E(t)$ denote the numbers of susceptible and infected human individuals and environmental contamination level at time t, respectively. Λ is the recruitment of hosts, β is the infection rate of susceptible individuals at population level, μ and α denote the natural and disease-induced death rate of hosts, respectively. a is the clearance rate of environmental contamination, ξ represents the release rate of contamination to the environment from the infected individuals. The increase in the concentration of parasite within the host produced by the contaminated environment is given by function $g(E)$. The whole system is decomposed into a fast-time subsystem and a slow-time subsystem. The authors observed when the slow-time subsystem is coupled, backward bifurcation will occur.

We found that the most works considered so far in above coupling epidemic models, the authors always assumed that there only exists one strain of pathogen in the transmission of disease [10, 23, 24]. However, as well known, viruses usually would mutate during replication within body of host, such as HIV [6], tuberculosis [12], COVID-19 [25], etc. It has been proven that plenty of diverse genetic variants can be coexisting in vivo in many viral infections, which would lead to more virulent infections [26]. Some two-strain coupled models have been studied which do not link the interaction between contaminated environment and virus in body [27, 28]. Li et al. [28] proposed a class of two-strain coinfection coupled model, which mainly focused on the coexistence equilibrium of two strains and the influence of within-host parameters on dynamics between host.

Usually, most of the multi-strain transmission models assumed that the interaction between two strains is competitive [6, 12, 27, 28]. However, it has been found that the relationship between various strains of pathogen is not only competitive, but also mutualistic, where one variant acts

as a helper virus for the other in the latter [29, 30]. There are many examples of mutualism between different strains of virus, e.g., H3N2 influenza [31], measles [32], etc. Bushman et al. [33] proposed an epidemic model within host, including wild-type strain, mutant strain and immune response. The authors assumed that the host was infected with both strains and showed that a mutant strain emerges and "rescues" a wild-type from extinction. Leeks et al. [26] showed that cells infected by both variants are more likely to be productive than by either variant alone. Therefore, it is necessary to study the mutualism between various strains in cases of co-infection during the disease transmission.

Furthermore, it is well known that the immune response of human body has an important role against virus infection, which usually includes cellular immunity and humoral immunity. The former aims to produce CTL immune cells to destroy infected cells, while the latter produces B cells to eliminate pathogens [34]. Roederer et al. [35] indicated that humoral immunity is more productive compared to cellular immunity in some kinds of infections. Aili et al. [23] developed a class of coupled model in body and vitro with humoral immunity, and showed if the antibody does not work well in host, there will exists backward bifurcation which make disease control and treatment with much difficulty. However, sustained antibody response can lead to the evolution of antigenic escape, which could help virus evade the host innate immunity [36, 37]. Therefore, it is necessary to study the immune evasion response due to mutant strains.

We establish an epidemic model with coupling transmission in vivo and vitro for environmentally-driven infectious disease including two mutualistic strains and immune evasion response in this paper. We will discuss the fast time subsystem with and without environmental contamination, and the slow time subsystem, respectively.

The rest of this paper is structured as below. In section 2, we give a detailed description of model establishment. In section 3, the within-host fast time subsystem is discussed. The various kinds of feasible equilibria and basic reproduction numbers are calculated, and the criteria on global stability of above equilibria are established. In section 4, the slow time subsystem between host is discussed. The nonnegativity, ultimate boundedness of solutions, the local stability of equilibria and uniform persistence of disease are proved, the existence of backward bifurcation is discussed as well based on the basic reproduction number R_0. In section 5, numerical simulations are provided to illustrate our results. In section 6, a brief conclusion is given.

2 Model description

Usually, the coinfection of multiple strains of pathogen mainly emerges simultaneously in a common host during disease transmission [26, 33]. We first introduce the following fast infection model within-body between two mutualistic strains with humoral immune response.

$$\begin{cases} \dot{X}(s) = \lambda - (k_1 Z_1(s) + k_2 Z_2(s))X(s) - dX(s), \\ \dot{Y}(s) = (k_1 Z_1(s) + k_2 Z_2(s))X(s) - (\delta + d)Y(s), \\ \dot{Z}_1(s) = p_1 Y(s) - bZ_1(s)M(s) - cZ_1(s), \\ \dot{Z}_2(s) = p_2 Y(s) - cZ_2(s), \\ \dot{M}(s) = eZ_1(s)M(s) - pM(s), \end{cases} \tag{3}$$

where $Z_i(s)$ represents the density of free virions of strain i at time s $(i = 1, 2)$, and there exists mutualistic interaction between strains 1 and 2 with coinfection on susceptible cell X. $M(s)$ represents the density of B cells at time s which is effective on strain 1, but ineffective on strain 2 due to immune evasion of mutation. k_i denotes the constant rate that healthy cells are infected by free virions of strain i. p_i is the production rate of strain i. Strains 1 and 2 have the same virion clearance rate c. b, e, p represent the neutralization rate, production rate and mortality rate of B cells, respectively.

For the disease transmission at the population level between hosts, we focus on indirect transmission through contact with virus contaminated environment. We introduce the following slow time epidemic model between hosts:

$$\begin{cases} \dot{S}(t) =\Lambda - (\beta_1 E_1(t) + \beta_2 E_2(t))S(t) - \mu S(t), \\ \dot{I}(t) =(\beta_1 E_1(t) + \beta_2 E_2(t))S(t) - (\mu + \alpha)I(t), \\ \dot{E}_1(t) =\xi I(1 - E_1) - aE_1, \\ \dot{E}_2(t) =\xi I(1 - E_2) - aE_2, \end{cases} \tag{4}$$

where $E_i(t)$ $(0 \leq E_i(t) \leq 1)$ represent the environmental pollution level of strain i at time t. β_i is the transmission rate of strain i in contamination environment $(i = 1, 2)$. The level of environmental contamination is correlated with the population of infected individuals which takes the form ξI. The other parameters are as the same as that of system (2).

We have proposed the models of viral infection within host (3) and infectious disease between hosts (4), respectively. In reality, however, the virus-contaminated environment causes an increase in virus density within host. Meanwhile, both the quantity of infected humans and the amount of virus in the host affect the rate of environmental contamination [9]. Thus, we can obtain the following coupled model within and between hosts:

$$\begin{cases} \dot{X}(s) =\lambda - (k_1 Z_1(s) + k_2 Z_2(s))X(s) - dX(s), \\ \dot{Y}(s) =(k_1 Z_1(s) + k_2 Z_2(s))X(s) - (\delta + d)Y(s), \\ \dot{Z}_1(s) =p_1 Y(s) - bZ_1(s)M(s) - cZ_1(s) + g_1(E_1), \\ \dot{Z}_2(s) =p_2 Y(s) - cZ_2(s) + g_2(E_2), \\ \dot{M}(s) =eZ_1(s)M(s) - pM(s), \end{cases} \tag{5}$$

$$\begin{cases} \dot{S}(t) =\Lambda - (\beta_1 E_1(t) + \beta_2 E_2(t))S(t) - \mu S(t), \\ \dot{I}(t) =(\beta_1 E_1(t) + \beta_2 E_2(t))S(t) - (\mu + \alpha)I(t), \\ \dot{E}_1(t) =\xi Z_1 I(1 - E_1) - aE_1, \\ \dot{E}_2(t) =\xi Z_2 I(1 - E_2) - aE_2, \end{cases} \tag{6}$$

functions $g_i(E_i)$ represent the density of strain i within body come from the contaminated environment. The level of environmental pollution can be correlated with the number of infected individuals and the concentration of virus within host which takes the form of $\xi Z_i I$. Obviously, as the number of environmental viruses increases, viral load in the host also rises. Thus, we can hypothesize the functions $g_1(E_1)$ and $g_2(E_2)$ as follows:

$$g_1(0)=0,\ g_1(E_1)\geq 0,\ \dot{g}_1(E_1)>0,\ \ddot{g}_1(E_1)\leq 0.$$
$$g_2(0)=0,\ g_2(E_2)\geq 0,\ \dot{g}_2(E_2)>0,\ \ddot{g}_2(E_2)\leq 0.$$

All of above parameters mentioned are positive in models (5) and (6).

3 Within-host fast time subsystem

The subsystem (5) can be considered as the fast system, therefore the variables E_1 and E_2 could be taken as constants (i.e., they do not vary with time on the fast time scale) [9].

3.1 Basic properties

The initial condition for subsystem (5) is taken as follows

$$X(0)>0,\ Y(0)>0,\ Z_1(0)>0,\ Z_2(0)>0,\ M(0)>0. \tag{7}$$

By the basic theory of ordinary differential equations [38], it can be proven that system (5) has the only solution $(X(s),Y(s),Z_1(s),Z_2(s),M(s))$ meeting the initial condition (7).

Firstly, regarding the positivity and boundedness of the solutions of subsystem (5), we have the result below.

Theorem 1. *All solutions of subsystem (5) with initial condition (7) are defined, positive and ultimately bounded for all $s\geq 0$.*

Proof. Assume that $\Gamma(s)=\min\{X(s),Y(s),Z_1(s),Z_2(s),M(s)\}$, then $\Gamma(0)=\min\{X(0),Y(0),Z_1(0),Z_2(0),M(0)\}>0$. Assume that $\Gamma(s)$ is not positive on $[0,\tau_1)$, where $\tau_1\leq\infty$ is the maximal existence time, then exists a $s_1\in[0,\tau_1)$ satisfying $\Gamma(s_1)=0$ and $\Gamma(s)>0$ for any $s\in[0,s_1)$. Obviously we can obtain $\dot{\Gamma}(s_1)\leq 0$. If $\Gamma(s_1)=X(s_1)$, then from the first equation of system (5) we easily have

$$\dot{X}(s_1)=\lambda-(k_1Z_1(s_1)+k_2Z_2(s_1)+d)X(s_1)=\lambda>0,$$

which leads to a contradiction. Similarly, if $\Gamma(s_1)=Y(s_1)$ or $\Gamma(s_1)=Z_1(s_1)$ or $\Gamma(s_1)=Z_2(s_1)$ or $\Gamma(s_1)=M(s_1)$, we also obtain a contradiction. Therefore, $\Gamma(s)>0$ on $[0,\tau_1)$, that is $X(s)>0,Y(s)>0,Z_1(s)>0,Z_2(s)>0,M(s)>0$ for any $s\in[0,\tau_1)$.

Next, we further study the boundedness of solutions of system (5) with initial condition (7).

Let $(X(s),Y(s),Z_1(s),Z_2(s),M(s))^T$ be any positive solution of system (5) with initial condition (7) defined on $[0,\tau_1)$. Let $L(s)=X(s)+Y(s)+\frac{\delta+d}{3p_1}Z_1(s)+\frac{\delta+d}{3p_2}Z_2(s)+\frac{(\delta+d)b}{3ep_1}M(s)$ and $\mu=\min\{d,\frac{\delta+d}{3},c,p\}$, we have

$$\begin{aligned}\dot{L}(s)=&\lambda+\frac{\delta+d}{3p_1}g_1(E_1)+\frac{\delta+d}{3p_2}g_2(E_2)-dX-\frac{\delta+d}{3}Y-\frac{(\delta+d)c}{3p_1}Z_1\\&-\frac{(\delta+d)c}{3p_2}Z_2-\frac{(\delta+d)bp}{3ep_1}M\\\leq&\lambda+\frac{\delta+d}{3p_1}g_1(E_1)+\frac{\delta+d}{3p_2}g_2(E_2)-\mu L.\end{aligned}$$

From the above equation, we have

$$\limsup_{s\to\infty} L(s) \leq \frac{\lambda + \frac{\delta+d}{3p_1}g_1(E_1) + \frac{\delta+d}{3p_2}g_2(E_2)}{\mu}.$$

Therefore, $L(s)$ is bounded on $[0, \tau_1)$, hence we have $\tau_1 = \infty$. □

3.2 The basic reproduction number and feasible equilibria

In this section, we discuss the existence of feasible equilibria of subsystem (5). In addition, we calculate the basic reproduction number of subsystem (5) by the existence of equilibria and the next generation approach [39].

The equilibria of subsystem (5) can be obtained from the following equations

$$\begin{cases} \lambda - (k_1Z_1(s) + k_2Z_2(s))X(s) - dX(s) = 0, \\ (k_1Z_1(s) + k_2Z_2(s))X(s) - (\delta + d)Y(s) = 0, \\ p_1Y(s) - bZ_1(s)M(s) - cZ_1(s) + g_1(E_1) = 0, \\ p_2Y(s) - cZ_2(s) + g_2(E_2) = 0, \\ eZ_1(s)M(s) - pM(s) = 0. \end{cases} \tag{8}$$

Since E_1, E_2 are constants, we discuss the existence of equilibria in four cases, i.e., (i) $E_1 = 0, E_2 = 0$, (ii) $E_1 > 0, E_2 > 0$, (iii) $E_1 > 0, E_2 = 0$, (iv) $E_1 = 0, E_2 > 0$.

(i) $E_1 = 0, E_2 = 0$. Denote

$$R_{w0} = \frac{(k_1p_1 + k_2p_2)X_0}{c(\delta + d)}, \quad R_{w1} = \max\{\frac{ep_1\widetilde{Y}}{cp}, \frac{ep_1Y^*}{cp}\}, \quad R_1 = \frac{k_1p_1X_0}{c(\delta + d)}, \quad R_2 = \frac{k_2p_2X_0}{c(\delta + d)},$$

where R_{w0} is called the basic reproduction number of immunity-inactivation which denotes the amount of newly infected cells generated by an infected cell during its lifecycle. R_{w1} is called the basic reproduction number of immunity-activation. R_i is the basic reproduction number induced by strain i $(i = 1, 2)$.

By calculation (8), we have the following results.

Theorem 2. (a) *Subsystem* (5) *always has a unique infection-free equilibrium* $E_0 = (X_0, 0, 0, 0, 0)$ *with* $X_0 = \frac{\lambda}{d}$;

(b) *If* $R_{w0} > 1$, $R_{w1} < 1$, *then subsystem* (5) *has an immunity-inactivated co-infection equilibrium* $E^* = (X^*, Y^*, Z_1^*, Z_2^*, 0)$ *with*

$$X^* = \frac{X_0}{R_{w0}}, \ Y^* = \frac{\lambda}{(\delta + d)}(1 - \frac{1}{R_{w0}}), \ Z_1^* = \frac{p_1\lambda}{c(\delta + d)}(1 - \frac{1}{R_{w0}}), \ Z_2^* = \frac{p_2\lambda}{c(\delta + d)}(1 - \frac{1}{R_{w0}});$$

(c) *If* $R_{w0} > 1$, $R_{w1} > 1$, *then subsystem* (5) *has an immunity-activated co-infection equilibrium* $\tilde{E} = (\tilde{X}, \tilde{Y}, \tilde{Z}_1, \tilde{Z}_2, \tilde{M})$ *with*

$$\tilde{X} = \frac{\lambda}{k_1\tilde{Z}_1 + k_2\tilde{Z}_2 + d}, \ \tilde{Y} = \frac{1}{2}(a_1 + \sqrt{a_1^2 + 4a_2}), \ \tilde{Z}_1 = \frac{p}{e}, \ \tilde{Z}_2 = \frac{p_2\tilde{Y}}{c},$$

$$\tilde{M} = \frac{ep_1\tilde{Y} - cp}{bp},\ a_1 = \frac{\lambda}{(\delta+d)} - \frac{ck_1p}{ek_2p_2} - \frac{cd}{k_2p_2},\ a_2 = \frac{\lambda ck_1p}{e(\delta+d)k_2p_2}.$$

Remark 1. *Mathematically, if $X > 0, Y > 0, Z_1 > 0, Z_2 = 0, M = 0$, from (8) we directly have $p_2Y = 0$ and then $Y = 0$, which leads to a contradiction. The result is also true if $Z_1 = 0, Z_2 > 0$. Therefore, the dominant-strain equilibria do not exist. Biologically, the article [40] shows that in the process of virus replication, if viral sequences damage owing to failure to integration, it could be rescued by the mechanism of mutualism between viruses. Mutualism of virus greatly increases the effective amount of cellular coinfection.*

(*ii*) $E_1 > 0,\ E_2 > 0$. Denote the basic reproduction number of immunity-activation as follows

$$R_{w2} = \max\{\frac{eg_1(E_1) + ep_1\hat{Y}}{cp}, \frac{eg_1(E_1) + ep_1\bar{Y}}{cp}\}.$$

Theorem 3. (*a*) *If $R_{w0} > 1, R_{w2} < 1$, then subsystem (5) has an immunity-inactivated co-infection equilibrium $\bar{E} = (\bar{X}, \bar{Y}, \bar{Z}_1, \bar{Z}_2, 0)$ with*

$$\bar{X} = \frac{1}{2}(b_1 - \sqrt{b_1^2 - 4b_2}),\ \bar{Y} = \frac{d}{(\delta+d)}(X_0 - \bar{X}),\ \bar{Z}_1 = \frac{1}{c}(g_1(E_1) + P_1\bar{Y}),\ \bar{Z}_2 = \frac{1}{c}(g_2(E_2) + P_2\bar{Y}),$$
$$b_1 = \frac{(k_1g_1(E_1) + k_2g_2(E_2))(\delta+d)}{(k_1p_1 + k_2p_2)d} + X_0(1 + \frac{1}{R_{w0}}),\ b_2 = \frac{X_0^2}{R_{w0}};$$

(*b*) *If $R_{w0} > 1, R_{w2} > 1$, then subsystem (5) has an immunity-activated co-infection equilibrium $\hat{E} = (\hat{X}, \hat{Y}, \hat{Z}_1, \hat{Z}_2, \hat{M})$ with*

$$\hat{X} = \frac{\lambda}{k_1\hat{Z}_1 + k_2\hat{Z}_2 + d},\ \hat{Y} = \frac{1}{2}(c_1 + \sqrt{c_1^2 + 4c_2}),\ \hat{Z}_1 = \frac{p}{e},\ \hat{Z}_2 = \frac{g_2(E_2) + p_2\hat{Y}}{c},$$
$$\hat{M} = \frac{eg_1(E_1) + ep_1\hat{Y} - cp}{bp},\ c_1 = \frac{\lambda}{(\delta+d)} - \frac{ck_1p}{ek_2p_2} - \frac{g_2(E_2)}{p_2} - \frac{cd}{k_2p_2},$$
$$c_2 = \frac{\lambda ck_1p}{(\delta+d)ek_2p_2} + \frac{\lambda g_2(E_2)}{(\delta+d)p_2}.$$

Proof. (*a*) We directly get $\bar{Z}_1 = \frac{1}{c}(g_1(E_1) + p_1\bar{Y}), \bar{Z}_2 = \frac{1}{c}(g_2(E_2) + p_2\bar{Y}), \bar{Y} = \frac{d}{(\delta+d)}(X_0 - \bar{X})$ and $\bar{X} < X_0$ from equations (8). Substituting above equations into the second equation of (8), we further get the following formula

$$\bar{X}^2 - b_1\bar{X} + b_2 = 0, \tag{9}$$

where $b_1 = \frac{(k_1g_1(E_1)+k_2g_2(E_2))(\delta+d)}{(k_1p_1+k_2p_2)d} + X_0(1 + \frac{1}{R_{w0}}),\ b_2 = \frac{X_0^2}{R_{w0}}$. Since

$$b_1^2 - 4b_2 > X_0^2(1 + \frac{1}{R_{w0}})^2 - \frac{4X_0^2}{R_{w0}} = X_0^2(1 - \frac{1}{R_{w0}})^2 \geq 0,$$

equation (9) has two positive roots as follows

$$\bar{X}_\pm = \frac{1}{2}(b_1 \pm \sqrt{b_1^2 - 4b_2}). \tag{10}$$

Let $g = k_1 g_1(E_1) + k_2 g_2(E_2)$, computing the derivative of $\bar{X}_\pm(g)$ with g, we have $\dot{\bar{X}}_\pm(g) = \frac{1}{2}\dot{b}_1(g)(1 \pm \frac{b_1(g)}{\sqrt{b_1^2(g)-4b_2}})$. Because of $b_2 > 0,\ \dot{b}_1(g) > 0$, we further have $\dot{\bar{X}}_+(g) > 0,\ \dot{\bar{X}}_-(g) < 0$. From (10) we can obtain

$$\bar{X}_+(0) = \begin{cases} X_0, & R_{w0} \geq 1, \\ \dfrac{X_0}{R_{w0}}, & R_{w0} < 1, \end{cases},\ \bar{X}_-(0) = \begin{cases} \dfrac{X_0}{R_{w0}}, & R_{w0} > 1, \\ X_0, & R_{w0} \leq 1. \end{cases} \tag{11}$$

Since $\bar{X}_+(g) \geq \bar{X}_+(0) \geq X_0,\ \bar{X}_-(g) \leq \bar{X}_+(0) \leq X_0$, we can get that system (5) has a unique immunity-inactivated co-infection equilibrium $\bar{E} = (\bar{X}, \bar{Y}, \bar{Z}_1, \bar{Z}_2, 0)$, where

$$\bar{X} = \frac{1}{2}(b_1 - \sqrt{b_1^2 - 4b_2}),\ \bar{Y} = \frac{d}{\delta}(X_0 - \bar{X}),\ \bar{Z}_1 = \frac{1}{c}(g_1(E_1) + P_1\bar{Y}),\ \bar{Z}_2 = \frac{1}{c}(g_2(E_2) + P_2\bar{Y}).$$

(b) By calculating system (8), we can directly obtain $\hat{X} = \frac{\lambda}{k_1\hat{Z}_1 + k_2\hat{Z}_2 + d},\ \hat{Z}_1 = \frac{p}{e},\ \hat{Z}_2 = \frac{1}{c}(g_2(E_2) + p_2\hat{Y}),\ \hat{M} = \frac{eg_1(E_1) + ep_1\hat{Y} - cp}{bp}$. By substituting above equations into the second equation of (8), we further obtain the following formula

$$\hat{Y}^2 + c_1\hat{Y} - c_2 = 0, \tag{12}$$

where $c_1 = \frac{\lambda}{(\delta+d)} - \frac{ck_1p}{ek_2p_2} - \frac{g_2(E_2)}{p_2} - \frac{cd}{k_2p_2},\ c_2 = \frac{\lambda ck_1p}{(\delta+d)ek_2p_2} + \frac{\lambda g_2(E_2)}{(\delta+d)p_2}$. According to Vieta Theorem, we can get that equation (12) has a unique positive root $\hat{Y} = \frac{1}{2}(c_1 + \sqrt{c_1^2 + 4c_2})$. Therefore, subsystem (5) has a unique immunity-activated co-infection equilibrium $\hat{E} = (\hat{X}, \hat{Y}, \hat{Z}_1, \hat{Z}_2, \hat{M})$, where

$$\hat{X} = \frac{\lambda}{k_1\hat{Z}_1 + k_2\hat{Z}_2 + d},\ \hat{Y} = \frac{1}{2}(c_1 + \sqrt{c_1^2 + 4c_2}),\ \hat{Z}_1 = \frac{p}{e},$$
$$\hat{Z}_2 = \frac{g_2(E_2) + p_2\hat{Y}}{c},\ \hat{M} = \frac{eg_1(E_1) + ep_1\hat{Y} - cp}{bp}.$$

□

(iii) $E_1 > 0,\ E_2 = 0$. Since the calculation is similar as case (ii), we only need to set E_2 to 0 in the equilibria in the case (ii). Denote the basic reproduction number of immunity-activation $\hat{R}^{(1)} = \max\{\frac{eg_1(E_1) + ep_1\hat{Y}^{(1)}}{cp}, \frac{eg_1(E_1) + ep_1\bar{Y}^{(1)}}{cp}\}$, we have the result below.

Theorem 4. (a) *If* $R_{w0} > 1, \hat{R}^{(1)} < 1$, *then subsystem* (5) *has an immunity-inactivated co-infection equilibrium* $\bar{E}^{(1)} = (\bar{X}^{(1)}, \bar{Y}^{(1)}, \bar{Z_1}^{(1)}, \bar{Z_2}^{(1)}, 0)$ *with*

$$\bar{X}^{(1)} = \frac{1}{2}(m_1 - \sqrt{m_1^2 - 4m_2}),\ \bar{Y}^{(1)} = \frac{d}{(\delta+d)}(X_0 - \bar{X}^{(1)}),\ \bar{Z_1}^{(1)} = \frac{1}{c}(g_1(E_1) + P_1\bar{Y}^{(1)}),$$
$$\bar{Z_2}^{(1)} = \frac{P_2\bar{Y}^{(1)}}{c},\ m_1 = \frac{k_1g_1(E_1)(\delta+d)}{(k_1p_1 + k_2p_2)d} + X_0(1 + \frac{1}{R_{w0}}),\ m_2 = \frac{X_0^2}{R_{w0}}.$$

(b) *If* $R_{w0} > 1, \hat{R}^{(1)} > 1$, *then subsystem* (5) *has an immunity-activated co-infection equilibrium* $\hat{E}^{(1)} = (\hat{X}^{(1)}, \hat{Y}^{(1)}, \hat{Z_1}^{(1)}, \hat{Z_2}^{(1)}, \hat{M}^{(1)})$ *with*

$$\hat{X}^{(1)}=\frac{\lambda}{k_1\hat{Z_1}^{(1)}+k_2\hat{Z_2}^{(1)}+d},\ \hat{Y}^{(1)}=\frac{1}{2}(n_1+\sqrt{n_1^2+4n_2}),\ \hat{Z_1}^{(1)}=\frac{p}{e},\ \hat{Z_2}^{(1)}=\frac{p_2\hat{Y}^{(1)}}{c},$$
$$\hat{M}^{(1)}=\frac{eg_1(E_1)+ep_1\hat{Y}^{(1)}-cp}{bp},\ n_1=\frac{\lambda}{(\delta+d)}-\frac{ck_1p}{ek_2p_2}-\frac{cd}{k_2p_2},\ n_2=\frac{\lambda ck_1p}{(\delta+d)ek_2p_2}.$$

(iv) $E_1=0,\ E_2>0$. Since the calculation is similar as case (iii), we have the similar results. Denote the basic reproduction number of immunity-activation $\hat{R}^{(2)}=\{\frac{ep_1\hat{Y}^{(2)}}{cp},\frac{ep_1\bar{Y}^{(2)}}{cp}\}$, we have the result below.

Theorem 5. *(a) If $R_{w0}>1,\hat{R}^{(2)}<1$, then subsystem (5) has an immunity-inactivated co-infection equilibrium $\bar{E}^{(2)}=(\bar{X}^{(2)},\bar{Y}^{(2)},\bar{Z_1}^{(2)},\bar{Z_2}^{(2)},0)$ with*

$$\bar{X}^{(2)}=\frac{1}{2}(l_1-\sqrt{l_1^2-4l_2}),\ \bar{Y}^{(2)}=\frac{d}{(\delta+d)}(X_0-\bar{X}^{(2)}),\ \bar{Z_1}^{(2)}=\frac{P_1\bar{Y}^{(2)}}{c},$$
$$\bar{Z_2}^{(2)}=\frac{g_2(E_2)+P_2\bar{Y}^{(2)}}{c},\ l_1=\frac{k_2g_2(E_2)(\delta+d)}{(k_1p_1+k_2p_2)d}+X_0(1+\frac{1}{R_{w0}}),\ l_2=\frac{X_0^2}{R_{w0}}.$$

(b) If $R_{w0}>1,\hat{R}^{(2)}>1$, then subsystem (5) has an immunity-activated co-infection equilibrium $\hat{E}^{(2)}=(\hat{X}^{(2)},\hat{Y}^{(2)},\hat{Z_1}^{(2)},\hat{Z_2}^{(2)},\hat{M}^{(2)})$ with

$$\hat{X}^{(2)}=\frac{\lambda}{k_1\hat{Z_1}^{(2)}+k_2\hat{Z_2}^{(2)}+d},\ \hat{Y}^{(2)}=\frac{1}{2}(c_1+\sqrt{c_1^2+4c_2}),\ \hat{Z_1}^{(2)}=\frac{p}{e},\ \hat{Z_2}^{(2)}=\frac{g_2(E_2)+p_2\hat{Y}^{(2)}}{c},$$
$$\hat{M}^{(2)}=\frac{ep_1\hat{Y}^{(2)}-cp}{bp},\ c_1=\frac{\lambda}{(\delta+d)}-\frac{ck_1p}{ek_2p_2}-\frac{g_2(E_2)}{p_2}-\frac{cd}{k_2p_2},\ c_2=\frac{\lambda ck_1p}{(\delta+d)ek_2p_2}+\frac{\lambda g_2(E_2)}{(\delta+d)p_2}.$$

3.3 Stability of equilibria

In this part, we focus on the globally asymptotically stable of every feasible equilibria of subsystem (5) by using LaSalle's invariance principle [41] and Lyapunov's stability theorem [42]. Here we only give results of the globally asymptotically stable of equilibria $E_0,E^*,\tilde{E},\bar{E},\hat{E}$, the proofs of other equilibria are similar.

Theorem 6. *If $R_{w0}<1$, the infection-free equilibrium E_0 of subsystem (5) is globally asymptotically stable.*

Proof. Define a Lyapunov function L_1 as follows

$$L_1=X_0\Big(\frac{X}{X_0}-1-\ln\frac{X}{X_0}\Big)+Y+v\frac{(\delta+d)}{p_1}Z_1+(1-v)\frac{(\delta+d)}{p_2}Z_2,$$

where $v=\frac{k_1p_1X_0}{(\delta+d)c}$. Taking the derivative of L_1 on both sides along with any positive solution of subsystem (5), we have

$$\begin{aligned}\frac{\mathrm{d}L_1(s)}{\mathrm{d}s}=&dX_0\Big(2-\frac{X_0}{X}-\frac{X}{X_0}\Big)+k_1Z_1X_0-v\frac{(\delta+d)c}{p_1}Z_1+k_2Z_2X_0-(1-v)\frac{(\delta+d)c}{p_2}Z_2\\&-v\frac{(\delta+d)b}{p_1}Z_1M\end{aligned}$$

$$
\begin{aligned}
=&dX_0\Big(2-\frac{X_0}{X}-\frac{X}{X_0}\Big)+\frac{(\delta+d)cZ_1}{p_1}\Big(\frac{k_1p_1X_0}{(\delta+d)c}-v\Big)+\frac{(\delta+d)cZ_2}{p_2}\Big(\frac{k_2p_2X_0}{(\delta+d)c}-(1-v)\Big)\\
&-v\frac{(\delta+d)b}{p_1}Z_1M\\
=&dX_0\Big(2-\frac{X_0}{X}-\frac{X}{X_0}\Big)+\frac{(\delta+d)cZ_2}{p_2}(R_{w0}-1)-v\frac{(\delta+d)b}{p_1}Z_1M.
\end{aligned}
$$

As a result, when $R_{w0}=\frac{(k_1p_1+k_2p_2)X_0}{(\delta+d)c}\leq 1$, we have $\dot{L}_1(s)\leq 0$. And $\dot{L}_1(s)=0$ if and only if $X=X_0, Z_1=0, Z_2=0$, according to the equations (8), we can obtain $Y=0, M=0$. According to the LaSalle's invariance principle [41], the equilibrium E_0 is globally asymptotically stable. □

Theorem 7. *If $R_{w0}>1$ and $R_{w1}<1$, then immunity-inactivated co-infection equilibrium E^* of subsystem (5) is globally asymptotically stable.*

Proof. Consider Lyapunov function L_2 as follows

$$
\begin{aligned}
L_2=&X^*\Big(\frac{X}{X^*}-1-\ln\frac{X}{X^*}\Big)+Y^*\Big(\frac{Y}{Y^*}-1-\ln\frac{Y}{Y^*}\Big)+\frac{k_1Z_1^*X^*}{cZ_1^*}Z_1^*\Big(\frac{Z_1}{Z_1^*}-1-\ln\frac{Z_1}{Z_1^*}\Big)\\
&+\frac{k_2Z_2^*X^*}{cZ_2^*}Z_2^*\Big(\frac{Z_2}{Z_2^*}-1-\ln\frac{Z_2}{Z_2^*}\Big)+\frac{bk_1X^*}{ec}M.
\end{aligned}
$$

Taking the derivative of L_2 on both sides along with any positive solution of subsystem (5), we can get

$$
\begin{aligned}
\frac{\mathrm{d}L_2(s)}{\mathrm{d}s}=&dX^*\Big(2-\frac{X^*}{X}-\frac{X}{X^*}\Big)+k_1Z_1^*X^*\Big(2-\frac{X^*}{X}-\frac{Z_1XY^*}{Z_1^*X^*Y}\Big)+k_2Z_2^*X^*\Big(2-\frac{X^*}{X}-\frac{Z_2XY^*}{Z_2^*X^*Y}\Big)\\
&+(k_1Z_1+k_2Z_2)X^*-(k_1Z_1^*+k_2Z_2^*)X^*\frac{Y}{Y^*}+\frac{k_1Z_1^*X^*}{cZ_1^*}\Big(\frac{Y}{Y^*}cZ_1^*-cZ_1\Big)-\frac{k_1Z_1^*X^*}{cZ_1^*}\frac{Z_1^*}{Z_1}\\
&\times\Big(\frac{Y}{Y^*}cZ_1^*-cZ_1\Big)+\frac{k_2Z_2^*X^*}{cZ_2^*}\Big(\frac{Y}{Y^*}cZ_2^*-cZ_2\Big)-\frac{k_2Z_2^*X^*}{cZ_2^*}\frac{Z_2^*}{Z_2}\Big(\frac{Y}{Y^*}cZ_2^*-cZ_2\Big)\\
&+\frac{k_1Z_1^*X^*}{cZ_1^*}(bZ_1^*M-bZ_1M)+\frac{bk_1X^*}{ec}(eZ_1M-pM)\\
=&dX^*\Big(2-\frac{X^*}{X}-\frac{X}{X^*}\Big)+k_1Z_1^*X^*\Big(3-\frac{X^*}{X}-\frac{Z_1XY^*}{Z_1^*X^*Y}-\frac{YZ_1^*}{Y^*Z_1}\Big)\\
&+k_2Z_2^*X^*\Big(3-\frac{X^*}{X}-\frac{Z_2XY^*}{Z_2^*X^*Y}-\frac{YZ_2^*}{Y^*Z_2}\Big)+\frac{bk_1X^*M}{c}\Big(Z_1^*-\frac{p}{e}\Big).
\end{aligned}
$$

Obviously, by calculating we can get $Z_1^*\leq\frac{p}{e}$ when $R_{w1}<1$. Hence, for any positive solution $(X(s),Y(s),Z_1(s),Z_2(s),M(s))$ of subsystem (5), we have $\dot{L}_2(s)\leq 0$. Furthermore, $\dot{L}_2(s)=0$ if and only if $X(s)=X^*, Y(s)=Y^*, Z_1(s)=Z_1^*, Z_2=Z_2^*, M(s)=0$. The equilibrium E^* is globally asymptotically stable by LaSalle's invariance principle [41]. □

Theorem 8. *If $R_{w0}>1, R_{w1}>1, \Big(1-\frac{\tilde{Z}_1}{Z_1}\Big)\Big(\frac{Y}{\tilde{Y}}-\frac{Z_1}{\tilde{Z}_1}\Big)\leq 0$ and $\Big(1-\frac{\tilde{Z}_2}{Z_2}\Big)\Big(\frac{Y}{\tilde{Y}}-\frac{Z_2}{\tilde{Z}_2}\Big)\leq 0$, then immunity-activated co-infection equilibrium $\tilde{E}$ of subsystem (5) is globally asymptotically stable.*

Proof. Defined a Lyapunov function L_3 as follows

$$L_3 = \tilde{X}\Big(\frac{X}{\tilde{X}} - 1 - \ln\frac{X}{\tilde{X}}\Big) + \tilde{Y}\Big(\frac{Y}{\tilde{Y}} - 1 - \ln\frac{Y}{\tilde{Y}}\Big) + \frac{(\delta+d)}{p_1}\tilde{Z}_1\Big(\frac{Z_1}{\tilde{Z}_1} - 1 - \ln\frac{Z_1}{\tilde{Z}_1}\Big) + \frac{(\delta+d)}{p_2}\tilde{Z}_2\Big(\frac{Z_2}{\tilde{Z}_2} - 1 - \ln\frac{Z_2}{\tilde{Z}_2}\Big) + \frac{b(\delta+d)}{p_1 e}\tilde{M}\Big(\frac{M}{\tilde{M}} - 1 - \ln\frac{M}{\tilde{M}}\Big).$$

Taking the derivative of L_3 along with any positive solution of subsystem (5) is given by

$$\begin{aligned}\frac{\mathrm{d}L_3(s)}{\mathrm{d}s} =& d\tilde{X}\Big(2 - \frac{\tilde{X}}{X} - \frac{X}{\tilde{X}}\Big) + k_1\tilde{Z}_1\tilde{X}\Big(1 - \frac{\tilde{X}}{X} + \frac{Z_1}{\tilde{Z}_1}\Big) + k_2\tilde{Z}_2\tilde{X}\Big(1 - \frac{\tilde{X}}{X} + \frac{Z_2}{\tilde{Z}_2}\Big) + k_1\tilde{Z}_1\tilde{X}\Big(1 - \frac{Y}{\tilde{Y}} \\ & - \frac{Z_1X\tilde{Y}}{\tilde{Z}_1\tilde{X}Y}\Big) + k_2\tilde{Z}_2\tilde{X}\Big(1 - \frac{Y}{\tilde{Y}} - \frac{Z_2X\tilde{Y}}{\tilde{Z}_2\tilde{X}Y}\Big) + (\delta+d)\tilde{Y}\Big(\frac{Y}{\tilde{Y}} - \frac{Z_1}{\tilde{Z}_1} - \frac{\tilde{Z}_1Y}{Z_1\tilde{Y}} + 1\Big) + (\delta+d)\tilde{Y} \\ & \times\Big(\frac{Y}{\tilde{Y}} - \frac{Z_2}{\tilde{Z}_2} - \frac{\tilde{Z}_2Y}{Z_2\tilde{Y}} + 1\Big) \\ =& d\tilde{X}\Big(2 - \frac{\tilde{X}}{X} - \frac{X}{\tilde{X}}\Big) + k_1\tilde{Z}_1\tilde{X}\Big(3 - \frac{\tilde{X}}{X} - \frac{Z_1X\tilde{Y}}{\tilde{Z}_1\tilde{X}Y} - \frac{\tilde{Z}_1Y}{Z_1\tilde{Y}}\Big) + k_2\tilde{Z}_2\tilde{X}\Big(3 - \frac{\tilde{X}}{X} - \frac{Z_2X\tilde{Y}}{\tilde{Z}_2\tilde{X}Y} \\ & - \frac{\tilde{Z}_2Y}{Z_2\tilde{Y}}\Big) + k_2\tilde{Z}_2\tilde{X}\Big(1 - \frac{\tilde{Z}_1}{Z_1}\Big)\Big(\frac{Y}{\tilde{Y}} - \frac{Z_1}{\tilde{Z}_1}\Big) + k_1\tilde{Z}_1\tilde{X}\Big(1 - \frac{\tilde{Z}_2}{Z_2}\Big)\Big(\frac{Y}{\tilde{Y}} - \frac{Z_2}{\tilde{Z}_2}\Big).\end{aligned}$$

We have $\dot{L}_3(s) \le 0$ for any positive solution $(X(s), Y(s), Z_1(s), Z_2(s), M(s))$ of subsystem (5). In addition, $\dot{L}_3(s) = 0$ if and only if $X(s) = \tilde{X}, Y(s) = \tilde{Y}, Z_1(s) = \tilde{Z}_1, Z_2(s) = \tilde{Z}_2$, we can obtain $M(s) = \tilde{M}$ when $Y(s) = \tilde{Y}$ and $Z_1(s) = \tilde{Z}_1$. Hence, by Lyapunov's stability theorem [42], we have equilibrium $\tilde{E}$ is globally asymptotically stable. □

Theorem 9. *If $R_{w0} > 1$, $R_{w2} < 1$, $\Big(1 - \frac{\bar{Z}_1}{Z_1}\Big)\Big(\frac{Y}{\bar{Y}} - \frac{Z_1}{\bar{Z}_1}\Big) \le 0$ and $\Big(1 - \frac{\bar{Z}_2}{Z_2}\Big)\Big(\frac{Y}{\bar{Y}} - \frac{Z_2}{\bar{Z}_2}\Big) \le 0$, then immunity-inactivated co-infection equilibrium $\bar{E}$ of subsystem (5) is globally asymptotically stable.*

Proof. We define Lyapunov function L_4 as follows

$$L_4 = \bar{X}\left(\frac{X}{\bar{X}} - 1 - \ln\frac{X}{\bar{X}}\right) + \bar{Y}\left(\frac{Y}{\bar{Y}} - 1 - \ln\frac{Y}{\bar{Y}}\right) + \frac{(\delta+d)}{p_1}\bar{Z}_1\left(\frac{Z_1}{\bar{Z}_1} - 1 - \ln\frac{Z_1}{\bar{Z}_1}\right) + \frac{(\delta+d)}{p_2}\bar{Z}_2\left(\frac{Z_2}{\bar{Z}_2} - 1 - \ln\frac{Z_2}{\bar{Z}_2}\right) + \frac{b(\delta+d)}{p_1 e}M.$$

The proof is similar to Theorem 7, here we omit it. □

Theorem 10. *If $R_{w0} > 1, R_{w2} > 1$, $\Big(1 - \frac{\hat{Z}_1}{Z_1}\Big)\Big(\frac{Y}{\hat{Y}} - \frac{Z_1}{\hat{Z}_1}\Big) \le 0$ and $\Big(1 - \frac{\hat{Z}_2}{Z_2}\Big)\Big(\frac{Y}{\hat{Y}} - \frac{Z_2}{\hat{Z}_2}\Big) \le 0$, then immunity-activated co-infection equilibrium $\hat{E}$ of subsystem (5) is globally asymptotically stable.*

Proof. We define Lyapunov functional L_5 as follows

$$L_5 = \hat{X}\Big(\frac{X}{\hat{X}} - 1 - \ln\frac{X}{\hat{X}}\Big) + \hat{Y}\Big(\frac{Y}{\hat{Y}} - 1 - \ln\frac{Y}{\hat{Y}}\Big) + \frac{(\delta+d)}{p_1}\hat{Z}_1\Big(\frac{Z_1}{\hat{Z}_1} - 1 - \ln\frac{Z_1}{\hat{Z}_1}\Big) + \frac{(\delta+d)}{p_2}\hat{Z}_2\Big(\frac{Z_2}{\hat{Z}_2} - 1 - \ln\frac{Z_2}{\hat{Z}_2}\Big) + \frac{b(\delta+d)}{p_1 e}\hat{M}\Big(\frac{M}{\hat{M}} - 1 - \ln\frac{M}{\hat{M}}\Big).$$

The proof is similar to Theorem 8, here we omit it. □

Remark 2. *About the assumptions of* $\left(1-\frac{\tilde{Z}_1}{Z_1}\right)\left(\frac{Y}{\tilde{Y}}-\frac{Z_1}{\tilde{Z}_1}\right)\leq 0$, $\left(1-\frac{\tilde{Z}_2}{Z_2}\right)\left(\frac{Y}{\tilde{Y}}-\frac{Z_2}{\tilde{Z}_2}\right)\leq 0$, $\left(1-\frac{\bar{Z}_1}{Z_1}\right)\left(\frac{Y}{\bar{Y}}-\frac{Z_1}{\bar{Z}_1}\right)\leq 0$, $\left(1-\frac{\bar{Z}_2}{Z_2}\right)\left(\frac{Y}{\bar{Y}}-\frac{Z_2}{\bar{Z}_2}\right)\leq 0$, $\left(1-\frac{\hat{Z}_1}{Z_1}\right)\left(\frac{Y}{\hat{Y}}-\frac{Z_1}{\hat{Z}_1}\right)\leq 0$ *and* $\left(1-\frac{\hat{Z}_2}{Z_2}\right)\left(\frac{Y}{\hat{Y}}-\frac{Z_2}{\hat{Z}_2}\right)\leq 0$, *it is a pity that we have only verified them by numerical simulation (details can be seen in Fig.1), and have not proved them reasonably, which will be an open question in the future.*

4 Between-host slow time subsystem

We further consider the between-host slow time subsystem (6). Usually, the process of disease transmission between hosts is slower than the speed of virus infection within host [9,22]. Therefore, during the transmission of disease, the virus always reach a steady state of infection in the host. Here, we only assume that there is immune response in the host, thus the within-host equilibrium $\hat{Z}_1=\frac{p}{e}$, $\hat{Z}_2=\frac{1}{c}(g_2(E_2)+p_2\hat{Y})$ when $E_1>0, E_2>0$ are substituted into subsystem (6), and we further have the following subsystem

$$\begin{cases} \dot{S}(t) =\Lambda-(\beta_1E_1(t)+\beta_2E_2(t))S(t)-\mu S(t),\\ \dot{I}(t) =(\beta_1E_1(t)+\beta_2E_2(t))S(t)-(\mu+\alpha)I(t),\\ \dot{E}_1(t) =\xi\frac{p}{e}I(1-E_1)-aE_1,\\ \dot{E}_2(t) =\xi\frac{1}{c}(g_2(E_2)+p_2\hat{Y})I(1-E_2)-aE_2. \end{cases} \tag{13}$$

Remark 3. *Similarly, when* $E_1>0, E_2=0$ *the equilibria of subsystem* (5) *are as follows*

$$\bar{Z_1}^{(1)}=\frac{g_1(E_1)+p_1\bar{Y}^{(1)}}{c},\ \bar{Z_2}^{(1)}=\frac{p_2\bar{Y}^{(1)}}{c},\ \hat{Z_1}^{(1)}=\frac{p}{e},\ \hat{Z_2}^{(1)}=\frac{p_2\hat{Y}^{(1)}}{c},$$

when $E_1=0, E_2>0$ *the equilibria of subsystem* (5) *are as follows*

$$\bar{Z_1}^{(2)}=\frac{p_1\bar{Y}^{(2)}}{c},\ \bar{Z_2}^{(2)}=\frac{g_2(E_2)+p_2\bar{Y}^{(2)}}{c},\ \hat{Z_1}^{(2)}=\frac{p}{e},\ \hat{Z_2}^{(2)}=\frac{g_2(E_2)+p_2\hat{Y}^{(2)}}{c},$$

also can be substituted into subsystem (6). *The analyses are similar, so we here only give the analysis of subsystem* (13).

In particular, the equilibrium $\bar{Z}_1=\frac{g_1(E_1)+p_1\bar{Y}}{c}$, $\bar{Z}_2=\frac{g_2(E_2)+p_2\bar{Y}}{c}$ *are substituted into subsystem* (6) *in the case of* $E_1>0$, $E_2>0$ *without humoral immunity, it is pity that it can hardly be solved for the endemic equilibrium. This would be an open question in the future.*

4.1 Basic properties

The initial condition for subsystem (13) takes the form

$$S(0)>0,\ I(0)>0,\ E_1(0)>0,\ E_2(0)>0. \tag{14}$$

The proof of positivity and boundedness of the solutions of subsystem (13) is similar to that of Theorem 1, here we omit it.

4.2 The basic reproduction number and feasible equilibria

In this section, we focus on the existence of equilibria of subsystem (13). Denote the basic reproduction number $R_0 = \frac{\Lambda\xi(\beta_1 cp+\beta_2 ep_2\tilde{Y})}{\mu eac(\mu+\alpha)}$.

Theorem 11. *(i) Subsystem (13) always has a disease-free equilibrium* $W_0 = (S_0, 0, 0, 0)$, *where* $S_0 = \frac{\Lambda}{\mu}$.

(ii) When $R_0 > 1$, *subsystem (13) exists an endemic equilibrium* $W^* = (S^*, I^*, E_1^*, E_2^*)$.

Proof. The proof of (i) is obvious, we now only prove (ii). The endemic equilibria can be obtained from the following equations

$$\begin{cases} \Lambda - (\beta_1 E_1^* + \beta_2 E_2^*)S^* - \mu S^* = 0, \\ (\beta_1 E_1^* + \beta_2 E_2^*)S^* - (\mu+\alpha)I^* = 0, \\ \xi\frac{p}{e}I^*(1-E_1^*) - aE_1^* = 0, \\ \xi\frac{1}{c}(g_2(E_2^*) + p_2\hat{Y})I^*(1-E_2^*) - aE_2^* = 0. \end{cases} \tag{15}$$

We directly get $S^* = \frac{\Lambda}{\beta_1 E_1^* + \beta_2 E_2^* + \mu}$, $I^* = \frac{caE_2^*}{\xi(g_2(E_2^*)+p_2\hat{Y})(1-E_2^*)}$, $E_1^* = \frac{\xi pI^*}{\xi pI^* + ae}$ from (15). Substituting above equations into the second equation of (15), we have

$$\begin{aligned} &\frac{\Lambda\beta_1 cp + \Lambda\beta_2 cpE_2^* + \Lambda\beta_2 e(g_2(E_2^*)+p_2\hat{Y})(1-E_2^*)}{P(E_2^*) + \beta_2 eE_2^*(g_2(E_2^*)+p_2\hat{Y})(1-E_2^*) + \mu e(g_2(E_2^*)+p_2\hat{Y})(1-E_2^*)} \\ =&(\mu+\alpha)\frac{ac}{\xi(g_2(E_2^*)+p_2\hat{Y})(1-E_2^*)}, \end{aligned}$$

where $P(E_2^*) = \beta_1 cpE_2^* + \beta_2 cp(E_2^*)^2 + \mu cpE_2^*$. Define the functions

$$H(E_2) = \frac{(\Lambda\beta_1 cp + \Lambda\beta_2 cpE_2 + \Lambda\beta_2 e(g_2(E_2)+p_2\hat{Y})(1-E_2))(1-E_2)}{P(E_2) + \beta_2 eE_2(g_2(E_2)+p_2\hat{Y})(1-E_2) + \mu e(g_2(E_2)+p_2\hat{Y})(1-E_2)},$$

$$G(E_2) = (\mu+\alpha)\frac{ac}{\xi(g_2(E_2)+p_2\hat{Y})}.$$

Then we can obtain

$$H(0) = \frac{\Lambda}{\mu}(\frac{\beta_1 cp}{ep_2\tilde{Y}} + \beta_2),\ H(1) = 0,\ G(0) = \frac{ac(\mu+\alpha)}{\xi p_2\tilde{Y}},\ G(1) = \frac{ac(\mu+\alpha)}{\xi(g_2(1)+p_2\hat{Y}(1))}.$$

Clearly, $H(0) > H(1)$, $G(1) > H(1)$, and because of $\dot{G}(E_2) < 0$, we can get $G(0) > G(1)$ (when $E_2 = 0$, $\hat{Y} = \tilde{Y}$; $E_2 = 1$, $\hat{Y} = \hat{Y}(1)$).

Consequently, we can see if $G(0) < H(0)$, then it must exist a solution E_2^*, such that $H(E_2^*) = G(E_2^*)$. Denote

$$R_0 = \frac{H(0)}{G(0)} = \frac{\Lambda\xi(\beta_1 cp + \beta_2 ep_2\tilde{Y})}{\mu eac(\mu+\alpha)}.$$

When $R_0 > 1$, the existence of endemic equilibrium $W^* = (S^*, I^*, E_1^*, E_2^*)$ is satisfied. □

4.3 Stability of equilibria

Theorem 12. *(i) When $R_0 < 1$, then the disease-free equilibrium $W_0 = (S_0, 0, 0, 0)$ of subsystem (13) is locally asymptotically stable.*

(ii) When $R_0 > 1$ and $\dot{H}(E_2^*) < 0$, the endemic equilibrium $W^* = (S^*, I^*, E_1^*, E_2^*)$ of subsystem (13) is locally asymptotically stable, where $\dot{H}(E_2^*) = \dot{Z}_2(E_2^*)(1 - E_2^*) - Z_2(E_2^*)$.

Proof. *(i)* We can obtain that the characteristic equation at the disease-free equilibrium W_0 is as follows

$$f(\lambda) = (\lambda + \mu)(\lambda + a)(-\frac{\xi p_2 \tilde{Y}}{c}\beta_2 S_0 - \frac{\xi p}{e}\beta_1 S_0 + (\lambda + a)(\lambda + \mu + \alpha)) = 0. \tag{16}$$

Clearly, the above equation has two roots of $\lambda_1 = -\mu$ and $\lambda_2 = -a$ respectively. Now we only need to solve the two roots λ_3 and λ_4 of following equation

$$\lambda^2 + (a + \mu + \alpha)\lambda + a(\mu + \alpha) - \frac{\xi p}{e}\beta_1 S_0 - \frac{\xi p_2 \tilde{Y}}{c}\beta_2 S_0 = 0.$$

Observing the constant term, we have

$$\frac{\frac{\xi p}{e}\beta_1 S_0 + \frac{\xi p_2 \tilde{Y}}{c}\beta_2 S_0}{a(\mu + \alpha)} = \frac{\Lambda\xi(\beta_1 cp + \beta_2 e p_2 \tilde{Y})}{\mu eac(\mu + \alpha)} = R_0.$$

When $R_0 < 1$, then $a(\mu + \alpha) > \frac{\xi p}{e}\beta_1 S_0 + \frac{\xi p_2 \tilde{Y}}{c}\beta_2 S_0$. According to the Vieta's formulas, we can get

$$\lambda_3 + \lambda_4 = -(a + \mu + \alpha) < 0,\ \lambda_3\lambda_4 = a(\mu + \alpha) - \frac{\xi p}{e}\beta_1 S_0 - \frac{\xi p_2 \tilde{Y}}{c}\beta_2 S_0 > 0.$$

Hence, λ_3 and λ_4 both have negative real parts. Therefore, the disease-free equilibrium W_0 is locally asymptotically stable.

(ii) We can obtain the Jacobian matrix at W^* is as follows

$J(W^*) =$

$$\begin{pmatrix} -(\beta_1 E_1^* + \beta_2 E_2^* + \mu) & 0 & -\beta_1 S^* & -\beta_2 S^* \\ \beta_1 E_1^* + \beta_2 E_2^* & -(\mu + \alpha) & \beta_1 S^* & \beta_2 S^* \\ 0 & \frac{\xi p}{e}(1 - E_1^*) & -(\frac{\xi p I^*}{e} + a) & 0 \\ 0 & \xi Z_2(E_2^*)(1 - E_2^*) & 0 & I^*\dot{Z}_2(E_2^*)(1 - E_2^*) - \xi Z_2(E_2^*)I^* - a \end{pmatrix}.$$

In order to facilitate the calculation, denote

$$B(E_1^*) = \frac{\xi p}{e}(1 - E_1^*),\ H(E_2^*) = Z_2(E_2^*)(1 - E_2^*),$$

then

$$\dot{H}(E_2^*) = \dot{Z}_2(E_2^*)(1 - E_2^*) - Z_2(E_2^*),$$

$$\xi I^*\dot{Z}_2(E_2^*)(1 - E_2^*) - \xi Z_2(E_2^*)I^* - a = -\frac{a(H(E_2^*) - E_2^*\dot{H}(E_2^*))}{H(E_2^*)}.$$

Denote $K(E_2) = H(E_2) - E_2\dot{H}(E_2)$, then $J(W^*)$ is equivalent to

$$\begin{pmatrix} -(\beta_1 E_1^* + \beta_2 E_2^* + \mu) & 0 & -\beta_1 S^* & -\beta_2 S^* \\ \beta_1 E_1^* + \beta_2 E_2^* & -(\mu+\alpha) & \beta_1 S^* & \beta_2 S^* \\ 0 & B(E_1^*) & -(\frac{\xi p I^*}{e} + a) & 0 \\ 0 & \xi H(E_2^*) & 0 & -\frac{aK(E_2^*)}{H(E_2^*)} \end{pmatrix}.$$

The characteristic equation at $J(W^*)$ is

$$f(\lambda) = \lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4 = 0, \tag{17}$$

where,

$$\begin{aligned}
b_1 &= \mu + \alpha + \frac{\xi p I^*}{e} + a + \frac{aK(E_2^*)}{H(E_2^*)} + \beta_1 E_1^* + \beta_2 E_2^* + \mu, \\
b_2 &= a_1 + (\mu + \alpha + \frac{\xi p I^*}{e} + a + \frac{aK(E_2^*)}{H(E_2^*)})(\beta_1 E_1^* + \beta_2 E_2^* + \mu), \\
b_3 &= a_2 + (\beta_1 E_1^* + \beta_2 E_2^* + \mu)a_1 + (\beta_1 E_1^* + \beta_2 E_2^*)(\beta_1 S^* B(E_1^*) + \beta_2 S^* \xi H(E_2^*)), \\
b_4 &= (\beta_1 E_1^* + \beta_2 E_2^* + \mu)a_2 + (\beta_1 E_1^* + \beta_2 E_2^*)(\beta_1 S^* B(E_1^*)\frac{aK(E_2^*)}{H(E_2^*)} + \beta_2 S^* \xi H(E_2^*)(\frac{\xi p I^*}{e} + a)), \\
a_1 &= (\mu+\alpha)(\frac{\xi p I^*}{e} + a) + \frac{aK(E_2^*)}{H(E_2^*)}(\mu + \alpha + \frac{\xi p I^*}{e} + a) - \beta_1 S^* B(E_1^*) - \beta_2 S^* \xi H(E_2^*), \\
a_2 &= \frac{aK(E_2^*)}{H(E_2^*)}(\mu+\alpha)(\frac{\xi p I^*}{e} + a) - \beta_1 S^* B(E_1^*)\frac{aK(E_2^*)}{H(E_2^*)} - \beta_2 S^* \xi H(E_2^*)(\frac{\xi p I^*}{e} + a).
\end{aligned}$$

Now we only need to prove $a_1 > 0,\ a_2 > 0$ and $K(E_2^*) > 0$. On substituting

$$(\mu+\alpha) = \frac{(\beta_1 E_1^* + \beta_2 E_2^*)S^*}{I^*},\ \frac{\xi p I^*}{e} + a = \frac{\xi p I^*}{e E_1^*},\ B(E_1^*) = \frac{\xi p}{e}(1 - E_1^*),$$

$$K(E_2^*) = H(E_2^*) - E_2^* \dot{H}(E_2^*),\ H(E_2^*) = \frac{aE_2^*}{\xi I^*},$$

into $a_1,\ a_2$, we obtain

$$\begin{aligned}
a_1 &= \frac{\xi p}{e}\frac{\beta_2 E_2^* S^*}{E_1^*} + \frac{\xi p}{e}\beta_1 S^* E_1^* + \frac{\xi I^* K(E_2^*)}{E_2^*}\Big(\frac{\beta_1 E_1^* S^*}{I^*} + \frac{\xi p I^*}{e E_1^*}\Big) - \xi \beta_2 E_2^* S^* \dot{H}(E_2^*), \\
a_2 &= \frac{\xi p}{e}\frac{\xi I^* K(E_2^*)}{E_2^*}\beta_1 S^* E_1^* - \frac{\xi p}{e}\frac{\beta_2 S^* E_2^*}{E_1^*}\xi I^* \dot{H}(E_2^*).
\end{aligned}$$

Assume that $\dot{H}(E_2^*) < 0$, then $K(E_2^*) = H(E_2^*) - E_2\dot{H}(E_2^*) > 0$, thus $a_1 > 0,\ a_2 > 0$ hold. Moreover, it is clear that $b_1 b_2 - b_3 > 0$. Summarize the above if $R_0 > 1$ and $\dot{H}(Z_2^*) < 0$, the endemic equilibrium W^* is locally asymptotically stable. □

Remark 4. *According to the Figure* 2 *(a), $H(E_2)$ is a monotone decreasing function. Therefore, it is reasonable that $\dot{H}(E_2^*) < 0$.*

4.4 Uniform persistence

Theorem 13. *If $R_0 > 1$, then subsystem (13) is uniformly persistent. That is, there exists a positive constant ε such that, for any positive solution $(S(t), I(t), E_1(t), E_2(t))$ of subsystem (13),*

$$\liminf_{t\to\infty} S(t) \geq \varepsilon, \quad \liminf_{t\to\infty} I(t) \geq \varepsilon, \quad \liminf_{t\to\infty} E_1(t) \geq \varepsilon, \quad \liminf_{t\to\infty} E_2(t) \geq \varepsilon.$$

Proof. Let $u(t, x_0) = (S(t, x_0), I(t, x_0), E_1(t, x_0), E_2(t, x_0))$ be any solution of subsystem (13) that meet the initial condition $u(0, x_0) = x_0$, where $x_0 = (S_0, I_0, E_{1_0}, E_{2_0}) \in R^4_+$, $R^4_+ := \{(x_1, x_2, x_3, x_4) : x_i \geq 0, i = 1, 2, 3, 4\}$. From subsystem (13), we have

$$\dot{S}(t) \geq A - \mu S(t).$$

By comparison principle, $\liminf_{t\to\infty} S(t) \geq \frac{\Lambda}{\mu}$, which means $S(t)$ is uniformly persistent.

Let $X = \{x = (I, E_1, E_2) \in R^3_+ : I > 0, E_1 > 0, E_2 > 0\}$. Then $\partial X = \{(I, E_1, E_2) \in R^3_+ : I = 0 \text{ or } E_1 = 0 \text{ or } E_2 = 0\}$ is the boundary of X. Denote $M_\partial = \{x_0 \in R^3_+ : u(t, x_0) \in \partial X, \forall t \geq 0\}$. Let $\omega(x_0)$ be the $\omega-$limit set of solution $u(t, x_0)$.

Define $M_0 = \{W_0\}$. Clearly, $M_0 \subset \bigcup_{x_0\in M_\partial} \omega(x_0)$. Due to $x_0 \in M_\partial$, we get $I \equiv 0$, $E_1 \equiv 0$ or $E_2 \equiv 0$. If $I \equiv 0$, then according to the subsystem (13), we know that $E_1 = 0$ and $E_2 = 0$. Thus, subsystem (13) becomes the following equation:

$$\dot{S}(t) = \Lambda - \mu S(t).$$

From this, we can obtain $\lim_{t\to\infty} S(t) = S_0$, which shows that $\omega(x_0) = W_0 \subset M_0$. If $E_i(t) = 0$ $(i = 1, 2)$, the discussions are similar to the above. Finally, we have $M_0 = \bigcup_{x_0\in M_\partial} \omega(x_0)$.

Now, we prove that $K^s(W_0) \cap X = \emptyset$, where $K^s(W_0)$ is the stable set of W_0. If not, then there exists a $x_0 \in X$ such that $\lim_{t\to\infty} u(t, x_0) = W_0$. Thus, for any constant $\varepsilon > 0$, there exists a $t_1 > 0$ so that $S(t) \geq S_0 - \varepsilon$, $I(t) < \varepsilon$, $E_1(t) < \varepsilon$, $E_2(t) < \varepsilon$ for all $t \geq t_1$. Moreover, from $\lim_{E_2\to\infty} \hat{Z}_2 = \frac{1}{c} p_2 \tilde{Y}$, we can obtain $\hat{Z}_2(E_2(t))) > \frac{1}{c} p_2 \tilde{Y} - \varepsilon$ for all $t \geq t_1$. Then we discuss the following two situations.

Case (1): If $\frac{\xi\beta_1 p S_0}{ea(\mu+\alpha)} < 1$. Since $R_0 = \frac{\xi\beta_1 cpS_0 + \xi\beta_2 ep_2\tilde{Y}S_0}{eac(\mu+\alpha)} > 1$, there exists a small enough constant $\varepsilon > 0$ so that

$$\frac{\xi\beta_1 cp(S_0 - \varepsilon) + \xi\beta_2 e(p_2\tilde{Y} - c\varepsilon)(S_0 - \varepsilon)}{eac(\mu + \alpha)} - \frac{f\xi\hat{Z}_1\varepsilon}{a} - \frac{(1 - f)\xi(\frac{1}{c}p_2\tilde{Y} - \varepsilon)\varepsilon}{a} - 1 > 0,$$

where $f = \frac{\xi\beta_1 p(S_0-\varepsilon)}{e(\mu+\alpha)(a+\xi\hat{Z}_1\varepsilon)} < 1$. Define the function

$$U_1(t) = I(t) + f\frac{\mu + \alpha}{\xi\hat{Z}_1}E_1(t) + (1 - f)\frac{\mu + \alpha}{\xi\hat{Z}_2}E_2(t).$$

We have $\lim_{t\to\infty} U_1(t) = 0$. Calculating the derivative of $U_1(t)$ when $t \geq t_1$,

$$\dot{U}_1(t) = \beta_1 E_1 S - f(\mu + \alpha)IE_1 - f\frac{(\mu + \alpha)a}{\xi\hat{Z}_1}E_1$$

$$
\begin{aligned}
&+\beta_2 E_2 S-(1-f)(\mu+\alpha) I E_2-(1-f)\frac{(\mu+\alpha)a}{\xi\hat{Z}_2}E_2\\
\geq&\big(\beta_1(S_0-\varepsilon)-f(\mu+\alpha)\varepsilon-f\frac{(\mu+\alpha)a}{\xi\hat{Z}_1}\big)E_1\\
&+\big(\beta_2(S_0-\varepsilon)-(1-f)(\mu+\alpha)\varepsilon-(1-f)\frac{(\mu+\alpha)a}{\xi(\frac{1}{c}p_2\tilde{Y}-\varepsilon)}\big)E_2\\
=&\big(\frac{\xi\beta_1 p(S_0-\varepsilon)}{ea(\mu+\alpha)}-\frac{f\xi\hat{Z}_1\varepsilon}{a}-f\big)\frac{(\mu+\alpha)a}{\xi\hat{Z}_1}E_1+\big(\frac{\xi\beta_2(p_2\tilde{Y}-c\varepsilon)(S_0-\varepsilon)}{ac(\mu+\alpha)}\\
&-(1-f)\frac{\xi(\frac{1}{c}p_2\tilde{Y}-\varepsilon)\varepsilon}{a}-(1-f)\big)\frac{(\mu+\alpha)a}{\xi(\frac{1}{c}p_2\tilde{Y}-\varepsilon)}E_2.
\end{aligned}
$$

According to $f=\frac{\xi\beta_1 p(S_0-\varepsilon)}{e(\mu+\alpha)(a+\xi\hat{Z}_1\varepsilon)}=\frac{\xi\beta_1 p(S_0-\varepsilon)}{ea(\mu+\alpha)}-\frac{f\xi\hat{Z}_1\varepsilon}{a}$, it is clear that $\dot{U}_1(t)>0$ for all $t\geq t_1$. Thus, $U_1(t)$ is monotone increasing for $t>t_1$. Hence, we have $\lim\limits_{t\to\infty}U_1(t)\neq 0$, which leads to a contradiction.

Case (2): If $\frac{\xi\beta_1 pS_0}{ea(\mu+\alpha)}>1$, there exists a small enough constant $\varepsilon>0$ so that $\frac{\xi\beta_1 p(S_0-\varepsilon)}{ea(\mu+\alpha)}-\frac{\xi\hat{Z}_1\varepsilon}{a}-1>0$. Define the function

$$
U_2(t)=I(t)+\frac{\mu+\alpha}{\xi\hat{Z}_1}E_1(t).
$$

Similar to the proof of case (1), we can obtain $\dot{U}_2(t)>0$ for all $t\geq t_1$. Hence, we have $\lim\limits_{t\to\infty}U_2(t)\neq 0$, which leads to a contradiction.

Above all, we have $K^s(W_0)\cap X=\emptyset$. By the theory of persistence in dynamic systems [43], a constant ε exists so that for any $x_0\in X$,

$$
\liminf_{t\to\infty}S(t)\geq\varepsilon,\quad \liminf_{t\to\infty}I(t)\geq\varepsilon,\quad \liminf_{t\to\infty}E_1(t)\geq\varepsilon,\quad \liminf_{t\to\infty}E_2(t)\geq\varepsilon.
$$

Thus subsystem (13) is uniformly persistent. □

4.5 Backward bifurcation analysis

Generally, the basic reproduction number can help us determine the conditions under which a disease can be controlled. In particular, the disease can be controlled when $R_0<1$. To further explore the complex dynamics, we discuss the possibility of backward bifurcation using the result given by Castillo-Chavez and Song [44].

For convenience, we change the notation by making $S=x_1, I=x_2, E_1=x_3, E_2=x_4$, then the subsystem (13) can be rewritten as $\dot{X}(t)=(f_1,f_2,f_3,f_4)^T$, where $X=(x_1,x_2,x_3,x_4)^T$. Thus we have

$$
\begin{cases}
\dot{x}_1=\Lambda-(\beta_1 x_3+\beta_2 x_4)x_1-\mu x_1,\\
\dot{x}_2=(\beta_1 x_3+\beta_2 x_4)x_1-(\mu+\alpha)x_2,\\
\dot{x}_3=\xi\frac{p}{e}x_2(1-x_3)-ax_3,\\
\dot{x}_4=\xi\frac{1}{c}(g_2(x_4)+p_2\hat{Y})x_2(1-x_4)-ax_4.
\end{cases}
\tag{18}
$$

We take β_1 as the bifurcation parameter, and get the value of β_1 by solving $R_0 = 1$ as follows

$$\beta_1 = \beta_1^* = \frac{\mu eac(\mu+\alpha) - \Lambda\xi\beta_2 ep_2\tilde{Y}}{\Lambda\xi cp}.$$

The Jacobian matrix of system (18) at the disease-free equilibrium W_0 as follows

$$J = \begin{pmatrix} -\mu & 0 & -\beta_1 x_1 & -\beta_2 x_1 \\ 0 & -(\mu+\alpha) & \beta_1 x_1 & \beta_2 x_1 \\ 0 & \frac{\xi p}{e} & -a & 0 \\ 0 & \frac{\xi p_2}{c}\tilde{Y} & 0 & -a \end{pmatrix}.$$

The Jacobian matrix J has a simple zero eigenvalue with $\beta_1 = \beta_1^*$, hence the center manifold theory [45] can be used to analyse the dynamic of system (13). It can be shown that J has a right eigenvector $\omega = (\omega_1, \omega_2, \omega_3, \omega_4)^T$, where

$$\omega_1 = -\frac{\beta_1 x_1\omega_3 + \beta_2 x_1\omega_4}{\mu},\ \omega_2 = \frac{\beta_1 x_1\omega_3 + \beta_2 x_1\omega_4}{\mu+\alpha},\ \omega_3 = \frac{\xi p}{ae}\omega_2,\ \omega_4 = \frac{\xi p_2\tilde{Y}}{ac}\omega_2.$$

Assuming that $\omega_2 = ace\mu > 0$, then $\omega_1 = -(\beta_1\xi pcx_1 + \beta_2 e\xi p_2\tilde{Y}x_1) < 0,\ \omega_3 = \xi pc\mu > 0,\ \omega 4 = e\xi\mu p_2\tilde{Y} > 0$. It can be shown that J has a left eigenvector $\upsilon = (\upsilon_1, \upsilon_2, \upsilon_3, \upsilon_4)$, where

$$\upsilon_1 = 0,\ \upsilon_2 = \frac{\frac{\xi p}{e}\upsilon_3 + \frac{\xi p_2\tilde{Y}}{c}\upsilon_4}{\mu+\alpha},\ \upsilon_3 = \frac{\beta_1 x_1}{a}\upsilon_2,\ \upsilon_4 = \frac{\beta_2 x_1}{a}\upsilon_2.$$

Assuming that $\upsilon_2 = a > 0$, then $\upsilon_3 = \beta_1 x_1 > 0,\ \upsilon_4 = \beta_2 x_1 > 0$.

Now we evaluate the constants a and b.

$$\upsilon_2\omega_1\omega_3\frac{\partial^2 f_2}{\partial x_1\partial x_3} = \upsilon_2\omega_1\omega_3\beta_1, \quad \upsilon_2\omega_1\omega_4\frac{\partial^2 f_2}{\partial x_1\partial x_4} = \upsilon_2\omega_1\omega_4\beta_2,$$
$$\upsilon_3\omega_2\omega_3\frac{\partial^2 f_3}{\partial x_2\partial x_3} - \upsilon_3\omega_2\omega_3\frac{\xi p}{e}, \quad \upsilon_4\omega_2\omega_4\frac{\partial^2 f_4}{\partial x_2\partial x_4} = \upsilon_4\omega_2\omega_4\frac{\xi}{c}(\dot{g}_2(x_4) + p_2\dot{\hat{Y}}(x_4) - p_2\hat{Y}(x_4)).$$

Therefore,

$$\begin{aligned} a = &\sum_{k,i,j=1}^{4}\upsilon_k\omega_i\omega_j\frac{\partial^2 f_k}{\partial x_i\partial x_j}(0,0) = 2\upsilon_2\omega_1\omega_3\beta_1 + 2\upsilon_2\omega_1\omega_4\beta_2 \\ &- 2\upsilon_3\omega_2\omega_3\frac{\xi p}{e} + 2\upsilon_4\omega_2\omega_4\frac{\xi}{c}(\dot{g}_2(0) + p_2\dot{\hat{Y}}(0) - p_2\hat{Y}(0)), \\ b = &\sum_{k,i=1}^{4}\upsilon_k\omega_i\frac{\partial^2 f_k}{\partial x_i\partial\beta_1}(0,0) = \upsilon_2\omega_3\frac{\partial^2 f_2}{\partial x_3\partial\beta_1} = \upsilon_2\omega_3 x_1 > 0. \end{aligned}$$

Regarding to the existence of backward bifurcation of subsystem (13), we have following theorem.

Theorem 14. *If $a > 0$, the system (13) will undergo a backward bifurcation when $R_0 = 1$.*

Figure 2 (b) numerically depicts the backward bifurcation phenomenon in the $R_0 - I$ plane. Let $\lambda = 550,\ k_1 = 10^{-6},\ k_2 = 1.5\times10^{-2},\ d = 0.1,\ \delta = 0.3,\ p_1 = 5,\ p_2 = 0.06,\ b = 0.03,\ c = 500,\ e = 10^{-3},\ p = 0.005,\ \Lambda = 80,\ \beta_2 = 0.5,\ \mu = 0.7,\ \xi = 1.5\times10^{-3},\ a = 0.009,\ \alpha = 0.3$.

In addition, $g_1(E_1) = h_1E_1,\ g_2(E_2) = h_2E_2,\ h_1 = 10,\ h_2 = 630$. As shown in Figure 2 (b), there exists endemic equilibria when $R_0 < 1$. When $R_0 > 1$, the system (13) has an unstable disease-free equilibrium and a stable endemic equilibrium. Figure 2 $(c-d)$ shows that when $R_0 = 0.4764$, the system (13) has a stable disease-free equilibrium W_0 and two positive equilibria: one is stable, another is unstable. This shows that the eradication of infectious diseases requires not only $R_0 < 1$, but also smaller enough, which will pose a greater challenge to the control of disease.

Remark 5. *When $\dot{g}_2(0) = 0$ and $p_2 = 0$, a is always less than 0, which means that there is no backward bifurcation. $p_2 = 0$ means that the release rate of strain 2 is 0, i.e., there is only a single strain and thus no backward bifurcation occurs.*

5 Numerical examples

Now, we illustrate and further validate the theoretical results by numerical simulations. In subsystems (5) and (13), for convenience, we take the functions $g_1(E_1) = h_1E_1,\ g_2(E_2) = h_2E_2$ with $h_1 = 10,\ h_2 = 10$. Moreover, we choose the parameters $d = 0.1,\ \delta = 0.2,\ p_1 = 5,\ p_2 = 2,\ \Lambda = 500,\ \beta_1 = 0.005,\ \beta_2 = 0.05,\ \mu = 0.44,\ \alpha = 0.15,\ c = 500,\ e = 10^{-3}$.

Case 1. For the subsystem (5), we take the parameters $\lambda = 60,\ k_1 = 10^{-6},\ k_2 = 1.5 \times 10^{-3},\ b = 0.003,\ c = 50,\ e = 10^{-5},\ p = 0.01$. By calculation, we have $R_{w0} = 0.1202,\ R_1 = 2 \times 10^{-4},\ R_2 = 0.12$, subsystem (5) has a unique infection-free equilibrium E_0. Figure 3 (a) illustrates that $E_0 = (600, 0, 0, 0, 0)$ is globally asymptotically stable. Thus, Theorem 6 is verified.

Case 2. For the subsystem (5), we choose the parameters $\lambda = 600,\ k_1 = 10^{-8},\ k_2 = 1.5 \times 10^{-3},\ b = 0.003,\ E_1 = 0.5,\ E_2 = 0.5,\ c = 15,\ e = 10^{-5},\ p = 0.01$. By calculation, we have $R_{w0} = 4.0001 > 1,\ R_1 = 6.6667 \times 10^{-5},\ R_2 = 4,\ R_{w2} = 0.5006 < 1$, subsystem (5) has a unique immunity-inactivated co-infection equilibrium $\bar{E}$. From the numerical simulation in Figure 3 (c), we can see that $\bar{E} = (1497.5, 1500.8, 500.6133, 200.4453, 0)$ is globally asymptotically stable. Thus, Theorem 9 is true.

Case 3. For the subsystem (5), we choose parameters $\lambda = 100,\ k_1 = 10^{-8},\ k_2 = 1.5 \times 10^{-2},\ b = 0.03,\ E_1 = 0.5,\ E_2 = 0.5,\ c = 50,\ e = 5 \times 10^{-3},\ p = 0.05$. By calculation, we have $R_{w0} = 2 > 1,\ R_1 = 3.3333 \times 10^{-6},\ R_2 = 2,\ R_{w2} = 1.7010 > 1$, subsystem (5) has a unique immunity-activated co-infection equilibrium $\hat{E}$. From the numerical simulation in Figure 3 (e), we can see that $\hat{E} = (492.7149, 169.095, 10, 6.8638, 1168.3)$ is globally asymptotically stable. Thus, Theorem 10 is verified.

Case 4. For the subsystem (13), we take parameters $\xi = 1.4 \times 10^{-6},\ a = 0.5,\ \lambda = 1000,\ k_1 = 10^{-8},\ k_2 = 1.5 \times 10^{-2},\ p = 0.005$. By calculation, we have $R_0 = 0.0019 < 1$, subsystem (13) has a disease-free equilibrium W_0. From the numerical simulation in Figure 3 (g), we can see that $W_0 = (1136.4, 0, 0, 0)$ is locally asymptotically stable. Thus, the result (i) of Theorem 13 is true.

Case 5. For the subsystem (13), we choose parameters $\xi = 1.4 \times 10^{-4},\ a = 0.005,\ \Lambda = 50,\ \lambda = 1000,\ k_1 = 10^{-8},\ k_2 = 1.5 \times 10^{-2},\ p = 0.005$. By calculation, we have $R_0 = 1.9325 > 1$, subsystem (13) has an endemic equilibrium $W^* = (107.4577, 4.6077, 0.3964, 0.4663)$. According to Figure 2 (a), the assumption $\dot{H}(E_2^*) < 0$ holds. From the numerical simulation in Figure 3

(i), we can see that W^* is locally asymptotically stable. Thus, the result (ii) of Theorem 13 is true.

5.1 The relationship of two-strain in host

As shown in Figure 4 $(a-b)$, we choose four sets of parameters such that 1) $R_1 = 0.6$, $R_2 = 0.48$; 2) $R_1 = 0.3$, $R_2 = 0.8$; 3) $R_1 = 1.0667$, $R_2 = 2 \times 10^{-4}$; 4) $R_1 = 1.1733$, $R_2 = 2 \times 10^{-5}$. When $R_{w0} = R_1 + R_2 > 1$ and $R_{w2} < 1$, there exists immunity-inactivated coinfection equilibrium. This means the presence of two mutualistic strains makes the disease more likely develop than single strain, even the basic reproduction number is small than 1 in each single strain. In addition, in cases 2 and 3, we make R_1 be 6.6667×10^{-5} and 3.3333×10^{-6}, both the strains 1 and 2 will be persistent.

5.2 The comparison of dynamics between single-strain and two-strain models

In this subsection, we mainly compare the dynamics in vitro between single-strain and two-strain. As shown in Figure 5 (a), there is only strain 1 in vivo, the basic reproduction number R_1 is 0.6667, we can see that diseases are extinct both within-host and between-host. As shown in Figure 5 (c), we introduce strain 2 into body, such that $R_1 = 0.6667$ and $R_2 = 0.8667$, i.e., $R_{w0} = R_1 + R_2 = 1.5334 > 1$. In this case, diseases are persist both within- and between-host. A comparison of these two graphs shows that simultaneous transmission of two strains is more advantageous than transmission of one strain. This phenomenon is common in infectious diseases, e.g., the combination of fungus and bacteria could aggravate dental decay [46], growth of the virus is facilitated by cooperation between two variants of H3N2 influenza [31].

5.3 Sensitivity analysis

In this subsection, we perform sensitivity analysis on the within-host basic reproduction number of immunity-activation R_{w2} and the between-host basic reproduction number R_0.

Figure 6 (a) shows the relationship between reproduction rate of strain i with R_{w2}, which means p_1 and p_2 are positively correlative variables with R_{w2}. In addition, when both p_1 and p_2 are less than 1, the effect of p_1 on R_{w2} is greater than p_2, while when both p_1 and p_2 are greater than 1, the effect of p_2 on R_{w2} is greater than p_1.

Next, we investigate the effect of e, p, c and p_2 on R_0. As seen in Figure 6 $(b-c)$, in order to reduce R_0 less than 1, measures can be taken to reduce the clearance rate p of B cells and the reproduction rate p_2 of strain 2, increase the clearance rate c of strains and the production rate e of B cells.

6 Discussion

In this paper, we proposed a coupled epidemic model with mutualistic two-strain of virus and humoral immunity, combining in vivo and vitro dynamics to explore the interactions of dynamic between different time scale.

For the between-host subsystem, in the case of two-strain mutualistic coinfection, more complex dynamics appear between hosts even there is humoral immunity in vivo. In addition,

by comparing single strain and two strains in vivo, it is known that simultaneous transmission of two strains is more advantageous than transmission of one strain for disease transmission. In reality, there are many such examples [30–32, 46].

When strain 1 and humoral immunity are removed, system (5)-(6) becomes a single strain coupled system [9,22]. Our two mutualistic strains coupled model has more complicated dynamic behavior compared to the single-strain coupled system. In contrast to epidemic model of two strains either transmission in body or vitro, our results suggest that dynamics within-host can interact with between-host. Therefore, system (5)-(6) is more practical with the real circumstance of disease spread and could offer better directions for controlling and preventing disease. Furthermore, there is a very interesting open question that whether the results are still true if there exists delays within-host and direct transmission between-host, which will be investigated in the future.

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Data availability

The datasets generated and/or analyzed during the current study are available on reasonable request to the corresponding author.

Conflict of interest

The authors have no conflicts of interest.

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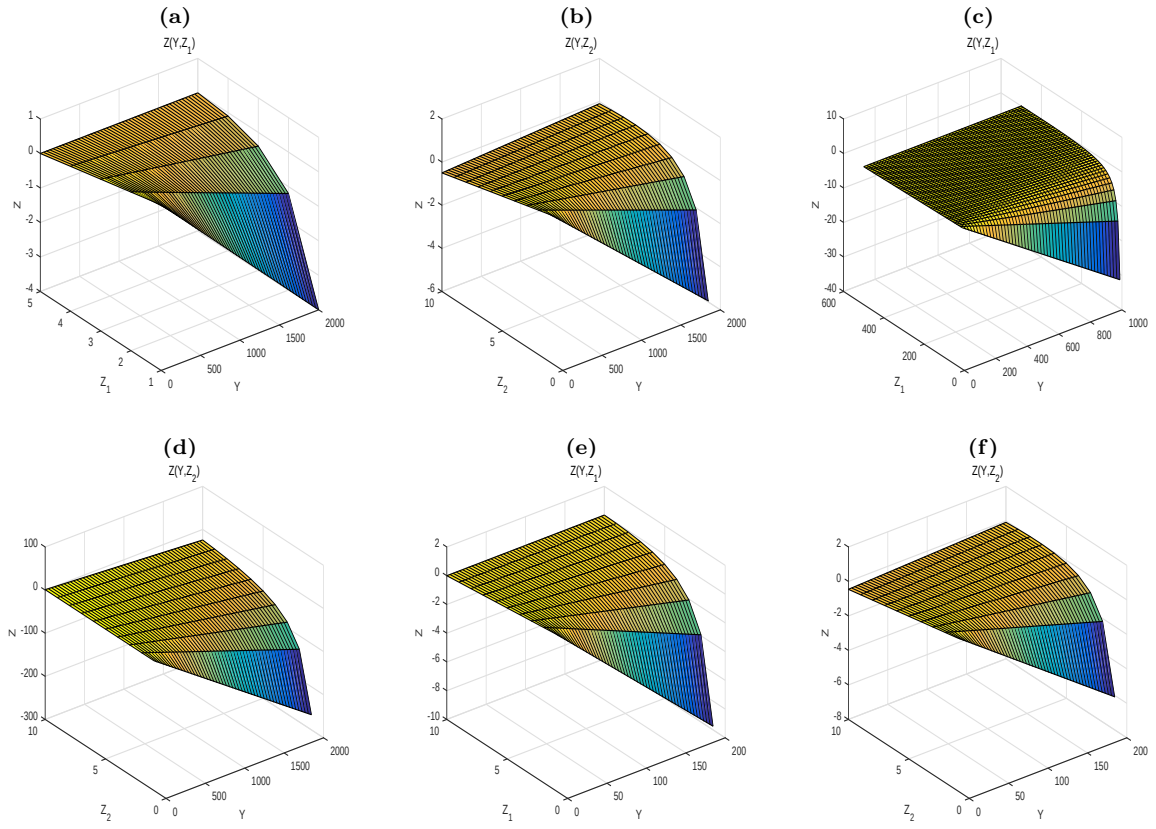


Figure 1: *(a-f): The images for functions* $(1-\frac{\bar{Z}_1}{Z_1})(\frac{Y}{\bar{Y}}-\frac{Z_1}{\bar{Z}_1})$, $(1-\frac{\bar{Z}_2}{Z_2})(\frac{Y}{\bar{Y}}-\frac{Z_2}{\bar{Z}_2})$, $(1-\frac{\bar{Z}_1}{Z_1})(\frac{Y}{Y}-\frac{Z_1}{\bar{Z}_1})$, $(1-\frac{\bar{Z}_2}{Z_2})(\frac{Y}{Y}-\frac{Z_2}{\bar{Z}_2})$, $(1-\frac{\hat{Z}_1}{Z_1})(\frac{Y}{\hat{Y}}-\frac{Z_1}{\hat{Z}_1})$ *and* $(1-\frac{\hat{Z}_2}{Z_2})(\frac{Y}{\hat{Y}}-\frac{Z_2}{\hat{Z}_2})$, *respectively. We can see that the vertical axes* Z *are all less than or equal to 0.*

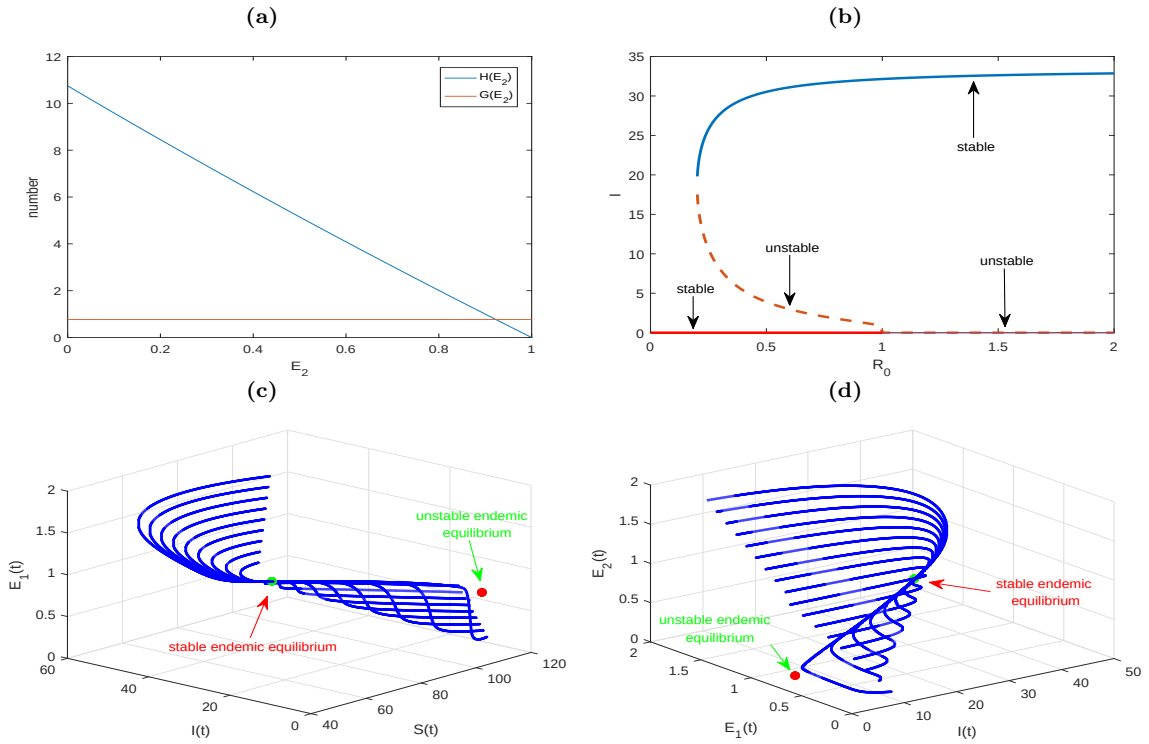
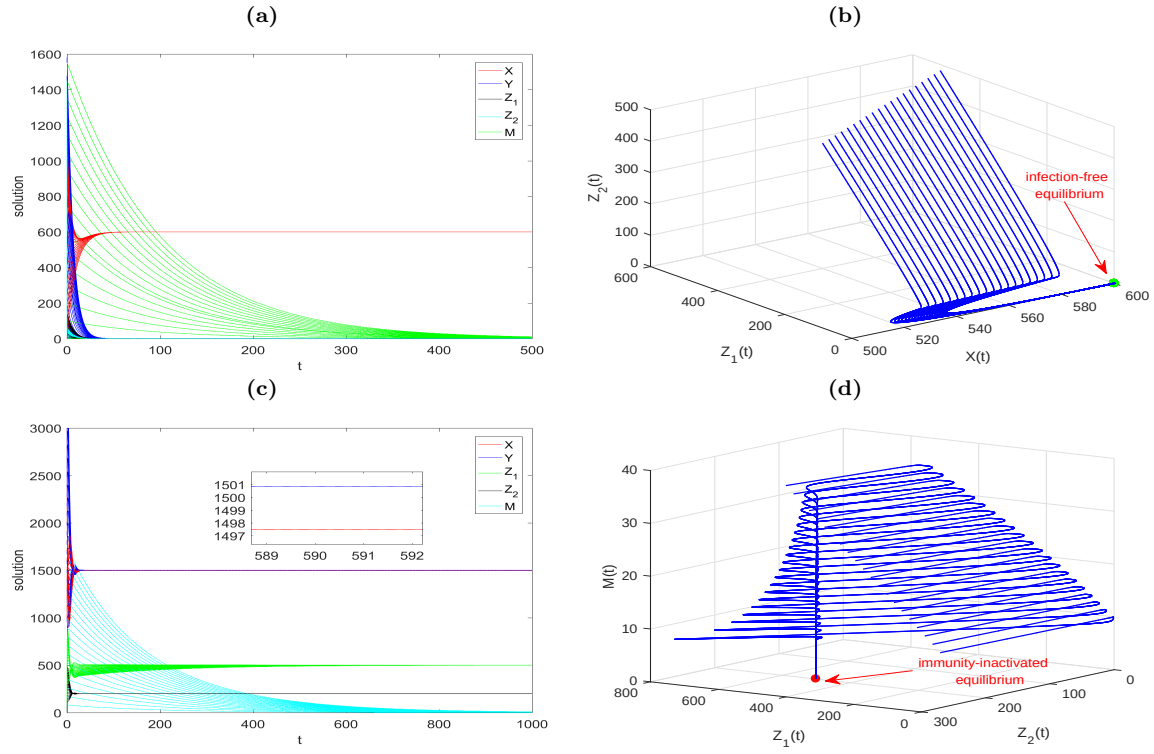


Figure 2: *(a): The image that $H(E2)$ and $G(E2)$ intersect when $R_0 = 1.9325$; (b): Backward bifurcation in $R_0 - I$ plane of subsystem (13); (c-d): The 3-dimensional phases of solutions for subsystem (13) when $R_0 = 0.4764$.*



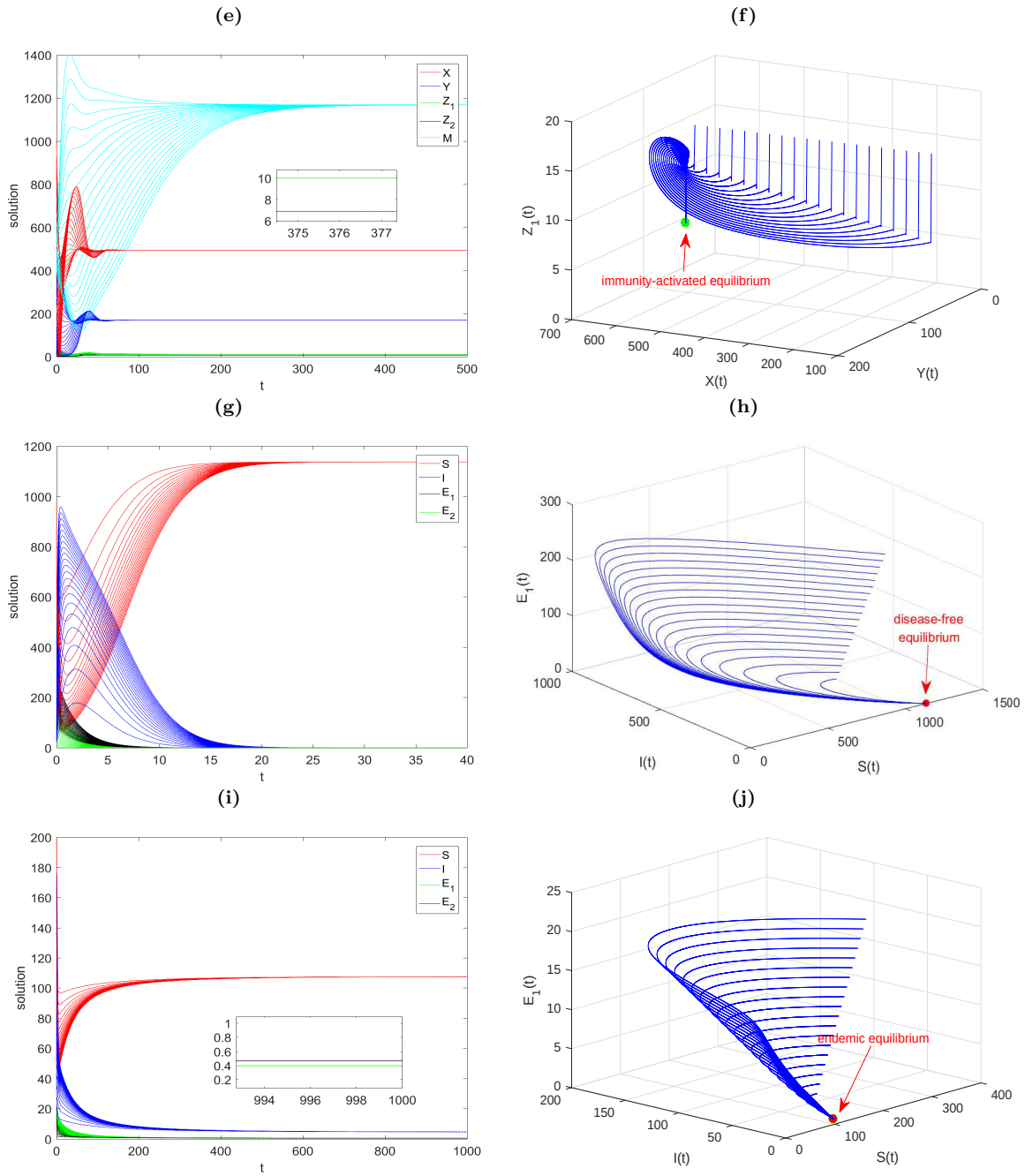


Figure 3: $(a-f)$: *Dynamical behaviors and 3-dimension phase of solutions* $(X(s), y(s), Z_1(s), Z_2(s), M(s))$ *of subsystem* (5) *when* $R_{w0} = 0.1202$*;* $(c-d)$*: Dynamical behaviors and 3-dimension phase of solutions* $(X(s), y(s), Z_1(s), Z_2(s), M(s))$ *of subsystem* (5) *when* $R_{w0} = 4.0001$, $R_{w2} = 0.5006$*;* $(e-f)$*: Dynamical behaviors and 3-dimension phase of solutions* $(X(s), y(s), Z_1(s), Z_2(s), M(s))$ *of subsystem* (5) *when* $R_{w0} = 2$, $R_{w2} = 1.7010$*;* $(g-h)$*: Dynamical behaviors and 3-dimension phase of solutions of* $(S(t), I(t), E_1(t), E_2(t))$ *of subsystem* (13) *when* $R_0 = 0.0019$*;* $(i-j)$*: Dynamical behaviors and 3-dimension phase of solutions of* $(S(t), I(t), E_1(t), E_2(t))$ *of subsystem* (13) *when* $R_0 = 1.9325$.

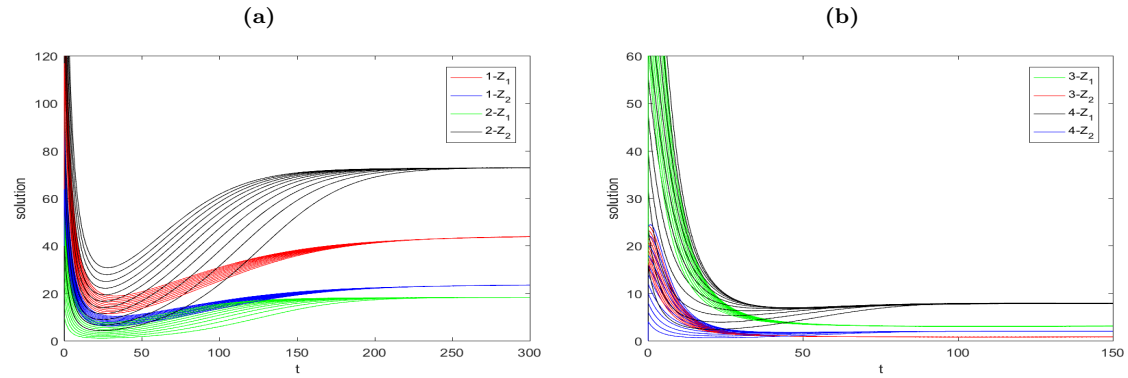


Figure 4: *(a-b): The coexistence condition of strains 1 and 2 under four sets of parameters:* 1) $R_1 = 0.6, R_2 = 0.48$; 2) $R_1 = 0.3, R_2 = 0.8$; 3) $R_1 = 1.0667, R_2 = 2 \times 10^{-4}$; 4) $R_1 = 1.1733, R_2 = 2 \times 10^{-5}$.

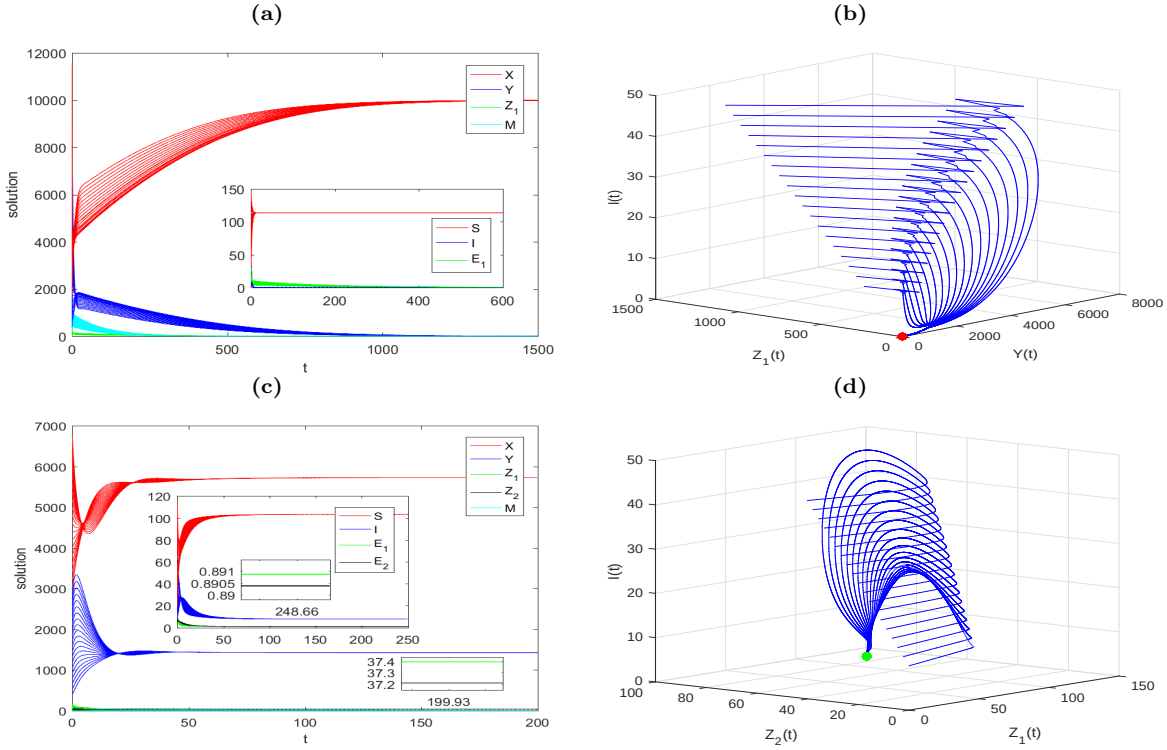


Figure 5: *(a-b): Dynamical behaviors and 3-dimension phase of solutions when strain 2 is removed from coupled system* (5)-(6)*; (c-d): Dynamical behaviors and 3-dimension phase of solutions of coupled system* (5)-(6).

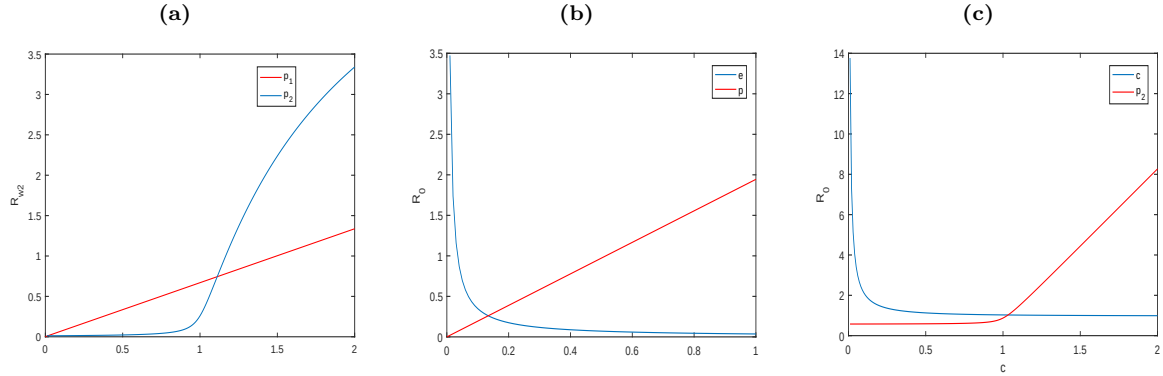


Figure 6: *(a): The effect of* p_1 *and* p_2 *on* R_{w2}*; (b-c): The effect of* e, p, c *and* p_2 *on* R_0.