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Global dynamics on a delayed double-strain influenza model with vaccination and cross-immunity

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Abstract

In this paper, a delayed double-strain influenza model with vaccination and cross-immunity is proposed to explore the effect of coinfection of double-strain on disease spread. First, the nonnegativity and ultimate boundedness of solution are proved. Second, the basic reproduction numbers of strains 1, 2, and the whole model are defined respectively, by which criteria on the local and global asymptotic stability of (disease-free, dominant) equilibria are established. The uniform persistence of (strains 1, 2 coexistent) disease is obtained as well. Finally, the validity of the theoretical results is demonstrated by numerical simulations. We find that neglecting cross-immunity and vaccination would misestimate the size of influenza outbreaks. Cross-type multivalent vaccines will be the main direction for effective control measure for influenza.

Keywords: Double-strain; Cross-immunity; Vaccination; Delay; Stability

1 Introduction

Influenza is a viral respiratory infection and usually includes four types, i.e., A, B, C, and D of the orthomyxoviridae family, in which the first three types of viruses can infect and spread between humans [1]. Influenza A and B viruses often appear with seasonal alternation, cause localized outbreaks, even worldwide pandemics [2]. Influenza virus can be transmitted not only by respiratory droplets and aerosols, but also by direct or indirect contact with mucous membranes [3]. Due to the rapid spread of influenza between the crowds, there are approximately 1 billion cases of influenza, with 290,000–650,000 respiratory disease-related deaths and 3–5 million severe cases globally a year, in which 99% of deaths in developing countries are among children under 5 years of age [1, 4], posing a serious threat to global human health.

Influenza can lead to nonrespiratory complications, e.g., it can further aggravate the condition with chronic illness even to death, such as cardiovascular diseases [5], especially dangerous for pregnant women, infants, young children, etc. [2, 4]. Vaccination is the most cost-effective preventive measure against influenza, which significantly reduces the risk of infection and serious complications [6]. However, current influenza vaccines mainly target the variable region of viral hemagglutinin surface glycoprotein, which cannot fully protect people against influenza before a pandemic, since it is only effective for routine immunization against specific variants of seasonal influenza and require annual vaccine updates [7]. Wu et al. [8] proposed a double-strain epidemic model with vaccination and amplification to research the interaction between amplified strain and common strain. Zou and Rahman [9] proposed a double-strain influenza model with single effective vaccine as follows:

$$\begin{cases} \dot{S}(t) = \Lambda - \beta_1 I_1 S - \beta_2 I_2 S - rS - \mu S, \\ \dot{V}_1(t) = rS - kI_2 V_1 - \mu V_1, \\ \dot{I}_1(t) = \beta_1 I_1 S - \gamma_1 I_1 - \mu I_1 - \nu_1 I_1, \\ \dot{I}_2(t) = \beta_2 I_2 S + kI_2 V_1 - \gamma_2 I_2 - \mu I_2 - \nu_2 I_2, \\ \dot{R}(t) = \gamma_1 I_1 + \gamma_2 I_2 - \mu R, \end{cases} \tag{1}$$

where S, V_1, I_1, I_2, R represent the number of susceptible, strain 1 vaccinated, strain 1 infected, strain 2 infected, and recovered individuals, respectively. The recruitment rate for susceptible individuals is Λ, β_i is the infection rate of strain i, k represents the infection rate of strain 1 vaccinated individuals, μ represents the natural mortality rate, r represents the vaccination rate, ν_i represents the cause-specific mortality rate of strain i infected individuals, γ_i represents the recovery rate of strain i infected individuals, where $i = 1, 2$. In addition, influenza virus coinfection with other respiratory viruses could lead to more serious complications, e.g., SARS-CoV-2 and influenza coinfection would be more severe than any single infection of one virus [10].

Due to the rapid evolution of recurrent influenza [11], seasonal influenza A and B viruses could evade human humoral immunity primarily through amino-acid substitutions, insertions, or deletions encoding epitopes of hemoglobin and neuraminidase, which allow the viruses to escape key antibodies induced by prior infection, vaccination, i.e., antigenic drift, and eventually drives the annual prevalence of influenza [2]. Due to antigenic drift, different strains of virus subtype could coexist, in which the antigenic deviation between two different strains could affect partial immunity to some extent, make the host acquire immunity with one strain but susceptible to the other, i.e., so called cross-immunity [12]. Casagrandi et al. [12] established SIRC epidemic models with cross-immunity to study the dynamic behavior of influenza. Chuang and Lui [13] found that if the cross-immune difference between two strains is large enough, then there is a risk that the stability of internal steady state may change and the cycle solution may bifurcate. Fudolig and Howard [14] established a type of SIR multistrain epidemic model with cross-immunity to explore the spread dynamic. Pell et al. [15] proposed the following delayed double-strain epidemic model:

$$\begin{cases} \dot{S}(t) = \Lambda - \beta_1 S I_1 - \beta_2 S I_2 - \mu S, \\ \dot{I}_1(t) = \beta_1 S I_1 - \gamma_1 I_1 - \mu I_1 - \nu_1 I_1, \\ \dot{I}_2(t) = \beta_2 S I_2 + \beta_2 R_l I_2 - \gamma_2 I_2 - \mu I_2 - \nu_2 I_2, \\ \dot{R}_l(t) = \gamma_1 I_1(t-\tau) - \beta_2 R_l I_2 - \mu R_l, \end{cases} \tag{2}$$

Table 1 Biological interpretations of parameters

Parameter	Description
Λ	Recruitment of individuals
$\frac{1}{\mu}$	Average time of life expectancy
r	Rate of vaccination with strain 1
k	Infection rate of vaccinated individuals to strain 2
β_i	Infection rate of strain i
μ_i	Mortality rate of individuals infected with strain i
γ_i	Recovery rate of individuals infected with strain i
τ_i	The incubation period of strain i
$e^{-\mu\tau_i}$	The probability of surviving time period from $t-\tau_i$ to time t

where R_I represents the number of strain 1 recovered individuals but susceptible to strain 2. τ represents the immune delay. They found that due to immune evasion, the basic reproduction number of original strain should be much higher than that of emerging strain to ensure the stability of the original strain dominant equilibrium.

Furthermore, the infection and recovery process of disease are usually not instantaneous processes, but with some time delays, e.g., COVID-19 and influenza [4, 16], which could greatly influence the dynamic of disease spread. Farah et al. [17] proposed a type of delayed double-strain epidemic model to investigate the effect of infection delay. Goel et al. [18] proposed an SIRC epidemic model to explore the impact of incubation and immunity delays on multistrain epidemics; they found that once the delays exceed a certain threshold, it could induce oscillatory behavior of the system. Chen et al. [19] proposed a class of delayed mixed-strain HIV infection models; they found that the infection delay could yield a Hopf branch and a chaotic phenomenon.

Motivated by the above consideration, we propose a delayed double-strain influenza model based on the following scenarios. Due to mutations (antigenic drift), the new strain shows cross-immunity with the original strain, and the vaccines are partially effective against the new influenza strain. Since the incubation period of influenza A virus infection is about 2–4 days [2, 4], latency delay is included in the model. The detailed model is as follows:

$$\begin{cases} \dot{S}(t) = \Lambda - \beta_1 I_1(t)S(t) - \beta_2 I_2(t)S(t) - rS(t) - \mu S(t), \\ \dot{V}(t) = rS(t) - kV(t)I_2(t) - \mu V(t), \\ \dot{I}_1(t) = \beta_1 S(t-\tau_1)I_1(t-\tau_1)e^{-\mu\tau_1} - \gamma_1 I_1(t) - \mu_1 I_1(t), \\ \dot{I}_2(t) = (\beta_2 S(t-\tau_2) + kV(t-\tau_2) + \beta_2 R_1(t-\tau_2))I_2(t-\tau_2)e^{-\mu\tau_2} - \gamma_2 I_2(t) - \mu_2 I_2(t), \\ \dot{R}_1(t) = \gamma_1 I_1(t) - \beta_2 R_1(t)I_2(t) - \mu R_1(t), \\ \dot{R}_2(t) = \gamma_2 I_2(t) - \mu R_2(t), \end{cases} \tag{3}$$

where R_i represents the number of recovered individuals of strains i. The parameter meanings are shown in Table 1, where $i = 1, 2$. Since the influenza vaccine may produce low levels of herd cross-immunity and reduce transmission and susceptibility [20], in this paper we assume $k \leq \beta_2$.

Since the sixth equation of model (3) is decoupled from the other equations, we can obtain the following degenerated model:

$$\begin{cases} \dot{S}(t) = \Lambda - \beta_1 I_1 S - \beta_2 I_2 S - rS - \mu S, \\ \dot{V}(t) = rS - kVI_2 - \mu V, \\ \dot{I}_1(t) = \beta_1 S(t-\tau_1) I_1(t-\tau_1) \mathrm{e}^{-\mu\tau_1} - \gamma_1 I_1 - \mu_1 I_1, \\ \dot{I}_2(t) = (\beta_2 S(t-\tau_2) + kV(t-\tau_2) + \beta_2 R_1(t-\tau_2)) I_2(t-\tau_2) \mathrm{e}^{-\mu\tau_2} - \gamma_2 I_2 - \mu_2 I_2, \\ \dot{R}_1(t) = \gamma_1 I_1 - \beta_2 R_1 I_2 - \mu R_1. \end{cases} \tag{4}$$

The organization of this article is as follows. In Sect. 2, the nonnegativity and boundedness of solution are proved, the basic reproduction numbers of strains 1, 2 and the whole model are derived, and the existence of equilibria are obtained. In Sect. 3, the threshold criteria on the stability of (disease-free, dominant) equilibria are obtained, and the uniform persistence of (strains 1, 2 coexistent) disease and the existence of strains 1, 2 coexistent equilibrium are discussed respectively. In Sect. 4, the theoretical results are demonstrated through numerical simulations. Finally, a brief conclusion and discussion are given in the last section.

2 Basic properties

Denote $\tau = \max\{\tau_1, \tau_2\}$, define the Banach space $\mathbf{C} := C([-\tau, 0], \mathbf{R}^5)$, and the positive cone of $\mathbf{C}$ is defined as $\mathbf{C}^+ := C([-\tau, 0], \mathbf{R}^5_+)$. $||\phi|| = \sum_{i=1}^{5} ||\phi_i||_\infty$, where $||\phi_i||_\infty = \sup_{-\tau \le \theta \le 0} |\phi_i(\theta)|$, $\theta = (\theta_1, \theta_2, \theta_3, \theta_4, \theta_5) \in \mathbf{C}$.

The initial conditions for model (4) are

$$S(\theta) = \phi_1(\theta), V(\theta) = \phi_2(\theta), I_1(\theta) = \phi_3(\theta), I_2(\theta) = \phi_4(\theta), R_1(\theta) = \phi_5(\theta), \theta \in [-\tau, 0], \tag{5}$$

where $\phi = (\phi_1(t), \phi_2(t), \phi_3(t), \phi_4(t), \phi_5(t)) \in C([-\tau, 0], \mathbf{R}^5_+)$, $\phi_i(0) > 0$, $i = 1, 2, \dots, 5$.

2.1 Nonnegativity and boundedness of solutions

In this subsection, with respect to the nonnegativity and boundedness of solutions for model (4), we have the following result.

Theorem 2.1 *Any solution of model* (4) *with initial condition* (5) *is nonnegative and ultimately bounded for all* $t \in [0, +\infty)$.

Proof For any $\phi \in \mathbf{C}^+$, define

$$f(t, \phi) = \begin{pmatrix} \Lambda - \beta_1 \phi_1(0)\phi_3(0) - \beta_2 \phi_1(0)\phi_4(0) - r\phi_1(0) - \mu\phi_1(0) \\ r\phi_1(0) - k\phi_2(0)\phi_4(0) - \mu\phi_2(0) \\ \beta_1 \phi_1(-\tau_1)\phi_3(-\tau_1)\mathrm{e}^{-\mu\tau_1} - \gamma_1\phi_3(0) - \mu_1\phi_3(0) \\ [\beta_2\phi_1(-\tau_2) + k\phi_2(-\tau_2) + \beta_2\phi_5(-\tau_2)]\phi_4(-\tau_2)\mathrm{e}^{-\mu\tau_2} - \gamma_2\phi_4(0) - \mu_2\phi_4(0) \\ \gamma_1\phi_3(0) - (\beta_2\phi_4(0) + \mu)\phi_5(0) \end{pmatrix}.$$

Since $f(t, \phi)$ is continuous and Lipschitz, we can obtain that model (4) has a unique solution $u(t, \phi)$ on its maximal existence interval $[0, \sigma_\phi)$, and by Theorems 2.2.1 and 2.2.3

of the existence of solution for delay differential equations (DDEs) in [21]. If $\phi_i(0) = 0$ for $i \in \{1, \ldots, 5\}$, then $f_i(t,\phi) \geq 0$. Therefore, by Theorem 5.2.1 in [21], it is obtained that $u_t(\phi) = u(t,\phi)$ is nonnegative.

Denote

$$K(t) = S(t) + \mathrm{e}^{\mu\tau_1} I_1(t+\tau_1) + V(t), M(t) = K(t) + \mathrm{e}^{\mu\tau_2} I_2(t+\tau_2) + R_1(t),$$

we have

$$\dot{K}(t) \leq \Lambda - \mu S(t) - \mu V(t) - \mu \mathrm{e}^{\mu\tau_1} I_1(t+\tau_1) \leq \Lambda - \mu K(t),$$

by the principle of comparison, $\limsup\limits_{t\to\infty} K(t) \leq \frac{\Lambda}{\mu}$, then $I_1(t) \leq \frac{\Lambda}{\mu}$.

Let $G(t) = M(t) + \gamma_1 \int_t^{t+\tau_1} I_1(s)\,\mathrm{d}s$, then we further have

$$\begin{aligned}
\dot{G}(t) &= \dot{S}(t) + \dot{V}(t) + \mathrm{e}^{\mu\tau_1} \dot{I}_1(t+\tau_1) + \mathrm{e}^{\mu\tau_2} \dot{I}_2(t+\tau_2) + \dot{R}_1(t) + \gamma_1 I_1(t+\tau_1) - \gamma_1 I_1(t) \\
&\leq \Lambda - \mu S(t) - \mu V(t) - \mu_1 \mathrm{e}^{\mu\tau_1} I_1(t+\tau_1) - \mu_2 \mathrm{e}^{\mu\tau_2} I_2(t+\tau_2) - \mu R_1(t) \\
&\leq \Lambda - \mu M(t) = \Lambda + \mu\gamma_1 \int_t^{t+\tau_1} I_1(s)\,\mathrm{d}s - \mu G(t) \\
&\leq \Lambda + \mu\gamma_1\tau_1 \frac{\Lambda}{\mu} - \mu G(t) = \Lambda + \gamma_1\tau_1\Lambda - \mu G(t),
\end{aligned}$$

by the comparison principle, we have $\limsup\limits_{t\to\infty} G(t) \leq \frac{\Lambda+\gamma_1\tau_1\Lambda}{\mu}$.

Since $M(t) \leq G(t)$, $M(t)$ is bounded on $[0,\sigma_\phi)$. By Theorem 2.3.1 in [22], the extension theorem for delayed differential equations: $\sigma_\phi = \infty$, i.e., the solution of model (4) is nonnegative and ultimately bounded on $[0,\infty)$. □

Further we obtain the positive invariant set of model (4):

$$\Gamma = \{(S(t), V(t), I_1(t), I_2(t), R_1(t)) \in \mathbf{C}_+^5 : M(t) \leq \frac{\Lambda + \gamma_1\tau_1\Lambda}{\mu}\}.$$

2.2 The existence of equilibria

In this subsection, the various types of equilibrium and basic reproduction number of model (4) are obtained.

Obviously, there exists a disease-free equilibrium (DFE) $E_0 = (S_0, V_0, 0, 0, 0) = (\frac{\Lambda}{r+\mu}, \frac{r\Lambda}{(r+\mu)\mu}, 0, 0, 0)$ for model (4). According to the next generation method of $\mathcal{R}_0$ for functional differential equations (FDEs) model in [23], we have

$$\mathcal{R}_0 = \rho(FV^{-1}) = \max\{\mathcal{R}_{01}, \mathcal{R}_{02}\},$$

where $\mathcal{R}_{01} = \frac{\beta_1\Lambda\mathrm{e}^{-\mu\tau_1}}{(r+\mu)(\gamma_1+\mu_1)}$, $\mathcal{R}_{02} = \frac{\beta_2\Lambda\mathrm{e}^{-\mu\tau_2}}{(r+\mu)(\gamma_2+\mu_2)} + \frac{kr\Lambda\mathrm{e}^{-\mu\tau_2}}{(r+\mu)(\gamma_2+\mu_2)\mu}$ denotes the basic reproduction number of strains 1, 2, respectively. Next, we will explain the meaning of each term in the $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$ expressions.

- $\frac{\beta_i\Lambda\mathrm{e}^{-\mu\tau_i}}{(r+\mu)(\gamma_i+\mu_i)}$ represents the average number of secondary infections caused by contact with susceptible individuals during the infection period of a strain i infected individual.
- $\frac{kr\Lambda\mathrm{e}^{-\mu\tau_2}}{(r+\mu)(\gamma_2+\mu_2)\mu}$ represents the average number of secondary infections caused by contact with vaccinated individuals during the infection period of a strain 2 infected individual.

Here, $\beta_i S_0 = \frac{\beta_i \Lambda}{(r+\mu)}$ is the product of the infection rates of susceptible individuals (unvaccinated) and individuals infected with strain i. $kV_0 = \frac{kr\Lambda}{(r+\mu)\mu}$ is the product of the infection rates of vaccinated individuals and individuals infected with strain 2. $\frac{1}{(\gamma_i+\mu_i)}$ is the average time duration of infection with strain i. $\mathrm{e}^{-\mu\tau_i}$ is the probability of surviving time period from $t-\tau_i$ to time t, $i=1,2$.

Remark 1 By the definition of $\mathcal{R}_0$ in [24], the basic reproduction number is defined as the expected number of secondary cases generated by a typical infected individual in a fully susceptible population. Since there are no recovered individuals infected with strain 1 in the completely susceptible population, the number of new infections generated by cross immunity will not affect the size of the basic reproduction number.

When $\mathcal{R}_{01} > 1$, model (4) has the strain 1 dominant equilibrium $E_1 = (\bar{S}, \bar{V}, \bar{I}_1, 0, \bar{R}_1)$, where

$$\bar{S} = \frac{(\gamma_1+\mu_1)\mathrm{e}^{\mu\tau_1}}{\beta_1}, \bar{I}_1 = \frac{\beta_1\Lambda \mathrm{e}^{-\mu\tau_1} - (r+\mu)(\gamma_1+\mu_1)}{\beta_1(\gamma_1+\mu_1)} = \frac{\mathcal{R}_{01}-1}{\beta_1(\gamma_1+\mu_1)},$$
$$\bar{V} = \frac{r(\gamma_1+\mu_1)\mathrm{e}^{\mu\tau_1}}{\beta_1\mu}, \bar{R}_1 = \frac{\gamma_1\beta_1\Lambda\mathrm{e}^{-\mu\tau_1} - \gamma_1(r+\mu)(\gamma_1+\mu_1)}{\beta_1\mu(\gamma_1+\mu_1)} = \frac{\gamma_1(\mathcal{R}_{01}-1)}{\beta_1\mu(\gamma_1+\mu_1)}.$$

When $\mathcal{R}_{02} > 1$, model (4) has the strain 2 dominant equilibrium $E_2 = (\tilde{S}, \tilde{V}, 0, \tilde{I}_2, 0)$, where

$$\tilde{S} = \frac{\Lambda}{\beta_2\tilde{I}_2 + r + \mu}, \tilde{V} = \frac{r\Lambda}{(\beta_2\tilde{I}_2 + r+\mu)(\mu + k\tilde{I}_2)},$$

$\tilde{I}_2$ is determined by the following quadratic equation:

$$\begin{aligned}&(\gamma_2+\mu_2)k\beta_2\tilde{I}_2^2 + [(\gamma_2+\mu_2)\Big(\mu\beta_2 + (r+\mu)k\Big) - \beta_2 k\Lambda\mathrm{e}^{-\mu\tau_2}]\tilde{I}_2\\ &+ [(r+\mu)(\gamma_2+\mu_2)\mu - \beta_2\mu\Lambda\mathrm{e}^{-\mu\tau_2} - kr\Lambda\mathrm{e}^{-\mu\tau_2}] = 0.\end{aligned} \tag{6}$$

Denote Eq. (6) as

$$a_2\tilde{I}_2^2 + a_1\tilde{I}_2 + a_0 = 0, \tag{7}$$

where $a_2 > 0$, $a_0 = (r+\mu)(\gamma_2+\mu_2)\mu(1-\mathcal{R}_{02}) < 0$, Eq. (7) has a unique positive root.

Using a similar method as discussed in [25], the following two thresholds are calculated:

$$\mathcal{R}_2^1 = \frac{\beta_2\mathrm{e}^{-\mu\tau_2}\bar{S} + k\mathrm{e}^{-\mu\tau_2}\bar{V} + \beta_2\mathrm{e}^{-\mu\tau_2}\bar{R}_1}{\gamma_2+\mu_2},\ \mathcal{R}_1^2 = \frac{\beta_1\mathrm{e}^{-\mu\tau_1}\tilde{S}}{\gamma_1+\mu_1},$$

where $\mathcal{R}_2^1$, $\mathcal{R}_1^2$ denote the number of invasion reproduction of strain 2 and strain 1, respectively.

There exists the strains 1, 2 coexistent equilibrium $E_c = (S^*, V^*, I_1^*, I_2^*, R_1^*)$ of system (4), where

$$S^* = \frac{(\gamma_1+\mu_1)\mathrm{e}^{\mu\tau_1}}{\beta_1}, I_2^* = \frac{r(\gamma_1+\mu_1)e^{\mu\tau_1} - \mu\beta_1 V^*}{k\beta_1 V^*},$$
$$R_1^* = \frac{\beta_1(\gamma_2+\mu_2)\mathrm{e}^{\mu\tau_2} - \beta_2(\gamma_1+\mu_1)\mathrm{e}^{\mu\tau_1} - \beta_1 kV^*}{\beta_1\beta_2},$$

$$I_1^* = \frac{(k\beta_1^2\Lambda + \mu\beta_1\beta_2(\gamma_1+\mu_1)e^{\mu\tau_1} - k\beta_1(r+\mu)(\gamma_1+\mu_1)e^{\mu\tau_1})V^* - \beta_2 r(\gamma_1+\mu_1)^2 e^{2\mu\tau_1}}{k\beta_1^2(\gamma_1+\mu_1)e^{\mu\tau_1}}.$$

V^* is determined by the following quadratic function:

$$\begin{aligned}&(k-\beta_2)k\mu(\gamma_1+\mu_1)\beta_1^2 e^{\mu\tau_1}(V^*)^2\\&\quad+\Big[k\gamma_1\beta_1^2\beta_2\Lambda + \beta_1\beta_2(\gamma_1+\mu_1)e^{\mu\tau_1}[\gamma_1\mu\beta_2 - k\gamma_1(r+\mu)\\&\quad+kr(\gamma_1+\mu_1)e^{\mu\tau_1}]\\&\quad+(k-\beta_2)\mu\beta_1(\gamma_1+\mu_1)e^{\mu\tau_1}[\beta_2(\gamma_1+\mu_1)e^{\mu\tau_1} - \beta_1(\gamma_2+\mu_2)e^{\mu\tau_2}]\Big]V^*\\&\quad+\beta_2 r(\gamma_1+\mu_1)^2 e^{2\mu\tau_1}[\beta_2(\gamma_1+\mu_1)e^{\mu\tau_1} - \beta_2\gamma_1 - \beta_1(\gamma_2+\mu_2)e^{\mu\tau_2}] = 0.\end{aligned} \tag{8}$$

Denote Eq. (8) as

$$s_2(V^*)^2 + s_1V^* + s_0 = 0, \tag{9}$$

since $k \le \beta_2$, it follows that $s_2 \le 0$. By the Descartes rule of signs [26], when $s_2 < 0$, the root V^* of Eq. (9) can be determined by the following cases:

Case 1. Equation (9) has no positive roots if $(a): s_0 < 0, s_1 < 0, s_2 < 0$ hold.

Case 2. Equation (9) has one root if one of the following cases holds:

$$(b): s_0 > 0, s_1 < 0, s_2 < 0; (c): s_0 > 0, s_1 > 0, s_2 < 0.$$

Case 3. Equation (9) has two or no positive roots if $(d): s_0 < 0, s_1 > 0, s_2 < 0$ hold.

Remark 2 Similar results can be obtained if one of the parameters s_1, s_0 is zero; here we assume that $s_1 \neq 0$, $s_0 \neq 0$.

When $s_2 = 0$, i.e., $\beta_2 = k$, Eq. (9) becomes a primary function, and we have $s_1 > 0$. There are the following two cases.

Case 4. Equation (9) has no positive roots if $(e): s_2 = 0, s_1 > 0, s_0 > 0$ hold.

Case 5. Equation (9) has a unique positive root if $(f): s_2 = 0, s_1 > 0, s_0 < 0$ hold.

Thus, we can conclude the following results and summarize them in Table 1.

Proposition 2.2 (1) *If the assumptions of Case* 1. (a): $s_0 < 0, s_1 < 0, s_2 < 0$ *and Case* 4. (e): $s_2 = 0, s_1 > 0, s_0 > 0$ *hold, Eq.* (9) *has no positive roots.*

(2) *If the assumptions of Case* 2. (b): $s_0 > 0, s_1 < 0, s_2 < 0$; ($c$): $s_0 > 0, s_1 > 0, s_2 < 0$, *and Case* 5. ($f$): $s_2 = 0, s_1 > 0, s_0 < 0$ *hold, Eq.* (9) *has a unique positive root.*

(3) *If the assumptions of Case* 3. (d): $s_0 < 0, s_1 > 0, s_2 < 0$ *hold, Eq.* (9) *has two or no positive roots.*

Remark 3 Proposition 2.2 can only give a sufficient condition for V^* to have positive roots, and the existence of coexistent equilibrium for model (4) requires the following additional condition:

$$r(\gamma_1+\mu_1)e^{\mu\tau_1} - \mu\beta_1V^* > 0,\ \beta_1(\gamma_2+\mu_2)e^{\mu\tau_2} - \beta_2(\gamma_1+\mu_1)e^{\mu\tau_1} - \beta_1kV^* > 0,$$

$$\Big(k\beta_1^2\Lambda + \mu\beta_1\beta_2(\gamma_1+\mu_1)e^{\mu\tau_1} - k\beta_1(r+\mu)(\gamma_1+\mu_1)e^{\mu\tau_1}\Big)V^* - \beta_2r(\gamma_1+\mu_1)^2e^{2\mu\tau_1} > 0.$$

Table 2 The situation of roots under different parameter symbols

Case 1	$s_0 < 0, s_1 < 0, s_2 < 0$	no positive roots
Case 4	$s_0 > 0, s_1 > 0, s_2 = 0$	
Case 2	$s_0 > 0, s_1 < 0, s_2 < 0$	a unique positive root
	$s_0 > 0, s_1 > 0, s_2 < 0$	
Case 5	$s_0 < 0, s_1 > 0, s_2 = 0$	
Case 3	$s_0 < 0, s_1 > 0, s_2 < 0$	two or no positive roots

3 Stability of equilibria

This section focuses on the stability of model (4), the criteria on the local and global asymptotic stability of equilibria E_0, E_1, and E_2 are obtained, and the uniform persistence of (strain 1, 2 coexistent) disease and the existence of strain 1, 2 coexistent equilibrium E_c are obtained.

3.1 Local stability of equilibria

In this subsection, we prove the local asymptotic stability (LAS) of all feasible equilibria, i.e., E_0, E_1, E_2 of model (4).

Theorem 3.1 *If $\mathcal{R}_0 < 1$, then DFE E_0 of model* (4) *is locally asymptotically stable.*

Proof The Jacobi matrix at E_0 is as follows:

$$J(E_0) = \begin{pmatrix} -(r+\mu) & 0 & -\beta_1 S_0 & -\beta_2 S_0 & 0 \\ r & -\mu & 0 & -kV_0 & 0 \\ 0 & 0 & A & 0 & 0 \\ 0 & 0 & 0 & B & 0 \\ 0 & 0 & \gamma_1 & 0 & -\mu \end{pmatrix},$$

where

$$A = \beta_1 \mathrm{e}^{(-\lambda\tau_1 - \mu\tau_1)} S_0 - (\gamma_1 + \mu_1),\ B = (\beta_2 S_0 + kV_0)\mathrm{e}^{(-\lambda\tau_2 - \mu\tau_2)} - (\gamma_2 + \mu_2).$$

The characteristic equation at E_0 can be calculated as

$$(\lambda + \mu)^2 (\lambda + r + \mu)(\lambda - A)(\lambda - B) = 0. \tag{10}$$

The characteristic equation (10) has characteristic roots $\lambda_1 = \lambda_2 = -\mu$, $\lambda_3 = -r - \mu$. The other characteristic roots are determined by $(\lambda - A)(\lambda - B) = 0$, i.e., $\lambda_4 = A$, $\lambda_5 = B$.

When $\tau_1 = 0$, $\tau_2 = 0$, $\mathcal{R}_{01} = \frac{\beta_1 \Lambda}{(r+\mu)(\gamma_1+\mu_1)}$, $\mathcal{R}_{02} = \frac{\beta_2 \mu \Lambda + kr\Lambda}{(r+\mu)(\gamma_2+\mu_2)\mu}$.

$$\lambda_4 = \beta_1 S_0 - (\gamma_1 + \mu_1) = \frac{\beta_1 \Lambda}{(r+\mu)} - (\gamma_1 + \mu_1) = (\gamma_1 + \mu_1)(\mathcal{R}_{01} - 1) < 0,$$

$$\lambda_5 = \beta_2 S_0 + kV_0 - (\gamma_2 + \mu_2) = (\gamma_2 + \mu_2)(\mathcal{R}_{02} - 1) < 0.$$

Thus, if $\tau_1 = 0$, $\tau_2 = 0$, then E_0 is LAS.

When $\tau_1 > 0$, $\tau_2 > 0$, λ_4 satisfies the following equation:

$$\lambda - \beta_1 e^{(-\lambda\tau_1 - \mu\tau_1)} S_0 + (\gamma_1 + \mu_1) = 0.$$

Let $\lambda = x_0 + y_0 i$, assuming $x_0 \geq 0$, we have

$$1 = \frac{e^{-\lambda\tau_1} \frac{\beta_1 \Lambda e^{-\mu\tau_1}}{r+\mu}}{\lambda + (\gamma_1 + \mu_1)} \leq \frac{|e^{-\lambda\tau_1}| \frac{\beta_1 \Lambda e^{-\mu\tau_1}}{r+\mu}}{|\lambda + (\gamma_1 + \mu_1)|} \leq \frac{e^{-x_0\tau_1} \frac{\beta_1 \Lambda e^{-\mu\tau_1}}{r+\mu}}{\gamma_1 + \mu_1} = e^{-x_0\tau_1} \mathcal{R}_{01},$$

since $x_0 \geq 0$, $e^{-x_0\tau_1} \mathcal{R}_{01} < 1$, this is a contradiction; therefore, λ_4 has a negative real part.

The characteristic root of λ_5 satisfies the following equation:

$$\lambda - \beta_2 e^{(-\lambda\tau_2 - \mu\tau_2)} S_0 - k e^{(-\lambda\tau_2 - \mu\tau_2)} V_0 + (\gamma_2 + \mu_2) = 0.$$

Let $\lambda = x_1 + y_1 i$, assuming $x_1 \geq 0$, we have

$$1 = \frac{e^{-\lambda\tau_2} \frac{\beta_2 \Lambda \mu e^{-\mu\tau_2} + kr\Lambda e^{-\mu\tau_2}}{(r+\mu)\mu}}{\lambda + (\gamma_2 + \mu_2)} \leq \frac{|\, e^{-\lambda\tau_2} \,| \frac{\beta_2 \Lambda \mu e^{-\mu\tau_2} + kr\Lambda e^{-\mu\tau_2}}{(r+\mu)\mu}}{|\, \lambda + (\gamma_2 + \mu_2) \,|} \leq e^{-x_1\tau_2} \mathcal{R}_{02},$$

since $x_1 \geq 0$, $e^{-x_1\tau_2} \mathcal{R}_{02} < 1$, this is a contradiction; therefore λ_5 has a negative real part as well. Thus, if $\tau_2 > 0$, $\tau_1 > 0$, then E_0 is LAS.

When $\tau_1 = 0$, $\tau_2 > 0$ and $\tau_1 > 0$, $\tau_2 = 0$, the proofs are the same as in the discussion above, so we omit them here. □

Using a similar method, we prove the LAS of E_1 in the next theorem.

Theorem 3.2 *If* $\mathcal{R}_{01} > 1$, $\mathcal{R}_2^1 < 1$, *then the strain* 1 *dominant equilibrium* E_1 *of model* (4) *is LAS.*

Proof The Jacobi matrix at E_1 is as follows:

$$J(E_1) = \begin{pmatrix} -\beta_1 \bar{I}_1 - (r+\mu) & 0 & -\beta_1 \bar{S} & -\beta_2 \bar{S} & 0 \\ r & -\mu & 0 & -k\bar{V} & 0 \\ \beta_1 e^{(-\lambda\tau_1 - \mu\tau_1)} \bar{I}_1 & 0 & A_1 & 0 & 0 \\ 0 & 0 & 0 & B_1 & 0 \\ 0 & 0 & \gamma_1 & -\beta_2 \bar{R}_1 & -\mu \end{pmatrix},$$

where

$$A_1 = \beta_1 e^{(-\lambda\tau_1 - \mu\tau_1)} \bar{S} - (\gamma_1 + \mu_1), B_1 = (\beta_2 \bar{S} + k\bar{V} + \beta_2 \bar{R}_1) e^{(-\lambda\tau_2 - \mu\tau_2)} - (\gamma_2 + \mu_2).$$

The characteristic equation at E_1 can be calculated as

$$\begin{aligned} &(\lambda + \mu)^2 (\lambda - B_1) \Big[\lambda^2 + \Big(\beta_1 \bar{I}_1 + (r+\mu) - \beta_1 e^{(-\lambda\tau_1 - \mu\tau_1)} \bar{S} + (\gamma_1 + \mu_1) \Big) \lambda \\ &+ (\beta_1 \bar{I}_1 + r + \mu)(\gamma_1 + \mu_1 - \beta_1 e^{(-\lambda\tau_1 - \mu\tau_1)} \bar{S}) + \beta_1^2 e^{(-\lambda\tau_1 - \mu\tau_1)} \bar{S} \bar{I}_1 \Big] = 0. \end{aligned} \tag{11}$$

Obviously, there are two characteristic roots $\lambda_1 = \lambda_2 = -\mu < 0$.

When $\tau_1 = \tau_2 = 0$, we have $\mathcal{R}_2^1 = \frac{\beta_2\bar{S}+k\bar{V}+\beta_2\bar{R}_1}{\gamma_2+\mu_2}$, the other characteristic roots of Eq. (11) satisfy

$$\begin{aligned}
&\lambda_3 = \beta_2\bar{S} + k\bar{V} + \beta_2\bar{R}_1 - (\gamma_2 + \mu_2) = (\gamma_2 + \mu_2)(\mathcal{R}_2^1 - 1) < 0,\\
&\lambda_4 + \lambda_5 = -(\beta_1\bar{I}_1 + (r + \mu) - \beta_1\bar{S} + (\gamma_1 + \mu_1)),\\
&\lambda_4\lambda_5 = (\beta_1\bar{I}_1 + r + \mu)(\gamma_1 + \mu_1 - \beta_1\bar{S}) + \beta_1^2\bar{S}\bar{I}_1.
\end{aligned}$$

Since $\tau_1 = 0$, $\beta_1\bar{S} = (\gamma_1 + \mu_1)$, therefore $\lambda_4 + \lambda_5 < 0$, $\lambda_4\lambda_5 > 0$, according to Veda's theorem, we have $\lambda_4 < 0$, $\lambda_5 < 0$. Thus, if $\tau_1 = 0$, $\tau_2 = 0$, then E_1 is LAS.

When $\tau_1 > 0$, $\tau_2 > 0$, from Eq. (11), we have λ_3 satisfying

$$\lambda - (\beta_2\bar{S} + k\bar{V} + \beta_2\bar{R}_1)e^{(-\lambda\tau_2-\mu\tau_2)} + (\gamma_2 + \mu_2) = 0.$$

Let $\lambda = x_2 + y_2 i$, assuming $x_2 \geq 0$, we have

$$1 = \frac{e^{-\lambda\tau_2}(\beta_2\bar{S} + k\bar{V} + \beta_2\bar{R}_1)e^{-\mu\tau_2}}{\lambda + \gamma_2 + \mu_2} \leq \frac{|\, e^{-\lambda\tau_2}\,|\,(\beta_2\bar{S} + k\bar{V} + \beta_2\bar{R}_1)e^{-\mu\tau_2}}{|\,\lambda + \gamma_2 + \mu_2\,|} \leq e^{-x_2\tau_2}\mathcal{R}_2^1,$$

since $x_2 \geq 0$, $e^{-x_2\tau_2}\mathcal{R}_2^1 < 1$, this is a contradiction, therefore λ_3 has a negative real part.

The rest two characteristic roots of Eq. (11) satisfy

$$\begin{aligned}
&\lambda^2 + \Big(\beta_1\bar{I}_1 + (r + \mu) - \beta_1 e^{(-\lambda\tau_1-\mu\tau_1)}\bar{S} + (\gamma_1 + \mu_1)\Big)\lambda\\
&\quad + (\beta_1\bar{I}_1 + r + \mu)(\gamma_1 + \mu_1 - \beta_1 e^{(-\lambda\tau_1-\mu\tau_1)}\bar{S}) + \beta_1^2 e^{(-\lambda\tau_1-\mu\tau_1)}\bar{S}\bar{I}_1 = 0,
\end{aligned} \tag{12}$$

if $\lambda = i\omega(\omega > 0)$ is a root of Eq. (12), substituting it into Eq. (12) and separating the real and imaginary parts leads to

$$\begin{aligned}
-\omega^2 + \beta_1\bar{I}_1(\gamma_1 + \mu_1) + (r + \mu)(\gamma_1 + \mu_1) &= (\gamma_1 + \mu_1)(\sin\omega\tau_1)\omega + (\gamma_1 + \mu_1)(r + \mu)\cos\omega\tau_1,\\
\Big(\beta_1\bar{I}_1 + (r + \mu) + (\gamma_1 + \mu_1)\Big)\omega i &= (\gamma_1 + \mu_1)(\cos\omega\tau_1)\omega i\\
&\quad - (\gamma_1 + \mu_1)(r + \mu)(\sin\omega\tau_1)i.
\end{aligned}$$

Squaring the above two equations and adding them together, we have

$$\begin{aligned}
&\omega^4 + (\beta_1^2\bar{I}_1^2 + 2(r + \mu)\beta_1\bar{I}_1\\
&\quad + (r + \mu)^2)\omega^2 + \beta_1^2\bar{I}_1^2(\gamma_1 + \mu_1)^2 + 2\beta_1\bar{I}_1(\gamma_1 + \mu_1)(r + \mu) = 0.
\end{aligned} \tag{13}$$

Denoting $\nu = \omega^2$, Eq. (13) is transformed as follows:

$$\begin{aligned}
&\nu^2 + (\beta_1^2\bar{I}_1^2 + 2(r + \mu)\beta_1\bar{I}_1\\
&\quad + (r + \mu)^2)\nu + \beta_1^2\bar{I}_1^2(\gamma_1 + \mu_1)^2 + 2\beta_1\bar{I}_1(\gamma_1 + \mu_1)(r + \mu) = 0.
\end{aligned} \tag{14}$$

Equation (14) has no positive root, so Eq. (12) cannot have any purely imaginary root. By Theorem 4.1 in [27], it can be shown that $\tau_1 > 0$, $\tau_2 > 0$, E_1 is LAS.

When $\tau_1 = 0$, $\tau_2 > 0$ and $\tau_1 > 0$, $\tau_2 = 0$, the proofs are the same as above, so we omit them here. □

Using a similar method as the above theorem, the following theorem proves the LAS of E_2.

Theorem 3.3 *If $\mathcal{R}_{02} > 1$, $\mathcal{R}_1^2 < 1$, the strain 2 dominant equilibrium E_2 of model (4) is LAS.*

Proof The Jacobi matrix at E_2 is as follows:

$$J(E_2) = \begin{pmatrix} -\beta_2\tilde{I}_2 - (r+\mu) & 0 & -\beta_1\tilde{S} & -\beta_2\tilde{S} & 0 \\ r & -k\tilde{I}_2 - \mu & 0 & -k\tilde{V} & 0 \\ 0 & 0 & A_2 & 0 & 0 \\ \beta_2 e^{(-\lambda\tau_2-\mu\tau_2)}\tilde{I}_2 & k e^{(-\lambda\tau_2-\mu\tau_2)}\tilde{I}_2 & 0 & B_2 & \beta_2 e^{(-\lambda\tau_2-\mu\tau_2)}\tilde{I}_2 \\ 0 & 0 & \gamma_1 & 0 & -\beta_2\tilde{I}_2 - \mu \end{pmatrix},$$

where

$$A_2 = \beta_1 e^{(-\lambda\tau_1-\mu\tau_1)}\tilde{S} - (\gamma_1+\mu_1), B_2 = (\beta_2\tilde{S} + k\tilde{V})e^{(-\lambda\tau_2-\mu\tau_2)} - (\gamma_2+\mu_2).$$

The characteristic equation at E_2 can be calculated as follows:

$$\begin{aligned} &(\lambda+\beta_2\tilde{I}_2+\mu)(\lambda-A_2)\Big[\lambda^3 + \Big((\beta_2\tilde{I}_2+r+\mu)+(k\tilde{I}_2+\mu)+(\gamma_2+\mu_2)\Big)\lambda^2 \\ &\quad + \Big((\beta_2\tilde{I}_2+r+\mu)(k\tilde{I}_2+\mu)+(\beta_2\tilde{I}_2+r+\mu)(\gamma_2+\mu_2)+(k\tilde{I}_2+\mu)(\gamma_2+\mu_2)\Big)\lambda \\ &\quad + (\beta_2\tilde{I}_2+r+\mu)(k\tilde{I}_2+\mu)(\gamma_2+\mu_2) \\ &\quad + \Big[-(\gamma_2+\mu_2)\lambda^2 + \Big(-(\beta_2\tilde{I}_2+r+\mu)(\gamma_2+\mu_2) \\ &\quad - (k\tilde{I}_2+\mu)(\gamma_2+\mu_2) + \beta_2^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{S} + k^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{V}\Big)\lambda + \beta_2 kr e^{-\mu\tau_2}\tilde{I}_2\tilde{S} + \beta_2^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{S} \\ &\quad \times (k\tilde{I}_2+\mu) + k^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{V}(\beta_2\tilde{I}_2+r+\mu) \\ &\quad - (\beta_2\tilde{I}_2+r+\mu)(k\tilde{I}_2+\mu)(\gamma_2+\mu_2)\Big]e^{-\lambda\tau_2}\Big] = 0. \end{aligned} \tag{15}$$

Equation (15) has a characteristic root $\lambda_1 = -\beta_2\tilde{I}_2 - \mu < 0$.

When $\tau_1 = \tau_2 = 0$, we have $\mathcal{R}_{02} = \frac{\beta_2\mu\Lambda + kr\Lambda}{(\gamma_2+\mu_2)(r+\mu)\mu}$, $\mathcal{R}_1^2 = \frac{\beta_1\tilde{S}}{\gamma_1+\mu_1}$. The characteristic root λ_2 of Eq. (15) satisfies

$$\lambda_2 = \beta_1\tilde{S} - (\gamma_1+\mu_1) = (\gamma_1+\mu_1)(\mathcal{R}_1^2 - 1) < 0.$$

Substituting $\tau_2 = 0$ and $\beta_2\tilde{S} + k\tilde{V} - (\gamma_2+\mu_2) = 0$ into Eq. (15), the rest of eigenvalues are determined by the following equation:

$$\begin{aligned} &\lambda^3 + \Big[(\beta_2\tilde{I}_2+r+\mu)+(k\tilde{I}_2+\mu)\Big]\lambda^2 + \Big[(\beta_2\tilde{I}_2+r+\mu)(k\tilde{I}_2+\mu)+\beta_2^2\tilde{S}\tilde{I}_2 + k^2\tilde{I}_2\tilde{V}\Big]\lambda \\ &+ \beta_2 kr\tilde{I}_2\tilde{S} + \beta_2^2\tilde{I}_2\tilde{S}(k\tilde{I}_2+\mu) + k^2\tilde{I}_2\tilde{V}(\beta_2\tilde{I}_2+r+\mu) = 0. \end{aligned} \tag{16}$$

Note that Eq. (16) can be denoted as $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$, where

$$\begin{aligned} &a_1 = (\beta_2\tilde{I}_2+r+\mu)+(k\tilde{I}_2+\mu), a_2 = (\beta_2\tilde{I}_2+r+\mu)(k\tilde{I}_2+\mu)+\beta_2^2\tilde{S}\tilde{I}_2 + k^2\tilde{I}_2\tilde{V}, \\ &a_3 = \beta_2 kr\tilde{I}_2\tilde{S} + \beta_2^2\tilde{I}_2\tilde{S}(k\tilde{I}_2+\mu) + k^2\tilde{I}_2\tilde{V}(\beta_2\tilde{I}_2+r+\mu). \end{aligned}$$

The sequential principal subequations are as follows:

$$\Delta_1 = a_1,\ \ \Delta_2 = \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix} = a_1 a_2 - a_3,$$
$$a_1 a_2 - a_3 = \beta_2^2 \Lambda \tilde{I}_2 + k^2 r \tilde{S}\tilde{I}_2 - \beta_2 k r \tilde{S}\tilde{I}_2 + \Big[(\beta_2\tilde{I}_2 + r + \mu) + (k\tilde{I}_2 + \mu)\Big](\beta_2\tilde{I}_2 + r + \mu).$$

Since $\beta_2 \geq k$, it can be obtained that

$$\beta_2^2 \Lambda \tilde{I}_2 - \beta_2 k r \tilde{S}\tilde{I}_2 \geq \beta_2 k \tilde{I}_2 (\Lambda - r\tilde{S}) > 0.$$

Therefore, $\Delta_1 > 0$, $\Delta_2 > 0$. By the Hurwitz criterion, λ_3, λ_4, λ_5 all have negative real parts. Therefore, if $\tau_1 = 0$, $\tau_2 = 0$, then E_2 is LAS.

When $\tau_1 > 0$, $\tau_2 > 0$, from Eq. (15), we have λ_2 satisfying

$$\lambda - \beta_1 \tilde{S} e^{(-\lambda\tau_1 - \mu\tau_1)} + (\gamma_1 + \mu_1) = 0.$$

Let $\lambda = x_3 + y_3 i$, if $x_3 \geq 0$, we have

$$1 = \frac{e^{-\lambda\tau_1}\beta_1\tilde{S}e^{-\mu\tau_1}}{\lambda + \gamma_1 + \mu_1} \leq \frac{|\ e^{-\lambda\tau_1}\ |\ \beta_1\tilde{S}e^{-\mu\tau_1}}{|\ \lambda + \gamma_1 + \mu_1\ |} \leq e^{-x_3\tau_2}\mathcal{R}_1^2,$$

since $x_3 \geq 0$, $e^{-x_3\tau_1}\mathcal{R}_1^2 < 1$, this is a contradiction; therefore λ_2 has a negative real part. The remaining three roots of (15) satisfy

$$\begin{aligned}
&\Big[\lambda^3 + \Big((\beta_2\tilde{I}_2 + r + \mu) + (k\tilde{I}_2 + \mu) + (\gamma_2 + \mu_2)\Big)\lambda^2 + \Big((\beta_2\tilde{I}_2 + r + \mu)(k\tilde{I}_2 + \mu) \\
&+ (\beta_2\tilde{I}_2 + r + \mu)(\gamma_2 + \mu_2) + (k\tilde{I}_2 + \mu)(\gamma_2 + \mu_2)\Big)\lambda + (\beta_2\tilde{I}_2 + r + \mu)(k\tilde{I}_2 + \mu) \\
&\times (\gamma_2 + \mu_2)\Big] + \Big[-(\gamma_2 + \mu_2)\lambda^2 + \Big(-(\beta_2\tilde{I}_2 + r + \mu)(\gamma_2 + \mu_2) - (k\tilde{I}_2 + \mu)(\gamma_2 + \mu_2) \\
&+ \beta_2^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{S} + k^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{V}\Big)\lambda + \beta_2 k r e^{-\mu\tau_2}\tilde{I}_2\tilde{S} + \beta_2^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{S}(k\tilde{I}_2 + \mu) \\
&+ k^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{V}(\beta_2\tilde{I}_2 + r + \mu) - (\beta_2\tilde{I}_2 + r + \mu)(k\tilde{I}_2 + \mu)(\gamma_2 + \mu_2)\Big]e^{-\lambda\tau_2} = 0.
\end{aligned} \tag{17}$$

Assume that $\lambda = i\omega(\omega > 0)$ is a root of Eq. (17); substituting it into Eq. (17) and separating the real and imaginary parts gives

$$\begin{aligned}
&\Big[(\beta_2\tilde{I}_2 + r + \mu)(k\tilde{I}_2 + \mu) + (\beta_2\tilde{I}_2 + r + \mu)(\gamma_2 + \mu_2) + (\beta_2\tilde{I}_2 + r + \mu)(\gamma_2 + \mu_2)\Big]\omega i - \omega^3 i \\
&\quad = \Big[(\gamma_2 + \mu_2)\omega^2 + \beta_2 k r e^{-\mu\tau_2}\tilde{I}_2\tilde{S} \\
&\qquad + \beta_2^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{S}(k\tilde{I}_2 + \mu) + k^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{V}(\beta_2\tilde{I}_2 + r + \mu) \\
&\qquad - (\beta_2\tilde{I}_2 + r + \mu)(k\tilde{I}_2 + \mu)(\gamma_2 + \mu_2)\Big](\sin\tau_2\omega)i + \Big[(\beta_2\tilde{I}_2 + r + \mu)(\gamma_2 + \mu_2) \\
&\qquad + (k\tilde{I}_2 + \mu)(\gamma_2 + \mu_2) - \beta_2^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{S} - k^2 e^{-\mu\tau_2}\tilde{I}_2\tilde{V}\Big](\cos\tau_2\omega)\omega i,
\end{aligned} \tag{18}$$

$$\begin{aligned}&\Big[(\beta_2\tilde{I}_2+r+\mu)+(k\tilde{I}_2+\mu)+(\gamma_2+\mu_2)\Big]\omega^2-(\beta_2\tilde{I}_2+r+\mu)(k\tilde{I}_2+\mu)(\gamma_2+\mu_2)\\&=\Big[(\gamma_2+\mu_2)\omega^2+\beta_2kr\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}+\beta_2^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}(k\tilde{I}_2+\mu)+k^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{V}(\beta_2\tilde{I}_2+r+\mu)\\&\quad-(\beta_2\tilde{I}_2+r+\mu)(k\tilde{I}_2+\mu)(\gamma_2+\mu_2)\Big](\cos\tau_2\omega)-\Big[(\beta_2\tilde{I}_2+r+\mu)(\gamma_2+\mu_2)\\&\quad+(k\tilde{I}_2+\mu)(\gamma_2+\mu_2)-\beta_2^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}-k^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{V}\Big](\sin\tau_2\omega)\omega.\end{aligned}\tag{19}$$

Squaring and adding both sides of Eq. (18) and Eq. (19), we have

$$\begin{aligned}&\omega^6+\Big[(\beta_2\tilde{I}_2+r+\mu)^2+(k\tilde{I}_2+\mu)^2\Big]\omega^4+\Big[((\beta_2\tilde{I}_2+r+\mu)(k\tilde{I}_2+\mu))^2-2\beta_2kr\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}\\&\times(\gamma_2+\mu_2)-(\beta_2^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S})^2-(k^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{V})^2+2k^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{V}(k\tilde{I}_2+\mu)(\gamma_2+\mu_2)\\&+2\beta_2^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}(\beta_2\tilde{I}_2+r+\mu)(\gamma_2+\mu_2)-2\beta_2^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}k^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{V}\Big]\omega^2\\&+\Big[2(\beta_2\tilde{I}_2+r+\mu)\\&\times(k\tilde{I}_2+\mu)(\gamma_2+\mu_2)-\beta_2kr\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}-\beta_2^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}(k\tilde{I}_2+\mu)\\&-k^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{V}(\beta_2\tilde{I}_2+r+\mu)\Big]\\&\times\Big[\beta_2kr\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}+\beta_2^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}(k\tilde{I}_2+\mu)+k^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{V}(\beta_2\tilde{I}_2+r+\mu)\Big]=0.\end{aligned}\tag{20}$$

Denote Eq. (20) as

$$\omega^6+b_1\omega^4+b_2\omega^2+b_3=0,\tag{21}$$

since $(\gamma_2+\mu_2)=\beta_2\mathrm{e}^{-\mu\tau_2}\tilde{S}+k\mathrm{e}^{-\mu\tau_2}\tilde{V}$, substituting it into b_2, b_3, we have

$$\begin{aligned}&(\beta_2\tilde{I}_2+r+\mu)(k\tilde{I}_2+\mu)(\beta_2\mathrm{e}^{-\mu\tau_2}\tilde{S}+k\mathrm{e}^{-\mu\tau_2}\tilde{V})-\beta_2kr\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}-\beta_2^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}(k\tilde{I}_2+\mu)\\&-k^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{V}(\beta_2\tilde{I}_2+r+\mu)=\beta_2k\mu\mathrm{e}^{-\mu\tau_2}\tilde{I}_2(\tilde{S}+\tilde{V})+(\beta_2\mu\mathrm{e}^{-\mu\tau_2}\tilde{S}+k\mu\mathrm{e}^{-\mu\tau_2}\tilde{V})(r+\mu),\end{aligned}$$

therefore $b_3>0$.

Due to

$$\begin{aligned}&2k^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{V}(k\tilde{I}_2+\mu)(\beta_2\mathrm{e}^{-\mu\tau_2}\tilde{S}+k\mathrm{e}^{-\mu\tau_2}\tilde{V})-2(k^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{V})^2>0,\\&2\beta_2^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}(\beta_2\tilde{I}_2+r+\mu)(\gamma_2+\mu_2)-2\beta_2kr\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S}(\gamma_2+\mu_2)-2(\beta_2^2\mathrm{e}^{-\mu\tau_2}\tilde{I}_2\tilde{S})^2>0,\end{aligned}$$

therefore $b_2>0$.

Let $p=\omega^2$, Eq. (21) is transformed as follows:

$$g(p)=p^3+b_1p^2+b_2p+b_3=0.\tag{22}$$

We further have

$$\dot{g}(p)=3p^2+2b_1p+b_2,$$

when $p \geq 0$, we have $\dot{g}(p) > 0$, $g(p)$ is monotonically increasing on $[0,+\infty)$, and $g(0) = b_3 > 0$.

Since Eq. (22) has no positive root, Eq. (17) cannot have any purely imaginary root. By Theorem 4.1 in [27], it can be seen that $\tau_1 > 0$, $\tau_2 > 0$, E_2 is LAS.

When $\tau_1 = 0$, $\tau_2 > 0$ and $\tau_1 > 0$, $\tau_2 = 0$, the proofs are the same as above, we omit them here. □

Remark 4 Since the existence of strains 1, 2 coexistent equilibrium E_c of model (4) is too complicated to obtain directly, we will deal with it by the uniform persistence of the strains 1, 2 coexistence through Theorem 3.7 and demonstrate its stability through numerical simulations.

3.2 Global stability of equilibria

Theorem 3.4 *If* $\mathcal{R}_0 < 1$, *then DFE* E_0 *of model* (4) *is globally asymptotically stable* (*GAS*).

Proof Construct the Lyapunov functional $U_0(t)$ as follows:

$$U_0(t) = I_1(t)e^{\mu\tau_1} + \beta_1 \int_{t-\tau_1}^{t} I_1(v)S(v)\,dv.$$

Deriving $U_0(t)$ along any positive solution of model (4), we have

$$\begin{aligned}\dot{U}_0(t) &= \beta_1 I_1(t-\tau_1)S(t-\tau_1) - (\gamma_1+\mu_1)e^{\mu\tau_1}I_1(t) + \beta_1 S(t)I_1(t) - \beta_1 I_1(t-\tau_1)S(t-\tau_1)\\ &\leq (\beta_1 S_0 - (\gamma_1+\mu_1)e^{\mu\tau_1})I_1(t)\\ &\leq (\gamma_1+\mu_1)e^{\mu\tau_1}(\mathcal{R}_{01}-1)I_1(t) \leq 0,\end{aligned}$$

$\dot{U}_0(t) = 0$ if and only if $I_1 = 0$, by applying LaSalle's invariance principle [28], all solutions of model (4) converge to $I_1 = 0$ as $t \to \infty$, i.e., $\lim_{t\to\infty} I_1 = 0$.

When $I_1 \to 0$, for sufficiently small constant $\varepsilon_1 > 0$, there exists constant $t_1 > 0$, for all $t > t_1$, such that $\gamma_1 I_1(t) < \varepsilon_1$. Thus

$$\dot{R}_1(t) = \gamma_1 I_1(t) - \beta_2 I_2(t)R_1(t) - \mu R_1(t) \leq \varepsilon_1 - \mu R_1(t).$$

Therefore, $\limsup_{t\to\infty} R_1(t) \leq \frac{\varepsilon_1}{\mu}$, when $\varepsilon_1 \to 0$, there is $\limsup_{t\to\infty} R_1(t) \leq 0$. Since R_1 is nonnegative, there is $\lim_{t\to\infty} R_1(t) = 0$.

Since $\lim_{t\to\infty} I_1(t) = 0$, $\lim_{t\to\infty} R_1(t) = 0$, the three-dimensional limit system is as follows:

$$\begin{cases}\dot{S}(t) = \Lambda - \beta_2 I_2(t)S(t) - rS(t) - \mu S(t),\\ \dot{V}(t) = rS(t) - kI_2(t)V(t) - \mu V(t),\\ \dot{I}_2(t) = (\beta_2 e^{-\mu\tau_2}S(t-\tau_2) + ke^{-\mu\tau_2}V(t-\tau_2))I_2(t-\tau_2) - (\gamma_2+\mu_2)I_2(t).\end{cases} \tag{23}$$

According to the limit system theory in [29], model (4) has the same dynamic behavior as model (23). Let $h(z) = z - \ln z - 1$ and construct the Lyapunov functional $U_1(t)$ as follows:

$$U_1(t) = S_0 h(\frac{S}{S_0}) + V_0 h(\frac{V}{V_0}) + e^{\mu\tau_2}I_2(t) + \beta_2 \int_{t-\tau_2}^{t} I_2(x)S(x)\,dx + k\int_{t-\tau_2}^{t} I_2(x)V(x)\,dx.$$

Deriving $U_1(t)$ along any positive solution of model (23), there are

$$\begin{aligned}
\dot{U}_1(t) =&\Big(1-\frac{S_0}{S(t)}\Big)\dot{S}(t)+\Big(1-\frac{V_0}{V(t)}\Big)\dot{V}(t)+\mathrm{e}^{\mu\tau_2}\dot{I}_2(t)+\beta_2[S(t)I_2(t)-I_2(t-\tau_2)S(t-\tau_2)]\\
&+k[S(t)I_2(t)-I_2(t-\tau_2)S(t-\tau_2)]\\
=&\Big(1-\frac{S_0}{S(t)}\Big)(\Lambda-(r+\mu)S(t))+\Big(1-\frac{V_0}{V(t)}\Big)(rS(t)-\mu V(t))+\beta_2 I_2(t)S_0+kI_2(t)V_0\\
&-\mathrm{e}^{\mu\tau_2}(\gamma_2+\mu_2)I_2(t)\\
=&\mu S_0\Big(2-\frac{S_0}{S(t)}-\frac{S(t)}{S_0}\Big)+rS_0\Big(3-\frac{S_0}{S(t)}-\frac{V(t)}{V_0}-\frac{V_0S(t)}{V(t)S_0}\Big)+(\beta_2S_0+kV_0\\
&-\mathrm{e}^{\mu\tau_2}(\gamma_2+\mu_2))I_2(t).
\end{aligned}$$

Since $\mathcal{R}_0=\max\{\mathcal{R}_{01},\mathcal{R}_{02}\}<1$, we further have

$$\begin{aligned}
&2-\frac{S_0}{S(t)}-\frac{S(t)}{S_0}\le 0,\ 3-\frac{S_0}{S(t)}-\frac{V(t)}{V_0}-\frac{V_0S(t)}{V(t)S_0}\le 0,\\
&\beta_2S_0+kV_0-\mathrm{e}^{\mu\tau_2}(\gamma_2+\mu_2)I_2(t)=\mathrm{e}^{\mu\tau_2}(\gamma_2+\mu_2)(\mathcal{R}_{02}-1)<0.
\end{aligned}$$

Therefore, $\dot{U}_1(t)\le 0$, $\dot{U}_1(t)=0$ if and only if $S(t)=S_0$, $V(t)=V_0$, $I_2=0$. The maximal invariant set is $\{(S,V,0,I_2,0)\in\mathbf{C}_5^+|S(t)=S_0,V(t)=V_0,I_2(t)=0\}$. By LaSalle's invariance principle [28], which implies that $S\to S_0$, $V\to V_0$, $I_2\to 0$ as $t\to\infty$, all solutions of model (4) converge to E_0, therefore E_0 is GAS. □

Theorem 3.5 *If* $\mathcal{R}_{01}>1$, $\mathcal{R}_2^1<1$, $\frac{\beta_2(\Lambda+\gamma_1\tau_1\Lambda)}{\mu(\gamma_2+\mu_2)\mathrm{e}^{\mu\tau_2}}<1$, *the strain* 1 *dominant equilibrium* E_1 *of model* (4) *is GAS.*

Proof Consider the Lyapunov functional $U_2(t)$ as follows:

$$U_2(t)=\mathrm{e}^{\mu\tau_2}I_2(t)+\beta_2\int_{t-\tau_2}^{t}I_2(v)S(v)\,\mathrm{d}v+k\int_{t-\tau_2}^{t}I_2(v)V(v)\,\mathrm{d}v+\beta_2\int_{t-\tau_2}^{t}I_2(v)R_1(v)\,\mathrm{d}v.$$

Deriving $U_2(t)$ along any positive solution of model (4), we have

$$\begin{aligned}
\dot{U}_2(t)&=\beta_2I_2(t)S(t)+kI_2(t)V(t)+\beta_2I_2(t)R_1(t)-\mathrm{e}^{\mu\tau_2}(\gamma_2+\mu_2)I_2(t)\\
&\le\beta_2(S(t)+V(t)+R_1(t))I_2(t)-\mathrm{e}^{\mu\tau_2}(\gamma_2+\mu_2)I_2(t)\\
&\le\beta_2\frac{\Lambda+\gamma_1\tau_1\Lambda}{\mu}I_2(t)-\mathrm{e}^{\mu\tau_2}(\gamma_2+\mu_2)I_2(t)\\
&=\mathrm{e}^{\mu\tau_2}(\gamma_2+\mu_2)I_2(t)\Big(\frac{\beta_2(\Lambda+\gamma_1\tau_1\Lambda)}{\mu(\gamma_2+\mu_2)\mathrm{e}^{\mu\tau_2}}-1\Big)\le 0,
\end{aligned}$$

$\dot{U}_2(t)=0$ if and only if $I_2=0$. According to LaSalle's invariant principle [28], all solutions of model (4) converge to $I_2=0$ as $t\to\infty$, i.e., $\lim_{t\to\infty}I_2=0$.

Since $\lim_{t\to\infty} I_2(t) = 0$, the four-dimensional limiting system of model (4) can be obtained as follows:

$$\begin{cases} \dot{S}(t) = \Lambda - \beta_1 S(t)I_1(t) - rS(t) - \mu S(t), \\ \dot{V}(t) = rS(t) - \mu V(t), \\ \dot{I}_1(t) = \beta_1 \mathrm{e}^{-\mu\tau_1} S(t-\tau_1)I_1(t-\tau_1) - \gamma_1 I_1(t) - \mu_1 I_1(t), \\ \dot{R}_1(t) = \gamma_1 I_1(t) - \mu R_1(t). \end{cases} \tag{24}$$

According to the limit system theory in [29], model (4) has the same dynamic behavior as model (24). Since $R_1(t)$ does not affect the model dynamics, only the behavior of the first three equations of the four-dimensional system is considered.

Using a similar method, constructing the Lyapunov functional $U_3(t)$, and deriving it along with any positive solution of model (24), we have

$$U_3(t) = \bar{S}h\Big(\frac{S}{\bar{S}}\Big) + \bar{V}h\Big(\frac{V}{\bar{V}}\Big) + \mathrm{e}^{\mu\tau_1}\bar{I}_1 h\Big(\frac{I_1}{\bar{I}_1}\Big) + \beta_1\bar{I}_1\bar{S}\int_{t-\tau_1}^{t} h\Big(\frac{I_1(x)S(x)}{\bar{I}_1\bar{S}}\Big)\,\mathrm{d}x.$$

$$\begin{aligned} \dot{U}_3(t) = {} & \Big(1 - \frac{\bar{S}}{S(t)}\Big)(\Lambda - \beta_1 I_1(t)S(t) - (r+\mu)S(t)) \\ & + \Big(1 - \frac{\bar{V}}{V(t)}\Big)(rS(t) - \mu V(t)) + (\gamma_1 + \mu_1)\mathrm{e}^{\mu\tau_1} \\ & \times (\bar{I}_1 - I_1(t)) - \frac{\beta_1 I_1(t-\tau_1)S(t-\tau_1)\bar{I}_1}{I_1(t)} \\ & + \beta_1 S(t)I_1(t) - \beta_1\bar{S}\bar{I}_1 \ln\frac{S(t)I_1(t)}{S(t-\tau_1)I_1(t-\tau_1)} \\ = {} & \mu\bar{S}\Big(2 - \frac{\bar{S}}{S(t)} - \frac{S(t)}{\bar{S}}\Big) + r\bar{S}\Big(3 - \frac{V(t)}{\bar{V}} - \frac{\bar{S}}{S(t)} - \frac{S(t)\bar{V}}{\bar{S}V(t)}\Big) \\ & + [\beta_1\bar{S} - (\gamma_1 + \mu)\mathrm{e}^{\mu\tau_1}]I_1(t) \\ & + \beta_1\bar{S}\bar{I}_1\Big(2 - \frac{S(t-\tau_1)I_1(t-\tau_1)}{\bar{S}I(t)} - \frac{\bar{S}}{S(t)} - \ln\frac{S(t)I_1(t)}{S(t-\tau_1)I_1(t-\tau_1)}\Big). \end{aligned}$$

Since

$$\begin{aligned} & 3 - \frac{V(t)}{\bar{V}} - \frac{\bar{S}}{S(t)} - \frac{S(t)\bar{V}}{\bar{S}V(t)} \le 0,\ 2 - \frac{\bar{S}}{S(t)} - \frac{S(t)}{\bar{S}} \le 0,\ \beta_1\bar{S} - (\gamma_1 + \mu_1)\mathrm{e}^{\mu\tau_1} = 0, \\ & 2 - \frac{S(t-\tau_1)I_1(t-\tau_1)}{\bar{S}I(t)} - \frac{\bar{S}}{S(t)} - \ln\frac{S(t)I_1(t)}{S(t-\tau_1)I_1(t-\tau_1)} \\ & \quad = -h\Big(\frac{\bar{S}}{S(t)}\Big) - h\Big(\frac{I_1(t-\tau_1)S(t-\tau_1)}{I(t)\bar{S}}\Big) \le 0, \end{aligned}$$

therefore, $\dot{U}_3(t) \le 0$. $\dot{U}_3(t) = 0$ if and only if $S(t) = \bar{S}$, $V(t) = \bar{V}$, $I_1(t) = \bar{I}_1$. Thus, the maximal invariant set is $\{(S, V, I_1, 0, R_1) \in \mathbf{C}_5^+ | S(t) = \bar{S}, V(t) = \bar{V}, I_1(t) = \bar{I}_1\}$. According to LaSalle's invariance principle [28],

$$\lim_{t\to\infty} S(t) = \bar{S},\ \lim_{t\to\infty} V(t) = \bar{V},\ \lim_{t\to\infty} I_1(t) = \bar{I}_1.$$

$$\dot{R}_1(t) = \gamma_1 I_1(t) - \mu R_1(t), \lim_{t\to\infty} R_1(t) = \frac{\gamma \bar{I}_1}{\mu} = \bar{R}_1.$$

all solutions of model (4) converge to E_1, E_1 is GAS. □

Theorem 3.6 *If* $\mathcal{R}_{02} > 1, \mathcal{R}_1^2 < 1, \mathcal{R}_{01} < 1$, *the strain* 2 *dominant equilibrium* E_2 *of model* (4) *is GAS.*

Proof Since $\mathcal{R}_{01} < 1$, referring to Theorem 3.4, we easily obtain $\lim_{t\to\infty} I_1(t) = 0$, $\lim_{t\to\infty} R_1(t) = 0$, which yields the three-dimensional limit system (23). Construct the Lyapunov functional $U_4(t)$ as follows:

$$\begin{aligned} U_4(t) =& \tilde{S}h\Big(\frac{S}{\tilde{S}}\Big) + \tilde{V}h\Big(\frac{V}{\tilde{V}}\Big) + \mathrm{e}^{\mu\tau_2}\tilde{I}_2 h\Big(\frac{I_2}{\tilde{I}_2}\Big) + \beta_2\tilde{I}_2\tilde{S}\int_{t-\tau_2}^{t} h\Big(\frac{I_1(x)S(x)}{\tilde{I}_1\tilde{S}}\Big)\,\mathrm{d}x \\ &+ \beta_2\tilde{I}_2\tilde{V}\int_{t-\tau_2}^{t} h\Big(\frac{I_2(x)V(x)}{\tilde{I}_2\tilde{V}}\Big)\,\mathrm{d}x. \end{aligned}$$

Derivative of $\dot{U}_4(t)$ along any positive solution of model (4) gives

$$\begin{aligned} \dot{U}_4(t) =& \Big(1 - \frac{\tilde{S}}{S(t)}\Big)(\Lambda - [\beta_2 I_2(t) + (r+\mu)]S(t)) \\ &+ \Big(1 - \frac{\tilde{V}}{V(t)}\Big)(rS(t) - kI_2(t)V(t) - \mu V(t)) \\ &+ \Big(1 - \frac{\tilde{I}_2}{I_2(t)}\Big)[(\beta_2 S(t-\tau_2) + kV(t-\tau_2))\mathrm{e}^{-\mu\tau_2} I_2(t-\tau_2) - \gamma_2 I_2(t) - \mu_2 I_2(t)] \\ &+ \Big(\beta_2 S(t)I_2(t) - \beta_2 S(t-\tau_2)I_2(t-\tau_2) - \beta_2\tilde{I}_2\tilde{S}\ln\frac{S(t)I_2(t)}{S(t-\tau_2)I_2(t-\tau_2)}\Big) \\ &+ \Big(kV(t)I_2(t) - kV(t-\tau_2)I_2(t-\tau_2) - k\tilde{I}_2\tilde{V}\ln\frac{V(t)I_2(t)}{V(t-\tau_2)I_2(t-\tau_2)}\Big) \\ =& \Big(1 - \frac{\tilde{S}}{S(t)}\Big)(\beta_2\tilde{I}_2\tilde{S} + (r+\mu)(\tilde{S} - S(t))) + \beta_2 I_2(t)\tilde{S} \\ &+ \Big(1 - \frac{\tilde{V}}{V(t)}\Big)\Big(rS(t) + k\tilde{I}_2(t)V(t) \\ &- \frac{r\tilde{S}V(t)}{\tilde{V}}\Big) + kI_2(t)\tilde{V} - \frac{\beta_2 S(t-\tau_2)I_2(t-\tau_2)\tilde{I}_2}{I_2(t)} - \frac{kV(t-\tau_2)I_2(t-\tau_2)\tilde{I}_2}{I_2(t)} \\ &- (\gamma_2 + \mu_2) \\ &\times \mathrm{e}^{\mu\tau_2} I_2(t) + \beta_2\tilde{I}_2\tilde{S} + k\tilde{I}_2\tilde{V} \\ &- \beta_2\tilde{I}_2\tilde{S}\ln\frac{S(t)I_2(t)}{S(t-\tau_2)I_2(t-\tau_2)} - k\tilde{I}_2\tilde{V}\ln\frac{V(t)I_2(t)}{V(t-\tau_2)I_2(t-\tau_2)} \\ =& r\tilde{S}\Big(3 - \frac{\tilde{S}}{S(t)} - \frac{V(t)}{\tilde{V}} - \frac{\tilde{V}S(t)}{\tilde{S}V(t)}\Big) + \mu\tilde{S}\Big(2 - \frac{\tilde{S}}{S(t)} - \frac{S(t)}{\tilde{S}}\Big) \\ &+ (\beta_2\tilde{S} + k\tilde{V} - (\gamma_2 + \mu_2)\mathrm{e}^{\mu\tau_2}) \\ &\times I_2(t) + \beta_2\tilde{I}_2\tilde{S}\Big(2 - \frac{\tilde{S}}{S(t)} - \frac{S(t-\tau_2)I_2(t-\tau_2)}{I_2(t)\tilde{S}} - \ln\frac{S(t)I_2(t)}{S(t-\tau_2)I_2(t-\tau_2)}\Big) \end{aligned}$$

Table 3 The existence and stability of the various types of equilibria

Equilibrium	Existence	LAS	GAS
E_0	always exist	$\mathcal{R}_0 < 1$	$\mathcal{R}_0 < 1$
E_1	$\mathcal{R}_{01} > 1$	$\mathcal{R}_{01} > 1, \mathcal{R}_2^1 < 1$	$\mathcal{R}_{01} > 1, \mathcal{R}_2^1 < 1, \frac{\beta_2(\Lambda+\gamma_1\tau_1\Lambda)}{\mu(\gamma_2+\mu_2)e^{\mu\tau_2}} < 1$
E_2	$\mathcal{R}_{02} > 1$	$\mathcal{R}_{02} > 1, \mathcal{R}_1^2 < 1$	$\mathcal{R}_{02} > 1, \mathcal{R}_1^2 < 1, \mathcal{R}_{01} < 1$
E_c	see Table 2	–	–

$$+ k\tilde{I}_2\tilde{V}\Big(\frac{V(t)}{\tilde{V}} - \frac{V(t-\tau_2)I_2(t-\tau_2)}{I_2(t)\tilde{V}} - \ln\frac{V(t)I_2(t)}{V(t-\tau_2)I_2(t-\tau_2)}\Big).$$

Note that $r\tilde{S} = k\tilde{I}_2\tilde{V} + \mu\tilde{V}$, we have

$$r\tilde{S}\Big(3 - \frac{\tilde{S}}{S(t)} - \frac{V(t)}{\tilde{V}} - \frac{\tilde{V}S(t)}{\tilde{S}V(t)}\Big) = (k\tilde{I}_2\tilde{V} + \mu\tilde{V})\Big(3 - \frac{\tilde{S}}{S(t)} - \frac{V(t)}{\tilde{V}} - \frac{\tilde{V}S(t)}{\tilde{S}V(t)}\Big).$$

Since

$$3 - \frac{\tilde{S}}{S(t)} - \frac{V(t)}{\tilde{V}} - \frac{S(t)\tilde{V}}{\tilde{S}V(t)} \le 0,\ 2 - \frac{S(t)}{\tilde{S}} - \frac{\tilde{S}}{S(t)} \le 0,\ \beta_2\tilde{S} + k\tilde{V} - (\gamma_2+\mu_2)e^{\mu\tau_2} = 0,$$

$$\begin{aligned}
&2 - \frac{\tilde{S}}{S(t)} - \frac{S(t-\tau_2)I_2(t-\tau_2)}{I_2(t)\tilde{S}} - \ln\frac{S(t)I_2(t)}{S(t-\tau_2)I_2(t-\tau_2)} \\
&= -h\Big(\frac{\tilde{S}}{S(t)}\Big) - h\Big(\frac{S(t-\tau_2)I_2(t-\tau_2)}{I_2(t)\tilde{S}}\Big), \\
&\Big(3 - \frac{\tilde{S}}{S(t)} - \frac{V(t)}{\tilde{V}} - \frac{\tilde{V}S(t)}{\tilde{S}V(t)}\Big) + \Big(\frac{V(t)}{\tilde{V}} - \frac{V(t-\tau_2)I_2(t-\tau_2)}{I_2(t)\tilde{V}} - \ln\frac{V(t)I_2(t)}{V(t-\tau_2)I_2(t-\tau_2)}\Big) \\
&= -h\Big(\frac{\tilde{V}S(t)}{\tilde{S}V(t)}\Big) - h\Big(\frac{\tilde{S}}{S(t)}\Big) - h\Big(\frac{V(t-\tau_2)I_2(t-\tau_2)}{I_2(t)\tilde{V}}\Big) \le 0,
\end{aligned}$$

therefore $\dot{U}_4(t) \le 0$ and $\dot{U}_4(t) = 0$ if and only if $S(t) = \tilde{S}, V(t) = \tilde{V}, I_2(t) = \tilde{I}_2$. Thus, the maximal invariant set is $\{(S, V, 0, I_2, 0) \in \mathbf{C}_5^+ | S(t) = \tilde{S}, V(t) = \tilde{V}, I_2(t) = \tilde{I}_2\}$. According to LaSalle's invariance principle [28], all solutions of system (4) converge to E_2, and E_2 is GAS. □

Based on the above theorem, we summarize the existence and stability of the various types of equilibria discussed in Table 3.

Remark 5 We do not derive the GAS of the strains 1, 2 coexistent equilibrium E_c of model (4), which is an interesting open question for the future. From numerical simulation, we will demonstrate the strains 1, 2 coexistent equilibrium E_c dynamic behavior (see Fig. 4a, 4b).

3.3 Uniform persistence

Theorem 3.7 *If* $\mathcal{R}_1^2 > 1$, $\mathcal{R}_0 > 1$, *and* $\mathcal{R}_2^1 > 1$, *model* (4) *is uniformly persistent, i.e., there exists constant* $\epsilon > 0$ *such that for all solutions of model* (4) *satisfying*

$$\liminf_{t\to\infty} S(t) > \epsilon,\ \liminf_{t\to\infty} V(t) > \epsilon,\ \liminf_{t\to\infty} I_i(t) > \epsilon,\ \liminf_{t\to\infty} R_1(t) > \epsilon,\ i = 1, 2,$$

for initial conditions $\phi = (S(\theta), V(\theta), I_1(\theta), I_2(\theta), R_1(\theta)) \in \Gamma$, *where* $I_1(0) + I_2(0) > 0$, *and model* (4) *has at least one coexistent equilibrium* $E_c = (S^*, V^*, I_1^*, I_2^*, R_1^*)$.

Proof Define

$$X_0 = \{(S,V,I_1,I_2,R_1) \in X : I_2 > 0, I_1 > 0\},$$

$$\partial X_0 = X \backslash X_0 = \{(S,V,I_1,I_2,R_1) \in X : I_2 = 0 \text{ } or \text{ } I_1 = 0\},$$

$$M_\partial = \{x_0 \in \partial X_0 : \phi_t(x_0) \in \partial X_0, \forall t \geq 0\}, M_0 = \{E_0, E_1, E_2\},$$

$$Q_1 = \{x_0 \in X : I_1 = 0\}, Q_2 = \{x_0 \in X : I_2 = 0\}.$$

First, we prove that $M_\partial = Q_1 \bigcup Q_2$, i.e., if $x_0 \in M_\partial$, then $x(t) \in Q_1$ or $x(t) \in Q_2$. Assume that there exists a constant $t_1 > 0$ such that $I_2(t_1) > 0$ and $I_1(t_1) > 0$. Notice that

$$\begin{cases} \dot{I}_1(t) \geq -(\gamma_1 + \mu_1) I_1, \\ \dot{I}_2(t) \geq -(\gamma_2 + \mu_2) I_2. \end{cases} \tag{25}$$

So, if there is a constant $t_1 > 0$ such that $I_2(t_1) > 0$, $I_1(t_1) > 0$, then we can obtain $I_2(t) > 0$, $I_1(t) > 0$ for any $t > t_1$. Therefore $(I_1(t), I_2(t)) \notin \partial X_0$, this is a contradiction. So, $M_\partial = Q_1 \bigcup Q_2$. $M_0 = \{E_0, E_1, E_2\}$ is isolated and acyclic. According to Theorem 4.6 in [30], we just need to prove that

$$X_0 \bigcap W^s(E_0) = \emptyset, \ X_0 \bigcap W^s(E_1) = \emptyset, \ X_0 \bigcap W^s(E_2) = \emptyset.$$

Next, we prove $X_0 \bigcap W^s(E_0) = \emptyset$. Suppose that there exists a solution $\phi_t(x_0) \in X_0$ such that: $\lim\limits_{t \to \infty} \phi_t(x_0) \in X_0 = E_0$ for $t \geq 0$, where $x_0 \in X_0$. That is, for any given sufficiently small constant $\delta > 0$, there exists a constant $t_2 > 0$ such that, for all $t \geq t_2$, we have

$$S_0 - \delta < S(t) < S_0 + \delta, \ V_0 - \delta < V(t) < V_0 + \delta, \ 0 < I_1(t) < \delta,$$

$$0 < I_2(t) < \delta, \ 0 < R_1(t) < \delta.$$

For large enough $t > t_2$, we have

$$\begin{cases} \dot{I}_1(t) \geq [\beta_1 \mathrm{e}^{-\mu\tau_1}(S_0 - \delta) - (\gamma_1 + \mu_1)] I_1, \\ \dot{I}_2(t) \geq [\beta_2 \mathrm{e}^{-\mu\tau_2}(S_0 - \delta) + k\mathrm{e}^{-\mu\tau_2}(V_0 - \delta) - (\gamma_2 + \mu_2)] I_2. \end{cases}$$

Define a linear comparison system

$$\frac{d\bar{I}(t)}{dt} = (F - V - \delta D)\bar{I}(t),$$

where $\bar{I}(t) = (\bar{I}_1(t), \bar{I}_2(t))^T$, $D = diag\{\beta_1 S_0 \frac{1-\mathrm{e}^{-\mu\tau_1}}{\delta} + \beta_1 \mathrm{e}^{-\mu\tau_1}, \beta_2 S_0 \frac{1-\mathrm{e}^{-\mu\tau_2}}{\delta} + \beta_2 \mathrm{e}^{-\mu\tau_2} + kV_0 \frac{1-\mathrm{e}^{-\mu\tau_2}}{\delta} + k\mathrm{e}^{-\mu\tau_2}\}$. Since $\sigma(F - V) > 0$ if and only if $\mathcal{R}_0 > 1$, here $\sigma(F - V)$ is the stable modulus of the matrix $F - V$. Thus, when $\mathcal{R}_0 > 1$, given sufficiently small constant $\delta_1 > 0$ such that

$$\sigma(F - V - \delta D) > 0 \text{ for } 0 \leq \delta \leq \delta_1.$$

Notice that $F - V - \delta D$ has a positive eigenvector with a positive eigenvalue $\sigma(F - V - \delta D)$. By the comparison principle, we have $\lim_{t\to\infty} I_1(t) = \infty$, $\lim_{t\to\infty} I_2(t) = \infty$, this is a contradiction. Therefore, $X_0 \bigcap W^s(E_0) = \emptyset$.

Suppose that there exists a solution $\phi_t(x_0) \in X_0$ such that: $\lim_{t\to\infty} \phi_t(x_0) = E_1$, where $x_0 \in X_0$. That is, for any fixed constant $\delta > 0$, there exists a constant $t_3 > 0$ such that, for all $t > t_3$, we have

$$\bar{S} - \delta < S(t), \bar{V} - \delta < V(t), 0 < I_2(t) < \delta, \bar{R}_1 - \delta < R_1(t).$$

For large enough $t > t_3$, we have

$$\dot{I}_2(t) \geq [\beta_2 \mathrm{e}^{-\mu\tau_2}(\bar{S} - \delta) + k\mathrm{e}^{-\mu\tau_2}(\bar{V} - \delta) + \beta_2 \mathrm{e}^{-\mu\tau_1}(\bar{R}_1 - \delta) - (\gamma_2 + \mu_2)]I_2.$$

Define the following auxiliary comparison system:

$$\frac{d\bar{I}(t)}{dt} = (F_1 - V_1 - \delta D_1)\bar{I}(t),$$

where $\bar{I}(t) = \bar{I}_2(t)$, $F_1 = \beta_2 \mathrm{e}^{-\mu\tau_2}\bar{S} + k\mathrm{e}^{-\mu\tau_2}\bar{V} + \beta_2\mathrm{e}^{-\mu\tau_1}\bar{R}_1$, $V_1 = (\gamma_2 + \mu_2)$, $D_1 = \Big(\beta_2\bar{S}\frac{1-\mathrm{e}^{-\mu\tau_2}}{\delta} + \beta_2\mathrm{e}^{-\mu\tau_2} + k\bar{V}\frac{1-\mathrm{e}^{-\mu\tau_2}}{\delta} + k\mathrm{e}^{-\mu\tau_2} + \beta_2\bar{R}_1\frac{1-\mathrm{e}^{-\mu\tau_2}}{\delta} + \beta_2\mathrm{e}^{-\mu\tau_2}\Big)$.

Since $\mathcal{R}_2^1 > 1$ if and only if $\sigma(F_1 - V_1) > 0$, here $\sigma(F_1 - V_1)$ is the stable modulus of the matrix $F_1 - V_1$. Therefore, when $\mathcal{R}_2^1 > 1$, given a sufficiently small constant $\delta_2 > 0$ such that

$$\sigma(F_1 - V_1 - \delta D_1) > 0 \;\text{ for } 0 \leq \delta \leq \delta_2.$$

Notice that $F_1 - V_1 - \delta D_1$ has a positive eigenvector with a positive eigenvalue $\sigma(F_1 - V_1 - \delta D_1)$. By the comparison principle, we have $\lim_{t\to\infty} I_2(t) = \infty$, this is a contradiction. Thus, $X_0 \bigcap W^s(E_1) = \emptyset$.

Similarly, $X_0 \bigcap W^s(E_2) = \emptyset$ ($\mathcal{R}_1^2 > 1$), the proofs are the same as above, so we omit them here.

From model (4), we can obtain that

$$\begin{aligned}\dot{S}(t) &= \Lambda - (\beta_2 I_2(t) + \beta_1 I_1(t) + r + \mu)S(t)\\ &\geq \Lambda - \Big(\max\{\beta_2, \beta_1\}\frac{\Lambda + \gamma_1\tau_1\Lambda}{\mu} + r + \mu\Big)S(t).\end{aligned}$$

By the comparison principle, we have $\liminf_{t\to\infty} S_i \geq \frac{\Lambda}{\max\{\beta_1,\beta_2\}\frac{\Lambda+\gamma_1\tau_1\Lambda}{\mu} + r + \mu}$.

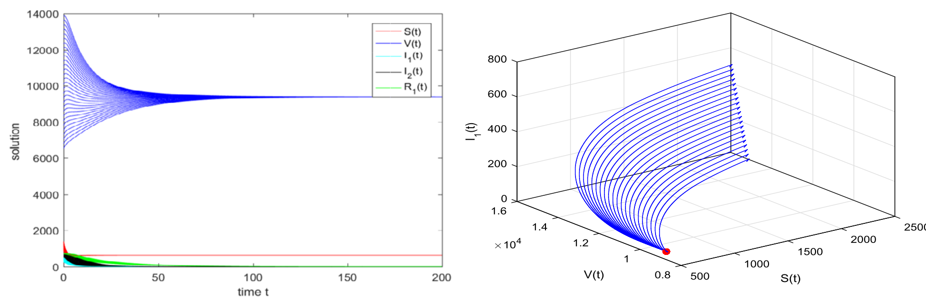
$$\dot{V}(t) = rS(t) - kI_2(t)V(t) - \mu V(t) \geq rS(t) - \Big(k\frac{\Lambda + \gamma_1\tau_1\Lambda}{\mu} + \mu\Big)V(t).$$

The uniform persistence of $V(t)$ can be guaranteed by the uniform persistence of $S(t)$.

$$\dot{R}_1(t) = \gamma_1 I_1(t) - \beta_2 R_1(t)I_2(t) - \mu R_1(t) \geq \gamma_1 I_1(t) - \Big(\beta_2\frac{\Lambda + \gamma_1\tau_1\Lambda}{\mu} + \mu\Big)R_1(t).$$

The uniform persistence of $R_1(t)$ can be guaranteed by the uniform persistence of $I_1(t)$.

From Theorem 4.6 in [30], we know that model (4) is uniformly persistent with respect to $(X_0, \partial X_0)$, Theorem 2.1 means that $\phi_t(x_0)$ is point dissipative. According to Theorem 2.4 in [31], model (4) has at least a strains 1, 2 coexistent equilibrium $E_c = (S^*, V^*, I_1^*, I_2^*, R_1^*)$. □



(1a) (1b)

Figure 1 Time series phases of solutions $(S(t), V(t), I_1(t), I_2(t), R_1(t))^T$ and 3-dimension phases of solutions $S(t)$, $V(t)$, $I_1(t)$ of model (4). (1a), (1b): initial functions $(S(i), V(i), I_1(i), I_2(i), R_1(i)) = (1000 + 20 * w + 10 * sin(i * h)$, $2000 + 20 * w + 10 * sin(i * h), 300 + 10 * w + 10 * sin(i * h), 300 + 12 * w + 10 * sin(i * h), 300 + 13 * w + 10 * sin(i * h))$, $w = 1, \dots, 15$, $i = 1, \dots, 100$, respectively

Remark 6 Based on the real circumstances of influenza transmission, the interaction between the two strains 1, 2 gradually shifts from coexistence to predominance of strain 2 (mutant strain) as it emerges, which is more consistent with the real disease spread.

4 Numerical simulation

This section focuses on the numerical simulation to illustrate the theoretical results of the four types of equilibria of model (4).

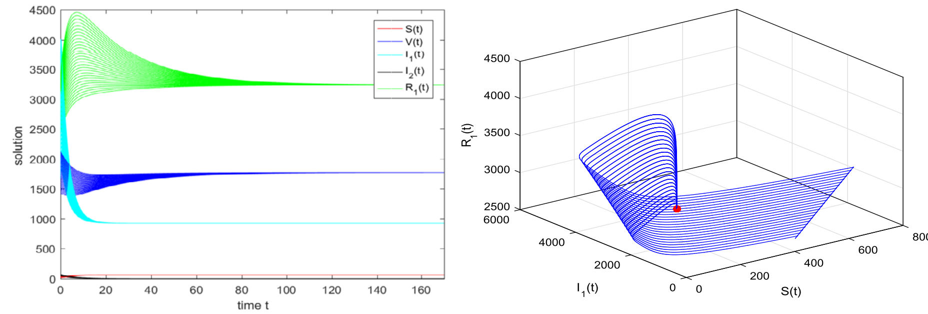
The DFE E_0 is simulated in Fig. 1, where $\Lambda = 200$, $\beta_1 = 0.00003$, $\beta_2 = 0.00002$, $k = 0.00001$, $r = 0.3$, $\mu = 0.02$, $\tau_1 = 2$, $\gamma_1 = 0.07$, $\mu_1 = 0.1$, $\tau_2 = 2$, $\gamma_2 = 0.09$, $\mu_2 = 0.1$. By calculation, we have $\mathcal{R}_{01} = 0.106 < 1$ and $\mathcal{R}_{02} = 0.5373 < 1$. As shown in Fig. 1, the DFE $E_0 = (625, 9375, 0, 0, 0)$ is GAS, which means that Theorem 3.4 is true.

The strain 1 dominant equilibrium E_1 is simulated in Fig. 2, where $\Lambda = 200$, $\beta_1 = 0.003$, $\beta_2 = 0.00002$, $k = 0.00001$, $r = 0.6$, $\tau_1 = 2$, $\gamma_1 = 0.07$, $\mu_1 = 0.1$, $\mu = 0.02$, $\mu_2 = 0.1$, $\tau_2 = 2$, $\gamma_2 = 0.09$. By calculation, we have $\mathcal{R}_{01} = 5.4694 > 1$ and $\mathcal{R}_{02} = 0.522 < 1$. As shown in Fig. 2, the strain 1 dominant equilibrium $E_1 = (59, 1769, 924, 0, 3233)$ is GAS, which means that Theorem 3.5 is true.

The strain 2 dominant equilibrium E_2 is simulated in Fig. 3, where $\Lambda = 200$, $\beta_1 = 0.00003$, $\beta_2 = 0.002$, $k = 0.00001$, $r = 0.6$, $\gamma_1 = 0.07$, $\mu = 0.02$, $\tau_1 = 2$, $\mu_1 = 0.1$, $\gamma_2 = 0.09$, $\tau_2 = 2$, $\mu_2 = 0.1$. By calculation, we have $\mathcal{R}_{01} = 0.0547 < 1$ and $\mathcal{R}_{02} = 3.7518 > 1$. As shown in Fig. 3, the strain 2 dominant equilibrium $E_2 = (89, 1908, 0, 809, 0)$ is GAS, which means that Theorem 3.6 is true.

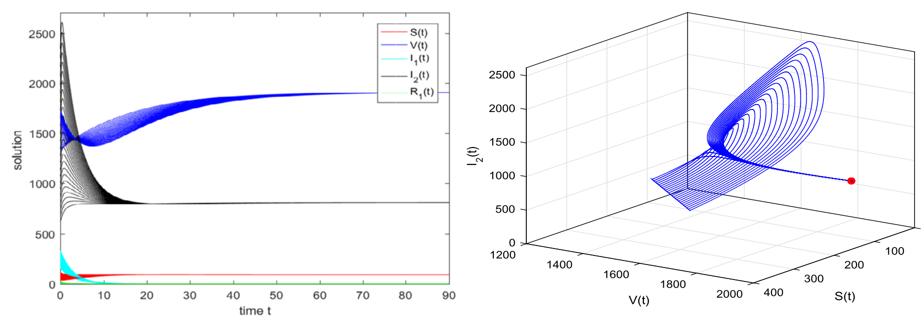
The strain 1, 2 coexistent equilibrium E_c is simulated in Fig. 4, where $\Lambda = 200$, $\beta_1 = 0.0005$, $\beta_2 = 0.0003$, $k = 0.0001$, $r = 0.4$, $\mu = 0.02$, $\tau_1 = 2$, $\gamma_1 = 0.1$, $\mu_1 = 0.03$, $\tau_2 = 2$, $\gamma_2 = 0.2$, $\mu_2 = 0.03$. By calculation, we have $\mathcal{R}_{01} = 1.7597 > 1$ and $\mathcal{R}_{02} = 4.5752 > 1$. As shown in Fig. 4, we can see that the strain 1, 2 coexistent equilibrium $E_c = (271, 1253, 240, 664, 110)$ is GAS.

As shown in Fig. 5, we compare the dynamical behavior of the strains 1, 2 coexistent equilibrium E_c between model (1) and models (2) and (4), corresponding to Fig. 5a (without cross-immunity), Fig. 5b (without vaccination), and Fig. 5c (with cross-immunity and vaccination), respectively. The values of the parameters in Fig. 5 are the same as in Fig. 4, except $r = 0$ and $k = 0$ in Fig. 5b.



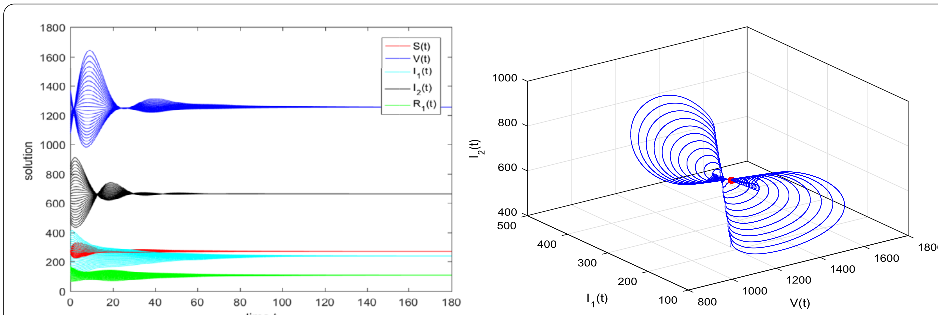
(2a) (2b)

Figure 2 Time series phases of solutions $(S(t), V(t), I_1(t), I_2(t), R_1(t))^T$ and 3-dimension phases of solutions $S(t)$, $I_1(t)$, $R_1(t)$ of model (4). (2a), (2b): initial functions $(S(i), V(i), I_1(i), I_2(i), R_1(i)) = (400 + 10 * w + 10 * sin(i * h)$, $1300 + 25 * w + 25 * sin(i * h), 600 + 10 * w + 5 * sin(i * h), 50 + 1 * w + 1 * sin(i * h), 2300 + 30 * w + 30 * sin(i * h))$, $w = 1, \ldots, 15$, $i = 1, \ldots, 100$, respectively



(3a) (3b)

Figure 3 Time series phases of solutions $(S(t), V(t), I_1(t), I_2(t), R_1(t))^T$ and 3-dimension phases of solutions $S(t)$, $V(t)$, $I_2(t)$ of model (4). (3a), (3b): initial functions $(S(i), V(i), I_1(i), I_2(i), R_1(i)) = (100 + 10 * w + 10 * sin(i * h)$, $1200 + 20 * w + 20 * sin(i * h), 200 + 10 * w + 5 * sin(i * h), 400 + 15 * w + 15 * sin(i * h), 100 + 10 * w + 10 * sin(i * h))$, $w = 1, \ldots, 15$, $i = 1, \ldots, 100$, respectively



(4a) (4b)

Figure 4 Time series phases of solutions $(S(t), V(t), I_1(t), I_2(t), R_1(t))^T$ and 3-dimension phases of solutions $V(t)$, $I_1(t)$, $I_2(t)$ of model (4). (4a), (4b): initial functions $(S(i), V(i), I_1(i), I_2(i), R_1(i)) = (150 + 10 * w + 10 * sin(i * h)$, $1000 + 15 * w + 20 * sin(i * h), 150 + 10 * w + 10 * sin(i * h), 500 + 10 * w + 15 * sin(i * h), 70 + 5 * w + 10 * sin(i * h))$, $w = 1, \ldots, 15$, $i = 1, \ldots, 100$, respectively

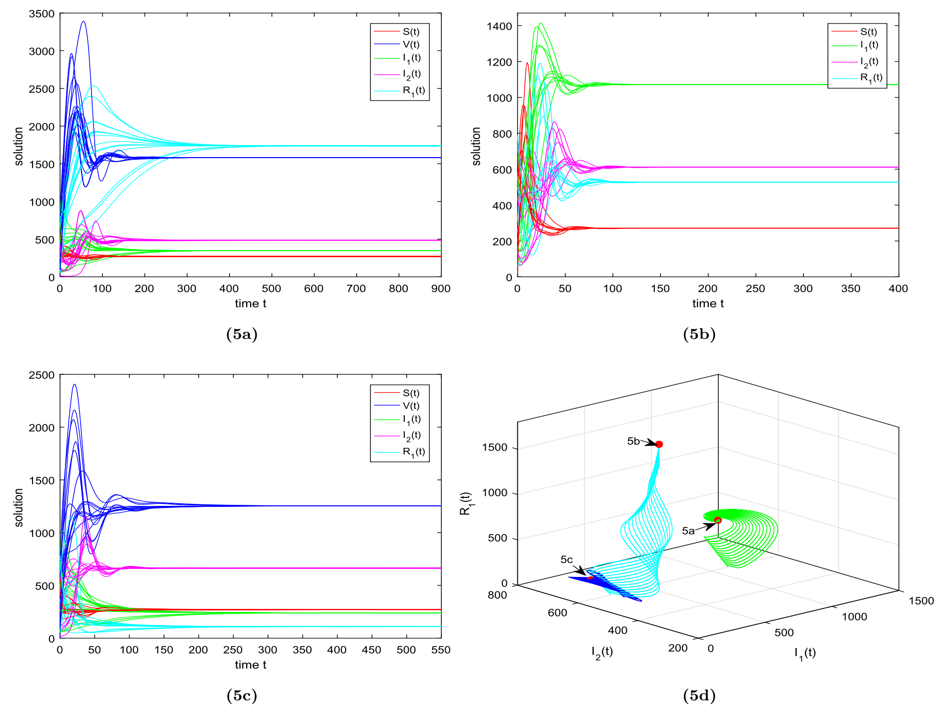


Figure 5 Time series phases of solutions $(S(t), V(t), I_1(t), I_2(t), R_1(t))^T$ and 3-dimension phases of solutions $I_1(t)$, $I_2(t)$, $R_1(t)$ of model (4). (5a), (5b), (5c): coexistence equilibrium E_c of model (1) without cross-immunity, model (2) without vaccination, model (4) with cross-immunity and vaccination

First, we compare Fig. 5a and 5c to research the effect of cross-immunity. As shown in Fig. 5c, the final size of the infected individuals of strains 1 and 2 is slightly higher than that in Fig. 5a, while the final size of the recovered individuals of strain 1 in Fig. 5a is much higher than that in Fig. 5c. According to the real circumstances of influenza [1, 2, 12], the recovered individuals of original strain would be most likely infected by the new strain with mutation (antigenic drift), so Fig. 5c (with cross-immunity) is more consistent with the actual situation of influenza transmission.

Next, we compare Figs. 5b and 5c to examine the impact of vaccines. As shown in Fig. 5b, the number of the infected and recovered individuals from strain 1 is much larger than that in Fig. 5c, the number of infected individuals from strain 2 in Fig. 5c is slightly larger than that in Fig. 5b, thus vaccination plays an important role in influenza prevention, although vaccines only target a single strain of the virus.

As with the above comparisons, we find that considering cross-immunity and vaccination in model (4) is necessary to research influenza transmission.

4.1 Sensitivity analysis

$\mathcal{R}_0$ plays an important role as a threshold for the spread of influenza. Sensitivity of model parameters may affect $\mathcal{R}_0$. Therefore, we used the latin hypercube sampling (LHS) method to rank the effects of model parameters on $\mathcal{R}_0$ from the perspective of global sensitivity analysis. The value ranges of parameters are shown in Table 4.

Figure 6 analyzes the influence of vaccination rate r on the final size of infected individuals of double strains, the values of the parameters in Fig. 6 are the same as in Fig. 4. From Fig. 6a, it can be seen that as the vaccination rate r increases, the number of infected

Table 4 The baseline values and ranges of parameters

Parameter	Baseline (Range)	Parameter	Baseline (Range)
Λ	100(0.1 – 200)	μ	0.02(0.001 – 0.3)
μ_1	0.1(0.001 – 0.5)	μ_2	0.1(0.001 – 0.5)
β_1	0.0003(0.00001 – 0.3)	β_2	0.0002(0.00001 – 0.2)
k	0.0001(0.00001 – 0.1)	r	0.3(0.0001 – 0.6)
γ_1	0.07(0.01 – 0.6)	γ_2	0.09(0.01 – 0.6)
τ_1	2(0.1 – 4)	τ_2	2(0.1 – 4)

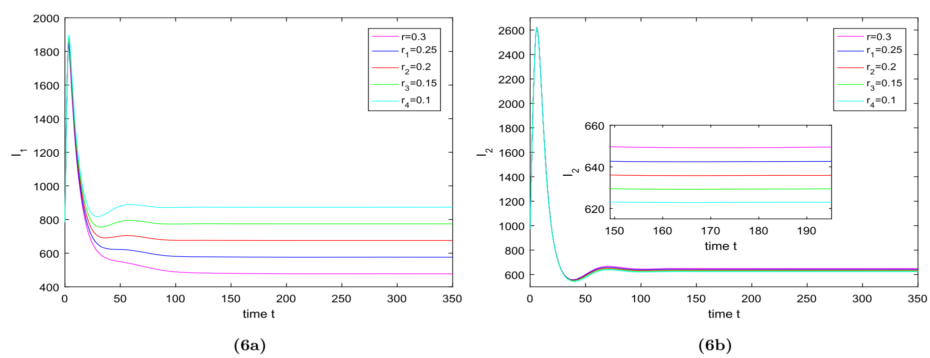


Figure 6 The impact of vaccination rate r on the number of infected individuals I_1 and I_2, with $r = 0.3$, $r_1 = 0.25$, $r_2 = 0.2$, $r_3 = 0.15$, $r_4 = 0.1$

individuals with strain 1 decreases. From Fig. 6b, we find that as the vaccination rate r increases, the final number of infected individuals with strain 2 slightly increases. Therefore, increasing the vaccination rate r would reduce the scale of influenza outbreaks, although vaccines are only effective against a single strain, the final size of influenza infections has significantly decreased.

Figure 7 analyzes the correlation between $\mathcal{R}_0$ and the rates of infection, recovery, mortality, as well as time delay. As shown in Fig. 7a, it can be seen that as β_1 and β_2 increase, $\mathcal{R}_0$ is positively correlated with β_1 and β_2. As shown in Fig. 7b, it can be seen that as γ_1 and γ_2 increase, $\mathcal{R}_0$ is negatively correlated with γ_1 and γ_2. As shown in Fig. 7c, it can be seen that as μ_1 and μ_2 increase, $\mathcal{R}_0$ is negatively correlated with μ_1 and μ_2. As shown in Fig. 7d, it can be seen that as τ_1 and τ_2 increase, $\mathcal{R}_0$ is negatively correlated with τ_1 and τ_2, which means that ignoring the delay may incorrectly estimate the outbreak and size of the disease. Increasing the rate of recovery from disease and decreasing the rate of infection through appropriate means would reduce the size of epidemic outbreaks. As seen from Fig. 7a, 7b, 7c, 7d, each plot is composed of two smooth surfaces, which is due to the fact that $\mathcal{R}_0 = \max\{\mathcal{R}_{01}, \mathcal{R}_{02}\}$, when the infection rate, recovery rate, and time delay of infection of two strains are variable, the basic reproduction number $\mathcal{R}_0$ will switch to $\mathcal{R}_{01}$ or $\mathcal{R}_{02}$ when the infection and recovery rates, and infection time delay of the two strains change.

Figure 8 analyzes the correlation between each parameter and $\mathcal{R}_0$ using the LHS and PRCC method. As seen from Fig. 8, these parameters Λ, β_i, k are positively correlated with $\mathcal{R}_0$, and γ_i, μ, μ_i, r are negatively correlated with $\mathcal{R}_0$, where $i = 1, 2$.

5 Conclusion

Based on the characteristics of influenza transmission, this paper proposes a class of delayed SVIR double-strain influenza model with vaccination and cross-immunity. The exis-

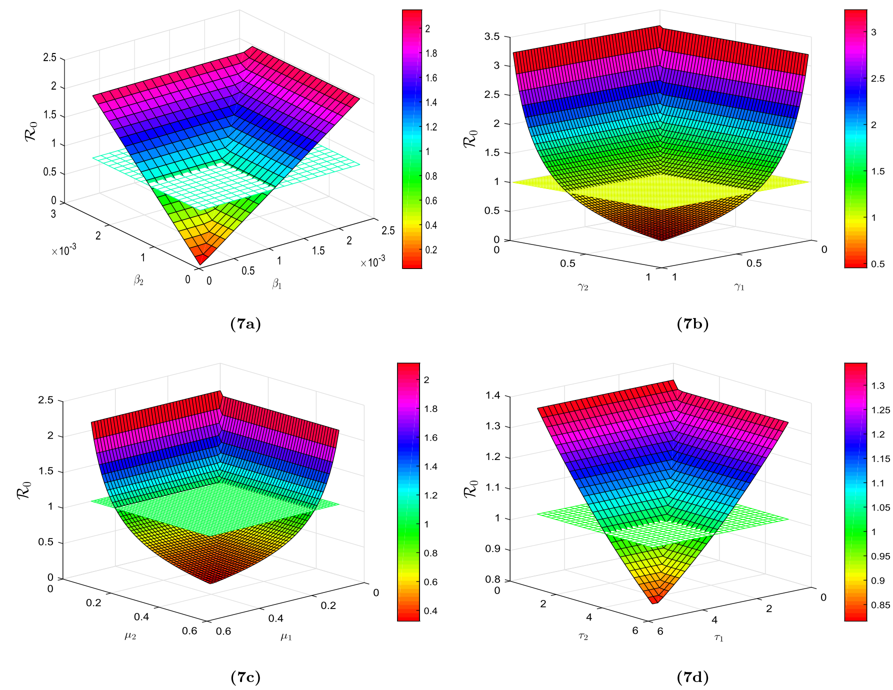


Figure 7 3-dimension phases, sensitivity analysis between $\mathcal{R}_0$ and infection, recovery and mortality rates, time delay, (7a): $\beta_1 \in [0, 0.0025]$, $\beta_2 \in [0, 0.003]$, (7b): $\gamma_1 \in [0, 1]$, $\gamma_2 \in [0, 1]$, (7c): $\mu_1 \in [0, 0.6]$, $\mu_2 \in [0, 0.6]$, (7d): $\tau_1 \in [0, 6]$, $\tau_2 \in [0, 6]$

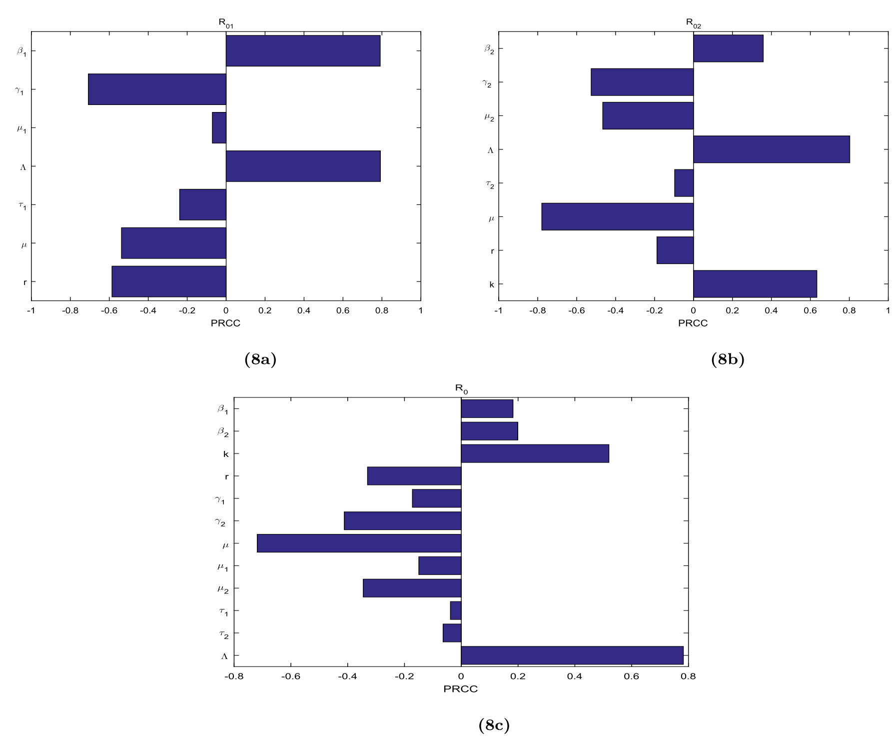


Figure 8 Sensitivity indicators of $\mathcal{R}_{01}$, $\mathcal{R}_{02}$, $\mathcal{R}_0$ for different parameters

tence of all feasible equilibria is obtained, and the basic reproduction number of strains 1, 2 and the whole model is derived, the threshold criteria on stability of equilibria E_0, E_1, and E_2 are established. The uniform persistence of disease and the existence of the strains 1, 2 coexistent equilibrium E_c are obtained. By numerical simulation, the theoretical results are illustrated, and sensitivity analysis of parameters is performed. The dependence of $\mathcal{R}_0$ on the parameters is analyzed based on LHS and PRCC, by which we can see that these parameters Λ, β_1, β_2, and k are crucial on disease control, there is a negative correlation between vaccination rate r and $\mathcal{R}_0$ as well. Overall, increase in the level of protection for susceptible and infected populations is critical to influenza control.

In addition, we compare the dynamical behavior of models (1), (2), and model (4), by which we find that neglecting cross-immunity and vaccination would misestimate the size of influenza outbreaks. Increasing the vaccination rate r would reduce the scale of influenza outbreaks, although vaccines are only effective against a single strain, the final size of influenza infections would significantly decreased.

Furthermore, vaccination is an effective control measure against influenza transmission and can prevent large-scale outbreaks. However, current vaccines are only used for routine immunization against specific variants of seasonal influenza and are not widely available, especially for new mutant strains. In [32], it is mentioned that current flu vaccines have some shortcomings, e.g., long production cycle, limited vaccine capacity, effectiveness in some populations, and lack of cross-reactivity. The variability of influenza viruses affects the effectiveness of influenza vaccines. Therefore, the cross-immunity mechanism should be emphasized on the spread of influenza viruses, which should be effectively designed in vaccine production and applicability.

This article does not obtain a specific expression for the coexistence equilibrium and further study of its stability other than illustrating it through numerical simulation, which would be an open question in the future. In addition, when considering the factor of vaccines, we did not take into account the factor of vaccine failure. On the other hand, we will investigate the influence of both mutation of strains and cross immunity on the transmission of disease.

Appendices

A.1 The derivation of model (3)

Before giving our final model, we first consider the following SVEIR influenza model:

$$\begin{cases} \dot{S}(t) = \Lambda - \beta_1 I_1(t)S(t) - \beta_2 I_2(t)S(t) - rS(t) - \mu S(t), \\ \dot{V}(t) = rS(t) - kV(t)I_2(t) - \mu V(t), \\ \dot{E}_1(t) = \beta_1 I_1(t)S(t) - \mu E_1(t) - G_1(t), \\ \dot{E}_2(t) = \beta_2 I_2(t)S(t) + kV(t)I_2(t) + \beta_2 R_1(t)I_2(t) - \mu E_2(t) - G_2(t), \\ \dot{I}_1(t) = G_1(t) - \gamma_1 I_1(t) - \mu_1 I_1(t), \\ \dot{I}_2(t) = G_2(t) - \gamma_2 I_2(t) - \mu_2 I_2(t), \\ \dot{R}_1(t) = \gamma_1 I_1(t) - \beta_2 R_1(t)I_2(t) - \mu R_1(t), \\ \dot{R}_2(t) = \gamma_2 I_2(t) - \mu R_2(t), \end{cases} \tag{26}$$

A.2 $G_1(t)$ is derived

We derived a functional differential equation from the Mckendrick–von Foersier equation [33] to describe the latent process from susceptibility to infection. When susceptible individuals come into contact with individuals infected with strain 1, strain 1 has a latent period τ in the susceptible individual's body, and $\tau \geq 0$. Susceptible individuals begin to infect and become latent individuals with no infectious ability at $t = 0$, and they become infected individuals with infectious ability at τ_1. Let $e_1(t,\tau)$ be the density of infected strain 1 latent individuals among susceptible individuals. So, when $\tau \in [0,\tau_1]$, the total number of strain 1 latent individuals at time t is

$$E_1(t) = \int_0^{\tau_1} e_1(t,\tau)\,\mathrm{d}\tau. \tag{27}$$

To obtain the equation to determine the change in the number of the latent compartment of strain 1, the Mckendrick–von Foersier equation [33] is used to describe the change of $e_1(t,\tau)$:

$$\frac{\partial e_1(t,\tau)}{\partial \tau} + \frac{\partial e_1(t,\tau)}{\partial t} = -\mu e_1(t,\tau),$$

where $\mu e_1(t,\tau)$ is the loss of strain 1 latent individuals due to natural death.

When $\tau = 0$, we have $e_1(t,0) = \beta_1 S(t) I_1(t)$. According to Eq. (27), we can get

$$\begin{aligned}\frac{dE_1(t)}{dt} &= \frac{\partial}{\partial t}\int_0^{\tau_1} e_1(t,\tau)\,\mathrm{d}\tau = \int_0^{\tau_1} \frac{\partial}{\partial t} e_1(t,\tau)\,\mathrm{d}\tau \\ &= \int_0^{\tau_1} (-\mu e_1(t,\tau) - \frac{\partial e_1(t,\tau)}{\partial \tau})\,\mathrm{d}\tau \\ &= -\mu \int_0^{\tau_1} e_1(t,\tau)\,\mathrm{d}\tau - \int_0^{\tau_1} (\frac{\partial e_1(t,\tau)}{\partial \tau})\,\mathrm{d}\tau \\ &= -\mu E_1(t) - e_1(t,\tau) + e_1(t,0).\end{aligned}$$

To determine $e_1(t,\tau)$, let $e_1^{\epsilon}(\tau) = e_1(\tau+\epsilon,\tau)$, we can obtain

$$\begin{aligned}\frac{e_1^{\epsilon}(\tau)}{d\tau} &= \frac{\partial e_1(\tau+\epsilon,\tau)}{\partial \tau} = \frac{\partial e_1(\tau+\epsilon,\tau)}{\partial(\tau+\epsilon)} + \frac{\partial e_1(\tau+\epsilon,\tau)}{\partial \tau} \\ &= -\mu e_1(\tau+\epsilon,\tau) = -\mu e_1^{\epsilon}(\tau).\end{aligned}$$

That is, $e_1^{\epsilon}(\tau) = e_1^{\epsilon}(0)\mathrm{e}^{-\mu\tau}$.

Let $\tau = \tau_1$, since

$$e_1^{t-\tau_1}(\tau) = e_1(t-\tau_1+\tau,\tau),\ e_1^{t-\tau_1}(0) = e_1(t-\tau_1,0),$$

we have

$$e_1(t,\tau_1) = e_1(t+\tau_1-\tau_1,\tau_1) = e_1(t-\tau_1,0)\mathrm{e}^{-\mu\tau} = \beta_1 S(t-\tau_1) I_1(t-\tau_1)\mathrm{e}^{-\mu\tau_1}.$$

We can get the equation for $E_1(t)$:

$$\dot{E}_1(t) = \beta_1 I_1(t) S(t) - \mu E_1(t) - \beta_1 S(t-\tau_1) I_1(t-\tau_1)\mathrm{e}^{-\mu\tau_1},$$

and then

$$G_1(t) = \beta_1 S(t-\tau_1)I_1(t-\tau_1)\mathrm{e}^{-\mu\tau_1}.$$

A.3 $G_2(t)$ is derived

Similar to the derivation process of $G_1(t)$. Let $e_2(t,\tau)$ be the density of infected strain 2 latent individuals among susceptible individuals. So, when $\tau \in [0,\tau_2]$, the total number of latent individuals at time t is

$$E_2(t) = \int_0^{\tau_2} e_2(t,\tau)\,\mathrm{d}\tau.$$

To obtain the equation to determine the change in the number of the latent compartment of strain 2, the Mckendrick–von Foersier equation is used to describe the change of $e_2(t,\tau)$:

$$\frac{\partial e_2(t,\tau)}{\partial \tau} + \frac{\partial e_2(t,\tau)}{\partial t} = -\mu e_2(t,\tau),$$

where $\mu e_2(t,\tau)$ is the loss of strain 2 latent individuals due to natural death.

When $\tau = 0$, $e_2(t,0) = \beta_2 I_2(t)S(t) + kV(t)I_2(t) + \beta_2 R_1(t)I_2(t)$. The rest of the derivation process is similar to the $G_1(t)$ derivation process, which will not be repeated here.

We can get the equation for $E_2(t)$:

$$\begin{aligned}\dot{E}_2(t) &= \beta_2 I_2(t)S(t) + kV(t)I_2(t) + \beta_2 R_1(t)I_2(t) - \mu E_2(t)\\ &\quad - (\beta_2 S(t-\tau_2) + kV(t-\tau_2) + \beta_2 R_1(t-\tau_2))I_2(t-\tau_2)\mathrm{e}^{-\mu\tau_2},\end{aligned}$$

and then

$$G_2(t) = (\beta_2 S(t-\tau_2) + kV(t-\tau_2) + \beta_2 R_1(t-\tau_2))I_2(t-\tau_2)\mathrm{e}^{-\mu\tau_2}.$$

Finally, based on the above derivation, substitute $G_1(t)$ and $G_2(t)$ into model (26). We can obtain an influenza model with latent time delay, vaccination, and cross immunity.

Decoupling $E_1(t)$ and $E_2(t)$ in model (26), we can obtain model (3).

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Author contributions
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Data availability
This manuscript has no associated data.

Declarations

Competing interests
The authors declare that they have no competing interests.

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