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Stability of delayed pathogen dynamics models with latency and two routes of infection

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Abstract

We consider a pathogen dynamics model with antibodies and both pathogen-to-susceptible and infected-to-susceptible transmissions. We consider two types of infected cells, latently infected cells, and actively infected cells. The model considers three types of discrete or distributed delays to characterize the time between the pathogen or the infected cell contacts a susceptible cell and the creation of mature pathogens. We deduct the basic reproduction number and antibody response activation number which determine the existence and stability of the steady states. The global stability analysis of the steady states is established using Lyapunov method. The theoretical results are confirmed by numerical simulations.

Keywords: Pathogen dynamics; Global stability; Time delay; Cellular and pathogenic infections; Antibody immune response; Latency

1 Introduction

Modeling and analysis of within-host human pathogen dynamics have been studied in several works (see, e.g., [1–23]). These works can help researchers to better understand the pathogen dynamical behavior and to provide new suggestions for clinical treatment. A vast amount of the mathematical models presented in the literature focused on modeling the interaction between three main compartments, susceptible cells (s), infected cells (y), and pathogens (p). B cell is one of the central components of the immune system against viral infections. The B cells create antibodies to neutralize the pathogens. Murase et al. [24] considered the effect of antibodies (x) on the pathogen infection model as follows:

$$
\begin{aligned}
\dot{s}(t) &= \omega - ds(t) - \pi_1 s(t)p(t),\\
\dot{y}(t) &= \pi_1 s(t)p(t) - \lambda y(t),\\
\dot{p}(t) &= n\lambda y(t) - cp(t) - ap(t)x(t),\\
\dot{x}(t) &= rp(t)x(t) - mx(t).
\end{aligned}
\tag{1}
$$

The susceptible cells are produced at rate ω, die at rate ds, and become infected at rate $\pi_1 sp$, where π_1 is the pathogen-susceptible incidence rate constant. λ is the death rate constant of the infected cells, a is the neutralization rate constant of the pathogens, and

c is the death rate constant of the pathogens. The infected cell releases a number n of pathogens during its lifespan. The B cells are proliferated and die at rates rpx and mx, respectively, where r and m are constants. The effect of antibody immune response on the pathogen dynamics has been studied in several works (see, e.g., [24–29]). In these works, it was assumed that the susceptible cells become infected by contacting with pathogens (pathogen-to-susceptible transmission). In [30–33], it was reported that the pathogens can also spread by infected-to-susceptible transmission. However, in these works the antibody immune response was neglected. In very recent works [34, 35], and [36], both pathogen-to-susceptible and infected-to-susceptible transmissions were incorporated in the pathogen dynamics models with antibody immune response. However, the latently infected cells were neglected in these models.

It is worth stressing that the introduction of delay equations has been widely applied to model complex systems in biology. Indeed, the introduction of delay terms can be viewed as a first step towards modeling multiscale dynamics and heterogeneity features in population dynamics [37].

In the present paper we investigate the global stability of pathogen dynamics models with antibodies and both pathogen-to-susceptible and infected-to-susceptible transmissions. We consider both latently infected cells and actively infected cells. We incorporate three types of discrete or distributed time delays to describe the time between the pathogen or the actively infected cell contacts a susceptible cell and the emission of new mature pathogens. We calculate two bifurcation parameters $\mathcal{R}_0$ (the basic reproduction number) and $\mathcal{R}_1$ (the antibody response activation number) which determine the existence and global stability of all steady states. Numerical simulations are performed to confirm the theoretical results.

2 Model with discrete-time delays

We investigate the following pathogen dynamics model with discrete-time delays:

$$\begin{aligned}
\dot{s}(t) &= \omega - ds(t) - s(t)\big[\pi_1 p(t) + \pi_2 y(t)\big], \\
\dot{u}(t) &= \rho e^{-\varepsilon_1\tau_1} s(t-\tau_1)\big[\pi_1 p(t-\tau_1) + \pi_2 y(t-\tau_1)\big] - (\alpha+\lambda_u)u(t), \\
\dot{y}(t) &= (1-\rho)e^{-\varepsilon_2\tau_2} s(t-\tau_2)\big[\pi_1 p(t-\tau_2) + \pi_2 y(t-\tau_2)\big] - \lambda y(t) + \alpha u(t), \\
\dot{p}(t) &= n\lambda e^{-\varepsilon_3\tau_3} y(t-\tau_3) - cp(t) - ap(t)x(t), \\
\dot{x}(t) &= rp(t)x(t) - mx(t).
\end{aligned} \tag{2}$$

The model assumes that the susceptible cells are infected by pathogens at rate $\pi_1 s(t)p(t)$ and by infected cells at rate $\pi_2 s(t)y(t)$. The fractions ρ and $(1-\rho)$ with $0 < \rho < 1$ are the proportions of infection that lead to latency and activation, respectively. λ_u is the death rate constant of the latently infected cells. Latently infected cells are activated at rate $\alpha u(t)$. Here, τ_1 is the time between pathogen entry a susceptible cell to become latent infected, and τ_2 is the time between pathogen entry a susceptible cell and the production of immature pathogens. The immature pathogens need time τ_3 to be mature. The factors $e^{-\varepsilon_1\tau_1}$, $e^{-\varepsilon_2\tau_2}$, and $e^{-\varepsilon_3\tau_3}$ represent the probability of surviving to the age of τ_1, τ_2, and τ_3, respectively, where ε_1, ε_2, and, ε_3 are positive constants.

We consider the initial conditions

$$\begin{aligned}
&s(\theta) = \phi_1(\theta), \qquad u(\theta) = \phi_2(\theta), \qquad y(\theta) = \phi_3(\theta), \\
&p(\theta) = \phi_4(\theta), \qquad x(\theta) = \phi_5(\theta), \\
&\phi_j(\theta) \geq 0, \quad \theta \in [-\kappa, 0], \\
&\phi_j \in C\big([-\kappa, 0], \mathbb{R}_{\geq 0}\big), \quad j = 1, \dots, 5,
\end{aligned} \tag{3}$$

where $\kappa = \max\{\tau_1, \tau_2, \tau_3\}$ and C is the Banach space of continuous functions mapping the interval $[-\kappa, 0]$ into $\mathbb{R}_{\geq 0}$ with norm $\|\phi_j\| = \sup_{-\kappa \leq \theta \leq 0} |\phi_j(\theta)|$. Then system (2) has a unique solution for $t > 0$ [38].

2.1 Properties of solution

Lemma 1 *The solutions of system* (2) *with initial conditions* (3) *are nonnegative and ultimately bounded for* $t > 0$.

Proof We have from Eq. $(2)_1$ that $\dot{s}|_{s=0} = \omega > 0$. Therefore $s(t) > 0$ for all $t \geq 0$. Moreover, for $t \in [0, \kappa]$, we have

$$\begin{aligned}
u(t) &= \phi_2(0)e^{-(\alpha+\lambda_u)t} + \int_0^t e^{-(\alpha+\lambda_u)(t-\theta)}\big\{\rho e^{-\varepsilon_1\tau_1} s(\theta - \tau_1)\big[\pi_1 p(\theta - \tau_1) + \pi_2 y(\theta - \tau_1)\big]\big\}\, d\theta \\
&\geq 0, \\
y(t) &= \phi_3(0)e^{-\lambda t} \\
&\quad + \int_0^t e^{-\lambda(t-\theta)}\big\{(1-\rho)e^{-\varepsilon_2\tau_2} s(\theta - \tau_2)\big[\pi_1 p(\theta - \tau_2) + \pi_2 y(\theta - \tau_2)\big] + \alpha u(\theta)\big\}\, d\theta \geq 0, \\
p(t) &= \phi_4(0)e^{-\int_0^t (c+ax(\upsilon))\, d\upsilon} + n\lambda e^{-\varepsilon_3\tau_3} \int_0^t e^{-\int_\theta^t (c+ax(\upsilon))\, d\upsilon} y(\theta - \tau_3)\, d\theta \geq 0, \\
x(t) &= \phi_5(0)e^{-mt + r\int_0^t p(\upsilon)\, d\upsilon} \geq 0.
\end{aligned}$$

By recursive argument we get $u(t) \geq 0$, $y(t) \geq 0$ and $p(t) \geq 0$ $\forall t \geq 0$. The nonnegativity of the model's solutions implies that $\dot{s}(t) \leq \omega - ds(t)$ and then $\lim_{t\to\infty} \sup s(t) \leq \frac{\omega}{d}$. Let us define $X_1(t) = \rho e^{-\varepsilon_1\tau_1} s(t - \tau_1) + (1-\rho)e^{-\varepsilon_2\tau_2} s(t - \tau_2) + u(t) + y(t)$. Then

$$\begin{aligned}
\dot{X}_1(t) &= \rho e^{-\varepsilon_1\tau_1}\big\{\omega - ds(t-\tau_1) - \pi_1 s(t-\tau_1)p(t-\tau_1) - \pi_2 s(t-\tau_1)y(t-\tau_1)\big\} \\
&\quad + (1-\rho)e^{-\varepsilon_2\tau_2}\big\{\omega - ds(t-\tau_2) - \pi_1 s(t-\tau_2)p(t-\tau_2) - \pi_2 s(t-\tau_2)y(t-\tau_2)\big\} \\
&\quad + \rho e^{-\varepsilon_1\tau_1} s(t-\tau_1)\big[\pi_1 p(t-\tau_1) + \pi_2 y(t-\tau_1)\big] - (\alpha + \lambda_u)u(t) \\
&\quad + (1-\rho)e^{-\varepsilon_2\tau_2} s(t-\tau_2)\big[\pi_1 p(t-\tau_2) + \pi_2 y(t-\tau_2)\big] - \lambda y(t) + \alpha u(t) \\
&= \omega\rho e^{-\varepsilon_1\tau_1} + \omega(1-\rho)e^{-\varepsilon_2\tau_2} \\
&\quad - \rho e^{-\varepsilon_1\tau_1}\, ds(t-\tau_1) - (1-\rho)e^{-\varepsilon_2\tau_2}\, ds(t-\tau_2) - \lambda_u u(t) - \lambda y(t) \\
&\leq \omega - \sigma_1\big[\rho e^{-\varepsilon_1\tau_1} s(t-\tau_1) + (1-\rho)e^{-\varepsilon_2\tau_2} s(t-\tau_2) + u(t) + y(t)\big] \\
&= \omega - \sigma_1 X_1(t),
\end{aligned}$$

where $\sigma_1 = \min\{d, \lambda_u, \lambda\}$. It follows that $\lim_{t\to\infty}\sup X_1(t) \le M_1$, where $M_1 = \frac{\omega}{\sigma_1}$. Since $s(t) > 0$, $u(t) \ge 0$, and $y(t) \ge 0$, then $\lim_{t\to\infty}\sup u(t) \le M_1$ and $\lim_{t\to\infty}\sup y(t) \le M_1$. Moreover, let $X_2(t) = p(t) + \frac{a}{r}x(t)$. Then

$$\begin{aligned}\dot{X}_2(t) &= n\lambda e^{-\varepsilon_3\tau_3}y(t-\tau_3) - cp(t) - \frac{am}{r}x(t)\\ &\le n\lambda M_1 - \sigma_2 X_2(t),\end{aligned}$$

where $\sigma_2 = \min\{c, m\}$. Then $\lim_{t\to\infty}\sup X_2(t) \le M_2$, where $M_2 = \frac{n\lambda M_1}{\sigma_2}$. The nonnegativity of the solution implies that $\lim_{t\to\infty}\sup p(t) \le M_2$ and $\lim_{t\to\infty}\sup x(t) \le M_3$, where $M_3 = \frac{r}{a}M_2$. This shows the ultimate boundedness of $s(t)$, $u(t)$, $y(t)$, $p(t)$, and $x(t)$. □

2.2 Steady states and threshold parameters

In the following, we derive the basic reproduction number from system (2) by using the next-generation method and calculate the steady states. We first define the matrices $\mathbb{F}$ and $\mathbb{V}$ as follows:

$$\mathbb{F} = \begin{bmatrix} 0 & \rho\pi_2 s_0 e^{-\varepsilon_1\tau_1} & \rho\pi_1 s_0 e^{-\varepsilon_1\tau_1}\\ 0 & (1-\rho)\pi_2 s_0 e^{-\varepsilon_2\tau_2} & (1-\rho)\pi_1 s_0 e^{-\varepsilon_2\tau_2}\\ 0 & 0 & 0\end{bmatrix}, \qquad \mathbb{V} = \begin{bmatrix}\alpha+\lambda_u & 0 & 0\\ -\alpha & \lambda & 0\\ 0 & -n\lambda e^{-\varepsilon_3\tau_3} & c\end{bmatrix},$$

where $s_0 = \frac{\omega}{d}$. Then

$$\mathbb{F}\mathbb{V}^{-1} = \begin{bmatrix}\psi_1 & \psi_2 & \psi_3\\ \psi_4 & \psi_5 & \psi_6\\ 0 & 0 & 0\end{bmatrix},$$

where

$$\begin{aligned}\psi_1 &= \frac{\alpha\rho\pi_2 s_0 e^{-\varepsilon_1\tau_1}}{(\alpha+\lambda_u)\lambda} + \frac{\alpha\rho\pi_1 s_0 n e^{-\varepsilon_1\tau_1}e^{-\varepsilon_3\tau_3}}{(\alpha+\lambda_u)c},\\ \psi_2 &= \frac{\rho\pi_2 s_0 e^{-\varepsilon_1\tau_1}}{\lambda} + \frac{\rho\pi_1 s_0 n e^{-\varepsilon_1\tau_1}e^{-\varepsilon_3\tau_3}}{c},\\ \psi_3 &= \frac{\rho\pi_1 s_0 e^{-\varepsilon_1\tau_1}}{c},\\ \psi_4 &= \frac{\alpha(1-\rho)\pi_2 s_0 e^{-\varepsilon_2\tau_2}}{(\alpha+\lambda_u)\lambda} + \frac{\alpha(1-\rho)\pi_1 s_0 n e^{-\varepsilon_2\tau_2}e^{-\varepsilon_3\tau_3}}{(\alpha+\lambda_u)c},\\ \psi_5 &= \frac{(1-\rho)\pi_2 s_0 e^{-\varepsilon_2\tau_2}}{\lambda} + \frac{(1-\rho)\pi_1 s_0 n e^{-\varepsilon_2\tau_2}e^{-\varepsilon_3\tau_3}}{c},\\ \psi_6 &= \frac{(1-\rho)\pi_1 s_0 e^{-\varepsilon_2\tau_2}}{c}.\end{aligned}$$

The basic reproduction number $\mathcal{R}_0$ can be computed as the spectral radius of $\mathbb{F}\mathbb{V}^{-1}$:

$$\mathcal{R}_0 = \frac{n\pi_1 s_0\gamma}{c} + \frac{\pi_2 s_0 e^{\varepsilon_3\tau_3}\gamma}{\lambda},$$

where

$$\gamma = \left(\frac{\alpha\rho}{\alpha+\lambda_u}e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3} + (1-\rho)e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}\right). \tag{4}$$

The parameter $\mathcal{R}_0$ can be written as $\mathcal{R}_0 = \mathcal{R}_{01} + \mathcal{R}_{02}$, where

$$\mathcal{R}_{01} = \frac{n\pi_1 s_0 \gamma}{c}, \qquad \mathcal{R}_{02} = \frac{\pi_2 s_0 e^{\varepsilon_3 \tau_3}\gamma}{\lambda}.$$

The model has three steady states:

(i) The pathogen-free steady state $\Omega_0 = (s_0, 0, 0, 0, 0)$.

(ii) The infected steady state without antibodies $\Omega_1 = (s_1, u_1, y_1, p_1, 0)$, where

$$s_1 = \frac{s_0}{\mathcal{R}_0}, \qquad y_1 = \frac{cd}{n\pi_1 \lambda e^{-\varepsilon_3\tau_3} + c\pi_2}(\mathcal{R}_0 - 1),$$
$$u_1 = \frac{\rho\omega e^{-\varepsilon_1\tau_1}}{(\alpha + \lambda_u)\mathcal{R}_0}(\mathcal{R}_0 - 1), \qquad p_1 = \frac{n\lambda e^{-\varepsilon_3\tau_3}}{c} y_1.$$

(iii) The infected steady state with antibodies $\Omega_2 = (s_2, u_2, y_2, p_2, x_2)$, where

$$\begin{aligned} s_2 &= \frac{(\alpha + \lambda_u)u_2}{\rho e^{-\varepsilon_1\tau_1}(\pi_1 p_2 + \pi_2 y_2)}, \qquad y_2 = \frac{-B + \sqrt{B^2 - 4AC}}{2A}, \\ u_2 &= \frac{\omega\rho e^{-\varepsilon_1\tau_1}(\pi_1 m + \pi_2 r y_2)}{(\alpha + \lambda_u)[rd + (\pi_1 m + \pi_2 r y_2)]}, \qquad p_2 = \frac{m}{r}, \\ x_2 &= \frac{c}{a}\left(\frac{n\lambda e^{-\varepsilon_3\tau_3} y_2}{c p_2} - 1\right), \end{aligned} \tag{5}$$

and

$$A = \lambda\pi_2 r, \qquad B = \lambda(rd + \pi_1 m) - \frac{\gamma\omega\pi_2 r}{e^{-\varepsilon_3\tau_3}}, \qquad C = -\frac{\gamma\omega\pi_1 m}{e^{-\varepsilon_3\tau_3}}. \tag{6}$$

We note that Ω_2 exists if $\frac{n\lambda e^{-\varepsilon_3\tau_3} y_2}{c p_2} > 1$. Now we can define antibody immune response activation number as follows:

$$\mathcal{R}_1 = \frac{n\lambda e^{-\varepsilon_3\tau_3} y_2}{c p_2}. \tag{7}$$

It follows that $x_2 = \frac{c}{a}(\mathcal{R}_1 - 1)$. Thus, an infected steady state with antibodies $\Omega_2 = (s_2, u_2, y_2, p_2, x_2)$ exists when $\mathcal{R}_1 > 1$.

Lemma 2 *Let* $\mathcal{R}_0 > 1$, *then* (i) *if* $\mathcal{R}_1 \leq 1$, *then* $p_1 \leq p_2$, *and* (ii) *if* $\mathcal{R}_1 > 1$, *then* $p_1 > p_2$.

Proof (i) Let $\mathcal{R}_1 \leq 1$, then $\frac{n\lambda e^{-\varepsilon_3\tau_3} y_2}{c p_2} \leq 1$. Using Eq. (5), we obtain

$$\frac{n\lambda e^{-\varepsilon_3\tau_3}}{c p_2}\left(\frac{-B + \sqrt{B^2 - 4AC}}{2A}\right) \leq 1,$$

which implies that

$$\left(\frac{2Acp_2}{n\lambda e^{-\varepsilon_3\tau_3}} + B\right)^2 \geq B^2 - 4AC.$$

Using Eq. (6), we get

$$\frac{4cm^2 e^{\varepsilon_3\tau_3}\pi_2(n\lambda\pi_1 + c\pi_2 e^{\varepsilon_3\tau_3})}{n^2 p_2}(p_2 - p_1) \geq 0.$$

Thus $p_1 \leq p_2$. The proof of (ii) can be done in a similar way. □

2.3 Global properties

We define a function $G(\theta) = \theta - 1 - \ln\theta$ and use the notation $(s,u,y,p,x) = (s(t),u(t),y(t),p(t),x(t))$.

Theorem 1 *The pathogen-free steady state Ω_0 of system (2) is globally asymptotically stable when $\mathcal{R}_0 \leq 1$.*

Proof Define $U_0(s,u,y,p,x)$ as follows:

$$\begin{aligned}
U_0 &= \gamma s_0 G\left(\frac{s}{s_0}\right) + \frac{\alpha}{\alpha+\lambda_u}e^{-\varepsilon_3\tau_3}u + e^{-\varepsilon_3\tau_3}y \\
&\quad + \frac{(1-\mathcal{R}_{02})}{n}p + \frac{a(1-\mathcal{R}_{02})}{rn}x \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\int_0^{\tau_1}\big(\pi_1 s(t-\theta)p(t-\theta) + \pi_2 s(t-\theta)y(t-\theta)\big)\,d\theta \\
&\quad + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\int_0^{\tau_2}\big(\pi_1 s(t-\theta)p(t-\theta) + \pi_2 s(t-\theta)y(t-\theta)\big)\,d\theta \\
&\quad + e^{-\varepsilon_3\tau_3}(1-\mathcal{R}_{02})\lambda\int_0^{\tau_3} y(t-\theta)\,d\theta,
\end{aligned}$$

where γ is defined by Eq. (4). We have $U_0(s,u,y,p,x) > 0$ for all $s,u,y,p,x > 0$, while $U_0(s_0,0,0,0,0) = 0$. Calculate $\frac{dU_0}{dt}$ along the solution of system (2) as follows:

$$\begin{aligned}
\frac{dU_0}{dt} &= \gamma\left(1-\frac{s_0}{s}\right)\{\omega - ds - \pi_1 sp - \pi_2 sy\} \\
&\quad + e^{-\varepsilon_3\tau_3}\frac{\alpha}{\alpha+\lambda_u}\big\{\rho e^{-\varepsilon_1\tau_1}s(t-\tau_1)\big[\pi_1 p(t-\tau_1) + \pi_2 y(t-\tau_1)\big] - (\alpha+\lambda_u)u\big\} \\
&\quad + e^{-\varepsilon_3\tau_3}\big\{(1-\rho)e^{-\varepsilon_2\tau_2}s(t-\tau_2)\big[\pi_1 p(t-\tau_2) + \pi_2 y(t-\tau_2)\big] - \lambda y + \alpha u\big\} \\
&\quad + \frac{(1-\mathcal{R}_{02})}{n}\big\{n\lambda y(t-\tau_3)e^{-\varepsilon_3\tau_3} - cp - apx\big\} + \frac{a(1-\mathcal{R}_{02})}{rn}\{rpx - mx\} \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\big\{\pi_1 sp + \pi_2 sy - \pi_1 s(t-\tau_1)p(t-\tau_1) - \pi_2 s(t-\tau_1)y(t-\tau_1)\big\} \\
&\quad + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\big\{\pi_1 sp + \pi_2 sy - \pi_1 s(t-\tau_2)p(t-\tau_2) - \pi_2 s(t-\tau_2)y(t-\tau_2)\big\} \\
&\quad + \lambda e^{-\varepsilon_3\tau_3}(1-\mathcal{R}_{02})\big\{y - y(t-\tau_3)\big\}.
\end{aligned} \tag{8}$$

Equation (8) can be simplified as follows:

$$\begin{aligned}
\frac{dU_0}{dt} &= -\gamma\frac{d(s-s_0)^2}{s} + \gamma(\pi_1 s_0 p + \pi_2 s_0 y) - \lambda e^{-\varepsilon_3\tau_3}y \\
&\quad - \frac{c(1-\mathcal{R}_{02})}{n}p - \frac{am(1-\mathcal{R}_{02})}{rn}x + \lambda(1-\mathcal{R}_{02})e^{-\varepsilon_3\tau_3}y
\end{aligned}$$

$$= -\gamma \frac{d(s-s_0)^2}{s} + \left(\gamma \pi_1 s_0 - \frac{c(1-\mathcal{R}_{02})}{n}\right)p + \left(\gamma \pi_2 s_0 - \lambda e^{-\varepsilon_3\tau_3}\mathcal{R}_{02}\right)y - \frac{am(1-\mathcal{R}_{02})}{rn}x.$$

We have

$$\gamma \pi_1 s_0 - \frac{c}{n}(1-\mathcal{R}_{02}) = \frac{c}{n}(\mathcal{R}_0 - 1), \qquad \gamma \pi_2 s_0 - \lambda e^{-\varepsilon_3\tau_3}\mathcal{R}_{02} = 0.$$

Therefore, we obtain

$$\frac{dU_0}{dt} = -\gamma \frac{d(s-s_0)^2}{s} + \frac{c}{n}(\mathcal{R}_0 - 1)p + \frac{am}{rn}(\mathcal{R}_{02} - 1)x.$$

Thus, $\frac{dU_0}{dt} \leq 0$ when $\mathcal{R}_0 \leq 1$ for all $s, p, x > 0$. Moreover, $\frac{dU_0}{dt} = 0$ if and only if $x(t) = 0$, $p(t) = 0$, and $s(t) = s_0$. Let $D_0 = \{(s, u, y, p, x) : \frac{dU_0}{dt} = 0\}$ and D_0' be the largest invariant subset of D_0. The solutions of system (2) tend to D_0' [38]. For each element in D_0', we have $p(t) = 0$. Thus Eq. $(2)_4$ yields

$$\dot{p}(t) = 0 = n\lambda e^{-\varepsilon_3\tau_3} y(t-\tau_3).$$

Then $y(t) = 0$. From Eq. $(2)_3$ we have

$$0 = \alpha u(t).$$

Then $u(t) = 0$. It follows that D_0' contains a single point that is $\{\Omega_0\}$. From LaSalle's invariance principle, Ω_0 is globally asymptotically stable when $\mathcal{R}_0 \leq 1$. □

Theorem 2 *For system* (2), *assume that* $\mathcal{R}_1 \leq 1 < \mathcal{R}_0$, *then* Ω_1 *is globally asymptotically stable.*

Proof Let $U_1(s, u, y, p, x)$ be given as follows:

$$\begin{aligned} U_1 &= \gamma s_1 G\left(\frac{s}{s_1}\right) + \frac{\alpha}{\alpha+\lambda_u} e^{-\varepsilon_3\tau_3} u_1 G\left(\frac{u}{u_1}\right) + e^{-\varepsilon_3\tau_3} y_1 G\left(\frac{y}{y_1}\right) \\ &+ \frac{\gamma \pi_1 s_1 p_1}{n\lambda e^{-\varepsilon_3\tau_3} y_1} p_1 G\left(\frac{p}{p_1}\right) + \frac{\gamma a \pi_1 s_1 p_1}{rn\lambda e^{-\varepsilon_3\tau_3} y_1} x \\ &+ e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3} \frac{\alpha\rho}{\alpha+\lambda_u} \pi_1 s_1 p_1 \int_0^{\tau_1} G\left(\frac{s(t-\theta)p(t-\theta)}{s_1 p_1}\right) d\theta \\ &+ e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3} (1-\rho) \pi_1 s_1 p_1 \int_0^{\tau_2} G\left(\frac{s(t-\theta)p(t-\theta)}{s_1 p_1}\right) d\theta \\ &+ e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3} \frac{\alpha\rho}{\alpha+\lambda_u} \pi_2 s_1 y_1 \int_0^{\tau_1} G\left(\frac{s(t-\theta)y(t-\theta)}{s_1 y_1}\right) d\theta \\ &+ e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3} (1-\rho) \pi_2 s_1 y_1 \int_0^{\tau_2} G\left(\frac{s(t-\theta)y(t-\theta)}{s_1 y_1}\right) d\theta \\ &+ \gamma \pi_1 s_1 p_1 \int_0^{\tau_3} G\left(\frac{y(t-\theta)}{y_1}\right) d\theta. \end{aligned}$$

We have $U_1(s,u,y,p,x) > 0$ for all $s,u,y,p,x > 0$ and $U_1(s_1,u_1,y_1,p_1,0) = 0$. Calculating $\frac{dU_1}{dt}$, we obtain

$$\begin{aligned}
\frac{dU_1}{dt} &= \gamma\left(1-\frac{s_1}{s}\right)(\omega - ds - \pi_1 sp - \pi_2 sy) \\
&\quad + e^{-\varepsilon_3\tau_3}\frac{\alpha}{\alpha+\lambda_u}\left(1-\frac{u_1}{u}\right)\bigl\{\rho e^{-\varepsilon_1\tau_1}s(t-\tau_1)\bigl[\pi_1 p(t-\tau_1)+\pi_2 y(t-\tau_1)\bigr] \\
&\quad - (\alpha+\lambda_u)u\bigr\} \\
&\quad + e^{-\varepsilon_3\tau_3}\left(1-\frac{y_1}{y}\right)\bigl\{(1-\rho)e^{-\varepsilon_2\tau_2}s(t-\tau_2)\bigl[\pi_1 p(t-\tau_2)+\pi_2 y(t-\tau_2)\bigr] - \lambda y + \alpha u\bigr\} \\
&\quad + \gamma\frac{\pi_1 s_1 p_1}{n\lambda e^{-\varepsilon_3\tau_3}y_1}\left(1-\frac{p_1}{p}\right)\bigl(n\lambda e^{-\varepsilon_3\tau_3}y(t-\tau_3) - cp - apx\bigr) \\
&\quad + \gamma\frac{a\pi_1 s_1 p_1}{rn\lambda e^{-\varepsilon_3\tau_3}y_1}(rpx - mx) \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\pi_1 s_1 p_1\left[\frac{sp}{s_1p_1} - \frac{s(t-\tau_1)p(t-\tau_1)}{s_1p_1} + \ln\left(\frac{s(t-\tau_1)p(t-\tau_1)}{sp}\right)\right] \\
&\quad + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\pi_1 s_1 p_1\left[\frac{sp}{s_1p_1} - \frac{s(t-\tau_2)p(t-\tau_2)}{s_1p_1} + \ln\left(\frac{s(t-\tau_2)p(t-\tau_2)}{sp}\right)\right] \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\pi_2 s_1 y_1\left[\frac{sy}{s_1y_1} - \frac{s(t-\tau_1)y(t-\tau_1)}{s_1y_1} + \ln\left(\frac{s(t-\tau_1)y(t-\tau_1)}{sy}\right)\right] \\
&\quad + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\pi_2 s_1 y_1\left[\frac{sy}{s_1y_1} - \frac{s(t-\tau_2)y(t-\tau_2)}{s_1y_1} + \ln\left(\frac{s(t-\tau_2)y(t-\tau_2)}{sy}\right)\right] \\
&\quad + \gamma\pi_1 s_1 p_1\left[\frac{y}{y_1} - \frac{y(t-\tau_3)}{y_1} + \ln\left(\frac{y(t-\tau_3)}{y}\right)\right]. \qquad (9)
\end{aligned}$$

Simplifying Eq. (9) and applying the steady state conditions for Ω_1

$$\begin{aligned}
&\omega = ds_1 + \pi_1 s_1 p_1 + \pi_2 s_1 y_1, \\
&e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}[\pi_1 s_1 p_1 + \pi_2 s_1 y_1] = \alpha e^{-\varepsilon_3\tau_3}u_1, \\
&e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}[\pi_1 s_1 p_1 + \pi_2 s_1 y_1] + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)[\pi_1 s_1 p_1 + \pi_2 s_1 y_1] = \lambda e^{-\varepsilon_3\tau_3}y_1, \\
&p_1 = \frac{n\lambda e^{-\varepsilon_3\tau_3}y_1}{c},
\end{aligned}$$

we get

$$\begin{aligned}
\frac{dU_1}{dt} &= \gamma\left(1-\frac{s_1}{s}\right)(ds_1 - ds) + \gamma\left(1-\frac{s_1}{s}\right)(\pi_1 s_1 p_1 + \pi_2 s_1 y_1) \\
&\quad - e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\left(\pi_1 s_1 p_1\frac{s(t-\tau_1)p(t-\tau_1)u_1}{s_1p_1u} + \pi_2 s_1 y_1\frac{s(t-\tau_1)y(t-\tau_1)u_1}{s_1y_1u}\right) \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_1 p_1 + \pi_2 s_1 y_1) \\
&\quad - e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\left(\pi_1 s_1 p_1\frac{s(t-\tau_2)p(t-\tau_2)y_1}{s_1p_1y} + \pi_2 s_1 y_1\frac{s(t-\tau_2)y(t-\tau_2)}{s_1y}\right) \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_1 p_1 + \pi_2 s_1 y_1) + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)(\pi_1 s_1 p_1 + \pi_2 s_1 y_1)
\end{aligned}$$

$$\begin{aligned}
&- e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_1 p_1+\pi_2 s_1 y_1)\frac{uy_1}{u_1 y}+\gamma\pi_1 s_1 p_1\left(1-\frac{y(t-\tau_3)p_1}{y_1 p}\right)\\
&+\frac{a}{c}\gamma\pi_1 s_1(p_1-p_2)x+e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\pi_1 s_1 p_1\ln\left(\frac{s(t-\tau_1)p(t-\tau_1)}{sp}\right)\\
&+e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\pi_1 s_1 p_1\ln\left(\frac{s(t-\tau_2)p(t-\tau_2)}{sp}\right)\\
&+e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\pi_2 s_1 y_1\ln\left(\frac{s(t-\tau_1)y(t-\tau_1)}{sy}\right)\\
&+e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\pi_2 s_1 y_1\ln\left(\frac{s(t-\tau_2)y(t-\tau_2)}{sy}\right)\\
&+\gamma\pi_1 s_1 p_1\ln\left(\frac{y(t-\tau_3)}{y}\right).
\end{aligned}$$

Consider the following equalities with ($i = 1$):

$$\begin{aligned}
&\ln\left(\frac{s(t-\tau_1)p(t-\tau_1)}{sp}\right)\\
&\quad=\ln\left(\frac{s(t-\tau_1)p(t-\tau_1)u_i}{s_i p_i u}\right)+\ln\left(\frac{uy_i}{u_i y}\right)+\ln\left(\frac{yp_i}{y_i p}\right)+\ln\left(\frac{s_i}{s}\right),\\
&\ln\left(\frac{s(t-\tau_2)p(t-\tau_2)}{sp}\right)=\ln\left(\frac{s(t-\tau_2)p(t-\tau_2)y_i}{s_i p_i y}\right)+\ln\left(\frac{yp_i}{y_i p}\right)+\ln\left(\frac{s_i}{s}\right),\\
&\ln\left(\frac{s(t-\tau_1)y(t-\tau_1)}{sy}\right)=\ln\left(\frac{s(t-\tau_1)y(t-\tau_1)u_i}{s_i y_i u}\right)+\ln\left(\frac{uy_i}{u_i y}\right)+\ln\left(\frac{s_i}{s}\right),\\
&\ln\left(\frac{s(t-\tau_2)y(t-\tau_2)}{sy}\right)=\ln\left(\frac{s(t-\tau_2)y(t-\tau_2)}{s_i y}\right)+\ln\left(\frac{s_i}{s}\right),\\
&\ln\left(\frac{y(t-\tau_3)}{y}\right)=\ln\left(\frac{y(t-\tau_3)p_i}{y_i p}\right)+\ln\left(\frac{y_i p}{yp_i}\right),
\end{aligned}\tag{10}$$

we obtain

$$\begin{aligned}
\frac{dU_1}{dt}=&-\gamma\frac{d(s-s_1)^2}{s}-\gamma(\pi_1 s_1 p_1+\pi_2 s_1 y_1)G\left(\frac{s_1}{s}\right)\\
&-e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\pi_1 s_1 p_1 G\left(\frac{s(t-\tau_1)p(t-\tau_1)u_1}{s_1 p_1 u}\right)\\
&-e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\pi_2 s_1 y_1 G\left(\frac{s(t-\tau_1)y(t-\tau_1)u_1}{s_1 y_1 u}\right)\\
&-e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\pi_1 s_1 p_1 G\left(\frac{s(t-\tau_2)p(t-\tau_2)y_1}{s_1 p_1 y}\right)\\
&-e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\pi_2 s_1 y_1 G\left(\frac{s(t-\tau_2)y(t-\tau_2)}{s_1 y}\right)\\
&-e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_1 p_1+\pi_2 s_1 y_1)G\left(\frac{y_1 u}{yu_1}\right)\\
&-\gamma\pi_1 s_1 p_1 G\left(\frac{y(t-\tau_3)p_1}{y_1 p}\right)+\frac{a}{c}\gamma\pi_1 s_1(p_1-p_2)x.
\end{aligned}$$

From Lemma 2, we have $p_1 \leq p_2$ when $\mathcal{R}_1 \leq 1$. Thus, $\frac{dU_1}{dt} \leq 0$ and $\frac{dU_1}{dt} = 0$ occur at the infected steady state without antibodies Ω_1. Let D_1' be the largest invariant subset of the set $D_1 = \{(s,u,y,p,x) : \frac{dU_1}{dt} = 0\}$. Thus, the solutions of system (2) tend to D_1'. It is clear that $D_1 = \{\Omega_1\}$. Using LaSalle's invariance principle, we conclude that Ω_1 is globally asymptotically stable when $\mathcal{R}_1 \leq 1$ and $\mathcal{R}_0 > 1$. □

Theorem 3 *For system* (2), *suppose that* $\mathcal{R}_1 > 1$, *then* Ω_2 *is globally asymptotically stable.*

Proof Consider $U_2(s,u,y,p,x)$:

$$\begin{aligned}
U_2 &= \gamma s_2 G\left(\frac{s}{s_2}\right) + \frac{\alpha}{\alpha+\lambda_u} e^{-\varepsilon_3\tau_3} u_2 G\left(\frac{u}{u_2}\right) + e^{-\varepsilon_3\tau_3} y_2 G\left(\frac{y}{y_2}\right) \\
&\quad + \gamma \frac{\pi_1 s_2 p_2}{n\lambda e^{-\varepsilon_3\tau_3} y_2} p_2 G\left(\frac{p}{p_2}\right) + \gamma \frac{a\pi_1 s_2 p_2}{rn\lambda e^{-\varepsilon_3\tau_3} y_2} x_2 G\left(\frac{x}{x_2}\right) \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3} \frac{\alpha\rho}{\alpha+\lambda_u} \pi_1 s_2 p_2 \int_0^{\tau_1} G\left(\frac{s(t-\theta)p(t-\theta)}{s_2 p_2}\right) d\theta \\
&\quad + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3} (1-\rho)\pi_1 s_2 p_2 \int_0^{\tau_2} G\left(\frac{s(t-\theta)p(t-\theta)}{s_2 p_2}\right) d\theta \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3} \frac{\alpha\rho}{\alpha+\lambda_u} \pi_2 s_2 y_2 \int_0^{\tau_1} G\left(\frac{s(t-\theta)y(t-\theta)}{s_2 y_2}\right) d\theta \\
&\quad + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3} (1-\rho)\pi_2 s_2 y_2 \int_0^{\tau_2} G\left(\frac{s(t-\theta)y(t-\theta)}{s_2 y_2}\right) d\theta \\
&\quad + \gamma \pi_1 s_2 p_2 \int_0^{\tau_3} G\left(\frac{y(t-\theta)}{y_2}\right) d\theta.
\end{aligned}$$

We have $U_2(s,u,y,p,x) > 0$ for all $s,u,y,p,x > 0$, while $U_2(s,u,y,p,x)$ reaches its global minimum at Ω_2. Calculate $\frac{dU_2}{dt}$ as follows:

$$\begin{aligned}
\frac{dU_2}{dt} &= \gamma\left(1-\frac{s_2}{s}\right)(\omega - ds - \pi_1 sp - \pi_2 sy) \\
&\quad + e^{-\varepsilon_3\tau_3} \frac{\alpha}{\alpha+\lambda_u}\left(1-\frac{u_2}{u}\right) \\
&\quad \times \left\{\rho e^{-\varepsilon_1\tau_1} s(t-\tau_1)\left[\pi_1 p(t-\tau_1) + \pi_2 y(t-\tau_1)\right] - (\alpha+\lambda_u)u\right\} \\
&\quad + e^{-\varepsilon_3\tau_3}\left(1-\frac{y_2}{y}\right)\left\{(1-\rho)e^{-\varepsilon_2\tau_2} s(t-\tau_2)\left[\pi_1 p(t-\tau_2) + \pi_2 y(t-\tau_2)\right] - \lambda y + \alpha u\right\} \\
&\quad + \gamma \frac{\pi_1 s_2 p_2}{n\lambda e^{-\varepsilon_3\tau_3} y_2}\left(1-\frac{p_2}{p}\right)\left(n\lambda y(t-\tau_3)e^{-\varepsilon_3\tau_3} - cp - apx\right) \\
&\quad + \gamma \frac{a\pi_1 s_2 p_2}{rn\lambda e^{-\varepsilon_3\tau_3} y_2}\left(1-\frac{x_2}{x}\right)(rpx - mx) \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3} \frac{\alpha\rho}{\alpha+\lambda_u} \pi_1 s_2 p_2 \left[\frac{sp}{s_2 p_2} - \frac{s(t-\tau_1)p(t-\tau_1)}{s_2 p_2} + \ln\left(\frac{s(t-\tau_1)p(t-\tau_1)}{sp}\right)\right] \\
&\quad + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3} (1-\rho)\pi_1 s_2 p_2 \left[\frac{sp}{s_2 p_2} - \frac{s(t-\tau_2)p(t-\tau_2)}{s_2 p_2} + \ln\left(\frac{s(t-\tau_2)p(t-\tau_2)}{sp}\right)\right] \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3} \frac{\alpha\rho}{\alpha+\lambda_u} \pi_2 s_2 y_2 \left[\frac{sy}{s_2 y_2} - \frac{s(t-\tau_1)y(t-\tau_1)}{s_2 y_2} + \ln\left(\frac{s(t-\tau_1)y(t-\tau_1)}{sy}\right)\right]
\end{aligned}$$

$$+ e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\pi_2 s_2 y_2\left[\frac{sy}{s_2y_2} - \frac{s(t-\tau_2)y(t-\tau_2)}{s_2y_2} + \ln\left(\frac{s(t-\tau_2)y(t-\tau_2)}{sy}\right)\right]$$
$$+ \gamma\pi_1 s_2 p_2\left[\frac{y}{y_2} - \frac{y(t-\tau_3)}{y_2} + \ln\left(\frac{y(t-\tau_3)}{y}\right)\right]. \quad (11)$$

Simplifying Eq. (11) and applying the steady state conditions for Ω_2:

$$\omega = ds_2 + \pi_1 s_2 p_2 + \pi_2 s_2 y_2,$$
$$e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}[\pi_1 s_2 p_2 + \pi_2 s_2 y_2] = \alpha e^{-\varepsilon_3\tau_3}u_2,$$
$$e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}[\pi_1 s_2 p_2 + \pi_2 s_2 y_2] + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)[\pi_1 s_2 p_2 + \pi_2 s_2 y_2] = \lambda e^{-\varepsilon_3\tau_3}y_2,$$
$$p_2 = \frac{m}{r}, \qquad n\lambda e^{-\varepsilon_3\tau_3}y_2 = cp_2 + ap_2x_2,$$

we get

$$\begin{aligned}\frac{dU_2}{dt} &= \gamma\left(1-\frac{s_2}{s}\right)(ds_2 - ds) + \gamma\left(1-\frac{s_2}{s}\right)(\pi_1 s_2 p_2 + \pi_2 s_2 y_2) \\
&\quad - e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\left(\pi_1 s_2 p_2\frac{s(t-\tau_1)p(t-\tau_1)u_2}{s_2p_2u} + \pi_2 s_2 y_2\frac{s(t-\tau_1)y(t-\tau_1)u_2}{s_2y_2u}\right) \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_2 p_2 + \pi_2 s_2 y_2) \\
&\quad - e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\left(\pi_1 s_2 p_2\frac{s(t-\tau_2)p(t-\tau_2)y_2}{s_2p_2y} + \pi_2 s_2 y_2\frac{s(t-\tau_2)y(t-\tau_2)}{s_2y}\right) \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_2 p_2 + \pi_2 s_2 y_2) + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)(\pi_1 s_2 p_2 + \pi_2 s_2 y_2) \\
&\quad - e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_2 p_2 + \pi_2 s_2 y_2)\frac{uy_2}{u_2y} + \gamma\pi_1 s_2 p_2\left(1-\frac{y(t-\tau_3)p_2}{y_2p}\right) \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\pi_1 s_2 p_2\ln\left(\frac{s(t-\tau_1)p(t-\tau_1)}{sp}\right) \\
&\quad + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\pi_1 s_2 p_2\ln\left(\frac{s(t-\tau_2)p(t-\tau_2)}{sp}\right) \\
&\quad + e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\pi_2 s_2 y_2\ln\left(\frac{s(t-\tau_1)y(t-\tau_1)}{sy}\right) \\
&\quad + e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\pi_2 s_2 y_2\ln\left(\frac{s(t-\tau_2)y(t-\tau_2)}{sy}\right) \\
&\quad + \gamma\pi_1 s_2 p_2\ln\left(\frac{y(t-\tau_3)}{y}\right).\end{aligned}$$

Applying equalities (10) when ($i = 2$), we obtain

$$\begin{aligned}\frac{dU_2}{dt} &= -\gamma\frac{d(s-s_2)^2}{s} - \gamma(\pi_1 s_2 p_2 + \pi_2 s_2 y_2)G\left(\frac{s_2}{s}\right) \\
&\quad - e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\pi_1 s_2 p_2 G\left(\frac{s(t-\tau_1)p(t-\tau_1)u_2}{s_2p_2u}\right) \\
&\quad - e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}\pi_2 s_2 y_2 G\left(\frac{s(t-\tau_1)y(t-\tau_1)u_2}{s_2y_2u}\right)\end{aligned}$$

$$
\begin{aligned}
&- e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\pi_1 s_2 p_2 G\left(\frac{s(t-\tau_2)p(t-\tau_2)y_2}{s_2 p_2 y}\right) \\
&- e^{-\varepsilon_2\tau_2-\varepsilon_3\tau_3}(1-\rho)\pi_2 s_2 y_2 G\left(\frac{s(t-\tau_2)y(t-\tau_2)}{s_2 y}\right) \\
&- e^{-\varepsilon_1\tau_1-\varepsilon_3\tau_3}\frac{\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_2 p_2 + \pi_2 s_2 y_2) G\left(\frac{y_2 u}{y u_2}\right) \\
&- \gamma\pi_1 s_2 p_2 G\left(\frac{y(t-\tau_3)p_2}{y_2 p}\right).
\end{aligned}
$$

Since $\mathcal{R}_1 > 1$, then s_2, u_2, y_2, p_2, and $x_2 > 0$. We obtain $\frac{dU_2}{dt} \leq 0$, and then the solutions of system (2) tend to D_2', the largest invariant subset of $D_2 = \{(s,u,y,p,x) : \frac{dU_2}{dt} = 0\}$. Clearly, $\frac{dU_2}{dt} = 0$ when $s = s_2$, $u = u_2$, $y = y_2$, and $p = p_2$. Since $p = p_2$ in D_2', then

$$
\dot{p} = 0 = n\lambda e^{-\varepsilon_3\tau_3} y_2 - c p_2 - a p_2 x,
$$

which gives $x = x_2$. Therefore, $\frac{dU_2}{dt} = 0$ when $s = s_2$, $u = u_2$, $y = y_2$, $p = p_2$, and $x = x_2$. The global asymptotic stability of Ω_2 is conducted from LaSalle's invariance principle. □

3 Model with distributed delays

We consider a pathogen dynamics model with distributed delays:

$$
\begin{aligned}
&\dot{s}(t) = \omega - ds(t) - s(t)\big[\pi_1 p(t) + \pi_2 y(t)\big], \\
&\dot{u}(t) = \rho \int_0^{h_1} f_1(\tau)e^{-\mu_1\tau} s(t-\tau)\big[\pi_1 p(t-\tau) + \pi_2 y(t-\tau)\big]\,d\tau - (\alpha+\lambda_u)u(t), \\
&\dot{y}(t) = (1-\rho)\int_0^{h_2} f_2(\tau)e^{-\mu_2\tau} s(t-\tau)\big[\pi_1 p(t-\tau) + \pi_2 y(t-\tau)\big]\,d\tau - \lambda y(t) + \alpha u(t), \\
&\dot{p}(t) = n\lambda \int_0^{h_3} f_3(\tau)e^{-\mu_3\tau} y(t-\tau)\,d\tau - cp(t) - ap(t)x(t), \\
&\dot{x}(t) = rp(t)x(t) - mx(t),
\end{aligned}
\tag{12}
$$

where $f_1(\tau)e^{-\mu_1\tau}$ is probability that susceptible host cells contacted by the pathogens at time $t-\tau$ survived τ time units and became latently infected at time t, $f_2(\tau)e^{-\mu_2\tau}$ is probability that susceptible host cells contacted by the pathogens at time $t-\tau$ survived τ time units and became actively infected at time t, and $f_3(\tau)e^{-\mu_3\tau}$ is the probability that an immature pathogen at time $t-\tau$ survived τ time units to become a mature pathogen at time t. The probability distribution functions $f_j(\tau)$, $j = 1,\ldots,3$, satisfy the following conditions:

(i) $f_j(\tau) > 0$, (ii) $\int_0^{h_j} f_j(\tau)\,d\tau = 1$, (iii) $\int_0^{h_j} f_j(\tau)e^{\ell\tau}\,d\tau < \infty$, where $\ell > 0$.

Let $\Theta_j(\tau) = f_j(\tau)e^{-\mu_j\tau}$ and $\eta_j = \int_0^{h_j}\Theta_j(\tau)\,d\tau$, $j = 1,2,3$, thus $0 < \eta_j \leq 1$.

The initial conditions for system (12) are the same as given by (3) where $\kappa = \max\{h_1, h_2, h_3\}$.

3.1 Properties of solution

Lemma 3 *The solutions* $(s(t), u(t), y(t), p(t), x(t))$ *of system* (12) *with initial conditions* (3) *are nonnegative and ultimately bounded for* $t > 0$.

Proof From Lemma 1 we have $s(t) > 0$ for all $t \geq 0$. For $t \in [0, \kappa]$, we have

$$\begin{aligned} u(t) &= \phi_2(0)e^{-(\alpha+\lambda_u)t} \\ &\quad + \int_0^t \biggl\{ \rho \int_0^{h_1} \Theta_1(\tau)s(\theta-\tau)\bigl[\pi_1 p(\theta-\tau)+\pi_2 y(\theta-\tau)\bigr] \biggr\} e^{-(\alpha+\lambda_u)(t-\theta)}\,d\tau\,d\theta, \\ y(t) &= \phi_3(0)e^{-\lambda t} + \int_0^t \biggl\{ (1-\rho)\int_0^{h_2} \Theta_2(\tau)s(\theta-\tau)\bigl[\pi_1 p(\theta-\tau)+\pi_2 y(\theta-\tau)\bigr]\,d\tau \\ &\quad + \alpha u(\theta) \biggr\} e^{-\lambda(t-\theta)}\,d\theta, \\ p(t) &= \phi_4(0)e^{-\int_0^t (c+ax(\upsilon))\,d\upsilon} + n\lambda \int_0^t e^{-\int_\theta^t (c+ax(\upsilon))\,d\upsilon} \int_0^{h_3} \Theta_3(\tau)y(\theta-\tau)\,d\tau\,d\theta, \\ x(t) &= \phi_5(0)e^{-mt+r\int_0^t p(\theta)\,d\theta}. \end{aligned}$$

We obtain by recursive argument that $u(t) \geq 0$, $y(t) \geq 0$, $p(t) \geq 0$, and $x(t) \geq 0$ $\forall t \geq 0$.

Clearly $\lim_{t\to\infty} \sup s(t) \leq \frac{\omega}{d}$. Let us define $Y_1(t) = \rho \int_0^{h_1} \Theta_1(\tau)s(t-\tau)\,d\tau + (1-\rho) \times \int_0^{h_2} \Theta_2(\tau)s(t-\tau)\,d\tau + u(t) + y(t)$. Then

$$\begin{aligned} \dot{Y}_1(t) &= \rho \int_0^{h_1} \Theta_1(\tau)\bigl\{\omega - ds(t-\tau) - s(t-\tau)\bigl[\pi_1 p(t-\tau)+\pi_2 y(t-\tau)\bigr]\bigr\}\,d\tau \\ &\quad + (1-\rho)\int_0^{h_2} \Theta_2(\tau)\bigl\{\omega - ds(t-\tau) - s(t-\tau)\bigl[\pi_1 p(t-\tau)+\pi_2 y(t-\tau)\bigr]\bigr\}\,d\tau \\ &\quad + \rho \int_0^{h_1} \Theta_1(\tau)s(t-\tau)\bigl[\pi_1 p(t-\tau)+\pi_2 y(t-\tau)\bigr]\,d\tau - (\alpha+\lambda_u)u(t) \\ &\quad + (1-\rho)\int_0^{h_2} \Theta_2(\tau)s(t-\tau)\bigl[\pi_1 p(t-\tau)+\pi_2 y(t-\tau)\bigr]\,d\tau - \lambda y(t) + \alpha u(t) \\ &= \omega\rho \int_0^{h_1} \Theta_1(\tau)\,d\tau + \omega(1-\rho)\int_0^{h_2} \Theta_2(\tau)\,d\tau - \rho\, d\int_0^{h_1} \Theta_1(\tau)s(t-\tau)\,d\tau \\ &\quad - (1-\rho)\,d\int_0^{h_2} \Theta_2(\tau)s(t-\tau)\,d\tau - \lambda_u u(t) - \lambda y(t) \\ &\leq \omega - \sigma_1\biggl(\rho\int_0^{h_1} \Theta_1(\tau)s(t-\tau)\,d\tau + (1-\rho)\int_0^{h_2} \Theta_2(\tau)s(t-\tau)\,d\tau + u(t) + y(t)\biggr) \\ &= \omega - \sigma_1 Y_1(t), \end{aligned}$$

where $\sigma_1 = \min\{d, \lambda_u, \lambda\}$. It follows that $\lim_{t\to\infty} \sup Y_1(t) \leq \tilde{M}_1$, where $\tilde{M}_1 = \frac{\omega}{\sigma_1}$. Since $s(t) > 0$, $u(t) \geq 0$, and $y(t) \geq 0$, then $\lim_{t\to\infty} \sup u(t) \leq \tilde{M}_1$ and $\lim_{t\to\infty} \sup y(t) \leq \tilde{M}_1$. Further, let us consider $Y_2(t) = p(t) + \frac{a}{r}x(t)$. Then

$$\begin{aligned} \dot{Y}_2(t) &= n\lambda \int_0^{h_3} \Theta_3(\tau)y(t-\tau)\,d\tau - cp(t) - \frac{am}{r}x(t) \\ &\leq n\lambda\tilde{M}_1 - \sigma_2 Y_2(t), \end{aligned}$$

where $\sigma_2 = \min\{c, m\}$. Then $\lim_{t\to\infty} \sup Y_2(t) \leq \tilde{M}_2$, where $\tilde{M}_2 = \frac{n\lambda\tilde{M}_1}{\sigma_2}$. The nonnegativity of the solution implies that $\lim_{t\to\infty} \sup p(t) \leq \tilde{M}_2$ and $\lim_{t\to\infty} \sup x(t) \leq \tilde{M}_3$, where $\tilde{M}_3 = \frac{r}{a}\tilde{M}_2$. This shows the ultimate boundedness of $s(t)$, $u(t)$, $y(t)$, $p(t)$, and $x(t)$. □

3.2 Steady states and threshold parameters

For system (12) the matrices $\mathbb{F}$ and $\mathbb{V}$ are given by

$$\mathbb{F} = \begin{bmatrix} 0 & \rho\pi_2 s_0\eta_1 & \rho\pi_1 s_0\eta_1 \\ 0 & (1-\rho)\pi_2 s_0\eta_2 & (1-\rho)\pi_1 s_0\eta_2 \\ 0 & 0 & 0 \end{bmatrix}, \qquad \mathbb{V} = \begin{bmatrix} \alpha+\lambda_u & 0 & 0 \\ -\alpha & \lambda & 0 \\ 0 & -n\lambda\eta_3 & c \end{bmatrix},$$

and then

$$\mathbb{F}\mathbb{V}^{-1} = \begin{bmatrix} \tilde{\psi}_1 & \tilde{\psi}_2 & \tilde{\psi}_3 \\ \tilde{\psi}_4 & \tilde{\psi}_5 & \tilde{\psi}_6 \\ 0 & 0 & 0 \end{bmatrix},$$

where

$$\begin{aligned}
\tilde{\psi}_1 &= \frac{\alpha\rho}{(\alpha+\lambda_u)\lambda}\pi_2 s_0\eta_1 + \frac{\alpha\rho}{(\alpha+\lambda_u)c} n\pi_1 s_0\eta_1\eta_3, \\
\tilde{\psi}_2 &= \frac{\rho}{\lambda}\pi_2 s_0\eta_1 + \frac{\rho}{c} n\pi_1 s_0\eta_1\eta_3, \\
\tilde{\psi}_3 &= \frac{\rho}{c}\pi_1 s_0\eta_1, \\
\tilde{\psi}_4 &= \frac{\alpha(1-\rho)}{(\alpha+\lambda_u)\lambda}\pi_2 s_0\eta_2 + \frac{\alpha(1-\rho)}{(\alpha+\lambda_u)c} n\pi_1 s_0\eta_2\eta_3, \\
\tilde{\psi}_5 &= \frac{(1-\rho)}{\lambda}\pi_2 s_0\eta_2 + \frac{(1-\rho)}{c} n\pi_1 s_0\eta_2\eta_3, \\
\tilde{\psi}_6 &= \frac{(1-\rho)}{c}\pi_1 s_0\eta_2.
\end{aligned}$$

Thus, $\tilde{\mathcal{R}}_0$ is given by

$$\tilde{\mathcal{R}}_0 = \tilde{\mathcal{R}}_{01} + \tilde{\mathcal{R}}_{02},$$

where

$$\tilde{\mathcal{R}}_{01} = \frac{n\pi_1 s_0\tilde{\gamma}}{c}, \qquad \tilde{\mathcal{R}}_{02} = \frac{\pi_2 s_0\tilde{\gamma}}{\lambda\eta_3} \quad \text{and} \quad \tilde{\gamma} = \left(\frac{\alpha\rho}{\alpha+\lambda_u}\eta_1\eta_3 + (1-\rho)\eta_2\eta_3\right). \tag{13}$$

The model has three steady states:

(i) The pathogen-free steady state $\Omega_0 = (s_0, 0, 0, 0, 0)$.

(ii) The infected steady state without antibodies $\Omega_1 = (s_1, u_1, y_1, p_1, 0)$, where

$$\begin{aligned}
s_1 &= \frac{s_0}{\tilde{\mathcal{R}}_0}, \qquad y_1 = \frac{cd}{n\pi_1\lambda\eta_3 + c\pi_2}(\tilde{\mathcal{R}}_0 - 1), \\
u_1 &= \frac{\omega\rho\eta_1}{(\alpha+\lambda_u)\tilde{\mathcal{R}}_0}(\tilde{\mathcal{R}}_0 - 1), \qquad p_1 = \frac{n\lambda\eta_3}{c} y_1.
\end{aligned}$$

(iii) The infected steady state with antibodies $\Omega_2 = (s_2, u_2, y_2, p_2, x_2)$, where

$$\begin{aligned} s_2 &= \frac{(\alpha + \lambda_u)u_2}{\rho\eta_1(\pi_1 p_2 + \pi_2 y_2)}, \qquad y_2 = \frac{-\tilde{B} + \sqrt{\tilde{B}^2 - 4\tilde{A}\tilde{C}}}{2\tilde{A}}, \\ u_2 &= \frac{\omega\rho\eta_1(\pi_1 m + \pi_2 r y_2)}{(\alpha + \lambda_u)[rd + (\pi_1 m + \pi_2 r y_2)]}, \qquad p_2 = \frac{m}{r}, \\ x_2 &= \frac{c}{a}\left(\frac{n\lambda\eta_3 y_2}{c p_2} - 1\right), \end{aligned} \tag{14}$$

where

$$\begin{aligned} \tilde{A} &= \lambda\pi_2 r, \qquad \tilde{B} = \lambda(rd + \pi_1 m) - \frac{\tilde{\gamma}\omega\pi_2 r}{\eta_3}, \\ \tilde{C} &= -\frac{\tilde{\gamma}\omega\pi_1 m}{\eta_3}. \end{aligned} \tag{15}$$

We note that Ω_2 exists when $\frac{n\lambda\eta_3 y_2}{c p_2} > 1$. Now we define

$$\tilde{\mathcal{R}}_1 = \frac{n\lambda\eta_3 y_2}{c p_2}. \tag{16}$$

Hence, $x_2 = \frac{c}{a}(\tilde{\mathcal{R}}_1 - 1)$. Thus, an infected steady state with antibodies $\Omega_2 = (s_2, u_2, y_2, p_2, x_2)$ exists when $\tilde{\mathcal{R}}_1 > 1$.

Lemma 4 *Let* $\tilde{\mathcal{R}}_0 > 1$, *then* (i) *if* $\tilde{\mathcal{R}}_1 \le 1$, *then* $p_1 \le p_2$, *and* (ii) *if* $\tilde{\mathcal{R}}_1 > 1$, *then* $p_1 > p_2$.

Proof (i) Let $\tilde{\mathcal{R}}_1 \le 1$, then $\frac{n\lambda\eta_3 y_2}{c p_2} \le 1$. Using Eq. (14), we obtain

$$\frac{n\lambda\eta_3}{c p_2}\left(\frac{-\tilde{B} + \sqrt{\tilde{B}^2 - 4\tilde{A}\tilde{C}}}{2\tilde{A}}\right) \le 1,$$

which gives

$$\left(\frac{2\tilde{A} c p_2}{n\lambda\eta_3} + \tilde{B}\right)^2 \ge \tilde{B}^2 - 4\tilde{A}\tilde{C}.$$

Using Eq. (15), we get

$$\frac{4m^2 c\pi_2(n\lambda\eta_3\pi_1 + c\pi_2)}{n^2(\eta_3)^2 p_2}(p_2 - p_1) \ge 0.$$

It follows that $p_1 \le p_2$. In a similar way, we can prove (ii). □

3.3 Global properties

Theorem 4 *The pathogen-free steady state* Ω_0 *of system* (12) *is globally asymptotically stable when* $\tilde{\mathcal{R}}_0 \le 1$.

Proof Let $V_0(s,u,y,p,x)$ be given as follows:

$$\begin{aligned} V_0 &= \tilde{\gamma} s_0 G\left(\frac{s}{s_0}\right) + \frac{\eta_3\alpha}{\alpha+\lambda_u} u + \eta_3 y + \frac{(1-\tilde{\mathcal{R}}_{02})}{n} p + \frac{a(1-\tilde{\mathcal{R}}_{02})}{rn} x \\ &\quad + \frac{\eta_3\alpha\rho}{\alpha+\lambda_u} \int_0^{h_1} \Theta_1(\tau) \int_0^{\tau} \bigl(\pi_1 s(t-\theta)p(t-\theta) + \pi_2 s(t-\theta)y(t-\theta)\bigr)\,d\theta\,d\tau \\ &\quad + \eta_3(1-\rho) \int_0^{h_2} \Theta_2(\tau) \int_0^{\tau} \bigl(\pi_1 s(t-\theta)p(t-\theta) + \pi_2 s(t-\theta)y(t-\theta)\bigr)\,d\theta\,d\tau \\ &\quad + \lambda(1-\tilde{\mathcal{R}}_{02}) \int_0^{h_3} \Theta_3(\tau) \int_0^{\tau} y(t-\theta)\,d\theta\,d\tau, \end{aligned}$$

where $\tilde{\gamma}$ is defined by Eq. (13). We get $V_0(s,u,y,p,x) > 0$ for all $s,u,y,p,x > 0$, $V_0(s_0,0,0,0,0) = 0$ and

$$\begin{aligned} \frac{dV_0}{dt} &= \tilde{\gamma}\left(1-\frac{s_0}{s}\right)(\omega - ds - \pi_1 sp - \pi_2 sy) \\ &\quad + \frac{\eta_3\alpha}{(\alpha+\lambda_u)} \left\{\rho \int_0^{h_1} \Theta_1(\tau)s(t-\tau)\bigl[\pi_1 p(t-\tau) + \pi_2 y(t-\tau)\bigr]\,d\tau - (\alpha+\lambda_u)u\right\} \\ &\quad + \eta_3 \left\{(1-\rho) \int_0^{h_2} \Theta_2(\tau)s(t-\tau)\bigl[\pi_1 p(t-\tau) + \pi_2 y(t-\tau)\bigr]\,d\tau - \lambda y + \alpha u\right\} \\ &\quad + \frac{(1-\tilde{\mathcal{R}}_{02})}{n}\left(n\lambda \int_0^{h_3} \Theta_3(\tau)y(t-\tau)\,d\tau - cp - apx\right) + \frac{a(1-\tilde{\mathcal{R}}_{02})}{rn}(rpx - mx) \\ &\quad + \frac{\eta_3\alpha\rho}{\alpha+\lambda_u} \int_0^{h_1} \Theta_1(\tau)\bigl\{s[\pi_1 p + \pi_2 y] - s(t-\tau)\bigl[\pi_1 p(t-\tau) + \pi_2 y(t-\tau)\bigr]\bigr\}\,d\tau \\ &\quad + \eta_3(1-\rho) \int_0^{h_2} \Theta_2(\tau)\bigl\{s[\pi_1 p + \pi_2 y] - s(t-\tau)\bigl[\pi_1 p(t-\tau) + \pi_2 y(t-\tau)\bigr]\bigr\}\,d\tau \\ &\quad + \lambda(1-\tilde{\mathcal{R}}_{02}) \int_0^{h_3} \Theta_3(\tau)\bigl(y - y(t-\tau)\bigr)\,d\tau \\ &= -\tilde{\gamma}\frac{d(s-s_0)^2}{s} + \tilde{\gamma}(\pi_1 s_0 p + \pi_2 s_0 y) - \frac{c(1-\tilde{\mathcal{R}}_{02})}{n} p - \frac{am(1-\tilde{\mathcal{R}}_{02})}{rn} x - \lambda\eta_3\tilde{\mathcal{R}}_{02} y \\ &= -\tilde{\gamma}\frac{d(s-s_0)^2}{s} + \frac{c}{n}(\tilde{\mathcal{R}}_0 - 1)p + \frac{am}{rn}(\tilde{\mathcal{R}}_{02} - 1)x. \end{aligned}$$

Thus, $\frac{dV_0}{dt} \le 0$ when $\tilde{\mathcal{R}}_0 \le 1$ for all $s,p,x > 0$. Similar to Theorem 1, we get $\frac{dV_0}{dt} = 0$ at Ω_0. Therefore, Ω_0 is globally asymptotically stable when $\tilde{\mathcal{R}}_0 \le 1$. □

Theorem 5 *For system* (12), *suppose that* $\tilde{\mathcal{R}}_1 \le 1 < \tilde{\mathcal{R}}_0$, *then* Ω_1 *is globally asymptotically stable.*

Proof Let us consider $V_1(s,u,y,p,x)$:

$$\begin{aligned} V_1 &= \tilde{\gamma} s_1 G\left(\frac{s}{s_1}\right) + \frac{\alpha\eta_3}{\alpha+\lambda_u} u_1 G\left(\frac{u}{u_1}\right) + \eta_3 y_1 G\left(\frac{y}{y_1}\right) \\ &\quad + \tilde{\gamma}\frac{\pi_1 s_1 p_1}{n\lambda\eta_3 y_1} p_1 G\left(\frac{p}{p_1}\right) + \tilde{\gamma}\frac{a\pi_1 s_1 p_1}{rn\lambda\eta_3 y_1} x \end{aligned}$$

$$
\begin{aligned}
&+\frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_1 s_1 p_1\int_0^{h_1}\Theta_1(\tau)\int_0^{\tau}G\left(\frac{s(t-\theta)p(t-\theta)}{s_1p_1}\right)d\theta\,d\tau\\
&+\eta_3(1-\rho)\pi_1 s_1 p_1\int_0^{h_2}\Theta_2(\tau)\int_0^{\tau}G\left(\frac{s(t-\theta)p(t-\theta)}{s_1p_1}\right)d\theta\,d\tau\\
&+\frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_2 s_1 y_1\int_0^{h_1}\Theta_1(\tau)\int_0^{\tau}G\left(\frac{s(t-\theta)y(t-\theta)}{s_1y_1}\right)d\theta\,d\tau\\
&+\eta_3(1-\rho)\pi_2 s_1 y_1\int_0^{h_2}\Theta_2(\tau)\int_0^{\tau}G\left(\frac{s(t-\theta)y(t-\theta)}{s_1y_1}\right)d\theta\,d\tau\\
&+\tilde{\gamma}\pi_1 s_1 p_1\frac{1}{\eta_3}\int_0^{h_3}\Theta_3(\tau)\int_0^{\tau}G\left(\frac{y(t-\theta)}{y_1}\right)d\theta\,d\tau.
\end{aligned}
$$

We have $V_1(s,u,y,p,x)>0$ for all $s,u,y,p,x>0$ and $V_1(s_1,u_1,y_1,p_1,0)=0$. Calculating $\frac{dV_1}{dt}$, we obtain

$$
\begin{aligned}
\frac{dV_1}{dt} = {}&\tilde{\gamma}\left(1-\frac{s_1}{s}\right)(\omega-ds-\pi_1sp-\pi_2sy)\\
&+\frac{\eta_3\alpha}{\alpha+\lambda_u}\left(1-\frac{u_1}{u}\right)\left\{\rho\int_0^{h_1}\Theta_1(\tau)s(t-\tau)\big[\pi_1p(t-\tau)+\pi_2y(t-\tau)\big]\,d\tau\right.\\
&\left.-(\alpha+\lambda_u)u\right\}\\
&+\eta_3\left(1-\frac{y_1}{y}\right)\left\{(1-\rho)\int_0^{h_2}\Theta_2(\tau)s(t-\tau)\big[\pi_1p(t-\tau)+\pi_2y(t-\tau)\big]\,d\tau\right.\\
&\left.-\lambda y+\alpha u\right\}\\
&+\tilde{\gamma}\frac{\pi_1s_1p_1}{n\lambda\eta_3y_1}\left(1-\frac{p_1}{p}\right)\left(n\lambda\int_0^{h_3}\Theta_3(\tau)y(t-\tau)\,d\tau-cp-apx\right)\\
&+\tilde{\gamma}\frac{a\pi_1s_1p_1}{rn\lambda\eta_3y_1}(rpx-mx)\\
&+\frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_1s_1p_1\int_0^{h_1}\Theta_1(\tau)\left[\frac{sp}{s_1p_1}-\frac{s(t-\tau)p(t-\tau)}{s_1p_1}+\ln\left(\frac{s(t-\tau)p(t-\tau)}{sp}\right)\right]d\tau\\
&+\eta_3(1-\rho)\pi_1s_1p_1\int_0^{h_2}\Theta_2(\tau)\left[\frac{sp}{s_1p_1}-\frac{s(t-\tau)p(t-\tau)}{s_1p_1}\right.\\
&\left.+\ln\left(\frac{s(t-\tau)p(t-\tau)}{sp}\right)\right]d\tau\\
&+\frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_2s_1y_1\int_0^{h_1}\Theta_1(\tau)\left[\frac{sy}{s_1y_1}-\frac{s(t-\tau)y(t-\tau)}{s_1y_1}+\ln\left(\frac{s(t-\tau)y(t-\tau)}{sy}\right)\right]d\tau\\
&+\eta_3(1-\rho)\pi_2s_1y_1\int_0^{h_2}\Theta_2(\tau)\left[\frac{sy}{s_1y_1}-\frac{s(t-\tau)y(t-\tau)}{s_1y_1}\right.\\
&\left.+\ln\left(\frac{s(t-\tau)y(t-\tau)}{sy}\right)\right]d\tau\\
&+\tilde{\gamma}\pi_1s_1p_1\frac{1}{\eta_3}\int_0^{h_3}\Theta_3(\tau)\left[\frac{y}{y_1}-\frac{y(t-\tau)}{y_1}+\ln\left(\frac{y(t-\tau)}{y}\right)\right]d\tau. \qquad (17)
\end{aligned}
$$

Simplifying Eq. (17) and applying the steady state conditions for Ω_1

$$\begin{aligned}
&\omega = ds_1 + \pi_1 s_1 p_1 + \pi_2 s_1 y_1,\\
&\frac{\eta_1\eta_3\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_1 p_1 + \pi_2 s_1 y_1) = \alpha\eta_3 u_1,\\
&\frac{\eta_1\eta_3\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_1 p_1 + \pi_2 s_1 y_1) + \eta_2\eta_3(1-\rho)(\pi_1 s_1 p_1 + \pi_2 s_1 y_1) = \lambda\eta_3 y_1,\\
&p_1 = \frac{n\lambda\eta_3}{c} y_1,
\end{aligned}$$

we get

$$\begin{aligned}
\frac{dV_1}{dt} &= \tilde{\gamma}\left(1-\frac{s_1}{s}\right)(ds_1 - ds) + \tilde{\gamma}\left(1-\frac{s_1}{s}\right)(\pi_1 s_1 p_1 + \pi_2 s_1 y_1)\\
&\quad + \frac{\eta_1\eta_3\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_1 p_1 + \pi_2 s_1 y_1)\\
&\quad - \frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\int_0^{h_1}\Theta_1(\tau)\left(\pi_1 s_1 p_1 \frac{s(t-\tau)p(t-\tau)u_1}{s_1 p_1 u} + \pi_2 s_1 y_1 \frac{s(t-\tau)y(t-\tau)u_1}{s_1 y_1 u}\right)d\tau\\
&\quad - \eta_3(1-\rho)\int_0^{h_2}\Theta_2(\tau)\left(\pi_1 s_1 p_1 \frac{s(t-\tau)p(t-\tau)y_1}{s_1 p_1 y} + \pi_2 s_1 y_1 \frac{s(t-\tau)y(t-\tau)}{s_1 y}\right)d\tau\\
&\quad + \frac{\eta_1\eta_3\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_1 p_1 + \pi_2 s_1 y_1) + \eta_2\eta_3(1-\rho)(\pi_1 s_1 p_1 + \pi_2 s_1 y_1)\\
&\quad - \frac{\eta_1\eta_3\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_1 p_1 + \pi_2 s_1 y_1)\frac{u y_1}{u_1 y} + \tilde{\gamma}\pi_1 s_1 p_1\left(1 - \frac{1}{\eta_3}\int_0^{h_3}\Theta_3(\tau)\frac{y(t-\tau)p_1}{y_1 p}\,d\tau\right)\\
&\quad + \tilde{\gamma}\frac{a\pi_1 s_1}{c}(p_1 - p_2)x + \frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_1 s_1 p_1\int_0^{h_1}\Theta_1(\tau)\ln\left(\frac{s(t-\tau)p(t-\tau)}{sp}\right)d\tau\\
&\quad + \eta_3(1-\rho)\pi_1 s_1 p_1\int_0^{h_2}\Theta_2(\tau)\ln\left(\frac{s(t-\tau)p(t-\tau)}{sp}\right)d\tau\\
&\quad + \frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_2 s_1 y_1\int_0^{h_1}\Theta_1(\tau)\ln\left(\frac{s(t-\tau)y(t-\tau)}{sy}\right)d\tau\\
&\quad + \eta_3(1-\rho)\pi_2 s_1 y_1\int_0^{h_2}\Theta_2(\tau)\ln\left(\frac{s(t-\tau)y(t-\tau)}{sy}\right)d\tau\\
&\quad + \tilde{\gamma}\pi_1 s_1 p_1\frac{1}{\eta_3}\int_0^{h_3}\Theta_3(\tau)\ln\left(\frac{y(t-\tau)}{y}\right)d\tau.
\end{aligned}$$

Consider the following equalities with ($i = 1$):

$$\begin{aligned}
&\ln\left(\frac{s(t-\tau)p(t-\tau)}{sp}\right) = \ln\left(\frac{s(t-\tau)p(t-\tau)u_i}{s_i p_i u}\right) + \ln\left(\frac{u y_i}{u_i y}\right) + \ln\left(\frac{y p_i}{y_i p}\right) + \ln\left(\frac{s_i}{s}\right),\\
&\ln\left(\frac{s(t-\tau)p(t-\tau)}{sp}\right) = \ln\left(\frac{s(t-\tau)p(t-\tau)y_i}{s_i p_i y}\right) + \ln\left(\frac{y p_i}{y_i p}\right) + \ln\left(\frac{s_i}{s}\right),\\
&\ln\left(\frac{s(t-\tau)y(t-\tau)}{sy}\right) = \ln\left(\frac{s(t-\tau)y(t-\tau)u_i}{s_i y_i u}\right) + \ln\left(\frac{u y_i}{u_i y}\right) + \ln\left(\frac{s_i}{s}\right),\\
&\ln\left(\frac{s(t-\tau)y(t-\tau)}{sy}\right) = \ln\left(\frac{s(t-\tau)y(t-\tau)}{s_i y}\right) + \ln\left(\frac{s_i}{s}\right),\\
&\ln\left(\frac{y(t-\tau)}{y}\right) = \ln\left(\frac{y(t-\tau)p_i}{y_i p}\right) + \ln\left(\frac{y_i p}{y p_i}\right),
\end{aligned} \tag{18}$$

we obtain

$$\begin{aligned}\frac{dV_1}{dt} &= -\tilde{\gamma}\frac{d(s-s_1)^2}{s} - \tilde{\gamma}(\pi_1 s_1 p_1 + \pi_2 s_1 y_1)G\left(\frac{s_1}{s}\right) \\ &\quad - \frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_1 s_1 p_1 \int_0^{h_1}\Theta_1(\tau)G\left(\frac{s(t-\tau)p(t-\tau)u_1}{s_1 p_1 u}\right)d\tau \\ &\quad - \frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_2 s_1 y_1 \int_0^{h_1}\Theta_1(\tau)G\left(\frac{s(t-\tau)y(t-\tau)u_1}{s_1 y_1 u}\right)d\tau \\ &\quad - \eta_3(1-\rho)\pi_1 s_1 p_1 \int_0^{h_2}\Theta_2(\tau)G\left(\frac{s(t-\tau)p(t-\tau)y_1}{s_1 p_1 y}\right)d\tau \\ &\quad - \eta_3(1-\rho)\pi_2 s_1 y_1 \int_0^{h_2}\Theta_2(\tau)G\left(\frac{s(t-\tau)y(t-\tau)}{s_1 y}\right)d\tau \\ &\quad - \frac{\eta_1\eta_3\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_1 p_1 + \pi_2 s_1 y_1)G\left(\frac{y_1 u}{y u_1}\right) \\ &\quad - \tilde{\gamma}\pi_1 s_1 p_1 \frac{1}{\eta_3}\int_0^{h_3}\Theta_3(\tau)G\left(\frac{y(t-\tau)p_1}{y_1 p}\right)d\tau + \tilde{\gamma}\frac{a\pi_1 s_1}{c}(p_1 - p_2)x.\end{aligned}$$

From Lemma 4, we have if $\tilde{\mathcal{R}}_1 \le 1$ then $p_1 \le p_2$. Thus $\frac{dV_1}{dt} \le 0$ and $\frac{dV_1}{dt} = 0$ occur at the infected steady state without antibodies Ω_1. Thus, Ω_1 is globally asymptotically stable when $\tilde{\mathcal{R}}_1 \le 1$ and $\tilde{\mathcal{R}}_0 > 1$. □

Theorem 6 *For system (12), suppose that $\tilde{\mathcal{R}}_1 > 1$, then Ω_2 is globally asymptotically stable.*

Proof Define $V_2(s,u,y,p,x)$ as follows:

$$\begin{aligned}V_2 &= \tilde{\gamma}s_2 G\left(\frac{s}{s_2}\right) + \frac{\alpha\eta_3}{\alpha+\lambda_u}u_2 G\left(\frac{u}{u_2}\right) + \eta_3 y_2 G\left(\frac{y}{y_2}\right) \\ &\quad + \tilde{\gamma}\frac{\pi_1 s_2 p_2}{n\lambda\eta_3 y_2}p_2 G\left(\frac{p}{p_2}\right) + \tilde{\gamma}\frac{a\pi_1 s_2 p_2}{rn\lambda\eta_3 y_2}x_2 G\left(\frac{x}{x_2}\right) \\ &\quad + \frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_1 s_2 p_2 \int_0^{h_1}\Theta_1(\tau)\int_0^{\tau}G\left(\frac{s(t-\theta)p(t-\theta)}{s_2 p_2}\right)d\theta\,d\tau \\ &\quad + \eta_3(1-\rho)\pi_1 s_2 p_2 \int_0^{h_2}\Theta_2(\tau)\int_0^{\tau}G\left(\frac{s(t-\theta)p(t-\theta)}{s_2 p_2}\right)d\theta\,d\tau \\ &\quad + \frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_2 s_2 y_2 \int_0^{h_1}\Theta_1(\tau)\int_0^{\tau}G\left(\frac{s(t-\theta)y(t-\theta)}{s_2 y_2}\right)d\theta\,d\tau \\ &\quad + \eta_3(1-\rho)\pi_2 s_2 y_2 \int_0^{h_2}\Theta_2(\tau)\int_0^{\tau}G\left(\frac{s(t-\theta)y(t-\theta)}{s_2 y_2}\right)d\theta\,d\tau \\ &\quad + \tilde{\gamma}\pi_1 s_2 p_2 \frac{1}{\eta_3}\int_0^{h_3}\Theta_3(\tau)\int_0^{\tau}G\left(\frac{y(t-\theta)}{y_2}\right)d\theta\,d\tau.\end{aligned}$$

We have $V_2(s,u,y,p,x) > 0$ for all $s,u,y,p,x > 0$, while $V_2(s,u,y,p,x)$ reaches its global minimum at Ω_2. Calculate $\frac{dV_2}{dt}$ as follows:

$$\begin{aligned}\frac{dV_2}{dt} &= \tilde{\gamma}\left(1-\frac{s_2}{s}\right)(\omega - ds - \pi_1 sp - \pi_2 sy) + \frac{\alpha\eta_3}{\alpha+\lambda_u}\left(1-\frac{u_2}{u}\right) \\ &\quad \times \left\{\rho\int_0^{h_1}\Theta_1(\tau)s(t-\tau)\big[\pi_1 p(t-\tau) + \pi_2 y(t-\tau)\big]d\tau - (\alpha+\lambda_u)u\right\}\end{aligned}$$

$$
\begin{aligned}
&+ \eta_3\left(1-\frac{y_2}{y}\right)\\
&\times \left\{(1-\rho)\int_0^{h_2}\Theta_2(\tau)s(t-\tau)\bigl[\pi_1 p(t-\tau)+\pi_2 y(t-\tau)\bigr]\,d\tau-\lambda y+\alpha u\right\}\\
&+ \tilde{\gamma}\frac{\pi_1 s_2 p_2}{n\lambda\eta_3 y_2}\left(1-\frac{p_2}{p}\right)\left(n\lambda\int_0^{h_3}\Theta_3(\tau)y(t-\tau)\,d\tau-cp-apx\right)\\
&+ \tilde{\gamma}\frac{a\pi_1 s_2 p_2}{rn\lambda\eta_3 y_2}\left(1-\frac{x_2}{x}\right)(rpx-mx)+\frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_1 s_2 p_2\\
&\times \int_0^{h_1}\Theta_1(\tau)\left[\frac{sp}{s_2p_2}-\frac{s(t-\tau)p(t-\tau)}{s_2p_2}+\ln\left(\frac{s(t-\tau)p(t-\tau)}{sp}\right)\right]d\tau\\
&+ \eta_3(1-\rho)\pi_1 s_2 p_2\\
&\times \int_0^{h_2}\Theta_2(\tau)\left[\frac{sp}{s_2p_2}-\frac{s(t-\tau)p(t-\tau)}{s_2p_2}+\ln\left(\frac{s(t-\tau)p(t-\tau)}{sp}\right)\right]d\tau\\
&+ \frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\pi_2 s_2 y_2\int_0^{h_1}\Theta_1(\tau)\left[\frac{sy}{s_2y_2}-\frac{s(t-\tau)y(t-\tau)}{s_2y_2}+\ln\left(\frac{s(t-\tau)y(t-\tau)}{sy}\right)\right]d\tau\\
&+ \eta_3(1-\rho)\pi_2 s_2 y_2\\
&\times \int_0^{h_2}\Theta_2(\tau)\left[\frac{sy}{s_2y_2}-\frac{s(t-\tau)y(t-\tau)}{s_2y_2}+\ln\left(\frac{s(t-\tau)y(t-\tau)}{sy}\right)\right]d\tau\\
&+ \tilde{\gamma}\pi_1 s_2 p_2\frac{1}{\eta_3}\int_0^{h_3}\Theta_3(\tau)\left[\frac{y}{y_2}-\frac{y(t-\tau)}{y_2}+\ln\left(\frac{y(t-\tau)}{y}\right)\right]d\tau. \qquad (19)
\end{aligned}
$$

Simplifying Eq. (19) and applying the steady state conditions for Ω_2

$$
\begin{aligned}
&\omega = ds_2+\pi_1 s_2 p_2+\pi_2 s_2 y_2,\\
&\frac{\eta_1\eta_3\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_2 p_2+\pi_2 s_2 y_2)=\alpha\eta_3 u_2,\\
&\frac{\eta_1\eta_3\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_2 p_2+\pi_2 s_2 y_2)+\eta_2\eta_3(1-\rho)(\pi_1 s_2 p_2+\pi_2 s_2 y_2)=\lambda\eta_3 y_2,\\
&p_2=\frac{m}{r},\qquad n\lambda\eta_3 y_2=cp_2+ap_2x_2,
\end{aligned}
$$

we get

$$
\begin{aligned}
\frac{dV_2}{dt} &= \tilde{\gamma}\left(1-\frac{s_2}{s}\right)(ds_2-ds)+\tilde{\gamma}\left(1-\frac{s_2}{s}\right)(\pi_1 s_2 p_2+\pi_2 s_2 y_2)\\
&- \frac{\eta_3\alpha\rho}{\alpha+\lambda_u}\int_0^{h_1}\Theta_1(\tau)\left(\pi_1 s_2 p_2\frac{s(t-\tau)p(t-\tau)u_2}{s_2p_2u}+\pi_2 s_2 y_2\frac{s(t-\tau)y(t-\tau)u_2}{s_2y_2u}\right)d\tau\\
&+ \frac{\eta_1\eta_3\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_2 p_2+\pi_2 s_2 y_2)\\
&- \eta_3(1-\rho)\int_0^{h_2}\Theta_2(\tau)\left(\pi_1 s_2 p_2\frac{s(t-\tau)p(t-\tau)y_2}{s_2p_2y}+\pi_2 s_2 y_2\frac{s(t-\tau)y(t-\tau)}{s_2y}\right)d\tau\\
&+ \frac{\eta_1\eta_3\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_2 p_2+\pi_2 s_2 y_2)+\eta_1\eta_3(1-\rho)(\pi_1 s_2 p_2+\pi_2 s_2 y_2)\\
&- \frac{\eta_1\eta_3\alpha\rho}{\alpha+\lambda_u}(\pi_1 s_2 p_2+\pi_2 s_2 y_2)\frac{uy_2}{u_2y}+\tilde{\gamma}\pi_1 s_2 p_2\left(1-\frac{1}{\eta_3}\int_0^{h_3}\Theta_3(\tau)\frac{y(t-\tau)p_2}{y_2p}\,d\tau\right)
\end{aligned}
$$

$$+ \frac{\eta_3 \alpha \rho}{\alpha + \lambda_u} \pi_1 s_2 p_2 \int_0^{h_1} \Theta_1(\tau) \ln\left(\frac{s(t-\tau)p(t-\tau)}{sp}\right) d\tau$$
$$+ \eta_3(1-\rho)\pi_1 s_2 p_2 \int_0^{h_2} \Theta_2(\tau) \ln\left(\frac{s(t-\tau)p(t-\tau)}{sp}\right) d\tau$$
$$+ \frac{\eta_3 \alpha \rho}{\alpha + \lambda_u} \pi_2 s_2 y_2 \int_0^{h_1} \Theta_1(\tau) \ln\left(\frac{s(t-\tau)y(t-\tau)}{sy}\right) d\tau$$
$$+ \eta_3(1-\rho)\pi_2 s_2 y_2 \int_0^{h_2} \Theta_2(\tau) \ln\left(\frac{s(t-\tau)y(t-\tau)}{sy}\right) d\tau$$
$$+ \tilde{\gamma} \pi_1 s_2 p_2 \frac{1}{\eta_3} \int_0^{h_3} \Theta_3(\tau) \ln\left(\frac{y(t-\tau)}{y}\right) d\tau.$$

Considering equalities (18) with ($i = 2$), we obtain

$$\begin{aligned}
\frac{dV_2}{dt} = {} & -\tilde{\gamma} \frac{d(s-s_2)^2}{s} - \tilde{\gamma}(\pi_1 s_2 p_2 + \pi_2 s_2 y_2) G\left(\frac{s_2}{s}\right) \\
& - \frac{\eta_3 \alpha \rho}{\alpha + \lambda_u} \pi_1 s_2 p_2 \int_0^{h_1} \Theta_1(\tau) G\left(\frac{s(t-\tau)p(t-\tau)u_2}{s_2 p_2 u}\right) d\tau \\
& - \frac{\eta_3 \alpha \rho}{(\alpha + \lambda_u)} \pi_2 s_2 y_2 \int_0^{h_1} \Theta_1(\tau) G\left(\frac{s(t-\tau)y(t-\tau)u_2}{s_2 y_2 u}\right) d\tau \\
& - \eta_3(1-\rho)\pi_1 s_2 p_2 \int_0^{h_2} \Theta_2(\tau) G\left(\frac{s(t-\tau)p(t-\tau)y_2}{s_2 p_2 y}\right) d\tau \\
& - \eta_3(1-\rho)\pi_2 s_2 y_2 \int_0^{h_2} \Theta_2(\tau) G\left(\frac{s(t-\tau)y(t-\tau)}{s_2 y}\right) d\tau \\
& - \frac{\eta_1 \eta_3 \alpha \rho}{\alpha + \lambda_u} (\pi_1 s_2 p_2 + \pi_2 s_2 y_2) G\left(\frac{y_2 u}{y u_2}\right) \\
& - \tilde{\gamma} \pi_1 s_2 p_2 \frac{1}{\eta_3} \int_0^{h_3} \Theta_3(\tau) G\left(\frac{y(t-\tau)p_2}{y_2 p}\right) d\tau.
\end{aligned}$$

Since $\tilde{\mathcal{R}}_1 > 1$, then s_2, u_2, y_2, p_2, and $x_2 > 0$. We have $\frac{dV_2}{dt} \leq 0$, then following the proof of Theorem 3, one can show that Ω_2 is globally asymptotically stable. □

4 Numerical simulations

We present some numerical simulations to approve our theoretical results of system (2) with parameter values given in Table 1. We consider different initial values:

IV$_1$: $\phi_1(\theta) = 800$, $\phi_2(\theta) = 2$, $\phi_3(\theta) = 2$, $\phi_4(\theta) = 6$, $\phi_5(\theta) = 2$,

Table 1 The data of model (2)

Parameter	Value	Parameter	Value	Parameter	Value
ω	10	τ_1	varied	m	0.1
d	0.01	τ_2	varied	r	varied
π_1	varied	τ_3	varied	ε_1	1
π_2	varied	ρ	0.5	ε_2	1
λ	0.5	α	0.05	ε_3	1
λ_u	0.5	n	10		
c	2	a	0.1		

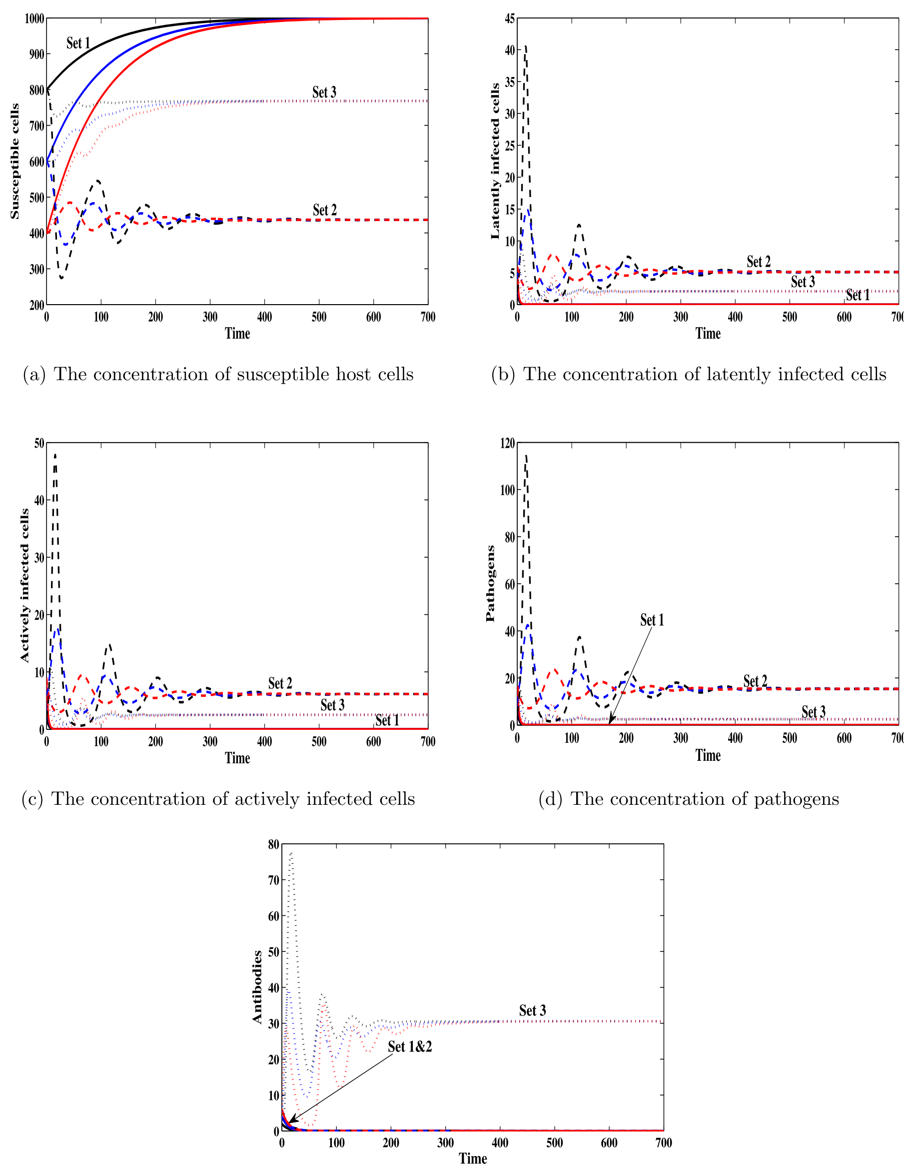
IV$_2$: $\phi_1(\theta) = 600$, $\phi_2(\theta) = 4$, $\phi_3(\theta) = 6$, $\phi_4(\theta) = 9$, $\phi_5(\theta) = 4$,
IV$_3$: $\phi_1(\theta) = 400$, $\phi_2(\theta) = 6$, $\phi_3(\theta) = 9$, $\phi_4(\theta) = 15$, $\phi_5(\theta) = 6$,
IV$_4$: $\phi_1(\theta) = 700$, $\phi_2(\theta) = 1$, $\phi_3(\theta) = 1$, $\phi_4(\theta) = 9$, $\phi_5(\theta) = 4$, $\theta \in [-\max\{\tau_1, \tau_2, \tau_3\}, 0]$.

The stability of the steady states will be investigated by varying six parameters r, π_1, π_2, τ_1, τ_2, and τ_3 and fixing the other parameters.

Case (I) Effect of the parameters π_1, π_2, and r:

We choose $\tau_1 = \tau_2 = \tau_3 = 0$ and π_1, π_2, and r are varied.

Set(1) $\pi_1 = 0.0001$, $\pi_2 = 0.0001$, and $r = 0.001$. This yields $\mathcal{R}_0 = 0.3818 < 1$ and $\mathcal{R}_1 = 0.1401 < 1$. Figure 1 shows that the concentration of susceptible cells increases and tends to the value $\omega/d = 1000$. In addition, the concentrations of infected cells, free pathogens,



(a) The concentration of susceptible host cells

(b) The concentration of latently infected cells

(c) The concentration of actively infected cells

(d) The concentration of pathogens

(e) The concentration of antibodies.

Figure 1 The simulation of trajectories of system (2) for Case (I) and antibodies are decreased and tend to zero for IV_1–IV_3. Therefore, there exists only one steady state that is Ω_0 and it is globally asymptotically stable. This shows the validity of Theorem 1.

Set(2) $\pi_1 = 0.0006$, $\pi_2 = 0.0006$, and $r = 0.001$. With these values we obtain $\mathcal{R}_0 = 2.2909 > 1$ and $\mathcal{R}_1 = 0.2367 < 1$. Figure 1 shows that the solutions of the system tend to the steady state $\Omega_1 = (436.5079, 5.1227, 6.1472, 15.368, 0)$ for all the three initial values IV_1–IV_3. Therefore, Ω_1 exists and it is globally asymptotically stable. Hence, the result of Theorem 2 is confirmed.

Set(3) $\pi_1 = 0.0006$, $\pi_2 = 0.0006$, and $r = 0.04$ and then $\mathcal{R}_0 = 2.2909 > 1$ and $\mathcal{R}_1 = 2.5285 > 1$. Figure 1 shows that the solutions of the system approach the steady state $\Omega_2 = (768.22, 2.1071, 2.5285, 2.5, 30.5702)$ for all the initial values IV_1–IV_3. Thus, Ω_2 exists and it is globally asymptotically stable. This validates the result of Theorem 3.

Case (II) Effect of time delay parameters:

For this case, we take IV_4 and choose the values $\pi_1 = 0.0006$, $\pi_2 = 0.0006$, and $r = 0.04$. Let us consider the case $\tau = \tau_1 = \tau_2 = \tau_3$. We compute the values of $\mathcal{R}_0$, $\mathcal{R}_1$ and the steady states of system (2) as a function of τ (see Table 2).

Table 2 shows that the values of $\mathcal{R}_0$ and $\mathcal{R}_1$ are decreased as τ is increased. Moreover, we have the following cases:

(i) Ω_2 exists and it is globally asymptotically stable when $0 \leq \tau < 0.368091$;
(ii) Ω_1 exists and it is globally asymptotically stable when $0.368091 \leq \tau < 0.499367$;
(iii) Ω_0 is globally asymptotically stable when $\tau \geq 0.499367$.

Figure 2 depicts that the numerical results are also compatible with the results of Theorems 1–3.

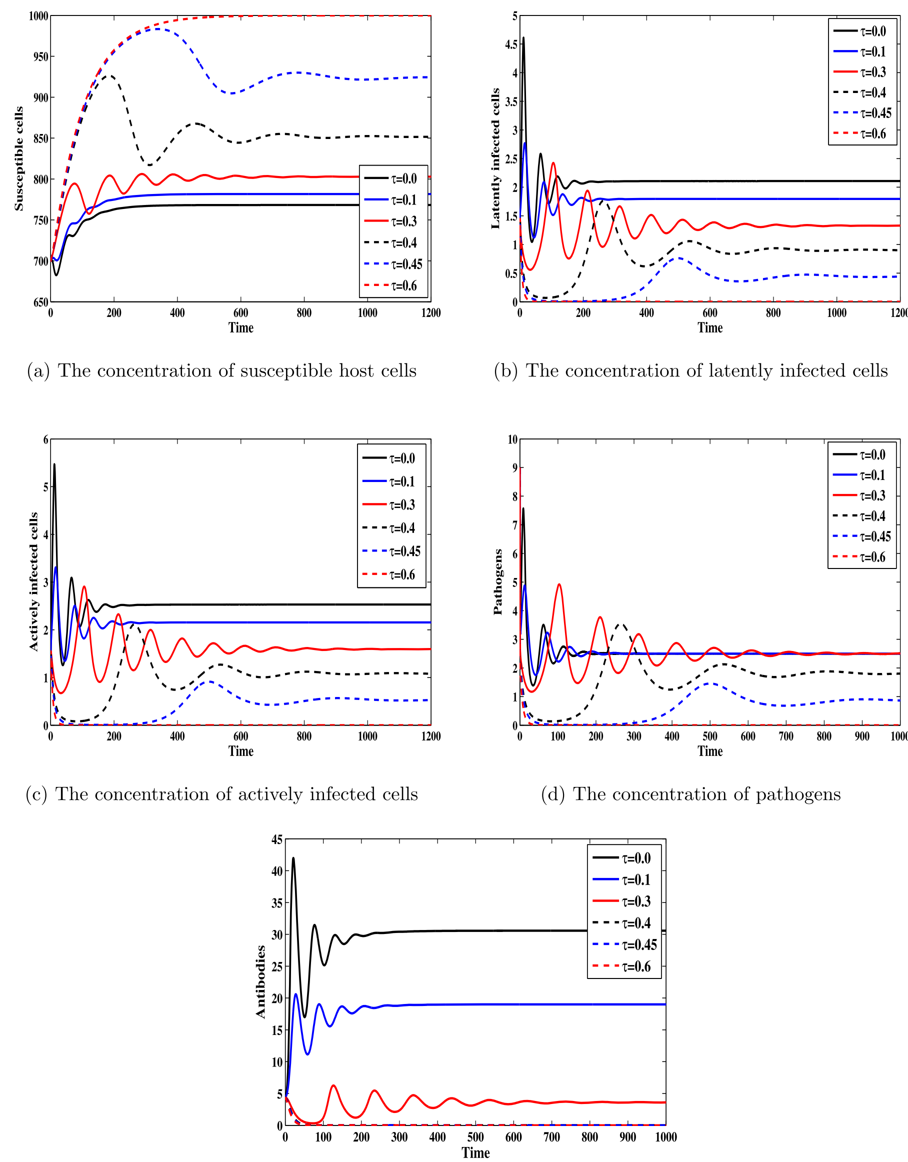
This means that the time delay can play the role of controller which can be designed to stabilize the system around the pathogen-free steady state Ω_0.

5 Conclusion

In this paper, we have studied two pathogen dynamics models with antibody immune response. Both pathogen-to-susceptible and infected-to-susceptible transmissions have been considered. We have considered two types of infected cells, latently infected cells, and actively infected cells. We have incorporated three types of discrete-time delays and distributed-time delays in the first and second models, respectively. We have shown that the solutions of the system are nonnegative and ultimately bounded, which ensures the well-posedness of the models. For each model, we have derived two threshold parameters $\mathcal{R}_0$ (the basic reproduction number) and $\mathcal{R}_1$ (the antibody response activation number), which fully determine the existence and stability of the three steady states of the model.

Table 2 The values of $\mathcal{R}_0$ and $\mathcal{R}_1$ for system (2) with different values of τ

τ	Steady state	$\mathcal{R}_0$	$\mathcal{R}_1$
0.0	$\Omega_2 = (768.22, 2.10709, 2.52851, 2.5, 30.5702)$	2.29091	2.52851
0.1	$\Omega_2 = (781.675, 1.7959, 2.15508, 2.5, 18.99995)$	1.932	1.95
0.3	$\Omega_2 = (802.817, 1.32797, 1.59356, 2.5, 3.61083)$	1.38295	1.18054
0.35	$\Omega_2 = (807.127, 1.2356, 1.48271, 2.5, 0.897031)$	1.27384	1.04485
0.368091	$\Omega_1 = (808.604, 1.20415, 1.44498, 2.5, 0)$	1.2367	1
0.4	$\Omega_1 = (851.774, 0.903263, 1.08392, 1.81643, 0)$	1.17402	0.92589
0.45	$\Omega_1 = (923.657, 0.442529, 0.531034, 0.846506, 0)$	1.08265	0.82142
0.499367	$\Omega_0 = (1000, 0, 0, 0, 0)$	1	0.73062
0.5	$\Omega_0 = (1000, 0, 0, 0, 0)$	0.99899	0.72953
0.6	$\Omega_0 = (1000, 0, 0, 0, 0)$	0.85209	0.57720



(a) The concentration of susceptible host cells

(b) The concentration of latently infected cells

(c) The concentration of actively infected cells

(d) The concentration of pathogens

(e) The concentration of antibodies.

Figure 2 The simulation of trajectories of system (2) with different values of τ for Case (II)

We have investigated the global stability of all steady states of the model by using Lyapunov method and LaSalle's invariance principle. We have proven that (i) if $\mathcal{R}_0 \leq 1$, then the pathogen-free steady state Ω_0 is globally asymptotically stable; (ii) if $\mathcal{R}_1 \leq 1 < \mathcal{R}_0$, then the infected steady state without antibodies Ω_1 is globally asymptotically stable; and (iii) if $\mathcal{R}_1 > 1$, then the infected steady state with antibodies Ω_2 is globally asymptotically stable. We have conducted numerical simulations and have shown that both the theoretical and numerical results are consistent.

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Competing interests
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Authors' contributions
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