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Research article

Analysis of a stochastic HBV infection model with delayed immune response

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Abstract: Considering the environmental factors and uncertainties, we propose, in this paper, a higher-order stochastically perturbed delay differential model for the dynamics of hepatitis B virus (HBV) infection with immune system. Existence and uniqueness of an ergodic stationary distribution of positive solution to the system are investigated, where the solution fluctuates around the endemic equilibrium of the deterministic model and leads to the stochastic persistence of the disease. Under some conditions, infection-free can be obtained in which the disease dies out exponentially with probability one. Some numerical simulations, by using Milstein's scheme, are carried out to show the effectiveness of the obtained results. The intensity of white noise plays an important role in the treatment of infectious diseases.

Keywords: HBV; Lyapunov functional; Milstein's scheme; non-linear perturbations; stationary distribution and ergodicity; time-delays

1. Introduction

Hepatitis B is a liver infection, caused by the hepatitis B virus (HBV), is responsible for more than 400 million chronic infections worldwide [1]. HBV is a leading cause of broad-spectrum liver diseases such as hepatitis, cirrhosis and liver cancer [2]. Some people with HBV are sick for only a few weeks (known as 'acute' infection), but for others, the disease progresses to a serious, lifelong illness known as 'chronic' hepatitis B. Majority of infected adults successfully clear the virus and acquires lifelong immunity [3]. The immune response to HBV-encoded antigens is responsible both for viral clearance and for disease pathogenesis during this infection. While the humoral antibody response to viral envelope antigens contributes to the clearance of circulating virus particles, the cellular immune response to the envelope, nucleocapsid, and polymerase antigens eliminates infected cells. During acute HBV infection, cytotoxic T lymphocytes (CTLs) can directly attack infected hepatocytes and

participate in the pathogenesis of liver disease by orchestrating diverse components of the immune system; see [4, 5].

In fact, the process intercellular transmission and virus-to-cell infection is not instantaneous but needs to be completed over a period of time, so it is necessary to consider the effect of time-delays on the HBV system [6–9]. Moreover, the parameters for growth and interactions depend on the state and nature of the virus, the condition of the immune system, and the environment in which the interaction takes place the body [10]. The environment of the body is determined by the overall health of the individual. One way to explore the impact of body environmental factors on the dynamics of HBV infection could be the extension of the deterministic description of the virus-CTL interaction to include the stochastic forcing either in an additive or multiplicative way. Mathematical models to investigate the dynamics of HBV transmission within environmental noise have been studied by many researchers, among them [11–14].

Many other mathematical models have been designed to evaluate the effect of public health programs and provided long-term predictions regarding the disease prevalence and control [15–19]. More and more attentions have been paid to the study of virus dynamics within-host, which can provide insights into virus infection and dynamics, as well as to how an infection can be reduced or even eradicated, see [20–24]. However, most of these approaches are based on deterministic models and do not consider the randomness in cell transmission and effect of environmental variability.

Motivated by the mentioned biological and mathematical considerations, in the present paper, we investigate the dynamics of stochastic delay differential equations (SDDEs) of HBV model with cell-to-cell transmission and CTLs immune response. For more realistic situation of the development process of the disease, we incorporate the effect of multiple time-delays and randomization within a host. The organization of the rest of this paper is as follows: In Section 2, we propose a stochastic delay differential model for HBV infection. In Section 3, we investigate existence and uniqueness of the global positive solution, and study existence of stationary distribution in Section 4. Possible extinction of the disease is studied in Section 5. Some numerical results and simulations are provided in Section 6 to show the effectiveness of the theoretical results. Concluding remarks are discussed in the last Section.

2. Time-delay dstochastic model of HBV

Although HBV replication at the cellular level is not fully understood, in this paper, we propose a new model of stochastic delay differential equations (SDDEs) for HBV replications in one host. We assume that during HBV infection, uninfected (healthy) hepatocytes can be infected not only by newly released free virus, but also by contacting with infected hepatocytes. We also assume that the cytotoxic T lymphocytes (CTLs) can specifically attack the target infected host cells. Of course there is an intracellular time-delay (time-lag) between the infection of a cell and the viral particles emission, and virus production. Time-delay is also required to represent incubation period, the time required for the production of new virus particles. Herein, based on the basic model of Nowak et al. [25], we introduce a delay differential model to combine the CTLs population with HBV infection. The model takes the

form

$$\begin{aligned}
\frac{dH(t)}{dt} &= \eta_1 - \alpha_1 H(t) - \beta_1 H(t)V(t) - \beta_2 H(t)I(t) \\
\frac{dI(t)}{dt} &= \beta_1 H(t-\tau_1)V(t-\tau_1) + \beta_2 H(t-\tau_1)I(t-\tau_1) - \beta_3 I(t)D(t) - \alpha_2 I(t) \\
\frac{dV(t)}{dt} &= aI(t-\tau_2) - \alpha_3 V(t) \\
\frac{dD(t)}{dt} &= \eta_2 - \alpha_4 D(t) + \beta_4 I(t)D(t).
\end{aligned} \tag{2.1}$$

$H(t)$, $I(t)$, $V(t)$, and $D(t)$, respectively, denote the healthy hepatocytes that are not infected by the viruses, the infected hepatocytes which are infected by viruses, hepatitis B viruses and CTLs. Time-delay τ_1 is considered, in the first term of the second equation, to justify the required time between initial infection of a cell by HBV and the release of new virions. It is also incorporated in the second term to consider the reaction time that healthy hepatocytes become infected by the infected cell contacts and then transformed into the infected hepatocytes; While τ_2 stands for the time necessary for the newly produced particles to become mature then infectious particles. The healthy cells become infected either by free viruses at rate $\beta_1 HV$ (virus-to-cell infection mode), or by direct contact with an infected cell at rate $\beta_2 HI$ (cell-to-cell transmission mode). Hence, the term $\beta_1 HV + \beta_2 HI$ represents the total infection rate of uninfected cells. Infected cells are eliminated by CTLs at rate $\beta_3 ID$, a is the production rate of free viruses by infected cells; While CTLs are produced at a constant η_2 from the thymus and at the rate $\beta_4 ID$ as a result of stimulation of infected cells (see Figure 1). (Existence of the equilibrium points and basic reproduction number $\mathcal{R}_0$ for the deterministic system (2.1) are given in the Appendix.) The description of the model parameters is presented in Table 1.

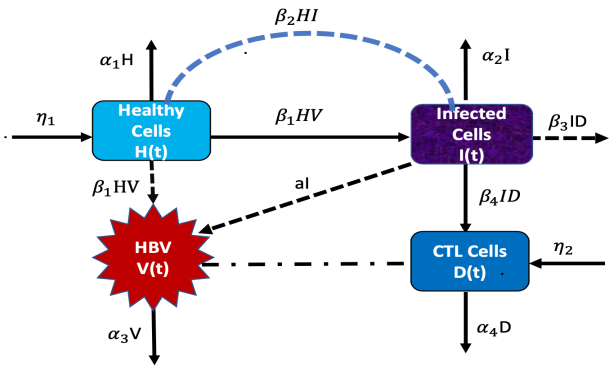

Figure 1. Mathematical scheme of system (2.1).

As a matter of fact, there are inevitably random disturbances in the process of HBV infection within-host, such as temperature fluctuation, mood fluctuation and other physiological rhythm changes, which may affect the dynamics of HBV infection. Taking this into consideration enables a lot of authors to introduce randomness into deterministic model of biological systems to reveal the effect of environmental variability, see [26–28].

For more realistic situation of the development process of the disease, we incorporate the effect of randomization within-host by introducing nonlinear perturbation on the natural death rate with white noise into each equation of system (2.1). In reality, the parameters associated with the Hepatitis B model are not certain, but the interval in which it belongs to can readily be determined. Therefore, we propose a delayed stochastic model of the form

$$\begin{aligned} dH(t) &= [\eta_1 - \alpha_1 H(t) - \beta_1 H(t)V(t) - \beta_2 H(t)I(t)]dt + (\nu_{11}H(t) + \nu_{12})H(t)dW_1 \\ dI(t) &= [\beta_1 H(t-\tau_1)V(t-\tau_1) + \beta_2 H(t-\tau_1)I(t-\tau_1) - \beta_3 I(t)D(t) - \alpha_2 I(t)]dt + \\ &\quad (\nu_{21} + \nu_{22}I(t))I(t)dW_2 \\ dV(t) &= [aI(t-\tau_2) - \alpha_3 V(t)]dt + (\nu_{31} + \nu_{32}V(t))V(t)dW_3 \\ dD(t) &= [\eta_2 - \alpha_4 D(t) + \beta_4 I(t)D(t)]dt + (\nu_{41} + \nu_{42}D(t))D(t)dW_4, \end{aligned} \tag{2.2}$$

subject to the initial conditions

$$\begin{aligned} H(\zeta) = \varphi_1(\zeta), \quad I(\zeta) = \varphi_2(\zeta), \quad V(\zeta) = \varphi_3(\zeta), \quad D(\zeta) = \varphi_4(\zeta), \\ \zeta \in [-\tau, 0], \quad \tau = \max\{\tau_1, \tau_2\}, \quad \varphi_i(\zeta) \in C, \quad i = 1, 2, 3, 4. \end{aligned} \tag{2.3}$$

Here, C is the family of Lebesgue integrable functions $C([-\tau, 0], \mathbb{R}^4_+)$. Such that, $\nu_{11}, \nu_{12}, \nu_{21}, \nu_{22}, \nu_{31}$, $\nu_{32}, \nu_{41}, \nu_{42}$, represent the intensities of the white noise and W_i, $(i = 1, 2, 3, 4)$ is a real-valued standard Brownian motion defined on a complete probability space $(\Omega, \mathcal{A}, \mathbb{P})$ satisfying the usual conditions [29]. We assume that the parameters α_i, $i = 1, 2, 3, 4$, are distributed by some non linear stochastic noise [30]. The random perturbation may be dependent on square of the state variables H, I, V and D of system (2.2), respectively, that is to say $\alpha_1 \to \alpha_1 - (\nu_{11}H + \nu_{12})dW_1$, $\alpha_2 \to \alpha_2 - (\nu_{21} + \nu_{22}I)dW_2$, $\alpha_3 \to \alpha_3 - (\nu_{31} + \nu_{32}V)dW_3$, $\alpha_4 \to \alpha_4 - (\nu_{41} + \nu_{42}D)dW_4$.

Table 1. Description of the model parameters.

Parameters	Description
η_1	Production rate of the uninfected hepatocytes from bone marrow and other organs
η_2	Production rate of the CTLs from the thymus
α_1	Natural death rate of the uninfected hepatocytes
α_2	Natural death rate of the infected hepatocytes
α_3	Decay rate of the free viruses
α_4	Death rate of the CTLs
β_1	Effective contact rate between uninfected hepatocytes and virus
β_2	Effective contact rate between uninfected and infected hepatocytes
β_3	Elimination rate of infected hepatocytes by CTLs
β_4	Production rate of CTLs due to the stimulation of infected cells
a	Production rate of free viruses from infected cells

3. Existence and uniqueness of the global positive solution

In this section, we provide some conditions that guarantee a unique global positive solution of the SDDEs system (2.2). This can be achieved that if the coefficients of the system realize the growth and

Lipschitzian conditions, then there will be a positive solution.

Theorem 1. *For any initial value system (2.3), there is a unique positive solution* $(H(t),I(t),V(t),D(t))$ *of system (2.2), on* $t \geq -\tau$ *and the solution will remain in* $\mathbb{R}^4_+$ *almost surely (a.s.).*

Proof. Since all the coefficients of system (2.2) are Lipschitz continuous, therefore, there is a unique local solution $(H(t), I(t), V(t), D(t))$ on $[-\tau, \tau_e)$, where τ_e is an explosion time. To show this solution is global, one may need to show $\tau_e = \infty$ a.s. (almost surely). Let $l_0 > 0$ be sufficiently large so that $(H(t), I(t), V(t), D(t)) = \{(\varphi_1(t), \varphi_2(t), \varphi_3(t), \varphi_4(t)) : -\tau \leq t \leq 0\} \in C([-\tau, 0]; \mathbb{R}^4_+)$ all lie within the interval $[\frac{1}{l_0}, l_0]$. For each integer $l \geq l_0$, define the stopping time

$$\tau_l = \inf\{t \in [-\tau, \tau_e) : \min\{H(t), I(t), V(t), D(t)\} \leq \frac{1}{l} \quad \text{or} \quad \max\{H(t), I(t), V(t), D(t)\} \geq l\},$$

let $\inf \phi = \infty$. τ_l is increasing with l and let $\tau_\infty = \lim_{l\to\infty} \tau_l$, then $\tau_\infty \leq \tau_e$ and by showing $\tau_\infty = \infty$ a.s., the aim is to conclude that $\tau_e = \infty$ a.s. If this assertion is erroneous, then there exists a pair of constants $T > 0$ and $\epsilon \in (0, 1)$ such that $\mathbb{P}\{\tau_\infty \leq T\} > \epsilon$. Therefore, there is an integer $l_1 \geq l_0$ such that

$$\mathbb{P}\{\tau_l \leq T\} > \epsilon, \quad \text{for all} \quad l \geq l_1. \tag{3.1}$$

Define a C^2-function $\mathcal{G} : \mathbb{R}^4_+ \to \mathbb{R}_+$ as follows:

$$\begin{aligned} \mathcal{G}(H, I, V, D) \equiv \mathcal{G}(.) &= (H - 1 - \ln H) + (I - 1 - \ln I) + l_2 V + l_2(D - 1 - \ln D) \\ &\quad + \int_{t-\tau_1}^{t} [\beta_1 H(s)V(s) + \beta_2 H(s)I(s)]ds + a l_2 \int_{t-\tau_2}^{t} I(s)ds, \end{aligned} \tag{3.2}$$

where l_2 is a positive constants to be determined later. By Itô's formula, we have

$$\begin{aligned} d\mathcal{G}(.) &= \Big(1 - \frac{1}{H}\Big)dH + \Big(1 - \frac{1}{I}\Big)dI + l_2 dV + l_2\Big(1 - \frac{1}{D}\Big)dD + \frac{1}{2}\frac{1}{H^2}(dH)^2 + \frac{1}{2}\frac{1}{I^2}(dI)^2 \\ &\quad + l_2\frac{1}{2}\frac{1}{D^2}(dD)^2 + [\beta_1 HV - \beta_1 H(t-\tau_1)V(t-\tau_1) + \beta_2 HI - \beta_2 H(t-\tau_1)I(t-\tau_1) \\ &\quad + a l_2 I - a l_2 I(t-\tau_2)] \\ &= \Big[\eta_1 - \alpha_1 H - \frac{\eta_1}{H} + \alpha_1 + \beta_1 V + \beta_2 I + \frac{\nu_{11}^2 H^2}{2} + \frac{\nu_{12}^2}{2} + \nu_{11}\nu_{12}H - \alpha_2 I - \beta_3 DI \\ &\quad - \frac{\beta_1 H(t-\tau_1)V(t-\tau_1)}{I} - \frac{\beta_2 H(t-\tau_1)I(t-\tau_1)}{I} + \alpha_2 + \beta_3 D + \frac{\nu_{21}^2}{2} + \nu_{21}\nu_{22}I \\ &\quad + \frac{\nu_{22}^2 I^2}{2} + l_2 aI - l_2\alpha_3 V + l_2\eta_2 - l_2\alpha_4 D + l_2\beta_4 ID - l_2\frac{\eta_2}{D} + l_2\alpha_4 - l_2\beta_4 I + l_2\frac{\nu_{41}^2}{2} \\ &\quad + l_2\nu_{41}\nu_{42}D + l_2\frac{\nu_{42}^2 D^2}{2}\Big]dt + (H-1)(\nu_{11}H + \nu_{12})dW_1 + (I-1)(\nu_{21} + \nu_{22}I)dW_2 \\ &\quad + l_2(\nu_{31} + \nu_{32}V)VdW_3 + l_2(D-1)(\nu_{41} + \nu_{42}D)dW_4 \\ &= \mathcal{L}\mathcal{G}(.)dt + (H-1)(\nu_{11}H + \nu_{12})dW_1 + (I-1)(\nu_{21} + \nu_{22}I)dW_2 + l_2(\nu_{31} + \nu_{32}V)VdW_3 \\ &\quad + l_2(D-1)(\nu_{41} + \nu_{42}D)dW_4. \end{aligned} \tag{3.3}$$

Here,

$$\begin{aligned}\mathcal{LG}(.) \leq\ & \eta_1 + \alpha_1 + \alpha_2 + l_2\eta_2 + l_2\alpha_4 + (\nu_{11}\nu_{12} - \alpha_1)H + (\beta_1 - l_2\alpha_3)V \\ & + (\beta_2 + \nu_{21}\nu_{22} + l_2 a - \alpha_2 - l_2\beta_4)I + (l_2\beta_4 - \beta_3)DI + (\beta_3 + l_2\nu_{41}\nu_{42})D \\ & + \frac{\nu_{11}^2 H^2}{2} + \frac{\nu_{12}^2}{2} + \frac{\nu_{21}^2}{2} + \frac{\nu_{22}^2 I^2}{2} + l_2\frac{\nu_{41}^2}{2} + l_2\frac{\nu_{42}^2 D^2}{2}.\end{aligned} \tag{3.4}$$

Choosing $l_2 = \beta_3/\beta_4$, yields

$$\begin{aligned}\mathcal{LG}(.) \leq\ & \sup_{H\in\mathbb{R}_+}\left\{(\nu_{11}\nu_{12} - \alpha_1)H + \frac{\nu_{11}^2 H^2}{2}\right\} + \sup_{I\in\mathbb{R}_+}\left\{(\beta_2 + \nu_{21}\nu_{22} + l_2 a - \alpha_2 - l_2\beta_4)I + \frac{\nu_{22}^2 I^2}{2}\right\} \\ & + \sup_{V\in\mathbb{R}_+}\left\{(\beta_1 - l_2\alpha_3)V\right\} + \sup_{D\in\mathbb{R}_+}\left\{(\beta_3 + l_2\nu_{41}\nu_{42})D + l_2\frac{\nu_{42}^2 D^2}{2}\right\} \\ & + \eta_1 + \alpha_1 + \alpha_2 + l_2\eta_2 + l_2\alpha_4 + \frac{\nu_{12}^2}{2} + \frac{\nu_{21}^2}{2} + l_2\frac{\nu_{41}^2}{2} \\ \leq\ & \mathcal{B},\end{aligned} \tag{3.5}$$

where $\mathcal{B}$ is a positive constant. It follows that $\mathcal{LG}(.)$ is bounded. Since the following proof is standard and it is similar to the method in the literature [31], so it is omitted. Therefore, the proof is completed.

4. Existence of ergodic stationary distribution

Herein, we construct a suitable stochastic Lyapunov function to study existence of a unique ergodic stationary distribution of the positive solutions to system (2.2). Ergodic stationary distribution of a stochastic model is one of the most important and significant characteristics. Ergodic property of a stochastic HBV epidemic model means that the stochastic model has a unique stationary distribution which predicts the persistence of the disease in the future under some restrictions on the intensity of white noise, that is the stochastic model fluctuate in a neighborhood of the infected equilibrium, $\mathcal{E}^*$ (defined in the Appendix) of the corresponding undisturbed model for all time regardless of the initial conditions.

First, assume that $X(t)$ is a regular time-homogenous Markov process in $\mathbb{R}^d$, illustrated by the SDDE

$$dX(t) = f(X(t), X(t-\tau), t)dt + \sum_{r=1}^{d} g_r(X(t), t)dW_r(t). \tag{4.1}$$

The diffusion matrix of the process $X(t)$ is

$$\Lambda(x) = (\lambda_{ij}(x)), \quad \lambda_{ij}(x) = \sum_{r=1}^{d} g_r^i(x)g_r^j(x).$$

Lemma 1. *[32]. The Markov process $X(t)$ has a unique ergodic stationary distribution $\pi(.)$ if there exist a bounded domain $\mathcal{U} \subset \mathbb{R}^d$ with regular boundary Γ and*

(i): there is a positive number $\mathcal{M}$ such that $\sum_{i,j=1}^{d} \lambda_{ij}(x)\xi_i\xi_j \geq \mathcal{M}|\xi|^2, x \in \mathcal{U}, \xi \in \mathbb{R}^d$.

(ii): there exists a nonnegative C^2-function V such that $\mathcal{L}V$ is negative for any $\mathbb{R}^d \setminus \mathcal{U}$.

Theorem 2. *Assume that*

$$\mathcal{R}_0^s = \frac{(\eta_1\beta_2)\psi_1 + (\eta_1 a\beta_1\alpha_1^{-1})\psi_0}{\psi_0\psi_1\psi_2} > 1, \tag{4.2}$$

where

$$\psi_0 = \alpha_1 + \frac{\nu_{12}^2}{2} + 2\sqrt{\eta_1\nu_{11}\nu_{12}} + 2\sqrt[3]{\eta_1^2\nu_{11}^2}, \quad \psi_1 = \alpha_3 + \frac{\nu_{31}^2}{2},$$

$$\psi_2 = \alpha_2 + \frac{\beta_3\eta_2}{\alpha_4} + \frac{\nu_{21}^2 + \nu_{41}^2}{2} + 2\sqrt[3]{\eta_1}(\sqrt[3]{\nu_{22}^2} + \sqrt[3]{\nu_{42}^2}) + \frac{4\sqrt[3]{\nu_{42}^2}\eta_2}{3\sqrt[3]{\eta_1}},$$

then system (2.2) admits a unique stationary distribution $\pi(.)$ and it has the ergodic property.

Proof. In order to prove Theorem 2, it is enough to validate conditions (i) and (ii) of Lemma 1.

We first prove condition (i). The diffusion matrix of system (2.2) is given by

$$\Lambda(H, I, V, D) = \begin{pmatrix} (\nu_{11}H + \nu_{12})^2H^2 & 0 & 0 & 0 \\ 0 & (\nu_{21} + \nu_{22}I)^2I^2 & 0 & 0 \\ 0 & 0 & (\nu_{31} + \nu_{32}V)^2V^2 & 0 \\ 0 & 0 & 0 & (\nu_{41} + \nu_{42}D)^2D^2 \end{pmatrix}.$$

Let $\mathcal{U}$ be any bounded domain in $\mathbb{R}_+^4$, then there exists a positive constant

$$\mathcal{M}_0 = \min_{(H,I,V,D)\in\bar{\mathcal{U}}_\sigma} \{(\nu_{11}H + \nu_{12})^2H^2, (\nu_{21} + \nu_{22}I)^2I^2, (\nu_{31} + \nu_{32}V)^2V^2, (\nu_{41} + \nu_{42}D)^2D^2\},$$

such that

$$\begin{aligned} \sum_{i,j=1}^{4} \lambda_{ij}(H, I, V, D)\xi_i\xi_j &= (\nu_{11}H + \nu_{12})^2H^2\xi_1^2 + (\nu_{21} + \nu_{22}I)^2I^2\xi_2^2 + (\nu_{31} + \nu_{32}V)^2V^2\xi_3^2 \\ &\quad + (\nu_{41} + \nu_{42}D)^2D^2\xi_4^2 \\ &\geq \mathcal{M}_0|\xi|^2, \end{aligned}$$

for any $(H, I, V, D) \in \bar{\mathcal{U}}_\sigma, \xi = (\xi_1, \xi_2, \xi_3, \xi_4) \in \mathbb{R}_+^4$. Thus, we have verified that condition (i) of Lemma 1 is satisfied. We then prove condition (ii) of Lemma 1. For any relatively small $\theta \in (0, 1)$, we define

$$\mathcal{R}_0^s(\theta) = \frac{(\eta_1\beta_2)\psi_1 + (\eta_1 a\beta_1\alpha_1^{-1})\hat{\psi}_0}{\hat{\psi}_0\psi_1\hat{\psi}_2}, \tag{4.3}$$

where,

$$\hat{\psi}_0 = \alpha_1 + \frac{\nu_{12}^2}{2} + 2\sqrt{\frac{\eta_1\nu_{11}\nu_{12}}{1-\theta}} + 2\sqrt[3]{\Big(\frac{\eta_1^2\nu_{11}^2}{(1-\theta)^2}\Big)},$$

$$\hat{\psi}_2 = \alpha_2 + \frac{\beta_3\eta_2}{\alpha_4} + \frac{\nu_{21}^2}{2} + \frac{\nu_{41}^2}{2} + 2\sqrt[3]{\eta_1}\Big(\frac{\sqrt[3]{\nu_{22}^2} + \sqrt[3]{\nu_{42}^2}}{\sqrt[3]{(1-\theta)^2}}\Big) + f_1 f_2^{\theta-1}\eta_2,$$

such that $f_1 = \dfrac{8}{3(1-\theta)f_2^\theta}$, $f_2 = 2\sqrt[3]{\dfrac{\eta_1}{(1-\theta)\nu_{42}^2}}$. Clearly, $\lim\limits_{\theta\to 0^+}\mathcal{R}_0^s(\theta) = \mathcal{R}_0^s$. Since $\mathcal{R}_0^s(\theta)$ is continuous and $\mathcal{R}_0^s > 1$, we can choose relatively small θ such that $\mathcal{R}_0^s(\theta) > 1$. By system (2.2), we have

$$\mathcal{L}(-\ln H) = -\frac{\eta_1}{H} + \alpha_1 + \beta_1 V + \beta_2 I + \frac{\nu_{12}^2}{2} + \nu_{11}\nu_{12}H + \frac{\nu_{11}^2}{2}H^2 \tag{4.4}$$

$$\begin{aligned}\mathcal{L}(-\ln I) = &-\frac{\beta_1 H(t-\tau_1)V(t-\tau_1)}{I} - \frac{\beta_2 H(t-\tau_1)I(t-\tau_1)}{I} + \alpha_2 + \beta_3 D\\ &+ \frac{\nu_{21}^2}{2} + \nu_{21}\nu_{22}I + \frac{\nu_{22}^2}{2}I^2\end{aligned} \tag{4.5}$$

$$\mathcal{L}(-\ln V) = -\frac{aI(t-\tau_2)}{V} + \alpha_3 + \frac{\nu_{31}^2}{2} + \nu_{31}\nu_{32}V + \frac{\nu_{32}^2}{2}V^2 \tag{4.6}$$

and

$$\mathcal{L}(-\ln D) = -\frac{\eta_2}{D} + \alpha_4 - \beta_4 + \frac{\nu_{41}^2}{2} + \nu_{31}\nu_{42}D + \frac{\nu_{42}^2}{2}D^2. \tag{4.7}$$

Define

$$\begin{aligned}\mathcal{V}_1(H) &= \sum_{i=1}^{2}\frac{c_i(H+h_i)^\theta}{\theta},\\
\mathcal{V}_2(H,I,D) &= k_1 H + \frac{k_2(I+k_3)^\theta}{\theta} + \frac{f_1(D+f_2)^\theta}{\theta} + k_2 k_3^{\theta-1}\int_{t-\tau_1}^{t}[\beta_1 H(s)V(s) + \beta_2 H(s)I(s)]ds\\
\mathcal{V}_3(V,I) &= -\ln V + \frac{m_1(\nu_{31}+\nu_{32}V)^\theta}{\theta} + \frac{\nu_{31}\nu_{32}}{\alpha_3}V + \frac{a\nu_{31}\nu_{32}(1+m_1\nu_{31}^{\theta-2}\alpha_3)}{\alpha_3}\int_{t-\tau_2}^{t}I(s)ds,\\
\mathcal{V}_4(H,I,V,D) &= \frac{(\nu_{11}H+\nu_{12})^\theta}{\theta} + \frac{(\nu_{21}+\nu_{22}I)^\theta}{\theta} + \frac{(\nu_{31}+\nu_{32}V)^\theta}{\theta} + \frac{(\nu_{41}+\nu_{42}D)^\theta}{\theta}\\
&\quad + \nu_{22}\nu_{21}^{\theta-1}\int_{t-\tau_1}^{t}[\beta_1 H(s)V(s) + \beta_2 H(s)I(s)]ds + \nu_{32}\nu_{31}^{\theta-1}a\int_{t-\tau_2}^{t}I(s)ds.\\
\mathcal{V}_5(H,I,V,D) &= \mathcal{V}_2(H,I,D) - \ln I - \ln D + m_2(\mathcal{V}_1(H) - \ln H) + m_3\mathcal{V}_3(V,I).\end{aligned}$$

where c_1, c_2, h_1, h_2, m_1, m_2, m_3 and k_1, k_2, k_3 are positive constants which will be determined later. By

Itô formula to $\mathcal{V}_1$, we obtain

$$\begin{aligned}
\mathcal{L}\mathcal{V}_1 &= \sum_{i=1}^{2}\Big[c_i(H+h_i)^{\theta-1}(\eta_1-\alpha_1 H-\beta_1 HV-\beta_2 HI)-\frac{c_i(1-\theta)}{2(H+h_i)^{2-\theta}}(\nu_{11}H+\nu_{12})^2H^2\Big]\\
&\le \sum_{i=1}^{2}\frac{c_i\eta_1}{h_i^{1-\theta}}-\frac{c_1(1-\theta)h_1^{\theta-2}\nu_{11}^2H^4}{2(\frac{H}{h_1}+1)^{2-\theta}}-\frac{c_2(1-\theta)h_2^{\theta-2}\nu_{11}\nu_{12}H^3}{(\frac{H}{h_2}+1)^{2-\theta}}\\
&\le \sum_{i=1}^{2}\frac{c_i\eta_1}{h_i^{1-\theta}}-\frac{c_1(1-\theta)h_1^{\theta+2}\nu_{11}^2(\frac{H}{h_1})^4}{2(\frac{H}{h_1}+1)^2}-\frac{c_2(1-\theta)h_2^{\theta+1}\nu_{11}\nu_{12}(\frac{H}{h_2})^3}{(\frac{H}{h_2}+1)^2}\\
&\le \sum_{i=1}^{2}\frac{c_i\eta_1}{h_i^{1-\theta}}-\frac{c_1(1-\theta)h_1^{\theta+2}\nu_{11}^2(\frac{H}{h_1})^4}{4((\frac{H}{h_1})^2+1)}-\frac{c_2(1-\theta)h_2^{\theta+1}\nu_{11}\nu_{12}(\frac{H}{h_2})^3}{2((\frac{H}{h_2})^2+1)}\\
&\le \sum_{i=1}^{2}\frac{c_i\eta_1}{h_i^{1-\theta}}-\frac{c_1(1-\theta)h_1^{\theta+2}\nu_{11}^2}{4}\Big[\frac{3}{4}\Big(\frac{H}{h_1}\Big)^2-\frac{1}{4}\Big]-\frac{c_2(1-\theta)h_2^{\theta+1}\nu_{11}\nu_{12}}{2}\Big(\frac{H}{h_2}-\frac{1}{2}\Big)\\
&= \Big(\frac{c_i\eta_1}{h_1^{1-\theta}}+\frac{c_1(1-\theta)h_1^{\theta+2}\nu_{11}^2}{16}\Big)+\Big(\frac{c_i\eta_1}{h_2^{1-\theta}}+\frac{c_2(1-\theta)h_2^{\theta+1}\nu_{11}\nu_{12}}{4}\Big)-\frac{3c_1(1-\theta)h_1^{\theta}\nu_{11}^2}{16}H^2\\
&\quad-\frac{c_2(1-\theta)h_2^{\theta}\nu_{11}\nu_{12}}{2}H.
\end{aligned}$$

Let

$$c_1=\frac{8}{3(1-\theta)h_1^{\theta}},\quad c_2=\frac{2}{(1-\theta)h_2^{\theta}},\quad h_1=2\sqrt[3]{\frac{\eta_1}{(1-\theta)\nu_{11}^2}},\quad h_2=2\sqrt{\frac{\eta_1}{(1-\theta)\nu_{11}\nu_{12}}}.$$

Therefore,

$$\mathcal{L}\mathcal{V}_1\le 2\sqrt{\frac{\eta_1\nu_{11}\nu_{12}}{1-\theta}}+2\sqrt[3]{\frac{\eta_1^2\nu_{11}^2}{(1-\theta)^2}}-\nu_{11}\nu_{12}H-\frac{\nu_{11}^2}{2}H^2. \tag{4.8}$$

Thus, from systems (4.4) and (4.8), we have

$$\mathcal{L}\mathcal{V}_1+\mathcal{L}(-\ln H)\le-\frac{\eta_1}{H}+\alpha_1+\beta_1V+\beta_2I+\frac{\nu_{12}^2}{2}+2\sqrt{\frac{\eta_1\nu_{11}\nu_{12}}{1-\theta}}+2\sqrt[3]{\frac{\eta_1^2\nu_{11}^2}{(1-\theta)^2}}. \tag{4.9}$$

By Itô's formula to $\mathcal{V}_2$, we get

$$
\begin{aligned}
\mathcal{L}\mathcal{V}_2 &= k_1\Big(\eta_1 - \alpha_1 H - \beta_1 HV - \beta_2 HI\Big) - \frac{k_2(1-\theta)}{2(I+k_3)^{2-\theta}}(\nu_{21}+\nu_{22}I)^2 I^2 \\
&\quad + k_2(I+k_3)^{\theta-1}[\beta_1 H(t-\tau_1)V(t-\tau_1) + \beta_2 H(t-\tau_1)I(t-\tau_1) - \alpha_2 I - \beta_3 ID] \\
&\quad + f_1(D+f_2)^{\theta-1}[\eta_2 - \alpha_4 D + \beta_4 ID] - \frac{f_1(1-\theta)}{2(D+f_2)^{2-\theta}}(\nu_{41}+\nu_{42}D)^2 D^2 \\
&\quad + k_2 k_3^{\theta-1}\beta_1[HV - H(t-\tau_1)V(t-\tau_1)] + k_2 k_3^{\theta-1}\beta_2[HI - H(t-\tau_1)I(t-\tau_1)] \\
&\le k_1\eta_1 + f_1 f_2^{\theta-1}\eta_2 + (k_2 k_3^{\theta-1} - k_1)\beta_1 HV + (f_1 f_2^{\theta-1}\beta_4 - k_2 k_3^{\theta-1}\beta_3)ID - k_1\beta_2 HI \\
&\quad + k_2 k_3^{\theta-1}\beta_2 HI - \frac{k_2(1-\theta)k_3^{\theta-2}}{2(\frac{1}{k_3}+1)^{2-\theta}}\nu_{22}^2 I^4 - \frac{f_1(1-\theta)f_2^{\theta-2}}{2(\frac{1}{f_2}+1)^{2-\theta}}\nu_{42}^2 D^4 \\
&\le k_1\eta_1 + f_1 f_2^{\theta-1}\eta_2 + (k_2 k_3^{\theta-1} - k_1)\beta_1 HV + (f_1 f_2^{\theta-1}\beta_4 - k_2 k_3^{\theta-1}\beta_3)ID \\
&\quad + (k_2 k_3^{\theta-1} - k_1)\beta_2 HI - \frac{k_2(1-\theta)k_3^{\theta-2}}{2(\frac{1}{k_3}+1)^{2-\theta}}\nu_{22}^2 I^4 - \frac{f_1(1-\theta)f_2^{\theta-2}}{2(\frac{1}{f_2}+1)^{2-\theta}}\nu_{42}^2 D^4,
\end{aligned}
$$

such that,

$$
\begin{aligned}
\mathcal{L}\mathcal{V}_2 &\le k_1\eta_1 + f_1 f_2^{\theta-1}\eta_2 + (k_2 k_3^{\theta-1} - k_1)\beta_1 HV + (f_1 f_2^{\theta-1}\beta_4 - k_2 k_3^{\theta-1}\beta_3)ID \\
&\quad - \frac{k_2(1-\theta)k_3^{\theta-2}}{2(\frac{1}{k_3}+1)^2}\nu_{22}^2 I^4 - \frac{f_1(1-\theta)f_2^{\theta-2}}{2(\frac{1}{f_2}+1)^2}\nu_{42}^2 D^4 + (k_2 k_3^{\theta-1} - k_1)\beta_2 HI \\
&\le k_1\eta_1 + f_1 f_2^{\theta-1}\eta_2 + (k_2 k_3^{\theta-1} - k_1)\beta_1 HV + (f_1 f_2^{\theta-1}\beta_4 - k_2 k_3^{\theta-1}\beta_3)ID \\
&\quad + (k_2 k_3^{\theta-1} - k_1)\beta_2 HI - \frac{k_2(1-\theta)k_3^{\theta+2}\nu_{22}^2(\frac{1}{k_3})^4}{4((\frac{1}{k_3})^2+1)} - \frac{f_1(1-\theta)f_2^{\theta+2}\nu_{42}^2(\frac{1}{f_2})^4}{4((\frac{1}{f_2})^2+1)} \\
&\le k_1\eta_1 + k_3\eta_1 + f_1 f_2^{\theta-1}\eta_2 + (k_2 k_3^{\theta-1} - k_1)\beta_1 HV + (f_1 f_2^{\theta-1}\beta_4 - k_2 k_3^{\theta-1}\beta_3)ID \\
&\quad - \frac{k_2(1-\theta)k_3^{\theta+2}\nu_{22}^2}{4}\Big[\frac{3}{4}\Big(\frac{I}{k_3}\Big)^2 - \frac{1}{4}\Big] - \frac{f_1(1-\theta)f_2^{\theta+2}\nu_{42}^2}{4}\Big[\frac{3}{4}\Big(\frac{D}{f_2}\Big)^2 - \frac{1}{4}\Big] \\
&\quad + (k_2 k_3^{\theta-1} - k_1)\beta_2 HI \\
&= k_1\eta_1 + k_3\eta_1 + f_1 f_2^{\theta-1}\eta_2 + (k_2 k_3^{\theta-1} - k_1)\beta_1 HV + (f_1 f_2^{\theta-1}\beta_4 - k_2 k_3^{\theta-1}\beta_3)ID \\
&\quad + (k_2 k_3^{\theta-1} - k_1)\beta_2 HI - \frac{3k_2(1-\theta)k_3^{\theta}\nu_{22}}{16}I^2 + \frac{k_2(1-\theta)k_3^{\theta+2}\nu_{22}^2}{16} \\
&\quad - \frac{3f_1(1-\theta)f_2^{\theta}\nu_{42}}{16}D^2 + \frac{f_1(1-\theta)f_2^{\theta+2}\nu_{42}^2}{16}.
\end{aligned}
$$

Let

$$
\begin{aligned}
&k_1 = k_2 k_3^{\theta-1}, \quad k_2 = \frac{8}{3(1-\theta)k_3^{\theta}}, \quad k_3 = 2\sqrt[3]{\frac{\eta_1}{(1-\theta)\nu_{22}^2}} \\
&f_1 = \frac{8}{3(1-\theta)f_2^{\theta}}, \quad f_2 = 2\sqrt[3]{\frac{\eta_1}{(1-\theta)\nu_{42}^2}}, \quad k_2 k_3^{\theta-1}\beta_3 > f_1 f_2^{\theta-1}\beta_4.
\end{aligned}
$$

Thus, we get

$$
\mathcal{L}\mathcal{V}_2 \le 2\sqrt[3]{\frac{\eta_1\nu_{22}^2}{(1-\theta)^2}} + 2\sqrt[3]{\frac{\eta_1\nu_{42}^2}{(1-\theta)^2}} - \frac{\nu_{22}^2}{2}I^2 - \frac{\nu_{42}^2}{2}D^2 + f_1 f_2^{\theta-1}\eta_2. \tag{4.10}
$$

From systems (4.5), (4.7) and (4.10), we have

$$\begin{aligned}\mathcal{L}(-\ln I)+\mathcal{L}(-\ln D)+\mathcal{L}\mathcal{V}_2 \le & -\frac{\beta_1 H(t-\tau_1)V(t-\tau_1)}{I}-\frac{\beta_2 H(t-\tau_1)I(t-\tau_1)}{I}\\ & -\frac{\eta_2}{D}-\beta_4+\alpha_2+\alpha_4+\beta_3 D+\frac{\nu_{21}^2}{2}+\frac{\nu_{41}^2}{2}+\nu_{31}\nu_{42}D+\nu_{21}\nu_{22}I+f_1 f_2^{\theta-1}\eta_2\\ & +2\sqrt[3]{\frac{\eta_1\nu_{22}^2}{(1-\theta)^2}}+2\sqrt[3]{\frac{\eta_1\nu_{42}^2}{(1-\theta)^2}}.\end{aligned} \tag{4.11}$$

Applying Itô formula to $\mathcal{V}_3$, one gets

$$\begin{aligned}\mathcal{L}\mathcal{V}_3 = & -\frac{aI(t-\tau_2)}{V}+\alpha_3+\nu_{31}\nu_{32}V+\frac{\nu_{32}^2}{2}V^2+m_1\nu_{32}(\nu_{31}+\nu_{32}V)^{\theta-1}(aI(t-\tau_2)-\alpha_3 V)\\ & -\frac{m_1\nu_{32}^2(1-\theta)}{2}(\nu_{31}+\nu_{32}V)^{\theta}V^2+\Big[\frac{\nu_{31}\nu_{32}}{\alpha_3}(aI(t-\tau_2)-\alpha_3 V)\Big]\\ & +\frac{\nu_{31}^2}{2}+\frac{a\nu_{31}\nu_{32}(1+m_1\nu_{31}^{\theta-2}\alpha_3)}{\alpha_3}I-\frac{a\nu_{31}\nu_{32}(1+m_1\nu_{31}^{\theta-2}\alpha_3)}{\alpha_3}I(t-\tau_2).\end{aligned} \tag{4.12}$$

Hence,

$$\mathcal{L}\mathcal{V}_3 \le -\frac{aI(t-\tau_2)}{V}+\alpha_3+\frac{\nu_{31}^2}{2}+\frac{\nu_{32}^2}{2}V^2+\frac{a\nu_{31}\nu_{32}(1+m_1\nu_{31}^{\theta-2}\alpha_3)}{\alpha_3}I-\frac{m_1\nu_{32}^2(1-\theta)\nu_{31}^{\theta}V^2}{2}. \tag{4.13}$$

Let $m_1=\dfrac{1}{(1-\theta)\nu_{31}^{\theta}}$. Therefore,

$$\mathcal{L}\mathcal{V}_3 \le -\frac{aI(t-\tau_2)}{V}+\alpha_3+\frac{\nu_{31}^2}{2}+\frac{a\nu_{31}\nu_{32}(1+m_1\nu_{31}^{\theta-2}\alpha_3)}{\alpha_3}I. \tag{4.14}$$

By Itô's formula to $\mathcal{V}_4$, we have

$$\begin{aligned}\mathcal{L}\mathcal{V}_4 = & \nu_{11}(\nu_{11}H+\nu_{12})^{\theta-1}\Big(\eta_1-\alpha_1 H-\beta_1 HV-\beta_2 HI\Big)-\frac{\nu_{11}^2}{2}(1-\theta)(\nu_{11}H+\nu_{12})^{\theta}H^2\\ & +\nu_{22}(\nu_{21}+\nu_{22}I)^{\theta-1}\Big(\beta_1 H(t-\tau_1)V(t-\tau_1)+\beta_2 HI-\alpha_2 I-\beta_3 ID\Big)\\ & -\frac{\nu_{22}^2}{2}(1-\theta)(\nu_{21}+\nu_{22}I)^{\theta}I^2+\nu_{32}(\nu_{31}+\nu_{32}V)^{\theta-1}\Big(aI(t-\tau_2)-\alpha_3 V\Big)\\ & +\nu_{42}(\nu_{41}+\nu_{42}D)^{\theta-1}\Big(\eta_2-\alpha_4 D+\beta_4 ID\Big)-\frac{\nu_{42}^2}{2}(1-\theta)(\nu_{31}+\nu_{32}D)^{\theta}D^2\\ & +\nu_{22}\nu_{21}^{\theta-1}\beta_1 HV-\nu_{22}\nu_{21}^{\theta-1}\beta_1 H(t-\tau_1)V(t-\tau_1)+\nu_{22}\nu_{21}^{\theta-1}\beta_2 HI\\ & -\nu_{22}\nu_{21}^{\theta-1}\beta_2 H(t-\tau_1)I(t-\tau_1)+\nu_{32}\nu_{31}^{\theta-1}aI-\nu_{32}\nu_{31}^{\theta-1}aI(t-\tau_2)\\ & -\frac{\nu_{32}^2}{2}(1-\theta)(\nu_{31}+\nu_{32}V)^{\theta}V^2\\ \le & \nu_{11}\nu_{12}^{\theta-1}\eta-\frac{1-\theta}{2}\nu_{11}^{\theta+2}H^{\theta+2}+\nu_{22}\nu_{21}^{\theta-1}\beta_1 HV+\nu_{22}\nu_{21}^{\theta-1}\beta_2 HI-\frac{1-\theta}{2}\nu_{22}^{\theta+2}I^{\theta+2}\\ & +\nu_{32}\nu_{31}^{\theta-1}aI-\frac{1-\theta}{2}\nu_{32}^{\theta+2}V^{\theta+2}+\nu_{42}\nu_{41}^{\theta-1}\eta_2+\nu_{42}\nu_{41}^{\theta-1}\beta_4 ID-\frac{1-\theta}{2}\nu_{42}^{\theta+2}D^{\theta+2}.\end{aligned} \tag{4.15}$$

Applying Itô's formula to $\mathcal{V}_5$, one obtains

$$\begin{aligned}\mathcal{L}\mathcal{V}_5 \leq & -\frac{\beta_1 H(t-\tau_1)V(t-\tau_1)}{I} - \frac{\beta_2 H(t-\tau_1)I(t-\tau_1)}{I} + \alpha_2 + \beta_3 D + \frac{\nu_{21}^2}{2} \\ & + \nu_{21}\nu_{22} I + \frac{\nu_{22}^2}{2} I^2 - \frac{\eta_2}{D} + \alpha_4 - \beta_4 + \frac{\beta_2\eta_2}{\alpha_4} + \frac{\nu_{41}^2}{2} + \nu_{31}\nu_{42} D + \frac{\nu_{42}^2}{2} D^2 \\ & + 2\sqrt[3]{\Big(\frac{\eta_1\nu_{22}^2}{(1-\theta)^2}\Big)} + 2\sqrt[3]{\Big(\frac{\eta_1\nu_{42}^2}{(1-\theta)^2}\Big)} - \frac{\nu_{22}^2}{2} I^2 - \frac{\nu_{42}^2}{2} D^2 + f_1 f_2^{\theta-1}\eta_2 \\ & + m_2\Big(-\frac{\eta_1}{H} + \alpha_1 + \beta_1 V + \beta_2 I + \frac{\nu_{12}^2}{2} + 2\sqrt{\frac{\eta_1\nu_{11}\nu_{12}}{1-\theta}} + 2\sqrt[3]{\Big(\frac{\eta_1^2\nu_{11}^2}{(1-\theta)^2}\Big)}\Big) \\ & + m_3\Big(-\frac{aI(t-\tau_2)}{V} + \alpha_3 + \frac{\nu_{31}^2}{2} + \Big[\frac{\nu_{31}\nu_{32}a}{\alpha_3} + m_1\nu_{32}\nu_{31}^{\theta-1}a\Big]I\Big).\end{aligned} \tag{4.16}$$

Additionally, we have

$$\begin{aligned}\mathcal{L}\mathcal{V}_5 \leq & -2\sqrt{\eta_1\beta_2 m_2} - 2\sqrt{a\beta_1 m_3} + \alpha_4 - \beta_4 + \alpha_2 + \beta_3 D + \frac{\nu_{21}^2}{2} + \frac{\nu_{41}^2}{2} + 2\sqrt[3]{\Big(\frac{\eta_1\nu_{22}^2}{(1-\theta)^2}\Big)} \\ & + 2\sqrt[3]{\Big(\frac{\eta_1\nu_{42}^2}{(1-\theta)^2}\Big)} + \frac{\beta_2\eta_2}{\alpha_4} + f_1 f_2^{\theta-1}\eta_2 + m_3(\alpha_3 + \frac{\nu_{31}^2}{2}) + m_2\beta_1 V + \nu_{31}\nu_{42} D \\ & + (\nu_{21}\nu_{22} + m_3(\frac{\nu_{31}\nu_{32}a}{\alpha_3} + m_1\nu_{32}\nu_{31}^{\theta-1}a))I \\ & + m_2(\alpha_1 + \frac{\nu_{12}^2}{2} + 2\sqrt{\frac{\eta_1\nu_{11}\nu_{12}}{1-\theta}} + 2\sqrt[3]{\Big(\frac{\eta_1^2\nu_{11}^2}{(1-\theta)^2}\Big)}).\end{aligned} \tag{4.17}$$

Let

$$m_2 = \frac{\eta_1\beta_2}{(\alpha_1 + \frac{\nu_{12}^2}{2} + 2\sqrt{\frac{\eta_1\nu_{11}\nu_{12}}{1-\theta}} + 2\sqrt[3]{\Big(\frac{\eta_1^2\nu_{11}^2}{(1-\theta)^2}\Big)})^2}, \quad m_3 = \frac{a\beta_1\eta_1\alpha_1^{-1}}{(\alpha_3 + \frac{\nu_{31}^2}{2})^2}.$$

Therefore, we obtain

$$\begin{aligned}\mathcal{L}V_5 \leq & -\frac{\eta_1\beta_2}{(\alpha_1 + \frac{\nu_{12}^2}{2} + 2\sqrt{\frac{\eta_1\nu_{11}\nu_{12}}{1-\theta}} + 2\sqrt[3]{\Big(\frac{\eta_1^2\nu_{11}^2}{(1-\theta)^2}\Big)})} - \frac{a\beta_1\eta_1\alpha_1^{-1}}{(\alpha_3 + \frac{\nu_{31}^2}{2})} + \alpha_4 - \beta_4 + \alpha_2 + \frac{\beta_2\eta_2}{\alpha_4} \\ & + 2\sqrt[3]{\Big(\frac{\eta_1\nu_{22}^2}{(1-\theta)^2}\Big)} + 2\sqrt[3]{\Big(\frac{\eta_1\nu_{42}^2}{(1-\theta)^2}\Big)} + f_1 f_2^{\theta-1}\eta_2 + m_2\beta_1 V + (\beta_3 + \nu_{31}\nu_{42})D \\ & + (\nu_{21}\nu_{22} + m_3(\frac{\nu_{31}\nu_{32}a}{\alpha_3} + m_1\nu_{32}\nu_{31}^{\theta-1}a))I + \frac{\nu_{21}^2}{2} + \frac{\nu_{41}^2}{2} \\ \leq & -(\hat{\psi}_2)(\mathcal{R}_0^s(\theta) - 1) + m_2\beta_1 V + (\beta_3 + \nu_{31}\nu_{42})D \\ & + (\nu_{21}\nu_{22} + m_3(\frac{\nu_{31}\nu_{32}a}{\alpha_3} + m_1\nu_{32}\nu_{31}^{\theta-1}a))I.\end{aligned} \tag{4.18}$$

Define a C^2-function $\tilde{\mathcal{V}} : \mathbb{R}^4_+ \to \mathbb{R}$ in the following form

$$\tilde{\mathcal{V}}(H, I, V, D) = \mathcal{M}\mathcal{V}_5 - \ln H - \ln V - \ln D + \mathcal{V}_4, \tag{4.19}$$

where $\mathcal{M} > 0$ is a sufficiently large number satisfying the following condition

$$-\mathcal{M}\hat{\psi}_2(\mathcal{R}_0^s(\theta) - 1) + \lambda_1 \leq -5, \tag{4.20}$$

and

$$\begin{aligned}\lambda_1 = \sup_{(H,I,V,D)\in\mathbb{R}^4_+} \Big\{&\alpha_1 + \beta_1 V + \beta_2 I + \frac{\nu_{12}^2}{2} + \nu_{11}\nu_{12}H + \frac{\nu_{11}^2}{2}H^2 + \alpha_3 + \frac{\nu_{31}^2}{2} + \nu_{31}\nu_{32}V \\ &+ \alpha_4 + \frac{\nu_{41}^2}{2} + \nu_{31}\nu_{42}D + \frac{\nu_{42}^2}{2}D^2 + \nu_{11}\nu_{12}^{\theta-1}\eta - \frac{1-\theta}{2}\nu_{11}^{\theta+2}H^{\theta+2} - \frac{1-\theta}{2}\nu_{22}^{\theta+2}I^{\theta+2} \\ &+ \nu_{22}\nu_{21}^{\theta-1}(\beta_1 H(t-\tau_1)V(t-\tau_1) + \beta_2 H(t-\tau_1)I(t-\tau_1)) + \nu_{32}\nu_{31}^{\theta-1}aI(t-\tau_2) \\ &+ \nu_{42}\nu_{41}^{\theta-1}\eta_2 + \nu_{42}\nu_{41}^{\theta-1}\beta_4 ID - \frac{1-\theta}{2}\nu_{42}^{\theta+2}D^{\theta+2} - \frac{1-\theta}{2}\nu_{32}^{\theta+2}V^{\theta+2} + \frac{\nu_{32}^2}{2}V^2\Big\}.\end{aligned} \tag{4.21}$$

Noting that $\tilde{\mathcal{V}}(H, I, V, D)$ is not only continuous, but also tends to $+\infty$ as (H, I, V, D) approches the boundary of $\mathbb{R}^4_+$, and $\|(H, I, V, D)\| \to \infty$. Hence, $\tilde{\mathcal{V}}$ must have a minimum point (H_0, I_0, V_0, D_0) in the interior of $\mathbb{R}^4_+$. We define a C^2-function $\mathcal{V} : \mathbb{R}^4_+ \to \mathbb{R}_+$ as follows:

$$\mathcal{V}(H, I, V, D) = \mathcal{M}\mathcal{V}_5 - \ln H - \ln V - \ln D + \mathcal{V}_4 - \tilde{\mathcal{V}}(H_0, I_0, V_0, D_0). \tag{4.22}$$

By Itô's formula, it follows that

$$\begin{aligned}\mathcal{L}\mathcal{V} \leq &-\mathcal{M}\hat{\psi}_2(\mathcal{R}_0^s(\theta) - 1) + \mathcal{M}(\beta_3 + \nu_{31}\nu_{42})D + \mathcal{M}(\nu_{21}\nu_{22} + m_3(\frac{\nu_{31}\nu_{32}a}{\alpha_3} + m_1\nu_{32}\nu_{31}^{\theta-1}a))I \\ &+ \mathcal{M}m_2\beta_1 V - \frac{\eta_1}{H} + \alpha_1 + \beta_1 V + \beta_2 I + \frac{\nu_{12}^2}{2} + \nu_{11}\nu_{12}H + \frac{\nu_{11}^2}{2}H^2 - \frac{aI(t-\tau_2)}{V} \\ &+ \alpha_3 + \frac{\nu_{31}^2}{2} - \frac{\eta_2}{D} + \alpha_4 - \beta_4 + \frac{\nu_{41}^2}{2} + \nu_{31}\nu_{42}D + \frac{\nu_{42}^2}{2}D^2 + \nu_{11}\nu_{12}^{\theta-1}\eta - \frac{1-\theta}{2}\nu_{11}^{\theta+2}H^{\theta+2} \\ &+ \nu_{22}\nu_{21}^{\theta-1}\beta_1 H(t-\tau_1)V(t-\tau_1) + \nu_{22}\nu_{21}^{\theta-1}\beta_2 HI - \frac{1-\theta}{2}\nu_{22}^{\theta+2}I^{\theta+2} + \frac{\nu_{32}^2}{2}V^2 + \nu_{31}\nu_{32}V \\ &+ \nu_{32}\nu_{31}^{\theta-1}aI(t-\tau_2) - \frac{1-\theta}{2}\nu_{32}^{\theta+2}V^{\theta+2} + \nu_{42}\nu_{41}^{\theta-1}\eta_2 + \nu_{42}\nu_{41}^{\theta-1}\beta_4 ID - \frac{1-\theta}{2}\nu_{42}^{\theta+2}D^{\theta+2}.\end{aligned} \tag{4.23}$$

Now, one can construct a bounded open domain $\mathcal{U}_\epsilon$ such that condition (*ii*) of Lemma 1 satisfies. Define a bounded open set, for arbitrary $\epsilon > 0$, as follows

$$\mathcal{U}_\epsilon = \Big\{(H, I, V, D) \in \mathbb{R}^4_+ : \epsilon < H < \frac{1}{\epsilon}, \epsilon^2 < I < \frac{1}{\epsilon^2}, \epsilon^3 < V < \frac{1}{\epsilon^3}, \epsilon < D < \frac{1}{\epsilon}\Big\}. \tag{4.24}$$

Therefore, we need to prove $\mathcal{LV} \leq -1$ for $(H, I, V, D) \in \mathbb{R}^4_+ \setminus \mathcal{U}_\epsilon$. Clearly, $\mathbb{R}^4_+ \setminus \mathcal{U}_\epsilon = \cup_{i=1}^8 \mathcal{U}_i$, such that

$$\begin{aligned}
&\mathcal{U}_1 = \{(H, I, V, D) \in \mathbb{R}^4_+ : H \leq \epsilon\}, \quad \mathcal{U}_2 = \{(H, I, V, D) \in \mathbb{R}^4_+ : H \geq \frac{1}{\epsilon}\},\\
&\mathcal{U}_3 = \{(H, I, V, D) \in \mathbb{R}^4_+ : H < \frac{1}{\epsilon}, I \leq \epsilon^2, V < \frac{1}{\epsilon^3}, D < \frac{1}{\epsilon}\}\\
&\mathcal{U}_4 = \{(H, I, V, D) \in \mathbb{R}^4_+ : I > \epsilon^2, V \leq \epsilon^3\}\\
&\mathcal{U}_5 = \{(H, I, V, D) \in \mathbb{R}^4_+ : D \leq \epsilon\}, \quad \mathcal{U}_6 = \{(H, I, V, D) \in \mathbb{R}^4_+ : I \geq \frac{1}{\epsilon^2}\},\\
&\mathcal{U}_7 = \{(H, I, V, D) \in \mathbb{R}^4_+ : V \geq \frac{1}{\epsilon^3}\}, \quad \mathcal{U}_8 = \{(H, I, V, D) \in \mathbb{R}^4_+ : D \geq \frac{1}{\epsilon}\}.
\end{aligned} \tag{4.25}$$

Choosing

$$\begin{aligned}
\lambda_2 = \sup_{(H,I,V,D)\in\mathbb{R}^4_+} \Big\{ & \mathcal{M}m_2\beta_1 V + \mathcal{M}(\beta_3 + \nu_{31}\nu_{42})D + \mathcal{M}(\nu_{21}\nu_{22} + m_3(\frac{\nu_{31}\nu_{32}a}{\alpha_3} + m_1\nu_{32}\nu_{31}^{\theta-1}a))I\\
&+ \alpha_1 + \beta_1 V + \frac{\nu_{12}^2}{2} + \nu_{11}\nu_{12}H + \frac{\nu_{11}^2}{2}H^2 + \alpha_3 + \frac{\nu_{31}^2}{2} + \nu_{31}\nu_{32}V + \frac{\nu_{32}^2}{2}V^2 + \alpha_4 + \frac{\nu_{41}^2}{2} + \nu_{31}\nu_{42}D\\
&+ \frac{\nu_{42}^2}{2}D^2 + \nu_{11}\nu_{12}^{\theta-1}\eta - \frac{1-\theta}{4}\nu_{11}^{\theta+2}H^{\theta+2} + \nu_{22}\nu_{21}^{\theta-1}\beta_1 HV + \nu_{22}\nu_{21}^{\theta-1}\beta_2 HI - \frac{1-\theta}{4}\nu_{22}^{\theta+2}I^{\theta+2}\\
&+ (\beta_2 + \nu_{32}\nu_{31}^{\theta-1}a)I - \frac{1-\theta}{4}\nu_{32}^{\theta+2}V^{\theta+2} + \nu_{42}\nu_{41}^{\theta-1}\eta_2 + \nu_{42}\nu_{41}^{\theta-1}\beta_4 ID - \frac{1-\theta}{4}\nu_{42}^{\theta+2}D^{\theta+2}\Big\}.
\end{aligned} \tag{4.26}$$

Case I: For any $(H, I, V, D) \in \mathcal{U}_1$, by system (4.23), one obtains

$$\begin{aligned}
\mathcal{LV} &\leq -\frac{\eta_1}{H} + \lambda_2\\
&\leq -\frac{\eta_1}{\epsilon} + \lambda_2.
\end{aligned} \tag{4.27}$$

Let $-\frac{\eta_1}{\epsilon} + \lambda_2 \leq -1$, yields $\mathcal{LV} \leq -1$.

Case II: For any $(H, I, V, D) \in \mathcal{U}_2$ from system (4.23), one may have

$$\begin{aligned}
\mathcal{LV} &\leq -\frac{1-\theta}{4}\nu_{11}^{\theta+2}H^{\theta+2} + \lambda_2\\
&\leq -\frac{(1-\theta)\nu_{11}^{\theta+2}}{4\epsilon^{\theta+2}} + \lambda_2,
\end{aligned} \tag{4.28}$$

choosing $-\frac{(1-\theta)\nu_{11}^{\theta+2}}{4\epsilon^{\theta+2}} + \lambda_2 \leq -1$, yields $\mathcal{LV} \leq -1$.

Case III: For any $(H, I, V, D) \in \mathcal{U}_3$ from system (4.23), we have

$$\begin{aligned}
\mathcal{LV} &\leq -\mathcal{M}\hat{\psi}_2(\mathcal{R}_0^s(\theta) - 1) + \nu_{22}\nu_{21}^{\theta-1}\beta_2 HI + \mathcal{M}m_2\beta_1 V + \mathcal{M}(\beta_3 + \nu_{31}\nu_{42})D\\
&\quad + \mathcal{M}(\nu_{21}\nu_{22} + m_3(\frac{\nu_{31}\nu_{32}a}{\alpha_3} + m_1\nu_{32}\nu_{31}^{\theta-1}a))I + \lambda_1\\
&\leq -\mathcal{M}\hat{\psi}_2(\mathcal{R}_0^s(\theta) - 1) + \lambda_1 + \nu_{22}\nu_{21}^{\theta-1}\beta_2\epsilon + \frac{\mathcal{M}m_2\beta_1}{\epsilon} + \frac{\mathcal{M}(\beta_3 + \nu_{31}\nu_{42})}{\epsilon}\\
&\quad + \mathcal{M}(\nu_{21}\nu_{22} + m_3(\frac{\nu_{31}\nu_{32}a}{\alpha_3} + m_1\nu_{32}\nu_{31}^{\theta-1}a))\epsilon^2,
\end{aligned} \tag{4.29}$$

we select ϵ small enough such that the following condition holds

$$\frac{\mathcal{M}(m_2\beta_1+\nu_{31}\nu_{42}+\beta_3)}{2}\leq\epsilon\leq\max\Big\{\frac{1}{\nu_{22}\nu_{21}^{\theta-1}\beta_2},\sqrt{\frac{1}{\mathcal{M}(\nu_{21}\nu_{22}+m_3(\frac{\nu_{31}\nu_{32}a}{\alpha_3}+m_1\nu_{32}\nu_{31}^{\theta-1}a))}}\Big\}.$$

Therefore, we have

$$\begin{aligned}\mathcal{LV}&\leq-5+2+1+1\\&\leq-1.\end{aligned}\tag{4.30}$$

Case V: For any $(H,I,V,D)\in\mathcal{U}_4$ from system (4.23), we have

$$\begin{aligned}\mathcal{LV}&\leq-\frac{aI}{V}+\lambda_2\\&\leq-\frac{a\epsilon^2}{\epsilon^3}+\lambda_2.\end{aligned}\tag{4.31}$$

Let $-\frac{a}{\epsilon}+\lambda_2\leq-1$, then we have $\mathcal{LV}\leq-1$.

Case VI: For any $(H,I,V,D)\in\mathcal{U}_5$ from system (4.23), we have

$$\begin{aligned}\mathcal{LV}&\leq-\frac{\eta_2}{D}+\lambda_2\\&\leq-\frac{\eta_2}{\epsilon}+\lambda_2,\end{aligned}\tag{4.32}$$

choose $-\frac{\eta_2}{\epsilon}+\lambda_2\leq-1$, yields $\mathcal{LV}\leq-1$.

Case VII: For any $(H,I,V,D)\in\mathcal{U}_6$ from system (4.23), we have

$$\begin{aligned}\mathcal{LV}&\leq-\frac{1-\theta}{4}\nu_{22}^{\theta+2}I^{\theta+2}+\lambda_2\\&\leq-\frac{(1-\theta)\nu_{22}^{\theta+2}}{4\epsilon^{2(\theta+2)}}+\lambda_2,\end{aligned}\tag{4.33}$$

let $-\frac{(1-\theta)\nu_{22}^{\theta+2}}{4\epsilon^{2(\theta+2)}}+\lambda_2\leq-1$, then we obtain $\mathcal{LV}\leq-1$.

Case IV: For any $(H,I,V,D)\in\mathcal{U}_7$ from system (4.23), we have

$$\begin{aligned}\mathcal{L}V&\leq-\frac{1-\theta}{4}\nu_{32}^{\theta+2}V^{\theta+2}+\lambda_2\\&\leq-\frac{(1-\theta)\nu_{32}^{\theta+2}}{4\epsilon^{3(\theta+2)}}+\lambda_2,\end{aligned}\tag{4.34}$$

choose $-\frac{(1-\theta)\nu_{32}^{\theta+2}}{4\epsilon^{3(\theta+2)}}+\lambda_2\leq-1$, we obtain that $\mathcal{LV}\leq-1$.

Case VI: For any $(H,I,V,D)\in\mathcal{U}_8$ from system (4.23), we have

$$\begin{aligned}\mathcal{LV}&\leq-\frac{1-\theta}{4}\nu_{42}^{\theta+2}D^{\theta+2}+\lambda_2\\&\leq-\frac{(1-\theta)\nu_{42}^{\theta+2}}{4\epsilon^{\theta+2}}+\lambda_2,\end{aligned}\tag{4.35}$$

let $-\frac{(1-\theta)\nu_{32}^{\theta+2}}{4\epsilon^{\theta+2}} + \lambda_2 \leq -1$, then $\mathcal{LV} \leq -1$. Therefore, condition (*ii*) of Lemma 1 satisfies, such that system (2.2) identifies a unique stationary distribution $\pi(.)$.

Remark 1. *If $\mathcal{R}_0^s > 1$ the solution of system (2.2) fluctuates around the endemic equilibrium of the undisturbed system (2.1) under certain conditions. This means that the disease will be persistent, provided that the intensities of white noise are adequately small; See Figure 2.*

5. Extinction of the disease

For the undisturbed system (2.1), if $\mathcal{R}_0 \leq 1$, the disease-free equilibrium $\mathcal{E}_0$ is globally asymptotically stability and HBV infection will die out. However, for $\mathcal{R}_0 > 1$, $\mathcal{E}^*$ is globally asymptotically stable and $\mathcal{E}_0$ is unstable; see [11]. Now, we investigate the possible extinction of the disease $I(t)$ for the stochastic system (2.2). Define

$$\begin{aligned}\mathcal{R}_0^e = (\beta_1+\beta_2)\int_0^\infty \Big|x-\frac{\eta_1}{\alpha_1}\Big|\pi(x)dx + \min\Big\{\alpha_1\alpha_3, \alpha_2 - \frac{\beta_2\eta_1}{\alpha_1}\Big\}(\chi_2-1)1_{(\Phi_0\leq 1)}\\ + \max\Big\{\alpha_1\alpha_3, \alpha_2 - \frac{\beta_2\eta_1}{\alpha_1}\Big\}(\chi_2-1)1_{(\Phi_0>1)} - \frac{1}{2(\nu_{21}^{-2}+\nu_{31}^{-2})}.\end{aligned}$$

Here,

$$\Phi_0 = \frac{\beta_2\eta_1}{\alpha_1(\alpha_2 - \frac{a\beta_1\eta_1}{\alpha_1\alpha_3})} > 0, \quad \chi_1 = \frac{a}{\alpha_3}, \quad \chi_2 = \sqrt{\frac{a\beta_1\eta_1}{\alpha_1\alpha_3(\alpha_2-\frac{\beta_2\eta_1}{\alpha_1})}}. \tag{5.1}$$

Theorem 3. *For any given initial value system (2.3) on $t \geq -\tau$, if $\mathcal{R}_0^e < 0$, the solution $(H(t), I(t), V(t), D(t))$ of system (2.2) satisfies the following:*

$$\limsup_{t\to\infty} \ln\Big(\frac{\chi_1}{(\alpha_2-\frac{\beta_2\eta_1}{\alpha_1})}I(t) + \frac{\chi_2}{\alpha_3}V(t)\Big) \leq \mathcal{R}_0^e < 0, \quad a.s. \tag{5.2}$$

Such that $\lim_{t\to\infty} I(t) = 0$ a.s., i.e., the disease, $I(t)$, will die out exponentially with probability one and $\lim_{t\to\infty} V(t) = 0$ a.s. Additionally, the distributions $H(t)$ and $D(t)$ converge weakly to the measures which have the densities $\pi(x)$ and $\pi(y)$, which will be determined later.

Proof. Assume the following auxiliary logistic equations with nonlinear stochastic perturbation

$$dX = [\eta_1 - \alpha_1 X]dt + (\nu_{11}X + \nu_{12})XdW_1(t), \tag{5.3}$$

with initial value $X_0 = H_0 > 0$.

$$dY = [\eta_2 - \alpha_4 Y]dt + (\nu_{41} + \nu_{42}Y)YdW_4(t), \tag{5.4}$$

with initial value $Y_0 = D_0 > 0$. Therefore, systems (5.3) and (5.4) have the ergodic property [30], such that the invariant densities are given by

$$\begin{aligned}\pi(x) &= \mathcal{N}_1 x^{-2-\frac{2(2\eta_1\nu_{11}+\alpha_1\nu_{12})}{\nu_{12}^3}}(\nu_{11}x+\nu_{12})^{-2+\frac{2(2\eta_1\nu_{11}+\alpha_1\nu_{12})}{\nu_{12}^3}} e^{-\frac{2}{\nu_{12}(\nu_{11}x+\nu_{12})}(\frac{\eta_1}{x}+\frac{2\eta_1\nu_{11}+\alpha_1\nu_{12}}{\nu_{12}})}, \quad x\in(0,\infty),\\ \pi(y) &= \mathcal{N}_2 y^{-2-\frac{2(2\eta_2\nu_{42}+\alpha_4\nu_{41})}{\nu_{41}^3}}(\nu_{42}y+\nu_{41})^{-2+\frac{2(2\eta_2\nu_{42}+\alpha_4\nu_{41})}{\nu_{41}^3}} e^{-\frac{2}{\nu_{41}(\nu_{42}y+\nu_{41})}(\frac{\eta_2}{y}+\frac{2\eta_2\nu_{42}+\alpha_4\nu_{41}}{\nu_{41}})}, \quad y\in(0,\infty),\end{aligned}$$

where $\mathcal{N}_1$ and $\mathcal{N}_2$ are constants such that

$$\int_0^\infty \pi(x)dx = 1, \qquad \int_0^\infty \pi(y)dy = 1.$$

Let $X(t)$ be the solution of system (5.3) with initial value $X_0 = H_0 > 0$, by the comparison theorem [33], one obtains $H(t) \le X(t)$ for any $t \ge 0$ a.s. Similarly, assume that $Y(t)$ be the solution of system (5.4) with initial value $Y_0 = D_0 > 0$, one may have $D(t) \le Y(t)$ such that $I(t) < 1/\beta_4$.

On the other hand, by [34], consider the vector $(\chi_1, \chi_2) = \Big(\frac{a}{\alpha_3}, \sqrt{\frac{a\beta_1\eta_1}{\alpha_1\alpha_3(\alpha_2-\frac{\beta_2\eta_1}{\alpha_1})}}\Big)$. Therefore, we can derive that there exists a left eigenvector of

$$\mathcal{A}_0 = \begin{pmatrix} 0 & \frac{\beta_1\eta_1}{\alpha_1(\alpha_2-\frac{\beta_2\eta_1}{\alpha_1})} \\ \frac{a}{\alpha_3} & 0 \end{pmatrix},$$

corresponding to the spectral radius of $\mathcal{A}_0$; $\rho(\mathcal{A}_0) = \sqrt{\frac{a\beta_1\eta_1}{\alpha_1\alpha_3(\alpha_2-\frac{\beta_2\eta_1}{\alpha_1})}}$, which can be denoted as $\sqrt{\frac{a\beta_1\eta_1}{\alpha_1\alpha_3(\alpha_2-\frac{\beta_2\eta_1}{\alpha_1})}}\Big)(\chi_1, \chi_2) = (\chi_1, \chi_2)\mathcal{A}_0$.

Consider a C^2-function $\hat{\mathcal{V}} : \mathbb{R}_+^2 \to \mathbb{R}_+$ by

$$\hat{\mathcal{V}}(I, V) = \varphi_1 I + \varphi_2 V, \tag{5.5}$$

where $\varphi_1 = \frac{\chi_1}{(\alpha_2-\frac{\beta_2\eta_1}{\alpha_1})}$ and $\varphi_2 = \frac{\chi_2}{\alpha_3}$, by Itô formula to $\hat{\mathcal{V}}$, one may have

$$d(\ln\hat{\mathcal{V}}) = \mathcal{L}(\ln\hat{\mathcal{V}})dt + \frac{\varphi_1(\nu_{21}+\nu_{22}I)I}{\hat{\mathcal{V}}}dW_2(t) + \frac{\varphi_2(\nu_{31}+\nu_{32}V)V}{\hat{\mathcal{V}}}dW_3(t), \tag{5.6}$$

such that

$$\begin{aligned}
\mathcal{L}(\ln\hat{\mathcal{V}}) &= \frac{\varphi_1}{\hat{\mathcal{V}}}\Big[\beta_1 H(t-\tau_1)V(t-\tau_1) + \beta_2 H(t-\tau_1)I(t-\tau_1) - \alpha_2 I - \beta_3 ID\Big] \\
&\quad + \frac{\varphi_2}{\hat{\mathcal{V}}}\Big[aI(t-\tau_2) - \alpha_3 V\Big] - \frac{\varphi_1^2(\nu_{21}+\nu_{22}I)^2I^2}{2\hat{\mathcal{V}}^2} - \frac{\varphi_2^2(\nu_{31}+\nu_{32}V)^2V^2}{2\hat{\mathcal{V}}^2} \\
&\le \frac{\varphi_1}{\hat{\mathcal{V}}}\Big[\beta_1 HV + \beta_2 HI - \alpha_2 I\Big] + \frac{\varphi_2}{\hat{\mathcal{V}}}\Big[aI - \alpha_3 V\Big] - \frac{\varphi_1^2\nu_{21}I^2 + \varphi_1^2\nu_{22}I^4}{2\hat{\mathcal{V}}^2} \\
&\quad - \frac{\varphi_2^2\nu_{31}V^2 + \varphi_2^2\nu_{32}V^4}{2\hat{\mathcal{V}}^2} \\
&= \frac{\varphi_1\beta_1}{\hat{\mathcal{V}}}\Big(H - \frac{\eta_1}{\alpha_1}\Big)V + \frac{\varphi_1\beta_2}{\hat{\mathcal{V}}}\Big(H - \frac{\eta_1}{\alpha_1}\Big)I + \frac{\varphi_1}{\hat{\mathcal{V}}}\Big(\frac{\beta_1\eta_1}{\alpha_1}V + \frac{\beta_2\eta_1}{\alpha_1}I - \alpha_2 I\Big) \\
&\quad + \frac{\varphi_2}{\hat{\mathcal{V}}}\Big[aI - \alpha_3 V\Big] - \frac{\varphi_1^2\nu_{21}I^2 + \varphi_1^2\nu_{22}I^4}{2\hat{\mathcal{V}}^2} - \frac{\varphi_2^2\nu_{31}V^2 + \varphi_2^2\nu_{32}V^4}{2\hat{\mathcal{V}}^2} \\
&\le \frac{\varphi_1\beta_1}{\hat{\mathcal{V}}}\Big(X - \frac{\eta_1}{\alpha_1}\Big)V + \frac{\varphi_1\beta_2}{\hat{\mathcal{V}}}\Big(X - \frac{\eta_1}{\alpha_1}\Big)I - \frac{\varphi_1^2\nu_{21}I^2 + \varphi_1^2\nu_{22}I^4}{2\hat{\mathcal{V}}^2} - \frac{\varphi_2^2\nu_{31}V^2 + \varphi_2^2\nu_{32}V^4}{2\hat{\mathcal{V}}^2} \\
&\quad + \frac{1}{\hat{\mathcal{V}}}\Big\{\frac{\chi_1}{(\alpha_2 - \frac{\beta_2\eta_1}{\alpha_1})}\Big(\frac{\beta_1\eta_1}{\alpha_1}V + \frac{\beta_2\eta_1}{\alpha_1}I - \alpha_2 I\Big) + \frac{\chi_2}{\alpha_3}\Big[aI - \alpha_3 V\Big]\Big\}.
\end{aligned}$$

Hence, we have

$$\begin{aligned}\mathcal{L}(\ln\hat{\mathcal{V}}) \leq & \frac{\varphi_1\beta_1}{\hat{\mathcal{V}}}\Big|X-\frac{\eta_1}{\alpha_1}\Big|V+\frac{\varphi_1\beta_2}{\hat{\mathcal{V}}}\Big|X-\frac{\eta_1}{\alpha_1}\Big|I+\frac{1}{\hat{\mathcal{V}}}(\chi_1,\chi_2)(\mathcal{A}_0(I,V)^T-(I,V)^T)\\ & -\frac{\varphi_1^2\nu_{21}I^2+\varphi_1^2\nu_{22}I^4}{2\hat{\mathcal{V}}^2}-\frac{\varphi_2^2\nu_{31}V^2+\varphi_2^2\nu_{32}V^4}{2\hat{\mathcal{V}}^2}\\ = & \frac{\varphi_1\beta_1}{\hat{\mathcal{V}}}\Big|X-\frac{\eta_1}{\alpha_1}\Big|V+\frac{\varphi_1\beta_2}{\hat{\mathcal{V}}}\Big|X-\frac{\eta_1}{\alpha_1}\Big|I+\frac{1}{\hat{\mathcal{V}}}\Big(\sqrt{\frac{a\beta_1\eta_1}{\alpha_1\alpha_3(\alpha_2-\frac{\beta_2\eta_1}{\alpha_1})}}-1\Big)(\chi_1 I+\chi_2 V)\\ & -\frac{\varphi_1^2\nu_{21}I^2+\varphi_1^2\nu_{22}I^4}{2\hat{\mathcal{V}}^2}-\frac{\varphi_2^2\nu_{31}V^2+\varphi_2^2\nu_{32}V^4}{2\hat{\mathcal{V}}^2},\end{aligned}$$

by substituting the values of χ_1 and χ_2 from system (5.1), we obtain

$$\begin{aligned}\mathcal{L}(\ln\hat{\mathcal{V}}) \leq & \frac{\varphi_1\beta_1}{\hat{\mathcal{V}}}\Big|X-\frac{\eta_1}{\alpha_1}\Big|V+\frac{\varphi_1\beta_2}{\hat{\mathcal{V}}}\Big|X-\frac{\eta_1}{\alpha_1}\Big|I+\frac{1}{\hat{\mathcal{V}}}\Big(\sqrt{\frac{a\beta_1\eta_1}{\alpha_1\alpha_3(\alpha_2-\frac{\beta_2\eta_1}{\alpha_1})}}-1\Big)\\ & \times\Big[(\alpha_2-\frac{\beta_2\eta_1}{\alpha_1})\varphi_1 I+\alpha_3\varphi_2 V\Big]-\frac{\varphi_1^2\nu_{21}I^2+\varphi_1^2\nu_{22}I^4}{2\hat{\mathcal{V}}^2}-\frac{\varphi_2^2\nu_{31}V^2+\varphi_2^2\nu_{32}V^4}{2\hat{\mathcal{V}}^2}\\ \leq & \beta_1\Big|X-\frac{\eta_1}{\alpha_1}\Big|+\beta_2\Big|X-\frac{\eta_1}{\alpha_1}\Big|+\min\Big\{\alpha_1\alpha_3,\alpha_2-\frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0-1\Big)1_{(\Phi_0\leq 1)}\\ & +\max\Big\{\alpha_1\alpha_3,\alpha_2-\frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0-1\Big)1_{(\Phi_0>1)}\\ & -\frac{\varphi_1^2\nu_{21}I^2+\varphi_1^2\nu_{22}I^4}{2\hat{\mathcal{V}}^2}-\frac{\varphi_2^2\nu_{31}V^2+\varphi_2^2\nu_{32}V^4}{2\hat{\mathcal{V}}^2}.\end{aligned}$$

Additionally, squaring both sides of system (5.5) and by Cauchy inequality, one may have

$$\hat{\mathcal{V}}^2=(\varphi_1\nu_{21}I\frac{1}{\nu_{21}}+\varphi_2\nu_{31}V\frac{1}{\nu_{31}})^2\leq(\varphi_1^2\nu_{21}^2I^2+\varphi_2^2\nu_{31}^2V^2)\Big(\frac{1}{\nu_{21}^2}+\frac{1}{\nu_{31}^2}\Big). \tag{5.7}$$

Hence,

$$\begin{aligned}\mathcal{L}(\ln\hat{\mathcal{V}}) \leq & (\beta_1+\beta_2)\Big|X-\frac{\eta_1}{\alpha_1}\Big|+\min\Big\{\alpha_1\alpha_3,\alpha_2-\frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0-1\Big)1_{(\Phi_0\leq 1)}\\ & +\max\Big\{\alpha_1\alpha_3,\alpha_2-\frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0-1\Big)1_{(\Phi_0>1)}-\frac{1}{2(\nu_{21}^{-2}+\nu_{31}^{-2})}\\ & -\frac{\varphi_1^2\nu_{22}^2I^4}{2\hat{\mathcal{V}}^2}-\frac{\varphi_2^2\nu_{32}^2V^4}{2\hat{\mathcal{V}}^2}.\end{aligned} \tag{5.8}$$

From systems (5.6), (5.7) and (5.8), we have

$$\begin{aligned}d(\ln\hat{\mathcal{V}}) \leq & (\beta_1+\beta_2)\Big|X-\frac{\eta_1}{\alpha_1}\Big|+\min\Big\{\alpha_1\alpha_3,\alpha_2-\frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0-1\Big)1_{(\Phi_0\leq 1)}\\ & +\max\Big\{\alpha_1\alpha_3,\alpha_2-\frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0-1\Big)1_{(\Phi_0>1)}-\frac{1}{2(\nu_{21}^{-2}+\nu_{31}^{-2})}-\frac{\varphi_1^2\nu_{22}^2I^4}{2\hat{\mathcal{V}}^2}\\ & -\frac{\varphi_2^2\nu_{32}^2V^4}{2\hat{\mathcal{V}}^2}+\frac{\varphi_1(\nu_{21}+\nu_{22}I)}{\hat{\mathcal{V}}}dW_2(t)+\frac{\varphi_2(\nu_{31}+\nu_{32}V)V}{\hat{\mathcal{V}}}dW_3(t).\end{aligned} \tag{5.9}$$

Integrating both sides of system (5.9) then dividing it by t, we obtain

$$\begin{aligned}\frac{\ln\hat{\mathcal{V}}(t)}{t} \leq \frac{\ln\hat{\mathcal{V}}(0)}{t} &+ \min\Big\{\alpha_1\alpha_3, \alpha_2 - \frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0 - 1\Big)1_{(\Phi_0\leq 1)} - \frac{1}{2(\nu_{21}^{-2} + \nu_{31}^{-2})}\\ &+ \max\Big\{\alpha_1\alpha_3, \alpha_2 - \frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0 - 1\Big)1_{(\Phi_0>1)} + \frac{(\beta_1+\beta_2)}{t}\int_0^t \Big|X(s) - \frac{\eta_1}{\alpha_1}\Big|ds\\ &- \frac{1}{t}\int_0^t \frac{\varphi_1^2\nu_{22}^2 I^4(s)}{2\hat{\mathcal{V}}^2(s)}ds - \frac{1}{t}\int_0^t \frac{\varphi_2^2\nu_{32}^2 V^4(s)}{2\hat{\mathcal{V}}^2(s)}ds + \frac{1}{t}\int_0^t \frac{\varphi_1\nu_{21}I(s)}{\hat{\mathcal{V}}(s)}dW_2(s)\\ &+ \frac{1}{t}\int_0^t \frac{\varphi_1\nu_{22}I^2(s)}{\hat{\mathcal{V}}(s)}dW_2(s) + \frac{1}{t}\int_0^t \frac{\varphi_2\nu_{31}V(s)}{\hat{\mathcal{V}}(s)}dW_3(s)\\ &+ \frac{1}{t}\int_0^t \frac{\varphi_2\nu_{32}V^2(s)}{\hat{\mathcal{V}}(s)}dW_3(s).\end{aligned} \tag{5.10}$$

Assume that $M_i(t)$, $i = 1, 2, 3, 4$, are real valued continuous local martingale vanishing at $t = 0$; Such that

$$\begin{aligned}M_1(t) &:= \int_0^t \frac{\varphi_1\nu_{21}I(s)}{\hat{\mathcal{V}}(s)}dW_2(s), \quad M_2(t) := \int_0^t \frac{\varphi_2\nu_{31}V(s)}{\hat{\mathcal{V}}(s)}dW_3(s),\\ M_3(t) &:= \int_0^t \frac{\varphi_1\nu_{22}I^2(s)}{\hat{\mathcal{V}}(s)}dW_2(s), \quad M_4(t) := \int_0^t \frac{\varphi_2\nu_{32}V^2(s)}{\hat{\mathcal{V}}(s)}dW_3(s).\end{aligned} \tag{5.11}$$

In addition, their quadratic form are given by

$$\begin{aligned}\langle M_1, M_1\rangle(t) &= \int_0^t \Big(\frac{\varphi_1\nu_{21}I(s)}{\hat{\mathcal{V}}(s)}\Big)^2 ds \leq \nu_{21}^2 t, \quad \langle M_2, M_2\rangle(t) = \int_0^t \Big(\frac{\varphi_2\nu_{31}V(s)}{\hat{\mathcal{V}}(s)}\Big)^2 ds \leq \nu_{31}^2 t,\\ \langle M_3, M_3\rangle(t) &= \int_0^t \Big(\frac{\varphi_1\nu_{22}I^2(s)}{\hat{\mathcal{V}}(s)}\Big)^2 ds, \quad \langle M_4, M_4\rangle(t) = \int_0^t \Big(\frac{\varphi_2\nu_{32}V^2(s)}{\hat{\mathcal{V}}(s)}\Big)^2 ds.\end{aligned} \tag{5.12}$$

By strong law of large numbers [35], one obtaines

$$\lim_{t\to 0}\frac{M_i(t)}{t} = 0 \quad a.s., \quad i = 1, 2. \tag{5.13}$$

Hence, we have

$$\begin{aligned}\frac{\ln\hat{\mathcal{V}}(t)}{t} \leq \frac{\ln\hat{\mathcal{V}}(0)}{t} &- \frac{1}{2(\nu_{21}^{-2} + \nu_{31}^{-2})} + \frac{(\beta_1+\beta_2)}{t}\int_0^t \Big|X(s) - \frac{\eta_1}{\alpha_1}\Big|ds - \frac{1}{t}\int_0^t \frac{\varphi_1^2\nu_{22}^2 I^4(s)}{2\hat{\mathcal{V}}^2(s)}ds\\ &- \frac{1}{t}\int_0^t \frac{\varphi_2^2\nu_{32}^2 V^4(s)}{2\hat{\mathcal{V}}^2(s)}ds + \min\Big\{\alpha_1\alpha_3, \alpha_2 - \frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0 - 1\Big)1_{(\Phi_0\leq 1)}\\ &+ \max\Big\{\alpha_1\alpha_3, \alpha_2 - \frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0 - 1\Big)1_{(\Phi_0>1)} + \frac{M_1(t)}{t} + \frac{M_2(t)}{t} + \frac{M_3(t)}{t} + \frac{M_4(t)}{t}.\end{aligned} \tag{5.14}$$

Let ϵ, ζ_1 and T_1 are positive constants, by the exponential martingale inequality [36], for each $T_1 \geq 1$, such that $j = 3, 4$, we have

$$\mathbb{P}\{\sup_{0\leq t\leq T_1}(M_j(t) - \frac{\epsilon}{2}\langle M_j(t), M_j(t)\rangle) > \zeta_1\} \leq e^{-\epsilon\zeta_1}.$$

Let $T_1 = n$, $\epsilon = 1$ and $\zeta_1 = 2\ln n$, we get

$$\mathbb{P}\{\sup_{0\le t\le n}(M_j(t) - \frac{1}{2}\langle M_j(t), M_j(t)\rangle) > 2\ln n\} \le \frac{1}{n^2}.$$

By using Borel-Cantelli Lemma [36], there is $\Omega_0 \subset \Omega$ with $\mathbb{P}(\Omega_0) = 1$ such that for $\rho \in \Omega_0$ there exists an integer $n_0 = n_0(\rho)$, such that

$$M_3(t) \le \frac{1}{2}\langle M_3(t), M_3(t)\rangle + 2\ln n = \frac{1}{2}\int_0^t \Big(\frac{\varphi_1 \nu_{22} I^2(s)}{\hat{\mathcal{V}}(s)}\Big)^2 ds. \tag{5.15}$$

$$M_4(t) \le \frac{1}{2}\langle M_4(t), M_4(t)\rangle + 2\ln n = \frac{1}{2}\int_0^t \Big(\frac{\varphi_2 \nu_{32} V^2(s)}{\hat{\mathcal{V}}(s)}\Big)^2 ds. \tag{5.16}$$

For all $0 \le t \le n \wedge n \ge n_0(\rho)$ a.s. That is, for $0 \le n-1 \le t \le n$, one obtains

$$\begin{aligned}\frac{\ln\hat{\mathcal{V}}(t)}{t} \le{}& \frac{\ln\hat{\mathcal{V}}(0)}{t} + \frac{(\beta_1+\beta_2)}{t}\int_0^t \Big|X(s) - \frac{\eta_1}{\alpha_1}\Big| ds + \frac{M_1(t)}{t} + \frac{M_2(t)}{t} \\ &+ \frac{4\ln n}{k-1} + \min\Big\{\alpha_1\alpha_3, \alpha_2 - \frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0 - 1\Big)1_{(\Phi_0\le 1)} \\ &+ \max\Big\{\alpha_1\alpha_3, \alpha_2 - \frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0 - 1\Big)1_{(\Phi_0>1)} - \frac{1}{2(\nu_{21}^{-2} + \nu_{31}^{-2})}.\end{aligned} \tag{5.17}$$

Noting that $X(t)$ is ergodic and $\int_0^\infty x\pi(x)dx < \infty$ a.s., therefore, we have

$$\lim_{t\to\infty}\frac{1}{t}\int_0^t \Big|X(s) - \frac{\eta_1}{\alpha_1}\Big| ds = \int_0^\infty \Big|x - \frac{\eta_1}{\alpha_1}\Big|\pi(x)dx. \tag{5.18}$$

In view of systems (5.13) and (5.18) by taking superior limit on both sides of system (5.17), one gets

$$\begin{aligned}\limsup_{t\to\infty}\frac{\ln\hat{\mathcal{V}}(t)}{t} \le{}& (\beta_1+\beta_2)\int_0^\infty \Big|x - \frac{\eta_1}{\alpha_1}\Big|\pi(x)dx + \min\Big\{\alpha_1\alpha_3, \alpha_2 - \frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0 - 1\Big)1_{(\Phi_0\le 1)} \\ &+ \max\Big\{\alpha_1\alpha_3, \alpha_2 - \frac{\beta_2\eta_1}{\alpha_1}\Big\}\Big(\Phi_0 - 1\Big)1_{(\Phi_0>1)} - \frac{1}{2(\nu_{21}^{-2} + \nu_{31}^{-2})} \\ :={}& \mathcal{R}_0^e.\end{aligned} \tag{5.19}$$

If $\mathcal{R}_0^e < 0$, then $\limsup_{t\to\infty}\frac{\ln I(t)}{t} < 0$, and $\limsup_{t\to\infty}\frac{\ln V(t)}{t} < 0$, a.s. which implies that $\lim_{t\to\infty} I(t) = 0$ and $\lim_{t\to\infty} V(t) = 0$ a.s. Therefore, the disease will die out exponentially with probability one.

We arrive at the following Remark.

Remark 2. *From $0 < \Phi_0 < 1$, when the stochastic perturbations ν_{21} and ν_{31} are sufficiently large so that $\mathcal{R}_0^e < 0$, the stochastic system (2.2) displays disease extinction with probability one. Also, stochastic perturbations lead to the eradication of the disease in the stochastic system faster than the undisturbed system; See Figure 3.*

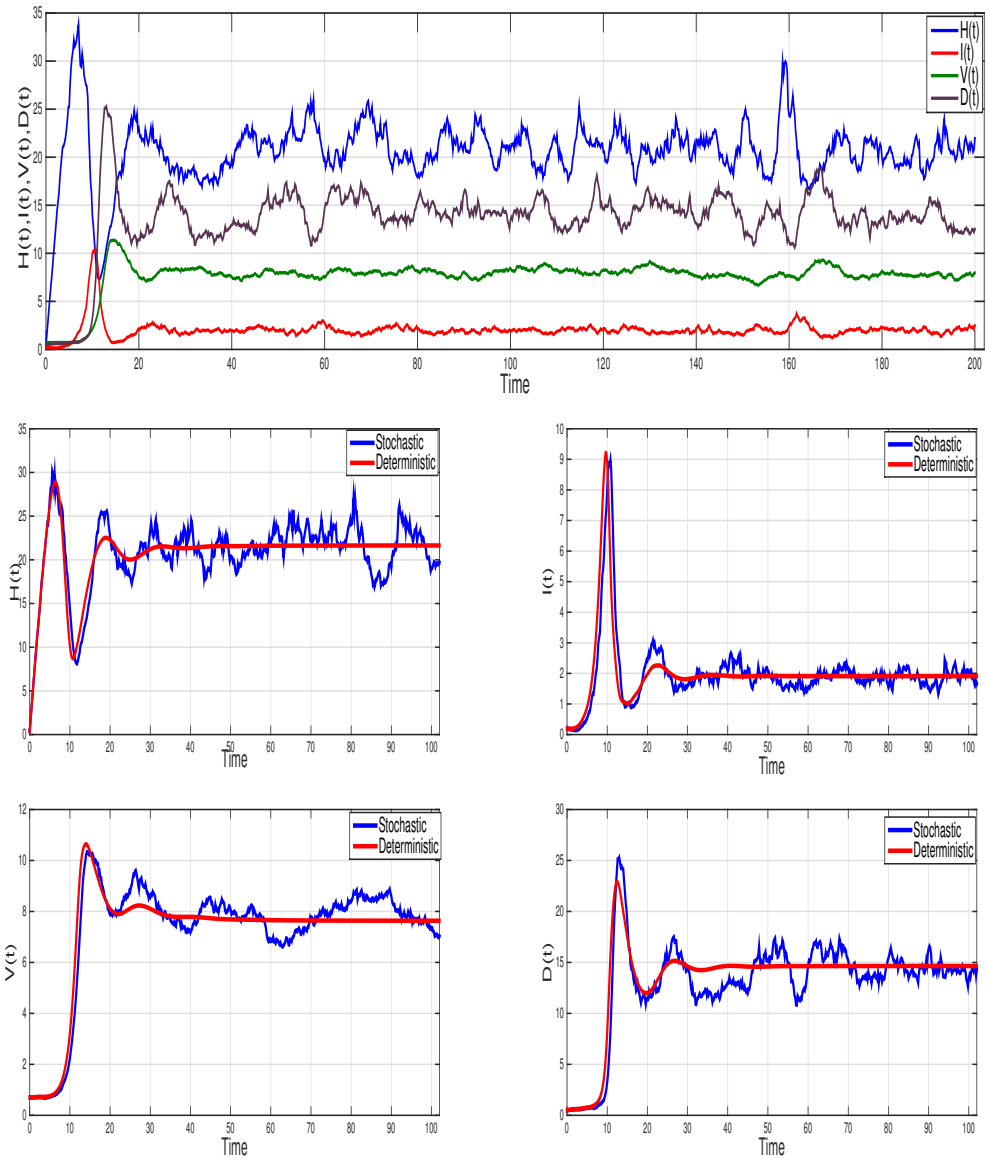

Figure 2. The top banner shows the numerical simulations of SDDEs system (2.2), $\nu_{11} = 0.003$, $\nu_{12} = 0.001$, $\nu_{21} = 0.004$, $\nu_{22} = 0.001$, $\nu_{31} = 0.001$, $\nu_{32} = 0.006$, $\nu_{41} = 0.003$, $\nu_{42} = 0.004$, and parameter values given in Table 2. When $\mathcal{R}_0^s > 1$, the model has a unique ergodic stationary distribution and the infection is persistent. The bellow banners show the stationary distribution and illustrate that the solution of the stochastic system (2.2) fluctuate in a neighborhood of the infected equilibrium, $\mathcal{E}^*$ of the corresponding undisturbed system (2.1).

6. Numerical simulations

In this section, some numerical simulations are given to validate the theoretical results, through Milstein's Higher order method [41, 42], to numerically solve SDDEs system (2.2). The discretization

Table 2. The list of parameter values for numerical simulations.

Parameters	Example 1	Example 2	Units
η_1	6	0.3	cell ml^{-1} day^{-1}
η_2	0.2 [10]	0.2 [10]	cell ml^{-1} day^{-1}
α_1	0.01 [37]	0.5	day^{-1}
α_2	0.1 [38]	0.9	day^{-1}
α_3	0.1	0.5	day^{-1}
α_4	0.3 [10]	0.1 [39]	day^{-1}
β_1	0.01 [40]	0.01	virions^{-1} day^{-1}
β_2	0.1	0.1	cell^{-1} day^{-1}
β_3	0.2 [39]	0.2 [39]	cell^{-1} day^{-1}
β_4	0.015	0.15	cell^{-1} day^{-1}
a	0.4 [39]	0.06	cell^{-1} day^{-1}

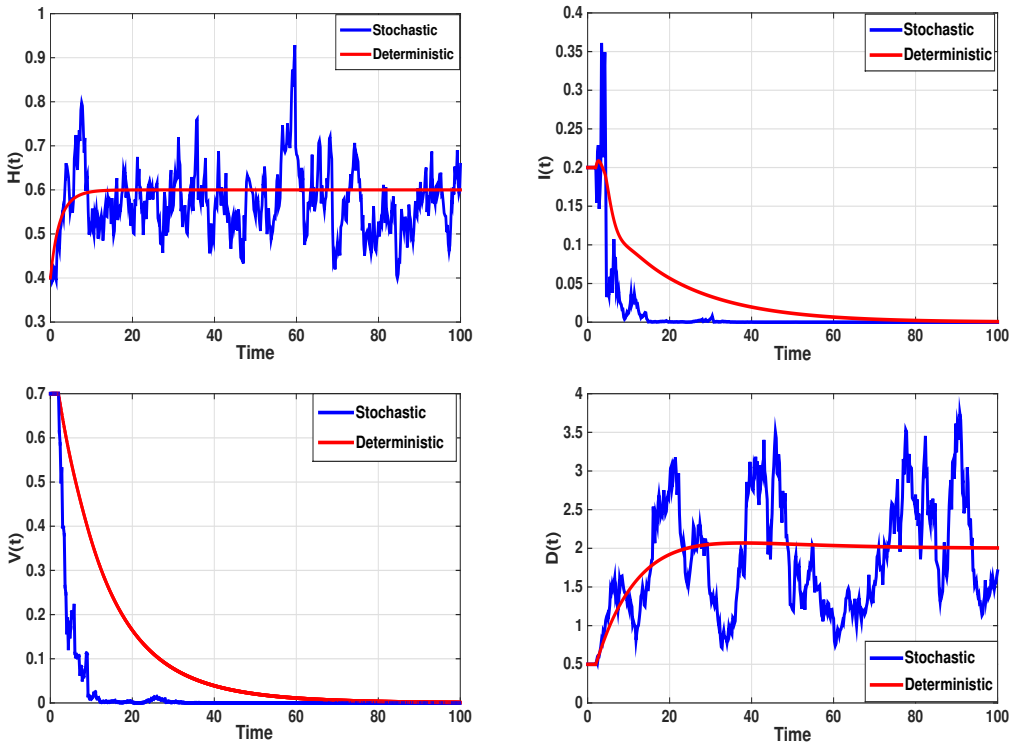

Figure 3. Time domain behavior of SDDEs system (2.2) (blue) and corresponding undisturbed system (2.1) (red), with $\tau_1 = 1$ and $\tau_2 = 2$, $\nu_{11} = 0.1$, $\nu_{12} = 0.1$, $\nu_{21} = 0.6$, $\nu_{22} = 0.6$, $\nu_{31} = 0.7$, $\nu_{32} = 0.3$, $\nu_{41} = 0.2$, $\nu_{42} = 0.1$, when $\Phi_0 < 1$ and $\mathcal{R}_0^e < 0$, the infection dies out in the stochastic model faster than the undisturbed model under the impact of stochastic perturbations.

transformation takes the form

$$H_{k+1} = H_k + [\eta_1 - \alpha_1 H_k - \beta_1 H_k V_k - \beta_2 H_k I_k]\Delta t + (\nu_{11} H_k + \nu_{12}) H_k \sqrt{\Delta t}\xi_{1,k} + \frac{H_k}{2}(2\nu_{11}^2 H_k^2 + 3\nu_{11}\nu_{12} H_k + \nu_{12}^2)$$

$$I_{k+1} = I_k + [\beta_1 H_k V_k + \beta_2 H_{k-m_1} I_{k-m_1} - \alpha_2 I_k - \beta_3 I_k D_k]\Delta t + (\nu_{21} + \nu_{22} I_k) I_k \sqrt{\Delta t}\xi_{2,k} + \frac{I_k}{2}(\nu_{21}^2 + 3\nu_{21}\nu_{22} I_k + 2\nu_{22}^2 I_k^2)$$

$$V_{k+1} = V_k + [aI_{k-m_2} - \alpha_3 V_k]\Delta t + (\nu_{31} + \nu_{32} V_k) V_k \sqrt{\Delta t}\xi_{3,k} + \frac{V_k}{2}(\nu_{31}^2 + 3\nu_{31}\nu_{32} V_k + 2\nu_{32}^2 V_k^2)$$

$$D_{k+1} = D_k + [\eta_2 - \alpha_4 D_k + \beta_4 I_k D_k]\Delta t + (\nu_{41} + \nu_{42} D_k) D_k \sqrt{\Delta t}\xi_{4,k} + \frac{D_k}{2}(\nu_{41}^2 + 3\nu_{41}\nu_{42} D_k + 2\nu_{42}^2 D_k^2).$$

The independent Gaussian random variables denoted as $\xi_{i,k}$, $(i = 1, 2, 3, 4)$, which follow the distribution $N(0, 1)$, m_1 and m_2 are integers such that the time-delays can be expressed in terms of the step-size Δt as $\tau_1 = m_1\Delta t$ and $\tau_2 = m_2\Delta t$. Initial values are taken fixed $(0.4, 0.2, 0.7, 0.5)$.

Example 1. *Herein, we use parameter values of Table 2 to analyze the dynamics of systems (2.1) and (2.2), with time-delays* $\tau_1 = 1$ *and* $\tau_2 = 2$*, we choose* $\nu_{11} = 0.003$*,* $\nu_{12} = 0.001$*,* $\nu_{21} = 0.004$*,* $\nu_{22} = 0.001$*,* $\nu_{31} = 0.001$*,* $\nu_{32} = 0.006$*,* $\nu_{41} = 0.003$*,* $\nu_{42} = 0.004$*. Direct calculations leads to* $\mathcal{R}_0^s > 1$*, the condition of Theorem 2 satisfies. The stationary distribution illustrates that the solution of the stochastic system (2.2) fluctuate in a neighborhood of the endemic equilibrium* $\mathcal{E}^*$ *of the corresponding undisturbed system (2.1), which means that the disease is persistent for all time regardless of the initial conditions if the scale of random perturbations is relatively small. Therefore, system (2.2) admits a unique ergodic stationary distribution* $\pi(.)$*. The simulation also indicates that the endemic equilibrium is asymptotically stable for the undisturbed system; See Figure 2.*

Example 2. *Now, we compare the solution of the SDDEs system (2.2) with the undisturbed system (2.1) around the disease free equilibrium point, using parameter values of Table 2. Figure 3 shows that the disease free equilibrium point is stable for the undisturbed system. However, for the SDDEs system (2.2), we choose* $\nu_{11} = 0.1$*,* $\nu_{12} = 0.1$*,* $\nu_{21} = 0.6$*,* $\nu_{22} = 0.6$*,* $\nu_{31} = 0.7$*,* $\nu_{32} = 0.3$*,* $\nu_{41} = 0.2$*,* $\nu_{42} = 0.1$*, by a simple calculation we have* $\Phi_0 \approx 0.067 < 1$ *and* $\mathcal{R}_0^e < 0$*, so that conditions of Theorem 3 hold, Therefore, the disease will be extinct with probability one. It is shown that the larger intensity of white noise set may help to eliminate the disease faster than the model without noise.*

7. Concluding remarks

In the present work, we investigated the impact of high-order stochastic perturbations on the dynamics of delay differential model of HBV infection with both virus-to-cell and cell-to-cell transmissions, intracellular delay, and immunity. The effect of stochastic perturbations on the persistence and possible extinction of the disease have been studied in detail. By utilizing Lyapunov functional, we proved the existence and uniqueness of an ergodic stationary distribution of positive solutions to the system, where the solution fluctuates around endemic equilibrium of the corresponding deterministic model and leads to the stochastic persistence of the disease with probability one. The model has a unique stationary distribution which is ergodic if $\mathcal{R}_0^s > 1$. In addition, we formulate sufficient conditions for complete extinction of the disease by constructing a suitable stochastic Lyapunov function. Under some conditions, the disease can die out exponentially with probability one. Some numerical simulations, by using Milstein's scheme, are carried out to show the effectiveness of the obtained results. The intensity of white noise plays an important role in the treatment of HBV and other infectious diseases.

The incorporation of intracellular time-delays and stochastic perturbations (noise) in the model is assumed to give a clearer view in the interpretation of the analytical result and this has important

implications on therapeutic options and drug development. Some other interesting topics deserve further investigation. One may take other kinds of environmental noise into account, such as the Levy noise [43]. In addition, motivated by the work in [44,45] the deterministic system (2.1) can be extended to include fractional derivatives in the model in order to consider long-run memory of the dynamic of the disease.

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Conflict of interest

The authors declare no conflict of interest in this paper.

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Appendix: Equilibrium points and $\mathcal{R}_0$ of the deterministic model

The deterministic system (2.1) admits two equilibrium points, namely; The disease-free equilibrium, $\mathcal{E}_0 = (H_0, 0, 0, D_0)$, where $H_0 = \frac{\eta_1}{\alpha_1}$ and $D_0 = \frac{\eta_2}{\alpha_4}$; The infected equilibrium, $\mathcal{E}^* = (H^*, I^*, V^*, D^*)$,

where

$$H^* = \frac{\eta_1\alpha_3}{\alpha_1\alpha_3 + (\beta_1 a + \beta_2\alpha_3)I^*}, \quad V^* = \frac{aI^*}{\alpha_3}, \quad D^* = \frac{\eta_2}{\alpha_4 - \beta_4 I^*},$$

with $\alpha_4 > \beta_4 I^*$ such that I^* is the positive root of

$$\begin{aligned}
&z_1 I^{*2} + z_2 I^* + z_3 = 0, \quad \text{where}\\
&z_1 = a\alpha_2\beta_1\beta_4 + \alpha_2\alpha_3\beta_2\beta_4\\
&z_2 = \alpha_1\alpha_2\alpha_3\beta_4 - (a\alpha_2\alpha_4\beta_1 + a\beta_1\beta_3\eta_2 + \alpha_3\beta_2\beta_3\eta_2 + a\beta_1\beta_4\eta_1 + \alpha_3\beta_2\beta_4\eta_1 + \alpha_2\alpha_3\alpha_4\beta_2)\\
&z_3 = a\alpha_4\beta_1\eta_1 + \alpha_3\alpha_4\beta_2 - (\alpha_1\alpha_3\beta_3\eta_2 + \alpha_1\alpha_2\alpha_3\alpha_4).
\end{aligned}$$

To determine the expression of the basic reproduction number, we utilize the next generation matrix approach [46]. Therefore, we have

$$\mathcal{F} = \begin{pmatrix} \frac{\beta_2\eta_1}{\alpha_1} & \frac{\beta_1\eta_1}{\alpha_1} \\ 0 & 0 \end{pmatrix}, \quad \mathbb{V} = \begin{pmatrix} \frac{\beta_3\eta_2}{\alpha_4} + \alpha_2 & 0 \\ -a & \alpha_3 \end{pmatrix},$$

$$\mathbb{V}^{-1} = \begin{pmatrix} \frac{\alpha_4}{\beta_3\eta_2 + \alpha_2\alpha_4} & 0 \\ \frac{a\alpha_4}{\alpha_3(\beta_3\eta_2 + \alpha_2\alpha_4)} & \frac{1}{\alpha_3} \end{pmatrix}.$$

The basic reproduction number is the spectral radius of $(\mathcal{F}\mathbb{V}^{-1})$, i.e. $\mathcal{R}_0 = \rho(\mathcal{F}\mathbb{V}^{-1})$. Hence,

$$\mathcal{R}_0 = \frac{\eta_1\alpha_4(a\beta_1 + \alpha_3\beta_2)}{\alpha_1\alpha_3(\beta_3\eta_2 + \alpha_2\alpha_4)} = \mathcal{R}_{01} + \mathcal{R}_{02},$$

where $\mathcal{R}_{01} = \dfrac{a\alpha_4\beta_1 H_0}{\alpha_3(\beta_3\eta_2 + \alpha_2\alpha_4)}$ and $\mathcal{R}_{02} = \dfrac{\alpha_4\beta_2 H_0}{\beta_3\eta_2 + \alpha_2\alpha_4}$. From biological point of view, $\mathcal{R}_{01}$ stands for the average number of secondary infected cells produced by an infectious virion and $\mathcal{R}_{02}$ represents the average number of secondary infected cells produced by an infected cell.