Bull. Malays. Math. Sci. Soc. (2021) 44:1345–1370
https://doi.org/10.1007/s40840-020-01014-6

BULLETIN *of the*
MALAYSIAN MATHEMATICAL
SCIENCES SOCIETY
http://www.springer.com/mathematics/journal/40840

On an Age-Structured Hepatitis B Virus Infection Model with HBV DNA-Containing Capsids

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Received: 8 October 2019 / Revised: 17 June 2020 / Accepted: 28 August 2020 /
Published online: 14 September 2020

Abstract

In this paper, we study an age-structured hepatitis B virus model with DNA-containing capsids. We obtain the well-posedness of the model by reformulate the model as an abstract Cauchy problem, and we find a threshold number $\Re_0$ for the existence of the steady states. The local stability of each steady states is established by linearizing the system and analyze the corresponding characteristic equation. Furthermore, we investigate the uniform persistence of the system and constructing Lyapunov functionals to show the global stability of each steady states. We observe that the virus-free steady state is globally asymptotically stable when $\Re_0 < 1$, while the infection steady state is globally asymptotically stable when $\Re_0 > 1$. Numerical simulations are also presented to support the analytical results.

Keywords HBV DNA-containing capsids · Age structure · Lyapunov functional · Stability · Hepatitis B virus

Mathematics Subject Classification 92D30 · 35B35 · 34K20

Communicated by Syakila Ahmad.

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1 Introduction

Viral hepatitis causes a life-threatening liver infection. World Health Organization estimated that there were about 325 millions people who living with chronic hepatitis infection or carriers and about 1.34 million deaths in 2015, where hepatitis B accounted for 80% of all hepatitis infection and 66% of all hepatitis mortality, respectively [44]. HBV infection can be acute or chronic in nature. Acute infection could last for several weeks and the acute patients eventually recover with immunity. However, chronic infection which lasts for several decades can potentially cause severe symptoms such as liver cirrhosis and hepatocellular carcinoma [36]. Therefore, HBV infection is a major concern for public health in the world.

Over the past two decades, many researchers have used mathematical models to describe the within-host viral infection of HBV. In 1996, Nowak et al. [33] proposed a simple ODE model to analyze the dynamical property of HBV. Their basic model consists of uninfected hepatocytes, infected hepatocytes and HBV. Uninfected hepatocytes are assumed to be produced at a constant rate and die at a constant rate. Infection between uninfected hepatocytes and free virus is assumed to satisfy the mass-action principle and infected hepatocytes die at a constant rate. To better understanding the viral dynamics of HBV infection, many authors have generalized the basic model of Nowark et al. by taking into account of some factors such as the delay during virion production, the therapeutic efficacy, the growth rate of uninfected cell and infection rate between uninfected cell and virus (see [9,12,15–17,28]).

During the process of hepatocyte infection, the HBV virions enter into hepatocyte, uncoat and transform relaxed circular DNA (rcDNA). The rcDNA is delivered into the nucleus and converted into covalently closed circular DNA (cccDNA) which is the template for the production of viral mRNA. After encapsidation, the full-length unspliced mRNA is reverse transcribed into DNA with the help of viral polymerase, which has reverse transcriptase function, for the formation of rcDNA. After maturation, a part of newly synthesized rcDNAs with nucleocapsid is transported to the nucleus to increase the pool size of cccDNA. The other part of rcDNA with nucleocapsid is released from the cytoplasm which implies new virion is developed [31,39]. In 2005, considering HBV DNA-containing capsids as an important factor, Murray et al. [30] constructed a multi-infection stage ODE model which consisted of infected hepatocytes with different copies of cccDNA, the amount of pregenome RNA (pgRNA) in the liver, the number of HBV DNA-containing capsids and free virus. They observed that their model fitted the experimental data in Chimpanzees very well. Murray et al. [29] also considered a simplified model consisted only the number of infected hepatocytes, the number of intracelluar HBV DNA-containing capsids, and the number of virions in plasma and used the model to estimate the half-life of HBV virions. Manna and Chakrabarty [24] combined the basic model of Nowark et al. [33] and the simplified model of Murray et al. [29] by adding the intracelluar HBV DNA-containing capsids, the corresponding mathematical model is as follows:

Table 1 The description of parameters of the HBV model (1)

Parameter	Description
Λ	The recruitment rate of uninfected cells
β	The rate of infection between uninfected cell and virus
μ_1	The natural death rate of uninfected cell
μ_2	The natural death rate of HBV DNA-containing capsid and the infected hepatocytes
μ_3	The natural death rate of virus
k	The production rate of virus from HBV DNA-containing capsid
v	The rate of production of intracellular HBV DNA-containing capsids associated with infection age a

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = \Lambda - \mu_1 T(t) - \beta T(t)V(t), \\ \dfrac{\mathrm{d}I(t)}{\mathrm{d}t} = \beta T(t)V(t) - \mu_2 I(t), \\ \dfrac{\mathrm{d}D(t)}{\mathrm{d}t} = vI(t) - (\mu_2 + k)D, \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = kD(t) - \mu_3 V(t), \end{cases} \tag{1}$$

where $T(t)$, $I(t)$, $D(t)$ and $V(t)$ denote the density of uninfected hepatocytes, infected hepatocytes, intracellular HBV DNA-containing capsids and the virions at time t, respectively. All parameters are assumed to be positive, and the description of parameters is listed in Table 1.

In [24], the authors shown that the global dynamics of model (1) is completely determined by the basic reproduction number, that is: the disease-free equilibrium is globally asymptotically stable if the basic reproduction number is less than one, while a positive endemic equilibrium exists and it is globally asymptotically stable if the basic reproduction number is greater than one. Consider time delay effect, Manna and Chakrabarty [25] investigated the Chronic hepatitis B infection models with one and two discrete delays, and they showed the global stability of the steady states. Geng et al. [6] studied a diffusive viral infection model with capsids and time delay, the global dynamical behaviors of the original model and the discrete model are investigated by constructing Lyapunov functionals, where the discrete model is obtained by applying the nonstandard finite difference (NSFD) scheme to the original continuous model. Guo et al. [7] formulated a diffusive and delayed HBV infection model with HBV DNA-containing capsids and general incidence rate, and they also studied the stability

of the model. In [26], Manna and Hattaf proposed a model incorporates the intracellular HBV DNA-containing capsids, spatial diffusion in both capsids and viruses, and adaptive immune response exerted by cytotoxic T lymphocytes and antibodies, and they have shown the global stability and instability of equilibria by Lyapunovs direct and indirect methods.

However, the above-mentioned models do not take into account the fact that the mortality rate and virus production rate of infected cells depend on the infection age of infected cells . Let $i(t,a)$ represent the density of infected cells with infection age a at time t. While the infection age a denotes the time since the infection began. Then, $\int_{a_1}^{a_2} i(t,a)\mathrm{d}a$ is the number of infected cells with infection age between a_1 and a_2 where $0 \leq a_1 < a_2 < +\infty$. Consider age as a continuous variable, writing the production rate of viral particles and the death rate of productively infected cells as two continuous functions of age, Nelson et al. [32] formulated a basic age-structured virus model, which governed by the first-order partial differential equations system. Nelson et al. analyzed the local stability of the model by evaluating eigenvalues and its related characteristic equation. In [37], Rong et al. extended the model with combination antiretroviral therapy and analyzed the local stability of the model. Huang et al. [14] have been further investigated the global stability of the model proposed in [32] by using Lyapunov direct method and LaSalle invariance principle. Hattaf and Yang [13] proposed an age-structured viral infection model with general incidence function that takes account of the loss of viral particles due to their absorption into susceptible cells, the global behavior of the model is investigated. For some recent works on viral models (HIV, HBV, etc) with age structure, we refer readers to the papers ([34,40–42,45] and the references therein).

Motivated by the above facts, in this paper, we establish a new within-host hepatitis B virus infection model with age structure and HBV DNA-containing capsids:

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = \Lambda - \mu_1 T(t) - \beta T(t) V(t), \\ \dfrac{\partial i(t,a)}{\partial t} + \dfrac{\partial i(t,a)}{\partial a} = -\delta(a) i(t,a), \\ \dfrac{\mathrm{d}D(t)}{\mathrm{d}t} = \displaystyle\int_0^{\infty} p(a) i(t,a)\mathrm{d}a - (\mu_2 + k) D, \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = kD(t) - \mu_3 V(t), \end{cases} \tag{2}$$

with boundary condition

$$i(t,0) = \beta T(t) V(t), \tag{3}$$

and initial condition

$$T(0) = T_0 > 0,\ i(0,\cdot) = i_0(a) \in L^1_+(0,\infty),\ D(0) = D_0 > 0,\ V(0) = V_0 > 0. \tag{4}$$

where $T(t)$, $i(t,a)$, $D(t)$ and $V(t)$ represent the density of uninfected cells, infected cells with infection age a, HBV DNA-containing capsids and infectious free virion at time t, respectively; $\delta(a)$ is the removal rate of infected cells associated with infection

age a and $L^1_+(0,\infty)$ is the nonnegative cone of $L^1(0,\infty)$. The biological meaning of all other parameters is the same with Model (1). At first, we make some assumptions about the coefficients.

(A1) The function $\delta(a),\ p(a) \in L^\infty_+(0,\infty)$. Denote

$$\bar{\delta} = \operatorname{ess\,sup}_{a\in\mathbb{R}_+} \delta(a),\ \bar{p} = \operatorname{ess\,sup}_{a\in\mathbb{R}_+} p(a),\ \underline{\delta} = \operatorname{ess\,inf}_{a\in\mathbb{R}_+} \delta(a) \text{ and } \underline{\mathrm{p}} = \operatorname{ess\,sup}_{\mathrm{a}\in\mathbb{R}_+} \mathrm{p(a)}.$$

(A2) There exists a positive constant $a_\dagger < +\infty$ such that $i(t,a) = 0$ for all $a \geq a_\dagger$. Here, $L^\infty_+(0,\infty)$ is the nonnegative cone of $L^\infty(0,\infty)$. Biologically, Assumption (A2) means that there is no individual can live forever. In addition, we denote the following notions for convenience:

$$\Phi(a) = \int_a^\infty p(s)e^{-\int_a^s \delta(\tau)\mathrm{d}\tau}\mathrm{d}s,\quad \Omega(a) = e^{-\int_0^a \delta(\tau)\mathrm{d}\tau},\quad \eta = \int_0^\infty p(a)\Omega(a)\mathrm{d}a. \quad (5)$$

It is clear that

$$\frac{\mathrm{d}\Phi(a)}{\mathrm{d}a} = \delta(a)\Phi(a) - p(a) \text{ and } \frac{\mathrm{d}\Omega(a)}{\mathrm{d}a} = -\delta(a)\Omega(a).$$

The aim of this paper is to analyze the global properties of the infection-age model (2). To analyze the global stability of steady states, we plan to construct some suitable Lyapunov functionals which involve some integrals with respect to the age-of-infection a which goes from 0 to infinity. However, the functional is infinite if the number of infected cells $i(a,t) = 0$ or if $i(a,t)$ is positive but close enough to 0. To solve this problem, we need to prove the uniform persistence of system (we point here that some recent results from the age-structured epidemic models would also be relevant for our discussion, for example, [18,20,46] and the references therein).

The article is organized as follows. In Sect. 2, we analyze the existence and uniqueness of solutions by rewriting model (2) as an abstract Cauchy problem in a Banach space. Existence and the local stability of steady states are discussed in Sect. 3. In Sect. 4, we study the asymptotically smooth and uniform persistence of solution semiflow. Global stability of steady states are stated in Sect. 5. In Sect. 6, we give some numerical simulations. A brief discussion is presented in the last section.

2 Existence and Uniqueness of Solutions

In this section, we study the existence and uniqueness of solutions to model (2) with boundary condition (3) and initial condition (4). We denote the following Banach spaces:

$$\begin{aligned}
\mathcal{X} &= \mathbb{R}\times\mathbb{R}\times L^1(\mathbb{R}_+,\mathbb{R})\times\mathbb{R}\times\mathbb{R},\\
\mathcal{X}_0 &= \mathbb{R}\times\{0\}\times L^1(\mathbb{R}_+,\mathbb{R})\times\mathbb{R}\times\mathbb{R},\\
\mathcal{X}_+ &= \mathbb{R}_+\times\mathbb{R}_+\times L^1_+(\mathbb{R}_+,\mathbb{R})\times\mathbb{R}_+\times\mathbb{R}_+,\\
\mathcal{X}_{0+} &= \mathcal{X}_+\cap\mathcal{X}_0,
\end{aligned}$$

with the norm

$$\left|\left|\left(\phi_1, \varphi(\cdot), \phi_2, \phi_3\right)\right|\right|_{\mathcal{X}} = |\phi_1| + \int_0^\infty |\varphi(a)|da + |\phi_2| + |\phi_3|.$$

In order to formulate system (2) as an abstract Cauchy problem, we define two operators on $\mathcal{X}_0$, which are the linear operator B and the nonlinear operator F.

The linear operator $B : \mathrm{Dom}(B) \subset \mathcal{X} \to \mathcal{X}$ is given as follows:

$$B\begin{pmatrix} \phi_1 \\ \begin{pmatrix} 0 \\ \varphi \end{pmatrix} \\ \phi_2 \\ \phi_3 \end{pmatrix} = \begin{pmatrix} -\mu_1\phi_1 \\ \begin{pmatrix} -\varphi(0) \\ -\varphi' - \delta\varphi \end{pmatrix} \\ -(\mu_2 + k)\phi_2 \\ -\mu_3\phi_3 \end{pmatrix},$$

with $\mathrm{Dom}(B) = \mathbb{R} \times \{0\} \times W^{1,1}(0, \infty) \times \mathbb{R} \times \mathbb{R}$, where $W^{1,1}$ denote the Sobolev space. The nonlinear map $F : \mathrm{Dom}(B) \subset \mathcal{X} \to \mathcal{X}$ is defined by

$$F\begin{pmatrix} \phi_1 \\ \begin{pmatrix} 0 \\ \varphi \end{pmatrix} \\ \phi_2 \\ \phi_3 \end{pmatrix} = \begin{pmatrix} \Lambda - \beta\phi_1\phi_3 \\ \begin{pmatrix} \beta\phi_1\phi_3 \\ 0 \end{pmatrix} \\ \int_0^\infty p(a)\varphi(a)da \\ k\phi_2 \end{pmatrix}.$$

Clearly, $\overline{\mathrm{Dom}(B)} = \mathcal{X}_0$ is not dense in $\mathcal{X}$ and F is Lipschitz continuous on $\mathrm{Dom}(B)$.

Let $u(t) = \left(T(t), \begin{pmatrix} 0 \\ i(t, \cdot) \end{pmatrix}, D(t), V(t)\right)^\intercal$, where $\intercal$ represents transposition of a vector. Then, we can rewrite system (2) as the following abstract Cauchy problem:

$$\begin{cases} \dfrac{\mathrm{d}u(t)}{\mathrm{d}t} = Bu(t) + F(u(t)), t \geq 0, \\ u(0) = u_0 \in \mathcal{X}_0 \bigcap \mathcal{X}_{0+}. \end{cases} \tag{6}$$

In order to establish the existence and uniqueness of solutions for system (2) by using [21, Theorem 5.2.7], we need to show that the operator B is a Hille–Yosida operator. Denote $\rho(B)$ be the resolvent set of B. The definition of Hille–Yosida operator is as following:

Definition 1 (*See* [21, Definition 2.4.1]) Let $B : \mathrm{Dom}(B) \subset \mathcal{X} \to \mathcal{X}$ be a linear operator. If there exist real constants $M \geq 1$, and $\omega \in \mathbb{R}$, such that $(\omega, +\infty) \subseteq \rho(B)$, and

$$\|(\lambda - B)^{-n}\| \leq \frac{M}{(\lambda - \omega)^n}, \quad \text{for } n \in \mathbb{N}_+, \quad \text{and all } \lambda > \omega.$$

Now, we show that the operator B is a Hille–Yosida operator.

Lemma 1 *The operator B is a Hille–Yosida operator.*

Proof Let the resolvent of operator B is defined by

$$(\lambda I - B)^{-1}\begin{pmatrix}\hat{\phi}_1\\ \begin{pmatrix}\hat{\varphi}_0\\ \hat{\varphi}\end{pmatrix}\\ \hat{\phi}_2\\ \hat{\phi}_3\end{pmatrix} = \begin{pmatrix}\phi_1\\ \begin{pmatrix}0\\ \varphi\end{pmatrix}\\ \phi_2\\ \phi_3\end{pmatrix}.$$

Then, we can obtain

$$\begin{pmatrix}\phi_1\\ \varphi\\ \phi_2\\ \phi_3\end{pmatrix} = \begin{pmatrix}\frac{1}{\lambda+\mu_1}\hat{\phi}_1\\ \hat{\varphi}_0 e^{-\int_0^a(\lambda+\delta(s))\mathrm{d}s} + \int_0^a \hat{\varphi} e^{-\int_\tau^a(\lambda+\delta(s))\mathrm{d}s}\mathrm{d}\tau\\ \frac{1}{\lambda+\mu_2+k}\hat{\phi}_2\\ \frac{1}{\lambda+\mu_3}\hat{\phi}_3\end{pmatrix}.$$

For $\int_0^\infty \varphi(a)\mathrm{d}a$, we make an estimation as follows:

$$\begin{aligned}\int_0^\infty \varphi(a)\mathrm{d}a &= \int_0^\infty \hat{\varphi}_0 e^{-\int_0^a(\delta(s)+\lambda)\mathrm{d}s}\mathrm{d}a + \int_0^\infty\int_0^a \hat{\varphi}(s)e^{-\int_s^a(\delta(\tau)+\lambda)\mathrm{d}\tau}\mathrm{d}s\mathrm{d}a\\ &\le \frac{|\hat{\varphi}_0|}{|\lambda+\underline{\delta}|} + \int_0^\infty\int_0^a \hat{\varphi}(s)e^{-(\lambda+\underline{\delta})(a-s)}\mathrm{d}s\mathrm{d}a\\ &= \frac{|\hat{\varphi}_0|}{|\lambda+\underline{\delta}|} + \int_0^\infty\int_s^\infty \hat{\varphi}(s)e^{-(\lambda+\underline{\delta})(a-s)}\mathrm{d}a\mathrm{d}s\\ &= \frac{|\hat{\varphi}_0|}{|\lambda+\underline{\delta}|} + \int_0^\infty \hat{\varphi}(s)e^{(\lambda+\underline{\delta})s}\int_s^\infty e^{-(\lambda+\underline{\delta})a}\mathrm{d}a\mathrm{d}s\\ &= \frac{|\hat{\varphi}_0|}{|\lambda+\underline{\delta}|} + \int_0^\infty \hat{\varphi}(s)e^{(\lambda+\underline{\delta})s}\frac{1}{\lambda+\underline{\delta}}e^{-(\lambda+\underline{\delta})s}\mathrm{d}s\\ &= \frac{|\hat{\varphi}_0|}{|\lambda+\underline{\delta}|} + \frac{||\hat{\varphi}||_{L_1}}{|\lambda+\underline{\delta}|}.\end{aligned}$$

Denote $\xi = \left(\hat{\phi}_1, \begin{pmatrix}\hat{\phi}_0\\ \hat{\varphi}(a)\end{pmatrix}, \hat{\phi}_2, \hat{\phi}_3\right)^{\mathsf{T}}$. Then, we have

$$\begin{aligned}||(\lambda I - B)^{-1}\xi||_{\mathcal{X}} &= |\phi_1| + |0| + \int_0^\infty \varphi(a)\mathrm{d}a + |\phi_2| + |\phi_3|\\ &= \frac{|\hat{\phi}_1|}{|\lambda+\mu_1|} + \int_0^\infty \varphi(a)\mathrm{d}a + \frac{|\hat{\phi}_2|}{|\lambda+\mu_2+k|} + \frac{|\hat{\phi}_3|}{|\lambda+\mu_3|}\\ &\le \frac{|\hat{\phi}_1|}{|\lambda+\mu_1|} + \frac{|\hat{\varphi}_0|}{|\lambda+\underline{\delta}|} + \frac{||\hat{\varphi}||_{L_1}}{|\lambda+\underline{\delta}|} + \frac{|\hat{\phi}_2|}{|\lambda+\mu_2+k|} + \frac{|\hat{\phi}_3|}{|\lambda+\mu_3|}.\end{aligned}$$

Choose $\mu = \min\{\mu_1, \mu_2 + k, \mu_3, \underline{\delta}\}$, then

$$||\,(\lambda I - B)^{-1}\,\xi\,||_{\mathcal{X}} \leq \frac{||\xi||_{\mathcal{X}}}{\lambda + \mu}.$$

Hence, by the definition of Hille–Yosida operator, the linear operator B is a Hille–Yosida operator. □

Let $X_0 = \left(T_0, \begin{pmatrix} 0 \\ i_0 \end{pmatrix}, D_0, V_0\right)^{\mathsf{T}} \in \mathcal{X}_{0+}$. Recalling that F is Lipschitz continuous on bounded set, then by [21][Theorem 5.2.7] (see also [19,22]), we have the following theorem.

Theorem 1 *There exists a uniquely determined semiflow $\{U(t)\}_{t\geq 0}$ on $\mathcal{X}_{0+}$ such that for each X_0, there exists a unique continuous map $U \in C([0,\infty), \mathcal{X}_{0+})$ which is an integrated solution of Cauchy problem (6), that is,*

$$\begin{cases} \displaystyle\int_0^t U(s)X_0 \mathrm{d}s \in \mathrm{Dom}(B), & \forall t \geq 0, \\ \displaystyle U(t)X_0 = X_0 + B\int_0^t U(s)X_0 \mathrm{d}s + \int_0^\infty F(U(s)X_0)\mathrm{d}s, & \forall t \geq 0. \end{cases} \tag{7}$$

Denote

$$\Upsilon = \left\{ (T(t), i(t,a), D(t), V(t)) \in \mathcal{X}_{0+} \;\middle|\; \begin{array}{l} T(t) \leq \dfrac{\Lambda}{\mu_1}, \quad T(t) + \displaystyle\int_0^\infty i(t,a)\mathrm{d}a \leq \frac{\Lambda}{\mu_0}, \\ D(t) \leq \dfrac{\bar{p}\Lambda}{\mu_0(\mu_2 + k)}, \quad V(t) \leq \dfrac{k\bar{p}\Lambda}{\mu_0(\mu_2 + k)\mu_3} \end{array} \right\} \tag{8}$$

where $\mu_0 = \min\left\{\mu_1, \underline{\delta}\right\}$. For the set Υ, we have the following proposition:

Proposition 1 *Υ is positively invariant set under the semiflow $\{U(t)\}_{t\geq 0}$. Moreover, the semiflow $\{U(t)\}_{t\geq 0}$ is point dissipative and attracts all positive solutions of system (2) in $\mathcal{X}_{0+}$.*

Proof First, we solve the second equation of system (2) along the characteristic line $t - a = c$ with boundary condition (3) and initial condition (4), where c is a constant. Set $a = a_0 + s$ and $t = t_0 + s$ for some variable s and (t_0, a_0) is a point in the first quadrant of the (t,a) plane. Denote $\hat{i}(s) := i(t_0 + s, a_0 + s) = i(t,a)$ and $\hat{\delta}(s) := \delta(a_0 + s) = \delta(a)$. Hence, we can rewrite the second equation of system (2) as

$$\frac{\mathrm{d}\hat{i}(s)}{\mathrm{d}s} = -\hat{\delta}(s)\hat{i}(s).$$

Solving the above ordinary differential equation give us

$$\hat{i}(s) = \hat{i}(0)e^{-\int_0^s \hat{\delta}(\tau)\mathrm{d}\tau}.$$

Consider the case $t \leq a$, we set $t_0 = 0$, $a_0 = a - t$ and $s = t$, one has that

$$i(t,a) = i_0(a-t)e^{-\int_0^t \delta(a-t-\tau)\mathrm{d}\tau} = i_0(a-t)\frac{\Omega(a)}{\Omega(a-t)}.$$

In the other case $t > a$, we set $t_0 = t - a$, $a_0 = 0$ and $s = a$. Recall that $\hat{i}(0) = i(0, t-a)$, we obtain that

$$i(t,a) = i(0,t-a)\Omega(a).$$

Overall, we obtain

$$i(t,a) = \begin{cases} \beta T(t-a)V(t-a)\Omega(a), & t > a, \\ i_0(a-t)\dfrac{\Omega(a)}{\Omega(a-t)}, & t \leq a. \end{cases} \tag{9}$$

Then, we have

$$\int_0^\infty i(t,a)\mathrm{d}a = \int_0^t \beta T(t-a)V(t-a)\Omega(a)\mathrm{d}a + \int_t^\infty i_0(a-t)\frac{\Omega(a)}{\Omega(a-t)}\mathrm{d}a$$

and

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty i(t,a)\mathrm{d}a = \int_0^\infty \frac{\partial}{\partial t}i(t,a)\mathrm{d}a = \beta T(t)V(t) - \int_0^\infty \delta(a)i(t,a)\mathrm{d}a.$$

From the first equation of (2), one has that

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} = \Lambda - \mu_1 T(t) - \beta T(t)V(t) \leq \Lambda - \mu_1 T(t),$$

which yields

$$T(t) \leq \frac{\Lambda}{\mu_1} + \left(T_0 - \frac{\Lambda}{\mu_1}\right)e^{-\mu_1 t}.$$

Considering the first and the second equations of (2), we have

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t}\left(T(t) + \int_0^\infty i(t,a)\mathrm{d}a\right) &= \Lambda - \mu_1 T(t) - \int_0^\infty \delta(a)i(t,a)\mathrm{d}a \\ &\leq \Lambda - \mu_1 T(t) - \underline{\delta}\int_0^\infty i(t,a)\mathrm{d}a \\ &\leq \Lambda - \mu_0\left(T(t) + \int_0^\infty i(t,a)\mathrm{d}a\right), \end{aligned}$$

and

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(T(t)+\int_0^\infty i(t,a)\mathrm{d}a\right)=\Lambda-\mu_1 T(t)-\int_0^\infty \delta(a)i(t,a)\mathrm{d}a$$
$$\geq -\mu_1 T(t)-\bar{\delta}\int_0^\infty i(t,a)\mathrm{d}a.$$

Hence,

$$x(0)e^{-\bar{\mu}_0 t}\leq T(t)+\int_0^\infty i(t,a)\mathrm{d}a\leq \frac{\Lambda}{\mu_0}+\left(x(0)-\frac{\Lambda}{\mu_0}\right)e^{-\mu_0 t}, \tag{10}$$

where $\bar{\mu}_0=\max\left\{\mu_1,\bar{\delta}\right\}$ and $x(0)=T(0)+\int_0^\infty i_0(a)\mathrm{d}a$.

Furthermore, we have

$$-(\mu_2+k)D(t)\leq \frac{\mathrm{d}D(t)}{\mathrm{d}t}$$
$$=\int_0^\infty p(a)i(t,a)\mathrm{d}a-(\mu_2+k)D(t)\leq \frac{\bar{p}\Lambda}{\mu_0}-(\mu_2+k)D(t)$$

and

$$D_0 e^{-(\mu_2+k)t}\leq D(t)\leq \frac{\bar{p}\Lambda}{\mu_0(\mu_2+k)}+\left(D_0-\frac{\bar{p}\Lambda}{\mu_0(\mu_2+k)}\right)e^{-(\mu_2+k)t}. \tag{11}$$

Similarly, we also have

$$V_0 e^{-\mu_3 t}\leq V(t)\leq \frac{k\bar{p}\Lambda}{\mu_0(\mu_2+k)\mu_3}+\left(V_0-\frac{k\bar{p}\Lambda}{\mu_0(\mu_2+k)\mu_3}\right)e^{-\mu_3 t}. \tag{12}$$

Hence,

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t}=\Lambda-\mu_1 T(t)-\beta T(t)V(t)\geq -\tilde{\mu}T(t),$$

where $\tilde{\mu}=\mu_1+\beta\frac{k\bar{p}\Lambda}{\mu_0(\mu_2+k)\mu_3}$. It yields that $T(t)\geq T(0)e^{-\tilde{\mu}t}$. Thus,

$$T(0)e^{-\tilde{\mu}t}\leq T(t)\leq \frac{\Lambda}{\mu_1}+\left(T(0)-\frac{\Lambda}{\mu_1}\right)e^{-\mu_1 t}. \tag{13}$$

Therefore, $U(t)\Upsilon\subset\Upsilon$, which implies Υ is a positively invariant set. Moreover, from (10), (11), (12) and (13), we can easily see that Υ attracts all positive solutions of (2). □

3 Existence and Local Stability of Steady States

3.1 Existence of Steady States

We define the basic reproductive number of system (2) as follows:

$$\Re_0 = \frac{\beta k \Lambda \eta}{\mu_1 \mu_3 (\mu_2 + k)}.$$

The existence of steady states of system (2) is stated as follows.

Theorem 2 *System (2) always has an virus-free steady state* $E_0 = (T^0, 0, 0, 0)$. *If* $\Re_0 > 1$, *system (2) also has an infection steady state* $E^* = (T^*, i^*(a), D^*, V^*)$, *where* $T^0 = \frac{\Lambda}{\mu_1}$, $T^* = \frac{\mu_3(\mu_2+k)\Lambda}{\mu_1\mu_3(\mu_2+k)+\beta i^*(0)k\eta}$, $i^*(a) = i^*(0)\Omega(a)$, $D^* = \frac{i^*(0)\eta}{\mu_2+k}$, $V^* = \frac{i^*(0)k\eta}{\mu_3(\mu_2+k)}$ *and* $i^*(0) = \frac{\mu_1\mu_3(\mu_2+k)}{\beta k\eta}(\Re_0 - 1)$.

Proof Let $(\hat{T}, \hat{i}(a), \hat{D}, \hat{V})$ be a steady state of (2), then

$$\begin{cases} \Lambda - \mu_1 \hat{T} - \beta \hat{T} \hat{V} = 0, \\ \dfrac{\mathrm{d}\hat{i}(a)}{\mathrm{d}a} = -\delta(a)\hat{i}(a), \\ \displaystyle\int_0^\infty p(a)\hat{i}(a)\mathrm{d}a - (\mu_2 + k)\hat{D} = 0, \\ k\hat{D} - \mu_3 \hat{V} = 0, \end{cases} \tag{14}$$

with initial condition

$$\hat{i}(0) = \beta \hat{T} \hat{V}. \tag{15}$$

From the second equation of system (14), we can obtain $\hat{i}(a) = \hat{i}(0)\Omega(a)$. Then, from the other equations of (14), we have

$$\begin{aligned} \hat{D} &= \frac{\hat{i}(0)\eta}{\mu_2 + k}, \\ \hat{V} &= \frac{k\hat{D}}{\mu_3} = \frac{\hat{i}(0)k\eta}{\mu_3(\mu_2 + k)}, \\ \hat{T} &= \frac{\Lambda}{\mu_1 + \beta\hat{V}} = \frac{\mu_3(\mu_2 + k)\Lambda}{\mu_1\mu_3(\mu_2 + k) + \beta\hat{i}(0)k\eta}. \end{aligned}$$

Plugging $\hat{T}$ and $\hat{V}$ into (15) yields

$$\hat{i}(0) = \frac{\beta\Lambda k\eta\hat{i}(0)}{\mu_1\mu_3(\mu_2 + k) + \beta k\eta\hat{i}(0)}.$$

Now, we consider the following two cases:

Case (i) If $\hat{i}(0) = 0$, then $\hat{D} = \hat{i}(a) = \hat{V} = 0$ and $\hat{T} = \frac{\Lambda}{\mu_1}$. Hence, system (2) has an virus-free steady state $E_0 = (T^0, 0, 0, 0)$.

Case (ii) If $\hat{i}(0) \neq 0$, then

$$\hat{i}(0) = \frac{\mu_1\mu_3(\mu_2+k)}{\beta\Lambda k\eta}\left(\frac{\beta k\Lambda\eta}{\mu_1\mu_3(\mu_2+k)} - 1\right) = \frac{\mu_1\mu_3(\mu_2+k)}{\beta\Lambda k\eta}(\Re_0 - 1).$$

Hence, the unique infection steady state $E^* = (T^*, i^*(a), D^*, V^*)$ exists if $\Re_0 > 1$. This ends the proof. □

3.2 Local Stability of Steady States

In this part, we analyze the local stability of steady states.

Theorem 3 (i) *The virus-free steady state E_0 is locally asymptotically stable if $\Re_0 < 1$ and unstable if $\Re_0 > 1$;* (ii) *the infection steady state E^* is locally asymptotically stable if $\Re_0 > 1$.*

Proof (i) Introduce the following perturbation variables

$$T_1(t) = T(t) - T^0,\ i_1(t,a) = i(t,a),\ D_1(t) = D(t) \text{ and } V_1(t) = V(t).$$

The linearized system of (2) around the virus-free steady state is given as follows

$$\begin{cases} \dfrac{\mathrm{d}T_1(t)}{\mathrm{d}t} = -\mu_1 T_1(t) - \beta T^0 V_1(t), \\ \dfrac{\partial i_1(t,a)}{\partial t} + \dfrac{\partial i_1(t,a)}{\partial a} = -\delta(a) i_1(t,a), \\ \dfrac{\mathrm{d}D_1(t)}{\mathrm{d}t} = \displaystyle\int_0^\infty p(a) i_1(t,a)\mathrm{d}a - (\mu_2+k) D_1(t), \\ \dfrac{\mathrm{d}V_1(t)}{\mathrm{d}t} = k D_1(t) - \mu_3 V_1(t), \end{cases} \tag{16}$$

with boundary condition

$$i_1(t,0) = \beta T^0 V_1(t), \tag{17}$$

Hence, the characteristic equation of (2) around the virus-free steady state E_0 is

$$\begin{vmatrix} \lambda+\mu_1 & 0 & 0 & \beta T^0 \\ 0 & 1 & 0 & -\beta T^0 \\ 0 & -\int_0^\infty p(a)\Omega(a)e^{-\lambda a}\mathrm{d}a & \lambda+\mu_2+k & 0 \\ 0 & 0 & -k & \lambda+\mu_3 \end{vmatrix} = 0,$$

After expanding, the characteristic equation is

$$(\lambda+\mu_1)\Delta(\lambda) = 0,$$

where $\Delta(\lambda) = \beta T^0 k \int_0^\infty p(a)\Omega(a)e^{-\lambda a}\mathrm{d}a - (\lambda+\mu_2+k)(\lambda+\mu_3)$.

It is obvious that the stability of E_0 is determined by the roots of $\Delta(\lambda) = 0$. If $\Re_0 > 1$, we have $\Delta(0) = \mu_3(\mu_2+k)(\Re_0 - 1) > 0$ and $\lim_{\lambda\to+\infty} \Delta(\lambda) = -\infty$. By Intermediate Value Theorem, there is at least one positive zero of $\Delta(\lambda)$. Hence, E_0 is unstable if $\Re_0 > 1$. Next, we assume $\Re_0 < 1$. We claim all zeros of $\Delta(\lambda)$ have negative real parts. In fact, by contradiction, we suppose λ_0 is a root of $\Delta(\lambda) = 0$ with $\mathrm{Re}(\lambda_0) \geq 0$, then we can obtain

$$\frac{(\lambda_0+\mu_3)(\lambda_0+\mu_2+k)}{k} = \beta T^0 \int_0^\infty p(a)\Omega(a)e^{-\lambda_0 a}\mathrm{d}a, \tag{18}$$

It follows that

$$\frac{\mu_3(\mu_2+k)}{k} \leq \left|\frac{(\lambda_0+\mu_3)(\lambda_0+\mu_2+k)}{k}\right| = \left|\beta T^0 \int_0^\infty p(a)\Omega(a)e^{-\lambda_0 a}\mathrm{d}a\right| \leq \beta T^0 A,$$

which contradicts with $\Re_0 < 1$. Therefore, if $\Re_0 < 1$, all the roots of $f(\lambda) = 0$ have negative real parts. Accordingly, the virus-free steady state E_0 is locally asymptotically stable.

(ii) With the same technique of (i), the characteristic equation of system (2) at the infection steady state E_1 is given by

$$\begin{vmatrix} r+\mu_1+\beta V^* & \beta T^* & 0 & 0 \\ \beta V^* & \beta T^* & 0 & -1 \\ 0 & 0 & -r-\mu_2-k & \int_0^\infty p(a)\Omega(a)e^{-ra}\mathrm{d}a \\ 0 & r+\mu_3 & -k & 0 \end{vmatrix} = 0.$$

After expanding, we have

$$(r+\mu_3)(r+\mu_2+k)(r+\mu_1+\beta V^*) = (r+\mu_1)\beta k T^* \int_0^\infty p(a)\Omega(a)e^{-ra}\mathrm{d}a. \tag{19}$$

Obviously, $r = -\mu_3$ and $r = -(\mu_2+k)$ are not the roots of Eq. (19). Then, we can rewrite Eq. (19) as follows:

$$r+\mu_1+\beta V^* = \frac{\beta k T^*(r+\mu_1)\int_0^\infty p(a)\Omega(a)e^{-ra}\mathrm{d}a}{(r+\mu_3)(r+\mu_2+k)}. \tag{20}$$

Notice that $\int_0^\infty p(a)i^*(a)\mathrm{d}a = (\mu_2+k)D^*$, $D^* = \frac{\mu_3 V^*}{k}$, $i^*(0) = \beta T^* V^*$ if $\Re_0 > 1$. Then, if r_0 is a root of Eq. (20) with $\mathrm{Re}(r_0) \geq 0$, we can obtain the following two inequalities

$$\left|r_0+\mu_1+\beta V^*\right| > \left|r_0+\mu_1\right|$$

and

$$
\begin{aligned}
&\left|\frac{\beta kT^*(r_0+\mu_1)\int_0^\infty p(a)\Omega(a)e^{-r_0 a}\mathrm{d}a}{(r_0+\mu_3)(r_0+\mu_2+k)}\right| \\
&\le \left|\frac{\beta kT^*\int_0^\infty p(a)\Omega(a)\mathrm{d}a}{\mu_3(\mu_2+k)}\right|\left|(r_0+\mu_1)\right| \\
&= \left|\frac{\beta kT^*\int_0^\infty p(a)\Omega(a)i^*(0)\mathrm{d}a}{i^*(0)\mu_3(\mu_2+k)}\right|\left|r_0+\mu_1\right| \\
&= \left|\frac{\beta kT^*\int_0^\infty p(a)i^*(a)\mathrm{d}a}{i^*(0)\mu_3(\mu_2+k)}\right|\left|r_0+\mu_1\right| \\
&= \left|\frac{\beta kT^*(\mu_2+k)D^*}{i^*(0)\mu_3(\mu_2+k)}\right|\left|r_0+\mu_1\right| \\
&= \left|\frac{\beta kT^*}{i^*(0)\mu_3(\mu_2+k)}\frac{(\mu_2+k)\mu_3V^*}{k}\right|\left|(r_0+\mu_1)\right| \\
&= \left|r_0+\mu_1\right|.
\end{aligned}
$$

The above inequalities contradicts with Eq. (20). Hence, all roots of Eq. (19) have negative real parts. Therefore, the infection steady state E_1 is locally asymptotically stable. □

4 Asymptotically Smooth and Uniform Persistence

In this section, we show that the semiflow $\{U(t)\}_{t\ge 0}$ is asymptotically smooth and uniform persistence. Because in the following section, we will use Lyapunov functionals and LaSalles invariance principle to show the global stability of each steady states. Since the state space $\mathcal{X}_{0+}$ is the infinite dimensional Banach space, we need the semiflow $\{U(t)\}_{t\ge 0}$ is asymptotically smooth. Furthermore, we need the semiflow generated by the system (2) is uniformly persistent to make sure the Lyapunov functional is well defined. Firstly, we show the semiflow is asymptotically smooth. Rewrite $U := \Phi + \Psi$, where

$$\Phi(t)X_0 := (0, \varpi_1(\cdot,t), 0, 0), \tag{21}$$

$$\Psi(t)X_0 := (T(t), \varpi_2(\cdot,t), D(t), V(t)), \tag{22}$$

with

$$\varpi_1(\cdot,t) = \begin{cases} 0, & t > a \ge 0, \\ i(t,a), & a \ge t \ge 0. \end{cases} \quad \text{and} \quad \varpi_2(\cdot,t) = \begin{cases} i(t,a), & t > a \ge 0, \\ 0, & a \ge t \ge 0. \end{cases}$$

We are now in the position to prove the following theorem.

Theorem 4 *For any $X_0 \in \Upsilon$, $\{U(t)X_0 : t \ge 0\}$ has compact closure in $\mathcal{X}$ if the following two conditions hold:*

(i) *There exists a function* $\Delta : \mathbb{R}_+ \times \mathbb{R}_+ \to \mathbb{R}_+$ *such that for any* $r > 0$, $\lim_{t\to\infty} \Delta(t, r) = 0$, *and if* $X_0 \in \Omega$ *with* $\|X_0\|_{\mathcal{X}} \le r$, *then* $\|\Phi(t)X_0\|_{\mathcal{X}} \le \Delta(t, r)$ *for* $t \ge 0$;
(ii) *For* $t \ge 0$, $\Psi(t)X_0$ *maps any bounded sets of* Υ *into sets with compact closure in* $\mathcal{X}$.

Proof Step I. To show (i) holds. Let $\Delta(t, r) := e^{-\underline{\delta}t} r$, where $\underline{\delta}$ is defined in (A1). It is obvious that $\lim_{t\to\infty} \Delta(t, r) = 0$. Then, for $X_0 \in \Upsilon$ satisfying $\|X_0\|_{\mathcal{X}} \le r$, we have

$$\begin{aligned}
\|\Phi(t)X_0\|_{\mathcal{X}} &= |0| + \int_0^\infty |\varpi_1(a, t)|\mathrm{d}a + |0| + |0| \\
&= \int_t^\infty \left| i_0(a-t)\frac{\Omega(a)}{\Omega(a-t)} \right| \mathrm{d}a \\
&= \int_0^\infty \left| i_0(s)\frac{\Omega(s+t)}{\Omega(s)} \right| \mathrm{d}s \\
&\le e^{-\underline{\delta}t} \int_0^\infty |i_0(s)|\mathrm{d}s \\
&\le e^{-\underline{\delta}t} \|X_0\|_{\mathcal{X}} \le \Delta(t, r), \quad t \ge 0.
\end{aligned}$$

Then, we completes the proof of condition (i).

Step II. To show (ii) holds. We need to show that $\varpi_2(t, a)$ remain in a precompact subset of $L^1_+(0, \infty)$. In order to prove it, we should show the following conditions hold (see [38][Theorem B.2]):

(a) The supremum of $\int_0^\infty \varpi_2(t, a)\mathrm{d}a$ with respect to $X_0 \in \Upsilon$ is finite;
(b) $\lim_{u\to\infty} \int_u^\infty \varpi_2(t, a)\mathrm{d}a = 0$ uniformly with respect to $X_0 \in \Upsilon$;
(c) $\lim_{u\to 0^+} \int_0^\infty (\varpi_2(t, a+u) - \varpi_2(t, a))\mathrm{d}a = 0$ uniformly with respect to $X_0 \in \Upsilon$;
(d) $\lim_{u\to 0^+} \int_u^\infty \varpi_2(t, a)\mathrm{d}a = 0$ uniformly with respect to $X_0 \in \Upsilon$.

Conditions (a), (b) and (d) hold since (8) holds. Next, we verify condition (c). For sufficiently small $u \in (0, t)$, we have

$$\begin{aligned}
&\int_0^\infty |\varpi_2(t, a+u) - \varpi_2(t, a)|\mathrm{d}a \\
&= \int_0^{t-u} |\beta T(t-a-u)V(t-a-u)\Omega(a+u) - \beta T(t-a)V(t-a)\Omega(a)|\mathrm{d}a \\
&\quad + \int_{t-u}^t |0 - \beta T(t-a)V(t-a)\Omega(a)|\mathrm{d}a \\
&\le \int_0^{t-u} \beta T(t-a-u)V(t-a-u)|\Omega(a+u) - \Omega(a)|\mathrm{d}a \\
&\quad + \int_0^{t-u} |\beta T(t-a-u)V(t-a-u) - \beta T(t-a)V(t-a)|\Omega(a)\mathrm{d}a \\
&\quad + u\left(\frac{\Lambda}{\mu_0}\right)^2 \frac{\beta k \bar{p}}{\mu_3(\mu_2 + k)}.
\end{aligned}$$

Since $\Omega(a)$ is non-increasing function with respect to a and $0 \leq \Omega(a) \leq 1$, we have

$$\begin{aligned}\int_0^{t-u} |\Omega(a+u) - \Omega(a)|\mathrm{d}a &= \int_0^{t-u} (\Omega(a) - \Omega(a+u))\mathrm{d}a \\ &= \int_0^{t-u} \Omega(a)\mathrm{d}a - \int_u^t \Omega(a)\mathrm{d}a \\ &= \int_0^u \Omega(a)\mathrm{d}a - \int_{t-u}^t \Omega(a)\mathrm{d}a \leq u.\end{aligned}$$

Then,

$$\int_0^\infty |\varpi_2(t, a+u) - \varpi_2(t,a)|\mathrm{d}a \leq 2u\left(\frac{\Lambda}{\mu_0}\right)^2 \frac{\beta k \bar{p}}{\mu_3(\mu_2+k)} + \Xi$$

where

$$\Xi = \int_0^{t-u} |\beta T(t-a-u)V(t-a-u) - \beta T(t-a)V(t-a)|\Omega(a)\mathrm{d}a.$$

Thanks to the argument in [27][Proposition 6], $T(\cdot)V(\cdot)$ is Lipschitz on $\mathbb{R}_+$, let M_1 be the Lipschitz coefficients of $T(\cdot)V(\cdot)$. Then,

$$\Xi \leq \beta M_1 u \int_0^{t-u} \Omega(a)\mathrm{d}a \leq \beta M_1 u \int_0^{t-u} \Omega(a)\mathrm{d}a \leq \frac{\beta M_1 u}{\underline{\delta}}.$$

Thus,

$$\int_0^\infty |\varpi_2(t, a+u) - \varpi_2(t,a)|\mathrm{d}a \leq 2u\left(\frac{\Lambda}{\mu_0}\right)^2 \left(\frac{\beta\bar{p}}{\mu_2} + \bar{k}\right) + \frac{\beta M_1 u}{\underline{\delta}}$$

which converges to 0 as $u \to 0^+$, then condition (c) holds. The proof is completed. □

Hence, Theorem 4 ensures the following proposition.

Proposition 2 *Let Assumption (A1) and (A2) hold, then the solution semiflow* $\{U(t)\}_{t\geq 0}$ *is asymptotically smooth.*

In the following of this section, we investigate the uniform persistence of system (2). Similar to the arguments in [4,34], we define

$$\widehat{M} = \left\{ \begin{pmatrix} T \\ \begin{pmatrix} 0 \\ i \end{pmatrix} \\ D \\ V \end{pmatrix} \in \mathcal{X}_{0+} : \int_0^\infty i(s)\mathrm{d}s + D + V > 0 \right\}$$

and

$$\partial \widehat{M} = \mathcal{X}_{0+} \backslash \widehat{M}.$$

Lemma 2 *The sets $\widehat{M}$ and $\partial \widehat{M}$ are both positively invariant under the semiflow $\{U(t)\}_{t\geq 0}$ generated by system (2) on $\mathcal{X}_{0+}$. Moreover, for each $\zeta \in \partial \widehat{M}$, $U(t)\zeta \to E_0$ as $t \to \infty$.*

Proof Let

$$G(t) = D(t) + V(t) + \int_0^\infty i(t,a)\mathrm{d}a.$$

We obtain that

$$\begin{aligned}\frac{\mathrm{d}G(t)}{\mathrm{d}t} &= \int_0^\infty p(a)i(t,a)\mathrm{d}a - \mu_2 D(t) - \mu_3 V(t) + \beta T(t)V(t) - \int_0^\infty \delta(a)i(t,a)\mathrm{d}a \\ &\geq -\mu_2 D(t) - \mu_3 V(t) - \bar{\delta}\int_0^\infty i(t,a)\mathrm{d}a \\ &\geq -a_1 G(t),\end{aligned}$$

where $a_1 = \max\{\mu_2, \mu_3, \bar{\delta}\}$. For any $\tilde{\zeta} = \left(\tilde{T}, (0,\tilde{i}), \tilde{D}, \tilde{V}\right)^T \in \widehat{M}$, we have $G(0) > 0$. Then, $G(t) \geq G(0)e^{-a_1 t} > 0$ which shows that $U(t)\widehat{M} \subset \widehat{M}$, that is, $\widehat{M}$ is positively invariant.

For any $\zeta = (T_0, (0, i_0), D_0, V_0)^T \in \partial \widehat{M}$, we have $V_0 = V(0) = 0$, $D_0 = D(0) = 0$, $\int_0^\infty i(a)\mathrm{d}a = 0$. Next, we prove $\partial \widehat{M}$ is positively invariant.

By using of Volterra formulation (9), the third equation of (2) is written as

$$\begin{aligned}\frac{\mathrm{d}D(t)}{\mathrm{d}t} &= \beta\int_0^t p(a)T(t-a)V(t-a)\Omega(a)\mathrm{d}a \\ &\quad + \int_t^\infty p(a)i_0(a-t)\frac{\Omega(a)}{\Omega(a-t)}\mathrm{d}a - (\mu_2 + k)D(t). \qquad (23)\end{aligned}$$

By the fourth equation of (2) and initial value $V(0) = 0$, it follows that $V(t) = k\int_0^t D(s)e^{-\mu_3(t-s)}\mathrm{d}s$. Substituting $V(t)$ into (23), we can obtain

$$\begin{aligned}\frac{\mathrm{d}D(t)}{\mathrm{d}t} &= \beta k\int_0^t p(a)T(t-a)\Omega(a)e^{-\mu_3(t-a)}\int_0^{t-a} D(s)e^{\mu_3 s}\mathrm{d}s\mathrm{d}a \\ &\quad + \int_t^\infty p(a)i_0(a-t)\frac{\Omega(a)}{\Omega(a-t)}\mathrm{d}a - (\mu_2 + k)D(t).\end{aligned}$$

We claim that $D(t) = 0$ and $V(t) = 0$ for all $t \geq 0$ if $D(0) = 0$ and $V(0) = 0$ (see [5][Lemma 4.3] for details). Hence, we have

$$0 \leq \int_0^\infty i(t,a)\mathrm{d}a = \int_0^t \beta T(t-a)V(t-a)\Omega(a)\mathrm{d}a + \int_t^\infty i_0(a-t)\frac{\Omega(a)}{\Omega(a-t)}\mathrm{d}a \leq 0$$

which implies that $\int_0^\infty i(t,a)\mathrm{d}a = 0$. Therefore, $\partial\widehat{M}$ is positively invariant.

Furthermore, $\int_0^\infty i(t,a)\mathrm{d}a = 0$ implies $\lim_{t\to\infty}||i(t,a)||_{L^1} = 0$. Since $(D(t),V(t)) \to (0,0)$ as $t\to\infty$, we have that $T(t)\to T^0$ as $t\to\infty$ from the system (2). Hence, it follows that $U(t)\zeta \to E_0$ as $t\to\infty$ for each $\zeta\in\partial\widehat{M}$. □

Followed by the results in [10,23], we have the following theorem.

Theorem 5 *If $\Re_0 > 1$, the semiflow $\{U(t)\}_{t\geq 0}$ generated by system (2) is uniformly persistent with respect to the pair $(\partial\widehat{M},\widehat{M})$; that is , there exists $\varepsilon > 0$ such that*

$$\lim_{t\to+\infty}\inf d\left(U(t)\zeta,\partial\widehat{M}\right)\geq\varepsilon$$

for any $\zeta\in\widehat{M}$.

Proof According to Lemma 2 and Theorem 1, the conditions (i)-(iii) of Theorem 4.1 in [10] are satisfied. Theorem 4.1 in [10] states that $\{U(t)\}_{t\geq 0}$ is uniformly persistent if and only if

$$W^s(E_0)\cap\widehat{M} = \varnothing, \tag{24}$$

where

$$W^s(E_0) = \left\{\zeta\in\Upsilon : \lim_{t\to+\infty}U(t)\zeta = E_0\right\}. \tag{25}$$

By way of contradiction, suppose that $\zeta_0\in W^s(E_0)\cap\widehat{M}$. Then, there exists $t_1 > 0$ such that $D(t_1)+V(t_1)+\int_0^\infty i(t_1,a)da > 0$ since $\zeta_0\in\widehat{M}$. Hence, $D(t)+V(t)+\int_0^\infty i(t,a)da > 0$ when $t\geq t_1$.

On the other hand, we can choose ε_0 small enough such that $\frac{k\beta\eta\left(T^0-\varepsilon_0\right)}{\mu_3(\mu_2+k)} > 1$ for $\Re_0 > 1$. And $\zeta_0\in W^s(E_0)$ implies that $\lim_{t\to+\infty}T(t) = T^0$. Then, for the above ε_0, there must exist some $t_2\geq 0$ such that $T(t) > T^0-\varepsilon_0$ for all $t\geq t_2$.

Let

$$G_1(t) = k\int_0^\infty \Phi(a)i(t,a)\mathrm{d}a + kD(t) + (\mu_2+k)V(t),$$

where $\Phi(a)$ is defined by (5). Notice that $\Phi(0)=\eta$. Then, for $t\geq t_2$, we have

$$\begin{aligned}\frac{\mathrm{d}G_1(t)}{\mathrm{d}t}\Big|_{(2)} &= -\mu_3(\mu_2+k)V(t) + k\Phi(0)i(t,0)\\ &= \left(k\beta\eta T(t) - \mu_3(\mu_2+k)\right)V(t)\\ &\geq \left(k\beta\eta\left(T^0-\varepsilon_0\right) - \mu_3(\mu_2+k)\right)V(t)\\ &\geq \mu_3(\mu_2+k)\left(\frac{k\beta\eta\left(T^0-\varepsilon_0\right)}{\mu_3(\mu_2+k)} - 1\right)V(t)\\ &\geq 0,\end{aligned} \tag{26}$$

which is a non-decreasing function for $t \geq t_2$. Therefore, $G_1(t) \geq G_1(t_0) > 0$ for all $t \geq t_0$ with $t_0 = \max\{t_1, t_2\}$, which prevents $(i(t,a), D(t), V(t))$ converging to $\left(0_{L^1}, 0, 0\right)$ as $t \to \infty$. A contradiction with $\zeta \in W^s(E_0)$. □

5 Global Stability of Steady States

In this section, we study the global stability of steady states by constructing appropriate Lyapunov functionals. For global stability of the virus-free steady state, we have the following result.

Theorem 6 *If $\Re_0 < 1$, the virus-free steady state E_0 is globally asymptotically stable.*

Proof We define the following function

$$H(x) = x - 1 - \ln x, \quad \forall x > 0,$$

and define the Lyapunov functional as:

$$L = L_1 + L_2 + \frac{\beta T^0}{\mu_3}\frac{k}{\mu_2 + k}D(t) + \frac{\beta T^0}{\mu_3}V(t),$$

where

$$L_1 = T^0 H\left(\frac{T}{T^0}\right) \text{ and } L_2 = \frac{\beta T^0}{\mu_3}\frac{k}{\mu_2 + k}\int_0^\infty \Phi(a) i(t,a)\mathrm{d}a.$$

Then, we have

$$\begin{aligned}\frac{\mathrm{d}L_1(t)}{\mathrm{d}t}\Big|_{(2)} &= \frac{T - T^0}{T}\Big(\Lambda - \mu_1 T(t) - \beta T(t) V(t)\Big)\\ &= -\frac{\mu_1}{T}(T - T^0)^2 - i(t,0) + \beta T^0 V(t)\end{aligned}$$

and

$$\begin{aligned}\frac{\mathrm{d}L_2(t)}{\mathrm{d}t}\Big|_{(2)} &= \int_0^\infty \Phi(a)\frac{\partial}{\partial t} i(t,a)\mathrm{d}a\\ &= -\int_0^\infty \Phi(a)\Big(\frac{\partial}{\partial a} i(t,a) + \delta(a) i(t,a)\Big)\mathrm{d}a\\ &= -\int_0^\infty \Phi(a)\delta(a) i(t,a)\mathrm{d}a - \int_0^\infty \Phi(a)\mathrm{d}i(t,a)\\ &= -\lim_{a\to+\infty} \Phi(a) i(t,a) + \Phi(0) i(t,0)\\ &\quad + \int_0^\infty \Big(\frac{\mathrm{d}\Phi(a)}{\mathrm{d}a} - \delta(a)\Phi(a)\Big) i(t,a)\mathrm{d}a.\end{aligned}$$

By Assumption (A2), we know that $\lim_{a\to+\infty}\Phi(a)i(t,a)=0$. Notice that $\Phi(0)=\eta$ and $\frac{\mathrm{d}\Phi(a)}{\mathrm{d}a}=\delta(a)\Phi(a)-p(a)$. Hence, we obtain that

$$\frac{\mathrm{d}L}{\mathrm{d}t}\Big|_{(2)}=-\frac{\mu_1}{T}(T-T^0)^2+(\Re_0-1)i(t,0).$$

It is clear that $\frac{\mathrm{d}L}{\mathrm{d}t}\le 0$ if $\Re_0<1$. Furthermore, when $\Re_0<1$, $\frac{\mathrm{d}L}{\mathrm{d}t}=0$ if and only if $T=T^0,\ V=0$. Hence, $\{((T,i,D,V))|\frac{\mathrm{d}L}{\mathrm{d}t}=0\}=\{E_0\}$, which is the largest invariant subset of $\{((T,i,D,V))|\frac{\mathrm{d}L}{\mathrm{d}t}=0\}$. Thanks the asymptotic smoothness of the semiflow as shown in Proposition 2, it follows from the arguments in [11,21] that the semiflow $\{U(t)\}_{t\ge0}$ admits a global attractor. According to the Lyapunov–LaSalle invariance principle, the virus-free steady state E_0 is globally asymptotically stable when $\Re_0<1$. □

Next, we discuss global stability of the infection steady state.

Theorem 7 *If $\Re_0>1$, the infection steady state E^* is globally asymptotically stable.*

Proof Let $\Phi(\theta)$ and η be defined in (5). We construct a Lyapunov functional as follows:

$$W=W_1+\frac{1}{\eta}W_2+\frac{1}{\eta}W_3+\frac{1}{\eta}\frac{\mu_2+k}{k}W_4,$$

where $W_1=T^*H\left(\frac{T(t)}{T^*}\right)$, $W_2=\int_0^\infty\Phi(\theta)i^*(\theta)H\left(\frac{i(t,\theta)}{i^*(\theta)}\right)\mathrm{d}\theta$, $W_3=D^*H\left(\frac{D(t)}{D^*}\right)$ and $W_4=V^*H\left(\frac{V(t)}{V^*}\right)$. We first calculate the derivative of W_1. Then, we obtain that

$$\begin{aligned}\frac{\mathrm{d}W_1}{\mathrm{d}t}\Big|_{(2)}&=\frac{T-T^*}{T}\big(\Lambda-\mu_1T(t)-\beta T(t)V(t)\big)\\&=\frac{T-T^*}{T}\big(\mu_1T^*+\beta T^*V^*-\mu_1T(t)-\beta T(t)V(t)\big)\\&=-\frac{\mu_1}{T}(T-T^*)^2+i^*(0)-i(t,0)-i^*(0)\frac{T^*}{T}+i(t,0)\frac{T^*}{T}\\&=-\frac{\mu_1}{T}(T-T^*)^2+i^*(0)-i(t,0)\\&\quad-\frac{1}{\eta}\int_0^\infty p(\theta)i^*(\theta)\frac{T^*}{T}\mathrm{d}\theta+\frac{1}{\eta}\int_0^\infty p(\theta)i^*(\theta)\frac{V}{V^*}\mathrm{d}\theta.\end{aligned}$$

Next, calculating the derivative of W_2, one has that

$$\begin{aligned}\frac{\mathrm{d}W_2}{\mathrm{d}t}\Big|_{(2)}&=\frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty\Phi(\theta)i^*(\theta)H\Big(\frac{i(t,\theta)}{i^*(\theta)}\Big)\mathrm{d}\theta\\&=\int_0^\infty\Phi(\theta)\Big(1-\frac{i^*(\theta)}{i(t,\theta)}\Big)\frac{\partial}{\partial t}i(t,\theta)\mathrm{d}\theta\\&=\int_0^\infty\Phi(\theta)\Big(1-\frac{i^*(\theta)}{i(t,\theta)}\Big)\Big(-\delta(\theta)i(t,\theta)-\frac{\partial}{\partial\theta}i(t,\theta)\Big)\mathrm{d}\theta\end{aligned}$$

$$
\begin{aligned}
&= -\int_0^\infty \Phi(\theta) i^*(\theta) \mathrm{d}\Big(\frac{i(t,\theta)}{i^*(\theta)} - 1 - \ln\frac{i(t,\theta)}{i^*(\theta)}\Big) \\
&= -\Phi(\theta) i^*(\theta)\Big(\frac{i(t,\theta)}{i^*(\theta)} - 1 - \ln\frac{i(t,\theta)}{i^*(\theta)}\Big)\Big|_{\theta=0}^{\theta=\infty} \\
&\quad + \int_0^\infty \Big(\frac{i(t,\theta)}{i^*(\theta)} - 1 - \ln\frac{i(t,\theta)}{i^*(\theta)}\Big)\Big(\frac{d\Phi(\theta)}{\mathrm{d}\theta} i^*(\theta) + \frac{\mathrm{d}i^*(\theta)}{\mathrm{d}\theta}\Phi(\theta)\Big)\mathrm{d}\theta.
\end{aligned}
$$

Since $\Phi(0) = \eta$, $\frac{\mathrm{d}\Phi(\theta)}{\mathrm{d}\theta} = \delta(\theta)\Phi(\theta) - p(\theta)$ and $\frac{\mathrm{d}i^*(\theta)}{\mathrm{d}\theta} = -\delta(\theta) i^*(\theta)$, we have

$$
\begin{aligned}
\frac{1}{\eta}\frac{\mathrm{d}W_2}{\mathrm{d}t}\Big|_{(2)} &= -\frac{1}{\eta}\Phi(\theta) i^*(\theta)\Big(\frac{i(t,\theta)}{i^*(\theta)} - 1 - \ln\frac{i(t,\theta)}{i^*(\theta)}\Big)\Big|_{\theta=0}^{\theta=\infty} \\
&\quad + \frac{1}{\eta}\int_0^\infty \Big(\frac{i(t,\theta)}{i^*(\theta)} - 1 - \ln\frac{i(t,\theta)}{i^*(\theta)}\Big)\Big(\frac{d\Phi(\theta)}{\mathrm{d}\theta} i^*(\theta) + \frac{\mathrm{d}i^*(\theta)}{\mathrm{d}\theta}\Phi(\theta)\Big)\mathrm{d}\theta \\
&= -\frac{1}{\eta}\Phi(\theta) i^*(\theta)\Big(\frac{i(t,\theta)}{i^*(\theta)} - 1 - \ln\frac{i(t,\theta)}{i^*(\theta)}\Big)\Big|_{\theta=\infty} \\
&\quad + \frac{1}{\eta}\int_0^\infty p(\theta) i^*(\theta)\Big(\frac{i(t,0)}{i^*(0)} - 1 - \ln\frac{i(t,0)}{i^*(0)}\Big)\mathrm{d}\theta \\
&\quad - \frac{1}{\eta}\int_0^\infty p(\theta) i^*(\theta)\Big(\frac{i(t,\theta)}{i^*(\theta)} - 1 - \ln\frac{i(t,\theta)}{i^*(\theta)}\Big)\mathrm{d}\theta.
\end{aligned}
$$

By some calculations, we also have

$$
\begin{aligned}
\frac{1}{\eta}\frac{\mathrm{d}W_3}{\mathrm{d}t}\Big|_{(2)} &= \frac{1}{\eta}\Big(1 - \frac{D^*}{D}\Big)\Big(\int_0^\infty \Phi(\theta) i(t,\theta)\mathrm{d}\theta - (\mu_2 + k)D\Big) \\
&= \frac{1}{\eta}\int_0^\infty p(\theta) i^*(\theta)\frac{i(t,\theta)}{i^*(\theta)}\mathrm{d}\theta - \frac{1}{\eta}\int_0^\infty p(\theta) i^*(\theta)\frac{D}{D^*}\mathrm{d}\theta \\
&\quad - \frac{1}{\eta}\int_0^\infty p(\theta) i^*(\theta)\frac{i(t,\theta)}{i^*(\theta)}\frac{D^*}{D}\mathrm{d}\theta + \frac{1}{\eta}\int_0^\infty p(\theta) i^*(\theta)\mathrm{d}\theta
\end{aligned}
$$

and

$$
\begin{aligned}
\frac{1}{\eta}\frac{\mu_2 + k}{k}\frac{\mathrm{d}W_4}{\mathrm{d}t}\Big|_{(2)} &= \frac{1}{\eta}\frac{\mu_2 + k}{k}\Big(1 - \frac{V^*}{V}\Big)\Big(kD - \mu_3 V\Big) \\
&= \frac{1}{\eta}\int_0^\infty p(\theta) i^*(\theta)\frac{D}{D^*}\mathrm{d}\theta - \frac{1}{\eta}\int_0^\infty p(\theta) i^*(\theta)\frac{V}{V^*}\mathrm{d}\theta \\
&\quad - \frac{1}{\eta}\int_0^\infty p(\theta) i^*(\theta)\frac{V^*}{V}\frac{D}{D^*}\mathrm{d}\theta + \frac{1}{\eta}\int_0^\infty p(\theta) i^*(\theta)\mathrm{d}\theta.
\end{aligned}
$$

Combining the above four parts, we have

$$
\begin{aligned}
\frac{\mathrm{d}W}{\mathrm{d}t}\Big|_{(2)} &= -\frac{\mu_1}{T}(T - T^*)^2 - \frac{1}{\eta}p(\theta) i^*(\theta) H\Big(\frac{i(t,\theta)}{i^*(\theta)}\Big)\Big|_{\theta=\infty} \\
&\quad - \frac{1}{\eta}\int_0^\infty p(\theta) i^*(\theta)\left\{H\Big(\frac{T^*}{T}\Big) + H\Big(\frac{V^*}{V}\frac{D}{D^*}\Big) + H\Big(\frac{i(t,\theta)}{i^*(\theta)}\frac{D^*}{D}\Big)\right\}\mathrm{d}\theta.
\end{aligned}
$$

Thus, $\frac{dW}{dt}\big|_{(2)} \leq 0$ and $\frac{dW}{dt}\big|_{(2} = 0$ if and only if $\frac{T}{T^*} = \frac{V^*}{V}\frac{D}{D^*} = \frac{i(t,\theta)}{i^*(\theta)}\frac{D^*}{D} = 1$, that is, $\{(T, i(t,a), D, V)\} = \{(T^*, i^*(a), D^*, V^*)\}$. Hence, $\left\{(T, i, D, V)\middle|\frac{dW}{dt}\big|_{(2)} = 0\right\} = \{E^*\}$, which is the largest invariant subset of $\left\{(T, i, D, V)\middle|\frac{dW}{dt}\big|_{(2)} = 0\right\}$. Thanks the asymptotic smoothness of the semiflow as shown in Proposition 2, it follows from the arguments in [11,21] that the semiflow $\{U(t)\}_{t\geq 0}$ admits a global attractor. By using Lyapunov–LaSalle invariance principle, we can conclude that the infection steady state E^* is globally asymptotically stable when $\Re_0 > 1$. □

6 Numerical Simulations

In this section, we perform some numerical simulations to illustrate our theoretical results. Here, we fix parameters $\Lambda = 2.6 \times 10^7$, $\mu_1 = 0.01$ which are from [3] and parameters $\mu_2 = 0.053,\ \mu_3 = 3.8,\ k = 0.87$ which come from [29].

Furthermore, we set the maximum age-infection for infected cells as $a_\dagger = 24$ and assume

$$\delta(a) = 0.053\left(1 + \sin\frac{(a-12)\,\pi}{24}\right),$$
$$p(a) = 150\left(1 + \sin\frac{(a-12)\,\pi}{24}\right),\quad 0 \leq a \leq 24,$$

so that each of the averages is equal to 0.053 and 150, respectively, which were in line with those in [29].

Let $a = 10$ and we observe the dynamical behavior of solutions when β varies.

If we choose $\beta = 1.67 \times 10^{-12}$ (which comes from [29]), then $\Re_0 = 3.9548 > 1$ and infection steady state is $E^* = (6.5742\times10^8, 1.7226\times10^7, 7.7282\times10^9, 1.7694\times 10^9)$. From Theorem 7, the infection steady state is globally asymptotically stable (see Fig. 1).

When we choose $\beta = 3 \times 10^{-13}$ (which is from [2]), thus $\Re_0 = 0.0710 < 1$ and virus-free steady states is $E_0 = (2.6000 \times 10^9, 0, 0, 0)$. From Theorem 6, the virus-free steady state is globally asymptotically stable (see Fig. 2).

7 Discussion

Many researchers have proposed models for HBV dynamics which manifest the relation of uninfected and infected hepatocytes along with the virions. Few models consider the virions produced from mature intracellular HBV DNA-containing capsids (see Murray et al. [30], Manna and Chakrabarty [24]). Taking into account the age-dependent mortality rate and virus production rate of infected cells, we generalized their models to an age-structured model of HBV infections with HBV DNA-containing capsids. By a standard theory of non-densely defined operator [21], we reformulated the model as an abstract Cauchy problem and we showed the existence and uniqueness of solutions for the original model. The existence of two steady states based on

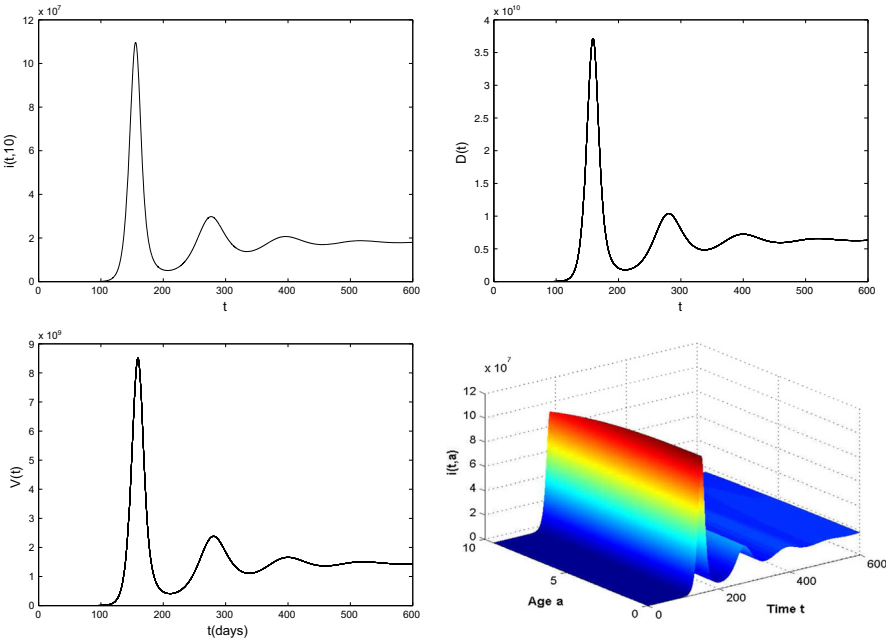

Fig. 1 The plots show variables $i(t, 10)$, $D(t)$, and $V(t)$ is converging to its infection steady state, respectively, as time t, where $\beta = 1.67 \times 10^{-11}$, $a = 10$ and $\Re_0 = 3.9548 > 1$

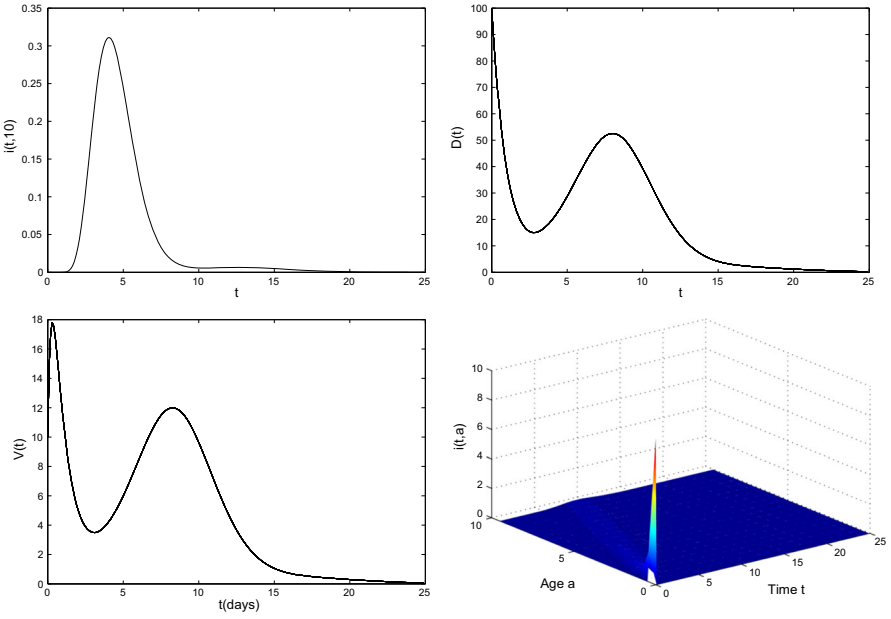

Fig. 2 The plots show that variables $i(t, 10)$, $D(t)$, $V(t)$ are converging to their virus-free steady state value, respectively, as time t increases, where $\beta = 3 \times 10^{-13}$, $a = 10$ and $\Re_0 = 0.0710 < 1$

basic reproduction number $\Re_0$ is obtained, and we proved the local stability of each steady states by linearizing the system and analyze the corresponding characteristic equation. In order to using Lyapunov–LaSalle invariance principle to prove the global asymptotical stability of the model, we showed the asymptotically smooth and uniform persistence of solution semiflow. Our main results are: if $\Re_0 < 1$, the virus-free steady state is globally asymptotically stable; otherwise, the virus-free steady state became unstable and the infection steady state is globally asymptotically stable if $\Re_0 > 1$. At last, we give some numerical simulations to support our theoretical analysis.

It should be pointed out, we have not studied the case $\Re_0 = 1$. In fact, in the proof of local stability of disease-free equilibrium, we can obtain the characteristic equation $\Delta(\lambda)$ and there may exist zero eigenvalue if $R_0 = 1$. This may lead to more complex dynamic behavior. For example, Qesmi et al. [35] propose a mathematical model describing the dynamics of hepatitis B or C virus infection with age-structure, and they found that the system may undergo a backward bifurcation when $\Re_0 = 1$. It is an ongoing project for us to study the dynamical behavior of system (2). The host immune system plays an important role in the progress of the viral infection. Many authors have considered the immune response in modeling viral infection, for example [1,8,43]. Based on the above facts, we propose an age-structured HBV infection with DNA-containing capsids by incorporating immune response with nonlinear incidence into the model (2) for our future work.

Acknowledgements The authors are very grateful to the editors and two reviewers for their valuable comments and suggestions that have helped us improving the presentation of this paper. S. Liu was partially supported by the National Natural Science Foundation of China (Grant No.11871060). R. Zhang was partially supported by the National Natural Science Foundation of China (Grant No.11871179). The authors would like to thank Professor Shigui Ruan for his supervision and suggestions. The authors would also acknowledge the kind hospitality received from the Department of Mathematics at University of Miami, where part of the work was completed.

References

1. Browne, C.: Immune response in virus model structured by cell infection-age. Math. Biosci. Eng. **13**, 887–909 (2016)
2. Ciupe, S., Ribeiro, R., Nelson, P., Perelson, A.: Modeling the mechanisms of acute hepatitis B virus infection. J. Theoret. Biol. **247**, 23–35 (2007)
3. Dahari, H., Ribeiro, R., Perelson, A.: Modeling hepatitis C virus dynamics: liver regeneration and critical drug efficacy. J. Theoret. Biol. **247**, 371–381 (2017)
4. Demasse, R.D., Ducrot, A.: An age-structured within-host model for multistrain malaria infections. SIAM J. Appl. Math. **73**, 572–593 (2013)
5. Frioui, M., Miri, S., Touaoula, T.: Unified Lyapunov functional for an age-structured virus model with very general nonlinear infection response. J. Appl. Math. Comp. **58**, 47–73 (2018)
6. Geng, Y., Xu, J., Hou, J.: Discretization and dynamic consistency of a delayed and diffusive viral infection model. Appl. Math. Comput. **316**, 282–295 (2018)
7. Guo, T., Liu, H., Xu, C., Yan, F.: Global stability of a diffusive and delayed HBV infection model with HBV DNA-containing capsids and general incidence rate. Discret. Contin. Dyn. Syst. Ser. B. **23**, 4223–4242 (2019)
8. Guo, T., Qiu, Z., Rong, L.: Analysis of an HIV model with immune responses and cell-to-cell transmission. Bull. Malays. Math. Sci. Soc. **43**, 581–607 (2020)
9. Gourley, S., Kuang, Y., Nagy, J.: Dynamics of a delay differential equation model of hepatitis B virus infection. J. Biol. Dyn. **2**, 140–153 (2008)

10. Hale, J., Waltman, P.: Persistence in infinite-dimensional systems. SIAM J. Math. Anal. **20**, 388–395 (1989)
11. Hale, J.K.: Asymptotic Behavior of Dissipative Systems, Mathematical Surveys and Monographs, vol. 25. American Mathematical Society, Providence (1988)
12. Hattaf, K., Yousfi, N.: Global properties of a diffusive HBV infection model with cell-to-cell transmission and three distributed delays. In: Boutayeb, A. (ed.) Disease Prevention and Health Promotion in Developing Countries, pp. 117–131. Springer, Cham (2020)
13. Hattaf, K., Yang, Y.: Global dynamics of an age-structured viral infection model with general incidence function and absorption. Int. J. Biomath. **11**, 1850065 (2018)
14. Huang, G., Liu, X., Takeuchi, Y.: Lyapunov functions and global stability for age-structured HIV infection model. SIAM J. Appl. Math. **72**, 25–38 (2012)
15. Lau, G., Cooksley, H., Ribeiro, R., et al.: Impact of early viral kinetics on T-cell reactivity during antiviral therapy in chronic hepatitis B. Antivir. Ther. **12**, 705–718 (2007)
16. Lewin, S., Ribeiro, R., Walters, T., et al.: Analysis of hepatitis B viral load decline under potent therapy: complex decay profiles observed. Hepatology **34**, 1012–1020 (2001)
17. Li, J., Wang, K., Yang, Y.: Dynamical behaviors of an HBV infection model with logistic hepatocyte growth. Math. Comput. Model. **54**, 704–711 (2011)
18. Liu, L., Feng, X.: A multigroup SEIR epidemic model with age-dependent latency and relapse. Math. Methods Appl. Sci. **41**, 6814–6833 (2018)
19. Magal, P.: Compact attractors for time-periodic age structured population models. Elect. J. Differ. Eqs. **65**, 1–35 (2001)
20. Magal, P., McCluskey, C.C., Webb, G.: Lyapunov functional and global asymptotic stability for an infection-age model. Appl. Anal. **89**, 1109–1140 (2010)
21. Magal, P., Ruan, S.: Theory and Applications of Abstract Semilinear Cauchy Problems, Applied Mathematical Sciences, vol. 201. Springer, Cham (2005)
22. Magal, P., Thieme, H.R.: Eventual compactness for a semiflow generated by an age-structured models. Commun. Pure Appl. Anal. **3**, 695–727 (2004)
23. Magal, P., Zhao, X.: Global attractors and steady states for uniformly persistent dynamical systems. SIAM J. Math. Anal. **37**, 51–275 (2005)
24. Manna, K., Chakrabarty, S.: Chronic hepatitis B infection and HBV DNA-containing capsids: modeling and analysis. Commun. Nonlinear Sci. Numer. Simul. **22**, 383–395 (2015)
25. Manna, K., Chakrabarty, S.: Global stability of one and two discrete delay models for chronic hepatitis B infection with HBV DNA-containing capsids. Comp. Appl. Math. **36**, 525–536 (2017)
26. Manna, K., Hattaf, K.: Spatiotemporal dynamics of a generalized HBV infection model with capsids and adaptive immunity. Int. J. Appl. Comput. Math. **5**, 65 (2019)
27. McCluskey, C.C.: Global stability for an SEI epidemiological model with continuous age-structure in the exposed and infectious classes. Math. Biosci. Eng. **9**, 819–841 (2012)
28. Min, L., Su, Y., Kuang, Y.: Mathematical analysis of a basic virus infection model with application to HBV infection. Rocky Mountain J. Math. **38**, 1573–1585 (2008)
29. Murray, J., Prucell, R., Wieland, S.: The half-life of hepatitis B virions. Hepatology **44**, 1117–1121 (2006)
30. Murray, J., Wieland, S., Prucell, R., Chisari, F.: Dynamics of hepatitis B virus clearance in chimpanzees. Proc. Natl. Acad. Sci. USA **102**, 17780–17785 (2005)
31. Nassal, M.: HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. Gut **64**, 1972–1984 (2015)
32. Nelson, P., Gilchrist, M., Coombs, D., et al.: An age-structured model of HIV infection that allow for variations in the production rate of viral particles and the death rate of productively infected cells. Math. Biosci. Eng. **1**, 267–288 (2004)
33. Nowak, M., Bonhoeffer, S., Hill, A., et al.: Viral dynamics in hepatitis B virus infection. Proc. Natl. Acad. Sci. USA **93**, 4398–4402 (1996)
34. Pang, J., Chen, J., Liu, Z., et al.: Local and global stabilities of a viral dynamics model with infection-age and immune response. J. Dyn. Differ. Equ. **31**, 793–813 (2019)
35. Qesmi, R., ElSaadany, S., Heffernan, J.M., et al.: A hepatitis B and C virus model with age since infection that exhibits backward bifurcation. SIAM J. Appl. Math. **71**, 1509–1530 (2011)
36. Ribeiro, R., Lo, A., Perelson, A.: Dynamics of hepatitis B virus infection. Microbes Infect. **4**, 829–835 (2002)

37. Rong, L., Feng, Z., Perelson, A.S.: Mathematical analysis of age-structured HIV-1 dynamics with combination antiretroviral therapy. SIAM J. Appl. Math. **67**, 731–756 (2007)
38. Smith, H.L., Thieme, H.R.: Dynamical Systems and Population Persistence, Graduate Studies in Mathematics, vol. 118. American Mathematical Society, Providence (2011)
39. Tuttleman, J., Pourcel, C., Summers, D.: Formation of the pool of covalently closed circular viral DNA in hepadnavirus-infected cells. Cell **47**, 451–460 (1986)
40. Wang, J., Zhang, R., Kuniya, T.: Global dynamics for a class of age-infection HIV models with nonlinear infection rate. J. Math. Anal. Appl. **432**, 289–313 (2015)
41. Wang, X., Lou, Y., Song, X.: Age-structured within-host HIV dynamics with multiple target cells. Stud. Appl. Math. **138**, 43–76 (2017)
42. Wang, X., Yang, J., Xu, F.: Analysis and control of an age-structured HIV-1 epidemic model with different transmission mechanisms. Adv. Differ. Equ. **36**, 1–24 (2018)
43. Wang, Y., Zhou, Y., Brauer, F., Heffernan, J.M.: Viral dynamics model with CTL immune response incorporating antiretroviral therapy. J. Math. Biol. **67**, 901–934 (2013)
44. WHO: Global Hepatitis Report 2017. https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/. Accessed 10 July 2019 (2017)
45. Yang, Y., Ruan, S., Xiao, D.: Global stability of an age-structured virus dynamics model with Beddington–DeAngelis infection function. Math. Biosci. Eng. **12**, 859–877 (2015)
46. Zhang, S., Guo, H.: Global analysis of age-structured multi-stage epidemic models for infectious diseases. Appl. Math. Comput. **337**, 214–233 (2018)