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STABILITY OF A DELAYED HEPATITIS B VIRUS INFECTION MODEL: EFFECT OF SPECIFIC FUNCTIONAL RESPONSE AND ABSORPTION

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Abstract

This work proposes and investigates a delayed cell population model of hepatitis B virus (HBV) infection. We use the Hattaf-Yousfi incidence function to describe viral infection. The model takes into account a specific functional response and the usually neglected absorption effect. Moreover, we introduce a time delay to account for the transformation processes necessary for actual

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HBV production. We naturally find a threshold parameter, namely, the basic reproduction number R_0 which ultimately determines the stability of the equilibria of the model obtained under other conditions. We determine the equilibria of our model known as uninfected equilibrium and infected equilibrium, and show that the model is well-posed, mathematically and biologically. By constructing appropriate Lyapunov functionals and using LaSalle's invariance principle, we show that, if $R_0 < 1$, the uninfected equilibrium is globally asymptotically stable. Furthermore, we prove that the uninfected equilibrium is locally asymptotically stable if $R_0 > 1$.

1. Introduction

Hepatitis B virus (HBV) infection is a hepatological condition leading to critical global health concern. According to [17, 29, 4], the pathogenesis of HBV infection is typically two types in nature: (a) acute illness which lasts for several weeks before eventually getting resolved in majority of cases in presence of dominant immune responses; and (b) chronic illness which can potentially give rise to a range of severe long-term implications such as acute necrotizing vasculitis, liver cirrhosis, membranous glomerulonephritis and hepatocellular carcinoma (HCC). Due to this spectrum of severe long-term complications, about 780 thousand individuals die annually with roughly 240 million chronically infected individuals [33]. Transmission of HBV generally occurs through two different routes: (a) vertical transmission where the virus carries to infant from mother at the time of birth; and (b) horizontal transmission where the virus passes through bites, sanitary habits and lesions in case of infants, and through sexual contacts, drug uses and medical procedures in case of adults [33, 6, 26]. The liver is the human organ that performs the greatest number of chemical transformations necessary for the smooth functioning of the body. The functional unit of liver is the hepatic lobule, which consists mainly of hepatocytes. The hepatitis B virus (HBV) is a major public health problem. It was first discovered in 1965 by Dr. Baruch Blumberg [3]. Originally, the virus was called the Australian antigen because it was named from Australian Aborigines

blood sample of that reacted with an antibody in the serum of an American hermophilia patient. It is called acute when it lasts less than six months, and chronic when it last more than six months. The evolution towards the chronicity is frequent with possible complications like cirrhosis and cancer. It is usually transmitted in the horst by two distinct modes of transmission either by a virus to healthy cells through the extracellular spaces or by a cell-to-cell infection involving direct contact between an infected cell and an uninfected cell [18, 21, 27]. Once in the blood the virus reaches the liver and multiplies itself in the liver cells (hepatocytes). The immune system destroy infected cells, by causing a liver inammation. Moreover, the hepatitis B virus infection usually disappears spontaneously and without treatment. On the other hand, vaccination against hepatitis B remains the principal and safest means to fight against this infection. If hepatitis B is not eliminated from the body by the immune system in the months following the onset of the infection it becomes chronic.

Traditionally several mathematical models have been introduced in order to gain insights into the pathogenesis of HBV infection by using ordinary differential equations (ODEs) and delay differential equations (DDEs). Nowak et al. [22] first introduced a basic ODE-driven model for HBV infection comprising uninfected hepatocytes, infected hepatocytes and free virus particles, and an extension of this basic viral infection model by including CTL immune responses was presented in [24]. Min et al. [20] presented an improved HBV infection model by incorporating standard incidence function for the infection process and they pointed out that basic model leads to unrealistic relationship between susceptibility to infection and number of hepatocytes due to mass action term for the infection process. A delayed version of HBV infection model with standard incidence function was proposed and analyzed in [8] by taking into account the time required for production of the matured virions from the exposed cells. Eikenberry et al. [7] showed the existence of sustained oscillations apart from the other two well-known dynamical behaviours

such as convergence to an infection-free steady state and to a chronic steady state for a delayed HBV infection model with logistic hepatocyte growth. In [32], Wang et al. performed the global stability analysis for an HBV infection model with standard incidence function and cytokine-mediated cure for infected hepatocytes based on empirical evidences. Hews et al. [15] proposed an improved HBV infection model by incorporating both logistic hepatocyte growth and standard incidence function.

WHO [33] showed in one of his reports that millions of people around the world are chronically suffering from HBV infection and thousands die from the complications mentioned above. Africa and Asia are the most affected continents but other parts of the world are concerned as well. The WHO has as goal to eradicate by 90% and reduce death due to viral hepatitis by 65% by the year 2030. Many mathematical models have been developed to help understand and control infectious diseases in general and hepatitis B in particular. Many early basic models were proposed and studied by many authors (for example, in [22, 23, 31, 32] and references therein). The various models don't really give account of experimental constants due to the fact that they don't really take into account the past(delay). Meanwhile the hepatitis B virus infection begins with a silent incubation period of about 2 months, but can extend to 6 months. In order to make the models more realistic and more adequate, a new features were introduced, known as delay and absorption effect, and from where we obtain a mathematical models of infection with delay and absorption.

This paper is organized as follows:

- We formulate and describe the mathematical model of hepatitis B infection in Section 2
- Section 3 is devoted to the existence and uniqueness, positivity, uniformly boundedness of solutions.
- In Section 4, the threshold parameter R_0 of model (1) is derived and the existence of the equilibria, known as uninfected equilibrium and infected equilibrium, are discussed in relation to the value of R_0 under some conditions.

• In Section 5, local stability and global stability of the uninfected equilibria are completely discussed.

• In Section 6, local asymptotic stability of the infected equilibrium is considered.

• Finally, a brief conclusion is presented in Section 7.

2. Description of the Model

The dynamics of HBV infection is the result of the dynamics of uninfected hepatocytes, infected hepatocytes, and virions particle and the various interactions between them. We propose the following model, which is a delayed system of three differential equations:

$$\begin{cases} \dfrac{dH(t)}{dt} = \lambda - dH(t) - \dfrac{(1-\eta)\beta H(t)V(t)}{1+\alpha_1 H(t)+\alpha_2 V(t)+\alpha_3 H(t)V(t)} + \rho I(t), \\ \dfrac{dI(t)}{dt} = e^{-m\tau}\dfrac{(1-\eta)\beta H(t-\tau)V(t-\tau)}{1+\alpha_1 H(t-\tau)+\alpha_2 V(t-\tau)+\alpha_3 H(t-\tau)V(t-\tau)} \\ \qquad\qquad - (a+\rho)I(t), \\ \dfrac{dV(t)}{dt} = (1-\varepsilon)k\, I(t) - \mu V(t) - \dfrac{(1-\eta)\beta H(t)V(t)}{1+\alpha_1 H(t)+\alpha_2 V(t)+\alpha_3 H(t)V(t)}, \end{cases} \tag{1}$$

where:

(1) The first equation of system (1) represents the dynamics of the concentration of healthy hepatocytes denoted by H where: the uninfected cells are produced in to the compartment at a rate λ from the bone marrow, die at the rate d and become infected by virus via the incidence force $\dfrac{\beta H}{1+\alpha_1 H+\alpha_2 V+\alpha_3 HV}$, (see [9, 10, 12] for details of such incidence and references therein) with β being the rate of transmission of infection, that is the proportion at which uninfected cells becomes infected. The rate of blocking new infection is given by $(1-\eta)$ and ρ is the cure rate of the infected cells. $\alpha_1 \geq 0$, $\alpha_2 \geq 0$, $\alpha_3 \geq 0$ are the saturation factors measuring the psychological or inhibitory effect.

(2) The second equation of system (1) represents the dynamics of the concentration of the infected hepatocytes denoted by I where: the infected hepatocytes may be killed due to viral or immune response or they may be lost by non cytolytic elimination of the CCCDNA in their nucleus at a rate $(a+\rho)I$, where a is the death rate of infected cells and ρ is the cure rate [11]. As we need some time for the healthy hepatocytes to become infected, we introduce the notion of delay. Thus, the healthy hepatocytes become infected at the rate

$$e^{-m\tau}\,\frac{\beta H(t-\tau)V(t-\tau)}{1+\alpha_1 H(t-\tau)+\alpha_2 V(t-\tau)+\alpha_3 H(t-\tau)V(t-\tau)}.$$

The parameter τ is a delay for the time between viral entry into target cells and production of new virus particles. The recruitment of virus producing cells at time t is given by the number of cells that were newly infected at time $t-\tau$ and are still alive at time t here, m is assumed to be a constant death rate for infected but not yet virus-producing cells. Thus the probability of surviving the time period from $t-\tau$ to t is $e^{-m\tau}$. This term contributes in increasing the number of infected cells with time.

(3) The third equation of system (1) represents the dynamics of the concentration of the virus particles denoted by V where: the infected hepatocytes produce virus at rate k. The term $(1-\varepsilon)k$ is the proportion at which infected cells become uninfected. The rate of blocking the viral production by infected cells is given by $1-\varepsilon$. We note that the treatment reduces the rate of virus production by cells from kI to $(1-\varepsilon)kI$. μ represents the rate of disappearance of virus particle. The term $-\dfrac{(1-\eta)\beta HV}{1+\alpha_1 H+\alpha_2 V+\alpha_3 HV}$ represents the absorption effect [28].

The model system (1) is subject to the following initial condition:

$$H(\theta)=\phi_1(\theta),\ I(\theta)=\phi_2(\theta),\ V(\theta)=\phi_3(\theta),\ -\tau\le\theta\le 0, \tag{2}$$

where $\phi = (\phi_1, \phi_2, \phi_3) \in \mathcal{C}([-\tau, 0], \mathbb{R}^3_+)$ which the Banach space of continuous functions from $[-\tau, 0]$ to $\mathbb{R}^3_+ = \{(H, I, V) \in \mathbb{R}^3 \setminus H \geq 0, I \geq 0, V \geq 0\}$.

3. Well Posedness

In this section, we show that model (1) is mathematically and biologically well posed.

Theorem 3.1. *The first quadrant* $\mathbb{R}^3_+$ *is positively invariant with respect to model* (1). *Moreover, under the initial condition* (2), *the solution* $(H(t), I(t), V(t))$ *of model* (1) *is existent, unique and all solutions of* (1) *are uniformly bounded in the compact subset*

$$\Gamma = \left\{(H, I, V) \in \mathbb{R}^3_+, H(t) \leq \frac{\lambda}{c}, I(t) \leq \frac{\lambda}{c}, V(t) \leq \frac{(1-\varepsilon)k\lambda}{\nu c}\right\},$$

where

$$c = \min\{a, d, m\}.$$

Proof. Firstly, since

$$\frac{dH}{dt}\Big|_{H=0} = \lambda + \rho H > 0,$$

$$\frac{dI}{dt}\Big|_{I=0} = e^{-m\tau} \frac{(1-\eta)\beta H(t-\tau)V(t-\tau)}{1 + \alpha_1 H(t-\tau) + \alpha_2 V(t-\tau) + \alpha_3 H(t-\tau)V(t-\tau)} > 0,$$

for all $H \geq 0, V \geq 0,$

$$\frac{dV}{dt}\Big|_{V=0} = (1-\varepsilon)kI > 0 \text{ for all } I \geq 0.$$

We deduce that $\mathbb{R}^3_+$ is positively invariant with respect to system (1).

Secondly, the existence and uniqueness of the solution $(H(t),\ I(t),\ V(t))$ can be easily proved by using the theorems in [16, 13, 14].

Finally, let us show that the solution $(H(t),\ I(t),\ V(t))$ is uniformly bounded.

For $t \geq 0$, define Z as below

$$Z(t) = H(t) + I(t) + (1-\eta)\beta \times \int_{t-\tau}^{t} e^{-m(t-s)} \frac{H(s)V(s)}{1+\alpha_1 H(s)+\alpha_2 V(s)+\alpha_3 H(s)V(s)}\, ds.$$

Taking the derivation of the previous expression along the solution, collecting and simplifying some terms, we obtain, for $t \geq 0$,

$$\begin{aligned}
\frac{dZ(t)}{dt} &= \lambda - dH(t) - \frac{(1-\eta)\beta H(t)V(t)}{1+\alpha_1 H(t)+\alpha_2 V(t)+\alpha_3 H(t)V(t)} + \rho I(t) \\
&\quad + e^{-m\tau}\frac{(1-\eta)\beta H(t-\tau)V(t-\tau)}{1+\alpha_1 H(t-\tau)+\alpha_2 V(t-\tau)} - (a+\rho)I(t) \\
&\quad + \alpha_3 H(t-\tau)V(t-\tau) \\
&\quad + \frac{(1-\eta)\beta H(t)V(t)}{1+\alpha_1 H(t)+\alpha_2 V(t)+\alpha_3 H(t)V(t)} \\
&\quad - e^{-m\tau}\frac{(1-\eta)\beta H(t-\tau)V(t-\tau)}{1+\alpha_1 H(t-\tau)+\alpha_2 V(t-\tau)+\alpha_3 H(t-\tau)V(t-\tau)} \\
&\quad - m\beta(1-\eta)\int_{t-\tau}^{t} e^{-m(t-s)}\frac{H(s)V(s)}{1+\alpha_1 H(s)+\alpha_2 V(s)+\alpha_3 H(s)V(s)}\, ds \\
&= \lambda - dH(t) - aI(t) - m(1-\beta)\beta \\
&\quad \times \int_{t-\tau}^{t} e^{-m(t-s)}\frac{H(s)V(s)}{1+\alpha_1 H(s)+\alpha_2 V(s)+\alpha_3 H(s)V(s)}\, ds.
\end{aligned}$$

It follows that

$$\frac{Z(t)}{dt} = \lambda - cZ(t),$$

where

$$c = \min\{a, d, m\}.$$

From where, we have

$$\limsup_{t\to+\infty} Z(t) \le \frac{\lambda}{c}.$$

From the third equation of system (1), it has that, for $t \ge 0$

$$\frac{dV(t)}{dt} \le (1-\varepsilon)kI(t) - \mu V(t),$$

from which we obtain

$$\limsup_{t\longrightarrow+\infty} V(t) \le \frac{(1-\varepsilon)k\lambda}{c\mu}.$$

This proves the uniform boundedness, and thus completes the proof of Theorem 3.1. □

Now, we determine the equilibria of system (1).

4. Basic Reproduction Number and Equilibria

4.1. Determination of the uninfected equilibrium point

In this subsection, we are going to determinate the uninfected equilibrium point which will help us in the calculation of the basic reproduction number by the van den Driessche's method [30]. It is easy to prove the following result:

Proposition 4.1. *The point* $E^0 = (H^0, 0, 0)$, *where* $H^0 = \frac{\lambda}{d}$ *is the uninfected equilibrium point of model* (1).

4.1.1. Determination of the basic reproduction number R_0 of our system

Theorem 4.2. *The basic reproduction number* R_0 *of system* (1) *is given by*

$$R_0 = \frac{(1-\eta)(1-\varepsilon)\beta k e^{-m\tau} H^0}{(a+\rho)((1-\eta)\beta H^0 + (1+\alpha_1 H^0)\mu)}.$$

Proof. We define the basic reproduction number R_0 of our model by

$$R_0 = \varphi(-DF(E^0)\cdot(DV(E^0)^{-1}) = \varphi(M),$$

where

$$\varphi(M) = \max_{\lambda \in sp(M)} |\lambda|,$$

$$DF(E^0) = \begin{pmatrix} 0 & (1-\eta)e^{-m\tau} f(H^0, 0, 0) H^0 \\ (1-\epsilon)K & 0 \end{pmatrix},$$

and

$$DV(E^0) = \begin{pmatrix} -(a+\rho) & 0 \\ 0 & -\mu - (1-\eta) f(H^0, 0, 0) \end{pmatrix},$$

with $f(H^0, 0, 0) = \dfrac{\beta H^0}{1+\alpha H^0}$.

Computation yields

$$R_0 = \frac{(1-\eta)(1-\epsilon) k f(H^0, 0, 0) e^{-m\tau}}{(a+\rho)(\mu + (1-\eta) f(H^0, 0, 0))}.$$

□

4.2. The infected equilibrium point

The following theorem presents the existence and uniqueness of uninfected equilibrium if $R_0 > 1$.

4.2.1. Existence and uniqueness

Theorem 4.3. *If* $R_0 > 1$ *and* $(1-\varepsilon)k - e^{-m\tau}(a+\rho) > 0$, *then system* (1) *has a unique infected equilibrium point* $E^* = (H^*, I^*, V^*)$ *with* $H^* \in]0; H^0[$, $I^* > 0$ *and* $V^* > 0$.

Proof. At any equilibrium, the following algebraic system holds:

$$\lambda - dH(t) - (1-\eta)f(H, I, V)V + \rho I = 0, \tag{3}$$

$$(1-\eta)f(H, I, V)V - (a+\rho)Ie^{m\tau} = 0, \tag{4}$$

$$(1-\epsilon)kI - \mu V - (1-\eta)f(H, I, V)V = 0, \tag{5}$$

where

$$f(H, I, V) = \frac{\beta H}{1 + \alpha_1 H + \alpha_2 V + \alpha_3 HV}.$$

By adding (3) and (4), we obtain

$$\lambda - dH(t) - e^{m\tau}(a+\rho)I + \rho I = 0.$$

We have $I = \dfrac{\lambda - dH(t)}{e^{m\tau}(a+\rho) + \rho} \geq 0$ implies that $H \geq \dfrac{\lambda}{d}$. Hence there is no equilibrium point if $H < \dfrac{\lambda}{d}$. Now, by adding Equations (4) and (5), we obtain

$$(1-\varepsilon)kI - \mu V - e^{m\tau}(a+\rho)I = 0,$$

this implies that

$$V = \frac{[(1-\varepsilon)k - e^{m\tau}(a+\rho)]I}{\mu}. \tag{6}$$

Since $(1-\varepsilon)k - e^{m\tau}(a+\rho) > 0$, V is positive. Next substituting (6) into (4), we have

$$\frac{1}{\mu}\{[(1-\varepsilon)k - e^{m\tau}(a+\rho)](1-\eta)f(H, I, V) - (a+\rho)e^{m\tau}\}I = 0,$$

which leads to

$$\frac{1}{\mu}\{[(1-\varepsilon)k - e^{m\tau}(a+\rho)](1-\eta)f(H, I, V) - (a+\rho)e^{m\tau}\} = 0$$

since $I > 0$. Now, we consider the function φ defined on interval $[0; H^0]$ by

$$\varphi(H) = [(1-\varepsilon)k - e^{m\tau}(a+\rho)](1-\eta)]f(H, I, V) - \mu(a+\rho)e^{m\tau}.$$

It follows that

$$\varphi(0) = -(\mu+\rho)e^{m\tau} < 0,$$

and

$$\begin{aligned}
\varphi(H^0) &= [(1-\varepsilon)k - e^{m\tau}(a+\rho)](1-\eta)f(H^0, 0, 0) - \mu(a+\rho)e^{m\tau} \\
&= (1-\varepsilon)(1-\eta)kf(H^0, 0, 0) - (a+\rho)(1-\eta)e^{m\tau}f(H^0, 0, 0) \\
&\quad - \mu(a+\rho)e^{m\tau} \\
&= (1-\varepsilon)(1-\eta)kf(H^0, 0, 0) - (a+\rho)e^{m\tau}[(1-\eta)f(H^0, 0, 0) + \mu] \\
&= \left[\frac{(1-\varepsilon)(1-\eta)ke^{-m\tau}f(H^0, 0, 0)}{(a+\rho)((1-\eta)f(H^0, 0, 0) + \mu)} - 1\right]((1-\eta)f(H^0, 0, 0) \\
&\quad + \mu)(a+\rho)e^{m\tau} \\
&= [R_0 - 1](a+\rho)e^{m\tau}(\mu + (1-\eta)f(H^0, 0, 0)).
\end{aligned}$$

Since $R_0 > 1$ it implies $\varphi(H^0) > 0$ but $\varphi(0) < 0$ thus this assures the existence of at least an $H \in]0; H^0[$.

We now prove the uniqueness of the H. We proceed as follows: the derivative of φ with respect to H yields

$$\varphi'(H) = [(1-\varepsilon)k - e^{m\tau}(a+\rho)(1-\eta)]\left(\frac{(1+\alpha_2 V)\beta}{(1+\alpha_1 H+\alpha_2 V+\alpha_3 HV)^2}\right.$$

$$\left. + \frac{H\beta(\alpha_2+\alpha_3 H)(k(1-\varepsilon)-e^{m\tau}(a+\rho))}{\mu(1+\alpha_1 H+\alpha_2 V+\alpha_3 HV)^2(e^{m\tau}(a+\rho)+\rho)}\right)$$

$$= [(1-\varepsilon)k - e^{m\tau}(a+\rho)(1-\eta)]$$

$$\times\left(\frac{\beta\mu(1+\alpha_2 V)e^{m\tau}((a+\rho)+\rho)}{\mu(1+\alpha_1 H+\alpha_2 V+\alpha_3 HV)^2(e^{m\tau}(a+\rho)+\rho)}\right.$$

$$\left. + \frac{H\beta(\alpha_2+\alpha_3 H)(k(1-\varepsilon)-e^{m\tau}(a+\rho))}{\mu(1+\alpha_1 H+\alpha_2 V+\alpha_3 HV)^2(e^{m\tau}(a+\rho)+\rho)}\right).$$

Moreover

$$\varphi'(H) > 0,$$

since

$$(1-\varepsilon)k - e^{m\tau}(a+\rho)(1-\eta) > 0.$$

Thus the function φ is strictly increasing on $[0;\ H^0]$ and according to the intermediate value theorem there exists a unique equilibrium point $H^* \in]0;\ H^0[$ such that $\varphi(H^*) = 0$. Thus, there exists a unique infected equilibrium point $E^*(H^*, I^*, V^*)$ with

$$H^* \in]0;\ H^0[,$$

$$I^* = \frac{\lambda - dH^*(t)}{e^{m\tau}(a+\rho)+\rho},$$

and

$$V^* = \frac{[(1-\varepsilon)k - e^{m\tau}(a+\rho)]I^*}{\mu}.$$

□

5. Asymptotic Stability Analysis of the Uninfected Equilibrium

The aim of this section is to study the local asymptotic stability of the uninfected and infected equilibria. For an arbitrary equilibrium $E = (H^*, I^*, V^*)$, the characteristic equation associated to system (1) is given by

$$\begin{vmatrix} d + (1-\eta)\beta L + x & -\rho & (1-\eta)\beta M \\ (1-\eta)\beta L e^{-(x+m)\tau} & (a+\rho) + x & (1-\eta)\beta M e^{-(x+m)\tau} \\ (1-\eta)\beta L & -(1-\varepsilon)k & (1-\eta)\beta M + x \end{vmatrix} = 0, \qquad (7)$$

where

$$L = \frac{(1-\eta)\beta(1+\alpha_2 V^*)V^*}{(1+\alpha_1 H^* + \alpha_2 v^* + \alpha_3 H^* V^*)^2},$$

and

$$M = \frac{(1-\eta)\beta(1+\alpha_1 H^*)H^*}{(1+\alpha_1 H^* + \alpha_2 v^* + \alpha_3 H^* V^*)^2}.$$

5.1. Local stability analysis of E^0

The characterization of the local stability of the uninfected equilibrium is given by the following proposition:

Proposition 5.1. (1) *If* $R_0 < 1$, *then the uninfected equilibrium point* $E^0 = \left(\frac{\lambda}{d}, 0, 0\right)$ *is locally asymptotically stable.*

(2) *If* $R_0 > 1$, *then the uninfected equilibrium point* E^0 *is unstable.*

Proof. (1) At E_0, (7) reduces to

$$\begin{vmatrix} -d-x & \rho & -(1-\eta)f(H^0,\,0,\,0) \\ 0 & -(a+\rho)-x & -(1-\eta)e^{-m\tau-x\tau}f(H^0,\,0,\,0) \\ 0 & (1-\epsilon)k & -\mu-(1-\eta)f(H^0,\,0,\,0)-x \end{vmatrix} = 0,$$

where

$$f(H^0,\,0,\,0) = \frac{\beta H^0}{1+\alpha_1 H^0}.$$

That is: the characteristic equation of our model at uninfected equilibrium is of the form:

$$(x+d)Z(x) = 0, \tag{8}$$

where

$$\begin{aligned} Z(x) = {} & x^2 + (\mu + (a+\rho) + (1-\eta)f(H^0,\,0,\,0))x \\ & + (a+\rho)(\mu + (1-\eta)f(H^0,\,0,\,0) \\ & - (1-\epsilon)k(1-\eta)f(H^0,\,0,\,0)e^{-(m+x)\tau}, \end{aligned} \tag{9}$$

which can rewritten as follows:

$$\begin{aligned} Z(x) = {} & x^2 + (\mu + (a+\rho) + (1-\eta)f(H^0,\,0,\,0))x \\ & + (a+\rho)(\mu + (1-\eta)f(H^0,\,0,\,0)(1 - R_0 e^{-x\tau}). \end{aligned} \tag{10}$$

It is clear that $x = -d$ is an eigenvalue for (8), and hence, the stability of E_0 is determined by the distribution of the roots of equation $Z(x) = 0$. For all solutions to have negative real part it suffices for the roots of the polynomial $Z(x)$ to have roots with negative real part, this polynomial can also be rewritten in the form:

$$Z(x) = P(x) + Q(x)e^{-m\tau},$$

with

$$P(x) = x^2 + (\mu + (a + \rho) + (1 - \eta)f(H^0, 0, 0))x$$

$$+ (a + \rho)(\mu + (1 - \eta)f(H^0, 0, 0)),$$

and

$$Q(x) = -(1 - \epsilon)k(1 - \eta)f(H^0, 0, 0)e^{-(m+x)\tau}.$$

Note that when $\tau = 0$, then Equation (10) becomes

$$Z(x) = x^2 + (\mu + (a + \rho) + (1 - \eta)f(H^0, 0, 0))x$$

$$+ (a + \rho)(\mu + (1 - \eta)f(H^0, 0, 0)(1 - R_0). \quad (11)$$

If $R_0 < 1$, then by Routh-Hurwitz criterion [1, 5], all the roots of Equation (11) have negative real parts. Thus the uninfected equilibrium E_0 is locally asymptotically stable when $\tau = 0$.

Next, we consider the case $\tau > 0$, and show that the polynomials P and Q verify the properties below:

(a) $P(x) \neq 0$ for $\mathrm{Re}(x) \geq 0$.

If $P(x) = 0$, we deduce from the Routh-Hurwitz criterion that $\mathrm{Re}(x) < 0$ for all x, since

$$(\mu + (a + \rho) + (1 - \eta)f(H^0, 0, 0)) > 0,$$

and

$$(a + \rho)(\mu + (1 - \eta)f(H^0, 0, 0)) > 0.$$

Hence $P(x) \neq 0$ for $\mathrm{Re}(x) \geq 0$.

(b) $\overline{P(-i\omega)} = P(i\omega)$ and $\overline{Q(i\omega)} = Q(i\omega)$ with $0 \leq \omega < \infty$.

Evaluating $P(x)$ and $Q(x)$ for $x = i\omega$ and for $x = -i\omega$ with $0 \le \omega < \infty$, we obtain:

$$P(i\omega) = -\omega^2 + i(\mu + (a+\rho) + (1-\eta)f(H^0, 0, 0))\omega$$

$$+ (a+\rho)(\mu + (1-\eta)f(H^0, 0, 0));$$

$$P(-i\omega) = -\omega^2 - i(\mu + (a+\rho) + (1-\eta)f(H^0, 0, 0))\omega$$

$$+ (a+\rho)(\mu + (1-\eta)f(H^0, 0, 0));$$

$$Q(i\omega) = -(1-\epsilon)k(1-\eta)f(H^0, 0, 0)e^{-(m+x)\tau};$$

$$Q(i\omega) = -(1-\epsilon)k(1-\eta)f(H^0, 0, 0)e^{-(m+x)\tau}.$$

Thus we have proved the following equalities: $\overline{P(-i\omega)} = P(i\omega)$ and $\overline{Q(i\omega)} = Q(i\omega)$ with $0 \le \omega < \infty$.

(c) $|Q(i\omega)| < |P(i\omega)|$ with $0 \le \omega < \infty$.

We have

$$|P(i\omega)|^2 = (\mu + (a+\rho) + (1-\eta)f(H^0, 0, 0))^2\omega^2$$

$$+ \left[(a+\rho)(\mu + (1-\eta)f(H^0, 0, 0)) - \omega^2\right]^2;$$

we obtain

$$|P(i\omega)|^2 = (\omega^2 + (a+\rho)^2)(\omega^2 + (\mu + (1-\eta)f(H^0, 0, 0))^2).$$

It follows that

$$|P(i\omega)| \ge (a+\rho)(\mu + (1-\eta)f(H^0, 0, 0)),$$

and since,

$$R_0 < 1,$$

then

$$(a+\rho)(\mu+(1-\eta)f(H^0,0,0)) > (1-\epsilon)k(1-\eta)f(H^0,0,0)e^{-(m+x)\tau}$$

moreover,

$$|Q(i\omega)| = (1-\epsilon)k(1-\eta)f(H^0,0,0)e^{-(m+x)\tau};$$

it follows that

$$|P(i\omega)| \geq (a+\rho)(\mu+(1-\eta)f(H^0,0,0))$$

$$> (1-\epsilon)k(1-\eta)f(H^0,0,0)e^{-(m+x)\tau} = |Q(i\omega)|.$$

That is,

$$|P(i\omega)| \geq |Q(i\omega)|;$$

hence for all, $0 \leq \omega < \infty$

$$|P(i\omega)| \geq |Q(i\omega)|.$$

(d) Finally we have

$$\lim_{\substack{|x|\to\infty \\ \mathrm{Re}(x)>0}} \left|\frac{Q(x)}{P(x)}\right| = \lim_{\substack{|x|\to\infty \\ \mathrm{Re}(x)>0}}$$

$$\times \frac{(1-\epsilon)k\,(1-\eta)f(H^0,0,0)e^{-(m+x)\tau}}{x^2+(\mu+(a+\rho)+(1-\eta)f(H^0,0,0))x+(a+\rho)(\mu+(1-\eta)f(H^0,0,0))}$$

$$= 0.$$

The solutions of equation $Z(x) = 0$ have negative real part if $R_0 < 1$ in the light of ([2], Theorem 1, p. 187). We can conclude that the equilibrium point E^0 is locally asymptotically stable.

(2) On the other hand, it is easy to show that (10) has a real positive root when $R_0 > 0$. Indeed, we put

$$\Phi(x) = x^2 + \big(\mu + (a+\rho) + (1-\eta)f(H^0, 0, 0)\big)x$$
$$+ (a+\rho)\,(\mu + (1-\eta)f(H^0, 0, 0)\,\big(1 - R_0 e^{-x\tau}\big).$$

We have $\Phi(0) = (a+\rho)(\mu + (1-\eta)f(H^0, 0, 0)(1-R_0)$ and $\lim_{x\longrightarrow+\infty} \Phi(x) = +\infty$. Therefore, Φ has a positive real root and the uninfected equilibrium is unstable. This proves the theorem. □

In what follows we will show that the global stability of the uninfected equilibrium point using a suitable Lyapunov functional.

5.2. Global stability of the uninfected equilibrium E^0

In this section, we will discuss the global stability of the uninfected equilibrium point E^0.

Theorem 5.2. *If* $R_0 \le 1$ *and* $(a+\rho) \neq k(1-\varepsilon)e^{-m\tau}$ *the uninfected equilibrium* E^0 *is globally asymptotically stable for any time delay* $\tau \ge 0$.

Proof. The proof of the theorem is done by using two cases. For convenience let us define the function g, by

$$g(H, V) = \frac{HV}{1 + \alpha_1 H + \alpha_2 V + \alpha_3 HV}.$$

Case I: $(a+\rho) < k(1-\varepsilon)e^{-m\tau}$.

Define the following Lyapunov functional:

$$L = H - H^0 - \int_{H^0}^{H} \lim_{V\mapsto 0^+} \frac{g(H^0, V)}{g(S, V)}\, dS + k_1 I + k_2 V + k_3 U,$$

where the constants k_1, k_2, and k_3 are to be determined later and

$$U = (1-\eta)\int_{-\tau}^{0} g(H(t+\theta), V(t+\theta))d\theta.$$

By computing the derivative of L along the solutions of model (1), we have that for $t \geq 0$,

$$\begin{aligned}\frac{dL}{dt} &= \left(1 - \lim_{V\mapsto 0^+}\frac{g(H^0, V)}{g(S, V)}\right)[\lambda - dH(t) - (1-\eta)\beta g(H, V) + \rho I] \\ &+ k_1[e^{-m\tau}\beta(1-\eta)g(H(t-\tau), V(t-\tau)) - (a+\rho)I] \\ &+ k_2[(1-\varepsilon)kI - \mu V - (1-\eta)\beta g(H, V)] \\ &+ k_3[(1-\eta)\beta g(H, V) - (1-\eta)\beta \cdot g(H(t-\tau), V(t-\tau))].\end{aligned}$$

Denoting that $\lambda = dH^0$ and letting $k_1 = \dfrac{(1-\varepsilon)k}{(1-\varepsilon)ke^{-m\tau} - (a+\rho)}$, $k_2 = \dfrac{k_1(a+\rho)}{(1-\varepsilon)k}$, and $k_3 = k_1 e^{-m\tau}$. We have that for $t \geq 0$,

$$\begin{aligned}\frac{dL}{dt} &= dH^0\left(1 - \frac{H}{H^0}\right)\left(1 - \lim_{V\mapsto 0^+}\frac{g(H^0, V)}{g(S, V)}\right) \\ &- \left(1 - \lim_{V\mapsto 0^+}\frac{g(H^0, V)}{g(S, V)}\right)(1-\eta)\beta g(H, V) + \left(1 - \lim_{V\mapsto 0^+}\frac{g(H^0, V)}{g(S, V)}\right)\rho I \\ &+ k_1 e^{-m\tau}\beta(1-\eta)g(H(t-\tau), V(t-\tau)) - (a+\rho)k_1 I \\ &+ k_2(1-\varepsilon)kI - \mu V k_2 - (1-\eta)\beta g(H, V)k_2 + k_1 e^{-m\tau}\beta(1-\eta)g(H, V) \\ &- k_1 e^{-m\tau}\beta(1-\eta)g(H(t-\tau), V(t-\tau)),\end{aligned}$$

since

$$k_1 = \frac{k_2(1-\varepsilon)k}{(a+\rho)}.$$

Then

$$\frac{dL}{dt} = dH^0\left(1-\frac{H}{H^0}\right)\left(1-\lim_{V\mapsto 0^+}\frac{g(H^0,V)}{g(H,V)}\right)$$

$$-\left(1-\lim_{V\mapsto 0^+}\frac{g(H^0,V)}{g(H,V)}\right)(1-\eta)\beta g(H,V)+\rho I\left(1-\lim_{V\mapsto 0^+}\frac{g(H^0,V)}{g(H,V)}\right)$$

$$+\frac{k_2 k e^{-m\tau}(1-\varepsilon)}{(a+\rho)}\beta(1-\eta)g(H(t-\tau),V(t-\tau))$$

$$-k_2k(1-\varepsilon)I+k_2k(1-\varepsilon)I-\mu V k_2-(1-\eta)\beta g(H,V)k_2$$

$$+\frac{k_2 k e^{-m\tau}(1-\varepsilon)}{(a+\rho)}\beta(1-\eta)g(H,V)$$

$$-\frac{k_2 k e^{-m\tau}(1-\varepsilon)}{(a+\rho)}\beta(1-\eta)g\left(H(t-\tau),V(t-\tau)\right).$$

As

$$\frac{k_2k(1-\varepsilon)}{(a+\rho)}=\frac{k(1-\varepsilon)}{e^{-m\tau}(1-\varepsilon)k-(a+\rho)}$$

implies that

$$(a+\rho)=\frac{k_2k(1-\varepsilon)e^{-m\tau}}{1+k_2}.$$

Then we have

$$\frac{dL}{dt} = dH^0\left(1-\frac{H}{H^0}\right)\left(1-\lim_{V\mapsto 0^+}\frac{g(H^0,V)}{g(H,V)}\right)$$

$$-\left(1-\lim_{V\mapsto 0^+}\frac{g(H^0,V)}{g(H,V)}\right)(1-\eta)\beta g(H,V)$$

$$+\rho I\left(1-\lim_{V\mapsto 0^+}\frac{g(H^0,V)}{g(H,V)}\right)-\mu V k_2$$

$$+ \frac{k_2 k e^{-m\tau}(1-\varepsilon)(1+k_2)}{k_2 k(1-\varepsilon)e^{-m\tau}}(1-\eta)\beta g(H, V),$$

$$= dH^0\left(1-\frac{H}{H^0}\right)\left(1-\lim_{V\mapsto 0^+}\frac{g(H^0, V)}{g(H, V)}\right)+\left(1-\lim_{v\mapsto 0^+}\frac{g(H^0, V)}{g(H, V)}\right)\rho I$$

$$+ k_2\mu V\left(\frac{(1-\eta)\beta g(H, V)}{k_2\mu V}\cdot\lim_{V\mapsto 0^+}\frac{g(H^0, V)}{g(H, V)}-1\right). \tag{12}$$

It is easy to see that the function g is positive, differentiable and increasing on $[0, +\infty[$. Furthermore, the function g is concave with respect to V, and satisfies the following properties:

(i) For all $H, V \geq 0$ $g(H, V)$, $g'_H(H, V)$ and $g'_V(H, V)$ are positive and $g''_V(H, V)$ is negative

(ii) $H > 0$, $g'_V(H, 0)$ is monotonically increasing that is

$$\frac{g'_V(H^0, 0)}{g'_V(H, 0)} > 1 \text{ for } H \in (0, H^0) \text{ and } \frac{g'_V(H^0, 0)}{g'_V(H, 0)} < 1 \text{ for } H > H^0. \tag{13}$$

From (12) and (13) we have that

$$\left(1-\frac{H}{H^0}\right)\left(1-\lim_{V\mapsto 0^+}\frac{g(H^0, V)}{g(H, V)}\right)=\left(1-\frac{H}{H^0}\right)\left(1-\frac{g'_V(H^0, 0)}{g'_V(H, 0)}\right)\leq 0,$$

and

$$\frac{g'_V(H^0, 0)}{g'_V(H, 0)} > 1 \text{ for } H \in (0, H) \text{ and for all } I > 0. \tag{14}$$

From (12) and (14) we have that

$$\left(1-\lim_{V\mapsto 0^+}\frac{g(H^0, V)}{g(H, V)}\right)\rho I=\left(1-\frac{g'_V(H^0, 0)}{g'_V(H, 0)}\right)I\leq 0.$$

Next, let us consider the term by concavity of the function g we have the following:

$$\frac{(1-\eta)\beta g(H, V)}{k_2\mu V} \cdot \lim_{v\mapsto 0^+} \frac{g(H^0, V)}{g(H, V)} - 1$$

$$= \frac{(1-\eta)\beta g(H, V)}{k_2\mu V} \frac{g'_V(H^0, 0)}{g'_V(H, 0)} - 1$$

$$\leq \frac{(1-\eta)\beta}{k_2\mu} g'_V(H^0, 0) - 1 \text{ since } 0 < \frac{g(H, V)}{Vg'_V(H, 0)} < 1$$

$$\leq \frac{(1-\eta)\beta(ke^{-m\tau}(1-\varepsilon) - (a+\rho))}{(a+\rho)\mu} g'_V(H^0, 0) - 1$$

$$\leq \frac{(1-\eta)\beta(ke^{-m\tau}(1-\varepsilon) - (a+\rho))}{(1+\alpha_1 H^0)(a+\rho)\mu} H^0 - 1 \text{ since } k_2 = \frac{(a+\rho)}{ke^{-m\tau}(1-\varepsilon) - (a+\rho)}$$

$$\leq \frac{(1-\eta)(1-\varepsilon)\beta ke^{-m\tau}H^0 - (a+\rho)((1-\eta)\beta H^0 + (1+\alpha_1 H^0)\mu)}{(1+\alpha_1 H^0)(a+\rho)\mu}$$

$$\leq \frac{(a+\rho)((1-\eta)\beta H^0 + (1+\alpha_1 H^0)\mu)}{(1+\alpha_1 H^0)(a+\rho)\mu}(R_0 - 1).$$

Then from (12), we have that for $t \geq 0$

$$\frac{dL}{dt} \leq dH^0\left(1 - \frac{H}{H^0}\right)\left(1 - \frac{g'_V(H^0, 0)}{g'_V(H, 0)}\right) + \left(1 - \frac{g'_V(H^0, 0)}{g'_V(H, 0)}\right)I$$

$$+ k_2\mu V\left(\frac{(a+\rho)((1-\eta)\beta H^0 + (1+\alpha_1 H^0)\mu)}{(1+\alpha_1 H^0)(a+\rho)\mu}(R_0 - 1)\right).$$

If $R_0 \leq 1$, we have that for $t \geq 0$, $\frac{dL}{dt} \leq 0$. This shows that the uninfected equilibrium E^0 is stable.

Next, we are going to show that the uninfected equilibrium E^0 is globally attractive. Let us define the subset

$$E = \left\{\varphi = (\varphi_1, \varphi_2, \varphi_3)^T \in \mathbb{C} / \frac{dL}{dt}(\varphi_1, \varphi_2, \varphi_3) = 0\right\}.$$

Let M be the largest invariance set with respect to the model (1) in E. It is easy to see that M includes at least one point E^0.

For any $\varphi = (\varphi_1, \varphi_2, \varphi_3)^T \in M$, let us use $(H(t), (I), (V))^T$ to denote the solution of model (1) with the initial condition, where

$$H(t) = H(t + \theta),\ I(t) = I(t + \theta),\ V(t) = V(t + \theta),\ (-\tau \le \theta \le 0,\ t \ge 0).$$

From the invariance of the subset M, we have that for all $t \in \mathbb{R}$, $(H(t), (I), (V))^T \in M \subset E$. Hence, it follows that for any $t \ge 0$, $H(t) = H^0$. Again from the invariance of the subset, we have that $H(t) \equiv \varphi_1 \equiv H^0$ for any $t \in \mathbb{R}$. Hence, from the equation of model (1) and the invariance of the subset M, we have that, for any, $t \ge 0$, $V(t) = I(t)$. This show that $M = \{E^0\}$. By means of the LaSalle's invariance principle, we have that the uninfected equilibrium E^0 is globally asymptotically stable when $R_0 \le 1$.

Case II: $(a + \rho) > k(1 - \varepsilon)e^{-m\tau}$.

Let us define a Lyapunov functional of the form

$$L_1 = c_1 I + c_2 V + (1 - \eta) \times \int_{-\tau}^{0} \frac{H(t + \theta)V(t + \theta)}{1 + \alpha_1 H(t + \theta) + \alpha_2 V(t + \theta) + \alpha_3 H(t + \theta)V(t + \theta)}\, d\theta,$$

where c_1 and c_2 are to be determined later. Then, it follows that, for $t \geq 0$

$$\frac{dL_1}{dt} = c_1\left[e^{-m\tau}\frac{(1-\eta)\beta H(t-\tau)V(t-\tau)}{1+\alpha_1 H(t-\tau)+\alpha_2 V(t-\tau)+\alpha_3 H(t-\tau)V(t-\tau)} - (a+\rho)I(t)\right]$$

$$+ c_2\left[(1-\varepsilon)kI - \mu V(t) - \frac{(1-\eta)\beta H(t)V(t)}{1+\alpha_1 H(t)+\alpha_2 V(t)+\alpha_3 H(t)V(t)}\right]$$

$$+ \frac{(1-\eta)HV}{1+\alpha_1 H(t)+\alpha_2 V(t)+\alpha_3 H(t)V(t)}$$

$$- e^{-m\tau}\frac{(1-\eta)H(t-\tau)V(t-\tau)}{1+\alpha_1 H(t-\tau)+\alpha_2 V(t-\tau)+\alpha_3 H(t-\tau)V(t-\tau)}.$$

By choosing $c_1 = \frac{e^{m\tau}}{\beta}$ and $c_2 = \frac{e^{-m\tau}(a+\rho)}{(1-\varepsilon)k\beta}$ we have that, for $t \geq 0$,

$$\frac{dL_1}{dt} = \frac{(1-\eta)H(t-\tau)V(t-\tau)}{1+\alpha_1 H(t-\tau)+\alpha_2 V(t-\tau)+\alpha_3 H(t-\tau)V(t-\tau)} - \frac{e^{m\tau}(a+\rho)}{\beta}I$$

$$+ \frac{e^{m\tau}(a+\rho)}{\beta}I - \frac{e^{m\tau}(a+\rho)\mu V}{(1-\varepsilon)k\beta} - \frac{e^{m\tau}(a+\rho)}{(1-\varepsilon)k}$$

$$\times \frac{HV(1-\eta)}{1+\alpha_1 H(t)+\alpha_2 V(t)+\alpha_3 H(t)V(t)}$$

$$+ \frac{HV(1-\eta)}{1+\alpha_1 H(t)+\alpha_2 V(t)+\alpha_3 H(t)V(t)}$$

$$- \frac{(1-\eta)H(t-\tau)V(t-\tau)}{1+\alpha_1 H(t-\tau)+\alpha_2 V(t-\tau)+\alpha_3 H(t-\tau)V(t-\tau)}.$$

We have

$$\frac{dL_1}{dt} = -\frac{e^{m\tau}(a+\rho)\mu V}{(1-\varepsilon)k\beta} + \frac{HV(1-\eta)}{1+\alpha_1 H(t)+\alpha_2 V(t)+\alpha_3 H(t)V(t)}\left(1-\frac{e^{m\tau}(a+\rho)}{(1-\varepsilon)k}\right),$$

$$= -\frac{e^{m\tau}(a+\rho)}{(1-\varepsilon)k\beta} + \frac{e^{m\tau}HV(1-\eta)}{1+\alpha_1 H(t)+\alpha_2 V(t)+\alpha_3 H(t)V(t)}\left(e^{-m\tau}-\frac{(a+\rho)}{(1-\varepsilon)k}\right),$$

$$= -\frac{e^{m\tau}(a+\rho)}{(1-\varepsilon)k\beta} + \frac{e^{m\tau}HV(1-\eta)((1-\varepsilon)e^{-m\tau}-(a+\rho))}{(1-\varepsilon)k(1+\alpha_1 H(t)+\alpha_2 V(t)+\alpha_3 H(t)V(t))}.$$

Similarly, let us also define the subset

$$E_1 = \left\{\varphi = (\varphi_1, \varphi_2, \varphi_3)^T \in \mathbb{C} / \frac{dL_1}{dt}(\varphi_1, \varphi_2, \varphi_3) = 0\right\}.$$

Let M_1 be the largest invariance set with respect to model (1) in E_1. It has that $E^0 \in M_1$. For any $\varphi = (\varphi_1, \varphi_2, \varphi_3)^T \in M_1$, let $(H_t, I_t, V_t)^T$ be the solution of model (1) with the initial condition (2). From the invariance of the subset M_1, it also has that, for all $t \in \mathbb{R}$, $(H_t, I_t, V_t)^T \in M_1 \subset E$. Hence, it has that, for any $t \geq 0$, $V(t) = 0$. From the invariance of the subset M_1, it further has that $V_t \equiv \phi_3 = 0$ for any $t \in \mathbb{R}$. From the second and first equation of model (1) and the invariance of the subset M_1, it finally has that, for any $t \geq 0$, $I(t) = 0$ and $H(t) = H^0$. This shows that $M_1 = E^0$. Therefore, it follows from LaSalle's invariance principle that the uninfected E^0 is globally asymptotically stable when $R_0 \leq 1$. This completes the proof. □

6. Local Asymptotic Stability Analysis of the Infected Equilibrium

The aim of this section is to study the local and global stability of the uninfected equilibrium.

Proposition 6.1. *If* $(a+\rho)^2(\mu+(1-\eta)\beta M)^2-(1-\varepsilon)^2(1-\eta)^2k^2\beta^2M^2 e^{-2m\tau}>0$, $(1-\eta)^2\beta^2LM-(d+(1-\eta)\beta L)^2>0$ *and* $(a+\rho)^2+d^2-2(1-\eta)\beta L(a+\rho)>0$, *then the infected equilibrium point* $E^*=(H^*, I^*, V^*)$ *is locally asymptotically stable for any time delay* $\tau\geq 0$.

Proof. At E^*, (7) reduces to

$$x^3+p_2x^2+p_1x+p_0+(q_1x+q_0)e^{-x\tau}=0, \tag{15}$$

where

$$p_2=(d+(1-\eta)\beta L)+(a+\rho)+(\mu+(1-\eta)\beta M),$$

$$p_1=(a+\rho)(d+(1-\eta)\beta+(\mu+(1-\eta)\beta M)$$
$$+d(\mu+(1-\eta)\beta M)+\mu(1-\eta)\beta M,$$

$$p_0=(d+(1-\eta)\beta L)(a+\rho)(\mu+(1-\eta)\beta M)-LM(a+\rho)(1-\eta)^2\beta^2,$$

$$q_1=(1-\epsilon)k(1-\eta)Me^{-(m\tau}-\rho(1-\eta)^2\beta^2LM(1-\varepsilon)ke^{-m\tau},$$

$$q_0=-(d+(1-\eta)\beta L)(1-\varepsilon)ke^{-m\tau}+LM(1-\eta)^2\beta^2e^{-m\tau}$$
$$-\rho(1-\eta)^2\beta^2L(\mu+(1-\eta)\beta M)(1-\varepsilon)ke^{-m\tau}.$$

If $\tau=0$, Equation (15) is reduced to the following form:

$$x^3+p_2x^2+(p_1+q_1)x+p_0+q_0=0.$$

Hence, it follows from the Routh-Hurwitz criterion that the infected equilibrium E^* of model (1) is locally asymptotically stable when $\tau=0$.

Now, let us consider the case $\tau > 0$. Let us show that Equation (15) has all its roots with real negative part. Let $p(x) = x^3 + p_2x^2 + p_1x + p_0$ and $q(x) = q_1x + q_0$. It follows that (15) is equivalent to

$$p(x) + q(x)e^{-x\tau} = 0. \tag{16}$$

We show that (16) only has solutions with negative real parts on the light of ([2], Theorem 1, p. 187).

If $p(x) = 0$, then from the Routh-Hurwitz criteria for all $x \in \mathbb{C}$ such that $p(x) = 0$ it is obvious that

$$p_0 > 0,\ p_1 > 0,\ p_2 > 0,$$

and

$$\begin{aligned} p_1p_2 - p_0 = {} & (d + (a + \rho))(d + (1 - \eta)\beta L)^2 \\ & + (a + \rho)^2((d + (1 - \eta)\beta L) + (\mu + (1 - \eta)\beta M)) \\ & + (a + \rho)(\mu + (1 - \eta)\beta M)(2d + (1 - \eta)\beta L) \\ & + (a + \rho)(\mu + (1 - \eta)\beta M)^2 \\ & + d(\mu + (1 - \eta)\beta M)(d + (1 - \eta)\beta L) \\ & + \mu(1 - \eta)\beta((a + \rho) + d) \\ & + \mu(1 - \eta)^2\beta^2L^2 + \mu(1 - \eta)\beta L(\mu + (1 - \eta)\beta M)) \\ & + LM(a + \rho)(1 - \eta)^2\beta^2 \geq 0. \end{aligned}$$

Since the hypothesis of Routh-Hurwitz criteria are satisfied, then the roots of $p(x)$ have negative real parts, hence $p(x) \neq 0$ for all $x \in \mathbb{C}$ such that $\mathrm{Re}(x) \geq 0$.

Evaluating now $p(x)$ and $q(x)$ for $x = iz$ and $x = -iz$ with $0 \le z < \infty$, for all $0 \le z < \infty$, we obtain

$$p(iz) = -iz^3 - p_2z^2 + ip_1z + p_0;$$

$$p(-iz) = iz^3 - p_2z^2 - ip_1z + p_0;$$

$$q(iz) = iq_1z + q_0;$$

$$q(-iz) = -iq_1z + q_0.$$

Hence we deduce that

$$\overline{p(-iz)} = p(iz);$$

$$\overline{q(-iz)} = q(iz).$$

For all $0 \le z < \infty$.

We now show that $|p(iz)| > |q(iz)|$ for all $0 \le z < \infty$. Let $z \in [0, \infty[$ we obtain

$$|p(iz)|^2 = (p_0 - p_2z^2)^2 + (p_1z - z^3)^2;$$

$$= z^6 + (p_2^2 - 2p_1)z^4 + (p_1^2 - 2p_0p_2)z^2 + p_0^2,$$

and

$$|q(iz)|^2 = q_0^2 + q_1^2z^2.$$

Thus,

$$|q(iz)|^2 - |q(iz)|^2 = z^6 + (p_2^2 - 2p_1)z^4 + (p_1^2 - 2p_0p_2)z^2 + p_0^2 - q_0^2 - q_1^2z^2;$$

$$= z^6 + (p_2^2 - 2p_1)z^4 + (p_1^2 - 2p_0p_2 - q_1^2)z^2 + p_0^2 - q_0^2.$$

Showing $|p(iz)|^2 > |q(iz)|^2$, is equivalent to showing that

$$|p(iz)|^2 - |q(iz)|^2 > 0.$$

That is,

$$a_2 = p_2^2 - 2p_1 > 0;$$

$$a_1 = p_1^2 - 2p_0p_2 - q_1^2 > 0;$$

$$a_3 = p_0^2 - q_0^2 > 0.$$

By simple computation we obtain

$$\begin{aligned} a_2 &= (a+\rho)^2 + (d+(1-\eta)\beta L)^2 + 2(d+(1-\eta)\beta L)(a+\rho) \\ &+ 2d + 2d(\mu+(1-\eta)\beta M) + 2(1-\eta)\beta L\mu + 2(1-\eta)^2\beta^2 LM \\ &+ 2(\alpha+\rho)(\mu+(1-\eta)\beta M) - 2(a+\rho)(d+(1-\eta)\beta L) \\ &- 2(a+\rho)(\mu+(1-\eta)\beta M) - 2d(\mu+(1-\eta)\beta M) - 2(1-\eta)\beta L\mu. \end{aligned}$$

We deduce that

$$p_2^2 - 2p_1 = (a+\rho)^2 + (d+(1-\eta)\beta L)^2 > 0.$$

Moreover,

$$\begin{aligned} a_1 &= 2(a+\rho)(\mu+(1-\eta)\beta M)((1-\eta)^2\beta^2 LM - (d+(1-\eta)\beta L)^2) \\ &+ 2(d+(1-\eta)\beta L)(1-\eta)^2 LM(a+\rho) + 2(a+\rho)^2(1-\eta)^2\beta^2 LM \\ &+ (\mu+(1-\eta)\beta M)^2((a+\rho)^2 + d^2 - 2(1-\eta)\beta L(a+\rho)) \\ &+ (a+\rho)^2(d+(1-\eta)\beta L) + \mu^2(1-\eta)^2\beta^2 L^2 \\ &+ 2d\mu(1-\eta)\beta L(\mu+(1-\eta)\beta M) \\ &+ 2(a+\rho)(d+(1-\eta)\beta L)(d(\mu+(1-\eta)\beta M) + \mu(1-\eta)\beta L) \\ &+ 2(a+\rho)(\mu+(1-\eta)\beta M)(\mu(1-\eta)\beta L) \\ &+ ((1-\varepsilon)k\beta Me^{-m\tau}(\rho(1-\eta)L+1))^2 > 0, \end{aligned}$$

since,

$$(1-\eta)^2\beta^2 LM - (d+(1-\eta)\beta L)^2 > 0,$$

and

$$(a+\rho)^2 + d^2 - 2(1-\eta)\beta L(a+\rho) > 0.$$

Therefore,

$$p_1^2 - 2p_0p_2 - q_1^2 > 0.$$

However

$$\begin{aligned} a_0 &= (d+(1-\eta)\beta L)^2((a+\rho)^2(\mu+(1-\eta)\beta M)^2 \\ &\quad - (1-\varepsilon)^2(1-\eta)^2k^2\beta^2M^2e^{-2m\tau}) \\ &\quad + (1-\eta)^4L^2\beta^4((a+\rho)^2M^2 - (\rho(1-\varepsilon)k(\mu+(1-\eta)\beta M) - M)^2e^{-2m\tau}) \\ &\quad + 2(d+(1-\eta)\beta L)(1-\eta)^2\beta^2LM((1-\eta)\beta k(1-\varepsilon) \\ &\quad \times(\rho(1-\varepsilon)k(\mu+(1-\eta)\beta M) - M)e^{-2m\tau}) > 0, \end{aligned}$$

since

$$(a+\rho)^2(\mu+(1-\eta)\beta M)^2 - (1-\varepsilon)^2(1-\eta)^2k^2\beta^2M^2e^{-2m\tau} > 0,$$

and

$$(a+\rho)^2M^2 - (\rho(1-\varepsilon)k(\mu+(1-\eta)\beta M) - M)^2 > 0.$$

We deduce that, $p_0^2 - q_0^2 > 0$, consequently,

$$|p(iz)|^2 - |q(iz)|^2 > 0.$$

Finally, we have

$$\lim_{\substack{|x|\to\infty \\ \mathrm{Re}(x)>0}} \left|\frac{Q(x)}{P(x)}\right| = \lim_{\substack{|x|\to\infty \\ \mathrm{Re}(x)>0}} \frac{q_1 x + q_0}{x^3 + p_2 x^2 + p_1 x + p_0} = 0.$$

Hence all solutions of the characteristics equation (16) have negative real parts according to ([2], Theorem 1, p. 187). Consequently E^* is locally asymptotically stable. This completes the proof. □

Remark 6.2. Most of the results obtained in this work generalize those of works that dealt with the stability of the basic models of the dynamics of HBV infection with the particular incidence function such as incidence function of: Crowley-Martin, Beddington-DeAngelis and without forgetting the saturated and standard incidence functions and that resulting from the mass action principle.

7. Conclusion

The study was centered on the analysis of the stability of a delayed hepatitis B virus infection model with a specific functional response and absorption effect. The originality of this work is to have studied the dynamics of hepatitis B virus with a generalized incidence function as well as absorption effect. First, we showed the existence of local and global existence of solutions and the positivity of solution of the model. Then we obtained sufficient conditions for the local asymptotic stability for the infected and uninfected equilibria as well as the global asymptotic stability for the uninfected and infected equilibria with the help of the basic reproduction number R_0. Moreover, we showed that when the basic reproduction number $R_0 < 1$, the uninfected equilibrium is globally asymptotically stable using a suitable Lyapunov functional and that when $R_0 > 1$, the infected equilibrium point is locally asymptotically stable. Therefore, the basic reproduction number R_0 directly involves deciding whether the host becomes infected or not. Regarding global

stability analysis, some elegant Lyapunov functionals have been constructed for various models (see, for example, [19] and [25] and the references therein). However, it is somewhat complicated to find a suitable Lyapunov functional to show global asymptotic stability of the infected equilibrium E^*. We left this for future investigation. We can also undertake an analysis of the bifurcation of the actual by following the work done in [37, 36, 34, 35]. Furthermore, for our future studies, we will extend our study on a more realistic model than the one on which we are working, which will take into account: the notion of diffusion, which will lead to partial delay differential equations, and we will replace discrete delay with a distributed delay.

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