International Journal of Advances in Mathematics
Volume 2018, Number 6, Pages 52-63, 2018
eISSN 2456-6098

Stability analysis of the transmission dynamics of hepatitis B Virus infection with controls in a population

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ABSTRACT. In this paper, the stability in the occurrence of HB Virus in a population was considered. The equilibrium states were examined. The stability in the occurrence of the HB Virus was verified using the Jacobian method. It was shown that the disease occurrence is unstable meaning that slight variation in the number of infected individuals can cause great positive increase in the endemicity of the disease.

1 Introduction

Hepatitis is a medical condition defined by the inflammation of the liver and characterized by the presence of inflammatory cells in the tissue of the Liver caused by a number of etiologic agents; including viruses and non-viral agents. The most infectious Hepatitis is of viral etiology, which includes among others Hepatitis type B..Hepatitis B is a serious viral infection that causes inflammation of the liver and affects how well the liver functions. It is one of the most prevalent diseases in the world. Hepatitis B may occur with limited or no symptoms but often leads to jaundice, anorexia and malaise. Some people go on to have chronic Hepatitis B, and are at a much higher risk for developing cirrhosis of the liver and liver cancer.

* Corresponding Author.
Received July 24, 2018; accepted September 30, 2018.
2010 Mathematics Subject Classification: 97Mxx and 92Bxx
Key words and phrases: Stability, Jacobian Method, equilibrium state, Unstable, endemicity.

Hepatitis B virus (HBV) is a noncytopathic, hepatotropic, DNA virus (hepadnavirus) [8]. It has a strong preference for infecting liver cells, but small amounts of hepadnaviral DNA can be found in the kidneys, pancreas and mononuclear cells [12]. HBV can be transmitted by sexual contact, through the skin, by inoculation with contaminated blood or blood products, by transplantation of organs from infected donors, and perinatally from infected mothers. Although HBV replication is only mildly cytopathic, cellular immune responses directed against the virus can produce substantial liver damage and result in chronic hepatitis, cirrhosis and hepatocellular carcinoma [12]. Chronic HBV infections remain a major public health problem worldwide. An estimated 350 million people worldwide have been infected with HBV [14], with 5% developing chronic HBV as a result [10].

Hepatitis B is a disease caused by hepatitis B virus (HBV). This disease reduces the livers ability to perform life-preserving functions, including filtering harmful infectious agents from the blood, storing blood sugar and converting it to usable energy forms, and producing many proteins necessary for life [5]. Hepatitis B is fifty to one hundred times more infectious than HIV [31]. It has caused epidemics in part of Asia and Africa, and it is endemic in China [30] and Nigeria [27]. About a third of the worlds population, more than two billion peoples have been infected with hepatitis B virus at some stage in their life time. Of these, about 360 million people remain chronically infected carriers of the disease, most of whom are unaware of their HBV status [13].

Transmission of hepatitis B virus results from exposure to infectious blood or body fluids containing blood. Possible forms of transmissions include (but are not limited to) unprotected sexual contact, blood transfusions, re-use of contaminated needles and syringes, and vertical transmission from mother to child during child birth [5]. Infection with the HBV has been a major public health problem. This has two phases: Acute and Chronic. The Acute phase causes liver inflammation, vomiting, and jaundice in which the individual is infectious. Chronic hepatitis B is an infection with hepatitis B virus that last longer than six months. Once the infection becomes chronic, it may never be cured completely, and may eventually cause liver cirrhosis and hepatocellular carcinoma (HCC) [5]. Hepatitis B virus (HBV) infection is among the most common causes of hepatitis and can result in serious liver diseases such as chronic hepatic insufficiency, hepatocellular carcinoma, and cirrhosis [9].
Over the last decade, much collaborated effort involving biologists and mathematicians has been devoted towards designing mathematical models of HBV dynamics [32, 4, 7, 15, and 19]. Mathematical modeling and model analysis of the HBV dynamics are important for exploring possible mechanisms and dynamical behaviors of the viral infection process, estimating key parameter values, and guiding development of efficient antiviral drug therapies [8]. Stability analysis of HBV dynamics models has been studied by many authors like [16, 20, 29, 28, 17, 18, 21] The aim of this paper is to develop a mathematical model with controls (enlightenment, condom use and therapy all at a time). We shall carry out equilibrium analysis of the modeled equations. The study will further verify the stability in the occurrence of Hepatitis B Virus using Jacobian method. The result(s) of the stability analysis will help give an insight on how best to control HBV infection in any given population.

2 Model formulation

Assumptions of the Model

The model is based on the following assumptions:

1. Individuals that make up the population are grouped into different compartments according to their epidemiological state
2. The population size in a compartment varies with respect to time.
3. The population mixes homogeneously. That is, all susceptible individuals are equally likely to be infected by infectious individuals if they come in contact with one another.
4. The infection does not confer immunity to the recovered individuals and so they can go back to the susceptible class at any given time.
5. The individuals in each compartment have equal natural death rate given as μ
6. The gain in the infectious class is at a rate proportional to the number of infectious and susceptible individuals, that is, βSI, where $\beta > 0$ is a contact parameter (effective contact rate).The susceptible are lost at the same rate
7. The rate of removal of infectious to the recovered or removed class is proportional to the number of infectious individuals.
8. Individuals that enter into the population will either go into the susceptible class or into the infectious class depending on their epidemiological condition as at the time of entering.
9. At all time, there must be individuals in the I compartment who are neither in I_T compartment nor in I_N compartment.

Variables underlying the Model

The following variables will be used in this model:

S The number of susceptible individuals.

E The number of exposed individuals.

I The number of infectious individuals.

R The number of individuals who have been treated and have recovered from the infection.

E_T The number of exposed individuals who are receiving treatment.

I_T The number of infectious individuals who are receiving treatment.

I_N The number of infectious individuals who are not receiving treatment.

Parameters of the Model

We shall use the following parameters in this model, they are:

π : The number of people that enter into the population or the number of individuals that enter into the susceptible class(recruitment).

β : Contact rate for HBV infectious individuals with the susceptible individuals. i.e., the rate at which susceptible individuals who had contact with the infected become exposed to HBV.

τ : The rate at which latently infected individuals become infectious (actively infected).

ω : The rate at which exposed individuals enter the exposed and treated class (E_T)

ρ_2 : The rate at which infectious individuals enter into the infectious and treated class (I_T)

α : The rate at which infectious and treated individuals go back to exposed class (E).

ρ_1 : The rate at which infectious individuals enter into the class of infected and not treated.

γ : The rate at which infectious and treated individuals recover from HBV (the rate at which infectious and treated individuals move to the recovered class R).

ϕ; The rate at which recovered individuals become susceptible to HBV again.

δ : HBV-induced mortality/death rate for the class of infectious and treated individuals.

δ_1 : HBV-induced mortality/death rate for the class of infectious and not treated individuals

μ : The natural mortality/death rate.

$\psi(1+\varphi)$: The rate at which exposed and treated individuals recover.

φ : Infectivity control; which include enlightenment, vaccine and the use of condom.

θ : The number of individuals already infected with HBV that goes into the population

ψ : Cure rate

Description of HBV Model

Base on the standard SEIR model, the population is partitioned into seven compartments or classes namely: Susceptible(S), Exposed(E), Infectious(I), Exposed and Treated(E_T), Infectious and Treated(I_T), Infectious and not Treated(I_N) and Recovered(R) Compartments.

Model Equations

$$\frac{ds}{dt} = \pi + \phi R - \beta SI - \mu S \tag{1.1}$$

$$\frac{dE}{dt} = \beta SI + \alpha I_T - \omega E - \tau E - \mu E \tag{1.2}$$

$$\frac{dE_T}{dt} = \omega E - \psi(1+\varphi)E_T - \mu E_T \tag{1.3}$$

$$\frac{dI}{dt} = \tau E + \theta I - \rho_1 I - \rho_2 I \tag{1.4}$$

$$\frac{dI_N}{dt} = \rho_1 I - \mu I_N - \delta_1 I_N \tag{1.5}$$

$$\frac{dI_T}{dt} = \rho_2 I - \alpha I_T - \gamma I_T - \mu I_T - \delta I_T \tag{1.6}$$

$$\frac{dR}{dt} = \gamma I_T + \psi(1+\varphi)E_T - \phi R - \mu R \tag{1.7}$$

$$N = S + E + E_T + I_N + I_T + R \tag{1.8}$$

Susceptible individuals acquire HBV infection following effective contact with individuals infected with HBV (i.e., those in the E, I_N and I_T classes) at a rate β, given by

$$\beta = \frac{\chi_B(E + \mu_1 I_N + \mu_2 I_T)}{N}; \quad N = S + E + I_N + I_T$$

where χ_B is the effective contact rate for HBV transmission. Further, the modification parameters $\mu_1 \geq 1$ and $\mu_2 < 1$ account for the relative infectiousness of individuals in the I_N and I_T classes in comparison to those in the E class. That is individuals in the I_N class are more infectious than those in the E class (because of their higher viral load), and likewise I_T, are less infectious than those in I_N class (because the use of treatment significantly reduces the viral load in those treated).

3 Analysis of the Model

The Disease-free Equilibrium (DFE) State of HBV:

The disease-free equilibrium state is the state of total absence of the disease.

Let $E^0 : (S^*, E^*, E_T^*, I^*, I_N^*, I_T^*, R^*)$ be the disease-free equilibrium state. At the disease-free equilibrium state, we have that the exposed, the exposed and treated, the infectious, the infectious and treated as well as the infectious and not treated classes must be equal to zero. That is, for disease-free equilibrium state, we must have that

$$E = E_T = I = I_N = I_T = 0 \tag{1.16}$$

Now by substituting the value of equation (1.16) into equations (1.9) (1.15) and solving simultaneously, we obtain the following results;

From equation (1.15); $-\mu R - \phi R = 0$. This implies that $-\mu R = \phi R$; $(\mu - \phi)R = 0 \Rightarrow R = 0$.

Hence, equation (1.9) becomes;

$$\pi - \mu S = 0 \tag{1.17}$$

This implies that $\pi - \mu S = 0$.

Hence $\pi = \mu S$.

$$Therefore \quad S = \frac{\pi}{\mu} \tag{1.18}$$

Therefore the disease- free equilibrium state of the model is thus;

$$E^0 : (S^*, E^*, E_T^*, I^*, I_N^*, I_T^*, R^*) = (\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0) \in R^7 \tag{1.19}$$

Stability Analysis: To determine the stability or otherwise of the disease-free equilibrium state E^0, we shall examine the behavior of the model population near this equilibrium solution. We shall determine the condition(s) that must be met for the disease-free equilibrium state to be stable. Hence, we shall determine the condition(s) that must be met if the disease is to be totally eradicated from the population.

We now linearize the system of equations to get the Jacobian Matrix J.

Now the values of the entries of the Jacobian Matrix are thus;

$$J = \begin{pmatrix} -\beta.I - \mu & 0 & 0 & -\beta.S & 0 & 0 & \phi \\ \beta.I & -(\omega+\tau+\mu) & 0 & \beta.S & 0 & \alpha & 0 \\ 0 & \omega & -[\mu+\psi(1+\Phi)] & 0 & 0 & 0 & 0 \\ 0 & \tau & 0 & (\theta-\rho_2-\rho_1) & 0 & 0 & 0 \\ 0 & 0 & 0 & \rho_1 & -(\mu+\delta_1) & 0 & 0 \\ 0 & 0 & 0 & \rho_2 & 0 & -(\alpha+\mu+\delta+\gamma) & 0 \\ 0 & 0 & \psi(1+\Phi) & 0 & 0 & \gamma & -(\mu+\phi) \end{pmatrix}$$

Now the Jacobian Matrix evaluated at the Disease-free equilibrium is given as;

$$J^* = \begin{pmatrix} -\mu & 0 & 0 & -\beta\frac{\pi}{\mu} & 0 & 0 & \phi \\ 0 & -(\omega+\tau+\mu) & 0 & \beta\frac{\pi}{\mu} & 0 & \alpha & 0 \\ 0 & \omega & -[\mu+\psi(1+\Phi)] & 0 & 0 & 0 & 0 \\ 0 & \tau & 0 & (\theta-\rho_1-\rho_2) & 0 & 0 & 0 \\ 0 & 0 & 0 & \rho_1 & -(\mu+\delta_1) & 0 & 0 \\ 0 & 0 & 0 & \rho_2 & 0 & -(\alpha+\mu+\delta+\gamma) & 0 \\ 0 & 0 & \psi(1+\Phi) & 0 & 0 & \gamma & -(\mu+\phi) \end{pmatrix}$$

Now the characteristic equation $|J^* - IE| = 0$ is obtained and evaluated thus;

$$\begin{bmatrix} -\mu & 0 & 0 & -\beta\frac{\pi}{\mu} & 0 & 0 & \phi \\ 0 & -(\omega+\tau+\mu) & 0 & \beta\frac{\pi}{\mu} & 0 & \alpha & 0 \\ 0 & \omega & -[\mu+\psi(1+\Phi)] & 0 & 0 & 0 & 0 \\ 0 & \tau & 0 & (\theta-\rho_1-\rho_2) & 0 & 0 & 0 \\ 0 & 0 & 0 & \rho_1 & -(\mu+\delta_1) & 0 & 0 \\ 0 & 0 & 0 & \rho_2 & 0 & -(\alpha+\mu+\delta+\gamma) & 0 \\ 0 & 0 & \psi(1+\Phi) & 0 & 0 & \gamma & -(\mu+\phi) \end{bmatrix} \begin{bmatrix} E & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & E & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & E & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & E & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & E & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & E & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & E \end{bmatrix}$$

which implies,

$$\begin{bmatrix} -\mu - E & 0 & 0 & -\beta\frac{\pi}{\mu} & 0 & 0 & \phi \\ 0 & -(\omega+\tau+\mu+E) & 0 & \beta\frac{\pi}{\mu} & 0 & \alpha & 0 \\ 0 & \omega & -[\mu+\psi(1+\Phi)+E] & 0 & 0 & 0 & 0 \\ 0 & \tau & 0 & (\theta-\rho_1-\rho_2-E) & 0 & 0 & 0 \\ 0 & 0 & 0 & \rho_1 & -(\mu+\delta_1-E) & 0 & 0 \\ 0 & 0 & 0 & \rho_2 & 0 & -(\alpha+\mu+\delta+\gamma+E) & 0 \\ 0 & 0 & \psi(1+\Phi) & 0 & 0 & \gamma & -(\mu+\phi+E) \end{bmatrix}$$

Let $F := -\mu - \tau - \omega$

$G := -\mu - \psi - \Phi\psi$

$H := \theta - \rho_1 - \rho_2$

$U := -\mu - \delta_1$

$V := -\mu - \alpha - \delta - \gamma$

$W := -\mu - \phi$

Therefore, the determinant of the above matrix will give us,

$$\begin{bmatrix} -\mu - E & 0 & 0 & -\beta\frac{\pi}{\mu} & 0 & 0 & \phi \\ 0 & F-E & 0 & \beta\frac{\pi}{\mu} & 0 & \alpha & 0 \\ 0 & \omega & G-E & 0 & 0 & 0 & 0 \\ 0 & \tau & 0 & H-E & 0 & 0 & 0 \\ 0 & 0 & 0 & \rho_1 & U-E & 0 & 0 \\ 0 & 0 & 0 & \rho_2 & 0 & V-E & 0 \\ 0 & 0 & \psi(1+\Phi) & 0 & 0 & \gamma & W-E \end{bmatrix}$$

$$-\frac{(G-E)(U-E)(W-E)(\mu+E)[-\mu E^3+(F\mu E^2+H\mu E^2+V\mu E^2)+(\pi\tau\beta E-FH\mu E-FV\mu E-HV\mu E)+(\mu\tau\alpha\rho_2+FHV\mu-\pi V\tau\beta)]}{\mu}$$

$$\frac{[-(G-E)(U-E)(W-E)(\mu+E)][\mu E^3+(-F\mu-H\mu-V\mu)E^2+(FH\mu-\pi\tau\beta+FV\mu+HV\mu)E+(\pi V\tau\beta-FHV\mu-\mu\tau\alpha\rho_2)]}{\mu} = 0$$

which implies,

$\frac{[-(G-E)(U-E)(W-E)(\mu+E)](AE^3+BE^2+CE+D)}{\mu} = 0$; where, $A := \mu,\ B := (-F\mu - H\mu - V\mu),\ C := FH\mu - \pi\tau\beta + FV\mu + HV\mu,\ D := \pi V\tau\beta - FHV\mu - \mu\tau\alpha\rho_2$.

4 Results and Discussion

Eigen value classification of stability(Eigen value of the Jacobean Matrix of the equilibrium point):

Assumption of the equilibrium:

We assumed that the equilibrium point is an isolated critical point or the zero solution or the null solution. It is upon this assumption that we discuss our results.

Now consider the results we got;

4.1 Result for Stability Analysis

Result for stability analysis was obtained as

$$AE^3 + BE^2 + CE + D = 0 \tag{1.21}$$

By substituting the numerical values(see table 4) of the parameters, we obtained A, B, C and D as:

$A = 0.02,\ B = -0.182,\ C = -185.12, D = -21.10$. The following theorems and definitions will validate our discussion, thus;

Theorem 1: Let A be a constant matrix in the system $\dot{x} = Ax$ with eigenvalues $\gamma i; i = 1, 2, ...n$.

1. If the system is stable, then $Re\{\gamma i\} \leq 0,\ i = 1, 2..n$
2. If either $Re\{\gamma i\} < 0,\ i = 1, 2..n$ or if $Re\{\gamma i\} \leq 0,\ i = 1, 2..n$ and there is no zero repeated eigenvalue; then the system is uniformly stable.

3. The system is asymptotically stable if and only if $Re\{\gamma i\} < 0,\ i = 1, 2..n$ (and then it is also uniformly stable, by (ii)).
4. If $Re\{\gamma i\} > 0$ for any i, the solution is unstable. In connection with (ii), note that if there is a zero repeated Eigen value the system may be stable or unstable. [1, 2, 3]

Theorem 2: Suppose that we have a set of autonomous ordinary differential equations, written in vector form:

$$\dot{x} = f(x) \tag{1.22}$$

Suppose that x^* is an equilibrium point. By definition, $f(x^*) = 0$ An equilibrium point x^* of the differential equation (1.22) is stable if all the eigenvalues of j^*, the Jacobian matrix evaluated at x^*, have negative real parts. The equilibrium point is unstable if at least one of the eigenvalues has a positive real part. [1, 2, 3].

Definition 1: An equilibrium state $x = 0$ is said to be:

(a). stable if for any positive scalar ϵ there exists a positive scalar δ such that $||x(t_0)|| < \delta$ implies $||x(t)|| < \epsilon$ for all $t \geq t_0$

(b). asymptotically stable if it is stable and if in addition $x(t) \to 0$ as $t \to \infty$

(c). unstable if it is not stable; that is, there exists an $\epsilon > 0$ such that for every $\delta > 0$, there exists an $x(t_0)$ with $||x(t_0)|| < \delta$, $||x(t_1)|| \geq \epsilon$ for some $t_1 > t_0$

(d). completely unstable if there exists an $\epsilon > 0$ such that for every $\delta > 0$ and for every $x(t_0)$ with $||x(t_0)|| < \delta$, $||x(t_1)|| \geq \epsilon$ for some $t_1 > t_0$

(Note: The definition (a) is often called "stability in the sense of Lyapunov") **Definition 2:** The equilibrium point q is said to be stable if given $\epsilon > 0$ there is a $\delta > 0$ such that $||\phi(t, p) - q|| < \epsilon$ for all $t > 0$ and for all p such that $||p - q|| < \delta$. If δ can be chosen not only so that the solution q is stable but also so that $\phi(t, p) \to q$ as $t \to \infty$, then q is said to be asymptotically stable. If q is not stable it is said to be unstable.[1, 2, 3]. Now considering equation (1.21);

i.e.,

$$AE^3 + BE^2 + CE + D = 0$$

This is a cubic equation, and the general formula for the roots, in terms of the coefficients of any cubic equation, is as follows:

$$E_k = \frac{1}{3A}(B + u_k L + \frac{\Delta_0}{u_k L}), k = 1, 2, 3 \tag{1.23}$$

where $u_1 = 1, u_2 = \frac{-1+i\sqrt{3}}{2}, u_3 = \frac{-1-i\sqrt{3}}{2}$ are the three cube roots of unity,[1, 2, 23, 24, 25, 26] and where $L = \sqrt[3]{\frac{\Delta_1 + \sqrt{\Delta_1^2 - 4\Delta_0^3}}{2}}$ with $\Delta_0 = B^2 - 3AC$ and $\Delta_1 = 2B^3 - 9ABC + 27A^2D$.

Now the three roots are:

When $k = 1$, we computed E_1 as:

$E_1 = -89.59817578924756142 + 40.00668578636637131922$ Similarly, we computed E_2 and E_3 when $k = 2$ and $k = 3$ respectively and obtain;

$E_2 = 98.37794138968132174 + 90.00607444194791010814$, $E_3 = -0.1130989337670936587 - 60.0127602283142814274$.

Using Eigen value classification of stability, we shall summarise our discussion of the roots of this equation using

table under the following headings: classification of the root, behaviour of the solution of the root and the nature of stability of the root as shown in table 1, table 2 and table 3 below for E_1, E_2 and E_3 respectively.

Table 1: For the first root (E_1):

Classification	Behaviour of the solution	The nature of Stability
Complex with negative real part	Spiral sink	Asymptotically stable

Table 2: For the second root (E_1):

Classification	Behaviour of the solution	The nature of Stability
Complex with positive real part	Spiral source	Unstable

Table 3: For the Third root (E_3):

Classification	Behaviour of the solution	The nature of Stability
Complex with negative real part	Spiral sink	Asymptotically stable

Computation of the Value of the Effective Reproduction Number (R_0) of HBV Infection by substituting the numerical values of the parameters of HBV using Mathcad:
The effective reproduction number of HBV Infection was calculated (Aja et al, 2017 [33]) as; $R_0 = \frac{[\pi\tau\beta(\alpha+\mu+\delta+\gamma)]+\sqrt{[\pi\tau\beta(\alpha+\mu+\delta+\gamma)]^2}}{2\mu[\tau\alpha\rho_2-(\omega+\tau+\mu)(-\theta+\rho_2+\rho_1)(\alpha+\mu+\delta+\gamma)]}$
Hence if we substitute the values of these parameters in (R_0) above we will obtain;
$R_0 = \frac{[10000\times500\times37(0.01+0.021+0.068+0.015)]+\sqrt{[10000\times500\times37(0.01+0.021+0.068+0.015)]^2}}{[2\times0.021[0.50\times0.01\times0.33-(0.02+0.50+0.021)\times(-10+0.33+0.33)\times(0.01+0.021+0.068+0.015)]]}$
$R_0 = 1738.46548920473270$; $R_0 > 1 \Rightarrow$ unstable.

4.2 Discussion of the results

From our results displayed in tables1, 2 and 3 above; we can see that the disease is unstable, this mean that any minor increase in the infection can cause epidemic in the population. Furthermore, the result shows that the disease is asymptotically stable; this implies that there are traces of the disease in the population, but it is no longer pronounced in the sense that a small control on the infected persons(individuals) can remove it completely from the population.

5 Conclusion

We built a new mathematical model for HBV with controls (enlightenment, condom use, vaccine and therapy). Furthermore, disease-free equilibrium was obtained. The results of the stability analysis showed that the disease is unstable which means that any minor increase in the infection of the disease can cause epidemic in the population. The result further shows that the disease is asymptotically stable which implies that there are traces of the disease in the population, but it is no longer pronounced in the sense that a small control on the infected persons (individuals) can remove it completely from the population.

Table 3: For the Third root (E_3):

Parameter	Value	Reference
μ	0.021	[5,6]
π	1000	Assumed
β	0.37	Assumed
τ	0.50	[22,11]
θ	10	Assumed
ω	0.02	Assumed
α	0.01	Assumed
γ	0.015	[5]
ϕ	0.92	Assumed
ψ	0.015	[5]
$\varphi \Rightarrow \Phi$	0.08	[5]
ρ_1	0.33	[22,11]
ρ_2	0.33	[22,11]
δ	0.068	[5]
δ_1	0.068	[5]

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