The Analysis of a HBV Model with Vaccination

Xiaoxia Yuan
Department of Applied Mathematics
North University of China
Taiyuan, Shanxi, P. R. China

Yakui Xue *
Department of Applied Mathematics
North University of China
Taiyuan, Shanxi, P. R. China
*Corresponding author

***Abstract*—In this paper, we introduce an improved hepatitis B virus(HBV) model to discuss the impact of vaccination. The basic reproductive number R_0 determine the extinction and the persistence of virus infection.When R_0 is less than one,the disease-free equilibrium is globally-asymptotically stable and the infection becomes extinct eventually;When R_0 is greater than one,the unique endemic equilibrium exists and endemic equilibrium is locally asymptotically.The results indicate that vaccination plays an importment role in preventing and controlling the spread of HBV.**

***Keywords*-hepatitis b virus; basic reproduction number; globally asymptotical stable**

I. INTRODUCTION

Recently, mathematical models have been used frequently to study the transmission dynamics of HBV in various regions. Long et al. (2008) considered the mathematical model of CTL immune response to HBV infection [1].Eikenberry et al.(2009)analyzed the hepatitis B virus infection in a delay model[2].Li et al.(2011)analyzed the dynamic behaviors of a HBV infection model with logistic hepatocyte growth and discuss the stability[3].These models provided useful information about the impact of various control measures.

II. MODEL

A deterministic compartmental model, a system of ordinary differential equations, is proposed to describe the dynamics of HBV transmission. The HBV transmission is complex and the detailed mechanism remains unclear, for the sake of simplicity, we make some assumptions:

(1)We class all the vertical infected infants into the chronic carriers.

(2)We assume that all the newborns are vaccinated at the same efficacy, since many countries have introducer HBV vaccination into their nation infant immunization program.

(3)The exposed compartment will shift either to the acute infection individuals or to the chronic HBV carriers, according to the medical journal by Cao(2010)[4].Attention that in this paper the chronic HBV carriers includes the so-called medically HBV carriers and the chronic infectious individuals.

Note that Medley et al. considered only five groups and did not distinguish the recovered and vaccinated subgroups[5].In fact ,the immunity after recovery is lifetime, while that following vaccination might wane after some time.

We divide the host population into six groups: the susceptible individuals S ; infected but not yet infectious individuals (exposed) E ; acute infectious individuals I ; chronic HBV carriers C ; recovered individuals R ; vaccinated individuals V .Of the six stages, both acute infection and chronic HBV carriers can spread the disease. $\mu(1-\omega)$ newborns successfully immunized move directly to the immune following vaccination, $\mu\omega\upsilon C$ babies have infected due to vertical transmission and access to chronic carrier class, the lest $\mu\omega(1-\upsilon C)$ newborns are unimmunized and become susceptible individual , q and ω is less than 1,all the parameters are nonnegative.

Based on the characteristics of HBV transmission, the relevant differential equations are

$$\begin{aligned}
\frac{dS}{dt} &= \mu\omega(1-\nu C)+\varepsilon V-\beta(I+\alpha C)S-\gamma_2 S-\mu S,\\
\frac{dE}{dt} &= \beta(I+\alpha C)S-\sigma E-\delta E-\mu E,\\
\frac{dI}{dt} &= \sigma E-\gamma_1 I-\mu I,\\
\frac{dC}{dt} &= \delta E+q\gamma_1 I-\mu\omega\nu C-\gamma_3 C-\mu C,\\
\frac{dR}{dt} &= (1-q)\gamma_1 I+\gamma_3 C-\mu R,\\
\frac{dV}{dt} &= \mu(1-\omega)+\gamma_2 S-\varepsilon V-\mu V.
\end{aligned} \tag{1}$$

Where, μ is the death rate(and equally the birth rate), ω is the proportion of failure immunization, υ is the proportion of children born to carrier mothers who have been infected, ε is the loss of immunity rate, β is the transmission coefficient, α is the infectiousness of the chronic carriers relative to acute infections, σ is the rate of exposed individuals becoming acute infectious individuals, δ is the rate of the exposed individuals becoming chronic carriers, q is the proportion of acute infection develops to chronic carriers , γ_1 is the rate of moving from acute class to chronic or recovery class, γ_2 is the vaccination rate, γ_3 is the rate of moving from chronic carrier to recovery.We assume all the newborns are vaccinated within 24 hours after birth, all the parameters are nonnegative.

Because R appears only in the fifth equation of the system(1), we can discuss the following reduced system:

$$\begin{aligned}
\frac{dS}{dt} &= \mu\omega(1-\nu C)+\varepsilon V-\beta(I+\alpha C)S-\gamma_2 S-\mu S,\\
\frac{dE}{dt} &= \beta(I+\alpha C)S-\sigma E-\delta E-\mu E,\\
\frac{dI}{dt} &= \sigma E-\gamma_1 I-\mu I,\\
\frac{dC}{dt} &= \delta E+q\gamma_1 I-\mu\omega\nu C-\gamma_3 C-\mu C,\\
\frac{dV}{dt} &= \mu(1-\omega)+\gamma_2 S-\varepsilon V-\mu V.
\end{aligned} \tag{2}$$

For the biological sense,

$$\Omega=\left\{(S,E,I,C,V)\middle|\begin{array}{l}S,E,I,C,V\ge 0,\\ S+E+I+C+V\le\omega\end{array}\right\}$$

is a positive invariant set of the system(2).

For convenience, let $a_1=\gamma_2+\mu, a_2=\sigma+\delta+\mu,$

$$a_3=\gamma_1+\mu, a_4=\gamma_3+\mu-\mu\omega\nu,\ \ a_5=\varepsilon+\mu.$$

III. BASIC REPRODUCTION NUMBER AND EQUILIBRIUM

System (2) have two equilibrias in Ω : the disease-free equilibria $P^0=\left(S^0,0,0,0,V^0\right)$, where

$$S^0=\frac{\varepsilon+\mu\omega}{\varepsilon+a_1} \qquad V^0=\frac{a_1-\mu\omega}{a_1+\varepsilon}$$

If $R_0>1$, the endemic equilibria $P^*=(S^*,E^*,I^*,C^*,V^*)$

$$S^*=\frac{a_2a_3a_4}{\beta\sigma a_4+\beta\alpha\sigma a_3+\beta\alpha\sigma q\gamma_1}=\frac{S^0}{R_0}$$

$$E^*=\frac{a_3a_4}{a_3\delta+q\gamma_1\sigma}C^* \qquad I^*=\frac{a_4\sigma}{a_3\delta+q\gamma_1\sigma}C^*$$

$$C^*=\frac{(\varepsilon+a_1)\mu S^0}{a_5\mu\omega\nu(a_3\delta+q\gamma_1\sigma)+a_2a_3a_4a_5}\left(1-\frac{1}{R_0}\right)$$

$$V^*=\frac{\mu(1-\omega)+\gamma_2S^*}{a_5}$$

Using the notation in van den Driessche and Watmough (2002) [6], we obtain the basic reproduction number R_0

$$F=\begin{pmatrix}0 & \beta S^0 & \beta\alpha S^0\\ 0&0&0\\0&0&0\end{pmatrix}, V=\begin{pmatrix}a_2&0&0\\-\sigma&a_3&0\\-\delta&-q\gamma_1&a_4\end{pmatrix}$$

$$R_0=\rho(FV^{-1})=\frac{a_4\beta\sigma S^0+\beta\alpha\sigma q\gamma_1S^0+a_3\beta\alpha\delta S^0}{a_2a_3a_4}.$$

IV. STABILITY OF EQUILIBRIUM

Theorem 4.1 For the system (2.2)

(1) If $R_0<1$,there is no positive equilibrium,and the disease-free equilibrium P^0 is locally stable.

(2)If $R_0>1$,the disease free equilibrium is unstable, the endemic equilibrium P^* exists, and it is locally stable.

Proof: The Jacobian matrix at P^0 is

$$J(P^0)=\begin{pmatrix}-a_1&0&-\beta S^0&-\beta\alpha S^0-\mu\omega\nu&\varepsilon\\0&-a_2&\beta S^0&\beta\alpha S^0&0\\0&\sigma&-a_3&0&0\\0&\delta&q\gamma_1&-a_4&0\\\gamma_2&0&0&0&-a_5\end{pmatrix}$$

The characteristic equation at P^0 is as follow,

$$\left|\lambda E-J(P^0)\right|=\left[(\lambda+a_1)(\lambda+a_5)+\gamma_2\varepsilon\right]\left|A\right|,$$

$$A=\begin{pmatrix}\lambda+a_2&-\beta S^0&-\beta\alpha S^0\\-\sigma&\lambda+a_3&0\\-\delta&-q\gamma_1&\lambda+a_4\end{pmatrix}$$

Let $f(\lambda)=(\lambda+a_1)(\lambda+a_5)+\gamma_2\varepsilon=\lambda^2+(a_1+a_5)\lambda+a_1a_5+\gamma_2\varepsilon,$ if $\nabla=(a_1+a_5)^2-4(a_1a_5+\gamma_2\varepsilon)\ge 0,$ there are two solutions, besides, $a_1a_5+\gamma_2\varepsilon>0, a_1+a_5>0,$ therefore, if there exist solutions,they must be negative.

Let $g(\lambda)=|A|=\lambda^3+l_1\lambda^2+l_2\lambda+l_3$, where

$$l_1=a_2+a_3+a_4>0\,,$$
$$l_2=a_2a_3+a_2a_4+a_3a_4-\beta\sigma S^0-\beta\alpha\delta S^0>0,$$
$$l_3=a_2a_3a_4-a_4\beta\sigma S^0-a_3\beta\alpha\delta S^0-\beta\alpha\sigma q\gamma_1S^0=a_2a_3a_4(1-R_0)>0$$

When $R_0<1$, we have $\frac{a_4\beta\sigma S^0+\beta\alpha\sigma q\gamma_1S^0+a_3\beta\alpha\delta S^0}{a_2a_3a_4}<1$,

$$\frac{a_3\beta\alpha\delta S^0}{a_2a_3a_4}<1, \frac{a_4\beta\sigma S^0}{a_2a_3a_4}<1$$

$$\begin{aligned}
l_1l_2-l_3 &= (a_2a_3+a_2a_4+a_3a_4)(a_2+a_3)+(a_2a_4+a_3a_4)a_4\\
&-(a_2+a_3)\beta\sigma S^0-(a_2+a_4)\beta\alpha\delta S^0+\beta\alpha\sigma q\gamma_1 S^0\\
&>2a_2a_3a_4+a_3^2a_4+a_3a_4^2>0.
\end{aligned}$$

Therefore, by Routh-Hurwitz criteria, all roots have negative real parts, and P^0 is locally stable.

Next we will discuss the properties of the endemic equilibrium $P*$,the jacobian matrix at P^* is $J(P^*)$

$$J(P^*)=\begin{pmatrix} -\beta(I^*+\alpha C^*)-a_1 & 0 & -\beta S^* & -\beta\alpha S^*-\mu\omega\nu & \varepsilon \\ \beta(I^*+\alpha C^*) & -a_2 & \beta S^* & \beta\alpha S^* & 0 \\ 0 & \sigma & -a_3 & 0 & 0 \\ 0 & \delta & q\gamma_1 & -a_4 & 0 \\ \gamma_2 & 0 & 0 & 0 & -a_5 \end{pmatrix}$$

We make an elementary row-transformation for $J(P^*)$, and we obtain the following matrix J^*.

$$J^*=\begin{pmatrix} -\beta(I^*+\alpha C^*)-a_1 & 0 & -\beta S^* & -\beta\alpha S^*-\mu\omega\nu & \varepsilon \\ 0 & -a_2 & M_1 & \alpha M_1-\mu\omega\nu M_2 & \varepsilon M_2 \\ 0 & 0 & -a_3+\frac{\sigma}{\sigma_2}M_1 & \frac{\sigma}{\sigma_2}(\alpha M_1-\mu\omega\nu M_2) & \frac{\sigma\varepsilon}{\sigma_2}M_2 \\ 0 & 0 & 0 & M_3-\mu\omega\nu M_4 & \varepsilon M_4 \\ 0 & 0 & 0 & 0 & M_5 \end{pmatrix}$$

Where

$$M_1=\frac{a_1\beta S^*}{\beta(I^*+\alpha C^*)+a_1}, M_2=\frac{\beta(I^*+\alpha C^*)}{\beta(I^*+\alpha C^*)+a_1}$$

$$M_3=-a_4+\alpha M_1(\delta+\frac{a_2q\gamma_1+\delta M_1}{a_2a_3-\sigma M_1}),$$
$$M_4=-\frac{\delta}{a_2}M_2+\frac{\delta}{a_2}\frac{a_2q\gamma_1+\delta M_1}{a_2a_3-\sigma M_1},$$
$$M_5=-\frac{\gamma_2(\beta\alpha S^*+\mu\omega\nu)}{\beta(I^*+\alpha C^*)+a_1}-\frac{\gamma_2\beta S^*}{\beta(I^*+\alpha C^*)+a_1}\frac{\varepsilon M_4}{\mu\omega\nu M_4-M_3}$$

The eigenvalues are:

$$\lambda_1=-\beta(I^*+\alpha C^*)-a_1<0, \lambda_2=-a_2<0,$$
$$\lambda_3=-a_3+\frac{\sigma}{a_2}M_1, \lambda_4=M_3-\mu\omega\upsilon M_4, \lambda_5=M_5.$$

Next we will check $\lambda_3,\lambda_4,\lambda_5<0$. Since P^* is the solution of (2.2), then we obtain $a_2=\frac{\beta(I^*+\alpha C^*)S^*}{E^*}, a_3=\frac{\sigma E^*}{I^*}$,

$$\lambda_3=-\frac{\sigma E^*}{I^*}+\frac{\sigma E^*}{\beta(I^*+\alpha C^*)S^*}\frac{a_1\beta S^*}{\beta(I^*+\alpha C^*)+a_1}$$

$$\lambda_3<0\Leftrightarrow\frac{a_1I^*}{[\beta(I^*+\alpha C^*)+a_1](I^*+\alpha C^*)}<1\Leftrightarrow\beta(I^*+\alpha C^*)^2+a_1\alpha C^*>0,$$

it holds as the endemic equilibrium P^* exists, at the same time we can know $M_4>0$. In addition, C^* and I^* satisfy

$$q\gamma_1=\frac{a_4C^*}{I^*}-\frac{\delta a_3}{\sigma}, a_4=\frac{\delta E^*+q\gamma_1 I^*}{C^*}$$
$$\lambda_4=M_3-\mu\omega\upsilon M_4=-a_4+\frac{1}{a_2}(\alpha M_1-\mu\omega\upsilon M_2)(\delta+\sigma\frac{a_2q\gamma_1+\delta M_1}{a_2a_3-\sigma M_1})$$

As the abo v e, we can obtain that $\lambda_4<0$,so $\mu\omega\upsilon M_4-M_3>0$, due to $M_4>0$ at the same time, we have $\lambda_5=M_5<0$. Therefore, all eigenvalues are negative, and we have the P^* is locally asymptotically stable.

In order to study the global stability of the disease-free equilibrium, we apply the novel approach in Kamgang and Sallet (2008)[7].

Before proving the main theorem we first give a lemma.

Lemma 4.1 If the following hypothesis $H_1 - H_5$ are satisfied, the disease-free equilibrium (DFE) is globally asymptotically stable for system

$$\dot{X}_1=A_1(X)(X_1-X_1^*)+A_{12}(X)X_2$$
$$\dot{X}_2=A_2(X)X_2$$

On the positively invariant set Ω, where $X=(X_1,X_2)$ and $X^*=(X_1^*,0)$ denote a disease-free equilibrium(DFE) of the system above.The variable X_1 denotes the numbers in the different compartments of susceptible, immune, recovered individuals ,in other words all the individuals who are not infected and who are not transmitting the disease. The varibal X_2 denotes the number of infected individuals, For example, exposed individuals, infectious, carrying individuals and so on.

H_1: The system is defined on a positively invariant set Ω of the nonnegative orthant. The system is dissipative on Ω

H_2: The sub-system $\dot{X}_1=A_1(X,0)(X-X_1^*)+A_{12}(X)X_2$ is globally asymptotically stable at the equilibrium X_1^* on the canonical projection of Ω.

H_3: The matrix is Metzler and irreducible for any given $X\in\Omega$.

H_4: There exists an upper-bound matrix $\bar{A}_2$ for $\Re=\{A_2(X)/X\in\Omega\}$ with the property that $\bar{A}_2=\max_\Omega\Re$ then for any $\bar{X}\in\Omega$,such that $\dot{X}_2=A_2(X)X_2$ (i. e, the point where the maximum is realized are contained in the disease-free sub-manifold).

H_5: $\alpha(\bar{A}_2)\le 0$,where $\alpha(\bar{A}_2)\le 0$ is spectral bound of $\bar{A}_2$.

Using the lemma (4.1), we can obtain that DFE is globally asymptotically stable ,next, we will prove that.

Proof: Set $X_1 = (S,V)^T, X_2 = (E,I,C)^T, X = (X_1, X_2)$ The invariant domain Ω is obviously positively compact set. $\dot{X}_1 = A_1(X)(X_1 - X_1^*) + A_{12}(X)X_2$

$$A_1(X) = \begin{pmatrix} -a_1 & \varepsilon \\ \gamma_2 & -a_5 \end{pmatrix}, \quad X_1^* = \begin{pmatrix} \dfrac{\varepsilon + \mu\omega}{\varepsilon + a_1} \\ \dfrac{a_1 - \mu\omega}{a_1 + \varepsilon} \end{pmatrix}$$

This is a linear system which is globally asymptotically stable at X_1^* , the hypothesis H_1,H_2 are satisfied.

$$\dot{X}_2 = A_2(X)X_2$$

$$A_2(X) = \begin{bmatrix} -a_2 & \beta S & \beta\alpha S \\ \sigma & -a_3 & 0 \\ \delta & q\gamma_1 & -a_4 \end{bmatrix}$$

As required by hypothesis H_3,for any $X \in \Omega$ the matrix $A_2(X)$ is Metzler and ireducible.

Now,let we check hypothesis H_4.There is a maximum which is uniquely realized in Ω when $x \in (S^0, V^0)$,this corresponds to P^0 ,the maximum $A_2(\bar{X})$ is given by

$$A_2(\bar{X}) = \begin{bmatrix} -a_2 & \beta S^0 & \beta\alpha S^0 \\ \sigma & -a_3 & 0 \\ \delta & q\gamma_1 & -a_4 \end{bmatrix}$$

The hypothesis H_5 requires that $\alpha(\bar{A}_2) \le 0$. Writing $A_2(\bar{X})$ as a block matrix

$$A_2(\bar{X}) = \begin{pmatrix} A & B \\ C & D \end{pmatrix}$$

where

$$A = -a_2, B = (\beta S^0, \beta\alpha S^0), \; C = \begin{pmatrix} \sigma \\ \delta \end{pmatrix}, D = \begin{pmatrix} -a_3 & 0 \\ q\gamma_1 & -a_4 \end{pmatrix}.$$

Since A is already a Metzler stable matrix, the condition $\alpha(A_2(\bar{X})) \le 0$ is equal to $\alpha(D - CA^{-1}B) \le 0$

$$M = D - CA^{-1}B = \begin{pmatrix} -a_3 + \dfrac{\sigma}{a_2}\beta S^0 & \dfrac{\sigma}{a_2}\beta\alpha S^0 \\ q\gamma_1 + \dfrac{\delta}{a_2}\beta S^0 & \dfrac{\delta}{a_2}\beta\alpha S^0 \end{pmatrix}.$$

The characteristic equation of M is given by

$$|\lambda E - M| = \lambda^2 + d_1\lambda + d_0$$

$$d_1 = \frac{1}{a_2}(a_2a_3 + a_2a_4 - \beta\sigma S^0 - \beta\alpha\delta S^0),$$

$$d_0 = \frac{1}{a_2}(a_2a_3a_4 - a_3\beta\alpha\delta S^0 - a_4\beta\sigma S^0 - \beta\alpha\sigma q\gamma_1 S^0).$$

When $R_0 < 1$, we have $d_1, d_0 > 0$ .It follows from the Routh-Hurwitz criterion that the two eigenvalues have negative real part if and only if $R_0 < 1$. When $R_0 = 1$, one eigenvalue is zero and another is negative real part root. Hence, M is a stable Metzler matrix if and only if $R_0 \le 1$, that is $\alpha(A_2) \le 0$ .We have seen that the hypotheses all are satisfied. Then by Lemma 4.1, we get the theorem 4.2.

Theorem 4.2 For the system (2.2), the disease-free equilibrium P^0 is globally asymptotically stable if $R_0 < 1$.

V. CONCLUSIONS

Hepatitis B is one of the top three infectious diseases reported by the Ministry of Health of China. Almost a third of the people infected with HBV worldwide in China. In this paper, we propose a mathematical model to study the transmission dynamics. We discussed the stability of the disease-free and disease-endemic equilibrium of the model. By analysis, we obtain that vaccine is important to control the hepatitis B virus. At last, we proposed a new method to prove the globally stability of disease-free equilibrium, the method effective for the high dimension ordinary differential equations.

ACKNOWLEDGMENTS

This work is fully supported by the National Sciences Foundation of China(11301491), the Top Young Academic Leaders of Higher Learning Institutions of Shanxi and the National Sciences Foundation of Shanxi Province (2012011002-1).

REFERENCES

[1] C. J. Long,,H .Qi and S.H. Huang, “Mathematical modeling of cytotoxic lymphocytemediated Immune response to hepatitis B virus infection, ” Journal of Biomedicine and Biotechnology,vol.2,pp.160-169,2008.

[2] S. Eikenberry,J.D. Nagy, “The dynamic of a delay model of hepatitis B virus infection with logistic Hepatocyte growth,”Mathematical Biosciences and Engineering, vol.6),pp.283-299, 2009.

[3] J.Q. Li,K.F. Wang, and Y.L. Yang, “Dynamical behaviors of an HBV infection model with logistic hepatocyte growth, ” Mathematical and computer modeling,vol.54 , pp.704-711,2011.

[4] C.L.Cao, “The difference between acute and chronic hepatitis B ,Liver Doctor,vol.4, pp.17-18, 2010.

[5] J.C.Kamgang and G.Sallet, “Computation of threshold conditions for epidemiological models and global stability of the disease-free equilibrium(DFE), ”Mathematical Biosciences, vol.213, pp.1-12,2008.

[6] G.F.Medley,N.A.Lindop,W.J.Edmunds,Heterogeneity,catastrophic dynamics and control,Nat.Med.,7(2001),619-624.

[7] Van den Driessche,P.and Watmough,J., “Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission”,Math. Biosci, vol.80,pp.290-292,2002.