

แบบจำลองทางคณิตศาสตร์ผลกระทบของการฉีดวัคซีน ป้องกันการติดเชื้อไวรัสตับอักเสบบีของประเทศไทย

Mathematical Modeling the Effects of Vaccination on HBV Infection in Thailand

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บทคัดย่อ

โรคไวรัสตับอักเสบบี เกิดจากการติดเชื้อไวรัสที่เซลล์ตับ โดยการติดเชื้อมีทั้งหมด 2 แบบได้แก่ การติดเชื้อแบบเฉียบพลันและการติดเชื้อแบบเรื้อรัง ซึ่งการติดเชื้อแบบเรื้อรังเป็นสาเหตุที่ทำให้เกิดโรคมะเร็งตับ ตับแข็ง และทำให้เกิดการเสียชีวิตในที่สุด ทั่วโลกมีผู้ติดเชื้อไวรัสตับอักเสบบี ประมาณ 350 ล้านคน และร้อยละ 75 เป็นคนเอเชีย และในประเทศไทยมีผู้ติดเชื้อนี้ประมาณร้อยละ 3 ของประชากรทั้งหมด ในปัจจุบันโรคไวรัสตับอักเสบบีมีแนวโน้มลดลงเนื่องจากการฉีดวัคซีนเพื่อป้องกัน อย่างไรก็ตามจำนวนผู้ที่ติดเชื้อนี้ก็ยังมีปริมาณไม่น้อย ดังนั้นผู้วิจัยจึงทำการศึกษากการแพร่ระบาดของโรคไวรัสตับอักเสบบีที่เกี่ยวข้องกับการฉีดวัคซีนในประเทศไทยโดยการสร้างและวิเคราะห์แบบจำลองทางคณิตศาสตร์ SVIR ซึ่งในงานวิจัยนี้ ผู้วิจัยได้วิเคราะห์แบบจำลองทั้งทางทฤษฎีและเชิงตัวเลข พร้อมทั้งหาค่า R_0 เพื่อตรวจสอบความเสถียรของแบบจำลองและนำไปสู่แนวทางการควบคุมการระบาดของโรคโดยการใช้วัคซีน เพื่อลดจำนวนของผู้ป่วยโรคไวรัสตับอักเสบบีในประเทศไทย

คำสำคัญ : โรคไวรัสตับอักเสบบี วัคซีน แบบจำลองทางคณิตศาสตร์ การวิเคราะห์เชิงตัวเลข

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Abstract

Hepatitis B virus (HBV) infection is a disease characterized by inflammation of the liver. There are two types of hepatitis B virus infection, acute hepatitis B and chronic hepatitis B. The chronic hepatitis B is the most significant factor leading to liver cancer and cirrhosis. There are approximately 350 million people infected with the HBV worldwide, and 75% of them are from Asia. In Thailand, there are approximately 3% of the populations who are infected by HBV. Nowadays, the number of people who are infected by HBV is decreased due to the present of vaccination. However, the number of infected people is still at high level and could be further reduced. Therefore, in this research we study and explore further by constructing and analyzing mathematical models relating to vaccination in the form of SVIR models. Numerical analysis is performed to explore the effect of some particular parameters to the overall dynamics. The basic reproduction number is also calculated. This is to find some approaches to control the epidemic or reduce number of patients with HBV in Thailand.

Keywords : hepatitis B, vaccine, mathematical model, numerical analysis

Introduction

Hepatitis B virus (HBV) infection is a serious health problem worldwide especially in Western Pacific and South-East Asia. There are two types of HBV which are acute and chronic one and it could lead to a high risk of death from cirrhosis of the liver including liver cancer (Richard, 2011; WHO, 2013; Henry, 2014). Infection of the hepatitis B virus can be transmitted in a variety of ways and is thought to be 100 times more infectious than HIV (Foundation for Liver Research, 2004). In general, anyone can get hepatitis B by contacting the blood or other body fluid from infected people, through injecting drug by sharing syringes, unprotected sexual intercourse and the most common way of infection is the vertical transmission from mother to infant at birth (Lim, 1997; Behrouz, 2011; NIDDK, 2012). The acute hepatitis B will last for a short term, the infection sometimes clears up because your body is able to fight off the infection and get rid of the virus. Most healthy adults and children older than 5 years old who get hepatitis B infection would get better without treatment. The chronic hepatitis B will last for more than six months. This type of hepatitis B will occur when the body cannot get rid of the hepatitis B virus which usually has no symptom until signs of liver damage appear. In the case without treatment, chronic hepatitis B can cause cirrhosis and liver cancer that lead to liver failure and death (WHO, 2013).

Currently, there is a high number of people who get infected with the hepatitis B virus worldwide, approximately 350 million people remain chronically infected carrier of the disease and 75% of them are in Asia (Bumrungrad, 2008). In addition, more than 686,000 people die yearly worldwide due to the hepatitis B virus infection (WHO, 2013). However, most of new infections could be prevented through vaccination. A vaccine against hepatitis B has been available since 1982. The vaccine is 95% effective in preventing infection (WHO, 2013). Worldwide, over 150 countries have implemented universal vaccination of newborns and adolescents.

For Thailand, there are approximately 3% of population who get HBV infected. At the present time, generally the HBV infection seems to be in the downward trend due to the fact that vaccine can effectively control the spread of the disease. Further, HBV vaccination can reduce the incidence of liver cancer (Chang, 1997; Chang, 2016; Foundation for Liver Research, 2004). Hence, it is essential to continue implementing HBV vaccination to reduce further disorders.

In this paper, we mainly focus on the infection in the form of chronic hepatitis B and therefore have extended a mathematical model of Dontwi *et al.*, 2014 by adding an HBV vaccination together with adapting the work by Kimbir *et al.*, 2014 to explore the overall HBV epidemic dynamics. We have analyzed the model both theoretical and numerical ways. Stability analysis is carried out and the basic reproduction number under vaccination (R_v) is determined to get some relevant input factors that could lead to a better control of HBV in Thailand.

Methods

Model Formulation

The transmission dynamics for HBV is developed, the population is divided into four subgroups at time t : S is the number of susceptible individuals, V is the number of vaccinated individuals, I is the number of HBV infected individuals and R is the number of recovered individuals from infection individuals, with the total population size $N(t)$ where $N = S + V + I + R$. The schematic diagram of this model is shown below.

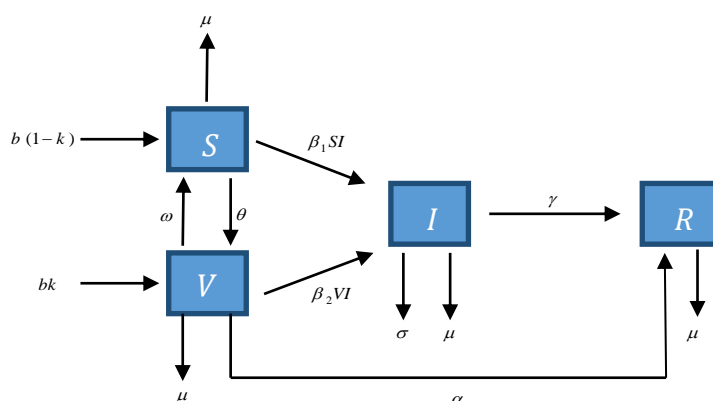


Figure1 A schematic diagram of HBV transmission dynamics under application of vaccination. S, V, I and R denote four compartment of susceptible, vaccinated, HBV infected and recovered individuals, respectively. The bk denotes the recruitment rate into vaccinated compartment where $b(1-k)$ is of susceptible compartment. $\beta_1 SI$ and $\beta_2 VI$ indicate the transmission from compartment S to I and from V to I , respectively. The ω denotes the vaccine efficacy wanes rate from V to S , whereas susceptible individuals subsequently obtain vaccination with a rate θ . α denotes a rate of vaccinated move to recovered compartment by vaccination. γ shows individuals' recovery and move from infected to recovered class, where σ denotes the death caused by HBV infection. Each compartment has its own natural death rate μ .

The corresponding differential equations are

$$\frac{dS}{dt} = b(1 - k) + \omega V - \mu S - \theta S - \beta_1 SI \quad (1)$$

$$\frac{dV}{dt} = bk + \theta S - \omega V - \mu V - \alpha V - \beta_2 VI \quad (2)$$

$$\frac{dI}{dt} = \beta_1 SI + \beta_2 VI - \mu I - \sigma I - \gamma I \quad (3)$$

$$\frac{dR}{dt} = \gamma I + \alpha V - \mu R \quad (4)$$

with initial condition

$$S(0) \geq 0, V(0) \geq 0, I(0) \geq 0, R(0) \geq 0 \quad (5)$$

where β_1 is the transmission rate of population without vaccination, β_2 is the transmission rate of population with vaccination, θ is the rate of susceptible who are subsequently vaccinated, α is the rate at which vaccination work efficiently, γ is the recovery rate of infected population, σ is the death rate caused by HBV infection, ω is the vaccine efficacy wanes rate, μ is the natural death rate of human population in Thailand, $b(1 - k)$ is the recruitment rate into susceptible population and bk is the recruitment rate into the vaccinated class. The total dynamics of human population is given by

$$\frac{dN}{dt} = b - \mu N - \sigma I. \quad (6)$$

1. Boundary of Solution

In this section, we determine the boundary of the solutions of system of equations (1)-(4). Consider

$$\frac{dN}{dt} = b - \mu N - \sigma I, \text{ we then obtain } \frac{dN}{dt} \leq b - \mu N. \text{ By taking integration to both sides of inequality, it}$$

gives $N \leq \frac{b}{\mu} - \left(\frac{b}{\mu} - N_0 \right) e^{-\mu t}$. As $t \rightarrow \infty$, then $N \rightarrow \frac{b}{\mu}$, implying that $0 \leq N \leq \frac{b}{\mu}$. Therefore, the

feasible solution set of system enter the region as $\Phi = \left\{ (S, V, I, R) \in \mathfrak{R}_+^4 : N \leq \frac{b}{\mu} \right\}$. Hence, every

solution with condition to \mathfrak{R}_+^4 , the region is positively invariant. It is sufficient to study the dynamics of the HBV model in Φ .

2. Equilibrium Points of the Model

Disease-free equilibrium state: this is when there is no infected individual,

$$E^0 = (S^0, V^0, I^0) = \left(\frac{b(1 - k) + \omega V^0}{\mu + \theta}, \frac{b(k\mu + \theta)}{(\mu\omega + (\mu + \alpha)(\mu + \theta))}, 0 \right)$$

The endemic equilibrium state: we obtain $E^* = (S^*, V^*, I^*)$ where $S^* = \frac{\mu + \sigma + \gamma - \beta_2 V^*}{\beta_1}$,

$$V^* = \frac{bk + \theta(\mu + \sigma + \gamma)}{\beta_1(\omega + \alpha + \mu + \beta_2 I^* + \frac{\beta_2 \theta}{\beta_1})} \text{ and}$$

$$I^* = \frac{(bk + \theta(\frac{\mu + \sigma + \gamma}{\beta_1}))(\omega\beta_1 - \mu\beta_2 + \theta\beta_2) - ((\mu + \alpha + \gamma)(\mu + \theta) + (1 - k)b\beta_1)(\omega + \alpha + \mu + \frac{\beta_2 \theta}{\beta_1})}{((\mu + \alpha + \gamma)(\mu + \theta) - b\beta_1(1 - k) - \beta_2(bk + \theta(\frac{\mu + \sigma + \gamma}{\beta_1})))\beta_1}.$$

3. The Basic Reproduction Number (R_v)

Using the next-generation operator approach (Diekmann, 1990; van den Driessche, 2002), we then obtain the basic reproduction number under vaccination (R_v) as

$$R_v = \frac{\beta_1 \left(\frac{b(1-k) + \omega V}{\mu + \theta} \right) + \beta_2 \left(\frac{b(k\mu + \theta)}{(\mu\omega + (\mu + \alpha)(\mu + \theta))} \right)}{\mu + \sigma + \gamma}.$$

In the absence of vaccination, $k = \theta = \omega = \alpha = 0$, we then obtain the basic reproduction number (R_0) as

$$R_0 = \frac{\beta_1 b}{\mu(\mu + \sigma + \gamma)}.$$

4. Stability Analysis

The local stability of this model is determined by constructing Jacobian matrix of the system of equations (1)-(3):

$$J(S, V, I) = \begin{bmatrix} -\mu - \theta - \beta_1 I & \omega & -\beta_1 S \\ \theta & -\omega - \mu - \alpha & -\beta_2 V \\ \beta_1 I & \beta_2 I & \beta_1 S + \beta_2 V - \mu - \sigma - \gamma \end{bmatrix}.$$

Theorem 1. (local stability at E^0) If $R_v < 1$, the disease-free equilibrium point (E^0) is locally asymptotically stable. If $R_v > 1$, the disease-free equilibrium point (E^0) is unstable.

Proof. The Jacobian matrix of the system of equations (1)-(3) at E^0 is

$$J(S^0, V^0, I^0) = \begin{bmatrix} -\mu - \theta & \omega & -\beta_1 S^0 \\ \theta & -\omega - \mu - \alpha & -\beta_2 V^0 \\ 0 & 0 & \beta_1 S^0 + \beta_2 V^0 - \mu - \sigma - \gamma \end{bmatrix}.$$

By finding the characteristic equation from $\det(J(E^0) - \lambda I) = 0$ where I is the identity matrix, we obtain

$$(\beta_1 S^0 + \beta_2 V^0 - \mu - \sigma - \gamma - \lambda)(\lambda^2 + (2\mu + \theta + \omega + \alpha)\lambda + (\mu(\mu + \omega + \alpha + \theta) + \alpha\theta)) = 0.$$

Hence, $\lambda_1 = \beta_1 S^0 + \beta_2 V^0 - \mu - \sigma - \gamma$ and the latter term is considered in the form of $\lambda^2 + a_1 \lambda + a_2 = 0$, we have $a_1 = 2\mu + \theta + \omega + \alpha > 0$, $a_2 = \mu(\mu + \omega + \alpha + \theta) + \alpha\theta > 0$, satisfying the Routh-Hurwitz criteria for $n = 2$ that are $a_1 > 0$ and $a_2 > 0$. Therefore, the disease-free equilibrium point at E^0 is locally asymptotically stable when $\beta_1 S^0 + \beta_2 V^0 < \mu + \sigma + \gamma$ (resulting in $\lambda_1 < 0$) that is when $R_v < 1$, whereas when $R_v > 1$, resulting in $\lambda_1 > 0$, the disease-free equilibrium point is unstable.

Theorem 2. (local stability at E^*) When $R_v > 1$, the endemic equilibrium point (E^*) is stable when satisfies the Routh-Hurwitz criteria.

Proof. The endemic equilibrium point (E^*) exists when $R_v > 1$ and the Jacobian matrix of the system of equations (1)-(3) at E^* is

$$J(S^*, V^*, I^*) = \begin{bmatrix} -\mu - \theta - \beta_1 I^* & \omega & -\beta_1 S^* \\ \theta & -\omega - \mu - \alpha & -\beta_2 V^* \\ \beta_1 I^* & \beta_2 I^* & 0 \end{bmatrix}.$$

By finding the characteristic equation from $\det(J(E^*) - \lambda I) = 0$ where I is the identity matrix, we obtain

$$\lambda^3 + (2\mu + \alpha + \omega + \theta + \beta_1 I^*)\lambda^2 + (\mu(\omega + \mu + \alpha + \theta) + \theta(2\omega + \alpha) + \beta_1 I^*(\omega + \mu - \beta_1 S^*))\lambda + \beta_1 I^*(\beta_2 V^*(\mu + \theta + \omega + \beta_1 I^*) - S^*(\beta_2 \theta + \beta_1(\omega + \mu + \alpha))) = 0.$$

Consider it in the form of $\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0$, we have $a_1 = (2\mu + \alpha + \omega + \theta + \beta_1 I^*) > 0$.

Therefore, by the Routh-Hurwitz criteria for $n = 3$ ($a_1 > 0$, $a_3 > 0$ and $a_1 a_2 > a_3$), the endemic equilibrium point at E^* is stable when

$$a_3 = \beta_1 I^*(\beta_2 V^*(\mu + \theta + \omega + \beta_1 I^*) - S^*(\beta_2 \theta + \beta_1(\omega + \mu + \alpha))) > 0 \text{ and } a_1 a_2 > a_3 \text{ i.e.}$$

$$(2\mu + \alpha + \omega + \theta + \beta_1 I^*)(\mu(\omega + \mu + \alpha + \theta) + \theta(2\omega + \alpha) + \beta_1 I^*(\omega + \mu - \beta_1 S^*)) >$$

$$\beta_1 I^*(\beta_2 V^*(\mu + \theta + \omega + \beta_1 I^*) - S^*(\beta_2 \theta + \beta_1(\omega + \mu + \alpha))).$$

Numerical Simulation

In this section, the system of equations (1)-(4) solved numerically. The parameters within this model are chosen as appropriate where some of them are the data of Thai population and are shown in Table 1. The numerical results are shown in Figure 2 and Figure 3.

Table 1 Parameters values used in numerical study

Parameter	Description	Value	Reference
b	The recruitment rate of human population in Thailand	2.298	National Statistical Office, Thailand, 2015
μ	The natural death rate of human population in Thailand	0.13281	National Statistical Office, Thailand, 2015
β_1	The transmission rate of population without vaccination	0.1	Variable
β_2	The transmission rate of population with vaccination	0.00001	Variable
θ	The rate of susceptible who are subsequently vaccinated	0.025	Estimate
α	The rate at which vaccination work efficiently	0.5	Estimate
γ	The recovery rate of infected population	0.1	Estimate
σ	The death rate caused by HBV infection	0.00001	Bureau of Epidemiology, 2015
ω	The vaccine efficacy wanes rate	0.1	Zou et al., 2009
k	Recruitment rate into the vaccinated class	0.5	Estimate

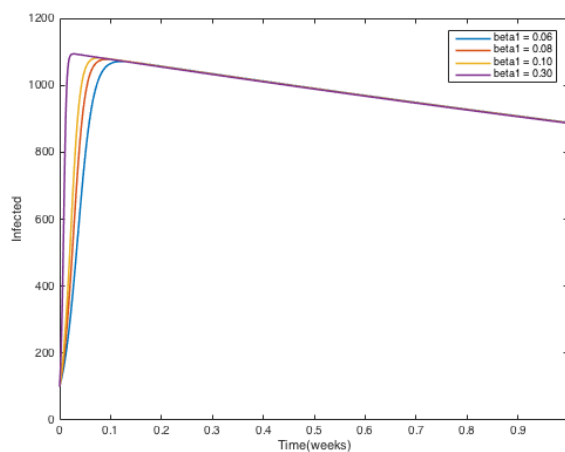


Figure 2 Numerical solutions of systems of equations (1)-(4) obtained using parameters: $b = 2.298$, $\mu = 0.13281$, $\theta = 0.025$, $\alpha = 0.5$, $\beta_2 = 0.00001$, $k = 0.5$, $\omega = 0.1$, $\sigma = 0.00001$ and $\gamma = 0.1$ when β_1 varies.

Figure 2 shows that when the transmission rate of population without vaccination (β_1) increases the number of infected increase and the epidemic time is faster than those of lower rate of β_1 . Furthermore, with lower β_1 , the result shows that the infected trend reaches the equilibrium value faster than those of greater β_1 . Therefore, we obtain that β_1 has a key effect on both the number of infected individuals and the time the epidemic occurs.

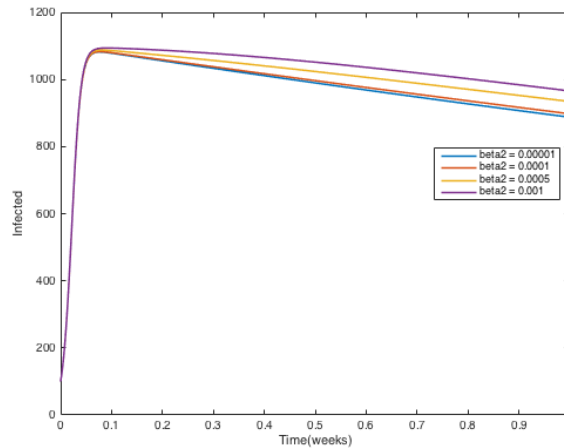


Figure3 Numerical solutions of system of equations (1)-(4) obtained using parameters: $b = 2.298$, $\mu = 0.13281$, $\theta = 0.025$, $\alpha = 0.5$, $\beta_1 = 0.1$, $k = 0.5$, $\omega = 0.1$, $\sigma = 0.00001$ and $\gamma = 0.1$ when β_2 varies.

Figure 3 shows that when the transmission rate of population with vaccination (β_2) increases, the number of infected at the peak and the time for the peak to occur remain the same. However, the trend after reaching the peak of infected individuals at lower β_2 tends to decrease faster than those of higher β_2 . These results demonstrate that β_2 does not have a clear effect on both the number of infected individuals and the epidemic time.

Conclusions

In this paper, we study the effects of vaccination on HBV infection in Thailand by developing $svIR$ model incorporating vital dynamics together with disease induced death. The $svIR$ model is formed by four dimensional differential equations. In order to understand the transmission of HBV, this model was analyzed qualitatively and there are two equilibrium points (disease-free and endemic ones). The basic reproduction

number under vaccination is $R_v = \frac{\beta_1 \left(\frac{b(1-k) + \omega V}{\mu + \theta} \right) + \beta_2 \left(\frac{b(k\mu + \theta)}{(\mu\omega + (\mu + \alpha)(\mu + \theta))} \right)}{\mu + \sigma + \gamma}$ and it

becomes a threshold condition for determining the stability of the model. If $R_v < 1$, the disease-free equilibrium point is locally asymptotically stable, where if $R_v > 1$, it is unstable. As for endemic equilibrium point, it is locally asymptotically stable when it satisfies the Routh-Hurwitz criteria. Furthermore, the numerical

simulations suggest that the transmission rate of population without vaccination (β_1) gives a positive effect on both the number of infected individuals and the epidemic occur time, whereas the transmission rate of population with vaccination (β_2) does not give a clear effect on the number of infected individuals or the epidemic occur time, this confirms the usefulness of vaccination i.e. although β_2 is higher, the peak of the number of infected individuals remain unchanged. Hence, both reducing the transmission rate of population without (β_1) and promoting people to get vaccination seems to be promising approach to lessen the HBV infected individuals. Hence, our model confirms that vaccination can be used to control the number of HBV infected individuals in Thailand.

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