On the sexual transmission dynamics of hepatitis B virus in China

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HIGHLIGHTS

- Sexual transmission is an important route of spread of HBV in China.
- Proposed a compartmental model including under-aged children, male and female adults.
- Studied the effect of sexual transmission on the spread and prevalence of HBV in China.
- Simulated the HBV data reported by the China CDC from 2002 to 2014.
- Immunization of both under-aged children and adults are crucial to control HBV in China.

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ABSTRACT

In a previous study we noticed that there might be co-infections of HBV and HIV by comparing incidence rates of these two diseases in China. The comparisons between the incidence data of HBV and sexually transmitted diseases (including AIDS, HIV, syphilis and gonorrhea) in China demonstrate that sexual transmission is an important route of spread of HBV in China. On the basis of this fact, in this paper we propose a compartmental model including under-aged children, male adults, and female adults. The effect of sexual transmission on the spread and prevalence of HBV in China is studied. The model is employed to simulate the HBV incidence data reported by the Chinese Center for Disease Control and Prevention for under-aged children, adult males, and adult females, respectively. The sensitivity analysis of the basic reproduction number indicates that it is important and crucial to increase the immunization rate for both under-aged children and adults in order to control the transmission of HBV in China. Our study suggests that effective control measures for hepatitis B in China include enhancing public education and awareness about hepatitis B virus, particularly about the fact that hepatitis B is a sexually transmitted disease, and increasing the immunization rate for both under-aged children and adults, especially for those groups of high risk.

1. Introduction

Hepatitis B, caused by the Hepatitis B Virus (HBV), is a major global health problem and the most serious type of viral hepatitis. Worldwide about 240 million people live with chronic infection and an estimation of 780,000 people die each year due to the acute or chronic consequences of hepatitis B (WHO, 2014). It is one of the top three infectious diseases and a leading cause of death in mainland China, as reported by the National Health and Family Planning Commission (the former Ministry of Health) of China. In China, around 130 million people are carriers of HBV, 30 million people are chronically infected, and 300,000 people die of HBV-related diseases annually (Liu et al., 2002; Jia and Zhuang, 2004). Fig. 1 shows the huge numbers of reported infections and deaths related to HBV from 2004 to 2011 reported by Chinese Center for Disease Control and Prevention (CCDC, 2004–2012; Public Health Science Data, 2004–2012).

The sex distributions of HBsAg carriers in Fig. 1(a) indicate that the number of males is obviously more than that of females (London and Drew, 1977). Female-to-male transmission of HBV between spouses appears to be more efficient (Ko et al., 1989). It is easier for

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females than males to recover after they are infected (London and Drew, 1977). On the other hand, the risk of becoming a carrier is also dependent on the age at infection (McLean and Blumberg, 1994; Williams et al., 1996; Zhao et al., 2000; Zou et al., 2010a). Infants infected perinatally (within the first 6 months) have a high probability (0.885) of becoming carriers, but the probability decreases sharply in early childhood age, while the probability for an infected adult is only about 0.1 (Edmunds et al., 1993).

The risk to be infected by hepatitis B is primarily related to sexual, household and perinatal exposure to infected individuals. Till now, there is no effective treatment available for chronic HBV carriers. Immunization with hepatitis B vaccine remains the most important prevention measure. It is known that blood transfusion was the main transmission route of HBV in China 10 years ago, but now the transmission rate by blood transfusion is evidently lower because the government has strengthened the management of blood productions recently. Starting from 2002, the Ministry of Health of China has integrated the infant HepB vaccination into the national immunization program with vaccine provided entirely by the government and it has been free for all newborn babies since 2005. In 2009, it was suggested to retroactively immunize teenagers (younger than 15 years old). Now the incidence in children is much better controlled, but the incidence in adults keeps increasing (see Fig. 2(a)).

It is known that sexual transmission plays an important role in the spread of hepatitis B (Alter et al., 1986, 1989). Struve et al. (1990) observed that heterosexual transmission is a major route of transmission of hepatitis B among adults but homosexual contact is responsible for only about 10% of all cases of hepatitis B. Recently, we proposed in Zou et al. (2010b) a deterministic model to study the transmission dynamics and prevalence of HBV infection in China and gave an approximate basic reproduction number $R_0 = 2.406$ by using the relevant data reported by the Ministry of Health of China, from which we asserted that hepatitis B is endemic in China and its transmission is approaching an equilibrium with the current immunization programme and control measures. Moreover, we noticed that there might be co-infections of HBV and HIV in China by comparing the HIV and HBV incidence rates there. Here we provide comparisons between the incidence of HBV and sexually transmitted diseases (including AIDS, HIV, syphilis and gonorrhea) in China. Fig. 2(a) and (b) present comparisons between HBV and sexually transmitted diseases in adults, which demonstrate that the incidence of both increased in the past few years. Fig. 3 provides a comparison for those diseases in China in 2011 by provinces, which indicates that both HBV and sexually transmitted diseases have high incidence rates in the provinces of Henan, Guangdong, Sichuan, Gansu and Xinjiang. Based on these data and comparisons, we conclude that sexual transmission is an important route of spread of HBV in China.

In this paper we propose a compartmental model, including under-aged children, male adults, and female adults, and study the effect of sexual transmission on the spread and prevalence of HBV in China. Firstly, we use the model to simulate the HBV data reported by the Chinese Center for Disease Control and Prevention (CCDC, 2004–2012) for under-aged children, female adults, and male adults, respectively. Then sensitivity analysis of the basic reproduction number will be carried out in terms of the model parameters, from which effective control measures will be discussed for the spread of HBV in China.
2. The model

Consider a compartmental model with three possible routes of transmission: (i) perinatal and vertical transmission from chronic carrier mothers to their newborn babies; (ii) non-sexual horizontal transmission amongst the whole population; (iii) heterosexual transmission in the adult population. Moreover, for the sake of simplicity we make the following assumptions:

(A1) the sexual transmission in homosexual population is negligible;
(A2) the loss of immunity after immunization is negligible;
(A3) the latent period after being infected is ignored, because the average latent period is about 3 months, quite short in comparison with years of the chronic period;
(A4) the size of female population is equal to that of male population (note that the current male-to-female ratio of population in China is 0.51:0.49, National Health and Family Planning Commission, 2012);
(A5) the under-aged children consist of those under 18 years of age who are not sexually active.

On the basis of the transmission dynamics of hepatitis B virus and Assumptions (A1)–(A5), we divide the population $N(t)$ into the following subgroups: susceptible, acute infected, chronic carrier, and immune.

Susceptible individuals are those who have never been infected with HBV and have never been successfully vaccinated. The numbers of susceptible under-aged children, female adults, and male adults at time $t$ are denoted by $S_u(t)$, $S_f(t)$, and $S_m(t)$, respectively. By assumption (A5), we assume that the growth rate is $\nu = 1/18$ as shown in Table 1. An individual leaves the susceptible compartment for three possible reasons: (a) he/she is infected with HBV with the force of infection $\lambda$, or $\lambda + \lambda_i$, $i = f, m$; (b) he/she dies with the natural mortality rate $\mu_0$; (c) he/she is vaccinated at an average rate $\nu_3$ (for an under-aged child) or $\nu_4$ (for an adult).
The acutely infected individuals are further divided into under-aged children $I_u(t)$, female adults $I_f(t)$, and male adults $I_m(t)$. The only way for under-aged children to enter this compartment is by non-sexual transmission with a force of infection $\lambda$. Female adults and male ones may be infected by either non-sexual contact with a force of infection $\lambda$, or sexual transmission with a force of infection $\lambda_i, i = f, m$. Moreover, the female-to-male transmission of HBV between spouses appears to be more efficient than male-to-female transmission (Ko et al., 1989). Thus, we conclude that $\lambda_m \geq \lambda_f$.

Some individuals who have been acutely infected may fail to clear hepatitis B and become chronic carriers (under-aged children $C_u(t)$, female adults $C_f(t)$, and male adults $C_m(t)$). The probability for one to fail to clear hepatitis B is different by age and gender. The probability for children $q_u$, which reaches as high as 95% is higher than adults, whose average probability of developing into carriers is 0.1 (Edmunds et al., 1993). The probability for men $q_f$ (McLean and Blumberg, 1994). Thus, we make assumptions for $q_u$, $q_f$ and $q_m$ as shown in Table 1.

Based on the above discussion and the forces of infection $\lambda_u$, $\lambda_f$, and $\lambda_m$, we assume the parameters are described in Table 1 and the forces of infection are given as follows:

$$
\begin{align*}
\frac{dS_u}{dt} &= \mu_u(1 - \nu C_f) - (\mu_0 + \lambda + \gamma_S + \psi) S_u, \\
\frac{dI_u}{dt} &= \lambda S_u - (\gamma_1 + \mu_1) I_u, \\
\frac{dC_u}{dt} &= \mu_u C_f + q_u f_f C_f - (\mu_0 + \mu_1 + \gamma_2) C_u, \\
\frac{dR_u}{dt} &= \mu (1 - \omega) + \gamma_S S_u + (1 - q_u) \gamma_f I_u + \gamma_2 C_u - \mu_0 R_u - \psi R_u, \\
\frac{dS_f}{dt} &= \frac{1}{2} \psi S_u - (\lambda + \lambda_f + \mu_0 + \gamma_4) S_f, \\
\frac{dI_f}{dt} &= (\lambda + \lambda_f) S_f - (\mu_0 + \gamma_1) I_f, \\
\frac{dC_f}{dt} &= \frac{1}{2} \psi C_u + q_f \gamma_f I_f - (\mu_0 + \mu_1 + \gamma_2) C_f, \\
\frac{dS_m}{dt} &= \frac{1}{2} \psi S_u + (\lambda + \lambda_m) S_m - (\mu_0 + \gamma_1) S_m, \\
\frac{dI_m}{dt} &= (\lambda + \lambda_m) S_m - (\mu_0 + \gamma_1) I_m, \\
\frac{dC_m}{dt} &= \frac{1}{2} \psi C_u + q_m \gamma_f I_m - (\mu_0 + \mu_1 + \gamma_2) C_m, \\
\frac{dR_m}{dt} &= \gamma_4 (S_f + S_m) + (1 - q_f) \gamma_f I_f + (1 - q_m) \gamma_f I_m + \gamma_2 (C_f + C_m) + \psi R_u - \mu_0 R_u,
\end{align*}
$$

where the parameters are described in Table 1 and the forces of infection are given as follows:

$$
\lambda = \beta (I_u + I_m + I_f) + \epsilon \beta (C_u + C_m + C_f),
\lambda_f = \beta_f C_f S_f + S_m + I_f + I_m + C_f + C_m + R_u
$$

$$
\begin{align*}
\lambda_m &= \beta_m C_m S_f + S_m + I_f + I_m + C_f + C_m + R_u.
\end{align*}
$$

Fig. 4. Flowchart of HBV transmission for the ODE model, where $i = f, m$. 

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**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda$</td>
<td>Rate of clearance of acute hepatitis B</td>
<td></td>
</tr>
<tr>
<td>$\lambda_f$</td>
<td>Sexual transmission between spouses</td>
<td></td>
</tr>
<tr>
<td>$\lambda_m$</td>
<td>Non-sexual transmission</td>
<td></td>
</tr>
<tr>
<td>$q_u$</td>
<td>Probability of developing into carriers</td>
<td></td>
</tr>
<tr>
<td>$q_f$</td>
<td>Probability of developing into carriers</td>
<td></td>
</tr>
<tr>
<td>$q_m$</td>
<td>Probability of developing into carriers</td>
<td></td>
</tr>
<tr>
<td>$\mu_u$</td>
<td>Mortality rate</td>
<td></td>
</tr>
<tr>
<td>$\mu_f$</td>
<td>Mortality rate</td>
<td></td>
</tr>
<tr>
<td>$\omega$</td>
<td>Vaccination rate</td>
<td></td>
</tr>
</tbody>
</table>
Let
\[ \lambda_m = \beta_m c_f \frac{2(I_f + eC_f)}{S_f} \]
where
\[ c_f = \psi \]
and
\[ \lambda_m = \beta_m c_f \frac{2(I_f + eC_f)}{S_f + S_m + I_f + I_m + C_f + C_m + R_0} \]

3. The results

3.1. The basic reproduction number

The disease-free equilibrium is
\[ E_0 = (S_f^0, 0, 0, R_f^0, S_m^0, 0, 0, S_m^0, 0, 0, R_f^0) \]
where
\[ S_f^0 = \frac{\mu \omega}{\mu_0 + \gamma_3 + \psi'} \]
\[ S_m^0 = \frac{\mu(1 - \omega)}{\mu_0 + \psi'} \]
\[ R_f^0 = \frac{\gamma_3 \psi' \mu \omega}{(\mu_0 + \gamma_3 + \psi')(\mu_0 + \gamma_3)} \]
\[ R_m^0 = \frac{\gamma_3 \psi' \mu \omega}{(\mu_0 + \gamma_3 + \psi')(\mu_0 + \gamma_3)} \]

Let
\[ F = \begin{pmatrix} \lambda S_u & 0 \\ (\lambda + \lambda_f) S_f \\ 0 \\ (\lambda + \lambda_m) S_m \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \]

Then, the linearization of system (2.1) at \( E_0 \) is given by
\[ DF(E_0) = \begin{pmatrix} F - V & 0 \\ -J_3 & -J_4 \end{pmatrix} \]

where \( J_3 \) and \( J_4 \) are 5 × 5 matrices, and
\[ F = \begin{pmatrix} \beta S_f^0 & \epsilon \beta S_f^0 \\ 0 & 0 \\ \beta S_f^0 & \epsilon \beta S_f^0 \\ 0 & 0 \\ \beta S_m^0 & \epsilon \beta S_m^0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{pmatrix} \]
Since all eigenvalues of \( J_f \) have positive real parts, the stability of \( E_0 \) is determined by the eigenvalues of matrix \( F - V \). Moreover, it follows from the results in Diekmann et al. (2010) and van den Driessche and Watmough (2002) that all eigenvalues of \( F - V \) have negative real parts if and only if \( \rho(FV^{-1}) < 1 \), where \( \rho(A) \) denotes the spectral radius of a matrix \( A \). One can compute \( FV^{-1} \), called the generation matrix (Diekmann et al., 2010; van den Driessche and Watmough, 2002), that is,

\[
FV^{-1} = \begin{pmatrix}
a_{11} & a_{12} & a_{13} & a_{14} & a_{15} & a_{16} \\
0 & 0 & 0 & 0 & 0 & 0 \\
a_{31} & a_{32} & a_{33} & a_{34} & a_{35} & a_{36} \\
0 & 0 & 0 & 0 & 0 & 0 \\
a_{51} & a_{52} & a_{53} & a_{54} & a_{55} & a_{56} \\
0 & 0 & 0 & 0 & 0 & 0 \\
\end{pmatrix}
\]

where

\[
a_{11} = \frac{\beta S_0^q (\mu_0 + \mu_1 + \gamma_1 + \psi_1 + \gamma_2 + \psi) + \beta \beta S_0^q q_1 Y_1 (\mu_0 + \mu_1 + \gamma_2 + \psi) + 2 \epsilon \beta S_0^q q_1 Y_1 \psi}{(\gamma_1 + \mu_0 + \mu_1 + \gamma_2 + \psi) (\mu_0 + \mu_1 + \gamma_2),}
\]

\[
a_{12} = \frac{\epsilon \beta S_0^q (\gamma_1 + \mu_0 + \mu_1 + \gamma_2) + 2 \psi}{(\mu_0 + \mu_1 + \gamma_2 + \psi) (\mu_0 + \mu_1 + \gamma_2),}
\]

\[
a_{13} = \frac{\epsilon \beta S_0^q (\mu_0 + \mu_1 + \gamma_2 + \psi) (\mu_0 + \mu_1 + \gamma_2 + \psi) + \epsilon \beta S_0^q q_1 Y_1 (\mu_0 + \mu_1 + \gamma_2 + \psi) + \epsilon \beta S_0^q q_1 Y_1 \psi}{(\gamma_1 + \mu_0) (\mu_0 + \mu_1 + \gamma_2 + \psi) (\mu_0 + \mu_1 + \gamma_2),}
\]

\[
a_{14} = \frac{\epsilon \beta S_0^q (\mu_0 + \mu_1 + \gamma_2) + \epsilon \beta S_0^q q_1 Y_1}{(\gamma_1 + \mu_0) (\mu_0 + \mu_1 + \gamma_2 + \psi) (\mu_0 + \mu_1 + \gamma_2),}
\]

\[
a_{15} = \frac{\epsilon \beta S_0^q (\mu_0 + \mu_1 + \gamma_2) + \epsilon \beta S_0^q q_1 Y_1}{(\gamma_1 + \mu_0) (\mu_0 + \mu_1 + \gamma_2 + \psi) (\mu_0 + \mu_1 + \gamma_2),}
\]

\[
a_{16} = \frac{\epsilon \beta S_0^q (\mu_0 + \mu_1 + \gamma_2) + \epsilon \beta S_0^q q_1 Y_1}{(\gamma_1 + \mu_0) (\mu_0 + \mu_1 + \gamma_2 + \psi) (\mu_0 + \mu_1 + \gamma_2),}
\]
We now use model (2.1) with parameters in Table 1 to simulate the infection rates for the three groups: under-aged children, female adults and male adults. The year 2005 is important because HepB vaccination has been free for every newborn baby since that year. Therefore, we choose year 2005 as the initial time in our simulations. Different from our previous study (Zou et al., 2010b), which distinguished neither ages nor genders, our new model and data include all three groups for mainland China. We estimate the unknown parameters by calculating the minimum sum of square:

$$
\min \sum (\text{Proportion of cases} - \text{Simulation})^2
$$

with MATLAB tool fminsearch. Fig. 7 shows that the simulations of our model with reasonable parameter values provide good matches with the data reported by China CDC on all three groups in China from 2005 to 2012. It is shown that the incidence rate for children is decreasing (Fig. 7(a)). Therefore, the measure to vaccinate newborn babies and children under 15 years old has been very effective. However, the incidence rates for both female and male adults keep increasing (Fig. 7(b) and (c)), which lead to the high incidence rate of HBV in...
China now. Therefore, in order to control and prevent the transmission of HBV in China, great attention should be paid to adults as well. Sexual transmission of hepatitis B needs to be controlled and prevented and more adults should be vaccinated.

From Fig. 8, we can see that the numbers of acute infections decrease quickly if either $\beta = 0$ or $\beta_f c_f = \beta_m c_m = 0$. For the male adults, the control of sexual transmission is mostly important since the number of male adult infections decreases fastest if $\beta_m c_m = 0$.

4. Conclusion

Hepatitis B vaccines have been available since 1982 (WHO, 2002). In 1983, WHO designed and initiated a Demonstration Project on a large scale controlled clinical trial to vaccinate 80,000 newborns in a high incidence area, Qidong City, Jiansu Province, China (Sun et al.,
The project ended in 1990 and it was found that HepB vaccination provided a 75% protective efficiency against hepatitis B infection in this area (Sun et al., 2002). In 1992, the World Health Assembly endorsed the recommendations of the Global Advisory Group of the Expanded Programme on Immunization that hepatitis B vaccine be integrated into national immunization systems of all countries by 1997 (WHO, 2002). In the same year, the Ministry of Health of China recommended routine vaccination of infants in China (Cui et al., 2007; Sun et al., 2002); however, it was not free. In 2002, the Ministry of Health of China integrated the infant HepB vaccination into the National Immunization Programme with vaccine provided entirely by the government (Cui et al., 2007; Sun et al., 2002). With the help of the joint project by the Chinese Ministry of Health and the Global Alliance for Vaccines and Immunization (GAVI Alliance) (Chee et al., 2012; Cui et al., 2007), which provided free HepB for children born each year in 12 western provinces and in government-designated poor counties in 10 middle provinces from 2002 to 2010 (Chee et al., 2012; Cui et al., 2007; Liang et al., 2013), the impact of HepB vaccination on HBsAg prevalence is observed in all of China as HBsAg prevalence is now less than 1% among children under 5 years (Liang et al., 2009; People's Daily Oversea Edition, 2013). In 2009, the Central Government of China issued the guidelines on the reform of health-care system for 2009–2011, in which it was suggested to retroactively immunize young adults (younger than 15 years old) on HBV for free (CPG, 2009; Zou et al., 2010b). Altogether, 62 million under-aged children were targeted for vaccination in 2009, 2010, and 2011 under this project (Liang et al., 2013). Thanks to the intensive and strong immunization campaign and programme by local and central governments, the hepatitis B incidence rate has decreased significantly and steadily in under-aged children in China in the last 10 years (see Fig. 2(a)). However, the hepatitis B incidence rate in adults in China still keeps increasing (see Fig. 1(a) and also Liang et al., 2009; Zhu et al., 2013).
It is known that sexual transmission may play an important role in the spread of hepatitis B (Alter et al., 1986, 1989; Struve et al., 1990). In Zou et al. (2010b) we noticed that there might be co-infections of HBV and HIV by comparing incidence rates of these two diseases in China. The comparisons between the incidence of HBV and sexually transmitted diseases (including AIDS, HIV, syphilis and gonorrhea) in China in Figs. 1–3 demonstrate that sexual transmission is an important route of spread of HBV in China. On the basis of this fact, in this paper we proposed a compartmental model including under-aged children, male adults, and female adults. It is assumed that all susceptible individuals can be infected via non-sexual contacts, while only adults can be infected via sexual contacts. The effect of sexual transmission of the spread and prevalence of HBV in China was studied. The model was employed to simulate the incidence rates reported by the Chinese Center for Disease Control and Prevention for under-aged children, adult males, and adult females, respectively.

The sensitivity analysis of the basic reproduction number on various model parameters indicates that it is important and crucial to increase the immunization rate for both under-aged children and adults in order to control the transmission of HBV in China. Our study shows that effective control measures for hepatitis B in China include enhancing public education and awareness about hepatitis B virus,
particularly about the fact that hepatitis B is a sexual transmitted disease, and increasing the immunization rate for both under-aged children and adults, especially for certain groups of high risk.

Finally, we should mention that, for the sake of simplicity, the homosexual transmission of hepatitis B virus was not considered in this study. It may affect the transmission dynamics of HBV as some studies suggested. We leave this for future consideration.

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References
