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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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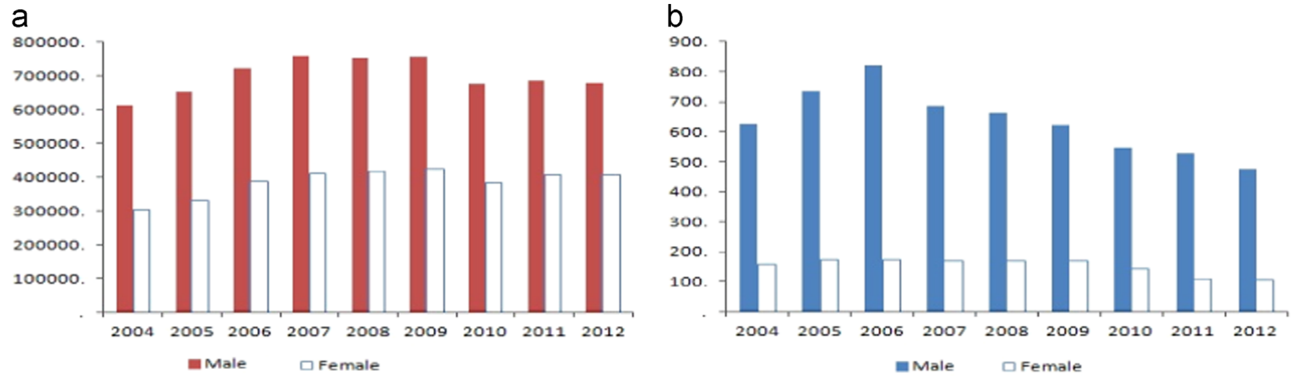

Fig. 1. Data on HBV and sexually transmitted diseases (including AIDS, HIV, gonorrhea and syphilis) in China from 2004 to 2012 (Public Health Science Data, 2004–2012): (a) infections with HBV for males and females; (b) deaths related to HBV for males and females.

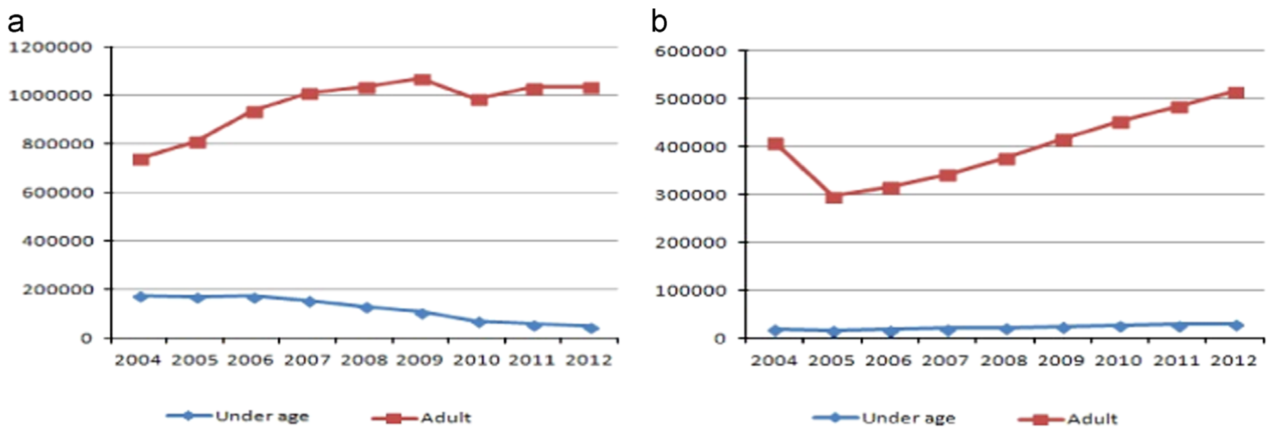

Fig. 2. Infection data on HBV and sexually transmitted diseases (including AIDS, HIV, gonorrhea and syphilis) in China for adults and children (Public Health Science Data, 2004–2012): (a) HBV and (b) sexually transmitted diseases.

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.

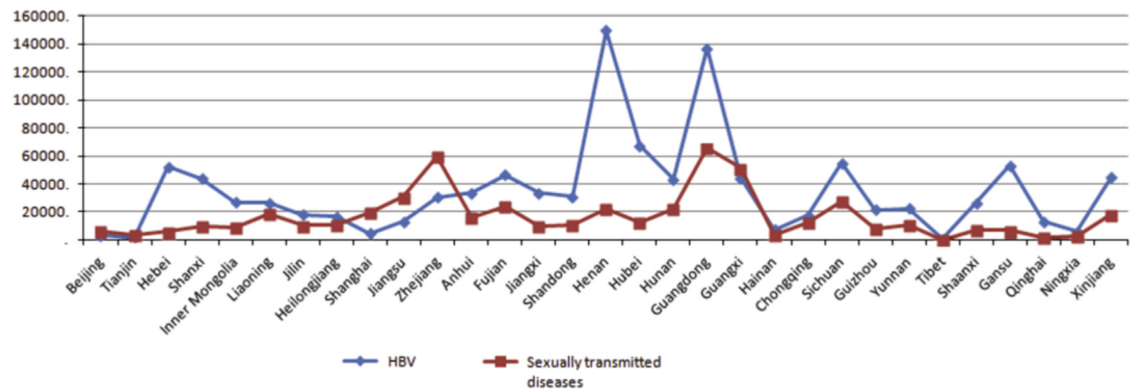

Fig. 3. Reported infections of HBV and sexually transmitted diseases (including AIDS, HIV, syphilis, gonorrhea) by provinces in 2011.

Table 1
Parameter description.

Parameter	Interpretation	Value (per year)	Reference
μ	Birth rate	0.012	National Health and Family Planning Commission (2012)
μ_0	Natural mortality rate	0.069	National Health and Family Planning Commission (2012)
μ_1	HBV related mortality rate	0.002	Cui et al. (2007)
ϵ	Reduced transmission rate	0.16	Edmunds et al. (1996)
γ_1	Progress rate from acute to carrier	4 per year	Edmunds et al. (1996)
γ_2	Progress rate from carrier to immune	0.025 per year	Edmunds et al. (1996)
γ_3	Vaccination rate for under-aged children	0.8	Assumption
γ_4	Vaccination rate for adults	0.05	Assumption
$1-\omega$	Proportion of births with successful vaccination	0.9	Assumption
q_u	Average probability an under age fails to clear an acute infection and develops to carrier state	0.95	Assumption
q_f	Average probability a female adult fails to clear an acute infection and develops to carrier state	0.08	Assumption
q_m	Average probability a male adult fails to clear an acute infection and develops to carrier state	0.7	Assumption
ψ	Growth rate from under-aged to adult	1/18	Assumption
ν	Proportion of perinatally infected (carrier mothers)	0.11	Edmunds et al. (1996)
β	Coefficient of transmission for non-sexual transmission	0.01	Fitting
β_f	The transmission probability for female per sex contact	0.0025	Fitting
β_m	The transmission probability for male per sex contact	0.02	Fitting
$c_j, j=f,m$	The average number of sex contacts of females with males (or males with females)	2 per year	Fitting

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 $\psi = 1/18$ 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 λ, or $\lambda+\lambda_i$, $i=f,m$; (b) he/she dies with the natural mortality rate μ_0; (c) he/she is vaccinated at an average rate γ_3 (for an under-aged child) or γ_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 λ. Female adults and male ones may be infected by either non-sexual contact with a force of infection λ or sexual transmission with a force of infection λ_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_m is higher than that for women q_f (McLean and Blumberg, 1994). Thus, we make assumptions for q_u, q_f and q_m as shown in Table 1. From National Health and Family Planning Commission, a newborn baby may be vaccinated successfully with a probability of 95% and the vaccination coverage is about 90% (National Health and Family Planning Commission, 2006–2010). Thus, we assume that $1-\omega=0.9$ as shown in Table 1.

Immune individuals are those who have recovered from the infection of hepatitis B or who have been vaccinated successfully. We use $R_u(t)$ and $R_a(t)$ to represent the number of under-aged immune children and immune adults at time t, respectively. Since free HBV vaccination is provided for newborn babies and children under 15 years, the vaccination rate for children (γ_3) is much higher than that for adults (γ_4) now. Moreover, free vaccination for newborns has started from 2005, while for children under 15 years started just from 2009. Therefore, γ_3 is less than $1-\omega$. Thus, we assume that $\gamma_3=0.8$ and $\gamma_4=0.05$ as shown in Table 1.

Based on the above discussion and the flowchart in Fig. 4, the model is formulated as follows:

$$\begin{cases}
\dfrac{dS_u}{dt}=\mu\omega(1-\nu C_f)-(\mu_0+\lambda+\gamma_3+\psi)S_u,\\
\dfrac{dI_u}{dt}=\lambda S_u-(\gamma_1+\mu_0)I_u,\\
\dfrac{dC_u}{dt}=\mu\omega\nu C_f+q_u\gamma_1 I_u-(\mu_0+\mu_1+\gamma_2+\psi)C_u,\\
\dfrac{dR_u}{dt}=\mu(1-\omega)+\gamma_3 S_u+(1-q_u)\gamma_1 I_u+\gamma_2 C_u-\mu_0 R_u-\psi R_u,\\
\dfrac{dS_f}{dt}=\frac{1}{2}\psi S_u-(\lambda+\lambda_f+\mu_0+\gamma_4)S_f,\\
\dfrac{dI_f}{dt}=(\lambda+\lambda_f)S_f-(\mu_0+\gamma_1)I_f,\\
\dfrac{dC_f}{dt}=\frac{1}{2}\psi C_u+q_f\gamma_1 I_f-(\mu_0+\mu_1+\gamma_2)C_f,\\
\dfrac{dS_m}{dt}=\frac{1}{2}\psi S_u-(\lambda+\lambda_m+\mu_0+\gamma_4)S_m,\\
\dfrac{dI_m}{dt}=(\lambda+\lambda_m)S_m-(\mu_0+\gamma_1)I_m,\\
\dfrac{dC_m}{dt}=\frac{1}{2}\psi C_u+q_m\gamma_1 I_m-(\mu_0+\mu_1+\gamma_2)C_m,\\
\dfrac{dR_a}{dt}=\gamma_4(S_f+S_m)+(1-q_f)\gamma_1 I_f+(1-q_m)\gamma_1 I_m+\gamma_2(C_f+C_m)+\psi R_u-\mu_0 R_a,
\end{cases} \tag{2.1}$$

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

$$\lambda=\beta(I_u+I_m+I_f)+\epsilon\beta(C_u+C_m+C_f),$$

$$\lambda_f=\beta_f c_f\frac{2(I_m+\epsilon C_m)}{S_f+S_m+I_f+I_m+C_f+C_m+R_a},$$

$$\lambda_m=\beta_m c_m\frac{2(I_f+\epsilon C_f)}{S_f+S_m+I_f+I_m+C_f+C_m+R_a}.$$

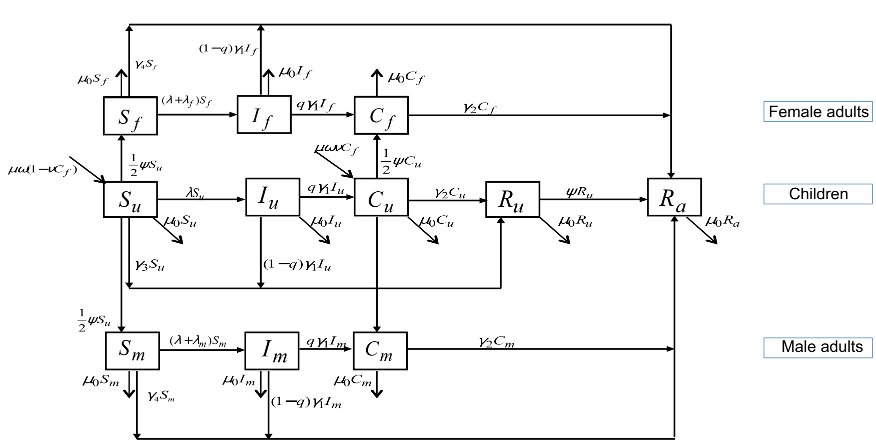

Fig. 4. Flowchart of HBV transmission for the ODE model, where $i=f,m$.

Note that the number of new sexual partnerships formed by adult males must be equal to the number of new partnerships formed by adult females. We have $2c_m(S_f+S_m+I_f+I_m+C_f+C_m+R_a)=2c_f(S_f+S_m+I_f+I_m+C_f+C_m+R_a)$. Thus, $c_f=c_m$ and

$$\lambda_m=\beta_m c_f\frac{2(I_f+\epsilon C_f)}{S_f+S_m+I_f+I_m+C_f+C_m+R_a}. \tag{2.2}$$

3. The results

3.1. The basic reproduction number

The disease-free equilibrium is $E_0=(S_u^0,0,0,R_u^0,S_f^0,0,0,S_m^0,0,0,R_a^0)$, where

$$S_u^0=\frac{\mu\omega}{\mu_0+\gamma_3+\psi},\quad R_u^0=\frac{\mu(1-\omega)}{\mu_0+\psi}+\frac{\gamma_3\mu\omega}{(\mu_0+\gamma_3+\psi)(\mu_0+\psi)},$$

$$S_f^0=S_m^0=\frac{\psi\mu\omega}{2(\mu_0+\gamma_3+\psi)(\mu_0+\gamma_4)},$$

$$R_a^0=\frac{\gamma_4\psi\mu\omega}{(\mu_0+\gamma_3+\psi)(\mu_0+\gamma_4)\mu_0}+\frac{\psi\mu(1-\omega)}{\mu_0(\mu_0+\psi)}+\frac{\gamma_3\psi\mu\omega}{\mu_0(\mu_0+\gamma_3+\psi)(\mu_0+\psi)}.$$

Let

$$\mathcal{F}=\begin{pmatrix}\lambda S_u\\0\\(\lambda+\lambda_f)S_f\\0\\(\lambda+\lambda_m)S_m\\0\\0\\0\\0\\0\\0\end{pmatrix},$$

$$\mathcal{V}=\begin{pmatrix}(\gamma_1+\mu_0)I_u\\-\mu\omega\nu C_f-q_u\gamma_1 I_u+(\mu_0+\mu_1+\gamma_2+\psi)C_u\\(\mu_0+\gamma_1)I_f\\-\frac{1}{2}\psi C_u-q_f\gamma_1 I_f+(\mu_0+\mu_1+\gamma_2)C_f\\(\mu_0+\gamma_1)I_m\\-\frac{1}{2}\psi C_u-q_m\gamma_1 I_m+(\mu_0+\mu_1+\gamma_2)C_m\\-(\mu\omega(1-\nu C_f)+(\mu_0+\lambda+\gamma_3+\psi)S_u\\-\mu(1-\omega)-\gamma_3 S_u-(1-q_u)\gamma_1 I_u-\gamma_2 C_u+\mu_0 R_0+\psi R_u\\-\frac{1}{2}\psi S_u+(\lambda+\lambda_f+\mu_0+\gamma_4)S_f\\-\frac{1}{2}\psi S_u+(\lambda+\lambda_m+\mu_0+\gamma_4)S_m\\-\gamma_4(S_f+S_m)-(1-q_f)\gamma_1 I_m-(1-q_m)\gamma_1 I_m-\gamma_2(C_f+C_m)-\psi R_u+\mu_0 R_a\end{pmatrix}.$$

Then, the linearization of system (2.1) at E_0 is given by

$$D\mathcal{F}(E_0)-D\mathcal{V}(E_0)=\begin{pmatrix}F-V&0\\-J_3&-J_4\end{pmatrix},$$

where J_3 and J_4 are 5×5 matrices, and

$$F=\begin{pmatrix}\beta S_u^0&\epsilon\beta S_u^0&\beta S_u^0&\epsilon\beta S_u^0&\beta S_u^0&\epsilon\beta S_u^0\\0&0&0&0&0&0\\\beta S_f^0&\epsilon\beta S_f^0&\beta S_f^0&\epsilon\beta S_f^0&\left(\beta+\frac{\beta_f c_f}{N_f^0}\right)S_f^0&\epsilon\left(\beta+\frac{\beta_f c_f}{N_f^0}\right)S_f^0\\0&0&0&0&0&0\\\beta S_m^0&\epsilon\beta S_m^0&\left(\beta+\frac{\beta_m c_f}{N_f^0}\right)S_m^0&\epsilon\left(\beta+\frac{\beta_m c_f}{N_f^0}\right)S_m^0&\beta S_m^0&\epsilon\beta S_m^0\\0&0&0&0&0&0\end{pmatrix},$$

$$V=\begin{pmatrix} \gamma_1+\mu_0 & 0 & 0 & 0 & 0 & 0 \\ -q_u\gamma_1 & \mu_0+\mu_1+\gamma_2+\psi & -\mu\omega\nu & 0 & 0 & 0 \\ 0 & 0 & \gamma_1+\mu_0 & 0 & 0 & 0 \\ 0 & -\frac{1}{2}\psi & -q_f\gamma_1 & \mu_0+\mu_1+\gamma_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & \gamma_1+\mu_0 & 0 \\ 0 & -\frac{1}{2}\psi & 0 & 0 & -q_m\gamma_1 & \mu_0+\mu_1+\gamma_2 \end{pmatrix}.$$

Since all eigenvalues of J_4 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,

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

where

$$a_{11}=\frac{\beta S_u^0(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)+\epsilon\beta S_u^0 q_u\gamma_1(\mu_0+\mu_1+\gamma_2)+2\epsilon\beta S_u^0 q_u\gamma_1\frac{\psi}{2}}{(\gamma_1+\mu_0)(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)},$$

$$a_{12}=\frac{\epsilon\beta S_u^0\left((\mu_0+\mu_1+\gamma_2)+2\frac{\psi}{2}\right)}{(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)},$$

$$a_{13}=\frac{\epsilon\beta S_u^0\mu\omega\nu(\mu_0+\mu_1+\gamma_2)+\beta S_u^0(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)+\epsilon\beta S_u^0(\mu_0+\mu_1+\gamma_2+\psi)q_f\gamma_1+2\epsilon\beta S_u^0\frac{\psi}{2}\mu\omega\nu}{(\gamma_1+\mu_0)(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)},$$

$$a_{14}=\frac{\epsilon\beta S_u^0}{(\mu_0+\mu_1+\gamma_2)},$$

$$a_{15}=\frac{\beta S_u^0(\mu_0+\mu_1+\gamma_2)+\epsilon\beta S_u^0 q_m\gamma_1}{(\gamma_1+\mu_0)(\mu_0+\mu_1+\gamma_2)},$$

$$a_{31}=\frac{\beta S_f^0(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)+\epsilon\beta S_f^0 q_u\gamma_1\left((\mu_0+\mu_1+\gamma_2)+\frac{\psi}{2}\right)+\epsilon\left(\beta+\frac{\beta_f c_f}{N_f^0}\right)S_f^0 q_u\gamma_1\frac{\psi}{2}}{(\gamma_1+\mu_0)(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)},$$

$$a_{32}=\frac{\epsilon\beta S_f^0((\mu_0+\mu_1+\gamma_2)+\frac{\psi}{2})+\epsilon\left(\beta+\frac{\beta_f c_f}{N_f^0}\right)S_f^0\frac{\psi}{2}}{(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)},$$

$$a_{33}=\frac{\beta S_f^0(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)+\epsilon\beta S_f^0\left(\mu\omega\nu(\mu_0+\mu_1+\gamma_2)+q_f\gamma_1(\mu_0+\mu_1+\gamma_2+\psi)+\frac{\psi}{2}\mu\omega\nu\right)+\epsilon\left(\beta+\frac{\beta_f c_f}{N_f^0}\right)S_f^0\frac{\psi}{2}\mu\omega\nu}{(\gamma_1+\mu_0)(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)},$$

$$a_{34}=\frac{\epsilon\beta S_f^0}{(\mu_0+\mu_1+\gamma_2)},$$

$$a_{35}=\frac{\left(\beta+\frac{\beta_f c_f}{N_f^0}\right)S_f^0(\mu_0+\mu_1+\gamma_2)+\epsilon\left(\beta+\frac{\beta_f c_f}{N_f^0}\right)S_f^0 q_m\gamma_1}{(\gamma_1+\mu_0)(\mu_0+\mu_1+\gamma_2)},$$

$$a_{36}=\frac{\epsilon\left(\beta+\frac{\beta_f c_f}{N_f^0}\right)S_f^0}{(\mu_0+\mu_1+\gamma_2)},$$

$$a_{51}=\frac{\beta S_f^0(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)+\epsilon\beta S_f^0\left(q_u\gamma_1(\mu_0+\mu_1+\gamma_2)+q_u\gamma_1\frac{\psi}{2}\right)+f_{64}q_u\gamma_1\frac{\psi}{2}}{(\gamma_1+\mu_0)(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)},$$

$$a_{52}=\frac{\epsilon\beta S_f^0(\mu_0+\mu_1+\gamma_2)+\epsilon\left(\beta+\frac{\beta_m c_f}{N_f^0}\right)S_f^0\frac{\psi}{2}+\epsilon\beta S_f^0\frac{\psi}{2}}{(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)},$$

$$a_{53}=\frac{S_f^0}{(\gamma_1+\mu_0)(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)}\left[\epsilon\beta\left(\mu\omega\nu(\mu_0+\mu_1+\gamma_2)+\mu\omega\nu\frac{\psi}{2}\right)\right.$$
$$\left.+\left(\beta+\frac{\beta_m c_f}{N_f^0}\right)(\mu_0+\mu_1+\gamma_2+\psi)(\mu_0+\mu_1+\gamma_2)\right.$$

$$+\epsilon\left(\beta+\frac{\beta_m c_f}{N_f^0}\right)\left((\mu_0+\mu_1+\gamma_2+\psi)q_f\gamma_1+\mu\omega\nu\frac{\psi}{2}\right)\Bigg],$$

$$a_{54}=\frac{\epsilon\left(\beta+\dfrac{\beta_m c_f}{N_f^0}\right)S_f^0}{(\mu_0+\mu_1+\gamma_2)},$$

$$a_{55}=\frac{\beta S_f^0(\mu_0+\mu_1+\gamma_2)+\epsilon\beta S_f^0 q_m\gamma_1}{(\gamma_1+\mu_0)(\mu_0+\mu_1+\gamma_2)}.$$

Its eigenvalues satisfy the characteristic equation

$$\lambda^3\{\lambda^3-(a_{11}+a_{33}+a_{55})\lambda^2-(a_{15}a_{51}+a_{35}a_{53}-a_{55}a_{33}-a_{11}a_{55}+a_{13}a_{31}-a_{11}a_{33})\lambda-a_{13}a_{35}a_{51}-a_{15}a_{31}a_{53}+a_{15}a_{33}a_{51}+a_{11}a_{35}a_{53}$$
$$+a_{13}a_{31}a_{55}-a_{11}a_{33}a_{55}\}=0. \tag{3.1}$$

In order to analyze the effect of sexual contacts on the transmission of HBV, we calculate the basic reproduction number under the following assumption:

(A6) Suppose that the sexual transmission probabilities for males and females are the same, i.e., $\beta_f=\beta_m\neq 0$.

With (A6) we see that $-a_{13}a_{35}a_{51}-a_{15}a_{31}a_{53}+a_{15}a_{33}a_{51}+a_{11}a_{35}a_{53}+a_{13}a_{31}a_{55}-a_{11}a_{33}a_{55}=0$ and therefore Eq. (3.1) becomes

$$\lambda^4(\lambda^2-(a_{11}+a_{33}+a_{35})\lambda-a_{31}a_{15}+a_{11}a_{35}-a_{31}a_{13}+a_{11}a_{33})=0, \tag{3.2}$$

which has eigenvalues

$$\lambda_1=0,$$
$$\lambda_{2,3}=\frac{1}{2}(a_{11}+a_{33}+a_{35}\pm\sqrt{(a_{11}+a_{33}+a_{35})^2-4(-a_{31}a_{15}+a_{11}a_{35}-a_{31}a_{13}+a_{11}a_{33})})$$
$$=\frac{r_2\pm\sqrt{r_2^2-4r_1r_3}}{2r_1},$$

where

$$r_1=2(\gamma_1+\mu_0)^2(\mu_0+\mu_1+\gamma_2)(\mu_0+\mu_1+\gamma_2+\psi),$$
$$r_2=(\mu_0+\gamma_1)\left\{2S_u^0\beta(\mu_0+\mu_1+\gamma_2+q_u\epsilon\gamma_1)(\mu_0+\mu_1+\gamma_2+\psi)+2S_f^0\left[(\mu_0+\mu_1+\gamma_2+\psi)\left(\left(\beta_f\frac{c_f}{N_f^0}+2\beta\right)(\mu_0+\mu_1+\gamma_2+\epsilon q_f\gamma_1)+\mu\nu\beta\epsilon\omega\right)+\mu\nu\psi\beta_f\frac{c_f}{N_f^0}\epsilon\omega)\right]\right\},$$
$$r_3=S_f^0S_u^0\beta\beta_f\frac{c_f}{N_f^0}[2(\mu_0+\mu_1+\gamma_2+\epsilon q_f\gamma_1)(\mu_0+\mu_1+\gamma_2+\psi+\epsilon q_u\gamma_1)+\mu\nu\psi\epsilon\omega].$$

Thus, the basic reproduction number can be expressed as

$$R_0=\frac{r_2+\sqrt{r_2^2-4r_1r_3}}{2r_1}. \tag{3.3}$$

Therefore, under the assumption (A6), the disease free equilibrium E_0 is stable if $R_0<1$ and unstable if $R_0>1$, where R_0 is defined in (3.3).

3.2. Sensitivity analysis and simulations

In Fig. 5(a), the solid red line describes the change of R_0 with respect to the non-sexual transmission coefficient β and the dashed blue line describes the change of R_0 with respect to the transmission probability for a female per sex contact β_f. It shows that the influence of β on R_0 is greater than β_f when β and β_f are very small. However, the situation changes as β and β_f increase, that is, controlling β_f is more important than controlling β if they are large. Fig. 5(b) and (c) shows that the basic reproduction number can be lowered by increasing the vaccine rate for either children γ_3 or adults γ_4. However, the influence of γ_4 on the basic reproduction number is greater than γ_3.

Fig. 6 shows that the basic reproduction number can be lowered by decreasing either the probability q_u (for under-age children to develop to carrier state), the probability q_m (for adults), or the averaged sex contact number c_m. However, the influence of q_u and q_m on R_0 is small and it is difficult to control those two parameters. Moreover, the basic reproduction number R_0 remains less than 1 if we can control $c_m=c_f=1$.

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 fminisearch. 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 vaccine 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

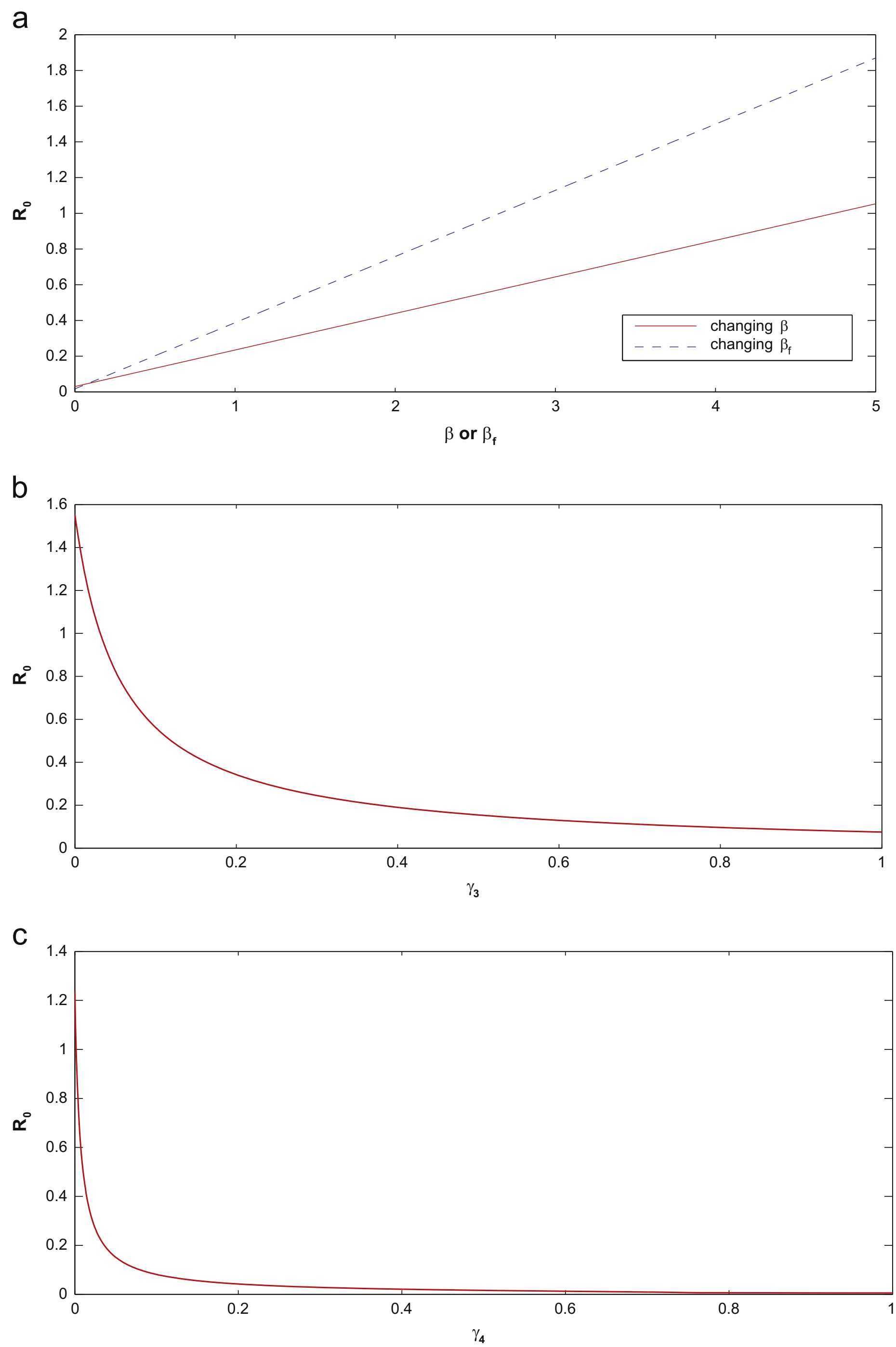

Fig. 5. The plots of the basic reproduction number R_0 in terms of model parameters: (a) the non-sexual transmission coefficient β and the transmission probability for females β_f; (b) the vaccine rate for children γ_3; and (c) the vaccine rate for adults γ_4. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

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.,

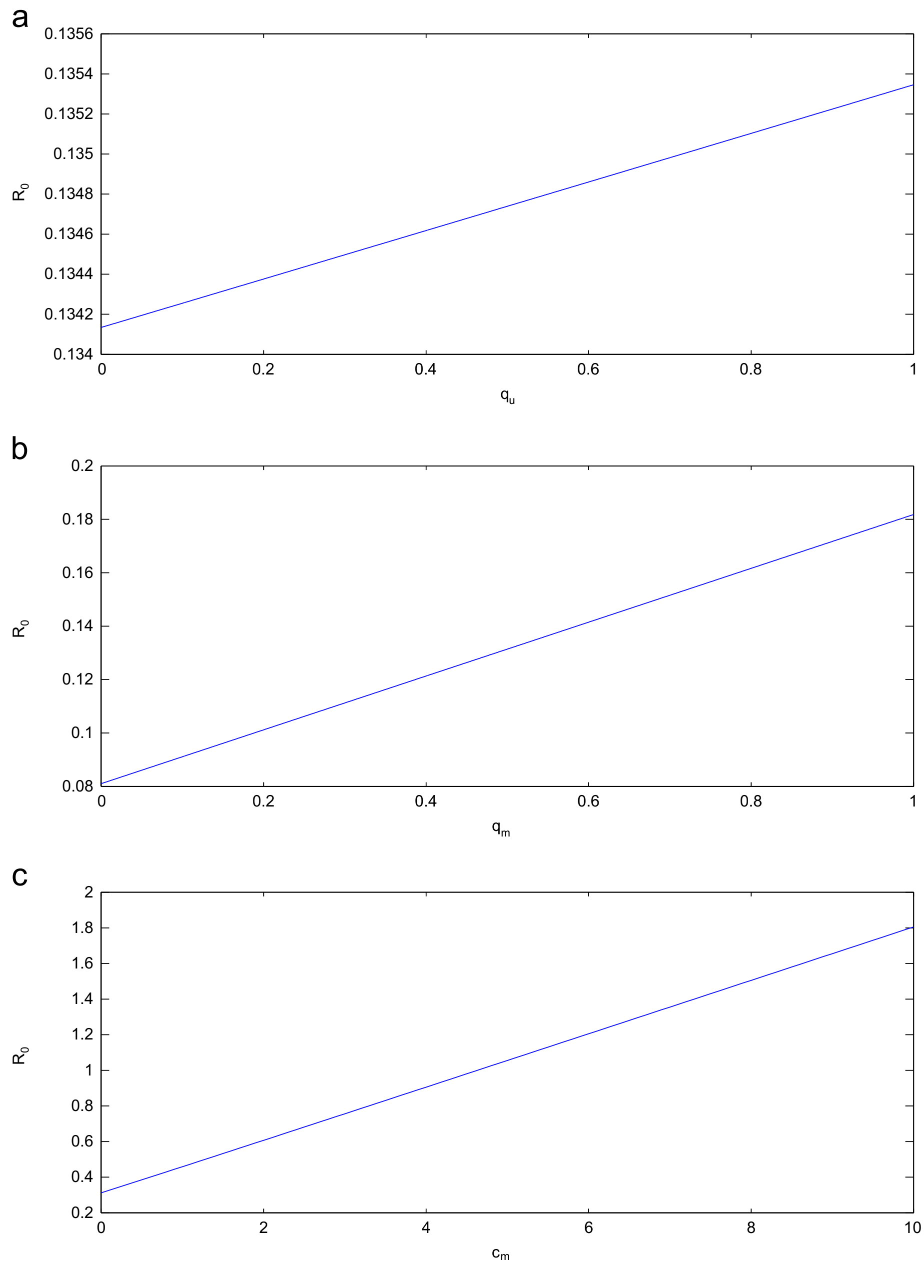

Fig. 6. The plots of the basic reproduction number R_0 in terms of model parameters: (a) average probability an under-age child fails to clear acute infection and develops to carrier state q_u; (b) average probability a male adult fails to clear acute infection and develops to carrier state q_m; and (c) the average number of sex contacts of females with males c_f.

2002). 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).

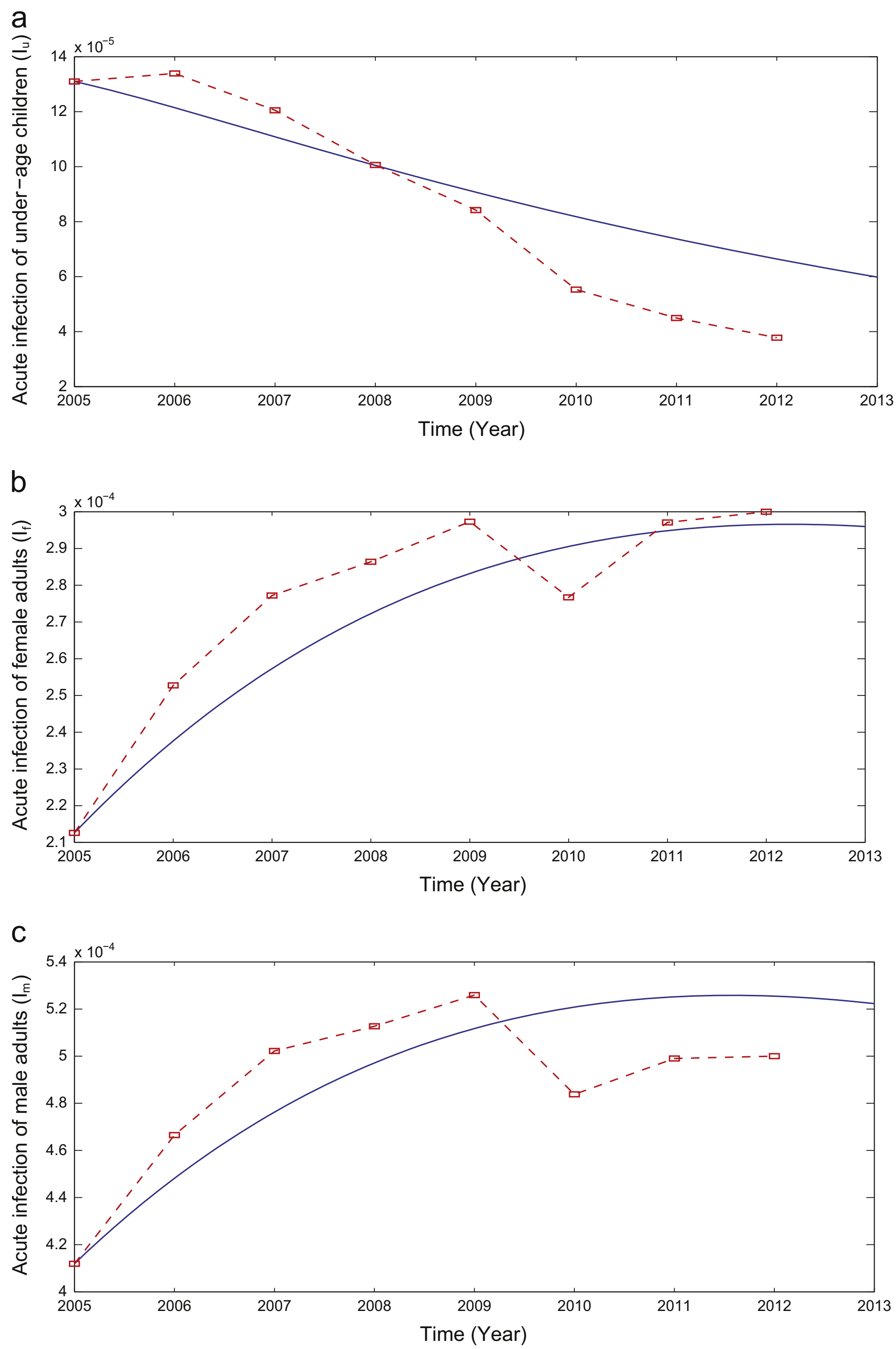

Fig. 7. Simulations of reported data on acute HBV infections in China from 2005 to 2012 using model (2.1) for (a) under-aged children; (b) female adults; and (c) male adults. The dashed lines are reported data and the solid lines represent simulations from model (2.1).

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,

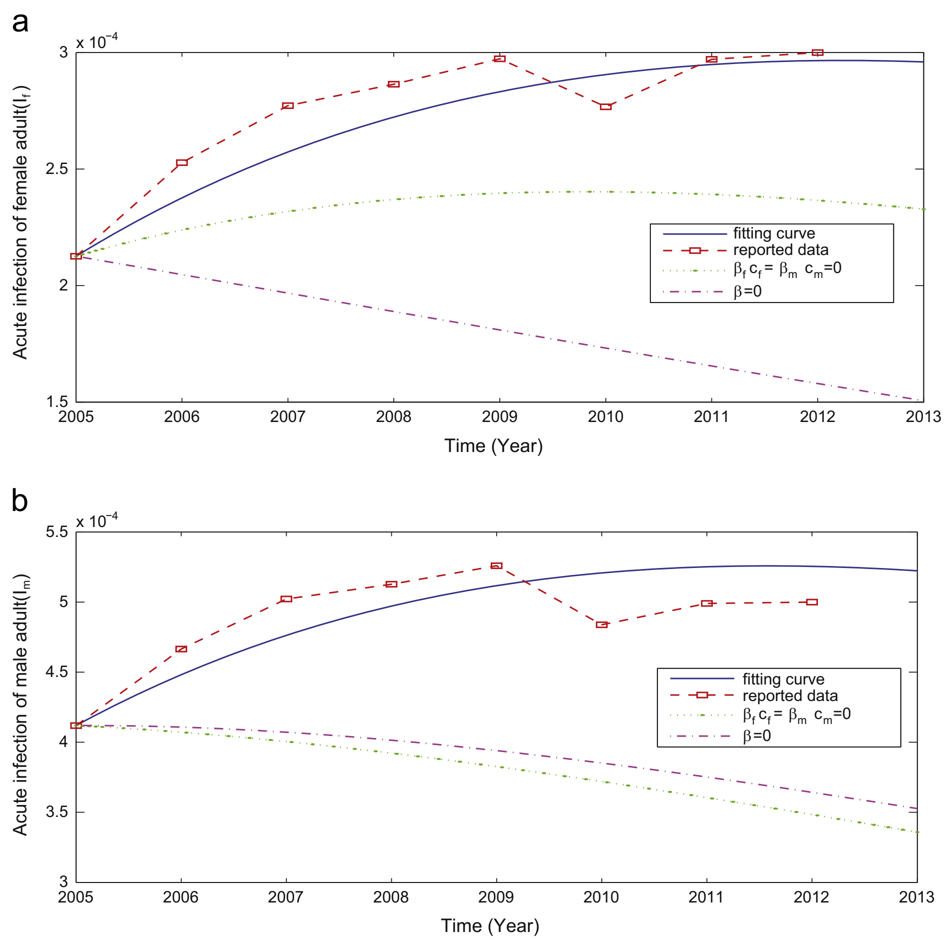

Fig. 8. Simulations of the numbers of acute infections with different control measures for (a) female adults and (b) male adults.

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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