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Modeling the transmission dynamics and control of hepatitis B virus in China ☆

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ABSTRACT

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV) and is a major global health problem. HBV is the most common serious viral infection and a leading cause of death in mainland China. Around 130 million people in China are carriers of HBV, almost a third of the people infected with HBV worldwide and about 10% of the general population in the country; among them 30 million are chronically infected. Every year, 300,000 people die from HBV-related diseases in China, accounting for 40–50% of HBV-related deaths worldwide. Despite an effective vaccination program for newborn babies since the 1990s, which has reduced chronic HBV infection in children, the incidence of hepatitis B is still increasing in China. We propose a mathematical model to understand the transmission dynamics and prevalence of HBV infection in China. Based on the data reported by the Ministry of Health of China, the model provides an approximate estimate of the basic reproduction number $R_0 = 2.406$. This indicates that hepatitis B is endemic in China and is approaching its equilibrium with the current immunization program and control measures. Although China made a great progress in increasing coverage among infants with hepatitis B vaccine, it has a long and hard battle to fight in order to significantly reduce the incidence and eventually eradicate the virus.

1. Introduction

Hepatitis B virus (HBV), an hepadnavirus with a circular genome composed of partially double-stranded DNA, replicates through an RNA intermediate form by reverse transcription (Locarnini, 2004). Hepatitis B is a potentially life-threatening liver infection caused by the HBV and is a major global health problem and the most serious type of viral hepatitis (WHO, 2008). It has caused epidemics in parts of Asia and Africa (Williams, 2006). Worldwide, about 2 billion people have been infected with the virus and about 360 million live with chronic infection. An estimated 600,000 persons die each year due to the acute or chronic consequences of hepatitis B (WHO, 2008; Shepard et al., 2006).

HBV is the most common serious viral infection and a leading cause of death in mainland China. Hepatitis B is one of the top three infectious diseases reported by the Ministry of Health of China. Around 130 million people in China are carriers of HBV, almost a third of the people infected with HBV worldwide and about 10% of the general population in the country; 30 million people in the country are chronically infected (Liu et al., 2002). Every year, 300,000 people die from HBV-related diseases in China, accounting for 40–50% of HBV-related deaths worldwide (Jia and Zhuang, 2004; Goldstein et al., 2005). Despite an effective vaccination program for newborn babies since the 1990s, which has reduced chronic HBV infection in children (Cui et al., 2006; MMWR, 2007), the incidence of hepatitis B is still increasing (Fig. 1(a)), from 21.9 in 100,000 people in 1990 to 53.3 in 100,000 in 2003 (Wang et al., 2004).

The risk of developing hepatitis B is primarily related to sexual, household or perinatal exposure to infected individuals. Prevention of perinatal HBV transmission is an important step in controlling hepatitis B in endemic countries. As infection by hepatitis B in the perinatal period leads to almost 90% development of chronic hepatitis, screening for HBsAg (hepatitis B surface antigen) positive mothers to determine newborns at risk and to target them for immunoprophylaxis has been one strategy used to break the cycle of transmission. Almost 90% of infants born to HBsAg-positive/HBeAg-positive women and 10% of infants born to HBsAg-positive/HBeAg-negative women become infected (Shepard et al., 2006; Goldstein et al., 2005). Also, infants infected perinatally have the highest probability of chronic infection (around 90%) and adults have the lowest (less than 5%) (Hyams, 1995).

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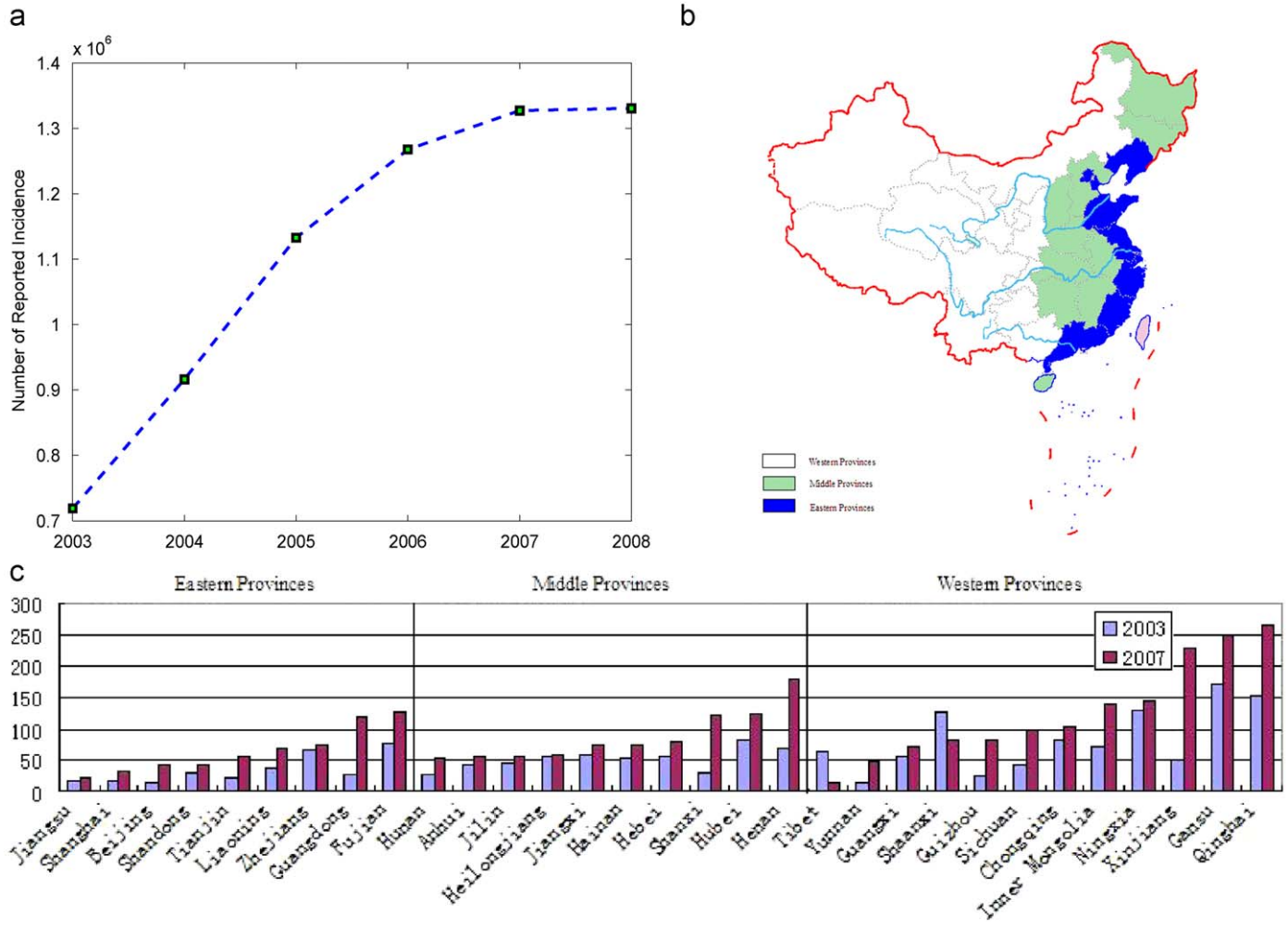

Fig. 1. (a) Hepatitis B data reported by the Ministry of Health of China from 2003 to 2008 (MOHC, 2009). (b) Estimated infant vaccination coverage with the 3-doses of hepatitis B vaccine (HepB3) and the timely administration of the HepB birth dose (HepB1), by regions in mainland China, 2001–2003. 94.1% of HepB1 and 81.9% of HepB1 in 9 eastern provinces (Beijing, Fujian, Guangdong, Jiangsu, Liaoning, Shandong, Shanghai, Tianjin, Zhejiang); 91.8% of HepB1 and 72.7% of HepB1 in 10 middle provinces (Anhui, Hainan, Hebei, Helongjiang, Henan, Hubei, Hunan, Jiangxi, Jilin, Shanxi); and 68.0% of HepB1 and 49.5% of HepB1 in 12 western provinces (Chongqing, Gansu, Guangxi, Guizhou, Inner Mongolia, Ningxia, Qinghai, Shaanxi, Sichuan, Tibet, Yunnan, Xinjiang) (MMWR, 2007). (c) Acute incidence rates (1/100,000) of HBV in mainland China by provinces in 2003 and 2007 (MOHC, 2009).

There is no widely available effective treatment for chronic HBV carriers. Immunization with hepatitis B vaccine (HepB) is the most important prevention measure (Shepard et al., 2006). Several vaccines have been developed for the prevention of HBV infection, which rely on the use of one of the viral envelope proteins (HBsAg). Vaccine can be received by infants to adults and provides protection for 85–90% of individuals (Shepard et al., 2006; Maynard et al., 1989). The main vaccinations include the 3-dose HepB vaccination and the timely HepB birth-dose (i.e., within 24 h of birth). In 1991, WHO recommended that hepatitis B vaccination should be included in national immunization system in all countries with an HBsAg carrier prevalence 8% by 1995 and all countries by 1997. By 2002, 154 countries had routine infant immunization with HepB (Lavanchy, 2004; Hou et al., 2005).

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 in Jiansu Province of China (Zuckerman et al., 1983; Sun et al., 1986, 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., 1986, 2002). Since about 20 million children are born in China each year, universal HepB immunization would protect 1.5 million from becoming HBV carriers in China every year. After reviewing these data, the Ministry of Health of China recommended routine vaccination of infants in China (MMWR, 2007; Sun et al., 2002). However, at that time infant HepB immunization was done mainly in the large cities of the richer eastern and coastal provinces (see Fig. 1(b)) because of high vaccine prices and user fees charged to parents (MMWR, 2007). Starting January 1, 2002, the Ministry of Health of China integrated the infant HepB vaccination into the national immunization program with vaccine provided entirely by the government (MMWR, 2007; Sun et al., 2002). Also starting from 2002, a 5-year joint project by the Chinese Ministry of Health and GAVI Alliance (GAVI, 2009) provided free HepB for approximately 5.6 million children born each year in 12 western provinces and in government-designated poor counties in 10 middle provinces (MMWR, 2007) (Fig. 1(b)). During 2003–2006, approximately 15.4 million children in China-GAVI project counties received the 3-dose HepB series.

The data from 2003 and 2007 clearly reveal this history and the consequences of the project. Although compared to 2003 the incidence increased in almost (29 of 31) all provinces in 2007, five of the eastern provinces had the lowest incidence in both years, indicating that these provinces benefited from the earlier immunization programme. The incidence in five of the middle provinces stabilized. The biggest changes occurred in the western

provinces although the situation varied from province to province. In 2007, the reported incidence rate of acute hepatitis B varied from 15.84 per 100,000 in Tibet (the lowest in the whole country) to 267.45 per 100,000 in Qinghai (the highest in the whole country, see Fig. 1(c)). More significantly, Tibet and Shaanxi were the only two provinces where the incidence rate decreased in 2007. This strongly demonstrates that the China-GAVI project is successful in some provinces.

The specific character of HBV infection in China is that there is a large number of HBV carriers. The purpose of this paper is to develop a mathematical model to study the transmission dynamics and control of HBV in mainland China, taking account the character of the virus infection in the country. After analyzing the existence and stability of the disease-free and disease-endemic equilibria of the model, we shall use the model to simulate the HBV data (Fig. 1(a)) reported by the Ministry of Health of China. By carrying out sensitivity analysis of the basic reproduction number on various parameters, we shall suggest some optimal strategies for control HBV infection in China.

The article is organized as follows. The model is presented in Section 2. In Section 3, we evaluate the basic reproduction number and determine the existence and stability of both the disease-free and disease-endemic equilibria of the model. Sensitivity analysis is performed in Section 4. In Section 5 we apply the model to simulate the HBV data in China and seek various control measures. A brief discussion is given in Section 6.

2. Mathematical modeling

In the last two decades, mathematical models have been used frequently to study the transmission dynamics of HBV in various regions. Anderson and May (1991) used a simple deterministic, compartmental mathematical model to illustrate the effects of carriers on the transmission of HBV. Anderson et al. (1992) and Williams et al. (1996) described models of the sexual transmission of HBV, which include heterogeneous mixing with respect to age and sexual activity. Edmunds et al. (1993) illustrated the relation between the age at infection with HBV and the development of the carrier state. Medley et al. (2001) gave a model to show that the prevalence of infection is largely determined by a feedback mechanism that relates the rate of transmission, average age at infection and age-related probability of developing carriage following infection. Thornley et al. (2008) applied the model of Medley et al. (2001) to predict chronic hepatitis B infection in New Zealand. The prevalence of HBV in developing countries is different from that in developed countries, since it appears that the rate of transmission in childhood is the major determinant of the level of HBV endemicity (Edmunds et al., 1996c), and little is known on the rates and patterns of sexual contact in developing countries. McLean and Blumberg (1994) and Edmunds et al. (1996a) studied models of HBV transmission on developing countries and Williams et al. (1996) described a model of HBV in the UK.

We propose a mathematical model to understand the transmission dynamics and prevalence of HBV in mainland China. The model is constructed based on the characteristics of HBV transmission in China and the model of Medley et al. (2001). Note that Medley et al. (2001) considered only five epidemiological groups and did not distinguish the recovered and vaccinated subgroups. In fact, the immunity after recovery is lifetime, while that following vaccination might wane after some time (Edmunds et al., 1996b). Therefore, we divide the host population into six epidemiological groups: the proportion susceptible to infection S; those latently infected L; acute infections I; carriers C; recovered and with protective immunity R; and immune following vaccination V. Fig. 2 illustrates the six compartments and model variables.

We assume that the population of newborn carriers born to carriers is less than the sum of the death of carriers and the population moving from carrier to immune state. In this case we have $\mu\omega v < \mu_0+\mu_1+\gamma_2$. Otherwise, carriers would keep increasing rapidly as long as there is infection; i.e., $dC/dt > 0$ for $C \neq 0$ or $I \neq 0$ and $t \geq 0$. The model is given by six ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \mu\omega(1-vC)+\psi V-(\mu_0+\beta I+\varepsilon\beta C+\gamma_3)S,\\
\frac{dL}{dt} &= (\beta I+\varepsilon\beta C)S-(\mu_0+\sigma)L,\\
\frac{dI}{dt} &= \sigma L-(\mu_0+\gamma_1)I,\\
\frac{dC}{dt} &= \mu\omega vC+q\gamma_1 I-(\mu_0+\mu_1+\gamma_2)C,\\
\frac{dR}{dt} &= \gamma_2 C+(1-q)\gamma_1 I-\mu_0 R,\\
\frac{dV}{dt} &= \mu(1-\omega)+\gamma_3 S-(\mu_0+\psi)V,
\end{aligned} \tag{2.1}$$

where the parameters are given in Table 1.

Following the recipe of van den Driessche and Watmough (2002), we obtain that the basic reproduction number, defined as the expected number of secondary infections produced by an index case (Anderson and May, 1991), is given by

$$R_0 = \frac{\mu(\psi+\mu_0\omega)}{\mu_0(\mu_0+\gamma_3+\psi)}\frac{\sigma\beta}{(\mu_0+\gamma_1)(\mu_0+\sigma)}\left[1+\frac{q\gamma_1\varepsilon}{\mu_0+\mu_1+\gamma_2-\mu\omega v}\right]. \tag{2.2}$$

Define

$$R_1 = \frac{\sigma\beta S_0}{(\mu_0+\gamma_1)(\mu_0+\sigma)},$$

$$R_2 = \frac{\sigma\beta q\gamma_1\varepsilon S_0}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)(\mu_0+\gamma_1)(\mu_0+\sigma)}.$$

Then we can see that

$$R_0 = R_1+R_2.$$

Remark. We can also follow Diekmann et al. (1990), evaluate the basic reproduction number by the formula $\tilde{R}_0 = \rho(FV^{-1})$ and obtain the following formula:

$$\tilde{R}_0 = \tfrac{1}{2}\{r_{01}+r_{02}+r_{03}+\sqrt{(r_{01}+r_{02}-r_{03})^2+4r_{02}r_{03}}\},$$

where

$$r_{01} = \frac{\sigma\beta S_0}{(\mu_0+\sigma)(\mu_0+\gamma_1)},$$

$$r_{02} = \frac{\varepsilon\beta q\sigma\gamma_1 S_0}{(\mu_0+\sigma)(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2)},$$

$$r_{03} = \frac{\mu\omega v}{\mu_0+\mu_1+\gamma_2}.$$

In fact, simple calculation shows that $R_0 < 1 (=1, >1)$ is equivalent to $\tilde{R}_0 < 1 (=1, >1)$.

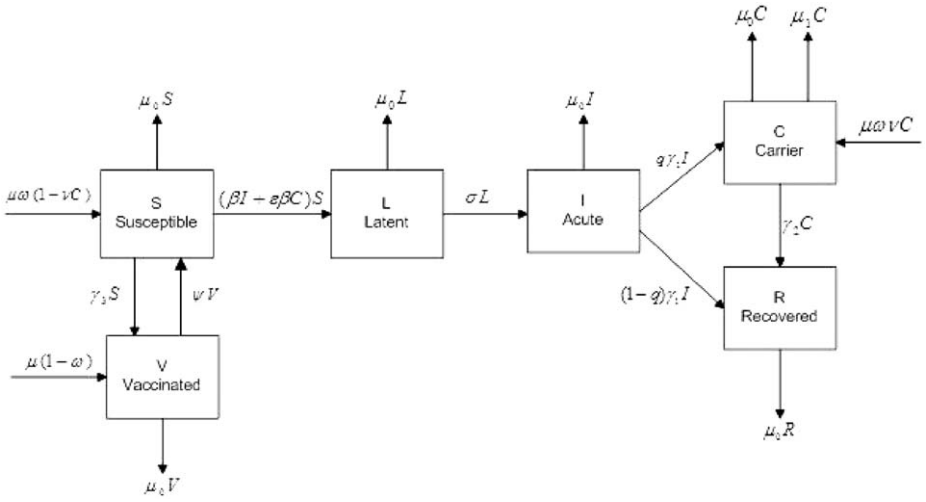

Fig. 2. Flowchart of HBV transmission in a population.

Table 1
Parameter values used in numerical simulations.

Parameter	Interpretation	Value	Reference
μ	Birth rate	0.0121	MOHC (2009)
μ_0	Natural mortality rate	0.00693	MOHC (2009)
μ_1	HBV related mortality rate	0.2%	MMWR (2007)
β	Transmission coefficient	0.95–20.49	Edmunds et al. (1996a)
ε	Reduced transmission rate	0.16	Edmunds et al. (1996a)
σ	Rate moving from latent to acute	6 per year	Edmunds et al. (1996a)
γ_1	Rate moving from acute to carrier	4 per year	Edmunds et al. (1996a)
γ_2	Rate moving from carrier to immune	0.025 per year	Edmunds et al. (1996a)
γ_3	Vaccination rate	0–100%	
ω	Proportion of births without successful vaccination	0–100%	
q	Average probability an individual fails to clear an acute infection and develops to carrier state	0.885	Hahnea et al. (2004)
ψ	Rate of waning vaccine-induced immunity	0.1	Edmunds et al. (1996b)
ν	Proportion of perinatally infected (carrier mothers)	0.11	Edmunds et al. (1996a)

3. Steady states analysis

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

$$\frac{dS}{dt} = \mu\omega(1-\nu C)+\psi V-(\mu_0+\beta I+\varepsilon\beta C+\gamma_3)S,$$

$$\frac{dL}{dt} = (\beta I+\varepsilon\beta C)S-(\mu_0+\sigma)L,$$

$$\frac{dI}{dt} = \sigma L-(\mu_0+\gamma_1)I,$$

$$\frac{dC}{dt} = \mu\omega\nu C+q\gamma_1 I-(\mu_0+\mu_1+\gamma_2)C,$$

$$\frac{dV}{dt} = \mu(1-\omega)+\gamma_3 S-(\mu_0+\psi)V, \tag{3.1}$$

which has a disease-free equilibrium $E_0=(S_0,0,0,0,V_0)$, where

$$S_0=\frac{\mu(\psi+\mu_0\omega)}{\mu_0(\mu_0+\gamma_3+\psi)},\quad V_0=\frac{\mu(\mu_0+\gamma_3-\mu_0\omega)}{\mu_0(\mu_0+\gamma_3+\psi)}.$$

There is an endemic equilibrium $E^*=(S^*,L^*,I^*,C^*,V^*)$ if $R_0>1$, where

$$S^*=\frac{(\mu_0+\mu_1+\gamma_2-\mu\omega\nu)(\mu_0+\sigma)(\gamma_1+\mu_0)}{(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega\nu)\beta\sigma}=\frac{S_0}{R_0},$$

$$L^*=\frac{\mu_0(\gamma_3+\mu_0+\psi)S^*(\mu_0+\mu_1+\gamma_2)(\gamma_1+\mu_0)(R_0-1)}{(\mu_0+\psi)\sigma[\beta S^*(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega\nu)+\mu\omega\nu q\gamma_1]},$$

$$I^*=\frac{\mu_0 S^*(\gamma_3+\mu_0+\psi)(R_0-1)(\mu_0+\mu_1+\gamma_2-\mu\omega\nu)}{(\mu_0+\psi)[\beta S^*(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega\nu)+\mu\omega\nu q\gamma_1]},$$

$$C^*=\frac{\mu_0\varepsilon\beta q\gamma_1(\mu_0+\gamma_1)(\gamma_3+\mu_0+\psi)(S^*)^2(R_0-1)}{(\mu_0+\psi)[\beta S^*(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega\nu)+\mu\omega\nu q\gamma_1]},$$

$$V^*=\frac{\mu(1-\omega)+\gamma_3 S^*}{\mu_0+\psi}.$$

Regarding the stability of the disease-free equilibrium E_0, we have the following result.

Theorem 1. *If $R_0<1$ then E_0 is stable; if $R_0>1$ then E_0 is unstable.*

Proof. The Jacobian matrix at E_0 is

$$J(E_0)=\begin{pmatrix} -(\mu_0+\gamma_3) & 0 & -\beta S_0 & -\mu\omega v-\varepsilon\beta S_0 & \psi \\ 0 & -(\mu_0+\sigma) & \beta S_0 & \varepsilon\beta S_0 & 0 \\ 0 & \sigma & -(\mu_0+\gamma_1) & 0 & 0 \\ 0 & 0 & q\gamma_1 & \mu\omega v-(\mu_0+\mu_1+\gamma_2) & 0 \\ \gamma_3 & 0 & 0 & 0 & -(\mu_0+\psi) \end{pmatrix}.$$

The characteristic equation is

$$\Phi_0(\lambda):=-(\mu_0+\lambda)(\psi+\mu_0+\gamma_3+\lambda)[\lambda^3+a_2\lambda^2+a_1\lambda+a_0]=0,$$

where

$$a_0=(\mu_0+\mu_1+\gamma_2-\mu\omega v)[(\mu_0+\gamma_1)(\mu_0+\sigma)-\sigma\beta S_0]-\sigma\beta q\gamma_1\varepsilon S_0,$$

$$a_1=(\mu_0+\gamma_1)(\mu_0+\sigma)+(2\mu_0+\gamma_1+\sigma)(\mu_0+\mu_1+\gamma_2-\mu\omega v)-\sigma\beta S_0,$$

$$a_2=3\mu_0+\sigma+\gamma_1-\mu\omega v+\mu_1+\gamma_2.$$

When $R_0<1$, we have $0<R_1<1$ and $0<R_2<1$. Thus,

$$a_0=(\mu_0+\mu_1+\gamma_2)(\mu_0+\gamma_1)(\mu_0+\sigma)(1-R_1-R_2)>0,$$

$$a_2>0,$$

$$\begin{aligned} a_1a_2-a_0&=(2\mu_0+\sigma+\gamma_1)[(\mu_0+\gamma_1)(\mu_0+\sigma)\\ &\quad-\sigma\beta S_0+(\mu_0+\mu_1+\gamma_2-\mu\omega v)(3\mu_0+\sigma+\gamma_1+\mu_1+\gamma_2-\mu\omega v)]\\ &\quad+\sigma\beta q\gamma_1\varepsilon S_0=(2\mu_0+\sigma+\gamma_1)(\mu_0+\gamma_1)(\mu_0+\sigma)\\ &\quad[1-R_1+\frac{(\mu_0+\mu_1+\gamma_2-\mu\omega v)}{(\mu_0+\sigma)(\mu_0+\gamma_1)}(3\mu_0+\sigma+\gamma_1+\mu_1+\gamma_2-\mu\omega v)]\\ &\quad+\sigma\beta q\gamma_1\varepsilon S_0>0. \end{aligned}$$

Therefore, by Routh–Herwitz criteria, all roots of $\Phi_0(\lambda)$ have negative real parts, and E_0 is stable.

Furthermore, if $R_0>1$ we have $a_0<0$ and E_0 is unstable. □

To discuss the properties of the endemic equilibrium $E^*=(S^*,L^*,I^*,C^*,V^*)$, we make an elementary row-transformation for the Jacobian matrix at E^* and obtain the following matrix:

$$J^*=\begin{pmatrix} -\mu_0-\beta I^*-\varepsilon\beta C^*-\gamma_3 & 0 & -\beta S^* & -\mu\omega v-\varepsilon\beta S^* & \psi \\ 0 & -\mu_0-\sigma & M_1 & \varepsilon M_1-\mu\omega v M_2 & \psi M_2 \\ 0 & 0 & -(\mu_0+\gamma_1)+\frac{\sigma M_1}{\mu_0+\sigma} & \frac{\sigma(\varepsilon M_1-\mu\omega v M_2)}{\mu_0+\sigma} & \frac{\psi\sigma M_2}{\mu_0+\sigma} \\ 0 & 0 & 0 & M_3-\mu\omega v M_4 & \psi M_4 \\ 0 & 0 & 0 & 0 & M_5 \end{pmatrix},$$

where

$$M_1=\frac{\beta S^*(\mu_0+\gamma_3)}{\mu_0+\beta I^*+\varepsilon\beta C^*+\gamma_3},$$

$$M_2=\frac{\beta(I^*+\varepsilon\beta C^*)}{\mu_0+\beta I^*+\varepsilon\beta C^*+\gamma_3},$$

$$\begin{aligned} M_3&=\mu\omega v-\mu_0-\mu_1-\gamma_2\\ &\quad-\frac{q\gamma_1\sigma\beta\varepsilon S^*(\mu_0+\gamma_3)}{\sigma\beta S^*(\mu_0+\gamma_3)-(\mu_0+\gamma_1)(\mu_0+\sigma)(\mu_0+\beta I^*+\varepsilon\beta C^*+\gamma_3)}, \end{aligned}$$

$$M_4=-\frac{q\gamma_1\sigma\beta(I^*+\varepsilon C^*)}{\sigma\beta S^*(\mu_0+\gamma_3)-(\mu_0+\gamma_1)(\mu_0+\sigma)(\mu_0+\beta I^*+\varepsilon\beta C^*+\gamma_3)},$$

$$\begin{aligned} M_5&=\frac{\gamma_3\psi M_4[q\gamma_1(\mu\omega v+\varepsilon\beta S^*)-\beta S^*(\mu\omega v-\mu_0-\mu_1-\gamma_2)]}{q\gamma_1(\mu_1+\beta I^*+\varepsilon\beta C^*+\gamma_3)(M_3-\mu\omega v M_4)}\\ &\quad-\frac{(\mu_0+\psi)(\mu_1+\beta I^*+\varepsilon\beta C^*)+\mu_0\gamma_3}{\mu_1+\beta I^*+\varepsilon\beta C^*+\gamma_3}. \end{aligned}$$

The eigenvalues are

$$\lambda_1=-\mu_0-\beta I^*-\varepsilon\beta C^*-\gamma_3<0,\quad \lambda_2=-\mu_0-\sigma<0,$$

$$\lambda_3=-(\mu_0+\gamma_1)+\frac{\sigma M_1}{\mu_0+\sigma},\quad \lambda_4=M_3-\mu\omega v M_4,\quad \lambda_5=M_5.$$

Since I^*, C^* and L^* are coordinates of the endemic equilibrium E^*, we have

$$\mu_0+\sigma=(\beta I^*+\varepsilon\beta C^*)\frac{S^*}{L^*},\quad \mu_0+\gamma_1=\sigma\frac{L^*}{I^*}.$$

Thus, $\lambda_3<0$ if and only if

$$\frac{(\mu_0+\gamma_3)I^*}{(\mu_0+\beta I^*+\varepsilon\beta C^*+\gamma_3)(I^*+\varepsilon C^*)}<1,$$

which is equivalent to

$$(\mu_0+\gamma_3)\varepsilon C^*+\beta(I^*+\varepsilon C^*)^2>0.$$

It holds as long as the endemic equilibrium E^* exists. In addition, C^* and I^* satisfy

$$q\gamma_1=(\mu_0+\mu_1+\gamma_2-\mu\omega v)\frac{C^*}{I^*}.$$

Similar to the proof of λ_3, we obtain that $\lambda_4<0$ if and only if

$$S^*\beta(I^*+\varepsilon C^*)+\mu\omega v C^*>0,$$

which holds as long as E^* exists. Furthermore, $\lambda_3<0$ implies that $M_4>0$. We have $\lambda_5<0$, since $\mu\omega v<\mu_0+\mu_1+\gamma_2$ and $\lambda_4<0$. Therefore, all eigenvalues are negative, and we have the following conclusion on the disease endemic equilibrium E^*.

Theorem 2. *E^* is a stable node if it exists.*

4. Sensitivity analysis

The parameters ω and γ_3 are important for the prevalence of HBV infection. They influence the dynamics of HBV, in particular the equilibrium states, including the states of susceptibles, acute infectives, and carriers. We can see from Fig. 1(c) that provinces with high rate of vaccination, i.e. the proportion of births with successful vaccination $1-\omega$ and the vaccination rate γ_3 are large (especially $1-\omega$, such as Tibet, Beijing and Shanghai), had low incidence in 2007. Especially in Tibet the incidence rate decreased from 64.42 in 2003 to 15.84 in 2007 after the China-GAVI project.

The existence and stability of equilibria are affected by the values of parameters. Fig. 3(a) shows the model output on the relationship between the equilibrium state of the seropositive $1-S$ and $1-\omega$. When $1-\omega$ is large so that $R_0<1$, only the disease-free equilibrium exists, which is stable. On the other hand when $1-\omega$ is small, the disease-free equilibrium is unstable and an endemic equilibrium appears. Note that for the disease-free equilibrium, the proportion of seropositive equals the proportion of immunization following vaccination, which increases as $1-\omega$ increases.

The equilibrium state of the carriers depends on both the proportion of births with successful vaccination $1-\omega$ and the rate of waning vaccine-reduced immunity ψ. From Fig. 3(b), we can see that when $R_0>1$, C becomes smaller if $1-\omega$ becomes small, although in all cases C increases as R_0 increases. Similarly, Fig. 3(c) shows that if the immunity does not wane vaccine-reduced, i.e. $\psi=0$, C is smaller despite of the same R_0. Fig. 3(d) shows that the carrier prevalence dynamic depends on ψ. If $\psi=0$, the maximum proportion of the carriers is lower than that of $\psi=0.1$, and the proportion of the carriers decreases faster (the dashed curve is below the solid one). Therefore, we distinguish the individuals of V and R in our model.

China has a huge number of HBV infections and carriers. This is one of the reasons that HBV infection is more serious in China than other countries. We want to see how the infection dynamics depend on the initial values. In Fig. 3(e)–(f), the curves are drawn with the same parameters but different initial values. In Fig. 3(e), the proportion of the carriers always keeps decreasing when the initial value for the acute infections is much smaller than the

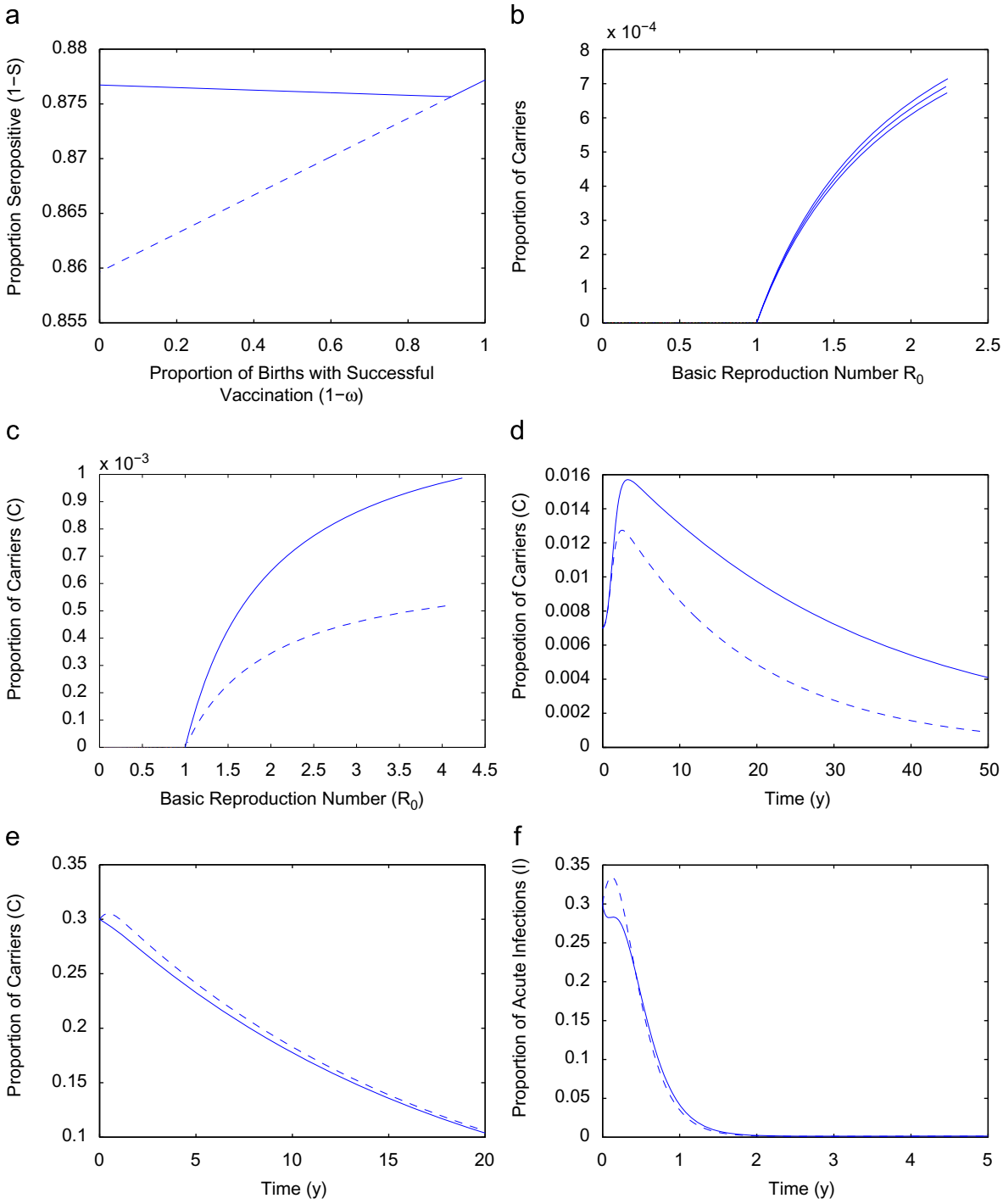

Fig. 3. Model output: (a) the relationship between the equilibrium proportion of seropositive $(1-S)$ and the proportion of births with successful vaccination $(1-\omega)$, (b) the equilibrium state of the carrier prevalence with immunization coverage $(1-\omega)$ at 50%, 70% and 90% (from left to right), (c) the equilibrium state diagram of the carrier prevalence with the rate of waning vaccine-reduced immunity (ψ) at $\psi=0.1$ (solid curve) and $\psi=0$ (dashed), (d) carrier prevalence dynamic consequences with the rate of waning vaccine-reduced immunity (ψ) at $\psi=0.1$ (solid curve) and $\psi=0$ (dashed), (e) carrier prevalence dynamic consequences with the initial values $(0.1, 0.03, 0.02, 0.3, 0.2, 0.35)$ (solid curve) and $(0.1, 0.1, 0.2, 0.3, 0.1, 0.2)$ (dashed), and (f) acute infection prevalence dynamic consequences with the initial values $(0.4, 0.1, 0.3, 0.2, 0, 0)$ (solid curve) and $(0.2, 0.3, 0.3, 0.2, 0, 0)$ (dashed).

initial carriers, while it increases in the first year then decreases when I_0 is close to C_0, although both curves approach the same value eventually. Similarly, in Fig. 3(f), the acute infections first increase in the first half year, then decrease when the initial value of the latent individuals L_0 equals to I_0. However, I is always non-increasing when $L_0=0.1$ and $I_0=0.3$.

5. Apply to the HBV transmission in China

In this section, we first use model (2.1) to simulate the reported HBV data (Fig. 1(a)) from the Ministry of Health of China (MOHC, 2009). Then we examine the current HBV control strategies in China. Based on the sensitivity analysis of the basic reproduction number on

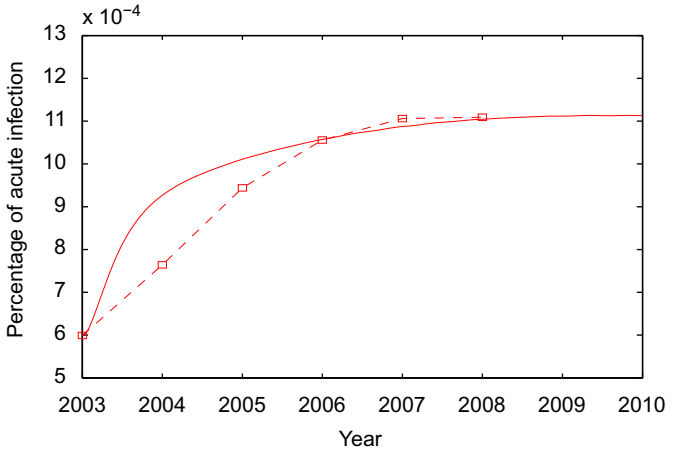

Fig. 4. The comparison between the reported acute hepatitis B data in mainland China since 2003 (MOHC, 2009; Fig. 1(a)) and the simulation of our model. The dashed curve is the data reported by Ministry of Health of China while the solid curve is simulated by using our model. Here $\omega = 0.7, \gamma_3 = 0.12, \beta = 1$, and all other parameters are given in Table 1.

parameters, we seek optimal measures to control the transmission of HBV in mainland China.

Using parameter values in Table 1, numerical simulations of the model give the percentage of acute hepatitis B infection in mainland China since 2003 (see Fig. 4). There is a small discrepancy between the data reported by Ministry of Health of China and the simulated solution due to the overestimation of some parameters and the initial proportion of latency. However, the simulated rates of 2007 and 2008 almost match the reported data for these two years. Thus, our model can mimic the reported data on HBV infection in mainland China. Based on the model and the used parameter values, we estimate the basic reproduction number $R_0 = 2.406$. This indicates that hepatitis B is endemic in mainland China: it stabilizes and is approaching its equilibrium. Therefore, the incidence will not vary significantly in the near future with the current control measures and immunization program.

To find better control strategies for HBV infection, we would like to see what parameters can reduce the basic reproduction number R_0 given by (2.2). From Fig. 5 we can see that R_0 decreases if $1-\omega$ increases, or β decreases, or γ_3 increases. If the transmission coefficient β is sufficiently small HBV could be eliminated even if $1-\omega = 0$. However, it is difficult to control β. From Figs. 5(a) and (b), we see that even if β is not small, R_0 might be smaller than 1 as long as γ_3 and $1-\omega$ are large enough. Therefore, immunization of both newborns and susceptible individuals is an efficient intervention. Figs. 5(a)–(c) show that combining immunization with reduction of contacts can reduce R_0 to be less than 1. The optimal control strategy will be a combination of immunization of newborns, immunization of susceptible individuals (at least young adults), and reduction of contacts.

The HBV infection in western provinces of China is the worst (see Fig. 1(c)), in particular in Xinjiang, Gansu and Qinghai. Increasing HepB coverage and timely administration of the birth dose in these areas is the best strategy to reduce the incidence and it has been successful in two other western provinces (Tibet and Shaanxi). The significant increase from 2003 to 2007 in two rich eastern provinces Guangdong and Fujian is perplexing. One of the reasons is probably that there is a very large number of immigrant workers in these two provinces. Administrating the immunization programme to the families of immigrant workers becomes important in reducing the infection in these provinces. The huge

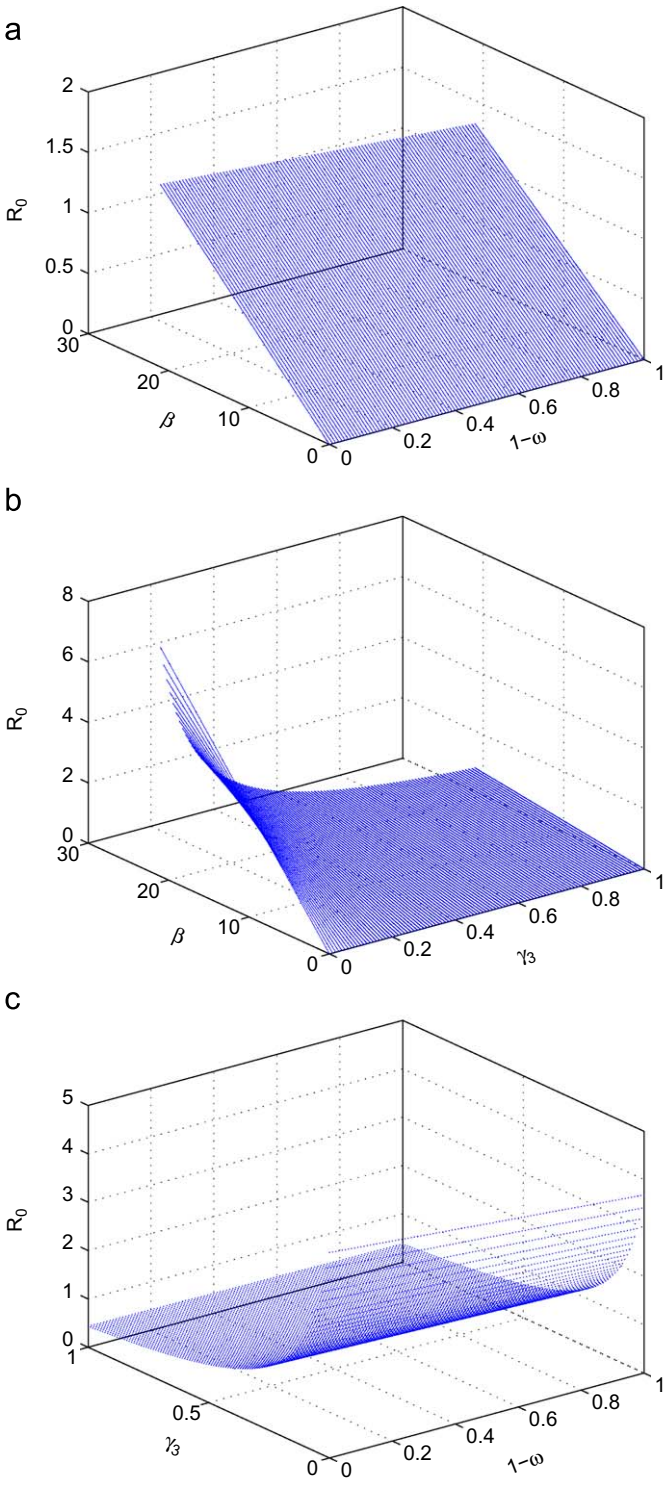

Fig. 5. The graphs of the basic reproduction number R_0 in terms of some parameters: (a) R_0 in terms of $1-\omega$ and β, (b) R_0 as a function of γ_3 and β, and (c) R_0 in terms of $1-\omega$ and γ_3.

increase in the middle province Henan, the most populated provinces (at the end of 2008 it had 88 million residents) and one of the provinces with most migration workers, is worrisome. With an increasing coverage of immunization on both newborns and young adults and an improvement of public health control measures, the burden of hepatitis B may will be lessened.

A comparison between the HIV and HBV incidence rates in mainland China leads to some questions and concerns (see Fig. 6).

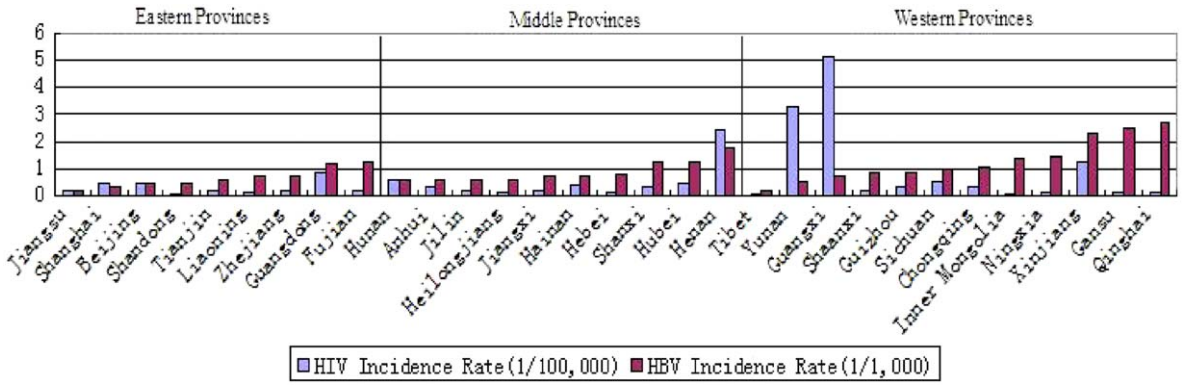

Fig. 6. Comparison of incidence rates of HIV (1/100,000) and HBV (1/1000) in mainland China by provinces in 2007 (MOHC, 2009).

Guangdong in the eastern, Henan in the middle, and Xianjiang in the western provinces had high incidence rates in both HIV and HBV infections in 2007. As HIV and HBV have very similar transmission routes, is there any correlation between the transmission of HIV and that of HBV in these provinces? Is there any case of coinfection of HIV and HBV? This certainly deserves further study. Unlike HIV, there is no large-scale national awareness campaign to educate the public and governmental officials in China about HBV. Yet the data in Fig. 6 indicates that it is HBV and not HIV that is the most common serious viral infection in China. Also, chronic hepatitis B is asymptomatic so most cases in China are undetected. Increasing the awareness of HBV is thus very important.

6. Discussion

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 is in China and about 10% of the general population in the country are carriers. In this paper, taking the specific feature of HBV infection in China into account, we proposed a mathematical model to study the transmission dynamics and control of HBV in mainland China. We discussed the existence and stability of the disease-free and disease-endemic equilibria of the model and performed sensitivity analysis of the parameters.

With suitable parameter values, our model can mimic the reported HBV data from the Ministry of Health of China. We estimated the basic reproduction number to be $R_0 = 2.406$ in China. This indicates that hepatitis B is endemic in China and is approaching its equilibrium with the current immunization programme and control measures. By carrying out sensitivity analysis of the basic reproduction number on various parameters, we think that the optimal control strategy is a combination of immunization of newborns, retroactive immunization of susceptible adults, and reduction of contacts.

It is interesting to notice that on April 7, 2009, the Central Government of China (CGC, 2009) 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. We expect that this will reduce the incidence rate of HBV infection in China significantly. This also suggests that it might be more reasonable and interesting to use age-structured models to study the transmission and control of HBV (Edmunds et al., 1993; McLean and Blumberg, 1994; Zhao et al., 2000). In a forthcoming paper we shall consider an age-structured version of our model (2.1).

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