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TRANSMISSION DYNAMICS AND THE CONTROL OF HEPATITIS B IN CHINA: A POPULATION DYNAMICS VIEW*

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Abstract Though the prevalence of hepatitis B began to decline for the first time in 2010, it remains unclear whether this downward trend is permanent and the disease will be eradicated in mainland China under the current measures. Because a large number of hepatitis B virus (HBV) carriers and unknown HBV infections is characteristic of HBV infections in China, a mathematical model was designed and fitted to the reported hepatitis B data. The estimated basic reproduction number is 1.2861 (95% confidence interval (CI) 1.2386-1.3302), which remains greater than one. Thus, the decline in 2010 may be part of the temporary benefits of public policy measures and should not be interpreted as indicative of successful intervention, although interventions do provide some benefits. To assess the effects of various interventions, the global uncertainty and sensitivity analyses revealed that the contribution of carriers is always greater than that of acute infections, and the prevalence of hepatitis B in China may be primarily a result of transmission by unknown patients. Therefore, strategies for controlling the HBV endemic, which target known patients, are unlikely to be highly effective. Additionally, three feasible strategies are proposed, although the benefits of these strategies may change radically over time.

Keywords Hepatitis B, mathematical modeling, basic reproduction number, equilibrium, control strategy.

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1. Introduction

Hepatitis B is a potentially life-threatening liver infection that is caused by the hepatitis B virus (HBV). Currently, HBV infection has become a serious public health problem because of its worldwide prevalence and potential adverse consequences, including cirrhosis, liver failure and hepatocellular carcinoma [5]. The World Health Organization (WHO) reported that more than 240 million people have a chronic (long-term) liver infection, more than 780,000 people die worldwide each year due to hepatitis B, and its prevalence is highest in sub-Saharan Africa and East Asia [24].

In mainland China, hepatitis B is one of the top three infectious diseases, and the prevalence of HBV surface antigen (HBsAg) among the general population is

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9.7%, based on a national survey conducted in 1992 [27]. With the use of the hematogenous hepatitis B vaccine beginning in 1984 and the vaccination program for newborn babies beginning in the 1990s [2], the overall prevalence of HBsAg carriers has decreased slightly from 9.7% in 1992 to 9% in 2002 [11]. However, the incidence of hepatitis B continues to increase, from 21.9 in 100,000 people in 1990 to 53.3 in 100,000 in 2003 [25]. As a result, the disease has become endemic in China [12]. The number of people living with HBV in China makes up almost one-third of the people infected with HBV worldwide [13], and 300,000 people die from HBV-related diseases in China every year, including 180,000 patients with hepatocellular carcinoma [10].

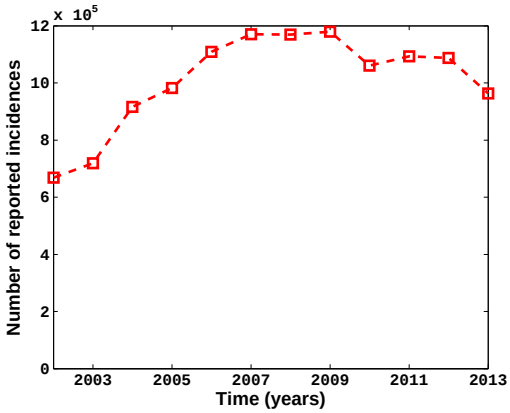

Figure 1. Hepatitis B data reported by the National Health and Family Planning Commission of the People's Republic of China from 2002 to 2013 [17].

To better survey the epidemic situation, the National Health and Family Planning Commission of the People's Republic of China (NHFPC) has published the "national statutory epidemic situation of infectious diseases" every year since 2003 [17]. Figure 1 illustrates the hepatitis B data from 2002 to 2013, which are reported by the NHFPC. Figure 1 shows that a decline in hepatitis B prevalence started in 2010. This decreased incidence is primarily due to the enactment of the 2006-2010 hepatitis B control plan, in which infant hepatitis B immunizations are administered, the modes of disease transmission were controlled, the infection situation of hepatitis B was monitored among key crowds, and so on [18]. However, it remains unknown whether the downward trend is permanent and will lead to hepatitis B eradication from mainland China under the current control measures.

In mainland China, because of the imbalance in economic develop among provinces, the existence of many remote mountainous and rural areas, and the fragmented health services, patients with HBV infection are often missed. Such patients do not know that they suffer from an HBV infection, use Chinese herbs and/or other improper agents to treat their symptoms [3, 14], and thus continue with their usual daily activities, which is also common in many developing countries. Hence, in addition to the large number of HBV carriers, another specific characteristic of the HBV infection endemic in China is that there are many unknown HBV infections, i.e., the infected persons but they do not know. Although the effect of carriers on the prevalence of hepatitis B in China has been explored by Zou et al. [29, 30], the effect of unknown HBV infections and their contribution has not been considered

and remains unclear.

Mathematical models can provide key insights into the course of an epidemic, potentially helping medical management by anticipating the impact of various interventions [8, 22, 26, 29–32]. The purpose of this study is to develop a mathematical model to study the transmission dynamics and control of HBV according to the specific characteristics of the viral infection in mainland China. The model is a compartment model expressed by a set of ordinary differential equations. Besides a comprehensive kinetic analysis of the proposed model, the reported hepatitis B data is further used to estimate the undetermined parameters and the basic reproduction number. In addition, a global uncertainty and sensitivity analysis of the model is performed to estimate the resultant effects of various interventions. As a result, the proposed interventions are assessed, and some projections and feasible control strategies of HBV infection in China are discussed.

2. Materials and Methods

2.1. Model structure

In the following, we describe the modified model structure of HBV transmission based on an existing model [29, 30]. According to the specific characteristics of HBV infection in China, the population at time t is divided into nine epidemiological groups: (1) the proportion susceptible to infection $S(t)$; (2) those latently infected $L(t)$; (3) unknown acute infections $I_1(t)$; (4) unknown carriers $C_1(t)$; (5) unknown carriers recovered and with protective immunity $R_1(t)$; (6) known acute infections $I_2(t)$; (7) known carriers $C_2(t)$; (8) known carriers recovered and with protective immunity $R_2(t)$; and (9) immune following vaccination $V(t)$. The values of all of the groups correspond to the proportion based on the population in 2002. Figure 2 illustrates the flowchart of nine compartments and model variables, which describes how individuals can move among the states.

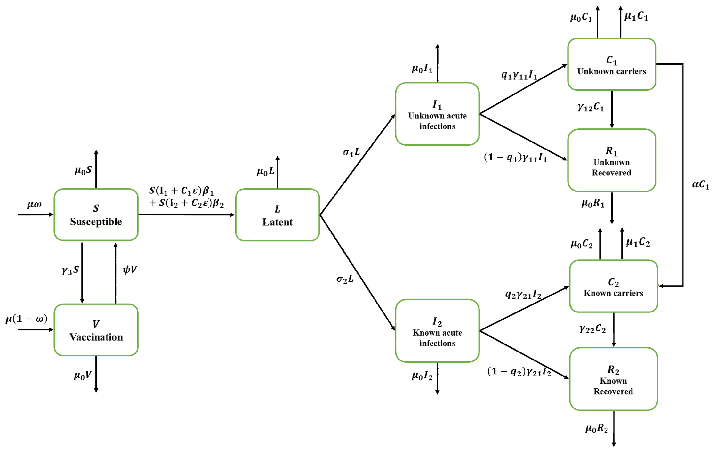

Figure 2. Flowchart of HBV transmission in a population.

Comparing the proposed model structure (Figure 2) with the previously reported model [29, 30], the potential HBV patients in China, i.e., the categorical variables

of unknown patients, including acute, carriers and recovered groups, are considered in our model. Additionally, because the prevalence of HBsAg among children aged 1 to 4 years decreased from over 8.5% in 1992 to less than 1% in 2006 in China [15], and because the GAVI project in China has been highly successful regarding HBV prevention and control [7, 9], the proportion of perinatally infected patients has become negligible. The perinatal exposure is neglected, and horizontal transmission is primarily considered in our model.

2.2. Dynamical model

According to the model structure shown in Figure 2, the dynamic model can be described by the following differential equations:

$$\begin{cases} S^{'} = \psi V + \mu\omega - \beta_1 S(I_1 + \varepsilon C_1) - \beta_2 S(I_2 + \varepsilon C_2) - (\mu_0 + \gamma_3)S, \\ L^{'} = \beta_1 S(I_1 + \varepsilon C_1) + \beta_2 S(I_2 + \varepsilon C_2) - (\mu_0 + \sigma_1 + \sigma_2)L, \\ I_1^{'} = \sigma_1 L - (\mu_0 + \gamma_{11})I_1, \\ I_2^{'} = \sigma_2 L - (\mu_0 + \gamma_{21})I_2, \\ C_1^{'} = q_1\gamma_{11}I_1 - (\mu_0 + \mu_1 + \alpha + \gamma_{12})C_1, \\ C_2^{'} = \alpha C_1 + q_2\gamma_{21}I_2 - (\mu_0 + \mu_1 + \gamma_{22})C_2, \\ V^{'} = \mu(1-\omega) + \gamma_3 S - (\mu_0 + \psi)V. \end{cases} \tag{2.1}$$

Note that there is no interaction between the unknown/known recovered groups and other groups, aside from the influx from acute infections and carriers to the recovered groups (Figure 2). Here, we omit the change in size of the unknown/known recovered groups over time. The interpretations and biologically plausible values of the variables and parameters are listed in Table S1 and Table S2 in Appendix A.

2.3. Basic reproduction number

Using the idea of the basic reproduction number in compartmental models [6,23], we obtain the basic reproduction number of model (2.1), which indicates the expected number of secondary infections produced by an index case.

$$R_0 = R_{I_1} + R_{I_1C_1} + R_{I_1C_1C_2} + R_{I_2} + R_{I_2C_2}. \tag{2.2}$$

Here,

$$\begin{aligned} &R_{I_1} = \tfrac{\beta_1\sigma_1 S_0}{l z_{11}}, \quad R_{I_1C_1} = \tfrac{\varepsilon g_1\beta_1\sigma_1 S_0}{l z_{11} z_{12}}, \quad R_{I_1C_1C_2} = \tfrac{\varepsilon g_1\alpha\beta_2\sigma_1 S_0}{l z_{11} z_{12} z_{22}}, \\ &R_{I_2} = \tfrac{\beta_2\sigma_2 S_0}{l z_{21}}, \quad R_{I_2C_2} = \tfrac{\varepsilon g_2\beta_2\sigma_2 S_0}{l z_{21} z_{22}} \end{aligned} \tag{2.3}$$

denote the contribution of unknown acute infections, unknown carriers, the conversions from unknown carriers to known carriers, known acute infections and known carriers, respectively. S_0 in these expressions denotes the steady state when HBV is eliminated, l, g_i, z_{ij}, $i = 1, 2, j = 1, 2$, are the combinations of some parameters, and the detailed expressions can be found in the kinetics analysis in the Appendix B. Briefly, the basic reproduction number R_0 can be divided into two scenarios, $R_I = R_{I_1} + R_{I_1C_1} + R_{I_1C_1C_2}$ and $R_{II} = R_{I_2} + R_{I_2C_2}$, which correspond to the basic reproduction number for unknown patients and known patients, respectively.

3. Results

3.1. Kinetics analysis

Regarding the kinetics of the proposed model (2.1), based on the Routh-Hurwitz criterion, a disease-free equilibrium always exists, and it is stable only if the basic reproduction number is less than one. Conversely, a disease-endemic equilibrium appears and is stable as long as it exists (see Appendix B for a detailed proof of the kinetics). According to the biological significance of the kinetics, the basic reproduction number is a critical value for the outbreak of hepatitis B. When the basic reproduction number is greater than one, the mean reproduction number of an HBV patient is greater than one during his or her lifetime in the absence of any control policies, i.e., the disease will continue to be prevalent or become an endemic. Otherwise, the disease can be controlled or eradicated.

3.2. Fitting the reported hepatitis B data and estimating the basic reproduction number

Using an adaptive Metropolis-Hastings algorithm to carry out an extensive Markov-chain Monte-Carlo (MCMC) simulation, we estimate the undetermined parameters and initial conditions in Table 1.

TABLE *1. Means and 95% confidence intervals (CI) for the estimated* parameters (Par.) and initial conditions (IC).

Par./IC	**Interpretation**	**Mean (95% CI)**
β_1	Unknown HBV transmission rate from susceptible to latent	5.3959 (5.3671, 5.4247)
β_2	Known HBV transmission rate from susceptible to latent	1.5906 (1.5734, 1.6295)
σ_1	Conversion rate from latent to unknown acute	1.6015 (1.5734, 1.6295)
γ_3	Vaccination rate	0.2539 (0.2491, 0.2587)
q_1	Average probability that an unknown HBV individual fails to clear an acute infection and develops into the carrier state	0.3759 (0.3726, 0.3792)
α	HBV conversion rate from unknown carrier to known carrier	9.3936×10^{-2} $(9.3679 \times 10^{-2}, 9.4193 \times 10^{-2})$
$S(0)$	Initial proportion of the susceptible population	3.2997×10^{-2} $(3.2708 \times 10^{-2}, 3.3285 \times 10^{-2})$
$L(0)$	Initial proportion of latently infections	7.1146×10^{-4} $(4.3943 \times 10^{-4}, 9.8349 \times 10^{-4})$
$I_1(0)$	Initial proportion of unknown acute infections	3.2929×10^{-4} $(4.0823 \times 10^{-4}, 6.1776 \times 10^{-4})$

Figure 3A illustrates the numerical simulation of the model with the fitted parameters, which provide the overall trend of the percentage of acute hepatitis B infections in mainland China. Furthermore, we estimate the basic reproduction number, $R_0 = 1.2861$ (95% CI 1.2386-1.3302). We conclude that the decrease in the

basic reproduction number compared to the previous estimation ($R_0 = 2.406$) [29] is due to better control precision and adaptability, based on the 2006-2010 hepatitis B control plan in China [18]. However, because the value remains greater than one, the incidences will rebound after a long-term decrease and tend toward the disease-endemic equilibrium (Figure 3B). Therefore, hepatitis B remains an endemic in China, even under the current control measures and immunization programs. Regarding the basic reproduction number, we can also estimate the contributions of unknown and known patients, which are $R_I = 0.9067$ (95% CI 0.8679-0.9500) and $R_{II} = 0.3794$ (95% CI 0.3660-0.3935), respectively. As a result, the transmission of hepatitis B in mainland China may be largely due to unknown patients because the contribution from unknown patients is greater than that of known patients ($R_I > R_{II}$). Ignoring the role of unknown HBV infections could underestimate the epidemiologic trend of hepatitis B in China.

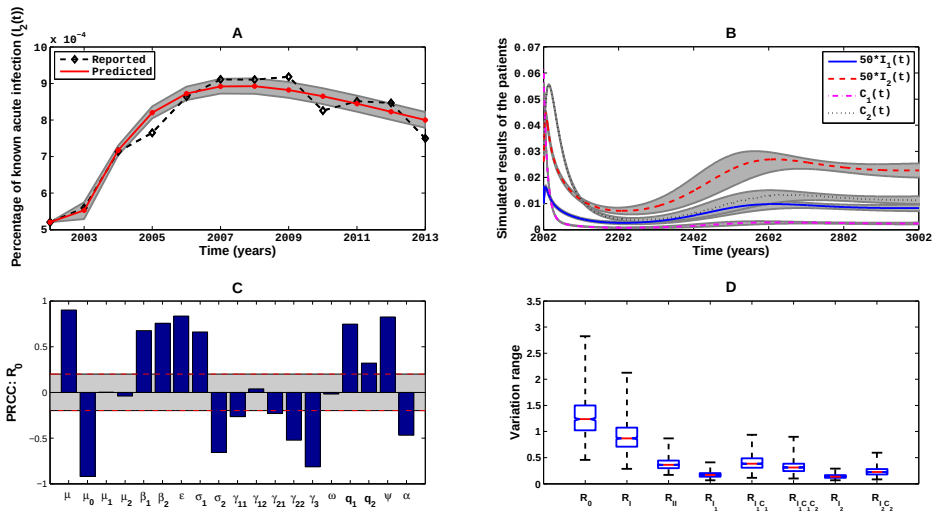

Figure 3. Illustration of the fitting prediction of the model and the uncertainty and sensitivity analysis on the basic reproduction number. (A) Result of the model that was fit to the reported acute hepatitis B data of 2002-2013. The black diamond curve shows the reported data, and the red star curve shows the simulated data. (B) Simulations of the long-term transmission outcome for the model. Here, the parameters and initial conditions are given in Table 1, Table S1 and Table S2. The gray areas indicate 95% CI of the fit lines. (C) Partial rank correlation coefficients (PRCCs) illustrating the dependence of R_0 on each parameter. The gray area represents the PRCC values that are not statistically significant. (D) Boxplot graph showing the variation in the basic reproduction number for the total patients and each sub-grouping R_i, $i = 0, I, II, I_1, I_1C_1, I_1C_1C_2, I_2, I_2C_2$.

3.3. Uncertainty and sensitivity analysis

To quantify the degree of confidence in the parameter values, Latin hypercube sampling (LHS) and PRCCs are performed to identify the critical parameters of our model and quantify how input uncertainty impacts the model outcomes [16, 28]. LHS is a stratified sampling without replacement technique, where the random parameter distributions are divided into N equal probability intervals, which are then sampled. N represents the sample size and is generally much larger than the number of parameters that are varied to ensure accuracy [16]. PRCC is calculated using the rank-transformed LHS matrix and output matrix to describe the influence of the

uncertainties on the model outcomes [16,28], i.e., to assess the sensitivity of the outcome variable to parameter variation [1,16]. Because there is no priori distribution on the parameters, a natural choice is a uniform distribution within $\pm 20\%$ variation with respect to the best point estimates of the corresponding parameters [16,21].

We set the sample size N to 1000, and each parameter is independently sampled from a uniform distribution. Figure 3C shows the PRCC results, which illustrate the dependence of the basic reproduction number R_0 on each parameter using the LHS/PRCC algorithm. According to the criterion that the absolute value of the PRCC is greater than 0.2 [16, 28], we find that there are fifteen parameters that have a significant impact on the basic reproduction number. The birth rate μ, the natural mortality rate μ_0, the HBV conversion rate from unknown/known acute to unknown/known carrier γ_{11}/γ_{21}, the HBV conversion rate from known carrier to known immune γ_{22}, the average probability that an unknown/known HBV individual fails to clear an acute infection and develops into a carrier state q_1/q_2 , and the rate of waning vaccine-induced immunity ψ usually remain unchanged and are difficult to regulate under the stable social circumstances and current treatments/vaccines in China. Because the sign of the PRCC indicates whether the basic reproduction number will increase or decrease, if we regulate the corresponding parameter [16] to decrease the basic reproduction number to control the disease, the following three feasible strategies emerge: strengthen the general education program for the entire population to decrease the unknown/known HBV transmission rate from susceptible to latent β_1/β_2 and the reduced transmission rate ε; implement a strict vaccination program for newborns and susceptible adults to further improve the vaccination rate γ_3; and mandate regular physical examinations and prompt reporting to decrease the conversion rate from latent to unknown acute σ_1, to increase the conversion rate from latent to known acute σ_2, and to increase the HBV conversion rate from unknown carrier to known carrier α.

To demonstrate a realistic variation in the basic reproduction number for the total population of patients and each sub-grouping $R_i, i = 0, I, II, I_1, I_1C_1, I_1C_1C_2, I_2$, I_2C_2, we produce a boxplot for R_i based on the Markov chains obtained from the parameter estimation processes. Figure 3D shows that the contribution of carriers on the basic reproduction number is always greater than the contribution of acute infections and that the transmission of unknown patients is the major contributor to the prevalence of hepatitis B in mainland China.

3.4. Time-varying sensitivity analysis

To further identify significant time-dependent relationships between the abovementioned seven parameters and hepatitis B patients with time, time-varying PRCCs are calculated for the variables of unknown/known acute infections and carriers, as shown in Figure 4. According to the results, we find that the final effects due to changes in the seven parameters with respect to the variables are identical: the signs of $\beta_1, \beta_2, \varepsilon, \sigma_1$ remain positive, and the signs of $\gamma_3, \sigma_2, \alpha$ remain negative, which is consistent with the results shown in Figure 3C. However, there are apparent pattern variations for time-varying PRCCs between unknown and known patients. For instance, regarding parameter σ_2 (the conversion rate from latent to known acute), both PRCCs remain negatively correlated over time for unknown patients (Figures 4A and 4C). However, for known patients, both PRCCs are significantly positively correlated at early time points and then become significantly negatively correlated

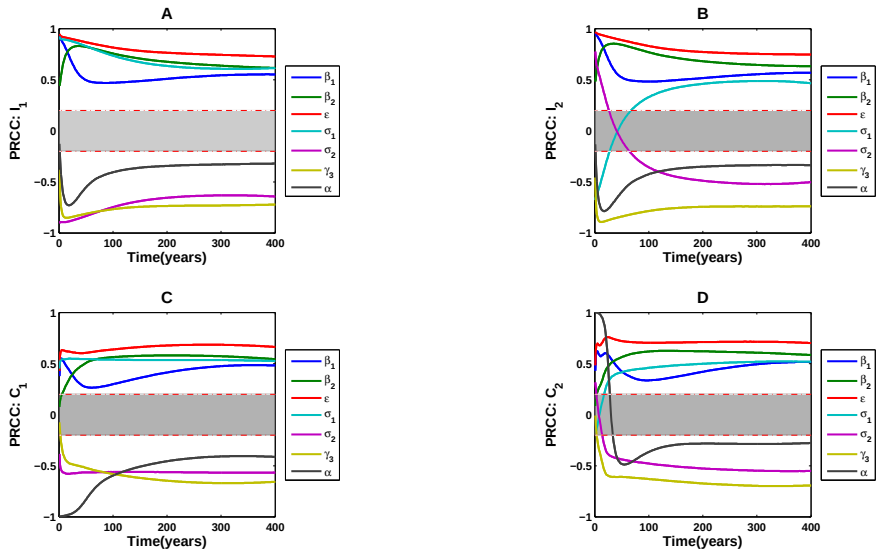

Figure 4. PRCCs plotted over time for identifying significant time-dependent relationships over a long-term course. PRCCs are calculated with respect to unknown acute infections in (A), known acute infections in (B), unknown carriers in (C) and known carriers in (D). The gray area represents PRCC values that are not significant. Note that the sensitivities of the parameters change as the system dynamics progress.

as the transmission progresses to steady state (Figures 4B and 4D). Thus, according to the sign of the PRCC, the conversion rate from latent to known acute (σ_2) is initially responsible for increasing the number known patients (likely due to an accumulative effect). Then, the parameter becomes a significant cause in decreasing the number of known patients (likely due to therapeutic effects under standard antiviral treatments).

4. Discussion

Hepatitis B and its related disorders are important public health issues in China, though considerable efforts have been made by the Central Government of China, including the 2006-2010 hepatitis B control plan [18], the global alliance for vaccines and immunization (GAVI) project [7, 9], and the guidelines on the reform of the health-care system for 2009-2011 [4]. How can the efficacy of such strategies be evaluated and the long-term trend of hepatitis B prevalence be predicted in China? Mathematical models have recently been used to examine the transmission dynamics and model the control of many epidemics [8, 22, 26, 29–32]. In China, in addition to a larger number of HBV carriers [29], a large quantity of unknown patients is another specific characteristic of the HBV endemic [3,14]. By combining the specific characteristics with the flowchart of HBV transmission, we propose a mathematical model to study the transmission dynamics and control of HBV in mainland China.

Kinetics analyses show that there is a critical threshold index to determine the outbreak of a disease, i.e., the basic reproduction number R_0, which is determined by five components and can be divided into two types: the basic reproduction numbers for unknown and known patients. When the basic reproduction number is

less than one, disease-free equilibrium is stable, and the disease can be controlled or eradicated. Conversely, the disease-endemic equilibrium is stable, hepatitis B will be prevalent or become an endemic.

Using a MCMC algorithm, we estimate the suitable parameter values and report a good fitting result based on the reported hepatitis B data by the National Health and Family Planning Commission of the People's Republic of China from 2002 to 2013 [17]. Using the estimated values, the basic reproduction number is calculated. In contrast to the previous estimation [29], our dynamic model predicts that hepatitis B remains an endemic in China, even under the current control measures and immunization programs, although the recent efforts have been beneficial and have contributed to a significant decline in the basic reproduction number. We find that the effect of unknown patients is greater than that of known patients on the prevalence of hepatitis B. Thus, unknown patients should be the focus of programs aimed to effectively control hepatitis B in mainland China in the future.

By performing the global uncertainty and sensitivity analysis of the model using various parameters, we identify three feasible strategies for efficiently decreasing the basic reproduction number, i.e., for containing hepatitis B epidemics. First, increasing the awareness of HBV throughout the population is expected to help decrease the HBV transmission rate from susceptible to latent and reduce the transmission rate due to increased knowledge of hepatitis B [14,18]. Second, implementing strict policies can further improve the vaccination rate, including vaccinations of newborns and susceptible adults [7, 9, 14, 18]. Third, implementing sensitive surveillance and prompt reporting, such as regular physical examinations, would directly reduce the conversion rate of latent to unknown patients and increase the conversion rate of unknown patients to known patients [3, 14]. However, the time-varying sensitivity analysis of the compartments of patients illustrates that there are variations with time that should be considered in the long and difficult battle for the prevention and control of hepatitis B.

In addition, the variation in the basic reproduction number for all patients and those for each sub-grouping indicates that the two specific characteristics of China mentioned above must be carefully considered in the battle for hepatitis B eradication. Currently, the main cause of the HBV epidemic may be the fact that the contribution of carriers is always greater than that of acute infections, and the transmission of unknown patients is the major contributor to the prevalence of hepatitis B. Thus, in addition to the carriers, unknown HBV infections represent an objective variable that is worth exploring as a potential epidemiologic factor in the transmission mechanism of hepatitis B in China.

Though the proposed model with the fitted parameters captures the trend of the reported hepatitis B data, our results are characterized by various limitations that should be acknowledged. For example, some factors are not incorporated in our analysis, such as neonatal infection, age structure, the cost of treatment, and overall socioeconomic development, which may be correlated with the prevalence of hepatitis B in mainland China over the long term [12, 14, 26, 29]. Moreover, demographics also influence the transmission of hepatitis B, and a stochastic model will be incorporated into future studies [19, 20]. Despite these caveats, our results strongly suggest that controls focused on the known patients are unlikely to be highly effective strategies for combating the HBV epidemic; instead, general education, vaccination programs, and regular physical examinations should be enhanced to effectively mitigate HBV infections.

Appendix

A. Description of initial conditions and parameters in our model

TABLE *S1. Description of initial conditions (IC) in our model.*

IC	Interpretation	Value	Reference
$S(0)$	Initial proportion of the susceptible population	$0-1$	Undetermined
$L(0)$	Initial proportion of latently infections	$0-1$	Undetermined
$I_1(0)$	Initial proportion of unknown acute infections	$0-1$	Undetermined
$I_2(0)$	Initial proportion of known acute infections	5.2029×10^{-4}	[10]
$C_1(0)$	Initial proportion of unknown carriers	0.0616	[10, 17]
$C_2(0)$	Initial proportion of known carriers	0.0293	[10, 17]
$V(0)$	Initial proportion of the immune following vaccination	0.3947	[10]

TABLE *S2. Description of parameters (Par.) in our model.*

Par.	Interpretation	Value	Reference
μ	Birth rate	0.0121/year	[5]
μ_0	Natural mortality rate	0.00693/year	[5]
μ_1	HBV-related mortality rate	0.002/year	[24]
β_1	Unknown HBV transmission rate from susceptible to latent	$\beta_1 \geq \beta_2$ [a]	Undetermined
β_2	Known HBV transmission rate from susceptible to latent	$0.95-20.49$ /person/year	[27]
ε	Reduced transmission rate	16%	[27]
σ_1	Conversion rate from latent to unknown acute	$\sigma_1 \leq \sigma_2$ [a]	Undetermined
σ_2	Conversion rate from latent to known acute	$\sigma_1+\sigma_2=6$ [b] /year	Undetermined
γ_{11}	HBV conversion rate from unknown acute to unknown carrier	4/year	[27]
γ_{12}	HBV conversion rate from unknown carrier to unknown immune	0 [c]	Assumed
γ_{21}	HBV conversion rate from known acute to known carrier	4/year	[27]
γ_{22}	HBV conversion rate from known carrier to known immune	0.025/year	[27]
γ_3	Vaccination rate	$0-1$/year	Undetermined
ω	Proportion of births that do not undergo a successful vaccination	14.5%	[2, 11]
q_1	Average probability that an unknown HBV individual fails to clear an acute infection and develops into the carrier state	$0-1$	Undetermined

TABLE *S2. (Cont.)*

q_2	Average probability that a known HBV individual fails to clear an acute infection and develops into the carrier state	0.0885	[2, 12, 25]
ψ	Rate of waning vaccine-induced immunity	0.1/year	[13]
α	HBV conversion rate from unknown carrier to known carrier	$0 - 1$/year	Undetermined

[a] $\beta_1 \geq \beta_2$ and $\sigma_1 \leq \sigma_2$ indicate that there are more infectious and a lower metastatic rate in unknown patients compared with known patients due to the increasing general education program for the whole population [18].

[b] $\sigma_1 + \sigma_2 = 6$ indicates that the average latent period persists for approximately two months, and then the individual becomes an acute HBV patient, including the unknown and known branches [27].

[c] Note that the use of solely Chinese herbs and/or other improper agents to treat hepatitis B may be ineffective for the cases of unknown carrier [18]. Therefore, the rate moving from unknown carriers to immune is estimated as zero.

B. Kinetics analysis

For the sake of notations, let

$$k = \mu_0 + \psi,\ m = \gamma_3 + \mu_0,\ l = \mu_0 + \sigma_1 + \sigma_2,\ z_{11} = \mu_0 + \gamma_{11},\ z_{21} = \mu_0 + \gamma_{21},$$
$$z_{12} = \mu_0 + \mu_1 + \gamma_{12} + \alpha,\ z_{22} = \mu_0 + \mu_1 + \gamma_{22},\ g_1 = q_1\gamma_{11},\ g_2 = q_2\gamma_{21}.$$

Note the model (2.1) in main text always has a disease-free equilibrium $E_0 = (S_0, 0, 0, 0, 0, 0, V_0)$, where

$$S_0 = \frac{\mu(\psi + k\omega - \psi\omega)}{km - \psi\gamma_3},\ \ V_0 = \frac{\mu(m - m\omega + \omega\gamma_3)}{km - \psi\gamma_3}.$$

Using those notations, the basic reproduction number of model (2.1) can be written as (2.2) and (2.3) in main text.

Furthermore, if $R_0 > 1$, there is an endemic equilibrium $E_1 = (S^*, L^*, I_1^*, I_2^*, C_1^*, C_2^*, V^*)$, in which

$$S^* = \frac{S_0}{R_0}, \qquad L^* = \frac{(km - \psi\gamma_3)(R_0 - 1)S^*}{kl}, \qquad I_1^* = \frac{L^*\sigma_1}{z_{11}},\ I_2^* = \frac{L^*\sigma_2}{z_{21}},$$
$$C_1^* = \frac{L^* g_1\sigma_1}{z_{11}z_{12}}, \quad C_2^* = \frac{L^*(g_1 z_{21}\alpha\sigma_1 + g_2 z_{11}z_{12}\sigma_2)}{z_{11}z_{12}z_{21}z_{22}}, \quad V^* = \frac{\mu - \mu\omega + \gamma_3 S^*}{k}.$$

On the stability of the equilibria, we first have

Proposition 4.1. *If $R_0 < 1$, then E_0 is stable; if $R_0 > 1$, E_0 is unstable.*

Proof. The Jacobian matrix at E_0 is

$$J_{(E_0)} = \begin{bmatrix} -m & 0 & -S_0\beta_1 & -S_0\beta_2 & -S_0\varepsilon\beta_1 & -S_0\varepsilon\beta_2 & \psi \\ 0 & -l & S_0\beta_1 & S_0\beta_2 & S_0\varepsilon\beta_1 & S_0\varepsilon\beta_2 & 0 \\ 0 & \sigma_1 & -z_{11} & 0 & 0 & 0 & 0 \\ 0 & \sigma_2 & 0 & -z_{21} & 0 & 0 & 0 \\ 0 & 0 & g_1 & 0 & -z_{12} & 0 & 0 \\ 0 & 0 & 0 & g_2 & 0 & -z_{22} & 0 \\ \gamma_3 & 0 & 0 & 0 & 0 & 0 & -k \end{bmatrix}.$$

With the aid of MATHEMATICA, the corresponding characteristic equation is

$$\Phi_0(\lambda) = ((\lambda+k)(\lambda+m) - \psi\gamma_3)(a_0\lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_4\lambda + a_5) = 0,$$

where $a_0 = 1$ and

$$\begin{aligned}
a_1 &= l + z_{11} + z_{12} + z_{21} + z_{22},\\
a_2 &= (1-R_{I_1})lz_{11} + (1-R_{I_2})lz_{21} + l(z_{12}+z_{22})\\
&\quad + z_{11}(z_{12}+z_{21}+z_{22}) + z_{12}(z_{21}+z_{22}) + z_{21}z_{22},\\
a_3 &= (1-R_{I_1}-R_{I_1C_1})lz_{11}z_{12} + (1-R_{I_1}-R_{I_2})lz_{11}z_{21}\\
&\quad + (1-R_{I_2}-R_{I_2C_2})lz_{21}z_{22} + (1-R_{I_1})lz_{11}z_{22} + (1-R_{I_2})lz_{12}z_{21} + lz_{12}z_{22}\\
&\quad + z_{11}z_{12}(z_{21}+z_{22}) + (z_{11}+z_{12})z_{21}z_{22},\\
a_4 &= (1-R_{I_1}-R_{I_1C_1}-R_{I_2})lz_{11}z_{12}z_{21} + (1-R_{I_1}-R_{I_1C_1}-R_{I_1C_1C_2})lz_{11}z_{12}z_{22}\\
&\quad + (1-R_{I_1}-R_{I_2}-R_{I_2C_2})lz_{11}z_{21}z_{22}\\
&\quad + (1-R_{I_2}-R_{I_2C_2})lz_{12}z_{21}z_{22} + z_{11}z_{12}z_{21}z_{22},\\
a_5 &= (1-R_0)lz_{11}z_{12}z_{21}z_{22}.
\end{aligned}$$

Clearly, all $a_i > 0$, $i = 1,2,3,4,5$, are valid when $R_0 < 1$. Furthermore, note that

$$(\lambda+k)(\lambda+m) - \psi\gamma_3 = 0 \Leftrightarrow (\lambda+\mu_0)(\lambda+\mu_0+\psi+\gamma_3) = 0$$

and

$$\begin{aligned}
\Delta_2 &= \begin{vmatrix} a_1 & a_0 \\ a_3 & a_2 \end{vmatrix}\\
&=(z_{12}+z_{21})(z_{12}+z_{22})(z_{21}+z_{22}) + z_{11}(z_{12}+z_{21}+z_{22})(z_{11}+z_{12}+z_{21}+z_{22})\\
&\quad + l^2((1-R_{I_1})z_{11} + (1-R_{I_2})z_{21} + z_{12} + z_{22})\\
&\quad + l((1-R_{I_1})z_{11}^2 + (1-R_{I_2})z_{21}^2 + (2+R_{I_2C_2})z_{21}z_{22} + z_{12}^2)\\
&\quad + l(z_{22}^2 + 2z_{12}(z_{21}+z_{22}) + z_{11}((2+R_{I_1C_1})z_{12} + 2z_{21} + 2z_{22})) > 0
\end{aligned}$$

are valid when $R_0 < 1$. To make the expressions of Δ_3 and Δ_4 simple, let $R_{I_1} = R_1, R_{I_1C_1} = R_2, R_{I_1C_1C_2} = R_3, R_{I_2} = R_4, R_{I_2C_2} = R_5$. Then

$$\begin{aligned}
\Delta_3 &= \begin{vmatrix} a_1 & a_0 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{vmatrix}\\
&=(z_{11}+z_{12})(z_{11}+z_{21})(z_{12}+z_{21})(z_{11}+z_{22})(z_{12}+z_{22})(z_{21}+z_{22})\\
&\quad + l\Delta_{31} + l^2\Delta_{32} + l^3\Delta_{33} > 0
\end{aligned}$$

because

$$\begin{aligned}
\Delta_{31} =& z_{21}^2z_{22}^2(z_{21}+z_{22})(1-R_4-R_5) + z_{12}^2(z_{21}+z_{22})(z_{21}^2(1-R_4)\\
&+ z_{21}z_{22}(3+R_5) + z_{22}^2) + z_{12}^3(z_{21}^2(1-R_4) + z_{21}z_{22}(2+R_5) + z_{22}^2)\\
&+ z_{12}z_{21}z_{22}(2z_{21}^2(1-R_4) + z_{21}z_{22}(4-R_4+R_5) + 2z_{22}^2)\\
&+ z_{11}^3(z_{12}^2(1-R_1-R_2) + z_{12}^2(1-R_1-R_4) + z_{21}z_{22}(2-2R_1+R_5)\\
&+ z_{11}^3z_{12}(2z_{21}(1-R_1) + z_{22}(2-2R_1+R_3) + z_{22}^2(1-R_1))
\end{aligned}$$

$$
\begin{aligned}
&+ z_{11}^2(z_{12}^3(1-R_1-R_2)+z_{12}^2(z_{21}(4-R_1+R_2)+z_{22}(4-R_1+R_2+2R_3)))\\
&+ z_{11}^2(z_{21}+z_{22})(z_{21}^3(1-R_1-R_4)+z_{21}z_{22}(3+R_5)+z_{22}^2(1-R_1))\\
&+ z_{11}^2z_{12}(z_{21}^2(4-R_1-R_4+R_2)+z_{21}z_{22}(8-R_0-R_1+3R_2+2R_3\\
&+ R_4+2R_5)+z_{22}^2(4-R_1+R_2+2R_3))+z_{11}(z_{12}^3(2z_{21}+z_{22}(2+R_3))\\
&+ z_{21}z_{22}(2z_{21}^2(1-R_4)+z_{21}z_{22}(4-R_4+R_5)+2z_{22}^2))+z_{11}(z_{12}^3(2z_{21}\\
&+ z_{22}(2+R_3))+z_{21}z_{22}(2z_{21}^2(1-R_4)+z_{21}z_{22}(4-R_4+R_5)+2z_{22}^2))\\
&+ z_{11}z_{12}^2(z_{21}^2(4+R_2-R_4)+z_{21}z_{22}(8-R_0+R_1+3R_2+2R_3+R_4+2R_5)\\
&+ z_{22}^2(4+R_2+2R_3))+z_{11}z_{12}(z_{21}^3(2+R_2-2R_4)\\
&+ z_{21}^2z_{22}(8-R_0+R_1+2R_2+R_3-R_4+3R_5))+z_{11}z_{12}(z_{21}z_{22}^2(8-R_0\\
&+ R_1+2R_2+2R_3+R_4+3R_5)+z_{22}^3(2+R_2+R_3))>0,
\end{aligned}
$$

$$
\begin{aligned}
\Delta_{32} =&(z_{21}^3z_{22}(1-R_4)+z_{21}^2z_{22}^2(2+R_5)+z_{21}z_{22}^3)(1-R_4-R_5)\\
&+ z_{12}^3(z_{21}(1-R_4)+z_{22})+z_{11}^3(z_{12}(1-R_1-R_2)+z_{21}(1-R_1-R_4)\\
&+ z_{22}(1-R_1))(1-R_1)+z_{12}^2(2z_{21}^2(1-R_4)+z_{21}z_{22}(4-R_4+R_5)+2z_{22}^2)\\
&+ z_{12}(z_{21}(1-R_4)+z_{22})(z_{21}^2(1-R_4)+z_{21}z_{22}(3+R_5)+2z_{22}^3)\\
&+ z_{11}^2(z_{12}^2(1-R_1-R_2)(2+R_2)+2z_{21}^2(1-R_1-R_4)\\
&+ z_{21}z_{22}(4-4R_1-R_4(1-R_1)+R_1+R_1R_5))+z_{11}^2(2z_{22}^2(1-R_1)\\
&+ z_{12}(z_{21}(4-4R_1-R_4+R_2(1-R_1-R_4)+R_1R_4)+z_{22}(4-4R_1\\
&+ R_2(1-R_1)+2R_3)))+z_{11}(z_{12}^3(1-R_1-R_2)+z_{21}^3(1-R_1-R_4)(1-R_4)\\
&+ z_{21}^2z_{22}(4-R_1-4R_4+R_5(1-R_1)+R_1R_4))+z_{11}(z_{21}z_{22}^2(4-R_1-R_4\\
&+ R_5(1-R_1))+z_{12}^2(z_{21}(4-R_1-R_4+R_2(1-R_4))\\
&+ z_{22}(4-R_1+R_2+2R_3)))+z_{11}z_{22}^3(1-R_1)\\
&+ z_{11}z_{12}z_{21}^2(4-R_1-4R_4+R_1R_4+R_2(1+R_4))\\
&+ z_{11}z_{12}(z_{22}^2(2-2R_1+R_3)+z_{21}z_{22}(8-2R_1-2R_4\\
&+ R_5(2-2R_2+R_1)+R_2(2-R_4)+R_3))>0,
\end{aligned}
$$

and

$$
\begin{aligned}
\Delta_{33} =&(z_{21}(1-R_4)+z_{22})(z_{12}^2+z_{21}z_{22}(1-R_4-R_5)+z_{12}(z_{21}(1-R_4)+z_{22}))\\
&+ z_{11}^2(z_{12}(1-R_1-R_2)+z_{21}(1-R_1-R_4)+z_{22}(1-R_1))(1-R_1)\\
&+ z_{12}(z_{21}(1-R_4)+z_{22})^2+z_{11}(z_{12}^2(1-R_1-R_2)\\
&+ z_{21}^2(1-R_1-R_4)(1-R_4)+z_{21}z_{22}(2(1-R_1)(1-R_4)+R_1R_5))\\
&+ z_{11}(z_{22}^2(1-R_1)+z_{12}(z_{21}(2(1-R_1-R_4)+2R_1R_4+R_2R_4)\\
&+ z_{22}(2-2R_1+R_3)))>0
\end{aligned}
$$

are valid when $R_0<1$. Similarly, we have

$$
\Delta_4=\begin{vmatrix} a_1 & a_0 & 0 & 0\\ a_3 & a_2 & a_1 & a_0\\ a_5 & a_4 & a_3 & a_2\\ 0 & 0 & a_5 & a_4 \end{vmatrix}
$$

$$
\begin{aligned}
=&z_{11}z_{12}z_{21}z_{22}(z_{11}+z_{12})(z_{11}+z_{21})(z_{12}+z_{21})(z_{11}+z_{22})(z_{12}+z_{22})(z_{21}+z_{22})\\
&+l\Delta_{41}+l^2\Delta_{42}+l^3\Delta_{43}+l^4\Delta_{44}>0
\end{aligned}
$$

because all $\Delta_{4i}>0$, $i=1,2,3,4$, are valid when $R_0<1$.

Thus, based on the Routh-Hurwitz criteria, we know that all roots of $\Phi_0(\lambda)$ have negative real parts if $R_0<1$, i.e., E_0 is stable. When $R_0>1$, $a_5<0$ is valid, so E_0 is unstable. □

Proposition 4.2. *E_1 is stable only if it exists, i.e., $R_0>1$.*

Proof. When $R_0>1$, E_1 exists and the Jacobian matrix at E_1 is

$$
J_{(E_1)}=\begin{bmatrix}
-m-M & 0 & -S^*\beta_1 & -S^*\beta_2 & -S^*\varepsilon\beta_1 & -S^*\varepsilon\beta_2 & \psi\\
M & -l & S^*\beta_1 & S^*\beta_2 & S^*\varepsilon\beta_1 & S^*\varepsilon\beta_2 & 0\\
0 & \sigma_1 & -z_{11} & 0 & 0 & 0 & 0\\
0 & \sigma_2 & \alpha & -z_{21} & 0 & 0 & 0\\
0 & 0 & g_1 & 0 & -z_{12} & 0 & 0\\
0 & 0 & 0 & g_2 & \alpha & -z_{22} & 0\\
\gamma_3 & 0 & 0 & 0 & 0 & 0 & -k
\end{bmatrix}.
$$

in which $M=(I_1^*+\varepsilon C_1^*)\beta_1+(I_2^*+\varepsilon C_2^*)\beta_2$.

Similarly, let $R_{I_1}=R_1, R_{I_1C_1}=R_2, R_{I_1C_1C_2}=R_3, R_{I_2}=R_4, R_{I_2C_2}=R_5$. With the aid of MATHEMATICA, the corresponding characteristic equation is

$$
\Phi_1(\lambda)=(b_0\lambda^7+b_1\lambda^6+b_2\lambda^5+b_3\lambda^4+b_4\lambda^3+b_5\lambda^2+b_6\lambda+b_7)=0,
$$

where $b_0=1$ and

$$
\begin{aligned}
b_1&=(k+m)+M+c_1,\\
b_2&=Q+(k+m)c_1+M(k+d_1)+c_2,\\
b_3&=Qc_1+(k+m)c_2+M(kd_1+d_2)+c_3,\\
b_4&=Qc_2+(k+m)c_3+M(kd_2+d_3)+c_4,\\
b_5&=Qc_3+(k+m)c_4+M(kd_3+d_4),\\
b_6&=Qc_4+M(kd_4+d_5),\\
b_7&=KMd_5,
\end{aligned}
$$

in which

$$
\begin{aligned}
Q&=km-\psi\gamma_3=\mu_0(\mu_0+\gamma_3+\psi),\\
c_1&=l+z_{11}+z_{12}+z_{21}+z_{22},\\
c_2&=l(z_{12}+z_{22}+z_{11}(1-\frac{R_1}{R_0})+z_{21}(1-\frac{R_4}{R_0}))+z_{11}(z_{12}z_{21}+z_{22})\\
&\quad+z_{12}(z_{21}+z_{22})+z_{21}z_{22},\\
c_3&=lz_{11}z_{12}(1-\frac{R_1}{R_0}-\frac{R_2}{R_0})+lz_{11}z_{21}(1-\frac{R_1}{R_0}-\frac{R_4}{R_0})+lz_{12}z_{21}(1-\frac{R_4}{R_0})\\
&\quad+z_{11}z_{12}z_{21}+lz_{11}z_{22}(1-\frac{R_1}{R_0})+lz_{21}z_{22}(1-\frac{R_4}{R_0}-\frac{R_5}{R_0})\\
&\quad+(l+z_{21})z_{12}z_{22}+z_{11}z_{22}(z_{12}+z_{21}),
\end{aligned}
$$

$$
\begin{aligned}
c_4 &= lz_{11}z_{12}z_{21}(1-\frac{R_1}{R_0}-\frac{R_2}{R_0}-\frac{R_4}{R_0})+lz_{11}z_{12}z_{22}(1-\frac{R_1}{R_0}-\frac{R_2}{R_0}-\frac{R_3}{R_0})\\
&\quad + lz_{11}z_{21}z_{22}(1-\frac{R_1}{R_0}-\frac{R_4}{R_0}-\frac{R_5}{R_0})+lz_{12}z_{21}z_{22}(1-\frac{R_4}{R_0}-\frac{R_5}{R_0})+z_{11}z_{12}z_{21}z_{22},\\
d_1 &= c_1,\\
d_2 &= l(z_{11}+z_{12}+z_{21}+z_{22})+z_{11}(z_{12}+z_{21}+z_{22})+z_{12}(z_{21}+z_{22})+z_{21}z_{22},\\
d_3 &= l(z_{11}(z_{12}+z_{21}+z_{22})+z_{12}(z_{21}+z_{22})+z_{21}z_{22})+z_{11}z_{12}(z_{21}+z_{22})\\
&\quad +(z_{11}+z_{12})z_{21}z_{22},\\
d_4 &= l(z_{11}z_{12}(z_{21}+z_{22})+(z_{11}+z_{12})z_{21}z_{22})+z_{11}z_{12}z_{21}z_{22},\\
d_5 &= lz_{11}z_{12}z_{21}z_{22}.
\end{aligned}
$$

It is easily to see that $b_1 > 0$ and $b_7 > 0$ when $R_0 > 1$. So we only need to judge the sign of Δ_i, $i = 2, 3, 4, 5, 6$, in order to show the stability of E_1. After some calculations, Δ_i can be expressed as a polynomial of Q, M, k, m, i.e., $\Delta_i = f_i(Q, M, k, m)$. Concretely, we have

$$
\begin{aligned}
\Delta_2 &= \begin{vmatrix} b_1 & b_0 \\ b_3 & b_2 \end{vmatrix} = f_2(Q,M,k,m)\\
&= h_{2,0}k^2M + h_{2,1}kmM + h_{2,2}kM^2 + h_{2,3}kQ + h_{2,4}mQ + h_{2,5}MQ + h_{2,6}k^2\\
&\quad + h_{2,7}km + h_{2,8}m^2 + h_{2,9}kM + h_{2,10}mM + h_{2,11}k + h_{2,12}m + h_{2,13}M\\
&\quad + h_{2,14} + h_{2,15}M^2 + h_{2,16}M,
\end{aligned}
$$

in which

$$
\begin{aligned}
&h_{2,0} = h_{2,1} = h_{2,2} = h_{2,3} = h_{2,4} = h_{2,5} = 1,\\
&h_{2,6} = h_{2,8} = h_{2,10} = h_{2,15} = c_1,\\
&h_{2,7} = h_{2,9} = h_{2,10} = 2c_1, \quad h_{2,11} = h_{2,12} = c_1^2,\\
&h_{2,13} = c_2, \ \ h_{2,14} = c_1c_2 - c_3, \ \ h_{2,16} = d_1d_2 - d_3.
\end{aligned}
$$

Using the expressions of c_1, c_2, c_3, d_1, d_2 and d_3, we know all $h_{2,j} > 0$, $j = 0, 1, 2, \cdots, 16$, are valid if $R_0 > 1$, i.e., $\Delta_2 > 0$.

Similarly, when $R_0 > 1$, after some tedious calculations, we have

$$
\Delta_3 = \begin{vmatrix} b_1 & b_0 & 0 \\ b_3 & b_2 & b_1 \\ b_5 & b_4 & b_3 \end{vmatrix} = f_3(Q,M,k,m) > 0,
$$

$$
\Delta_4 = \begin{vmatrix} b_1 & b_0 & 0 & 0 \\ b_3 & b_2 & b_1 & b_0 \\ b_5 & b_4 & b_3 & b_2 \\ b_7 & b_6 & b_5 & b_4 \end{vmatrix} = f_4(Q,M,k,m) > 0,
$$

$$
\Delta_5 = \begin{vmatrix} b_1 & b_0 & 0 & 0 & 0 \\ b_3 & b_2 & b_1 & b_0 & 0 \\ b_5 & b_4 & b_3 & b_2 & b_1 \\ b_7 & b_6 & b_5 & b_4 & b_3 \\ 0 & 0 & b_7 & b_6 & b_5 \end{vmatrix} = f_5(Q,M,k,m) > 0,
$$

$$\Delta_6 = \begin{vmatrix} b_1 & b_0 & 0 & 0 & 0 & 0 \\ b_3 & b_2 & b_1 & b_0 & 0 & 0 \\ b_5 & b_4 & b_3 & b_2 & b_1 & b_0 \\ b_7 & b_6 & b_5 & b_4 & b_3 & b_2 \\ 0 & 0 & b_7 & b_6 & b_5 & b_4 \\ 0 & 0 & 0 & 0 & b_7 & b_6 \end{vmatrix} = f_6(Q, M, k, m) > 0,$$

Thus, by Routh-Hurwitz criteria, all roots of $\Phi_1(\lambda)$ have negative real parts if $R_0 > 1$, i.e., E_1 is stable only if it exists. □

References

[1] S.M. Blower and H. Dowlatabadi, *Sensitivity and uncertainty analysis of complex-models of disease transmission–an HIV model, as an example*, Int. Stat. Rev., 62(1994), 229–243.

[2] F.Q. Cui, X.J. Wang and X.F. Liang, *Epidemiological analysis on reported hepatitis B under 15 years in China: the report from Chinese Center for Disease Control and Prevention*, Chin. J. Vaccines Immunization, 12(2006), 206–208.

[3] F.Q. Cui, Y. Lu, F.Z. Wang, Y.S. Chen, H. Zheng, Y. Zhang, X.H. Gong, L.L. Han, H.J. Dong, C. Chen, L.Y. Ling, L. Zhang, L.Q. Diao, X.P. Shao, G. Fang, L. Gao and X.F. Liang, *Analysis on the proportion of reported hepatitis B cases through pilot surveillance in China during 2006*, Chin. J. Epidemiol., 28(2007), 872–874.

[4] CGC, *The Central Government of the People's Republic of China, Guidelines on Deepening the Reform of Health-care System (2009-2011)*, `http://www.gov.cn/zwgk/2009-04/07/content_1279256.htm`, (accessed April 7, 2014).

[5] J.L. Dienstag, *Hepatitis B virus infection*, N. Engl. J. Med., 359(2008), 1486–1500.

[6] O. Diekmann, J.A. Heesterbeek and J.A. Metz, *On the definition and the computation of the basic reproduction ratio R0 in models fo rinfectious diseases in heterogeneous populations*, J. Math. Biol., 28(1990), 365–382.

[7] GAVI, *The Global Alliance for Vaccines and Immunization*, `http://www.gavialliance.org/performance/country_results/index.php?countID=75`, (accessed February 21, 2014).

[8] D.W. Hutton and M.L. Brandeau, *Too much of a good thing? When to stop catch-up vaccination*, Med. Deci. Making, 33(2013), 920–936.

[9] S.C. Hadler, F.Q. Cui, F. Averhoff, T. Taylor, F.Z. Wang, L. Li, X.F. Liang and W.Z. Yang, *The impact of hepatitis B vaccine in China and in the China GAVI Project*, Vaccine, 31(2013), J66–J72.

[10] J.D. Jia and H. Zhuang, *The overview of seminar on chronic hepatitis B*, Chin. J. Hepatol., 12(2004), 698–699.

[11] X.F. Liang, Y.S. Chen, X.J. Wang, X. He, L.J. Chen, J. Wang, C.Y. Lin, H.Q. Bai, J. Yan, G. Cui and J.J. Yu, *A study on the sero-epidemiology of hepatitis B in Chinese population aged over 3-years old: the report from Chinese Center for Disease Control and Prevention*, Chin. J. Epidemiol., 26(2005), 655–658.

[12] J. Liu and D.M. Fan, *Hepatitis B in China*, Lancet, 369(2007), 1582–1583.

[13] G.T. Liu, C.W. Si, Q.H. Wang, L.H. Chen, H.S. Chen, D.Z. Xu, L.X. Zhang, B.E. Wang, L.T. Wang and Y. Li, *Comments on the prevention and research of chronic hepatitis in China*, Nat. Med. J. China, 82(2002), 74–76.

[14] F.M. Lu and H. Zhuang, *Management of hepatitis B in China*, Chinese Med. J., 122(2009), 3–4.

[15] Z. Luo, L. Li and B. Ruan, *Impact of the implementation of a vaccination strategy on hepatitis B virus infections in China over a 20-year period*, Int. J. Infect. Dis., 16(2012), e82–e88.

[16] S. Marino, I.B. Hogue, C.J. Ray and D.E. Kirschner, *A methodology for performing global uncertainty and sensitivity analysis in systems biology*, J. Theor. Biol., 254(2008), 178–196.

[17] NHFPC, *National statutory epidemic situation of infectious diseases*, `http://www.nhfpc.gov.cn/zhuzhan/yqxx/lists.shtml`, (accessed February 21, 2014).

[18] NHFPC, *Control projection of national hepatitis B during 2006-2010*, `http://www.nhfpc.gov.cn/zhuzhan/zcjd/201304/72ea886b4f6c416fae8bdb38634b0620.shtml`, (accessed February 21, 2014).

[19] E. Brooks-Pollock, G.O. Roberts and M.J. Keeling, *A dynamic model of bovine tuberculosis spread and control in Great Britain*, Nature, 511(2014), 228–231.

[20] A. Pandey, K.E. Atkins, J. Medlock, N. Wenzel, J.P. Townsend, J.E. Childs, T.G. Nyenswah, M.L. Ndeffo-Mbah and A.P. Galvani, *Strategies for containing Ebola in West Africa*, Science, 346(2014), 991–995.

[21] A. Rinaldo, E. Bertuzzo, L. Mari, L. Righetto, M. Blokesch, M. Gatto, R. Casagrandi, M. Murray, S.M. Vesenbeckh and I. Rodriguez-Iturbe, *Reassessment of the 2010-2011 Haiti cholera outbreak and rainfall-driven multiseason projections*, Proc. Natl. Acad. Sci. USA, 109(2012), 6602–6607.

[22] S. Thornley, C. Bullen and M. Roberts, *Hepatitis B in high prevalence New Zealand population: a mathematical model applied to infection control policy*, J. Theor. Biol., 254(2008), 599–603.

[23] P. van den Driessche and J. Watmough, *Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission*, Math. Biosci., 180(2002), 29–48.

[24] WHO, *Hepatitis B*, `http://www.who.int/mediacentre/factsheets/fs204/en/index.html`, (accessed July 30, 2014).

[25] X.J. Wang, R.Z. Zhang, Y.S. Hu and X.F. Liang, *Analysis on epidemic status of viral hepatitis in China: the report from Chinese center for Disease Control and Prevention*, Dis. Surveillance, 19(2004), 290–292.

[26] J.R. Williams, D.J. Nokes, G.F. Medley and R.M. Anderson, *The transmission dynamics of hepatitis B in the UK: a mathematical model for evaluating costs and effectiveness of immunization programmes*, Epidemiol. Infect., 116(1996), 71–89.

[27] G.L. Xia, C B. Liu, H L. Cao, S L. Bi, M Y. Zhan, C A. Su, J H. Nan and X Q. Qi, *Prevalence of hepatitis B and C virus infections in the general Chinese*

population. Results from a nationwide cross-sectional seroepidemiologic study of hepatitis A, B, C, D, and E virus infections in China, 1992, Int. Hepatol. Commun., 5(1996), 62–73.

[28] Y. Xiao, S. Tang, Y. Zhou, R.J. Smith, J. Wu and N. Wang, *Predicting the HIV/AIDS epidemic and measuring the effect of mobility in mainland China*, J. Theor. Biol., 317(2013), 271–285.

[29] L. Zou, W. Zhang and S. Ruan, *Modeling the transmission dynamics and control of hepatitis B virus in China*, J. Theor. Biol., 262(2010), 330–338.

[30] L. Zou, W. Zhang and S. Ruan, *Corrigendum to "Modeling the transmission dynamics and control of hepatitis B virus in China" [J. Theor. Biol. 262 (2010) 330-338]*, J. Theor. Biol., 317(2013), 425–427.

[31] S. Zhao, Z. Xu and Y. Lu, *A mathematical model of hepatitis B virus transmission and its application for vaccination strategy in China*, Int. J. Epidemiol., 29(2000), 744–752.

[32] J. Zhang, Z. Jin, G.Q. Sun, X.D. Sun, Y.M. Wang and B. Huang, *Determination of Original Infection Source of H7N9 Avian Influenza by Dynamical Model*, Sci. Rep., 4(2014), DOI:10.1038/srep04846.