Estimating the impact of test-and-treat strategies on hepatitis B virus infection in China by using an age-structured mathematical model

Jian Zu, PhD\textsuperscript{*},
Miaolei Li, MD\textsuperscript{*},
Guihua Zhuang, PhD\textsuperscript{b,\textsuperscript{*}}
Peifeng Liang, PhD\textsuperscript{c}
Fuqiang Cui, PhD\textsuperscript{d}
Fuzhen Wang, MD\textsuperscript{e}
Hui Zheng, MD\textsuperscript{e}
Xiaofeng Liang, MD\textsuperscript{e,\textsuperscript{*}}

Abstract

The potential impact of increasing test-and-treat coverage on hepatitis B virus (HBV) infection remains unclear in China. The objective of this study was to develop a dynamic compartmental model at a population level to estimate the long-term effect of this strategy.

Based on the natural history of HBV infection and 3 serosurvey data of hepatitis B in China, we proposed an age- and time-dependent discrete model to predict the number of new HBV infection, the number of chronic HBV infection, and the number of HBV-related deaths for the time from 2018 to 2050 under 5 different test-and-treat coverage and compared them with current intervention policy.

Compared with current policy, if the test-and-treat coverage was increased to 100% since 2018, the numbers of chronic HBV infection, new HBV infection, and HBV-related deaths in 2035 would be reduced by 26.60%, 24.88%, and 26.55%, respectively, and in 2060 it would be reduced by 44.93%, 43.29%, and 43.67%, respectively. In contrast, if the test-and-treat coverage was increased by 10% every year since 2018, then the numbers of chronic HBV infection, new HBV infection, and HBV-related deaths in 2035 would be reduced by 21.81%, 20.10%, and 21.40%, respectively, and in 2060 it would be reduced by 41.53%, 39.89%, and 40.32%, respectively. In particular, if the test-and-treat coverage was increased to 75% since 2018, then the annual number of HBV-related deaths would begin to decrease from 2018. If the test-and-treat coverage was increased to above 25% since 2018, then the hepatitis B surface antigen (HBsAg) prevalence for population aged 1 to 59 years in China would be reduced to below 2% in 2035. Our model also showed that in 2035, the numbers of chronic HBV infection and HBV-related deaths in 65 to 69 age group would be reduced the most (about 1.6 million and 13 thousand, respectively).

Increasing test-and-treat coverage would significantly reduce HBV infection in China, especially in the middle-aged people and older people. The earlier the treatment and the longer the time, the more significant the reduction. Implementation of test-and-treat strategy is highly effective in controlling hepatitis B in China.

Abbreviations: ADV = adefovir dipivoxil, CHB = chronic hepatitis B, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, IFN = interferon, TDF = tenofovir disoproxil fumarate.

Keywords: age-structured model, antiviral therapy, HBsAg prevalence, Hepatitis B virus, infectious disease dynamics, test-and-treat strategies, transmission dynamics

1. Introduction

Hepatitis B virus (HBV) infection remains a serious public health problem in China.\textsuperscript{11–14} Despite the availability of hepatitis B vaccine for 3 decades, the prevalence of chronic HBV infection in China had only declined slightly, from 9.8% in 1992 to 7.2% in 2006.\textsuperscript{15,16} A recent national serosurvey of hepatitis B in China revealed that the hepatitis B surface antigen (HBsAg) prevalence for population aged 1 to 29 years was 2.6% in 2014.\textsuperscript{17,18} Based on these surveys, it was estimated that in 2014, there were more than 71 million people with chronic HBV infection in China, about 28 million people were patients with chronic hepatitis B disease (defined as someone who has chronic hepatitis disease due to chronic HBV infection), and approximately 25% to 40% of these chronic HBV carriers (defined as someone who carries HBsAg for >6 months) would develop into cirrhosis and hepatocellular carcinoma (HCC).\textsuperscript{12–15} Hepatitis B virus had become the primary cause of mortality in China.\textsuperscript{11–13}

The government of China adopted comprehensive strategies to prevent HBV transmission, including hepatitis B vaccination and antiviral therapy.\textsuperscript{11–10} Several studies had shown that interferon (IFN) treatment enhanced HBsAg seroclearance by approximately sixfold in Asian studies.\textsuperscript{11–13} Lin et al\textsuperscript{12} followed-up 233 IFN-treated patients and 233 well-matched untreated controls
from Taiwan and found that the annual rate of HBsAg seroclearance was 3% and 0.4%, respectively. Another prospective study of 411 Chinese patients with chronic HBV infection (208 treated with IFN-α and 203 as control) indicated that HBsAg seroclearance occurred at an average rate of 2.4% per year in IFN-α treated patients and 0.49% in control patients. Moreover, Hadziyannis et al.[14] found that 5% of patients with hepatitis B virus antigen (HBeAg)-negative chronic hepatitis B (CHB) had HBsAg loss after 196 weeks of treatment with adefovir dipivoxil (ADV). Through 8 years of treatment with tenofovir disoproxil fumarate (TDF) in mostly naive patients, Marcellin et al.[15] reported that 13% of patients with HBeAg-positive chronic hepatitis B had experienced loss of HBsAg. Long-term treatment with tenofovir disoproxil fumarate for patients with chronic hepatitis B disease was safe and effective with no evidence of resistance.[13-18] Therefore, it can be seen that antiviral therapy had played an important role in reducing HBsAg prevalence in both Western and Eastern countries.[11-18]

Since 1992, both interferon treatment and nucleos(t)ide analog therapy had been introduced and approved for the treatment of patients with chronic hepatitis B disease in China.[1] Currently, due to the high cost of treatment, only about 12.5% of patients with chronic hepatitis B disease in China have received antiviral therapy.[2,3] But with the development of economy and society, it is believed that more and more patients with chronic hepatitis B disease would receive antiviral therapy in China. However, there have been few studies modeling the potential impact of increasing test-and-treat coverage on HBV infection in China. In general, accurate estimate of the long-term effect of test-and-treat policy would not only help us assess the burden of hepatitis B in China, but also help us design a new prevention and treatment strategy.

The objective of this study was to develop a dynamic compartmental model of HBV transmission to estimate the impact of increasing test-and-treat coverage on HBV infection in China. Overall, based on 3 national survey data of hepatitis B in 1992, 2006, and 2014,[28-31] we predicted the number of new HBV infection, the number of chronic HBV infection, and the number of HBV-related deaths in China for the time from 2018 to 2050 under 5 different test-and-treat coverage and compared them with the current intervention policy.

2. Materials and methods

2.1. Compartmental model of HBV transmission

According to the natural history of HBV infection and main features of HBV transmission in China, we constructed a dynamic compartmental model of HBV transmission.[18,19,23] In this model, the total population was divided into 3 compartments: susceptible to HBV infection \( S(t) \); chronic HBV carriers \( C(t) \); recovered and obtained immunity due to HBV infection or vaccination \( R(t) \); where \( a \) represented age and \( t \) represented time. We took “year” as a basic unit of time. Particularly, in this study we considered mother-to-child transmission of HBV and catch-up vaccination for adolescents. After combination immunization of hepatitis B immunoglobulin (HBIG) and birth dose vaccine, on average the mother-to-child transmission rate \( \mu \) might be reduced to below 7.6%.[1,10] We assumed that the maximum age of people was 100 years old and further divided population into 101 age groups. The susceptible people in age group \( a \) (\( a = 1, 2, \ldots, 100 \)) might be infected by all age groups of HBV infection. Moreover, we assumed that the people were homogeneously mixed and we used a standard incidence rate to describe the transmission process of HBV in China. Therefore, we obtained the following age-structured transmission model of HBV in China (Eqs. (1) and (2)).

For population aged 0 year (0 ≤ \( a \) ≤ 1):

\[
\begin{align*}
S(t+1) + b(t)N(t)\left(1 - pr(t) - ca\left(\sum_{a=1}^{49} C(t) / \sum_{a=1}^{49} N(t)\right)\right), \\
C(t+1) = q_a b(t)N(t)\left(1 - \sum_{a=1}^{49} C(t) / \sum_{a=1}^{49} N(t)\right), \\
R(t+1) = b(t)\left(p_r(t) + (1 - q_r)b(t)N(t)\left(\sum_{a=1}^{15} C(t) / \sum_{a=1}^{49} N(t)\right)\right).
\end{align*}
\]

For population aged 1 to 100 years:

\[
\begin{align*}
S(t+1) + (1 - \mu_a(t))S(t) - b(t)N(t)S(t) - \lambda(t)S(t), \\
C(t+1) = (1 - \mu_a(t))C(t) + q_{ap}(t)S(t) - m_aC(t) + r_aC(t), \\
R(t+1) = (1 - \mu_a(t))R(t) + b(t)N(t)S(t) + (1 - q_r)b(t)N(t) + r_aC(t).
\end{align*}
\]

where \( N(t) = S(t) + C(t) + R(t), N(t) = \sum_{a=0}^{100} N(t). \) (\( C(t) = \sum_{a=15}^{100} C(t), \) and \( \lambda(t) = \beta(t)C(t)/N(t) \) represent the force of HBV infection, \( \beta(t) \) the average transmission rate in age group \( a \) in year \( t \). The meanings of other parameters were described in Table 1.

2.2. Model input parameters

Parameter estimation was mainly based on 3 national serosurvey data of hepatitis B in China.[15-18] The demographic data were obtained from National Bureau of Statistics of China and adjusted according to national census data of China in 1990, 2000, and 2010.[24-28] Specifically speaking, the birth rate \( b(t) \) was obtained from the National Bureau of Statistics of China.[24] if \( t \geq 2016, \) then \( b(t) = b(2015) \) (Supplementary Fig. 1A, http://links.lww.com/MD/C207). The 3 doses of vaccination coverage rate of newborns \( v(t) \) was obtained from the immunization history report of national serosurvey in 2006 and 2014.[6,7,10] Since 2005, hepatitis B virus vaccine was administered to all infants freely in China.[2,3,6,7] Therefore, it can be seen that the 3 doses of vaccination coverage rate of newborns in China reached up to 99.67% since 2012.[15,17] If \( t \geq 2015, \) then \( v(t) = (2014) \) (Supplementary Fig. 1B, http://links.lww.com/MD/C207). The age-specific death rate of HBV-related diseases among chronic HBV carriers \( m_a \) was determined from mortality curves of HBV-related cirrhosis and hepatocellular carcinoma (Supplementary Fig. 1C, http://links.lww.com/MD/C207).[20] The total death rate \( d_a(t) \) was obtained from national census data of China in 1990, 2000, 2010 and 1% of population sampling survey in 2005 (Supplementary Fig. 1D, http://links.lww.com/MD/C207).[25-28] Consequently, the age-specific death rate of non-HBV related diseases was given by \( \mu_a(t) = d_a(t)N(t) - m_aC(t) / N(t) \). The other parameter values except the HBsAg seroclearance rate and HBV transmission rate were determined from published literatures and were summarized in Table 1.[11-31]

Moreover, based on the HBsAg prevalence for population aged 1 to 59 years in 1992 and 2006 and transmission models (1) and (2), we used the method of nonlinear least squares to estimate the annual rate of HBsAg seroclearance \( r_a \) and HBV transmission rate \( \beta(t) \). Particularly, the transmission rate of HBV in 1992, \( \beta(1992) \), was estimated by using a catalytic model.[21,22] The initial conditions of the model were determined according to national serosurvey of hepatitis B in 1992.[5] For simplicity of estimation, we assumed that the transmission rate of HBV \( \beta(t) \) decreased exponentially since 1992. Because in China besides the implementation of newborn hepatitis B vaccination, we also adopted other prevention and control strategies to reduce the
transmission risk of HBV since 1992, such as safe injection, health education, and HBsAg screening before blood transfusion. \[^{1-11}\] With the aid of MATLAB software (MathWorks, Inc.), we obtained the annual rate of HBsAg seroclearance \(\beta_a(t)\) (Table 1) and transmission rate \(\beta_a(t)\), that is,

\[
\beta_a(t) = (0.5308\exp(-0.3853(t - 1992)) + 0.4692)\beta_a(1992), \quad \text{if } t \geq 1993. \quad (3)
\]

In this study, the ethical approval was not necessary and this study did not involve patient consent because all of the data were collected from published literatures.

### 2.3. Model validation

We compared the estimated age-specific HBsAg prevalence by model with national survey data in 2006 and 2014. \[^{6-8,12,33}\] Compared with the national survey data in 2006, \[^{11}\] we can see that the estimated values from our model fitted very well with survey data in 2006 and the maximum absolute error was 0.0028. All estimated values fell into the 95% confidence intervals of observed values (Supplementary Fig. 2A, http://links.lww.com/MD/C207). Moreover, we found that the estimated HBsAg prevalence for population aged 1 to 29 years was also consistent with the survey data in 2014 (Supplementary Fig. 2B, http://links.lww.com/MD/C207). \[^{7,8,12,33}\] This comparison analysis demonstrated that our model and estimated parameters were credible and can be used to predict the prevalence of HBsAg in the future.

### 2.4. Evaluation of the impact of test-and-treat strategy

Based on the transmission rate (3) and estimated parameters, we used transmission models (1) and (2) to evaluate the impact of increasing test-and-treat coverage on HBV infection in China. We assumed that different test-and-treat coverage mainly influenced the HBsAg seroclearance rate of chronic HBV carriers. According to the guideline of prevention and treatment for chronic hepatitis B in China, both interferon and nucleos(t)ide analog were used for the treatment of patients with chronic hepatitis B disease. \[^{5-4}\] For simplicity, we assumed that if the patients with chronic hepatitis B disease received antiviral therapy, then their HBsAg seroclearance rate was sixfold higher than that of patients without treatment. \[^{11-18}\]

Currently, it is estimated that about 30% of people with chronic HBV infection have chronic hepatitis disease (28 million people) and require receiving antiviral therapy in China. \[^{11-7}\] but due to the high cost of treatment, only about 12.5% of patients

### Table 1

| Description of parameters | Values | References |
|---------------------------|--------|------------|
| \(a(t)\): birth rate in year \(t\) | | |
| \(v(t)\): 3 doses of vaccination coverage rate of newborns in year \(t\) | | |
| \(p(t)\): vaccination protection rate per year | | |
| \(\alpha\): mother-child transmission rate per year | | |
| \(w\): proportion of HBsAg-positive mothers in total prevalence of HBsAg aged 15–49 years | | |
| \(q_c\): probability of acute HBV infection that became chronic due to mother-child transmission | | |
| \(m_p\): age-specific mortality rate of HBV-related diseases per year | | |
| \(d_{p/t}\): age-specific total death rate in year \(t\) | | |
| 1990 < \(t\) < 1995 | | |
| 1996 < \(t\) < 2002 | | |
| 2003 < \(t\) < 2007 | | |
| 2008 < \(t\) < 2014 | | |
| 2015 < \(t\) < 2050 | | |
| \(\mu_1\): age-specific death rate of non-HBV related diseases in year \(t\) | | |
| \(d_{c/t}\): catch-up vaccination coverage rate for population aged 8–15 years in 2009–2011 | | |
| \(q_c\): age-specific probability of acute HBV infection that became chronic per year | | |
| 0 < \(a\) < 1 (not due to mother-child transmission) | | |
| 1 < \(a\) < 4 | | |
| 5 < \(a\) < 15 | | |
| 16 < \(a\) < 100 | | |
| \(\beta_0(1992)\): age-specific transmission rate of HBV in 1992 | | |
| \(r_x\): annual rate of HBsAg seroclearance in chronic HBV carriers (%/yr) | | |
| 1 < \(a\) < 4 | | |
| 5 < \(a\) < 9 | | |
| 10 < \(a\) < 14 | | |
| 15 < \(a\) < 19 | | |
| 20 < \(a\) < 24 | | |
| 25 < \(a\) < 29 | | |
| 30 < \(a\) < 34 | | |
| 35 < \(a\) < 39 | | |
| 40 < \(a\) < 49 | | |
| 50 < \(a\) < 59 | | |
| Other age groups | | |

HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus.
with chronic hepatitis B disease have received antiviral therapy.[12-4] Therefore, if we assumed that the HBsAg seroclearance rate of chronic HBV carriers without treatment was \( r \), then we had

\[
(30\% \times C) \times 12.5\% \times 6 + (30\% \times C) \times 87.5\% \times r + (70\% \times C) \times r = C \times r_d
\]

where \( C \) was the total number of chronic HBV carriers and \( r_d \) was the current estimated seroclearance rate of HBsAg. This implies that

\[
 r = 0.8421 \times r_d
\]

Consequently, if the test-and-treat coverage was increased to 25\%, then we had

\[
(30\% \times C) \times 25\% \times 6 + (30\% \times C) \times 75\% \times r + (70\% \times C) \times r = C \times 1.1579 \times r_d
\]

That is to say, if the test-and-treat coverage was increased to 25\%, then the annual rate of HBsAg seroclearance in chronic HBV carriers would become 1.1579\%. Similarly, if the test-and-treat coverage was increased to 50\%, 75\% and 100\%, respectively, then the annual rate of HBsAg seroclearance would become 1.4737\%, 1.7895\% and 2.1053\%, respectively. In other words, the influence of increasing test-and-treat coverage was transformed into the effect of increasing HBsAg seroclearance rate.

In general, we predicted the number of chronic HBV infection, the number of new HBV infection, and the number of HBV-related deaths in China for the time from 2018 to 2050 under the following conditions: current practice: 12.5\% of test-and-treat coverage; 25\% of test-and-treat coverage since 2018; 50\% of test-and-treat coverage since 2018; 75\% of test-and-treat coverage since 2018; 100\% of test-and-treat coverage since 2018; and gradually increase to 100\% since 2018: test-and-treat coverage increasing by 10\% every year from 2018 to 2026 and thereafter remaining at 100\% till 2030. Compared with the current practice, we estimated how many chronic HBV carriers and HBV-related deaths would be reduced due to the increase of test-and-treat coverage and how many people were prevented to be infected by HBV. We also estimated in which age group the number of chronic HBV infection, the number of new HBV infection, and the number of HBV-related deaths would reduce the most in 2035.

2.5. Testing and treatment strategy

If the resource of HBV testing and treatment was limited, we estimated in which age group the test-and-treat coverage was singly increased to 100\% since 2018, the number of chronic HBV infection in 2030 would be reduced the most, the total number of new HBV infection, and the number of HBV-related deaths in 2018 to 2030 would be reduced the most, compared with the current policy. In particular, we divided the chronic HBV carriers aged 1 to 59 years into 12 age groups.

2.6. Sensitivity analysis

We performed sensitivity analysis to assess which critical parameters affected our prediction in terms of chronic HBV infection, new HBV infection and HBV-related deaths. Parameters included the HBsAg seroclearance rate \( (r_d) \), transmission rate of HBV \( (\beta_{x}(t)) \), proportion of patients with chronic hepatitis B disease, and HBsAg seroclearance rate of patients with treatment. The parameter value was cut down or increased by 20\% since 2018, or was varied in a reasonable range.[11,13,22] But we assumed that each parameter was changed, one at a time, while the others were held constant. When we performed sensitivity analysis, we also assumed that the test-and-treat coverage rate was increased to 100\% since 2018.

3. Results

3.1. Reduction of chronic HBV carriers

Compared with the current policy, we found that the larger the test-and-treat coverage, the more the reduction of chronic HBV carriers. Specifically, if the current coverage of testing and treatment (12.5\%) remained unchanged till 2035, the number of chronic HBV infection in 2035 would be more than 38.93 million (Fig. 1A). However, if the test-and-treat coverage was increased to 50\% since 2018, then compared with the current policy, the number of chronic HBV infection in 2035 would be reduced by 12.41\% (34.1 million vs 38.93 million) (Fig. 1A and B). Furthermore, if the test-and-treat coverage was increased to 100\% since 2018, then the number of chronic HBV infection in 2035 would be reduced by 26.61\% (28.57 million vs 38.93 million) (Fig. 1A and B). The test-and-treat coverage should be increased to above 75\% since 2018 for achieving 20\% reduction of chronic HBV carriers in 2035. More interestingly, from Fig. 1B we can see that the longer the time, the more significant the reduction of chronic HBV carriers. Compared with the current policy, the number of chronic HBV infection in 2050 would be reduced by 44.94\% (10.45 million vs 18.98 million) if the test-and-treat coverage was increased to 100\% since 2018. However, if the test-and-treat coverage was increased by 10\% every year since 2018, then the number of chronic HBV infection in 2035 and 2050 would be reduced by 21.81\% and 41.53\%, respectively (Table 2), which was less than the situation that the test-and-treat coverage was increased to 100\% since 2018 (Table 2). This implied that the earlier the testing and treatment, the more the reduction of chronic HBV carriers.

Moreover, compared with the current policy, we found that the HBV prevalence in the middle-aged people and older people would reduce more due to the increase of test-and-treat coverage. From Fig. 1C, we can see that if the test-and-treat coverage was increased to 100\% since 2018, then in 2035 there were 3 peaks in the age-specific reduced number of chronic HBV infection, which were in 15 to 19, 50 to 54, and 65 to 69 age groups, the largest peak age distribution was in 65 to 69 age group and in this age group the number of chronic HBV infection would be reduced by 1,608,407.

In addition, from Fig. 1D, we can see that if the HBsAg prevalence for population aged 1 to 59 years required reducing to below 2\% in 2035, then the test-and-treat coverage should be above 25\% since 2018. Whereas if the test-and-treat coverage was increased to 50\% since 2018, then the HBsAg prevalence for population aged 1 to 59 years would become 1.88\% in 2035, which would be decreased by 10.9\% compared with the current policy (2.11\% vs 1.88\%).

3.2. Reduction of new HBV infection

Compared with the current policy, we found that the larger the test-and-treat coverage, the more the reduction of new HBV infection. If the coverage of testing and treatment was increased
Table 2

Percentage reduction in chronic HBV infection, new HBV infection and HBV-related deaths under different test-and-treat strategies.

| Coverage rate of testing and treatment | 12.5% (current practice) | 25% | 50% | 75% | 100% | Gradually increase to 100% |
|---------------------------------------|---------------------------|-----|-----|-----|------|---------------------------|
| Number of chronic HBV infection in 2035 | 38,930,311                | 37,249,398 | 34,100,973 | 31,216,677 | 28,573,930 | 30,439,987 |
| Decrease from current practice (%)     | –                         | 4.32 | 12.41 | 19.81 | 26.61 | 21.81 |
| Number of chronic HBV infection in 2050 | 18,978,155                | 17,433,226 | 14,796,184 | 12,400,296 | 10,450,729 | 1,1097,155 |
| Decrease from current practice (%)     | –                         | 8.14 | 22.51 | 34.66 | 44.94 | 41.53 |
| Total number of new HBV infection in 2018-2035 | 21,428,871               | 21,052,109 | 20,328,291 | 19,642,163 | 18,991,546 | 19,896,431 |
| Decrease from current practice (%)     | –                         | 1.76 | 5.14   | 8.34  | 11.40 | 7.15 |
| Total number of new HBV infection in 2018-2050 | 29,912,601               | 29,054,693 | 27,450,573 | 25,982,956 | 24,638,339 | 25,884,301 |
| Decrease from current practice (%)     | –                         | 2.87 | 8.23   | 13.14 | 17.63 | 13.47 |
| Total number of HBV-related deaths in 2018-2035 | 4,247,014                | 4,153,439 | 3,974,363 | 3,805,500 | 3,646,225 | 3,856,757 |
| Decrease from current practice (%)     | –                         | 2.20 | 6.42   | 10.40 | 14.15 | 9.19 |
| Total number of HBV-related deaths in 2018-2050 | 7,247,542               | 6,972,118  | 6,461,795  | 6,000,683  | 5,583,553  | 5,919,046  |
| Decrease from current practice (%)     | –                         | 3.80 | 10.84  | 17.20 | 22.96 | 18.33 |
| Peak time of HBV-related deaths (year) | 2029                      | 2027 | 2022   | 2018  | 2018  | 2022 |
| Number of HBV-related deaths in peak time | 240,723                   | 234,502 | 226,785  | 224,513  | 224,513  | 229,130 |
| Decrease from current practice (%)     | –                         | 2.58 | 5.79   | 6.73  | 6.73  | 4.82 |

HBV = hepatitis B virus.
to 50% since 2018, then compared with the current policy, the number of new HBV infection in 2035 would be reduced by 11.52% (738,822 vs 834,976) (Fig. 2A and B). By contrast, if the test-and-treat coverage was increased to 100% since 2018, then the number of new HBV infection in 2035 would be reduced by 24.88% (627,213 vs 834,976) (Fig. 2A and B). The test-and-treat coverage should be increased to above 75% since 2018 for achieving 20% reduction of new HBV infection in 2035. In particular, from Fig. 2A and B we can see that the longer the time, the more significant the reduction of new HBV infection. In 2050, compared with the current policy, the number of new HBV infection would be reduced by 43.29% (204,923 vs 361,330) if the test-and-treat coverage was increased to 100% since 2018. While if the test-and-treat coverage was increased by 10% every year since 2018, the number of new HBV infection in 2035 and 2050 would be reduced by 20.10% and 39.89%, respectively, which was less than the situation that the test-and-treat coverage was increased to 100% since 2018. This means that the earlier the treatment, the more the reduction of new HBV infection.

More interestingly, from Fig. 2C we can see that if the HBV test-and-treat coverage was increased to 100% since 2018, then compared with the current policy, in 2035 the number of new HBV infection in 0 to 4 age group would be reduced the most (about 41,332). The second peak age distribution was in 45 to 49 age group and in this age group the number of new HBV infection would be reduced by 25,695.

Moreover, compared with the current policy, we found that increasing test-and-treat coverage would significantly reduce the total number of new HBV infection in China. If the test-and-treat coverage was increased to 100% since 2018, the total number of new HBV infection in 2018 to 2035 would be reduced by 11.40% and in 2018 to 2050 it would be reduced by 17.63% (Table 2). By contrast, if the test-and-treat coverage was increased by 10% every year since 2018, the total number of new HBV infection over 33 years (2018-2050) would be reduced by 13.47%, which was less than 17.63% (Table 2). Particularly, we found that if the test-and-treat coverage was increased to 100% since 2018, then in 2018 to 2035 the total number of new HBV infection in 0 to 4 age group would be reduced the most (about 464,615). The second peak age distribution was in 40 to 44 age group, which would be reduced by 234,340 (Fig. 2D).
3.3. Reduction of HBV-related deaths

Compared with the current policy, we found that the larger the test-and-treat coverage, the more the reduction of HBV-related deaths. If the test-and-treat coverage was increased to 50% since 2018, the number of HBV-related deaths in 2035 would be reduced by 12.39% (204,956 vs 233,836) (Fig. 3A and B). By contrast, if the test-and-treat coverage was increased to 100% since 2018, then the number of HBV-related deaths in 2035 would be reduced by 26.55% (171,756 vs 233,836). Particularly, the test-and-treat coverage should be increased to above 75% since 2018 for achieving 20% reduction of HBV-related deaths in 2035. Moreover, from Fig. 3A and B we can see that the longer the time, the more significant the reduction of HBV-related deaths. If the test-and-treat coverage was increased to 100% since 2018, then the number of HBV-related deaths in 65 to 69 age group would begin to decrease since 2018 and reach a level of 106,795 in 2050. However, if the current coverage (12.5%) remained unchanged, the annual number of HBV-related deaths would continue to increase, it would begin to decrease after 2029, and reach to a level of 160,734 in 2050.

More interestingly, from Fig. 3C we can see that if the test-and-treat coverage was increased to 100% since 2018, then compared with the current policy, the number of HBV-related deaths in 2035 would be reduced the most (about 13,320).

Figure 3. Reduction of HBV-related deaths under different test-and-treat strategies. (A) The number of HBV-related deaths, 2014 to 2050. (B) Percentage reduction in HBV-related deaths compared with current practice, 2018-2050. (C) Age-specific reduced number of HBV-related deaths in 2035 compared with current practice. (D) Age-specific reduced number of HBV-related deaths in 2018 to 2035 compared with current practice. HBV = hepatitis B virus.

In addition, from Fig. 3A we can see that if the test-and-treat coverage was increased to 75% since 2018, then the annual number of HBV-related deaths would begin to decrease since 2018 and reach a level of 106,795 in 2050. However, if the current coverage (12.5%) remained unchanged, the annual number of HBV-related deaths would continue to increase, it would begin to decrease after 2029, and reach to a level of 160,734 in 2050.

Furthermore, compared with the current policy, we found that increasing test-and-treat coverage would significantly reduce the total number of HBV-related deaths in China. If the coverage of testing and treatment was increased to 100% since 2018, the total number of HBV-related deaths in 2018 to 2035 would be reduced by 14.15% and in 2018 to 2050 it would be reduced by 22.96% (Table 2). If the test-and-treat
Current practice 18,978,155 – 29,912,603 – 7,247,544 –
1–4 18,650,361 1.73 29,757,632 0.52 7,246,758 0.01
5–9 18,656,267 1.70 29,768,690 0.48 7,246,452 0.02
10–14 18,931,337 0.25 29,891,943 0.07 7,247,274 0.00
15–19 18,831,619 0.77 29,844,293 0.23 7,245,712 0.03
20–24 18,352,637 3.30 29,572,469 1.14 7,229,308 0.25
25–29 18,978,155 0.00 29,912,603 0.00 7,247,544 0.00
30–34 18,978,155 0.00 29,912,603 0.00 7,247,544 0.00
35–39 16,902,629 10.94 28,474,642 4.81 6,992,073 3.52
40–44 18,978,155 0.00 29,912,603 0.00 7,247,544 0.00
45–49 18,978,155 0.00 29,912,603 0.00 7,247,544 0.00
50–54 16,856,062 11.18 28,825,091 3.64 6,797,381 6.21
55–59 16,741,151 11.79 28,637,471 4.26 6,799,209 6.19

HBV = hepatitis B virus.

Coverage was increased by 10% every year since 2018, the total number of HBV-related deaths over 33 years (2018–2050) would be reduced by 18.33% (Table 2). Particularly, from Fig. 3D we found that if the test-and-treat coverage was increased to 100% since 2018, then in 2018 to 2035 the total number of HBV-related deaths in the 60 to 64 age group would be reduced the most (about 120,046).

### 3.4. Optimal strategy of testing and treatment

Compared with the current policy, we found that if the test-and-treat coverage in 55 to 59 age group was singly increased to 100% since 2018, then the number of chronic HBV infection in 2050 would be reduced by 11.79% (about 2,237,004), the total number of new HBV infection in 2018 to 2050 would be reduced by 4.26% (about 1,275,132) and the total number of HBV-related deaths in 2018 to 2050 would be reduced by 6.19% (about 448,335) (Table 3). Compared with other age groups, we can see that a 100% of testing and treatment in 55 to 59 age group was an optimal strategy if the resource of testing and treatment was limited. The second optimal strategy was a 100% of testing and treatment in the 50–54 age group and the third optimal strategy was that in 35 to 39 age group.

### 3.5. Sensitivity analysis results

Sensitivity analysis indicated that the rate of HBsAg seroclearance ($r_a$) was the most sensitive parameter on estimation of chronic HBV infection in 2050 and the total number of HBV-related deaths in 2018 to 2050. If the HBsAg seroclearance rate was cut down by 20% since 2018, the percentage reduction in chronic HBV infection in 2050 would decrease from 44.93% to 30.83% and the percentage reduction in HBV-related deaths in 2018 to 2050 would decrease from 22.96% to 15.15% under a test-and-treat coverage of 100% (Tables 2 and 4).

Moreover, we found that the transmission rate of HBV ($b_a(t)$) was the most sensitive parameter on estimation of the total number of new HBV infection in 2018 to 2050. Under a test-and-treat coverage of 100%, if the transmission rate of HBV was cut down by 20% since 2018, then the percentage reduction in new HBV infection in 2018 to 2050 would increase from 17.63% to 33.56% (Tables 2 and 4).

### Table 4

| Scenarios | Number of chronic HBV infection in 2050 | Decrease from current practice (%) | Total number of new HBV infection (2018–2050) | Decrease from current practice (%) | Total number of HBV-related deaths (2018–2050) | Decrease from current practice (%) |
|-----------|----------------------------------------|----------------------------------|-----------------------------------------------|----------------------------------|-----------------------------------------------|----------------------------------|
| Current practice | 18,978,155 | – | 29,912,603 | – | 7,247,544 | – |
| Rate of HBsAg seroclearance ($r_a$) | | | | | | |
| Cut down by 20% since 2018 | 13,126,310 | 30.83% | 26,457,830 | 11.55% | 6,149,246 | 15.15% |
| Increased by 20% since 2018 | 8,312,176 | 56.20% | 23,016,214 | 23.06% | 5,087,855 | 29.80% |
| Transmission rate of HBV ($b_a(t)$) | | | | | | |
| Cut down by 20% since 2018 | 10,343,916 | 45.50% | 19,873,306 | 33.56% | 5,579,111 | 22.86% |
| Increased by 20% since 2018 | 10,557,199 | 44.37% | 19,379,495 | 1.78% | 5,591,111 | 22.86% |
| HBsAg seroclearance rate of patients with treatment $b_a(t)$ | | | | | | |
| 5r | 11,984,155 | 36.85% | 25,704,826 | 14.07% | 5,913,976 | 18.40% |
| 7r | 9,110,715 | 51.99% | 23,653,206 | 20.96% | 5,278,424 | 27.17% |
| Proportion of patients with chronic hepatitis B disease | | | | | | |
| 25% | 11,714,169 | 38.28% | 25,521,997 | 14.68% | 5,857,082 | 19.19% |
| 35% | 9,321,725 | 50.88% | 23,804,377 | 20.42% | 5,327,625 | 26.49% |

$r_a$ was the HBsAg seroclearance rate of patients without treatment. HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus.
4. Discussion and conclusions

Understanding the potential impact of increasing test-and-treat coverage on HBV infection is very important for controlling hepatitis B in China. In this study, based on the natural history of HBV infection and three serosurvey data of hepatitis B in China, we proposed an age- and time-dependent discrete model to estimate the long-term effect of increasing HBV test-and-treat coverage in China. We predicted the number of chronic HBV infection and the number of HBV-related deaths for the time from 2018 to 2050 under 5 different test-and-treat coverages and compared them with current intervention policy. Our modeling study indicated that increasing the test-and-treat coverage would significantly reduce the number of chronic HBV infection, the number of new HBV infection and the number of HBV-related deaths in China, especially in the middle-aged people and older people.[1-4,11,31-33]

The earlier the treatment and the longer the time, the more significant the reduction. In particular, if the test-and-treat coverage was increased to 75% since 2018, then the annual number of HBV-related deaths would begin to decrease from 2018. If the test-and-treat coverage was increased to above 25% since 2018, then the HBsAg prevalence for population aged 1 to 59 years would be reduced to below 2% in 2035.

The limitations of the present study mainly derive from the uncertainties that remain in some of the model assumptions. First, the acute HBV infection was not considered as a compartment of the model. Because the average duration of acute HBV infection was relatively short (about 3 months), and it was almost impossible to determine its initial number from the national survey data. Second, for simplicity, the transmission rate was assumed to decrease exponentially in all age groups at the same rate. To be more reasonable, the transmission rate in different age groups might change differently over time. Particularly, in some age groups the frequency of high-risk behavior might increase over time, which might increase the transmission rate. Third, due to the data quality problem, the HBV-related death rate of chronic HBV carriers was estimated from international reports, which might cause some deviations of the estimated results from China’s realities. Besides, the nucleos(t)ide analog therapy for hypertension B disease might have different seroclearance rate of HBsAg, which might have a certain influence on the estimated results in this paper.[1,4-19]

In conclusion, this study developed a novel method to predict the long-term effect of increasing HBV treatment coverage at a population-level. Except for hepatitis B vaccination strategy, implementation of test-and-treat strategy is highly effective in controlling hepatitis B in China. Great efforts need to be made to increasing the test-and-treat coverage among patients with chronic hepatitis B disease. Moreover, our findings also provided some quantitative and new information that might be useful for improving the prevention and treatment strategies of hepatitis B in China and other high endemic areas.

Acknowledgments

We are very grateful to referees and editors for their careful reading and valuable comments. We would also like to thank Profs Yicang Zhou, Yanni Xiao, and Xiaodan Sun for their valuable discussion on this work.

Author contributions

Conceptualization: Jian Zu, Guihua Zhuang, Fuqiang Cui, Xiaofeng Liang.

Data curation: Jian Zu, Miaolei Li, Peifeng Liang, Fuqiang Cui, Fuzhen Wang, Hui Zheng, Xiaofeng Liang.

Formal analysis: Jian Zu, Peifeng Liang.

Funding acquisition: Jian Zu, Guihua Zhuang, Fuqiang Cui, Xiaofeng Liang.

Investigation: Jian Zu, Fuzhen Wang, Hui Zheng.

Methodology: Jian Zu, Miaolei Li, Guihua Zhuang, Peifeng Liang, Fuqiang Cui, Hui Zheng, Xiaofeng Liang.

Project administration: Guihua Zhuang.

Resources: Guihua Zhuang, Fuzhen Wang, Hui Zheng.

Software: Jian Zu, Miaolei Li, Peifeng Liang.

Supervision: Guihua Zhuang, Fuqiang Cui, Fuzhen Wang, Xiaofeng Liang.

Validation: Jian Zu, Fuqiang Cui, Fuzhen Wang, Hui Zheng, Xiaofeng Liang.

Visualization: Miaolei Li, Peifeng Liang.

Writing – original draft: Jian Zu.

Writing – review & editing: Miaolei Li.

References

[1] Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009;373:582–92.
[2] Chinese Society of Hepatology and Chinese Society of Infectious Diseases. Chinese Medical Association The guideline of prevention and treatment for chronic hepatitis B: a 2015 update. Chin J Hepatol 2015;23:888-905. (in Chinese).
[3] Cui EQ, Zhuang H. Hepatitis B control in China: progress, challenges and strategies. Chin J Viral Dis 2016;6:81–7. (in Chinese).
[4] Zhang S, Ma Q, Liang S, et al. Annual economic burden of hepatitis B virus-related diseases among hospitalized patients in twelve cities in China. J Viral Hepat 2016;23:202–10.
[5] Cui GL, Liu CB, Cao HL, et al. 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 1996;6:62–73.
[6] Liang XF, Bi SL, Yang WZ, et al. Epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. Vaccine 2009;27:6550–7.
[7] Cui EQ, Shen LP, Li L, et al. Prevention of chronic hepatitis B after 3 decades of escalating vaccination policy, China. Emerg Infect Dis 2017;23:765–72.
[8] Zu J, Zhuang GH, Liang P, et al. Estimating age-related incidence of HBsAg seroclearance in chronic hepatitis B virus infections by using a dynamic compartmental model. Sci Rep 2017;7:2912.
[9] Wei F, Zheng Q, Li M, et al. The association between hepatitis B mutants and hepatocellular carcinoma: a meta-analysis. Medicine 2017;96:e6835.
[10] Liang XF, Bi SL, Yang WZ, et al. Evaluation of the impact of hepatitis B vaccination among children born during 1992-2005 in China. J Infect Dis 2009;200:39-47.
[11] Chu CM, Liaw YF. Hepatitis B surface antigen seroclearance during chronic HBV infection. Antivir Ther 2010;15:133–43.
[12] Lin SM, Yu ML, Lee CM, et al. Interferon therapy in HBeAg-positive chronic hepatitis B reduces progression to cirrhosis and hepatocellular carcinoma. J Hepatol 2007;46:45–52.
[13] Yuen MF, Hui CK, Cheng CC, et al. Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: the effect on hepatitis B e antigen serocconversion and the development of cirrhosis-related complications. Hepatology 2001;34:139–45.
[14] Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology 2006;131:1743–51.
[15] Marcellin P, Gane EJ, Flisiak R, et al. Long term treatment with tenofovir disoproxil fumarate for chronic hepatitis B infection is safe and well tolerated and associated with durable virologic response with no detectable resistance: 8 year results from two phase 3 trials. Hepatology 2014;60:313A–4A.
[16] Ungtrakul T, Suprayoon T, Kusuman P, et al. Role of quantitative hepatitis B surface antigen in predicting inactive carriers and HBeAg seroclearance in HBeAg-negative chronic hepatitis B patients. Medicine 2017;96:e5554.

[17] Wu W, Zhu Y, Yu C, et al. Clinical features of treatment-naive patients with hepatitis B virus infection: A community-based survey from high- and intermediate-hepatitis B endemicity regions in Southeast China. Medicine 2017;96:e6660.

[18] Pan AN, Xu WW, Luo YL, et al. A novel system for predicting liver histopathology in patients with chronic hepatitis B. Medicine 2017;96:e6465.

[19] Zhao SJ, Xu ZY, Lu Y. A mathematical model of hepatitis B virus transmission and its application for vaccination strategy in China. Int J Epidemiol 2000;29:744–52.

[20] Goldstein ST, Zhou F, Hadler SC, et al. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int J Epidemiol 2005;34:1329–39.

[21] Grenfell BT, Anderson RM. The estimation of age-related rates of infection from case notifications and serological data. J Hyg (Lond) 1985;95:419–36.

[22] Liang PF, Zu J, Yin J, et al. The independent impact of newborn hepatitis B vaccination on reducing HBV prevalence in China, 1992–2006: a mathematical model analysis. J Theor Biol 2015;386:115–21.

[23] Medley GF, Lindop NA, Edmunds WJ, et al. Hepatitis B virus endemicity: heterogeneity, catastrophic dynamics and control. Nat Med 2001;7:619–24.

[24] National Bureau of Statistics of China. Birth rate per year. Available at: http://data.stats.gov.cn/easyquery.htm?cn=C01. Accessed 21 July, 2017.

[25] National Bureau of Statistics of China. Tabulation on the 1990 Population Census of the People’s Republic of China. 1993;China Statistics Press, Beijing:Table 3–5.

[26] Zhang W, Cui H. An evaluation on the accuracy of 2000 population census of China. Population Res 2002;4:25–35.

[27] National Bureau of Statistics of China. The age-specific death rate in 2000. Available at: http://www.stats.gov.cn/tjsj/tzjs/datareleasing/2000pucha/2000pucha/htmlt/0604.htm. Accessed 21 July, 2017.

[28] Cui H, Xu L, Li R. An evaluation of data accuracy of the 2010 population census of China. Popul Res 2013;37:10–21.

[29] Edmunds WJ, Medley GF, Nokes DJ, et al. The influence of age on the development of the hepatitis B carrier state. Proc R Soc Lond B 1993;253:197–201.

[30] Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. Clin Infect Dis 1995;20:992–1000.

[31] Liao X, Liang Z. Strategy vaccination against hepatitis B in China. Hum Vaccin Immunother 2015;11:1534–9.

[32] Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015;386:1546–55.

[33] Ott JJ, Horn J, Krause G, et al. Time trends of chronic HBV infection over prior decades—a global analysis. J Hepatol 2017;66:48–54.