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

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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%, 26.55%, respectively, and in 2050 it would be reduced by 44.93%, 43.29%, 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%, 21.40%, respectively, and in 2050 it would be reduced by 41.53%, 39.89%, 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.[1–4] 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.[5,6] 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.[7,8] 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).[2–10] Hepatitis B virus had become the primary cause of mortality in China.[1–3]

The government of China adopted comprehensive strategies to prevent HBV transmission, including hepatitis B vaccination and antiviral therapy.[1–10] Several studies had shown that interferon (IFN) treatment enhanced HBsAg seroclearance by approximately sixfold in Asian studies.[11–13] Lin et al[12] followed-up 233 IFN-treated patients and 233 well-matched untreated controls

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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.[13] Moreover, Hadziyannis et al[14] found that 5% of patients with hepatitis B e 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.[15–18] 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 treatment had been introduced and approved for the treatment of patients with chronic hepatitis B disease in China.[1–7] 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.[2–4] 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,[5–8] 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.[8,19–23] In this model, the total population was divided into 3 compartments: susceptible to HBV infection $S_a(t)$; chronic HBV carriers $C_a(t)$; recovered and obtained immunity due to HBV infection or vaccination $R_a(t)$; 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 ε might be reduced to below 7.6%.[1–3] 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 ($0 \le a < 1$):

$$\begin{cases} S_o(t+1) = b(t)N(t)\left(1 - pv(t) - \varepsilon w\left(\sum_{a=15}^{49} C_a(t) / \sum_{a=15}^{49} N_a(t)\right)\right), \\ C_o(t+1) = q_p b(t)N(t)\varepsilon w\left(\sum_{a=15}^{49} C_a(t) / \sum_{a=15}^{49} N_a(t)\right), \\ R_o(t+1) = b(t)N(t)pv(t) + (1-q_p)b(t)N(t)\varepsilon w\left(\sum_{a=15}^{49} c_a(t) / \sum_{a=15}^{49} N_a(t)\right). \end{cases} \quad (1)$$

For population aged 1 to 100 years:

$$\begin{cases} S_{a+1}(t+1) = (1-\mu_a(t))S_a(t) - p\theta_a(t)S_a(t) - \lambda_a(t)S_a(t), \\ C_{a+1}(t+1) = (1-\mu_a(t))C_a(t) + q_a\lambda_a(t)S_a(t) - m_a C_a(t) - r_a C_a(t), \\ R_{a+1}(t+1) = (1-\mu_a(t))R_a(t) + p\theta_a(t)S_a(t) + (1-q_a)\lambda_a(t)S_a(t) + r_a C_a(t). \end{cases} \quad (2)$$

where $N_a(t) = S_a(t) + C_a(t) + R_a(t)$, $N(t) = \sum_{a=0}^{100} N_a(t)$, $C(t) = \sum_{a=0}^{100} C_a(t)$, and $\lambda_a(t) = \beta_a(t)C(t)/N(t)$ represent the force of HBV infection, $\beta_a(t)$ 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.[5–11] 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 $t \ge 2016$, 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 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.[2,3,7] If $t \ge 2015$, 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 $\mu_a(t) = (d_a(t)N_a(t) - m_a C_a(t))/N_a(t)$. The other parameter values except the HBsAg seroclearance rate and HBV transmission rate were determined from published literatures and were summarized in Table 1.[1–31]

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 $\beta_a(t)$. Particularly, the transmission rate of HBV in 1992, $\beta_a(1992)$, 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 $\beta_a(t)$ 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

Table 1

Parameter values for input into compartmental models (1) and (2) and references.

Description of parameters	Values	References
$b(t)$: birth rate in year t	Supplementary Figure 1A	[24]
$v(t)$: 3 doses of vaccination coverage rate of newborns in year t	Supplementary Figure 1B	[1,3,5–8,10,22]
p: vaccination protection rate per year	0.85 (0.75–0.95)	[1,3,5–8,10,22]
ε: mother-to-child transmission rate per year	0.06 (0.03–0.09)	[1–3]
w: proportion of HBsAg-positive mothers in total prevalence of HBsAg aged 15–49 years	0.8491 (Calculated according to survey data in 1992 and 2006)	[5–7]
q_p: probability of acute HBV infection that became chronic due to mother-to-child transmission	0.90	[1,29,30]
m_a: age-specific mortality rate of HBV-related diseases per year	Supplementary Figure 1C	[8,20,22]
$d_a(t)$: age-specific total death rate in year t	Supplementary Figure 1D	[25–28]
$1990 \le t \le 1995$	$d_a(t)=d_a(1990)$,	
$1996 \le t \le 2002$	$d_a(t)=d_a(2000)$,	
$2003 \le t \le 2007$	$d_a(t)=d_a(2005)$,	
$2008 \le t \le 2014$	$d_a(t)=d_a(2010)$,	
$2015 \le t \le 2050$	$d_a(t)=d_a(2010)$.	
$\mu_a(t)$: age-specific death rate of non-HBV related diseases in year t	$\mu_a(t) = (d_a(t)N_a(t) - m_a C_a(t))/N_a(t)$	[8,20,25–28,22]
$\theta_a(t)$: catch-up vaccination coverage rate for population aged 8–15 years in 2009–2011	0.95	[2,3,6,7,31]
q_a: age-specific probability of acute HBV infection that became chronic per year		[1,29,30]
$0 \le a \le 1$ (not due to mother-to-child transmission)	0.30	
$1 \le a \le 4$	0.25	
$5 \le a \le 15$	0.06	
$16 \le a \le 100$	0.03	
$\beta_a(1992)$: age-specific transmission rate of HBV in 1992	Supplementary Figure 1E	[5,8,19,21,22]
r_a: annual rate of HBsAg seroclearance in chronic HBV carriers (%/yr)		[1,2,8,11–18,22]
$1 \le a \le 4$	8.01	
$5 \le a \le 9$	4.62	
$10 \le a \le 14$	0.56	
$15 \le a \le 19$	1.44	
$20 \le a \le 24$	4.37	
$25 \le a \le 29$	0.00	
$30 \le a \le 34$	0.00	
$35 \le a \le 39$	3.42	
$40 \le a \le 49$	0.00	
$50 \le a \le 59$	2.58	
Other age groups	1.50	

HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus.

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 r_a (Table 1) and transmission rate $\beta_a(t)$, that is,

$$\beta_a(t) = (0.5308\exp(-0.3853(t-1992)) + 0.4692)\beta_a(1992), \quad \text{if } t \ge 1993. \tag{3}$$

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.[6–8,32,33] Compared with the national survey data in 2006,[6] 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).[7,8,32,33] 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.[2–4] 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,[1–7] but due to the high cost of treatment, only about 12.5% of patients

with chronic hepatitis B disease have received antiviral therapy.[2–4] Therefore, if we assumed that the HBsAg seroclearance rate of chronic HBV carriers without treatment was r, then we had

$$(30\% \times C) \times 12.5\% \times 6r + (30\% \times C) \times 87.5\% \times r + (70\% \times C) \times r = C \times r_a$$

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

$$r = 0.8421 \times r_a$$

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

$$(30\% \times C) \times 25\% \times 6r + (30\% \times C) \times 75\% \times r + (70\% \times C) \times r = C \times 1.1579\, r_a$$

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 $1.1579r_a$. Similarly, if the test-and-treat coverage was increased to 50%, 75% and 100%, respectively, then the annual rate of HBsAg seroclearance would become $1.4737r_a$, $1.7895r_a$ and $2.1053r_a$, 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 2050. 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 2050 would be reduced the most, the total number of new HBV infection, and the number of HBV-related deaths in 2018 to 2050 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_a), transmission rate of HBV ($\beta_a(t)$), 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.[1–8,11–15,22] 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

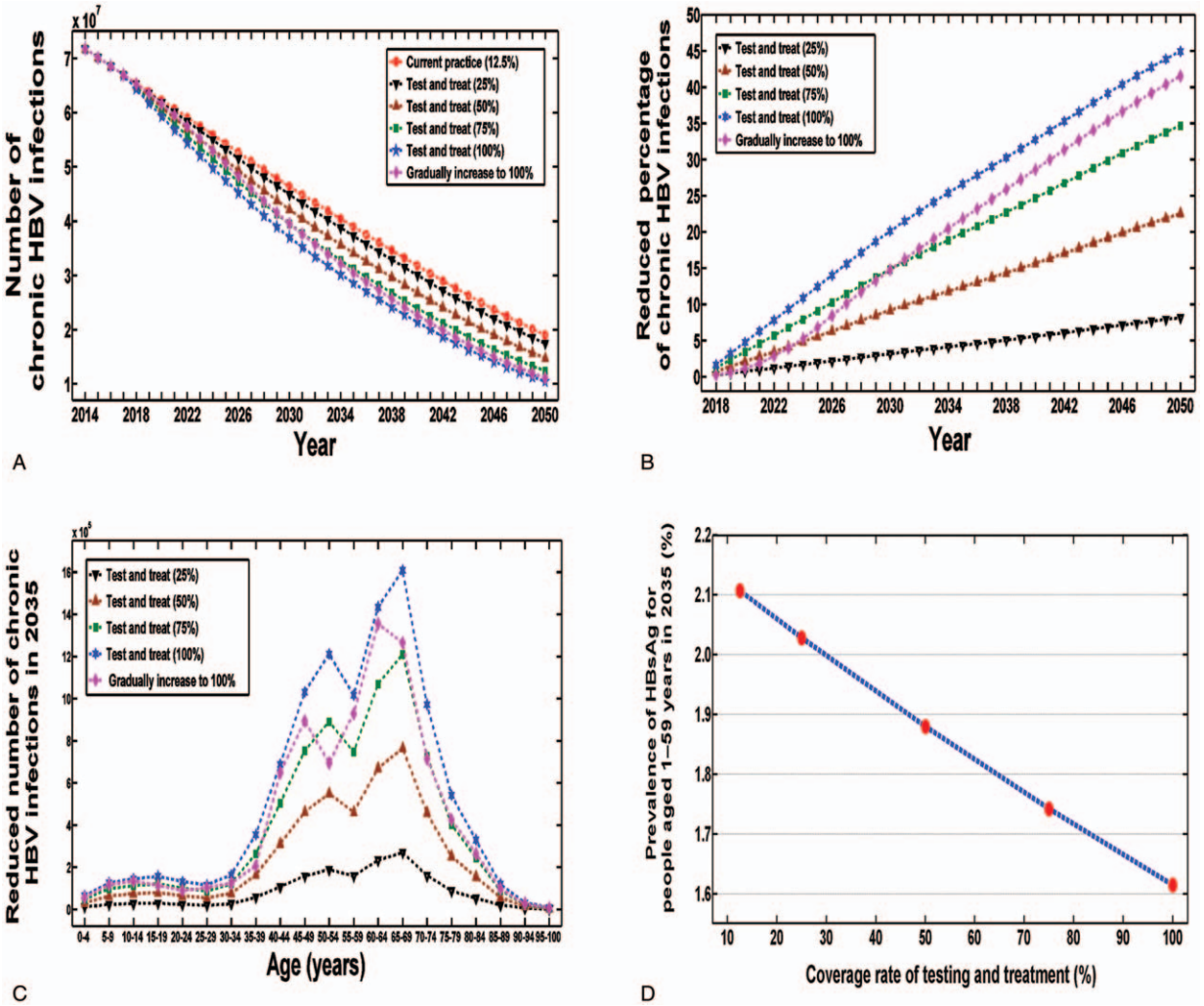

Figure 1. Reduction of chronic HBV infection under different test-and-treat strategies. (A) The number of chronic HBV infection, 2014-2050. (B) Percentage reduction in chronic HBV infection compared with current practice, 2018-2050. (C) Age-specific reduced number of chronic HBV infection in 2035 compared with current practice. (D) Prevalence of HBsAg for population aged 1 to 59 years in 2035 when the test-and-treat coverage was 12.5%, 25%, 50%, 75% and 100%. HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus.

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	14,706,184	12,400,298	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	22,4513	224,513	229,130
Decrease from current practice (%)	–	2.58	5.79	6.73	6.73	4.82

HBV = hepatitis B virus.

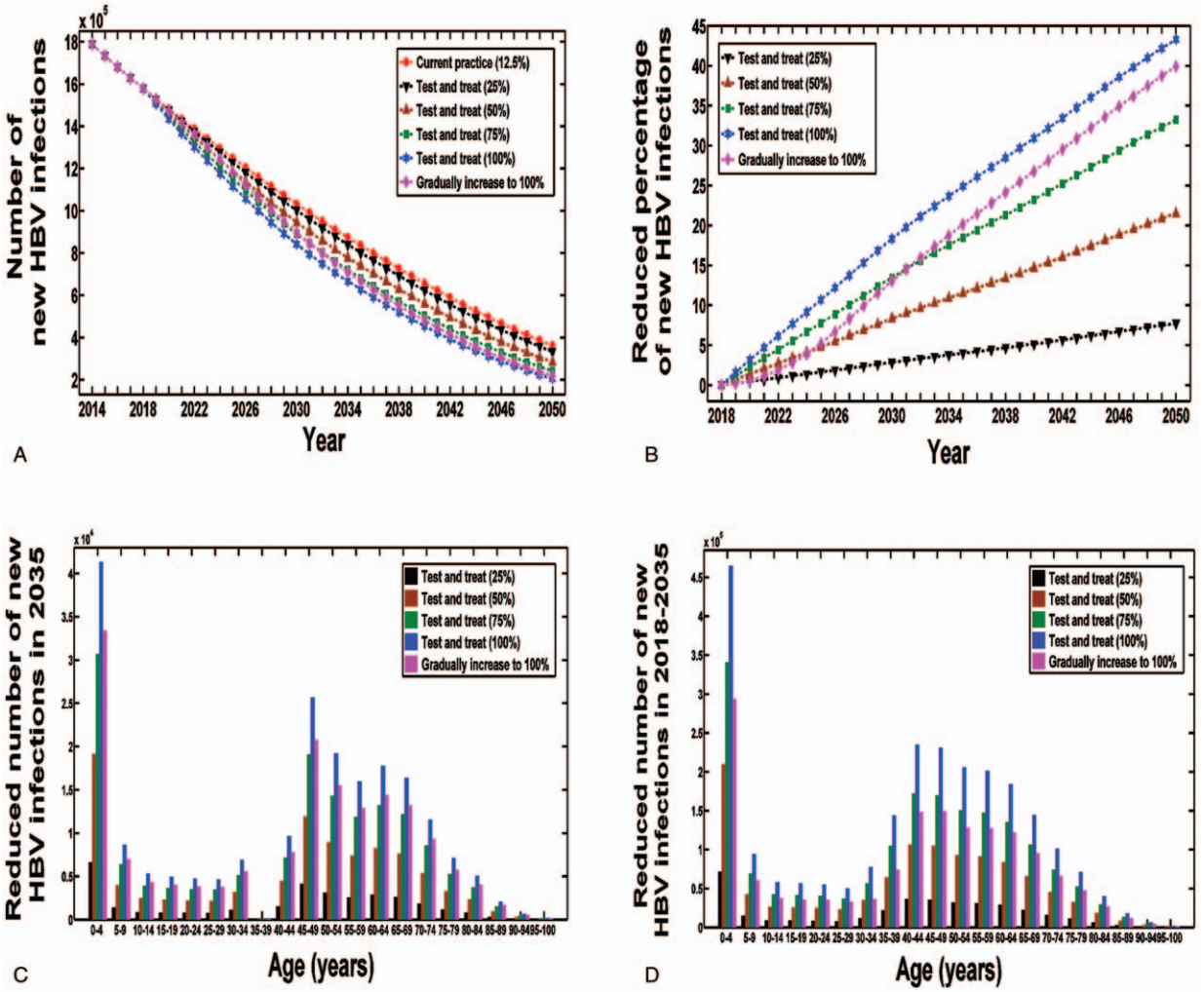

Figure 2. Reduction of new HBV infection under different test-and-treat strategies. (A) The number of new HBV infection, 2014 to 2050. (B) Percentage reduction in new HBV infection compared with current practice, 2018 to 2050. (C) Age-specific reduced number of new HBV infection in 2035 compared with current practice. (D) Age-specific reduced number of new HBV infection in 2018 to 2035 compared with current practice. 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).

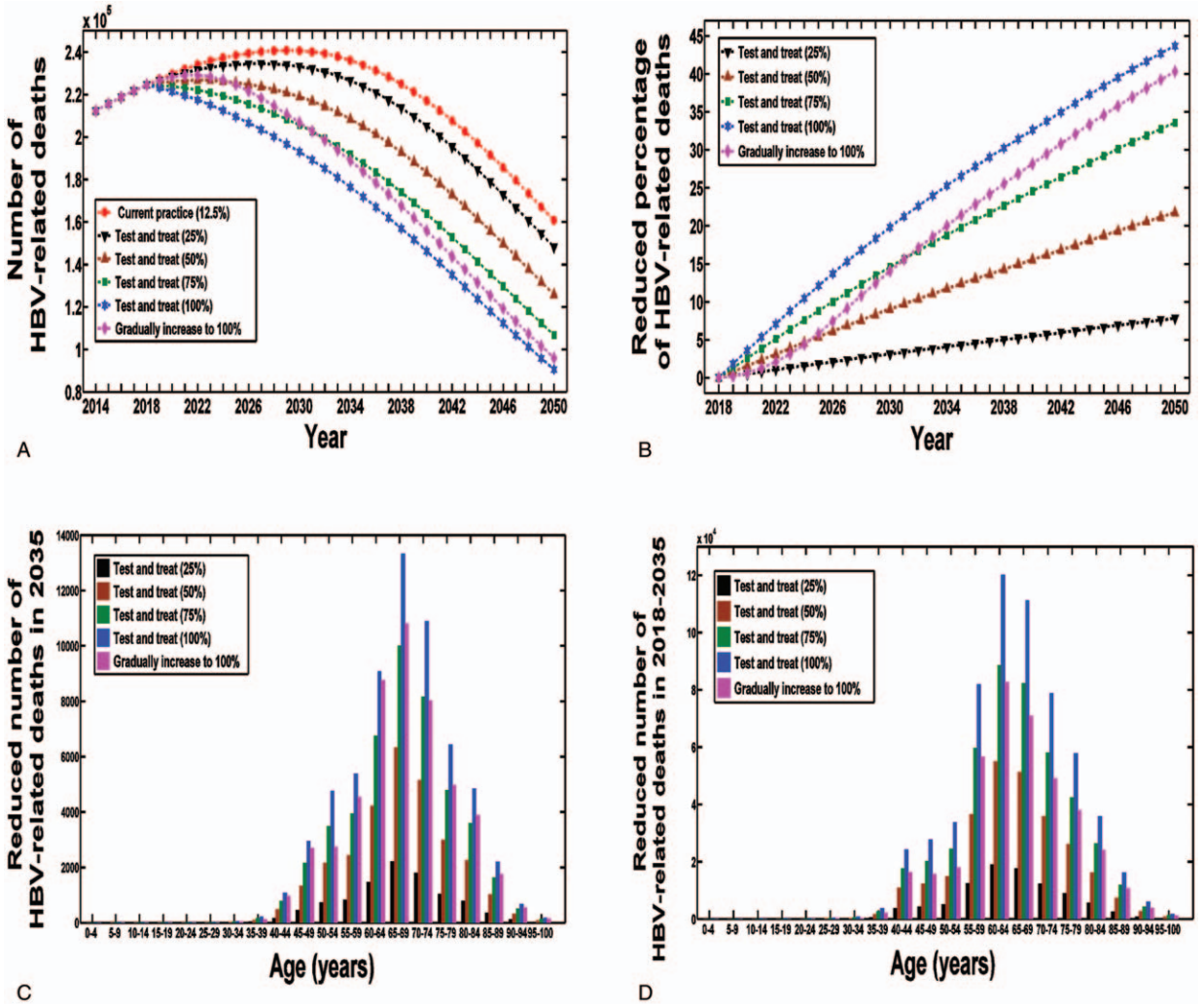

Figure 3. Reduction of HBV-related deaths under different test-and-treat strategies. (A) The number of HBV-related deaths, 2014 to 2050. (B) Percentage reduction in HBV-related deaths compared with current practice, 2018-2050. (C) Age-specific reduced number of HBV-related deaths in 2035 compared with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

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 2050 would be reduced by 43.67% (90,549 vs. 160,734). However, if the test-and-treat coverage was increased by 10% every year since 2018, the number of HBV-related deaths in 2035 and 2050 would be reduced by 21.40% and 40.32%, respectively, which was less than the situation that the test-and-treat coverage was increased to 100% since 2018. This also implied that the earlier the treatment, the more the reduction of HBV-related deaths. 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.

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, in 2035 the number of HBV-related deaths in 65 to 69 age group would be reduced the most (about 13,320).

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

Table 3

Reduction of HBV infection under a test-and-treat coverage of 100% in each age group.

Age group of testing and treatment	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	–
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 ($\beta_a(t)$) 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

Sensitivity analysis for HBV infection under a test-and-treat coverage of 100%.

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	–	29,912,601	–	7,247,542	–
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 ($\beta_a(t)$)						
Cut down by 20% since 2018	10,343,916	45.50%	19,873,306	33.56%	5,575,962	23.06%
Increased by 20% since 2018	10,557,199	44.37%	29,379,495	1.78%	5,591,111	22.86%
HBsAg seroclearance rate of patients with treatment						
5r	11,984,155	36.85%	25,704,862	14.07%	5,913,976	18.40%
7r	9,110,715	51.99%	23,643,206	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 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, the number of new 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 treatment for patients with chronic hepatitis B disease might have different seroclearance rate of HBsAg, which might have a certain influence on the estimated results in this paper.[14–18]

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.

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