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Modeling hepatitis B-related deaths in China to achieve the WHO's impact target

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ABSTRACT

Background: The World Health Organization (WHO) targets a 65% reduction in hepatitis B-related deaths by 2030 compared to 2015 to eliminate viral hepatitis as a major public health threat. It is unknown whether and how China can achieve this target despite significant intervention achievements. We aimed to predict the hepatitis B-related deaths in China and identify key developments needed to achieve the target.

Methods: An age- and time-dependent dynamic hepatitis B virus (HBV) transmission compartmental model was developed to predict the trend of hepatitis B-related deaths under base-case and subsequent scenarios from 2015 to 2040. In base-case scenario, we assumed the diagnosis and treatment (D&T) rate would reach 72% in 2030, as proposed by WHO. Subsequent scenarios were set based on the results of base-case and one-way sensitivity analysis.

Results: Compared with 2015, hepatitis B-related deaths would be reduced by 23.89% in 2030 and 51.79% in 2040, respectively, and the WHO's impact target of 65% reduction would not be achieved until 2038 at the earliest under base-case scenario. HBV clearance rate and current treatment effectiveness were the most sensitive parameters that significantly influenced the decline of hepatitis B-related deaths from 2015 to 2040. In the subsequent scenario, when D&T rate improving to 90% by 2030, with the current treatment effectiveness and HBV clearance rate being optimized from 2016, the WHO's impact

Abbreviations: WHO, World Health Organization; HBV, hepatitis B virus; D&T, diagnosis and treatment; HBsAg, hepatitis B virus surface antigen; HCC, hepatocellular carcinoma; AC, asymptomatic carriers; CHB, chronic hepatitis B; CC, compensated cirrhosis; DC, decompensated cirrhosis; MCMC, Markov Chain Monte Carlo; HR, hazard ratio; RR, relative risk; HBIG, hepatitis B immunoglobulin; MTCT, mother-to-child transmission.

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target would be achieved in 2038. Increasing the clearance rate further from 2% to 2.8% during 2016–2030 linearly, the impact target would be achieved on time.

Conclusions: It is difficult for China to achieve the WHO's impact target of 65% reduction in hepatitis B-related deaths by 2030 even we assumed the D&T rate would reach 72% in 2030 and beyond. A comprehensive scale-up of available strategies, especially innovative drugs and technologies will ensure that China achieves the target on schedule.

1. Introduction

Hepatitis B virus (HBV) infection has long been a major health problem in China. Although universal neonatal hepatitis B vaccination has been introduced for 30 years with brilliant achievements, the prevalence of HBV surface antigen (HBsAg) in the whole population is still maintained at 5–6%, approximately 90 million people living with chronic HBV infection (Cui et al., 2017; Liu et al., 2019). In 2015, China has become one of the first group of countries to initiate an investment case for viral hepatitis, then the government has gradually begun to focus on improving the diagnosis and treatment (D&T) coverage for people with chronic HBV infection, especially included tenofovir disoproxil fumarate (TDF) in national reimbursement drug list (Nayagam et al., 2021). However, the new cases and mortality of hepatocellular carcinoma (HCC) in China still accounts for about 50% of the total patients worldwide, and more than 80% of HCC cases are related to HBV infection and are associated with cirrhosis (Xie et al., 2018).

In 2016, the World Health Organization (WHO) released the first global health sector strategy on viral hepatitis for contributing to the achievement of the 2030 Agenda for Sustainable Development. The strategy calls for global action to eliminate viral hepatitis as a public health problem by 2030. For hepatitis B-related deaths, a 65% reduction compared with 2015 was proposed as a key impact target, and increasing the D&T rate of eligible persons with chronic HBV infection to 72% (90% diagnosis coverage and 80% treatment coverage among eligible individuals) was proposed as service target to facilitate achievement of this impact target (WHO, 2016). In 2021, WHO adopted another interim plan, which considered that the 65% reduction in hepatitis B-related deaths was equivalent to reducing hepatitis B-related mortality to less than 4 per 100,000 (WHO, 2021).

Several studies have addressed the hepatitis B-related deaths issue and concluded that the target could be achieved by expanded screening and treatment coverage for chronic hepatitis B infection individuals in some low HBV-endemic countries (Cuadrado et al., 2020; McCulloch et al., 2020; Posuwan et al., 2020). In China, Wang et al. proposed that universal HBV screening may be essential in China (Wang & Cui, 2022). Li et al. developed a dynamic sex- and age-stratified model of the HBV transmission and demonstrated that improved diagnosis, linkage to care and treatment coverage will be crucial in further reducing HBV-related mortality and removing HBV as a public health threat (Li et al., 2023). Zhang et al. used a decision-tree Markov state-transition model to assess the cost-effectiveness of expanding antiviral treatment for chronic HBV infection, and they showed that 80% coverage of HBsAg-positive individuals aged 18–80 years was optimal, and early implementation of expanded antiviral therapy with modified alanine aminotransferase thresholds could reduce HBV-related complications and deaths to support the target of 65% reduction in hepatitis B-related deaths (Zhang et al., 2023). However, none of these studies explored specific key developments that would enable the achievement of impact target on time. This study aimed to predict the decline of hepatitis B-related deaths in China by using a mathematical model and identify key developments needed to achieve the target on 2030. Our findings will inform policy-makers to improve D&T strategies and programs for chronic HBV infection further.

2. Methods

2.1. Model construction

We have previously constructed an age- (a) and time- (t) dependent dynamic compartmental model to simulate HBV transmission in China based on the natural history of HBV infection and the national history and current status of hepatitis B control (Liu et al., 2022). The population was divided into susceptible to HBV ($S_{a,t}$), immune due to infection or vaccination ($I_{a,t}$) and chronic infection ($C_{a,t}$), respectively. In addition, acute infection ($A_{a,t}$) is not a compartment but rather a transient process by which a susceptible person moves to other compartments or dies (Liu et al., 2022). In this paper, we further divided the chronic infection compartment ($C_{a,t}$) into five additional hepatitis B-related health compartments, including asymptomatic carriers ($AC_{a,t}$), chronic hepatitis B ($CHB_{a,t}$), compensated cirrhosis ($CC_{a,t}$), decompensated cirrhosis ($DC_{a,t}$) and hepatocellular carcinoma ($HCC_{a,t}$), to describe the progression of chronic HBV infection. The model was run from 2015 to 2040 annually. All individuals in our model were divided into 101 age groups (one for each age, from 0 to 100 years). When the model was running a year, then the age of all individuals increased by one year (Fig. 1).

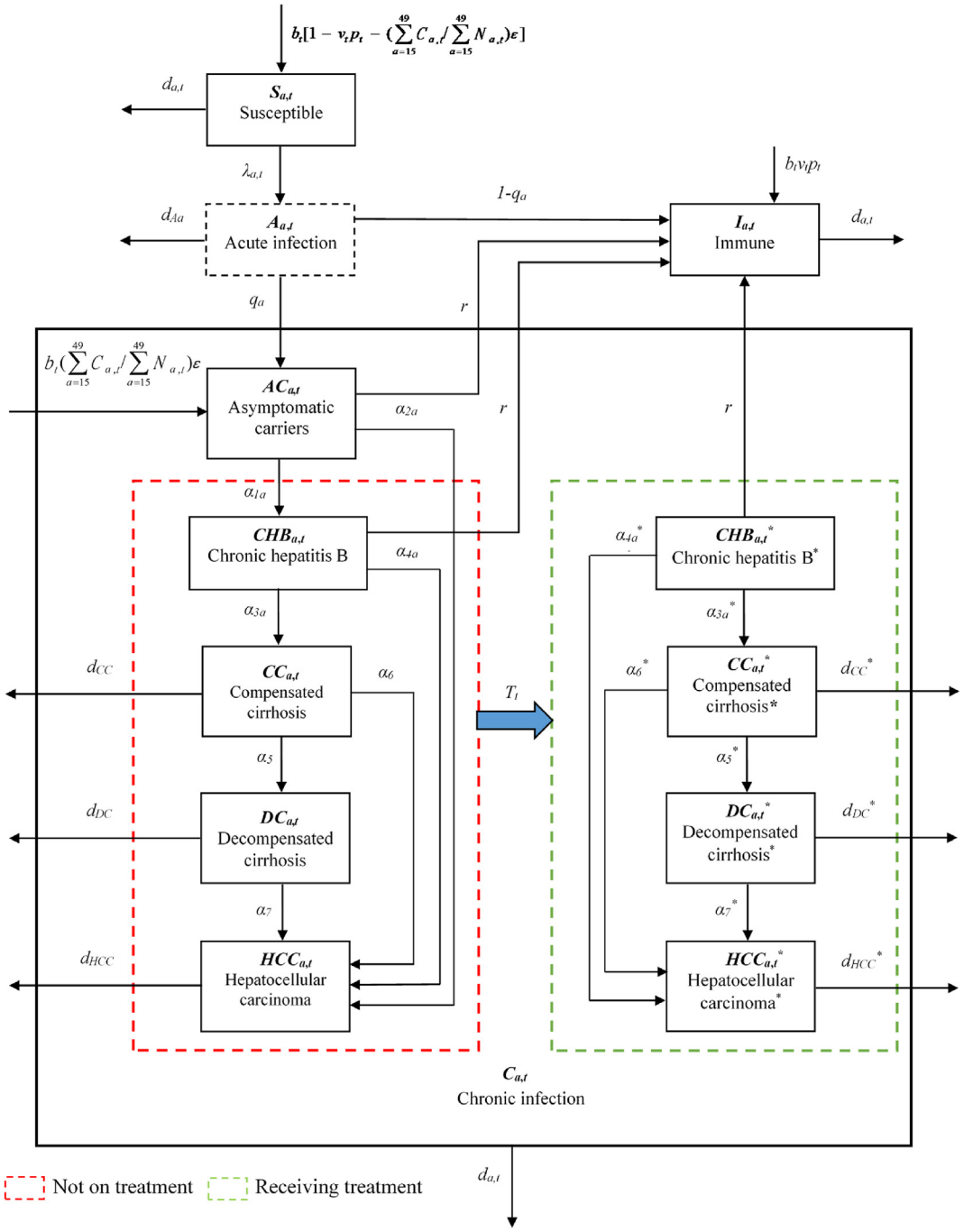

Fig. 1. Age- and time-dependent dynamic compartmental model of chronic HBV infect progression. b_t, birth rate at a given time; v_t, vaccine coverage of newborns in 2015 and beyond; p_t, vaccine protection against HBV infection in 2015 and beyond; ε, HBV intrauterine infection rate in infected pregnant women; $d_{a,t}$, age- and time-dependent background death rate; $\lambda_{a,t}$, age- and time-dependent force of HBV infection as in (Liu et al., 2022); d_{Aa}, age-dependent mortality of acute infection; q_a, age-dependent proportion of acute infection become chronic; r, HBV clearance rate; α_{1a}, age-dependent progression rate from asymptomatic carriers to chronic hepatitis B; α_{2a}, age-dependent progression rate from asymptomatic carriers to HCC; α_{3a}, age-dependent progression rate from chronic hepatitis B to compensated cirrhosis; α_{4a}, age-dependent progression rate from chronic hepatitis B to HCC; α_5, progression rate from compensated cirrhosis to decompensated cirrhosis; α_6, progression rate from decompensated cirrhosis to HCC; α_7, progression rate from decompensated cirrhosis to HCC; d_{CC}, progression rate from compensated cirrhosis to death; d_{DC}, progression rate from decompensated cirrhosis to death; d_{HCC}, progression rate from HCC to death; T_t, receiving treatment rate in 2017 and beyond; α_{3a}*, age-dependent progression rate from chronic hepatitis B to compensated cirrhosis after treatment; α_{4a}*, age-dependent progression rate from chronic hepatitis B to HCC after treatment; α_5*, progression rate from compensated cirrhosis to decompensated cirrhosis after treatment; α_6*, progression rate from decompensated cirrhosis to HCC after treatment; α_7*, progression rate from decompensated cirrhosis to HCC after treatment; d_{CC}*, progression rate from compensated cirrhosis to death after treatment; d_{DC}*, progression rate from decompensated cirrhosis to death after treatment; d_{HCC}*, progression rate from HCC to death after treatment.

In the model, individuals in the susceptible compartment can first transition to the hepatitis B-related asymptomatic carriers state through vertical transmission during childbirth or later infection in life. The risks of asymptomatic carriers developing chronic hepatitis B (CHB) or hepatocellular carcinoma (HCC), and CHB developing compensated cirrhosis or HCC are both related to age (Chinese Society of Hepatology & Chinese Medical Association, 2019; Wang et al., 2020). Individuals within asymptomatic carriers or CHB can also transit into the immune compartment at HBV clearance rate (Wang et al., 2020). The risks of compensated cirrhosis developing decompensated cirrhosis or HCC, and decompensated cirrhosis developing HCC are both related to hepatitis B virus-deoxyribonucleic acid or the degree of liver injury (Chinese Society of Hepatology & Chinese Medical Association, 2019). Hepatitis B-related deaths can occur through acute infection, the compensated cirrhosis, decompensated cirrhosis or HCC.

According to the guidelines for the prevention and treatment of chronic hepatitis B infection in China (2019 version), antiviral therapy is only indicated for patients with CHB status, cirrhosis (both compensated cirrhosis and decompensated cirrhosis) and HCC with detectable hepatitis B replication (Chinese Society of Hepatology & Chinese Medical Association, 2019). All eligible persons with chronic HBV infection are stratified into those receiving treatment, and those not on treatment. We assumed that treatment could reduce the risk of progression to cirrhosis and/or HCC and the death due to cirrhosis and/or HCC, which leads to different transition rates between those receiving treatment and those who are not on treatment. These rates are represented by hazard ratio (HR) or relative risk (RR). The relevant discrete difference equations are shown below.

For individuals aged 0 year:

$$\begin{cases} S_{0,t} = b_t N_t \left[1 - v_t p_t - \left(\sum_{a=15}^{49} C_{a,t} \Big/ \sum_{a=15}^{49} N_{a,t}\right)\varepsilon\right] \\ AC_{0,t} = b_t N_t \left(\sum_{a=15}^{49} C_{a,t} \Big/ \sum_{a=15}^{49} N_{a,t}\right)\varepsilon \\ I_{0,t} = b_t N_t v_t p_t \end{cases} \tag{1}$$

For individuals aged 1–100 years:

$$\begin{cases} S_{a+1,t+1} = S_{a,t}(1 - \lambda_{a,t} - d_{a,t} - \theta_{a,t} p_t) \\ AC_{a+1,t+1} = AC_{a,t}(1 - d_{a,t} - \gamma - \alpha_{1a} - \alpha_{2a}) + S_{a,t}(1 - d_{Aa}) q_a \lambda_{a,t} \\ CHB_{a+1,t+1} = CHB_{a,t}(1 - d_{a,t} - \gamma - \alpha_{3a} - \alpha_{4a})(1 - T_t) + AC_{a,t}\alpha_{1a} \\ CC_{a+1,t+1} = CC_{a,t}(1 - d_{a,t} - \alpha_5 - \alpha_6 - d_{CC})(1 - T_t) + CHB_{a,t}\alpha_{3a} \\ DC_{a+1,t+1} = DC_{a,t}(1 - d_{a,t} - \alpha_7 - d_{DC})(1 - T_t) + CC_{a,t}\alpha_5 \\ HCC_{a+1,t+1} = HCC_{a,t}(1 - d_{a,t} - d_{HCC})(1 - T_t) + AC_{a,t}\alpha_{2a} + CHB_{a,t}\alpha_{4a} + CC_{a,t}\alpha_6 + DC_{a,t}\alpha_7 \\ CHB_{a+1,t+1}{}^{*} = CHB_{a,t}{}^{*}(1 - d_{a,t} - \gamma - \alpha_{3a}{}^{*} - \alpha_{4a}{}^{*}) + CHB_{a,t}(1 - d_{a,t} - \gamma - \alpha_{3a} - \alpha_{4a})T_t \\ CC_{a+1,t+1}{}^{*} = CC_{a,t}{}^{*}(1 - d_{a,t} - \alpha_5{}^{*} - \alpha_6{}^{*} - d_{CC}{}^{*}) + CHB_{a,t}{}^{*}\alpha_{3a}{}^{*} + CC_{a,t}(1 - d_{a,t} - \alpha_5 - \alpha_6 - d_{CC})T_t \\ DC_{a+1,t+1}{}^{*} = DC_{a,t}{}^{*}(1 - d_{a,t} - \alpha_7{}^{*} - d_{DC}{}^{*}) + CC_{a,t}{}^{*}\alpha_5{}^{*} + DC_{a,t}(1 - d_{a,t} - \alpha_7 - d_{DC})T_t \\ HCC_{a+1,t+1}{}^{*} = HCC_{a,t}{}^{*}(1 - d_{a,t} - d_{HCC}{}^{*}) + CHB_{a,t}{}^{*}\alpha_{4a}{}^{*} + CC_{a,t}{}^{*}\alpha_6{}^{*} + DC_{a,t}{}^{*}\alpha_7{}^{*} + HCC_{a,t}(1 - d_{a,t} - d_{HCC})T_t \\ I_{a+1,t+1} = I_{a,t}(1 - d_{a,t}) + S_{a,t}(1 - d_{Aa})(1 - q_a)\lambda_{a,t} + S_{a,t}\theta_{a,t}p_t + AC_{a,t}\gamma + CHB_{a,t}\gamma + CHB_{a,t}{}^{*}\gamma \end{cases} \tag{2}$$

Where, $C_{a,t}$=$AC_{a,t} + CHB_{a,t} + CC_{a,t} + DC_{a,t} + HCC_{a,t} + CHB_{a,t}{}^{*}$+$CC_{a,t}{}^{*}$+$DC_{a,t}{}^{*}$+$HCC_{a,t}{}^{*}$, $N_{a,t}$=$S_{a,t} + C_{a,t} + I_{a,t}$, $\sum_{a=15}^{49} C_{a,t} / \sum_{a=15}^{49} N_{a,t}$ denotes HBV carriage rate of women with childbearing age (15–49 years) at a given time.

2.2. Model parameters

Model parameters including b_t, v_t, p_t, ε, $\lambda_{a,t}$, $e_{a,t}$, r, d_{Aa} and q_a were applied from our previous study directly (Liu et al., 2022). Meanwhile, we chose v_t, p_t, and $\lambda_{a,t}$ to the optimum limits within their respective ranges simultaneously, with the explicit assumption that hepatitis B prevention efforts in China have been maximal.

Due to the incomplete information and poor quality of reported data in China, we used a variety of methods to specify other model parameters from expanded compartments. To be specific, we estimated the initial population in compensated/decompensated cirrhosis and HCC compartmens (represented as $CC_{0\text{-}100,2006}$, $DC_{0\text{-}100,2006}$, $HCC_{0\text{-}100,2006}$, respectively), and the age-dependent progression rates from asymptomatic carriers to CHB or HCC, CHB to compensated cirrhosis or HCC (represented as α_{1a}, α_{2a}, α_{3a} and α_{4a}, respectively) by using Markov Chain Monte Carlo (MCMC) method based on China cancer registry annual report data in 2006–2015.

First, the total number and the age distribution characteristics of $S_{0\text{-}100,2006}$, $I_{0\text{-}100,2006}$ and chronic HBV infectors ($C_{0\text{-}100,2006}$) were determined (Liu et al., 2022). Because no people aged >59 years were enrolled in the hepatitis B serosurvey, the hepatitis B data of people aged 55–59 years were assumed the same as these elderly >59 years. The total number of $CHB_{0\text{-}100,2006}$ was assumed to be 25 million (Chinese Society of Hepatology & Chinese Medical Association, 2019), and the age distribution characteristics were the same as $C_{0\text{-}100,2006}$, so we calculated $CHB_{a,\ 2006} = C_{a,2006}/C_{0\text{-}100,2006} \times 25000000$. Then $AC_{a,2006}$ were calculated as $AC_{a,2006} = C_{a,2006} - CHB_{a,\ 2006} - CC_{a,2006} - DC_{a,2006} - HCC_{a,2006}$.

According to the general progression of HCC and previous literatures, we assumed the total population in each state satisfied $CC_{0\text{-}100,2006}$>$HCC_{0\text{-}100,2006}$>$DC_{0\text{-}100,2006}$, and we assumed their population ratios were about 3:2:1 (Chinese Society of Hepatology & Chinese Medical Association, 2019; Department of Medical Administration et al., 2020). Then we calculated the total number of deaths due to liver cancer in 2006 through China cancer registry annual report, 2009 and China Population and Employment Statistics Yearbook, 2007. We adjusted the total number of deaths due to liver cancer as hepatitis B-related HCC deaths based on the studies that HCC accounted for nearly 90% of all liver cancer, and hepatitis B-related HCC accounted for nearly 80% of HCC, so hepatitis B-related HCC deaths was equaled to liver cancer deaths multiplied by 0.9 and 0.8 (Department of Medical Administration et al., 2020; Venook et al., 2010; WHO, 2015). Subsequent adjust of hepatitis B-related HCC incidence or death rate were both based on this method. We finally obtained the range of $HCC_{0\text{-}100,2006}$ was 0.7–1.4 million, the range of $CC_{0\text{-}100,2006}$ was 1.05–2.1 million, and the range of $DC_{0\text{-}100,2006}$ was 0.35–0.7 million. In the meantime, we determined the proportion of population in different age of cirrhosis and HCC at the initial state based on the results of multiple epidemiological cohort studies on patients with cirrhosis in different regions of China (Table S1) and the incidence of liver cancer in different age groups in 2006 (Fig. S1).

Second, we assumed a growth curve function to characterize the relationship between age and progression rates α_{1a}, α_{2a}, α_{3a}, α_{4a} (Aho et al., 2014; Hens et al., 2012; Nagelkerke et al., 1999). The relevant equations are shown below.

$$\alpha_{1a} = h_1 + (h_2 - h_1) / (1 + exp(-h_3(a - h_4))) \ (h_1, h_2, h_3, h_4 > 0) \tag{3}$$

$$\alpha_{2a} = j_1 + (j_2 - j_1) / (1 + exp(-j_3(a - j_4))) \ (j_1, j_2, j_3, j_4 > 0) \tag{4}$$

$$\alpha_{3a=} k_1 + (k_2 - k_1) / (1 + exp(-k_3(a - k_4))) \ (k_1, k_2, k_3, k_4 > 0) \tag{5}$$

$$\alpha_{4a=} l_1 + (l_2 - l_1) / (1 + exp(-l_3(a - l_4))) \ (l_1, l_2, l_3, l_4 > 0) \tag{6}$$

Third, combining parameters $CC_{0\text{-}100,2006}$, $HCC_{0\text{-}100,2006}$, $DC_{0\text{-}100,2006}$ and $h_{1\text{-}4}$, $j_{1\text{-}4}$, $k_{1\text{-}4}$, $l_{1\text{-}4}$ from Equations (3)–(6) together, then we estimated their values by MCMC method with a Metropolis-Hastings algorithm (Haario et al., 2006; Morton et al., 2005; Trentini et al., 2017). Prior distributions of these parameters were assumed to be uniform, and they were sampled from their respective ranges as inputs to enter our model (Fig. 1). The model was run from 2006 to 2015 for 10,000 iterations, the first 5000 iterations were taken as the burn-in period, and the last 5000 iterations were taken as the stable parameter estimation results to obtain their posteriori normal distributions. The mean value of these parameters were selected as the best fitting of the baseline value, and the mean value ± 1.96 × standard deviation was selected as 95% confidence interval (CI) (Guo et al., 2018; Harms & Roebroeck, 2018). Inputs of the other model parameters were fixed at their respective baseline values, as showed in Table 1. Liver cancer incidence from China cancer registry annual report in 2007–2015 were adjusted to hepatitis B-related HCC incidence and used as calibration of the model outputs. The results of each parameter's baseline value and 95% CI were shown in Table S2 and Fig. S2, and the comparison of model outputs in 2007–2015 with the hepatitis B-related HCC incidence was shown in Fig. S3.

Finally, the model was further run from 2015 to 2017. We selected the liver cancer death rate from China cancer registry annual report in 2015–2017, adjusted them to hepatitis B-related HCC death rate and then compared the adjusted results with the model outputs to validate our model (Fig. S4).

For the progression rates of decompensated cirrhosis to death (d_{DC}) and HCC to death (d_{HCC}), as many clinical pathologies are associated with decompensated cirrhosis (including ascites, gastrointestinal varicose bleeding, sepsis, hepatorenal syndrome, hepatic encephalopathy and other organ function injuries), so there is a wide range of mortality in chronic HBV infectors with decompensated cirrhosis from 10% to 87% (Chinese Society of Hepatology & Chinese Medical Association, 2019). In order to obtain a more accurate d_{DC} as the baseline value, we need transform the relationship between the death rate d and the death probability P for the occurrence of an event during the time period t (Briggs et al., 2006), $P=1-\exp(-dt)$, *which yields the rate* $d=-\ln(1-P)/t$. For example, assuming 100 patients are followed up for 5 years after which 20 have died, then the 5-year probability of death is $P = 0.2$, which gives the death rate $d=-\ln(1-0.2)/5=0.0446$ per year. Combining with previous studies on the final outcome of patients with decompensated cirrhosis, and the probability of death from decompensated cirrhosis in other similar literatures, d_{DC} was finally determined to be 0.24 per year and we varied it from 0.1533 to 0.5589 per year, following a triangular distribution (Chinese Society of Hepatology & Chinese Medical Association, 2019) (Table S3). The probability of death from HCC was calculated in the same way as 0.34 per year, ranging from 0.22 to 0.45 per year, with a uniform distribution (Nguyen et al., 2009; Thiele et al., 2014) (Table S4).

The D&T rate of chronic HBV infectors in China is relatively low, still far from the WHO target in 2030 (Cui & Zhuang, 2021). In order to make sure the D&T rate T_t can reach 72% on schedule, we assumed the value of T_t would increase linearly from 2017 to 2030 because TDF was officially included in Chinese's national insurance since 2017 and the diagnosis and treatment coverage for people with chronic HBV infection after that would increase, with the D&T rate of 72% after 2030. Finally, we calculated the value of T_t from 2017 to 2030 and obtained the D&T rate at the same time (Fig. S5). Individuals with chronic hepatitis B infection on treatment had a reduced rate of progression and the probability of death, compared with those untreated, as expressed as the product of the raw parameter values and HR or RR.

Time-dependent birth rates (b_t) and age-, time-dependent background death rate ($d_{a,t}$) during 2015–2021 were obtained from the corresponding yearbooks, but after 2021, they were assumed to follow the 2021 data. For b_t, an annual change by

Table 1
Parameters of the compartmental model of chronic HBV infect progression.

Parameter	Baseline value	Range	Distribution	References
α_{1a}, age- dependent progression rate from asymptomatic carriers to chronic hepatitis B	Fig. S3: baseline sets	Fig. S3: 95% CI interval sets	Uniform	
α_{2a}, age- dependent progression rate from asymptomatic carriers to HCC	Fig. S3: baseline sets	Fig. S3: 95% CI interval sets	Uniform	
α_{3a}, age- dependent progression rate from chronic hepatitis B to compensated cirrhosis	Fig. S3: baseline sets	Fig. S3: 95% CI interval sets	Uniform	
α_{4a}, age- dependent progression rate from chronic hepatitis B to HCC	Fig. S3: baseline sets	Fig. S3: 95% CI interval sets	Uniform	
α_5, progression rate from compensated cirrhosis to decompensated cirrhosis	0.04	0.03–0.05	Uniform (0.03, 0.05)	Wang et al. (2020)
α_6, progression rate from compensated cirrhosis to HCC	0.045	0.03–0.06	Uniform (0.03, 0.06)	Wang et al. (2020)
α_7, progression rate from decompensated cirrhosis to HCC	0.045	0.03–0.06	Uniform (0.03, 0.06)	Wang et al. (2020)
d_{CC}, progression rate from compensated cirrhosis to death	0.0175	0.015–0.02	Uniform (0.015, 0.02)	Chinese Society of Hepatology and Chinese Medical Association (2019)
d_{DC}, progression rate from decompensated cirrhosis to death	0.24	0.1533–0.5589	Triangular (0.1533, 0.24, 0.5589)	
d_{HCC}, progression rate from HCC to death	0.34	0.22–0.45	Uniform (0.22, 0.45)	
Tt, receiving treatment rate in 2017 and beyond	Fig. S6: baseline sets			
HR[a] of α_{3a}, receiving treatment versus not on treatment	0.09	0.038–0.221	Uniform (0.038, 0.221)	(Hou et al., 2020; Li et al., 2017; Ren et al., 2018)
HR of α_{4a}, receiving treatment versus not on treatment	0.03	0.009–0.113	Uniform (0.009, 0.113)	Zhang et al. (2018)
RR[b] of α_{5a}, receiving treatment versus not on treatment	0.45	0.28–0.73	Lognormal (−0.79, 0.24)	Liaw et al. (2004)
RR of α_{6a}, receiving treatment versus not on treatment	0.75	0.63–1.0	Lognormal (−0.26, 0.13)	Xia et al. (2015)
RR of α_{7a}, receiving treatment versus not on treatment	0.75	0.63–1.0	Lognormal (−0.26, 0.13)	Xia et al. (2015)
RR of d_{CC}, receiving treatment versus not on treatment	0.46	0.29–0.73	Lognormal (−0.74, 0.22)	Xia et al. (2015)
RR of d_{DC}, receiving treatment versus not on treatment	0.81	0.37–1.0	Lognormal (−0.50, 0.25)	Ye and Su (2013)
RR of d_{HCC}, receiving treatment versus not on treatment	0.57	0.47–0.7	Lognormal (−0.56, 0.1)	He et al. (2017)

[a] Hazard ratio.
[b] Relative risk.

±5% was introduced after 2021 to cover its uncertainty given changes of the family planning policy in China. Other model parameters were estimated from published literatures. Model parameters were summarized in Table 1. A relatively wide range was given to each parameter according to previous studies.

2.3. Prediction analysis

In the base-case scenario, we used the model to generate predictions on hepatitis B-related deaths under the assumption that the D&T rate reaching 72% in 2030 and beyond due to improving the treatment rate for people with chronic HBV infection. Then, by comparing the results with the model prediction that the D&T rate still remained at the 2016 level, we estimated the effectiveness of increasing the D&T rate to reduce hepatitis B-related deaths (Liu & Liu, 2019; Polaris Observatory Collaborators, 2018). After base-case analysis, a probabilistic sensitivity analysis was conducted using the results from multiple iterations obtained during the MCMC analysis to elucidate the potential impact of uncertainty in all parameters. In addition, one-way sensitivity analysis was done to identify sensitive parameters, in which each parameter was adjusted independently in their respective ranges. Meanwhile, all HR and RR values were adjusted to their optimum or worst limits simultaneously to represent the change of current treatment effectiveness, which were also included in the one-way sensitivity analysis.

Subsequent scenarios were set according to the model predicting results in base-case analysis and one-way sensitivity analysis. We further assumed that the D&T rate would increasing to 80% and 90% in 2030. Sensitive parameters were adjusted individually or in combination. The other parameters were fixed at the baseline values.

All analysis and simulations were performed in Matlab 2023b (The MathWorks, Inc. Natick, Massachusetts, United States).

3. Results

3.1. Hepatitis B-related deaths under base-case scenario

Fig. 2 showed the results of base-case analysis and probabilistic sensitivity analysis under assumption that the D&T rate would reach 72% in 2030 and beyond. According to our model prediction, the number of hepatitis B-related deaths would decrease by 33.11% in 2030 (307,912 vs. 460,357) and 51.57% in 2040 (195,025 vs. 402,689) compared to the scenario that the D&T rate remained at 2016 level, as shown in Table 2. However, with only 23.89% reduction in the number of hepatitis B-related deaths in 2030 compared to 2015, even if the D&T rate reach 72% in 2030, the likelihood of achieving the WHO impact target by 2038 is extremely low (less than 1%) based on probabilistic sensitivity analysis.

One-way sensitivity analyses showed that four sensitivity parameters significantly influenced hepatitis B-related deaths when they were varied within the pre-set range. The most sensitive parameter was HBV clearance rate, which came closest to making the impact target achievable after 2040 (Fig. 3).

3.2. Hepatitis B-related deaths under subsequent scenarios

Based on the results of the model predictions in base-case scenario and one-way sensitivity analysis, we assumed four development factors under four subsequent scenarios: (I) the D&T rate increasing to 80% and 90% by 2030, respectively, because the standardization management of D&T was implemented from 2017, (II) the standardization management of D&T affect the current treatment effectiveness, which is improved to a higher level (the optimum limits of all HR and RR), (III) the standardization management of D&T also affect the HBV clearance rate, reaching the optimal limit from 2016 (2%), and (IV) as a result of using innovative medicines during the period 2016–2030, HBV clearance rate could rise linearly from 2 % to a higher level, potentially allowing the achievement of the WHO's impact target by 2030. The development factors in each subsequent scenario were individually or in combination as scenario A: (I); scenario B: (I) and (II); scenario C: (I), (II) and (III); and scenario D: (I), (II) and (IV), respectively.

As shown in Fig. 4, the WHO's impact target would not be achieved before 2040 under scenario A or B (Fig. 4A and B). Even if the D&T rate improving to 90% by 2030, the current treatment effectiveness to a higher level and HBV clearance rate to 2% from 2016 (scenario C), the WHO's impact target would not be achieved until 2038 (Fig. 4C). This impact target will be met on time by 2030 only if the HBV clearance rate linearly increases from 2% to 2.8% during the period 2016–2030 (scenario D, Fig. 4D).

4. Discussion

A comprehensive public health program for hepatitis B with full coverage of neonatal vaccination, hepatitis B immunoglobulin (HBIG) and antiviral prophylaxis for preventing HBV mother-to-child transmission (MTCT) were taken by Chinese government to reduce new chronic HBV infections and decrease hepatitis B prevalence for over three decades (Liu et al., 2019; Wang et al., 2015). With these interventions, our previous study has demonstrated an optimistic outcome for China to achieve the WHO's target of 0.1% prevalence in children under 5 years old by 2030 (Liu et al., 2022). Now the major problem will come from averting hepatitis B-related deaths in adults. In May 2016, the Chinese government has successfully negotiated the price reduction of tenofovir to less than one-third of its original price (from 1500 RMB to 490 RMB per month) (China to cut prices of, 2016). Simultaneously, the price of generic entecavir has fell to about 300 RMB per month. These two WHO recommended first-line anti-HBV medications were included in the national reimbursement drug list, allowing more patients to access to the medications in 2017, and then the prices were further reduced to nearly 70 RMB per person-year in 2019 (Nayagam et al., 2021). The implementation of these measures have increased the opportunity of eligible people with chronic hepatitis B infection for receiving treatment. Yet, the D&T rate is still low so far, which brings a new challenge to China to achieve the

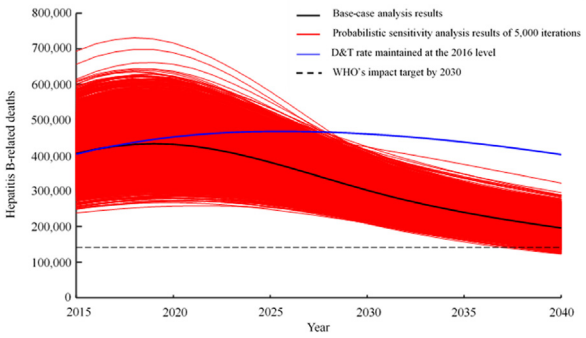

Fig. 2. Hepatitis B-related deaths in China under base-case scenario.

Table 2
The number of hepatitis B-related deaths under base-case scenario.

Years	D&T rate maintained at the 2016 level	D&T rate would reach 72% in 2030 and beyond	Reduction (%)
2015	404557	404557	0.00
2016	417021	417021	0.00
2017	427372	425878	0.35
2018	437069	432293	1.09
2019	445264	435216	2.26
2020	452067	434677	3.85
2021	457489	430738	5.85
2022	461665	423701	8.22
2023	464692	413937	10.92
2024	466641	401869	13.88
2025	467597	387983	17.03
2026	467684	372810	20.29
2027	466927	356795	23.59
2028	465413	340395	26.86
2029	463164	323965	30.05
2030	460357	307912	33.11
2031	456804	292312	36.01
2032	452773	278024	38.60
2033	448184	264833	40.91
2034	443029	252600	42.98
2035	437405	241271	44.84
2036	431290	230726	46.50
2037	424733	220892	47.99
2038	417738	211691	49.32
2039	410368	203077	50.51
2040	402689	195025	51.57
Total	11549992	8700200	24.67

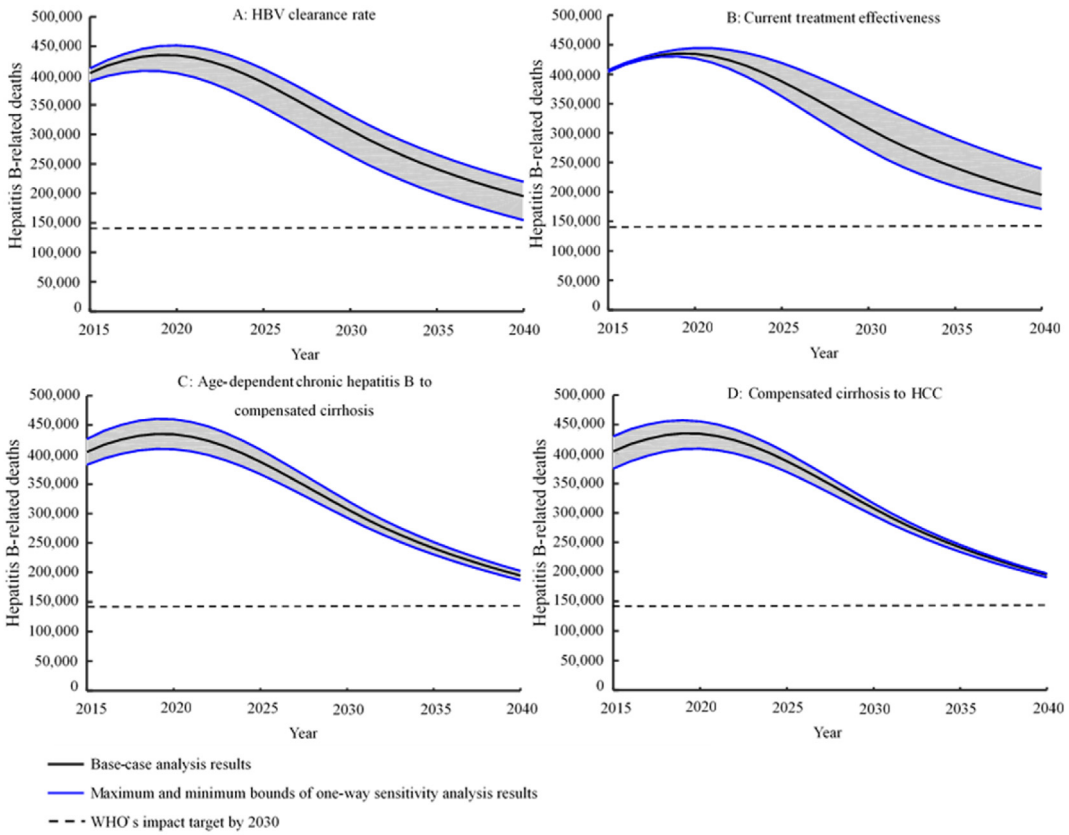

Fig. 3. Impacts of sensitive parameters on hepatitis B-related deaths under base-case scenario.

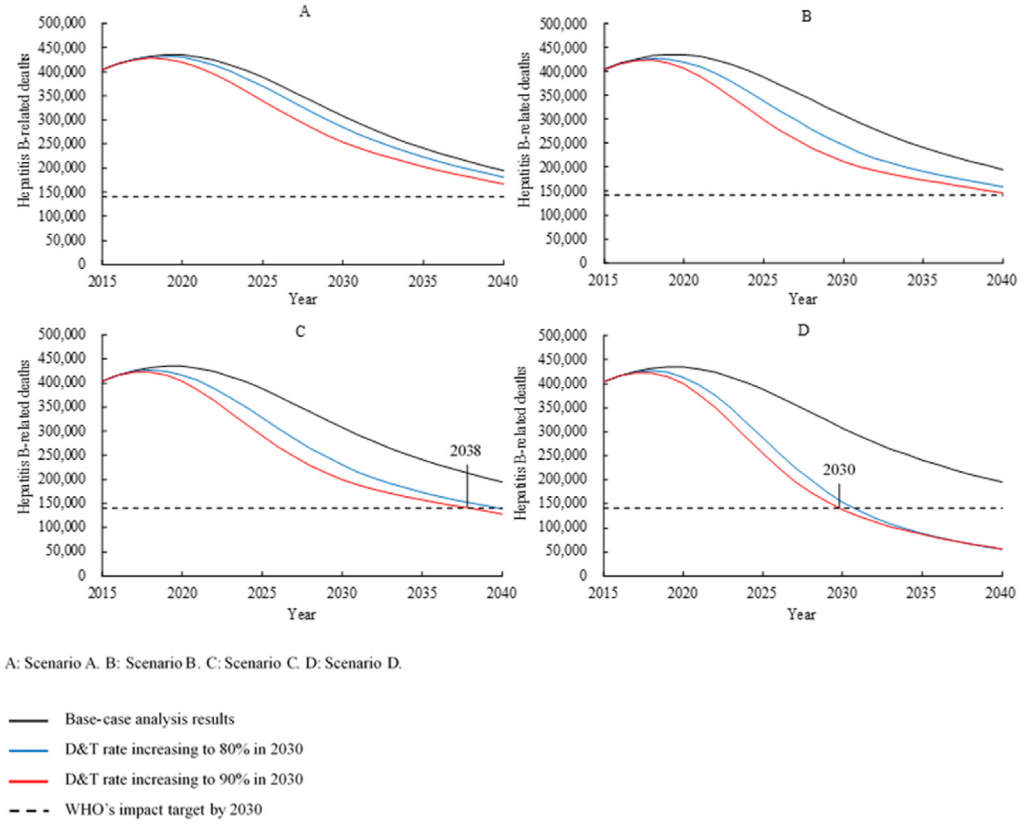

Fig. 4. Hepatitis B-related deaths in China under four subsequent scenarios.

WHO impart target of reducing hepatitis B-related deaths (Cui & Zhuang, 2021). Achieving this target on schedule is not only important for controlling hepatitis B in China, but also can make a significant global impact on the HBV epidemic (Nayagam et al., 2016).

Due to uneven distribution of economic and medical resources, as well as specialized healthcare professionals, many chronic HBV infectors do not receive timely diagnosis and treatment (Cui & Zhuang, 2016; Liu & Liu, 2019; Wang et al., 2019). Research indicates that implementing a universal screening strategy for individuals aged 18–70 over the next decade and expanding treatment coverage for chronic HBV infection people with cirrhosis and HCC are the optimal D&T strategies for reducing hepatitis B-related mortality risk (Nayagam et al., 2021; Su et al., 2022). Although our study similarly found that improving the D&T rate is crucial for reducing hepatitis B-related deaths in China, it differs from other similar mathematical model studies twhich adjust D&T rate to its maximum value at the initial stage (Li et al., 2023; Zhang et al., 2023). Our model suggests that D&T growth should be constrained by various factors, such as comorbidities or co-infections, population compliance, and accessibility issues for residents in remote rural areas. Therefore, our model assumes a linear increase in D&T. Then according to our model results, without a scale-up of diagnosis and receiving treatment for individuals with chronic HBV infection (the D&T rate remained at the 2016 level), China would continue to face a high burden of hepatitis B in the future, and hepatitis B-related deaths in 2030 would increase by 13.79% compared to 2015, and the total number of this deaths would be 11 million between 2015 and 2040. Conversely, if the D&T rate increased to 72% in 2030, hepatitis B-related deaths would reduce by 23.89% and 51.79% compared to 2015 by 2030 and 2040, respectively. The total number of this deaths between 2015 and 2040 would reduce by 24.67% compared with the scenario that the D&T rate remained at the 2016 level (Table 2). However, it is difficult for China to achieve the WHO's impact target of 65% reduction of hepatitis B-related deaths by 2030 at the current conditions with high HBsAg prevalence in the whole population and a large number of people living with chronic HBV infection. Our sensitivity analysis confirms the reliability of this result.

Building on these findings, we further hypothesized in subsequent scenario A, B, and C that with the substantial reduction in antiviral drug prices since 2017, both the D&T rate and the current treatment effectiveness would be improved to a higher level, which could further reduce hepatitis B-related deaths in China and significantly shorten the time required to meet the 65% reduction target for chronic HBV carriers. This finding is also of significant relevance to other countries with high HBsAg infection rates. However, this measure alone is insufficient to ensure that China will meet the impact target on schedule.

As our subsequent scenario D shows, only by combining standardised management of D&T with innovative technologies to improve HBV clearance rate can China potentially achieve WHO impact target of 65% reduction with hepatitis B-related deaths by 2030. However, current antiviral drugs have little success in improving natural HBV clearance in chronically HBV-infected individuals. These antiviral drugs only provide an opportunity to bring HBV under control, slow the progression of cirrhosis, reduce the incidence of HCC, and improve long-term survival, but do not completely clear HBV from infected cells (Testoni et al., 2017). Therefore, we suggest that the development of new drugs similar to those used for the complete eradication of hepatitis C virus is the most critical factor in the reduction of hepatitis B-related deaths (Bulterys et al., 2018). It has been reported that nucleic acid polymers, as a novel broad-spectrum antiviral compound, can inhibit the release of HBsAg from HBV-infected hepatocytes, which can lead to the reduction of HBsAg levels in chronically HBV-infected patients and improve the clearance rate of chronic HBV infection after antiviral therapy (Bazinet et al., 2020; Vaillant, 2019). In addition, another study have reported that the presence of a bispecific molecule (ImmTAV) within the body's immune system that binds with high affinity to T-lymphocyte antigen receptors and CD3 (ScFv)-activated T-lymphocytes, which is capable of specifically clearing hepatocytes that have been infected with HBV, has shown a significant therapeutic effect in patients with hepatitis B chronic infection (Bertoletti, 2020). The above studies have demonstrated the great potential of new therapeutic tools in clearing HBV, but as these studies are still in the early stage of experimental exploration, more in-depth discussions are needed in the future regarding the effectiveness and safety of treatment for chronic hepatitis B individuals.

Although our study has important findings revealing the possibility of China achieving the WHO impact target of reducing hepatitis B-related deaths, it does have limitations. First, we didn't consider the gender of the entire population and its potential influence on our model prediction outcomes. Second, due to a lack of data, we adjusted hepatitis B-related HCC incidence or death rate by multiplying liver cancer incidence or death rate by 0.9 and 0.8 (Department of Medical Administration et al., 2020; Venook et al., 2010; WHO, 2015). Third, the COVID-19 pandemic might have short-term and long-term effects on hepatitis B-related deaths, which were not included in the model. Fourth, we did not focus on the cost-effectiveness of various D&T strategies, which may limit policy-makers in making clear choices and judgments. Fifth, we did not perform mathematical analysis of our age-structured dynamic model, including calculating the basic reproduction number, and proving the existence and stability of the disease-free and endemic steady state (Cao & Zhou, 2012; Zhang & Zhou, 2014; Zou et al., 2010), which can be left for the further study. Despite these limitations, our main conclusions remain unchanged.

5. Conclusions

Our model predicted that it is difficult for China to achieve the WHO's impact target of 65% reduction in hepatitis B-related deaths by 2030, even we assumed the D&T rate would reach 72% in 2030 and beyond. Increase D&T rate to a higher level and the standardization management of D&T coverage rapidly may shorten the time to achieve the target. A comprehensive scale-up of available strategies, especially innovative new drugs and technologies will ensure that China achieves the target on schedule.

CRediT authorship contribution statement

Wenjun Liu: Writing – original draft, Software, Methodology, Formal analysis. **Renjie Liu:** Formal analysis, Data curation. **Peng Li:** Formal analysis. **Ruyi Xia:** Data curation. **Zhuoru Zou:** Formal analysis. **Lei Zhang:** Supervision, Methodology. **Mingwang Shen:** Writing – review & editing, Validation. **Guihua Zhuang:** Writing – review & editing, Validation.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The data of this study are from national hepatitis B serosurveys in China and our previous results which were published in references (Liu et al., 2022).

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Declaration of competing interests

I am writing to declare that, to the best of my knowledge, I have no conflicts of interest in article writing. I understand the importance of maintaining the highest standards of integrity, professionalism, and ethical conduct. I can confirm that I have no personal relationships, financial interests, business connections or other factors that could compromise or appear to compromise impartiality, fairness and ethical conduct with any other organization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idm.2025.02.010.

References

Aho, K., Derryberry, D., & Peterson, T. (2014). Model selection for ecologists: The worldviews of AIC and BIC. *Ecology, 95*(3), 631–636.

Bazinet, M., Pântea, V., Placinta, G., et al. (2020). Safety and efficacy of 48 Weeks REP 2139 or REP 2165, tenofovir disoproxil, and pegylated interferon alfa-2a in patients with chronic HBV infection naïve to nucleos(t)ide therapy. *Gastroenterology, 158*(8), 2180–2194.

Bertoletti, A. (2020). ImmTAV, a new immunotherapy targeting the source of HBV infection. *Hepatology, 72*(5), 1514–1517.

Briggs, A., Claxton, K., & Sculpher, M. (2006). *Decision modelling for health economic evaluation*. New York: Oxford University Press.

Bulterys, M., & Sadiq Hamid, S. (2018). Treatment of people diagnosed with chronic hepatitis C virus infection. *Bulletin of the World Health Organization, 96*(8), 515.

Cao, H., & Zhou, Y. (2012). The discrete age-structured SEIT model with application to tuberculosis transmission in China. *Mathematical and Computer Modelling, 55*(3–4), 385–395.

China to cut prices of expensive patent drugs. China Daily. Available at: http://www.chinadaily.com.cn/china/2016-05/20/content_25393469.htm, (2016)–. (Accessed 29 March 2022).

Chinese Society of Hepatology, Chinese Medical Association. (2019). Chinese guidelines on the management of liver cirrhosis. *Chinese Journal of Hepatology, 27*(11), 846–865 ((Chinese)).

Cuadrado, A., Perelló, C., Cabezas, J., et al. (2020). Update on epidemiology of hepatitis B in a low-endemic European country: There is still much to do. *Journal of Viral Hepatitis, 27*(11), 1261–1265.

Cui, F., Shen, L., Li, L., et al. (2017). Prevention of chronic hepatitis B after 3 decades of escalating vaccination policy, China. *Emerging Infectious Diseases, 23*(5), 765–772.

Cui, F., & Zhuang, H. (2016). Hepatitis B control in China: Progress, challenges and strategies. *Chin J Viral Dis., 6*(2), 81–87 ((Chinese)).

Cui, F. Q., & Zhuang, H. (2021). Progress in prevention and control viral hepatitis since the establishing of the People's Republic of China. *Chinese Journal of Hepatology, 29*(8), 725–731 ((Chinese)).

Department of Medical Administration, National Health and Health Commission of the People's Republic of China. (2020). Guidelines for diagnosis and treatment of primary liver cancer in China (2019 edition). *Chinese Journal of Hepatology, 28*(2), 112–128 ((Chinese)).

Guo, P., Zhu, B., Niu, H., et al. (2018). Fast genomic prediction of breeding values using parallel Markov chain Monte Carlo with convergence diagnosis. *BMC Bioinformatics, 19*(1), 3.

Haario, H., Laine, M., Mira, A., et al. (2006). Dram: Efficient adaptive MCMC. *Statistics and Computing, 16*, 339–354.

Harms, R. L., & Roebroeck, A. (2018). Robust and fast Markov chain Monte Carlo sampling of diffusion MRI microstructure models. *Front Neuroinform, 12*, 97.

He, L., Liu, X., Zhao, Y., et al. (2017). Efficacy of nucleot(s)ide analogs therapy in patients with unresectable HBV-related hepatocellular carcinoma: A systematic review and meta-analysis. *Disease Markers, 2017*, Article 7075935.

Hens, N., Shkedy, Z., Aerts, M., et al. (2012). *Modeling infectious disease parameters based on serological and social contact data: A modern statistical perspective*. New York: Springer.

Hou, J. L., Zhao, W., Lee, C., et al. (2020). Outcomes of long-term treatment of chronic HBV infection with entecavir or other agents from a randomized trial in 24 countries. *Clinical Gastroenterology and Hepatology, 18*(2), 457–467.

Li, S. Y., Li, H., Xiong, Y. L., et al. (2017). Peginterferon is preferable to entecavir for prevention of unfavourable events in patients with HBeAg-positive chronic hepatitis B: A five-year observational cohort study. *Journal of Viral Hepatitis, 24*(Suppl 1), 12–20.

Li, R., Shen, M., Ong, J. J., et al. (2023). Blueprint to hepatitis B elimination in China: A modelling analysis of clinical strategies. *JHEP Rep, 5*(10), Article 100833.

Liaw, Y. F., Sung, J. J., Chow, W. C., et al. (2004). Lamivudine for patients with chronic hepatitis B and advanced liver disease. *New England Journal of Medicine, 351*(15), 1521–1531.

Liu, J., Liang, W., Jing, W., et al. (2019). Countdown to 2030: eliminating hepatitis B disease, China. *Bulletin of the World Health Organization, 97*(3), 230–238.

Liu, J., & Liu, M. (2019). Progress and challenges in achieving the WHO goal on "Elimination of Hepatitis B by 2030" in China. *Chinese Journal of Epidemiology, 40*(6), 605–609 ((Chinese)).

Liu, W., Zhuang, T., Xia, R., et al. (2022). Modelling the prevalence of hepatitis B towards eliminating it as a major public health threat in China. *BMC Public Health, 22*(1), 1179.

McCulloch, K., Romero, N., MacLachlan, J., et al. (2020). Modeling progress toward elimination of hepatitis B in Australia. *Hepatology, 71*(4), 1170–1181.

Morton, A., & Finkenstädt, B. F. (2005). Discrete time modelling of disease incidence time series by using Markov chain Monte Carlo methods. *Appl Statist., 54*, 575–594.

Nagelkerke, N., Heisterkamp, S., Borgdorff, M., et al. (1999). Semi-parametric estimation of age-time specific infection incidence from serial prevalence data. *Statistics in Medicine, 18*(3), 307–320.

Nayagam, S., Chan, P., Zhao, K., et al. (2021). Investment case for a comprehensive package of interventions against hepatitis B in China: Applied modeling to help national strategy planning. *Clinical Infectious Diseases, 72*(5), 743–752.

Nayagam, S., Thursz, M., Sicuri, E., et al. (2016). Requirements for global elimination of hepatitis B: A modelling study. *The Lancet Infectious Diseases, 16*(12), 1399–1408.

Nguyen, V. T., Law, M. G., & Dore, G. J. (2009). Hepatitis B-related hepatocellular carcinoma: Epidemiological characteristics and disease burden. *Journal of Viral Hepatitis, 16*(7), 453–463.

Polaris Observatory Collaborators. (2018). Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: A modelling study. *Lancet Gastroenterol Hepatol, 3*(6), 383–403.

Posuwan, N., Wanlapakorn, N., Sintusek, P., et al. (2020). Towards the elimination of viral hepatitis in Thailand by the year 2030. *J Virus Erad, 6*(3), Article 100003.

Ren, P., Cao, Z., Mo, R., et al. (2018). Interferon-based treatment is superior to nucleos(t)ide analog in reducing HBV-related hepatocellular carcinoma for chronic hepatitis B patients at high risk. *Expert Opinion on Biological Therapy, 18*(10), 1085–1094.

Su, S., Wong, W. C., Zou, Z., et al. (2022). Cost-effectiveness of universal screening for chronic hepatitis B virus infection in China: An economic evaluation. *Lancet Global Health, 10*(2), e278–e287.

Testoni, B., Durantel, D., & Zoulim, F. (2017). Novel targets for hepatitis B virus therapy. *Liver International, 37*(Suppl 1), 33–39.

Thiele, M., Gluud, L. L., Fialla, A. D., et al. (2014). Large variations in risk of hepatocellular carcinoma and mortality in treatment naïve hepatitis B patients: Systematic review with meta-analyses. *PLoS One, 9*(9), Article e107177.
Trentini, F., Poletti, P., Merler, S., et al. (2017). Measles immunity gaps and the progress towards elimination: A multi-country modelling analysis. *The Lancet Infectious Diseases, 17*(10), 1089–1097.
Vaillant, A. (2019). Rep 2139: Antiviral mechanisms and applications in achieving functional control of HBV and HDV infection. *ACS Infectious Diseases, 5*(5), 675–687.
Venook, A. P., Papandreou, C., Furuse, J., et al. (2010). The incidence and epidemiology of hepatocellular carcinoma: A global and regional perspective. *The Oncologist, 15*(Suppl 4), 5–13.
Wang, C., & Cui, F. (2022). Expanded screening for chronic hepatitis B virus infection in China. *Lancet Global Health, 10*(2), e171–e172.
Wang, A. L., Qiao, Y. P., Wang, L. H., et al. (2015). Integrated prevention of mother-to-child transmission for human immunodeficiency virus, syphilis and hepatitis B virus in China. *Bulletin of the World Health Organization, 93*(1), 52–56.
Wang, G., Wang, F., Zhuang, H., et al. (2020). Guidelines for the prevention and treatment of chronic hepatitis B (2019 version). *Chin J Viral Dis, 10*(1), 1–25 ((Chinese)).
Wang, F. Z., Zheng, H., Su, X. J., et al. (2019). Achievements and prospects for hepatitis B prevention and control in China. *Chin J Vaccine, 25*(5), 487–492 ((Chinese)).
WHO. (2015). *Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection*. Geneva: World Health Organization.
WHO. (2016). *Global health sector strategy on viral hepatitis 2016-2021*. Geneva: World Health Organization.
WHO. (2021). *Interim guidance for country validation of viral hepatitis elimination*. Geneva: World Health Organization.
Xia, B. W., Zhang, Y. C., Wang, J., et al. (2015). Efficacy of antiviral therapy with nucleotide/nucleoside analogs after curative treatment for patients with hepatitis B virus-related hepatocellular carcinoma: A systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol, 39*(4), 458–468.
Xie, L., Yin, J., Xia, R., et al. (2018). Cost-effectiveness of antiviral treatment after resection in hepatitis B virus-related hepatocellular carcinoma patients with compensated cirrhosis. *Hepatology, 68*(4), 1476–1486.
Ye, X. G., & Su, Q. M. (2013). Effects of entecavir and lamivudine for hepatitis B decompensated cirrhosis: Meta- analysis. *World Journal of Gastroenterology, 19*(39), 6665–6678.
Zhang, S., Wang, C., Liu, B., et al. (2023). Cost-effectiveness of expanded antiviral treatment for chronic hepatitis B virus infection in China: An economic evaluation. *Lancet Reg Health West Pac, 35*, Article 100738.
Zhang, W., Zhang, D., Dou, X., et al. (2018). Consensus on pegylated interferon alpha in treatment of chronic hepatitis B. *J Clin Transl Hepatol., 6*(1), 1–10.
Zhang, S., & Zhou, Y. (2014). Dynamic analysis of a hepatitis B model with three-age-classes. *Communications in Nonlinear Science and Numerical Simulation, 19*(7), 2466–2478.
Zou, L., Ruan, S., & Zhang, W. (2010). An age-structured model for the transmission dynamics of hepatitis B. *SIAM Journal on Applied Mathematics, 70*(8), 3121–3139.