Disease burden of chronic hepatitis B and complications in China from 2006 to 2050: an individual-based modeling study

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Abstract

Background: Chronic hepatitis B has become a major public health problem in China. An accurate depiction of the disease burden has not yet been thoroughly conducted. We aimed to project the disease burden of chronic hepatitis B virus infection and related complications by modeling various scenarios. Method : An individual-based Markov model was used to predict disease burden from 2006 through 2050. We simulated 5 scenarios with different annual incidences, diagnosis and nucleotide analogs (NAs) treatment rates as well as treatment eligibility, which included a natural history without diagnosis or NAs therapy, a base-case, a World Health Organization proposed target case and two ideal cases. Result: Natural history scenario is projected to have the fewest HBsAg loss (27.59 million) and highest HBV-related deaths (27.19 million). With improved diagnosis and treatment rates of NAs therapy, ideal cases have fewer HBV-related deaths (14.46-14.77 million) than WHO (15.13 million) and base-case (16.89 million), but proportion of HBsAg loss is similar among them. With reduced new infections, prevalence of chronic HBV in 2050 is expected minimally to be 27.03-27.49 million under WHO and ideal cases. Conclusion: If the future disease burden of chronic HBV is to be lowered dramatically, reducing new infection is more effective than increasing diagnosis, treatment rate and treatment eligibility. Additionally, without high potency new drugs, it will be hard to avert increasing trend of cumulative cirrhosis, DC, HCC, LT and HBV-related death.

Introduction

Chronic hepatitis B virus (HBV) infection has always been a major public health issue in China. In the latest nationwide seroepidemiologic survey, conducted in 2006, the prevalence rate of HBsAg positivity in the general population was 7.18% (1). Although an updated survey was re-conducted in 2014, it only covered 1–29 years old age population (2). Based on this data, approximately 93 million people were chronically infected with HBV. People living with chronic HBV infection can be classified into several categories according to serum markers and liver function (3, 4), including immune-tolerant carrier, inactive carrier, HBeAg positive hepatitis, HBeAg negative hepatitis. In 2006, the estimated 63–73 million inactive carriers made up the largest group (4–6).

A main concern about chronic HBV infection is its long-term complications. Chronic HBV infection carries a risk of developing primary liver cancer, which ranks as the sixth most common cancer worldwide (7). It also leads to 786,000 HBV-related deaths per year, making it the tenth leading cause of death worldwide (8). Over their lifetimes, 15–40% of people with chronic HBV infection can develop complications ranging from hepatocellular carcinoma (HCC) to HBV-related death (9).

Considering these potential progressions and adverse outcomes, the World Health Organization (WHO) endorsed its first global health sector strategy on viral hepatitis in 2016 with the goal of eliminating hepatitis B and C by 2030 (10). There are various ways to achieve this goal, including preventing new infections and treating current cases. For those already infected, a ‘functional cure’ (HBsAg loss) is the only method available. The international guidelines also suggested treatment for those who are eligible as well as continued monitoring of all currently infected individuals (11). Nucleos(t)ide analogs (NAs) therapy was first introduced around 2000. Since 2005, high-potency NAs with minimal risk and side effects, such as Entecavir (ETV), have been widely applied in China as the first-line recommendation (12, 13). Recently China has updated chronic HBV treatment guideline expanding NAs treatment eligibility (14).

There were several HBV modeling studies evaluated the epidemiology of chronic HBV infection in China (15–17). Those studies found that increasing screen and treatment were effective in reducing chronic HBV infection, enhancing vaccination was beneficial for eliminating transmission. However, previous studies barely projected HBV complicated diseases including cirrhosis, DC, HCC, liver transplantation clearly. Meanwhile, there is no cohort study in China so far could accurately follow up long-term outcomes of all HBV infected population, which is quite important to systematic

assessment of health consequence and decision-making. Therefore, our study developed an individual-level Markov model aiming to project the disease burden of total chronic HBV infections, cirrhosis, DC, HCC, LT, and HBV-related from 2006 to 2050 under various scenarios representing different level of diagnosis, treatment rate, treatment eligibility, and annual new infection.

Materials And Methods

Overview

We developed an individual-level Markov model to simulate HBV infection outcomes in individuals with chronic HBV infection from 2006 to 2050. The model projects the prevalence of total chronic HBV infection, HBsAg loss population, incidences of progressing to cirrhosis, decompensated cirrhosis (DC), HCC, liver transplantation (LT), and HBV-related deaths. Model construction was done using TreeAge Pro 2011 Suite (TreeAge Software, Williamstown, MA). Data analysis was performed using R version 3.5.3. Figures were drawn with R version 3.5.3 plus Tableau Desktop 2018 (Tableau Software, Inc. Seattle, WA).

Patient demographics

Our study constructed a simulated chronic HBV-infected population representing nationwide baseline in 2006 using results of national survey of chronic HBV infection epidemiologic study (18, 19) (Supplementary Table 3 and Supplementary Table 10). New HBV infections after 2006 were added into simulated population annually based on reports by the Chinese Center for Disease Control and Prevention, and the age distribution was derived from published data. Since there is no data regarding to age structure after 2017, we adopted the same distribution as 2017 (20–22) (Supplementary Table 4).

Model schematics

In natural history, we simplified and organized chronic HBV infection status into three ‘CHB states’ including HBsAg-positive inactive carrier, HBeAg-negative hepatitis, HBeAg-positive hepatitis, four ‘Complication states’ including cirrhosis, DC, HCC, LT, and three absorbing states including HBsAg loss, background death, HBV-related death (Supplementary Fig. 2). Each ‘CHB state’, at predefined probability rates, could either progress into cirrhosis and HCC states, or undergo HBsAg loss or background death as absorbing states. All of ‘Complication states’ could transfer to each other or undergo HBV-related death (Supplementary Fig. 2 and Supplementary Table 1). We also modeled annual probability of non-liver death. Background mortality of age-standardized rate (ASR) was estimated from the National Bureau of Statistics of China (23).

We didn’t consider immune tolerance as one of states here, which is common among infants and children, due to less epidemiologic data are available and the largest population consist of chronic HBV infection in adults is inactive carriers in China (5, 24–26).

We also assumed those who met treatment criteria in Chinese Medical Association and Asian Pacific Association for the Study of the Liver (APASL) guidelines in HBeAg-negative hepatitis, HBeAg-positive hepatitis and cirrhosis states could receive NAs therapy and achieve virological response (defined as undetectable serum HBV DNA during therapy), thereafter progress at different probability rates in Supplementary Table 2 (4, 27). For those who did not achieve virological response, we assumed them to have same progression as natural history. For DC, HCC, or LT patients, we assumed the progression rate was relatively constant regardless of NAs therapy.

We did not different strategies of HBV vaccination in our model because currently it has already covered universally with more than 95% coverage and vertical transmission block is also highly effective with less than 10/100 000 new

HBV infection incidence (28, 29). Meanwhile, vaccine's effect have already been shown as new infection number every year in our model. And we simulated only NAs therapy, electing not to include interferon therapy due to its finite coverage, numerous side effects and contraindications (13).

HBV diagnosis, awareness, and treatment

We adopted a recent study summarized diagnosis and treatment rates (treatment/treatment eligible) in China (18.7% and 10.8%, respectively, in 2016) as the base-case parameters in our model (20). Under WHO targets and ideal cases scenario, we used data from WHO proposed 'elimination of viral hepatitis' in 2016 as diagnosis and treatment rates. We assumed that newly enrolled individuals were neither undiagnosed nor unaware at first, and they could become diagnosed at a certain probability. Once diagnosed, patients were assumed to accept their condition and awareness of HBV infection. Newly treated individuals were divided into virological response or non- virological response state, which were permanent until simulation ended.

Simulation scenarios

We simulated five scenarios with different diagnosis rate, treatment rate, treatment eligibility and new infection annually (Table 1). 1) Natural history scenario. No interventions (diagnosis and awareness, treatment) were applied. 2) Base-case scenario. Current diagnosis and treatment rate simulated applied throughout 2004 to 2050. 3) WHO proposed target scenario. Higher diagnosis and treatment rates and reduced new infection cases proposed by WHO were simulated (Supplementary Table 4–5). 4) Ideal case 1—full capacity of diagnosis and treatment. This scenario simulated that all existing HBV-infected patients would be diagnosed, and all treatment eligible patients could receive and benefit from NAs therapy. However, annual new infection cases and treatment eligibility were not changed compared with WHO target scenario (Supplementary Table 4). 5) Ideal case 2—full treatment-eligible proportion. This scenario simulated that all hepatitis and cirrhosis patients were treatment-eligible. However, annual new infection number, diagnosis rate and treatment rate were not changed compared with WHO target scenario (Supplementary Table 4–5).

Table 1

Parameters of Simulated scenarios

Scenarios	Assumption	2006–2017	2018–2020	2021–2030	2031–2050
Natural	incidence	historical data	851659(2017 incidence)	851659(2017 incidence)	85159(2017 incidence)
	diagnosis	no diagnosis	no diagnosis	no diagnosis	no diagnosis
	treatment	no treatment	no treatment	no treatment	no treatment
Base-case	incidence	historical data	851659(2017 incidence)	851659(2017 incidence)	851659(2017 incidence)
	Dx%	18.70%	18.70%	18.70%	18.70%
	Tx/eligible%	10.83%	10.83%	10.83%	10.83%
WHO target	incidence	historical data	555858 in 2020 (70% of 2015)*	79408 in 2030 (10% of 2015)*	79408(2030 incidence)
	Dx%	18.70%	30% in 2020*	90% in 2030*	90%(2030 rate)
	Tx/eligible%	10.83%	10.83%	80.00% in 2030*	80.00%(2030 rate)
Ideal 1 (Dx%=1; Tx/eligible%=1)	incidence	historical data	555858 in 2020 (70% of 2015)*	79408 in 2030 (10% of 2015)*	79408(2030 incidence)
	Dx%	18.70%	100%	100%	100%
	Tx/eligible%	10.83%	100%	100%	100%
Ideal 2	incidence	historical data	555858 in 2020 (70% of 2015)*	79408 in 2030 (10% of 2015)*	79408(2030 incidence)
(eligible%=1)	Dx%	18.70%	30% in 2020*	90% in 2030*	90%(2030 rate)
	Tx/eligible%	10.83%	10.83%	80.00% in 2030*	80.00%(2030 rate)
Dx%: diagnosis rate					
Tx/eligible%: treatment/treatment eligible					
Eligible%: eligible proportion					
*Dx% and Tx/eligible% in 2018–2019 and 2021–2029 were estimated through linear regression (Supplementary Tables 4 and 5).					

Validation

We validated our model's results using authoritative public health data sources. These included the annual HCC incidence number provided by WHO CI5plus/IARC 2010–2012, WHO Globocan 2018, Polaris, HBV-related deaths with WHO Globocan 2018, and total chronic HBV infection prevalence according to studies published by Chinese hepatology experts for the base-case scenario (30–33). In addition, in the natural history scenario, we compared our predicted

cumulative 10-year probabilities of HBsAg loss and chronic hepatitis with published studies on inactive carriers (34) (Supplementary S 5).

Sensitivity analysis

We did a 1-way sensitivity analysis on the model in base-case parameters by considering uncertainty in all probability rates. We defined each annual transition probability using the upper range and lower range values, then compared upper or lower values of cirrhosis, DC, HCC, LT cumulative incidence and cumulative death with base-case values. (Supplementary S 6).

Result

Validation and sensitivity analysis

Our model projected that the total number of chronic HCV infection in 2016 was 86 million, which is equal to the reported epidemiologic data. The projected annual incidence of HCC in 2010 to 2018 and HBV-related death in 2018 were within 13% of the reported values except one data (30–33) (Supplementary Table 6). Finally, our model's 10-year cumulative incidence rates of HBsAg loss, hepatitis in inactive carrier closely matched those of a published real-world study (34) (Supplementary Table 7).

Sensitivity analysis revealed that 81.75% (327/400) of all predicted upper or lower values of cirrhosis, DC, HCC, LT cumulative incidence and cumulative death fluctuated within 10%, 96% (384/400) were fluctuated within 20%. (Supplementary Table 8)

Table 2
Cumulative number and percent of chronic HBV infection, cured, and HBV-related death till 2030 and 2050.

	Natural		Base-case		WHO		Ideal 1		Ideal 2	
Year	2030	2050	2030	2050	2030	2050	2030	2050	2030	2050
Total CHB	73.74	43.18	73.53	43.59	68.07	27.49	67.50	27.03	67.51	27.08
Δ CHB	40.14	87.74	40.34	87.32	39.48	81.65	40.06	82.11	40.05	82.07
HBsAg loss	18.79	27.59	23.26	35.33	22.69	32.67	23.42	33.42	23.45	33.58
Percent	46.81%	31.45%	57.65%	40.46%	57.47%	40.01%	58.46%	40.70%	58.55%	40.92%
HBV-RD	13.24	27.19	9.02	16.89	8.77	15.13	8.57	14.77	8.53	14.46
Percent	32.99%	31.00%	22.37%	19.35%	22.21%	18.53%	21.39%	17.99%	21.29%	17.62%
BD	8.11	32.96	8.06	35.10	8.02	33.85	8.07	33.92	8.07	34.03
Percent	20.20%	37.57%	19.98%	40.20%	20.31%	41.46%	20.14%	41.31%	20.15%	41.46%
reflecting the reduced number of chronic HBV infection										
CHB = chronic HBV infection; HBV-RD = HBV-related death; BD = Background death										

Cumulative incidence of HBsAg loss and HBV-related deaths

Figure 1A showed cumulative HBsAg loss in China from 2006 to 2050 under five scenarios. Under the natural history scenario, HBsAg loss was projected to be 27.59 million, which was lowest among all scenarios. 32.67 million HBsAg loss was predicted under WHO target scenario, slightly less than ideal 1 with 33.42 million and ideal 2 with 33.58 million. The highest occurred under base-case with 35.33 million. The proportion of HBsAg loss among base-case (40.46%), WHO (40.01%), ideal 1(40.71%) and ideal 2 (40.92%) scenarios were extremely close, but each of them exceeded natural history (31.45%) obviously (Table 2). Figure 1B revealed cumulative HBV-related deaths under the different scenarios. Under the natural history scenario, as many as 27.19 million patients were predicted to die of HBV-related reasons by 2050. This number reduced to 16.89 million under base-case, and dropped even lower to 15.13 million, 14.77 million, and 14.46 million under scenarios 3–5. Similarly, proportion of HBV-related among base-case (19.35%), WHO (18.53%), ideal 1(17.99%) and ideal 2 (17.62%) scenarios were far less than natural history (31.00%) (Table 2).

Incidence of chronic HBV complications and death

The cumulative and annual incidence of HBV-related complications and death were presented in Fig. 2 and Supplementary Fig. 3. We projected that there would be a total of 379.66 million cumulative incidence of HBV-related complications and 241.61 million death under natural history scenario (Supplementary Table 11). Compared to natural history, cumulative incidence of HBV-related complications was predicted to reduce significantly to 251.59 million, 230.38 million, 215.19 million, and 218.32 million under scenarios 2–5. Among four complications, cumulative incidence of cirrhosis was found to have the largest decline with 39.87%, 49.09%, 51.61%, and 52.77% reduction under four non-natural history scenarios. Annual incidence of HBV-related complications and death were presented in Fig. 3 and Supplementary Fig. 4. In 2050, HCC death was predicted to be the most common cause of both HBV-related complications and death; corresponding annual incidence of HCC yielded to 411440, 258010, 168840, 147270, and 165330 respectively under five scenarios.

Annual incidence of HBeAg negative and positive hepatitis B

Our model also predicted a decreasing trend of annual incidence of HBeAg negative and positive hepatitis in Fig. 4. We estimated annual incidence of HBeAg negative hepatitis was lowest among all the scenarios under natural history from 2006 (1.69 million) to 2023 (1.13 million). Thereafter the annual incidence in natural and base-case became close and higher than the other three scenarios. (Fig. 4A). Estimated annual incidence of HBeAg-positive hepatitis under natural history was constantly highest among all the scenarios; the incidence in 2050 yielded to 294430, more than five times than ideal 2 (54255) (Fig. 4B).

Prevalence of total chronic HBV infection

The trend of total chronic HBV infection prevalence over time was presented in Supplementary Fig. 5. Estimated prevalence was projected to decrease over time under all scenarios, from 93 million in 2006 to 43.18 million, 43.59 million, 27.49 million, 27.03 million, and 27.08 million in 2050 under scenarios 1–5 respectively. (Table 2)

Discussion

Our model used the most updated domestic data on Chinese hepatitis B epidemiologic studies, national notifiable disease surveillance, published cohort data, and other similar models to systematically and prospectively project chronic HBV infection disease burden in China through 2050. We estimated that cumulative incidence of cirrhosis, DC, HCC, LT, HBV-related death would still increase, and total chronic HBV-infected prevalence would decrease over time under all scenarios. Among them, ideal 1 and 2 scenarios were predicted to have the lowest disease burden of

complication and chronic infection. In addition, reducing new infection is projected to be the most effective method now available.

100% diagnostic modalities and treatment rates simulated in ideal 1 scenario projected more HBsAg loss, less HBV-related death and less total chronic HBV infected prevalence than gradually increased diagnosis and treatment rates under WHO targeted scenario. Current HBV screen in China only includes childbirth screen and vaccination, blood products screen, and safe injection practices screen (35). More than 80% HBV infections are unaware about their HBV status (20).In the United States, screen is recommended for those who are at high risk including immigrants from places with > 2% prevalence, HIV-infected people, and pregnant women at their first prenatal visits (36, 37). According to that standard, implementing 100% HBV screen and achieving full diagnosis to all Chinese is clinically significant due to medium-high prevalence nationwide.

Similarly, ideal 2 scenario led to fewer HBV-related deaths and more HBsAg loss than WHO targeted scenario, which proved increased treatment eligibility was beneficial in reducing chronic HBV disease burden. In the past, only hepatitis patients with 2 times higher upper limit of normal ALT met the treatment eligibility in China; but recently newest Chinese guideline suggested full treatment to all hepatitis patients with elevated ALT (14). Our model result provided theoretical evidence and clearly endorsed the recommendation of increasing treatment eligibility by newest Chinese guideline.

We also observed a huge disparity of total prevalence between base-case and WHO targeted scenario, which mostly derived from different setting of annual new infection. Diagnosis and treatment rate only contributed minor difference compared with reduced new infection. Therefore, controlling new infection is the most effective method to lower chronic HBV disease burden now available. Although Chinese government administered birth immunization after birth since 1992 and achieved significant reduction on total HBV prevalence, there are still 50,000 vertical transmission and 800 thousands new infection every year.(1, 20, 38, 39) New infections were found to be more common in undeveloped region and those who born before 1992 without vaccine protection (40).Thus, more efforts are still needed especially on birth immunization of remote region and catch-up vaccine for susceptible adults.

In addition, cumulative incidences of cirrhosis, DC, HCC, and related deaths were predicted increasing over time under all scenarios, implying that NAs therapy could only decelerate but not reverse the growing trend. The potential attribution was supposed that only a small group of patients receiving NAs therapy would reach ‘functional cure’ status (41). Even with the help of Peg-IFN therapy, 3–7% of patients would loss HBsAg, far less than 97% of HCV elimination using DAAs (3, 42, 43). Also, the huge baseline of infected population would generate large disease burden of hepatitis and complications every year, largely exceeded HBsAg loss individuals in number. These two reasons explain why DAAs could convert the increasing trend of HCV complications as shown in our previous modeling study but not NAs therapy in HBV (44). Hence, we suggest that without high potency new drugs, it will be hard to avert increasing trend of cumulative cirrhosis, DC, HCC, LT and HBV-related death.

Our study has several limitations as a modeling study could never exactly simulate an actual situation, particularly with such complicated disease progression. 1) The parameters chosen in the model were selected from different published articles. We selected updated and large-scale population studies of Asian published in high impact factor journals. Probabilities can’t be found were assumed based on Chinese public data and studies. 2) Further cost-effectiveness analysis is still warranted considering the expense of diagnosis and treatment. 3) Data from a national open public health database might be underreported. But we tried to find unpublished data from expert review. 4) HBV pathogenesis and clinical progression are complicated. Our model simplified and focused on majority part.

Conclusion And Implication

Our finding suggested that if the future disease burden of chronic HBV is to be lowered dramatically, the government needs to control new infection as priority such as consolidate and further expand birth immunization, and catch-up vaccine for adults. Meanwhile, without high potency new drugs, it will be hard to avert increasing trend of cumulative cirrhosis, DC, HCC, LT and HBV-related death.

Abbreviations

WHO, world health organization; HBV, hepatitis B virus; NAs, nucleos(t)ide analogs; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; DAA, direct-acting antiviral agent; LT, liver transplantation.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: All the authors consent to publish

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: LL, YZ, and JW designed the study. YZ and JW analyzed the data and interpreted the results. YZ wrote the manuscript. CD, KX and SY revised the manuscript from preliminary draft to submission. LL supervised the whole study.

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References

1. Wang FS, Fan JG, Zhang Z, Gao B, Wang HY. The global burden of liver disease: the major impact of China. Hepatology 2014;60:2099-2108.
2. Cui F, Shen L, Li L, Wang H, Wang F, Bi S, Liu J, et al. Prevention of Chronic Hepatitis B after 3 Decades of Escalating Vaccination Policy, China. Emerg Infect Dis 2017;23:765-772.
3. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS, Jr., et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-1599.
4. Hou JL, lai W. [The guideline of prevention and treatment for chronic hepatitis B: a 2015 update]. Zhonghua Gan Zang Bing Za Zhi 2015;23:888-905.
5. Toy M, Salomon JA, Jiang H, Gui H, Wang H, Wang J, Richardus JH, et al. Population health impact and cost-effectiveness of monitoring inactive chronic hepatitis B and treating eligible patients in Shanghai, China. Hepatology 2014;60:46-55.
6. Lu FM, Zhuang H. Management of hepatitis B in China. Chin Med J (Engl) 2009;122:3-4.

7. Valery PC, Laversanne M, Clark PJ, Petrick JL, McGlynn KA, Bray F. Projections of primary liver cancer to 2030 in 30 countries worldwide. Hepatology 2017.
8. Liu J, Zhang S, Wang Q, Shen H, Zhang M, Zhang Y, Yan D, et al. Seroepidemiology of hepatitis B virus infection in 2 million men aged 21-49 years in rural China: a population-based, cross-sectional study. Lancet Infect Dis 2016;16:80-86.
9. Abara WE, Qaseem A, Schillie S, McMahon BJ, Harris AM. Hepatitis B Vaccination, Screening, and Linkage to Care: Best Practice Advice From the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2017;167:794-804.
10. Shah D. Impact of comprehensive exercise program on quality of life and psychopathology in kidney transplant population: A pilot study: ProQuest Information & Learning; 2016.
11. Rosen HR, Ghany MG, Chung RT, Lok ASF. NAM 2017 report: A national plan to eliminate hepatitis B and C in the United States by 2030 and the AASLD's response. Hepatology 2017;66:1020-1022.
12. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong DK, Pham B, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology 2010;139:1218-1229.
13. Tang CM, Yau TO, Yu J. Management of chronic hepatitis B infection: current treatment guidelines, challenges, and new developments. World J Gastroenterol 2014;20:6262-6278.
14. Chinese Society of Infectious Diseases, Chinese Medical Association; Chinese Society of Hepatology, Chinese Medical Association. [Guidelines for the prevention and treatment of chronic hepatitis B (version 2019)]. J Clin Hepatol 2019;35:2648 -2669. (in Chinese).
15. Zu J, Li M, Zhuang G, Liang P, Cui F, Wang F, Zheng H, et al. Estimating the impact of test-and-treat strategies on hepatitis B virus infection in China by using an age-structured mathematical model. Medicine (Baltimore) 2018;97:e0484.
16. Zhao S, Xu Z, Lu Y. A mathematical model of hepatitis B virus transmission and its application for vaccination strategy in china. Int J Epidemiol 2000;29:744-752.
17. Zhang T, Wang K, Zhang X. Modeling and Analyzing the Transmission Dynamics of HBV Epidemic in Xinjiang, China. PLoS One 2015;10:e0138765.
18. Lu FM, Li T, Liu S, Zhuang H. Epidemiology and prevention of hepatitis B virus infection in China. J Viral Hepat 2010;17 Suppl 1:4-9.
19. Wang SFC, X. P. [Overview of the development of liver transplantation in China](in Chinese). Chinese Journal of Organ Transplantation 2018;39(5).
20. Fu-Qiang C, Hui Z. Epidemics and control of hepatitis B in China. Chinese Journal of Viral Diseases 2018.
21. Chinese Center for Disease Control and Prevention. The Data-center of China Public Health Science. In. http://www.phsciencedata.cn/Share/en/index.jsp; 2019.
22. Zhang Q, Qi W, Wang X, Zhang Y, Xu Y, Qin S, Zhao P, et al. Epidemiology of Hepatitis B and Hepatitis C Infections and Benefits of Programs for Hepatitis Prevention in Northeastern China: A Cross-Sectional Study. Clin Infect Dis 2016;62:305-312.
23. National Bureau of Statistics of China. Chinese Statistical Yearbook. In. http://www.stats.gov.cn/english/Statisticaldata/AnnualData/; 2019.
24. Sharma SK, Saini N, Chwla Y. Hepatitis B virus: inactive carriers. Virol J 2005;2:82.
25. Wang H, Ru GQ, Yan R, Zhou Y, Wang MS, Cheng MJ. Histologic Disease in Chinese Chronic Hepatitis B Patients With Low Viral Loads and Persistently Normal Alanine Aminotransferase Levels. J Clin Gastroenterol 2016;50:790-

796.
26. Tseng TC, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, Hsu CA, et al. Serum hepatitis B surface antigen levels help predict disease progression in patients with low hepatitis B virus loads. Hepatology 2013;57:441-450.
27. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1-98.
28. Sun M, Li C, Li P, Lu J, Wang Y, Chang F, Li X, et al. Impact evaluation of the routine hepatitis B vaccination program of infants in China. J Public Health (Oxf) 2019;41:158-163.
29. World Health Organization. China: WHO and UNICEF estimates of immunization coverage: 2018 revision. In. https://www.who.int/immunization/monitoring_surveillance/data/chn.pdf; 2018.
30. World Health Organization; International Agency for Research on Cancer. Cancer Incidence in Five Continents Time Trends(CI5plus). In. http://ci5.iarc.fr/CI5plus/Default.aspx; 2019.
31. CDA Foundation. POLARIS observatory: hepatitis B in China. In. http://cdafound.org/polaris-hepB-dashboard/; 2019.
32. World Health Organization; International Agency for Research on Cancer. Globocan: 2018 China. In. http://gco.iarc.fr/today/data/factsheets/populations/160-china-fact-sheets.pdf; 2019.
33. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-132.
34. Chu CM, Liaw YF. HBsAg seroclearance in asymptomatic carriers of high endemic areas: appreciably high rates during a long-term follow-up. Hepatology 2007;45:1187-1192.
35. World Health Organization. Hepatitis B control. In. http://www.wpro.who.int/china/mediacentre/factsheets/hepatitis/en/; 2019.
36. U.S. Preventive Services Task Force. Hepatitis B Virus Infection: Screening, 2014. In. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-b-virus-infection-screening-2014; 2014.
37. Centers for Disease Control and Prevention. Hepatitis B Questions and Answers for Health Professionals. In: Who should be screened for HBV? https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm; 2018.
38. Fan R, Yin X, Liu Z, Liu Z, Lau G, Hou J. A hepatitis B-free generation in China: from dream to reality. Lancet Infect Dis 2016;16:1103-1105.
39. World Health Organization. Tenofovir reduces mother-to-child transmission of hepatitis B: new study. In. https://www.who.int/hepatitis/news-events/hbv-mtct-tenofovir/en/; 2016.
40. Zhang M, Wu R, Xu H, Uhanova J, Gish R, Wen X, Jin Q, et al. Changing incidence of reported viral hepatitis in China from 2004 to 2016: an observational study. BMJ Open 2019;9:e028248.
41. Huang H, Wang J, Li W, Chen R, Chen X, Zhang F, Xu D, et al. Serum HBV DNA plus RNA shows superiority in reflecting the activity of intrahepatic cccDNA in treatment-naive HBV-infected individuals. J Clin Virol 2018;99-100:71-78.
42. Yapali S, Talaat N, Lok AS. Management of hepatitis B: our practice and how it relates to the guidelines. Clin Gastroenterol Hepatol 2014;12:16-26.
43. Lim SG, Aghemo A, Chen PJ, Dan YY, Gane E, Gani R, Gish RG, et al. Management of hepatitis C virus infection in the Asia-Pacific region: an update. Lancet Gastroenterol Hepatol 2017;2:52-62.
44. Wu J, Zhou Y, Fu X, Deng M, Zheng Y, Tian G, Li Y, et al. The Burden of Chronic Hepatitis C in China From 2004 to 2050: An Individual-Based Modeling Study. Hepatology 2018.

Supplementary Materials Legends

Model construction methods

Supplementary Figure 1.Schematic of Markov model in TreeAge Pro software

Supplementary Figure 2. Markov chain diagram

CHB=chronic hepatitis B infected; DC=decompensated cirrhosis; HCC=hepatic cell carcinoma; LT=liver transplantation

Supplementary Table 1. Annual transition probabilities of chronic HBV infection in natural history

Figures in the table were cited from a hepatitis B model study performed in Shanghai, China. Since dramatically unbalanced medical and economic development across the whole country, further adjustment according to approved LT centers distribution, economic level and population of each province, previous LT statistical reviews and reports were necessary to accurately approach to the real figure. We hereby assume the probability of receiving LT was same as Shanghai's condition, however, only limited population was able to get access to or afford LT. The proportion was estimated to be 6%.

Supplementary Table 2. Annual transition probabilities of chronic HBV infection related to treatment

Supplementary Table 3. Estimated annual chronic HBV incidence and age distribution from 2006 to 2050

Estimated incidence and age distribution in 2006 derived from nation-wide survey data and population census data in National Bureau of Statistics of China; Thereafter annual incidence derived from China CDC; However, about 85% of reported incidence were chronic HBV infection according to Hui Zhuang's (expert in hepatology) article and China CDC unpublished data. Age distribution from published epidemiologic study. And we assumed incidence and age distribution after 2017 were the same.

Supplementary Table 4. Estimated annual chronic HBV incidence and age distribution from 2018 to 2050 in WHO target, ideal 1, ideal 2 scenarios

Estimated incidence derived from WHO global health sectors strategy on viral hepatitis. Age distribution was supposed to be the same with 2017.

Supplementary Table 5. Parameters of WHO target and ideal 2 scenarios

Figures in the years of 2017, 2020, 2030 were cited from published articles or WHO official data.

Red figures: Dx% and Tx/eligible% figures were calculated directly by linear estimation.

Tx|Dx% figures were calculated through the formula.

Supplementary Table 6. Validation of base-case intermediate model results to published data

Supplementary Table 7. Validation of modeled natural history to published data

Supplementary Table 8. Results of 1-way sensitivity analysis (Part I)

C, DC, HCC items' unit: million

LT items' unit: thousand

Supplementary Table 9. Results of 1-way sensitivity analysis (part II)

C, DC, HCC items' unit: million

LT items' unit: thousand

Additional results

Supplementary Figure 3. Cumulative Cirrhosis, DC, HCC, LT death

A: cirrhosis death; B: decompensated cirrhosis death; C: hepatocellular carcinoma death; D: liver transplantation death

Supplementary Figure 4. Annual Cirrhosis, DC, HCC, LT death number

A: cirrhosis death; B: decompensated cirrhosis death; C: hepatocellular carcinoma death; D: liver transplantation death

Supplementary Figure 5. Total chronic HBV infection prevalence

Supplementary Table 10. Population characteristics of chronic HBV infected in 2006

Supplementary Table 11. Cumulative and annual incidence number of complications and related-death

Figures

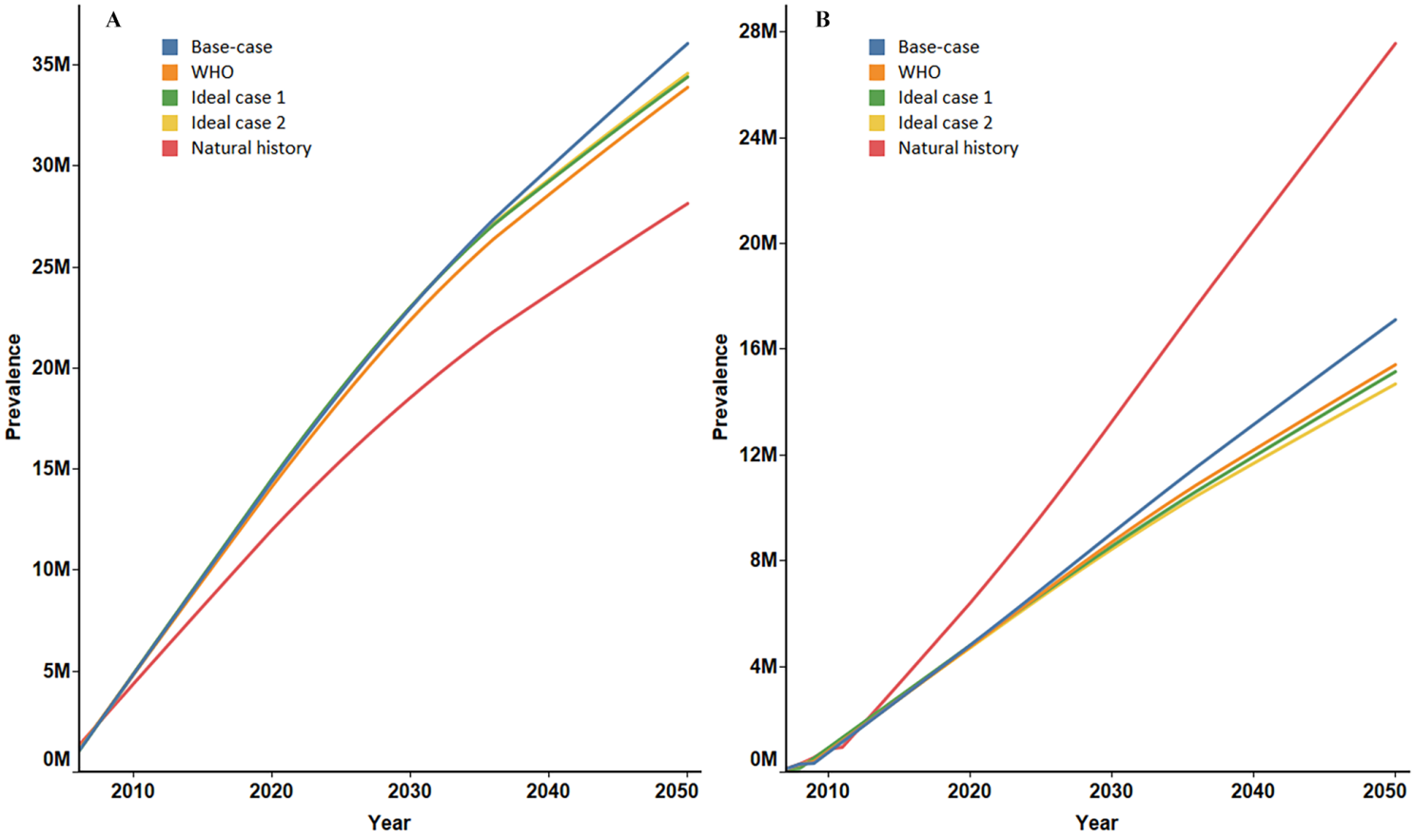

Figure 1

Cumulative incidence of HBsAg loss and HBV-related death A: HBsAg loss number; B: HBV-related death number HBV = hepatitis B virus

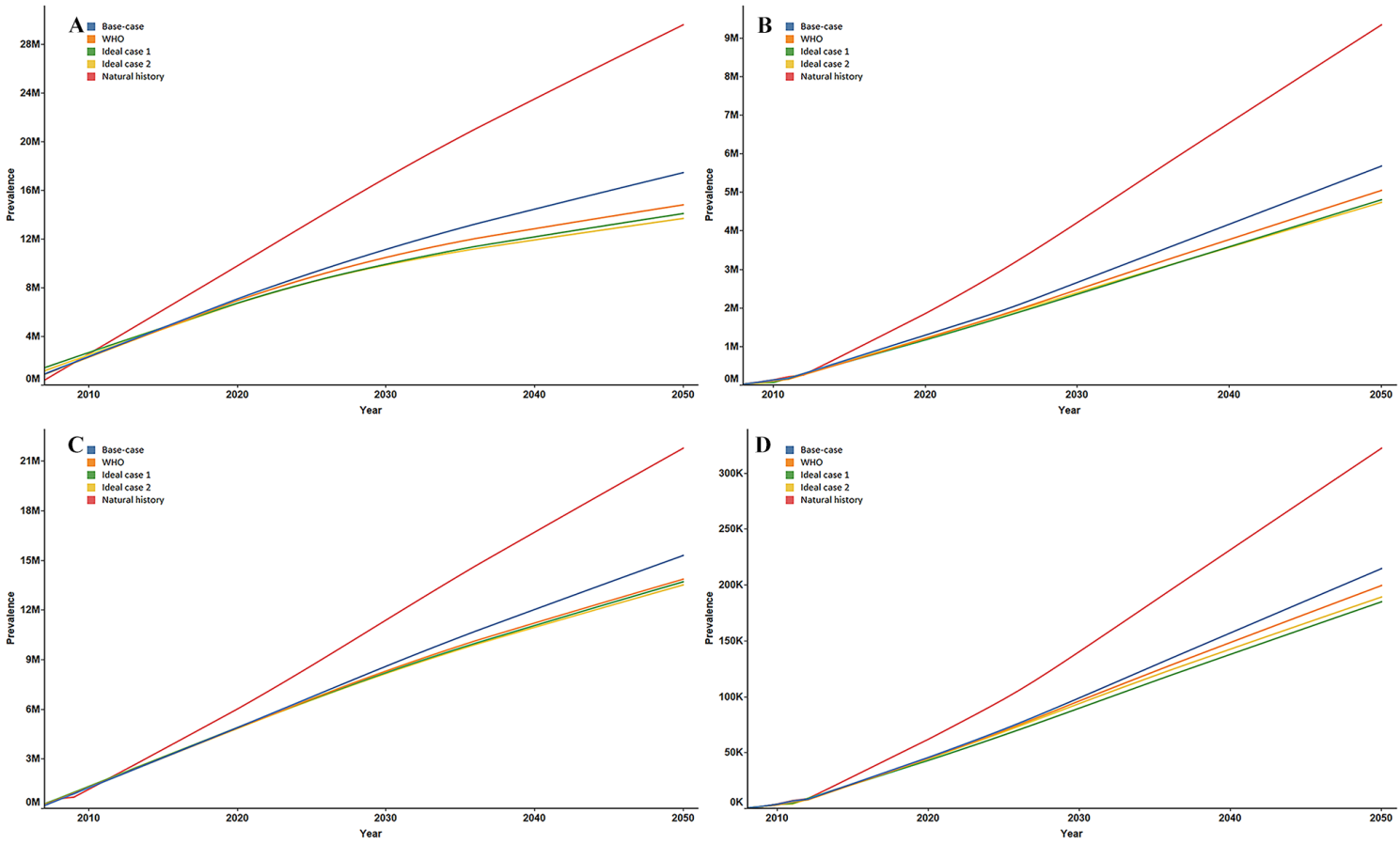

Figure 2

Cumulative incidence of Cirrhosis, DC, HCC, LT A: Cirrhosis incidence; B: DC incidence; C: HCC incidence; D: LT incidence DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LT = liver transplantation

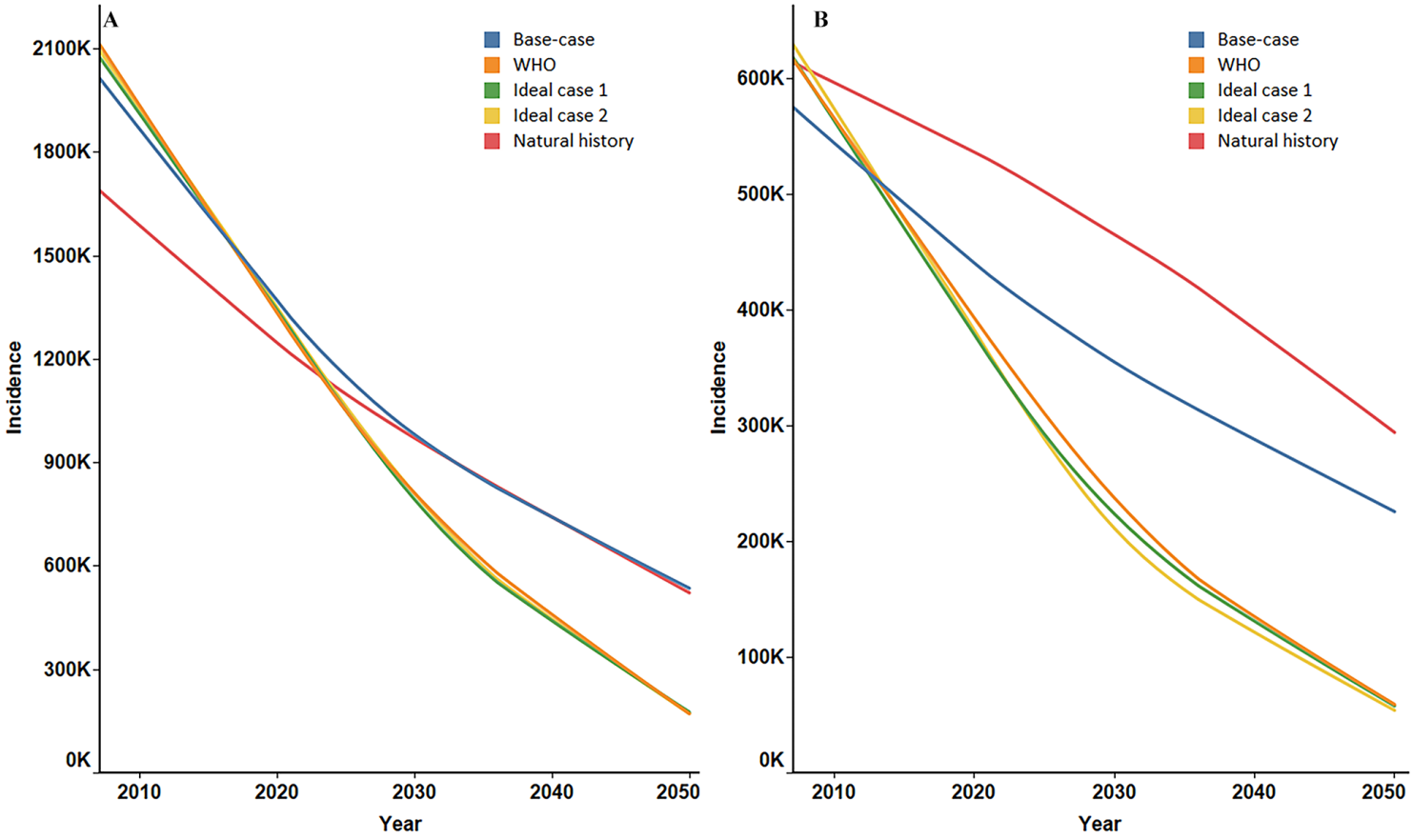

Figure 3

Annual incidence of Cirrhosis, DC, HCC, LT A: Cirrhosis incidence; B: DC incidence; C: HCC incidence; D: LT incidence DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LT = liver transplantation

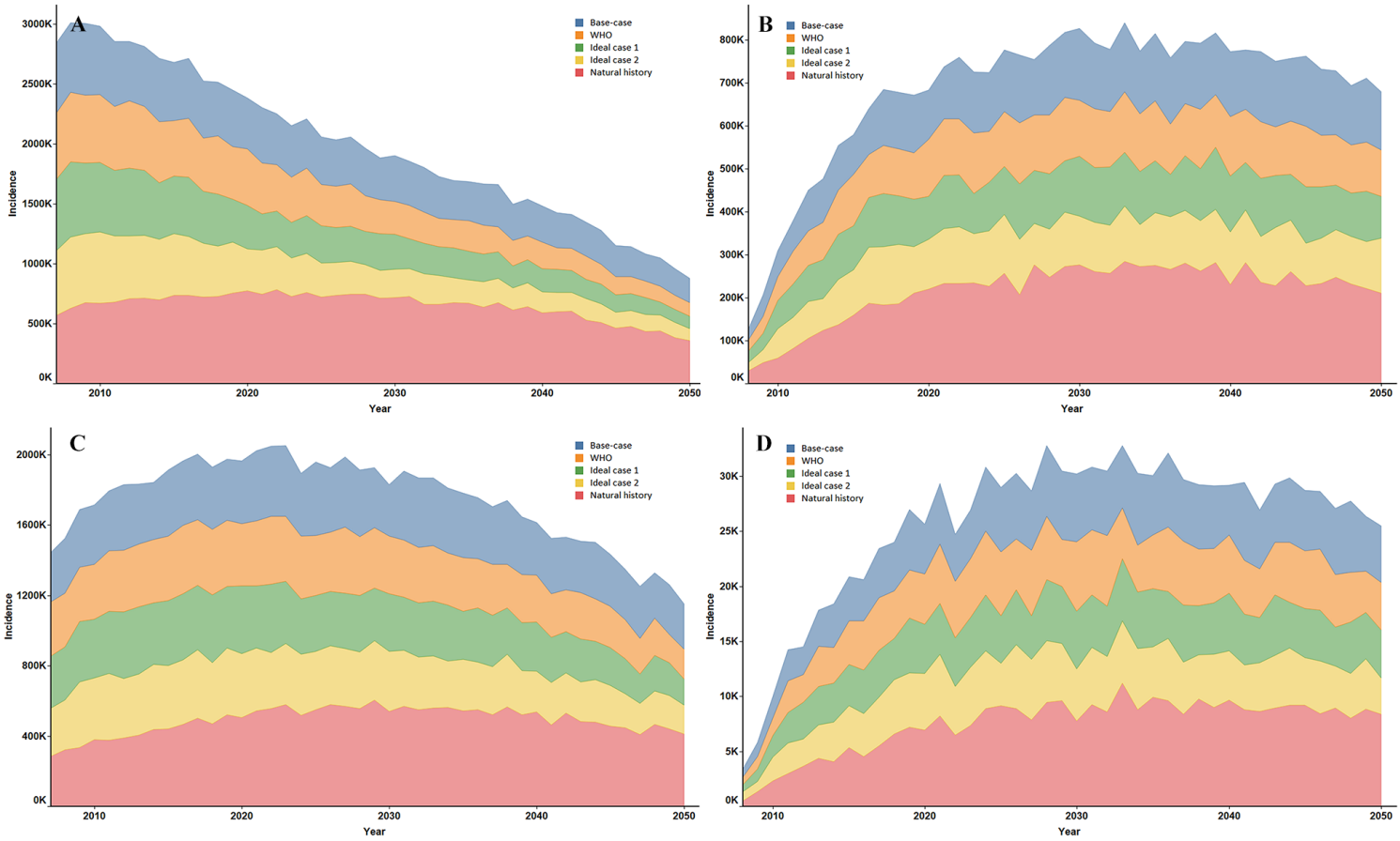

Figure 4

Annual incidence of HBeAg negative and positive hepatitis A: HBeAg positive hepatitis incidence; B: HBeAg negative hepatitis incidence HBeAg = hepatitis B e antigen

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials1.17VJ.docx