

Methods and Applications

Cost-Effectiveness Analysis of Sequential Screening Strategies for Hepatitis B Virus Infection by Birth Cohort — China

Lei Wang¹; Hui Zheng¹; Lanfang Xia¹; Guomin Zhang¹; Fuzhen Wang¹; Zundong Yin¹; Huaqing Wang^{1,*}

ABSTRACT

Introduction: Eliminating hepatitis B virus (HBV) as a major public health threat is a global health priority that requires cost-effective screening strategies. This study evaluated the cost-effectiveness of sequential birth cohort HBV screening strategies in China.

Methods: Using a Markov model, we compared five screening strategies with current practice, calculating HBV-related deaths averted, quality-adjusted life years (QALYs) gained, and incremental cost-effectiveness ratios (ICER). One-way deterministic and probabilistic sensitivity analyses were conducted to evaluate the robustness of the results.

Results: The sequential birth cohort screening strategy (Sequential Screening 1: screening the 1991–2000 cohort in 2025–2026, the 1971–1990 cohort in 2027–2028, and the 1951–1970 cohort in 2029–2030) was the most cost-effective, with an ICER of 58,523 Chinese Yuan (CNY) per QALY at a willingness-to-pay threshold of three times the per-capita Gross Domestic Product (GDP). An alternative strategy that prioritized the 1951–1970 cohort in 2025–2026 averted the most HBV-related deaths (approximately 3.44 million) and gained 24.9 million QALYs, with an ICER of 60,113 CNY per QALY, also showing cost-effectiveness.

Discussion: Our findings support sequential birth cohort screening as an optimal and innovative approach to achieving the WHO HBV elimination targets, offering evidence-informed guidance for policymakers to optimize screening programs and resource allocation.

Hepatitis B virus (HBV) infection poses a major global health challenge, with far-reaching implications for public health systems and individual well-being (1). Despite advances in medical science and availability of effective treatment, HBV remains a substantial health

burden worldwide. HBV is a major cause of cirrhosis of the liver and hepatocellular carcinoma, which are associated with high morbidity and mortality (2). The World Health Organization (WHO) has a goal of eliminating viral hepatitis as a major public health threat, aiming to reduce new infections by 90% and deaths by 65% by 2030 (3). Achieving these ambitious targets requires multi-faceted approaches, with effective screening being a cornerstone (4–5).

China has the heaviest burden of hepatitis B globally, with approximately 75 million people living with chronic HBV infection, accounting for nearly one-third of the infected population worldwide. In 2022, there were 450,000 deaths attributed to HBV-related diseases in China (6). Among the 75 million people living with chronic HBV infection, approximately 30 million are unaware of their infection status and, consequently, are unable to undergo standardized diagnosis and treatment. Among those who are aware of their HBV infection, 17 million require antiviral treatment, but only 3 million are receiving antivirals (7).

Screening for HBV is essential for detection and timely initiation of treatment to prevent disease progression (2,8). However, implementing a comprehensive screening program is challenging, particularly in resource-constrained settings. Costs associated with screening, including test kits, healthcare personnel, and infrastructure, must be carefully weighed against potential benefits. Cost-effective screening strategies are crucial to ensure that limited resources are allocated in a way that maximizes health outcomes (9).

This study evaluated the cost-effectiveness of birth cohort HBV screening strategies, focusing on sequential birth cohort screening with model-based simulations. Using advanced modeling techniques, we simulated the natural history of HBV infection, the impact of screening and treatment on disease progression, and the associated costs. Through a comprehensive analysis of different sequential birth cohort screening strategies, we identified the most cost-

effective approach.

METHODS

A Markov model was developed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA) to assess the cost-effectiveness of five HBV screening strategies in China. The model schematic is shown in [Figure 1](#). The model incorporated 6 disease states: chronic HBV carrier (Carrier), chronic hepatitis B (CHB), compensated cirrhosis (CC), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and HBV-related death; along with 3 care cascade states: undiagnosed, diagnosed but not on treatment, and on treatment. Annual disease progression probabilities (both natural and treatment-modified), along with cost and utility parameters derived from literature review, are presented in [Supplementary Table S1](#) (available at <https://weekly.chinacdc.cn/>). The model simulated long-term outcomes, including HBV-related deaths, costs, and quality-adjusted life years (QALYs). The initial population comprised 66,728,602 HBsAg-positive individuals aged 20–69 years (1951–2000 birth cohort), based on China's 2020 national HBV seroepidemiological survey (7). The initial distribution of health status and healthcare cascade among HBsAg-positive individuals is shown in [Supplementary](#)

[Table S2](#) (available at <https://weekly.chinacdc.cn/>).

Six Scenarios Were Compared

Status quo: maintaining current HBV testing practices without change, the diagnosis rate is predicted to reach 90% by 2040 and the treatment rate is predicted to reach 80% by 2050.

Targeted Screening 1951–2000: conduct targeted general population screening for the 1951–2000 birth cohort starting in 2025, aiming to achieve the WHO targets of 90% diagnosed and 80% under treatment by 2030.

Targeted Screening 1961–2000: conduct targeted general population screening for the 1961–2000 birth cohort starting in 2025, aiming to achieve the WHO targets of 90% diagnosed and 80% under treatment by 2030.

Targeted Screening 1951–1990: conduct targeted general population screening for the 1951–1990 birth cohort starting in 2025, aiming to achieve the WHO targets of 90% diagnosed and 80% under treatment by 2030.

Sequential Screening 1: screen the 1991–2000 birth cohort in 2025–2026, the 1971–1990 birth cohort in 2027–2028, and the 1951–1970 birth cohort in 2029–2030. Each stage aims to meet the WHO targets of 90% diagnosed and 80% under treatment.

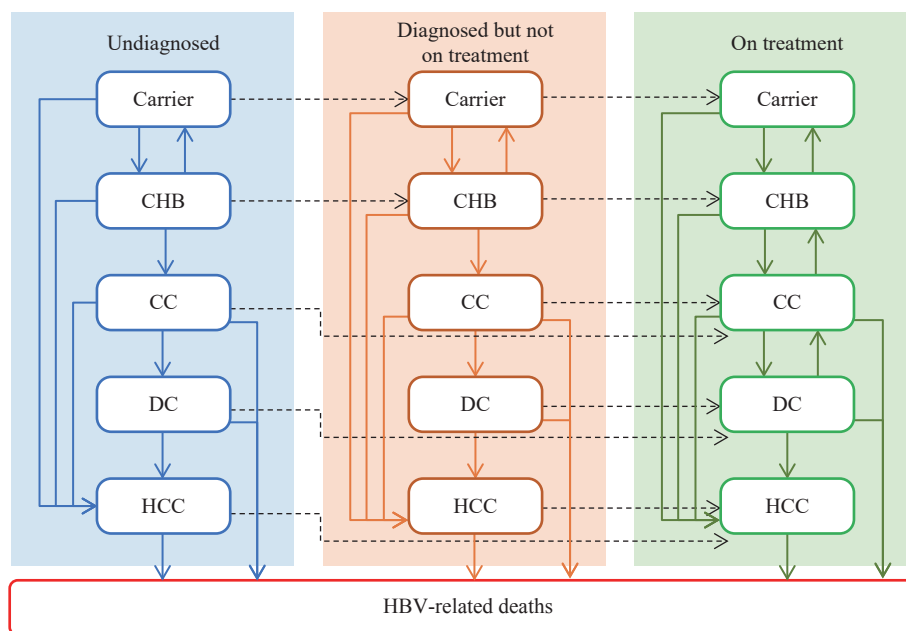


FIGURE 1. Markov model schematic for CHB natural history and care cascade transition simulation.

Note: Carrier, CHB, and CC can lead to natural, unrelated death (not shown).

Abbreviation: CHB=chronic hepatitis B; CC=compensated cirrhosis; DC=decompensated cirrhosis; HCC=hepatocellular carcinoma.

Sequential Screening 2: screen the 1951–1970 birth cohort in 2025–2026, the 1971–1990 birth cohort in 2027–2028, and the 1991–2000 birth cohort in 2029–2030. Each stage aims to meet the WHO targets of 90% diagnosed and 80% under treatment.

The screening approach used was the HBsAg/HBcAb rapid test. The treatment criteria adhered to the WHO guidelines for the prevention, diagnosis, care, and treatment of people with chronic hepatitis B infection (2). We calculated ICER to identify the additional cost per QALY gained between the status quo and the five screening strategies and determine the cost-effectiveness of each strategy. We adopted the WHO definition of cost-effectiveness, which is less than three times the per capita Gross Domestic Product (GDP) (10). Accordingly, the cost-effectiveness threshold was set at 287,247 Chinese Yuan (CNY, 2024). Future costs and QALYs were discounted at 3% per year.

We conducted probabilistic sensitivity analyses to characterize all model parameters' combined uncertainty with 1,000 Monte Carlo simulations. We conducted one-way deterministic sensitivity analyses to determine the effect of parameter uncertainty and model robustness.

RESULTS

Under the status quo, HBV-related deaths are projected to peak in 2029 at approximately 330,000 deaths annually. Based on the Global Health Sector

Strategy (GHSS) target of a 65% reduction in mortality, China will not meet this target until 2053 without intervention. The three targeted screening scenarios would significantly reduce HBV deaths, achieving the GHSS target by 2044. The Sequential Screening 1 strategy could achieve the GHSS target by 2036, while the Sequential Screening 2 strategy could achieve it by 2035 (Figure 2). The Targeted Screening 1951–2000, Targeted Screening 1961–2000, and Targeted Screening 1951–1990 strategies could avert 2.34 million, 2.33 million, and 2.13 million HBV-related deaths, respectively. The Sequential Screening 1 and Sequential Screening 2 strategies demonstrated superior outcomes, potentially averting 3.18 million and 3.44 million HBV-related deaths, respectively (Table 1).

Results of the cost-effectiveness analyses are presented in Table 1. Targeted Screening 1951–2000 was estimated to cost 2,454.3 billion CNY, with an incremental cost of 956.2 billion CNY, gaining 15.2 million QALYs and resulting in an ICER of 62,974 CNY per QALY gained. Targeted Screening 1961–2000 was estimated to cost 2,306.9 billion CNY, with an incremental cost of 935.1 billion CNY, gaining 15.7 million QALYs and yielding an ICER of 59,551 CNY per QALY gained. Targeted Screening 1951–1990 was estimated to cost 2,231.9 billion CNY, with an incremental cost of 893.0 billion CNY, gaining 13.6 million QALYs and producing an ICER of 65,519 CNY per QALY gained. Sequential Screening 1 was estimated to cost 2,843.1 billion

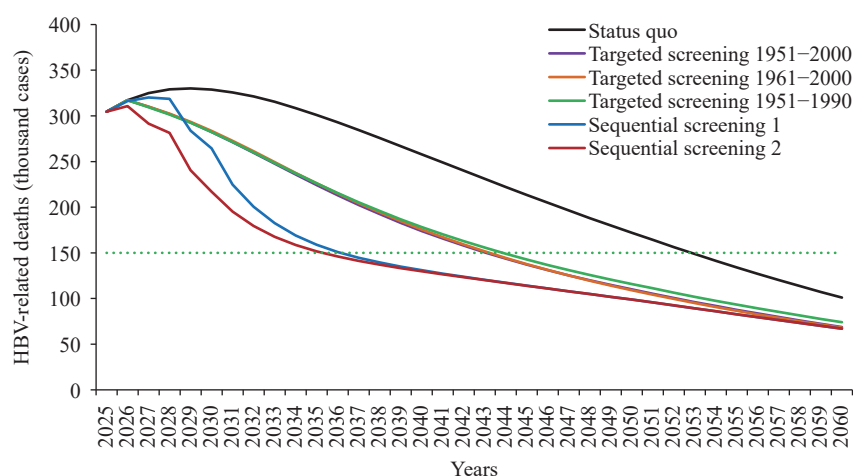


FIGURE 2. Impact of HBV screening strategies on HBV-related deaths from 2025 to 2060.

Note: The green dashed line represents the GHSS target of reducing HBV-related deaths by 65% in China (<150,000). In 2019, an estimated 470,800 hepatitis B-related deaths occurred in the Western Pacific Region, with China accounting for 90% (around 420,000). To meet the target, annual deaths need to be less than 150,000.

Abbreviation: HBV=hepatitis B virus; GHSS=Global Health Sector Strategy.

CNY, with an incremental cost of 1,345.0 billion CNY, gaining 23.0 million QALYs, with an ICER of 58,523 CNY per QALY gained. Sequential Screening 2 was estimated to cost 2,997.6 billion CNY, with an incremental cost of 1,499.6 billion CNY, gaining 24.9 million QALYs, with an ICER of 60,113 CNY per QALY gained. All strategies demonstrated cost-effectiveness under the threshold of three times per-capita GDP (287,247 CNY). The most cost-effective strategy was Sequential Screening 1.

As shown in Figure 3, the probability of a strategy being cost-effective depended on the willingness-to-pay threshold (0–3 times per-capita GDP). At a threshold of 287,247 CNY (3 times per-capita GDP), Sequential Screening 2 had a 100% probability of being cost-effective, outperforming the other strategies. Sequential Screening 2 remained the leading cost-effective strategy

until the threshold decreased to 0.78 times the GDP per capita (130,000 CNY), after which Sequential Screening 1 became the most cost-effective, with an 86.5% probability of being cost-effective at a threshold of 100,000 CNY. If willingness-to-pay decreased to 75,000 CNY, the Targeted Screening 1951–2000 strategy would become the most cost-effective. Sensitivity analyses demonstrated that variations in all parameters did not substantially affect the conclusion that the sequential birth cohort screening strategy was cost-effective under the threshold of 3 times per-capita GDP (Supplementary Figure S1, available at <https://weekly.chinacdc.cn/>).

DISCUSSION

WHO recommends HBV screening for individuals

TABLE 1. Effectiveness and cost-effectiveness for HBV screening strategies in China.

Scenario	HBV-related deaths averted (million)	Costs (billion CNY)	Incremental costs (billion CNY)	QALYs gained (million)	ICER cost/QALY gained
Targeted Screening 1951–2000	2.34	2,454.3	956.2	15.2	62,974
Targeted Screening 1961–2000	2.33	2,306.9	935.1	15.7	59,551
Targeted Screening 1951–1990	2.13	2,231.9	893.0	13.6	65,519
Sequential Screening 1	3.18	2,843.1	1,345.0	23.0	58,523
Sequential Screening 2	3.44	2,997.6	1,499.6	24.9	60,113

Abbreviation: HBV=hepatitis B virus; CNY=Chinese Yuan; QALY=quality-adjusted life years; ICER=incremental cost-effectiveness ratio.

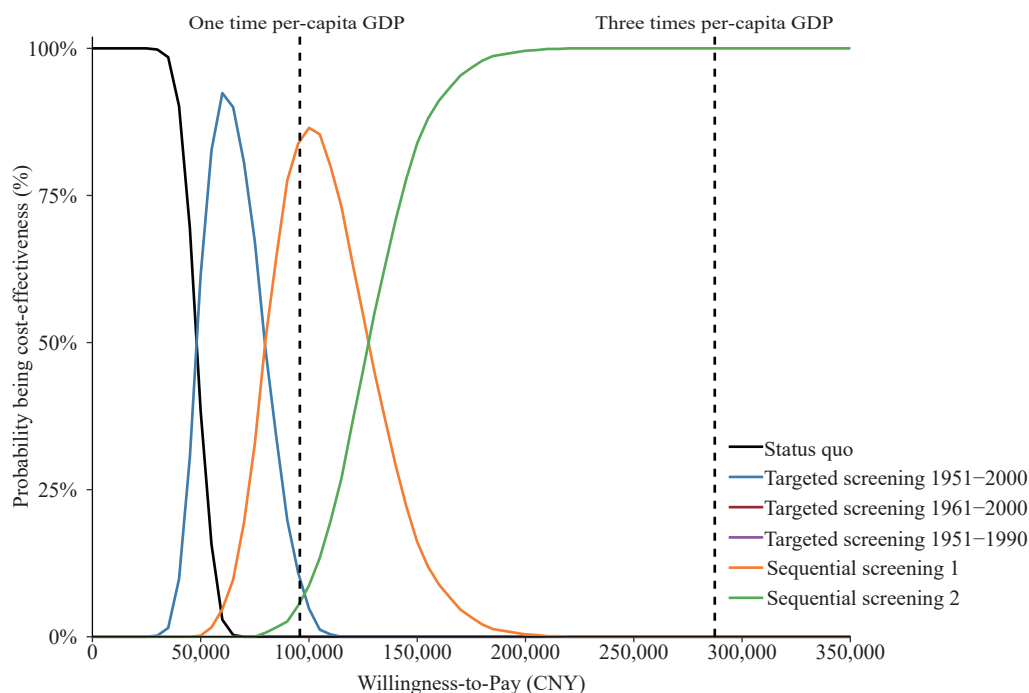


FIGURE 3. Cost-effectiveness acceptability curves for HBV screening strategies.

Abbreviation: GDP=gross domestic product; CNY=Chinese Yuan.

born in regions with HBsAg seroprevalence of 2% or higher (11–12). Traditional approaches such as universal population screening may not be economically viable, particularly in a large, populous country like China. While high-risk population screening reduces initial investment and can be implemented in resource-limited settings, it faces significant challenges in accurately identifying key risk groups — a process requiring extensive resources to establish reliable criteria and screening methods (13). In contrast, birth cohort screening offers a more targeted approach that accounts for the epidemiological characteristics of HBV infection. To our knowledge, this is the first economic evaluation of sequential birth cohort screening and treatment strategies for HBV in China.

Our study has several important program implications. First, without implementing a screening strategy, China will not achieve the GHSS target of a 65% reduction in mortality until after 2050, consistent with predictions by the Polaris Observatory Collaborators (14). If China implements HBV screening starting in 2025, the likelihood of achieving the GHSS targets of a 90% diagnosis rate and an 80% treatment rate by 2030 is small. Second, both targeted cohort screening and sequential cohort screening strategies are cost-effective, with targeted younger birth cohorts showing a lower ICER compared to older cohorts. Screening the 1951–2000 birth cohort, which includes people aged 60–69 years, resulted in a less favorable ICER due to the reduced lifespan of the older population compared with the 1961–2000 cohort. Screening younger people with longer life expectancy contributes more QALYs gained, similar to findings from a previous study of universal HBV screening in China (15). Third, sequential birth cohort screening averts more HBV-related deaths and gains more QALYs, with a lower ICER, compared to targeted cohort screening. Sequential screening enables each birth cohort to be screened more quickly, meeting the WHO targets of 90% diagnosis and 80% treatment sooner, thereby significantly averting more HBV-related deaths and gaining more QALYs. Fourth, our findings are robust and applicable to China as a whole or to individual provinces. Given the substantial variation in per-capita GDP across provinces, our probabilistic sensitivity analyses confirmed that sequential cohort screening strategies remain cost-effective even if the willingness-to-pay threshold is lowered to 0.78 times per-capita GDP (Figure 3). Understanding the cost-effectiveness of these strategies

provides valuable insights for policymakers and healthcare providers, enabling informed decision-making about resource allocation and implementation.

The Markov model constructed in this study and the innovative HBV screening strategy have several considerations for future application. First, this model is applicable in scenarios where data on HBsAg prevalence and disease distribution status of HBV-infected individuals are available. Second, for accurate predictions, model parameters need adjustment based on the efficacy of hepatitis B treatment medicines during application. Third, the model is not applicable in scenarios involving dynamic increases in HBsAg-positive individuals, liver transplantation, natural HBsAg loss, or hepatitis B medicine resistance.

In conclusion, this study strongly supports implementation of a sequential birth cohort screening strategy as a cost-effective approach to screening for HBV infection. Sequential birth cohort screening represents an optimal and innovative HBV screening strategy for China that can significantly contribute to achieving the WHO targets for HBV elimination. Our results provide valuable evidence for policymakers to optimize HBV screening programs and allocate resources efficiently.

Conflicts of interest: No conflicts of interest.

Acknowledgements: Dr. Lance Rodewald from the Chinese Center for Disease Control and Prevention for his valuable comments and assistance with editing the English language.

Funding: Beijing Natural Science Foundation (L212058).

doi: 10.46234/ccdcw2025.096

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Submitted: March 18, 2025

Accepted: April 16, 2025

Issued: April 25, 2025

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Parameters used in the Markov model.

Parameters	Base case	Lower bound	Upper bound	Data source
Natural disease progression				
From Carrier to				
CHB (Aged 20–39)	0.0023	0.0012	0.0035	(1–2)
CHB (Aged ≥40)	0.0054	0.0027	0.0081	(1–2)
HCC (Aged 20–29)	0.0018	0.0014	0.0022	(3–4)
HCC (Aged 30–39)	0.0019	0.0015	0.0023	(3–4)
HCC (Aged ≥40)	0.0033	0.0026	0.0040	(3–4)
From CHB to				
Carrier	0.0600	0.0480	0.0720	(3,5)
CC	0.0380	0.0220	0.0880	(3,6)
HCC (Aged 20–39)	0.0030	0.0024	0.0036	(3)
HCC (Aged ≥40)	0.0061	0.0049	0.0073	(3)
From CC to				
DC	0.0730	0.0350	0.1000	(1)
HCC	0.0340	0.0100	0.1200	(1)
HBV-related death	0.0310	0.0310	0.0380	(1)
From HCC to				
HBV-related death	0.4500	0.2200	0.7000	(1)
Disease progression on treatment				
From Carrier to				
CHB (Aged 20–39)	0.0012	0.0006	0.0017	(1–2) Assumed 50% reduction
CHB (Aged ≥40)	0.0027	0.0014	0.0041	(1–2) Assumed 50% reduction
HCC (Aged 20–29)	0.0012	0.0010	0.0014	(3)
HCC (Aged 30–39)	0.0014	0.0011	0.0016	(3)
HCC (Aged ≥40)	0.0018	0.0014	0.0022	(3)
From CHB to				
Carrier	0.0780	0.0624	0.0936	(7)
CC	0.0012	0.0012	0.0030	(8)
HCC (Aged 20–39)	0.0016	0.0013	0.0019	(3)
HCC (Aged ≥40)	0.0047	0.0033	0.0060	(3)
From CC to				
CHB	0.1350	0.0950	0.2420	(9)
DC	0.0050	0.0045	0.0190	(8)
HCC	0.0068	0.0028	0.0169	(8)
HBV-related death	0.0170	0.0120	0.0480	(1)
From DC to				
CC	0.2840	0.2530	0.3160	(10)
HCC	0.0217	0.0185	0.0249	(8)
HBV-related death	0.0790	0.0110	0.1440	(8)
From HCC to				
HBV-related death	0.1750	0.1000	0.2500	(8)

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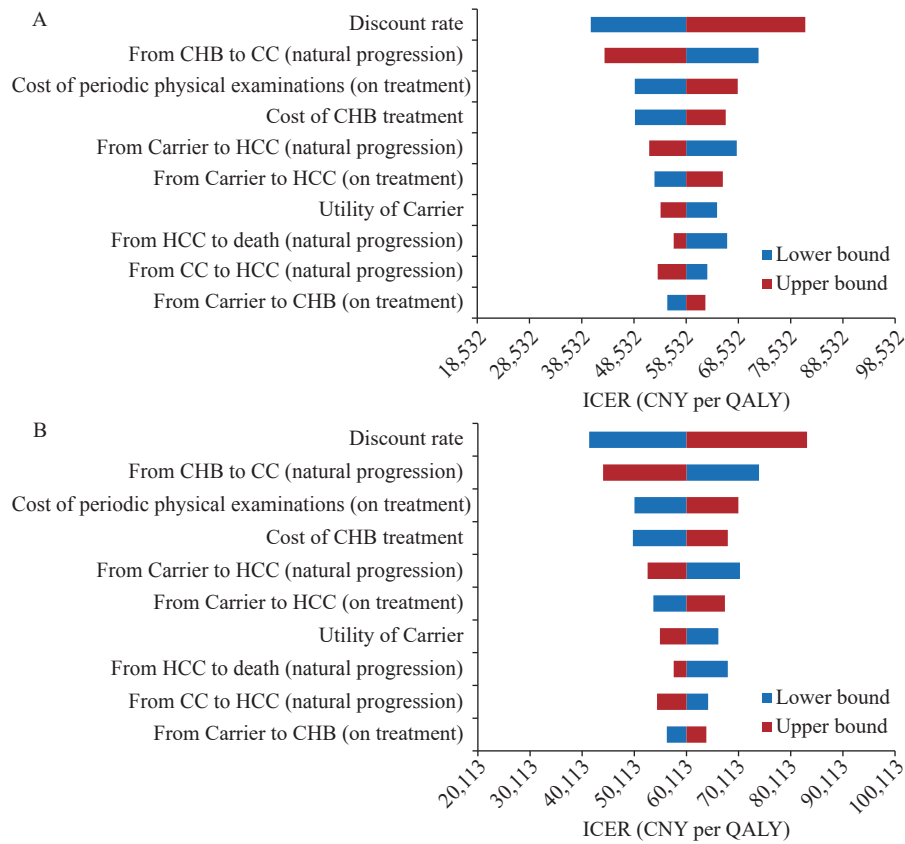
Parameters	Base case	Lower bound	Upper bound	Data source
Costs (CNY)				
HBsAg and HBcAb rapid test	5.0000	2.5000	7.5000	(11)
Screening program setup	28.0000	14.0000	42.0000	(12)
Follow-up management	5.0000	2.5000	7.5000	(13)
Generic entecavir or tenofovir	80.0000	60.0000	100.0000	(14)
CHB treatment	12,093.8800	6,953.3800	16,062.3100	(3)
CC treatment	30,108.1400	24,058.6900	36,157.5800	(1)
DC treatment	38,403.5200	30,733.9400	46,100.9100	(1)
HCC treatment	50,766.6300	40,607.7400	60,911.6100	(1)
Utility weight				
Carrier	0.7900	0.7400	0.8400	(1)
CHB	0.7500	0.7200	0.7900	(15)
CC	0.7300	0.6900	0.7800	(1)
DC	0.6500	0.6300	0.6700	(1)
HCC	0.3800	0.3600	0.4100	(1)
Discount rate: cost (%)	3.0000	0	6.0000	(16–17)
Discount rate: health outcome (%)	3.0000	0	6.0000	(16–17)

Abbreviation: HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; CHB=chronic hepatitis B; CC=compensated cirrhosis; DC=decompensated cirrhosis; HCC=hepatocellular carcinoma; CNY=Chinese Yuan.

SUPPLEMENTARY TABLE S2. Initial distribution of health status and health care cascade among HBsAg-positive individuals aged 20–69 years.

Gender	Age (years)	Undiagnosed						Diagnosed but not on treatment						On treatment						Total
		Carrier	CHB	CC	DC	HCC		Carrier	CHB	CC	DC	HCC		Carrier	CHB	CC	DC	HCC		
Male	20–24	317,747	94,235	2,577	0	0		444,151	131,723	3,602	0	0		28,125	8,341	228	0	0		1,030,729
	25–29	734,210	217,746	5,955	0	0		1,026,287	304,368	8,324	0	0		64,987	19,273	527	0	0		2,381,678
	30–34	1,236,095	472,137	18,173	0	5,117		1,727,828	659,958	25,402	0	7,152		109,411	41,790	1,609	0	453		4,305,123
	35–39	1,373,271	524,532	20,189	0	5,684		1,919,574	733,197	28,221	0	7,946		121,553	46,428	1,787	0	503		4,782,886
	40–44	1,273,107	495,821	16,280	2,171	5,246		1,779,565	693,064	22,757	3,034	7,333		112,687	43,887	1,441	5,397	484		4,462,254
	45–49	1,798,075	700,273	22,993	3,066	7,409		2,513,371	978,851	32,140	4,285	10,356		159,153	61,983	2,035	7,623	656		6,302,270
	50–54	1,817,219	496,986	46,781	5,546	10,851		2,540,131	694,693	65,391	7,753	15,168		160,848	43,990	4,141	13,790	960		5,924,248
	55–59	1,134,066	310,153	29,194	3,461	6,772		1,585,212	433,535	40,808	4,838	9,466		100,380	27,453	2,584	8,606	599		3,697,127
	60–64	886,172	213,868	14,265	9,130	17,575		1,238,702	298,948	19,940	12,762	24,567		78,438	18,930	1,263	22,700	1,556		2,858,815
	65–69	663,487	160,125	10,681	6,836	13,159		927,430	223,825	14,930	9,555	18,393		58,727	14,173	945	16,996	1,165		2,140,426
Subtotal		11,233,449	3,685,877	187,089	30,209	71,813		15,702,250	5,152,163	261,516	42,227	100,381		994,308	326,249	16,560	75,110	6,356		37,885,557
Female	20–24	174,970	49,233	0	0	0		244,575	68,818	0	0	0		15,487	4,358	0	0	0		557,441
	25–29	513,206	144,405	0	0	0		717,365	201,851	0	0	0		45,425	12,782	0	0	0		1,635,035
	30–34	1,227,544	180,630	0	0	4,112		1,715,876	252,486	0	0	5,747		108,654	15,988	0	0	364		3,511,401
	35–39	992,924	146,106	0	0	3,326		1,387,922	204,229	0	0	4,649		87,887	12,932	0	0	294		2,840,269
	40–44	1,277,043	254,880	6,527	1,865	4,507		1,785,067	356,275	9,124	2,607	6,300		113,035	22,560	578	4,637	399		3,845,404
	45–49	1,465,074	292,409	7,489	2,140	5,171		2,047,898	408,732	10,468	2,991	7,228		129,678	25,882	663	5,320	458		4,411,599
	50–54	1,411,760	287,905	23,428	3,991	7,809		1,973,375	402,438	32,748	5,579	10,916		124,959	25,483	2,074	9,924	691		4,323,083
	55–59	1,078,765	219,997	17,902	3,050	5,967		1,507,911	307,514	25,024	4,263	8,341		95,485	19,473	1,585	7,583	528		3,303,388
	60–64	661,592	106,519	5,619	6,331	12,187		924,781	148,894	7,854	8,850	17,035		58,560	9,428	497	15,741	1,079		1,984,967
	65–69	810,075	130,426	6,880	7,752	14,922		1,132,332	182,311	9,617	10,836	20,859		71,702	11,544	609	19,274	1,321		2,430,460
Subtotal		9,612,954	1,812,510	67,845	25,129	58,002		13,437,102	2,533,548	94,834	35,126	81,075		850,873	160,431	6,005	62,479	5,134		28,843,045
Total		20,846,403	5,498,387	254,934	55,338	129,814		29,139,352	7,685,711	356,350	77,353	181,456		1,845,181	486,680	22,565	137,589	11,490		66,728,602

Abbreviation: HBsAg=hepatitis B surface antigen; CHB=chronic hepatitis B; CC=compensated cirrhosis; DC=decompensated cirrhosis; HCC=hepatocellular carcinoma.



SUPPLEMENTARY FIGURE S1. Tornado diagram showing the 10 most impactful parameters from the one-way sensitivity analysis. (A) Scenario : Sequential screening 1; (B) Scenario : Sequential screening 2.

Abbreviation: CHB=chronic hepatitis B; CC=compensated cirrhosis; HCC=hepatocellular carcinoma; CNY=Chinese Yuan; QALY=quality-adjusted life years; ICER=incremental cost-effectiveness ratio.

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