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Research Paper

Cost-effectiveness of couple-based immunization strategy to prevent mother-to-child transmission of hepatitis B virus in China: A decision-analytic Markov model

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ABSTRACT

Background: Mother-to-child transmission (MTCT) is the major route of HBV transmission in many parts of the world. We designed couple-based immunization strategy and aimed to assess the cost-effectiveness of this strategy in China.

Methods: We constructed a decision-analytic Markov model to compared current immunization strategy consisting of hepatitis B vaccination (HepB) for all infants and extra hepatitis B immunoglobulin for infants with HBsAg-positive mothers versus couple-based immunization strategy including additional HBV screening for pre-pregnant couples and HepB for high-risk wives. Costs were assessed from a healthcare system perspective. Number of infants with perinatal HBV infection, life-years (LYs), quality-adjusted life-years (QALYs), and disability-adjusted life-years (DALYs) were used to access effects. We calculated incremental cost-effectiveness ratios (ICERs) and performed sensitivity analysis.

Findings: Based on the birth cohort of 17,578,815 livebirths in China in 2017, couple-based immunization strategy reduced perinatal HBV infection by 18% (9194/51,365) with cost increase of ¥ 41 million, saved 49,986 LYs (ICER: ¥819 per LY saved), gained 48,879 QALYs (ICER: ¥837 per QALY gained) and averted 63,362 DALYs (¥646 per DALY averted) compared with current immunization strategy. These ICERs were below willingness-to-pay levels of China's once GDP per capita (¥59,660), remaining robust in sensitivity analysis.

Interpretation: Under the intermediate endemic of HBV infection in China, implementation of couple-based immunization strategy can improve the efficiency of preventing MTCT of HBV, and is highly cost-effective. This strategy can be a new immunization strategy choice to achieve the target of eliminating hepatitis B by 2030.

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1. Introduction

Mother-to-child transmission (MTCT) is the major route of HBV transmission, and an important factor for the reservoir of chronic HBV infection in the populations of many parts of the world, especially in China and South-East Asia [1]. A literature has reported [2] that in the absence of prophylaxis, approximately 90% of the hepatitis B e antigen (HBeAg)-positive mothers transmit HBV to their offspring, compared with 10%–20% of HBeAg-negative carrier mothers. The risk of developing chronic HBV infection is 90% following acute infection in neonates [1,3].

In 1992, China actively responded to the call of WHO to include the infant hepatitis B vaccination (HepB) in the routine childhood immunization programme [4]. Since 2002, China integrated HepB into the expanded programme on immunization and provided free three doses of HepB for all newborns [5]. Reported coverages of three doses of HepB and timely birth-dose of HepB for infants was 99.58% and 95.61% in 2015, respectively [6]. At the end of 2010, China's Integrated Prevention of Mother-to-Child Transmission of HIV, Syphilis and Hepatitis B Virus programme (iPMTCT programme) was launched in 1156 counties (covering 41% of the country) [7], and iPMTCT programme has been extended nationwide since 2015 [8]. In iPMTCT programme, children born to screened mothers with hepatitis B surface antigen (HBsAg)-positive were extra provided with free hepatitis B immunoglobulin (HBIG; 100 IU) within 24 h after birth, in addition to three doses of HepB [7]. As of 2017, the national coverage of HBsAg screening test among pregnant women exceeded 99.5% and almost all (99.7%) of infants exposed to HBV received HBIG at birth [8].

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Research in context

Evidence before this study

We searched PubMed for articles published in English or Chinese before April 2019, with the terms "hepatitis B virus (HBV)", "economic" or "cost-effective", and "mother-to-child transmission (MTCT)" or "perinatal transmission". We identified cost-effectiveness of current immunization strategy consisting of HBsAg screening for pregnant women, HepB for all infants and extra HBIG for infants born to HBsAg-positive mothers to prevent MTCT of HBV has been reported in some studies. And some studies reported the cost-effectiveness of antiviral prophylaxis during pregnancy to prevent MTCT of HBV. However, no previous studies describing health effects or cost-effectiveness of couple-based immunization strategy including additional HBV screening for pre-pregnant couples and HepB for high-risk wives to prevent MTCT of HBV worldwide.

Added value of this study

In this study, using decision-analytic Markov model to access the cost-effectiveness of couple-based immunization strategy versus current immunization strategy to prevent MTCT of HBV in China. To our knowledge, this study first compared the lifetime costs and effectiveness in the couple-based immunization strategy versus the current immunization strategy under the intermediate endemic of HBV infection in China. Furthermore, the parameter data of the prevalence of HBV infection in pre-pregnant couples was from our group's published research on the nationwide level population-based HBV sero-epidemiological survey in China. Our findings add to the understanding of comprehensive prevention and control MTCT of HBV by additional immunization intervention basing on the current immunization strategy in developing countries.

Implications of all the available evidence

Preventing MTCT of HBV is one of the five core interventions to achieve the goals of World Health Organization to eliminate hepatitis B as a major public health threat by 2030. Evidence on how to achieve the target will be needed to help guide national policies. This study found that couple-based immunization strategy is more effective to prevent MTCT of HBV, is cost-effective at the threshold of one-time GDP per capita, and is feasible and affordable under the current conditions of China. Our results suggested that the couple-based immunization strategy could use as a new immunization strategy to control MTCT of HBV and to achieve the target of eliminating hepatitis B by 2030 in other countries with high or intermediate endemic of HBV. Future research should explore the effective strategies on curb HBV transmission in reproductive women and pregnant women to improve the efficiency of preventing MTCT of HBV.

However, the current immunization strategy does not completely block the MTCT of HBV. A meta-analysis in 2014 [9] has reported that the failure rate of the HBIG plus HepB prophylaxis for infants born to HBsAg-positive mothers was 4.87% in Chinese population. According to WHO estimates and the national serological survey in 2014 [5,10], under the intermediate endemic of HBV infection in China [11], about 50,000 children are born with HBV every year despite of the implementation of current immunization strategy. Although a few studies [12,13] have explained that antiviral therapy for pregnant women with high HBV-DNA load in the third trimester effectively decreased MTCT of HBV, it is still controversial whether antiviral therapy could be promoted as a public health strategy [1,14].

In order to reduce the failure rate of the current immunization strategy, it is vital to explore a new immunization strategy for China to prevent MTCT of HBV, and to achieve the target of 90% reduction of new cases of chronic HBV infections by 2030. Therefore, we designed a new immunization strategy, including additional HBV serological screening for pre-pregnant couples as well as HepB for HBsAg-negative wives of HBsAg-positive husbands basing on the current immunization strategy (named couple-based immunization strategy), to improve the efficiency of preventing MTCT of HBV. The aims of the couple-based immunization strategy were to reduce HBV infection in reproductive women, thereby reduce HBV infection in pregnancy and reduce the risk of MTCT of HBV. The aims of this study were to access the cost-effectiveness of couple-based immunization strategy by a decision-analytic Markov model; to access the costs, expected effects and feasibility of this immunization strategy; and to provide a new strategy proposal for controlling MTCT of HBV in China.

2. Methods

2.1. Comparator strategies

2.1.1. Current immunization strategy

This strategy includes universal HepB for all infants and extra HBIG for infants born to HBsAg-positive mothers. HBsAg screening is performed for all pregnant women. All infants receive the first dose of HepB within 24 h of birth, followed by the second and third dose of HepB at 1 and 6 months, respectively. In addition, extra HBIG ($\geq$100 IU) is provided within 24 h of birth (preferably within 12 h of birth) for infants born to HBsAg-positive mothers.

2.1.2. Couple-Based immunization strategy

This strategy includes universal HepB for all infants, HBIG for infants born to HBsAg-positive mothers, additional HBV serological screening for pre-pregnant couples and HepB for HBsAg-negative wives of HBsAg-positive husbands. That is, based on the current immunization strategy, additional HBV serological screening (including HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc) is provided for all pre-pregnant couples and HepB is given for all HBsAg-negative wives of HBsAg-positive husbands.

2.2. Model structure

In this economic evaluation, we constructed a decision-analytic Markov model to compare the costs and effects of the two immunization strategies to prevent MTCT of HBV. The baseline parameter values and plausible ranges were obtained from the literatures, and were summarized in Table 1.

We developed a decision tree (Figure S1) representing the two immunization strategies to prevent MTCT of HBV. According to internationally accepted definitions [1], we constructed a Markov model representing the health states of chronic HBV infection and progression (Figure S2), which consisted of nine health states: immune tolerant, immune active, inactive carrier, immune due to infection, HBeAg-negative chronic hepatitis B, compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC) and death. Transition parameters between health states were obtained from the published literatures home and abroad (Table 1). Population-based age-specific mortality rates were obtained from China Population & Employment Statistics Yearbook, 2018 [42].

2.3. Costs estimations

Costs in this study were assessed from a healthcare system perspective, including direct intervention costs and direct medical costs,

Table 1
Main model parameters.

Parameter	Base-case value	Deterministic range	PSA distribution	PSA parameters	Source
Epidemiological parameters					
Proportion of couples both tested HBsAg+ (%)	0.69%	±10%	Triangular	–	[15]
Proportion of couples only the wives tested HBsAg+ (%)	4.18%	±10%	Triangular	–	[15]
Proportion of couples only the husbands tested HBsAg+ (%)	5.6%	±10%	Triangular	–	[15]
Risk of HBsAg- wives being infected with HBV by HBsAg+ husbands after receiving HepB (%)	1%	0–5%	Uniform	low=0,high=5	[16,17]
Prevalence of HBsAg+ among pregnant women (%)	6%	±10%	Triangular	–	[10,18]
Risk of perinatal HBV transmission with HBIG and HepB (%)	4.87%	3.58–6.59%	Triangular	–	[9]
Risk of symptomatic HBV after perinatal infection (%)	1%	±50%	Beta	α=15.2,β=1505.07	[19]
Risk of infant fulminant hepatitis B after symptomatic infection (%)	0.1%	±50%	Beta	α=15.35,β=15,334.68	[20]
Risk of infant death from fulminant hepatitis B infection (%)	60%	–	–	–	[21,22]
Risk of infant chronic HBV infection after fulminant hepatitis (%)	33.3%	–	–	–	[22]
Risk of chronic HBV infection after perinatal infection (%)	89%	80–90	Beta	α=133,β=16.44	[19]
Discount: cost (%)	3%	0–6	Point estimate	–	[23]
Discount: effect (%)	3%	0–6	Point estimate	–	[23]
Livebirths in 2017	17,578,815	–	–	–	[24]
Life expectancy in 2015 (year)	76.3	–	–	–	[24]
Annual disease transition rates					
From immune tolerant to					
Immune active	Age<18:0.017	±50%	Beta	α=15.09,β=872.45	[25]
	Age≥19:0.1423	0.12–0.16	Beta	α=166.66,β=1004.52	[26]
Hepatocellular carcinoma	0.003	0–0.006	Beta	α=3.83,β=1271.86	[27]
From immune active to					
inactive carrier	0.125	0.1–0.15	Beta	α=83.91,β=587.37	[1]
HBeAg-negative chronic hepatitis B	0.005	0–0.05	Beta	α=0.15,β=29.43	[27]
Compensated cirrhosis	0.038	0.022–0.088	Beta	α=4.86,β=123.09	[26,28]
Hepatocellular carcinoma	0.011694	0.007999–0.016509	Beta	α=28.67,β=2422.6	[29]
From inactive carrier to					
HBsAg negative	0.014	0.005–0.03	Beta	α=4.74,β=333.65	[30-33]
immune active	0.0048	0.004–0.018	Beta	α=1.79,β=371.72	[26]
HBeAg-negative chronic hepatitis B	0.0268	0.0155–0.0471	Beta	α=10.73,β=389.63	[27]
Compensated cirrhosis	0.001	0.001–0.002	Beta	α=15.35,β=15,334.68	[20,26]
Hepatocellular carcinoma	0.00064	±50%	Beta	α=15.36,β=23,978.28	[34]
From HBeAg-negative chronic hepatitis B to					
Compensated cirrhosis	0.029	0.015–0.058	Beta	α=6.76,β=226.26	[26]
Hepatocellular carcinoma	0.003243	0.002407–0.004275	Beta	α=46.16,β=14,187.75	[29]
From compensated cirrhosis to					
Decompensated cirrhosis	0.039	0.032–0.046	Beta	α=114.56,β=2822.8	[35]
Hepatocellular carcinoma	0.048	0.030–0.066	Beta	α=25.96,β=514.85	[35]
Death	0.0555	0.031–0.080	Beta	α=18.56,β=315.92	[35]
From decompensated cirrhosis to					
Hepatocellular carcinoma	0.071	0.01–0.113	Beta	α=6.71,β=87.82	[26,35]
Death	0.17	0.10–0.25	Beta	α=16.21,β=79.15	[35,36]
From hepatocellular carcinoma to					
Death	0.34	0.22–0.45	Beta	α=21.82,β=42.36	[37]
Intervention costs (Chinese yuan ¥)					
HepB cost per infant	21	16–25	Triangular	–	[38]
HBsAg screening cost per pregnant women	8	6–10	Triangular	–	[38]
HBIG vaccination cost per infant	152	145–176	Triangular	–	[38]
HBV serological screening cost per couple	50	30–70	Triangular	–	Assumption
HepB cost per adult	60	40–80	Triangular	–	Assumption
Cost of HBV-related diseases (Chinese yuan ¥)					
Infant acute hepatitis B (symptomatic)	16,368	±20%	Triangular	–	[39,40]
Infant acute, fulminant hepatitis B	60,184	±20%	Triangular	–	[39,40]
Immune tolerant	440	±20%	Triangular	–	[41]
Immune active	3304	±20%	Triangular	–	[39,40]
Inactive carrier	440	±20%	Triangular	–	[41]
HBeAg-negative chronic hepatitis B	3241	±20%	Triangular	–	[39,40]
Compensated cirrhosis	35,764	20–120%	Triangular	–	[39,40]
Decompensated cirrhosis	45,611	±20%	Triangular	–	[39,40]
Hepatocellular carcinoma	60,302	±20%	Triangular	–	[39,40]
Health Utilities					
General population	0.82	0.800–0.840	Beta	α=1161.57,β=254.98	[38]
Immune tolerant	0.795	0.760–0.820	Beta	α=552.25,β=142.4	[38]
Immune active	0.76	0.660–0.795	Beta	α=116.12,β=36.67	[38]
Inactive carrier	0.795	0.760–0.820	Beta	α=552.25,β=142.4	[38]
HBeAg-negative chronic hepatitis B	0.75	0.720–0.795	Beta	α=383.41,β=127.8	[38]
Compensated cirrhosis	0.72	0.660–0.750	Beta	α=274.65,β=106.81	[38]
Decompensated cirrhosis	0.57	0.470–0.610	Beta	α=108.96,β=82.2	[38]
Hepatocellular carcinoma	0.51	0.390–0.570	Beta	α=59.94,β=57.59	[38]

See appendix for the disability weights of HBV-related diseases used for disability-adjusted life-years. PSA=probabilistic sensitivity analysis. HBsAg=Hepatitis B surface antigen. HBV=hepatitis B virus. HBIG= hepatitis B immunoglobulin. HepB=hepatitis B vaccination. HBeAg=hepatitis B e antigen.

measured in Chinese yuan (¥; ¥ 1 equivalent to 0.15 United states dollars) (Table 1).

Direct intervention costs were composed of the costs of HepB for infants, HBsAg screening for pregnant women, HBIG vaccination for infants born to HBsAg-positive mothers, HBV serological screening for pre-pregnant couples, and HepB for HBsAg-negative wives of HBsAg-positive husbands.

Direct medical costs were composed of the treatment costs and monitoring costs directly incurred by HBV infected persons.

2.3.1. Treatment costs of HBV-related diseases

This study determined the treatment cost parameters based on the results of the economic burden survey of HBV-related diseases among hospitalized patients in 12 cities in China in 2010 [39], and adjusted to the price level of 2017 with healthcare consumer price index [24]. One-time direct treatment costs of acute HBV infections and the annual direct treatment costs of chronic HBV infections were calculated. The treatment costs of immune active and HBeAg-negative chronic hepatitis B phases were determined based on the annual outpatient average direct medical costs, because we assumed that rarely hospitalizations were incurred for the initial stages of chronic HBV infection. The treatment costs of HBV-related CC, DCC and HCC phases were determined according to the annual average direct medical costs (including outpatient expenditure, inpatient expenditure, and expenditure of medicines self-purchased in retail). We used 20% of the CC cost for the lower range as hospitalizations were less common among patients with CC.

2.3.2. Monitoring costs of HBV-related diseases

WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection [1] recommend that treatment is not generally indicated in the immune tolerant and inactive carrier phases, but monitoring is required for disease progression at least once a year. Monitoring generally includes assessment of HBV serologic status, HBV-DNA load, blood routine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, serum albumin, prothrombin time, alpha-fetoprotein, liver ultrasound and liver stiffness measurement [43].

2.4. Health outcomes

We estimated the number of infants with perinatal HBV infection, and their lifetime advanced HBV-related diseases (CC, DCC, HCC) and HBV-related deaths, as well as life-years (LYs), quality-adjusted life-years (QALYs), and disability-adjusted life-years (DALYs) in the total birth cohort under each strategy. LYs represent an objective measure, but do not consider morbidity. Health utilities of HBV from the relevant domestic studies [38] were used for QALYs of HBV-related diseases (Table 1). Disability weights from the Global Burden of Disease Study 2013 [44] were used for DALYs of HBV-related diseases (Table S1).

2.5. Measurement of cost-effectiveness

We calculated the incremental cost-effectiveness ratio (ICER) between the current immunization strategy and the couple-based immunization strategy, which was defined as $\frac{Cost_2 - Cost_1}{Effectiveness_2 - Effectiveness_1}$.

Following the cost-effectiveness thresholds recommended by the WHO' Choosing Interventions that are Cost-Effective project when evaluating health interventions [23], the strategy was deemed cost-effective if the ICER was below the willingness-to-pay (WTP) threshold of three times of the country's annual gross domestic product (GDP) per capita. Highly cost-effective was defined if the ICER was below the WTP threshold of once the annual GDP per capita. According to China Health Statistics Yearbook [24], China's GDP per capita was ¥59,660 in 2017.

2.6. Statistical analysis

A decision-analytic Markov model was constructed in TreeAge Pro 2019, R1 (TreeAge Software, Inc., MA, USA, serial number: AMVLA-VQHD3-GBNQM-B). This decision-analytic Markov model was used to simulate costs and health outcomes in a birth cohort of 17,578,815 livebirths in China in 2017 [24], and was specified a 76-year cycle with a 1-year interval in accordance with the life expectancy of 76.3 years in China in 2015 (the life expectancy of China was unavailable in 2017) [24]. A half cycle correction was applied to estimate the costs and effectiveness. According to WHO guide to cost-effectiveness analysis, 3% discount rate was used for costs and effects [23,27].

2.7. Sensitive analysis

To access the robustness of the results, we performed both one-way deterministic sensitivity analysis and probabilistic sensitivity analysis. In the one-way sensitivity analysis, parameters were varied over plausible ranges to evaluate the impact of the parameters changes on the ICER. Probabilistic sensitivity analysis (PSA) was done to characterize the overall combined uncertainty of all the model parameters by using Monte Carlo simulations. The result of PSA was also presented in a cost-effectiveness acceptability curve, indicating the probability of cost-effectiveness through a variation of WTP.

3. Results

3.1. Costs of the two immunization strategies

We used the birth cohort of 17,578,815 livebirths in China in 2017, and calculated the total direct costs and Incremental direct costs (Table 2).

As shown in Table 2, the total direct costs in the current immunization strategy and the couple-based immunization strategy were close (¥ 5521 million vs. ¥ 5562 million, respectively). The direct intervention cost in the current immunization strategy was lower than the couple-based immunization strategy (¥ 670 million vs. ¥ 1579 million), while the direct medical cost of HBV-related diseases in the current immunization strategy was higher than the couple-based immunization strategy (¥ 4851 million vs. ¥ 3983 million). The couple-based immunization strategy required an additional ¥ 909 million direct intervention cost than the current immunization strategy, but avoided ¥ 868 million direct medical cost of HBV-related diseases, with a total direct cost increase of only ¥ 41 million.

Table 2
Costs of the two immunization strategies.

Immunization strategy	Total direct cost (CNY¥, millions)			Incremental direct cost (CNY¥, millions)		
	Intervention	HBV-related diseases	Total	Intervention	HBV-related diseases	Total
Current (Reference)	670	4851	5521	–	–	–
Couple-based	1579	3983	5562	909	−868	41

Table 3
Effects of the two immunization strategies.

Health outcomes Cases		Current (Reference)	Couple-based	Incremental
Perinatal HBV infection		51,365	42,171	−9194
HBV-related advanced diseases	Compensated cirrhosis	887	728	−159
	Decompensated cirrhosis	184	151	−33
	Hepatocellular carcinoma	237	195	−42
	Total	1308	1074	−234
HBV-related deaths		35,472	29,123	−6349
Life-years				
Life-years		519,479,550	519,529,536	49,986
Quality-adjusted life-years		425,929,148	425,978,028	48,879
Disability-adjusted life-years		12,437,165	12,373,804	−63,362

3.2. Effects of the two immunization strategies

We estimated the number of infants with perinatal HBV infection, and their lifetime HBV-related advanced diseases (CC, DCC, HCC) and HBV-related deaths, as well as LYs, QALYs, and DALYs in the total birth cohort under each strategy.

As shown in Table 3, under the current immunization strategy, 51,365 infants were perinatal HBV infection, with approximately 1308 of them developing HBV-related advanced disease (including 887 CC, 184 DCC, and 237 HCC) and 35,472 HBV-related deaths, and there were 519.48 million LYs, 425.93 million QALYs and 12.44 million DALYs in the total birth cohort. Under the couple-based immunization strategy, 42,171 infants were infected with HBV during perinatal period, with about 1074 of them developing HBV-related advanced disease (including 728 CC, 151 DCC, and 195 HCC) and 29,123 HBV-related deaths, and there were 519.53 million LYs, 425.98 million QALYs and 12.37 million DALYs in the total birth cohort. Compared with the current immunization strategy, the couple-based immunization strategy reduced perinatal HBV infection by 18% (9194/51365), correspondingly reduction of 234 HBV-related advanced disease (145 CC, 30 DCC, 39 HCC) and 6349 HBV-related deaths, meanwhile, saved 49,986 LYs, gained 48,879 QALYs and averted 63,362 DALYs in the total birth cohort.

3.3. Cost-effectiveness

As shown in Table 4, compared with the current immunization strategy, the couple-based immunization strategy was highly cost-effective, with ICER of ¥819 per LY saved, ¥837 per QALY gained and ¥646 per DALY averted, which were lower than China's once GDP per capita (¥59,660 in 2017).

3.4. Sensitive analysis

To access the robustness of the results, we performed both one-way sensitivity analysis and probabilistic sensitivity analysis.

In one-way sensitive analysis, we compared the couple-based immunization strategy versus the current immunization strategy (Fig. 1). The ICER remained below once GDP per capita for plausible ranges of all parameters, representing highly cost-effectiveness of the couple-based immunization strategy. Varying the proportion of couples only the wives testing HBsAg-positive between 3.76% and 4.60%, the ICER was always lower than once GDP per capita. Increasing the intervention cost of HBV serological screening for pre-pregnant couples from ¥50 to ¥70, the couple-based immunization strategy was still highly cost-effective, with an ICER increased from ¥837 to ¥8030 per QALY gained, while the cost was gradually reduced from ¥50 to ¥30, this strategy would have better cost-effective. When the risk of HBV transmission after receiving HepB for HBsAg-negative wives of HBsAg-positive husbands was 5%, the ICER was ¥5895 per QALY gained, while the risk was gradually decreased, the couple-based immunization strategy cost lower and accumulated more QALYs than the current immunization strategy.

The probability sensitivity analysis showed that the baseline result was reliable within 95% confidence interval of 1000 Monte Carlo simulation results (Figure S3). As the majority of points lay below and to the right of the WTP line of once GDP per capital, the dominance of the couple-based immunization strategy over the current immunization strategy was almost certain. This finding was also supported by the result of the cost-effectiveness acceptability curve in Fig. 2, indicating the probability of cost-effectiveness over a range of WTP thresholds, which showed that, couple-based immunization strategy had a 99.1% probability to be cost-effective at the WTP threshold of once GDP per capital.

Additionally, as today's children become tomorrow's adults, the infants born to HBsAg-positive mothers will decrease markedly. Extrapolating to 2030, the prevalence of HBsAg among pregnant women will be under 2%. To access the cost-effectiveness of the couple-based immunization strategy in the future, another probability sensitivity analysis was done (Figure S4), indicating that this strategy is still cost-effective but not as high as it is currently.

4. Discussion

In order to achieve the goals of WHO to eliminate hepatitis B as a major public health threat by 2030, exploring and implementing a more efficient immunization strategy to prevent MTCT of HBV is particular importance for either China or other low- and middle-income countries [45,46]. Based on the universal HepB for infants, Chinese government has added free HBsAg screening for all pregnant women, and the extra HBIG for all newborns born to HBsAg-positive mothers since the end of 2010, which has interrupted 97%

Table 4
Summary results for the two immunization strategies.

Immunization strategy	Average per person				ICER		
	Costs (CNY¥)	LY	QALY	DALY	CNY¥ per LY saved	CNY¥ per QALY gained	CNY¥ per DALY averted
Current (Reference)	314.09	29.5515	24.2297	0.7075	–	–	–
Couple-based	316.42	29.5543	24.2325	0.7039	819	837	646

LY=life-year. QALY=quality-adjusted life-year. DALY=disability-adjusted life-year. ICER= incremental cost-effectiveness ratio.

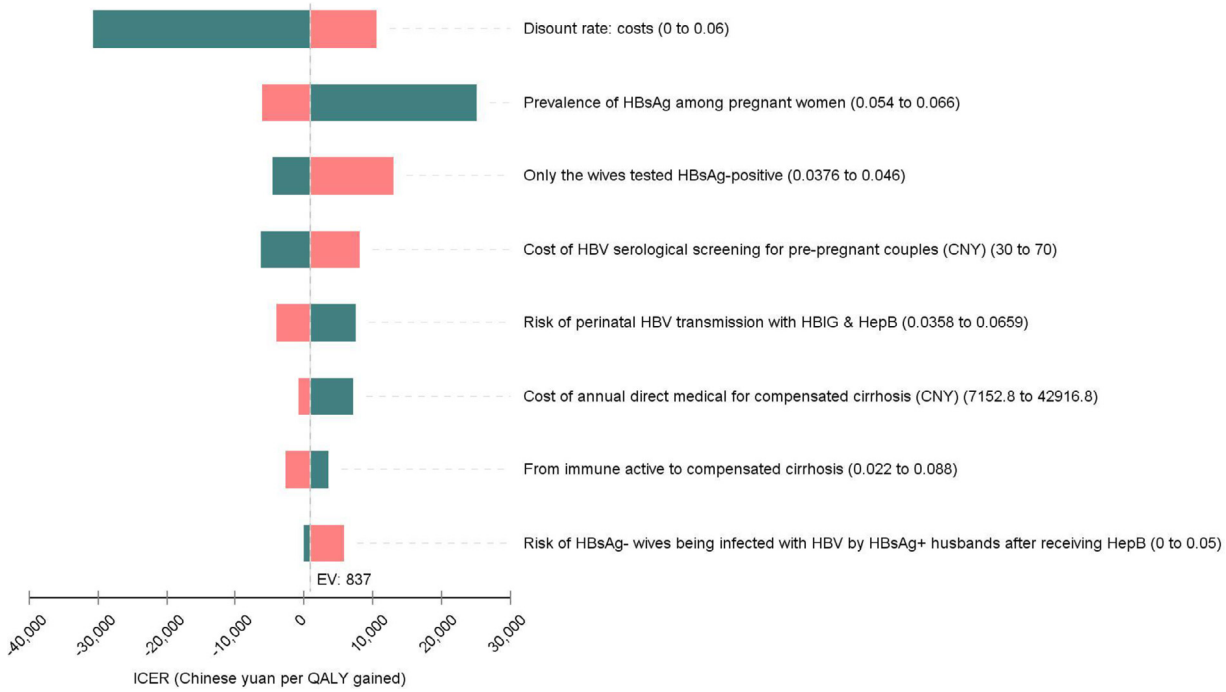

Fig. 1. Tornado diagram presenting one-way sensitive analyses. The bars are colored by parameter range: red represents higher range, and green represents lower range. ICER = incremental cost-effectiveness ratio. QALY = quality-adjusted life-year. HBsAg = hepatitis B surface antigen. CNY = Chinese yuan. HBIG = hepatitis B immunoglobulin. HepB = hepatitis B vaccination.

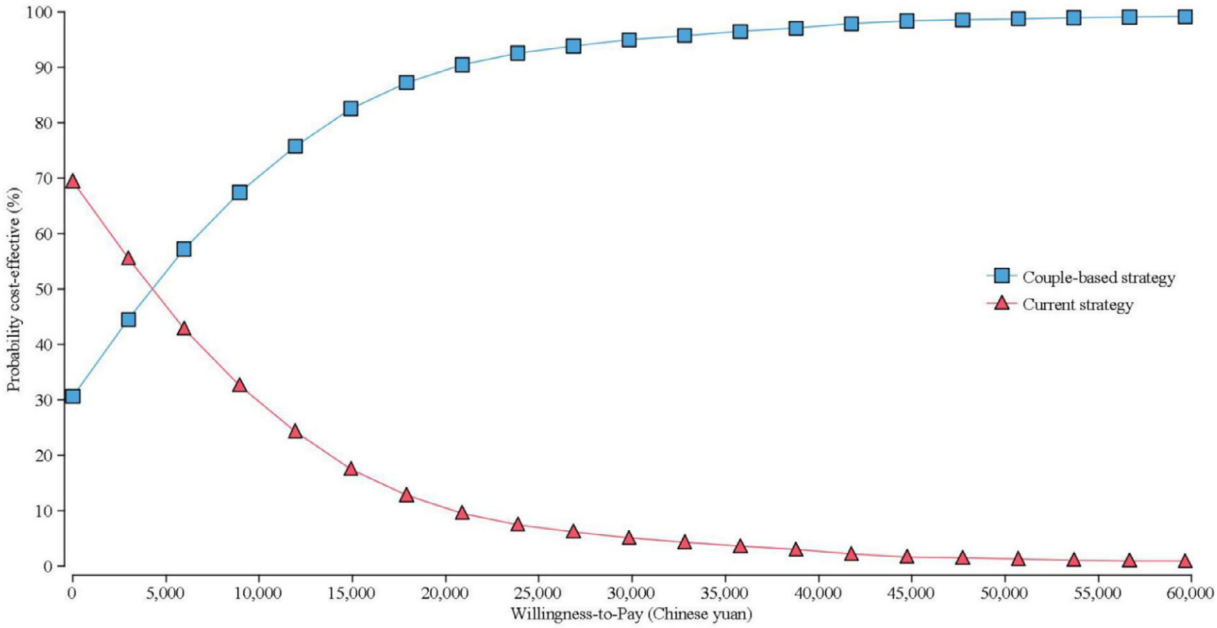

Fig. 2. Cost effectiveness acceptability curve. This figure represents the probability of cost-effectiveness over a range of willingness-to-pay thresholds per quality-adjusted life-year (QALY) gained.

of perinatal HBV infection [5]. Although the perinatal HBV infection has significantly reduced since the implementation of the current immunization strategy, 50,000 children are born with HBV every year in China [5,10]. Therefore, based on the current immunization strategy, this study designed couple-based immunization strategy to prevent MTCT of HBV, including additional HBV serological screening for pre-pregnant couples as well as HepB for HBsAg-negative wives of HBsAg-positive husbands, to reduce HBV infection in reproductive women, thereby reduce HBV infection in pregnancy and reduce the risk of MTCT of HBV.

The decision-analytic Markov model is widely used in the economic evaluation of hepatitis B worldwide, and it is also an important evidence for WHO's assessment of the resources needed to eliminate hepatitis B globally [21,47,48]. This study accessed the costs, effects and cost-effectiveness of the current immunization strategy versus the couple-based immunization strategy to prevent MTCT of HBV by a decision-analytic Markov model, and provided a new strategy proposal for controlling MTCT of HBV in China.

The results indicated that, in the birth cohort of China in 2017, the total direct costs in the current immunization strategy and the

couple-based immunization strategy were ¥ 5521 million and ¥ 5562 million, respectively. Under the current immunization strategy, 51,365 infants were perinatal HBV infection, with approximately 1308 of them developing HBV-related advanced disease and 35,472 HBV-related deaths, and there were 519.48 million LYs, 425.93 million QALYs and 12.44 million DALYs in the total birth cohort. Under the couple-based immunization strategy, 42,171 infants were infected with HBV during perinatal period, with about 1074 of them developing HBV-related advanced disease and 29,123 HBV-related deaths, and there were 519.53 million LYs, 425.98 million QALYs and 12.37 million DALYs in the total birth cohort.

Existing health economic analyses suggested that based on the universal HepB for infants, the HepB plus HBIG immunization for infants born to HBsAg-positive mothers was cost-effective to prevent MTCT of HBV. According to Donghoon Lee' study in South Korea [49], compared with the infant universal HepB strategy, the current immunization strategy had lower cost and higher effect. Lin Fan's research in American [22] showed that the current immunization strategy was cost-effective with ICER of $6957 per QALY gained compared with the infant universal HepB strategy. Yali Cai's study in China [41] indicated that the current immunization strategy reduced the cost by ¥502.09 while obtained 0.0059 QALY per capita, achieved better effect with lower cost.

Our analyses suggested that compared with the current immunization strategy, the couple-based immunization strategy reduced perinatal HBV infection by 18% (9194/51365) with cost increase of only ¥ 41 million, correspondingly reduction of 234 HBV-related advanced disease and 6349 HBV-related deaths. This strategy saved 49,986 LYs (ICER: ¥819 per LY saved), gained 48,879 QALYs (ICER: ¥837 per QALY gained) and averted 63,362 DALYs (¥646 per DALY averted) in the total birth cohort. According to China Health Statistics Yearbook [24], China's GDP per capita was ¥59,660 in 2017. The couple-based immunization strategy was highly cost-effective with ICER less than once the GDP per capita by the economic modelling analysis in the birth cohort of China in 2017.

Since 2010, Chinese government has launched the national preconception health examination project, and expanded it nationally in 2013, including free HBV serological screening for reproductive couples to prevent birth defects. Currently, Chinese government has implemented the infant universal HepB programme, the national preconception health examination project and the iPMTCT programme, which provided free HepB for infants, HBV serological screening for pre-pregnant couples, HBsAg screening for pregnant women and HBIG vaccination for infants born to HBsAg-positive mothers in all regions. Due to the high coverage of the above programmemes, each region already has corresponding health human resources and technical resources to find more HBsAg-positive couples, HBsAg-negative spouses of HBsAg-positive persons and HBsAg-positive pregnant women. Additionally, since September 2019, the National Health Commission incorporated the national preconception health examination project into the national basic public health service project, which further ensured the compliance of this project, thereby increased compliance with the new immunization strategy implementation. In a word, the excellent implementation of these national large-scale projects provides feasibility to implement the couple-based immunization strategy to prevent MTCT of HBV in China.

This study estimated that based on the current invests of the infant universal HepB programme, preconception health examination project and iPMTCT programme, according to the cost of HepB ¥60 per adult, Chinese government need to invest an additional ¥59 million to achieve the effects of the couple-based immunization strategy to prevent MTCT of HBV. The results of this study suggested that the implementation of couple-based immunization strategy was affordable under the level of China' economic development.

From our knowledge, this study first used the birth cohort of China in 2017 to do a decision-analytic Markov model of the immunization strategies to prevent MTCT of HBV. And this study first compared the number of infants with perinatal HBV infection, and their lifetime advanced HBV-related diseases (CC, DCC, HCC) and HBV-related deaths, as well as LYs, QALYs and DALYs in the total birth cohort under the couple-based immunization strategy versus the current immunization strategy. This study found that the couple-based immunization strategy was priority to prevent MTCT of HBV, and was feasible and affordable under the current conditions of China. Our results could provide a new immunization strategy to control MTCT of HBV, which will help to achieve the target of eliminating hepatitis B by 2030 in China.

It's worth noting that despite the implementation of the couple-based immunization strategy, a gap still remains to eliminate hepatitis B by 2030 in China. In addition to immunization strategies, antiviral therapy in the third trimester is the global focus. Some studies reported that antiviral therapy was effective in lowering the risk of MTCT among infants born to mothers with high HBV-DNA level when also given with birth dose vaccine and HBIG [12,13]. Additionally, a few studies have accessed the cost-effectiveness of antiviral therapy strategy [22,49]. However, a recent high-quality study of Jourdain [14] failed to show positive results of antiviral therapy to prevent MTCT of HBV, possibly warning against overtreatment. Maybe we should wait for the new WHO guidelines for preventing MTCT of HBV, which scheduled to be completed by mid-2020, [50] to discuss whether antiviral therapy could be promoted as a public health strategy. If antiviral therapy strategy is feasible, it will become a competing strategy for the couple-based immunization strategy in the coming years. As today's children become tomorrow's adults, the prevalence of HBsAg will gradually decrease, which will decrease the cost-effectiveness of the couple-based strategy. Therefore, the comparison between these two strategies would be useful for further research.

This study has several limitations to consider. Firstly, the validity of models depends largely on the veracity and reliability of the parameters in the models, however, we used some parameters of other countries, local areas or specific populations to estimate the lifetime costs and effects of the national birth cohort in China, which might have bias. For example, the parameters of the HBsAg prevalence among pre-pregnant couples is based on a single study that was conducted in rural China. Secondly, we assumed that all HBV-related mortality was due to CC, DCC and HCC, without considering liver transplantation or post-transplantation complications, because of the few applications relative to the large patient population in China. Thirdly, there are unmeasured potential costs and benefits of the couple-based immunization strategy. For ethical considerations, HepB should be offered/recommended to the HBsAg-negative husbands of HBsAg-positive wives in the couple-based immunization strategy, costs of which were not included in the current cost-effectiveness analysis. And we did not include the benefits of screening almost all young adults in China, contributing to achievement of the WHO target for identifying people with CHB, and the benefits of protecting the high-risk woman from HBV infection. Fourthly, the closer to pregnancy that the HBV screening for couples occurs, the less effective and cost-effective will be the strategy because risk would accrue between the start of intimacy until screening/vaccination. However, there is currently no relevant research evidence for us to conduct relevant sensitivity analysis. Finally, the WTP threshold depending on GDP per capital is a theoretical one to indicate whether an intervention is priority in the health-care agenda, which means other factors should be considered before an intervention is adopted on a national level.

In conclusion, our results suggest that under the intermediate endemic of HBV infection in China, the couple-based immunization strategy to prevent MTCT of HBV is highly cost-effective, feasible and affordable. Couple-based immunization strategy can be a new immunization strategy proposal for controlling MTCT of HBV and helping to achieve the target of eliminating hepatitis B by 2030. In the future,

with the changes in the prevalence of HBsAg among the population and the emergence of other strategies to prevent MTCT of HBV, further researches will be needed to clarify the more appropriate strategies.

Contributors

ML and JL conceived, designed, interpreted, and revised the report. WJ did a literature search, analysis and interpretation, compiled tables and figures, and drafted the report. YW and QM did a literature search, data collection. All authors participated in data analysis, interpretation, discussion, and writing of the report.

Ethics

Not required.

Declaration of competing interest

Authors declare no conflict of interest with the content of this article.

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Patient and other consents

Not applicable.

Data sharing

No additional data available.

Supplementary materials

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Reference

[1] WHO. Guidelines for the prevention, care and treatment of persons with chronic hepatitis b infection. http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf;jsessionid=C45FBB6C849F7F96F2213274A3FE2336?sequence=1 [Accessed March 2015].
[2] Okada K, Kamiyama I, Inomata M, Imai M, Miyakawa Y. e antigen and anti-e in the serum of asymptomatic carrier mothers as indicators of positive and negative transmission of hepatitis b virus to their infants. N Engl J Med 1976;294:746–9.
[3] Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009;373:582–92.
[4] Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Epidemiological serosurvey of hepatitis B in China—declining Hbv prevalence due to hepatitis B vaccination. Vaccine 2009;27:6550–7.
[5] Cui F, Shen L, Li L, Wang H, Wang F, Bi S, et al. Prevention of Chronic Hepatitis B after 3 decades of Escalating Vaccination Policy, China. Emerg Infect Dis 2017;23:765–72.
[6] Cui J, Cao L, Zheng J, Cao L, Duo M, Xiao Q. Reported coverage of vaccines in the National Immunization Programme of China. Chin J vacc and imm 2015;2017:601–7.
[7] Wang AL, Qiao YP, Wang LH, Fang LW, Wang F, Jin X, et al. Integrated prevention of mother-to-child transmission for human immunodeficiency virus, syphilis and hepatitis b virus in China. Bull World Health Organ 2015;93:52–6.
[8] Wang A, Qiao Y, Dou L, Wang Q, Wang X, Su M, et al. Challenges of eliminating mother-to-child transmission of HIV, syphilis and hepatitis B in China: a cross-sectional survey. Lancet 2018;392:S55.
[9] Lin X, Guo Y, Zhou A, Zhang Y, Cao J, Yang M, et al. Immunoprophylaxis failure against vertical transmission of hepatitis B virus in the Chinese population: a hospital-based study and a meta-analysis. Pediatr Infect Dis J 2014;33:897–903.
[10] WHO. Tenofovir reduces mother-to-child transmission of hepatitis B: new study. 2016. https://www.who.int/hepatitis/news-events/hbv-mtct-tenofovir/en/ [Accessed 2 April 2019].
[11] Liu J, Zhang S, Wang Q, Shen H, Zhang M, Zhang Y, 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;16:80–6.
[12] Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, et al. Tenofovir to prevent Hepatitis B transmission in mothers with high viral load. N Engl J Med 2016;374:2324–34.
[13] Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis b virus in real-life practice. Hepatology 2014;60:468–76.
[14] Jourdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khamduang W, Tierney C, et al. Tenofovir versus placebo to prevent perinatal transmission of Hepatitis B. N Engl J Med 2018;378:911–23.
[15] Liu J, Zhang S, Wang Q, Shen H, Zhang M, Zhang Y, et al. Prevalence of HBsAg/HBeAg amongst 1 936 801 couples preparing for pregnancy in rural China: an observational study. J Viral Hepat 2017;24:679–86.
[16] Liu C, Tang Y, Wang R, Sui J, Cai X, Zhang W. Evaluation of the immune effect of Chinese hamster ovary cell derived hepatitis b vaccine among adults. Chin Prev Med 2012;9:701–3.
[17] Zhang W, Han L, Lin C, Li L, Gao P, Lin H, et al. Study on the cellular and humoral immunity effect of recombinant Chinese hamster ovary cell hepatitis B vaccine in adults. Chin Prev Med 2010;10:918–22.
[18] Yin X, Liu Z, Liu Z, et al. Getting to zero mother-to-child transmission of hepatitis b virus: dream and challenge. Chin J Hepatol 2018;4:262–5.
[19] WHO. Hepatitis B vaccines: Who position paper - July 2017. Wkly Epidemiol Rec 2017;92:369–92.
[20] Hung HF, Chen TH. Probabilistic cost-effectiveness analysis of the long-term effect of universal hepatitis B vaccination: an experience from Taiwan with high hepatitis B virus infection and Hepatitis B e antigen positive prevalence. Vaccine 2009;27:6770–6.
[21] Yang P, Zhang S, Sun P, Cai Y, Lin Y, Zou Y. Development of Markov models for economics evaluation of strategies on hepatitis B vaccination and population-based antiviral treatment in China. Chin J Epidemiol 2017;7:845–51.
[22] Fan L, Owusu-Edusei Jr. K, Schillie SF, Murphy TV. Cost-effectiveness of active-passive prophylaxis and antiviral prophylaxis during pregnancy to prevent perinatal hepatitis b virus infection. Hepatology 2016;63:1471–80.
[23] WHO. WHO guide to cost-effectiveness analysis. 2003. https://www.who.int/choice/publications/p_2003_generalised_cea.pdf [Accessed 1 May 2019].
[24] National Health Commission of the People's Republic of China. The 2018 China health statistics yearbook. Beijing: China Union Medical University Press; 2018.
[25] Hong SJ, Park HJ, Chu MA, Choi BS, Choe BH. The rate of conversion from immune-tolerant phase to early immune-clearance phase in children with chronic hepatitis B virus infection. Pediatr Gastroenterol Hepatol Nutr 2014;17:41–6.
[26] Wong WW, Woo G, Heathcote EJ, Krahn M. Disease burden of chronic hepatitis B among immigrants in Canada. Can J Gastroenterol 2013;27:137–47.
[27] Nayagam S, Conteh L, Sicuri E, Shimakawa Y, Suso P, Tamba S, et al. Cost-effectiveness of community-based screening and treatment for chronic hepatitis B in the Gambia: an economic modelling analysis. Lancet Glob Health 2016;4:e568–78.
[28] Barbosa C, Smith EA, Hoerger TJ, Fenlon N, Schillie SF, Bradley C, et al. Cost-effectiveness analysis of the national perinatal hepatitis b prevention programme. Pediatrics 2014;133:243–53.
[29] Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168–74.
[30] Lim TH, Gane E, Moyes C, Borman B, Cunningham C. Serological and clinical outcomes of horizontally transmitted chronic hepatitis B infection in New Zealand Maori: results from a 28-year follow-up study. Gut 2015;64:966–72.
[31] EASL. 2017 Clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–98.
[32] Liu J, Lee MH, Batrla-Utermann R, Jen CL, Iloeje UH, Lu SN, et al. A predictive scoring system for the seroclearance of HBsAg in HBeAg-seronegative chronic hepatitis B patients with genotype B or C infection. J Hepatol 2013;58:853–60.
[33] Kobayashi M, Hosaka T, Suzuki F, Akuta N, Sezaki H, Suzuki Y, et al. Seroclearance rate of hepatitis B surface antigen in 2,112 patients with chronic hepatitis in Japan during long-term follow-up. J Gastroenterol 2014;49:538–46.
[34] Chen JD, Yang HI, Iloeje UH, You SL, Lu SN, Wang LY, et al. Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. Gastroenterology 2010;138:1747–54.
[35] Lin X, Robinson NJ, Thursz M, Rosenberg DM, Weild A, Pimenta JM, et al. Chronic hepatitis B virus infection in the Asia-Pacific region and Africa: review of disease progression. J Gastroenterol Hepatol 2005;20:833–43.
[36] Yin J, Ji Z, Liang P, Wu Q, Cui F, Wang F, et al. The doses of 10 mug should replace the doses of 5 mug in newborn hepatitis B vaccination in China: a cost-effectiveness analysis. Vaccine 2015;33:3731–8.
[37] Thiele M, Gluud LL, Fialla AD, Dahl EK, Krag A. Large variations in risk of hepatocellular carcinoma and mortality in treatment naive hepatitis B patients: systematic review with meta-analyses. PLoS One 2014;9:e107177.
[38] Lin Y, Zhang S, Yang P, Cai Y, Zou Y. Cost-effectiveness and affordability of strategy for preventing mother-to-child transmission of hepatitis B in China. Chin J Epidemiol 2017;7:852–9.
[39] Ma Q, Liang S, Xiao H, Zhang S, Zhuang G, Zou Y, et al. Survey of economic burden of hepatitis B-related diseases in 12 areas in China. Chin J Epidemiol 2017;7:868–76.
[40] Zhang S, Ma Q, Liang S, Xiao H, Zhuang G, Zou Y, et al. Annual economic burden of hepatitis B virus-related diseases among hospitalized patients in twelve cities in china. J Viral Hepat 2016;23:202–10.

[41] Cai Y. Economic evaluation of preventing for mother-to-child transmission of Hepatitis B virus and Prophylactic Entecavir use for community-based population in Shenzhen [Master]. Zhengzhou University; 2016.
[42] Department of Population and Employment Statistics NBoSoC. China population and employment statistics yearbook 2018. Beijing: China Statistics Press; 2019.
[43] Hou J, Wang G, Wang F, Cheng J, Ren H, Zhuang H, et al. Guideline of prevention and treatment for chronic Hepatitis B (2015 update). J Clin Transl Hepatol 2017;5:297–318.
[44] Salomon JA, Haagsma JA, Davis A, de Noordhout CM, Polinder S, Havelaar AH, et al. Disability weights for the global burden of disease 2013 study. Lancet Glob Health 2015;3:e712–23.
[45] Thomas DL. Global elimination of chronic hepatitis. N Engl J Med 2019; 380:2041–50.
[46] Liu J, Liang W, Jing W, Liu M. Countdown to 2030: eliminating hepatitis B disease, China. Bull World Health Organ 2019;97:230–8.
[47] Zhang S. Promoting hepatitis B elimination and laying emphasis on its economics evaluation. Chin J Epidemiol 2017;7:841–4.
[48] Nayagam S, Thursz M, Sicuri E, Conteh L, Wiktor S, Low-Beer D, et al. Requirements for global elimination of hepatitis B: a modelling study. Lancet Infect Dis 2016;16:1399–408.
[49] Lee D, Shin HY, Park SM. Cost-effectiveness of antiviral prophylaxis during pregnancy for the prevention of perinatal hepatitis B infection in South Korea. Cost Eff Resour Alloc 2018;16:6.
[50] WHO. WHO begins guideline development to stop mother-to-child transmission of hepatitis B. 2019. https://www.who.int/hepatitis/news-events/hbv-mtc-guidelines-development/en/. [Accessed 11 Nov 2019].