

RESEARCH PAPER



Cost-effectiveness of augmenting universal hepatitis B vaccination with immunoglobulin treatment: a case study in Zhejiang Province, East China

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ABSTRACT

Objective: To evaluate the cost-effectiveness of the current strategy combining universal vaccination with hepatitis B immunoglobulin (HBIG) treatment for infants of hepatitis B surface antigen (HBsAg) positive mothers compared with universal vaccination with hepatitis B vaccine only.

Methods: A decision tree model with a Markov process was constructed and used to simulate the lifetime of the birth cohort in Zhejiang Province during 2016. The current strategy was compared against universal vaccination with respect to costs and health effects. Costs were assessed from the health care system perspective. Health effects were measured by the number of hepatitis B virus (HBV) related diseases and deaths avoided and quality-adjusted life-years (QALYs) gained. The incremental cost-effectiveness ratio (ICER) is calculated and compared to standard willingness-to-pay thresholds. A one-way sensitivity analysis and a probabilistic sensitivity analysis (PSA) were performed to assess parameter uncertainties.

Results: Over the cohort's lifetime, 182 acute symptomatic infections, 2215 chronic infections, 872 cases of cirrhosis, 595 cases of hepatocellular carcinoma (HCC) and 1,350 HBV-related deaths among the cohort of 624,000 infants would be further avoided by the current strategy compared to universal vaccination. Universal vaccination was dominated by the current strategy that produced not only higher total QALYs, but also had lower costs. The results remained robust over a wide range of assumptions.

Conclusions: The current strategy was cost saving compared to universal vaccination, and continuing the current strategy is recommended to further decrease the burden of hepatitis B.

ARTICLE HISTORY

Received 21 May 2019
Revised 3 October 2019
Accepted 19 October 2019

KEYWORDS

Hepatitis B; mother-to-child; infection; cost-effectiveness; QALY

Introduction

The hepatitis B virus (HBV) is a well-known risk factor for liver diseases, including chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC)¹. In China, 78 million people are currently estimated to carry the hepatitis B surface antigen (HBsAg), amounting to almost a third of the chronic infections worldwide. Every year, approximately 300,000 Chinese people die from HBV-related liver cirrhosis and HCC, accounting for 37%–50% of worldwide mortality.² China has made great achievements in hepatitis B immunization. The hepatitis B vaccine (HepB) was first recommended for inclusion in the routine vaccination schedule for infants in 1992 and was subsequently integrated into the National Expanded Program of Immunization in 2002, contributing to the birth-dose HepB coverage of 70.7% in 1992 increase to 95.0% in 2014;³ the prevalence of HBsAg positivity in persons aged ≤5 years dropped nearly 30 times from 9.67% in 1992 to 0.32% in 2014.^{4,5} Currently, mother-to-child transmission (MTCT) has been a major mode of HBV transmission in China. Hepatitis B immunoglobulin (HBIG) in combination with HepB vaccination could generally further reduce MTCT to as low as 5%.⁶ In 2011, China launched a program for preventing mother-to-child transmission (PMTCT) of hepatitis B and has since augmented universal vaccination with

maternal screening and HBIG treatment. This program provides infants born to HBsAg-positive women with HepB plus HBIG within 24 h after birth, followed by completion of the HepB series, and infants born to HBsAg-negative women receive routine HepB series only.

Zhejiang is a relatively developed province in eastern China. However, the HBV disease burden in Zhejiang once was as high as many other places in China with high endemicity of HBV infection via MTCT.⁷ Since 1992, the HepB coverage rates for the birth dose and 3-dose schedule in Zhejiang Province have both remained above 90%, and the prevalence of HBsAg decreased from 2.16% in 2006 to 1.05% in 2014 in the age group of 1–29 years.⁸ Great improvements have been seen in HBV infection control in Zhejiang Province, which might be considered a representative sample for research.

Economic analyses of universal infant hepatitis B vaccination have been carried out by several studies in China and it has been shown to be cost-effective.^{9–11} However, most previous studies focused on the economic analysis of vaccines alone and did not include combinations of maternal screening test and the use of HBIG to augment a universal vaccination. Few economic studies have examined the current strategy of augmenting universal hepatitis B vaccination with immunoglobulin treatment. The

purpose of this study was to compare the current strategy combining universal vaccination with HBIG treatment for infants of carrier mothers versus no screening and with hepatitis B vaccine only. The results from this study will provide important and useful evidence and technical support for health policymakers to select the optimal HBV prevention strategy for eradicating the HBV infection.

Methods

Comparator strategies

In this economic evaluation, we compared the current strategy versus universal vaccination. The details of each strategy are as follows:

Universal vaccination: regardless of the HBsAg status of mothers, infants receive the initial dose of HepB within 24 h of birth, followed by the 2nd dose and the 3rd dose at 1 month and 6 months. Together, these doses constitute the primary 3-dose hepatitis B vaccination series (HepB3). No pregnant women are screened for hepatitis B surface antigen (HBsAg); no infants receive HBIG.

Current strategy: universal vaccination plus maternal screening for HBsAg. Infants born to HBsAg-positive women receive the first dose of HepB and HBIG within 24 h after birth, followed

by completion of the HepB series. Infants born to HBsAg-negative mothers receive the first dose of HepB within 24 h of birth and followed by completion of the HepB series; none receive HBIG.

Model

A decision tree was developed to represent the intervention characteristics of the current strategy, and Markov models combined with the decision tree were built to represent the protection state or the natural history of chronic HBV infection. The model is a single cohort analysis based on a closed population (no births) static model, in which both the number of cohort that change over time and herd immunity were ignored. Two preventive strategies against HBV infection were illustrated in our decision tree model (Figure 1). We identified ten mutually exclusive health states that indicate the progression of HBV morbidity from the susceptible state: susceptible to HBV, immune tolerance, HBeAg-positive chronic hepatitis B (CHB), inactive state, HBeAg-negative CHB, HBsAg clearance, compensated cirrhosis (CC), decompensated cirrhosis (DC), HCC, and death. The Markov process with annual cycles terminates either when all newborns expire or reach the life expectancy age of 81 (Figures 2–4).¹² The parameters used in the model were obtained from field surveys, program files,

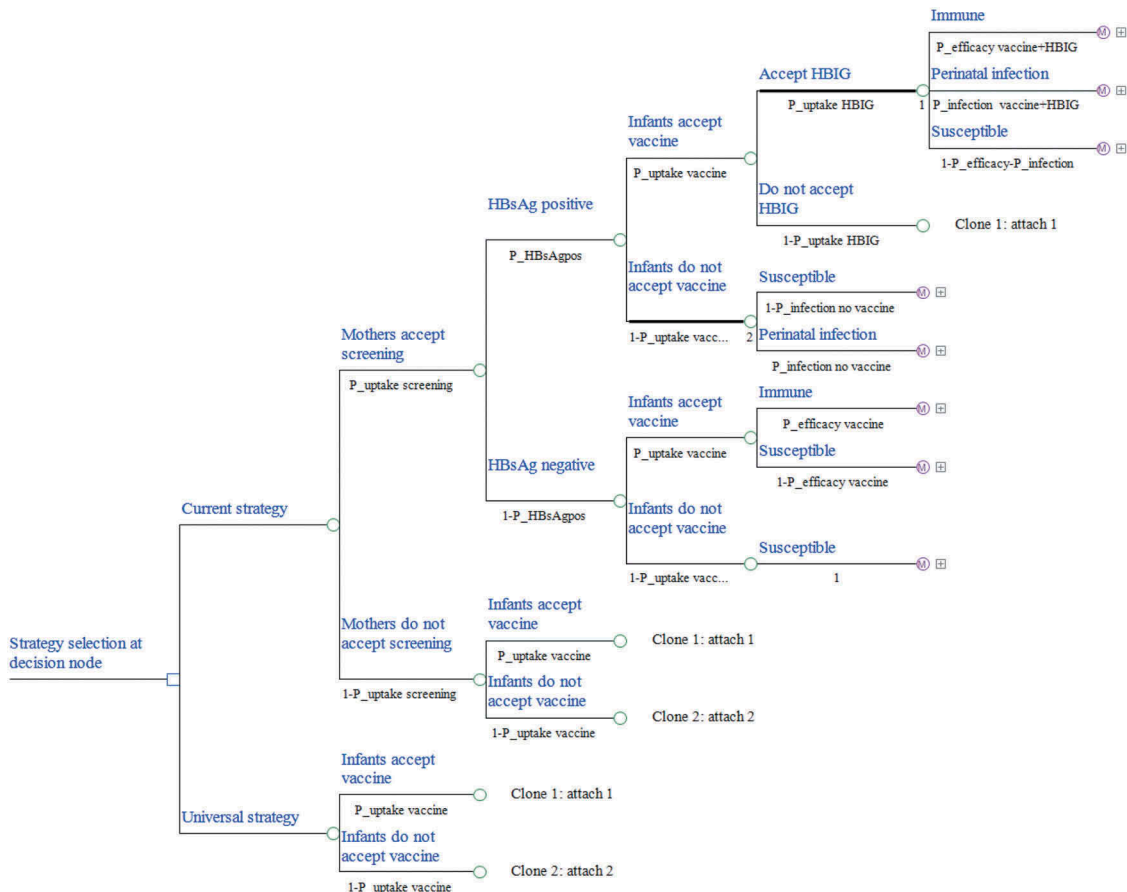


Figure 1. Decision tree model. A square node represents the decision node, a circular node represents a chance node and represents a Markov model. At the end of each branch of the decision tree there is one of three types of Markov models either corresponding to i. infants under immune ii. infants have got perinatal infection or iii. infants are susceptible. Under each line is a probability represented by P.; HBIG, hepatitis B immunoglobulin. If the tree is cloned, it means that the tree is copied, and a corresponding number will appear under the node of the tree.

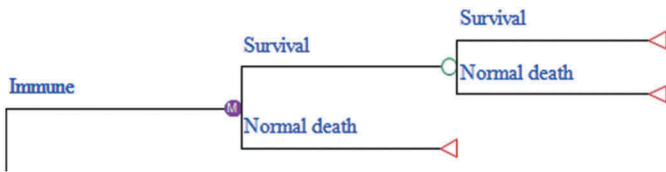


Figure 2. Markov model of protection.

published literature, and unpublished data from the Zhejiang Provincial CDC. The model was created in TreeAge Pro 2016 (TreeAge Software, Inc., Williamstown, MA).

Intervention coverage and epidemiological and efficacy parameters

According to the PMTCT project report, the HBsAg screening rate among pregnant women was 99.0%, and 99% of the infants born to HBsAg-positive mothers were administered HBIG. According to the China Information Management System for Immunization Programming (CIMSIP), the reported HepB3 coverage was 99.0% among all infants. The efficacy of immunization and the risk of perinatal infection varied according to maternal HBsAg status, vaccine and HBIG administration. For the infants of HBsAg-positive mothers administered HBIG plus the HepB3 vaccine, the efficacy could be 96.0%, compared to 90.6% for the HepB3 vaccine only. The rate of perinatal infection was 2.9% from HBsAg-positive mothers under immunoprophylaxis with HBIG and HepB3, compared to 5.9% under HepB3 only. The HBsAg-positive rate among pregnant women was 8.0%, which was derived from a meta-analysis by our team, including 10 studies conducted in Zhejiang Province. We made some assumptions that all individuals who are vaccinated would adhere to the full 3-dose vaccination series and that vaccine protection lasts for a lifetime. Detailed information is listed in Table 1.

The annual transition probabilities of health states in the Markov model were primarily obtained from the published literature, mainly from Chinese or Asian populations. A wide range was given to each of these parameters to cover the majority of reported data. For those parameters considered to be age-dependent, we adjusted the age-specific base-case values simultaneously by ±50% in the sensitivity analyses. All-cause mortality was taken from Zhejiang Provincial Bureau of Statistics. Specific values of the transition probabilities are listed in Table 2.

Cost estimations and health outcome measures

Costs in this study were assessed from a health care system perspective, including vaccination program costs and direct medical costs of HBV-related diseases.⁹ The vaccination program costs comprised the cost of the vaccine and the implementation cost. The implementation cost included the following five parameters: Administration, regular maintenance, low-value consumables and materials, immunization digital system

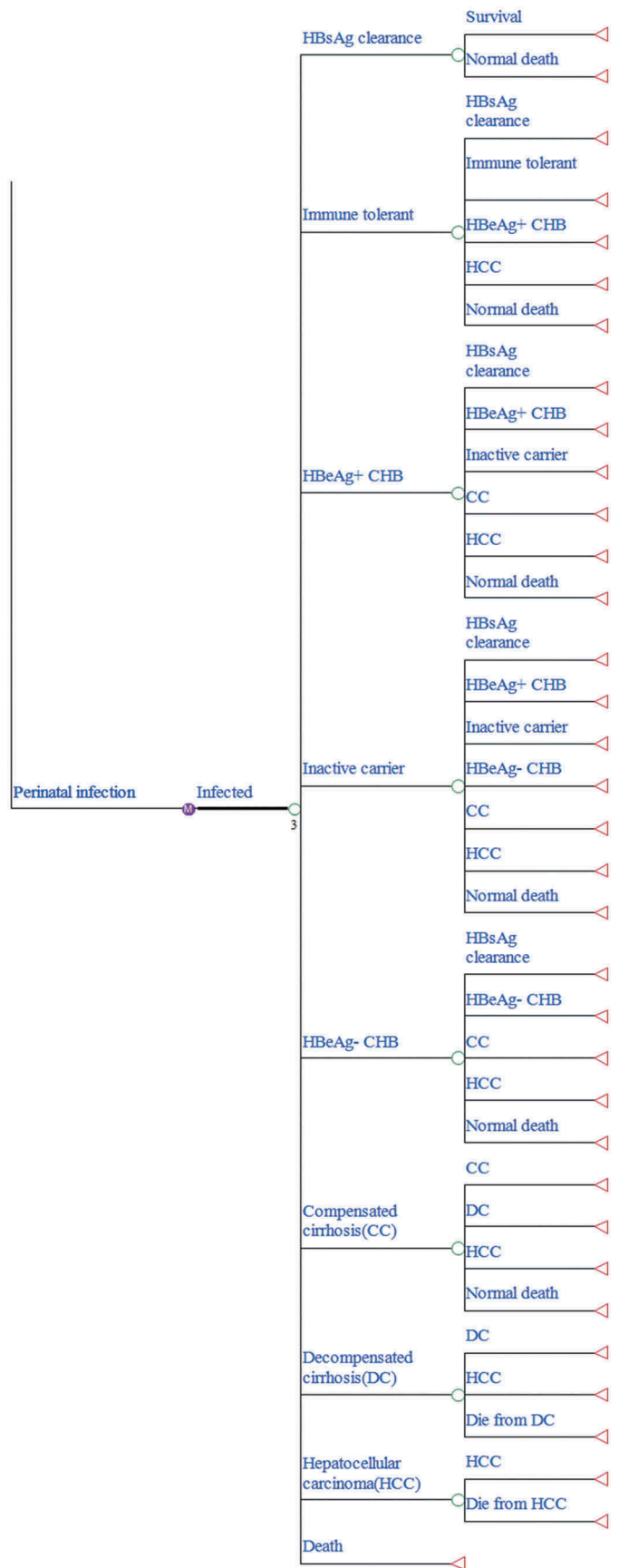


Figure 3. Markov model of perinatal infection and progression. A person in any state may die due to the other causes, but a person with decompensated cirrhosis or hepatocellular carcinoma may also die due to HBV infection.

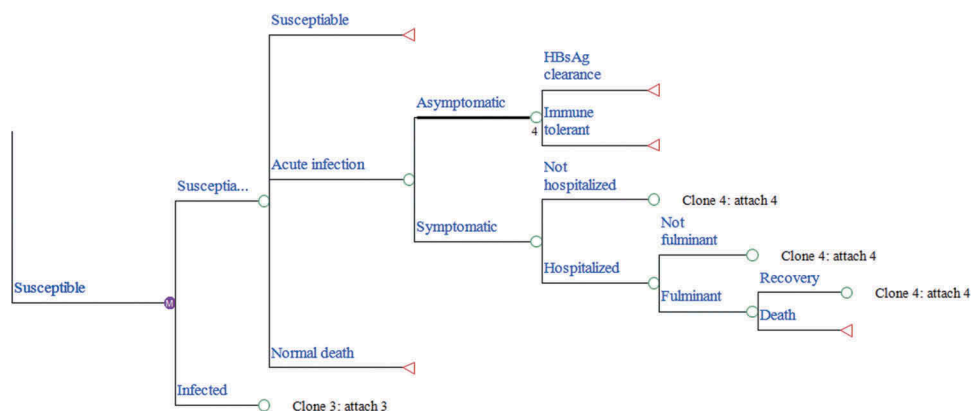


Figure 4. Markov model of hepatitis B virus (HBV) infection and progression. A susceptible individual would follow the HBV infection rate by age (see Table 2 for the detail formula).

Table 1. Parameter values including ranges used in the sensitivity analyses.

Parameters	Base-case value	Range	Reference
Newborns in 2016	624,000		
Vaccination-related data			
Cost of implementation (CNY/per dose)	19.55	± 25%	13
Vaccine price (CNY/per dose)	3.10	± 25%	a
HBIG price (CNY/per dose)	120.0	± 25%	a
Screening			
Maternal screening rate (%)	99.0	95-100	b
Cost (CNY/person)	15.0	± 25%	a
Coverage (%)			
HepB3 coverage	99.0	95-100	c
HBIG injection rate	99.0	95-100	b
Efficacy (%)			
HepB3 for general newborns	96.36	92.13-98.00	14-16
HepB3+ HBIG: HBsAg+	96.0	91.00-97.00	17-19
HepB3: HBsAg+	90.9	83.60-93.00	20-22
HepB3: HBsAg-	97.51	95.06-97.67	23-25
Epidemiology data (%)			
HBsAg positive rate among pregnant women	8.0	5.9-13.6	Meta,26
Prenatal infection rate			
HepB3 for general newborns	0.93	0.41-1.82	14,27,28
HepB3+ HBIG: HBsAg+	2.9	1.50-3.58	21,29,30
HepB3: HBsAg+	5.9	3.70-6.99	21,22,31
HBsAg+ mothers without vaccination	40.34	32.28-48.40	32,33
General newborns without vaccination	3.22	2.58-3.87	
Direct medical costs (CNY)			
Acute infection			
Not hospitalize after symptomatic	273.00	± 25%	d
Hospitalization after symptomatic	9,661.82		d
Fulminant	49,304.40		34
Immune tolerant	1,614.94		d
HBeAg-positive CHB	16,504.05		d
Inactive carrier	1,614.94		d
HBeAg-negative CHB	13,835.49		d
CC	19,139.21		d
DC	36,428.94		d
HCC	35,225.18		d
Utility score			
General Population	0.90	0.84-0.95	35
Acute infection			
Asymptomatic carrier/Not fulminant	0.75	0.66-0.84	d
Fulminant	0.46	0.24-0.68	36
Immune tolerant	0.81	0.81-0.82	36,37
HBeAg-positive CHB	0.77	0.75-0.79	d
Inactive carrier	0.81	0.80-0.82	36,37
HBeAg-negative CHB	0.77	0.74-0.79	d
CC	0.66	0.60-0.73	d
DC	0.56	0.53-0.60	d
HCC	0.58	0.52-0.65	d
Duration of protection	lifelong		38
Discount rate (%)	3	0 ~ 6	39

a: procurement prices by government in 2016; b: unpublished data from the Zhejiang Provincial CDC; c: reported coverage data from the China Information Management System for Immunization Program; d: data from the field survey

Table 2. Transition probabilities for each cycle of the Markov model.

Parameters	Base-case value	Range	Reference
HBV infection rate in susceptible people by age	$(b1 + b2 * \text{Exp}(b3 * \text{age})) * (1 - P_decrease)^{(24 + \text{age})}$		10,40
≥ 1 year	b1 = 0.034435 b2 = 0.494480 b3 = -0.729443 P_decrease = 0.02162	0.023542–0.045328 0.371654–0.617305 -0.942076~0.516809 0.02162–0.03243	
Outcome probabilities of acute infection			
Symptomatic			
< 15 years	0.05	0–0.5	9,41–43
≥ 15 years	0.3	0–0.5	
Hospitalization after symptomatic presentation	0.3	0.1–0.5	44
Fulminant cases among symptomatic presentation			
< 20 years	0.05	0–0.1	44
≥ 20 years	0.04	0–0.1	
Death among fulminant patients			
< 20 years	0.6	0.04–0.8	45,46
≥ 20 years	0.7	0.04–0.8	
Acute infections that become immune tolerant			
< 1 year	0.89	± 50%	47
≥ 1 year	$e^{(-0.65 * \text{age}^{0.46})}$		
From immune tolerant to:			
HBsAg positive CHB			
< 7 years	0.0043	± 50%	48
7–12 years	0.0067		
13–18 years	0.0294		
≥ 19 years	0.1423		49
HBsAg clearance			
< 19 years	0.0105	± 50%	50
20–39 years	0.0155		
≥ 40 years	0.043		
HCC			
< 30 years	0.0000288	± 50%	51,52
≥ 30 years	0.0003216		
From HBsAg positive CHB to:			
Inactive carrier	0.078	0.063–0.093	53
HBsAg clearance	0.013	0.002–0.028	54
CC	0.038	0.022–0.088	55
HCC			
< 30 years	0.0000288	± 50%	56
≥ 30 years	0.001175		
From inactive carrier to:			
HBsAg clearance	0.0342	0.0171–0.0513	54,57
HBsAg negative CHB	0.0427	0.02–0.05	57
HBsAg positive CHB	0.006	0–0.011	53
CC	0.001	0.0005–0.0015	49
HCC			
< 30 years	0.0000288	± 50%	56
≥ 30 years	0.0006		
From HBsAg negative CHB to:			
HBsAg clearance	0.02	0.0050–0.0262	58–61
CC	0.029	0.015–0.058	49
HCC			
< 30 years	0.0000288	± 50%	62
≥ 30 years	0.000286		
From CC to			
DC	0.073	0.035–0.1	63
HCC	0.0316	0.0258–0.0374	
From DC to			
HCC	0.0316	0.0258–0.0374	63
Death	0.17	0.1–0.25	
From HCC to death	0.34	0.22–0.45	63

maintenance and other relative items. The cost of fixed assets and cold chain equipment purchase were excluded.⁶⁴ The direct medical costs included the outpatient expenditure and inpatient expenditure. Effectiveness was quantified by quality-adjusted life years (QALYs), as well as new cases of HBV-related morbidity and disease-specific mortality.

The cost of the vaccine and HBIG were determined to be 3.1 Chinese yuan (CNY) and 120 CNY per dose, respectively, according to the current government contract price. The implementation cost was 19.55 CNY per dose, which was obtained from a field

survey that covered 1 provincial CDC, 3 municipal CDCs, 9 county CDCs, 27 township hospitals and 91 village clinics.⁶⁴

We performed a field survey in 8 hospitals from 3 cities in Zhejiang Province to assess the disease burden and QALYs of HBV-related diseases. The 3-level version of EQ-5D was used to determine the QALYs of the target population. Face-to-face interviews with patients were conducted to complete the questionnaire. A total of 626 outpatients and 523 inpatients with different types of HBV-related diseases were enrolled. Costs and the QALYs were analyzed following the analysis

framework published by Zhang SL³⁴ and Jia YX.³⁷ The base-case values of these direct costs were simultaneously adjusted by $\pm 25\%$, and the 95% CI estimates of QALYs were used in the sensitivity analyses. The QALYs of asymptomatic carriers, immune-tolerant patients and inactive carriers were obtained from the published literature. All costs are from 2016. Costs and QALYs predicted in future years were discounted to the values of 2016 at an annual discount rate of 3%.

Measurement of cost-effectiveness

The expected costs and effectiveness were compared between the two strategies, and the incremental cost-effectiveness ratio (ICER) was calculated based on QALYs. The ICER is the difference in costs between the reference strategy and the comparative strategy divided by the difference in their QALYs.⁶⁵ According to the WHO recommendation, an intervention is often deemed to be very cost-effective if the ICER is less than the annual per capita gross domestic product (GDP), which was 84,916 CNY in Zhejiang Province in 2016. New cases of HBV-sequelae over the lifetime of the 2016 birth cohort were derived from the Markov cohort analysis.

Sensitivity analyses

A series of one-way deterministic sensitivity analyses that varied the parameters individually over plausible ranges were performed to test the robustness of our findings and to identify key uncertainties. In addition, a probabilistic sensitivity analysis based on Monte Carlo simulations with 10,000 iterations was performed to evaluate the impact of the overall combined uncertainty of all the model parameters on the ICER. The parameter of all costs of investigation were assigned log-normal distribution found by drawing a distribution histogram. Some parameters were assigned a beta distribution estimated from the mean and 95% CI presented in reference, others were assigned triangular distributions because the distributions of parameters were unclear due to limited literature-based estimates.

Results

Base-case analysis

We estimated the number of infants with HBV infection and their lifetime complications under each strategy (Table 3). The

universal vaccination had a greater number of infants who developed HBV-related diseases and deaths. Compared with universal vaccination, 182 acute symptomatic infections, 2,215 chronic infections, 872 cases of cirrhosis, 595 cases of HCC and 1,350 HBV-related deaths would be further avoided under the current strategy among the cohort of 624,000 infants and would result in an additional 17,435 QALYs saved. The cost of providing maternal screening and HBIG to infants born to HBsAg-positive mothers was lower compared to the lifetime cost incurred by patients who acquired CHB at birth. The current strategy dominated universal vaccination since it not only produced higher total QALYs but also resulted in lower costs. The results are summarized in Tables 3 and 4.

Sensitivity analyses

Key parameters were evaluated using a series of one-way sensitivity analyses, and the ICERs were presented in a tornado diagram (Figure 5). The results showed that the direct medical costs associated with HBV-related diseases were among the most important parameters that could impact the ICER. However, the ICER remained well cost-saving regardless of changes in key parameter values, which demonstrated that none of the single parameters could change the conclusion that the current strategy was cost saving.

The results of the probabilistic sensitivity analysis are presented as the incremental cost-effectiveness scatter plot in Figure 6. For 1,000 Monte-Carlo simulations, the incremental cost-effectiveness scatter plot showed that 96% of the incremental cost-effectiveness ratios fell below at a willingness-to-pay threshold of 84,916 CNY, indicating a 96% likelihood of being cost-effective compared to universal vaccination. In addition, 92.8% of the incremental cost-effectiveness ratios accumulated in the fourth quadrant of the cost-effectiveness plane, indicating that the current strategy dominated universal vaccination with increased QALYs and with reduced costs in most case.

Discussion

China has experienced a significant reduction in perinatal HBV transmission rates and childhood HBV infections since implementing a universal vaccination strategy. Despite this

Table 3. New cases of HBV-related diseases and deaths in the birth cohort.

Strategy	Acute symptomatic infection	Chronic infection	Cirrhosis	HCC	HBV-related deaths
Universal vaccination	2,154	5,352	2,338	1,587	3,634
Current PMTCT	1,972	3,137	1,466	992	2,284
Current PMTCT vs Universal vaccination	-182	-2,215	-872	-595	-1,350

Table 4. Per capital costs, QALYs, and the ICERs of two strategies.

Strategy	Costs*(CNY)			Incremental costs	QALYs	Incremental QALYs	ICER
	Program costs	Illness costs	Total				
Universal vaccination	67.27	2,158.47	2,225.74	-	26.88	-	-
Current	91.44	1,341.74	1,433.18	-792.56	26.91	0.03	dominate

*Expressed as the value from 2016

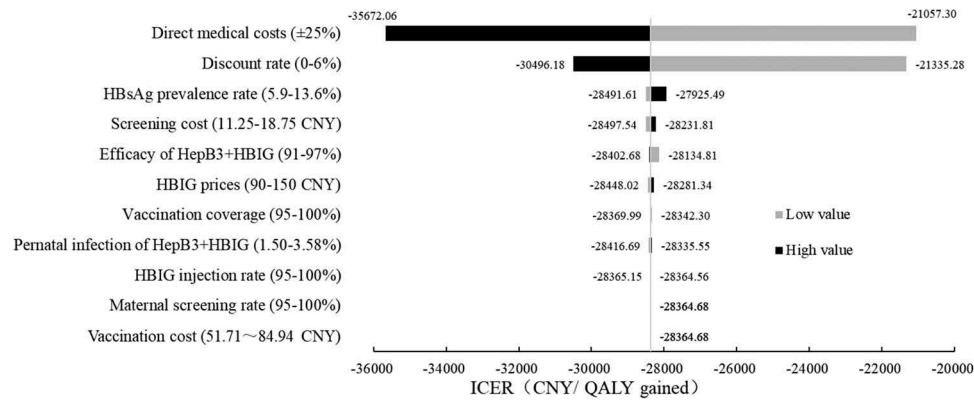


Figure 5. Tornado diagram presenting one-way sensitivity analyses. HepB3, 3-dose hepatitis B vaccination series. HBIG, hepatitis B immunoglobulin. HBsAg, hepatitis B surface antigen. QALY, quality-adjusted life year.

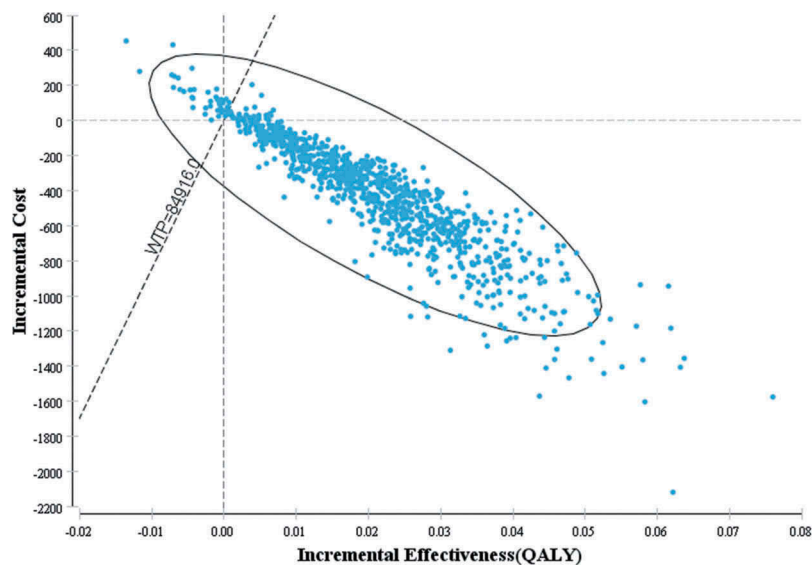


Figure 6. Incremental cost-effectiveness scatter plot for the current strategy compared to universal vaccination. WTP, willingness-to-pay threshold. QALY, quality-adjusted life year.

trend, there are still a large number of HBsAg-positive pregnant women, and perinatal transmission has become the predominant mode of HBV transmission. The combination of HBIG and HepB has been confirmed as a more effective preventive intervention, which was reported to further reduce the perinatal breakthrough infections.^{66,67} Our study demonstrated that augmenting universal hepatitis B vaccination with maternal screening and supplemental use of HBIG for high risk infants continues to be cost saving compared to universal vaccination.

The current strategy was more beneficial with respect to QALYs gained and was less costly, as savings from less disease treatment outweigh the costs of HBsAg testing for pregnant women and HBIG administration to infants. Our results were consistent with and are supported by results from earlier studies. A study conducted in Taiwan found that the combination of maternal screening for HBsAg, HBIG administration to all neonates born to HBsAg carrier mothers was cost-effective at all levels of prevalence.⁶⁸ A US study showed that the universal

vaccination with screening plus HBIG administration remains cost-effective compared to the universal strategy even with a prevalence as low as 0.2% among pregnant women. However, as prevalence decreased, the current strategy became less cost-effective, since the prevalence among pregnant women dropped from 7% to 0.2%, ICER increased from \$2,886/QALY saved to \$15,552/QALY saved.⁶⁹ Strategies involving prenatal maternal screening were also shown to be cost-effective compared to vaccination HepB alone in resource-constrained settings.⁷⁰ These evaluations indicated that augment universal vaccination with immunoglobulin treatment, providing HepB plus HBIG to infants born to HBsAg-positive mothers could be cost-effective, even cost saving. Although there was a large variation in the prevalence of HBsAg in pregnant women in these studies (from 0.6% in the US to 7% in Thailand), the robustness of outcomes was not susceptible to the epidemiological status of HBsAg in each country.

Importantly, the current strategy was consistently a cost-saving option in the one-way sensitivity analysis. The direct

medical costs of HBV-related diseases had the greatest impact on the results of the one-way sensitivity analysis. The economic effect of the strategy becomes more obvious when the costs increase, which may be related to treatment costs accounting for the majority of the total cost of the strategy. Although increased uptake of interventions is needed to maximize health gains, in our study, uptake of screening and HBIG administration were not large drivers of cost-effectiveness mainly because low rates reduce both the impact and the costs, which scale together. These losses and frailties are also seen in a similar economic evaluation study.⁷¹

Our study had both advantages and limitations. One of its major advantages was that the critical parameter inputs in our model, such as the direct medical costs and vaccination costs, were obtained from field surveys conducted in Zhejiang Province, which are more reliable and transparent than sources from the literature. Second, the HepB3 coverage rate, screening rate and HBIG injection rate, which were critical for this model, were obtained from the national surveillance system or the official report on the PMTCT project, which are more reliable and comprehensive than sources used in previous studies.

This study was subject to several limitations. A static rather than a dynamic model was used to simulate the HBV infection rate, static models can only simulate fixed populations, in which the force of infection remains constant and herd-immunity is ignored. Thus, the observed incidence over one year was used to estimate the number of cases as the cohort ages by one year in one discrete markov cycle. We found that a birth cohort that were offered universal infant vaccination with Hep B vaccine and HBIG had a lower incidence of HBV infection compared with a cohort offered universal vaccine only. A dynamic model might be considered more realistic in simulating the transmission of HBV and in capturing the impact of herd immunity.⁷² However, in endemic areas such as China, which have a high prevalence of HBV carriers, a static model such as the current one is probably sufficient to simulate the predominantly perinatal transmission, even if it may underestimate the impact of vaccination.⁹ The validity of models and the results rely largely on the availability and reliability of the model parameter inputs, which varied substantially in the literature. However, the main findings remained stable when parameters and assumptions were varied in the sensitive analyses. A probabilistic sensitivity analysis was conducted by applied triangular distributions in the models, while beta and gamma distributions were more recommended. However, a previous study that applied triangular distributions had approved that comparing with studies used other parameter distributions arriving at the same conclusion, and it would not affect the accuracy and reliability of parameters.⁴² In addition, antiviral prophylaxis can reduce high HBV-DNA loads in pregnant women and reduce the probability of perinatal HBV transmission, which has been reported.^{65,69} However, due to specific economic and medical system issues, antiviral drugs have not been widely used by Chinese patients, and thus we did not take these drugs into account in our model. Further research may take antiviral prophylaxis for pregnant women into consideration.

In summary, the present study provides important insights into the value of HepB immunization and an understanding of economic evidence. Our results suggest that that maternal screening for HBsAg and HBIG treatment for infants of carrier mothers could be cost saving addition to universal vaccination, and could further reduce HBV-related morbidity and mortality. These results support a recommendation to China's health policy makers for the continued allocation of central and regional funding for HBV vaccination combined with HBIG for high-risk infants.

Acknowledgments

We gratefully acknowledge the efforts made by the health workers from the CDC in 3 cities for their excellent collaboration in conducting this survey.

Disclosure of potential conflicts of interest

The authors declare that they have no competing interests and that there has been no significant financial support for this work that could have influenced its outcome.

Ethics

The ethics committee of Zhejiang Provincial CDC approved this study. The purpose of the study was explained to the patients, and written informed consent was obtained before the interview.

Funding

This work was supported by the National Natural Science Foundation of China [71874147; 81573257]; the project of Natural Science Fund of Fujian Province [2017J01133].

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