International Journal of Infectious Diseases 78 (2019) 130–139

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Cost-effectiveness analysis of hepatitis B vaccine booster in children born to HBsAg-positive mothers in rural China

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ARTICLE INFO

Article history:
Received 8 May 2018
Received in revised form 19 August 2018
Accepted 21 August 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Hepatitis B vaccine
Adolescent booster
Cost-effectiveness analysis

ABSTRACT

Objective: In rural areas of China with highly endemic for hepatitis B virus (HBV) infection, protective efficacy was observed in adulthood when a one-dose HBV vaccine booster was administered to high-risk children born to mothers who were positive for hepatitis B surface antigen (HBsAg). The aim of this study was to estimate the cost-effectiveness of an HBV vaccine booster in this specific group of children when given at 10 years of age.

Methods: Two potential strategies were considered: strategy 1 was a one-dose booster given if the child was negative on HBsAg screening; strategy 2 was a one-dose booster given if the child was negative on both HBsAg plus anti-HBs screening. A decision tree combined with a Markov model was developed to simulate the booster intervention process and to simulate the natural history of HBV infection in a cohort of 10-year-old children who were born to HBsAg-positive mothers. The model was calibrated based on multiple selected outcomes. Costs and quality-adjusted life years (QALYs) were measured from a societal perspective. Cost-effectiveness ratios (CERs) of the different strategies were compared in both base-case and one-way sensitivity analyses.

Results: Compared to the current practice of 'no screening and no booster', both strategy 1 and strategy 2 were cost-saving, with CERs estimated at US$ −6961 and US$ −6872 per QALY gained, respectively. In the one-way sensitivity analysis for strategy 1, all the CERs were found to be less than US$ −5000 per QALY gained after considering the uncertainty of all the variables, including vaccination protective efficacy, natural history, behavior, and various costs and utility weights. In a 'worst case' scenario (all parameter values simultaneously being at the worst), the CER of strategy 1 increased to US$ 3263 per QALY gained, which was still less than the GDP per capita of China in 2016 (US$ 8126).

Conclusions: A hepatitis B vaccine booster given to children born to HBsAg-positive mothers in rural China would be cost-effective and could be considered in HBV endemic areas.

Introduction

In China, chronic infection with hepatitis B virus (HBV) is estimated to be associated with 60% of cirrhosis and 80% of liver cancer (Wang et al., 2014). Due to the heavy disease burden, the Chinese government recommended HBV vaccination in 1992. In 2002, the vaccine was added to the National Immunization Program schedule for all neonates/infants, with the cost being fully paid for by the government. The latest nationwide study found that the prevalence of hepatitis B surface antigen (HBsAg) had reduced

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https://doi.org/10.1016/j.ijid.2018.08.024

to 0.32% in the age group 1–4 years and to 0.94% in the age group 5–14 years in 2014, from 9.67% and 10.74%, respectively, in 1992 (Wang et al., 2017a; Xia et al., 1996). Consistent with reports from other areas and countries (Trépo et al., 2014), the immunization program for infants in China has proven very successful in decreasing HBV infection in children and in preventing mother-to-children transmission.

It has long been observed that neutralizing antibodies (anti-HBs) conferred by HBV vaccination wane in many individuals after 10–15 years (Ni et al., 2007). In recent years, breakthrough HBV infections in adults who were vaccinated during infancy have been documented in different areas, especially among individuals who were born to HBsAg-positive mothers (Wu et al., 2013; Xu et al., 2010; Shahmoradi et al., 2012). The use of a vaccine booster test in children/young adults to measure HBsAg anamnestic immune responses has led to controversial conclusions regarding the necessity of an adolescent booster, due to the different or unknown maternal HBsAg status of the populations enrolled (But et al., 2008; Jan et al., 2010; Wu et al., 2013; Zanetti et al., 2005).

A recent study involving 9793 individuals found that HBV breakthrough infection did occur and that chronicity developed in around 0.51% of adults who had been protected in childhood by the neonatal vaccination series. The children born to HBsAg-positive mothers, mainly those who had lost anti-HBs, were at high risk of becoming HBsAg-positive (4.32%, 4/370). However, for the individuals who were born to HBsAg-negative mothers, HBV breakthrough infection only occurred and developed chronicity in about 0.25% (22/8850) of adults, and no vaccine booster protective efficacy was found among them, even for those who had become negative for anti-HBs (Wang et al., 2017b). Notably, a one-dose vaccine booster given at 10–14 years of age to the children who were born to HBsAg-positive mothers was found to be beneficial (Wang et al., 2017b).

Currently, approximately 6% of women of child-bearing age in rural China have a chronic HBV infection, and in recent years, an estimated 1 000 000 infants have been born to HBsAg-positive mothers every year (Zheng et al., 2010). The latest nationwide study showed that HBsAg seroprevalence was still as high as 4.38% in the age group 15–29 years (Wang et al., 2017a), indicating the high risk of HBV infection via sexual transmission among peers, parenteral transmission, or horizontal (household) HBV exposure. It is imperative to protect those who are susceptible from horizontal transmission to consolidate the protective efficacy of vaccination. Although the cost-effectiveness is unknown, some medical doctors still recommend adolescent boosters, especially for high-risk individuals (Lu et al., 2004, 2008; Chinchai et al., 2009; Wu et al., 2013; Qu et al., 2014).

Several previous studies have analyzed the cost-effectiveness of different strategies for primary HBV vaccination and have concluded that primary HBV vaccination of populations at certain ages in China are all cost-saving (Hutton et al., 2010; Yin et al., 2015; Zheng et al., 2015). This study was performed to analyze the cost-effectiveness of the potential booster vaccination of the specific group of children born to HBsAg-positive mothers.

Methods

Decision tree–Markov model

A cohort of children born to HBsAg-positive mothers in 2006, who were 10 years old in 2016, was assumed for enrollment. In China, HBV vaccines have been fully paid for by the government for all neonates/infants since 2002 (Sun et al., 2002), and no vaccine booster protection was found among children who were born to HBsAg-negative mothers (Wang et al., 2017b). A screening process before booster vaccination was assumed for this specific group of children who were born to HBsAg-positive mothers. This would allow individuals with an existing infection to be identified and to be informed of their infection status so that appropriate therapy could be given. Some individuals in the real world would like to know their anti-HBs status in order to relieve anxiety.

Two booster vaccination strategies were considered: strategy 1 was a one-dose booster given if the child was negative on HBsAg screening; strategy 2 was a one-dose booster given if the child was negative on both HBsAg plus anti-HBs screening (Figure 1A). The current practice of 'no screening and no booster' was set as the comparison group. A decision tree–Markov model was constructed using TreeAgePro 2014 (TreeAge Software, Inc., Williamstown, MA, USA). The decision tree model was used to simulate compliance with and the protective efficacy of the booster, and to compare cost-effectiveness among the different strategies. The Markov model (Figure 1B) was used to simulate the disease progression and calculate the health and economic outcomes.

Eleven health states were set based on the updated guidelines of the Chinese Society of Hepatology, Chinese Medical Association (Chinese Society of Hepatology, Chinese Medical Association, 2015), European Association for the Study of the Liver (EASL) (EASL, 2017), and available parameters from HBV natural history studies published in the literature (Figure 1B). These were (1) susceptible, (2) immune, (3) immune tolerant, (4) inactive HBsAg carriage, (5) hepatitis B e antigen (HBeAg)-positive chronic hepatitis B, (6) HBeAg-negative chronic hepatitis B, (7) HBsAg seroclearance, (8) compensated cirrhosis, (9) decompensated cirrhosis, (10) hepatocellular carcinoma (HCC), and (11) death.

The Markov model was set with a cycle length of 1 year from 10 years to 76 years (the average life expectancy in China in 2015; http://www.stats.gov.cn/tjsj/ndsj/2016/indexch.htm). The model was built with the following assumptions: (1) the National Health and Family Planning Commission of the People's Republic of China recommends screening-based HBV booster vaccination for high-risk children; the costs would be paid by the parents; (2) serum anti-HBs-positive status indicates protection from HBV infection; (3) there is no vaccine-induced herd-immunity; and (4) adverse events following booster are rare and negligible.

Model parameters

Values for the model parameters were chosen from the cost-effectiveness analyses of primary HBV vaccination conducted in the Chinese population, or from original studies published in English or in Chinese before August 2017.

Parameters of behavior and protective efficacy of booster vaccination

No publication was found about the rate of awareness of HBsAg-positive status among women of reproductive age in rural China in 2006. The rate of HBsAg screening before delivery among pregnant women from 1992 to 2005 was 94.6% in developed Beijing (Wang et al., 2007) and was 79.36% in 2007 in Shandong Province, where rural areas were more developed compared to the other areas of China (Song et al., 2008). In the current study, it was assumed that 70% of HBsAg-positive mothers were aware of their infection status. Information from the school-based vaccination system was used in a previous economic analysis on catch-up vaccination (Hutton et al., 2010). However, it was considered that this would not be appropriate or efficacious for the current situation, because maternal HBsAg status is considered confidential information in China. Thus, a school-based health education and information program was considered more appropriate. Parents would be informed of the booster vaccination by the teachers so that the parents of the target children would be prompted to take them to the nearest clinic for screening and to receive the booster.

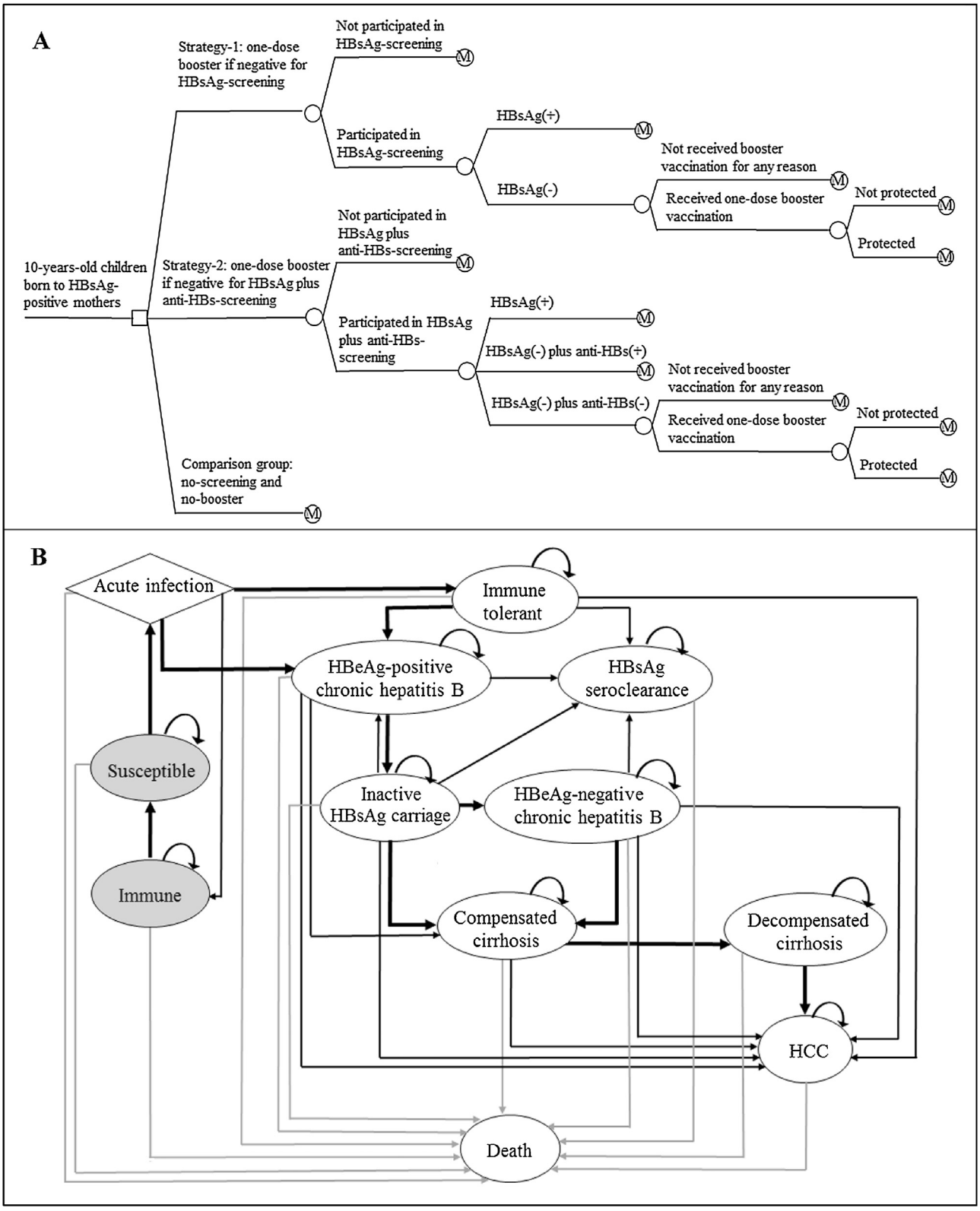

Figure 1. (A) Decision tree for the intervention comparison, and (B) Markov model for the natural history of hepatitis B virus infection. (Abbreviations: HBsAg, hepatitis B surface antigen; anti-HBs, antibodies against hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma).

No publication was found on the willingness of those in this specific high-risk population to receive the booster. Experts in the National Immunization Programs, Chinese Center for Disease Control and Prevention (CDC) were consulted. These experts stated that compliance with screening should be more than 70% in rural China. Based on the compliance reported in the economic analysis of catch-up vaccination (Hutton et al., 2010) and adult HBV vaccination (Zheng et al., 2015), the following was assumed for strategy 1: that 70% of individuals would participate in HBsAg screening and that 80% would receive the one-dose booster if

Table 1
Model parameters for intervention, behavior, natural history, and others.

Parameter	Base-case value	Range for sensitivity analysis	Notes and references
Compliance to screening and booster vaccination			
HBsAg screening	0.70	0.20–0.90	Assumed based on Hutton et al. (2010) and Zheng et al. (2015)
HBsAg screening plus anti-HBs screening	0.65	0.20–0.85	
One-dose booster vaccination	0.80	0.55–0.95	
Efficacy of booster vaccination			Based on a previous study in Qidong, China (Wang et al., 2017b)
10 μg for one dose	0.57	0.45–0.75	Assumed based on the anti-HBs seroprotective rates after HBV vaccination
10 μg for two doses	0.90	0.57–0.95	booster studies of Jan et al. (2010) and Chen et al. (2011)
10 μg for three doses	0.93	0.57–0.98	
Awareness rate of HBsAg status among HBsAg-positive mothers	0.70	0.50–0.80	Wang et al. (2007), Song et al. (2008)
Initial probabilities			Results of maternal HBsAg-positive children aged 1–14 years in a hepatitis B
Already infected (HBsAg screening positive rate)	0.0571	0.02–0.07	national serosurvey in 2014 (Wang et al., 2017c)
Immune (anti-HBs screening positive rate)	0.5640	0.48–0.65	
Acute infection			
Outcome probabilities of acute infection			
Symptomatic	0.30	0.15–0.45	Jia et al. (2014), Kim et al. (2006), Liaw and Chu (2009), Lu et al. (2013), Trépo et al. (2014), Yin et al. (2015), Zheng et al. (2015)
Symptomatic infection requiring hospitalization	0.12	0.01–0.50	Hutton et al. (2010), Trépo et al. (2014), Yin et al. (2015)
Hospitalized cases with fulminant hepatitis	0.04	0.01–0.10	Hutton et al. (2010), Trépo et al. (2014), Yin et al. (2015)
Fulminant cases resulting in death	0.70	0.40–0.80	Choi et al. (2011), Hutton et al. (2010), Liaw and Chu (2009), Trépo et al. (2014), Yin et al. (2015), Zheng et al. (2015)
Symptomatic infection becoming chronic	10∼: 0.06; 20∼: 0.04	±50%	Kim et al. (2006), Trépo et al. (2014), Yin et al. (2015), Zheng et al. (2015)
Asymptomatic acute infection becoming chronic	$\exp(-0.65 \times age^{0.46})$	–	Edmunds et al. (1993), Hung and Chen (2009), Jia et al. (2014), Lu et al. (2013)
Disease progression parameters of chronic HBV infection (annual transition probabilities)			
Immune tolerant			
To HBsAg seroclearance	10∼: 0.0035; 20∼: 0.0052; 40∼: 0.0140	±50%	Lim et al. (2015), Qu et al. (2014)
To HBeAg-positive chronic hepatitis B	10∼: 0.0119; 13∼: 0.0535; 19∼: 0.1423	±50%	Hong et al. (2014), Wong et al. (2013)
To HCC	10∼: 0.0000288; 30∼: 0.0003216	±50%	Chen et al. (2010b), Gambarin-Gelwan (2013), Yang et al. (2002), Yang et al. (2017)
HBeAg-positive chronic hepatitis B			
To inactive HBsAg carriage	0.078	0.063–0.093	Yang et al. (2017), Yuen et al. (2003)
To HBsAg seroclearance	0.0043	0.0007–0.0093	Chu and Liaw (2007a), Qu et al. (2014)
To compensated cirrhosis	10∼: 0.01; 20∼: 0.02; 40∼: 0.027	±50%	Lu et al. (2013), Yin et al. (2015)
To HCC	10∼: 0.0000288; 30∼: 0.001175; 40∼: 0.0064	±50%	Wen et al. (2004), Yang et al. (2017), Yin et al. (2015)
Inactive HBsAg carriage			
To HBeAg-positive chronic hepatitis B	0.006	0–0.011	Hsu et al. (2002), Yang et al. (2017)
To HBeAg-negative chronic hepatitis B	0.0427	0.02–0.05	Chu and Liaw, (2007b), Yang et al. (2017)
To HBsAg seroclearance	0.0114	0.0057–0.0171	Qu et al. (2014), Simonetti et al. (2010), Trépo et al. (2014)
To compensated cirrhosis	0.00102	±50%	Hung and Chen (2009), McMahon et al. (1990), Yu et al. (1997)
To HCC	10∼: 0.0000288; 30∼: 0.0006; 40∼: 0.0061	±50%	Chen et al. (2010a), Wen et al. (2004), Yin et al. (2015)
HBeAg-negative chronic hepatitis B			
To HBsAg seroclearance	0.0067	0.0017–0.0087	Kwak et al. (2011), Liu et al. (2013), Liu et al. (2010), Qu et al. (2014)
To compensated cirrhosis	10∼: 0.01; 20∼: 0.02; 40∼: 0.027	±50%	Lu et al. (2013), Wu et al. (2002), Yin et al. (2015)
To HCC	10∼: 0.0000288; 30∼: 0.000286; 40∼: 0.0064	±50%	Wen et al. (2004), Yang et al. (2017), Yin et al. (2015)
Compensated cirrhosis			
To decompensated cirrhosis	0.036	0.025–0.050	Jia et al. (2014), Xu et al. (2002)
To HCC	0.0316	0.0258–0.0374	Thiele et al. (2014), Yang et al. (2017)
Decompensated cirrhosis			
To HCC	0.034	0.01–0.10	Wu et al. (2010), Yin et al. (2015)
To death (disease-specific)	0.17	0.10–0.25	Nguyen et al. (2009), Wu et al. (2010), Yang et al. (2017), Yin et al. (2015)
HCC to death (disease-specific)	0.34	0.30–0.70	Thiele et al. (2014), Yang et al. (2017)

HBsAg, hepatitis B surface antigen; anti-HBs, antibodies against hepatitis B surface antigen; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma.

negative. For strategy 2, it was assumed that 65% of individuals would participate in the HBsAg plus anti-HBs-screening and that 80% would receive the one-dose booster if both were negative. The protective efficacy of the one-dose booster was calculated as 57% using the formula (7.21 − 3.09%)/7.21%, based on a previous study that showed that the booster reduced the HBsAg-positive rate from 7.21% to 3.09% in adulthood in this specific population (Wang et al., 2017b). The use of a two- or three-dose booster was not considered in the base-case analysis, because no report of protective efficacy was available.

In the sensitivity analysis, the cost-effectiveness of two- or three-dose booster was considered. Booster test studies among children/young adults with unknown maternal HBsAg status have reported 95% anti-HBs-positive seroconversion after the two-dose booster and 98% after the three-dose booster (Chen et al., 2011; Jan et al., 2010). In the present study, a conservative assumption was made by deducting 5% from the anti-HBs-positive seroconversion rates as the protective efficacy, thus 90% for the two-dose booster and 93% for the three-dose booster. Considering 80% compliance for the one-dose booster, compliance of 78% was assumed for the two-dose booster and 76% for the three-dose booster if negative on HBsAg screening (Table 1).

Incidence and transition probabilities of HBV infection

Based on the report from a nationwide serological survey of hepatitis in China, 2014 (Wang et al., 2017c), the initial probabilities were set at 0.0571 for the HBsAg-positive rate and 0.564 for the anti-HBs-positive rate (Table 1) for the cohort of children who were born to HBsAg-positive mothers and who were 10 years old in 2016. In order to estimate the age-specific annual incidence of HBV infection in susceptible individuals in the high-risk population who were born to HBsAg-positive mothers, the age-specific annual incidence in the general population was calculated using the non-linear least-squares method based on the nationwide HBV prevalence in China in 1992 (Yang et al., 2017; Yin et al., 2015). This would characterize natural HBV infections without vaccination, because the time was just before HBV vaccination was recommended for newborns (Xia et al., 1996). Based on the theoretical expression of the incidence (details showed in the Supplementary material) and the difference in HBsAg prevalence between 1992 and 2006 (Liang et al., 2009; Xia et al., 1996), it was estimated that the average annual decline in incidence in the general population was 2.16%. The age-specific incidence of HBV infection in susceptible individuals in the high-risk population who were born to HBsAg-positive mothers in 2016 was based on the increased risk (odds ratio 7.38) of chronic HBV infection among the high-risk population and the annual decline in incidence in the general population. There are currently no available data on the occurrence of chronic HBV infection in susceptible individuals after 25 years of age; thus it was assumed that new HBV infection only occurred during the age range 10–25 years. A detailed description of the methodology is provided in the Supplementary material.

The probabilities of progression or regression of HBV infection (Table 1) were obtained from economic analyses, meta-analyses, and observational epidemiological studies that were mainly conducted in Chinese populations. Age-specific probabilities were applied when necessary and feasible.

Costs

All costs were measured from the societal perspective. Costs of screening and booster vaccination were derived from a nationwide economic analysis of adult HBV vaccination conducted by the Chinese CDC in 2014, which covered the screening and vaccination delivery costs (Zheng et al., 2015). Considering the cost differences of screening and vaccination among different regions, and the waste of screening and vaccination resources due to over-screening and over-provision of booster among children born to HBsAg-negative mothers, four-fold the base-case value was set as the higher bound in the sensitivity analysis. It was assumed that a target child could walk to the nearest clinic escorted by one of their parents with no additional travel costs. The productivity loss due to the time spent by the parents was considered an indirect cost. It was assumed that each visit would take 1.5 h on average, at US$ 1.84/h (Zheng et al., 2015), and that the current multi-level immunization system in each province of China would be able to provide HBV screening and booster vaccination. Based on the economic analysis on catch-up vaccination (Hutton et al., 2010), a setup cost of US$ 0.40 per child was assumed in the base-case analysis. In the sensitivity analysis, the range of the setup cost was assumed to be US$ 0.20 to US$ 0.60 per child.

The annual costs per patient of HBV-related diseases consisted of direct medical costs, direct non-medical costs, and the indirect costs of the escorted persons. These data were derived from a nationwide multicenter survey on the HBV-associated economic burden that was conducted in 27 general and specialized hospitals located in six provinces of China, with 4726 patients enrolled in 2010 (Zhang et al., 2016). As no data were available from this survey on the costs of asymptomatic HBsAg carriers, eight hepatologists from Beijing You'an Hospital, Qidong People's Hospital, and Qidong Hospital for Infectious Diseases were consulted (Wang et al., 2017d). In the sensitivity analysis, the costs of HBV-related diseases varied from 50% to 150% of the base-case values to cover the majority of reported data and variation across different regions of China. According to a community-based nationwide survey on health-seeking behaviors among HBsAg-positive adults, the Chinese CDC reported that 18% of asymptomatic HBsAg carriers underwent a medical examination at least once a year and 11% of chronic hepatitis B patients received various treatments (Zheng et al., 2016). All costs are presented in US$, with the exchange rate of 1 US$ = 6.6423 CNY in 2016 (Table 2).

Utility weights

There are currently no available data from the nationwide survey on the utility weights of HBV-related diseases. Data on QALY-related utility weights (Table 2) for HBV-related diseases from a cost-effectiveness analysis for preventing mother-to-child transmission of HBV in China in 2017 were used (Lin et al., 2017). In this study, the meta-analysis was conducted to pool the utility weights of cirrhosis and HCC.

Cost-effectiveness analysis

The cost-effectiveness ratio (CER) for each of the booster strategies compared with the current practice of no screening and no booster was used as the key indicator, by dividing the difference of the discounted cost by the difference of the discounted QALYs. All costs and QALYs were discounted at a 3% annual rate. One-way sensitivity analyses were performed to assess the uncertainty of the primary results with the range of variables listed in Tables 1 and 2. The CERs under a most pessimistic scenario (the 'worst case') were also calculated to make a most conservative estimation, that is, when all the parameters were simultaneously at the worst for the booster strategy.

Results

Model validation

The model predicted outcomes were compared with the observed outcomes from previous reports (Table 3). Observational studies reported that about 10–25% of individuals chronically infected with HBV developed HCC (Omata et al., 2017), that 70–90%

Table 2
Model parameters for costs and utility weights.

Parameter	Base-case value	Range for sensitivity analysis	Notes and references
Costs associated with screening and vaccination, US$			
Direct costs			
HBsAg screening and delivery cost	2.10	1.75–8.40	Zheng et al. (2015) and Lin et al. (2017)
HBsAg and anti-HBs screening and delivery cost	3.33	2.98–8.40	
Per-dose vaccine and delivery cost	2.67	2.14–10.68	
Indirect costs			Assumed based on results from Zheng et al. (2015)
Work loss for one-visit screening or vaccination (US$ per visit)	2.76	1.84–7.36	
Annual cost per patient with different HBV-related disease, US$			
Direct costs			
Acute hepatitis B	2555	±50%	Based on results from Zhang et al. (2016), a nationwide multicenter survey of the HBV-associated economic burden in China (N = 4726)
Fulminant hepatitis	8971	±50%	
Chronic hepatitis B	3436	±50%	
Compensated cirrhosis	5428	±50%	
Decompensated cirrhosis	6903	±50%	
Hepatocellular carcinoma	9070	±50%	
Immune tolerant/inactive HBsAg carriage	228	±50%	
Indirect costs			
Acute hepatitis B	377	±50%	
Fulminant hepatitis	2316	±50%	
Chronic hepatitis B	544	±50%	
Compensated cirrhosis	844	±50%	
Decompensated cirrhosis	1280	±50%	
Hepatocellular carcinoma	3913	±50%	
Utility weights			
Health/asymptomatic infection	0.82	0.80–0.84	From Lin et al. (2017), a cost-effectiveness analysis of the strategy for preventing mother-to-child transmission of hepatitis B in China; the utility weights of cirrhosis and hepatocellular carcinoma were obtained by meta-analysis
Acute hepatitis B	0.76	0.66–0.78	
Fulminant hepatitis	0.26	0.15–0.35	
HBeAg-positive chronic hepatitis B	0.76	0.66–0.78	
HBeAg-negative chronic hepatitis B	0.75	0.72–0.78	
Immune tolerant/inactive HBsAg carriage	0.795	0.76–0.82	
Compensated cirrhosis	0.72	0.66–0.75	
Decompensated cirrhosis	0.57	0.47–0.61	
Hepatocellular carcinoma	0.51	0.39–0.57	
Discount rate	0.03	0.01–0.06	

HBsAg, hepatitis B surface antigen; anti-HBs, antibodies against hepatitis B surface antigen; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma. All costs and QALYs were discounted to year 2016 at 3%.

Table 3
Model validation: comparison between values predicted by the model and observed outcomes, prior to any intervention.

Selected outcomes	Proportion predicted by the model	Proportion observed in the literature	
		Value range	Data sources
HCC/chronic HBV infection	21.3%	10–25%	Reported by Omata et al. in a guideline, 2017 (Omata et al., 2017) and in a WHO review, 2017
Cirrhosis-associated HCC/HCC	71.3%	70–90%	Reported by Omata et al. in a guideline, 2017 (Omata et al., 2017)
HBV-related death[a]/chronic HBV infection	30.5%	25–40%	Review by Kao and Chen (2002); review by Trépo et al. (2014)

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; WHO, World Health Organization.
[a] Deaths due to decompensated cirrhosis or HCC.

of HCC cases were associated with cirrhosis (Omata et al., 2017), and that 25–40% of HBV-infected individuals might die of cirrhosis and/or HCC (Kao and Chen, 2002; Trépo et al., 2014). Our model predicted that the proportion of HCC in chronic HBV-infected individuals was 21.3%, the proportion of cirrhosis-associated HCC was 71.3%, and the proportion of death after chronic HBV infection was 30.5% (Table 3). The values predicted by the model were all within the observed ranges.

Base-case results

Compared with the current no-screening and no-booster intervention, booster vaccination reduced the number of cases of HBV-related diseases. By taking strategy 1–one-dose booster if negative on HBsAg screening – among 100 000 high-risk children, 485 chronic HBV-infected cases and 153 HBV-related deaths could be avoided if 36 962 children received the booster. By taking strategy 2–one-dose booster if negative on both HBsAg plus anti-HBs screening – among 100 000 high-risk children, 365 chronic HBV-infected cases and 115 HBV-related deaths could be avoided if 13 792 children received the booster vaccination (Table 4).

During the simulated lifetime from age 10 years to 76 years, strategy 1 and strategy 2 were both cost-saving when compared to no screening and no booster, with US$ 78 (strategy 1) and US$ 59 (strategy 2) saved per person; the CERs were US$ −6961/QALY and US$ −6872/QALY, respectively. Both strategies led to greater effectiveness but lower costs (Table 5).

Sensitivity analysis

Strategy 1 appeared slightly more favorable than strategy 2 (Table 5). Therefore, a one-way sensitivity analysis for strategy 1 was conducted among more than 60 variables, including protective efficacy, natural history of HBV infection, behavior, and various

Table 4
Predicted numbers of events or various diseases caused by HBV with different intervention strategies, per 100 000 10-year-old children born to HBsAg-positive mothers.

Vaccination event or HBV-related diseases	No screening and no booster (Comparison group)	Strategy 1: one-dose booster if negative on HBsAg screening[a]	Strategy 2: one-dose booster if negative on both HBsAg plus anti-HBs screening[a]
Booster vaccinated	0	36 962	13 792
Hospitalized acute symptomatic hepatitis B	773	581 (192)	636 (137)
Fulminant hepatitis	32	24 (8)	26 (6)
Chronic HBV infection	1991	1506 (485)	1626 (365)
Compensated cirrhosis	191	144 (47)	156 (35)
Decompensated cirrhosis	251	190 (61)	205 (46)
Hepatocellular carcinoma	423	320 (103)	345 (78)
HBV-related death[b]	629	476 (153)	514 (115)

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HBs, antibodies against hepatitis B surface antigen.
[a] Numbers in parentheses are the numbers of cases prevented by the booster intervention.
[b] Deaths due to decompensated cirrhosis, hepatocellular carcinoma, or fulminant hepatitis.

Table 5
Cost-effectiveness analysis of a one-dose adolescent booster vaccination, compared to no intervention.

Different strategies taken in high-risk children at 10 years old	Discounted cost, US$	Discounted QALYs	Cost-effectiveness ratio, US$/QALY
Comparison group No screening and no booster	1290	23.2486	–
Strategy 1 One-dose booster if negative on HBsAg screening	1212	23.2599	−6961
Strategy 2 One-dose booster if negative on HBsAg plus anti-HBs screening	1231	23.2572	−6872

HBsAg, hepatitis B surface antigen; QALY, quality-adjusted life year; anti-HBs, antibodies against hepatitis B surface antigen.

costs and utility weights. All CERs were less than US$ −5000 per QALY gained. The following parameters showed a great impact on the CERs: the annual cost per patient due to compensated cirrhosis, utility of chronic hepatitis B, annual cost per patient due to chronic hepatitis, and utility of inactive HBsAg carriage (Figure 2).

The CERs related to the parameters of screening and booster vaccination were found to be robust, such as work loss for one-visit screening or vaccination, HBsAg screening and delivery cost, per-dose vaccine and delivery cost, compliance with screening or one-dose booster, and protective efficacy of booster vaccination. When all the parameters were simultaneously set at the values most unfavorable to the booster strategy (the 'worst case' scenario), strategy 1 was not cost-saving anymore, with the CER increased to US $ 3263/QALY. However, it was still lower than the GDP per capita of China in 2016 (US$ 8126). The one-dose booster vaccination of high-risk children if negative on HBsAg screening was cost-effective.

The cost-effectiveness of two-dose and three-dose booster vaccination was further analyzed based on strategy 1. The CER of two-dose booster vaccination was US$ −6966/QALY (range US$ −7037/QALY to US$ −6565/QALY) and the CER of three-dose booster vaccination was US$ −6910/QALY (range US$ −7000/QALY to US$ −6066/QALY), after considering the parameter values (Table 1), including compliance, per-dose vaccine cost, and work loss for one-visit vaccination. Both the two-dose and three-dose booster provided more benefits and saved more costs.

Discussion

This study analyzed the cost-effectiveness of HBV booster vaccination in the assumed 10-year-old children born to HBsAg-positive mothers who had completed the vaccination series during infancy in China. A decision tree–Markov model was constructed and parameter values were selected from previous cost-effectiveness analysis and original studies published in English or in Chinese that were mainly conducted in Chinese populations. The natural history model was calibrated based on multiple selected

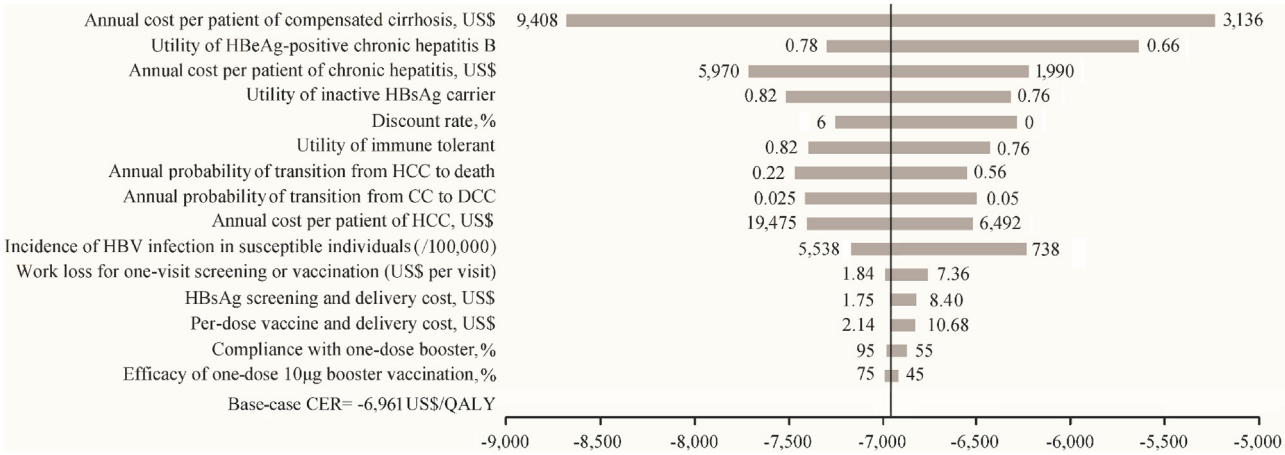

Figure 2. One-way sensitivity analysis for the one-dose adolescent booster vaccination, given if negative for HBsAg on screening, compared to the current practice of no screening and no booster.

outcomes. The values predicted by the model were all within the observed ranges documented in clinical practice. From the societal perspective, both strategy 1 and strategy 2 were cost-saving compared with the current no-screening and no-booster intervention, with CERs estimated at US$ −6961 and US$ −6872 per QALY gained, respectively. In the one-way sensitivity analysis for strategy 1, after considering the uncertainty of all the variables, including vaccination efficacy, natural history, behavior, and various costs and utility weights, all CERs were less than US$ −5000/QALY. In the 'worst case' scenario (all parameters simultaneously being at the worst), by taking strategy 1, the CER increased to US$ 3263/QALY, still less than the GDP per capita of China in 2016 (US$ 8126). The real cost-effectiveness of booster vaccination with more than one dose might be uncertain, as the compliance might be lower than our assumption and no report was available about the protective efficacy of more than one dose. Nevertheless, based on the current assumptions, the two- or three-dose booster would provide more benefits and cost less than the one-dose booster. Thus, it is suggested that at least one dose of booster vaccination in adolescence should be considered for high-risk children born to HBsAg-positive mothers when they have lost anti-HBs.

Several studies have evaluated the cost-effectiveness of neonatal HBV vaccination, or catch-up vaccination for children or adults in China. All of them have come to the conclusion that primary HBV vaccination given to populations at certain ages is cost-saving, with the incremental cost-effectiveness ratio (ICER) ranging from US$ −13 238/QALY for universal HBV vaccination in Taiwan to US$ −1909/QALY for catch-up vaccination among children/adolescents in China (Hung and Chen, 2009; Hutton et al., 2010; Jia et al., 2014; Lu et al., 2013). The present study is the first to report a cost-effectiveness analysis of booster vaccination for a high-risk population. The one-dose booster given in the case of a negative HBsAg screening result was also cost-saving, with a CER estimated at US$ −6961/QALY, indicating this strategy to be favorable when compared with catch-up vaccination in general children/adolescents. The parameters that showed a great impact on CERs – costs of HBV-related diseases, annual transition probabilities, and incidence of HBV infection – were similar to the findings of other health economic evaluations conducted in the Chinese population (Supplementary material Table 1). Therefore, the parameter values and ranges in our model appear reasonable.

Following the effective protection achieved by neonatal immunization, further benefit could be provided by booster vaccination to prevent horizontal transmission in this high-risk population when they participate in certain activities, such as unsafe sexual activities, dental treatments, razor sharing, tattoos, acupuncture, and body care and beauty treatments in public places. In December 2016, the National Health and Family Planning Commission recommended that vaccinated infants should be tested for the presence of HBsAg and the anti-HBs titer at 1–2 months after completion of the third dose of vaccine if they have been born to an HBsAg-positive mother. If the child is seronegative for HBsAg and has an anti-HBs of <10 mIU/ml, the fourth dose of vaccine should be given (Qu et al., 2017). As the fourth dose of HBV vaccine was only given starting in 2017, high-risk children should consider the vaccine booster when their anti-HBs has disappeared. In China, the provincial CDC immunization offices have branches to serve the immunization needs in various districts. The target population could go to the nearest clinic for screening and to receive the booster, if the Health and Family Planning Commission recommends the screening-based HBV booster. Therefore, HBsAg screening-based booster vaccination is not only cost-saving, but also feasible.

It was assumed that chronic infection only occurred during the age range of 10 years to 25 years based on our previous study (Wang et al., 2017b). This might have led to an underestimation of the superiority of booster vaccination. Considering the cost variation in different regions, four-fold the base-case value of costs associated with screening and vaccination was set as the higher bound in the sensitivity analysis and the costs of HBV-related diseases were assumed to vary from 50% to 150% of the base-case values to cover the majority of the reported data. Under these conservative assumptions, booster vaccination was still cost-saving. Even in the 'worst case' scenario, the CER was still less than the GDP per capita in China in 2016 (US$ 8126). The conclusion appears to be robust.

This study has several limitations. The protective effect of adolescent booster was only observed in one high endemic rural area. Generalization of the study findings to HBV prevention in populations with a very low prevalence of HBsAg might be limited. It was noted that the HBsAg seroclearance rate was much lower in the neonatal vaccinated population (0.36% annually) than in the unvaccinated population (1.49% annually) (Qu et al., 2014). Hence, a lower HBsAg seroclearance rate was set in the current model. However, beyond that, most of the natural history parameters were derived from the unvaccinated population, due to the absence of data for the vaccinated population. There was no report from a national survey of the utility weights of HBV-related diseases; the utility weights pooled by meta-analysis were therefore used. The various survey instruments used in the original utility weights studies would have led to bias. Therefore, a wide range was given to the utility weights in the sensitivity analysis to cover the uncertainty. This study was based on the current incidence of HBV infection, treatment options, costs, and vaccination policy. The incidence of HBV infection will decrease with the wide use of HBV vaccination and the advent of antiviral therapy. Chronic HBV-infected patients may live with the disease for many years. Their costs and utility weights may change in the future with the development of new treatments. Since 2017, high-risk children negative for HBsAg at 1–2 months after completion of the third dose have been eligible for a fourth dose of the vaccine. Their risk of breakthrough infection later in life would be changed. All of the above changes would lead to uncertainty. Considering the disparate accessibility of antiviral therapy in different regions of China, booster vaccination should be preferred.

Hepatitis B booster vaccination of children born to HBsAg-positive mothers in rural China would be cost-effective. We recommend that at least one dose of hepatitis B adolescent booster vaccination should be considered if anti-HBs has been lost, as these individuals are still at high risk of horizontal transmission in endemic areas after being protected by the neonatal HBV vaccination.

Funding

The project was funded by State Key Projects Specialized on Infectious Diseases (2017ZX10201201-006-003) to CQ, (2017ZX10201201-008-002) to JFS, and Key Research Projects for Precision Medicine (2017YFC0908103) to CQ. YW was supported by the Graduate Innovation Funding of Peking Union Medical College (2015-1001-09). The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Conflict of interest

The authors have no financial or other interests with regard to the submitted manuscript that might be construed as a conflict of interest.

Author contributions

Chunfeng Qu participated in the study design, revised and finalized the manuscript, and gave technical support. Yuting Wang participated in the study design, statistical analyses, and data collection and drafted the manuscript. Ju-Fang Shi participated in the study design, drafted the manuscript, and gave technical support. Le Wang participated in the statistical analyses and data collection. Yongfeng Yan, Hongyu Yao, and Taoyang Chen participated in data collection. Min Dai advised on data analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.08.024.

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