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Targeted hepatitis E vaccination for women of childbearing age is cost-effective in China

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ABSTRACT

Background: Hepatitis E virus (HEV) infection is hyper-endemic in China, it is characterized with a high morbidity of fulminant hepatitis and mortality in pregnant women. The first hepatitis E vaccine, HEV 239, was licensed in China in 2011 which provides an effective preventive measure.
Objective: To evaluate the cost-effectiveness of vaccination with HEV 239 in women of childbearing age in China and whether HEV antibody screening should be considered before vaccination.
Methods: A decision tree-Markov model was constructed to simulate HEV infection in a closed female cohort with an average first-marriage age of 25 years and evaluate health and economic outcomes of two potential vaccination strategies, direct vaccination and combined screening and vaccination, from a societal perspective. An incremental cost-effectiveness ratio (ICER, additional costs per disability-adjusted life-year (DALY) averted) was calculated for each vaccination strategy versus no vaccination and between two vaccination strategies. Univariate and probabilistic sensitivity analyses were conducted to assess the robustness of the model findings.
Results: ICERs of direct vaccination and combined screening and vaccination versus no vaccination were $4040 and $3114 per DALY averted, respectively, much lower than 1-time Chinese per-capita GDP ($8127). Direct vaccination would need additional $45,455 for each DALY averted compared with combined screening and vaccination, far more than the 3-time per-capita GDP. Probabilistic sensitivity analyses confirmed our findings that two vaccination strategies would be cost-effective if the willingness-to-pay reached the 1-time per-capita GDP, and that combined screening and vaccination would be more cost-effective than direct vaccination strategy.
Conclusion: Vaccinating women of childbearing age with HEV 239 would cost less than the 1-time per-capita GDP for each DALY averted in China, and the vaccination with a prior screening would be the optimal option.

1. Introduction

Hepatitis E is an acute viral hepatitis caused by hepatitis E virus (HEV) that is transmitted primarily through contaminated drinking water. The infection usually is self-limiting and resolves within 2–6 weeks, but occasionally it develops into a serious disease known as fulminant hepatitis. The World Health Organization (WHO) estimated that every year, HEV causes 20 million infections worldwide which lead to 3.3 million symptomatic cases and 44,000 deaths [1,2]. In addition, 3000 stillbirths are associated with HEV annually [1]. China is a highly HEV-endemic country where hepatitis E outbreak has been reported many times [3–5]. The

Abbreviations: HEV, hepatitis E virus; WHO, world health organization; CI, confidence interval; $, US dollar; DALY, disability-adjusted life-year; YLL, year of life lost; YLD, year lost due to disability; ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay; GDP, gross domestic product.

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overall case fatality rate of hepatitis E is reported between 1% and 3%, but in pregnant women it can reach 4–30% [6–8]. Pregnant women are most likely to progress to fulminant hepatitis if infected by HEV, especially in late pregnancy and puerperium [6,9,10]. Hepatitis E often leads to adverse fetal outcomes in pregnant women, including increased rates of premature delivery, miscarriage, and stillbirth [7,10]. Furthermore, vertical transmission may also contribute directly to infant morbidity and mortality in early postpartum period [11].

Public hygiene is the first line of defense against HEV infection. Nevertheless, typical interventions including improvement in sanitation and treatment of drinking water can not prevent all the infections, just like the experience during outbreaks in southern Sudan and northern Uganda not long ago [12,13]. Furthermore, there is no specific treatment capable of altering the course of hepatitis E. Prompt administration of an effective vaccine could be a powerful way to prevent the transmission [14]. In 2011, a recombinant subunit vaccine (HEV 239, Xiamen Innovax Biotech, Xiamen, China) was licensed in China. It is available only in Chinese market at present. A phase III clinical trial showed that the vaccine efficacy was 85.1% for participants who received at least one dose and reached 93.3% after full three doses [15,16]. The vaccine efficacy did not decrease much over time during a 4.5-year follow-up [16], and statistical models estimated that the median duration of detectable protective antibody was up to 13 years [17]. Studies revealed that HEV 239 was well-tolerated: side-effects were few and mild, and no vaccination-related serious adverse events were noted [15,18].

The World Health Organization has not recommended HEV 239 for routine use in national programs up to now. Nevertheless, it mentioned that the use of the vaccine might mitigate consequences in high risk groups such as pregnant women [19]. Economic evaluation data are needed for the decision making. Vaccination during pregnancy is generally contraindicated because of safety concerns, although preliminary analysis found that HEV 239 was safe and immunogenic among 37 pregnant women who inadvertently received the vaccine during pregnancy [20]. Larger studies and further clinical trials are needed to support this finding. Therefore, we conducted this model-based cost-effectiveness analysis to evaluate (1) the cost-effectiveness of vaccination with HEV 239 in women of childbearing age in China and (2) whether HEV antibody (anti-HEV) screening should be considered before vaccination.

2. Methods

2.1. Decision tree-Markov model

We constructed a decision tree-Markov model to evaluate the cost-effectiveness of potential vaccination strategies for women aged 25 years from the societal perspective, using the software of TreeAge Pro 2016 (TreeAge Software, Inc., MA, USA). This population is most likely to benefit from vaccination according to the average first-marriage age of Chinese women and the ongoing threat in pregnant women. HEV 239 was used according to the 3-dose series at 0, 1 and 6 months recommended by the manufacturer. A closed cohort of 100,000 women was assumed to enter the model and followed three alternative strategies: direct vaccination; combined screening and vaccination, i.e. screening everyone and vaccinating those negative for anti-HEV; and no vaccination. The cohort members were followed until the age of 45 years given the concern about the duration of vaccine protection. We assumed that these women could have one child at most and, in addition, we did not consider the impact of HEV infection during pregnancy on the fetus itself in order to simplify the model and to conservatively estimate the effectiveness of the new vaccine.

The decision tree was used to simulate screening test characteristics, compliance with full 3-dose vaccination and efficacies of the vaccination, and to perform the comparisons among the strategies (Fig. 1(A)). The Markov model was used to simulate HEV infection and its consequences and as the calculator to calculate health and economic outcomes of HEV infection. As shown in Fig. 1(B), the Markov model consisted of seven health states: susceptible to HEV (before pregnancy); susceptible to HEV (after childbearing); natural immunity (before pregnancy); natural immunity (after childbearing); vaccine immunity (before pregnancy); vaccine immunity (after childbearing); and death. Whether before pregnancy or after childbearing, a woman in the state of natural immunity or vaccine immunity may retune to the state of susceptible to HEV due to the loss of protective antibody. The Markov model was run with a cycle length of 1 year for 21 cycles to cover the experiences of cohort members from the age of 25 years to the age of 45 years.

2.2. Model parameters

Base-case values, ranges and distributions of parameters used in the model were estimated from published literatures and government documents. They were described below and summarized in Table 1.

2.2.1. Prevalence and incidence of HEV infection

To determine the initial proportion of the cohort members who had been infected and maintained the protective antibody, we used data that reported Chinese prevalence of anti-HEV. The Third National Viral Hepatitis Prevalence Survey reported 28.04% in the general Chinese population aged 15–60 years [21], but there were no data stratified by gender or age. In a study including 990 pregnant women and 965 non-pregnant women matched for age and residence, the overall prevalence was 25.3% (95% confidence interval (CI): 22.5–28.0%), and age-specific prevalences were 21.8%, 25.6%, and 29.6% (95% CIs: 16.7–26.9%, 22.0–29.2%, and 22.6–36.7%) for women aged <25, 26–35 and >35 years, respectively, without statistical differences between pregnant women and non-pregnant women [22]. The data are close to those reported in another study: the prevalence in 10,741 women of childbearing age was 24.24%, which increased with age [23]. According to these reports, the base-case value of anti-HEV prevalence in women aged 25 years was determined to be at 21.8%, and the 95% CI was used in sensitivity analyses.

In an extension of the phase III trial of HEV 239 [24], 3.16% of the initially seronegative subjects underwent positive seroconversion over the 7-month period, presumably in response to HEV infection. Therefore, we assumed that the annual incidence of HEV infection was about 5.42%. In the same study, the incidence of HEV asymptomatic infection was much higher than symptomatic infection. Rein et al. published their modeled estimates of the global incidence of HEV infection, and suggested that the probability of symptomatic cases in infected adults was 19.8% (95% CI: 16.7–22.9%) [1]. A wide range was given to each of these parameters due to the poor quality of reported incidence data of HEV infection in China. They were adjusted by ±50% in sensitivity analyses, but a very low value (0.5%) was assumed as the lower bound of annual HEV infection incidence in order to cover possible low incidences.

2.2.2. Screening test characteristics

The diagnosis of HEV infection was based on the detection of anti-HEV. The new Wantai anti-HEV rapid test (Wan Tai Pharmaceutical Co., Beijing, China) was easy to use and effective and rapid to detect HEV infection; it also displayed higher sensitivity and specificity than other assays [25,26]. In one study which assessed

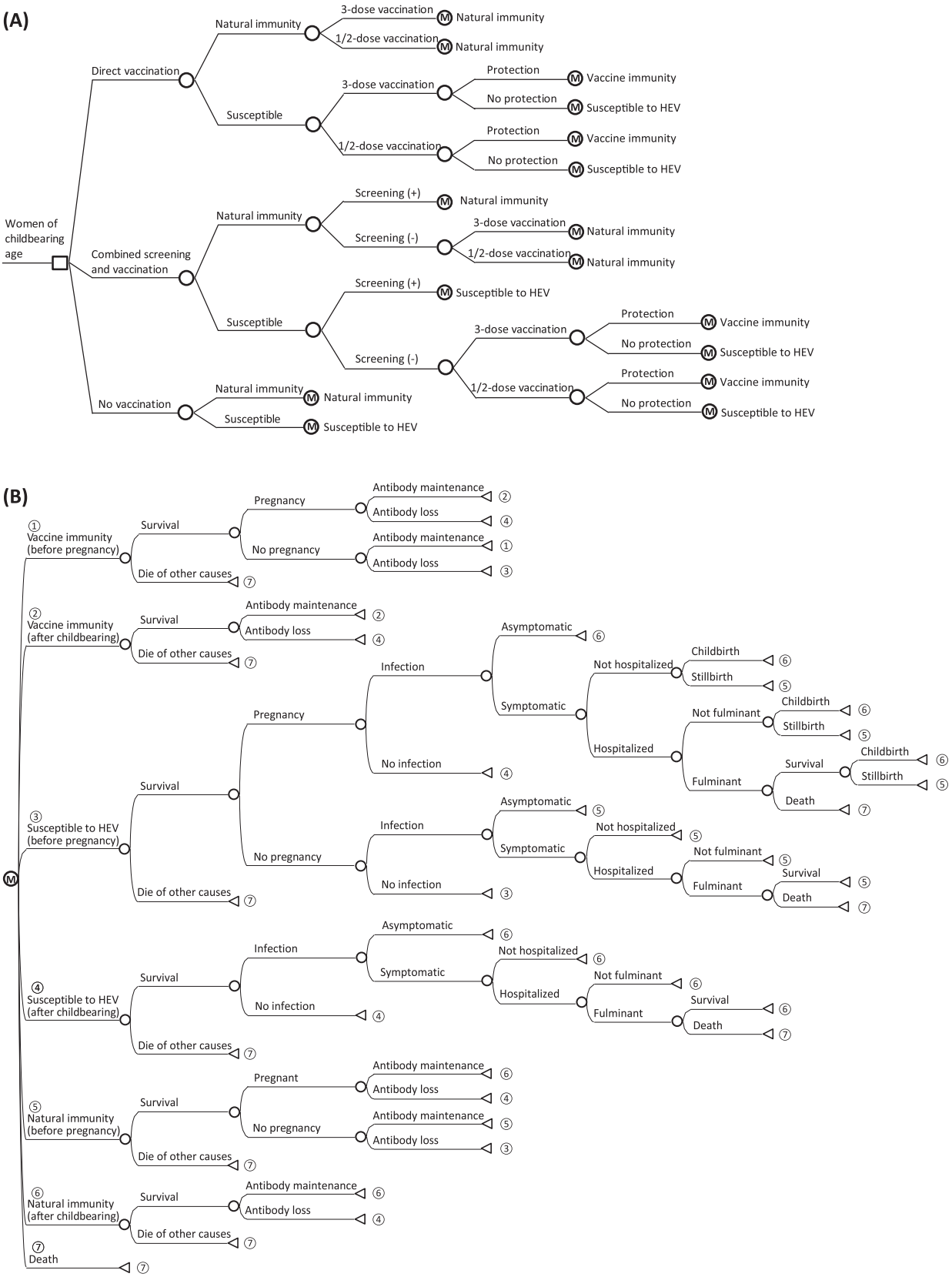

Fig. 1. Decision tree-Markov model of HEV vaccination in women of childbearing age. As shown in (A), the decision tree considers three alternative strategies and describes possible events following each strategy. After traversing the decision tree, a woman will enter one of pre-pregnancy health states of the Markov model according to her path in the decision tree, as shown in (B). Transitions occur between health states by the end of each cycle, as indicated by digital labels. The death state is the absorbing state of the Markov model, a woman may die due to fulminant hepatitis or other death causes.

Table 1
Base-case values, ranges and distributions of parameters used in the model.

Parameter	Base-case value	Range	Distribution	Reference
Screening test characteristics for anti-HEV				
Sensitivity	0.932	0.813–0.986	Beta (42.97, 3.14)	[25–27,29]
Specificity	0.978	0.895–0.993	Beta (182.82, 4.11)	[27]
Diagnostic odds ratio	601	301–902	Lognormal (6.4, 0.28)	[27,28]
Vaccination coverage				
Three-dose schedule	0.8	0.7–0.95	Triangular (0.7, 0.8, 0.95)	[30]
One/two doses	0.2	0.05–0.3	Triangular (0.05, 0.2, 0.3)	[30]
Vaccine protection				
Following three-dose vaccination	0.933	0.786–0.979	Triangular (0.786, 0.933, 0.979)	[15,16]
Following one/two-dose vaccination	0.851	0.671–0.933	Triangular (0.671, 0.851, 0.933)	[15,16]
Annual loss of protective antibody	0.034	0.017–0.051	Triangular (0.017, 0.034, 0.051)	[15,16,24]
Anti-HEV prevalence	0.218	0.167–0.269	Beta (54.76, 196.43)	[21–23]
Annual HEV infection incidence	0.054	0.005–0.081	Beta (172.35, 3019.4)	[24]
Symptomatic cases in infected women	0.198	0.099–0.297	Beta (122.62, 496.68)	[1,31]
Symptomatic cases that require hospitalization				[15,32]
Pregnant women	0.328	0.164–0.5	Triangular (0.164, 0.328, 0.5)	
Non-pregnant women	0.1	0.05–0.15	Triangular (0.05, 0.1, 0.15)	
Fulminant cases in hospitalized pregnant women	0.34	0.222–0.55	Triangular (0.222, 0.34, 0.55)	[4,33,34]
Fulminant cases in hospitalized non-pregnant women	0.04	0.01–0.1	Triangular (0.01, 0.04, 0.1)	[30]
Fulminant cases that result in death	0.612	0.503–0.72	Beta (47.43, 30.07)	[34,35]
Stillbirth in symptomatic pregnant women	0.214	0.146–0.292	Beta (26.08, 95.79)	[34]
Direct costs ($)				
Vaccination (per dose)	31	16–47	Triangular (16, 31, 47)	Government contract price and retail markup rate
Anti-HEV screening	4	2–6	Triangular (2, 4, 6)	National and local government pricing
Outpatient of acute viral hepatitis	95	48–143	Triangular (48, 95, 143)	[36–38]
Inpatient of acute viral hepatitis	3079	1540–4619	Triangular (1540, 3079, 4619)	[36,37,39,40]
Inpatient of fulminant hepatitis	5260	2630–7890	Triangular (2630, 5260, 7890)	[36,37,40,41]
Induced labor	707	354–1061	Triangular (354, 707, 1061)	[42,43]
Work loss days				
Inpatient of acute viral hepatitis	16	8–24	Triangular (8, 16, 24)	[30]
Inpatient of fulminant hepatitis	33	17–50	Triangular (17, 33, 50)	[30]
Induced labor	6	4–8	Triangular (4, 6, 8)	[42]
Average daily wage in 2016 ($)	28	14–42	Triangular (14, 28, 42)	China Statistical Yearbook, 2017
Annual daily wage increase	0.04	0–0.08	Triangular (0, 0.04, 0.08)	Indexes of average real wage since 1995
Disability weight				
Symptomatic infection (non-hospitalized)	0.058	0.029–0.087	Triangular (0.029, 0.058, 0.087)	[44]
Symptomatic infection (hospitalized)	0.353	0.177–0.53	Triangular (0.177, 0.353, 0.53)	[44]
Stillbirth (to impair the health of women)	0.02	0.01–0.03	Triangular (0.01, 0.02, 0.03)	[45]
Symptomatic infection duration (days)	40	20–60	Triangular (20, 40, 60)	[30]
Discount rate	0.05	0–0.1		[47]

the sensitivity and specificity of the Wantai rapid test respectively using blood samples from acutely-infected patients and uninfected children [27], the sensitivity was 93.2% (95% CI: 81.3–98.6%) and the specificity was 97.8% (95% CI: 95.6–99.9%). Given the inverse relationship between sensitivity and specificity, we modeled the specificity as a function of the sensitivity and the diagnostic odds ratio (DOR), i.e, specificity = $(1 - \text{sensitivity}) \cdot \text{DOR}/[\text{sensitivity} + (1 - \text{sensitivity}) \cdot \text{DOR}]$. The DOR was calculated according to a published literature by Genders et al. [28]. The sensitivity in other studies of assessing the Wantai rapid test varied from 91% (95% CI: 81–97%) to 96.1% (95% CI: 79.6–99.9%) [26,29]. In this study, the base-case value of sensitivity was determined to be at 93.2%, and the 95% CI was used in sensitivity analyses. The DOR was adjusted by ±50% in sensitivity analyses to cover uncertainties.

2.2.3. Vaccine coverage and protective efficacy

Due to the sufficient availability of HEV 239 for women of childbearing age in China, we estimated that 80% of the cohort members would receive 3-dose vaccination [30], and the remainders would receive 1- or 2-dose vaccination. The rate was adjusted between 70% and 95% according to the difference in the coverage of the 3-dose vaccination between rural and urban areas [30]. The vaccine protective efficacy was reported as 93.3% (95% CI: 78.6–97.9%) with 3-dose regimen and 85.1% (95% CI: 67.1–93.3%) with the 1- or 2-dose regimen in healthy adults aged 16–65 years in the phase III trial, respectively [15,16], but no data stratified by gender or age. So we made a homogeneous assumption that women of childbearing age had the same vaccine protective efficacy as healthy adults aged 16–65 years. The phase III trial showed that HEV 239 was well-tolerated and side-effects were few and mild which did not require medical treatment [15]. In addition, the preliminary observation suggested that HEV 239 was safe for both mother and fetus when analyzing the records of women who were pregnant at the time of enrollment or became pregnant during the course of the trial and were inadvertently given the vaccine [20]. So adverse effects of HEV 239 were ignored in our study. The protective antibody obtained from vaccination or infection had been found to wane over a period of time [16]. It was supposed in our model that the protective antibody loses according to a certain proportion every year and a person who loses the protective antibody has the same risk of infection as those who are susceptible to HEV. Based on published data, 99% of those vaccinated with 3-dose regimen developed the protective antibody and 4 years later, 87% still had the protective antibody [15,16], and in another study 2.59% of the initially seropositive participants underwent negative seroconversion over the 7-month period [24], we estimated an annual loss of protective antibody at about 3.39% for both vaccine and natural immunity. It was raised and reduced by 50% in sensitivity analyses.

2.2.4. Outcome and transition probabilities of HEV infection

HEV infection is a transient process, and only the patients with fulminant hepatitis may die due to the infection. Probabilities of symptomatic cases that required hospitalization were estimated based on previous studies [15,32]. Probabilities of pregnant and non-pregnant women with symptomatic infection that progressed to fulminant hepatitis were derived from previous systematic reviews and published studies [4,30,33,34]. The case fatality rate of fulminant hepatitis was determined based on previous studies [34,35]. The probability of stillbirth in symptomatic pregnant women was determined based on published literatures [34], which was used as the likelihood of induced labor. A wide range was given to each of these parameters to cover the majority of reported data in sensitivity analyses.

Population-based age-specific mortality rates were obtained from the China Statistics Yearbook, 2017. Age-specific pregnancy rates were obtained from the tabulation in the Population Census of China, 2010. The rates were transformed to the probabilities by the formula embedded in TreeAge.

2.2.5. Costs

Costs were converted from Chinese dollar to US dollar ($) at an average exchange rate of 6.6423 in 2016. The cost of vaccination was determined at $31 per dose based on the current government contract price of HEV 239 (No. JKZX-2016-11-01 from the Chinese Government Procurement Network) and the permitted retail markup rate for vaccines which are not introduced into the national immunization program, which included the cost of vaccine and syringe, the cost of storage and transportation of vaccine, and the cost of administration of vaccination. The cost of screening was determined at $4 according to the national and local government pricing, including the expenses of test and administration. Because obtaining vaccination or screening is convenient, we did not consider the potential costs of travel and time loss for getting the services.

For the cost of hepatitis E, we considered direct costs, which were further divided into direct medical costs and direct nonmedical costs, and indirect costs. Direct medical costs included HEV-related outpatient expenditure, inpatient expenditure, and expenditure for medicines self-purchased in retail pharmacies. Direct nonmedical costs included the family's travel expenses for getting treatment and the patient's extra health product expenses. Indirect costs were the productivity losses caused by illness. Direct costs of acute viral hepatitis and fulminant hepatitis were estimated from economic burden surveys on hepatitis E and other types of viral hepatitis in China [36,37,40,41]. These direct costs are close between different types of viral hepatitis. Direct costs of induced labor for stillbirth were determined according to published studies from China [42,43]. Due to the large differences in reported costs from different regions of China, a wide range (±50%) was given in sensitivity analyses to cover uncertainties.

Indirect costs were estimated by the Human Capital Approach. The work-loss days of acute viral hepatitis and fulminant hepatitis were determined based on previous publications [30]. The work-loss days of induced labor were derived from a previous study [42]. The average daily wage in 2016 was determined from the China Statistical Yearbook, 2017. According to the national indexes of average real wages since 1995, we conservatively estimated a 4% annual increase for daily wage that was used during the entire time horizon of analysis. This parameter was adjusted between 0 and 8%.

2.2.6. Disability weights and discount rate

Disability-adjusted life-year (DALY) was used to evaluate the effectiveness of each alternative strategy. DALYs were the sum of years of life lost (YLLs) and years lost due to disability (YLDs). Disability weights of non-hospitalized and hospitalized symptomatic infections were determined according to a published study [44], and the disability weight of stillbirth to impair the health of women was derived from another study [45]. The symptomatic infection duration was considered as the duration of disability [30]. DALYs were calculated by the published formula [46]. The discount rate was set at 5% because of the expectation of continuous high economic growth in China [47], and was adjusted between 0% and 10% in sensitivity analyses. Costs, YLLs, YLDs and DALYs predicted to occur in future years were discounted to the present values in 2016 using the same discount rate.

2.3. Cost-effectiveness analysis

The expected cost and effectiveness were obtained for each of three strategies by running the model. They were compared between three strategies and incremental cost-effectiveness ratios (ICERs) were calculated based on the measures of YLL and DALY, respectively. If YLL was used all costs were considered, but if DALY only direct costs. The ICER calculated based on DALY (i.e. additional costs per DALY averted) was used as the key indicator to decide whether a strategy is cost-effective compared with another. Due to the lack of data of Chinese willingness-to-pay (WTP), we compared the ICER with Chinese per-capita gross domestic product (GDP), which was $8127 in 2016, according to the recommendation of the World Health Organization [48].

2.4. Sensitivity analysis

A series of sensitivity analyses were performed to evaluate the uncertainty of parameter estimates and the robustness of the model. Univariate sensitivity analyses were done for all parameters within their respective ranges to show how each parameter impacted the results and to identify main influential parameters. Threshold analyses were followed to identify the thresholds of main influential parameters for the ICERs <0, <1 or >3 times per-capita GDP. Probabilistic sensitivity analyses using second-order Monte Carlo simulation were further conducted to estimate the simultaneous impact of parameter uncertainty on the base-case results. The choice of distribution was based on consideration of the properties of the parameters and data informing the parameters. The results of 1000 iterations were plotted as cost-effectiveness acceptability curves.

3. Results

3.1. Base-case results

As shown in Table 2, each of two vaccination strategies would obviously reduce HEV-related clinical outcomes compared with no vaccination. If direct vaccination or combined screening and vaccination was administered to 100,000 women aged 25 years, 7442 or 7279 symptomatic hepatitis cases, 65 or 64 fulminant hepatitis cases, and 40 or 39 deaths due to HEV could be averted compared with no vaccination, and thus a certain number of YLLs (999 or 977) and DALYs (1510 or 1477) could be averted. With large per-capita intervention costs ($89 or $73), each of two vaccination strategies would need more total direct costs (per-capita $61 or $46) and total costs (per-capita $26 or $12) compared with no vaccination. Together with the results of health benefit, the ICERs based on DALY of two vaccination strategies versus no vaccination were $4040 and $3114, respectively, much lower than the per-capita GDP ($8127). The similar results appeared when the ICERs were calculated based on YLL. Compared with combined screening and vaccination, direct vaccination would need $45,455 additional

Table 2
HEV-related health and economic outcomes and ICERs between strategies.

	No vaccination	Direct vaccination	Combined screening and vaccination
HEV-related health outcomes (100,000 cohort members)			
No. of symptomatic hepatitis	12,759	5317	5480
Pregnant women	425	98	106
Non-pregnant women	12,334	5219	5374
No. of fulminant hepatitis	97	32	33
Pregnant women	47	11	12
Non-pregnant women	50	21	21
No. of HEV-related death	59	19	20
Pregnant women	29	7	7
Non-pregnant women	30	12	13
YLLs*	1353	354	376
YLDs*	783	272	283
DALYs*	2136	626	659
Per-capita HEV-related costs ($)*			
Screening and vaccination costs	0	89	73
Direct medical and nonmedical costs	41	13	14
Total direct costs	41	102	87
Indirect costs (productivity lost)	59	24	25
Total costs	100	126	112
ICERs of vaccination strategies versus no vaccination*			
Additional costs ($) per YLL averted	/	2603	1228
Additional costs ($) per DALY averted	/	4040	3114
ICERs of direct vaccination versus combined screening and vaccination*			
Additional costs ($) per YLL averted	/	63,636	/
Additional costs ($) per DALY averted	/	45,455	/

*Expressed as the present value in 2016.
Abbreviations: ICER, incremental cost-effectiveness ratio; YLL, year of life lost; YLD, year lost due to disability; DALY, disability-adjusted life-year.

costs for each DALY averted, which is far more than the 3-time per-capita GDP ($24,381).

3.2. Sensitivity analysis results

Univariate sensitivity analyses found that annual HEV infection incidence was a main influential parameter (Fig. 2(A)). With its decrease to a low level (1.0% for direct vaccination and 0.8% for combined screening and vaccination), the ICERs of each vaccination strategy compared with no vaccination would exceed the 3-time per-capita GDP. All other parameters would not produce this result when they change independently in respective estimated ranges. The cost of vaccination was a main influential parameter that significantly affected the ICER of direct vaccination versus combined screening and vaccination (Fig. 2(B)). When the cost of vaccination per dose decreased to $20.6, slightly higher than $16 (the estimated lower bound), the ICER would fall below the 3-time per-capita GDP. If it continued to decrease to $11.8, and even to $7.4, the ICER would fall below the 1-time per-capita GDP and 0, respectively. Anti-HEV prevalence was another potential parameter to affect the ICER of direct vaccination versus combined screening and vaccination (Fig. 2(C)). When it decreased to 14.7%, 7.6% and 3.6%, the ICER would fall below the 3-time, 1-time per-capita GDP and 0, respectively. However, the 14.7% of anti-HEV prevalence was already lower than the estimated lower bound 16.7%.

The probabilistic sensitivity analyses conducted respectively for each vaccination strategy versus no vaccination showed that two

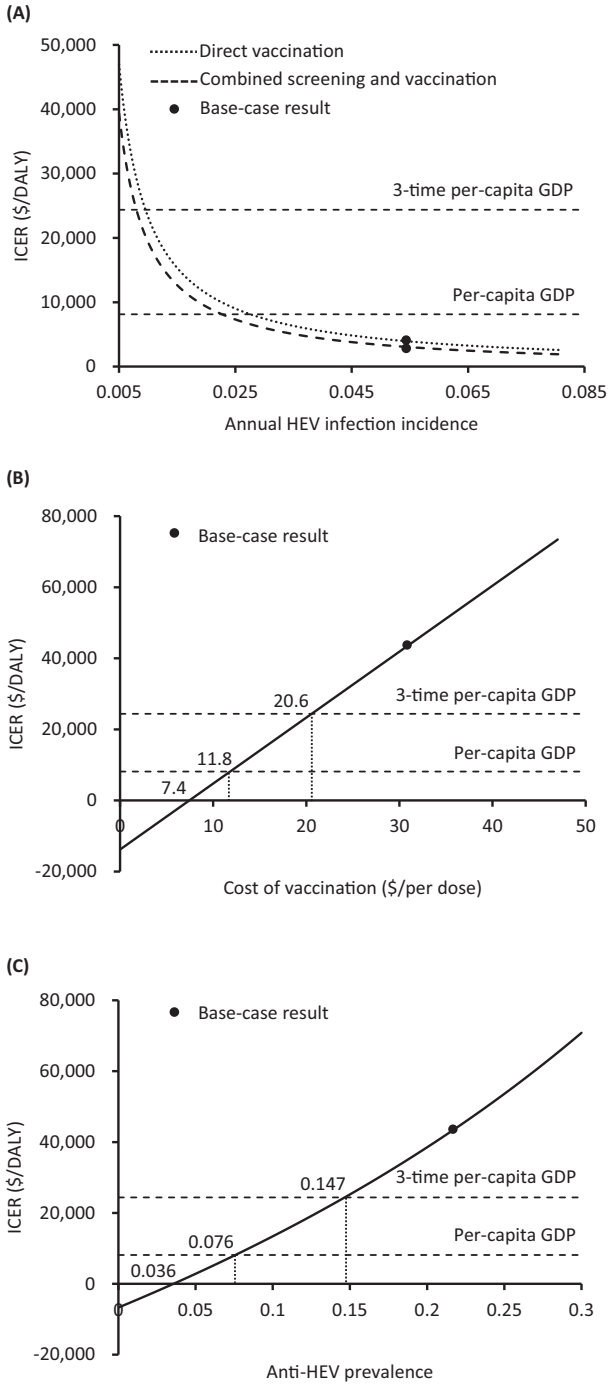

Fig. 2. Univariate sensitivity analysis results of main influential parameters. (A) ICERs of two vaccination strategies versus no vaccination, respectively, with the change of annual HEV infection incidence. (B) ICERs of direct vaccination versus combined screening and vaccination with the change of the cost of vaccination. (C) ICERs of direct vaccination versus combined screening and vaccination with the change of anti-HEV prevalence. Abbreviations: ICER, incremental cost-effectiveness ratio; DALY, disability-adjusted life-year; GDP, gross domestic product.

vaccination strategies could have a high probability of being cost-effective when the WTP reached the 1-time per-capita GDP, 0.984 for direct vaccination and 0.998 for combined screening and vaccination (Fig. 3(A)). The probabilistic sensitivity analysis conducted for all three strategies competing with each other showed that with the increase of WTP, combined screening and vaccination and direct vaccination would successively exceed no vaccination in the probability of being optimal, and that combined

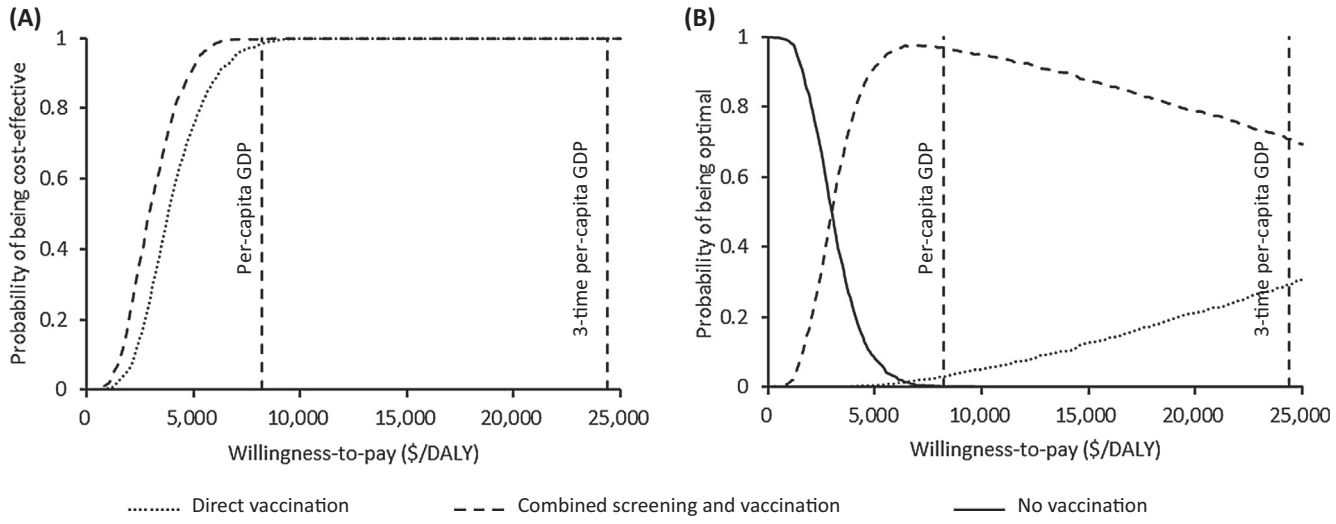

Fig. 3. Probabilistic sensitivity analysis results. (A) Cost-effectiveness acceptability curves of each vaccination strategy versus no vaccination, respectively. (B) Cost-effectiveness acceptability curves of all strategies competing with each other. Abbreviations:DALY, disability-adjusted life-year; GDP, gross domestic product.

screening and vaccination could maintain its dominance from a WTP less than the 1-time per-capita GDP to the WTP equal to the 3-time per-capita GDP (with a probability of 0.97 and 0.709 of being optimal at the 1- and 3-time per-capita GDP, respectively) (Fig. 3(B)). It is therefore quite certain that two vaccination strategies all would be cost-effective compared with no vaccination if the WTP reached the 1-time per-capita GDP, and that combined screening and vaccination would be more cost-effective compared with direct vaccination within the WTP of the 3-time per-capita GDP.

4. Discussion

Hepatitis E is an important global public health concern, occurring sporadically or as disease outbreaks in at least 63 countries [19]. A distinctive characteristic of hepatitis E is the high morbidity of fulminant hepatitis and the resulting deaths in pregnant women [1]. Besides, the infection during pregnancy is associated with poor fetal outcomes [7,10]. Hepatitis E prevention through vaccination would be a realistic possibility and most useful in developing countries where the virus is endemic [49]. Currently, there are two vaccines for hepatitis E that have been tested in human clinical trials, of which one, HEV 239, has been licensed and used in China.

This cost-effectiveness analysis showed that compared with no vaccination, two potential vaccination strategies all would be cost-effective in women of childbearing age of China under the base-case scenario from the societal perspective if the WTP reached the 1-time per-capita GDP, consistent with findings of a previous study [32]. We tried to make relatively accurate estimates for each parameter through various available methods. Nevertheless, data on the incidence of HEV infection is limited in China. So we assumed a very wide range for this parameter. Univariate sensitivity analyses found that annual HEV infection incidence was the only parameter, and with its change in the estimated possible range the ICERs of two vaccination strategies could exceed the 3-time per-capita GDP. However, the threshold 1.0% or 0.8% for the result to be reversed is far lower than reported annual HEV infection incidences in China [3,24]. It should be a small probability event to encounter such a scenario, at least for now. The results of probabilistic sensitivity analysis confirmed the robustness of the finding that two vaccination strategies would be cost-effective.

Our study found that combined screening and vaccination would be more cost-effective compared with direct vaccination. Although direct vaccination could obtain more heath benefit than combined screening and vaccination, the resulting increase in costs for a DALY averted is too high, far more than the 3-time per-capita GDP. The results of probabilistic sensitivity analysis confirmed this finding. Generally, whether or not screening should be done before vaccination largely depends on costs of vaccination and prevalence of infection. The univariate sensitivity analysis found that direct vaccination could be cost-effective and even cost-saving compared with combined screening and vaccination if the cost of vaccination per dose dropped to a corresponding low level. The price of HEV 239 is high now, which as a major component determines the cost of vaccination. A decline in the vaccine price can be expected in the future with the increase of application and the expansion of output, especially if the vaccine is introduced into the national immunization program. Direct vaccination could be preferred if anti-HEV prevalence decreased to a low level. However, high anti-HEV prevalence was continuously reported in China [21–23], and it is unrealistic to meet the low anti-HEV prevalence at present.

To our knowledge, this study was the first cost-effectiveness analysis to account for vaccination with HEV 239 in women of childbearing age. The only previous study about the cost-effectiveness of HEV 239 was published in 2016 by Zhao et al. [32], which focused on pregnant women in epidemic regions of China by using a decision tree model. In the current study, we took pains to ensure the reliability of results. First, the model structure was communicated repeatedly with clinical experts to align with the clinical practices to the greatest extent possible. Only hospitalized symptomatic infection may progress to fulminant hepatitis with different probabilities according to whether or not the patient was pregnant. Only patients with fulminant hepatitis may die due to HEV infection. Second, the conservative strategy was adhered as much as possible in simplifying modeling to avoid the overestimation of benefit of a new vaccine. We assumed the cohort members could have only one child at most, and we did not consider the impact of HEV infection during pregnancy on the fetus itself.

There were several limitations in our study. First, simple triangular distribution was used for the majority of model parameters in probabilistic sensitivity analyses, due to the lack of data. Generally, probability and disability weight parameters should be specified as a beta distribution, and cost parameters should as a gamma

distribution. This may result in a bias of our results, but the direction of bias is unclear. Second, side-effects following vaccination were not considered based on several limited studies on HEV 239 [15,18,20]. Further studies are needed with the emergence of solid side-effects data in the future. Third, the high efficacy of the vaccine was primarily against genotype 4 of HEV in China, possibly resulting in an overestimation of effectiveness for vaccination strategies. Nevertheless, all the genotypes belong to a single serotype, and therefore HEV 239 may be expected to protect against infection with all four genotypes [19].

In conclusion, the current study found that from the societal perspective, vaccinating women of childbearing age with HEV 239 would cost less than the 1-time per-capita GDP for each DALY averted in China, and the vaccination with a prior screening would be the optimal option. It is important to emphasize that information of cost-effectiveness can guide policy-makers, but should never be used as a stand-alone criterion for decision-making. Whether or not a new intervention is introduced needs to analyze and judge comprehensively combining with other information including affordability, budget impact, fairness and feasibility in the local context [50].

Contributions

Ruyi Xia participated in the design, conducted statistical analyses and drafted the manuscript. Shuliu Sun participated in the design and data collection. Mingwang Shen and Lei Zhang helped to revise the manuscript. Guihua Zhuang participated in the design, revised the draft and gave the technical support. All authors read and approved the final manuscript.

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Declaration of Competing Interest

There is no conflict of interest in this paper.

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