



## Tenofovir prophylaxis for preventing mother-to-child hepatitis B virus transmission in China: A cost-effectiveness analysis



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### ABSTRACT

**Objectives:** This study aimed to evaluate whether tenofovir prophylaxis for mothers with high viral loads in late pregnancy is a cost-effective way to prevent mother-to-child hepatitis B virus (HBV) transmission in China.

**Methods:** A decision tree Markov model was constructed for a cohort of infants born to HBV surface antigen-positive mothers in China, 2016. The expected cost and effectiveness were compared between the current active-passive immunoprophylaxis strategy and the tenofovir prophylaxis strategy, and the incremental cost-effectiveness ratio was calculated. One-way and multi-way probabilistic sensitivity analyses were performed.

**Results:** For 100,000 babies born to mothers positive for hepatitis B surface antigen, tenofovir prophylaxis strategy will prevent 2213 perinatal HBV infections and will gain 931 quality-adjusted life years when compared with the current active-passive immunoprophylaxis strategy. The incremental cost-effectiveness ratio was ¥ 59,973 (\$9087) per quality-adjusted life years gained. This result was robust over a wide range of assumptions.

**Conclusions:** Tenofovir prophylaxis for mothers with high viral loads in late pregnancy was found to be more cost-effective than the current active-passive immunoprophylaxis alone. Embedding tenofovir prophylaxis for mothers with high virus loads into the present hepatitis B prevention strategies should be considered to further prevent mother-to-child hepatitis B transmission in China.

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### Introduction

Mother-to-child transmission (MTCT) is the most common mode of hepatitis B virus (HBV) transmission in highly endemic areas and accounts for 35–50% of chronic HBV infections in China (Yao, 1996). To prevent MTCT, active-passive immunoprophylaxis of hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) is recommended worldwide for infants born to Hepatitis B surface antigen (HBsAg)-positive mothers. Although this strategy has been

demonstrated to be very effective, a small proportion of infants remain infected (Wen et al., 2013). To further reduce the risk of MTCT, many guidelines recommend prophylactic use of antiviral treatment for mothers with high viral load during late pregnancy (Terrault et al., 2016; European Association for the Study of the Liver, 2017; Sarin et al., 2020). Among the available nucleos(t)ide analogues for pregnant women, tenofovir is recommended as the preferred choice because of its high antiviral potency and low resistance (European Association for the Study of the Liver, 2017).

In China, as many as 5.2% of childbearing-age women remain positive for HBsAg and 28.78% are positive for HBeAg which indicates a large number of newborn HBV infections (Zhang et al., 2017). Thus, prevention of MTCT is thought to be the main task of hepatitis B control in China. However, the high cost of tenofovir has hindered the scale-up use in hepatitis B prevention. After the

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National Drug Price negotiations in May 2016, the price of tenofovir (Viread, GlaxoSmithKline Inc.) plummeted to an all-time low (¥16.3/300 mg) and is now covered by health insurance in China. The China Foundation of Hepatitis Prevention and Control has recently published a management algorithm for interrupting MTCT, recommending antiviral use during late pregnancy for women with high viral loads (Hou et al., 2018). However, the Chinese government has not currently added antiviral prophylaxis in the prevention strategy of hepatitis B. Economic evaluation studies from the United States and Korea have proven that an antiviral prophylaxis strategy is more cost-effective than each country's current preventive strategy alone (Fan et al., 2016; Lee et al., 2018). Whether China should adopt tenofovir prophylaxis as a prevention strategy for further interrupting MTCT is unknown as there is no economic evaluation using the latest data.

This study aimed to evaluate whether tenofovir prophylaxis for mothers with high viral loads in late pregnancy is a cost-effective way to prevent MTCT of HBV in China. This research could provide important data for the policy-makers to improve the hepatitis B prevention strategy in China and be a reference for other Asian countries with similar prevalence and incidence of hepatitis B.

**Methods**

*Study population*

A decision tree Markov model was constructed for a closed cohort of infants born to HBsAg-positive mothers (Figure 1). Two alternative strategies were considered, based on the current hepatitis B prevention strategy in China: (1) V&H: all infants born to HBsAg-positive mothers receive a dose of 200 IU HBIG and a dose of 10 µg hepatitis B vaccine within 24 hours of birth. A further two doses of 10 µg vaccine are given at 1 and 6 months after birth, respectively. For accurate calculation, the branches of this strategy (V&H) in the decision tree were constructed the same as for tenofovir prophylaxis (TDF + V&H); (2) TDF + V&H: all HBsAg-positive mothers receive an HBV DNA quantitative test during the 24th and 28th weeks of pregnancy. The sensitivity and specificity of quantitative HBV DNA test for detecting 10<sup>5</sup> IU/ml are

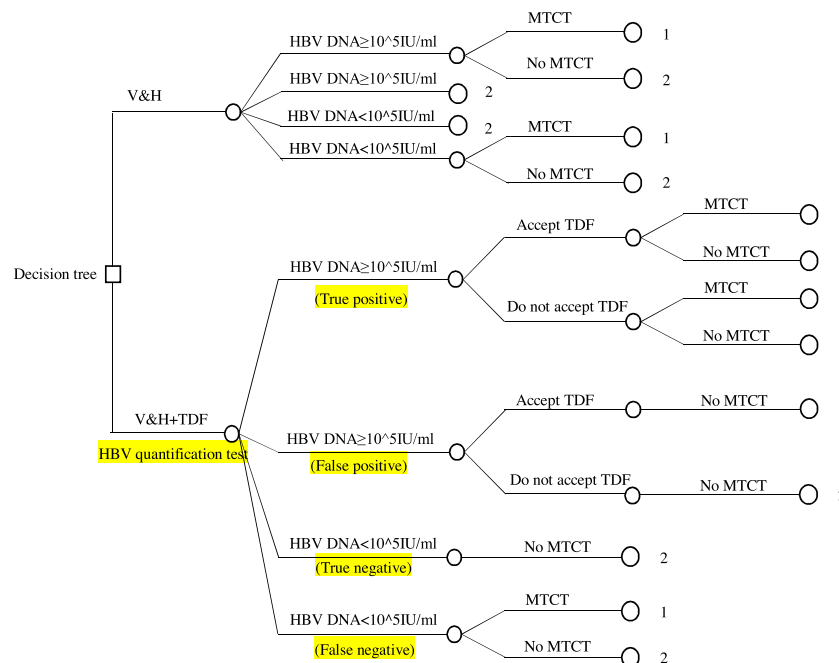
considered. Based on the results, mothers with HBV DNA ≥10<sup>5</sup> IU/ml (whether the result was true or not) are given tenofovir treatment (300 mg/day, orally) from the 28th week of pregnancy until 4 weeks postpartum. Otherwise, mothers are given no intervention. The acceptance rate of tenofovir prophylaxis is considered and assumed to be 1.0 in the base-case analysis. HBV DNA ≥10<sup>5</sup> IU/ml is chosen as the cut-off based on the recommendation of the American Association for the Study of Liver Diseases (AASLD) guideline. Babies should receive the same management as the V&H strategy. It is assumed that all cohort members will receive the active-passive immunoprophylaxis according to the high coverage of vaccination in newborn babies in China (>95%). It is also assumed that all HBsAg-positive mothers would accept HBV DNA quantification.

*Measures*

The Markov model consisted of seven health states based on a previous publication (Yin et al., 2015): immunity due to vaccination or perinatal infection; asymptomatic carriage; chronic hepatitis; compensated cirrhosis; decompensated cirrhosis; hepatocellular carcinoma; and death (Figure S1). Symptomatic acute hepatitis (rare in perinatal infections) and liver transplantation (with few applications relevant to the large patient population in China) were not considered in the model. The model was run for 91 cycles with a 1-year cycle length, in order to cover lifelong experiences of the vast majority of cohort members.

Base-case values, ranges and distributions of parameters used in the model were derived from published studies, government documents, and surveys from the current institutions. They are described below and summarized in Table 1.

The proportion of mothers with HBV DNA ≥10<sup>5</sup> IU/ml among HBsAg-positive mothers was calculated by pooling the results of a meta-analysis and two large cohort studies in China (Chen et al., 2018; Peng et al., 2018; Lu et al., 2017). The base-case value was 0.288 and ranged from 0.28–0.297 in deterministic sensitivity analyses based on the 95% CIs. The risk of MTCT for mothers with HBV DNA ≥10<sup>5</sup> IU/ml under the V&H strategy was conservatively estimated to be 9.93%, based on a recently published meta-analysis



**Figure 1.** Decision tree.

**Table 1**

Base-case values, ranges and distributions of parameters used in the model exploring the cost-effectiveness of tenofovir prophylaxis in China, 2016.

Parameter	Base-case value	Range	Distribution	Reference
<b>Annual transition probabilities</b>				
<b>Asymptomatic carrier</b>				
To immune (clearance of HBV)	0.01	0–0.015	Beta (76, 7,514)	Simonetti et al., 2010
<b>To chronic hepatitis</b>				
0–19 years	0.0012	±50%		Hung and Chen, 2009;
20–39 years	0.0023	±50%		Jacobs et al., 2003
≥40 years	0.0054	±50%		
<b>To hepatocellular carcinoma</b>				
0–19 years	0.0005	±50%		Jacobs et al., 2003;
20–39 years	0.002	±50%		Tilson et al., 2008
≥40 years	0.0061	±50%		
<b>Chronic hepatitis</b>				
To asymptomatic carrier	0.015	0–0.05	Beta (222, 14,553)	Hung and Chen, 2009;
<b>To compensated cirrhosis</b>				
0–19 years	0.015	±50%		Jacobs et al., 2003;
20–39 years	0.02	±50%		Jacobs et al., 2003;
≥40 years	0.027	±50%		Tilson et al., 2008
<b>To hepatocellular carcinoma</b>				
0–19 years	0.003	±50%		Jacobs et al., 2003;
20–39 years	0.005	±50%		Tilson et al., 2008
≥40 years	0.0064	±50%		
<b>Decompensated cirrhosis</b>				
To decompensated cirrhosis	0.073	0.03–0.1	Beta (142, 1,807)	Hutton et al., 2010;
To hepatocellular carcinoma	0.034	0.01–0.1	Beta (66, 1,886)	Chen et al., 2007
<b>Hepatocellular carcinoma</b>				
To death (disease-specific)	0.17	0.1–0.25	Beta (28, 138)	Liaw and Chu, 2009;
To death (disease-specific)	0.56	0.3–0.7	Beta (16,987, 13,347)	Liaw, 2009
<b>Cost (CNY)</b>				
<b>Chronic infections (per year)</b>				
Chronic hepatitis	6,400	±50%	Triangular (3,200, 6,400, 9,600)	
Compensated cirrhosis	10,872	±50%	Triangular (5,436, 10,872, 16,308)	
Decompensated cirrhosis	19,569	±50%	Triangular (9,785, 19,569, 29,354)	
Hepatocellular carcinoma	69,081	±50%	Triangular (34,541, 69,081, 103,622)	
<b>Vaccination</b>				
HBIG	200	100–300	Triangular (100, 200, 300)	
HBV DNA quantification	100	70–150	Triangular (70, 100, 150)	
TDF (per 300mg)	16.3	0.59–19.56	Triangular (0.59, 16.3, 19.56)	
<b>Work loss days (per year)</b>				
Chronic hepatitis	18	±50%		Jacobs et al., 2003;
Compensated cirrhosis	26	±50%		Zhang et al., 2016
Decompensated cirrhosis	40	±50%		
Hepatocellular carcinoma	150	±50%		
<b>Utility scores</b>				
Asymptomatic carrier	1	0.95–1	Triangular (0.99, 1, 1)	Hung and Chen, 2009; Hutton et al., 2007; Zhuang et al., 2014
Chronic hepatitis	0.9	0.8–1	Triangular (0.8, 0.9, 1)	
Compensated cirrhosis	0.8	0.7–0.93	Triangular (0.7, 0.8, 0.93)	
Decompensated cirrhosis	0.75	0.5–0.93	Triangular (0.5, 0.75, 0.93)	
Hepatocellular carcinoma	0.73	0.5–0.8	Triangular (0.5, 0.73, 0.8)	

Abbreviations: MTCT, mother-to-child transmission; V&amp;H, active-passive immunoprophylaxis; TDF, tenofovir; HBV, hepatitis B virus; CNY, Chinese Yuan.

# Government guidance price

(Chen et al., 2018). The 95% CIs (6.35–13.52%) of this parameter were used as the range in the deterministic sensitivity analyses. The relative risk (RR) of MTCT was 0.23 for mothers with HBV DNA  $\geq 10^5$  IU/ml under the TDF + V&H strategy compared with the V&H strategy (Brown and McMahon, 2016; Hyun et al., 2017). This parameter fluctuated from 0.10–0.52 in deterministic sensitivity analyses based on the 95% CIs. The risk of MTCT among mothers with HBV DNA  $< 10^5$  IU/ml was set to 0 in the model because studies have reported few infections under this concentration (Lu et al., 2017; Zou et al., 2012). The potential adverse effect of antiviral prophylaxis was not considered in the model. The

protection obtained from vaccination was considered to be lifelong.

Annual transition probabilities related to chronic HBV infection were determined based on published studies that have been used in many hepatitis B-related economic evaluation studies. A wide range was given to each of these parameters to cover the majority of reported data. For variables thought to be age-dependent, age-specific base-case values were adjusted simultaneously by  $\pm 50\%$  in deterministic sensitivity analyses. Population-based age-specific mortality rates were obtained from the China Population & Employment Statistics Yearbook, 2017. The rates were transformed

to probabilities by the formula embedded in TreeAge software to predict deaths due to other causes ([www.treeage.com](http://www.treeage.com)). Both the sensitivity and specificity of quantitative HBV DNA test for detecting  $10^5$  IU/ml were estimated to be 0.985 based on the performance of a domestic real-time fluorescence quantitative PCR kit (Huosheng et al., 2006). Wide ranges were given in the sensitivity analysis to cover the efficacy of variety kinds of kits used across health agencies in China (sensitivity: 0.500–0.985; specificity: 0.500–0.985).

The cost of the three-dose 10 µg series was estimated at ¥20, based on the current national and local government contract prices for 10 µg vaccines and syringes and on subsidies to the health system for the administration of vaccinations. The cost of HBIG (200 IU) was estimated at ¥200, ranging between 100 and 300, based on local government contract prices. The cost of HBV DNA quantification was estimated at ¥100 by averaging government guidance prices for public hospitals in various provinces in China. The range of this parameter was 70–150, covering the prices of most provinces in China. The cost of tenofovir prophylaxis was calculated by multiplying the daily dose cost with the average days of treatment (119 days). Daily dose cost of tenofovir was estimated at ¥16.3, according to the Chinese government guidance prices published in 2016 (Viread, GlaxoSmithKline Inc.). The range was from 0.59–19.56 in deterministic sensitivity analyses.

The total cost of each type of chronic HBV-related disease consisted of two parts: direct cost, which was further divided into direct medical cost and direct nonmedical cost; and indirect cost. The direct medical cost included outpatient expenditures, inpatient expenditures, and self-medication expenditures. A survey in 27 hospitals from 12 cities of six provinces across eastern, central and western areas of China was conducted to assess the economic burden of HBV-related diseases. The following were calculated: per-capita outpatient expenditures, inpatient expenditures, self-medication expenditures, and direct nonmedical costs in a single visit or admission for each type of HBV-related diseases in this survey (Zhang et al., 2016). The costs in 2016 were calculated by multiplying the results in the survey mentioned above with the medical care consumer price index from 2009 to 2016. Together with other domestic reports, the per-capita annual outpatient visit rate and annual inpatient admission rate were determined for each type of chronic HBV-related diseases. Using these data, the annual direct cost for each type of chronic HBV-related diseases was calculated. The economic burden of asymptomatic HBV carrier was not considered in the model. The base-case values of these direct costs were simultaneously adjusted by ±50% in deterministic sensitivity analyses to cover the differences among the provinces.

Indirect costs – the productivity losses caused by HBV-related disease – were estimated using the human capital approach. Work loss days for each type of chronic HBV-related diseases were determined according to studies, and the base-case values were adjusted simultaneously by ±50% in deterministic sensitivity analyses (Jacobs et al., 2003; Zhang et al., 2016). If patients were aged 18–59 years, only patient productivity losses were considered; otherwise, only productivity losses of the family caregiver were considered, which was assumed to be half of the patient

productivity loss. The average daily wage in 2016 was ¥270, which was obtained from the China Statistical Yearbook 2017. It dropped by as much as 50% in deterministic sensitivity analyses because of the potential overestimation of the human capital approach to productivity loss. According to the national indexes of average real wages since 1995, a 4% annual increase for daily wage was conservatively estimated, which was used during the entire time horizon of the analysis.

This study investigated the health-related quality of life of chronic hepatitis B patients using the SF-36 questionnaire and the scores were transformed into utility using the Hong Kong algorithm (Zhuang et al., 2014). Together with other reports, this study determined the utility of each type of chronic hepatitis B patient (Hutton et al., 2007; Hung and Chen, 2009; Zhuang et al., 2014). The ranges of utilities covered the majority of data reported in the literature. The discount rate was determined to be 5% because of the expectation of continuous and high economic growth in China, adjusted to between 0% and 8%.

### Statistical analysis

The expected costs were calculated from both a healthcare perspective and societal perspective. A series of life-long HBV-related health outcomes were predicted, including perinatal infections, chronic hepatitis, cirrhosis, hepatocellular carcinoma, death, life-years lost, and quality-adjusted life-years (QALYs) lost. The health outcomes were calculated based on 100,000 babies born to HBsAg-positive mothers in 2016. The incremental cost-effectiveness ratio (ICER) was calculated based on the measures of life-years and QALYs, respectively. If life-year was used, all costs were considered; if QALY was used, only the direct costs were considered, according to the expert panel recommendation. Costs, life-years and QALYs predicted to occur in future years were discounted to the values in 2016 by the same discount rate. The ICER based on QALYs was used as the key indicator to decide which strategy was more cost-effective. Following the recommendation of the World Health Organization, a strategy is considered to be highly cost-effective, cost-effective or cost-ineffective compared with another if the ICER is <1, 1–3 or >3 times per-capita gross domestic product (GDP), respectively. The per-capita GDP of China was ¥53,980 (\$8179) in 2016.

One-way deterministic sensitivity analysis was performed to preliminarily test the robustness of the base-case results and to determine the most sensitive parameters. Multi-way probabilistic sensitivity analysis using Monte Carlo simulation was performed to further test the robustness of the base-case results. The probability parameters were specified as beta distributions. The cost parameters were simply specified as triangular distributions to match the differences among the provinces. The utility parameters were also modelled by triangular distributions.

### Results

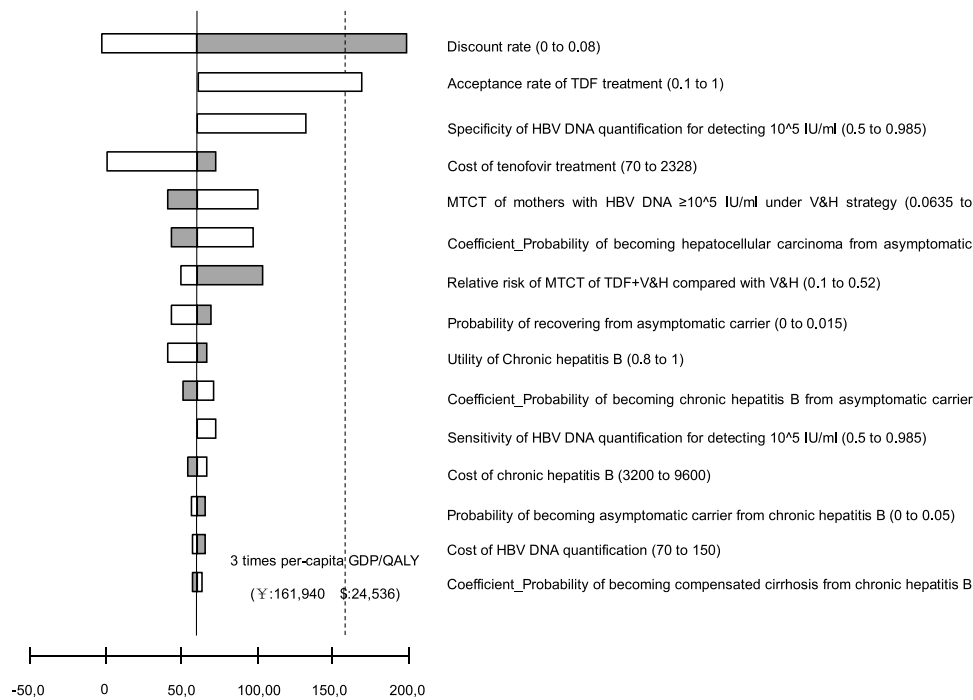
For every 100,000 babies born to HBsAg-positive mothers, the TDF + V&H strategy will save 2213 perinatal infections, 305 chronic hepatitis, 365 hepatocellular carcinomas, and 416 hepatitis B-

**Table 2**

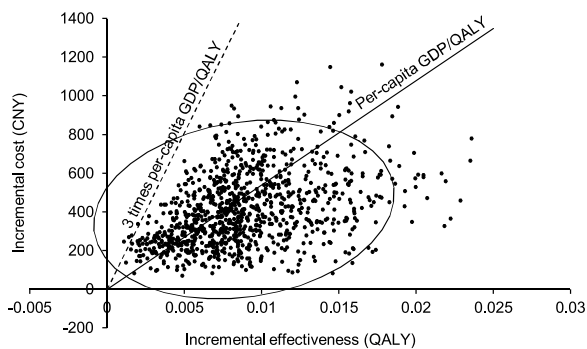
Base-case result of lifetime cost, quality-adjusted life years, and life-years of the two alternative strategies in China, 2016.

	Direct cost (¥)	Incremental cost (¥)	QALY	Incremental QALYs	ICER
V&H (Reference)	368	–	19.846418	–	–
TDF + V&H	927	559	19.855734	0.009316	59973

Abbreviation: QALY, quality-adjusted life year; ICER, incremental cost-effective ratio; V&H, active-passive immunoprophylaxis; TDF, tenofovir.



**Figure 2.** Tornado diagram: ICERs of TDF + V&H strategy compared with V&H strategy when each parameter is varying in its range. Abbreviations: MTCT, mother-to-infant transmission; V&H, active-passive immunoprophylaxis; TDF, tenofovir; GDP, gross domestic product; QALY, quality-adjusted life-years



**Figure 3.** Incremental cost-effectiveness scatterplots of 1000 iterations for tenofovir prophylaxis strategy compared with active-passive immunoprophylaxis strategy in China, 2016.

Note: The ellipse shows the 95% confidence interval.

Abbreviations: CNY, Chinese Yuan; GDP, gross domestic product; QALY, quality-adjusted life-years

related deaths compared with the V&H strategy. Furthermore, 822 life-years and 931 QALYs will be gained (Table S2).

As shown in Table 2, the ICER of TDF + V&H strategy compared with that of the V&H strategy was ¥59,973 (\$9087), between one and three times per capita GDP of China 2016. When calculated by total cost divided by life-years, the ICER (¥32,112) was lower than per capita GDP. This result suggests that the TDF + V&H strategy is more cost-effective than the V&H strategy.

One-way sensitivity analysis revealed that the parameter that most influenced cost-effectiveness was the discount rate, with the ICER exceeding three times per-capita GDP/QALY when varying in its range. The ICER remained less than three times per-capita GDP/QALY when the other parameters fluctuated separately in their ranges. Details are shown in Figure 2.

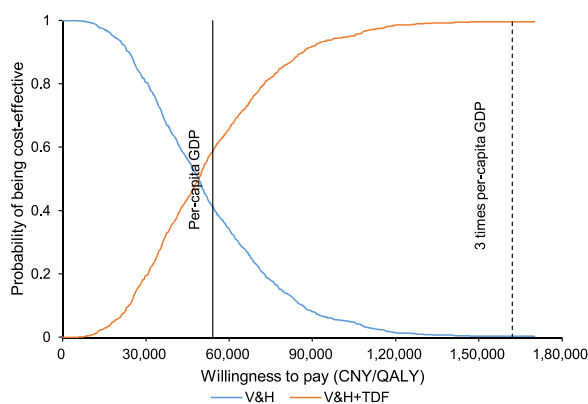
The results of multi-way probabilistic sensitivity analysis with 1000 iterations are shown in Figures 3 and 4. As shown in the

scatter plot, 99.9% of dots were in the lower right of the three times per-capita GDP/QALY threshold line and 40.9% of dots were under the one time per-capita GDP/QALY threshold line. This indicates that the TDF + V&H strategy is cost-effective and has a 40.9% possibility of being highly cost-effective compared with the V&H strategy. The cost-effectiveness accessibility curve in Figure 4 shows how preferable a strategy is as the willingness-to-pay increases. The TDF + V&H strategy has a higher probability of being cost-effective than that of the V&H strategy when the decision-maker pays more than ¥59,700 (\$9045) for an additional QALY.

## Discussion

The high risk of infection and development of chronic conditions suggests that infants are a key target population for hepatitis B prevention. The most important strategy to interrupt mother-to-infant HBV transmission is to deliver timely and complete active-passive immunoprophylaxis. Nevertheless, this strategy is ineffective in a certain proportion of infants born to highly viremic mothers. To achieve the goal of global eradication of HBV infection, better strategies are essential for this high-risk group. Using a growing body of evidence, updated guidelines from various international bodies and countries (Terrault et al., 2016; European Association for the Study of the Liver, 2017) – especially in the Asian-Pacific region, including China (Sarin et al., 2020; Chinese Society of Hepatology, 2015) have suggested prophylactic antiviral treatment for pregnant women with high viral loads, although it is not yet a routine strategy. Tenofovir is the first choice among all available agents because of its substantial effects in terms of interrupting MTCT and its low rate of side effects. Such treatment should last for limited periods for the benefit and lowest risk for mothers and fetuses, and it may be discontinued 1–3 months after delivery.

This study showed that, compared with current active-passive immunoprophylaxis, the TDF + V&H strategy would be more cost-effective for further interrupting MTCT in China. This result was



**Figure 4.** Cost-effectiveness acceptability curves for TDF + V&H strategy compared with V&H strategy in China, 2016.

Abbreviations: GDP, gross domestic product; CNY, Chinese Yuan; QALY, quality-adjusted life-years; V&H, active-passive immunoprophylaxis; TDF, tenofovir.

robust across a wide range of assumptions. In a previous study, Wang et al. evaluated the cost-effectiveness of an antiviral treatment strategy in China comparing three different antiviral agents (lamivudine, telbivudine and tenofovir) with active-passive immunoprophylaxis (Wang et al., 2016). Their findings suggested that telbivudine was the most cost-effective strategy for China. This conclusion was based on the cost of telbivudine and tenofovir at that time. However, the price of tenofovir is lower than that of telbivudine. With much lower cost and better effect, tenofovir will surely dominate the telbivudine strategy.

As the cost of tenofovir was one of the most sensitive parameters, this study explored how it would affect the ICER if it decreased in the future. When the price of tenofovir dropped to ¥14.71/300 mg, the TDF + V&H strategy became highly cost-effective compared with the V&H strategy, while all the other parameters kept the base-case value. Moreover, the TDF + V&H strategy became cost-saving with a price of ¥0.35 per day. Generic tenofovir became available in China in February 2018 and was on the list of government procurement at the price of ¥0.59/300 mg. However, the clinical effect for interrupting MTCT had not been reported. It is predicted that if the Chinese government adopted generic tenofovir as the preventive treatment agent for mothers, the TDF + V&H strategy would be highly cost-effective, as long as it can further reduce MTCT by 15.1% compared with active-passive immunoprophylaxis.

There are several assumptions regarding the strategies that were used in the model. First, HBV DNA quantification was considered for HBsAg-positive mothers because testing for HBsAg is a part of routine prenatal care in China. It is unnecessary to consider the cost of the HBsAg test in this model. Second, among the three available antiviral agents for pregnant women, only tenofovir was considered. The decision was made for the following reasons: lamivudine is not recommended by the guidelines because of its potential resistance (Terrault et al., 2016); tenofovir has the best treatment effect and the lowest side-effect rate; and the price of tenofovir is currently lower than that of telbivudine in China. Third, real-time fluorescence HBV DNA quantitative detection was used to examine the HBV DNA level in this model because it is one of the most widely used methods in China. However, various kinds of test kits and machines are used for HBV DNA quantification across China; therefore, the specificity and sensitivity of HBV DNA quantification were given wide ranges in the sensitivity analysis (0.500–0.985) to cover the efficacy of all kinds of tests. Finally, HBV DNA  $\geq 10^5$  IU/ml was chosen as the cut-

off point rather than  $10^6$  IU/ml, with a view to more mothers being eligible for TDF prophylaxis and thus potentially preventing more newborns from HBV infection. Also, selecting a lower HBV DNA level will lead to a conservative estimate of cost-effectiveness of TDF prophylaxis.

### Limitations

There were two limitations in this study. First, consistent with all previous studies, the adverse effect of the antiviral treatment was not considered in the modelling, possibly resulting in an overestimation of cost-effectiveness for tenofovir prophylaxis strategies. Further studies will be needed if solid adverse effect evidence arises in the future. Second, because of absence of the latest national data, the cost of HBV-related disease was estimated based on a large-scale investigation in 2009. Although the medical costs were adjusted to the price in 2016 by the medical care consumer price index, this approximate estimation may have introduced inaccuracy to the outcome.

### Conclusion

This study showed that tenofovir prophylaxis for highly viremic mothers in the third trimester is a cost-effective method for further preventing MTCT in China. The Healthcare Department of China may consider embedding tenofovir prophylaxis for highly viremic mothers into its hepatitis B prevention strategy for infants.

### Ethical approval

Not applicable.

**Disclosure statement:** All the authors reported no conflict of interest. The National T&S Major Project of China (grant no. 2018ZX10721202) founded this research. The authors have no industrial links or affiliations with the funder.

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### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2020.03.036>.

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