Expanding Antiviral Prophylaxis During Pregnancy to Prevent Perinatal Hepatitis B Virus Infection: A Cost-effectiveness Study

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Background. Mother-to-child transmission (MTCT) cannot be completely prevented by the administration of active-passive immunoprophylaxis in pregnant women with hepatitis B virus (HBV) DNA levels <10^6 copies/mL. This study will assess the economic outcomes of expanding antiviral prophylaxis in pregnant women with HBV DNA levels <10^6 copies/mL.

Methods. A decision model was adopted to measure the economic outcomes of expanded antiviral prophylaxis at different cutoff values of HBV DNA in HBsAg(+) pregnant women in the context of the United States and China. The model inputs, including clinical, cost, and utility data, were extracted from published studies. Sensitivity analyses were carried out to examine the uncertainty of the model outputs. Quality-adjusted life-years (QALYs) and direct medical costs were expressed over a lifetime horizon.

Results. Compared with standard antiviral prophylaxis at HBV DNA ≥10^5 copies/mL, expanded antiviral prophylaxis improved the health outcomes, and the incremental cost of expanded antiviral prophylaxis varied from $2063 in pregnant women with HBV DNA ≥10^5 copies/mL to $14,925 in all HBsAg(+) pregnant women per QALY gained in the United States, and from $1624 to $12,348 in China. The model outcome was considerably influenced by the discount rate, key clinical parameters related to the incidence of MTCT, and efficacy of the prophylaxis strategy.

Conclusions. This study indicates that antiviral prophylaxis using tenofovir among pregnant women with HBV DNA <10^6 copies/mL may be a cost-effective option, and the cutoff value of the HBV DNA load for antiviral prophylaxis needs to be tailored.

Keywords. antiviral prophylaxis; cost-effectiveness; hepatitis B virus; mother-to-child transmission.

Hepatitis B virus (HBV) infection remains a substantial global public health problem due to subsequent complications, including compensated cirrhosis (CC), decompensated cirrhosis (DC), and hepatocellular carcinoma (HCC) [1]. The World Health Organization (WHO) estimated that 350 million to 400 million individuals are chronically infected by HBV [1–3]. The 2030 elimination targets reported by the WHO aim to achieve a 90% reduction in cases of chronic hepatitis B and C and a 65% reduction in mortality by 2030 [4]. Mother-to-child transmission (MTCT) plays a major role in the acquisition of HBV infection, especially in endemic regions [5]. Without prophylaxis, up to 90% of infants born to mothers with chronic hepatitis B (CHB) develop chronic HBV infection [6–8], leading to a 25% risk of premature death from complications. Although active-passive immunoprophylaxis (APIP) based on hepatitis B vaccination and hepatitis B immune-globulin (HBIG) can reduce the risks of MTCT by 85% to 95% [5], nearly 10%–30% of immunoprophylaxis fails [9].

Recent studies have found that the maternal HBV viral load is an important predictor of MTCT, and lowering the HBV DNA level during pregnancy can effectively reduce the risk of MTCT in mothers with high viremia [10]. The clinical guidelines recommended nucleo(t)side analogue (NA) in the third trimester for decreasing the risk of MTCT. However, the HBV DNA threshold to start antiviral therapy varies from 4 log10 IU/mL (American Association for the Study of Liver Diseases [AASLD] evidence level 1, grade 1 recommendation; European Association for the Study of the Liver [EASL] evidence level 1, grade 1 recommendation) to >6 log10 IU/mL (Asian Pacific Association for the Study of the Liver [APASL] B2). The WHO did not make recommendations for antiviral therapy to reduce MTCT due to a lack of evidence when the guidelines were drafted [11]. Due to its favorable efficacy and safety profiles, tenofovir is recommended as the preferred option [1, 9, 12]. However, there is no consensus regarding whether antiviral prophylaxis should be recommended for those with HBV DNA levels <10^6 copies/mL, although the infection risk is not completely prevented even...
following the administration of APIP. In a recent real-world prospective cohort study, immunoprophylaxis failure was observed in 10.1% of low viremic cohorts [13]. A meta-analysis revealed that the pooled incidence of MTCT was 2.754% (95% confidence interval [CI], 1.198%–4.310%) in pregnant women, with HBV DNA <10^6 copies/mL [10]. This meta-analysis included 20 studies in the Chinese population with a significant heterogeneity ($I^2 = 81\%$ and evidence of publication bias). These findings suggest that antiviral prophylaxis should be administered to mothers who are HBV DNA positive rather than only those with $>10^6$ copies/mL.

One potential reason that antiviral prophylaxis is not recommended for pregnant women with HBV DNA levels <10^6 copies/mL is its considerable cost, which may not offset its purported benefit. However, no economic study addressing this issue has been conducted. The purpose of the current study was to examine the economic value of antiviral prophylaxis in preventing MTCT when a lower cutoff HBV DNA load value is applied. For enhancing the transferability of the economic results, the contexts of the United States and China were adopted, which represented high-income and middle-income regions, respectively.

**METHODS**

**Analytic Overview**

A mathematical model was adopted to examine the lifetime cost-effectiveness of different prophylaxis strategies for the prevention of vertical transmission in pregnant women with HBsAg (+) in the contexts of the United States and China. Both of the 2 countries would share the same model inputs, except for background mortality and cost data, which would adopt country-specific inputs. Based on the current guidelines, the cutoff HBV DNA level value for antiviral prophylaxis is $\geq 10^6$ copies/mL (usual care strategy). The following expanded cutoff HBV DNA level values for antiviral prophylaxis were evaluated: $\geq 10^5$ (expanded strategy 1), $\geq 10^4$ (expanded strategy 2), $\geq 10^4$ (expanded strategy 3), and universal prophylaxis regardless of the DNA level (expanded strategy 4). Our target population was pregnant women diagnosed with HBsAg (+). Because the efficacy of antiviral prophylaxis was absent in the scenario without APIP [5], we assumed that the population in this analysis would receive the background APIP. The proportions of HBV DNA levels $<10^3$, $10^3$–$10^4$, $10^4$–$10^5$, $10^5$–$10^6$, and $\geq 10^6$ copies/mL in the HBsAg (+) pregnant women were 45.2%, 11.2%, 7.8%, 4.8%, and 30.9% [14, 15], respectively.

APIP with hepatitis B vaccine and immune-globulin could be administered to infants born to HBV-infected mothers who might incur HBV infection. These infected offspring could develop symptomatic acute and chronic diseases related to HBV. As performed in the previous study, the chronic diseases related to HBV were assumed to begin at the age of 20 [16]. The connections between acute and chronic diseases were bridged by a decision tree (Figure 1A) and a Markov model (Figure 1B). The offspring with chronic HBV infection in the decision tree would enter into the “inactive carrier” state in the Markov model, and the rest of the living offspring would enter into the “normal & recovery” state. The Markov model could track the long-term outcomes of HBV infection, including the following 9 health states: normal health and recovery, inactive carrier (loss of HBeAg, normal alanine aminotransferase [ALT]; $<40$ IU/L), and HBV DNA load $<10^6$ copies/mL, active CHB (ALT $\geq 40$ IU/L or HBV DNA $\geq 10^4$ copies/mL), CC, cirrhosis regression, DC, HCC, liver transplantation, and death. The Markov cycle length was 1 year, and the time horizon was a lifetime (death or until 100 years).

The health end points included the cumulative probabilities of CC, DC, HCC, expected life-years (LYs), and quality-adjusted life-years (QALYs). The cost and QALYs were discounted at an annual rate of 3% in the United States and 5% in China. Incremental cost-effectiveness ratios (ICERs) were examined. We used US $50,000 and $91,177 (the per capita gross domestic product in China in 2017) as the local willingness-to-pay (WTP) threshold [17, 18].

**Clinical and Utility Data**

The key model inputs are summarized in Table 1. The risk of MTCT in women with HBV DNA $\geq 10^6$ copies/mL was 0.593 (95% CI, 0.345–0.897), which was estimated from 3 clinical trials [6–8]. The odds ratio (OR) of MTCT risk per HBV DNA log10 copy/mL increase was 3.44 and was used to estimate the risk of MTCT incidence in women with HBV DNA $<10^6$ copies/mL [10, 19, 20]. The MTCT risks in the women with $<10^3$, $10^3$–$10^4$, $10^4$–$10^5$, and $10^5$–$10^6$ HBV DNA copies/mL were calculated by multiplying the in women with HBV DNA $\geq 10^6$ copies/mL and their relative risks. Previous studies indicated low risk of MTCT infection when the maternal HBV-DNA load was $<10^6$ copies/mL [10]. For this reason, the OR provides a reasonable approximation of the risk ratio (RR) [21]. The relative risks in the subgroup with $<10^3$, $10^3$–$10^4$, $10^4$–$10^5$, and $10^5$–$10^6$ HBV DNA copies/mL were estimated based on the following formula: $1/\text{OR}^n(7-n)$, $n = 2, 3, 4, 5, 6$.

By adopting a recent network meta-analysis of randomized controlled trials [5], we updated the comparative effectiveness of prophylactic strategies for MTCT of the hepatitis B virus by adding the latest clinical trial [12]. The risk ratios of APIP vs no prevention and prophylaxis with TDF vs APIP were 0.159 and 0.101, respectively [9, 12].

After MTCT infection, ~1% of children develop symptomatic acute hepatitis [22], including 0.1% of children developing fulminant hepatitis [23]. The case fatality rate of fulminant hepatitis is 58.8%, including 35.7% of patients who develop CHB, and the remaining patients recover [16, 23]. Among the children with asymptomatic infection, 8% clear HBsAg, 45% gain inactive carrier status, 45% progress into active CHB.
status, 1% develop HCC, and 1% develop cirrhosis [16]. As reported in a previous economic study, the Markov process could start at age 20 years because the immunotolerant phase lasts for ~20 years after MTCT [39]. The annual transition probabilities among the health states related to chronic HBV infection were derived from published data [16, 24–38]. Age- and region-specific probabilities, such as the rate of liver transplantation and annual mortalities due to DCC and HCC caused by HBV, were used in the Markov model if data were available. The probability of transition to death in the inactive carrier, active CHB, and CC were estimated as background mortalities and obtained from the life tables of the World Health Organization (WHO) member states (2011) [40]. The risk data would be converted into annually transition probabilities by the following formula: \(1 - \exp(-\lambda t)\), where \(\lambda\) is the risk and \(t\) is time.

Utility scores were assigned to each health state in the Markov model based on the literature (Table 1).

**Cost Data**

This analysis adopted the third-party payer and health care perspectives in the United States and China and only considered direct medical costs (Appendix Table 1). For comparability, the costs in the 2 countries were reported in 2018 US dollars. Chinese yuan were converted into US dollars using the following exchange formula: 1 US $ = CNY 6.8. The US costs associated with health care services were inflated to 2018 values according to the US Consumer Price Index [41].

The costs included antiviral therapy and the management of complications associated with HBV disease. Antiviral prophylaxis with 300 mg per day of tenofovir could be initiated at week...
Table 1. Clinical and Utility Inputs

| Parameters                                                                 | Expected Value (Range) | Reference   |
|---------------------------------------------------------------------------|------------------------|-------------|
| **Clinical data**                                                        |                        |             |
| Phase of the decision tree                                               |                        |             |
| MTCT incidence with HBV DNA ≥6 log10 copies/mL                            | 0.593 (0.345–0.897)    | [6–8]       |
| OR of MTCT risk per HBV DNA log10 copy/mL increase                       | 3.44 (1.39–7.48)       | [10, 19, 20]|
| RR of MTCT of APIP vs no prevention                                      | 0.159 (0.1–0.25)       | [5]         |
| RR of MTCT of tenofovir vs APIP                                          | 0.101 (0.013–0.79)     | [9, 12]     |
| Probability of symptomatic AHB after perinatal infection                 | 0.01 (0.008–0.013)     | [22]        |
| Proportion of fulminant hepatitis in symptomatic AHB                     | 0.001 (0.00075–0.00125) | [22]       |
| Case fatality rate of fulminant AHB                                      | 0.588 (0.476–0.7)      | [16, 23]    |
| Probability of developing active CHB from fulminant AHB                  | 0.357 (0.333–0.381)    | [16, 23]    |
| Probability of recovery from asymptomatic perinatal infection            | 0.08 (0.06–0.1)        | [16]        |
| Probability of becoming an inactive carrier from asymptomatic perinatal  | 0.45 (0.338–0.563)     | [16]        |
| Probability of developing active CHB from asymptomatic perinatal infection| 0.45 (0.338–0.563)     | [16]        |
| Probability of developing CC from asymptomatic perinatal infection       | 0.01 (0.0075–0.0125)   | [16]        |
| Probability of developing HCC from asymptomatic perinatal infection      | 0.01 (0.008–0.013)     | [16]        |
| Phase of the Markov model (per year)                                     |                        |             |
| Probability of developing active CHB from inactive carrier              | 0.012 (0.006–0.018)    | [24]        |
| Probability of developing CC from inactive carrier                       | 0.007 (0.004–0.01)     | [25]        |
| Probability of developing HCC from inactive carrier                      | 0.0006 (0.0003–0.0009) | [26–28]    |
| Probability of becoming an inactive carrier from active CHB in 20–29 years| 0.07 (0.06–0.08)       | [29]        |
| Probability of becoming an inactive carrier from active CHB in subsequent years| 0.119 (0.097–0.14)   | [30]        |
| Probability of developing CC from active CHB in 20–29 years              | 0.007 (0.004–0.01)     | [16, 28]    |
| Probability of developing CC from active CHB in subsequent years         | 0.002 (0.001–0.004)    | [31]        |
| Probability of developing HCC from active CHB in 20–29 years             | 0.001 (0–0.001)        | [27, 28]    |
| Probability of developing HCC from active CHB in subsequent years        | 0.003 (0.002–0.007)    | [31]        |
| Probability of developing cirrhosis regression from CC                   | 0.24 (0.12–0.36)       | [31, 32]    |
| Probability of developing DC from CC                                     | 0.015 (0.008–0.023)    | [31]        |
| Probability of developing HCC from CC                                     | 0.004 (0.002–0.006)    | [31, 32]    |
| Probability of developing HCC from DC                                    | 0.08 (0.04–0.12)       | [16]        |
| Probability of receiving a liver transplantation for DCC in the United States | 0.018 (0.014–0.023)    | [33]        |
| Probability of receiving a liver transplantation for HCC in the United States | 0.046 (0.035–0.058)    | [33]        |
| Survival probability of DC in the United States                          | 0.075 (0.06–0.032)     | [34–37]     |
| Survival probability of HCC in the United States                         | 0.091 (0.052–0.129)    | [34–37]     |
| Survival probability of liver transplantation in the first year in the United States | 0.15 (0.113–0.188)     | [16]        |
| Survival probability of liver transplantation in the subsequent year in the United States | 0.015 (0.011–0.019)   | [16]        |
| Probability of receiving a liver transplantation for DC in China         | 0.00032 (0.00017–0.00018) | [38]       |
| Probability of receiving a liver transplantation for HCC in China        | 0.00047 (0–0.00244)    | [38]        |
| Survival probability of DC in China                                      | 0.052 (0.032–0.084)    | [38]        |
| Survival probability of HCC in China                                     | 0.368 (0.36–0.375)     | [38]        |
| Survival probability of liver transplantation in the first year in China | 0.219 (0.164–0.273)    | [38]        |
| Survival probability of liver transplantation in the subsequent year in China | 0.067 (0.05–0.084)    | [38]        |
| **Utility data**                                                         |                        |             |
| Inactive carrier                                                        | 1 (0.95–1)             | [16]        |
| Active CHB                                                               | 0.99 (0.9–1)           | [16]        |
| CC                                                                       | 0.7 (0.7–0.9)          | [16]        |
| DCC                                                                      | 0.6 (0.5–0.7)          | [16]        |
| HCC                                                                      | 0.73 (0.5–0.8)         | [16]        |
| Transplantation                                                          | 0.86 (0.7–0.9)         | [16]        |

Abbreviations: CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma.

28 of gestation and continue up to 4 weeks after delivery. All infants received 200 IU hepatitis B immune globulin intramuscularly and 10 μg of the HBV vaccine (GlaxoSmithKline) within 12 hours after birth. The prices of tenofovir, HBIG, and the vaccine were obtained from public databases and the literature [16, 39, 42, 43]. Due to the availability of generic tenofovir, the current analysis used the prices of the generic agents in both the United States and China. One hundred percent compliance with APIP (HBIG and vaccination) was assumed for all newborns of women with HBsAg(+). Using the universal strategy,
the quantitative HBV DNA test could not be performed because all women who are HBsAg(+) receive antiviral prophylaxis. The HBV infection status of the infants could be determined within 1 year after delivery. Approximately 25% of children could receive a 1-year treatment with tenofovir before the age of 20, and all children receive an assessment of disease progression twice a year [16]. The costs related to acute symptomatic and fulminant HBV infection were estimated based on previous reports involving any child or infant acute infection before the age of 20 [2, 16, 39, 44]. The direct medical costs in the Markov model were annually determined for each health state and derived from previous reports based on the population in the United States [3, 33, 45, 46] and China [2, 38, 44]. Patients with inactive carrier and active CHB status receive an assessment of disease progression once and twice a year, respectively [16]. Once active CHB is diagnosed, patients could receive tenofovir therapy. The costs for “cirrhosis regression” health states were assumed to be equivalent to the costs of inactive carriers. These costs were assumed to be incurred regardless of previous diagnoses or interventions and, thus, were unaffected by any medical care assessment.

Sensitivity Analyses
In the probabilistic sensitivity analysis, 1000 Monte Carlo simulations were run by inputting parameters sampled from statistical distributions. A cost-effectiveness acceptability curve representing the uncertainty in the model was generated to show the probability of the cost-effective simulations at various willingness-to-pay thresholds. Using a 1-way sensitivity analysis, the gaps in the ICERs of an individual parameter between the low and high values (Tables 1–2) were measured, and the results are shown as a tornado chart. In 2-way sensitivity analyses, we assessed the impact of varying the MTCT incidence of HBV DNA $\geq 6 \log_{10}$ copies/mL and OR of MTCT risk per HBV DNA $\log_{10}$ copy/mL increase.

### RESULTS

#### Base Case Analysis
Considering that antiviral prophylaxis for HBV DNA $\geq 10^6$, which is the recommended strategy for preventing MTCT, was set as the reference, there were 15.35, 2.14, 1.50, and 0.24 new cases of CHB, CC, DC, and HCC per 100 000 offspring of HBsAg(+) American women, respectively (Table 2). Compared with reference strategy, expanding antiviral prophylaxis averted cases of CHB from 3.33 (using expanded strategy 1) to 6.34 (using expanded strategy 4), CC from 0.47 to 0.89, DC from 0.33 to 0.62, and HCC from 0.05 to 0.10 per 100 000 offspring over the lifetime. Compared with the reference strategy, the expected LYs and QALYs were improved from 0.07 and 0.02 using expanded strategy 1 to 0.13 and 0.03 using expanded strategy 4 per offspring of HBsAg(+) American women. In the Chinese setting, the health benefits gained by the expanded strategies were comparable to those in the United States.

The reference strategies are shown as the cheapest strategy, followed by expanded strategies 1, 2, 3, and 4. In the United States, compared with the reference strategy, the marginal cost of the expanded strategies ranged from $38 in expanded strategy 1 to $519 in expanded strategy 4, which led to ICERs ranging from $2063 to $14 925 per QALY gained. In China, compared with the reference strategy, the marginal cost per QALY gained ranged from $1624 using expanded strategy 1 to $12 348 using expanded strategy 4.

#### Sensitivity Analysis
The tornado diagrams show the comparison between expanded strategy 4 and the reference strategy because expanded strategy 4 achieved the greatest health outcomes (Figure 2). The 1-way sensitivity analyses revealed that the results of the model in the United States were more sensitive to the cost of tenofovir, discount rate, and RR of MTCT of tenofovir vs APIP. The upper values of these parameters could lead the ICERs of expanded

### Table 2. Base Case Cost and Health Outcomes

|                  | Cost, $ | QALYs | Expected LYs | CHB per 100 000 | CC per 100 000 | DCC per 100 000 | HCC per 100 000 | ICER, $/QALY* |
|------------------|---------|-------|--------------|-----------------|---------------|-----------------|----------------|---------------|
| **United States** |         |       |              |                 |               |                 |                |               |
| Usual care strategy | 1012    | 30.40 | 78.19        | 15.35           | 2.14          | 1.50            | 0.24           | NA            |
| Expanded strategy 1 | 1049    | 30.42 | 78.26        | 12.01           | 1.68          | 1.17            | 0.19           | 2063          |
| Expanded strategy 2 | 1133    | 30.43 | 78.29        | 10.43           | 1.46          | 1.02            | 0.16           | 4486          |
| Expanded strategy 3 | 1261    | 30.44 | 78.30        | 9.77            | 1.36          | 0.96            | 0.15           | 8152          |
| Expanded strategy 4 | 1531    | 30.44 | 78.32        | 9.00            | 1.26          | 0.88            | 0.14           | 14 925         |
| **China**         |         |       |              |                 |               |                 |                |               |
| Usual care strategy | 235     | 20.15 | 74.21        | 14.96           | 2.03          | 1.42            | 0.22           | NA            |
| Expanded strategy 1 | 249     | 20.16 | 74.28        | 11.71           | 1.59          | 1.11            | 0.17           | 1624          |
| Expanded strategy 2 | 274     | 20.16 | 74.31        | 10.17           | 1.38          | 0.97            | 0.15           | 3024          |
| Usual care strategy | 310     | 20.16 | 74.32        | 9.53            | 1.30          | 0.90            | 0.14           | 5141          |
| Expanded strategy 1 | 441     | 20.16 | 74.33        | 8.77            | 1.19          | 0.83            | 0.13           | 12 348         |

Abbreviations: CC, compensated cirrhosis; CHB, chronic hepatitis B; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; LY, life-years; NA, nucleotide analog; QALY, quality-adjusted life-years.

*Compared with the reference strategy.
strategy 4 vs the reference strategy to be higher than the threshold ($50,000/QALY). In the Chinese setting, the results were more sensitive to the following parameters: RR of MTCT of tenofovir vs APIP, discount rate, OR of MTCT risk per HBV DNA log10 copies/mL increase, RR of MTCT of APIP vs no prevention, and the cost of tenofovir. Adjusting some of these factors could lead the ICERs of expanded strategy 4 vs the reference strategy to be lower than the threshold ($9,117/QALY).

To explore the potential impact of the key parameters identified in the 1-way sensitivity analyses, further 1-way sensitivity analyses were performed by adjusting the following 4 parameters with wider ranges: RR of MTCT of tenofovir vs APIP, RR of MTCT of APIP vs no prevention, MTCT incidence of HBV DNA ≥ 6 log10 copies/mL, and OR of MTCT risk per HBV DNA log10 copy/mL increase (Figure 3). The expanded prophylaxis strategies were not cost-effective if the assumed extensions of the 95% CI of the 4 parameters were used, except for the variation in RR of MTCT of APIP vs no prevention in the United States.

We performed 2-way sensitivity analyses of MTCT incidence of HBV DNA ≥ 6 log10 copies/mL and OR of MTCT risk per HBV DNA log10 copy/mL increase in the context of the United States. Using a willingness-to-pay threshold of $50,000 per QALY (Appendix Figure 1), expanded strategy 4 could be kept cost-effective when the population had high MTCT incidence of HBV DNA ≥ 6 log10 copies/mL and low OR of MTCT risk per HBV DNA log10 copy/mL increase.

Compared with the usual care strategy, the cost-effectiveness acceptability curves showed that expanded strategies 1, 2, 3, and 4 produced 99.8%, 97.8%, 93.4%, and 82.5% probabilities of cost-effectiveness at the threshold of $50,000/QALY in the United States and 99.7%, 94.2%, 78.4%, and 39.0% at the threshold of $9,117/QALY in China, respectively (Appendix Figure 2).
DISCUSSION

The strengths of this study are notable. To the best of our knowledge, this study is the first to evaluate the optimal cutoff value of maternal viral load for antiviral prophylaxis. Previous economic evaluations of antiviral prophylaxis for preventing MTCT in pregnant women with HBV DNA levels ≥10^6 copies/mL have shown antiviral prophylaxis to be cost-effective [16, 46, 47]. Our analysis demonstrates that the expanded introduction of maternal antiviral prophylaxis for women with a low viral load of HBV (<10^6 copies/mL) may prevent more MTCT infection and avert more HBV-related complications in offspring than the present recommendation of antiviral prophylaxis for women with HBV DNA levels ≥10^6 copies/mL. Moreover, this evaluation indicates that the expanded antiviral prophylaxis strategies for all HBsAg(+) pregnant women may be cost-effective at the WTP threshold of $50,000/QALY in the context of the United States and Chinese pregnant women with HBV DNA levels ≥10^3 copies/mL at the WTP threshold of $9117/QALY. Antiviral prophylaxis for Chinese women with HBV DNA levels <10^3 copies/mL was not cost-effective because the ICER ($12,348/QALY) was higher than the threshold of $9117/QALY (per capita GDP of China in 2017). However, if 3 times the per capita GDP is used as the WTP threshold, as performed in other Chinese economic evaluations [38], the expanded antiviral prophylaxis in this Chinese subgroup becomes cost-effective.

The model outcome is sensitive to several factors. A higher discount rate could result in less favorable ICERs due to the effect of discounting the cost-effectiveness of expanded strategies because costs related to antiviral prophylaxis occur early and most economic and health benefits are realized in the future. In cases in which the key clinical parameters are related to the incidence of MTCT and the efficacy of the prophylaxis strategy, the ICERs of the expanded strategies vs the usual care strategy could also become less favorable because adjusting these parameters weakens the efficacy of antiviral prophylaxis. For example, if the higher OR of MTCT risk per HBV DNA log10 copy/mL increase is used, the model outcome would be more favorable. Additionally, if 3 times the per capita GDP is used as the WTP threshold, as performed in other Chinese economic evaluations [38], the expanded antiviral prophylaxis in this Chinese subgroup becomes cost-effective.
DNA $\geq 10^6$ copies/mL decreased and no prophylaxis was applied, the MTCT incidence could decrease in women with HBV DNA $<10^6$ copies/mL, which could lead the economic outcomes of the expanded strategies to be less favorable. Furthermore, the lower efficacy of tenofovir and higher efficacy of APIP are expected to result in higher ICERs of the expanded strategies over the usual care strategy. However, these clinical factors could influence real-world practices. Due to delayed vaccination and inadequate initial injections in real-world practice [48], immunoprophylaxis failure is still common, although recent findings show that few MTCTs occur in women with HBV DNA $<10^6$ copies/mL who are receiving APIP [1]. A recent study found that HBV DNA is increased in 9% of women during pregnancy [49], which could also increase the risk of MTCT in those with low viremia during early pregnancy. Therefore, the risks of MTCT HBV infection could be underestimated in real-world practice.

These results should be carefully interpreted due to several weaknesses. A major weakness was that the efficacy data in the women with HBV DNA levels $<10^6$ copies/mL receiving antiviral prophylaxis were sparse because a paucity of health benefits is difficult to observe in small sample sizes. Thus, our estimates of MTCT following antiviral prophylaxis in these women were obtained using an indirect approach. However, the sensitivity analyses indicated that antiviral prophylaxis could remain preferable, except for in specific situations, such as the RR of MTCT of tenofovir vs APIP $>0.7$ in the subgroup with HBV DNA levels $<10^3$ copies/mL in the United States and $>0.6$ in Chinese women with HBV DNA levels $<10^5$ copies/mL. Furthermore, our model did not consider the benefits of mothers receiving antiviral prophylaxis during pregnancy due to the absence of robust evidence. A recent study found that hepatitis B virus titers at baseline were strongly associated with hepatic flares during the early postpartum period [50], indicating that those receiving antiviral prophylaxis might have lower risks of hepatic flare. Third, the current analysis did not estimate the value of initiating antiviral prophylaxis during the second trimester due to inconsistency in the current evidence [51, 52]. However, an additional economic analysis introducing antiviral prophylaxis during the second trimester needs to be implemented to address this issue in the future, especially for those with HBV DNA levels $\geq 10^5$ copies/mL. Fourth, due to the lack of direct data, the current analysis used ORs for estimating the relative risk of MTCT in women with HBV DNA levels $<10^6$ copies/mL, although the approach is likely to be reasonable when the outcome is $<10\%$ [21]. Finally, HBeAg status is a strong predictor of MTCT [53]. However, the current analysis did not incorporate it in order to simplify the model and match the guidelines, whose recommendation was based on the HBV DNA level.

In summary, we found that antiviral prophylaxis for pregnant women with HBV DNA $<10^6$ copies/mL seems to be a cost-effective option that is likely to effectively decrease the disease burden related to hepatitis B by avoiding MTCT of HBV. However, the cutoff values need to be tailored based on individual risks and the local context, and further large-scale studies are necessary to determine the benefits of antiviral prophylaxis in women with low viremia. When more robust data become available, it might be advisable to lower the cutoff value of the HBV DNA load for antiviral prophylaxis and administer tenofovir to women with HBV infection during their late pregnancy in high- and middle-income regions.

**Supplementary Data**

Supplementary material are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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**Data sharing.** No additional data are available.

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