Cost-effectiveness Analysis of the National Perinatal Hepatitis B Prevention Program

WHAT’S KNOWN ON THIS SUBJECT: Infant postexposure prophylaxis prevents perinatal hepatitis B (HepB) virus transmission and mortality and morbidity caused by chronic HepB virus infection. The US Perinatal Hepatitis B Prevention Program (PHBPP) identifies and manages infants born to HepB surface antigen–positive women.

WHAT THIS STUDY ADDS: It presents the first estimates of the long-term costs and outcomes of postexposure prophylaxis with the PHBPP. It analyzes the effects of the PHBPP, and alternative immunization scenarios, on health and economic outcomes for the 2009 US birth cohort.

OBJECTIVE: To analyze the cost-effectiveness of the national Perinatal Hepatitis B Prevention Program (PHBPP) over the lifetime of the 2009 US birth cohort and compare the costs and outcomes of the program to a scenario without PHBPP support. PHBPP’s goals are to ensure all infants born to hepatitis B surface antigen–positive women receive timely postexposure prophylaxis, complete HepB vaccine series, and obtain serologic testing after series completion.

METHODS: A decision analytic tree and a long-term Markov model represented the risk of perinatal and childhood infections under different prevention alternatives, and the long-term health and economic consequences of HepB infection. Outcome measures were the number of perinatal infections and childhood infections from infants born to HepB surface antigen–positive women, quality-adjusted life-years (QALYs), lifetime costs, and incremental cost per QALY gained. The health outcomes and total costs of each strategy were compared incrementally. Costs were evaluated from the health care system perspective and expressed in US dollars at a 2010 price base.

RESULTS: In all analyses, the PHBPP increased QALYs and led to higher reductions in the number of perinatal and childhood infections than no PHBPP, with a cost-effectiveness ratio of $2602 per QALY gained. The health outcomes and total costs of each strategy were compared incrementally. Costs were evaluated from the health care system perspective and expressed in US dollars at a 2010 price base.

CONCLUSIONS: This study indicated that the current PHBPP represents a cost-effective use of resources, and ensuring the program reaches all pregnant women could present additional public health benefits. Pediatrics 2014;133:1–11

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KEY WORDS

cost-effectiveness, QALY, cost, perinatal, infection, hepatitis B, immunization programs

ABBREVIATIONS

ACIP—Advisory Committee on Immunization Practices
CDC—Centers for Disease Control and Prevention
CEAC—cost-effectiveness acceptability curve
CI—confidence interval
HBIG—hepatitis B immune globulin
HBsAg—hepatitis B surface antigen
HBV—hepatitis B virus
HepB—hepatitis B
ICER—incremental cost-effectiveness ratio
PEP—postexposure prophylaxis
PHBPP—Perinatal Hepatitis B Prevention Program
PVST—postvaccination serologic testing
QALY—quality-adjusted life-year

Dr Barbosa participated in the concept and design of the study; the collection, analysis, and interpretation of data; and drafted and revised the manuscript. Ms Smith, Ms Fenlon, Dr Schillie, and Dr Murphy participated in the concept and design of the study; the collection, analysis, and interpretation of data; and revised the manuscript. Dr Hoerger participated in the concept and design of the study, the analysis and interpretation of data, and drafted and revised the manuscript. Ms Bradley participated in the collection of data and revised the manuscript. All authors approved the manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-0718
doi:10.1542/peds.2013-0718
Accepted for publication Nov 1, 2013
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(Continued on last page)
Each year, an estimated 25,000 infants are born to hepatitis B surface antigen (HBsAg)-positive women in the United States. With no intervention, these infants have a 40% to 90% risk of hepatitis B virus (HBV) infection. Approximately 90% of infected infants develop chronic HBV infection, which carries a 25% risk of premature death from progressive damage to the liver, leading to cirrhosis, or cancer of the liver. Postexposure prophylaxis (PEP), from progression of the liver, carries a 25% risk of premature death.

Barbosa et al

From approximately 90% of infected infants develop chronic HBV infection, which are born to hepatitis B surface antigen (HBsAg)-positive women. The Advisory Committee on Immunization Practices (ACIP) recommends that all pregnant women receive HBsAg screening to ensure that infants of HBsAg-positive women receive PEP. ACIP recommends that infants of HBsAg-positive women receive HBIG and HepB vaccine administered at birth, followed by completion of a 3-dose HepB vaccine series is 65% to 95% effective in preventing perinatal HBV infection.

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends that all pregnant women receive HBsAg screening to ensure that infants of HBsAg-positive women receive PEP. ACIP recommends that infants of HBsAg-positive women receive HBIG and HepB vaccine within 12 hours of birth, complete the HepB series, and receive serologic testing (HBsAg and antibody to HBsAg) 1 to 2 months after completing the HepB vaccine series to determine outcomes (HepB immunity by vaccination, nonresponse to vaccination, or chronic HBV infection) and future management. ACIP also recommends that the small percentage (5%) of infants who fail to respond to an initial HepB vaccine series and remain uninfected receive an additional HepB vaccine series and repeat postvaccination serologic testing (PVST).

In 1990, the CDC began funding Perinatal Hepatitis B Prevention Programs (PHBPP) in all 64 immunization grantees through the 317 program. PHBPP's goals are to ensure all infants born to HBsAg-positive women receive timely PEP, complete HepB vaccine series, obtain PVST after series completion, and continue medical care appropriate to their outcomes. These goals are accomplished through case management activities. Programs report outcomes annually to the CDC. In 2008, provisional estimates were that 48% of the 25,600 annual estimated births to HBsAg-positive women were identified and case-managed by PHBPP. Most HBsAg-positive women and infants case-managed by PHBPP receive medical care funded by private insurance or Medicaid, although data on the exact proportions of each have not been collected.

More information on PHBPP activities is described in Appendix A of the Supplemental Information. Although economic analyses of the burden and prevention impact of HBV transmission have been conducted, no study has focused on the long-term costs and outcomes of PEP through the current national PHBPP. This study analyzes the effects of the PHBPP on health and economic outcomes attributable to perinatal and early childhood infection (postnatal infection, before age 5 years), determined over the lifetime of the 2009 US birth cohort. Costs and outcomes of the current PHBPP (“PHBPP” strategy) are compared incrementally to a strategy represented by the ACIP recommendations without PHBPP support (“No PHBPP” strategy). The study’s main hypotheses were as follows: the number of perinatal and childhood infections will be lower in the PHBPP strategy, the higher quality-adjusted life-years (QALYs) gained with PHBPP will justify the higher program costs, and the program will be cost-effective when compared with the No PHBPP strategy.

METHODS

Overview

Economic evaluation provides a framework to allocate resources to effective strategies. Full economic evaluations are evaluations where the costs and consequences of at least 2 strategies are compared and can help with understanding the value for money of each strategy. Where 1 strategy does not dominate (ie, is not both more effective and less costly), costs and effects are combined in the form of incremental cost-effectiveness ratios (ICERs), defined as the difference in costs (C) divided by the difference in mean effectiveness (E), 

\[
\text{ICER} = \frac{(C_j - C_i)}{(E_j - E_i)}
\]

where \( j \) is a more costly strategy than \( i \). The ICER represents the additional cost required to achieve 1 additional unit of outcome. An optimal intervention is one with an ICER that is not more than the decision maker’s intrinsic valuation for an additional unit of the outcome.

In a cost-effectiveness analysis, health benefits associated with the strategies under comparison can be measured and valued by using natural units of outcome (eg, life-years), number of infections, or they can reflect the value individuals place on their health, called utilities. QALYs are a widely used measure of health benefits that incorporate mortality and morbidity estimates in a single index. Cost per QALY estimates allow a comparison between different health care interventions that compete for the same pool of resources.

This cost-effectiveness analysis compared 2 strategies. In the base-case analysis, the No PHBPP strategy assumes that there is no program targeted at identification and management of infants born to HBsAg-positive mothers and that infants do not receive HBIG or PVST. In the PHBPP strategy, a proportion of the infants born to HBsAg-positive mothers are identified prospectively and managed through the national PHBPP. Those not captured by the PHBPP follow the No PHBPP strategy.

The costs and outcomes of the strategies analyzed in this study were calculated by using a decision-analytic model. The model was constructed in 2 parts, a decision analytic tree and a...
long-term Markov model, both following a cohort simulation approach.\textsuperscript{13,14}

**Decision Analytic Tree**

The decision tree estimated the expected number of infants, born to HBsAg-positive women, who were perinatally and postnatally infected and was used in all cost-effectiveness analyses. The decision tree was built in TreeAge Pro 2011 (TreeAge Software, Inc, Williamstown, MA) (Fig 1). All infants born to HBsAg-positive women follow either the No PHBPP or the PHBPP strategy. Four mutually exclusive outcomes were modeled: seroprotection, susceptibility, perinatal infection, and childhood infection. The cost-effectiveness analysis focused on the last 2 outcomes and QALYs lost with each type of infection. The decision tree model base-case parameters and sources are summarized in Table 1. The 24,784 cohort considered in this analysis was the estimated number of infants born to HBsAg-positive mothers in 2009.\textsuperscript{1,15,16} More than 95% of women were screened for HBsAg in the United States in 2003–2004.\textsuperscript{4,15} Consistent with this estimate, and so that all infants born to HBsAg-positive women are modeled, both strategies assume a 100% screening coverage. Vaccine efficacy is assumed to confer immunity to chronic and acute HBV infection acquired perinatally and during childhood before age 5 years. Efficacy varies by the time of first dose of HBIG and HepB vaccine administration, or HepB vaccine without HBIG, and by completion of vaccine series within 9 months or longer periods. The major determinant of the effectiveness of PEP for infants of HBsAg-positive mothers is on-time administration of the initial dose of HepB vaccine and HBIG.\textsuperscript{17} Because most available data use $<$24 hours of life as the optimal timing for administering the first dose of HepB vaccine and HBIG, we also use $<$24 hours rather than the ACIP-recommended $\leq$12 hours. Infants born to HBsAg-positive

![Figure 1](https://example.com/figure1.png)

**FIGURE 1**

Decision tree model. Decision node represented by squares, chance node by circles, and terminal nodes by triangles. Markov model entered in M circles. HBsAg+, hepatitis B surface antigen positive; Hep1Vacc, first dose of HepB vaccine; Vacc., vaccine; m, months; PVST, postvaccination serologic test.
<table>
<thead>
<tr>
<th>Parameter Name, Reference No.</th>
<th>Base-Case</th>
<th>SA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Probabilistic SA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upper Value</td>
<td>Lower Value</td>
<td>Assumption</td>
</tr>
<tr>
<td><strong>Population and risk of infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Births per year&lt;sup&gt;16&lt;/sup&gt;</td>
<td>4 130 685</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>P mother is HBsAg&lt;sup&gt;&lt;sup&gt;+&lt;/sup&gt;&lt;/sup&gt;&lt;sup&gt;1,15&lt;/sup&gt;</td>
<td>0.006</td>
<td>0.008</td>
<td>0.004</td>
</tr>
<tr>
<td>N infants to HBsAg&lt;sup&gt;&lt;sup&gt;+&lt;/sup&gt;&lt;/sup&gt; mother&lt;sup&gt;24,784&lt;/sup&gt;</td>
<td>24 784</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>P HBsAg&lt;sup&gt;&lt;sup&gt;+&lt;/sup&gt;&lt;/sup&gt; mother is HBeAg&lt;sup&gt;+&lt;/sup&gt;&lt;sup&gt;&lt;sup&gt;15,42&lt;/sup&gt;&lt;/sup&gt;</td>
<td>0.3</td>
<td>0.36</td>
<td>0.24</td>
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<tr>
<td>P transmission HBeAg&lt;sup&gt;+&lt;/sup&gt;&lt;sup&gt;15,42&lt;/sup&gt;</td>
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<td>0.734</td>
</tr>
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<td>P transmission HBeAg&lt;sup&gt;-&lt;/sup&gt;&lt;sup&gt;3,39-42&lt;/sup&gt;</td>
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<td>0.314</td>
<td>0.037</td>
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<td>P of transmission HBsAg&lt;sup&gt;+&lt;/sup&gt;</td>
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<tr>
<td>P of childhood infection among not seroprotected&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>0.36</td>
<td>0.24</td>
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<td><strong>Vaccination coverage for No PHBPP</strong></td>
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<td></td>
<td></td>
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<tr>
<td>P Hep1Vacc ≤24 h&lt;sup&gt;27,28&lt;/sup&gt;</td>
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<td>0.544</td>
<td>0</td>
</tr>
<tr>
<td>P Hep1Vacc+HBIG ≤24h</td>
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<td>0.544</td>
<td>0</td>
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<tr>
<td>P Hep1Vacc 24–72 h&lt;sup&gt;27,28&lt;/sup&gt;</td>
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<td>0.081</td>
<td>0.000</td>
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<tr>
<td>P Hep1Vacc+HBIG 24–72h</td>
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<tr>
<td>P Hep1Vacc 72 h–3 mo&lt;sup&gt;27,28&lt;/sup&gt;</td>
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<tr>
<td>P no dose&lt;sup&gt;17&lt;/sup&gt;</td>
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<td>—</td>
<td>—</td>
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<tr>
<td>P completion in 9 mo&lt;sup&gt;29&lt;/sup&gt;</td>
<td>0.032</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
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<tr>
<td>P Hep1Vacc+HBIG 24–72 h</td>
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<td>—</td>
<td>—</td>
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<tr>
<td>P Hep1Vacc 24–72 h</td>
<td>0.001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>P Hep1Vacc 72 h–3 mo</td>
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<td>—</td>
<td>—</td>
</tr>
<tr>
<td>P no dose</td>
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<tr>
<td>P completion in 9 mo</td>
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<tr>
<td>P PVST</td>
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<tr>
<td>P HBs&lt;sup&gt;&lt;sup&gt;+&lt;/sup&gt;&lt;/sup&gt; woman is identified and captured by PHBPP</td>
<td>0.479</td>
<td>1</td>
<td>0.479</td>
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<td><strong>Efficacy of HBV vaccine and HBIG by time of administration and completion of vaccination series</strong></td>
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<td>HBIG+Hep1Vacc =24 h and remaining doses on time&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.920</td>
<td>0.970</td>
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<tr>
<td>HBIG+Hep1Vacc =24 h and remaining doses on time&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.830</td>
<td>0.970</td>
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<tr>
<td>HBIG+Hep1Vacc 24–72 h and remaining doses on time&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.616</td>
<td>0.828</td>
<td>0.460</td>
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<tr>
<td>HBIG+Hep1Vacc 24–72 h and remaining doses not on time&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>0.747</td>
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<td>0.720</td>
<td>0.800</td>
<td>0.600</td>
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<td>Hep1Vacc ≤24 h and remaining doses not on time&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.600</td>
<td>0.800</td>
<td>0.600</td>
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<tr>
<td>Hep1Vacc 24–72 h and remaining doses on time&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.482</td>
<td>0.648</td>
<td>0.360</td>
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<tr>
<td>Parameter Name, Reference No.</td>
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<td>SA(^b)</td>
<td>Probabilistic SA</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td></td>
<td>Upper Value</td>
<td>Lower Value</td>
<td>Assumption</td>
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<tr>
<td>Hep1Vacc 24–72 h and remaining doses not on time(^i)</td>
<td>0.402</td>
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<td>Hep1Vacc 72 h–3 mo and remaining doses not on time(^k)</td>
<td>0.269</td>
<td>0.540</td>
<td>0.201</td>
</tr>
</tbody>
</table>

Cost parameters

- Cost per 1 vaccine dose\(^l\) $22
- Administrative costs for 1 vaccine dose\(^m\) $14
- Cost of HBIG\(^o\) $121 $146 $97
- Cost of anti-HBsAg Test\(^o\) $15
- Blood drawn cost\(^n\) $3
- Cost of HBsAg screening test\(^n\) $15
- Cost of outpatient consultation\(^n\) $61
- Cost of identification in PHBPP per infant\(^n\) $783 $929 $472 For upper value the bootstrapped CI used, for lower value the total cost for all grantees divided by the total number of infants was used
- Cost of management in PHBPP per infant\(^n\) $769 $890 $552

Markov model inputs\(^n\)

- Cost due to HBV perinatal and childhood infection
  - Cost of perinatal infection diagnosed at infection $24 117 $28 941 $19 294 ±20% $\gamma$ 9454 7 3706
  - Cost of perinatal infection not diagnosed at infection $8931 $11 787 $7865 ±20% $\gamma$ 3854 7 1511
  - Cost of childhood infection diagnosed at infection $11 643 $13 972 $9315 ±20% $\gamma$ 4564 7 1789
  - Cost of childhood infection not diagnosed at infection $37 137 $44 555 $29 870 ±20% $\gamma$ 1455 7 570

- QALYs loss due to HBV perinatal and childhood infection
  - QALY loss due to perinatal infection diagnosed at infection 0.7656 0.9187 0.6125 ±20% $\gamma$ 0.3001 7 0.1
  - QALY loss due to perinatal infection not diagnosed at infection 1.1851 1.4221 0.9481 ±20% $\gamma$ 0.4846 7 0.2
  - QALY loss due to childhood infection diagnosed at infection 0.2560 0.3072 0.2048 ±20% $\beta$ 0.1003 5 13
  - QALY loss due to childhood infection not diagnosed at infection 0.5161 0.6193 0.4129 ±20% $\beta$ 0.2023 3 2

HBeAg+, hepatitis B e antigen positive; HBsAg+, hepatitis B surface antigen positive; Hep1Vacc, first dose of HepB vaccine; NA, not applicable; NIS, National Immunization Survey; P, probability; SA, sensitivity analysis; —, no value was assumed in the sensitivity analysis or no distribution was assigned to the parameter.

\(^a\) Calculation of all inputs detailed in Appendix A of the Supplemental Information.

\(^b\) Upper and lower values for sensitivity analyses were informed by the CI of the parameter estimate or if CIs were not available, upper and lower values were set at ±20% of the base value. For other variables, upper and lower values were based on previous studies and educated guesses.

\(^c\) Calculated as the transmission HBeAg+*P HBsAg+mother HBe+ + (P transmission HBeAg-*(1 – P HBsAg+mother HBe+)).

\(^d\) Assuming low end of Lee et al\(^o\) CI for HBIG+Hep1Vacc ≤24 h and remaining doses on time.

\(^e\) Calculated as 0.92*0.67, assuming a decrease in efficacy of 33%.

\(^f\) Assuming low end of Lee et al\(^o\) CI for HBIG+Hep1Vacc ≤24 h and remaining doses on time.

\(^g\) Calculated as 0.87*0.67, assuming a decrease in efficacy of 33%.

\(^h\) Calculated as 0.72*0.67, assuming a decrease in efficacy of 33%.

\(^i\) Calculated as 0.6*0.67, assuming a decrease in efficacy of 33%.

\(^j\) Calculated as 0.482*0.67, assuming a decrease in efficacy of 33%.

\(^k\) Calculated as 0.402*0.67, assuming a decrease in efficacy of 33%.

\(^l\) Authors’ calculations by using self-reported grantee data to CDC from PHBPP grantees in 49 US states (excluding Alaska), 5 cities (Chicago, Houston, New York City, Philadelphia, San Antonio), and the District of Columbia. CIs around individual cost estimates were calculated by using bootstrapping.

\(^m\) Inputs from Markov model described in Appendix A of the Supplemental Information; and Markov model structure described in Appendix B of the Supplemental Information and in Hoerger et al.49
women who do not complete the HepB vaccine series, or who have delays in completing the series, are significantly more likely to develop chronic infection than infants who receive timely PEP.\textsuperscript{18,19} The number of children receiving PHBPP services was calculated from PHBPP data reported to the CDC (infants born in 2008\textsuperscript{3} and 2009, CDC unpublished data), which included the number of identified and case-managed infants born to HBsAg-positive women and the number receiving HBIG and HepB vaccine.\textsuperscript{1} Unit costs included HepB vaccine dose, vaccine administration, program costs, screening all pregnant women, HBIG, and PVST with outpatient consultation.

Markov Model

A Markov model of disease progression was used to estimate the HepB-related lifetime medical costs and QALY losses associated with perinatal and childhood HBV infections. These were then used as inputs to the decision tree. The Markov model was built in Microsoft Visual Studio 2008.

We defined early diagnosis as diagnosis of infection soon after infection (100% probability of diagnosis for infants who are serologically tested) and late diagnosis as detection of infection at a 1% annual rate,\textsuperscript{20-22} or when the infection becomes symptomatic. We estimated hepatitis-related costs and QALY loss for early and late diagnosis and for perinatal and childhood infection. Table 1 shows that perinatal infections have higher costs and greater QALY losses than childhood infections, because chronic HBV infection is more common after perinatal infection (90% vs 30%).\textsuperscript{4} For both types of infections, early diagnosis leads to earlier and more monitoring, and more effective treatment than late diagnosis, resulting in higher costs but lower QALY loss. Appendices A and B in the Supplemental Information provide detailed explanations of the calculation of each parameter in Table 1 and a detailed description of the Markov model, respectively.

Analysis Outcomes

The combined decision tree and Markov models quantified the number of perinatal and early childhood infections from infants born to HBsAg-positive women. The other main outcome measures were QALYs, lifetime costs, and incremental cost per QALY gained. Costs were evaluated from the health care system perspective and expressed in 2010 US dollars. Future costs and QALYs were discounted at a 3% annual rate.\textsuperscript{11,12} For each strategy, expected health outcomes were the number of perinatal and childhood infections and QALYs lost with infection. Expected total costs were the sum of strategy costs and the present value of discounted future health care costs associated with monitoring and treating HBV infection and its complications.

Cost-effectiveness Analysis

ICERs were estimated.\textsuperscript{23} The ICER represents the additional cost to achieve 1 less QALY loss due to infection. The preferred strategy is determined by comparing the ICER to what decision makers are willing to pay for an additional QALY. No consensus has been reached on decision makers’ willingness to pay in the United States, although a $50 000/QALY benchmark has been used in several studies.\textsuperscript{24} Probabilistic sensitivity analysis was conducted to incorporate uncertainty in model parameters. Monte Carlo simulation was used to calculate the combined impact of the model’s various uncertainties.\textsuperscript{25} The distributions used are presented in Table 1. Uncertainty in the model was described using a cost-effectiveness acceptability curve (CEAC)\textsuperscript{25} to graphically show the probability that 1 strategy is more cost-effective than the other based on decision makers’ willingness to pay for an additional QALY.\textsuperscript{11,25}

Sensitivity Analyses

One-way sensitivity analyses were conducted to estimate the impact of changing each key parameter individually. A series of multiway sensitivity analyses changed several variables simultaneously to create 6 hypothetical scenarios: (1) pessimistic and optimistic vaccine efficacy scenarios, using lower or upper bounds of the confidence interval (CI) from Lee et al\textsuperscript{26} for first dose of vaccine and HBIG and 50% or 10% cut in the remaining variables’ efficacy, respectively; (2) no maternal screening cost: the cost of screening all pregnant women in both strategies was excluded; (3) same diagnosis probability: assumed all perinatal and childhood infections were diagnosed at infection (early diagnosis); (4) perfect PHBPP: assumed that all infants born to HBsAg-positive women were identified and managed by a perfect program (100% coverage), all infants received HBIG and HepB vaccine within 24 hours and completed all doses within 9 months, and all infants were serologically tested post-vaccination; (5) No PHBPP, where all first HepB doses ≤72 hours are given with HBIG, no PVST after completion; and (6) No PHBPP, where all first HepB doses ≤72 hours are given with HBIG, with PVST after completion. The 2 last scenarios relax the assumption of no administration of HBIG and PVST under No PHBPP. They estimate the impact on the ICER of compliance with recommended PEP in the absence of the PHBPP. In the absence of PHBPP, a proportion of infants born to HBsAg-positive women likely still receive HBIG and possibly PVST. Because there are no data on administration rates of HBIG and PVST rates after series completion among infants not followed by PHBPP, scenarios 5 and 6 assumed that all first doses of HepB given before 72 hours, based on National Immunization Survey data,\textsuperscript{27-29} were accompanied by
HBIG. Scenario 6 also assumed that PVST would be done at the same rate as in the program strategy. Because program costs relied on self-reported data (as detailed in Appendix A in the Supplemental Information), which might not have captured all the identification and management-related costs, a threshold analysis on program costs was conducted.

RESULTS

Base-Case Results

Table 2 presents the cost-effectiveness results for the base-case analysis. The lifetime costs for the No PHBPP strategy were the costs of screening all pregnant women ($60,018,562), the cost of routine vaccination ($1,943,035), and the long-term medical costs associated with late diagnosis of perinatal and childhood infections ($52,364,741). The PHBPP had higher lifetime costs ($120,319,857) and better health outcomes relative to No PHBPP. The lifetime costs of the PHBPP included the costs of screening all pregnant women ($60,018,562), identifying infants born to HBsAg-positive women ($9,304,521), managing those infants ($8,977,101), the cost of PEP with HBIG and HepB vaccine, with additional HepB series and PVST for infants who failed to respond to the initial HepB vaccine series ($4,221,035), and long-term HepB-related medical costs ($37,798,101). Compared with No PHBPP, the PHBPP was associated with 2351 fewer total infections (1485 perinatal and 866 childhood), 2304 less QALYs lost, and an ICER of $2602 per QALY. Hence, if decision makers are willing to pay at least $2602 per QALY gained, the PHBPP can be considered cost-effective.

Figure 2 presents the CEAC. The probability that the PHBPP is cost-effective increases as health gains are more highly valued; if decision makers are willing to pay $6000 for an additional QALY, the PHBPP is cost-effective.

Sensitivity Analyses

Figure 3 shows the effect of the 1-way sensitivity analyses on the ICERs. The probability of HBV transmission had the highest impact on the ICER. With higher transmission probabilities, the program was more cost-effective, and with lower transmission probabilities, the ICER was higher. Overall, changing each variable had a moderate to small effect, and the ICER never surpassed $6500 per QALY.

Table 3 presents the results of the multiway sensitivity analyses. Under a pessimistic vaccine efficacy scenario, the PHBPP was slightly more costly and less effective than in the base-case scenario, with a slightly higher ICER ($3060 per QALY). Under the optimistic vaccine efficacy scenario, the PHBPP had lower costs and higher QALYs gained than in the base-case scenario. Excluding the cost of screening all pregnant women did not have an impact on the ICER. With early diagnosis of all infections, the PHBPP was cost-saving (less costly and more effective than vaccination only). This is caused by the higher cost and lower QALY loss related to early diagnosis of perinatal infections for the PHBPP strategy.
FIGURE 3
Sensitivity analysis. Shows the range of ICERs (horizontal axis; $/QAL Y) for lower and upper bound input values (vertical axis), when the PHBPP is compared with no program. For example, higher transmission rate leads to a more cost-effective program and vice versa.

TABLE 3 Multiway Sensitivity Analysis: What-If Scenarios

<table>
<thead>
<tr>
<th>Total Cost, $</th>
<th>Total</th>
<th>Total</th>
<th>Total</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infections</td>
<td>Perinatal Infections</td>
<td>Childhood Infections</td>
<td>QALYs Lost*</td>
</tr>
<tr>
<td>(1a) Pessimistic vaccine efficacy scenario</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PHBPP</td>
<td>124 070 020</td>
<td>8084</td>
<td>5246</td>
<td>2838</td>
</tr>
<tr>
<td>PHBPP</td>
<td>131 789 282</td>
<td>5571</td>
<td>3682</td>
<td>1889</td>
</tr>
<tr>
<td>(1b) Optimistic vaccine efficacy scenario</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PHBPP</td>
<td>95 893 164</td>
<td>4430</td>
<td>2874</td>
<td>1555</td>
</tr>
<tr>
<td>PHBPP</td>
<td>104 482 875</td>
<td>2969</td>
<td>1752</td>
<td>918</td>
</tr>
<tr>
<td>(2) No maternal screening cost</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PHBPP</td>
<td>54 307 179</td>
<td>6816</td>
<td>4423</td>
<td>2393</td>
</tr>
<tr>
<td>PHBPP</td>
<td>80 301 294</td>
<td>4664</td>
<td>2938</td>
<td>1527</td>
</tr>
<tr>
<td>(3) Same diagnosis probability (all diagnosed at infection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PHBPP</td>
<td>196 488 335</td>
<td>6816</td>
<td>4423</td>
<td>2393</td>
</tr>
<tr>
<td>PHBPP</td>
<td>170 856 338</td>
<td>4414</td>
<td>2938</td>
<td>1476</td>
</tr>
<tr>
<td>(4) Perfect PHBPP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PHBPP</td>
<td>114 325 741</td>
<td>6816</td>
<td>4423</td>
<td>2393</td>
</tr>
<tr>
<td>PHBPP</td>
<td>133 862 135</td>
<td>1257</td>
<td>1109</td>
<td>148</td>
</tr>
<tr>
<td>(5) No PHBPP where all first HepB doses ≤72 h are given with HBIG, no PVST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PHBPP</td>
<td>103 458 773</td>
<td>5098</td>
<td>3308</td>
<td>1790</td>
</tr>
<tr>
<td>PHBPP</td>
<td>114 658 168</td>
<td>3570</td>
<td>2357</td>
<td>1212</td>
</tr>
<tr>
<td>(6) No PHBPP where all first HepB doses ≤72 h are given with HBIG, with PVST</td>
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<td></td>
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</tr>
<tr>
<td>No PHBPP</td>
<td>119 464 037</td>
<td>4941</td>
<td>3308</td>
<td>1632</td>
</tr>
<tr>
<td>PHBPP</td>
<td>122 998 909</td>
<td>3487</td>
<td>2357</td>
<td>1130</td>
</tr>
</tbody>
</table>

* Costs and QALYs are discounted at a 3% annual rate. Costs in US dollars at a 2010 price base.
and childhood infections. Under the assumption of a perfect program, the higher costs of the program ($133,862 vs $120,319 in the base-case) led to many more infections avoided and hence, less QALYs lost. Under this assumption, there were only 1257 infections and the ICER was $3517 per QALY. Providing HBIG to all infants who received a first dose of HepB within 72 hours in the No PHBPP strategy resulted in an ICER of $7358 per QALY. This is related to the higher impact of this assumption in the No PHBPP strategy where the higher costs related to HBIG administration are offset by lower future complication costs and QALYs lost related to HepB infections. However, also providing PVST in the No PHBPP strategy reduced the ICER of scenario 5 to $2804 per QALY because PVST leads to earlier treatment but reduces only childhood infections and not perinatal infections, which are associated with higher future costs.

The threshold analysis on the program costs showed that assuming a $50,000 per QALY maximum willingness to pay, the cost of PHBPP identification could be up to $54,000 per infant and the costs of PHBPP management could be up to $88,000 per infant. This is well above the base-case values of $783 and $769 for the costs of identification and management per infant.

DISCUSSION

When the PHBPP is compared with a strategy that follows ACIP recommendations without the support of the program, the ICER is $2602 per QALY, and when this strategy also considers HBIG and HBIG with PVST, the ICER is between $7358 and $2804 per QALY, which by most standards suggests that the PHBPP is cost-effective in avoiding perinatal and childhood infections. The costs and outcomes of immunization strategies to prevent HBV transmission in the United States have been evaluated. Comparing prevention of perinatal HBV infection with a situation of no immunization, in 1991 Margolis et al reported a total of 4703 perinatal and childhood infections prevented from 11400 HBsAg-positive women. To understand our results within the context of those presented by Margolis et al, we compared the PHBPP to a hypothetical scenario of no vaccination in a separate analysis (results available on request). Scaled to our estimate of 24784 HBsAg-positive mothers, the number of infections prevented in Margolis et al would be analogous to 10224 infections avoided, close to our estimate of 19159 infections prevented when the PHBPP is compared with a situation of no immunization. The slightly lower number of infections prevented in our models is caused by the use of a lower transmission rate (updated to take into account current seroprevalence estimates), and a slightly lower efficacy of PEP that takes into account current compliance rates by timing of first and remaining doses of PEP doses. Margolis et al did not account for PEP compliance (they assumed the same value as routinely administered vaccines) and did not cost a specific perinatal prevention program. Therefore, program cost estimates are not directly comparable. Margolis et al presented cost-effectiveness results from a third-part payer's perspective in which only direct medical costs were included. They also presented net benefit estimates from a broader perspective in which medical direct costs and morbidity and mortality-related work-loss costs were included. When a broader perspective was adopted, Margolis et al reported that the perinatal prevention strategy generated cost savings. Following our health care system perspective on costs and health economic guidelines that recommend that mortality-related productivity losses should not be included in cost-effectiveness studies with QALYs, we excluded mortality-related work-loss costs. Thus, we do not compare our ICER with that presented by Margolis et al, because the authors did not present ICERS in the form of cost per QALY and included different cost categories.

Other data limitations could have affected the results. The HepB vaccine efficacy with HBIG within 24 hours of birth was taken from a recent meta-analysis based on 3 trials, and HepB vaccine efficacy without HBIG was based on 4 trials. Despite the small number of studies, the estimates are within the range of results from studies not included because they were not randomized controlled trials. The efficacy of HepB vaccine and HBIG when the first dose is delayed and when all vaccine doses are not completed on time was determined by the authors' calculations relying on 2 studies. These areas of uncertainty were considered in the probabilistic and multi-way sensitivity analyses.

Another important data limitation relates to the cost of the PHBPP. Program costs were based on aggregate data reported by PHBPP grantees. We excluded outliers and used bootstrap techniques to account for imperfections of the data. However, it is possible that cross-subsidies (eg, office space, utilities, shared equipment, hospital personnel time for communication, and liaising with PHBPP staff) were not captured in the reports. More accurate costs are needed for future analyses.

In addition to the data limitations, more general issues remain. Some benefits of the PHBPP have been underestimated. Recent evidence suggests vaccination confers immunity into early adulthood. This study did not account for infections avoided at later stages in life (eg, during adolescence and adulthood). We focused on the impact of perinatal vaccination in the cohort of infants born to HBsAg-positive mothers in 2009. Our approach also did not take into account...
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CONCLUSIONS

This study presents the first cost-
effectiveness analysis of the US PHBPP. The simulation of a perfect PHBPP sce-
ario showed that an expansion of the current recommendations to all infants at risk would lead to a reduced number of perinatal and childhood infections, with an ICER of $3517 per QALY. Our model pre-
dicted that the current PHBPP represented a cost-effective use of resources, and that expansion of the program could represent an economically efficient method to pre-
vent further morbidity and mortality.

ACKNOWLEDGMENTS

We acknowledge the contributions by Perinatal Hepatitis B Prevention Coordi-
nators Julie Lazaroff, New York City Department of Health and Mental Hy-
giene, and Patrick Fineis, Michigan De-
partment of Community Health, for providing useful comments on the model, and by Qian Li from the CDC’s National Center for Immunization and Respira-
tory Diseases who analyzed data from the 2010 National Immunization Pro-
gram to determine HepB vaccine cover-
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