SUPPLEMENTAL ONLINE APPENDIX

For Cost-Effectiveness of Ensuring Hepatitis B Protection for Previously Vaccinated Healthcare Personnel

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The cost-effectiveness of ensuring hepatitis B protection among healthcare personnel (HCP) with unknown response to vaccination by evaluating antibody to hepatitis B surface antigen (anti-HBs) at matriculation or hire (pre-exposure), or by evaluating HCP for post-exposure management after a reported blood or body fluid (BBF) exposure (post-exposure) has been evaluated and published (Hoerger TJ, Bradley C, Schillie S, Reilly M, Murphy T. Cost-effectiveness of ensuring hepatitis B protection for previously vaccinated healthcare personnel. ICHE. 201X Month; XX(XX):XXXX-X). This online appendix provides additional details on model inputs. It also presents cost-effectiveness results for 2 additional strategies for ensuring hepatitis B protection among HCP with unknown response: pre-exposure challenge dose of hepatitis B (HepB) vaccine and post-exposure evaluation with follow-up only for HCP exposed to source patients with positive or unknown hepatitis B surface antigen (HBsAg) status. This supplemental appendix presents the cost-effectiveness results of these 2 additional strategies for trainees and non-trainees and provides greater detail on selected model inputs.

Model Inputs

Key model input variables are presented in Table 1 of the published article. Decision tree diagrams for the pre-exposure anti-HBs testing strategy and the post-exposure management strategy are included in Figures A-1 and A-2. Exposure, seroprotection, and intervention cost variables are described in more detail below.
Exposure Variables

Probability of Blood and Body Fluid Exposure

The annual probability of BBF exposure was calculated as the sum of the annual probability of percutaneous exposure and the annual probability of mucosal exposure. The annual probability of percutaneous exposure was set equal to the median self-reported probability of exposure of HCP from 5 studies of percutaneous exposures published after 2000 (the Needlestick Safety and Prevention Act was signed into law in 2000).\textsuperscript{1-5} For one-way sensitivity analyses, we used the lowest and highest reported values. The annual probability of mucosal exposure was determined in a similar fashion, based on 4 studies.\textsuperscript{1-4} Based on evidence that the percutaneous exposures are up to twice as likely among trainees as among non-trainees, a panel of experts\textsuperscript{6} recommended multiplying the median percutaneous and mucosal rates by 1.75 to set the value for trainees. In addition, both probabilities included all exposures experienced by the HCP, not just those the HCP reported to his or her employer. More than half of percutaneous exposures were reported to the employer, compared with only 17\% of mucosal exposures. We accounted for reporting when we calculated the probability of infection from source patients who are HBsAg-positive.\textsuperscript{6}

Probability that Source Patient has Hepatitis B

The probability that the source patient is HBsAg-positive was 0.009. This figure was a weighted average of figures from 3 healthcare systems in the United States (personal communication, D. Nace, January 11, 2012; D. Weber, August 30, 2011, January 20, 2012; B. McMahon, February 1, 2012), covering the years 2000–2012 and representing 7,170 exposures. This figure assumes that the rate of HBsAg-positivity for unknown sources (estimated to account for 6\% of exposures) is the same as that for known sources. The value reflects the current
prevalence of hepatitis B virus (HBV) infection, which is lower now than in the 1990s and earlier.

**Probability of Serologic Evidence of Protection**

The proportion of HCP with serologic evidence of protection (anti-HBs ≥10 mIU/mL) differs between trainees and non-trainees. Trainees are more likely to have completed vaccination at age <1 year. The median proportion of anti-HBs levels ≥10 mIU/mL approximately 20 years later is 0.2 for persons vaccinated at <1 year of age, based on data extrapolated from subjects followed for approximately 5 to 15 years.⁷-¹¹ Most non-trainees completed vaccination at age ≥1 year. The median proportion of anti-HBs levels ≥10 mIU/mL measured approximately 20 years later is 0.8 for persons vaccinated at ≥1 year of age, based on subjects followed for approximately 5 to 30 years.¹²-²⁰ Low and high values for the one-way sensitivity analyses are drawn from the range of proportions in studies for vaccination at age <1 and at age ≥1 year.

Among HCP whose anti-HBs level is <10 mIU/mL at time distant from vaccination, a response to a single challenge dose of HepB vaccine is assumed to be evidence of protection. For the model, response to a challenge dose of HepB vaccine is defined as the probability that an HCP who received a complete series of HepB vaccine in the remote past and who currently has anti-HBs <10 mIU/mL will reach anti-HBs ≥10 mIU/mL after the challenge dose. For trainees, the proportion of responders (60%) is derived from U.S. subjects vaccinated at age <1 year who were followed for approximately 5 to 15 years.⁸-¹¹ For non-trainees, the proportion of responders (75%) is derived from U.S. subjects vaccinated at age ≥1 year who were followed for approximately 5 to 22 years.¹⁴,¹⁷,¹⁹ These values were extrapolated using linear trend lines fit to available data.
Probability of Hepatitis Infection if BBF Exposure Occurs, Source Patient Has Hepatitis B, and HCP Is Not Protected

The probability of infection varies depending on whether the exposure was percutaneous or mucosal. The probability for percutaneous injuries is based on the probability of serological evidence of HBV among HCP after sustaining a needlestick injury from a needle contaminated with blood containing HBV (figures for needlestick injury were applied to all percutaneous exposures). Specifically, the probability was calculated as follows:

\[
\text{Probability of infection when source HBeAg} + [0.50] \times \text{Probability HBeAg} + [0.345] + \text{Probability of infection when source HBeAg} - [0.30] \times \text{Probability HBeAg} - [0.655] = 0.369
\]

The equation accounts for the fact that source patients who are hepatitis B e-antigen (HBeAg) positive are more infectious than source patients who are HBsAg-positive and HBeAg-negative.

Similar data on infectivity do not exist for mucosal exposures. Because mucosal exposures are considered to be less infectious than percutaneous exposures, we set the mucosal probability of infection equal to half the percutaneous value.

Because percutaneous exposures are more infectious and more likely to be reported than mucosal exposures, the probability of infection after a reported BBF exposure differs from the probability of infection after an unreported BBF exposure. Accordingly, we calculated separate values for the probability of infection after a reported BBF exposure and the probability of infection after an unreported BBF exposure.

Overall Probability of HBV Infection

The probability of infection in a 1-year period is calculated as follows:
(probability of BBF exposure) * (probability the source patient is HBsAg-positive) * 
(probability HCP is not protected) * (probability of infection given source patient is HBsAg-
positive and HCP is not protected)

Total intervention costs of each strategy depend on the number of anti-HBs tests, number 
of HepB vaccine doses, costs of source patient testing, additional costs to the employer 
occupational health department, and—for infected HCP—medical costs of hepatitis B-related 
treatment. HCP who become infected experience utility loss arising from hepatitis-related 
complications. Parameters for these variables are shown in Table 1 in the published article.

Impact of Hepatitis B Infection

We used a hepatitis B cost-effectiveness model to calculate the lifetime consequences 
of HBV infection. The model accounts for the fact that some acute HBV infections are 
asymptomatic, whereas others require treatment that may include hospitalization or liver 
transplantation; it also accounts for the 6% of acute infections in adults that progress to chronic 
infection. For trainees, we calculated the present value of future hepatitis-related medical costs 
and QALY losses for an acute infection at age 25. For non-trainees, we assumed that the 
infection occurred at age 35. The choice of age at infection has relatively small effects on the 
projected lifetime costs and QALY losses.

Protection after Revaccination (Challenge Dose plus Two Additional Doses)

Protection after revaccination was defined as the probability that an HCP who had 
received a complete series of HepB vaccine in the remote past with anti-HBs <10 mIU/mL and 
failed to reach anti-HBs ≥10 mIU/mL after a single additional (challenge) dose of vaccine will 
reach anti-HBs ≥10 mIU/mL after 2 more doses of vaccine (complete revaccination). A value of
0.8 for both trainees and non-trainees was derived from 3 studies\textsuperscript{8,11,17} conducted in the United States. Subjects in the studies were vaccinated both at \textless 1 and \textgeq 1 year of age.

\textit{Efficacy of HBIG}

HBIG is provided to an HCP who is not protected and has been exposed to an HBsAg-positive source patient. The efficacy of HBIG represents the probability that a non-protected HCP would be protected against a recent HBV exposure after one dose of HBIG. A value of 0.8 for the efficacy of HBIG was derived from a review article and was based on 216 persons who sustained percutaneous exposure to HBsAg positive material and 25 spouses exposed to acute HBV infection.\textsuperscript{24}

\textbf{Intervention Cost Components}

Intervention cost components and sources are shown in Table 1 in the published article. Costs for laboratory tests come from the Medicare Clinical Laboratory Fee Schedule. For one-way sensitivity analyses, low values were set 25\% lower than base values. High values were based on the list price that a medical student might be charged by a hospital laboratory, under the assumption that such tests would not be covered by insurance because they are not medically necessary. For probabilistic sensitivity analyses, the costs for laboratory tests are drawn from a normal distribution with 95\% confidence intervals that are \pm 25\% of the base values.

\textbf{Sensitivity Analyses}

One-way and probabilistic sensitivity analyses are performed. For each run in probabilistic sensitivity analyses, key input parameters are drawn from appropriate distributions (beta and normal distributions for probabilities and costs, respectively). For the probability that the source patient has HBV infection, we use a beta distribution with a mean of 0.009, based on 7,170 observations from 3 healthcare institutions. The resulting range of values in the
probabilistic sensitivity analysis is narrower than in the one-way sensitivity analysis (which ranges from 0.003 to 0.10) (personal communication, D. Nace, January 11, 2012; D. Weber, August 30, 2011, January 20, 2012; B. McMahon, February 1, 2012; A. Elward, September 1, 2011; H. Keyseling, August 31, 2011). The range in the one-way sensitivity analysis provides information for HCP who serve patients at very low risk or very high risk for HBsAg-positivity. The cost of vaccine and the cost of administering the vaccine are separately varied by a multiplicative factor between 0.75 and 1.25 for one-way sensitivity analyses, with corresponding normal distributions in the probabilistic sensitivity analyses.

Additional Strategies

Pre-Exposure “Challenge” Dose of HepB Vaccine

Under this strategy, the HCP receives 1 additional dose of HepB vaccine followed by anti-HBs testing upon matriculation or hire. If the anti-HBs is $\geq 10$ mIU/mL after the first dose, the HCP is protected. If the anti-HBs is $<10$ mIU/mL after this dose, the HCP will receive 2 more doses of HepB vaccine and post-vaccination anti-HBs testing. If the HCP does not show serologic evidence of protection after these additional doses, the HCP will be considered a known non-responder.

Post-Exposure Evaluation with Follow-up Only for HCP Exposed to Source Patients with Positive or Unknown HBsAg Status

Under this strategy, management only occurs if BBF exposure occurs, is recognized by the HCP, and is reported to the employer. If no BBF exposure occurs, the HCP is not infected, and no costs are incurred. If BBF exposure occurs but is not recognized or reported, the probability of infection depends on the probability that the source patient is HBsAg-positive, the probability the HCP is not protected, and the probability of infection given those parameters. If
BBF exposure occurs and is reported, the HCP will receive an anti-HBs test and the source patient will be tested for hepatitis B surface antigen (HBsAg) simultaneously. If the anti-HBs is ≥10 mIU/mL, the HCP has serologic evidence of protection, and no further management occurs. If the anti-HBs is <10 mIU/mL, management depends on whether the source patient is HBsAg-positive or HBsAg-negative: if the source patient is HBsAg-positive, the HCP receives Hepatitis B Immune Globulin (HBIG) and 1 additional dose of HepB vaccine, completes revaccination (a total of 3 additional doses), and is tested for anti-HBs 1 to 2 months after the last HepB vaccine dose. If the HCP still does not show serologic evidence of protection after these doses, the HCP may be a nonresponder or be HBV infected based on the probability of infection given that the source patient is HBsAg-positive and the HCP is not protected. If the source patient is unknown, or unavailable for testing, management proceeds as if the source was HBsAg-positive. If the source patient is HBsAg-negative, the HCP receives no HepB vaccine doses or HBIG.

Under each of the above scenarios, if the HCP is known to be protected, he or she is deemed a known responder, no further management will occur, and the HCP will not become infected. If a known non-responder has a reported BBF exposure and the source patient is HBsAg-positive (or unknown), the HCP will receive 2 doses of HBIG. The HBIG will provide additional protection against infection; however, some HCP will remain unprotected and face the probability of infection given that the source patient is HBsAg-positive and the HCP is not protected.

RESULTS

The probability that an HCP will be infected with HBV is shown for each management strategy, applying the 95% assumption of sustained vaccine-induced protection (Table A-1). With no intervention, the probability of infection is 4.779 per 100,000 HCP. The interventions
increase the probability that the HCP is protected. The pre-exposure challenge dose of HepB vaccine produces the lowest probability of infection (0.652 per 100,000 HCP), followed by post-exposure evaluation with follow-up only for HCP exposed to source patients with positive or unknown HBsAg status (2.955 per 100,000 HCP). In the 1-year model, the pre-exposure “challenge” dose of HepB vaccine has an incremental cost-effectiveness ratio (ICER) of $4,507,834 and $6,352,660 per QALY relative to no intervention for trainees and non-trainees, respectively. The post-exposure evaluation with follow-up only for HCP exposed to source patients with positive or unknown HBsAg status has an ICER of $1,639,968 and $1,497,845 per QALY relative to no intervention for trainees and non-trainees, respectively. When the analysis is extended for 10 years, the ICERs (calculated relative to the no intervention scenario) for trainees and non-trainees improve.

Table A-2 shows the results of the probabilistic sensitivity analyses for trainees in the 1-year model. The median ICERs are relatively close to the base case analysis, while the mean ICERs are higher because we assumed a high initial probability of protection resulting in low incremental QALYs. The credible interval is wide, reflecting the uncertainty about initial probability of protection.
REFERENCES FOR ONLINE APPENDIX


6. Centers for Disease Control and Prevention (CDC). CDC guidance for hepatitis B virus protection for healthcare personnel. MMWR. October XX, 2013 / XX(RRXX);X-XX.


15. McMahon BJ. 30 year follow-up after hepatitis B vaccination in adults and children. Presented at the Viral Hepatitis Prevention Board Meeting, Milan, Italy; November 2011.


Table A-1. Results, 1- and 10-Year Analysis, Assuming 95% Sustained Vaccine Protection

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Probability of Infection</th>
<th>Cost</th>
<th>QALY Loss</th>
<th>Cost per QALY Saved (Relative to No Intervention)</th>
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<tr>
<td><strong>1-Year Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Trainees</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No intervention</td>
<td>0.00004779</td>
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<td>−0.0000372</td>
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<td>Pre-exposure “challenge” dose of HepB vaccine</td>
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<td>−0.000051</td>
<td>$4,507,834</td>
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<td>Post-exposure evaluation with follow-up only for HCP exposed to source patients with positive or unknown HBsAg status</td>
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<td>$23.66</td>
<td>−0.000230</td>
<td>$1,639,968</td>
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<td>(b) Non-trainees</td>
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<td></td>
<td></td>
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<tr>
<td>No intervention</td>
<td>0.000273</td>
<td>$0.19</td>
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<td>Pre-exposure “challenge” dose of HepB vaccine</td>
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<td>Post-exposure evaluation with follow-up only for HCP exposed to source patients with positive or unknown HBsAg status</td>
<td>0.000169</td>
<td>$10.50</td>
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<td>$1,497,845</td>
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<td><strong>10-Year Analysis</strong></td>
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<tr>
<td>(a) Trainees</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No intervention</td>
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<td>$3.00</td>
<td>−0.00033</td>
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<tr>
<td>Pre-exposure “challenge” dose of HepB vaccine</td>
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<td>$253.28</td>
<td>−0.00004</td>
<td>$889,659</td>
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<tr>
<td>Strategy</td>
<td>Probability of Infection</td>
<td>Cost</td>
<td>QALY Loss</td>
<td>Cost per QALY Saved (Relative to No Intervention)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
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<tr>
<td>Post-exposure evaluation with follow-up only for HCP exposed to source patients with positive or unknown HBsAg status</td>
<td>$199.90</td>
<td>−0.000130896</td>
<td>$1,009,594</td>
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<td><strong>(b) Non-trainees</strong></td>
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<tr>
<td>No intervention</td>
<td>$1.66</td>
<td>−0.0001581</td>
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<td>Pre-exposure “challenge” dose of HepB vaccine</td>
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<td>Post-exposure evaluation with follow-up only for HCP exposed to source patients with positive or unknown HBsAg status</td>
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<td>Initial Decision</td>
<td>Mean ICER (Relative to No Intervention)</td>
<td>Median ICER (Relative to No Intervention)</td>
<td>Credible Interval (2.5 Percentile)</td>
<td>Credible Interval (97.5 Percentile)</td>
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<td>Pre-exposure “challenge” dose of HepB vaccine</td>
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<td>$53,286,004.75</td>
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Figure A-1. Pre-exposure anti-HBs testing strategy—TreeAge Decision Tree
Figure A-2. Post-exposure management strategy—TreeAge Decision Tree