Hepatitis B Protection Among Health Care Personnel: Cost-Effectiveness Considerations

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Conflict of Interest Statements

- Dr. Hoerger: No conflicts of interest
- Ms. Bradley: No conflicts of interest

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Methods

Study Question

- How to manage health care personnel (HCP) who are known to have received a full series of hepatitis B vaccination previously, but whose current seroprotection status is unknown?

    - We don't know if they have a current anti-HBs level ≥ 10 mIU/mL or ever had an anti-HBs ≥ 10 mIU/mL after vaccination (anti-HBs = antibody to hepatitis B surface antigen [HBsAg])

Importance

- HCP are at risk for exposure to hepatitis B infected blood and body fluids (BBF) through percutaneous injury and mucosal exposure
  - Appropriate management strategies may reduce the probability of transmitting hepatitis B from infected patients to HCP
  - Management strategies have costs
  - Does the cost of management provide good value?

Three Primary Management Strategies

1. Post-exposure: All sources
    –   If HCP exposed and exposure is reported, conduct anti-HBs testing. If anti-HBs < 10 mIU/mL, HCP receives either hepatitis B vaccine or hepatitis B vaccine plus HBIG, depending on whether source patient is negative or positive for HBsAg.

2. Pre-exposure: anti-HBs testing; HepB dose if necessary
    –   All HCP initially receive an anti-HBs test. If anti-HBs < 10 mIU/mL, the HCP receives 1 dose of hepatitis B vaccine and later receives another anti-HBs test. If anti-HBs remains < 10 mIU/mL, the HCP receives 2 additional doses of vaccine.

3. Pre-exposure: HepB dose, anti-HBs testing
    –   All HCP initially receive 1 dose of hepatitis B vaccine and subsequent anti-HBs test. If anti-HBs < 10 mIU/mL, the HCP receives 2 additional doses of vaccine.

Comparator Strategy

- 3 primary strategies compared to
  - Each other
  - A "do nothing" strategy where no management is provided
    - Provides useful benchmark for the probability of infection and associated cost of infections if no management occurs
    - The "best" a strategy can do is completely eliminate infections

Alternative Strategies

- **Variant (b):** Post-exposure: HBV positive or unknown sources
  - Variant to Strategy 1, but does not include HCP vaccination if source patient is HBV negative
  - Produces same protection as Strategy 1 in first year but lower costs
- **Variant (a):** Hybrid: Pre-exposure HepB dose; post-exposure, all sources
  - Variant to Strategy 3, but does not have anti-HBs testing prior to exposure
  - Results in slightly more infections than Strategy 3 but costs less

Separate Analyses for Trainees and Non-trainees

- Trainees
  - More likely to have been vaccinated at age < 1 year →
    - Less likely to have current anti-HBs ≥ 10 mIU/mL
    - Lower response rates to additional doses of hepatitis B vaccine
  - More likely to have BBF exposure
  - Assumed to be 10 years younger than non-trainees →
    - Medical costs and QALY loss associated with an infection are slightly higher

General Model Framework

- **Intervention time frame:**
  - 1-Year analysis and
  - Multi-Year analysis covering up to 10 years of exposure

- **Analytic horizon**
  - For hepatitis B infections, consider hepatitis-related costs and QALY losses for HCP's remaining lifetime

- **Discounting: 3% annual rate**

- **Perspective: Societal**

- **All costs are in year 2010 $**

General Model Framework (cont'd)

- **Decision tree analysis for each management strategy**
  - Determines intervention cost and probability of infection for strategy

- **CDC Hepatitis B Cost-Effectiveness Model (Zhou et al., *Pediatrics*, 2003)**
  - Estimates hepatitis-related costs and QALY loss associated with an acute hepatitis B infection in an adult HCP
  - Accounts for asymptomatic infections and 6% probability of chronic infection
  - Estimated hepatitis-related cost = $7,176
  - Estimated QALY loss = -0.7794

Analytic Method

- Cost-effectiveness analysis
- Summary measures
  - Incremental cost-effectiveness ratios (ICERs) = change in net costs divided by change in quality-adjusted life-years (QALYs) =

$$\frac{(\text{intervention cost}) - (\text{hepatitis-related costs averted})}{\text{change in QALYs from averting infections}}$$

Exposure Variables

Probability of	Trainee	Non-trainee (if different than Trainee)
Mucosal exposure	0.221	0.126
Percutaneous exposure	0.177	0.101
Blood and body fluid (BBF) exposure (Sum of mucosal and percutaneous exposures)	0.398	0.227
Source patient has hepatitis B	0.009	--
Reporting the incident (mucosal)	0.17	--
Reporting the incident (percutaneous)	0.54	--
Reporting a BBF exposure incident	0.33	--
Infection after mucosal exposure, source patient +	0.185	--
Infection after percutaneous exposure, source patient +	0.369	--

Seroprotection Variables

Probability of	Trainee	Non-trainee (if different from Trainee)
Evidence of Seroprotection prior to any intervention	0.2	0.8
Evidence of Seroprotection after a single challenge dose of vaccine*	0.6	0.75
Evidence of Seroprotection among challenge dose non-responders after 2 additional vaccine doses*	0.8	--
Efficacy of HBIG	0.8	--

*In addition to the original three-dose series of the Hepatitis B vaccine

Cost Inputs

Variable	Cost
Administrative costs for vaccine	$14.42
Blood drawing cost for anti-HBs test	$3.00
Cost of anti-HBs test	$15.12
Cost of discovering exposure source's status (HBsAg test)	$14.53
Cost of hepatitis B core antibody	$16.96
Cost per vaccine dose	$52.50
Occupational health costs associated with an injury	$85.30
Cost of HBIG	$745.42
Office: outpatient visit cost	$61.31

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Sensitivity Analyses

- Incremental cost-effectiveness ratios
  - One-way sensitivity analyses
    - Low, high clinically relevant values
  - Probabilistic sensitivity analyses
    - Draw input values from distributions simultaneously
    - Run 10,000 draws

Results

Probability of Hepatitis B Infection, 1 Year

Strategy	Trainees	Non-trainees
Do nothing	0.00076	0.00011
1. Post-exposure: All sources	0.00047	0.00007
b. Post-exposure: HBV positive or unknown sources	0.00047	0.00007
a. Hybrid: Pre-exposure HepB dose; post-exposure, all sources	0.00019	0.00002
2. Pre-exposure: anti-HBs testing; HepB dose if necessary	0.00004	0
3. Pre-exposure: HepB dose, anti-HBs testing	0.00004	0

Comments

- Infections are relatively rare in the primary analysis
  - For trainees, the "do nothing" probability of infection is 0.00076
  - = (probability of BBF exposure) * (probability source patient is HBsAg+) * (probability HCP is not seroprotected [= 1 minus the probability of seroprotection prior to intervention]) * (probability of infection given source patient is HBsAg+ and HCP is not seroprotected)
  - = 0.398 * 0.009 * (1 – 0.2) * 0.267

- Strategies 2 and 3 and Variant (a) provide protection against unrecognized/unreported exposures

- Probability of infection lower for non-trainees than for trainees
  - Biggest reason: probability of prior seroprotection is higher for non-trainees (0.8 vs. 0.2)

Cost-Effectiveness, Trainees, 1-Year Analysis

Strategy	Cost	Incremental Cost	Probability of Infection	QALY Loss	Incremental Change in QALYs	ICER (Relative to Above Strategy)	ICER (Relative to Do Nothing)
Do nothing	$5.49	—	0.00076	−0.0006	—	—	—
b. Post-exposure: HBV positive or unknown sources	$26.44	$20.95	0.00047	−0.00037	0.00023	$91,087	$91,087
1. Post-exposure: All sources	$35.06	$8.62	0.00047	−0.00037	0	Dominated by b	$128,565
a. Hybrid: Pre-exposure HepB dose; post-exposure, all sources	$91.15	$56.09	0.00019	−0.00015	0.00022	$254,955	$190,356
3. Pre-exposure: HepB dose, anti-HBs testing	$145.60	$54.45	0.00004	−0.00003	0.00012	$453,750	$245,807
2. Pre-exposure: anti-HBs testing; HepB dose if necessary	$146.71	$1.11	0.00004	−0.00003	0	Dominated by 3	$247,754

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Comments: Trainee, 1-Year analysis

- Strategies 2 and 3 provide the most protection and have the highest costs; their ICERs are similar and well above $50,000 per QALY

- Strategy 1 provides less protection, costs less, and has a lower ICER than Strategies 2 and 3; still above $50,000 per QALY

- Variant (a) costs less than Strategies 2 and 3, yields more infections, somewhat lower ICER

- Variant (b) costs less than Strategy 1, has same number of infections, lower ICER

Cost-Effectiveness, Non-trainees, 1-Year Analysis

Strategy	Cost	Incremental Cost	Probability of Infection	QALY Loss	Incremental Change in QALYs	ICER (Relative to Above Strategy)	ICER (Relative to Do Nothing)
Do nothing	$0.76	—	0.00011	−0.00007	—	—	—
b. Post-exposure: HBV positive or unknown sources	$10.57	$9.81	0.00007	−0.00004	0.00003	$326,967	$326,967
1. Post-exposure: All sources	$11.57	$1.00	0.00007	−0.00004	0	Dominated by b	$360,416
2. Pre-exposure: anti-HBs testing; HepB dose if necessary	$49.26	$37.69	0	0	0.00004	$942,145	$692,833
a. Hybrid: Pre-exposure HepB dose; post-exposure, all sources	$76.83	$27.57	0.00002	−0.00001	−0.00001	Dominated by 2	$1,267,840
3. Pre-exposure: HepB dose, anti-HBs testing	$99.17	$22.34	0	0	0.00001	Dominated by 2	$1,405,861

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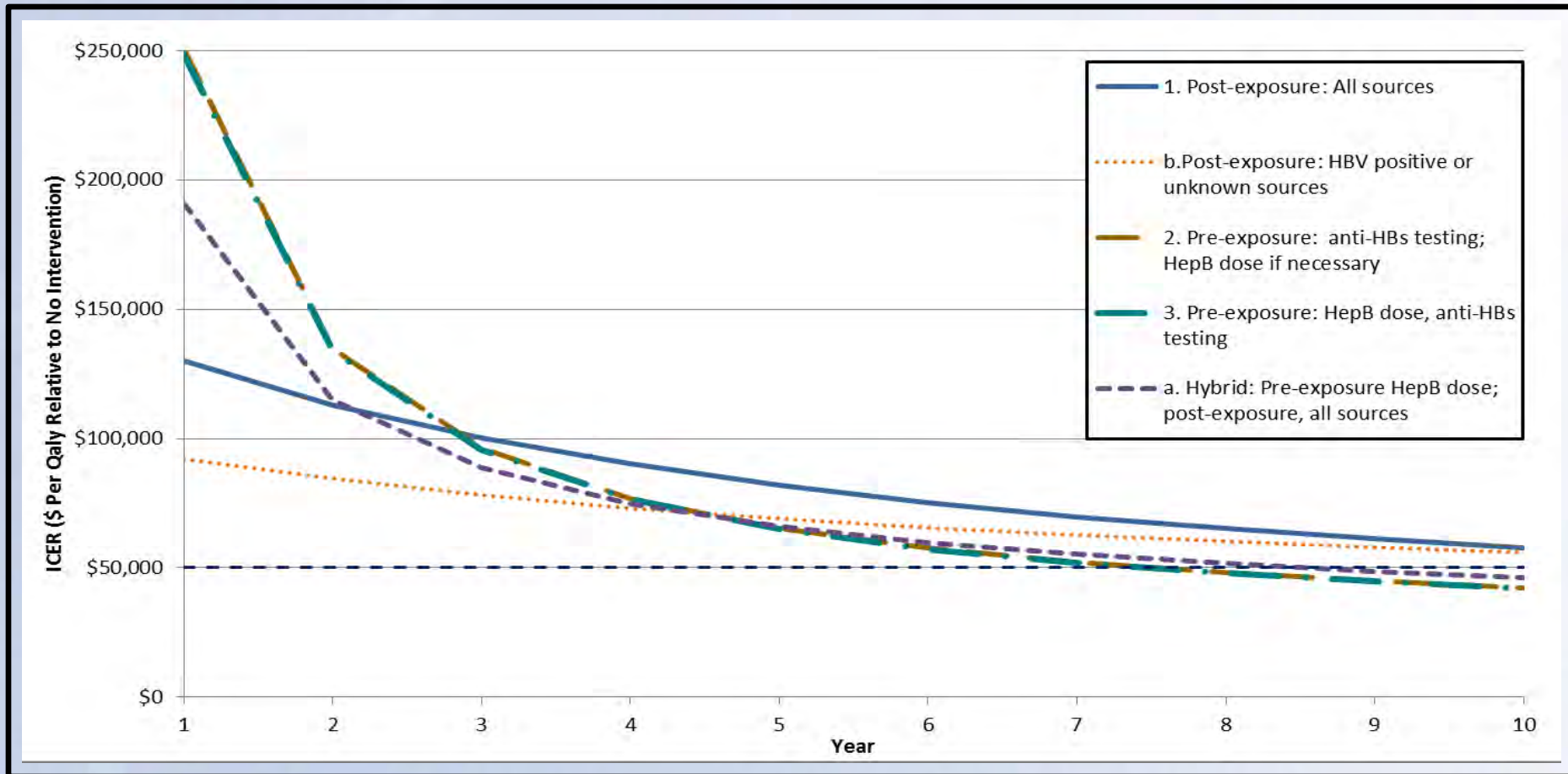
Comments: Non-trainees, 1-Year Analysis

- ICERs for all strategies are much higher than for trainees
  - Main reason: Probability of prior seroprotection is higher for non-trainees (0.8 vs. 0.2) → fewer infections, even in the do-nothing case

- All of the strategies now have ICERs > $300,000 per QALY

- Strategy 2 is now less costly than Strategy 3 (both have same probability of infection)
  - Only a small share receive vaccine under Strategy 2, while all receive vaccine in Strategy 3

Multi-Year Analysis: Trainees

	Cost per QALY saved relative to "Do nothing even if exposed"		
	1st Year ($)	10th Year ($)	Year when < $50,000
Do nothing even if exposed			
1. Post-exposure: All sources	$128,565	$57,756	> 10
b. Post-exposure: HBV positive or unknown sources	$91,087	$56,056	> 10
2. Pre-exposure: anti-HBs testing; HepB dose if necessary	$247,754	$42,275	~ 7th
3. Pre-exposure: HepB dose, anti-HBs testing	$245,807	$ 42,047	~ 7th
a. Hybrid: Pre-exposure HepB dose; post-exposure, all sources	$190,356	$46,298	~ 8th

Cost-effectiveness, Trainees, Multi-Year Analysis

Note: For trainees, curves for Strategies 2 and 3 virtually overlap

Comments: Trainees, Multi-Year Analysis

- ICERs fall, because management today provides protection against exposure in subsequent years

- Strategies 2 and 3 provide protection upfront to almost all trainees
  - Costs in later years are relatively small
  - ICERs fall more rapidly, eventually are lower than for Strategy 1

Multi-Year Analysis: Non-trainees

|	Cost per QALY saved relative to "Do nothing even if exposed"		
	1st Year ($)	10th Year ($)	Year when < $50,000
Do nothing even if exposed			
1. Post-exposure: All sources	$360,416	$252,970	> 10
b. Post-exposure: HBV positive or unknown sources	$326,967	$267,446	> 10
2. Pre-exposure: anti-HBs testing; HepB dose if necessary	$692,833	$169,334	> 10
3. Pre-exposure: HepB dose, anti-HBs testing	$1,405,861	$250,833	> 10
a. Hybrid: Pre-exposure HepB dose; post-exposure, all sources	$1,267,840	$260,627	> 10

Cost-effectiveness, Non-trainees, Multi-Year Analysis
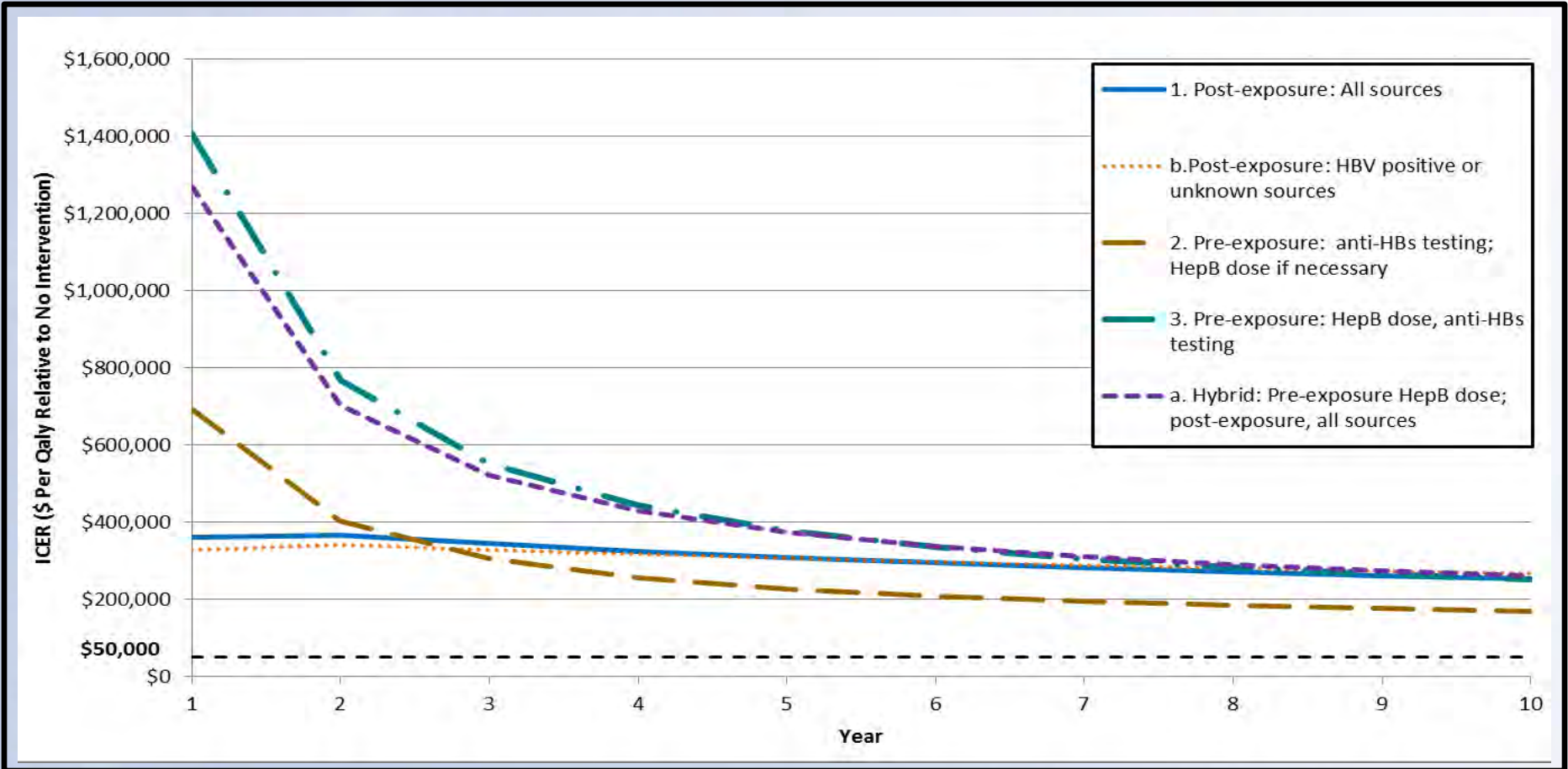
Comments: Non-trainees, Multi-Year Analysis

- ICERs again fall as the duration of exposure increases
- Strategy 2 always much lower than Strategy 3, and lower than Strategy 1 after a couple of years
- All of the ICERs remain above $150,000 per QALY

One-Way Sensitivity Analyses, Strategy 1, Trainee, One-Year Model
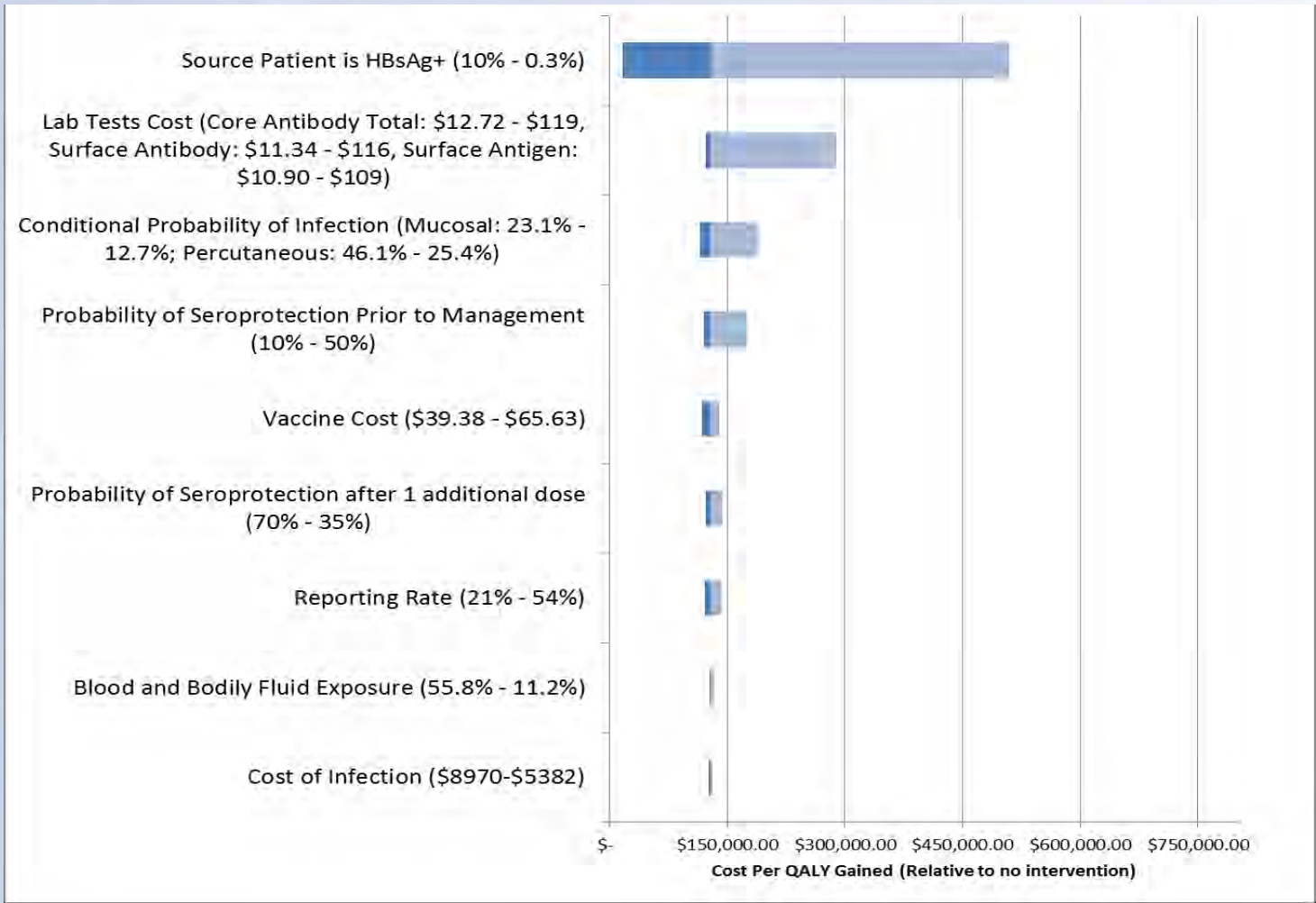
Probabilistic Sensitivity Analyses, $ per QALY, Trainees, One-Year Analysis, Based on 10,000 Simulations

Initial Decision	Mean ICER (Relative to Do Nothing)	Median ICER (Relative to Do Nothing)	Credible Interval (2.5 97.5 Percentile)
b. Post-exposure: HBV positive or unknown sources	$104,092	$97,785	$48,134 - $197,444
1. Post-exposure: All sources	$146,119	$137,441	$70,226 - $271,231
a. Hybrid: Pre-exposure HepB dose; post-exposure, all sources	$224,695	$206,530	$94,048 - $459,413
2. Pre-exposure: anti-HBs testing; HepB dose if necessary	$290,014	$267,501	$124,334 - $580,978
3. Pre-exposure: HepB dose, anti-HBs testing	$290,731	$266,014	$120,972 - $599,324

Limitations and Possible Impact on ICERs

- Assumed that HCP with anti-HBs < 10 mIU/mL are not seroprotected. Achieving anti-HBs ≥ 10 mIU/mL after additional vaccine dose moves person from no seroprotection to seroprotection.
    - An alternative: some persons with measured anti-HBs < 10 mIU/mL actually have immunity
    - Having immunity in the absence of evidence of serologic protection would increase ICERs for all strategies
- We used average values of BBF exposure and the probability that the source patient is HBsAg+
    - Some HCP face higher probability of BBF exposure → ICERs decrease
    - Some serve a higher share of HBsAg+ patients → ICERs decrease

Limitations and Possible Impact on ICERs (cont'd)

- Unrecognized exposures are not included
  - No data on probability available

- QALY losses and costs associated with a hepatitis B infection are based on a simulation model of lifetime outcomes for persons infected with hepatitis B
  - Model generally considered valid

- Adverse events associated with vaccination are not included
  - Hepatitis B vaccine generally considered safe

Summary

Comparison of Options: Trainees

	Cost per QALY saved relative to "Do nothing even if exposed"			Protection for unrecognized/ unreported exposures	Incidence of HBV infection/10^5 1 Year
	1st Year ($)	10th Year ($)	Year when < $50,000		
Do nothing even if exposed					76
1. Post-exposure: All sources	$128,565	$57,756	> 10	No	47
b. Post-exposure: HBV positive or unknown sources	$91,087	$56,056	> 10	No	47
2. Pre-exposure: anti-HBs testing; HepB dose if necessary	$247,754	$42,275	~ 7th	Yes	4
3. Pre-exposure: HepB dose, anti-HBs testing	$245,807	$ 42,047	~ 7th	Yes	4
a. Hybrid: Pre-exposure HepB dose; post-exposure, all sources	$190,356	$46,298	~ 8th	Some	19

Comparison of Options: Non-trainees

	Cost per QALY saved relative to "Do nothing even if exposed"			Protection for unrecognized/ unreported exposures	Incidence of HBV infection/10^5 1 Year
	1st Year ($)	10th Year ($)	Year when < $50,000		
Do nothing even if exposed					11
1. Post-exposure: All sources	$360,416	$252,970	> 10	No	7
b. Post-exposure: HBV positive or unknown sources	$326,967	$267,446	> 10	No	7
2. Pre-exposure: anti-HBs testing; HepB dose if necessary	$692,833	$169,334	> 10	Yes	0
3. Pre-exposure: HepB dose, anti-HBs testing	$1,405,861	$250,833	> 10	Yes	0
a. Hybrid: Pre-exposure HepB dose; post-exposure, all sources	$1,267,840	$260,627	> 10	Some	2

Questions