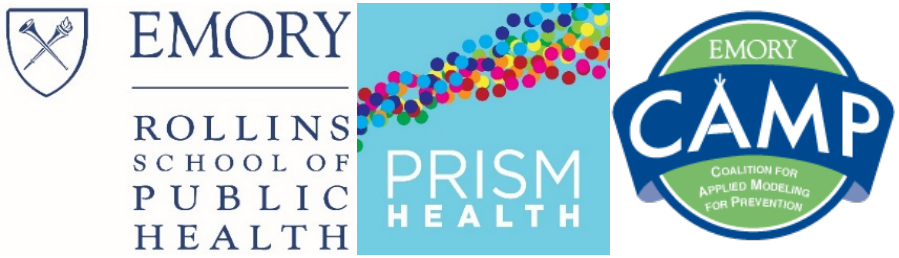
Economic Evaluation of Universal Hepatitis B Vaccination Among Adults

Eric Hall, PhD
Rollins School of Public Health
Emory University

Eli Rosenberg, PhD
School of Public Health
University at Albany



Conflicts of Interest Statements

None of the authors have conflicts of interest

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Methods: Study Question

Evaluate the cost-effectiveness of a universal hepatitis B vaccination recommendation of all adults ≥19 years of age.

General approach:

1) Define Strategies

- *Baseline strategy:* Status-quo, comparison strategy
- *Alternate strategy:* Intervention being evaluated

2) Define Base Case

- Use point estimates (“best guesses”) for all inputs
- Serves as an anchor for other sensitivity analyses

3) Sensitivity Analyses

- Vary inputs individually to their extreme values
- Vary all inputs probabilistically
- Define specific scenarios

Methods: Study Question

Evaluate the cost-effectiveness of a universal hepatitis B vaccination recommendation of all adults ≥19 years of age.

Baseline strategy

- Current vaccination recommendations and coverage with 3-dose vaccine

Alternate (intervention) strategies

- Universal vaccination with 3-dose vaccine (*Engerix-B/TWINRIX)*
- Universal vaccination with 2-dose vaccine (*HEPLISAV-B)*

Methods: Intervention(s)

Alternate strategies

- Initiation of a hepatitis B vaccination series among adults aged 19 years of age or older *that are not currently recommended to receive vaccination*.
- Under base case assumptions:
  - Intervention only applies to non-high risk persons.
  - No additional vaccination among high-risk persons.
- Allows for unnecessary vaccination of
  - persons currently infected and unaware.
  - persons that forgot they were vaccinated.

Intervention time frame: 1 year

- Single point in time vaccination process

Methods: Economic Model

Decision Tree Model

Cohort

1,000,000

microsimulation trials

Age heterogeneity representative of the U.S. population

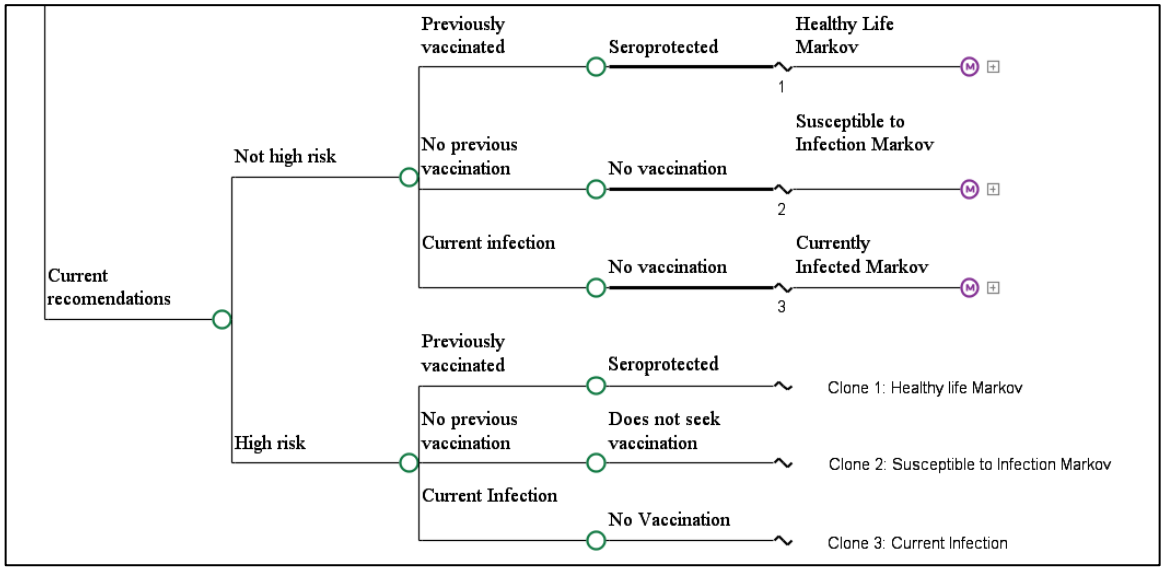
Two population groups:

- Non-high risk

(general population)

- High-risk

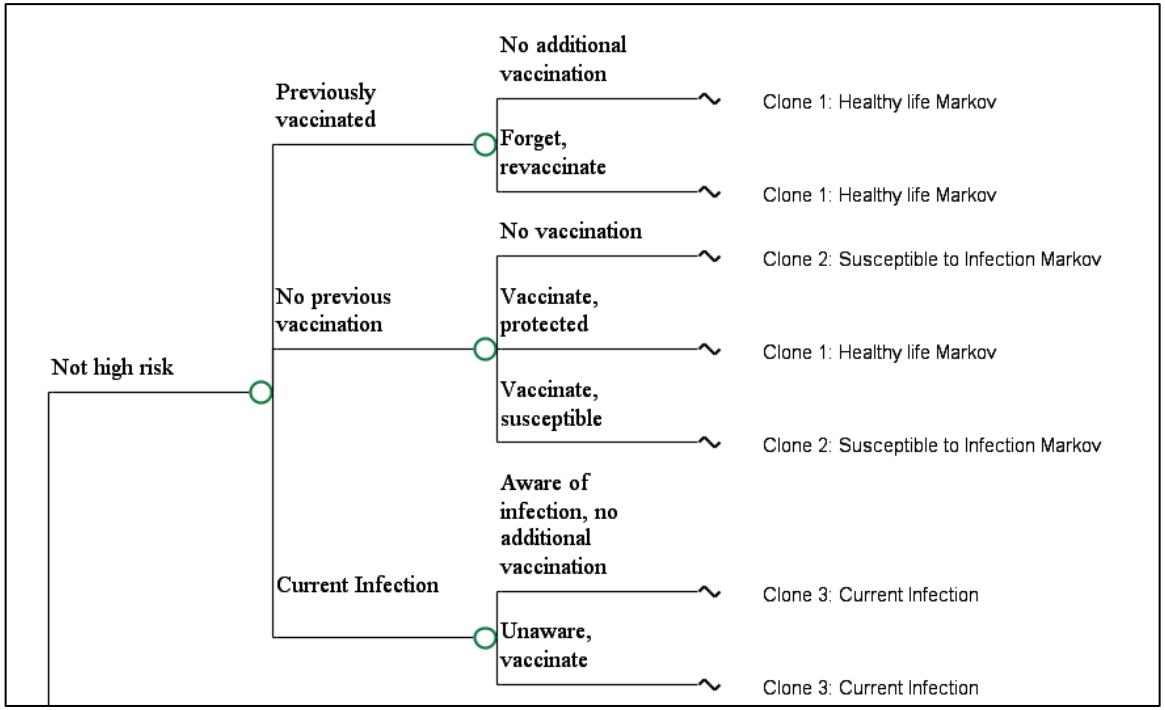
Baseline Strategy



Methods: Economic Model

Decision Tree Model

Alternate Strategy



Cohort

1,000,000

microsimulation trials

Age heterogeneity representative of the U.S. population

Two population groups:

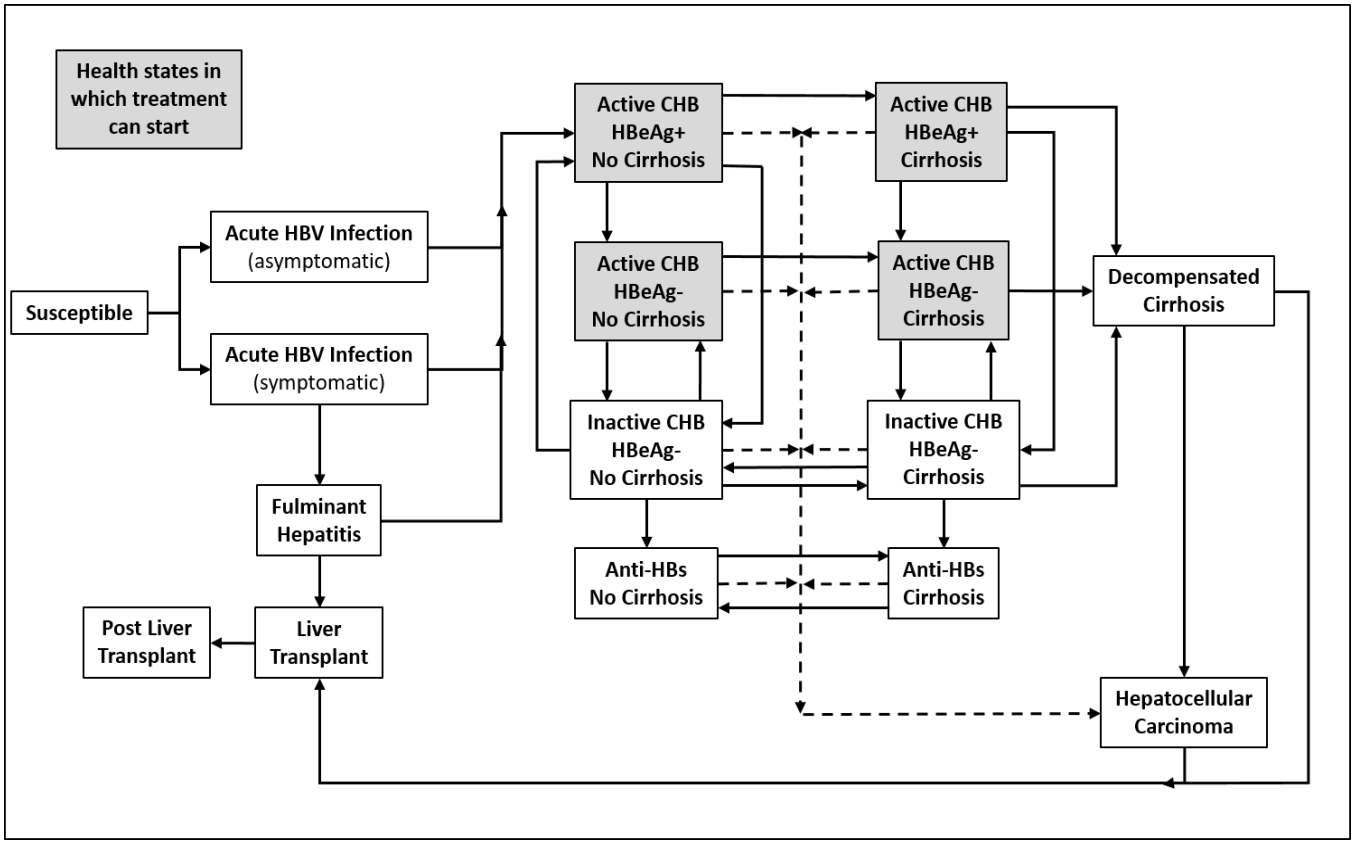
- Non-high risk

(general population)

- High-risk

Methods: Epidemiological Model

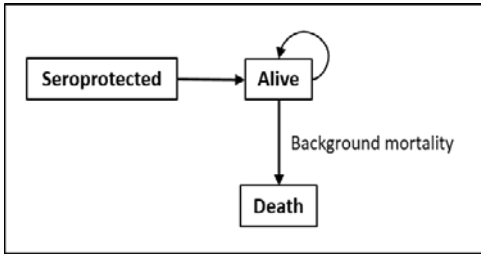
Susceptible to Infection Markov



Time step: 1 year

Each health state includes background mortality defined by single year of age.

Healthy Life Markov



Abbreviations: HBV, hepatitis B virus; CHB, chronic hepatitis B infection; HBeAg+, hepatitis B e-antigen positive; HBeAg-, hepatitis B e-antigen negative; anti-HBs, hepatitis B surface antibody. All health states can transition to death, either by background mortality or hepatitis B-related death.

Chahal 2018[1]

Methods: Health Outcomes

Analytic horizon:

- Lifetime of the cohort

Costs:

- 2019 USD

Discounting

- 3% per year

Health outcomes:

- Quality-adjusted life years (QALYs)
- Life-years
- Acute HBV infections
- Chronic HBV infections
- Deaths related to HBV infection
- Vaccine doses administered
- Persons protected against infection

Primary summary measure:

- Incremental cost-effectiveness ratio (ICER)
- ICER= Δ cost per person / Δ QALYs per person

Methods: Inputs

Baseline Strategy Vaccination Coverage

Input	Base Case	Lower	Upper
Proportion of population that is high risk[2]	0.300	0.150	0.450
Proportion aware of CHB infection[3]	0.339	0.167	0.511
Current vaccination coverage (non-high risk)[4,5]			
19-29 years	0.921	0.700	0.990
30+ years	0.000	0.000	0.200
Current vaccination coverage (high risk)[4,5]			
19-29 years	0.921	0.700	0.990
30-49 years	0.329	0.100	0.500
50+ years	0.159	0.100	0.350
Proportion that forget about vaccination[6]			
19-49 years	0.300	0.236	0.364
50+ years	0.192	0.138	0.245
Proportion that receive dose 2, given dose 1[16]	0.819	0.716	0.819
Proportion that receive dose 3, given dose 2[16]	0.800	0.542	0.800

Methods: Inputs

Costs Associated with Vaccination (2019 USD)

Input	Base Case	Lower	Upper
One dose of HepB (3-dose series)[14]	**58.95**	44 (-25%)	74 (+25%)
One dose of HepB (2-dose series)[14]	**115.75**	87 (-25%)	145 (+25%)
Administration of one dose of HepB[15,18]	27.85	21 (-25%)	35 (+25%)
Hepatitis B surface antibody test[19]	10.74	8 (-25%)	13 (+25%)
Hepatitis B core antibody total test[19]	12.05	9 (-25%)	15 (+25%)
Hepatitis B surface antigen test[19]	10.33	8 (-25%)	13 (+25%)
Time for receiving one dose of HepB[18]	82.65	62 (-25%)	103 (+25%)
Travel to receive one dose of HepB	20.00	10 (-50%)	30 (+50%)

Abbreviations: HepB, hepatitis B vaccine

Methods: Sensitivity Analyses

Base Case

- Dose-specific vaccine coverage: Initial dose= 50% coverage in the general population
- No additional vaccination among high-risk persons

Sensitivity Analyses

1. Interval sensitivity analyses on vaccination coverage inputs
2. One-way sensitivity analyses on all inputs
   - Tornado diagram (individual inputs)
   - Tornado diagram (groups on inputs)
3. Probabilistic sensitivity analysis that varied all inputs simultaneously
   - Triangle distribution for each input
4. Two-way sensitivity analysis on vaccination coverage by risk of infection

Results: Base Case Results

Outcome	3-dose strategy	2-dose strategy
Vaccination Outcomes		
Percent protected (current strategy)	23.7%	23.7%
Percent protected (alternate strategy)	44.9%	45.7%
Epidemiologic Outcomes		
Percent of chronic HBV infections averted	24.2%	24.0%
Percent of HBV deaths averted	22.8%	22.2%
NNV (acute infection)	372	386
Cost outcomes (2019 USD)		
Incremental USD per person	$130	$129
ICER (USD/QALY)	$152,722	$155,429
USD per life-year gained	$67,567	$69,947
USD per acute HBV infection averted	$226,845	$227,113
USD per HBV death averted	$1,295,407	$1,322,837

Abbreviations: HBV, hepatitis B virus; NNV, number needed to vaccinate; USD, 2019 U.S. Dollars. Base case assumes 50% of non-high risk persons initiate vaccination and no additional vaccination among high-risk persons. Base case results are based on the median value of 100 stochastic runs with 1,000,000 microsimulations per run.

Results: Intermediate Outcomes

Intermediate Outcome	Baseline strategy	3-dose strategy	2-dose strategy
Incident Health Outcomes			
Acute HBV infections	570,735	428,485	428,733
Fulminant hepatitis	7,063	5,204	5,576
Chronic HBV infections	45,847	34,200	34,447
Hepatocellular carcinoma	81,410	59,477	60,964
Liver transplants	2,230	<2,000	<2,000
HBV-related deaths	104,953	78,808	78,808
Vaccination Outcomes			
Number of vaccine doses	176,117,095	352,138,654	310,701,976
Trials protected	58,705,698	111,232,436	113,205,352

Note: Analytic horizon is the lifetime of the cohort, which is, on average, ~35 years per person. U.S. adult population of 247,822,574.

Abbreviations: HBV, hepatitis B virus. Alternate strategy assumes coverage in the youngest group (19-29 years) does not decrease below current coverage (91.3%). Base case assumes 50% of non-high risk persons initiate vaccination and no additional vaccination among high-risk persons. Base case results are based on the median value of 100 stochastic runs with 1,000,000 microsimulations per run. Population-level results are scaled to U.S. adult population size.

Results: Base Case Results by Age Group

Age group	% protected (current)	% protected (alternate)	% of acute HBV infections averted	NNV	ICER (USD/QALY)
3-dose strategy					
19-29 years	91.4%	93.9%	26.9%	108	$128,416
30-39 years	9.6%	38.6%	25.6%	193	$58,573
40-49 years	9.6%	38.4%	26.9%	301	$117,410
50-59 years	4.6%	28.0%	19.1%	642	$371,606
60+ years	4.6%	28.4%	20.8%	>1,000	$518,337
2-dose strategy					
19-29 years	91.4%	92.7%	12.6%	105	$113,483
30-39 years	9.6%	39.8%	27.4%	190	$57,944
40-49 years	9.6%	38.5%	27.3%	296	$95,564
50-59 years	4.6%	30.2%	21.0%	661	$509,911
60+ years	4.6%	29.9%	24.1%	>1,000	$541,461

Abbreviations: HBV, hepatitis B virus; USD, 2019 U.S. Dollars; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; NNV, number needed to vaccinate to prevent an acute infection. Alternate strategy assumes coverage in the youngest group (19-29 years) does not decrease below current coverage (91.3%). Base case assumes 50% of non-high risk persons initiate vaccination and no additional vaccination among high-risk persons. Base case results are based on the median value of 100 stochastic runs with 1,000,000 microsimulations per run.

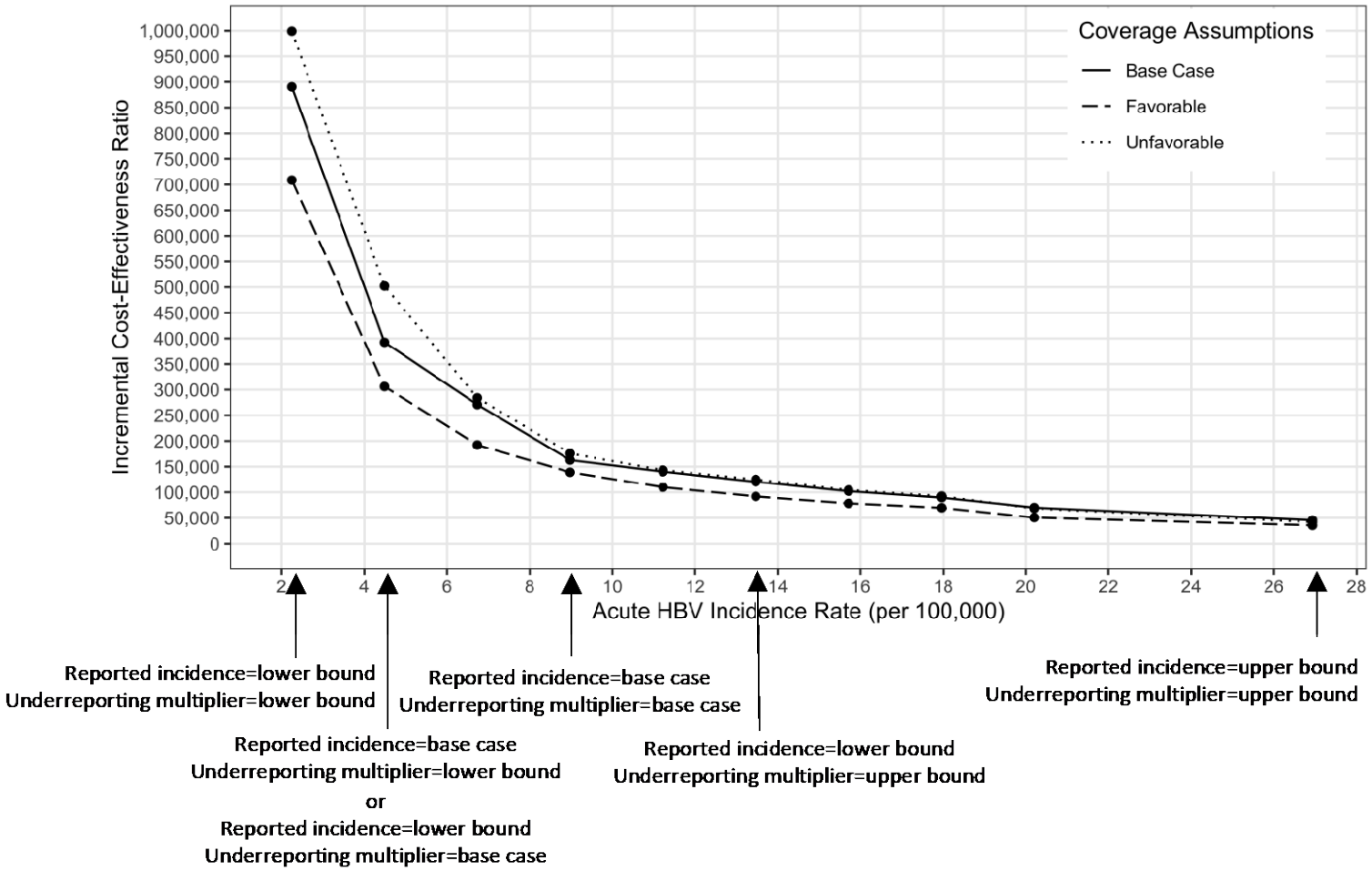
Results: Sensitivity Analysis

Outcome	Base Case	20% additional vaccination among high-risk
3-dose vaccination strategy		
Percent of acute HBV infections averted	24.8%	31.2%
Percent of HBV deaths averted	22.8%	40.5%
ICER (USD/QALY)	$152,722	$137,111
USD per life-year gained	$67,567	$62,588
USD per acute HBV infection averted	$226,845	$205,508
USD per HBV death averted	$1,295,407	$919,649
2-dose vaccination strategy		
Percent of acute HBV infections averted	24.6%	30.9%
Percent of HBV deaths averted	22.2%	40.5%
ICER (USD/QALY)	$155,429	$134,589
USD per life-year gained	$69,947	$61,661
USD per acute HBV infection averted	$227,113	$206,495
USD per HBV death averted	$1,322,837	$913,739

Abbreviations: HBV, hepatitis B virus; USD, 2019 U.S. Dollars; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; NNV, number needed to vaccinate. Alternate strategy assumes coverage in the youngest group (19-29 years) does not decrease below current coverage and vaccination 50% of non-high risk adults.

Results: Sensitivity Analysis

3-dose vaccination strategy



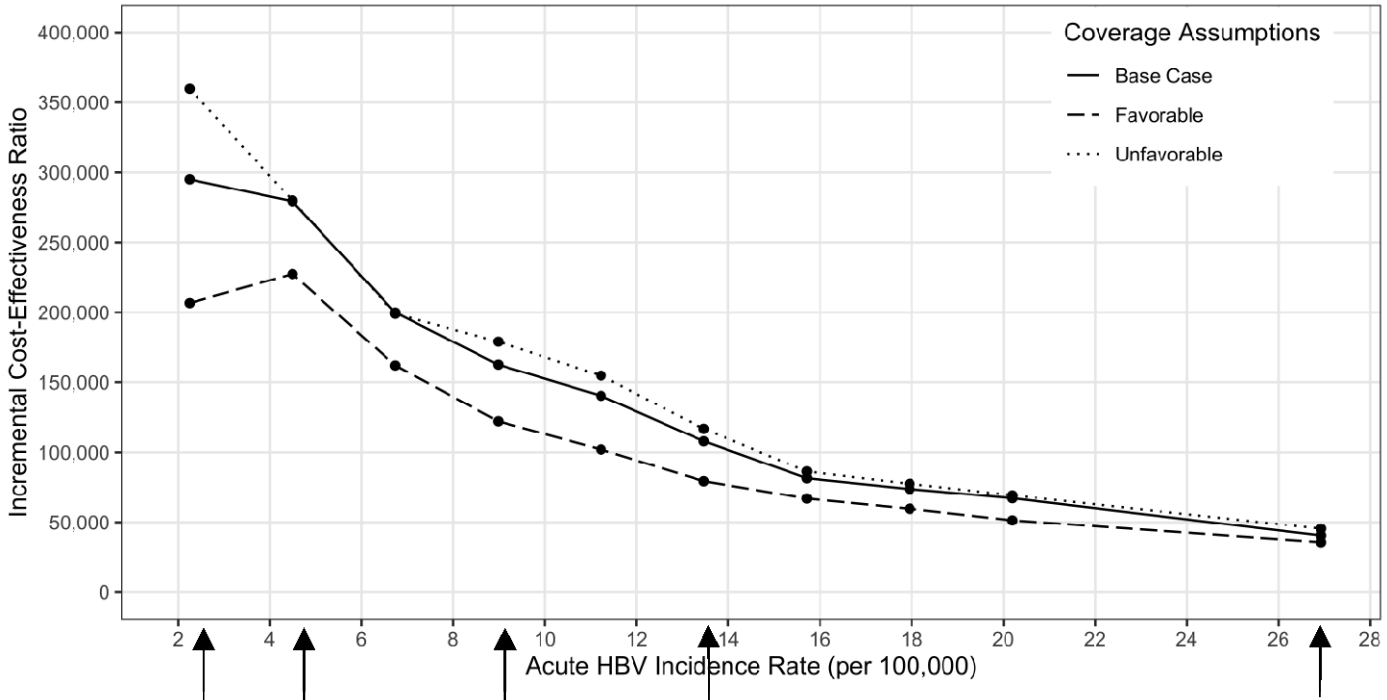
Base Case
- 50% general
- 0% high-risk

Favorable
- 70% general
- 60% high-risk

Unfavorable
- 30% general
- 0% high-risk

Results: Sensitivity Analysis

2-dose vaccination strategy



Reported incidence=lower bound
Underreporting multiplier=lower bound

Reported incidence=base case
Underreporting multiplier=lower bound
or
Reported incidence=lower bound
Underreporting multiplier=base case

Reported incidence=base case
Underreporting multiplier=base case

Reported incidence=lower bound
Underreporting multiplier=upper bound

Reported incidence=upper bound
Underreporting multiplier=upper bound

Base Case
- 50% general
- 0% high-risk

Favorable
- 70% general
- 60% high-risk

Unfavorable
- 30% general
- 0% high-risk

Summary

Base Case Assumptions

(50% vaccination initiation among general population; no additional vaccination among high-risk persons).

3-dose strategy:

- ICER=$152,722
- 100% increase in # of doses; avert 24% of incident acute HBV infections

2-dose strategy:

- ICER=$155,429
- 76% increase in # of doses; avert 24% of incident acute HBV infections

Increased (20%) vaccination in high-risk persons yields greater benefits

- ICERs ≈ $135,000; avert ~31% of acute HBV infections

Limitations

Used a static model that assumes risk of infection estimates do not change over time.

- Does not include indirect effects of vaccination.
- Results are a conservative estimate of effects.

Assumed vaccination occurred at a single point in time, protection was instantaneously effective, and protection did not wane.

Did not model coinfections (e.g. HIV, HCV).

We only assessed vaccination strategies in the absence of alternate screening or linkage to care programs.

- Possible understatement of costs

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Extra Slides

Similarity in 2-dose & 3-dose Results

Driven by vaccination input variables.

- Combination of dose-specific efficacy, coverage and costs.
  1) 2-dose vaccine requires less visits, but costs more per dose.
  2) Modeling drop off between doses and potential for protection from incomplete series results in a similar total number of persons protected in each strategy.

Example: Expected values for persons 40-49 years old

	2-dose		3-dose	
	Distribution	Vaccination costs	Distribution	Vaccination costs
No vaccination	50.0%	0	50.0%	0
1 dose, protected	1.7%	$246.25	2.8%	$189.45
1 dose, susceptible	7.4%	$246.25	6.3%	$189.45
2 doses, protected	40.0%	$492.50	6.4%	$378.90
2 doses, susceptible	1.6%	$492.50	1.8%	$378.90
3 doses, protected	N/A	N/A	32.3%	$568.35
3 doses, susceptible	N/A	N/A	0.5%	$568.35
	Weighted average:	**$227**	**Weighted average:**	**$235**
	Total protected:	**41.7%**	**Total protected:**	**41.5%**

Methods: Inputs

Vaccine Efficacy Inputs

Input	Base Case	Lower	Upper
Efficacy of 3-dose vaccine strategy			
(Engerix-B/TWINRIX)			
1 dose only (all ages)[7]	0.308	0.200	0.400
2 doses only (all ages)[7]	0.782	0.700	0.800
3 doses (<50 years)[7]	0.985	0.750	1.000
3 doses (50+ years)[8]	0.840	0.750	1.000
Efficacy of 2-dose vaccine strategy			
(HEPLISAV-B)			
1 dose only (19-39 years)[8]	0.305	0.270	0.340
1 dose only (40+ years)[8]	0.185	0.159	0.210
2 doses (19-29)[20]	0.999	0.999	0.999
2 doses (30-39 years)[20]	0.989	0.981	0.997
2 doses (40-49 years)[20]	0.972	0.962	0.982
2 doses (50-59 years)[20]	0.952	0.941	0.963
2 doses (60+ years)[20]	0.916	0.900	0.932

Methods: Inputs

Risk of acute HBV infection among unvaccinated, uninfected adults

$$Inc.Rate = \frac{reported\ incidence * underreporting\ multiplier}{1-(p)-(\sum_{dose=1}^{dose=3}(vax_{dose} * eff_{dose}))+((\sum_{dose=1}^{dose=3} p * vax_{dose} * eff_{dose}))} \times \frac{pInfHR}{pPopHR}$$

Input	Base Case	Lower	Upper	Reference
Reported Acute HBV Incidence				
19-29 years	0.60	0.30	1.20	9
30-39 years	2.32	1.16	4.64	9
40-49 years	2.54	1.26	5.08	9
50-59 years	1.62	0.81	3.24	9
60+ years	0.56	0.28	1.12	9
Under-reporting multiplier	6.48	3.24	9.72	10
Acute HBV Prevalence				
19-29 years	0.033	0.028	0.038	11
30-39 years	0.033	0.028	0.038	11
40-49 years	0.033	0.028	0.038	11
50-59 years	0.067	0.058	0.077	11
60+ years	0.067	0.058	0.077	11
Proportion of infections (high-risk)	0.478	0.359	0.598	13
Proportion of population (high-risk)	0.300	0.150	0.450	13

Methods: Inputs

Annual Health State Costs for HBV Infection (2019 USD)

Health State/Cost	Base Case	Lower	Upper	Reference
Acute Hepatitis, asymptomatic	0.00	0.00	671.34	1,17
Acute Hepatitis, symptomatic	385.32	199.68	671.34	1,17
Fulminant Hepatitis*	18,739.30	18,682.10	50,176.90	1,17
HBeAg+, Active CHB, Non-Cirrhotic	1,395.57	698.33	4,187.79	1,17
HBeAg+, Active CHB, Cirrhotic	2,929.30	1,464.65	8,786.81	1,17
HBeAg-, Active CHB, Non-Cirrhotic	1,395.57	698.33	4,187.79	1,17
HBeAg-, Active CHB, Cirrhotic	2,929.30	1,464.65	8,786.81	1,17
HBeAg-, Inactive CHB, Non-Cirrhotic	698.33	348.62	2,093.90	1,17
HBeAg-, Inactive CHB, Cirrhotic	1,464.65	731.78	4,392.87	1,17
Decompensated Cirrhosis	34,683.14	32,551.47	36,816.97	1,17
Hepatocellular Carcinoma	55,324.22	49,651.27	60,989.61	1,17
Liver Transplant*	219,631.47	202,537.06	236,721.55	1,17
Post Liver Transplant	47,833.68	39,085.72	56,581.64	1,17
Anti-HBs, Non-Cirrhotic	348.62	174.85	1,046.95	1,17
Anti-HBs, Cirrhotic	731.78	365.89	2,196.43	1,17
Initial tests and evaluations for new infections*	356.09	178.09	534.18	1,17
Annual Treatment Cost	9,576.00	5,988.00	11,976.00	1
Annual Cost of Monitoring Treatment Tests	690.89	345.54	1,036.00	1
Annual Cost of Adverse Events	732.00	366.00	1,098.00	1

Methods: Inputs

Annual Health State Utility Values

Health State	Base Case	Lower	Upper	Reference
Susceptible	0.990	0.980	1.000	1
Immune	0.990	0.980	1.000	1
Acute HBV, asymptomatic	0.990	0.950	1.000	1
Acute HBV, symptomatic	0.700	0.630	0.770	1
Active CHB, Non-Cirrhotic	0.670	0.603	0.737	1
Active CHB, Cirrhotic	0.660	0.594	0.726	1
Inactive CHB, cirrhotic and non-cirrhotic	0.850	0.765	0.935	1
Fulminant Hepatitis	0.370	0.333	0.407	1
Decompensated Cirrhosis	0.370	0.333	0.407	1
Hepatocellular Carcinoma	0.430	0.387	0.473	1
Liver Transplant	0.570	0.513	0.627	1
Post Liver Transplant	0.640	0.576	0.704	1
anti-HBs	0.860	0.774	0.946	1
Annual utility loss while on treatment	0.031	0.000	0.047	1

Results: Base Case Ranges

Outcome	3-dose strategy n (IQR)	2-dose strategy n (IQR)
Vaccination Outcomes		
% protected (current strategy)	23.7% (23.7%, 23.7%)	23.7% (23.7%, 23.7%)
% protected (alternate strategy)	44.9% (44.9%, 44.9%)	45.7% (45.6%, 45.7%)
Epidemiologic Outcomes		
% of acute HBV infections averted	24.8% (23.4%, 25.7%)	24.6% (23.2%, 25.5%)
% of chronic HBV infections averted	24.2% (18.2%, 30.0%)	24.0% (18.0%, 29.7%)
% of HBV deaths averted	22.8% (17.3%, 27.3%)	22.2% (16.7%, 27.0%)
NNV (acute infection)	372 (355, 398)	386 (370, 414)
NNV (hospitalization)	341 (263, 748)	359 (221, 548)
Effectiveness Outcomes		
Incremental QALYs per person	0.0008 (0.0005, 0.0011)	0.0008 (0.0005, 0.0010)
Incremental life-years per person	0.0018 (0.0012, 0.0026)	0.0018 (0.0012, 0.0025)
Cost outcomes (2019 USD)		
Incremental USD per person	$130 ($126, $132)	$129 ($125, $131)
ICER (USD/QALY)	$152,722 ($119,113, $235,086)	$155,429 ($120,302, $242,226)
USD per life-year gained	$67,567 ($49,808, $99,258)	$69,947 ($49,569, $99,139)
USD per acute HBV infection averted	$226,845 ($212,478, $243,129)	$227,113 ($212,475, $241,453)
USD per HBV death averted	$1,295,407 ($988,565, $1,718,223)	$1,322,837 ($1,014,550, $1,726,958)

Abbreviations: HBV, hepatitis B virus; n, number; IQR, interquartile range; %, percent; USD, 2019 U.S. Dollars; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; NNV, number needed to vaccinate. Alternate strategy assumes coverage in the youngest group (19-29 years) does not decrease below current coverage (91.3%). Base case assumes 50% of non-high risk persons initiate vaccination and no additional vaccination among high-risk persons. Base case results are based on the median value of 100 stochastic runs with 1,000,000 microsimulations per run.

Results: Probabilistic Sensitivity Analysis

3-Dose Vaccination Strategy

		Probabilistic Sensitivity Analysis		
Outcome	**Base Case**	**Median**	**5th**	**95th**
Vaccination Outcomes				
Percent protected (current strategy)	23.7%	26.9%	22.1%	32.4%
Percent protected (alternate strategy)	44.9%	45.9%	42.4%	50.8%
Epidemiologic Outcomes				
Acute HBV infections averted	141,011	158,359	79,731	259,613
Chronic HBV infections averted	11,152	6,443	<1,000	15,130
HBV deaths averted	24,163	37,421	15,068	59,279
NNV (acute infection)	372	301	168	578
Effectiveness Outcomes				
QALYs gained per person	0.0008	0.0012	0.0004	0.0020
Life-years gained per person	0.0018	0.0023	0.0005	0.0040
Cost outcomes (2019 USD)				
Incremental USD per person	$130	$122	$95	$151
ICER (USD/QALY)	$152,722	$105,898	$64,560	$276,552
USD per life-year gained	$67,567	$51,813	$30,432	$239,897
USD per acute HBV infection averted	$226,845	$193,563	$105,208	$382,210
USD per HBV death averted	$1,295,407	$842,404	$466,672	$2,009,627

Results: Probabilistic Sensitivity Analysis

2-Dose Vaccination Strategy

		Probabilistic Sensitivity Analysis		
Outcome	**Base Case**	**Median**	**5th**	**95th**
Vaccination Outcomes				
Percent protected (current strategy)	23.7%	26.9%	22.1%	32.4%
Percent protected (alternate strategy)	45.7%	47.1%	43.9%	52.1%
Epidemiologic Outcomes				
Acute HBV infections averted	142,622	165,793	87,463	280,647
Chronic HBV infections averted	11,152	5,948	<1,000	16,369
HBV deaths averted	25,030	39,156	19,919	66,008
NNV (acute infection)	386	308	171	578
Effectiveness Outcomes				
QALYs gained per person	0.0008	0.0012	0.0005	0.0020
Life-years gained per person	0.0018	0.0025	0.0007	0.0045
Cost outcomes (2019 USD)				
Incremental USD per person	$129	$122	$95	$148
ICER (USD/QALY)	$155,429	$101,489	$57,130	$253,554
USD per life-year gained	$69,947	$48,853	$27,761	$141,828
USD per acute HBV infection averted	$227,113	$182,721	$96,613	$346,385
USD per HBV death averted	$1,322,837	$778,710	$435,255	$1,450,081

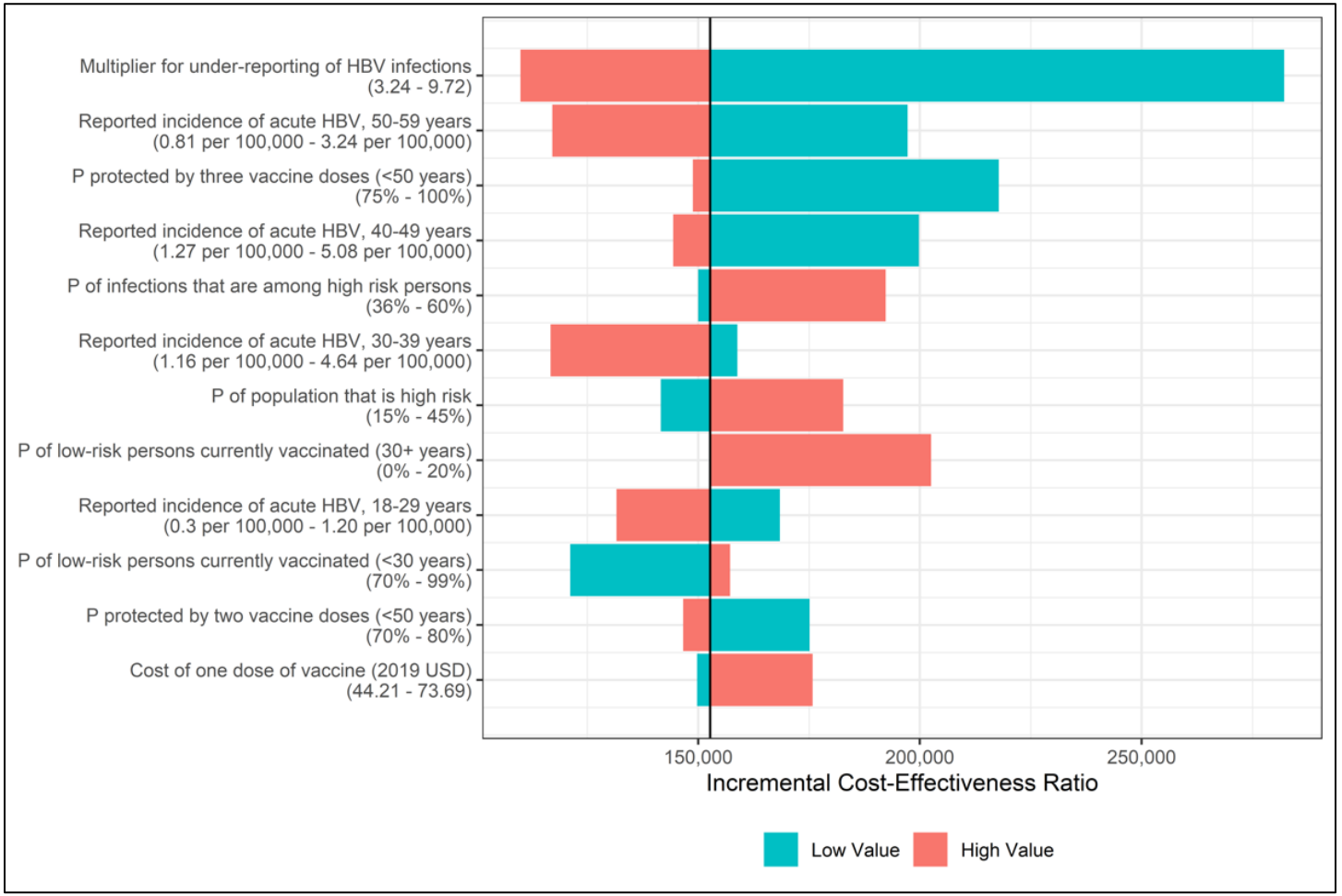
Results: Sensitivity Analysis

Outcome	Vaccination coverage among non-high risk adults				
	30%	40%	50%	60%	70%
3-dose vaccination strategy					
Percent of acute HBV infections averted	14.3%	19.9%	25.1%	29.7%	33.4%
Percent of HBV deaths averted	21.3%	28.4%	32.7%	38.5%	42.3%
ICER (USD/QALY)	$175,650	$165,866	$162,780	$155,627	$155,009
USD per life-year gained	$86,988	$79,548	$79,535	$74,211	$74,076
USD per acute HBV infection averted	$245,534	$231,841	$227,262	$229,705	$237,894
USD per HBV death averted	$955,828	$943,924	$1,012,989	$1,030,649	$1,091,179
2-dose vaccination strategy					
Percent of acute HBV infections averted	14.3%	19.8%	24.7%	29.9%	34.1%
Percent of HBV deaths averted	21.3%	28.1%	32.4%	38.7%	42.5%
ICER (USD/QALY)	$179,058	$169,837	$162,691	$153,809	$154,290
USD per life-year gained	$89,923	$81,518	$79,568	$74,180	$74,491
USD per acute HBV infection averted	$243,919	$231,625	$229,163	$225,784	$231,285
USD per HBV death averted	$949,542	$947,367	$1,015,120	$1,012,338	$1,076,577

Abbreviations: HBV, hepatitis B virus; USD, 2019 U.S. Dollars; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; NNV, number needed to vaccinate. Alternate strategy assumes coverage in the youngest group (19-29 years) does not decrease below current coverage (91.3%). Alternate strategy assumes no additional vaccination among high-risk persons.

Results: Sensitivity Analysis

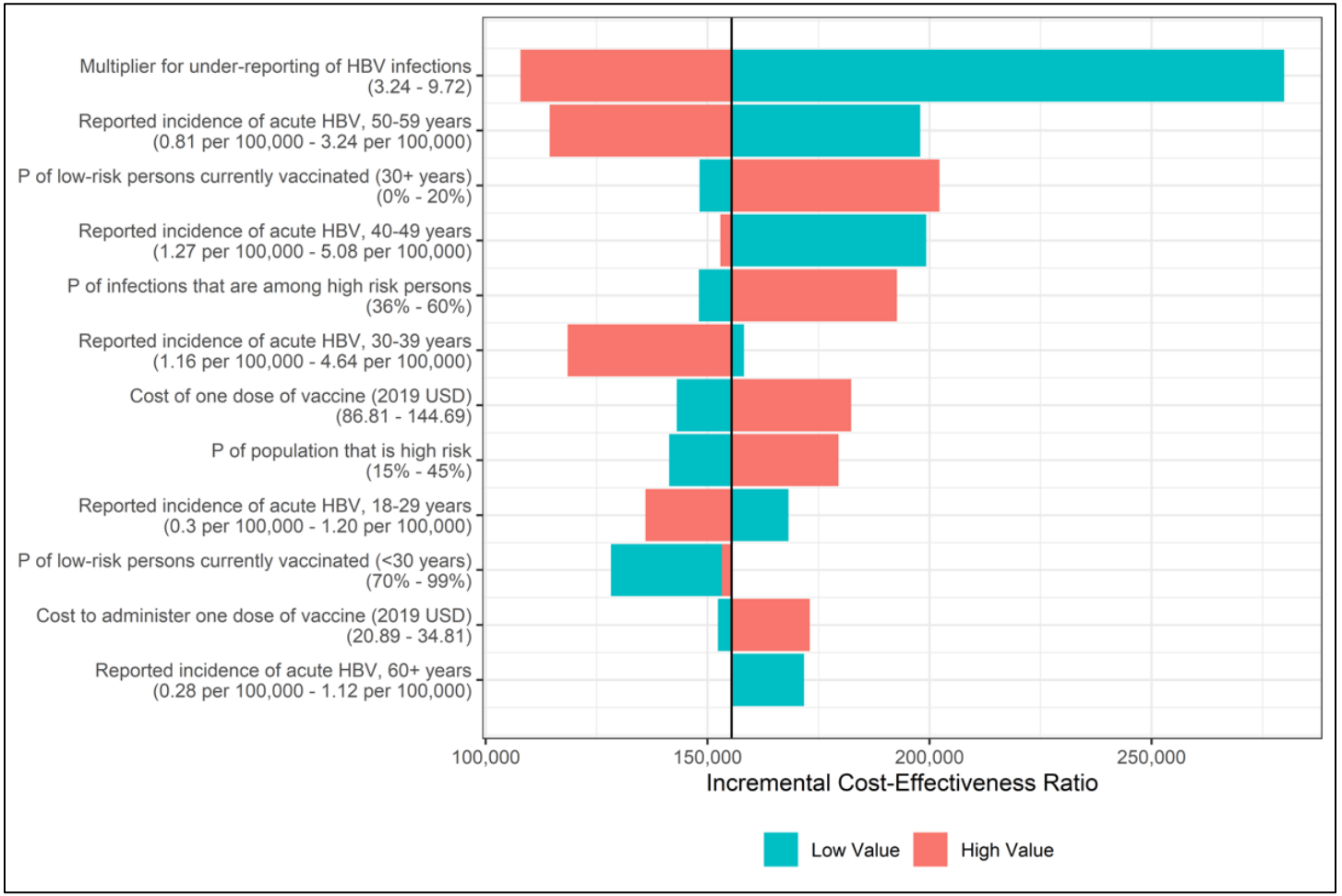
3-Dose Vaccination Strategy



Abbreviations: HBV, hepatitis B virus; P, proportion

Results: Sensitivity Analysis

2-Dose Vaccination Strategy



Abbreviations: HBV, hepatitis B virus; P, proportion

Results: Probabilistic Sensitivity Analysis