Cost-effectiveness of 3-Antigen vs. Single-Antigen Vaccine for Prevention of Hepatitis B in Adults in the United States

Anderson SA,[1] Talbird SE,[1] Nossov M,[2] Beattie N,[2] Diaz-Mitoma F[2]

[1]RTI Health Solutions, Research Triangle Park, NC, United States; [2]VBI Vaccines, Cambridge, MA, United States

BACKGROUND

- Hepatitis B is a liver infection spread through exposure to infectious bodily fluid and blood; up to 12% of adults with an acute hepatitis B virus (HBV) infection develop chronic HBV infections.[1] Long-term complications of both acute and chronic HBV infections can be fatal.
- In the United States (US), incidence of acute HBV infections has been approximately 20,000 cases per year. There are between 850,000 and 2.2 million prevalent chronic HBV infections among US adults. Overall, 15% of adults with chronic HBV infections will die prematurely.[2]
- Vaccination rates remain low, with only 40.3% of adults aged 19 to 49 years and only 19.1% of adults aged ≥ 50 years receiving 3 doses of hepatitis B vaccine in 2018.[3]
- The Centers for Disease Control and Prevention updated its hepatitis B vaccination guidance in April 2022.[4] It recommends universal HBV vaccination of adults through age 59 years and vaccination of all adults with risk factors aged 60 years and older. Furthermore, any adult aged 60 years or older may be vaccinated.
- PREHEVBRIO™ [Hepatitis B Vaccine (Recombinant)], the first 3-antigen hepatitis B vaccine, was approved by the Food and Drug Administration in November 2021. In the phase 3 PROTECT trial, the 3-antigen vaccine elicited noninferior seroprotection rates (SPR) in adults aged 18 years and older and statistically significantly higher SPRs compared with ENGERIX-B™, a single-antigen hepatitis B vaccine, in adults aged 45 years and older.

OBJECTIVE

- This analysis estimated the cost-effectiveness of this 3-antigen vaccine relative to a 3-dose, single-antigen vaccine to prevent HBV infection among adults in the US.

METHODS

Model Structure

- A cost-effectiveness model was developed using a combined decision tree and Markov structure to follow 100,000 adults vaccinated against HBV infection with either a 3-antigen or single-antigen vaccine (Figure 1 and Figure 2).
- Societal and healthcare sector perspectives were modeled, and a lifetime time horizon was used.
- The following populations were modeled, with an assumed age at vaccination based on the median age of the cohort or from published literature (shown in parentheses):
  - Adults aged 18-44 (31.0 years)
  - Adults aged 45-64 years (54.5 years)
  - Adults aged ≥ 65 years (74.5 years)
  - Diabetic adults (61.9 years)
  - Obese adults (48.5 years)
- The cycle length was 1 month for the first 12 modeled months; subsequently, the cycle length was 1 year.

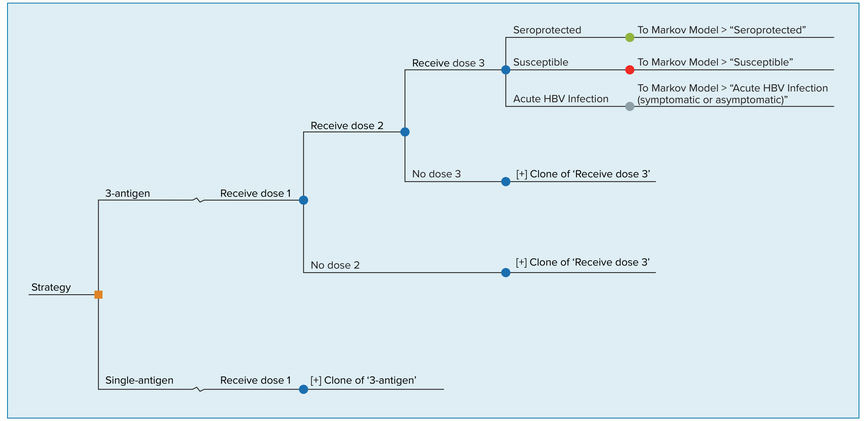
Model Inputs

- SPRs were obtained from the pivotal, phase 3, head-to-head PROTECT trial (NCT03393754) (Table 1) and adjusted for reported adherence rates to hepatitis B vaccine dose regimen (Table 2) to estimate effective, real-world SPRs.
- Vaccine acquisition costs were **$64.75** per dose for the 3-antigen vaccine and **$63.55** for the single-antigen vaccine.[5,6]
- Direct and indirect costs, utilities, transition probabilities, and mortality were obtained from Rosenthal et al.[7]
- HBV incidence was based on the most recently available US data (2018)[8]; age-specific incidence was calculated using the same method as Rosenthal et al.[7]
- Health outcomes and costs (2020 US dollars) were discounted 3% annually,[9] and costs were inflated to 2020 US dollars.

Model Outcomes and Analyses

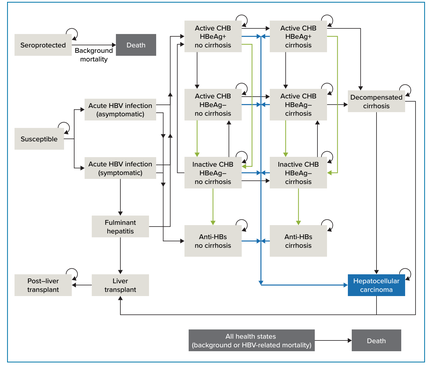
- Total and incremental health and cost outcomes were reported by vaccine and population.
- The primary outcome was incremental cost per quality-adjusted life-year (QALY) gained (incremental cost-effectiveness ratio [ICER]).
- One-way sensitivity and scenario analyses were conducted using 95% confidence intervals, ranges from the published literature, or assumption.

Figure 1. Decision-Tree Model Structure (Year 1)



Note: The orange square represents the initial decision node: vaccination with a 3-dose single-antigen vaccine or with a 3-dose 3-antigen vaccine. Blue circles represent chance nodes where the transition is governed by an input probability. Green, red, and gray circles represent the transition to the state named in the subsequent Markov model structure.

Figure 2. Markov Model Structure



anti-HBs = antibody to hepatitis B surface antigen; CHB = chronic hepatitis B virus infection; HBeAg– = hepatitis B e antigen negative; HBeAg+ = hepatitis B e antigen positive.

Notes: Green arrows show transition probabilities altered by treatment of chronic HBV infection. Blue arrows show transitions to hepatocellular carcinoma. There is an increased mortality risk for individuals in any chronic HBV infection, fulminant hepatitis, decompensated cirrhosis, liver transplant, post–liver transplant, or hepatocellular carcinoma state. All patients remain in a liver transplant state for 1 year.

Table 1. Vaccine Seroprotection Rates (PROTECT Trial Per-Protocol Analysis, % Achieving Anti-HBs Titers ≥ 10 mIU/mL)

		Age group			High risk	
		18-44	45-64	≥ 65	Diabetic	Obese
Day 28 (4 weeks after dose 1)	3-antigen	28.8%	17.2%	8.6%	11.3%	19.0%
	Single-antigen	9.6%	7.7%	6.7%	11.5%	10.1%
Day 56 (4 weeks after dose 2)	3-antigen	76.0%	54.6%	36.2%	27.8%	49.3%
	Single-antigen	37.0%	27.4%	13.1%	18.0%	20.5%
Day 168 (20 weeks after dose 2)	3-antigen	87.2%	72.0%	48.7%	44.4%	60.2%
	Single-antigen	39.0%	30.2%	18.3%	23.0%	22.5%
Day 196 (4 weeks after dose 3)	3-antigen	99.2%	94.8%	83.6%	83.3%	89.2%
	Single-antigen	91.1%	80.1%	64.7%	58.3%	68.1%

Sources: VBI Vaccines data on file[11]; Vesikari et al.[12]

Table 2. Adherence to 3-Dose Adult Hepatitis B Vaccine

	Vaccine adherence			Series completion
Age group, years	Dose 1	Dose 2 conditional on receiving previous dose	Dose 3 conditional on receiving previous dose	Calculated % vaccinated with 3 doses
18-29	100%	74.3%	71.5%	53.1%
30-39	100%	81.9%	80.0%	65.5%
40-49	100%	81.9%	80.0%	65.5%
50-64	100%	84.9%	83.9%	71.2%
≥ 65	100%	81.7%	84.7%	69.2%

Source: Nelson et al.[13]

RESULTS

Base-Case Results

- The 3-antigen vaccine reduced acute and chronic HBV infections, reduced cases of long-term complications (Table 3), and increased QALYs (Table 4) for all populations compared with the single-antigen vaccine.
- The 3-antigen vaccine reduced disease-related costs and fully offset modestly higher vaccination costs, making the 3-antigen vaccine dominant (cost saving) compared with the single-antigen vaccine for adults aged 18-64 years and adults with diabetes and obesity (Table 4).
- Incremental cost per QALY gained is the same for both the healthcare sector and societal perspectives because there is no difference in indirect costs between the two vaccine strategies given both are 3-dose regimens.

Sensitivity Analysis Results

- One-way sensitivity analysis found that there were only two populations in which varying parameters resulted in ICERs of over $10,000 per QALY gained (Figure 3 and Figure 4).
- The variation in the ICER for each of the other populations was:
  - Aged 18-44 years: −$7,118 to −$1,946 (3-antigen vaccine dominant)
  - Aged 45-64 years: −$11,950 to $9,856
  - Obese adults: −$10,946 to $4,393

Table 3. Health Outcomes

	Seroprotection and infection[a]	Long-term complications and death[a]					
	No. (%) seroprotected[b]	Acute HBV infections	Fulminant hepatitis	Chronic HBV infections	Hepatocellular carcinoma	Liver transplants	HBV-related deaths
18-44 years							
3-antigen	85,066 (85.1%)	67	1	5	8	0	9
Single-antigen	70,594 (70.6%)	130	2	10	15	1	17
45-64 years							
3-antigen	82,720 (82.7%)	31	0	2	3	0	3
Single-antigen	67,176 (67.2%)	57	1	4	5	0	5
≥ 65 years							
3-antigen	72,086 (72.1%)	14	0	1	1	0	1
Single-antigen	54,769 (54.8%)	21	0	2	1	0	1
High risk: diabetic adults							
3-antigen	72,288 (72.3%)	53	1	4	4	0	4
Single-antigen	55,762 (55.8%)	79	1	6	5	0	6
High risk: obese adults							
3-antigen	78,810 (78.8%)	44	1	4	4	0	4
Single-antigen	59,051 (59.1%)	83	1	7	7	0	7

Note: These results are based on a cohort of 100,000 vaccinated adults in each modeled cohort, discounted using a 3% annual discount rate.

[a] Differences and totals may not sum to expected values due to rounding.

[b] Percentage seroprotected is based on both the vaccine SPRs reported in Table 1 and the vaccine adherence rates reported in Table 2 to estimate real-world SPR.

Table 4. Total and Incremental Cost Outcomes (2020 US Dollars)

	Vaccine-related costs[a]	Total direct medical costs[b]	Total societal costs[c]	Total QALYs	Incremental cost per QALY gained[d]
18-44 years					
3-antigen	$20,137,507	$22,011,986	$47,859,106	2,529,680	3-antigen vaccine dominant
Single-antigen	$19,842,700	$23,481,788	$49,328,908	2,529,378	
45-64 years					
3-antigen	$20,817,666	$21,431,837	$48,151,963	1,844,400	3-antigen vaccine dominant
Single-antigen	$20,512,902	$21,615,920	$48,336,045	1,844,326	
≥ 65 years					
3-antigen	$20,566,003	$20,684,818	$47,081,927	1,034,102	$26,237
Single-antigen	$20,264,923	$20,447,921	$46,845,030	1,034,093	
High risk: diabetic adults					
3-antigen	$20,641,191	$21,471,271	$47,964,886	1,145,780	3-antigen vaccine dominant
Single-antigen	$20,339,010	$21,578,381	$48,071,995	1,145,724	
High risk: obese adults					
3-antigen	$20,536,303	$21,404,752	$47,763,739	1,388,248	3-antigen vaccine dominant
Single-antigen	$20,235,657	$21,849,686	$48,208,673	1,388,144	

Note: These results are based on a cohort of 100,000 vaccinated adults in each modeled cohort, discounted using a 3% annual discount rate. Dominant indicates that the intervention strategy had lower costs and higher QALYs than the baseline strategy.

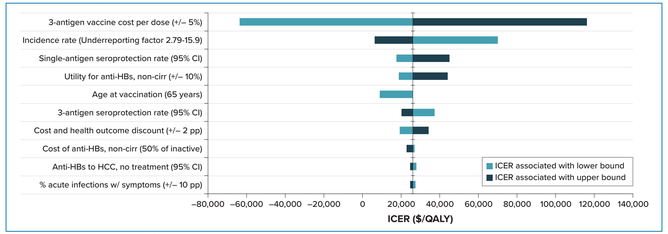
[a] Vaccine-related costs include vaccine administration and acquisition costs.

[b] Total direct medical costs include vaccine acquisition and administration costs and direct disease-related costs.

[c] Societal costs include indirect costs for time for vaccination and costs of travel to vaccination. Indirect costs are equal across vaccines because both are 3-dose regimens.

[d] Incremental cost per QALY gained are the same for both the healthcare sector and societal perspectives because there is no difference in indirect costs between the 2 vaccine strategies.

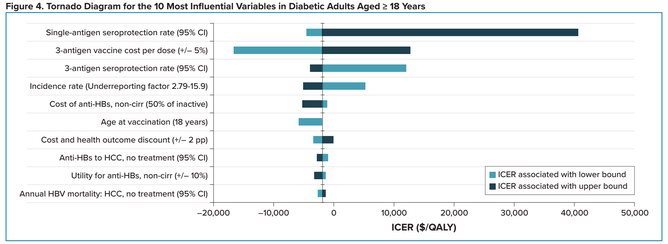
Figure 3. Tornado Diagram for the 10 Most Influential Variables in Adults Aged ≥ 65 Years



CI = confidence interval; cirr = cirrhosis; HCC = hepatocellular carcinoma; pp = percentage point.

Note: The y-axis is centered at the base-case ICER. Positive ICERs indicate that the 3 antigen vaccine resulted in more costs and QALYs than the single-antigen vaccine. Negative ICERs indicate that the 3-antigen vaccine was the dominant strategy (i.e., resulted in lower costs and higher QALYs than the single-antigen vaccine).

Figure 4. Tornado Diagram for the 10 Most Influential Variables in Diabetic Adults Aged ≥ 18 Years



Note: The y-axis is centered at the base-case ICER. Positive ICERs indicate that the 3 antigen vaccine resulted in more costs and QALYs than the single-antigen vaccine. Negative ICERs indicate that the 3-antigen vaccine was the dominant strategy (i.e., resulted in lower costs and higher QALYs than the single-antigen vaccine).

CONCLUSIONS

- The 3-antigen vaccine is estimated to lead to fewer HBV infections, long-term complications, and deaths compared with the single-antigen vaccine due to higher SPRs.
- Compared with the single-antigen vaccine, the 3-antigen vaccine is dominant (cost saving) from both societal and healthcare sector perspectives in adults aged 18-64 years and adults with diabetes and obesity and has a cost per QALY gained of $26,237 in adults aged ≥ 65 years.
- A 3-antigen vaccine is an additional cost-effective tool in implementation of recently expanded Centers for Disease Control and Prevention recommendations for adult hepatitis B vaccination.

REFERENCES

1. Hyams KC. Clin Infect Dis. 1995;20(4):992-1000.
2. Schillie S, et al. MMWR Recomm Rep. 2018;67(1):1.
3. Lu P-J, et al. MMWR Surveill Summ. 2021;70(3):1-26. (Suppl Box 3).
4. Weng MK, et al. MMWR Morb Mortal Wkly Rep 2022;71:477-83.
5. Analysource. https://www.analysource.com/. Accessed 2 February 2022.
6. Analysource. https://www.analysource.com/. Accessed 2 February 2022.
7. Rosenthal EM, et al. Vaccine. 2020;38(51):8206-15.
8. Centers for Disease Control and Prevention, Viral Hepatitis Surveillance, United States, 2018. Division of Viral Hepatitis; 2020.
9. Sanders GD, et al. JAMA. 2016;316(10):1093-103.
10. US Bureau of Economic Analysis. Table 2.4.4U. 2021. https://www.bea.gov/data/consumer-spending/main. Accessed 12 December 2021.
11. VBI Vaccines data on file. A phase 3 double-blind randomized controlled trial to compare the immunogenicity and safety of a three-dose regimen of Sci-B-Vac™ to a three-dose regimen of ENGERIX B® in adults (PROTECT) clinical study report. 26 August 2020.
12. Vesikari T, et al. Lancet Infect Dis. 2021 Sep;21(9):1271-81.
13. Nelson JC, et al. Am J Public Health. 2009 Oct;99 suppl 2:S389-97.

DISCLOSURES

Funding for this study was provided by VBI Vaccines. Authors maintained independent scientific control of the study design and analyses.

CONTACT INFORMATION

Seri Anderson, MPH, PhD
Senior Research Economist

RTI Health Solutions
3040 East Cornwallis Road
Post Office Box 12194
Research Triangle Park,
NC 27709-2194

Phone: +1.919.541.7427
Email: saanderson@rti.org