Vaccine 41 (2023) 3506–3517

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness of a 3-antigen versus single-antigen vaccine for the prevention of hepatitis B in adults in the United States

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ARTICLE INFO

Article history:
Received 23 December 2022
Received in revised form 31 March 2023
Accepted 5 April 2023
Available online 3 May 2023

Keywords:
Cost-effectiveness
Hepatitis B
HBV
Vaccine
3-antigen
Universal vaccination

ABSTRACT

Objectives: The first 3-antigen hepatitis B vaccine was approved by the United States (US) Food and Drug Administration in November 2021 and was recommended by the Centers for Disease Control and Prevention in 2022. We estimated the cost-effectiveness of this 3-antigen vaccine (PreHevbrio™) relative to the single-antigen vaccine, Engerix-B™, to prevent hepatitis B virus (HBV) infection among US adults.
Methods: A cost-effectiveness model was developed using a combined decision-tree and Markov structure to follow 100,000 adults over their remaining lifetimes after vaccination with either the 3-antigen or single-antigen vaccine. Outcomes from societal and healthcare sector perspectives were calculated for adults aged 18–44, 45–64, and ≥65 years; adults with diabetes; and adults with obesity. Seroprotection rates were obtained from the phase 3, head-to-head PROTECT trial (NCT03393754). Incidence, vaccine costs, vaccine adherence rates, direct and indirect costs, utilities, transition probabilities, and mortality were obtained from published sources. Health outcomes and costs (2020 USD) were discounted 3% annually and reported by vaccine and population. One-way sensitivity and scenario analyses were conducted.
Results: In the model, the 3-antigen vaccine led to fewer HBV infections, complications, and deaths compared with the single-antigen vaccine in all modeled populations due to higher rates and faster onset of seroprotection. Compared with the single-antigen vaccine, the 3-antigen vaccine had better health outcomes, more quality-adjusted life-years (QALYs), and lower costs in adults aged 18–64 years, adults with diabetes, and adults with obesity (dominant strategy). For adults aged ≥65 years, the 3-antigen vaccine was cost-effective compared with the single-antigen vaccine ($26,237/QALY gained) below common willingness-to-pay thresholds ($50,000-$100,000/QALY gained). In sensitivity analyses, results were sensitive to vaccine cost per dose, incidence, and age at vaccination.
Conclusion: The recently approved 3-antigen vaccine is a cost-saving or cost-effective intervention for preventing HBV infection and addressing the long-standing burden of hepatitis B among US adults.
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1. Introduction

In the United States (US), there are an estimated 20,000 acute hepatitis B virus (HBV) infections each year [1]. Rates of HBV infection in the US increased by 11% between 2014 and 2018 [2], and approximately half of incident acute infections in the US now occur among adults aged 30–49 years [3]. Similarly, there are between 850,000 and 2.2 million prevalent chronic HBV infections in the US [4], of which as many as 66% have been undiagnosed [5], increasing the risk of transmission and delaying treatment. As a result, thousands of deaths are attributable to hepatitis B each year [4]. Chronic hepatitis B is life threatening, with 15% of infected individuals dying from cirrhosis or hepatocellular carcinoma (HCC) [4]. Acute infection carries its own risks. Symptomatic acute infections progress into fulminant hepatitis in 4% of adult cases; and even once natural immunity (antibody to hepatitis B surface antigen [anti-HBs]) is achieved, an increase in the risk of HCC persists [6,7].

Abbreviation: ACIP, Advisory Committee on Immunization Practices; anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; 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; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; NA, not applicable; NNV, number needed to vaccinate; SPR, seroprotection rate.

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https://doi.org/10.1016/j.vaccine.2023.04.022
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The Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) has recommended routine hepatitis B vaccination for infants and vaccination of adults at high risk for hepatitis B infection since 1991 [4]. Despite these recommendations, only 30.0% of all adults aged ≥19 years, 40.3% of adults aged 19–49 years, and only 19.1% of adults aged ≥50 years reported receiving at least 3 doses of hepatitis B vaccine in 2018 [8]. Vaccination rates also remain low for high-risk populations, such as adults with diabetes, who are at a higher risk for infection [9], and adults with obesity, who have a higher risk for nonresponse to vaccination [10].

To better address the persistence of hepatitis B as a significant public health problem in the US, the ACIP has recently updated the routine hepatitis B vaccination recommendation for adults, adopting a universal vaccination recommendation for all adults aged 19–59 years. Additionally, the new guidance reiterated that adults aged > 60 years with risk factors for hepatitis B should receive hepatitis B vaccine, and adults aged > 60 years without risk factors may receive the vaccine [3]. This universal hepatitis B vaccination for adults aged 19–59 years has the potential to improve vaccination rates and better prevent the spread of HBV infections among adults [11,12].

Although there are several hepatitis B vaccines approved by the US Food and Drug Administration (FDA), PreHevbrio™ [Hepatitis B vaccine (recombinant)] is the first FDA-approved 3-antigen vaccine containing all 3 HBV surface antigens (S, pre-S1, and pre-S2) [13]. The pre-S1 and pre-S2 proteins play a significant part in the viral invasion of hepatocytes, as well as in viral infection, viral assembly, viral replication, and stimulation of immune responses in the body [14]. Additionally, pre-S1 and pre-S2 regions are significantly more immunogenic at T and B cell levels than S regions and have shown to be able to overcome non-responsiveness to the S antigen through expanded T cell epitopes and distinct regulation pathways [15]. Response to pre-S antigens is also seen with more rapid-onset and pronounced antibody response compared with the S antigen alone [16,17]. In the phase 3 PROTECT trial (NCT03393754), the 3-antigen vaccine elicited non-inferior seroprotection rates (SPRs) compared with the single-antigen hepatitis B vaccine (ENGERIX-B) in adults aged ≥18 years, and statistically significant higher SPRs in adults aged ≥45 years [18,19]. Based on these results, the 3-antigen vaccine is a differentiated new tool to help healthcare providers protect their adult patients against HBV infection, addressing the long-standing burden of hepatitis B among adults on the US public health system. The 3-antigen vaccine was included in the ACIP's 2022 updated hepatitis B vaccination recommendation for adults [3].

The objective of this study was to estimate the incremental cost-effectiveness of the 3-antigen vaccine compared with the single-antigen vaccine, based on head-to-head phase 3 trial data, for the prevention of hepatitis B in US adults aged 18–44, 45–64, and ≥65 years, as well as adults with diabetes (aged ≥18 years) and adults with obesity (aged ≥18 years).

2. Materials and methods

2.1. Model overview

The model uses a deterministic decision tree in year 1 to calculate the number of vaccinated and seroprotected individuals and the number of acute infections. A deterministic Markov model structure was used after year 1 to estimate long-term outcomes. Base-case analyses are conducted from the societal and healthcare sector perspectives for a lifetime time horizon. A lifetime time horizon was selected to fully capture the long-term outcomes of HBV infection that can take many years to manifest. All health and cost outcomes are discounted annually at a 3% rate [20]. The model was programmed in Excel (Microsoft Corporation).

2.2. Modeled population

The cost-effectiveness model calculates outcomes for a cohort of 100,000 US adults who, at time 0, are vaccinated with at least 1 dose of the 3-antigen or single-antigen hepatitis B vaccine and have no current or prior HBV infection. The modeled populations included US adults aged 18–44, 45–64, and ≥65 years, as well as adults (aged ≥18 years) with controlled type 2 diabetes mellitus (having hemoglobin A1c > 8.5%), and adults with obesity (aged ≥18 years) (with body mass index > 30).

For each of the 3 age groups in the model, the 2019 US age distribution and age-specific incidence, mortality, seroprotection rates, and vaccine adherence rates are used to calculate age-weighted results [21]. For adults with diabetes and obesity, age-specific inputs are applied to a cohort age weighted to reflect the prevalence of diabetes or obesity by age in the US general population [22,23]. These age-weighted results for all modeled groups are then scaled to a cohort of 100,000. Age at vaccination was assumed to be the median age of the cohort for the 3 age groups or based on the average age of adults with diabetes (61.9 years) and adults with obesity (48.5 years) in the US [6]. The sex distribution is assumed to match the PROTECT trial [24].

2.3. Model structure

The decision tree is presented in Fig. 1. For both intervention strategies, vaccination of the entire modeled population with the first dose of the 3-dose series occurs at time 0. The decision tree then calculates the number of individuals receiving the second and third doses of vaccine using real-world adherence data, as compliance can be a concern for vaccine series completion [25]. Among those receiving 1, 2, or 3 doses of the vaccine, the number of individuals who achieve seroprotection, develop an acute HBV infection, or remain susceptible is calculated each month after vaccination at time 0 (this year will hereafter be referred to as "year 1") based on PROTECT trial data for the percentage of patients achieving seroprotection at months 1, 2, 6, and 7 [18,24]. Seroprotected individuals (those achieving anti-HB titers ≥10 mIU/mL, or those achieving natural immunity following clearance of an acute HBV infection [4,26]) are assumed to have lifelong immunity [27,28]. Throughout year 1, individuals who are not seroprotected are vulnerable to infection. Based on individuals' progression through the decision-tree model in year 1, they begin the Markov model in the susceptible, seroprotected, or acute HBV infection (symptomatic or asymptomatic) states.

The Markov model follows a cohort of 100,000 individuals vaccinated with either the 3-antigen or the single-antigen vaccine for the cohort's remaining lifetime to track infections and disease progression over time (Fig. 2). As the cohort progresses to different health states, individuals incur costs and quality-of-life decrements. The cohort ages according to US population estimates until death or a maximum age of 100 years. The cycle length was 1 month for the first 12 months modeled (in the decision tree); subsequently, the cycle length was 1 year (in the Markov model).

The model includes both asymptomatic and symptomatic infections; the percent of acute infections with symptoms is 30% (range, ± 10 percentage points) [6]. Once an individual develops a symptomatic acute HBV infection, they are at risk of developing fulminant hepatitis. All acute HBV infections are at risk of progressing to chronic HBV infection. Chronic HBV infection has features that affect the likelihood of progression to more severe hepatic health

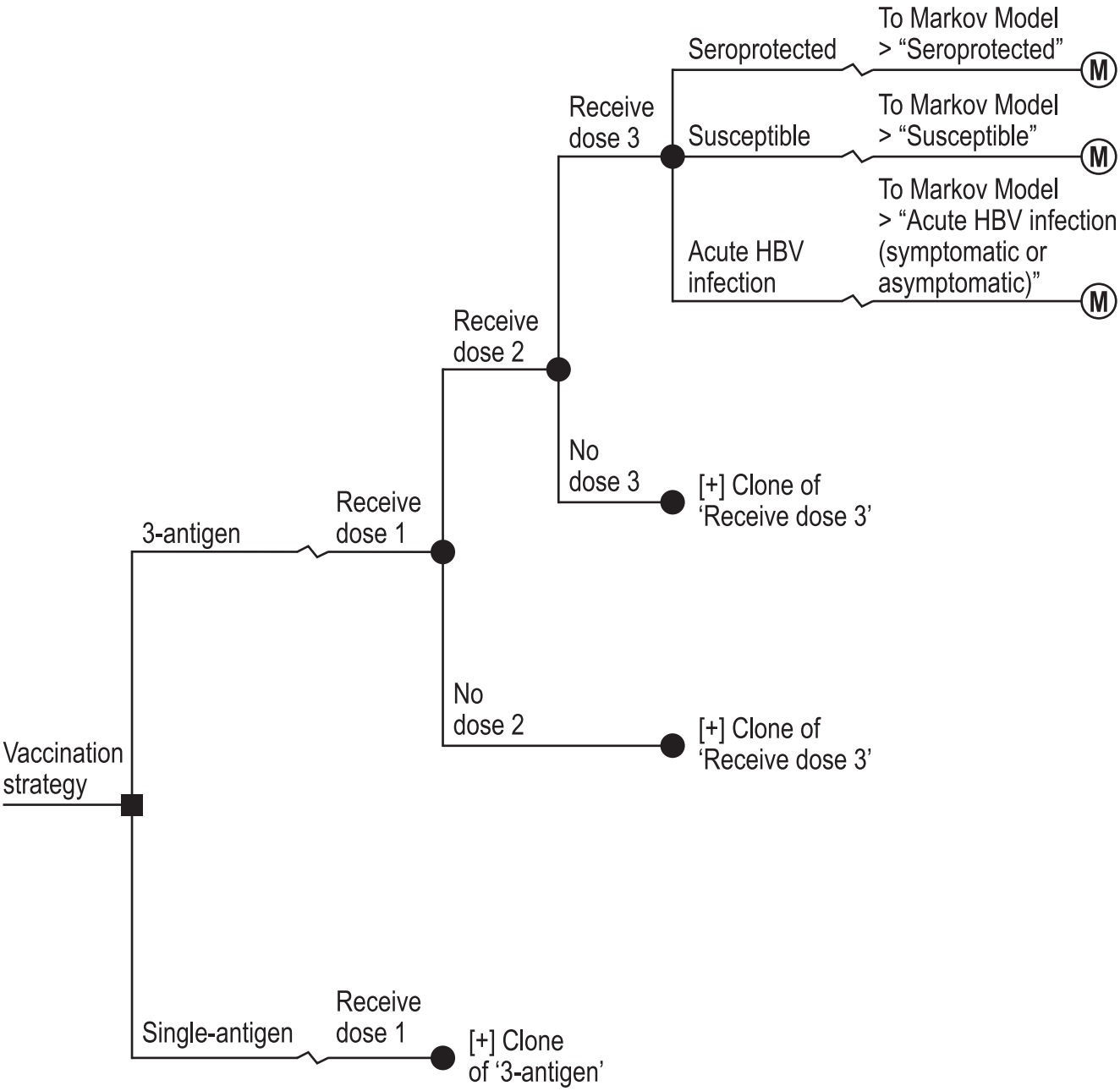

Fig. 1. Decision-Tree Model Structure. HBV = hepatitis B virus.Note: The square represents the initial decision node: vaccination with a 3-antigen vaccine or with a single-antigen vaccine. Circles represent chance nodes where the transition is governed by an input probability. The letter *M* enclosed in a circle represents the transition to the state named in the subsequent Markov model structure (see Fig. 2).

states, including the following: active versus inactive, hepatitis B e antigen negative (HBeAg−) versus hepatitis B e antigen positive (HBeAg+), and cirrhotic versus noncirrhotic.

A proportion of patients begin treatment with antivirals each year, which reduces the likelihood of progressing to more severe health states and the risk of death [6]. We assume treatment only begins in active chronic HBV infection states and continues while individuals are in any chronic HBV infection state, active or inactive [7]. An annual probability of discontinuation of treatment is assumed [6].

Death due to non–HBV-related causes may occur in any disease state; death due to HBV-related causes can occur in any disease state, except acute HBV infection, after accounting for the risk of non–HBV-related death.

2.4. Model inputs

2.4.1. HBV incidence

Annual incidence of HBV infection in an unvaccinated, uninfected population is calculated using the method described in Rosenthal et al. [6] (Supplementary Table S1). That method uses the CDC-reported incidence of acute HBV infection by age and adjusts for underreporting [29], as well as for the prevalence of immunity to HBV infection through previous exposure [30] and/or vaccination. For adults with diabetes, annual incidence and prevalence are adjusted using multipliers to account for their higher risk of HBV infection [9] and higher prevalence [31]. In this model, susceptible individuals are at risk of contracting hepatitis B every year until death.

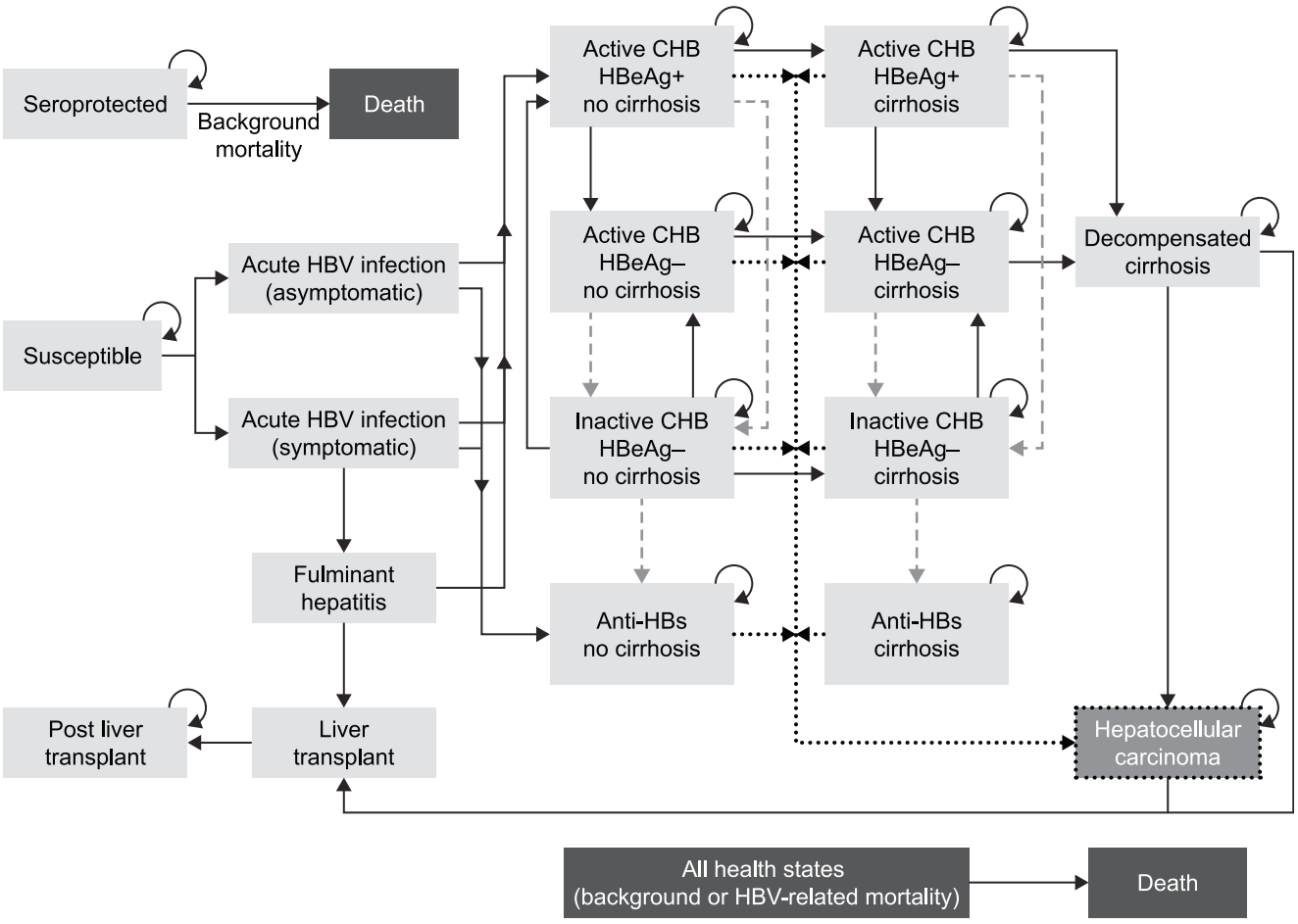

Fig. 2. Markov Model Structure. anti-HBs = antibody to hepatitis B surface antigen; CHB = chronic hepatitis B virus infection; HBeAg– = hepatitis B e antigen negative; HBeAg + = hepatitis B e antigen positive; HBV = hepatitis B virus. Notes: Light gray, dashed arrows show transition probabilities altered by treatment of chronic HBV infection. Black dashed 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. For the acute HBV infection, fulminant hepatitis, and liver transplant health states, adults transition to another health state or death within 1 year.

2.4.2. Vaccine efficacy

Among those receiving 1, 2, or 3 doses of either vaccine, the percentage of individuals who achieved seroprotection (defined as anti-HB titers ≥10 mIU/mL) and the 95% confidence intervals are taken from PROTECT trial data at days 28, 56, 168, and 196 (Table 1) [18,24]. Using SPRs after dose 2 at both day 56 and day 168 allows the model to capture the incremental difference between the 3-antigen and single-antigen vaccines in terms of real-world effectiveness for individuals who fail to complete the 3-dose series of either vaccine.

2.4.3. Vaccine adherence

To account for real-world adherence, the percentage vaccinated is based on US hepatitis B vaccine adherence data [25]. Nelson et al. [25] analyzed data from Vaccine Safety Datalink, 1996–2004, to estimate the percentage of people who receive the second and third doses of a hepatitis B vaccine after receiving the first dose (Table 2). The percentage vaccinated with 3 doses (series completion) is calculated according to the following formula:

$$\%\ vaccinated\ with\ 3\ doses\ among\ those\ vaccinated\ with\ the\ first\ dose = dose\ 2\ vaccine\ adherence \times dose\ 3\ vaccine\ adherence$$

2.4.4. Transition probabilities

Annual transition probabilities for the Markov model are taken from the published literature (Supplementary Table S2) [6,7]. The model captures treatment of HBV infections by including annual transition probabilities with and without treatment. The percentage of individuals with chronic infections who start treatment annually is 0.6% (range, 0.2%-1.8%), derived using the same method as in Rosenthal et al. [6]. The percentage of those on treatment who discontinue annually is 3.2% (range, 1.8%-5.2%) [6].

The model accounts for the competing risk of HBV-related death and general mortality. General mortality can occur in any state; the annual probability of mortality is based on the 2018 general US adult population mortality by single-year age group [32]. For the 2 high-risk groups modeled, excess mortality rates are used to capture increased risk of death for adults with diabetes and adults with obesity [6,34,34].

2.4.5. Costs and quality of life

One-time costs for acute infections as well as annual disease management costs for chronic infections and advanced disease states are taken from the published literature (Table 3) [6]. A one-time cost for initial tests and evaluation is incurred for all new chronic infections. The initial tests reflect standard of care in

Table 1
Vaccine Seroprotection Rates.

Vaccine/modeled population	3-antigen vaccine			Single-antigen vaccine		
	Base-case value	Range[a]			Range[a]	
		Lower bound	Upper bound	Base-case value	Lower bound	Upper bound
Adults aged 18–44 years						
Day 28 (4 weeks after dose 1)[b]	28.8%	21.1%	37.6%	9.6%	5.2%	15.8%
Day 56 (4 weeks after dose 2)[b]	76.0%	67.5%	83.2%	37.0%	28.9%	45.8%
Day 168 (20 weeks after dose 2)[b]	87.2%	80.1%	92.5%	39.0%	30.7%	47.7%
Day 196 (4 weeks after dose 3)[b]	99.2%	95.6%	100.0%	91.1%	85.0%	95.3%
Adults aged 45–64 years						
Day 28 (4 weeks after dose 1)[b]	17.2%	13.3%	21.8%	7.7%	5.0%	11.2%
Day 56 (4 weeks after dose 2)[b]	54.6%	49.0%	60.1%	27.4%	22.6%	32.6%
Day 168 (20 weeks after dose 2)[b]	72.0%	66.8%	76.8%	30.2%	25.2%	35.5%
Day 196 (4 weeks after dose 3)[b]	94.8%	91.8%	96.9%	80.1%	75.3%	84.3%
Adults aged ≥65 years						
Day 28 (4 weeks after dose 1)[b]	8.6%	5.5%	12.7%	6.7%	4.0%	10.5%
Day 56 (4 weeks after dose 2)[b]	36.2%	30.4%	42.3%	13.1%	9.3%	17.7%
Day 168 (20 weeks after dose 2)[b]	48.7%	42.6%	54.9%	18.3%	13.8%	23.4%
Day 196 (4 weeks after dose 3)[b]	83.6%	78.6%	87.8%	64.7%	58.6%	70.4%
Adults with diabetes (aged ≥18 years)[c]						
Day 28 (4 weeks after dose 1)	11.3%	4.3%	23.0%	11.5%	4.7%	22.2%
Day 56 (4 weeks after dose 2)	27.8%	16.5%	41.6%	18.0%	9.4%	30.0%
Day 168 (20 weeks after dose 2)	44.4%	30.9%	58.6%	23.0%	13.2%	35.5%
Day 196 (4 weeks after dose 3)[b]	83.3%	70.7%	92.1%	58.3%	44.9%	70.9%
Adults with obesity (aged ≥18 years)[c]						
Day 28 (4 weeks after dose 1)	19.0%	14.5%	24.2%	10.1%	6.7%	14.5%
Day 56 (4 weeks after dose 2)	49.3%	43.1%	55.4%	20.5%	15.8%	26.0%
Day 168 (20 weeks after dose 2)	60.2%	54.1%	66.1%	22.5%	17.5%	28.1%
Day 196 (4 weeks after dose 3)[b]	89.2%	84.9%	92.7%	68.1%	62.0%	73.8%

anti-HBs = antibody to hepatitis B surface antigen.
Sources: Vesikari et al. [18],VBI Vaccines Inc. Data on File [46].
[a] The 95% confidence intervals are from the PROTECT trial clinical study report [24].
[b] Seroprotection data are taken from the per-protocol analysis of the PROTECT trial and were defined as the percentage achieving anti-HBs titers ≥10 mIU/mL [18].
[c] High-risk groups use a single seroprotection rate regardless of age due to the small sample size in PROTECT.

Table 2
Vaccine adherence.

Age group, years	Vaccine adherence (range)			Series completion (range), calculated % vaccinated with all 3 doses
	Dose 1	Dose 2 conditional on receiving previous dose[a]	Dose 3 conditional on receiving previous dose[a]	
18–29	100%	74.3% (63.2%-84.0%)	71.5% (60.3%-81.1%)	53.1% (38.1%-68.1%)
30–39	100%	81.9% (72.0%-90.7%)	80.0% (70.1%-88.8%)	65.5% (50.4%-80.5%)
40–49	100%	81.9% (72.0%-90.7%)	80.0% (70.1%-88.8%)	65.5% (50.4%-80.5%)
50–64	100%	84.9% (75.5%-93.4%)	83.9% (74.5%-92.3%)	71.2% (56.2%-86.2%)
≥ 65	100%	81.7% (72.2%-90.2%)	84.7% (75.2%-93.2%)	69.2% (54.3%-84.2%)

[a] To calculate the range tested in the one-way sensitivity analysis, we used Goal Seek in Excel to develop a single parameter, which was added to the dose 2 and dose 3 vaccine adherence values by age group and produced the required series completion. For example, for patients aged 18–29 years for the lower bound, we subtracted 11.1% from the dose 2 adherence (74.3% − 11.1% = 63.2%) and the dose 3 adherence (71.5% − 11.1% = 60.3%) to change the series completion for ages 18–29 years from 53.1% − 15% = 38.1%. Source: Nelson et al. [25].

the US and include tests for HBeAg, antibody to hepatitis B e antigen (anti-HBe), anti-HBs, antibody to hepatitis B core antigen, hepatitis C virus, hepatitis D virus, and human immunodeficiency virus; HBV-DNA quantification; liver enzyme tests; complete blood count; a renal function panel; and an ultrasound [7]. Treatment for chronic infections is associated with an additional annual cost for antiviral drug treatment (cost for tenofovir assumed [6,7]), monitoring treatment, and treatment-related adverse events. Monitoring includes the following performed annually: tests for HBeAg, anti-HBe, anti-HBs, and HBsAg (for seroconverted patients); HBV-DNA quantification; liver function tests; complete blood count; renal function panel; bone density scan/dual-energy X-ray absorptiometry alpha-fetoprotein serum; and an ultrasound [7].

Vaccine acquisition and administration costs for each vaccine are based on 2022 wholesale acquisition costs [35,36] (Table 3). The difference in price per dose between the two vaccines is varied in one-way sensitivity analysis, from a difference (3-antigen – single-antigen) of +$1.20 in the base case to a minimum of -$2.04 and a maximum of $4.44. Indirect costs related to time for vaccination and travel costs are included in the model as a per-dose cost associated with each dose received based on time loss estimates and US wage data [6] (Table 3). Productivity loss for individuals with acute or chronic HBV infections or long-term complications are excluded from the model, in keeping with other recent models of vaccination against HBV infection that take a societal perspective [6,6,37]. Thus, the results reflect a modified reference case because certain costs from the societal perspective were not included (e.g., patient time costs, unpaid caregiver costs) due to paucity of reliable data estimates [20]. Costs and disutilities for vaccine-related adverse events were assumed equivalent between the 2 vaccines and excluded from the model.

Table 3
Direct and indirect costs.

Category/input	Base-case value	Range		Source
		Lower bound	Upper bound	
Vaccine costs				
3-antigen vaccine cost, per dose	$64.75	NA	NA	[36]
Single-antigen vaccine cost, per dose	$63.55	NA	NA	[35]
Incremental vaccine cost, per dose (3-antigen minus single antigen)	$1.20	-$2.04	$4.44	Calculated
Vaccine administration, per dose	$17.22	$12.91	$21.52	[6]; costs were inflated from 2019 to 2020 US dollars [47]
Indirect costs				
Time costs to receive one dose of vaccine	$84.71	$63.53	$105.89	[6]; costs were inflated from 2019
Travel costs to receive one dose of vaccine	$20.50	$10.25	$30.75	to 2020 US dollars [47]
Annual disease management cost				
Seroprotected	$0.00	NA	NA	[6]; costs were inflated from 2019
Susceptible	$0.00	NA	NA	to 2020 US dollars [47]
Asymptomatic acute HBV infection[a]	$0.00	$0.00	$688.08	
Symptomatic acute HBV infection[a]	$394.93	$204.66	$688.08	
Active chronic HBV infection (no cirrhosis)[a]	$1,430.37	$715.74	$4,292.22	
Inactive chronic HBV infection (no cirrhosis)[b]	$715.74	$357.31	$2,146.11	
Anti-HBs (natural immunity, no cirrhosis)[b]	$357.31	$179.21	$1,073.06	
Active chronic HBV infection (with cirrhosis)[a]	$3,002.35	$1,501.17	$9,005.92	
Inactive chronic HBV infection (with cirrhosis)[b]	$1,501.17	$750.03	$4,502.41	
Anti-HBs (natural immunity, with cirrhosis)[b]	$750.03	$375.01	$2,251.20	
Fulminant hepatitis[a]	$19,206.58	$19,147.96	$51,428.11	
Decompensated cirrhosis[a]	$35,548.00	$33,363.17	$37,735.04	
Liver transplant[a]	$225,108.20	$207,587.52	$242,624.44	
Post liver transplant[a]	$49,026.46	$40,060.36	$57,992.56	
Hepatocellular carcinoma[a]	$56,703.78	$48,122.05	$62,510.45	
Diagnosis, treatment, monitoring, and adverse event costs				
Cost for initial tests and evaluations for new chronic infections[c]	$364.97	$182.53	$547.50	
Annual cost of treatment[d]	$9,814.79	$6,137.32	$12,274.63	
Annual cost of monitoring treatment tests[e]	$708.12	$354.16	$1,061.83	
Annual cost of treatment-related adverse events[f]	$750.25	$375.13	$1,125.38	

anti-HBs = antibody to hepatitis B surface antigen; anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NA = not applicable; US = United States.

[a] Range is 95% of confidence interval from source [6].

[b] Source assumes that costs for inactive disease would be one-half of active disease-state costs and that costs for anti-HBs states would be one-quarter of active disease-state costs [6]. The range is calculated using the same relation with active disease-state costs as the base case [6].

[c] Source calculates assuming a one-time cost upon initial infection that includes tests for HBeAg, anti-HBe, anti-HBs, anti-HBc, hepatitis C virus, hepatitis D virus, and human immunodeficiency virus; HBV-DNA quantification; liver enzyme tests; complete blood count; a renal function panel; and an ultrasound [7]. Range is 95% confidence interval from the source [7].

[d] Annual cost of antiviral treatment with tenofovir [6,7]. Base case is 80% and range is 50%-100% of wholesale acquisition cost [6].

[e] Source calculates assuming these include tests for HBeAg, anti-HBe, anti-HBs, and HBsAg (for seroconverted patients); HBV-DNA quantification; liver function tests; complete blood count; a renal function panel; bone density scan/dual-energy X-ray absorptiometry alpha-fetoprotein serum; and an ultrasound [7]. Range is ±50% of base case [7].

[f] Source calculates value by weighting the frequency of common and serious adverse events from key clinical trials [7]. Range is ±50% of base case [7].

To capture quality of life and calculate quality-adjusted life-years (QALYs), utility values associated with disease states and disutility values associated with treatment of HBV infections are taken from the published literature (Supplementary Table S3) [6].

3. Analyses

3.1. Base-case analyses

The model estimated health and economic outcomes for each of the modeled populations by vaccine. Health outcomes included the number and percentage of seroprotected individuals 1 year after vaccination and lifetime case counts for acute HBV infections, fulminant hepatitis, chronic HBV infections, HCC, liver transplants, and HBV-related deaths, as well as QALYs. Economic outcomes included total direct medical costs (consisting of vaccination acquisition costs, vaccination administration costs, and disease-related costs), and total societal costs (consisting of the total direct medical costs and indirect costs for time for vaccination and costs of travel to vaccination).

Relative differences for the 3-antigen vaccine compared with the single-antigen vaccine for the number of seroprotected individuals, case counts, and costs were calculated using the number or dollar amount and the following formula:

$$\frac{Outcome\ \ for\ \ 3\ antigen\ \ vaccine - Outcome\ \ for\ \ single\ \ \ antigen\ \ vaccine}{Outcome\ \ for\ \ single\ antigen\ \ \ vaccine}$$

Incremental outcomes were calculated as outcome for the 3-antigen vaccine minus outcome for the single-antigen vaccine. We calculated the incremental costs for each cost category, incremental QALYs, and the incremental cost per QALY gained. All outcomes are presented as discounted over the cohort's remaining lifetime.

The undiscounted number needed to vaccinate (NNV) to avoid 1 HBV-related death was calculated according to the ACIP guidelines for health economics studies [38] using the following formula:

$$\frac{Number\ \ fully\ \ \ vaccinated}{\#\ \ deaths\ \ with\ \ no\ \ \ vaccination - \#\ \ deaths\ \ with\ \ \ vaccination}$$

The NNV for each vaccine compared with no vaccination is interpreted as the number of people that would need to be vaccinated to avoid 1 HBV-related death.

Table 4
Total and Incremental Health Outcomes per 100,000 Vaccinated.

Modeled population	Seroprotection and infection[a]		Long-term complications and death, n[a]				
	Seroprotected individuals, n (%)[b]	Acute HBV infections, n	Fulminant hepatitis	Chronic HBV infections	Hepatocellular carcinoma	Liver transplants	HBV-related deaths
18–44 years							
3-antigen	85,066 (85.1%)	67.0	0.8	5.4	7.9	0.5	8.5
Single-antigen	70,594 (70.6%)	130.3	1.5	10.4	15.4	0.9	16.6
Relative difference (%)	*20.5%*	*−48.6%*	*−48.6%*	*−48.6%*	*−48.5%*	*−48.5%*	*−48.5%*
45–64 years							
3-antigen	82,720 (82.7%)	31.5	0.4	2.5	2.6	0.2	2.8
Single-antigen	67,176 (67.2%)	57.0	0.7	4.5	4.7	0.3	5.0
Relative difference (%)	*23.1%*	*−44.8%*	*−44.8%*	*−44.8%*	*−44.3%*	*−44.5%*	*−44.3%*
≥ 65 years							
3-antigen	72,086 (72.1%)	13.6	0.1	1.0	0.5	0.0	0.5
Single-antigen	54,769 (54.8%)	21.2	0.2	1.6	0.8	0.1	0.8
Relative difference (%)	*31.6%*	*−35.9%*	*−35.8%*	*−35.8%*	*−35.0%*	*−35.5%*	*−35.0%*
High risk: Adults with diabetes							
3-antigen	72,288 (72.3%)	52.5	0.6	4.1	3.5	0.3	3.7
Single-antigen	55,762 (55.8%)	79.3	0.9	6.2	5.3	0.4	5.5
Relative difference (%)	*29.6%*	*–33.8%*	*–33.7%*	*–33.7%*	*–33.0%*	*–33.3%*	*–33.0%*
High risk: Adults with obesity							
3-antigen	78,810 (78.8%)	44.4	0.5	3.5	3.7	0.3	3.9
Single-antigen	59,051 (59.1%)	83.2	0.9	6.6	6.9	0.5	7.3
Relative difference (%)	*33.5%*	*−46.6%*	*−46.5%*	*−46.5%*	*−46.2%*	*−46.3%*	*−46.2%*

HBV = hepatitis B virus; SPR = seroprotection rate. 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] Percentages of seroprotected individuals are based on both the vaccine SPRs reported in Table 1 and the vaccine adherence rates reported in Table 2 to estimate real-world outcomes per 100,000 vaccinated adults.

3.2. One-Way sensitivity and scenario analysis

Deterministic one-way sensitivity analysis was conducted for each of the 5 modeled populations to test the sensitivity of the incremental cost-effectiveness ratio (ICER) when each of the inputs or groups of related inputs were varied one at a time. Groups of related inputs that were varied together included discount rates for cost and health outcomes, vaccine adherence for doses 2 and 3 (varying series completion rates by ±15 percentage points), risk reduction in HBV-related mortality due to treatment, and utilities for seroprotected/susceptible individuals and those with asymptomatic acute HBV infection. Results are presented in tornado diagrams showing the variation in the incremental cost per QALY gained from the base-case value for the 3-antigen versus the single-antigen vaccine. Results are shown for the 5 most influential input parameters.

Scenario analyses were conducted to evaluate key policy questions regarding the impact of series completion for 3-dose vaccines for each modeled population and the impact of the age at vaccination on the cost-effectiveness results for adults with diabetes. In the first scenario, adherence rates for doses 2 and 3 varied by ±20%, resulting in series completion rates ranging from 34% to 100% depending on the age group. In the second scenario, the age at vaccination varied from 20 to 70 years.

4. Results

4.1. Base-case results

For all modeled populations, more individuals were seroprotected with the 3-antigen vaccine than with the single-antigen vaccine because of the higher SPRs for the 3-antigen vaccine (Table 4). In addition, individuals receiving the 3-antigen vaccine had higher SPRs after the first and second doses than individuals receiving the single-antigen vaccine, leading to better protection in those individuals not completing the full course. As a result, vaccination with the 3-antigen vaccine reduced the number of acute and chronic HBV infections and long-term complications compared with the single-antigen vaccine in all modeled populations. Specifically, vaccination with the 3-antigen vaccine reduced acute and chronic HBV infections by a range of 33.7% (for adults with diabetes) to 48.6% (for adults aged 18–44 years) compared with the single-antigen vaccine. The number of acute infections avoided with the 3-antigen vaccine compared with single-antigen vaccine was greatest in adults aged 18–44 years, with 63.3 acute and 5.1 chronic infections avoided per 100,000 people vaccinated. Similarly, the number of long-term complications avoided due to vaccination with the 3-antigen vaccine compared with the single-antigen vaccine was greatest in adults aged 18–44 years, with approximately 8.0 HBV-related deaths, 7.5 cases of HCC, 0.7 cases of fulminant hepatitis, and 0.5 liver transplants avoided per 100,000 people vaccinated (Table 4).

For all modeled populations, disease-related costs (including testing and evaluation costs for new chronic infections and hepatitis B treatment costs) were lower for the 3-antigen vaccine than for the single-antigen vaccine due to fewer acute and chronic infections and fewer long-term complications (Table 5). Vaccine acquisition costs for the 3-antigen vaccine were higher than for the single-antigen vaccine based on a higher per dose cost for the 3-antigen vaccine ($64.75 vs. $63.55). Vaccine administration costs as well as travel expenses and productivity loss costs associated with time for vaccination were equal for the 2 vaccine strategies because both vaccines are indicated as a 3-dose regimen. For all populations except adults aged ≥65 years, the reductions in disease-related costs offset the increased vaccine acquisition costs, resulting in lower total costs with the 3-antigen vaccine compared with the single-antigen vaccine from both the societal and healthcare sector perspectives (Table 5). Costs related to HBV were reduced by a range of 33.0% (adults

Table 5
Total and Incremental Cost Outcomes per 100,000 Vaccinated (2020 US Dollars).

Modeled population	Vaccine costs	Disease-related costs	Total direct medical costs	Total societal costs[a]	Total QALYs	Incremental cost per QALY gained[b]
18–44 years						
3-antigen	$20,137,507	$1,874,479	$22,011,986	$47,859,106	2,529,680	3-antigen vaccine dominant strategy
Single-antigen	$19,842,700	$3,639,088	$23,481,788	$49,328,908	2,529,378	
Difference	$294,807	−$1,764,609	−$1,469,802	−$1,469,802	302	
Relative difference (%)	*1.5%*	*−48.5%*	*−6.3%*	*−3.0%*	*0.01%*	
45–64 years						
3-antigen	$20,817,666	$614,171	$21,431,837	$48,151,963	1,844,400	3-antigen vaccine dominant strategy
Single-antigen	$20,512,902	$1,103,018	$21,615,920	$48,336,045	1,844,326	
Difference	$304,764	−$488,846	−$184,082	−$184,082	74	
Relative difference (%)	*1.5%*	*−44.3%*	*−0.9%*	*−0.4%*	*0.004%*	
≥65 years						
3-antigen	$20,566,003	$118,815	$20,684,818	$47,081,927	1,034,102	$26,237
Single-antigen	$20,264,923	$182,998	$20,447,921	$46,845,030	1,034,093	
Difference	$301,080	−$64,183	$236,897	$236,897	9	
Relative difference (%)	1.5%	−35.1%	1.2%	0.5%	0.001%	
High risk: adults with diabetes						
3-antigen	$20,641,191	$830,080	$21,471,271	$47,964,886	1,145,780	3-antigen vaccine dominant strategy
Single-antigen	$20,339,010	$1,239,371	$21,578,381	$48,071,995	1,145,724	
Difference	*$302,181*	*−$409,290*	*−$107,110*	*−$107,110*	*56*	
Relative difference (%)	*1.5%*	*−33.0%*	*−0.5%*	*−0.2%*	*0.005%*	
High risk: adults with obesity						
3-antigen	$20,536,303	$868,450	$21,404,752	$47,763,739	1,388,248	3-antigen vaccine dominant strategy
Single-antigen	$20,235,657	$1,614,029	$21,849,686	$48,208,673	1,388,144	
Difference	$300,645	−$745,580	−$444,934	−$444,934	104	
Relative difference (%)	*1.5%*	*−46.2%*	*−2.0%*	*−0.9%*	*0.01%*	

QALY = quality-adjusted life-year. 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 strategy indicates that the intervention strategy had lower costs and higher QALYs than the baseline strategy.

[a] Societal costs include total direct medical costs plus indirect costs for time for vaccination and costs of travel to vaccination. Indirect costs are equal across vaccines because both vaccines are 3-dose regimens, making the difference in total direct medical costs and total societal costs the same.

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

with diabetes) to 48.5% (adults aged 18–44 years) with the 3-antigen vaccine compared with the single-antigen vaccine. For a cohort of 100,000 vaccinated individuals, cost savings ranged from $107,000 (adults with diabetes) to $1.5 million (adults aged 18–44 years), representing a cost savings from the societal perspective ranging from −0.2% to −3.0%, respectively. For adults aged ≥65 years, total costs from the societal perspective were approximately 0.5% higher for the 3-antigen vaccine compared with the single-antigen vaccine.

The model estimated that the 3-antigen vaccine resulted in lower costs and more QALYs (i.e., a dominant strategy) compared with the single-antigen vaccine in adults aged 18–64 years, adults with diabetes, and adults with obesity. For adults aged ≥65 years, the 3-antigen vaccine resulted in higher costs and more QALYs compared with the single-antigen vaccine, leading to an ICER of $26,237, which is below common willingness-to-pay thresholds of $50,000-$100,000 per QALY gained [39].

The number of people that would need to be vaccinated with either the 3-antigen vaccine or single-antigen vaccine to avoid 1 HBV-related death was lower for the 3-antigen vaccine compared with the single-antigen vaccine for all populations modeled. The NNV to avoid 1 HBV-related death was lowest for adults aged 18–44 years (565 and 686 for 3-antigen vaccine and single-antigen vaccine, respectively) and highest for adults aged ≥65 years (43,177 and 57,505 for 3-antigen vaccine and single-antigen vaccine, respectively) (Table 6).

4.2. One-way sensitivity analysis results

One-way sensitivity analyses are presented in Fig. 3 for the 5 most influential variables in each modeled population. For adults aged 18–44 years, the ICER was not sensitive to changes in input parameters, as the 3-antigen vaccine remained the dominant strategy compared with the single-antigen vaccine for all parameter changes. For the other populations, ICERs ranged from < $0 (3-antigen dominant strategy) to upper-bound ICERs of: $3,532 per QALY gained (adults with obesity); $8,631 per QALY gained (adults aged 45–64 years); $40,602 per QALY gained (adults with diabetes); and $116,201 per QALY gained (adults aged ≥65 years).

Table 6
Number Needed to Vaccinate to Avoid 1 HBV-Related Death.

Vaccine	Age group			High-risk population	
	18–44 years	45–64 years	≥65 years	Adults with diabetes (≥18 years)	Adults with obesity (≥18 years)
3-antigen	565	3,452	43,177	5,262	2,759
Single-antigen	686	4,306	57,505	6,824	3,713
Incremental NNV	−121	−854	−14,329	−1,563	−954

HBV = hepatitis B virus; NNV = number needed to vaccinate. Note: All outcomes are undiscounted.

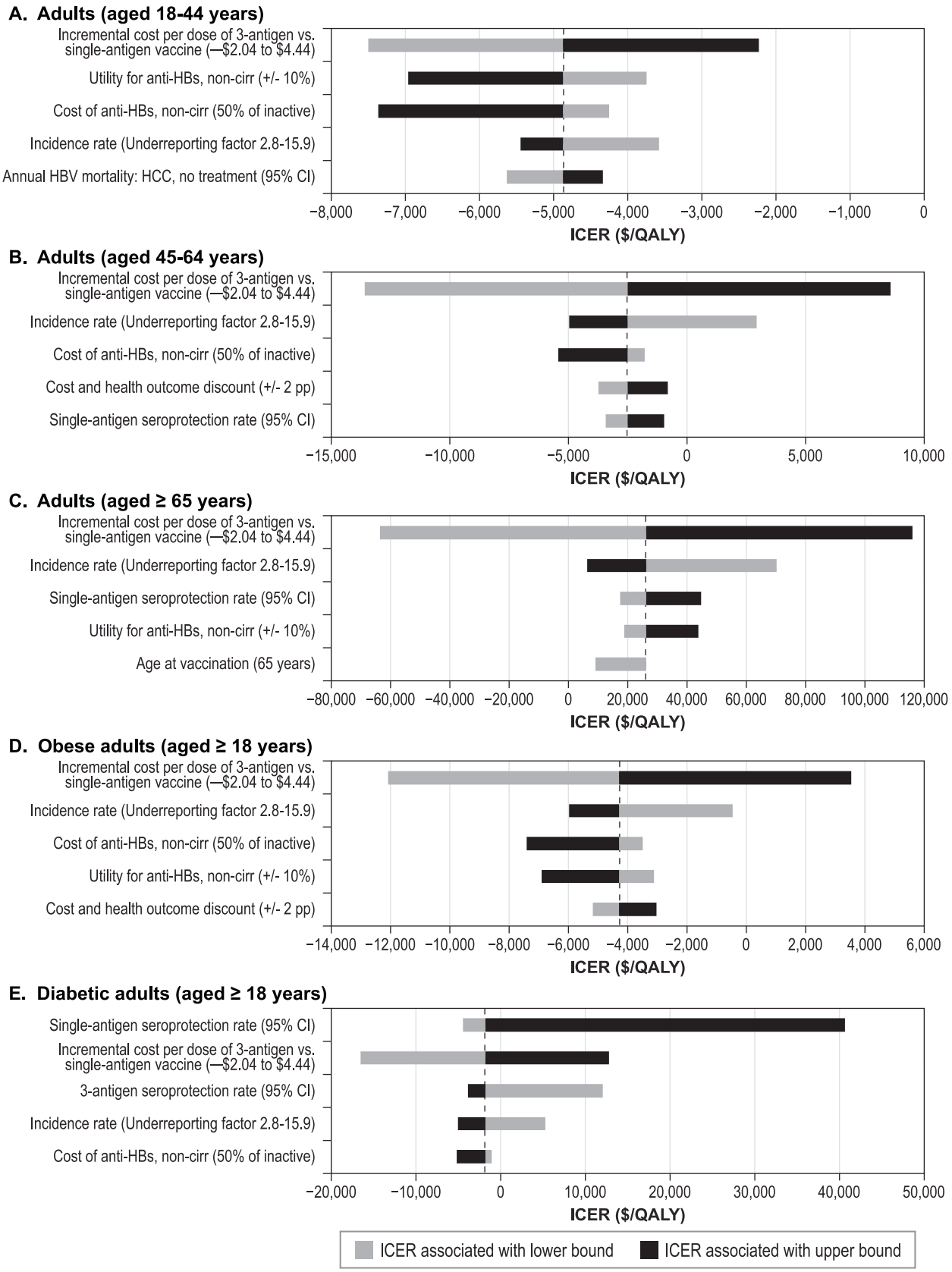

Fig. 3. One-Way Sensitivity Analysis Results: Impact on ICER of the 5 Most Influential Variables by Modeled Population.Notes: The x-axis is centered at the base-case ICER. Negative ICERs indicate that the 3-antigen vaccine was the dominant strategy (i.e., resulted in fewer costs and more QALYs than the single-antigen vaccine). Positive ICERs indicate that the 3–antigen vaccine resulted in higher costs and QALYs than the single-antigen vaccine. anti-HBs = antibody to hepatitis B surface antigen; CI = confidence interval; cirr = cirrhosis; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; ICER = incremental cost-effectiveness ratio; pp = percentage point; QALY = quality-adjusted life-year.

Table 7
Incremental Costs, Incremental QALYs, and ICERs for Adults With Diabetes by Age at Vaccination.

Age at vaccination	Incremental total costs	Incremental QALYs	ICER ($/QALY)
Base case (61.9 years)	−$107,110	56	3-antigen dominant strategy
20 years	−$3,036,673	517	3-antigen dominant strategy
30 years	−$2,991,144	498	3-antigen dominant strategy
40 years	−$2,131,271	356	3-antigen dominant strategy
50 years	−$845,021	161	3-antigen dominant strategy
60 years	−$173,602	65	3-antigen dominant strategy
70 years	$162,747	19	$8,708

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year. 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 strategy indicates that the intervention strategy had lower costs and higher QALYs than the baseline strategy.

4.3. Scenario results

When vaccination adherence rates were varied ± 20% for both the second and third dose, the 3-antigen vaccine was the dominant strategy compared with the single-antigen vaccine in all scenarios and all modeled populations except for adults aged ≥65 years, wherein ICERs increased as series completion increased (range: $24,500- $28,754 per QALY gained for lower and higher series completion rates, respectively).

Table 7 reports the results for varying ages at vaccination for adults with diabetes. Incremental costs saved and incremental QALYs gained increased as individuals were vaccinated at younger ages, meaning the younger the age at vaccination, the more benefit an individual with diabetes would receive from being vaccinated with the 3-antigen vaccine relative to the single-antigen vaccine. Vaccination of adults with diabetes with the 3-antigen vaccine was the dominant strategy compared with the single-antigen vaccine up to age 70; for vaccination at age 70 years, the ICER was $8,708 per QALY gained. Varying age at vaccination was also tested for the other modeled cohorts; in general, earlier age at vaccination was associated with increased cost-savings for the 3-antigen vaccine compared with the single-antigen vaccine (results not shown).

5. Discussion

From both the societal and healthcare sector perspectives, based on the modelled results, the 3-antigen vaccine is a cost-saving intervention and would be expected to reduce costs and improve health outcomes compared with the single-antigen vaccine for the prevention of hepatitis B in US adults aged 18–64 years, adults with diabetes, and adults with obesity. The 3-antigen vaccine is a cost-effective intervention in US adults aged 65 and older, with an incremental cost per QALY gained of $26,237. The 3-antigen vaccine is estimated to lead to fewer acute and chronic HBV infections, long-term complications, and deaths compared with the single-antigen vaccine due to higher SPRs after each vaccination. These results were robust to a wide range of uncertainties in key parameters that influenced the benefits and costs of the vaccine intervention, as well as in scenarios examining vaccine adherence (i.e., series completion rates) and age at vaccination. The ICER in the cohort of adults aged ≥65 years was at or below $50,000 per QALY gained in all scenarios except at the upper-bound scenario of the price of the 3-antigen vaccine and the lower-bound scenario of HBV incidence (underreporting factor of 2.8). Extrapolating these results to the US population level and assuming 2019 vaccination coverage levels, we found that vaccination with the 3-antigen instead of the single-antigen vaccine would have averted an additional 34,000 acute HBV infections, 2,800 chronic HBV infections, and 6,800 HBV-related deaths among adults aged 18–44 years in the US over the remaining lifetime of the cohort. Among adults aged 45–64 years and ≥65 years, the 3-antigen vaccine would have averted an additional 8,700 and 1,200 acute HBV infections compared with the single-antigen vaccine, respectively. These population-level reductions in infection would improve further if vaccination coverage rates were to increase as a result of the recently expanded ACIP adult hepatitis B vaccination recommendation.

This is the first cost-effectiveness evaluation of the recently approved 3-antigen vaccine compared with the single-antigen vaccine. Recently, 3 cost-effectiveness analyses comparing a 2-dose and 3-dose single-antigen hepatitis B vaccine were conducted in high-risk populations [6] as well as in the US general adult population and diabetic subgroups [40,41]. Both Rosenthal et al. [6] and Hirst et al. [41] found that the 2-dose single-antigen vaccine was associated with better health outcomes than the 3-dose single-antigen vaccine. Rosenthal et al. found that the 2-dose single-antigen vaccine was also associated with lower costs. Our cost-effectiveness analysis showed that the only available, recently approved 3-antigen hepatitis B vaccine also results in lower costs and better health outcomes than the 3-dose single-antigen vaccine in US adults aged 18–64 years, adults with diabetes, and adults with obesity.

Strengths of this analysis include that the model used SPR data from a head-to-head phase 3 randomized control trial (PROTECT) [18] and adherence data from a real-world analysis of hepatitis B vaccine series completion rates in the US [25] (used by other cost-effectiveness models). All input parameters were based on the most current data available, which may be from different years, based on reporting lag times.

This analysis has several important assumptions and limitations. First, the cost-effectiveness model uses a static model structure, excluding indirect effects of vaccination, such as herd immunity or averted subsequent transmission of HBV. Second, as in other economic models of hepatitis B vaccines, we assumed seroprotected individuals have lifelong immunity after vaccination or HBV infection. This simplifying assumption would mostly affect results for high-risk populations known to be at risk for nonresponse to vaccination. Revaccination (i.e., boosting) of individuals who did not attain seroprotection or who had declining seroprotection was beyond the scope of our analysis. Third, we assumed that vaccine-related adverse events were comparable for the 2 vaccines and, thus, could be excluded from this analysis. This assumption was made based on the safety reported in the PROTECT trial [18] as well as exclusion of adverse events in previous economic models of hepatitis B vaccines [6,42,42]. We have also excluded productivity losses for individuals with hepatitis B infection or its long-term complications. Although exclusion of disease-related productivity losses is aligned with a previous cost-effectiveness analysis comparing hepatitis B vaccines from the societal perspective [6], this exclusion is conservative when comparing the incremental value of the 3-antigen vaccine with single-antigen vaccine; including these productivity costs would result in greater cost savings for society with the 3-antigen vaccine. Fourth, cost data for treatment of HBV infection and chronic HBV were based

on data from the previous cost-effectiveness models, where costs are not available separately by HBeAg status, and costs for advanced liver disease are oftentimes based on studies of patients with advanced liver disease from hepatitis C. These gaps in the literature persist for accurately estimating the cost of treatment of hepatitis B in the US. Fifth, vaccine seroprotection data from the clinical study was used rather than real-world effectiveness; while this analysis did use real-world adherence data, real-world effectiveness data would capture further effects of access, acceptability, health-seeking behaviors, and stock availability. Sixth, the results of this analysis were not validated against any real-world data sources. The model was validated through a quality-control review by an independent researcher, and the model results were validated against Rosenthal et al. [6]. Finally, we simplified treatment for HBV infection in the model, assuming that all health states had the same probability of treatment discontinuation and that treatment was equally effective in all years it was delivered. These assumptions were tested in sensitivity analysis and, even varying the percent of treated HBV infections to 0% or to 100%, had little impact on the cost-effectiveness results.

It is important to note that this model was not designed to capture the effect of individuals protected from HBV infection through pediatric vaccination aging into adulthood, which would require a population-level analysis and possibly a full dynamic transmission model. With the implementation of a universal pediatric vaccination recommendation in the US in 1991 [43], the size of the unvaccinated adult population is expected to decrease over time; however, there remains a significant bolus of unvaccinated adults in the US, as reflected in the recently expanded ACIP recommendation. This unmet need is particularly apparent among adults aged > 30 years, who would not have been vaccinated as an infant and who have the highest burden of HBV infections (50% of infections occur in adults 30–49 years of age). The new routine universal hepatitis B vaccination recommendation for adults aged 19–59 will hopefully increase vaccination rates in this population.

Hepatitis B remains a persistent health problem that will require new solutions. Without a cure, vaccination is the primary means of further reducing the transmissions, and this preventative 3-antigen vaccine provides an additional differentiated intervention to help meet the US and World Health Organization's goals of a 90% reduction in HBV infections by 2030 [44,45].

6. Source(s) of Support and Role of the Funding Source

The financial support for this study was provided by VBI Vaccines Inc. RTI Health Solutions received funding under a research contract with VBI Vaccines Inc. to conduct this study and to provide editorial support in the form of manuscript writing, styling, and submission.

7. Contributions

The manuscript has been read and approved by all authors, each of whom has met the requirements for authorship. S.E.T. and S.A. contributed to the design and programming of the model, acquisition of publicly available data, identification and selection of the input values, interpretation of the study results, and drafting and revising the manuscript. M.N, N.B, and A.T.R. contributed to the study design, acquisition of data, interpretation of the analyses, and reviewing and revising the manuscript. F.D. contributed to the interpretation of the analyses, clinical content in the manuscript, and reviewing the manuscript.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: S.E. Talbird and S.A. Anderson are employees of RTI Health Solutions, an independent nonprofit research organization, which received funding pursuant to a contract from VBI Vaccines Inc. M. Nossov, N. Beattie, A.T. Rak, and F. Diaz-Mitoma are employees of VBI Vaccines Inc. VBI Vaccines Inc. is the manufacturer of PreHevbrio™, which is referred to as the 3-antigen vaccine in this manuscript.

Acknowledgements

Funding for this study was provided by VBI Vaccines Inc. The authors acknowledge John Forbes, Emily Gill, and Adele C Monroe of RTI Health Solutions for editorial and graphics support and technical assistance in the preparation of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.04.022.

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