Cost-Effectiveness of an Adjuvanted Hepatitis B Vaccine (HEPLISAV-B) in Patients With Inflammatory Bowel Disease

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Background: Compare the cost-effectiveness of 2 recombinant hepatitis B virus (HBV) vaccines in patients with inflammatory bowel disease (IBD).

Methods: Markov models were developed for 2 IBD cohorts: (1) 40-year-old patients prior to starting IBD treatment and (2) 40-year-old patients already receiving therapy. Cohort A received full vaccination series, cohort B had primary vaccine failure and received a vaccine booster. Two vaccines were compared: adjuvanted HEPLISAV-B and nonadjuvanted Engerix-B. Clinical probabilities of acute hepatitis, chronic hepatitis, cirrhosis, fulminant hepatic failure and death, treatment costs, and effectiveness estimates were obtained from published literature. A lifetime analysis and a US payer perspective were used. Probabilistic sensitivity analyses were performed for different hypothetical scenarios.

Results: Analysis of cohort A showed moderate cost-effectiveness of HEPLISAV-B ($88,114 per quality-adjusted life year). Analysis of cohort B showed increased cost-effectiveness ($35,563 per quality-adjusted life year). Changing Engerix-B to HEPLISAV-B in a hypothetical group of 100,000 patients prevented 6 and 30 cases of acute hepatitis; and 4 and 5 cases of chronic hepatitis annually for cohorts A and B, respectively. It also prevented 1 and 2 cases of cirrhosis, and 1 and 2 deaths over 20 years for each cohort. Cost-effectiveness was determined by vaccination costs, patient age, and progression rate from chronic hepatitis to cirrhosis.

Conclusions: HEPLISAV-B is cost-effective over Engerix-B in patients receiving immunosuppressive therapy for IBD. Benefits increase with population aging and lower costs of vaccines. We advocate measuring levels of HBV antibodies in patients with IBD and favor adjuvanted vaccines when vaccination is needed.

Lay Summary

Treatments for inflammatory bowel disease can reactivate hepatitis B. We used a computer model to evaluate the costs and the protection provided by a new adjuvanted vaccine. The benefits of HEPLISAV-B preventing hepatitis, cirrhosis, and deaths justify the higher costs.

Key Words: hepatitis B, vaccination, Crohn disease, ulcerative colitis, preventive services

INTRODUCTION

Vaccinations are a cornerstone in the treatment of patients living with inflammatory bowel disease (IBD). These patients frequently require long-term immune-suppressive therapies and are at an increased risk for preventable infections, including infections with hepatitis B virus (HBV).[1]

One of the biggest achievements in reducing liver-related disability and cancer-related deaths is associated with

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HBV vaccination in the United States. These recommendations started in June 1982, when the Advisory Committee on Immunization Practices (ACIP) published their initial recommendations on the use of HBV vaccine.[2] Subsequently, in 1991, the same committee recommended that HBV vaccination should be universally administered to newborns in the United States.[3] Even though the absolute risk is low in patients with IBD, treatment with antitumor necrosis factor (TNF) and other immunosuppressive agents can cause reactivation of HBV.[4] As a result, there have been fatal cases of HBV reactivation after initiating immunosuppressive therapy.[5] As such, current evidence and guidelines strongly recommend vaccination for HBV in patients with IBD.[1,6] Specifically, HBV vaccination should be provided to any nonimmune patient with IBD, regardless of immunosuppression status. This is critical since they are less likely to seroconvert while on systemic immunosuppression such as anti-TNF therapy. Adjuvanted vaccines have higher seroconversion rates than previous vaccines in both healthy volunteers and immunosuppressed patients.[7]

The HEPLISAV-B vaccine is a new HBV vaccine that has been recommended by the ACIP since 2018.[8] HEPLISAV-B is an inactivated, yeast-derived vaccine that uses a novel immunostimulatory adjuvant and is approved by the U.S. Food and Drug Administration (FDA) for the prevention of HBV in any adult 18 years or older. To date, 4 clinical trials have shown that HEPLISAV-B is more effective than a presently available vaccine, Engerix-B in healthy volunteers and have reported 90%–100% seroprotective anti-HBs levels for HEPLISAV-B as opposed to 70.5%–90.2% for Engerix-B. Further, HEPLISAV-B requires only 2 doses, 1 month apart; while Engerix-B is administered in 3 doses over a period of 6 months, thus the former allowing a shorter period to acquire HBV protection. However, clinical trials suggested a marginal increase in risk of developing cardiac events and autoimmune diseases in patients receiving HEPLISAV-B.[8,9] Postvaccination serologic testing is recommended in patients with IBD by the American College of Gastroenterology (ACG) 1–2 months after the final dose to confirm a protective level of antibodies against HBV (anti-HBs >10 IU/L).[1] The ACIP recommends postvaccination serologic testing to be performed in immunocompromised patients.

Initial efficacy trials on this adjuvanted vaccine did not include patients with IBD or other immunocompromised conditions.[10] Literature using Engerix-B suggests that most healthy infants and children achieve seroprotective titers but 5%–40% of individuals have waning of anti-HBs titers to <10 IU/L in adulthood.[7,11–13] In these patients, a challenge dose of the HBV vaccine may be given to assess for an anamnestic response. Approximately 88% of patients who receive a challenge dose of HBV vaccine, develop an antibody response of >10 IU/L indicating persistent immunity to HBV infection.[14,15] Current ACIP guidelines do not generally recommended for persons of normal immune status to be revaccinated if anti-HBs is <10 IU/L, unless they are infants born to hepatitis B surface antigen (HBsAg)-positive mothers, health care personnel, hemodialysis, or immunocompromised patients.[8] Some professional HIV societies do recommend checking annual anti-HBs concentrations and a booster dose to individuals whose anti-HBs concentrations have decreased <10 IU/L. In patients with IBD, it is recommended to test for HBV immunity and administer 1 or 2 challenge doses prior to starting biologics or other immunosuppressive therapy.[13] As a result, it is not currently clear which of the available HBV vaccines is more effective, particularly when considering cost differences that result from additional doses required to achieve HBV protection.

The objective of this study was to perform an economic analysis comparing 2 available HBV vaccines (HEPLISAV-B vs Engerix-B) in patients with IBD. The secondary goal was to measure the clinical benefits of the vaccine and other parameters under which vaccination is more cost-effective.

METHODS

A Markov model was created comparing 2 available HBV vaccines in patients with IBD with changing stages every year over a lifetime analysis. We adhered to the recommendations from the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) group for conducting and reporting an economic analysis.[16] The primary analysis was performed from the perspective of a third-party payer.

Markov Model and Clinical Probabilities

We created a Markov model where patients would transition among 10 different stages: seroprotected, susceptible, acute HBV infection, chronic HBV infection, fulminant hepatic failure, cirrhosis (compensated and decompensated), hepatocellular carcinoma (HCC), liver transplant (subdivided in first year after transplant and subsequent years), and death. The model was adapted from a previous cost-effectiveness analysis for different adult conditions (Fig. 1).[17]

Two cohorts were evaluated:

- Cohort A (IBD treatment naive, never vaccinated): 40-year-old patients who never received HBV vaccination. They were tested prior to starting biologics and confirmed anti-HBs titers <10 IU/L. This cohort received full series of Engerix-B (3 doses of 20 mcg HBsAg at 0, 1, and 6 months) or full series of HEPLISAV-B (2 doses of 20 mcg adjuvanted HBsAg at 0 and 1 month). This cohort included analysis of cardiovascular and autoimmune events associated with HEPLISAV-B administration.
- Cohort B (immunosuppressed, primary vaccination failure): 40-year-old patients receiving treatment. This cohort was similar to the cohort presented by Pratt et al.[18] Most patients (78%) were receiving treatment [ie, 50% immunomodulators, 40% anti-TNF, and 17% on corticosteroids (categories are not mutually exclusive)]. Previous vaccination was not documented.[19–21] They never achieved seroconversion after initial immunization, confirmed by checking anti-HBs status and titer level being >0 and <10 IU/L after immunization.[4] Revaccination attempts were provided at the discretion of treating

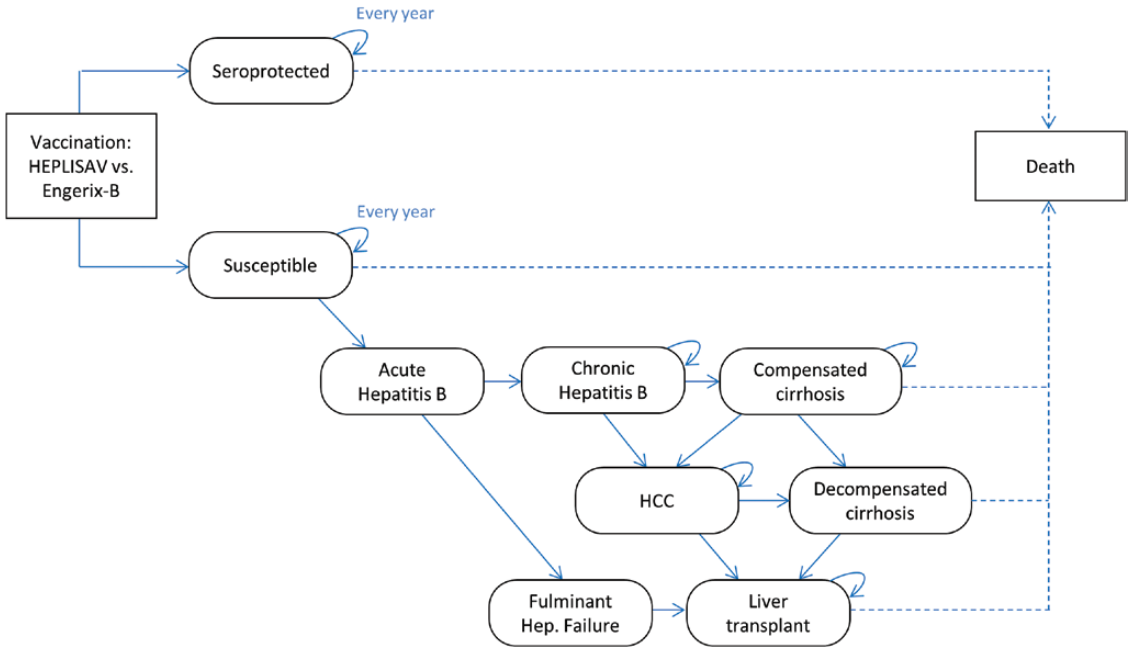

FIGURE 1. Markov model for hepatitis B vaccination in patients with IBD. (Liver transplant was subdivided in first year and subsequent years post-transplant.)

clinician (patients can receive 1–3 doses of Engerix-B, and 1–2 doses of HEPLISAV-B). Anti-HBs titers were measured a second time after receiving the first vaccination booster.

All patients included in the vaccination program were diagnosed with Crohn disease or ulcerative colitis without other significant comorbidities. We assumed none of them ever had HBV infection [typically seronegative for antibody against hepatitis B core protein (anti-HBc), HBsAg, and negative viral DNA]. None of them had cirrhosis or significant liver disease. An appointment with a registered nurse or nurse practitioner was necessary for administration of each vaccine dose. We did not perform half cycle corrections (all events were assumed to happen at the beginning of each cycle).

Probabilities to progressing into different clinical scenarios were obtained from published literature (Table 1). Considering that the main transmission routes for HBV are vertical, sexual, blood transfusions, and needle sticks, we assumed the probability of developing acute HBV in IBD was similar to that for healthy adults.[22] Seroprotection rates from both vaccines were obtained from 3 clinical trials.[19,23–25] Survival was defined based on the most recent US actuarial life tables.[26]

Patients living with IBD lose HBV antibody protection after vaccination. In general, 81% [95% confidence interval (CI), 78%–96%] of volunteers respond to a Engerix-B booster, achieving anti-HBs titers >10 IU/L at 60 days.[28] Response rates to a similar booster dose of HEPLISAV-B in IBD patients have not been measured. We estimated seroconversion to be 65% (95% CI, 55%–75%) in cohort B, adapting results from Pratt et al (details in Supplementary Table S1).[18]

Cost Estimates

Cost estimates were obtained from multiple sources, but most estimates were based on 2 published economic analysis for HBV in the United States.[29,30] Initial analysis was conducted using vaccines cost for the private sector, secondary analysis was conducted using costs for the U.S. Centers for Disease Control and Prevention (CDC) (Table 2). Calculations for vaccination cost in cohort B were adapted from Pratt et al (details in Supplementary Table S2).[21]

Patients who acquired HBV infection and developed any of the clinical consequences were assumed to receive adequate medical treatment including oral antiviral medications for HBV, hospitalization, cancer treatment, and liver transplant evaluation.

Because payments and costs vary geographically, depending on local operating costs, we varied our baseline costs through sensitivity analysis using a gamma distribution and the ranges shown in Table 2. Only direct costs were considered. Costs were adjusted to the 2019 US dollar using the gross domestic product implicit price deflator. We consider that preventing cases of acute HBV has similar value in upcoming years and opted not to include discounting rates.

Effectiveness Estimates

Effectiveness of vaccination was measured in quality-adjusted life years (QALYs). Life expectancy of patients with IBD was assumed to be similar to the general population.[34] Utilities for decreased quality of life caused by IBD were adapted from a systematic review and published surveys and

TABLE 1. Probabilities for Health State Transitions and Other Inputs

Description		Range	Reference
Clinical assumptions			
Age-specific mortality for healthy person	US life tables		[26]
Seroconversion rates after Engerix-B series (0, 1, and 6 months)	0.690	0.610–0.770	[19,23–25]
Seroconversion rates after HEPLISAV-B series (0 and 1 months)	0.925	0.901–0.949	[23–25]
Seroconversion rate after Engerix-B rescue (immunosuppressed patient, 1 dose)	0.500	0.400–0.600	[18]
Seroconversion rate after HEPLISAV-B rescue (immunosuppressed patient, 1 dose)	0.650	0.550–0.750	Expert
Probabilities for health state transitions	Annual estimates		
Susceptible to acute HBV infection (cohort A, never vaccinated)	0.00027	Ages 40–44	[17,22]
	0.00023	Ages 45–49	
	0.00018	Ages 50–54	
	0.00014	Ages 55–59	
	0.00004	Ages 60+	
Susceptible to acute HBV infection (cohort B, immunosuppressed)	0.00059	Ages 40–49	Supplement[4]
	0.00036	Ages 50–59	
	0.00004	Ages 60+	
Acute HBV infection to chronic infection	0.077	0.05–0.10	[17]
Acute HBV infection to FHF	0.003		[17]
Chronic HBV infection to compensated cirrhosis	0.059		[17]
Chronic HBV infection to HCC	0.005		[17]
Chronic HBV infection to seroprotected	0.001		[17]
Compensated cirrhosis to death	0.150		[17]
Compensated to decompensated cirrhosis	0.050		[17]
Compensated cirrhosis to HCC	0.022		[17]
Decompensated cirrhosis to death	0.190		[17]
Decompensated cirrhosis to HCC	0.025		[17]
Decompensated cirrhosis to liver transplant	0.018		[17]
FHF to death	0.247		[27]
FHF to liver transplant (only 47% of 30% who survive FHF)	0.198		[27]
HCC to death	0.433		[17]
HCC to liver transplant	0.046		[17]
Liver transplant to death (first year)	0.080		[17]
Liver transplant to death (subsequent years)	0.069		[17]
Cardiac deaths associated with HEPLISAV-B	0.00054		[9]
Cardiac deaths associated with Engerix-B	0.00036		[9]

Seroconversion rates and probability to develop chronic HBV follow a beta distribution. Lower and upper values are 2 SDs from mean estimate.
FHF, fulminant hepatic failure.

followed a normal distribution. Using 3 different scales, utility values of IBD range from 0.96 on remission, to 0.51 living with chronically active-therapy resistant disease.[35] Crohn disease has a worse quality of life in remission and severe disease. Ulcerative colitis has a worse quality of life in moderate disease.

For cohort A, we included the risk of developing autoimmune disease, and cardiac events after receiving HBV vaccination. The attributable risk of autoimmune/granulomatous disease was 0.0005 (0/1088 vs 2/3789), myocardial infarction was 0.002 (19/5587 vs 3/2781), and cardiac death was 0.0004 (8/5587 vs 3/2781).[9] The relative risk for myocardial infarction was 3.15 (95% Koopman score CI 1.00, 9.98). All the patients who developed cardiac events had history of cardiac ischemia, type 2 diabetes, hypertension, hyperlipidemia, active smoking, or obesity. Mortality was accounted for by assigning a utility value of 0. Lifetime horizon was capped at 110 years. No adjustments were made for opportunity costs (Table 3).

Outcomes and Sensitivity Analysis

Results are reported as incremental cost-effectiveness ratios (ICERs) and net monetary benefit (NMB). ICER and NMB values were calculated according to previously reported methodology.[38] Our

TABLE 2. Annual Costs for Markov Model Health States

Interventions	Costs Mean USD	Range and Comments	Reference
Anti-HBs titers	$45	Once	31
One dose of Engerix-B	$59	Cost for private sector (CDC price $34)	32
One dose HEPLISAV-B	$116	Cost for private sector (CDC price $70)	32
Appointment for vaccination	$17	$13.45–20.01 CPT code 90471	33
Health States	**Mean USD**	**SD ± USD**	
HBV seroprotected/susceptible	$0	No changes	
Acute HBV infection	$947	±$95	30
Chronic HBV infection	$2088	±$261	29
Compensated cirrhosis	$7832	±$979	30
Decompensated cirrhosis	$41,192	±$5149	30
Fulminant hepatic failure	$22,180	±$2772	30
HCC	$36,544	±$4568	30
Liver transplant, first year	$453,958	±$56,745	30
Liver transplant, subsequent years	$43,792	±$5474	30

Costs variations follow a gamma distribution, following mean ± SD, $\alpha = 2$ and $\lambda = 1$. Adjusted to 2019 dollars.
FHF, fulminant hepatic failure; USD, United States dollars.

TABLE 3. Utility Values for Hepatitis B-Related Disease

Utility Values	Estimate	Range	Reference
IBD, HBV susceptible, or HBV seroprotected after vaccination	0.71	0.51 chronically active, therapy resistant disease—0.91 on remission	32,35
Acute HBV infection	0.69	0.59–0.79	17,36,37
Chronic HBV infection	0.67	0.57–0.77	17,36,37
Compensated cirrhosis	0.66	0.56–0.76	17,36,37
Decompensated cirrhosis	0.37	0.27–0.47	17,36,37
FHF	0.37	0.27–0.47	17,36,37
HCC	0.43	0.33–0.53	17,36,37
Liver transplant, first year	0.57	0.47–0.67	17,36,37
Liver transplant, subsequent years	0.64	0.54–0.74	17,36,37

Utility estimates follow a normal distribution. SD of 0.05, lower and upper ranges are 2 SDs (0.1) from mean estimate.
FHF, fulminant hepatic failure.

model was recreated on a cohort of 100,000 individuals to measure the health outcomes avoided by HEPLISAV-B vs Engerix-B.

The robustness of the model was tested by performing probabilistic sensitivity analysis with variations in the important clinical variables and cost estimates. Seroconversion rates and probability to develop chronic HBV followed a beta distribution (Tables 1–3). Tornado diagrams were created to compare the weight of different variables on cost-effectiveness. A second-order Monte Carlo simulation was performed for a willingness-to-pay analysis. Acceptability curves were created within a willingness-to-pay range from $0 to $100,000.

When estimates were unavailable or significant discrepancies were found in published literature, 3 authors (J.E.C., J.Y.K., and F.A.F.) would discuss and agree on a final estimate. The Markov model was built and analyzed using the decision analysis software TreeAge (TreeAge Pro Version 2020; Williamstown, MA).

Ethical Considerations

This study is based on publicly available data and was not submitted for IRB review.

RESULTS

Analysis of cohort A showed moderate cost-effectiveness of HEPLISAV-B ($88,114 per QALY). Cost-effectiveness of HEPLISAV-B substantially increased in cohort B ($35,563 per QALY) (Fig. 2). NMB indices showed similar results as ICERs (Table 4). The subsequent analysis, in which vaccination costs of the private sector were replaced with CDC costs, demonstrated increased cost-effectiveness with ICERs of $41,492 and $12,682 per QALY gained, for cohorts A and B, respectively (Supplementary Table S3).

Changing Engerix-B to HEPLISAV-B showed clinical gains in preventing liver-related morbidity and mortality. In a hypothetical group of 100,000 patients, this change prevented 6 and 30 cases of acute hepatitis; and 4 and 5 cases of chronic hepatitis annually for cohorts A and B, respectively. It also prevented 1 and 2 cases of cirrhosis, and 1 and 2 deaths over 20 years for each cohort (Table 5).

Administration of HEPLISAV-B to 100,000 patients in cohort A was potentially associated with 232 cardiac events and 35 cardiac-related deaths. Additionally, HEPLISAV-B would potentially lead to 52 autoimmune/granulomatous diseases.[9]

Sensitivity and Willingness-to-Pay Analysis

Analysis of tornado diagrams showed that the model is sensitive to initial cost of vaccination, how long the patient was in the model and progression rates from chronic hepatitis to compensated cirrhosis. Transition between different health stages is illustrated in Supplementary Fig. S1. Quality of life living with IBD, progression rate from acute hepatitis to chronic hepatitis and clinical severity of acute hepatitis were also important modifiers (Supplementary Fig. S2).

The Monte Carlo analysis generated acceptability curves with a willingness to pay of $100,000. Curves favored the HEPLISAV-B vaccine in both cohorts, using either private sector or CDC vaccination costs (Supplementary Fig. S3).

DISCUSSION

Hepatitis B screening and vaccination is recommended in patients living with IBD.[1,39] To our knowledge, this is the first economic analysis to compare 2 vaccine alternatives in a population residing in the United States. We found that HEPLISAV-B is a cost-effective vaccination strategy, but results greatly vary by patient cohort, vaccination costs and progression rates from chronic HBV infection to compensated cirrhosis. Our results are aligned with prior studies showing HEPLISAV-B is a cost-effective vaccine in healthy adults, travelers, healthcare workers, and patients with diabetes or chronic kidney disease.[17]

HEPLISAV-B demonstrated significant clinical gains by preventing acute hepatitis, cirrhosis, and death. Clinical gains however did not translate into cost-effectiveness for all patient groups. Our estimates are more conservative than those published previously. Our ICER estimates ranged from $88,114 to $35,563. Kuan et al reported ICERs of $14,788 for patients with diabetes and $12,969 for healthcare workers (adjusted to 2019 US dollars).[17] Part of the difference seen is attributed to vaccination costs. Modeling with CDC vaccination costs made our results comparable to Kuan et al's study with an ICER of $12,682 for cohort B. Additionally, previous models utilized higher effectiveness for patients with end stage renal disease who are more exposed to HBV (ie, blood transfusions and hemodialysis). Our results show a significant difference in cost-effectiveness between treatment naive and immunosuppressed patients with IBD (ie, those receiving steroids, immunomodulators, and/or biologics). Cohort B represents a closer representation of patients seen in clinical practice. Some of these patients are offered a double-dose protocol of Engerix-B. This protocol might change with HEPLISAV-B higher response rates, requiring less booster doses.[18,21]

In the present analysis, comparative effectiveness of HEPLISAV-B vaccination was moderate. This is attributed

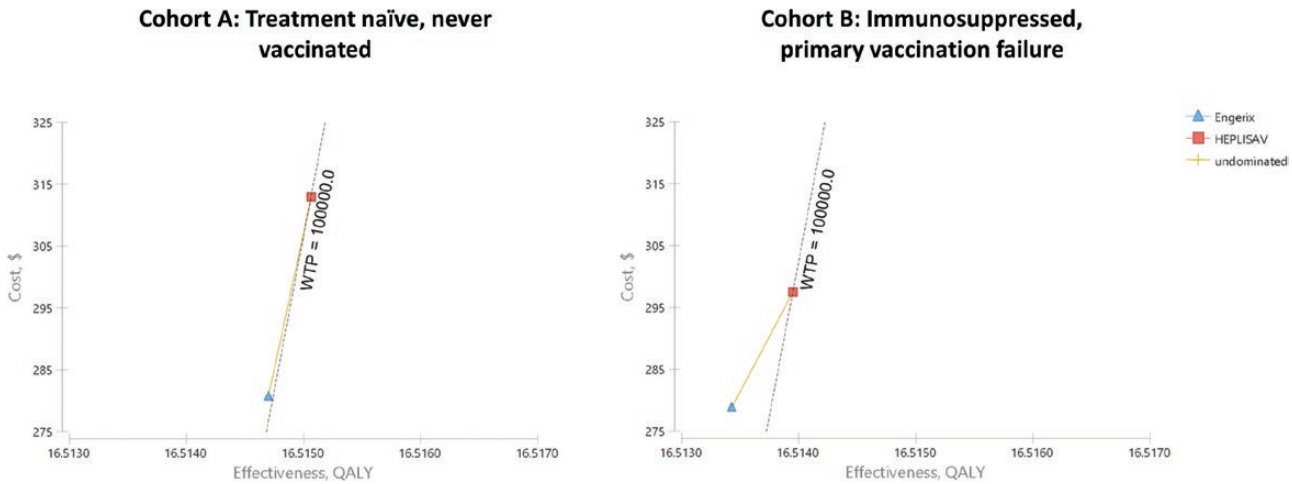

FIGURE 2. Cost-effectiveness diagram for 2 cohorts of patients with IBD receiving hepatitis B vaccination.

TABLE 4. ICERs for Hepatitis B Vaccination Alternatives in IBD Patients

	Cost (US Dollars)	Incremental Cost (US Dollars)	Effectiveness (QALYs Gained)	Incremental Effectiveness (QALYs Gained)	ICER ($/QALY)	NMB
Cohort A: treatment naive, never vaccinated						
Engerix-B	$281	Ref.	16.5147	Ref.	Ref.	825,454
HEPLISAV-B	$313	$32	16.5151	0.0004	88,114	825,440
Cohort B: immunosuppressed, primary vaccination failure						
Engerix-B	$279	Ref.	16.5134	Ref.	Ref.	825,393
HEPLISAV-B	$297	$19	16.5140	0.0005	35,563	825,400

TABLE 5. Health Outcomes Avoided in 100,000 IBD Patients Receiving Engerix-B and HEPLISAV-B

Years After Intervention	Seroprotected	Susceptible	Acute HBV	Chronic HBV	FHF	Compensated Cirrhosis	Death
Cohort A: treatment naive, complete Engerix-B series							
1 year	68,868	30,932	8	0	0	0	191
2 years	68,730	30,870	8	1	0	0	392
3 years	68,583	30,803	8	1	0	0	604
5 years	68,260	30,657	8	2	0	0	1072
10 years	67,195	30,177	7	4	0	1	2616
20 years	63,160	28,363	4	5	0	1	8466
Cohort A: treatment naive, complete HEPLISAV-B series							
1 year	92,323	7484	2	0	0	0	191
2 years	92,138	7468	2	0	0	0	392
3 years	91,941	7452	2	0	0	0	604
5 years	91,508	7417	2	1	0	0	1072
10 years	90,080	7301	2	1	0	0	2616
20 years	84,671	6862	1	1	0	0	8465
Cohort B: immunosuppressed, Engerix-B booster							
1 year	49,904	49,875	30	0	0	0	191
2 years	49,804	49,772	29	2	0	0	392
3 years	49,698	49,664	29	4	0	0	604
5 years	49,464	49,425	29	8	0	1	1072
10 years	48,692	48,642	29	16	0	3	2618
20 years	45,768	45,718	17	18	0	5	8473
Cohort B: immunosuppressed, HEPLISAV-B booster							
1 year	64,876	34,912	0	0	0	0	191
2 years	64,745	34,841	2	0	0	0	392
3 years	64,607	34,765	3	0	0	0	604
5 years	64,303	34,598	20	6	0	0	1072
10 years	63,300	34,050	20	11	0	2	2617
20 years	59,499	32,002	12	13	0	3	8471

No patients developed decompensated cirrhosis, HCC, or required liver transplant in the first 10 years of our model.
FHF, fulminant hepatic failure.

to the small number of patients who eventually develop decompensated cirrhosis, HCC, and subsequently die from liver-related complications across a diverse population of IBD patients. With current HBV treatments and advances in HCC treatment and liver transplantation, the mortality associated with HBV has decreased substantially. However, ICERs do not reflect all the benefits of preventing HBV in the community. Preventing 1 case of acute hepatitis may save

only a few QALYs, but also reduces vertical transmission and transmission to sexual partners. These benefits from a society perspective are beyond the scope of this analysis.

Patients with IBD frequently achieve seroprotective titers but later see them decline to subprotective levels over years. It remains an issue of debate as to what degree of protection these individuals retain against HBV. The current belief is that lower titers translate into reduced protection. One suggested strategy is to serially monitor at-risk vaccinated patients and administer a booster dose each time titers fall <10 IU/L. This approach is difficult to implement given cost issues, manpower, and follow-up. Therefore, the higher titers generated by HEPLISAV-B represent an important advance. Prospective research should measure the adequate booster frequency to maintain seroprotective titers before antibody titers decay after receiving adjuvanted vaccines.

Implications and Future Directions

Current ACG clinical guidelines highly recommend vaccination of HBV in patients with IBD,[1] but were published prior to the approval of HEPLISAV-B. The 2020 ACIP guidelines state that HEPLISAV-B may be used in persons aged ≥18 years for vaccination against HBV, but there are no current recommendations on using it preferentially instead of Engerix-B or other vaccines.[8] Changing vaccination strategies based solely on requiring that ICERs are below the national income has significant shortcomings. By including modeling of acute hepatitis, cirrhosis, and deaths prevented, we were able to show that in patients with IBD, adjuvanted vaccines may have social value in the United States.

Adverse events from HBV vaccination are considered rare but were included in cohort A. Based on 3 clinical trials, the U.S. FDA concluded that major adverse events and severe adverse events were similar over a 56-week period.[9] However, 1 trial showed increased cardiac adverse events with HEPLISAV-B (cardiac events Engerix-B 0.9% and HEPLISAV-B 0.5%, myocardial infarction Engerix-B 0.04% and HEPLISAV-B 0.25%). All these patients had preexisting coronary artery disease, diabetes, hypertension, hyperlipidemia, smoking within the last year, or obesity. HEPLISAV-B was recently approved in 2018 and long-term implications on safety are under study. The cardiology adjudication panel agreed that additional postmarketing monitoring is crucial. A post hoc analysis of the Phase 3 trials showed no significant adverse cardiovascular outcomes and currently the manufacturer (Dynavax) is conducting a postmarketing study following patients until December 2020 to assess cardiovascular risk. In the interim, we advocate discussing cardiac risks of vaccinations in elderly patients with cardiovascular risk factors.[40–42] Additional research and postmarketing surveillance are needed to establish if there is an association between HEPLISAV-B and autoimmune conditions.[27]

Initial trials also showed more autoimmune events in the HEPLISAV-B group: 1 case of granulomatosis with polyangitis, Tolosa–Hunt syndrome, alopecia areata, polymyalgia rheumatica, and autoimmune thyroiditis, none of them seen with Engerix-B. Associations with autoimmune processes were inconclusive given disease chronicity/previous onset, or having incomplete evaluation. The risks of these conditions in patients with IBD remain unknown and we assumed it would cause minimal impact on utility values.

Strengths and Limitations

In any decision analysis, the quality of the input data is critical. In our analysis, the most important probabilities were obtained from 3 recently conducted clinical trials.[19,23–25] Another strength is achieved through accounting for clinical uncertainties and valid statistical measures with a second-order Monte Carlo simulation.

Despite the sensitivity analysis and Monte Carlo simulation, our model represents a simplification of a complex process. Patients on remission have a quality of life similar to healthy individuals (utility of 1). However, hospitalizations and mortality in patients with severe IBD or colorectal adenocarcinoma are difficult to include in our model. Another limitation was the inability to include loss of protection (HBsAb <10 IU/L) over subsequent years. We presumed that those patients who developed HBV-related complications would have been diagnosed until the next iteration of the cycle (ie, a year later).

Additionally, the benefits of HBV vaccination have significant geographical variability. Our analysis was done in a US setting. In other countries with higher HBV incidence like Sub-Saharan Africa (eg, Mozambique) or Western Pacific (eg, Philippines, and Vietnam), the difference in effectiveness (and therefore cost-effectiveness) would be higher provided that the cost of vaccines is proportionately lower.

Finally, we assumed that HBV acquisition rate increases between 25 and 49 years (Table 1). While this is an intuitive assumption, as those patients are sexually active; there are arguments that the chance of developing HCC peak later in life (around 60–65 years of age). Hepatocellular carcinogenesis is not a linear process in which low-grade dysplastic lesions develop slowly years before they transform into cancer, and more likely progress in an accelerated fashion after having cirrhosis.

CONCLUSIONS

This economic analysis shows that HEPLISAV-B vaccination is cost-effective compared to Engerix-B vaccination in patients receiving therapy for IBD. Benefits increase with population aging and lower costs of both vaccines but decrease in immunocompetent patients who need full vaccination series. We advocate to measure protective level of antibodies against HBV in patients with IBD to assure sustained immunity, and favor adjuvanted vaccines when vaccination is needed.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Crohn's & Colitis 360* online.

DATA AVAILABILITY

Data available at https://drive.google.com/file/d/1YGCrxigboyrUeWZ_4wdVrCPwM0SxNQRR/view?usp=sharing and https://drive.google.com/file/d/1MG8oLEC0yiQVvxcJX9D9cmSIv6Ayg1g6/view?usp=sharing.

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