

Evolving Considerations for Choice of Hepatitis B Vaccine

HIGHLIGHTS

- › Disease Burden of Hepatitis B Virus (HBV) in the United States
- › 2022 Recommendations Provided by the Advisory Committee on Immunization Practices
- › Considerations for Improved HBV Vaccine Practices

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Evolving Considerations for Choice of Hepatitis B Vaccine

OVERVIEW

This supplement to *The American Journal of Managed Care*[®] provides an overview of emerging considerations based on CDC recommendations and new clinical data around hepatitis B virus (HBV) vaccines. Additionally, this manuscript highlights the potential of Heplisav-B in fulfilling unmet needs that currently exist in the HBV prevention landscape.

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Evolving Considerations for Choice of Hepatitis B Vaccine

Dalga D. Surofchy, PharmD, APH; Neil Shieh, PharmD; and Iris Tam, PharmD

Introduction

Hepatitis B virus (HBV) is among the most common causes of chronic viral liver disease and remains a major public health burden in the United States. No cure for HBV infection is known, and as such, the US Department of Health and Human Services (HHS) has emphasized prevention through vaccination as a main focus in significantly reducing its incidence by the year 2030.¹ In fact, the HHS has established a Viral Hepatitis National Strategic Plan with the goal of eliminating HBV infection in the United States by the year 2030. This goal will be achieved by reducing the incidence of new HBV infections by 90% and mortality by 65%.¹

Currently, 4 HBV vaccines (excluding bivalent vaccines) are available in the United States for use in adults and all are equally recommended as options for the prevention of HBV infection by the Advisory Committee on Immunization Practices (ACIP).² One of the vaccines is Heplisav-B which contains cytosine phosphoguanine (CpG) 1018 adjuvant and is administered as a 2-dose series at months 0 and 1. The other 3 HBV vaccines are aluminum hydroxide–adjuvanted vaccines (Engerix-B, Recombivax-HB, and PreHevbrio), each of which is administered as a 3-dose series at months 0, 1, and 6 (Table 1).²⁻⁶

The following discussion provides an overview of emerging considerations based on CDC recommendations and new clinical data around HBV vaccines. Additionally, this manuscript highlights the potential of Heplisav-B in fulfilling unmet needs that currently exist in the HBV prevention landscape.

Disease Burden of HBV in the United States

Since the introduction of the first HBV vaccine in 1982, the overall rate of reported acute HBV infections has declined across all age groups in the United States. This decline is mostly attributed to the implementation in 1991 of universal HBV vaccination of infants and, in 1999, the inclusion of children and adolescents through age 18 years who have not received the HBV vaccine.⁷

However, according to the CDC's 2019 Viral Hepatitis Surveillance Report, the incidence of HBV infection among adults in the United States remains a serious public health concern due to the increased

ABSTRACT

There is currently no known cure for hepatitis B virus (HBV) infection, and HBV remains a major public health burden in the United States. The US Department of Health and Human Services has established a Viral Hepatitis National Strategic Plan with the goal of eliminating HBV infection in the United States by the year 2030. This goal will be achieved by reducing the incidence of new HBV infections by 90% and mortality by 65%, with a main focus on prevention of HBV infection through vaccination. Currently, 4 HBV vaccines (excluding bivalent vaccines) are available in the United States for use in adults, including Heplisav-B, which was approved by the FDA in November 2017 for use in adults 18 years and older. All 4 HBV vaccines are equally recommended as options for the prevention of HBV infection by the Advisory Committee on Immunization Practices. This article provides an overview of emerging considerations based on CDC recommendations and new clinical data around HBV vaccines, as well as the potential of Heplisav-B in fulfilling unmet needs that currently exist in the HBV prevention landscape.

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For author information and disclosures, see end of text.

TABLE 1. General Adult Dosing of FDA-Approved Monovalent HBV Vaccines^{2-6,a,b}

	Heplisav-B ^c	Engerix-B	Recombivax-HB	PreHevbrion ^d
FDA approval date	2017 ³	1989 ⁵	1986 ⁴	2021 ⁴
General adult dosing ²	2 doses (20 mcg/0.5 mL each) IM on a 0- and 1-month schedule	3 doses (20 mcg/1.0 mL each) IM on a 0-, 1-, and 6-month schedule	3 doses (10 mcg/1.0 mL each) IM on a 0-, 1-, and 6-month schedule	3 doses (10 mcg/1.0 mL each) IM on a 0-, 1-, and 6-month schedule

CpG, cytosine phosphoguanine; HBV, hepatitis B virus; IM, intramuscular.

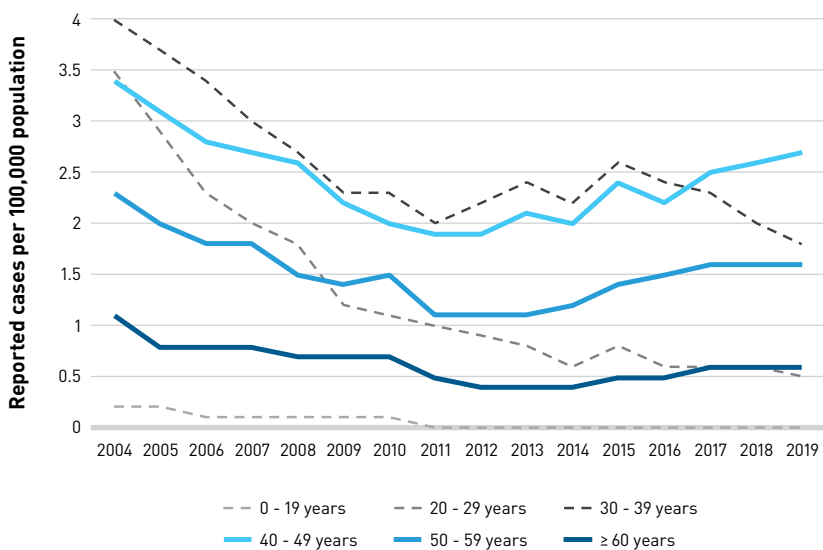
^aDoes not include bivalent HBV vaccines (eg, Twinrix, Pediarix, Vaxelis).

^bThe focus of this table is general adult dosing of monovalent HBV vaccines. See appropriate prescribing information for each product for all dosing schedules.

^cHeplisav-B vaccine uses recombinant hepatitis B surface antigen and CpG 1018 toll-like receptor 9 agonist adjuvant.

^dPreHevbrion is a 3-antigen vaccine.

FIGURE 1. Rates of Reported Acute HBV Infection in the United States by Age Group^{8,a}



HBV, hepatitis B virus.

^aSource: Centers for Disease Control and Prevention (CDC), National Notifiable Diseases Surveillance System.

Repurposed from materials developed by the CDC. Use of this figure does not imply the CDC's endorsement of the material contained in this publication. This figure and related material are available, free of charge, at <https://www.cdc.gov/hepatitis/statistics/2019surveillance/Figure2.4.htm>

risk for cirrhosis and liver cancer among those who develop chronic HBV infection. Immunosuppressed persons, such as hemodialysis (HD) recipients and individuals with HIV or diabetes, develop chronic HBV more frequently. It is estimated that 25% of persons chronically infected with HBV during childhood, and 15% of those infected after childhood, will die prematurely as a result of liver complications.⁷

In 2019, the CDC estimated 20,700 infections in the United States, and an estimated 730,000 to 2,400,000 residents were living with HBV.⁸⁻¹² Although reported HBV cases have continued trending downward since 2004, a majority of new cases since 2011 have been reported among adults aged between 40 and 59 years. Between 2011 and 2019, increases of approximately 42.1% and 45.5% in HBV incidence were documented in adults aged 40 to 49 years

and those aged 50 to 59 years, respectively. These increases are attributed to this cohort not being directly impacted by the universal vaccination measures as well as the low (30%) reported overall HBV vaccination coverage rate (receiving 3 or more doses) among adults.

In contrast, adults aged 20 to 29 years had a 50% reduction in HBV cases reported during those same years as individuals in this cohort were impacted by the 1991 universal HBV vaccination measures. The reduction in HBV cases among persons aged 20 to 29 years occurred because many in this cohort received HBV vaccination as a part of their childhood immunization schedule. ACIP added universal recommendations for childhood HBV vaccinations in 1991 (Figure 1).⁸

2022 Recommendations Provided by ACIP

To address the increasing rates of HBV associated with individuals not captured in the universal childhood recommendations, the ACIP vaccine recommendations for HBV (Table 2) were updated on April 1, 2022.²

ACIP recommends HBV vaccination for:

- all adults aged 19 to 59 years (universal expansion);
- adults 60 years or older with risk factors;
- adults 60 years or older without risk factors, involving shared clinical decision-making (SCDM); and
- infants and all other persons 18 years and younger.

As updated, the universal expansion recommendation steps away from previous recommendations for adults that focused on vaccinating at-risk or high-risk individuals only. The newly expanded adult recommendation, also referred to as an “adult catch-up recommendation,” eliminates one of the many barriers

physicians have reportedly faced in determining risk-based vaccination eligibility of patients and further streamlines HBV vaccination efforts for all adults.²

Additionally, the CDC included new language focused on SCDM, which aims to prompt all providers to offer the HBV vaccine to adults 60 years and older who have no known risk factors. For these adults, SCDM puts the onus on the health care provider to actively engage patients in discussions around their vaccination needs instead of waiting for a patient to request vaccination.²

Despite ACIP evidence-based recommendations, survey data from 2018 highlight that only 30% of all US adults 19 years and older are protected against HBV (ie, have received 3 or more doses of HBV vaccine).² This statistic is of particular concern, as it has been estimated that 80% of HBV-infected persons are undiagnosed and therefore are unaware of their infection status, resulting in asymptomatic carriers (or reservoirs) continuing to transmit virus for many years.¹³ Given the current lack of curative treatment options, chronic HBV infection can lead to inflammation, cirrhosis, fibrosis, hepatocellular carcinoma (HCC), and a 15% lifetime risk of premature mortality.¹⁴ This burden is particularly pronounced among at-risk and high-risk populations (Table 2), including persons living with HIV (PLWH) and those receiving HD, who traditionally have suboptimal immune responses to HBV vaccinations and consequently bear a greater clinical burden of disease.^{2,14-16}

Heplisav-B Efficacy and Safety Summary

Efficacy

Heplisav-B is a single-antigen HBV vaccine approved by the FDA in November 2017 for prevention of HBV infection of all known subtypes. FDA approval was based on immunogenicity results of three randomized, multicenter phase 3 clinical trials (Table 3), including adult participants who had received either 2-dose Heplisav-B administered over 1 month, or 3-dose Engerix-B administered over 6 months.^{3,17-19}

These pivotal noninferiority trials evaluated immunogenicity induced by Heplisav-B compared with Engerix-B by examining seroprotection rates (SPRs), defined as the percentage of participants who developed antibody concentrations ≥ 10 mIU/mL or less; criteria for noninferiority were met if the lower bound of the 95% CI for the difference in SPR (Heplisav-B minus Engerix-B) was greater than -10%. In Study 1 and Study 2, statistical superiority in SPR was declared if the lower bound of the 95% CI for the difference in SPR was above 0%. A summary of each trial is presented in Table 3, and efficacy data from all 3 trials are shown in Figure 2 and Figure 3.¹⁷⁻¹⁹

Study 1 and Study 2 were primarily designed to demonstrate the noninferiority in SPRs between Heplisav-B and Engerix-B; however, statistical superiority was declared in the studies based on prespecified superiority criteria. Study 1 and Study 2 were conducted in healthy adults with no history of HBV infection or immunization

TABLE 2. 2022 ACIP Recommendations for Persons Recommended to Receive HBV Vaccination²

All infants

Persons 18 years and younger

Adults aged 19-59 years

Adults 60 years and older with risk factors for HBV:

- Persons at risk for infection by sexual exposure
 - » Sex partners of persons testing positive for HBsAg
 - » Sexually active persons who are not in a long-term, mutually monogamous relationship (eg, persons with more than 1 sex partner during the previous 6 months)
 - » Persons seeking evaluation or treatment for a sexually transmitted infection
 - » Men who have sex with men
- Persons at risk for infection by percutaneous or mucosal exposure to blood
 - » Persons with current or recent injection drug use
 - » Household contacts of persons testing positive for HBsAg
 - » Residents and staff members at facilities for persons with developmental disabilities
 - » Health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
 - » Persons on maintenance HD, including in-center or home HD and peritoneal dialysis, and predialysis persons
 - » Persons with diabetes, at the discretion of the treating clinician
- Others
 - » International travelers to countries with high or intermediate levels of or endemic HBV infection (HBsAg prevalence $\geq 2\%$)
 - » Persons with hepatitis C virus infection
 - » Persons with chronic liver disease (including, but not limited to, persons with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and ALT or AST level > 2 times ULN)
 - » Persons with HIV infection
 - » Persons who are incarcerated

Adults 60 years and older without known risk factors for HBV may receive HBV vaccines

ACIP, Advisory Committee on Immunization Practices; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HD, hemodialysis; ULN, upper limit of normal.

Repurposed from Weng MK, Doshani M, Khan MA, et al. Universal hepatitis B vaccination in adults aged 19-59 years: updated recommendations of the Advisory Committee on Immunization Practices—United States, 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71(13):477-483. doi:10.15585/mmwr.mm7113a1

and were seronegative for hepatitis B surface antigen (HBsAg), antibody level to HBsAg (anti-HBs), antibody against hepatitis B core antigen, and HIV.^{17,18}

For the primary immunogenicity outcome in Study 1, the SPR at week 12 (8 weeks after second dose) in the Heplisav-B group

TABLE 3. Summary of Pivotal Clinical Trials for Heplisav-B^{17-19,a}

	Study 1	Study 2	Study 3
Date published	2012 ¹⁷	2013 ¹⁸	2018 ¹⁹
Participant population	Healthy adults aged 18-55 years; no history of HBV infection or immunization	Healthy adults aged 40-70 years; no history of HBV infection or immunization	Healthy adults aged 18-70 years; analysis also included populations shown in the literature to have immunogenic hyporesponsiveness to HBV vaccines (elderly, men, obese, smokers, those with diabetes)
Study design	Randomized, active controlled, subject and observer blinded, multicenter study	Randomized, active controlled, subject and observer blinded, multicenter study	Randomized, active controlled, observer blinded, multicenter study
Treatment arms, (n = participants completing study)	Heplisav-B administered as 2 doses at 0 and 4 weeks, with a third placebo dose at week 24 (n = 1746) Engerix-B administered at weeks 0, 4, and 24 (n = 588)	Heplisav-B administered as 2 doses at 0 and 4 weeks, with a third placebo dose at week 24 (n = 1123) Engerix-B administered at weeks 0, 4, and 24 (n = 359)	Heplisav-B administered as 2 doses at 0 and 4 weeks, with a third placebo dose at week 24 (n = 640) Engerix-B administered at weeks 0, 4, and 24 (n = 321)
Primary objective	Demonstrate noninferiority in SPRs at week 12 for Heplisav-B (8 weeks after second dose) to week 28 for Engerix-B (4 weeks after third dose)	Demonstrate noninferiority in SPRs of Heplisav-B at week 12 compared with Engerix-B at week 32 (8 weeks following the last dose)	Demonstrate noninferiority in SPRs of Heplisav-B to Engerix-B at week 28 and to evaluate overall safety in participants with diabetes
Secondary objectives	Compare SPR and geometric mean antibody concentrations at various time points, and safety outcomes Evaluate statistical superiority of the immune response if noninferiority is established between Heplisav-B and Engerix-B	Compare safety between Heplisav-B and Engerix-B Evaluate statistical superiority of the immune response if noninferiority is established between Heplisav-B and Engerix-B	Demonstrate noninferiority in the SPRs measured at week 24 for Heplisav-B compared with Engerix-B at week 28 in the total study population, including subgroup analyses Demonstrate that the SPR induced by Heplisav-B was statistically significantly higher than that induced by Engerix-B
Testing strategy	Designed to test for noninferiority; however, statistical superiority was declared based on prespecified criteria	Designed to test for noninferiority; however, statistical superiority was declared based on prespecified criteria	Designed to primarily test for noninferiority
Primary results summary	The difference in SPR between the Heplisav-B group and the Engerix-B group was greater than -10% (difference in SPRs, 13.9%; 95% CI, 10.6%-17.6%)	The SPR in the Heplisav-B group was noninferior and superior to that of the Engerix-B group (difference in SPRs, 19.5%; 95% CI, 14.7%-24.7%)	The SPR in the Heplisav-B group was noninferior and superior to that of the Engerix-B group (difference in SPRs, 24.9%; 95% CI, 19.3%-30.7%)

HBsAg, hepatitis B surface antigen; SPR, seroprotection rate.

^aSPR is defined as seroprotection rate: the percent of individuals who reach an antibody level to HBsAg of 10 mIU/mL or greater.

was 95.1%, as compared with the SPR of 81.1% at week 28 (4 weeks after third dose) for Engerix-B (Figure 2a). The difference in the SPRs was 13.9% (95% CI, 10.6%-17.6%), establishing noninferiority between Heplisav-B and Engerix-B as well as statistical superiority of Heplisav-B. Figure 2a highlights the greater number of participants achieving faster and higher SPRs as early as week 4 and continuing throughout week 28. The authors concluded that Heplisav-B demonstrated superior immunogenicity and earlier onset of protection in healthy adults compared with currently licensed aluminum-adjuncted vaccines (Figure 2a).¹⁷

In Study 2, the primary end point of SPR for the Heplisav-B group at week 12 was 90.0%, compared with the SPR at week 32 (8 weeks

after the last dose) in the Engerix-B group at 70.5% (SPR difference, 19.5%; 95% CI, 14.7%-24.7%). Based on the prespecified noninferiority criteria of -10%, Heplisav-B was declared to be both noninferior and superior to the SPR of Engerix-B. The ability of Heplisav-B to induce both earlier and higher levels of SPR compared with Engerix-B in this older adult population (Figure 2b) is particularly highlighted given the lower immune response and increasing HBV incidence in this age group, as discussed earlier (Figure 1).^{8,18}

In addition to the high SPRs induced by Heplisav-B in older adults known to have immunogenic hyporesponsiveness to HBV vaccines, as shown in Study 2, Study 3 (Figure 3) further focused on the immunogenic potential of Heplisav-B compared with Engerix-B in other

known hyporesponsive or higher-risk populations, particularly patients with diabetes. The primary end point of SPR at 28 weeks among participants with type 2 diabetes mellitus in the Heplisav-B group was 90.0%, and the SPR in the Engerix-B group was 65.1% (SPR difference, 24.9%; 95% CI, 19.3%-30.7%). This difference met the primary end point criteria for noninferiority, and the secondary end point of being statistically significantly higher.¹⁹

Safety

The safety profile of Heplisav-B has been demonstrated in 9597 participants across 5 clinical trials. The most common adverse effects (AEs) across both Heplisav-B and Engerix-B populations from Study 1 and Study 2 were local injection site pain and systemic reactions, such as fatigue, headache, and malaise. In Study 1 specifically, local injection site pain was measured after each injection for Heplisav-B and Engerix-B, and rates ranged from 34.8% to 38.5% and 20.2% to 33.6%, respectively. The ranges for fatigue, headache, and malaise were 13.8% to 17.4%, 12.8% to 16.9%, and 7.6% to 9.2% for Heplisav-B, respectively. The ranges for fatigue, headache, and malaise were 10.0% to 16.7%, 9.5% to 19.2%, and 6.4% to 8.9% for Engerix-B, respectively. Safety profiles for Study 2 are consistent with those of Study 1 and are available in the full prescribing information for Heplisav-B.³

Serious AEs

Participants were monitored for serious AEs in the pivotal trials for up to 13 months after receiving the first dose of vaccine. In the Heplisav-B group, 6.2% of participants reported serious AEs, compared with 5.3% in the Engerix-B group. Acute myocardial infarction (AMI) was reported in 0.25% (n = 14) of Heplisav-B recipients compared with 0.04% (n = 1) of Engerix-B recipients.³

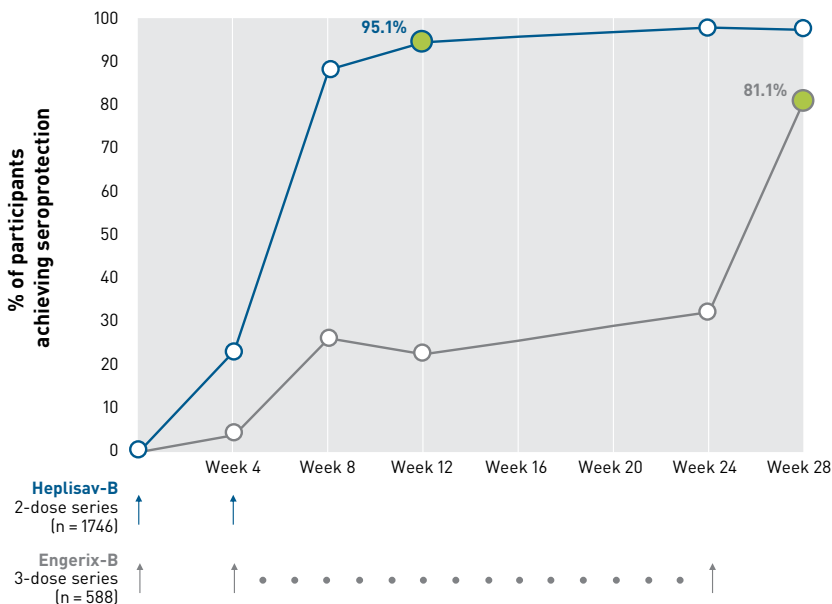
Real-world Postmarketing Safety

Data: AMI

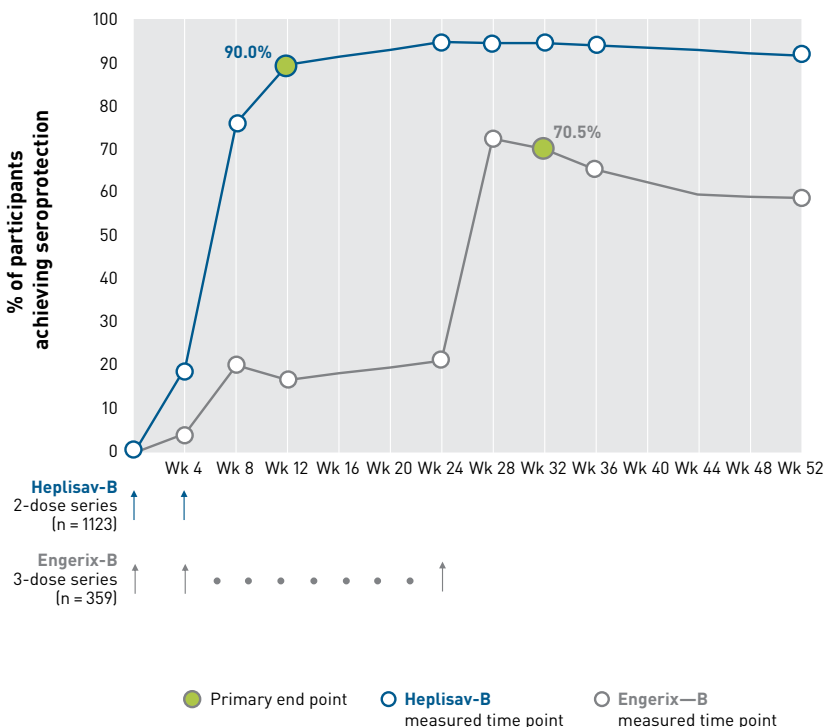
Recently published Heplisav-B postmarketing data from a large, prospective cohort noninferiority study revealed postvaccination occurrence

FIGURE 2. Percentage of Adults Achieving Protective Immunity in Study 1 and Study 2^{17,18,a}

A. Study 1: Seroprotection in Adults 18-55 Years of Age

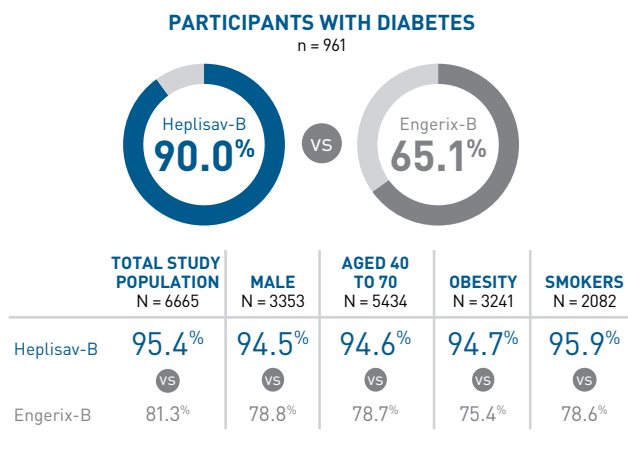


B. Study 2: Seroprotection in Adults 40-70 Years of Age



^aSeroprotection is defined as antibody level to hepatitis B surface antigen ≥ 10 mIU/mL.

FIGURE 3. Comparison of SPRs in Participants Who Received Heplisav-B (Week 24) vs Those Who Received Engerix-B (Week 28)¹⁹



SPR, seroprotection rate.

TABLE 4. American Medical Association CPT Codes for Heplisav-B²²

Drug and administration codes	Description
CPT drug code 90739 ^a	CpG-adjuvanted HBV vaccine (Heplisav-B), adult dosage, 2-dose or 4-dose schedule, for IM use
CPT administration code 90471	Immunization administration (includes percutaneous, intradermal, subcutaneous, or IM injection); 1 vaccine (single or combination vaccine/toxoid)

CpG, cytosine phosphoguanine; CPT, Current Procedural Terminology; HBV, hepatitis B virus; IM, intramuscular.
^aThis code went into effect on July 1, 2022, following a 6-month implementation period that began on January 1, 2022.

of AMI events with Heplisav-B (N = 31,183) and with Engerix-B (N = 38,442). This study reported 52 AMIs among recipients of Heplisav-B compared with 71 AMIs in the Engerix-B group, translating to AMI rates of 1.67 and 1.86 per 1000 person-years for Heplisav-B and Engerix-B, respectively. The absolute AMI rate difference was -0.19 (95% CI, -0.82 to 0.44) with an adjusted HR of 0.92 (1-sided 97.5% CI, ∞ to 1.32), which was below the predefined noninferiority margin (P < .001 for noninferiority). Authors concluded that Heplisav-B was not significantly associated with increased risk of AMI compared with Engerix-B.²⁰

Real-World Postmarketing Safety Data: Pregnancy

According to the ACIP, clinical studies of Heplisav-B vaccine in pregnant women are insufficient to inform vaccine-associated risks in this population.² In 2022, safety and immunogenicity of

Heplisav-B among women who became pregnant following vaccine administration were evaluated in a postmarketing study published by Kushner et al. These authors identified and compared SPRs between treatment arms of participants in the Heplisav-B clinical trials who had documented pregnancy during vaccine trial participation and during the follow-up period. Among participants with documented SPR, 97.2% (95% CI, 85.5%-99.9%) of those in the Heplisav-B arm (n = 40) were seroprotected (anti-HBs ≥ 10 mIU/mL), as were 66.7% (95% CI, 41.0%-86.7%) of those in the Engerix-B arm (n = 19). These limited data suggest that Heplisav-B is immunogenic in women who become pregnant after vaccination, and pregnancy outcomes appear to be similar to those of women who received Engerix-B prior to pregnancy.²¹

Billing and Coding

Heplisav-B is supplied as a 0.5 mL-dose prefilled syringe (NDC 43528-003-01) sold in a package of 5 single-dose prefilled syringes (NDC 43528-003-05). Each 0.5-mL dose is formulated to contain 20 mcg of HBsAg and 3000 mcg of CpG 1018 adjuvant.³ On March 7, 2022, the American Medical Association released an updated vaccine Current Procedural Terminology (CPT) drug code for Heplisav-B, as shown in Table 4.²²

**Considerations for Improved HBV Vaccine Practices
 Vaccination Series Completion Rates**

Despite ACIP recommendations, 2018 data show that about 70% of US adults 19 years or older are not protected against HBV. Only 40.3% of those aged between 19 and 49 years and 19.1% of those 50 years or older are vaccinated against HBV.² Vaccination rates are low, and multiple studies have reported suboptimal series completion rates among adults, ranging from 22% to 51% for 3-dose adult HBV vaccines, depending on the age group studied.²³⁻²⁶ Protection against HBV requires administration of adequate numbers of properly timed vaccine doses.³⁻⁶ Incomplete vaccine regimens place individuals at risk for HBV infection. With a vaccination schedule of only 2 rather than 3 doses, evidence suggests that individuals who initiate vaccination with Heplisav-B have a greater likelihood of completing the full vaccination regimen compared with those who initiate vaccination with a 3-dose product.²⁵

A large cohort study within an integrated health care system assessed adherence to the HBV vaccine schedule among individuals who initiated vaccination with Heplisav-B (n = 4727) compared with those who initiated vaccination with Engerix-B (n = 6161). The primary adherence outcome for the study was vaccination series completion rate based on the recommended vaccine schedule plus 3 months (4 months after the date of the first dose of Heplisav-B and 9 months after the date of the first dose of Engerix-B); the secondary adherence outcome was vaccination series completion rate within 1 year of receiving the first dose. Individuals who initiated the 2-dose

Heplisav-B regimen were significantly more likely to complete the vaccine schedule compared with those receiving the 3-dose Engerix-B regimen (44.7% vs 26.1%, respectively). Within 1 year of receiving the first dose, 60.5% of individuals vaccinated with Heplisav-B completed the full series compared with 32.3% of those vaccinated with Engerix-B, representing a 77% higher likelihood of completing the series with Heplisav-B vaccination (adjusted relative risk, 1.77; 95% CI, 1.68-1.87). See **Figure 4**.²⁵

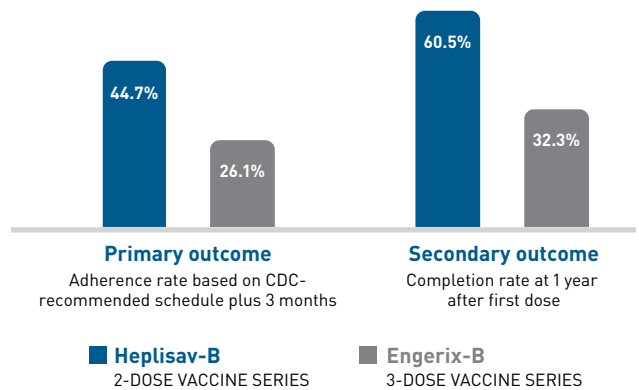
LaMori et al (2022) conducted a retrospective study analyzing HBV vaccination rates among a large (N = 356,828) representative sample of US adults. This study included data on hepatitis A and HBV vaccinations derived from an administrative claims database spanning more than 10 years (from January 1, 2010, to June 30, 2020). The investigators examined data to determine vaccination adherence (receipt of second or third dose within specified assessment period per labeled dose schedule) and completion rates (receipt of all doses assessed at 6, 12, 18, and 24 months) for each of the 4 vaccines included in the study. Across all 4 studied vaccines, results revealed low vaccination adherence (14%-32%) and low completion rates (28%-45% at 24 months). Among individuals who received the 2-dose vaccine series, Heplisav-B, adherence rates were more than 2-fold higher (32.2%) than in individuals who received traditional 3-dose (Engerix-B and Recombivax-HB) HBV vaccines (14.3%). This difference in adherence rates was consistent across all age groups.²⁷

Supplemental data further highlighted vaccination adherence and completion (24 months) rates for hepatitis A, hepatitis B (3-dose series), and combination hepatitis A and B vaccines (3-dose series) among special at-risk or high-risk populations with chronic comorbidities (diabetes with and without chronic complications, mild to severe liver disease, and renal disease). These data did not include an analysis of Heplisav-B. The overall reported adherence was 14.3% (range, 13.8%-18.3%) for the 3-dose HBV vaccines and 15.3% (range, 9.9%-16.1%) for the combined hepatitis A and B vaccines (3-dose vaccines). Overall reported completion rates were 37.3% (range, 40.7%-45.5%) for the 3-dose HBV vaccines and 33.8% (range, 25%-32.3%) for the combined hepatitis A and B vaccines. The adherence and completion rates reported for 2-dose series hepatitis A vaccines were as follows: adherence rate: 27% overall (range, 27%-34.4%); completion rate: 28.4% (range, 27.8%-35.7%).²⁸

Interchangeability of HBV Vaccines

Given the availability of 4 HBV vaccines (excluding bivalent vaccines), the ACIP has provided guidance on the interchangeability of HBV vaccines. The ACIP recommends completing a vaccine series using the same product when feasible, and if a dosing regimen consists of 2 different vaccine products it should consist of a total of 3 doses to be considered completed. For example, individuals who start a vaccination series with a 3-dose vaccine can complete this series

FIGURE 4. Primary and Secondary Vaccination Completion Rates With 2- and 3-Dose HBV Vaccines²⁵



HBV, hepatitis B virus.

with 2 additional doses of Heplisav-B.^{3,5,7,14} **Figure 5** highlights the approved dosing schedule for Heplisav-B as compared with traditional 3-dose aluminum-adsjuvanted vaccines and compares various vaccination scenarios to ensure vaccine series completion based on ACIP guidance.^{3,5,7,14}

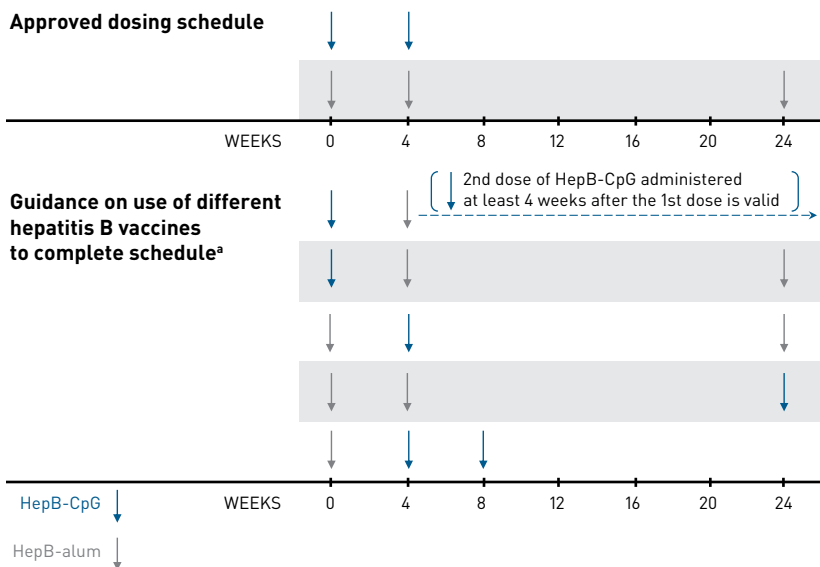
Interchangeability can remove patient barriers to becoming fully seroprotected from HBV when the manufacturer of the previously administered vaccine is unknown, or when vaccine from the same manufacturer is unavailable, further contributing to attainment of 2030 goals as outlined by the HHS. **Figure 5** highlights various scenarios in which Heplisav-B can be interchanged with a traditional aluminum-based vaccine (Engerix-B, Recombivax-HB, or PreHevbrio).^{3,5,7,14}

Special Patient Populations

Health Care Personnel

Health care personnel (HCP) are included in special populations known to be at increased risk of acquiring HBV infection due to occupational exposure. CDC data from 2018 show overall vaccination coverage of 67.2% among HCP. Although rates of vaccination coverage are higher in the HCP population than among adults in the general public (30%),²⁹ HCP remain at occupational risk until the time of completion of their vaccination series and development of HBV seroprotection. Evolving literature suggests that HCP who initiate vaccination with Heplisav-B would benefit from faster time to seroprotection than those who initiate vaccination with a 3-dose vaccine product.³⁰

Stevenson et al (2021) published results from a model developed to assess the health and economic impact over a 1-year period when Heplisav-B or Engerix-B was administered to HCP newly entering a health care system. Primary outcomes of the study included the number of additional HCP protected against HBV and the cost of

FIGURE 5. ACIP Vaccine Interchangeability and Dosing Schedule^{3,5,7,14}

ACIP, Advisory Committee on Immunization Practices; HBV, hepatitis B virus; HepB-alum, aluminum-adjuvanted HBV vaccines; HepB-CpG, Heplisav-B.

^aData on the safety and immunogenicity effects when Heplisav-B is interchanged with HBV vaccines from other manufacturers are limited. The CDC's ACIP guidance for interchangeability indicates that, when feasible, the same manufacturer's vaccines should be used to complete an HBV series. Heplisav-B vaccine series consist of 2 doses administered 4 weeks apart, while HepB-alum vaccine series consist of 3 doses administered at weeks 0, 4, and 24. A dosing regimen consisting of 2 different vaccine products should consist of a total of 3 doses in the possible combinations shown above. Adhere to minimum windows: 4 weeks between doses 1 and 2, 8 weeks between doses 2 and 3, and 16 weeks between doses 1 and 3. Doses administered at less than the minimal interval should be repeated. However, a series containing 2 doses of Heplisav-B administered at least 4 weeks apart is valid, even if the patient received a single earlier dose from another manufacturer.

potential postexposure prophylaxis in this high-risk population. The model predicted that Heplisav-B would protect an additional 77% of HCP compared with Engerix-B after 2 doses, and an additional 24% upon completion of all 3 doses of Engerix-B. Projected health care spending for prophylaxis for HCP initiating Heplisav-B vs Engerix-B was approximately \$63,000 compared with \$100,000, for a cost savings of about 37%. This study showed that Heplisav-B has the potential to provide faster and more substantial immunity among HCP, as well as among other high-risk special populations (Table 2), along with cost savings for institutions/employers.³⁰

HIV

Special at-risk or high-risk populations (Table 2) such as PLWH show particularly poor immune response to HBV vaccination.^{2,15} Globally, it is estimated that about 5% to 20% of PLWH are co-infected with chronic HBV.³¹ Co-infected patients are at increased risk for cirrhosis, HCC, end-stage liver disease, and other liver-related morbidities and mortality.³² Specifically, co-infected patients have a 4-fold higher risk of HCC, a 1.5-fold increase in all-cause mortality, and a 3-fold

increase in liver-related mortality.³³ As a result, joint HIV guidelines developed by the National Institutes of Health, the CDC, the HIV Medicine Association, and the Infectious Diseases Society of America highly recommend primary HBV vaccination for all non-HBV-immune patients co-infected with HIV. This is consistent with the universal HBV vaccination recommendation from the ACIP for adults aged 19 to 59 years, and with HIV being a risk factor that supports vaccination in those 60 years and older (Table 2).² For vaccine nonresponders, these guidelines recommend an alternative vaccine dose and duration consisting of a 4-dose series using double doses of Engerix-B or Recombivax-HB at 0, 1, 2, and 6 months.³² This strategy, along with variation in high-dose regimens and alternative dosing schedules, has yielded low SPRs in published studies—between 17% and 89%.³⁴ This range in HIV-infected patients is attributed to variable immune response associated with dysfunction of CD4 T cells, specific B-cell defects, and hyperimmune activation status and genes within the human leukocyte antigen complex.³⁵ If a 2-dose vaccine is preferred, Heplisav-B can be administered in PLWH. However, this recommendation is based on expert opinion from the joint HIV guidelines because of a gap in robust literature on Heplisav-B for PLWH.³²

The authors of a retrospective chart review identified 67 HIV-positive adults with a documented history of nonresponse to prior 3-dose aluminum-based vaccines who subsequently received 2 single doses of Heplisav-B. The primary efficacy outcome was the percentage of PLWH who developed seroprotection 2 months post Heplisav-B vaccination. This study found that 87% of patients developed seroprotection (anti-HBs positive at levels > 10 mIU/mL), highlighting the immunogenicity of Heplisav-B in PLWH who did not respond to previous HBV vaccination series. It is important to note that a subgroup analysis indicated that those with detectable HIV RNA and low CD4 counts were 85% and 96% less likely to develop seroprotection, respectively.³⁶

In 2021, Schnittman et al published a retrospective cohort study of 64 adults from a quaternary care center HIV clinic without HBV seroprotection who subsequently received standard dosing of Heplisav-B. The primary outcome was SPR at any point after the first Heplisav-B vaccination (median time, 13 weeks after vaccination). Overall SPRs (antibody titer levels ≥ 10 mIU/mL) were 81% (95% CI, 72%-91%), with 63% (95% CI, 51%-74%) of participants achieving

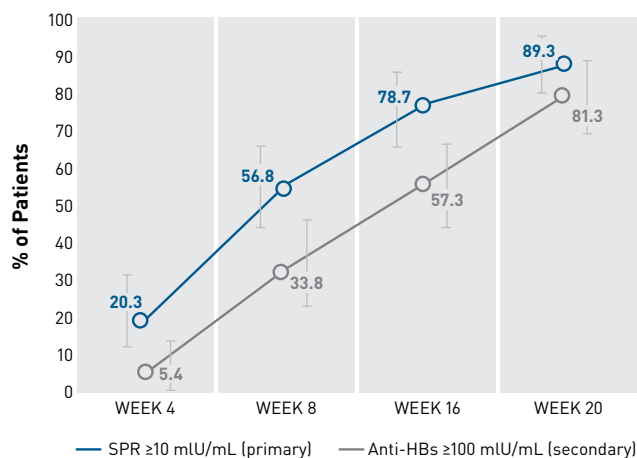
antibody titer levels ≥ 100 mIU/mL³⁷; notably, higher antibody titer levels may be associated with duration of protection, such that the higher the antibody titer level, the longer the anticipated duration of protection.³⁵ Subgroup analysis highlighting persons considered nonresponders to prior primary HBV vaccination revealed an SPR of 84% (95% CI, 72%-96%). Furthermore, study authors emphasized that higher baseline levels (≥ 350 cells/mm³) of CD4 cell counts predict higher SPRs, suggesting that PLWH who are treated with antiretroviral therapy could develop SPRs similar to those of persons who do not have HIV.³⁷ A randomized controlled trial including PLWH (NCT04193189) is currently investigating the use of Heplisav-B compared with Engerix-B in PLWH who are naive to HBV vaccination, as well as in prior nonresponders. This open-label study is evaluating whether Heplisav-B is noninferior to the standard dose of Engerix-B as well as if Heplisav-B (given as a 3-dose series) achieves superior seroprotection rates compared with the standard dose of Engerix-B. This study is set to be completed by June 1, 2024.³⁸

Hemodialysis

Information from the US Renal Data System shows that more than 550,000 patients with chronic kidney disease (CKD) were on long-term HD in the United States at the end of 2018.³⁹ Patients receiving HD are at increased risk of HBV exposure, have lower seroconversion rates (44.3%), and have more rapidly declining antibody titers than individuals not receiving HD.^{40,41} As such, adults receiving HD are vaccinated with higher doses of Recombivax-HB (40-mcg vs 10-mcg single dose) or Engerix-B (40-mcg vs 20-mcg single dose) at months 0, 1, and 6 (Recombivax-HB) and 0, 1, 2, and 6 (Engerix-B).⁴⁵ Heplisav-B does not provide specific FDA-labeled dosing for patients undergoing HD. However, evidence from 2013 indicates that 3 single doses of Heplisav-B showed higher, earlier, and more durable seroprotection in patients with CKD compared with 4 double doses of Engerix-B.⁴¹ Rapid and increased seroprotection is particularly crucial for patients undergoing HD, and new evidence is emerging to inform use of Heplisav-B in this population.

In an open-label, single-arm, multicenter trial, 4 single 20-mcg doses of Heplisav-B were administered at weeks 0, 4, 8, and 16 to the per-protocol population of 75 non-HBV-immune adults initiating or undergoing HD, with no active comparator vaccine. The primary objective was to evaluate safety and immunogenicity induced by Heplisav-B at week 20 as measured by SPR. Results show that Heplisav-B was able to seroprotect approximately 89% of patients receiving HD, and it induced increasing SPRs up until week 20. The secondary objective was to evaluate the immunogenicity induced by Heplisav-B at week 20 as measured by the percentage of patients achieving antibody titer levels ≥ 100 mIU/mL (Figure 6).¹⁶ Rapid achievement of seroprotection for patients undergoing HD can be important, given increased HBV exposure risk in this population.¹⁶

FIGURE 6. Percent of Hemodialysis Patients Above Anti-HBs Thresholds^{16,a}



Anti-HBs, antibodies to hepatitis B virus surface antigen; SPR, seroprotection rate.
*Study injections were administered at weeks 0, 4, 8, and 16.

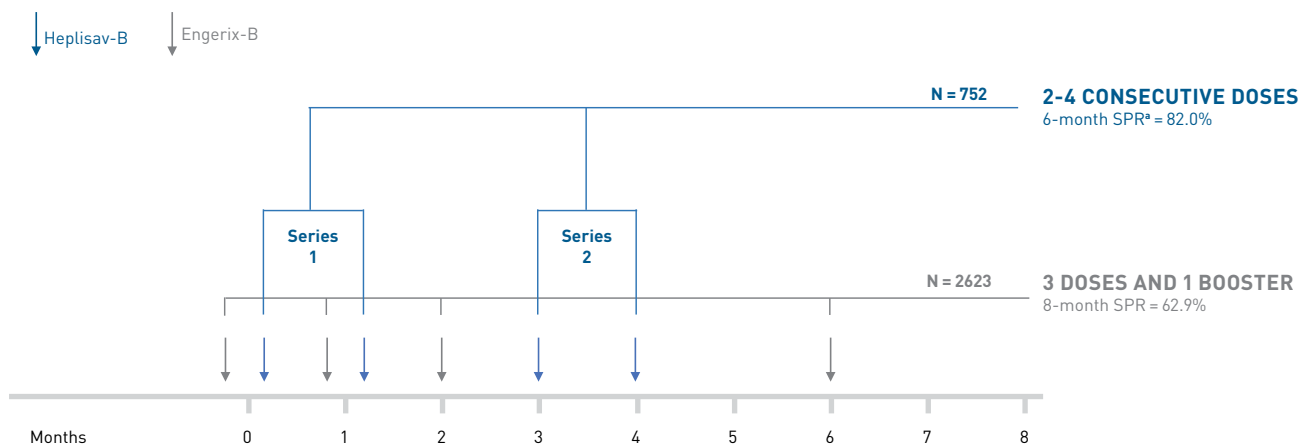
Manley et al (2022) conducted a retrospective cohort analysis of 3949 HBV vaccine-naïve patients on HD who received either standard dosing (2 single doses) of Heplisav-B or HD dosing (4 double doses) of Engerix-B. Patients who completed 1 round of vaccination (series 1) but failed to reach seroprotection (anti-HBsAg > 10 mIU/mL) at least 2 months after the last vaccine (primary end point) received a subsequent round (series 2) of Heplisav-B or Engerix-B. Any patient who initially developed but later lost seroprotection received a single dose of Engerix-B or Heplisav-B as a booster. Patients in series 1 who received 4 double doses of Engerix-B had higher SPRs than those receiving the standard 2 doses of Heplisav-B. No difference in SPRs was noted between groups receiving subsequent vaccine series and groups receiving booster doses.⁴²

Post hoc analysis of data from patients who received up to 4 single doses of Heplisav-B (2 doses in series 1, followed by 2 additional doses in series 2) revealed higher SPRs than for patients who received 4 increased doses (40 mcg) of Engerix-B (82.0% vs 62.9%; $P < .0001$). Due to the shortened dosing schedule of Heplisav-B, seroprotection was achieved faster in this group than in the Engerix-B group (6 months vs 8 months), highlighting the potential benefit of better and faster immunogenicity with Heplisav-B for patients on HD (Figure 7).⁴²

Health Care Costs

A recent analysis of 3 US payer databases revealed that patients with HBV infection had a higher comorbidity burden, greater health care utilization, and a heavier cost burden when compared with non-HBV matched controls.⁴³ Although an economic evaluation found that universal adult vaccination against HBV would avert nearly

FIGURE 7. Post Hoc Analysis SPRs of Heplisav-B vs Engerix-B⁴²



SPR, seroprotection rate.

**P* < .0001 compared with Engerix-B’s SPR at 8 months.

TABLE 5. Cost-Effectiveness Model Results (2020 USD) for Heplisav-B vs Engerix-B^{45,46}

Special at-risk or high-risk populations	ICER ^a
Diabetes	Dominant, ⁴⁶ \$47,744 ⁴⁵
CKD	Dominant ^{45,46}
Older adults	Dominant ⁴⁶
Obesity	Dominant ⁴⁶
Nonresponders	\$22,470 ⁴⁶
HIV	Dominant ⁴⁶
PWID	Dominant ⁴⁶
Health care personnel	\$36,829 ⁴⁵
Travelers	\$11,287 ⁴⁵
CLD	\$45,384 ⁴⁵
ESRD	Dominant ⁴⁵

CKD, chronic kidney disease; CLD, chronic liver disease; ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio; PWID, people who inject drugs; QALY, quality-adjusted life-year; USD, US dollars.

^aDominant ICER: Heplisav-B was cost-saving and provided increased benefits or QALYs compared with Engerix-B.

In a CDC-sponsored study, Rosenthal et al (2020) assessed the cost utility of providing 2-dose Heplisav-B vs 3-dose Engerix-B to the following 7 special populations: nonresponders to the 3-dose vaccine; older adults; persons who inject drugs (PWID); PLWH; and persons with diabetes, obesity, or CKD. Study authors found that use of Heplisav-B resulted in dominant (lower costs and higher quality-adjusted life-years [QALYs]) incremental cost-effectiveness ratios (ICERs) for all modeled populations except nonresponders. Although not dominant for nonresponders, Heplisav-B was still identified as being cost-effective for this group. In addition to yielding better health outcomes in all special populations, the 2-dose regimen of Heplisav-B particularly benefited populations with increased incidence of HBV infection and reduced adherence, such as PWID and PLWH. Study authors also found that SPRs attained by Heplisav-B led to fewer HBV infections (37.5%-59.8% averted infections), sequelae, and HBV-related deaths (36.3%-71.4% averted deaths) than were reported for those receiving Engerix-B across all populations. Authors of this study noted that although the analysis considers only Engerix-B for comparison, these results are generalizable to other 3-dose HBV vaccines with similar costs and efficacies.⁴⁶

Similarly, a 2021 US study examined cost-effectiveness of Heplisav-B vs Engerix-B using an established Markov model and ICERs in special adult populations with diabetes, chronic liver or kidney disease, and end-stage renal disease (ESRD); HCP; travelers to countries with endemic HBV; and a public health population, defined as government-funded population sites with a high percentage of patients receiving HBV vaccinations (Table 5).^{45,46} This analysis did not capture indirect costs—only differences in lifetime spending

one-fourth of acute HBV infections and related deaths compared with the previous strategy, the fact remains that the burden of HBV infection is more pronounced in at-risk and high-risk populations (Table 2).^{2,44} These special populations benefit greatly from earlier and higher immune protection. Multiple papers have reported on the economic advantages of the 2-dose vaccine (Heplisav-B) compared with the 3-dose vaccine (Engerix-B) for adults at high risk for HBV infection.^{45,46}

and survival from the perspective of a US managed care payer. Heplisav-B showed favorable cost-effectiveness for all studied populations. For those with CKD and ESRD, use of Heplisav-B resulted in dominant ICERs (Table 5).^{45,46}

This study also reported an ICER value of \$47,744/QALY (2020 US dollars [USD]) for patients with diabetes. An age-based subpopulation analysis conducted for patients with diabetes revealed that Heplisav-B was more cost-effective compared with Engerix-B for patients aged 20 to 59 years (ICER \$9147/QALY [2020 USD]) but was not more cost-effective for patients aged 60 to 70 years (ICER \$290,171/QALY [2020 USD]). This study reported ICER values for the following additional at-risk groups: patients with chronic liver disease (ICER \$45,384/QALY [2020 USD]), HCP (ICER \$36,829/QALY [2020 USD]), and travelers (ICER \$11,287/QALY [2020 USD]).⁴⁵

In addition to cost-utility and cost-effectiveness studies conducted in the high-risk groups described above, Oster et al (2022) published a decision analytic model conducted in the general population. This study compared expected levels of adherence, overall seroprotection, and total costs of HBV vaccination at 1 year among a hypothetical cohort of 1 million previously unvaccinated adults receiving Heplisav-B or Engerix-B.⁴⁷ At the time of study analysis, the private sector acquisition costs for Heplisav-B (\$126.50/dose) and Engerix-B (\$61.86/dose) were based on the August 1, 2021, update to the CDC's publicly available Vaccine Price List.⁴⁸ Study authors found that use of a 2-dose HBV vaccine (Heplisav-B) compared with a 3-dose HBV vaccine (Engerix-B) would increase the number of adults fully seroprotected at 1 year by 275,000 per 1 million persons. The magnitude of this difference was large enough that the cost per person seroprotected with Heplisav-B was 15% lower than with Engerix-B, despite the higher cost per dose of Heplisav-B.⁴⁷

Summary

HBV is a highly infectious disease that remains a public health burden in the United States. The estimated number of persons in the United States living with chronic HBV ranges from 730,000 to 2,400,000 persons, including both US-born and foreign-born individuals.⁹⁻¹² In 2019, 20,700 new acute cases were estimated, with almost 80% of these acute cases to occur among persons aged 30 to 59 years.⁸ The persistence in incidence of new acute HBV cases has elucidated an unmet need, prompting public health organizations such as HHS to establish the Viral Hepatitis National Strategic Plan, with the goal of eliminating HBV infection in the United States by the year 2030.

HBV infection is preventable through vaccination—a major focus toward reaching 2030 goals. Heplisav-B was approved by the FDA in November 2017 for use in adults 18 years and older. The ACIP included Heplisav-B in its list of recommended adult HBV vaccines in February 2018. The dosing schedule includes fewer intramuscular injections than are required for 3-dose aluminum-adjuvanted

HBV vaccines. Use of Heplisav-B led to faster and higher rates of seroprotection than were seen with the use of Engerix-B in pivotal trials. Heplisav-B is playing an important role in helping to reach 2030 public health goals through its demonstrated immunogenicity among both the general public and high-risk special populations. Additionally, Heplisav-B provides a flexible and efficient option in prevention of HBV, as well as cost savings that benefit the health care system and, ultimately, patients. ■

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