Cost-Effectiveness of Hepatitis B Testing and Vaccination of Adults Seeking Care for Sexually Transmitted Infections

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Abstract

**Background.**—The estimated number of people living with hepatitis B virus (HBV) infection acquired through sexual transmission was 103,000 in 2018, with an estimated incidence of 8,300 new cases per year. While hepatitis B (HepB) vaccination is recommended by the Advisory Committee for Immunization Practices for persons seeking evaluation and treatment for sexually transmitted infections (STI), pre-vaccination testing is not yet recommended. Screening may link persons with chronic hepatitis B (CHB) to care and reduce unnecessary vaccination.

**Methods.**—We used a Markov model to calculate the health impact, and cost-effectiveness of one-time HBV testing combined with the first dose of the hepatitis B vaccine for adults seeking care for STI. We ran a lifetime, societal perspective analysis for a hypothetical population of 100,000 ages 18–69 years. The disease progression estimates were taken from recent cohort studies and meta-analyses. In the US, an intervention that costs less than $100,000 per quality adjusted life year (QALY) is generally considered cost-effective. The strategies that were compared were: 1) vaccination without HBV screening, 2) vaccination and HBsAg screening, 3) vaccination and screening with HBsAg and anti-HBs, and 4) vaccination and screening with HBsAg, anti-HBs and anti-HBc. Data were obtained from Centers for Medicare and Medicaid services reimbursement, the CDC vaccine price list, and additional cost-effectiveness literature.

**Results.**—Compared with current recommendations, the addition of one-time HBV testing is cost saving and would prevent an additional 138 cases of cirrhosis, 47 cases of decompensated cirrhosis, 90 cases of hepatocellular carcinoma, 33 liver transplants, and 163 HBV-related deaths,

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and gain 2185 QALYs, per 100,000 adults screened. Screening with the 3-tests panel would save $41.6-$42.7 million/100,000 adults tested compared with $41.5-$42.5 million for the 2-tests panel and $40.2-$40.3 million for HBsAg alone.

**Conclusions.**—One-time HBV pre-vaccination testing in addition to HepB vaccination for unvaccinated adults seeking care for STI would save lives, prevent new infections and unnecessary vaccination, and is cost saving.

**Summary**

HBV testing of adults seeking evaluation and treatment of STI who are unvaccinated and do not know their HBV infection status is cost saving compared with the current recommendation for vaccination alone.

**Keywords**

sexually transmitted diseases; chronic hepatitis B; antiviral treatment; hepatitis B vaccination; cost-saving

**Introduction**

Hepatitis B virus (HBV) can be efficiently transmitted by sexually active persons, and sexual transmission is a common route of HBV infection in low endemic countries. The risks of HBV transmission between persons with acute or chronic hepatitis B and an unprotected or unvaccinated partner is as high as 40% through sexual contact. The Centers for Disease Control and Prevention (CDC) estimated that from 2013 to 2018, an estimated 47,000 or 38% of acute HBV infections in the United States were attributable to sexual transmission. The estimated prevalence of sexually transmitted HBV infections in the United States in 2018 was 103,000, with an estimated incidence of 8,300 new cases.

To decrease the risk of sexually transmitted HBV infection, the CDC Advisory Committee for Immunization Practices (ACIP) recommends hepatitis B (HepB) vaccination for persons seeking evaluation or treatment for STI who reported not completing a HepB vaccine series. Although there are many hepatitis B cost-effectiveness analyses, very few examine vaccination in high-risk populations, and very few examine pre-vaccination screening. A study published in 2008 suggested universal hepatitis B vaccination of persons at STI clinics who reported no prior vaccination would be cost-saving to society. However, that was based on a cohort aged 25 years with only 10% self reported prior vaccination or infection, and based on the much lower prior federal contract price for the 3 dose HepB vaccine of $24 per dose. HBV pre-vaccination testing is not currently recommended in the absence of other risk factors for persons seeking evaluation and treatment for STI. One-time HBV testing would provide a diagnosis for those living with chronic hepatitis B (CHB) enabling linkage to care and treatment. Testing could also save vaccine costs by identifying persons with natural immunity or current infection who would not require second or third doses of the vaccine, and identifying people with vaccine induced immunity who might not need further doses.

The purpose of this study was to assess the cost-effectiveness of one-time pre-vaccination HBV testing of adults seeking evaluation and treatment for STI in any clinical setting, who
reported no prior hepatitis B vaccination and do not know their HBV infection status. We compared screening strategies using the hepatitis B surface antigen (HBsAg) test for CHB or a 2-tests panel (HBsAg and hepatitis surface antibody [anti-HBs]) for CHB and immunity or a 3-tests panel (HBsAg, hepatitis B core antibody [anti-HBc] and anti-HBs) for CHB, prior infection, and immunity, and CHB treatment and HepB vaccination compared with HepB vaccination alone.

**Methodology**

Because the impact of HepB vaccination and infection may take place over many years or decades, we used a Markov model (Appendix Figure 1) to simulate progression through a discrete series of health states in response to alternative screening, treatment, and vaccination policies. Markov models are appropriate for simulating people moving from health state to health state over time, such as how persons with inactive or latent chronic hepatitis B infection can reactivate to cause active hepatitis with liver inflammation. The model starts with a cohort of the eligible population distributed across health states of susceptible, immune (from vaccination or prior infection), inactive CHB, active CHB, and cirrhosis. Events and outcomes measured in the model included CHB screening, monitoring and treatment costs, quality adjusted life years (QALYs), and clinical endpoints. This mathematical model has been shown to closely match HBV natural history, cirrhosis incidence, and survival. We use age proportions based on the age distribution seen at STI clinics is shown in Table 1. The estimated HBsAg prevalence in the STI population in the United States was 4.2%. We assumed, as with the general population, 67% of adults with CHB are not aware of their infection. Results were presented as weighted averages over age and gender where 61.9% of the risk group were male. The proportion with reported prior HepB vaccination ranged across age-groups from 15.9% to 91.3%, (Table 1). The age-group-specific annual incidence of developing acute HBV infection ranged between 0.33% and 1.0%. We ran a lifetime analysis to compute results for a hypothetical population of 100,000 men and women ages 18–69 years eligible to be screened due to seeking care for an STI.

The following scenarios (Appendix Figure 2) were assessed:

1. **Vaccination without HBV screening (Current practice):** Offer HepB vaccination (2 dose or 3 dose vaccines) if the adult reported no prior vaccination. No HBV testing.

2. **HepB vaccination and HBsAg screening:** Offer HepB vaccination (2 dose or 3 dose vaccines) if the adult reported no prior vaccination. If the HBsAg test is positive, no further vaccine doses are given, and the patient is connected to CHB care and treatment.

3. **HepB vaccination and screening with HBsAg and anti-HBs:** Offer HepB vaccination if the adult reported no prior vaccination. If the tests are positive for HBsAg or anti-HBs ≥10 mIU/mL, no further vaccine doses are given. An adult testing positive for HBsAg is connected to CHB care and treatment.
4. **HepB vaccination and screening with HBsAg, anti-HBs and anti-HBc**: Offer HepB vaccination if the adult reported no prior vaccination. If the tests are positive for HBsAg or anti-HBc or anti-HBs >10 mIU/mL, no further vaccine doses are given. An adult testing positive for HBsAg is connected to CHB care and treatment.

In sensitivity analyses, we explored comparisons with two additional strategies with no HepB vaccination for comparison:

- **a.** No HepB vaccination or HBV screening
- **b.** HBV screening, and CHB care and treatment. No HepB vaccination.

### Vaccination

HepB vaccination was modeled including both the dollar costs of vaccination and the productivity costs for patient time. We modeled a vaccine-specific visit at the physician’s office or pharmacy for subsequent doses. The proportion of patients receiving subsequent doses of HepB vaccine in a pharmacy setting was 30%\(^{12}\). Age-group-specific seroprotection rates for the three dose HepB vaccines (Twinrix\(^\circledR\) or Engerix-B\(^\circledR\) or Recombinvax HB\(^\circledR\)) and the two dose vaccine (Heplisav-B\(^\circledR\)) by age are shown in Table 1. Based on the reported HepB vaccination coverage among individuals seeking care for STI who reported no prior vaccination, 74% received the first HepB vaccine dose\(^{4}\). Among persons who received the first dose, 61% received a second dose and 32% received a third dose\(^{13}\) as shown in Table 1. We assumed 70% of the adults age 19–49 years and 80.8% of adults age 50 years and older were aware whether they have been vaccinated\(^{14}\). See additional details on vaccination rates in the appendix (Appendix Table 1).

### Disease progression and treatment related estimates:

Disease transition estimates for acute infection are shown in Table 1 and were obtained from Chahal et al.\(^{15}\) and Hutton et al.\(^{16}\). The natural history of CHB and disease progression rates were derived from recent cohort studies and meta-analyses mainly from North America for HBV mono-infected patients (Appendix Tables 2–3)\(^{17–27}\). A 50% reduction in disease progression estimates was applied for female patients, based on recent sex-specific studies\(^{28–30}\). Treatment effectiveness estimates were expressed as reductions in disease progression risks for treatment-naïve patients (Appendix Table 4)\(^{31–36S}\). We assumed effective antiviral suppression would reduce liver cancer risks in cirrhotic and non-cirrhotic patients by 50% and 70%, respectively, compared with natural history\(^{33S, 34S, 36S}\). Disease progression between health states, conditional on treatment, age (where available) and gender was simulated in one-year cycles. Causes of death that were not related to CHB were included in the model, based on age-specific mortality rates from life tables in the National Statistics Report\(^{37S}\).

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\(^{1}\)Assumes that anti-HBs ≥10 mIU/mL alone indicates a complete HepB vaccine series if records are not available; and that persons without knowledge or records of prior vaccination with anti-HBs <10 mIU/mL, might have been fully vaccinated in the past, but have waning antibody and not necessarily waning immunity.

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**Costs and utilities:**

The costs of HBsAg ($10.33), anti-HBc ($10.74), anti-HBs ($12.05) tests, and a three hepatitis B tests package ($28.27) were based on Medicare reimbursement. For our base case analysis, we used the private sector costs for the three dose monovalent HepB vaccines (Engerix-B® and Recombivax-HB®) at $61.86-$61.22 per dose, the three dose combination hepatitis A and hepatitis B vaccine (Twinrix®) at $112.35 per dose, and the two dose monovalent vaccine (Heplisav-B®) at $121.25 per dose. The lower CDC federal contract prices for the vaccines were also used in the sensitivity analysis. The analysis included administration costs of $25.84 at the providers’ office or clinic and $17.50 at the pharmacy. Although the lowest price for antiviral drugs is generic tenofovir disoproxil fumarate at $325 per year [RedBook 2021], we used an annual antiviral drug cost of $502 with the assumption that 60% of the patients will be dispensed generic tenofovir disoproxil fumarate and 40% generic entecavir. We obtained other medical management costs for CHB, cirrhosis, decompensated cirrhosis, and liver cancer from Liu et al. Medical management costs were adjusted for inflation using the personal consumption expenditure index to reflect 2021 US dollars. For patients diagnosed with CHB and linked to care, we assumed they will receive initial baseline tests (HBeAg, CBC, CMP, HBV DNA), and twice yearly clinic visits with ALT blood tests, yearly HBV DNA viral load tests, and that eligible patients (50%) would receive additional hepatocellular carcinoma (HCC) surveillance consisting of liver ultrasound and alpha fetoprotein (AFP) every 6 months as recommended by the American Association for the Study of Liver Diseases (AASLD) (Table 1). Costs of testing and clinic visits were based on Medicare reimbursement rates (Table 1). We assumed patients who achieved HBsAg loss would continue to incur annual costs for long-term CHB monitoring. All costs and quality adjusted life years (QALYs) were discounted at a rate of 3% per year. The analysis was performed from the societal perspective. We used EQ5D utility assessments calculated by Woo et al. based on a Canadian CHB patient sample and included age adjustments, and for the immune and susceptible health states we used Chahal et al. estimates.

In our analysis, we evaluated the costs and QALYs for each testing and vaccination strategy combination. We rank-ordered the strategies in terms of lowest to highest costs. In cases where an intervention had higher costs, but better health outcomes, we calculated an incremental cost-effectiveness ratio (ICER) between the more expensive strategy and the less-expensive strategy. In some sensitivity analyses, we calculated a Net Monetary value which converting dollars and QALYs into a single measure where QALYs are valued at $100,000 each. Our main goal was to evaluate the impact of the HBV testing strategies. In a secondary analysis, we evaluated the cost-effectiveness of HepB vaccination compared to no vaccination.

In addition to conducting a base-case analysis, we also conducted sensitivity analyses. We first conducted one-way sensitivity analyses where we varied each parameter one-at-a-time. We also examined results assuming 3-dose vaccination. We next evaluated several pairs of parameters in two-way sensitivity analysis. Finally, we conducted a Monte-Carlo simulation where each parameter was varied according to probability distributions (described in...
the appendix) in order to get a distribution of outcomes with which we created cost-effectiveness acceptability curves.

The disease model was created using TreeAge Pro Healthcare 2011 and analyzed with Microsoft Excel 365.

Results

Among adults seeking care for an STI, pre-vaccination HBV testing for HepB unvaccinated persons and CHB care and treatment improved health outcomes while lowering overall net costs when compared with vaccination alone of adults who reported no prior HepB vaccination (Figure 1). The addition of one-time adult pre-vaccination HBV testing and connection to CHB care would prevent an additional 138 cases of cirrhosis, 90 cases of HCC, and 163 HBV-related deaths and would gain 2,185 QALYs for every 100,000 adults screened, irrespective of the HepB vaccine used (Table 2, Appendix Table 5). Because CHB treatment is so inexpensive and these disease outcomes are so costly, a strategy that combined HepB vaccination with CHB screening with HBsAg and treatment produced an estimated $40.2 - $40.3 million in net savings for every 100,000 adults tested depending on the vaccine used (Table 2, Appendix Table 5). HBV testing that includes anti-HBc to test for prior infection or anti-HBs to test for immunity would identify people who would not benefit from vaccination, saving the cost of a second or third dose of vaccine. Screening with the 2-tests panel “HBsAg, anti-HBs” would lower costs by $41.5 - $42.5 million when compared to the current practice that only offers vaccination. Testing with the hepatitis B 3-tests panel “HBsAg, anti-HBs, anti-HBc” would have the highest cost savings compared with vaccination alone, but it only had an additional $0.44 - $1.84 in savings per person than testing with the 2-tests panel.

The cost-effectiveness of HepB vaccination of adults seeking care for an STI, compared to no vaccination, varied depending on the vaccine used. Vaccination with the 2-dose Heplisav® vaccine would cost $5.4 million, prevent 1,490 acute infections, prevent 6 HBV-related deaths, and would have an ICER of $96,794/QALY for every 100,000 adults seen at STI clinics (Appendix Table 5). Using the Engerix-B® or Recombivax HB vaccine had an ICER of $68,225 per QALY and the Twinrix® vaccine had an ICER of $141,297 per QALY.

Vaccination of the cohort with the two dose vaccine (Heplisav®) was $1.94 million more expensive than vaccination with the three dose monovalent vaccines (Engerix-B®/Recombivax HB®), but added 5 more QALYs per 100,000 population. Heplisav® was $1.76 million less expensive and had better protection against HBV infection than Twinrix®, adding 5 more QALYs (Appendix Tables 5,6a–c).

Sensitivity Analysis

The main conclusion that HBV screening and CHB treatment was cost-effective did not change because parameter assumptions were varied (Figure 2, Appendix Figs. 3a–3c). If CHB prevalence in the STI population were zero instead of 4.2%, the benefits of screening were smaller, but screening would still be less costly than the status quo because it would identify people who had already been vaccinated and would not need additional vaccine...
doses (Appendix Figures 4a–4c). Anti-HBc prevalence did not substantially affect the value of screening (Appendix Figures 5a–5c).

Because the three tests (HBsAg, anti-HBs, anti-HBc) strategy only saved a net $0.44 - $1.84 above the two test (HBsAg, anti-HBs) strategy, many small changes in test costs could lead to a switch between which of these testing strategies were the lowest-cost. However, the net cost difference between these two strategies did not vary more than a few dollars per person as parameters were varied (Appendix Figure 6a–6c).

The appendix contains comparisons of policies of screening and vaccination to strategies with screening without HepB vaccination. Screening and vaccination helps avoid unnecessary vaccine doses, so under these conditions, vaccination is much more cost-effective when compared to no-vaccination strategies.

Sensitivity analysis results were similar with all three types of vaccines (Appendix Figures 3–6).

Using CDC federal contract vaccine pricing instead of private payer pricing would make immunization much more cost-effective. The ICER of current practice (vaccination alone) compared to no HepB vaccination would become much more favorable at $44,374 per QALY for Heplisav®, $16,298 for Engerix-B®/Recombivax HB®, and $68,944 for Twinrix® (Appendix Tables 7a–c).

Probabilistic sensitivity analysis highlights overall uncertainty about which specific testing and vaccination strategy is the most cost-effective, given joint uncertainty around all model parameters (Figure 3). When evaluating various screening policies with vaccination and using the Heplisav® vaccine, screening with the 2 tests (HBsAg, anti-HBs) and HepB vaccination was optimal in 40–49% of simulations and screening with the 3 tests (HBsAg, anti-HBs, anti-HBc) and vaccination was optimal in 47–55% of simulations; HBsAg screening with vaccination was optimal in 4–8% of simulations. Current practice (HepB vaccination alone) was not optimal compared to the strategies involving screening. If using the other vaccines, it was slightly more likely that screening with the 3 tests (HBsAg, anti-HBs, anti-HBc) was cost-effective compared to the 2 tests (HBsAg, anti-HBs), but there still was substantial uncertainty and the status quo was highly unlikely to be cost-effective (Appendix Figures 12a, 12b). If considering policies without vaccination, there was additional uncertainty (Appendix Figures 13a, 13b, 13c).

**Discussion**

Adding a one-time HBV testing for adults at STI clinics who reported they have not been vaccinated and have not been previously tested to the current recommendation to offer HepB vaccination would be cost saving. Pre-vaccination testing with HBsAg, and linking those diagnosed with CHB to care and antiviral treatment will prevent costly complications and deaths, and can reduce sexual transmission of HBV to sex partners. The current approach of vaccinating without pre-vaccination testing likely results in missed opportunities for CHB diagnosis. The optimal cost savings was seen screening using the 3-tests panel, which also detected past infection or immunity to reduce unnecessary vaccine doses. However, the cost
difference between testing with the 3-tests panel and the 2-tests panel was minor: only $0.44 - $1.84 per person.

The conclusion that HBV pre-vaccination testing of adults and referral for CHB treatment is valuable is consistent with other studies of the value of screening and treating high-risk groups\(^{15, 16, 46}\). Hutton et al. found screening and treatment to be cost-effective for Asian and Pacific Islanders in the United States. They found ring vaccination of partners of identified positive individuals may be cost-effective, but that broad vaccination of these adults would not be cost-effective. However, that analysis is from 2007 and the adult Asian and Pacific Islander population may have lower infection risk than individuals seeking care for STI\(^{16}\). A 2018 study by Toy et al. of reaching WHO screening and treating goals would be highly cost-effective or cost-saving\(^{465}\). But, it did not focus on vaccination or people at higher risk of STI. A 2019 study by Chahal et al. found screening, treatment, and vaccination of men who have sex with men (MSM) to be highly cost-effective\(^{15}\).

Our analysis is the first to specifically evaluate HBV screening and vaccination policies for individuals at risk of STI. We show the current ACIP recommendation to vaccinate persons seeking care for STI who reported no prior hepatitis B vaccination would likely prevent 1,338–1,490 acute hepatitis B infections and 6 HBV-related deaths for every 100,000 persons evaluated for STI. The current recommendation (HepB vaccination alone) based on the commercial vaccine prices has an ICER of $68,225 for the 3 dose Engerix-B\(^{®}\) or Recombivax HB vaccine, $141,297 for the 3 dose Twinrix\(^{®}\) combined hepatitis A and hepatitis B vaccine, and $96,794 for the 2 dose Heplisav-B\(^{®}\) vaccine.

The value of HepB vaccination in this high-risk STI population was addressed by Miriti et al. in 2008\(^{4}\). In a base case analysis of people aged 25 years with only 10% reported having prior HepB vaccination, Miriti’s study suggested that a national program for routine HepB vaccination would likely be cost saving for the society if loss productivity from illness was included in the analysis. Since that study was published, many adolescents and young adults have received HepB vaccination\(^{10}\). The CDC estimated that among adults ages 18–29 years, about 91% have received the HepB vaccine\(^{11}\). We calculated that only 24% of individuals at STI clinics would benefit from HepB vaccination because today’s population seen at STI clinics is mostly young with high vaccination coverage. And, of those unprotected, about 30% are age 40 years and older and face a higher incidence of acute infection. Miriti’s analysis used federal contract vaccine pricing for the three dose monovalent HepB vaccines at $24.25/dose whereas in this study, we used the commercial pricing for the HepB vaccines that ranged from $61.86 to $121.25 per dose. If CDC federal contract vaccine prices were used, our study found vaccination alone with the 3 dose monovalent vaccines (Engerix-B\(^{®}\) or Recombivax HB\(^{®}\)) and the 2 dose monovalent vaccine (Heplisav-B\(^{®}\)) would be cost-effective at $27,778/QALY and $55,969/QALY, respectively. The ICER for vaccination alone with the combined hepatitis A and hepatitis B vaccine (Twinrix\(^{®}\)) was $80,424/QALY. Miriti’s study did not consider the impact of CHB treatment, but included the costs of productivity loss from disease complications that were not included in this study. Since 2005, CHB antiviral drug treatment costs have dramatically dropped, lowering the costs of chronic infection treatment. Thus, it has become less expensive to treat persons diagnosed with CHB.
Our study has several limitations. We did not evaluate all possible screening, vaccination, and treatment policies. We only included vaccination policies with the first dose given at the initial visit because of concerns about loss to follow-up and because that policy is in line with ACIP recommendations. In addition, we did not further stratify the population of individuals seeking care for an STI, either based on patient characteristics (e.g., MSM) or setting of care. Presumably, higher-risk populations would benefit more from vaccination. However, even moderate-risk groups are likely to benefit from screening that would link patients to highly cost-effective care.

Like all modeling studies, the quality of the results are predicated upon the quality of the input assumptions. Data are somewhat scarce on the prevalence and incidence of hepatitis B in STI clinic populations. Because of this limitation, we conducted a sensitivity analysis on these parameters, and found they did not have a meaningful impact on the overall conclusions. Many of our costs are based on Medicare fee schedules. Although Medicare payments are commonly used for cost-effectiveness analyses, the rates are designed for other purposes, and in addition, the average patient age is older than the population studied here. However, we assume the economic costs of testing and clinic visits may not be substantially different even given the age differences. We did not include the benefits of prevention of secondary infections, which may be a concern in a population that engages in higher levels of sexual activity. However, the secondary benefits could be attenuated if younger people with higher levels of sexual activity assortatively mix with younger people with higher baseline levels of HBV vaccination. We also did not include productivity losses from disease, which may underestimate cost savings from screening and vaccination. We did not include the added benefit in protecting against hepatitis A if the combined hepatitis A and hepatitis B vaccine (Twinrix®) was used for vaccination. Our model did not include any impact of the clinical value from knowing anti-HBc status beyond avoiding unnecessary vaccine doses. However, it may be possible that knowing anti-HBc status may be useful knowledge for certain patients like patients who would be at risk for hepatitis B reactivation when receiving immunosuppressive therapy.

A one-time HBV pre-vaccination testing of adults seeking evaluation and treatment of STI in addition to the current recommendation to vaccinate persons who reported no prior hepatitis B vaccination is cost saving. Compared with HepB vaccination alone, a combined strategy that includes immunization, screening with the HBV 3-tests panel and treatment of CHB would save over $40 million and prevent 163 HBV-related deaths/100,000 adults screened.

Supplementary Material
Refer to Web version on PubMed Central for supplementary material.

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Figure 1: Comparison in costs and QALYs of status quo (HepB vaccination with Heplisav®) with the various pre-vaccination HBV testing strategies combined with vaccination among a cohort of 100,000 persons.

Footnote: The HBsAg, + Vacc; HBsAg, anti-HBs + Vacc; HBsAg, anti-HBs, anti-HBC + Vacc all are very closely overlapping. All have the same QALYs. See Figure 3 for a closer examination of the cost differences. Results for Engerix®/Recombivax® and Twinrix® are similar and can be found in Appendix Table 4.
Figure 2: Net Monetary Value Increase with HBsAg, anti-HBs, anti-HBc + Vacc vs. Status Quo for a single person screened. Heplisav® vaccine

Net Monetary value calculates the incremental value of the HBsAg, anti-HBs, anti-HBc + Vacc strategy compared to the status quo strategy by valuing dollars at a rate of $1 = $1 and QALYs gained at a value of 1 QALY = $100,000. Positive values indicate the HBsAg, anti-HBs, anti-HBc + Vacc strategy is preferred when compared to the status quo if a policymaker is willing to pay $100,000 per QALY gained.
Figure 3: Probability strategy is preferred under various thresholds for willingness to pay for one quality adjusted life year

Footnote: Evaluated for Heplisav®. The QALY differences do not vary substantially, so these results are relatively stable for other willingness-to-pay values between $0 and $100,000 per QALY.
### Table 1.

Key input variables and ranges

| Variable                                                                 | Base Case | Range          | Distribution | Reference                   |
|-------------------------------------------------------------------------|-----------|----------------|--------------|-----------------------------|
| Age/birth cohort                                                        | 18 yrs    | 18–69 yrs      |              |                             |
| Proportion of population (at an STI clinic)                             |           |                |              | Hechter, 2014⁶               |
| 18–24                                                                   | 35%       |                |              |                             |
| 25–34                                                                   | 39%       |                |              |                             |
| 35–44                                                                   | 17%       |                |              |                             |
| 45–54                                                                   | 7%        |                |              |                             |
| 55+                                                                    | 3%        |                |              |                             |
| HBsAg prevalence in STI US population                                  | 4.17%     |                |              | Marseille, 2021⁷             |
| Male to female ratio within the risk group                              | 61.9%     |                |              | Pathela, 2015⁹              |
| Ratio of Prevalence in Men vs. Women                                    | 1.38      |                |              | Patel, 2019⁸                |
| Proportion With Prior Vaccination                                       |           |                |              |                             |
| 18–29                                                                  | 91.3%     | 16–95          | beta         | Rosenthal, 2020¹¹           |
| 30–39                                                                   | 40.1%     | 37.0–91.3      | beta         | Lu et al.¹⁰, CDC, 2021, unpublished |
| 40–49                                                                   | 31.9%     | 29.1–40.1      | beta         | Lu et al.¹⁰, CDC, 2021, unpublished |
| 50–59                                                                  | 24.9%     | 22.6–31.9      | beta         | Lu et al.¹⁰, CDC, 2021, unpublished |
| 60+                                                                    | 15.6%     | 14.3–24.9      | beta         | Lu et al.¹⁰, CDC, 2021, unpublished |
| Proportion unvaccinated who have prior infection (anti-HBc positive regardless of anti-HBs) |           |                |              |                             |
| 18–24                                                                  | 8.8%      | (4.2%–13.3%)   | beta         | Trepka, 2003⁸⁵             |
| 25–34                                                                   | 26.1%     | (20.1%–32.1%)  | beta         | Trepka, 2003⁸⁵             |
| 35+                                                                    | 33.1%     | (27.4%–38.8%)  | beta         | Trepka, 2003⁸⁵             |
| Annual incidence of developing acute HBV infection                      |           |                |              |                             |
| 18–39                                                                   | 1.0%      |                | beta         | Miriti, 2008⁴              |
| 40+                                                                    | 0.33%     |                | beta         | Miriti, 2008⁴              |
| Percent not aware of their infection                                    | 67%       | 49–82%         | beta         | Patel, 2019⁸                |
| Percent aware of prior vaccination                                      |           |                |              |                             |
| 19–49 years                                                             | 70%       | 63.6–97.6%     | beta         | Rolnick¹⁴                  |
| 50+ years                                                               | 80.8%     | 75.5–86.2%     | beta         | Rolnick¹⁴                  |
| Variable                                                                 | Base Case | Range    | Distribution | Reference  |
|--------------------------------------------------------------------------|-----------|----------|--------------|------------|
| Proportion adults diagnosed with CHB and linked to care and received antiviral treatment | 18%       | 17–19%  | beta         | Harris, 2020 |
| Screening Costs (U.S. dollars) $                                          |           |          |              |            |
| Cost of hepatitis B serologic tests                                       |           |          |              | CMS, 2021  |
| Hepatitis B surface antigen (HBsAg)                                      | $10.33    | $7.50-$20.00 | gamma        |            |
| Hepatitis B core antibody (anti-HBc)                                    | $12.05    | $7.50-$20.00 | gamma        |            |
| Hepatitis B surface antibody (anti-HBs)                                  | $10.74    | $7.50-$20.00 | gamma        |            |
| All 3 hepatitis B tests                                                   | $28.27    | $25.00-$40.00 | gamma        |            |
| Vaccination Costs (U.S. dollars) $                                        |           |          |              |            |
| Engerix-B® / Recombivax HB private sector cost per dose                  | $61.54    | $25.43-$73.85 | gamma        | CDC, 2021  |
| Twinrix® private sector cost per dose                                    | $112.35   | $62.04-$134.83 | gamma        | CDC, 2021  |
| Heplisav-B® private sector cost per dose                                 | $121.25   | $73.05-$145.50 | gamma        | CDC, 2021  |
| Vaccine Administration (physician)                                       | $25.84    | $20.67-$31.01 | gamma        | Tsai, 2019 |
| Vaccine Administration (pharmacist)                                     | $17.50    | $14-$21 | gamma        | Tsai, 2019 |
| Patient time, vaccination-specific visit, physician’s office (hour)      | 2.00      |          |              | Ray, 2015  |
| Patient time, vaccination-specific visit, pharmacy (hour)                | 0.20      | 0.17–0.29 | gamma        | Prosser, 2008 |
| Proportion of patients requiring vaccination-specific visit               |           |          |              |            |
| First dose                                                               | 0         |          |              |            |
| Second and third doses                                                    | 0.5       | 0–1     | beta         | CDC, 2013  |
| Proportion of patients receiving vaccine in pharmacy setting              | 0.3       |          |              | Singhal, 2014 |
| Mean hourly earnings                                                     | $29.96    |          |              | BLS, 2021  |
| Linkage to Care and Treatment Costs                                      |           |          |              |            |
| Antiviral drug costs per year                                            | $502.00   | $326.00–16,464.00 | gamma‡       | CMS, 2021  |
| Initial Baseline Tests (HBeAg, CBC, CMP, HBV DNA)                        | $71.40    | $35.70-$107.10 | gamma        | CMS, 2021  |
| Total Annual monitoring costs‡                                           | $355.00   | $177.50-$332.50 | gamma        | CMS, 2021  |
| Clinic visit × 2                                                         | $74.00    | $        |              | CMS, 2021  |
| Ultrasound × 1 (50% none, 50% × 2)                                       | $125.0    | $        |              | CMS, 2021  |
| AFP × 1 (50% none, 50% x2)                                               | $17.00    | $        |              | CMS, 2021  |
| CMP × 2                                                                 | $11.00    | $        |              | CMS, 2021  |
| HBV DNA × 1                                                              | $43.00    | $        |              | CMS, 2021  |
| Variable                                      | Base Case | Range              | Distribution | Reference                 |
|-----------------------------------------------|-----------|--------------------|--------------|---------------------------|
| **Annual Disease Management Costs**           |           |                    |              |                           |
| **Medical Costs**                             |           |                    |              |                           |
| Chronic Hepatitis B                           | $1,694.00 | $183.00 – $5,061.00| gamma        | Liu, 2012 ^25S           |
| Cirrhosis                                     | $5,057.00 | $183.00 – $5,061.00| gamma        | Liu, 2012 ^25S           |
| Decompensated cirrhosis                       | $13,405.00| $6,709.00 – $20,115.00| gamma        | Liu, 2012 ^25S           |
| Hepatocellular carcinoma                      | $53,366.00| $26,761.00 – $80,054.00| gamma        | Liu, 2012 ^24S           |
| Liver Transplant 1st year                     | $175,745.00| $87,879.00 – $263,612.00| gamma        | Liu, 2012 ^25S           |
| Liver Transplant 2nd year                     | $30,687.00| $15,343.00 – $46,043.00| gamma        | Liu, 2012 ^25S           |
| Acute symptomatic (not hospitalized)          | $591.00   | $306.00 – $1,029.00 | gamma        | Kim,                      |
| Acute symptomatic (hospitalized)              | $17,340.00| $3,691.00 – $17,340.00| gamma        | Kim,                      |
| Fulminant hepatitis                           | $27,707.00| $27,791.00 – $74,414.00| gamma        | Kim,                      |
| **Patient and Caregiver Time Costs**          |           |                    |              |                           |
| Active HBV (w/o cirrhosis)                    | $5,876.00 | $3,289.00 – $8,462.00| gamma        | Federico et al, 2012 ^55S |
| Cirrhosis                                     | $8,639.00 | $6,139.00 – $11,241.00| gamma        | Federico et al, 2012 ^55S |
| HCC                                           | $7,816.00 | $5,317.00 – $10,316.00| gamma        | Federico et al, 2012 ^55S |
| Transplant                                    | $16,440.00| $13,940.00 – $18,940.00| gamma        | Federico et al, 2012 ^55S |
| Sustained Viral Response                      | $960.00   | $0.00 – $7,311.00  | gamma        | Assumption: 32 hours per year |
| **Health State Utilities**                    |           |                    |              |                           |
| Immune state                                  | 0.99      | 0.98 – 1.00        | beta         | Chahal, 2019 ^15          |
| Susceptible state                             | 0.99      | 0.98 – 1.00        | beta         | Chahal, 2019 ^15          |
| Active CHB                                    | 0.88      | (0.80 – 0.92)      | beta         | Woo, 2012 ^65S            |
| Cirrhosis                                     | 0.73      | (0.49 – 0.82)      | beta         | Woo, 2012 ^65S            |
| Inactive CHB                                  | 0.81      | (0.77 – 0.85)      | beta         | Woo, 2012 ^65S            |
| Decompensated cirrhosis                       | 0.84      | (0.72 – 0.84)      | beta         | Woo, 2012 ^65S            |
| Hepatocellular carcinoma                      | 1         | (0.95 – 1.00)      | beta         | Woo, 2012 ^65S            |
| Liver Transplant                              | 1         | (0.95 – 1.00)      | beta         | Woo, 2012 ^65S            |
| HBsAg seroclearance                           | 1         | (0.95 – 1.00)      | beta         | Woo, 2012 ^65S            |
| Viral suppression                             | 1         | (0.95 – 1.00)      | beta         | Woo, 2012 ^65S            |
| **Vaccination**                               |           |                    |              |                           |
| Fraction receiving 1st dose                   | 74%       | 66.6 – 81.4        | beta         | Mirri, 2008 ^4             |
| Variable | Base Case | Distribution | Reference |
|----------|-----------|--------------|-----------|
| Fraction receiving 2nd dose (of those receiving 1st dose) | 61% | beta | Bruxvoort, 2020 |
| Fraction receiving 3rd dose (of those receiving 1st dose) | 32% | beta | Bruxvoort, 2020 |
| Vaccine Effectiveness, 1st dose | | | |
| 18–29 years | 20.4% | 4%-28.8% | beta | Leve 2002* |
| 30–39 years | 20.4% | 4%-28.8% | beta | Leve 2002* |
| 40–49 years | 12% | 4%-17.2% | beta | Treadwell 1993* |
| 50–59 years | 12% | 4%-17.2% | beta | Treadwell 1993* |
| 60+ years | 7.5% | 4%-8.6% | beta | Joines 2001* |
| Vaccine Effectiveness, 2nd dose | | | |
| 18–29 years | 77.0% | 24%-87.2% | beta | Leve 2002* |
| 30–39 years | 77.0% | 24%-87.2% | beta | Leve 2002* |
| 40–49 years | 63% | 24%-72.0% | beta | Treadwell 1993* |
| 50–59 years | 63% | 24%-72.0% | beta | Treadwell 1993* |
| 60+ years | 50.4% | 24%-60% | beta | Joines 2001* |
| Vaccine Effectiveness, 3rd dose | | | |
| 18–29 years | 99.3% | 80%-100% | beta | Hirst 2021* |
| 30–39 years | 99.3% | 80%-100% | beta | Hirst 2021* |
| 40–49 years | 97% | 80%-100% | beta | Hirst 2021* |
| 50–59 years | 97% | 80%-100% | beta | Hirst 2021* |
| 60+ years | 92.2% | 80%-100% | beta | Hirst 2021* |
| Seroprotection rate for Heplisav-B® (0,1 month schedule) | | | |
| 18–29 years | 22% | 12%-32% | beta | Hirst 2021* |
| 30–39 years | 22% | 12%-32% | beta | Hirst 2021* |
| 40–49 years | 22% | 12%-32% | beta | Hirst 2021* |
| 50–59 years | 22% | 12%-32% | beta | Hirst 2021* |
| 60+ years | 22% | 12%-32% | beta | Hirst 2021* |
| Variable       | Base Case | Range      | Distribution* | Reference  |
|---------------|-----------|------------|---------------|------------|
| 18–29 years   | 96%       | 80%-100%   | beta          | Hirst 2021 |
| 30–39 years   | 96%       | 80%-100%   | beta          | Hirst 2021 |
| 40–49 years   | 96%       | 80%-100%   | beta          | Hirst 2021 |
| 50–59 years   | 96%       | 80%-100%   | beta          | Hirst 2021 |
| 60+ years     | 96%       | 80%-100%   | beta          | Hirst 2021 |
| Discount Rate | 3%        | 0%-5%      | beta          | Hirst 2021 |

* These are the distributions used for the probabilistic sensitivity analysis. The distributions are set such that the means are centered on the base-case value and the standard deviations of the distributions are set to match one quarter of the ranges specified in the “Range” column of this table. Parameters with no distribution identified were not varied in probabilistic sensitivity analysis. More details are described in the Appendix.

† The 2013 NIS indicate 91.3% of 17 year olds received three doses of HepB vaccine in 2013. This coverage estimate of 17-year-olds from 2013 would be 25 years old in 2021, so we used this estimate for those aged 18–29 years of age for vaccination coverage.

‡ The range of $326.00–16,464.00 is for one-way sensitivity analysis, but for the probabilistic sensitivity analysis, a standard deviation of 173 is used.

§ Annual monitoring costs are implemented as a single parameter in the model. The sub-components are shown to explain how the annual monitoring costs were calculated. But, for purposes of sensitivity analysis, only the total annual monitoring costs are varied.

Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase; CBC, complete blood count; CHB, chronic hepatitis B; CMP, complete metabolic panel; HBeAg, hepatitis B e antigen; STI, sexually transmitted infections.

All costs in 2021 USD, with inflation adjusting using the personal consumption expenditures index.
Table 2:

Health and Economic Results of Screening Interventions for a Population of 100,000 adults

| Strategy                                      | Cost       | QALYs     | Cirrhosis | Decompensated Cirrhosis | HCC | Transplants | HBV Deaths |
|-----------------------------------------------|------------|-----------|-----------|--------------------------|-----|-------------|------------|
| **Heplisav-B ®**                              |            |           |           |                          |     |             |            |
| Status Quo                                    | 407,218,391| 2,377,829 | 461       | 131                      | 431 | 156         | 690        |
| HBsAg + Vacc                                 | 367,022,663| 2,380,014 | 323       | 84                       | 341 | 123         | 526        |
| HBsAg, anti-HBs + Vacc                      | 365,641,803| 2,380,014 | 323       | 84                       | 341 | 123         | 526        |
| HBsAg, anti-HBs, anti-HBc + Vacc             | 365,591,884| 2,380,014 | 323       | 84                       | 341 | 123         | 526        |
| **Engerix-B®/Recombivax HB®**                |            |           |           |                          |     |             |            |
| Status Quo                                    | 405,264,020| 2,377,824 | 462       | 131                      | 431 | 156         | 690        |
| HBsAg + Vacc                                 | 365,073,912| 2,380,009 | 324       | 84                       | 341 | 123         | 527        |
| HBsAg, anti-HBs + Vacc                      | 363,727,272| 2,380,009 | 324       | 84                       | 341 | 123         | 527        |
| HBsAg, anti-HBs, anti-HBc + Vacc             | 363,683,205| 2,380,009 | 324       | 84                       | 341 | 123         | 527        |
| **Twinrix®**                                  |            |           |           |                          |     |             |            |
| Status Quo                                    | 408,974,805| 2,377,824 | 462       | 131                      | 431 | 156         | 690        |
| HBsAg + Vacc                                 | 368,650,275| 2,380,009 | 324       | 84                       | 341 | 123         | 527        |
| HBsAg, anti-HBs + Vacc                      | 366,485,066| 2,380,009 | 324       | 84                       | 341 | 123         | 527        |
| HBsAg, anti-HBs, anti-HBc + Vacc             | 366,300,996| 2,380,009 | 324       | 84                       | 341 | 123         | 527        |

QALYs: Quality-Adjusted Life-Years

ICER: Incremental Cost-Effectiveness Ratio

Cost: in US dollars

Dominant: the intervention has lower costs and higher QALYs than the Status Quo