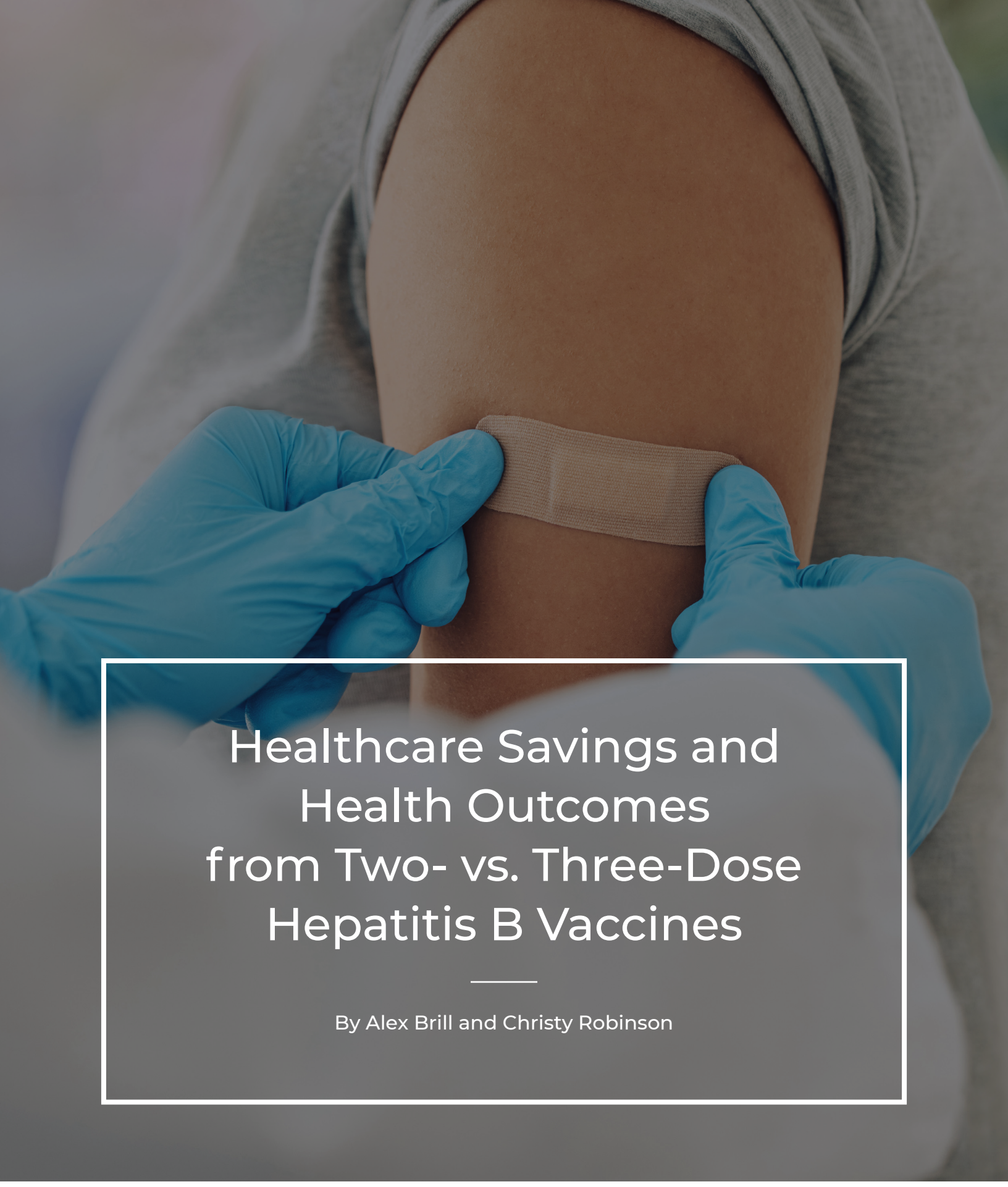

Healthcare Savings and Health Outcomes from Two- vs. Three-Dose Hepatitis B Vaccines

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August 2026

MATRIX GLOBAL ADVISORS

Executive Summary

This report estimates the changes in healthcare spending and health outcomes that would result from broader US adoption of the two-dose hepatitis B vaccine, Heplisav-B.

Despite public health efforts, hepatitis B, a virus that can cause severe liver disease and death, remains a serious concern and significant driver of healthcare spending in the United States. In 2023, there were 14,400 acute hepatitis B infections, 17,650 newly reported chronic hepatitis B cases, and 1,769 hepatitis B–related deaths. The rate of new chronic hepatitis B cases is higher among males than females and significantly higher among Blacks and Asians than whites or Hispanics.

Thankfully, available vaccines can reduce the risk of transmission. However, many adults are unvaccinated, and many who begin the vaccination process do not complete it and remain susceptible. Moreover, the effectiveness of available vaccines varies considerably.

Since 1982, a three-dose vaccine, administered over six months, has been available in the United States. Heplisav-B, administered in two doses four weeks apart, entered the US market in 2017.

Compared with the three-dose vaccine, Heplisav-B has a higher series completion rate and results in higher rates of seroprotection—that is, the immune response to a vaccine that generates antibodies necessary to protect against a virus. After receiving both doses of Heplisav-B, 96 percent of adults are seroprotected, compared with 24 percent after two doses of a three-dose vaccine and 80 percent after the third dose.

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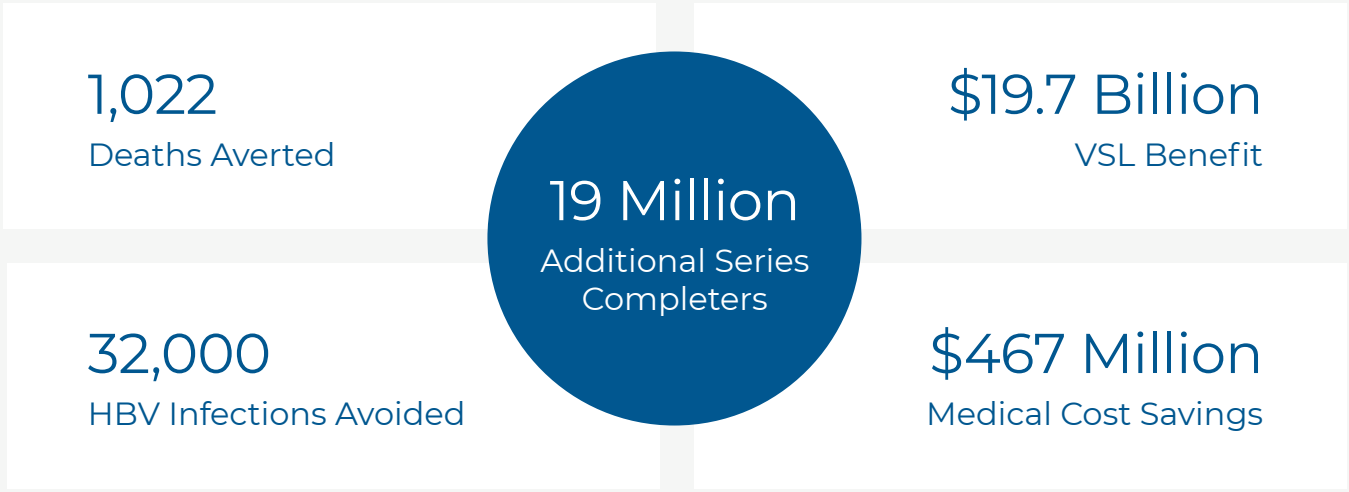
In this report, through the use of an original vaccination and disease progression model, we evaluate the changes in population-wide healthcare spending and health outcomes from broader adoption of the two-dose vaccine. Specifically, we estimate the increase in the number of adults who complete the vaccine series; the reduction in hepatitis B infections and deaths; the medical cost savings; and the benefit in terms of the value per statistical life (VSL), a commonly used metric in cost-benefit analyses that calculates the benefit of avoiding a fatality. (See **Figure 1** for a summary of results.)

As our results show, broader adoption of the two-dose vaccine could save more than a thousand lives and hundreds of millions of dollars in healthcare spending.

Healthcare leaders in the private sector and policymakers in government should evaluate the benefits of the two-dose vaccine and consider strategies for increasing its utilization.

Broader adoption of the two-dose vaccine could save more than a thousand lives and hundreds of millions of dollars in healthcare spending.

FIGURE 1. BENEFITS OF 100% UTILIZATION OF TWO-DOSE HEPATITIS B VACCINE



Source: Authors' calculations based on hepatitis B vaccination and disease progression model for the US population. For additional details, see the full report and appendix.

Introduction

Hepatitis B is a virus that can cause severe liver disease and death for those who contract it. Since 1982, a three-dose vaccine to protect against the hepatitis B virus (HBV) has been available in the United States. Since 2017, a two-dose vaccine has also been available, and its market share has been increasing. Despite the availability of these products, hepatitis B continues to spread and cause significant health burdens. This report investigates the health and cost implications of broader adoption of the two-dose vaccine.

In the early 1990s, the Advisory Committee on Immunization Practices (ACIP) within the Centers for Disease Control and Prevention (CDC) recommended universal childhood vaccination for HBV, prompting the vaccination rate among children age 19–35 months to rise from 16 percent in 1993 to 90 percent in 2000 (*CDC, 2002*). The childhood vaccination rate for HBV has since remained at roughly 90 percent.[1] While adult vaccination was initially recommended only for those at higher risk of contracting HBV, ACIP expanded its recommendation in 2022 to include vaccination for all adults age 19–59 (*Weng et al., 2022*). However, only 34 percent of adults report that they have been vaccinated (*CDC, 2024*).

For the first 25 years that hepatitis B vaccines were available in the United States, vaccines were administered in three successive doses over six months. In 2017, a two-dose adult vaccine was introduced in the United States. This version, with the second dose administered four weeks after the first, has demonstrated clinical advantages compared with three-dose vaccines. For example, one study found that 45 percent of adults who started the two-dose series completed it, while only 26 percent completed the three-dose series (*Bruxvoort et al., 2020*). See also Trantham et al. (*2018*), Bridges et al. (*2019*), LaMori et al. (*2022*), and Oster et al. (*2022*).

Additionally, the two-dose vaccine results in higher rates of seroprotection—that is, the immune response to a vaccine that generates antibodies necessary to protect against a virus—than three-dose vaccines (*Halperin et al., 2012*; *Heyward et al., 2013*; and *Jackson et al., 2018*). Researchers have also found that the two-dose vaccine results in lower net costs in studied populations (*Rosenthal et al., 2020*).

There are obvious implications for both health outcomes and healthcare costs arising from these distinctions and the choice between vaccine type. In this report, we compare two-dose and three-dose hepatitis B vaccines and, through the use of an original vaccination and disease progression model, evaluate the changes in population-wide healthcare spending and health outcomes that would result from broader adoption of the two-dose vaccine.

[1] *In December 2025, CDC adopted ACIP's amended recommendation for childhood vaccination for HBV, changing the recommendation from universal to individual-based or shared clinical decision-making.*

Background

HEPATITIS B IN THE UNITED STATES

Hepatitis B is transmitted through blood or body fluids and can result in chronic HBV infection, liver failure, cirrhosis, liver cancer, and death. Vaccines drastically reduced the number of new (acute) cases of HBV in the United States. The incidence of acute hepatitis B fell more than 90 percent from the early 1980s to the early 2010s (*Ly, Xing, and Spradling, 2021*). But the virus remains of great concern because of its costly and burdensome health implications and the low adult vaccination rate, 34 percent in 2021.

The CDC estimates that, in 2023, there were 14,400 acute HBV infections,[2] 17,650 newly reported chronic hepatitis B cases, and 1,769 hepatitis B–related deaths. Forty-eight percent of acute cases occurred among people age 40–59 years, and 46 percent of newly reported chronic hepatitis B cases occurred among people age 30–49 (*CDC, 2025a*).

For adults with acute hepatitis B infections, 95 percent make a full recovery, while 5 percent become chronically infected (*CDC, 2025b*).[3]

For new chronic hepatitis B cases, the rate among males is 1.4 times the rate among females (7.1 and 5.1 cases per 100,000, respectively), while rates for whites and Hispanics are similar (1.9 and 2 cases per 100,000, respectively) but significantly higher for Blacks (9.5 cases per 100,000) and Asians (18.9 cases per 100,000) (*CDC, 2025a*).

ADULT VACCINATION

In 2020, the Department of Health and Human Services (HHS) released the Viral Hepatitis National Strategic Plan, offering an assessment of the progress made on the targets for 2020 established in the previous action plan, released in 2017. While affirming positive trends in vaccinations for hepatitis B at birth and for healthcare workers, the 2020 report warned that new HBV infections, particularly among people age 20–49, were not on track to reach targeted levels (*HHS, 2020*). In a new set of targets, the report established a goal of reducing acute hepatitis B infections by 90 percent by 2030. Key to reaching this goal is an increase in adult vaccinations, as affirmed by ACIP's expanded recommendation (*Weng et al., 2022*).

The seroprotection rate after two doses of a three-dose vaccine is only 24 percent, compared with 96 percent for Heplisav-B.

As noted above, US adults can receive either a two-dose vaccine—Heplisav-B, introduced in 2017—or one of two traditional three-dose vaccines, Engerix-B or Recombivax HB. Heplisav-B reached 46 percent market share in 2025. While typically more expensive than the three-dose vaccines,

[2] *The actual number of new cases of acute hepatitis B reported in 2023 was 2,214, but CDC's estimate adjusts for underreporting.*

[3] *This differs drastically for children, with chronic hepatitis B developing among 90 percent of infected infants and 30 percent of children infected between one and five years of age (*CDC, 2025b*).*

Heplisav-B has demonstrated higher series completion and results in higher seroprotection in less time—inducing seroprotection in 96 percent of adults in four weeks versus 80 percent in six months. Significantly, as **Table 1** shows, the seroprotection rate after two doses of a three-dose vaccine is only 24 percent, compared with 96 percent for Heplisav-B. Given these advantages, the remainder of this paper quantifies and compares the benefits of US adults receiving the two-dose vaccine instead of a three-dose vaccine.

TABLE 1. CHARACTERISTICS OF TWO- AND THREE-DOSE HEPATITIS B VACCINES

BRAND NAME	# of Doses	Schedule	Completion Rate	Seroprotection		
				1 Dose	2 Doses	3 Doses
Heplisav-B	2	4 weeks	56%	22%	96%	N/A
Engerix-B	3	6 months	38%	4%	24%	80%

Source: Hirst, Hyer, and Janssen (2021).

Analysis

The analysis presented here estimates health outcomes and healthcare cost savings for the US adult population from broader adoption of the two-dose hepatitis B vaccine.

ANALYTICAL FRAMEWORK

In simple terms, an adult (in real life and in our analysis) starts out vaccinated or unvaccinated. Some adults will get vaccinated, some will contract hepatitis B, and some will do neither. Both vaccination against hepatitis B and disease progression among those infected with hepatitis B evolve over time.

Upon beginning a multi-dose vaccine, adults enter one of two pathways where at each step they either proceed to the next dose or stop. After each vaccination dose, an individual can either be seroprotected (partially depending on which vaccine was used and how many doses were received) or susceptible (meaning they did not develop immunity after vaccination and remain at risk). The evolution over time from the initial state is determined by adherence and seroprotection probabilities observed from the literature.

Similarly, in the case of acute HBV infections, adults also enter one of two pathways: the majority will recover, but some will progress to chronic HBV and other diseases, the likelihood (and cost) of which vary. Given the evolving nature of infection, we model the transition from healthy to sick as a discrete time Markov stochastic process, which provides the probability that an individual is in a particular state at time $t + 1$, dependent only on the individual's state at time t.

In the appendix to this paper, we provide a detailed description of the model. In brief, it reflects the protection each vaccine dose affords adults at each stage of the vaccination process—accounting for the higher series completion and higher immunogenicity of a two-dose vaccine compared with a three-dose vaccine—and captures the probabilities of progression from acute HBV infection to more serious conditions, including cirrhosis, liver failure, and liver cancer.

The model reflects the protection each vaccine dose affords adults at each stage of the vaccination process—accounting for the higher series completion and higher immunogenicity of a two-dose vaccine compared with a three-dose vaccine.

DATA AND METHODOLOGY

Here, we provide a high-level overview of the data and methodology used to construct our model. For a technical explanation, please see the appendix.

Data

The US adult population in our model is based on US Census Bureau data for 2024. We draw our estimates of vaccine adherence rates, seroprotection rates, disease transition probabilities, and annual costs associated with each disease state from Hirst, Hyer, and Janssen (*2021*). Our estimates of annual death probabilities are derived from Social Security Administration (SSA) Period Life Tables. For the value per statistical life (VSL), we use the central VSL estimate for 2025 ($14 million) from HHS guidelines for regulatory analysis (*Kearsley, 2026*). (See the accompanying box for definitions of key terms.)

Current vaccination rates by age group are drawn from CDC (*2002 and 2024*). We derive current rates of acute HBV from CDC (*2025a*) and chronic HBV from Lim et al. (*2020*).

Key Terms

Vaccine Adherence Rate. Percentage of people who come back for their second and, if applicable, third shot.

Seroprotection Rate. Percentage of people who develop immunity after one, two, or (if applicable) three doses.

Disease Transition Probability. Annual probability that a susceptible person gets HBV or someone with a chronic disease develops a major condition.

Death Probability. Annual probability that a person dies from natural causes or a major HBV-related condition.

Value per Statistical Life. A commonly used metric in cost-benefit analyses that calculates the benefit of avoiding a fatality.

Methodology

The model is based on two transition matrices—one for vaccination and one for disease progression—that repeat each year. The vaccination matrix comprises the initial state, vaccination states, and post-vaccination outcome states, while the disease progression matrix comprises the disease states identified in the accompanying box.

The population in the model is divided into cohorts representing US Census data on adults by race (Black, white, Asian, and other); sex (male and female); and age (19–29, 30–39, 40–49, 50–64, and 65+). There are 40 distinct cohorts in total in the model. The population reflects estimated current

Disease States

Acute HBV Infection. The initial, short-term illness that occurs after infection.

Chronic HBV Infection. A long-term infection that occurs when the immune system cannot fight off the virus.

Fulminant Hepatic Failure (FHF). A rare but severe complication of acute HBV leading to rapid liver failure.

Compensated Cirrhosis. Significant scarring of the liver, but the liver can still perform most of its functions.

Decompensated Cirrhosis. More severe liver scarring, where the liver can no longer function properly.

Hepatocellular Carcinoma (HCC). Liver cancer, a common outcome of chronic HBV infection and cirrhosis.

Liver Transplant. A state for patients who receive a transplant due to FHF, decompensated cirrhosis, or HCC.

vaccination rates and current rates of acute and chronic HBV among US adults.

We run the model for a period of 60 years, with new adults (age 19) entering the model each year at a rate of 1.6 percent of the adult US population. (See **Table 2** for a summary of key assumptions.) Vaccine completion and seroprotection rates for two- and three-dose vaccines mimic those identified in **Table 1**.

TABLE 2. KEY ASSUMPTIONS

US adult population	258 million
Time horizon	60 years
Annual entrant rate (age 19)	1.6%
% population with chronic HBV	0.65%
% population with acute HBV	0.0056%
% already vaccinated	
19–29 and new entrants	90%
30–39	42%
40–49	36%
50–64	28%
65+	20%

The model allows us to estimate the number of individuals in each disease or vaccination state over the time horizon and quantify avoided diseases and disease costs from various vaccine uptake scenarios. As noted above, we derive estimates of the annual cost of managing an individual in each disease state from Hirst, Hyer, and Janssen (*2021*). We then extrapolate these costs to the number of individuals in each disease state estimated in the model and sum over the time horizon to calculate total costs avoided by using two- and three-dose vaccines. To measure the benefit of vaccines preventing death, we apply the midrange VSL estimate ($14 million) from HHS guidelines for regulatory analysis (*Kearsley, 2026*) to the number of deaths prevented by vaccination.

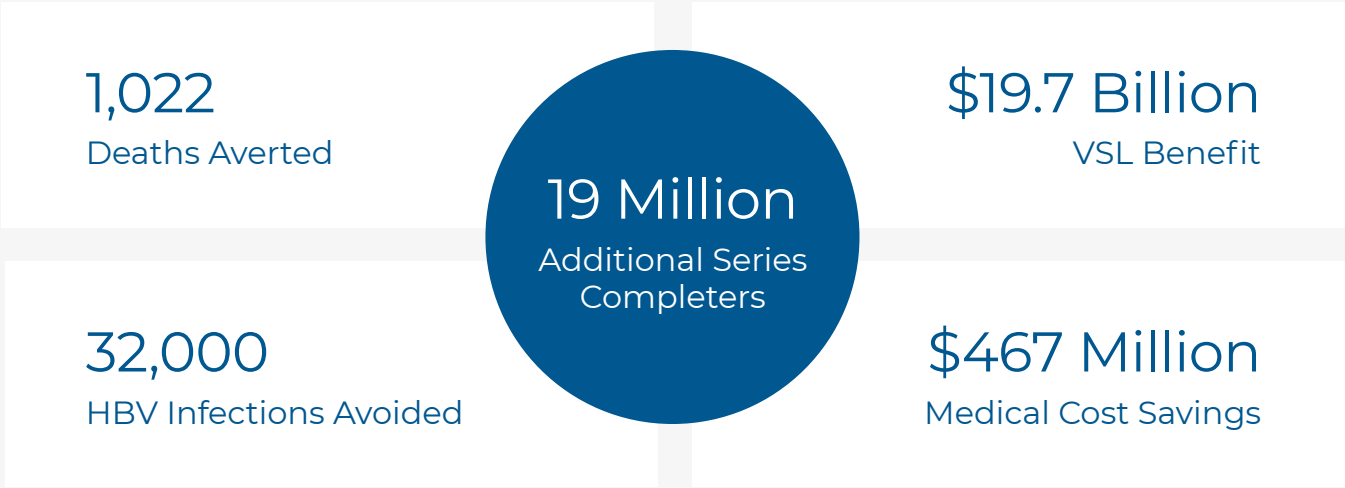
Finally, we assume that 5 percent of susceptible adults initiate vaccination annually. This assumption is derived from a retrospective study of health insurance claims for individuals in the United States over the age of 18 initiating hepatitis B vaccination between 2008 and 2015 (*Trantham et al., 2018*).

Results

In our baseline, the two-dose vaccine comprises 46 percent of hepatitis B vaccines, reflecting Heplisav-B's current market share. It is important to note that benefits in terms of health outcomes and savings are already anticipated from current utilization of the two-dose vaccine. The baseline in our analysis represents a significant improvement relative to a baseline before 2017, when Heplisav-B was not yet available and all initiating adults received a three-dose vaccine.

It is important to note that benefits in terms of health outcomes and savings are already anticipated from current utilization of the two-dose vaccine.

FIGURE 1. BENEFITS OF 100% UTILIZATION OF TWO-DOSE HEPATITIS B VACCINE



Source: Authors' calculations.

We model the impact of moving from 46 percent to 100 percent of initiating adults receiving the two-dose vaccine over a 60-year time horizon. Our model estimates that the number of adults who would complete the vaccine series would increase by nearly 19 million. Nearly 32,000 HBV infections and more than 1,000 HBV-related deaths would be avoided. The VSL benefit from the averted deaths would total nearly $20 billion, and nearly $470 million in medical cost savings would be realized. (See **Figure 1** for a summary of results.)

It should be noted that this analysis does not include the cost of the vaccines themselves because drug prices vary by payer. And, outside of the VSL estimates, the analysis excludes non-medical savings from preventing infection, such as savings from avoiding lost work due to illness.

BUDGETARY AND CLINICAL IMPACTS OVER TIME

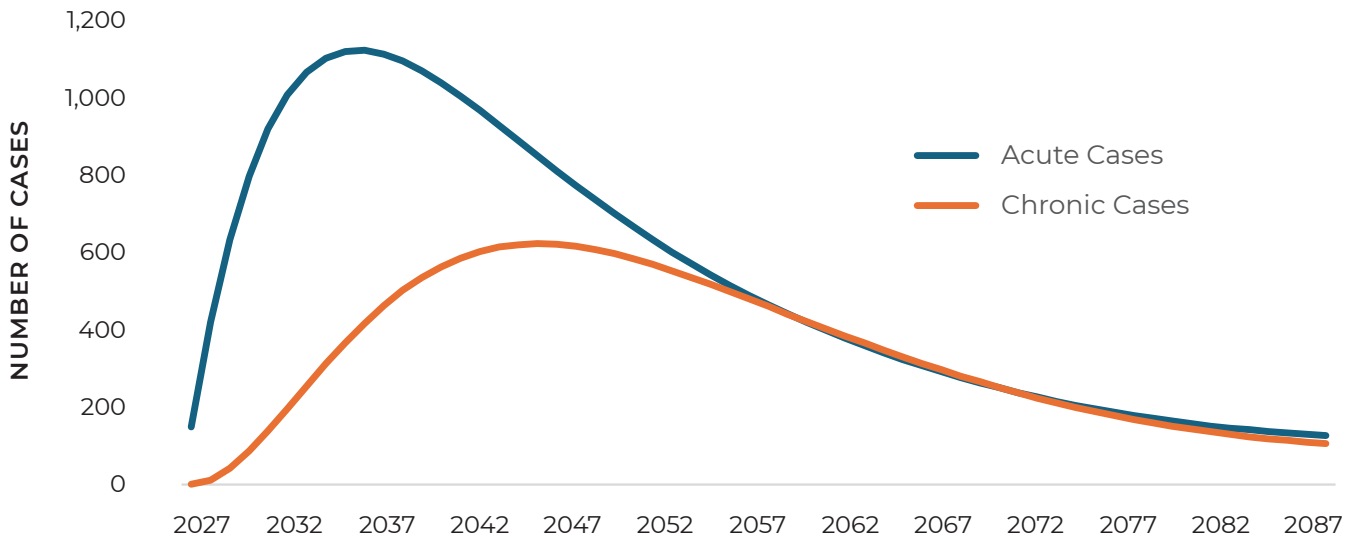
The results presented above reflect the aggregate impact over the model's 60-year time horizon. This timeframe captures roughly the entire adult lives of all individuals in the model when the model begins. It is a duration significantly longer than traditional budget analyses for the simple reason that much of the benefit of all vaccine initiators receiving the two-dose vaccine materializes over time. As **Charts 1–3** demonstrate, the dynamic nature of the model leads to differences in the pace of progress by metric.

Chart 1 shows acute and chronic HBV cases avoided per year. The gains are quite large in the first two decades before slowing significantly by the end of the model horizon. Avoided acute HBV cases per year peak at nearly 1,100 in the tenth year, while avoided chronic cases per year peak at approximately 600 almost a decade later.

Chart 2 illustrates that the nearly $500 million in medical cost savings accrue more slowly than avoided cases, peaking in the twenty-fifth year before accumulating more slowly in the latter half of the period.

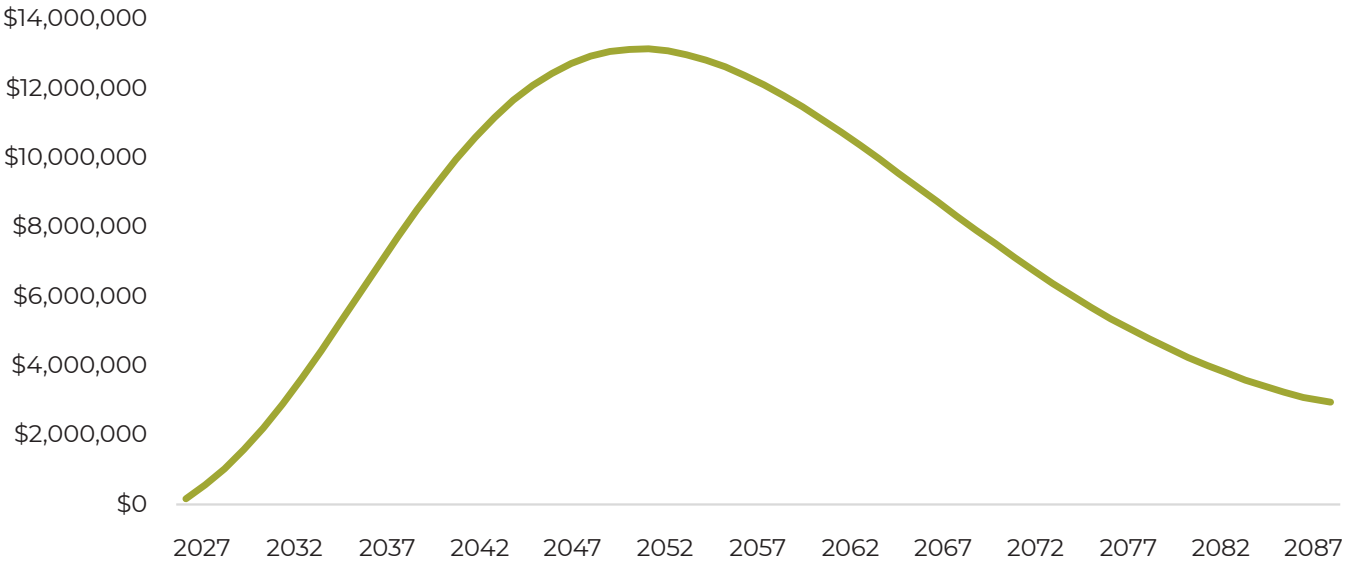
Finally, **Chart 3** reports the cumulative impact in terms of avoided deaths. Due to the nature of hepatitis B and the typical length of disease states, most HBV-related deaths are avoided in the third and fourth decades.

CHART 1. ANNUAL ACUTE AND CHRONIC HBV CASES AVOIDED



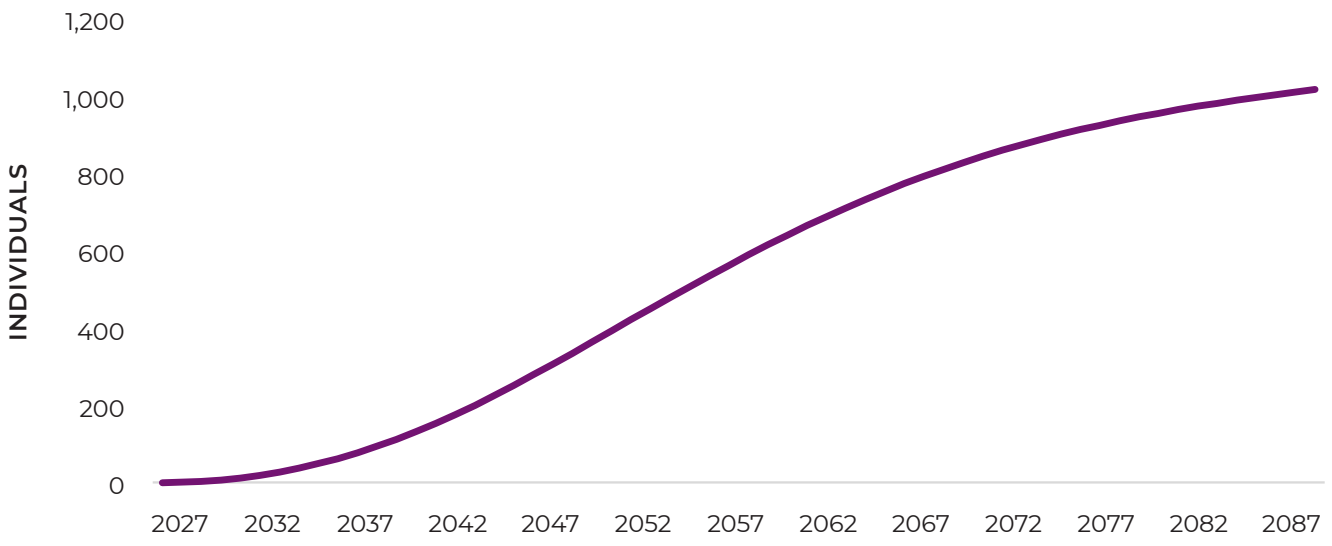
Source: Authors' calculations.

CHART 2. ANNUAL MEDICAL COSTS AVOIDED



Source: Authors' calculations.

CHART 3. CUMULATIVE HBV DEATHS AVOIDED



Source: Authors' calculations.

Discussion

Increasing the adoption of the two-dose vaccine can dramatically reduce the incidence of hepatitis B in the future. While the benefits will not accrue immediately, over decades tens of thousands of new cases can be avoided.

To put the potential benefits of wide adoption of the two-dose vaccine in context, we note that an alternative strategy, increasing the annual vaccination rate, would also reduce the incidence of hepatitis B. However, the public health challenge involved in administering millions more vaccines is likely far greater than simply administering the two-dose vaccine.

To illustrate this, we model a scenario where more adults initiate vaccination while utilization of the two-dose vaccine remains unchanged at 46 percent. The vaccination rate would need to increase from 5 percent to 7 percent of susceptible adults to lower the number of new HBV infections to the same level achieved by exclusively using the two-dose vaccine. Vaccinating 40 percent more people each year, 3 million additional vaccine initiators in the first year, would achieve comparable outcomes but with far greater burdens on providers and patients.

Conclusion

The incidence of new hepatitis B cases in the United States is significantly lower today than 40 years ago thanks largely to vaccines. However, the disease remains a significant burden on the healthcare system and on the thousands of individuals who contract it annually. Despite public health efforts, millions of adults remain without seroprotection. In short, hepatitis B persists as a public health challenge.

This paper demonstrates the powerful impact of utilizing the two-dose hepatitis B vaccine, which has been demonstrated to have both a higher completion rate and a higher seroprotection rate. Healthcare leaders in the private sector and policymakers in government keen to address the significant burden of hepatitis B in the United States can consider strategies to increase vaccination rates or increase utilization of the two-dose vaccine, or both.

While increasing the vaccination rate is a vital goal, our analysis shows that simply switching to the two-dose vaccine would have as great a benefit as vaccinating millions more people. Our results clearly demonstrate the potential benefit of successful efforts to further raise the adoption rate of the two-dose vaccine. More than a thousand lives can be saved as well as hundreds of millions of dollars in healthcare spending.

ABOUT THE AUTHORS

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ABOUT MGA

MGA specializes in healthcare, tax, and fiscal policy. Drawing on years of policy experience, the MGA team uses analytics to help identify, quantify, and solve economic policy problems.

This report was sponsored by the Immunization Alliance for Equity and Access. The authors are solely responsible for the content. Any views expressed here represent only the view of the authors.

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Appendix

This appendix provides a detailed description of the methodology used in constructing the hepatitis B vaccination and disease progression model presented in this paper. The core model operates in two parts:

1. **Vaccination.** A baseline (t = 0) calculation that determines how many individuals are in each initial state (Protected, Susceptible, Chronic, and Acute), followed by continuous vaccination beginning in year t = 1, when the model can vaccinate a user-set fraction of the remaining susceptible population each year based on vaccine initiation rates, return rates for subsequent doses, and seroprotection rates.

2. **Disease Progression.** An annual Markov simulation that iteratively applies a transition matrix to the state vector, tracking how the population moves through disease states over the time horizon, adding a new inflow of adults each year and moving them through the same Markov system.

COHORT GENERATION

The model tracks multiple cohorts with different characteristics to capture heterogeneity. As parameterized, it is set to match the US adult population, with 40 demographic cohorts stratified by race (white, Black, Asian, and other); sex (each race is split 50/50 by sex, male and female); and age group (19–29, 30–39, 40–49, 50–64, and 65+).

Each cohort's share is calculated as:

$$\text{share} = \text{race}_{share} \times 0.5 \text{ x age}_{weight}$$

Where *race_share* is the population share of each race in the 2024 population distribution, 0.5 assumes that each race is split 50/50 by sex, and *age_weight* is the population weight of each age group.

The model assumes that some portion of each cohort is already seroprotected from prior vaccination (by age), and that a fixed proportion of each cohort begins the model with baseline acute and chronic HBV.

THE STATE SPACE

The model tracks individuals across 11 mutually exclusive health states. At any point in time, each person in the simulation occupies one state.

The last two states, *Death_HBV* and *Death_Other*, are absorbing. Once an individual reaches these states, they never leave. The distinction between HBV-related death and other-cause death allows the user to track mortality attributable to hepatitis B versus background death from aging and other causes across vaccination scenarios.

State	Symbol	Description
Protected	P	Seroprotected (immune). The individual has developed protective antibody levels.
Susceptible	S	Not immune and at risk of infection.
Acute	A	Acute HBV infection. A short-term illness that occurs shortly after exposure.
Chronic	C	Chronic HBV infection. A long-term infection the immune system cannot clear.
FHF	FHF	Fulminant hepatic failure. A rare but severe complication causing rapid liver failure.
CompCirr	CC	Compensated cirrhosis. Significant liver scarring, but the liver still functions.
DecompCirr	DCC	Decompensated cirrhosis. Severe scarring where the liver can no longer function properly.
HCC	HCC	Hepatocellular carcinoma. Liver cancer, often a consequence of chronic infection.
Transplant	TX	Liver transplant. The patient has received a transplant.
Death_HBV	D_HBV	Death from HBV-related causes.
Death_Other	D_Other	Death from non-HBV causes (background mortality).

PART 1 – VACCINATION PHASE

The initial vaccination phase determines baseline conditions for the Markov model at $t = 0$. The vaccination phase takes as given:

- Total individuals in the cohort (population size × cohort share)
- Initiation rate of individuals starting the vaccine series
- Vaccine configuration
- Baseline number of individuals already seroprotected, chronically infected, and acutely infected (parameterized in the model)

Calculation Steps

Step 1: Determine Eligibility

Before agents in the model are vaccinated, the model accounts for those already protected (from prior vaccination), already chronically infected, or who have acute infection. Only those who meet none of these criteria are eligible for vaccination:

$$N_{eligible} = N_{total} - N_{already\ protected} - N_{chronic} - N_{acute}$$

Step 2: Apply Initiation Rate

The initiation rate (α) determines the fraction of eligible individuals that start the vaccine series:

$$N_{initiators} = N_{eligible} \times \alpha$$

$$N_{noninitiators} = N_{eligible} - N_{initiators}$$

Those individuals who do not initiate the vaccine remain in the susceptible state.

Step 3: Process Through Vaccine Series

Everyone who initiates receives Dose 1. After each dose (except the final one), some people return for the next dose and some drop out. Dropouts receive whatever protection level they have achieved so far.

For each dose i from 1 to $n - 1$:

$$N_{return} = N_{atdose} \times r_{i+1}$$

$$N_{dropout} = N_{atdose} - N_{return}$$

Where r_{i+1} is the return rate for the next dose. Among dropouts:

$$N_{dropoutprotected} = N_{dropout} \times SPR_i$$

$$N_{dropoutsusceptible} = N_{dropout} \times (1 - SPR_i)$$

Where SPR_i is the cumulative seroprotection rate, that is,

SPR_1 = protection rate after Dose 1 only
SPR_2 = protection rate after Doses 1 and 2
SPR_3 = protection rate after Doses 1, 2, and 3

Step 4: Final Dose Outcomes

Those who reach the final dose either become protected or remain susceptible based on the final seroprotection rate:

$$N_{completers} = N_{atfinaldose}$$

$$N_{protectedfromcompletion} = N_{completers} \times SPR_{final}$$

$$N_{susceptiblefromcompletion} = N_{completers} \times (1 - SPR_{final})$$

The model then vaccinates a fraction ρ of the remaining susceptible population in each simulation year $t \geq 1$. For cohort g in year t, the offered group is $O_{g,t} = \rho \times S_{g,t}$. That offered group is then split by vaccine mix share: $O^A_{g,t} = (1 - S_B)O_{g,t}$ and $O^B_{g,t} = S_B\ O_{g,t}$.

Within the offered groups, vaccine initiation rate is set to 1 (all receive the first dose), and baseline protected, chronic, and acute are set to 0 because these individuals are already known to be susceptible.

The same dose completion and seroprotection logic from the baseline vaccination phase is then applied.

If $P_{g,t}^{new}$ and $S_{g,t}^{return}$ denote the new protected and residual susceptible counts generated from the offered groups progressing through the vaccination phase, the state update is: $S_{g,t} \leftarrow S_{g,t} - O_{g,t} + S_{g,t}^{return}$ and $P_{g,t} \leftarrow P_{g,t} + P_{g,t}^{new}$.

PART 2 – DISEASE PROGRESSION (MARKOV MODEL)

Once the initial distribution of individuals across the Protected, Susceptible, Chronic, and Acute states is determined, the model simulates how this population evolves over time using a Markov process.

The Markov Model Framework

A Markov model is a mathematical framework that describes a system moving through discrete states over time. The key feature is that the probability of transitioning to the next state depends only on the current state.

The State Vector

At any point in time *t*, the population distribution is described by a state vector v_t. This is a row vector where each element represents the number of individuals (*n*) in each health state:

$$v_t = [n_p, n_s, n_A, n_C, n_{FHF}, n_{CC}, n_{DCC}, n_{HCC}, n_{TX}, n_{D_{HBV}}, n_{D\_Other}]$$

The sum of all elements in v_t equals the current modeled population at time *t*.

The Transition Matrix

The heart of the Markov model is the transition matrix P. This is an 11×11 matrix where each element P[*i*,*j*] represents the probability of moving from state *i* to state *j* in one time step (one year). Each row of the transition matrix is constructed to sum to 1. This ensures that every individual transitions to some state (including possibly staying in the same state).

Transition Probabilities by State

Protected State (P)

Individuals who are seroprotected have developed immunity and are protected from HBV infection. The only way they leave this state is through death from other causes (background mortality).

Let p_{bg} = probability of background (non-HBV) death:

$$P\,[Protected \rightarrow Death\_Other] = p_{bg}$$

$$P\,[Protected \rightarrow Protected] = 1 - p_{bg}$$

Background mortality probability is calculated using an exponential function of age with an adjustment for gender.

Susceptible State (S)

Susceptible individuals can either become infected (transition to Acute), die from other causes, or remain susceptible.

Let FOI = Force of Infection (annual probability of becoming infected):

$$P\,[Susceptible \rightarrow Death\_Other] = p_{bg}$$

$$P\,[Susceptible \rightarrow Acute] = (1 - p_{bg}) \times FOI$$

$$P\,[Susceptible \rightarrow Susceptible] = (1 - p_{bg}) \times (1 - FOI)$$

The term $(1 - p_{bg})$ appears because individuals must survive background mortality before potentially becoming infected. Background mortality is applied first; then disease-specific transitions are applied to the survivors.

Acute HBV Infection State (A)

Acute HBV infection has several possible transitions:

$$P\,[Acute \rightarrow Death\_Other] = p_{bg}$$

$$P\,[Acute \rightarrow Protected] = (1 - p_{bg}) \times p\_acute\_clear$$

$$P\,[Acute \rightarrow Chronic] = (1 - p_{bg}) \times p\_acute\_to\_chronic$$

$$P\,[Acute \rightarrow FHF] = (1 - p_{bg}) \times p\_acute\_to\_fhf$$

$$P\,[Acute \rightarrow Death\_HBV] = (1 - p_{bg}) \times p\_death\_acute$$

Chronic HBV Infection State (C)

Chronic HBV infection is a long-term condition with annual probabilities of progression to compensated cirrhosis, HCC, and death. The probability of staying in the Chronic state is:

$$P\,[Chronic \rightarrow Chronic] = (1 - p_{bg}) \times (1 - pchronic\_to\_cirrhosis - pchronic\_to\_hcc - pdeath\_chronic)$$

Other Disease States

The remaining disease states (FHF, compensated cirrhosis, decompensated cirrhosis, HCC, and transplant) follow the same logic. Each has probabilities of transitioning to more severe states, receiving a transplant, dying from HBV-related causes, or remaining stable.

Running the Simulation

With the initial state vector v_0 and transition matrix P defined, running the simulation follows:

$$v_{t+1} = v_t \times P$$

To get the distribution of the cohort in the next year $t + 1$, multiply the current year state vector by the transition matrix.

Because transitions occur throughout the year rather than instantaneously at the start or end, the model uses the average of the state vectors at the beginning and end of each period:

$$v_{avg} = (v_t + v_{t+1}) / 2$$

The FOI depends on the acute and chronic infections across all living cohorts, creating a feedback loop where higher vaccination reduces transmission:

$$prevalence = \frac{(N_{acute} = N_{chronic})}{N_{alive}}$$

$$FOI = 1 - e^{-\beta \times prevalence}$$

Where β is the transmission coefficient. Higher β means faster transmission for a given prevalence.