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Economic Evaluation of Delivering Hepatitis B Vaccine to Injection Drug Users

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Abstract

Background—Injection drug users (IDUs) are at high risk of hepatitis B (HBV) infection, and HBV vaccination coverage in IDUs is low. Recent studies demonstrate that syringe exchange programs are effective venues to reach and immunize IDUs. The purpose of this paper was to determine if targeting IDUs for HBV vaccination through syringe exchange programs is economically desirable for the healthcare system and to assess the relative effectiveness of several different vaccination strategies.

Methods—Active IDUs in Chicago IL and Hartford and Bridgeport CT (N=1964) were recruited and screened through local syringe exchange programs, randomized to a standard (0, 1, 6 months) or accelerated (0, 1, 2 months) vaccination schedule, and followed from May 2003 to March 2006. Analyses were conducted in 2007. The vaccination program's costs were balanced against future HBV-associated medical costs. Benefits in terms of prevented acute HBV infections and quality-adjusted life years were estimated based on a Markov model.

Results—HBV vaccination campaigns targeting IDUs through syringe exchange programs are cost-saving. The most cost-saving strategies include giving the first dose to everyone at screening, administering the vaccination under the accelerated schedule (0, 1, 2 months), and obtaining highly discounted vaccine from local health departments.

Conclusions—It is economically inappropriate to offer HBV screening in the absence of vaccination. Existing syringe exchange programs in the U.S. should include HBV vaccination.

Introduction

Since the first safe and effective hepatitis B vaccine was approved in 1982, vaccination campaigns have been successful in controlling hepatitis B virus (HBV) infection in the general U.S. population. However, HBV infection remains a major health threat to individuals who

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engage in high-risk behaviors, especially injection drug users (IDUs).[1] Among the estimated 1.3 million IDUs in the U.S.,[2–4] the prevalence of HBV infection ranges from 40% to 80%,[5–12] and the incidence rate ranges between 8% and 12%.[13–15] The Advisory Committee on Immunization Practices recommended vaccination of IDUs as long ago as 1991,[16] but the current vaccination coverage among IDUs remains low.[17–19] Vaccination programs targeting IDUs are uncommon, mainly due to a lack of funds, the lack of reliable delivery venues, and expectations of poor adherence to a complicated hepatitis B vaccination schedule.

The mortality and morbidity associated with HBV infection (e.g., treatment of serious acute HBV infection and illnesses associated with chronic infection) impose a sizable economic burden on the healthcare system. To date, no study has undertaken a comprehensive evaluation of the costs and benefits of a hepatitis B vaccination program that targeted IDUs. Previous studies have shown that hepatitis B vaccination targeting other high-risk groups is cost effective and even cost saving. The hepatitis B vaccination of prison inmates in the U.S. would realize savings for the healthcare system, although it would cost the prison system $415 per infection averted.[20] A recent study in England and Wales found that the vaccination of high-risk adults in genitourinary clinics was more cost effective than universal infant vaccination.[21] Also, U.S. and Italian studies yielded similar conclusions among hemodialysis patients.[22,23] Therefore, hepatitis B vaccination targeting IDUs was anticipated to be cost effective or cost saving if IDUs could be successfully reached and immunized.

Analysis of recent studies revealed that it is possible to successfully reach and immunize IDUs by implementing vaccine programs through syringe exchange programs and providing modest payments to clients as incentives.[24–26] It was hypothesized that adherence could also be increased by adopting an accelerated (2-month) hepatitis B vaccination schedule without a substantial reduction of immune protection.[27] The purpose of the present study was to determine the economic and clinical consequences of vaccinating IDUs against hepatitis B after implementing these approaches. Two vaccination schedules (standard 0, 1, 6 months versus accelerated 0, 1, 2 months) and two screening strategies (giving the first dose only to susceptible people who return following screening versus giving the first dose to every participant at the screening visit) were compared. This study set out to ascertain whether hepatitis B vaccination campaigns targeting IDUs are economically desirable for the healthcare system and which screening strategy would be the most effective.

Methods

Study Population

The assessment of hepatitis B vaccination of IDUs was based on data from the Hepatitis Vaccine Study (HVS) of active IDUs in Chicago IL and Hartford and Bridgeport CT. Data were collected between May 2003 and March 2006. The primary inclusion criteria were that participants be aged≥18 years and had injected drugs in the past 30 days as indicated by self-report and the evidence of injection stigmata. The HVS research protocol was approved by the Yale Human Investigation Committee as well as the IRBs at DePaul University (Chicago) and the Hispanic Health Council (Hartford). Blood samples, collected at screening, were tested to determine HBV serostatus. First, Abbott Corzyme B® and Abbott Ausab® enzyme immunoassays (EIAs) were used to detect HBV core antibody (HBcAb) and HBV surface antibody (HBsAb), respectively. When necessary, sera were further tested with the Auszyme® EIA to detect HBV surface antigen (HBsAg), a marker for active infection. Among a total of 1964 recruits, 860 (44%) individuals were susceptible to HBV infection (i.e., their sero-samples tested negative for HBsAb, HBcAb, and HBsAg) and therefore were eligible to receive a vaccination. All others were excluded from the vaccination program.

Participants who returned for their serologic results and received the first dose of vaccine were randomized to either the standard (0, 1, and 6 months) or accelerated (0, 1, and 2 months) vaccination schedules. In Hartford and Bridgeport, all vaccinees received TWINRIX (GlaxoSmithKline, [GSK]). In Chicago, some of vaccinees received Recombvax (Merck) + HAVRIX (GSK) instead. Blood samples were collected again at the Dose-3 visit (i.e., Month 2 or Month 6) and at the exit visit (Month 7) to assess successful immunization rates for two doses and three doses, respectively. Those who reached or surpassed the immunization threshold of 10 mIU/ml of HBsAb were considered to be successfully immunized. Across the three sites, an average of $15 was paid to each participant at each visit as an incentive.

A total of 595 eligible participants (69.2% of the 860 who tested susceptible) returned and received the first dose of vaccine. Among those who received the first dose, 76.4% completed two doses, and 52.0% completed three doses in the standard arm; 78.1% completed two doses, and 63.6% completed three doses in the accelerated arm. The successful immunization rates of three doses in the standard and accelerated vaccination schedules were 85.7% and 78.3%, respectively. The overall successful immunization rate of two doses was 60%. More details of the setting of the HVS and the demographic details of the study population are available in Heimer et al.[28]

Model

This study compared the economic performances of four vaccination strategies to that of a no-vaccination strategy in a cohort of 1964 IDUs (Figure 1). In the no-vaccination strategy, all susceptible IDUs were assumed to be at risk of HBV infection for the rest of their lives. The first vaccination strategy was *standard vaccination with first dose after screening visit;* this is the current standard recommended practice for high-risk populations,[29] which assumed the standard 6-month vaccination schedule, with the first dose given only to susceptible IDUs after having received their serologic tests results. The second vaccination strategy was *standard vaccination with first dose at screening visit*, where every recruit was given the first dose at the screening visit (i.e., prior to obtaining serologic test results). For those who returned, second and third doses were given 1 and 6 months later only to those susceptible at screening.

The third vaccination strategy was *accelerated vaccination with first dose after screening visit*, which is similar to the first strategy except that the third and final dose was given after 2 instead of 6 months. The fourth vaccination strategy was *accelerated vaccination with first dose at screening visit*, which gave the first dose to every recruit at the screening visit; the second and third doses were given 1 and 2 months later only to those susceptible at screening. IDUs successfully immunized in the four vaccination strategies included those successfully immunized after three doses and those successfully immunized after only two doses. Successfully immunized individuals were assumed to have a life-long protection against HBV. Individuals who completed the three-dose vaccine series but were not successfully immunized were assumed to have the same risk of infection as those who were unvaccinated.

By extending a Markov model simulating the natural history of HBV infection (Figure 2),[21] the long-term clinical consequences and medical costs of those who remain susceptible as a result of failing to begin or complete the vaccine series or who fail to become successfully immunized were analyzed. The model was analyzed using TreeAge Pro 2007. A total of ten health states were followed in the model until all people in the cohort died; the analyses were conducted in 2007. A specified percentage of each state moves into other states according to a set of transition probabilities (Table 1[1,13–15,20,30–51]) during a time interval called the Markov cycle. The Markov cycle in this model was set to 1 year. Because the annual rate of IDUs who permanently stop drug injection is unknown and recidivism is very common, it was assumed that the IDU cohort in this model was a closed population in the baseline analysis, and a range of permanent cessation rates was tested using the sensitivity analysis. Those IDUs

who permanently stopped injection were assumed to have the same low risk of infection as the general population for the rest of their lives.

The model estimated the number of new acute HBV infections, quality-adjusted life years (QALYs), and the future medical costs in each strategy. QALYs and future medical costs were discounted at a 3% annual rate. The quality-of-life scale ranging from 0 (death) to 1 (full quality) for HBV-related illnesses was obtained from Kim et al.[36] Economic results were summarized as the difference between the total costs (the sum of costs of the vaccination program and future medical costs) of each vaccination strategy and those costs incurred in the no-vaccination strategy (i.e., net cost). Benefits were expressed as acute HBV infections prevented and as QALYs gained.

Epidemiologic Data

The incidence of HBV and the transition probabilities used in the Markov model were estimated from the published literature (Table 1). It is known that the probabilities of progressing from acute to chronic infection and from chronic infection to cirrhosis differ between adults and children. Because participants in this study were all aged ≥18 years and the average age was 40, the probabilities used in this model were those characteristics of the adult group.

Costs

This economic evaluation was designed to assess vaccination strategies with respect to the allocation of healthcare funds, and therefore the analysis was conducted from the perspective of the healthcare sector. As such, only the direct medical costs of HBV-associated illnesses and the direct costs of the vaccination program targeting IDUs were considered in the model (Table 2[36,52,53]). The medical costs associated with HBV morbidity and mortality by other diseases in co-infected individuals[54] were not considered in this model. The annual medical costs of acute infections were obtained from Margolis et al.,[52] and the annual medical costs of chronic infection and its associated illnesses were obtained from Kim et al.[36] All these costs were updated to 2003 by using the medical care component of the Consumer Price Index. Vaccination program costs included (1) staff salaries and benefits associated with time spent on recruiting, serologic testing, and vaccine administration; (2) supply costs (e.g., serologic testing supplies, paper, and miscellaneous office supplies); (3) the cost of participant incentives; and (4) the cost of the vaccine. The baseline analysis assumed the availability of a discounted vaccine price of $10 (i.e., provided by health departments), but additional models using the standard retail vaccine price of $55 were analyzed. Future costs were discounted to 2003 at 3% per year.

Sensitivity Analysis

Sensitivity analyses examined the effect of variations in the probabilities of disease progression, the incidence rate of acute infection, the percentage of the susceptible IDUs, vaccine completion rates, successful immunization rates, the rates at which IDUs stop injecting, and access to medical care.

Results

Baseline Results

Table 3 presents the baseline results for each strategy. It shows that the accelerated vaccination schedule prevented 17% more acute infections and gained 14%–20% more QALYs per person than the standard vaccination schedule. Also, the vaccination strategy with the first dose administered to everyone at the screening visit prevented 45% more acute infections and saved 43%–50% more QALYs per person than the strategy that administered the first dose only to

susceptible persons who returned for their test results. Compared with the no-vaccination strategy, the net costs of the four vaccination strategies were all cost saving. (i.e., negative net costs). The accelerated vaccination schedule realized 32%–51% more savings than the standard vaccination schedule, and the strategy with the first dose administered to everyone at the screening visit realized 99%–127% more savings than the strategy that administered the first dose only to susceptible persons. Therefore, the accelerated vaccination schedule with the first dose given at the screening visit was the most cost-saving and cost-effective strategy. It should be remembered that the vaccination programs analyzed here were furnished with vaccine from local health departments that obtain their vaccine from the CDC for approximately $10 per dose. If vaccines were obtained at retail, the cost would be $55 per dose. This higher vaccine price decreased the magnitude of savings, but it did not change the cost-saving result and the relative order of magnitude of the savings of the four vaccination strategies.

Sensitivity Analysis

When each disease-progression factor was varied within a plausible range (Table 1), none changed the relative order of the number of acute infections prevented or the dominant position of the accelerated vaccination with the first dose at screening. Among the variables tested, the total cost of each strategy was most sensitive to the probabilities of developing chronic hepatitis from acute infection, developing compensated cirrhosis from chronic hepatitis, and mortality rates.

Successful immunization rates in IDUs were 10% lower than those in healthy young adults.[27] But the results were less sensitive to the successful immunization rates than to the vaccine-completion rates. When both two-dose and three-dose successful immunization rates increased by 10%, the savings of the four vaccination strategies increased by 4% to 10%, and the benefits increased by 2% to 3%, respectively. When both two-dose and three-dose completion rates increased by 10%, the savings of the four vaccination strategies increased by 24% to 52%, and the benefits increased by 15% to 18%, respectively.

A lower susceptibility rate, a lower incidence rate, or both, decreased the number of acute infections prevented and the savings realized from each vaccination strategy. The CDC recommendation is that the prevaccination screening may be considered when the prevalence of HBV infection is >20%.[55] The analyses in this paper determined that the standard vaccination program, with the first dose given after the screening visit, was cost saving when susceptibility was not less than 25% (i.e., prevalence is not greater than 67%) and the vaccination and laboratory costs did not exceed $500,000. When the susceptibility rate was less than 17% (i.e., prevalence greater than 75%) or the annual incidence of acute infection was lower than 2.5%, the future HBV-related medical costs saved by the four vaccination strategies did not offset the vaccination program costs, and the four vaccination strategies were no longer cost saving compared with the no-vaccination strategy.

When the cessation rate of drug injection was considered in the model (i.e., when the annual percentage of IDUs permanently stopping drug injection increased), an increase in QALYs gained was found. This is because the life-saving effect of hepatitis B vaccination diminished due to the high mortality rate of IDUs, and the effect is more obvious in the general population due to the relatively lower mortality rate. When injection-cessation rates increased, there was a decrease in the number of acute infections prevented and in the magnitude of savings in each vaccination strategy. This is attributed to the significantly lower HBV incidence rate in the general population. When more than 29% of IDUs permanently stopped drug injection per year, all four vaccination strategies were no longer cost saving compared with the no-vaccination strategy.

In the baseline analysis, it was assumed that 100% of IDUs had access to medical care after they were infected. The sensitivity analysis demonstrated that all four vaccination strategies were cost saving compared to the no-vaccination strategy once more than 70% of IDUs had access to medical care. When less than 46% of IDUs had access to medical care, all four vaccination strategies were no longer cost-saving, because 54% of medical costs were no longer spent.

Discussion

This study demonstrated that integrating hepatitis B vaccination into existing syringe exchange programs would realize an economic benefit for the healthcare system. The most cost-saving and cost-effective vaccination strategy included giving the first dose to all screened participants prior to knowing their serological results and administering the vaccination under the accelerated schedule (0, 1, 2 months); this strategy saved almost a half-million dollars, realized a gain of 0.12 QALYs per person, and prevented 382 acute HBV infections for a cohort of 860 susceptible IDUs.

The cost saving of a hepatitis B vaccination program as demonstrated in this study was based on several factors. First, the target population had a comparatively high incidence rate of infection.[13–15] Second, a high proportion (44%) of the target population remained susceptible to infection. Third, the medical costs of chronic HBV-associated illnesses are expensive, ranging from $1003 to $328,407 per person per year.[36] Fourth, the sensitivity analysis indicated that at least 46% of the target population should have access to medical care when they get infected. Although health data were not collected in this study, 79.7% active IDUs in Connecticut are insured (unpublished data, 2002). However, it should be noted that having health insurance does not guarantee access to medical care. Fifth, the program is cost saving if less than 29% of IDUs permanently stop drug injecting annually. To our knowledge, there is no information in the literature concerning permanent injection-cessation rates. In fact, this rate would be difficult if not impossible to ascertain; it is imagined that a 29% cessation rate surpasses the actual rate. Economic benefit would be expected when implementing similar vaccination campaigns in other U.S. cities that satisfy the above conditions.

In addition, this study demonstrated that an investment in hepatitis B vaccination targeting IDUs through syringe exchange programs compared favorably to other HBV interventions targeting other high-risk groups in the U.S. The vaccination of hemodialysis patients was found to cost $261 per patient from the perspective of the healthcare sector.[23] A recent study showed that routine hepatitis B vaccination costs $6.80 per adult client through HIV counseling and testing sites, and costs $7.40 per adult client through sexually transmitted disease clinics from the societal perspective.[36] Only one previous hepatitis B vaccination study with the perspective of the healthcare sector also identified cost savings, and it demonstrated that providing hepatitis B vaccine for prison inmates would realize a saving of $45,000,000 for 381,646 inmates, approximately $118 per inmate involved.[20] In contrast, the most cost-saving strategy in the current study could save $473,999 for 1964 IDUs, approximately $241 per IDU involved.

These estimates are conservative and likely underestimate the benefits of a hepatitis B vaccination program for IDUs. Only participants who were successfully protected by completing two or three doses were considered in this model. But those who completed only one dose were found to have successful immunization rates ranging from 5.4% to 20.4% in healthy adults in previous studies.[56] Although the one-dose successful immunization rate would probably be lower among IDUs, one might reasonably expect some increase in protection by factoring that rate into the model. Furthermore, occult HBV infection was not taken into account in the current study's model. A previous study showed that those with occult HBV infection might have higher probabilities of developing cirrhosis and hepatocellular

carcinoma,[57] which may incur greater medical costs for infected people compared to vaccinated people and increase the savings from vaccination. Moreover, because most HBV transmission is from individuals engaged in high-risk behaviors, the benefits of vaccination will be greater if secondary transmission to non-IDUs is considered in the model. In addition, the average age of IDUs in this study was 40. More savings would be realized by enrolling younger IDUs, because they may have a higher likelihood of developing protective antibody levels.[58] The cohort effect of universal vaccination (implemented by the U.S. Public Health Service in the 1990s) should be considered in future models.

In conclusion, existing syringe exchange programs in the U.S. should include hepatitis B vaccination programs because they are effective in protecting IDUs against HBV infection and are economically beneficial to the healthcare system. This logic can be extended to any program or service that comes into repeated contact with high HBV-incidence populations such as IDUs.

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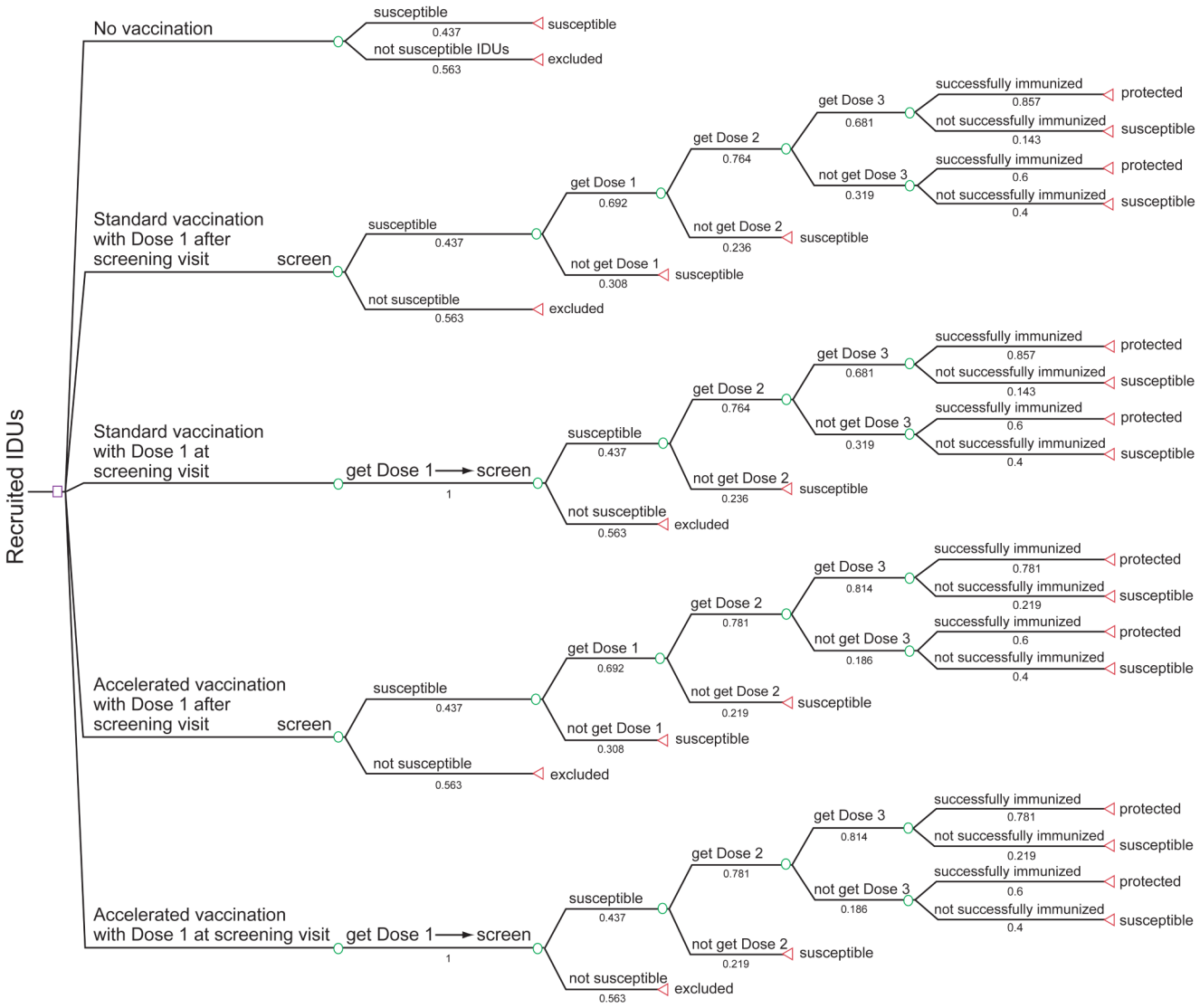

Figure 1. Decision model for hepatitis B vaccination at syringe-exchange programs

This figure depicts four vaccination strategies and the no-vaccination strategy considered in the model. Depending on the strategy chosen, participants would receive the first dose either prior to knowing their serologic results or after learning they are susceptible according to their serologic results; the third dose would be administered on either a standard or accelerated schedule. Once participants initiate vaccination, they either return for their follow-up doses or fail to complete the vaccine series. The completion rates, successful immunization rates, and percentage of the susceptible were based on data obtained from the HVS study. Those who remain susceptible as a result of failing to begin the vaccine series, to complete the vaccine series, or to become successfully immunized were entered into a Markov model simulating the natural history of HBV infection.

IDU, injection drug user

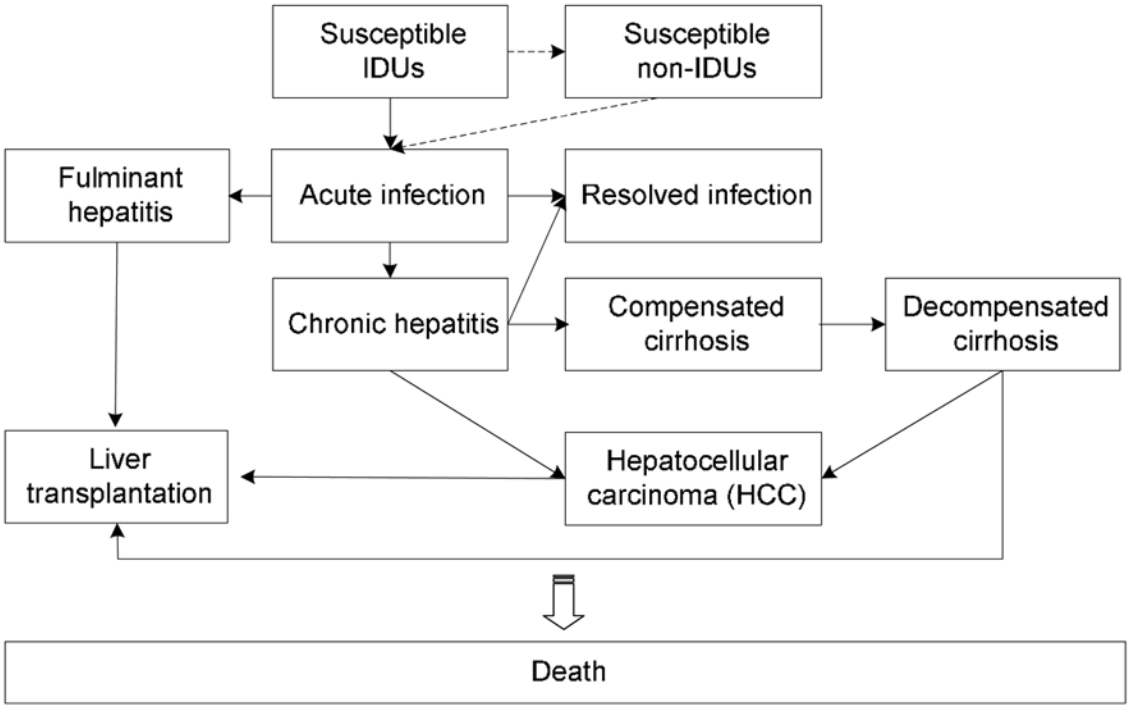

Figure 2. Markov model of disease states following HBV infection

This figure shows the dynamic flow of health states included in the model. People who develop acute infections could have three possible manifestations: asymptomatic, non-hospitalized symptomatic, and hospitalized symptomatic. These three manifestations were not explicitly stated in the Markov model, but different medical costs would be considered in the analysis. Some acute infections can progress to fulminant hepatitis. Although most acute infections are resolved in adults, a percentage—about 5%—develop chronic infection. The chronic infections may progress to compensated cirrhosis, to hepatocellular carcinoma (HCC), or to both. Compensated cirrhosis may progress to decompensated cirrhosis and subsequent HCC. Patients with fulminant or chronic hepatitis may subsequently undergo liver transplantation. The dotted line in this model describes the dynamic of permanent cessation of drug injection in the sensitivity analysis.

Table 1

Estimation for parameters in the Markov model

Parameter	Baseline	Range	Sources
Susceptible IDUs			
Probability of developing acute infection	0.1	0.08–0.12	13–15
Probability of stopping injecting drugs	0	0–0.8	Estimated
Probability of disease-free mortality	0.035	0.033–0.081	30,31
Susceptible non-IDUs			
Probability of developing acute infection	0.0004	0.0004–0.0006	1
Probability of disease-free mortality	0.017	0.013–0.017	Estimated
Acute infection state			
Proportion of asymptomatic infection	0.6		20
Proportion of symptomatic infection	0.4		20
Proportion of hospitalization	0.12		20
Proportion of non-hospitalization	0.88		20
Probability of developing fulminant hepatitis	0.005	0.001–0.01	32,33
Probability of developing chronic hepatitis	0.05	0.02–0.1	34
Probability of recovery	0.94		35
Probability of disease-specific excess mortality	0.005	0.005–0.01	35
Fulminant hepatitis state			
Probability of undergoing liver transplantation	0.2	0.11–0.3	36
Probability of disease-specific excess mortality	0.7	0.6–0.8	37–39
Chronic hepatitis state			
Probability of developing compensated cirrhosis	0.121	0.004–0.142	36
Probability of developing HCC	0.005	0.002–0.007	36
Probability of recovery	0.1	0.095–0.105	36
Probability of disease-specific excess mortality	0.025	0.018–0.036	33,40
Compensated cirrhosis state			
Probability of developing decompensatedcirrhosis	0.044	0.028–0.083	41–43
Probability of developing HCC	0.024	0.013–0.055	44–47
Probability of disease-specific excess mortality	0.036	0.03–0.044	36
Decompensated cirrhosis state			
Probability of developing HCC	0.024	0.013–0.055	44–47
Probability of disease-specific excess mortality	0.275	0.225–0.325	42,44,48
Probability of undergoing liver transplantation	0.018	0.015–0.024	36
HCC state			
Probability of disease-specific excess mortality	0.429	0.259–0.503	36
Probability of undergoing liver transplantation	0.045	0.036–0.071	36
Liver transplantation for fulminant			
Probability of disease-specific excess mortality	0.07	0.066–0.104	49–51

IDU, injection drug user; HCC, hepatocellular carcinoma

Table 2

Medical costs of hepatitis B-associated illnesses and vaccination costs

Costs	Estimate ($ per person)	Source
Annual medical costs[a]		
Acute infection[b] **(one-time costs)**		
Nonhospitalized	309	52
Hospitalized	9,173	52
Fulminant	17,407	52
Chronic carrier	1,003	36
Compensated cirrhosis	5,666	36
Decompensated cirrhosis	29,800	36
Hepatocellular carcinoma	26,425	36
Liver transplantation		
First year	328,407	36
Follow-up years	31,681	36
HBV-unrelated medical expenditure	2,416	53
Costs of vaccination program		
Recruiting	42	Estimated
Blood drawing	15	Estimated
Vaccine administering	13	Estimated
Serologic test cost	34	Estimated
Supply cost	8	Estimated
Payment per visit	15	Estimated
Vaccine	10–55 per dose	Estimated

[a] All medical costs are expressed in 2003 U.S. dollars.

[b] Only medical costs for acute infection are one-time costs.

Table 3

The baseline cost–benefit result of the syringe exchange program-delivered hepatitis B vaccination involving 1964 IDUs in Chicago IL and Hartford and Bridgeport CT

Strategy	Acute infections prevented	Discounted QALYs Gained	Discounted HBV-related medical costs ($)	Program cost ($)		Net cost ($)	
				$10 vaccine	$55 vaccine	$10 vaccine	$55 vaccine
No vaccination	0	0	1,414,526	0	0	/	/
Standard vaccination with first dose after screening	225	0.07	914,508	342,052	403,207	−157,967	−96,812
Accelerated vaccination with first dose after screening	264	0.08	827,333	348,926	413,636	−238,267	−173,557
Standard vaccination with first dose at screening	326	0.10	690,815	364,783	503,129	−358,928	−220,582
Accelerated vaccination with first dose at screening	382	0.12	565,811	374,717	518,192	−473,999	−330,524

HBV, hepatitis B virus; IDU, injection drug user; QALY, quality-adjusted life year