MAJOR ARTICLE

The Cost-effectiveness of Screening for Chronic Hepatitis B Infection in the United States

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(See the editorial commentary by Lo Re III, on pages 1307–1309.)

Background. Hepatitis B virus (HBV) continues to cause significant morbidity and mortality in the United States. Current guidelines suggest screening populations with a prevalence of ≥2%. Our objective was to determine whether this screening threshold is cost-effective and whether screening lower-prevalence populations might also be cost-effective.

Methods. We developed a Markov state transition model to examine screening of asymptomatic outpatients in the United States. The base case was a 35-year-old man living in a region with an HBV infection prevalence of 2%. Interventions (versus no screening) included screening for Hepatitis B surface antigen followed by treatment of appropriate patients with (1) pegylated interferon-α2a for 48 weeks, (2) a low-cost nucleoside or nucleotide agent with a high rate of developing viral resistance for 48 weeks, (3) prolonged treatment with low-cost, high-resistance nucleoside or nucleotide, or (4) prolonged treatment with a high-cost nucleoside or nucleotide with a low rate of developing viral resistance. Effectiveness was measured in quality-adjusted life years (QALYs) and costs in 2008 US dollars.

Results. Screening followed by treatment with a low-cost, high-resistance nucleoside or nucleotide was cost-effective ($29,230 per QALY). Sensitivity analyses revealed that screening costs <$50,000 per QALY in extremely low-risk populations unless the prevalence of chronic HBV infection is <.3%.

Conclusions. The 2% threshold for prevalence of chronic HBV infection in current Centers for Disease Control and Prevention/US Public Health Service screening guidelines is cost-effective. Furthermore, screening of adults in the United States in lower-prevalence populations (eg, as low as .3%) also is likely to be cost-effective, suggesting that current health policy should be reconsidered.

Hepatitis B virus (HBV) infection continues to be a major cause of morbidity and mortality in the United States despite strategies developed to eliminate its transmission. The estimated number of new infections in 2007 was 43,000 [1]. The recent Institute of Medicine (IOM) report on hepatitis and liver cancer notes that up to 2 million Americans are chronically infected, although upward of 75% may not know their status and thus present with late disease [2]. These individuals also serve as reservoirs for disease propagation. The IOM committee concluded that hepatitis B is an important public health problem and that lack of awareness among health care providers, at-risk populations, and the public presents significant barriers to its control.

Guidelines such as those of the US Preventive Services Task Force do not recommend screening for HBV infection in the general adult population [3]. In 2008 the Centers for Disease Control and Prevention (CDC) modified its recommendations to include "individuals born in Asia, Africa, and other geographic regions with 2% or higher prevalence of chronic HBV infections" [4]. Previous CDC recommendations called for testing of people born in areas with 8% prevalence or higher.

Chronic HBV infection leads to cirrhosis, liver failure, or hepatocellular carcinoma (HCC) in 15%–40% of patients and to liver transplantation in roughly 25% of

Received 10 November 2010; accepted 2 February 2011.

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Clinical Infectious Diseases 2011;52(11):1294–1306

1058-4838/2011/5211-0005$14.00
DOI: 10.1093/cid/cir199

patients per year with decompensated cirrhosis [5]. The goal of treatment is the prevention or reversal of decompensated cirrhosis and reduction in the risk of HCC [6–8].

The full economic impact of chronic HBV infection remains unknown. While previously reported analyses have focused on prevention (primarily through vaccination) [9], the cost-effectiveness of treatment strategies [5, 10–15], or screening and vaccinating high-risk populations [16], none have evaluated the larger question of screening and subsequent treatment in the general adult population. Therefore, we developed a decision analytic model that can be used to make assessments of the effectiveness and cost-effectiveness of screening in populations with varying prevalence of HBV infection.

METHODS

Population Prevalence

On the basis of data from the National Health and Nutrition Examination Surveys between 1988 and 1994, the prevalence of chronic hepatitis B (CHB; Hepatitis B surface antigen [HBsAg] positivity) in the general population of the United States is 0.42% (95% confidence interval, .32%–.55%) [17]. Among US-born, noninstitutionalized persons the prevalence is lowest, 0.1%, whereas foreign-born residents of the United States have a prevalence of 1.0%–2.6%. Among persons living in group quarters, such as college dormitories, military barracks, nursing homes, and long-term care facilities, the prevalence is roughly 0.5% [18].

Natural History of CHB

HBeAg seroconversion occurs in 50%–75% of patients within 5–10 years. Cirrhosis develops in a small proportion of patients and is correlated with both viral load and HBeAg status. Approximately 41% of patients with compensated cirrhosis progress to decompensated cirrhosis over a period of 15 years. HCC can develop at any stage of chronic infection with HBV, although it is more likely in patients with cirrhosis (see the Supplementary Appendix for further details).

Treatment of CHB

Management guidelines, including those from the American Association for the Study of Liver Diseases (AASLD), the US HBV Consensus Panel, and most recently the National Institutes of Health [6–8, 19], generally agree on which patient subgroups are treatment candidates—patients with chronic HBV infection, high HBV DNA levels, and active liver inflammation as reflected by elevated levels of alanine aminotransferase (ALT). Consistent with recommendations by the AASLD, we observe HBeAg-positive patients for 6 months and initiate therapy in those without spontaneous seroconversion. Patients who are HBeAg negative begin treatment without a period of observation. Liver biopsy is recommended for these patients. Duration of treatment is different for patients with HBeAg-positive and HBeAg-negative CHB. In the prolonged treatment strategies, treatment of HBeAg-positive patients is discontinued after an additional 6 months of consolidation therapy if they seroconvert, whereas those who are HBeAg negative are treated indefinitely. Among patients who have been screened, we assume that liver disease is not detected until they develop decompensated cirrhosis, in which case salvage therapy with 2 nucleoside or nucleotide agents is recommended. For patients who develop resistance, guidelines recommend the addition of a second agent or a switch to another agent (guided by viral resistance profiling).

Description of Decision Model

We used a commercially available computer program (DECISION MAKER) [20] to develop a Markov state transition model, analyze decision trees, and perform sensitivity analyses, using a lifelong time horizon and a societal perspective. We considered 5 strategies for a hypothetical 35-year-old man (see Figure 1):

1. No screening versus screening followed by treatment of HBsAg-positive patients with
2. Pegylated interferon-α2a for 48 weeks;
3. A low-cost nucleoside or nucleotide agent with a high rate of developing viral resistance for 48 weeks;
4. Prolonged treatment with a low-cost, high-resistance nucleoside or nucleotide followed by salvage therapy with the high-cost, low-resistance nucleoside or nucleotide for those who develop resistance; or
5. Prolonged treatment with a high-cost, low-resistance nucleoside or nucleotide.

Assumptions regarding efficacy, cost, and resistance were developed from data reported in the literature for lamivudine (low cost, high resistance) and tenofovir (high cost, low resistance). In order to bias results against screening, we assumed that screening would require a separate visit to a health care provider and result in the cost of a visit along with that of the blood test for HBsAg (see the Supplementary Appendix). We assume 100% compliance with treatment, as efficacy from clinical trials is based on intention to treat. However, we explore the impact of this assumption in sensitivity analyses (see Figure 2). Regardless of whether or not screening is performed, patients may have CHB, be immune (ie, have antibody to HBsAg), or be uninfected and unexposed. Asymptomatic patients found to have CHB may have elevated liver function test results (ALT) and may also be HBeAg positive. In the screening strategies, patients with elevated ALT level undergo abdominal ultrasound and HBV DNA load quantification. HBeAg-positive patients are stratified into those with viral loads of $\geq$20,000 IU/mL or

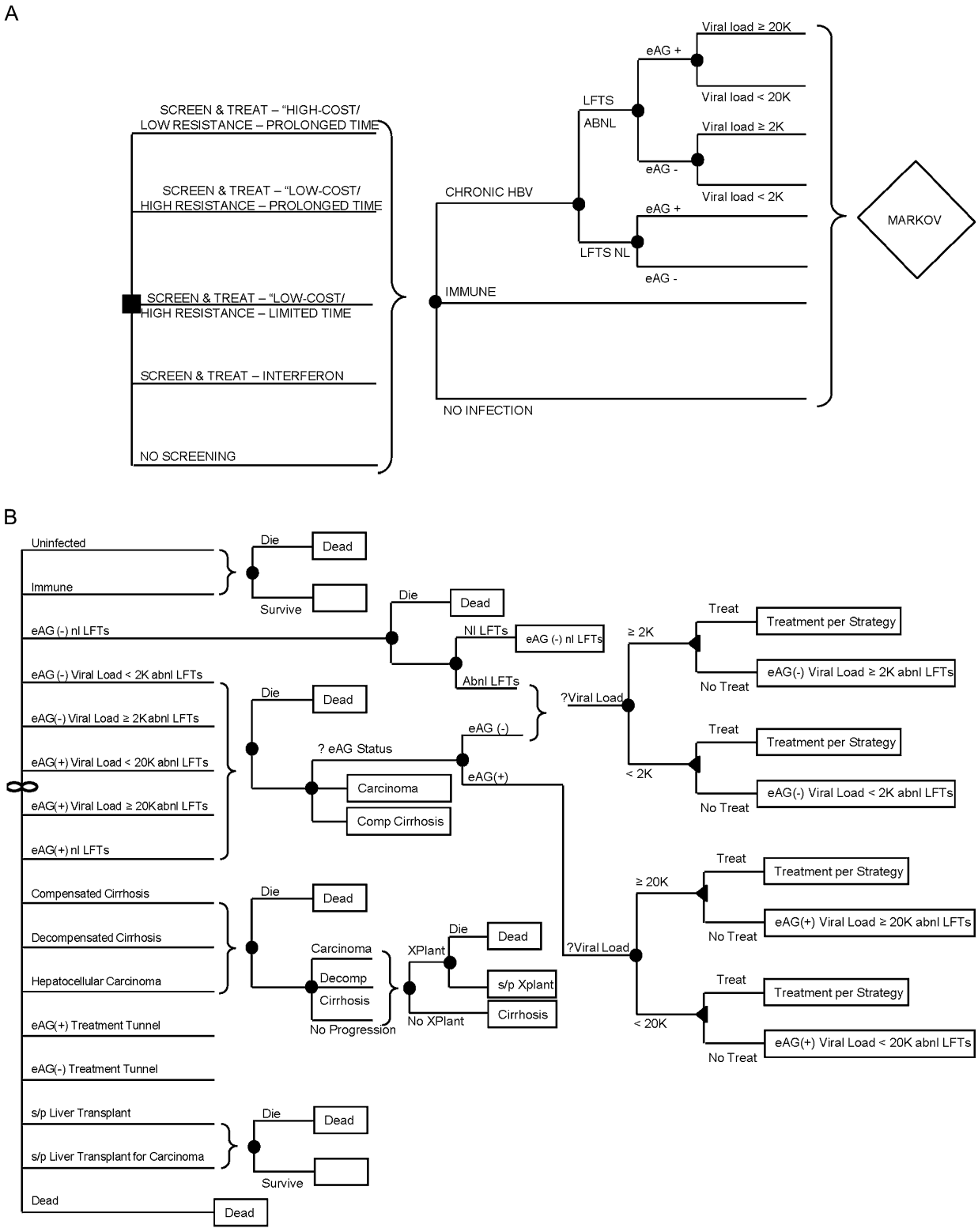

Figure 1. *A*, decision tree model showing the 5 screening and treatment strategies at the initial square decision node. As indicated at the first round chance node, at the time of screening patients may have chronic hepatitis B virus (HBV) infection, be immune, or not be infected. Patients with chronic HBV infection may or may not have abnormal liver function tests (LFTs); HBeAg status may be positive or negative, and viral load may be elevated or not in those with abnormal LFTs. After initial screening, all patients proceed to the Markov simulation. *B*, Simplification of the actual Markov model, which contains 52 states of health. During each monthly cycle, patients face a series of different chance events that depend on the state of health in which they started that cycle. In general, these events include elevation or normalization of alanine aminotransferase (ALT), increase or decrease in HBV DNA load,

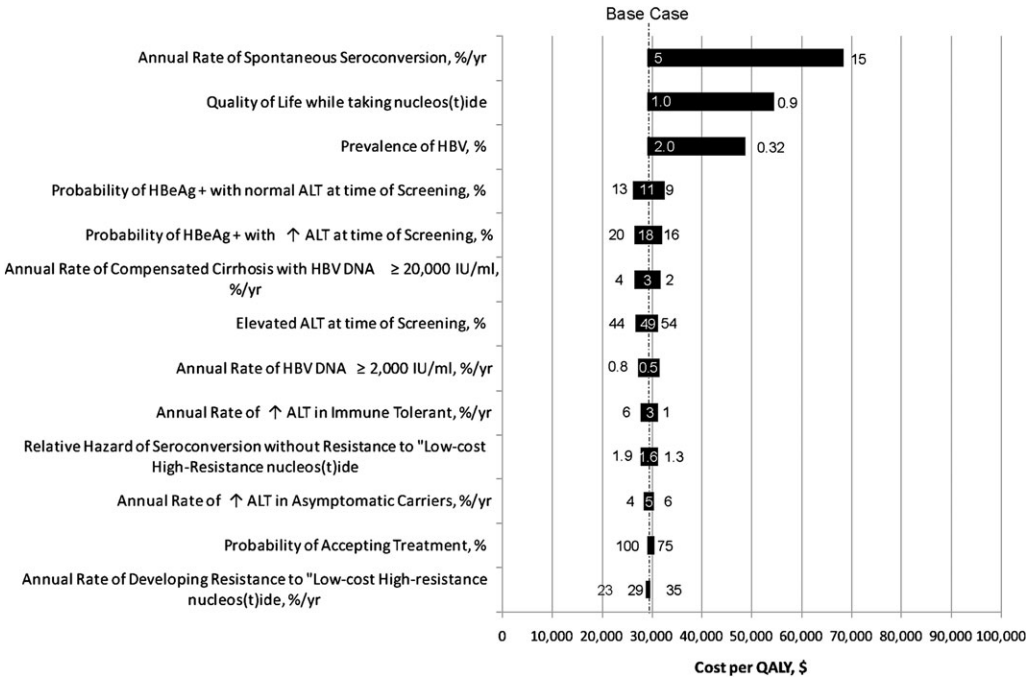

Figure 2. Tornado diagram of 1-way sensitivity analyses for the strategy of screening followed by prolonged treatment with the low-cost, high-resistance nucleoside or nucleotide and salvage therapy with the high-cost, low-resistance nucleoside or nucleotide if resistance develops. The marginal cost-effectiveness ratio (mCER) in dollars per quality-adjusted life year (QALY) is shown on the horizontal axis ranging between $0 and $100,000 per QALY. For each parameter examined, the upper and lower limits of the sensitivity analysis (labels appear at either end of each band) are based on either the 95% confidence intervals or a clinically reasonable range.

<20,000 IU/mL, whereas HBeAg-negative patients are stratified into those with viral loads of ≥2,000 IU/mL or <2,000 IU/mL. We assume that a fraction (5%) of patients with elevated ALT level and high viral loads (≥20,000 IU/mL in HBeAg-positive patients and ≥2,000 IU/mL in HBeAg-negative patients) undergo ultrasound-guided liver biopsy. Patients enter the Markov model that simulates the natural history of CHB progression in starting health states determined by (1) initial ALT level, (2) HBeAg status, and (3) viral load. HBeAg-positive patients with elevated ALT level and high viral loads are observed for 6 months. If spontaneous HBeAg conversion does not take place, treatment is started. HBeAg-negative patients with elevated ALT level and high viral loads are started on treatment without a period of observation. Treatments are characterized by their impact on viral load, seroconversion in HBeAg-positive patients, and the development of resistance. Baseline values for parameters used in the decision analytic model are summarized in Table 1.

Costs

Costs are expressed in 2008 US dollars. Details of the micro-costing models are described in Table 2 and the Supplementary Appendix. Future costs and effectiveness were discounted at 3% per year [51]. Costs were subjected to sensitivity analyses.

Quality of Life

Numerous studies have examined the impact of CHB on health-related quality of life [12, 46, 52–55]. We used standard gamble utility assessments elicited by Levy et al [46] from uninfected respondents living in the United States to provide quality of life adjustment factors for CHB—compensated cirrhosis, decompensated cirrhosis, HCC, and liver transplantation (first year and subsequent years). We used time trade-off assessments from a panel of hepatologists described in a study by Bennett et al [12] to adjust quality of life while receiving interferon. We assumed that oral antiviral agents did not diminish quality of life in an appreciable manner.

Figure 1 continued.

HBeAg seroconversion, development of compensated cirrhosis, progression to decompensated cirrhosis, development of hepatocellular carcinoma (HCC), and liver transplantation. We assume that disease progresses in a linear fashion, such that only patients with compensated cirrhosis may develop decompensated cirrhosis. The risk of developing cirrhosis or HCC is dependent on HBV DNA load. HCC can develop at any stage of chronic HBV infection. Patients with decompensated cirrhosis or HCC may be eligible for liver transplantation. In any cycle patients may die from disease-related causes or nonexplicitly modeled causes based on life tables stratified by age, sex, and race.

Table 1. Data Required in the Analysis: Probabilities, Rates, and Quality of Life

Variable	Base-case value (95% confidence interval or clinically plausible range) [reference]	Distribution type
Patient characteristic at time of screening		
Prevalence of HBV	.0042 (.0032–.0055) [17, 21]	Uniform
Elevated ALT level	.35 (85 abnormal, 242 at risk) [22]	β
HBeAg positive		
With elevated ALT level	.18 (44 abnormal, 251 at risk) [23]	β
With normal ALT level	.11 (19 abnormal, 177 at risk) [23]	β
HBV DNA level of ≥20,000 IU/mL in HBeAg-positive patients	.93 (523 abnormal, 565 at risk) [24]	β
HBV DNA level of ≥2,000 IU/mL in HBeAg-negative patients	.35 (1,078 abnormal, 3,088 at risk) [24]	β
Natural history parameter		
Annual rate of elevated ALT level		
Asymptomatic carriers	.0469 (.0378–.0569) [25]	Lognormal
Immunotolerant	.0344 (.0135–.0577) [25]	Lognormal
Annual rate of HBV DNA level of ≥2,000 IU/mL		
Asymptomatic carriers	.0050 (.0022–.0079) [25]	Lognormal
HBeAg negative, elevated ALT level, and HBV DNA level of ≥2,000 IU/mL	1.0	
Annual rate of HBV DNA level of ≥20,000 IU/mL		
Asymptomatic carriers	.0050 (.0022–.0079) [25]	Lognormal
HBeAg negative, elevated ALT level, HBV DNA level of ≥20,000 IU/mL	1.0	
Annual rate of compensated cirrhosis		
Immunotolerant	.0	
Asymptomatic carriers	.0095 (.0055–.0136) [26]	Lognormal
HBV DNA level of <2,000 IU/mL	.0047 (.0031–.0075) [26]	Lognormal
HBV DNA level of ≥2,000 and <20,000 IU/mL	.0085 (.0054–.0129) [26]	Lognormal
HBV DNA level of ≥20,000 IU/mL	.0285 (.0193–.0423) [26]	Lognormal
Annual rate of hepatocellular carcinoma		
Immunotolerant	.0221 (.0059–.0286) [24]	Lognormal
HBV DNA level of <2,000 IU/mL	.0021 (.0005–.0023) [24]	Lognormal
HBV DNA level of ≥2,000 and <20,000 IU/mL	.0028 (.0011–.0051) [24]	Lognormal
HBV DNA level of ≥20,000 IU/mL	.0243 (.0065–.0314) [24]	Lognormal
Compensated cirrhosis	.0220 (.0171–.0271) [27]	Lognormal
Decompensated cirrhosis	.0619 (.0096–.1192) [28]	Lognormal
Annual rate of decompensated cirrhosis		
Compensated cirrhosis	.0352 (.0251–.0498) [29]	Lognormal
Annual rate of spontaneous seroconversion (HBeAg negative)	.05 (.05–.15) [30–32]	Uniform
Annual rate of liver transplantation		
Decompensated cirrhosis	.9370 (.7931–1.1096) [33]	Lognormal
Hepatocellular carcinoma	4.96 (4.0806–5.6222) [33]	Lognormal
30-d mortality following transplantation	.0528 (.0489–.0567) [34]	Lognormal
Annual excess mortality rate following transplantation		
Without HCC	.0505 (.0488–.0521) [34]	Lognormal
With HCC	.0762 (.0747–.1003) [34]	Lognormal
Annual excess mortality rate		
Compensated cirrhosis	.0325 (.0201–.0457) [35]	Lognormal
Decompensated cirrhosis	.3794 (.2546–.3932) [26, 35]	Lognormal
Hepatocellular carcinoma	.4330 (.319–.499) [5, 36]	Lognormal

Table 1. (*Continued*)

Variable	Base-case value (95% confidence interval or clinically plausible range) [reference]	Distribution type
Treatment-related parameter		
Liver biopsy among patients considered for treatment	.05 (.05–.15)	Uniform
Peginterferon α-2		
HBeAg seroconversion at 72 weeks	.32 (.266–.38) [19, 37]	Logit
HBV DNA level of <20,000 IU/mL in HBeAg-positive patients at 72 weeks	.32 (.262–.376) [19, 37]	Logit
HBV DNA level of <2,000 IU/mL in HBeAg-negative patients at 72 weeks	.19 (.137–.258) [38]	Logit
Annual rate of developing resistance	.00 [39]	
Low-cost, high-resistance nucleoside or nucleotide, 48-week course		
HBeAg seroconversion at 72 weeks	.19 (.146–.243) [19, 37]	Logit
HBV DNA level of <20,000 IU/mL in HBeAg-positive patients at 72 weeks	.22 (.173–.275) [19, 37]	Logit
HBV DNA level of <2,000 IU/mL in HBeAg-negative patients at 72 weeks	.07 (.035–.113) [38]	Logit
Annual rate of developing resistance	.2854 (.2343–.3544) [39–41]	Lognormal
Low-cost, high-resistance nucleoside or nucleotide, prolonged course		
HBeAg seroconversion at 72 weeks	.19 (.146–.243) [19, 37]	Logit
Annual rate of HBeAg seroconversion[a]	.139 (.1266–.1514) [6, 40–44]	Lognormal
Relative hazard of HBeAg seroconversion without resistance mutation	1.57 (1.29–1.85) [40]	Lognormal
HBV DNA level of <20,000 IU/mL in HBeAg-positive patients at 48 weeks	.62 (.561–.679) [19, 37]	Logit
HBV DNA level of <2,000 IU/mL in HBeAg-negative patients at 48 weeks	.73 (.664–.798) [38]	Logit
Annual rate of developing resistance	.2854 (.2343–.3544) [39–41]	Lognormal
Relative hazard of developing cirrhosis	.45 (.28–.73) [43]	Lognormal
Relative hazard of developing HCC	.47 (.22–1.00) [43]	Lognormal
High-cost, low-resistance nucleoside or nucleotide, prolonged course		
HBeAg seroconversion at 48 weeks	.21 (32 events, 153 at risk) [19, 45]	β
Annual rate of HBeAg seroconversion[a]	Assumed same as for low-cost, high-resistance nucleoside or nucleotide	
HBV DNA level of <20,000 IU/mL in HBeAg-positive patients at 48 weeks	.76 (134 events, 176 at risk) [45]	β
HBV DNA level of <2,000 IU/mL in HBeAg-negative patients at 48 weeks	.93 (233 events, 250 at risk) [39, 45]	β
Annual rate of developing resistance	.00 [39, 45]	
Relative hazard of developing cirrhosis	.45 (.28–.73) [43]	Lognormal
Relative hazard of developing HCC	.47 (.22–1.00) [43]	Lognormal
Quality of life		
Chronic HBV infection	.86 [46]	
Compensated cirrhosis	.85 [46]	
Decompensated cirrhosis	.39 [46]	
Liver transplant		
First year	.69 [46]	
Subsequent years	.80 [46]	
Hepatocellular carcinoma	.43 [46]	
Interferon	.93 [12]	

NOTE. ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

[a] This rate of seroconversion applies to the first 5 years following start of treatment. After this time, the rate of seroconversion reverts to the spontaneous rate in nontreated patients.

Table 2. Costs Used in Decision Analysis

Variable	Cost, 2008 US $ [Reference]
Disease state	
Chronic hepatitis B[a]	1,062 [47]
Compensated cirrhosis[b]	1,194 [12, 36]
Decompensated cirrhosis[a]	15,986 [47]
Hepatocellular carcinoma[b]	47,903 [12, 36]
Liver transplant[b]	
First year	157,758 [12, 36]
Subsequent years	27,550 [12, 36]
Drug	
Peginterferon α-2	2,189/month [48]
Low-cost, high-resistance nucleoside or nucleotide, lamivudine	340/month [48]
High-cost, low-resistance nucleoside or nucleotide, tenofovir	614/month [48]
Laboratory testing and office visit (CPT code)	
HBsAg (87340)	14.43 [49]
HBeAg (87350)	16.10 [49]
Antibody to HBeAg (86707)	16.16 [49]
HBV DNA quantitative assay (87517)	59.85 [49]
Hepatic function panel (80076)	11.42 [49]
Complete blood count (85025)	10.86 [49]
Renal panel (80069)	12.13 [49]
Thyroid stimulating hormone (84443)	23.47 [49]
Office outpatient visit, established patient	
Level 1 visit (99211)	19.04 [50]
Level 3 visit (99213)	65.13 [50]
Level 4 visit (99214)	97.88 [50]
Screening	
Screening[c]	33.47
Ultrasound examination of abdomen (76705)[d]	116.55
Ultrasound-guided needle biopsy of the liver with pathologic examination[e]	1,152.13
Treatment	
Peginterferon α-2, stable HBV infection[f]	
First year	
HBeAg positive	25,489.82
HBeAg negative	25,457.56
Following years	
HBeAg positive	157.24
HBeAg negative	124.98
Peginterferon α-2, compensated cirrhosis[f]	
First year	
HBeAg positive	NA
HBeAg negative	NA
Following years	
HBeAg positive	157.24
HBeAg negative	124.98
Peginterferon α-2, HCC before transplant and s/p transplant[f]	
First year	
HBeAg positive	NA
HBeAg negative	NA
Following years	
HBeAg positive	92.11
HBeAg negative	59.85

Table 2. (*Continued*)

Variable	Cost, 2008 US $ [Reference]
Low-cost, high-resistance nucleoside or nucleotide, stable HBV infection[g]	
First year	
HBeAg positive	4,779.89
HBeAg negative	4,747.63
Following years	
HBeAg positive	4,395.60
HBeAg negative	4,363.34
Low-cost, high-resistance nucleoside or nucleotide, compensated cirrhosis[g]	
First year	
HBeAg positive	NA
HBeAg negative	NA
Following years	
HBeAg positive	4,297.72
HBeAg negative	4,265.46
Low-cost, high-resistance nucleoside or nucleotide, decompensated cirrhosis, HCC before transplant, and s/p transplant[g]	
First year	
HBeAg positive	NA
HBeAg negative	NA
Following years	
HBeAg positive	4,297.72
HBeAg negative	4,265.46
High-cost, low-resistance nucleoside or nucleotide, stable HBV infection[g]	
First year	
HBeAg positive	8,073.11
HBeAg negative	8,040.85
Following years	
HBeAg positive	7,688.82
HBeAg negative	7,656.56
High-cost, low-resistance nucleoside or nucleotide, compensated cirrhosis[g]	
First year	
HBeAg positive	7,975.23
HBeAg negative	7,942.97
Following years	
HBeAg positive	7,590.94
HBeAg negative	7,558.68
High-cost, low-resistance nucleoside or nucleotide, decompensated cirrhosis, HCC before transplant, and s/p transplant[g]	
First year	
HBeAg positive	7,779.46
HBeAg negative	7,747.20
Following years	
HBeAg positive	7,590.94
HBeAg negative	7,558.68

NOTE. CPT, *Current Procedural Terminology*; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NA, not available; US, United States.

[a] Year 2000 US dollars, inflated to 2008 US dollars using the medical care component of the Consumer Price Index (2000, 4.6%; 2001, 4.7%; 2002, 4.0%; 2003, 4.4%; 2004, 4.2%; 2005, 4.0%; 2006, 4.4%; 2007, 3.7%).

[b] Year 2001 US dollars, inflated to 2008 US dollars using the medical care component of the Consumer Price Index.

[c] HBsAg test and level 1 office visit (99211).

Table 3. Results of Base-Case Analysis

Strategy	Cost, US $	Effectiveness, QALYs	Marginal cost, US $	Marginal effectiveness, QALYs	Marginal cost-effectiveness, US $/QALY
No screening	914.76	23.2228	…	…	…
Screening for HBV, then treatment with low-cost, high-resistance nucleoside or nucleotide for 48 weeks	1,170.07	23.2236	255.3055	.0008	[a]
Screening for HBV, then prolonged treatment with low-cost, high-resistance nucleoside or nucleotide, then salvage with high-cost, low-resistance nucleoside or nucleotide	1,177.96	23.2319	263.1976	.0090	29,232.14
Screening for HBV, then treatment with interferon	1,209.95	23.2241	31.9901	–.0077	[b]
Screening for HBV, then prolonged treatment with high-cost, low-resistance nucleoside or nucleotide	1,286.72	23.2314	108.7611	–.0005	[b]

NOTE. Discount is 3% per year. HBV, hepatitis B virus; QALY, quality-adjusted life year; US, United States.

[a] Extended dominance—the marginal cost-effectiveness of this strategy is larger than that of the next more costly strategy that has a nonnegative marginal cost-effectiveness ratio.

[b] A dominated strategy—one that is both more costly and less effective than its comparator.

Calculation of Marginal Cost-effectiveness Ratios and Issues of Dominance and Extended Dominance

Strategies are rank ordered by increasing cost, and marginal cost-effectiveness ratios (mCERs) are calculated between each progressively more expensive but more effective strategy. A strategy is dominated if it costs more but yields lower effectiveness than the prior ''cheapest'' strategy. Extended dominance occurs when the mCER of one strategy is larger than that of the next more costly strategy that has a nonnegative mCER. When a strategy is dominated by standard or extended dominance it is eliminated from the analysis, and the mCER is not calculated.

Sensitivity Analyses

We performed both deterministic and probabilistic sensitivity analyses (PSAs) to examine the impact of uncertainty in parameter estimates and population-level variation in parameters. We conducted PSA using second-order Monte Carlo simulation [56]. Distributions for parameter values were developed (see Table 1) using beta and logit distributions for probabilities and lognormal distributions for relative risks, hazard ratios, and rates. Deterministic sensitivity analyses were performed by systematically varying 1 or more parameter values over clinically relevant ranges.

Model Calibration and Validation

We compared predicted survival in our natural history model of patients with CHB diagnosed at the time of screening with observations from a large Mediterranean cohort study of blood donors among whom 2,352 were found to be HBsAg positive [57]. Overall survival among men who entered the study at a mean age of 33.1 years was 88.8% at 20.5 years after study entry. For a similar cohort of 33.1-year-old men with asymptomatic CHB, our model predicted an overall survival of 88.2%.

RESULTS

In the base case (US population of males with a mean age of 35 years and a 2.0% prevalence of CHB) (Table 3), not screening

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[d] Performed for all screened patients with elevated alanine aminotransferase levels.

[e] Includes ultrasound guidance for biopsy (CPT 76942; $213.26), needle biopsy liver (CPT 47000; $369.06), pathological examination (CPT 88307; $233.09), and special pathological stains ×4 (CPT 88313; $336.69).

[f] Incremental costs in patients treated with interferon include drug costs, HBV DNA testing 4 times per year during the first year and once per year during following years, hepatic and renal function panels, complete blood count (CBC) monthly during the 11 months of treatment, thyroid-stimulating hormone test every 2 months during treatment, HBeAg testing once per year in HBeAg-positive patients, and level 3 office visit (99213) every 6 weeks during treatment and once per year thereafter.

[g] Incremental costs in patients treated with nucleosides or nucleotides include drug costs, HBV DNA testing, hepatic and renal function panels, CBC 4 times per year during the first year and twice per year during following years (if stable), HBeAg testing once per year in HBeAg-positive patients, and level 4 office visit (99214) 3 times during the first year and then once per year during following years. Note that costs of treatment in following years for those receiving nucleoside or nucleotide therapy include ongoing drug costs; however, in patients not continuing to receive treatment, drug costs are eliminated.

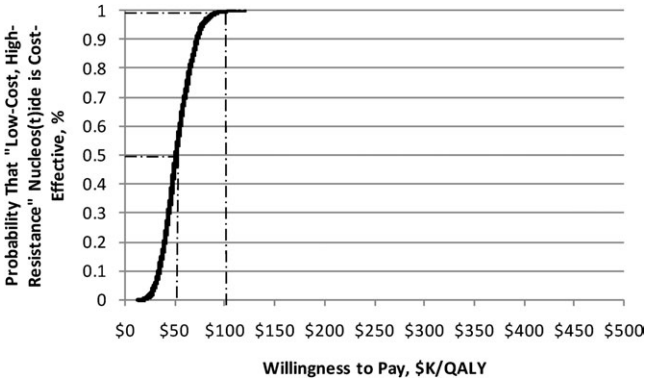

Figure 3. Probabilistic sensitivity analysis showing a cost-effectiveness acceptability curve comparing no screening with screening followed by prolonged treatment with a low-cost, high-resistance nucleoside or nucleotide followed by salvage therapy with the high-cost, low-resistance nucleoside or nucleotide in those who develop resistance. We calculated the marginal cost-effectiveness ratios for this comparison based on 10,000 second-order Monte Carlo simulations. Values were varied simultaneously based on picks from their respective distributions. Screening cost <$50,000 per quality-adusted life year (QALY) in >49% of the simulations and cost <$100,000 per QALY >99% of the time.

is both the least effective and the least costly strategy. Screening followed by prolonged treatment of HBsAg-positive patients with a low-cost, high-resistance nucleoside or nucleotide and salvage therapy with the high-cost, low-resistance agent should resistance develop is slightly more costly and more effective than no screening and has an mCER of $29,230 per additional quality-adjusted life year (QALY). Screening followed by a 48-week course of treatment with a low-cost, high-resistance nucleoside or nucleotide has a larger mCER and is eliminated due to extended dominance. Screening followed by prolonged treatment of HBsAg-positive patients with a high-cost, low-resistance nucleoside or nucleotide is the most expensive and is slightly less effective than screening followed by indefinite treatment with the low-cost, high-resistance nucleoside or nucleotide.

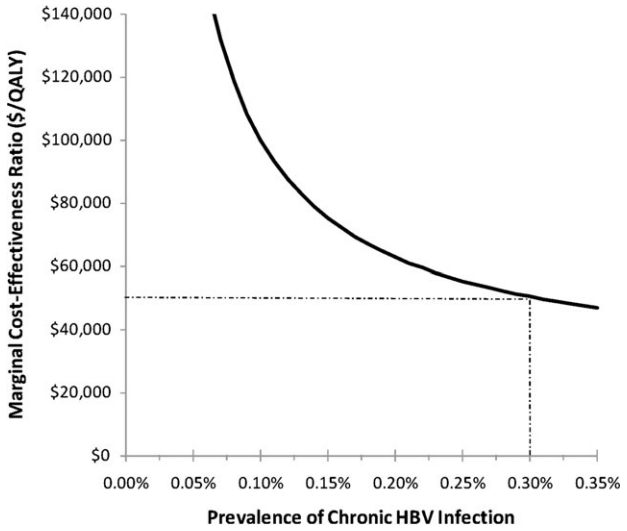

Figure 4. Prevalence of chronic hepatitis B virus (HBV) infection. The marginal cost-effectiveness ratio (mCER) of screening followed by prolonged treatment with the low-cost, high-resistance nucleoside or nucleotide decreases as the prevalence in the screening population increases. The mCER is <$50,000 per quality-adjusted life year (QALY) above a screening population prevalence of 0.3%.

Probabilistic Sensitivity Analysis

Over 10,000 iterations, screening followed by prolonged treatment with a low-cost, high-resistance nucleoside or nucleotide was preferred 80% of the time, whereas screening followed by treatment with a high-cost, low-resistance nucleoside or nucleotide was preferred 20% of the time. As shown in the cost-effectiveness acceptability curve (Figure 3), in a comparison of screening followed by prolonged treatment with a low-cost, high-resistance nucleoside or nucleotide with no screening, screening had an mCER <$50,000 per QALY >49% of the time and <$100,000 per QALY >99% of the time. Table 1 shows confidence intervals and types of distributions used in the PSA.

Deterministic Sensitivity Analyses

The overall prevalence in the United States is reported to be 0.3%–0.5%, whereas the prevalence among foreign-born immigrants may be as high as 2.6%. As shown in Figure 4, the marginal cost-effectiveness of screening followed by treatment with a low-cost, high-resistance nucleoside or nucleotide decreases as the prevalence increases. Below a prevalence of 0.3%, the mCER is >$50,000 per QALY.

Although data are available to describe the impact of low-cost, high-resistance nucleoside or nucleotide agents on the relative hazard of developing both cirrhosis and HCC, similar data do not exist for newer high-cost, low-resistance agents. In our base case, we assumed that the high-cost, low-resistance agents were no better in this regard. As shown in Figure 5, the mCER of screening followed by treatment with the high-cost, low-resistance nucleoside or nucleotide decreases as the relative hazard of either compensated cirrhosis or HCC decreases.

Few studies have explored the efficacy of salvage therapy in patients who have developed resistance to initial treatment with a high-resistance nucleoside or nucleotide. In our base case, we assumed that the high-cost, low-resistance agent has the same efficacy in suppressing viral load in the salvage therapy setting as in nucleoside- or nucleotide-naive patients. Sensitivity analyses across a clinically plausible range demonstrate only a slight increase in the mCER of screening as the efficacy of salvage therapy decreases.

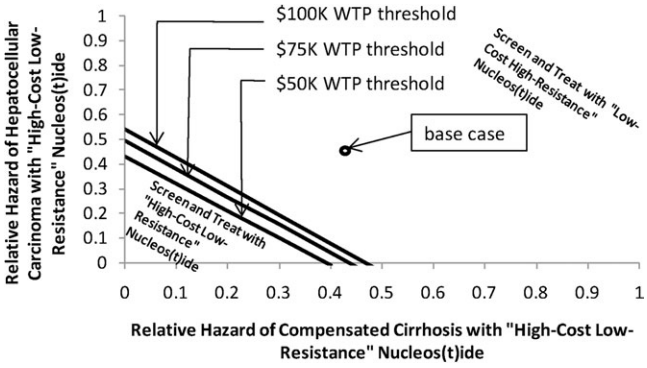

Figure 5. Three-way sensitivity analysis: relative hazard of compensated cirrhosis and relative hazard of hepatocellular carcinoma in patients receiving prolonged treatment with high-cost, low-resistance nucleoside or nucleotide. The 3 lines represent willingness-to-pay thresholds of $50,000, $75,000, and $100,000 per quality-adjusted life year (QALY). For points falling above each line, the cost-effectiveness of this strategy exceeds the willingness-to-pay threshold, and the less costly screening followed by prolonged treatment with the low-cost, high-resistance nucleoside or nucleotide is preferred.

Figure 2 summarizes the results of multiple 1-way sensitivity analyses using a tornado plot to examine the cost-effectiveness of screening followed by prolonged treatment with the low-cost, high-resistance nucleoside or nucleotide compared with that of no screening. Although the cost-effectiveness of screening followed by the low-cost, high resistance agent was sensitive to a number of parameters, only changes in 2 parameters (annual rate of spontaneous seroconversion and quality of life while receiving nucleoside or nucleotide therapy) increased the cost-effectiveness of this strategy to >$50,000 per QALY.

DISCUSSION

Current guidelines, such as those of the US Preventive Services Task Force [3], do not recommend universal screening for HBV infection in the general population and utilize relatively high rates of prevalence (2%) in targeted populations. Our analysis suggests that screening becomes cost-effective at a population prevalence of >0.3%. This threshold is at the lower end of the confidence limit for general population estimates of chronic HBV infection in the United States, 0.3%–0.5%, although it is slightly above the prevalence for the lowest-risk segment of the population, US-born, noninstitutionalized persons [58].

It is important to note that this analysis did not address the cost-effectiveness of universal screening versus current guidelines promulgated by the CDC supporting selective screening of higher-prevalence populations. This is a more complex question that requires accurate estimates of prevalence in both the group to be screened and the group not undergoing screening. However, we performed a subanalysis examining the cost-effectiveness of liberalizing the current CDC guidelines suggesting that foreign-born residents of the United States undergo screening if they have emigrated from a region with a prevalence of ≥2% to a slightly lower prevalence threshold. A recent estimate, based on 2008 data, indicates that prevalence varies from 1.3% to 11.8% among foreign-born residents of the United States depending on country of origin [59]. While the mean prevalence among those who emigrated from Asia, Africa, the Caribbean, and Eastern Europe is 6.7%, that of those who emigrated from Central America or other regions not explicitly noted above is 1.3%. In addition, this lower-risk group makes up >55% of the foreign-born residents in the United States. Our analysis showed that the mCER of screening foreign-born residents with a prevalence of ≥2% (ie, the current CDC guideline) is favorable at $31,600 per QALY compared with no screening. The marginal cost-effectiveness of liberalizing the current CDC guideline to also include foreign-born residents with a prevalence of 1.3% is $33,500 per QALY compared with the current CDC guideline.

It also is important to note that results of a cost-effectiveness analysis such as ours provide insights into policy-level decision making for large groups of patients. The best practice for individual patients must also account for patient-to-patient variability in preferences for health outcomes and treatment side effects, as well as more complex and subtle differences such as racial differences in the risk of hepatocellular carcinoma or variability in HBV genotype, which might impact response to interferon.

The superiority of screening was a robust result, insensitive to variations in most parameter values within clinically plausible ranges. One of the few parameters that might make screening cost >$50,000 per QALY was the underlying rate of spontaneous HBeAg seroconversion. However, spontaneous seroconversion would have to exceed 10% per year (base case value, 5% per year) for screening to no longer be cost-effective.

Our analysis examined several treatment options for chronically infected patients for whom treatment was warranted by current guidelines. In the base case, screening followed by prolonged treatment with the high-cost, low-resistance nucleoside or nucleotide was less effective than screening followed by prolonged treatment with the low-cost, high-resistance agent followed by salvage therapy for those who develop resistance. However, changes in the efficacy of this agent, particularly in salvage versus primary treatment settings, could result in this screening strategy becoming cost-effective. Although the main focus of our analysis was the question of screening, due to controversy about using a high-resistance agent as first-line therapy, we also performed a subanalysis that did not include this strategy. In this analysis, the marginal cost-effectiveness of the high-cost, low-resistance nucleoside or nucleotide versus no screening was still reasonable at $43,500 per QALY.

Although we did not model immunization following screening, the major impact of immunization would be to slightly improve the overall life expectancy of noninfected patients who were not already immune (by preventing future infection) and to add up-front cost for these patients. In addition, there are complex, population-level interactions that result from a decreasing prevalence of HBV infection, which our simulation was not designed to model. Ignoring the beneficial impact of immunization, we performed a separate scenario analysis in which we added costs of immunization ($113.22; vaccine cost + level 2 established patient visit) to screening costs for nonimmune patients. This worst-case estimate increased slightly the mCER of screening to $41,800 per QALY, still below a societal willingness-to-pay threshold of $50,000 per QALY. Our analysis also did not address the issue of human immunodeficiency virus (HIV) screening. The complexity of the decision tree in HIV-infected subjects requires additional modeling that is beyond the scope of this analysis.

Prior cost-effectiveness analyses have not focused on screening followed by HBV infection treatment. However, several analyses have examined treatment alternatives for patients with already-diagnosed HBV [14, 60]. Kanwal et al [5] found that a hybrid strategy consisting of lamivudine followed by adefovir salvage was cost-effective in patients without cirrhosis, whereas entecavir was cost-effective in patients with cirrhosis. Lacey [13] reports similar results for lamivudine followed by adefovir salvage or adefovir followed by lamivudine salvage in Singapore, whereas Yuan et al [15] report that entecavir was ''highly cost-effective'' compared with lamivudine.

How should this analysis impact policy and practice? While the most cost-effective treatment strategy for those found to be infected with HBV may evolve in the future, given newer and more effective agents or consideration of more complex salvage therapies for patients who develop resistance, screening for chronic HBV infection is likely to be cost-effective, even in low-prevalence populations (eg, as low as .3%) in the United States. These findings suggest that current health policy with regard to screening for CHB should be reconsidered.

Supplementary Material

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Acknowledgments

Financial support. This work was supported by Gilead Sciences; the National Center for Research Resources (grant 1UL1RR026314 to M. H. E.); the National Institute of Diabetes and Digestive and Kidney Diseases (grant K23 DK075599 to M. H. E. and grant K24 DK070528 to K. E. S.); the National Heart, Lung, and Blood Institute (grant K30 HL078581-01 to M. H. E.); and the National Library of Medicine (grant R01 LM009533 to M. H. E.).

Potential conflicts of interest. K. E. S. has served on an advisory board for BMS, Merck, SciClone, Vertex, GSK, Regulus, Three Rivers, J&J, Valeant, Anadys, Schering, Baxter, and Astellas; received grant support from Roche (Genentech), Schering (Merck), Vertex, Gilead, BMS, SciClone, Anadys, HGS, and Gilead; received royalties from the US Army and UpToDate; and received payment for the development of educational presentations from Chronic Liver Disease Foundation. M. H. E. is a consultant for Savient Pharmaceuticals. T. E. K.: no conflicts.

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