Estimating Future Hepatitis C Morbidity, Mortality, and Costs in the United States

John B. Wong, MD, Geraldine M. McQuillan, PhD, John G. McHutchison, MD, and Thierry Poynard, MD

ABSTRACT

Objectives. This study estimated future morbidity, mortality, and costs resulting from hepatitis C virus (HCV).

Methods. We used a computer cohort simulation of the natural history of HCV in the US population.

Results. From the year 2010 through 2019, our model projected 165 900 deaths from chronic liver disease, 27 200 deaths from hepatocellular carcinoma, and $10.7 billion in direct medical expenditures for HCV. During this period, HCV may lead to 720 700 years of decompensated cirrhosis and hepatocellular carcinoma and to the loss of 1.83 million years of life in those younger than 65 at a societal cost of $21.3 and $54.2 billion, respectively. In sensitivity analysis, these estimates depended on (1) whether patients with HCV and normal transaminase levels develop progressive liver disease, (2) the extent of alcohol ingestion, and (3) the likelihood of dying from other causes related to the route of HCV acquisition.

Conclusions. Our results confirm prior Centers for Disease Control and Prevention projections and suggest that HCV may lead to a substantial health and economic burden over the next 10 to 20 years. (*Am J Public Health.* 2000; 90:1562–1569)

During the 1980s, 230 000 cases of acute hepatitis C virus (HCV) occurred annually, most of which were associated with blood transfusions or injection drug use.[1] Because of changes in the blood donor population and transfusion practice, mandatory screening of donated blood, and declines in injection drug users, only 28 000 to 36 000 cases of acute HCV now occur annually. Chronic hepatitis develops in about 85% of those infected.[1–3] Thus, HCV is the etiology in 40% of the patients with chronic liver disease.[1,4] Antibody screening in 1988 through 1994 suggested that 3.9 million people in the United States were infected, 4 times the number infected with HIV.[1,3,5] Some 2.7 million of these individuals have detectable HCV RNA in their blood.[6]

In the United States, chronic HCV infection accounts for 8000 to 10 000 related deaths annually.[1,3] It has become the leading cause of liver transplantation, accounting for 30% of all liver transplants.[1,7] The Centers for Disease Control and Prevention (CDC) conservatively estimates expenditures devoted to HCV to be more than $600 million annually.[1] The goals for *Healthy People 2000: National Health Promotion and Disease Prevention Objectives* included reducing hepatitis C cases by one fourth and cirrhosis deaths by one third.[8] Although the targeted decline in the incidence of HCV already has been achieved,[9] annual deaths attributable to liver disease in the 1990s have remained relatively constant at about 25 000, making it the 10th leading cause of death, despite declining alcohol-related liver deaths.[1,10,11] The CDC predicts that HCV-related mortality might double or triple over the next 10 to 20 years.[1]

We modified a previously published computer cohort simulation model for the natural history of hepatitis C to estimate the future long-term morbidity, mortality, and costs that might be expected from cases of hepatitis C that existed in 1991.[12,13]

Methods

Decision Analytic Model

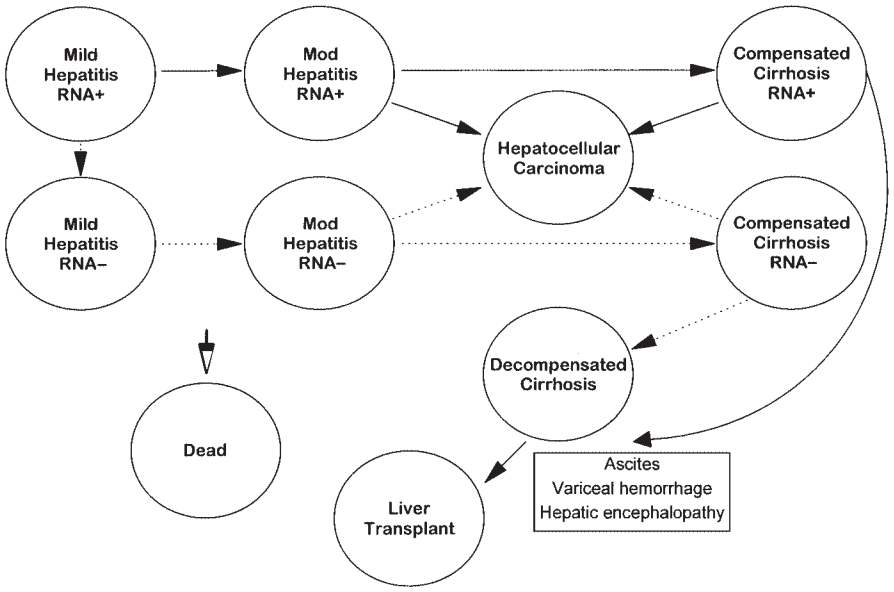
We used a Markov computer simulation to model prognosis by following up over time a cohort representative of the HCV-infected cohorts for each age group within the National Health and Nutrition Examination Survey III (NHANES III).[14,15] Details of the computer model have been published elsewhere.[13,16] Briefly, in a Markov simulation, cohort members move among predefined states of health over time periods or cycles (e.g., 1 year) until all members have died. By tracking the proportion of the cohort developing complications each year and their care costs, the computer simulation estimates future HCV-related morbidity, mortality, and expenditures.

The health states were based on liver histology, presence or absence of hepatitis C viremia, decompensated liver disease, hepatocellular carcinoma, or liver transplantation (Figure 1). The 3 histologic states considered were mild hepatitis, moderate hepatitis, and a cirrhotic stage.[17] From each histologic state, individuals could progress over time to a more advanced clinical or histologic state or

John B. Wong is with the Division of Clinical Decision Making, Informatics and Telemedicine, Department of Medicine, New England Medical Center, Tupper Research Institute, Tufts University School of Medicine, Boston, Mass. Geraldine M. McQuillan is with the National Center for Health Statistics, Hyattsville, Md. John G. McHutchison is with the Division of Gastroenterology–Hepatology, Scripps Clinic and Research Foundation, La Jolla, Calif. Thierry Poynard is with Groupe Hospitalier, Pitié-Salpêtrière, Paris, France.

Requests for reprints should be sent to John B. Wong, MD, New England Medical Center, 750 Washington St, Box 302, Boston, MA 02111 (e-mail: jwong@lifespan.org).

This article was accepted March 7, 2000.



Note. Overall, there were 190 states of health. Each circle represents a state of health for a segment of the US population with chronic hepatitis C. Each arrow represents possible changes in health status that may occur each year. Dotted arrows represent lower probabilities of transition, reflecting the viral-negative state (the odds-likelihood ratio for progression is reduced by 0.0002 for mild hepatitis, 0.001 for moderate hepatitis, 0.4 for cirrhosis to hepatocellular carcinoma, and 0.32 for cirrhosis to decompensated cirrhosis). The decompensated cirrhosis state shown here represents separate states of health in the model for diuretic-sensitive and diuretic-refractory ascites, first year and subsequent years after initial variceal hemorrhage, and first year and subsequent years after initial hepatic encephalopathy. Similarly, the liver transplant state has separate states of health for the first year and subsequent years posttransplant. For individuals who are hepatitis C RNA-positive with mild hepatitis, moderate hepatitis, or compensated cirrhosis, additional separate states of health exist for those with normal transaminases and those with elevated transaminases. For those with elevated transaminases, separate states of health exist for those known to have chronic hepatitis C and those whose infection is unknown and clinically silent unless they develop decompensated cirrhosis or hepatocellular carcinoma. In the base case, individuals with normal transaminases do not develop progressive disease or hepatocellular carcinoma. In addition, each of these states of health exists separately for each of the 9 age groups categorized by NHANES III. Individuals in any state of health may die from causes related to their age and sex as occurs in the general population, and individuals with decompensated cirrhosis or hepatocellular carcinoma may die from liver-related causes.

FIGURE 1—Simplified schematic of Markov model.

remain in the same state of health. For example, each year, individuals with mild chronic hepatitis could develop moderate chronic hepatitis or remain stable with mild chronic hepatitis. Likewise, individuals with moderate chronic hepatitis could progress to a compensated cirrhosis state or remain stable. Individuals in the cirrhotic state could progress to either hepatocellular carcinoma or 1 of 3 modes of hepatic decompensation: (1) ascites (diuretic-sensitive or diuretic-refractory), (2) variceal hemorrhage, or (3) hepatic encephalopathy. Once individuals developed decompensated cirrhosis, they could die from liver disease, receive a liver transplant, or remain alive with liver failure. Individuals in any state of health could die from other causes (as occurs in an age- and sex-matched general population).

The likelihood of these health state transitions was based on probabilities derived from a review of the literature in which actuarial techniques were used; expert opinion was used when such data were unavailable. For this study, the previously published model was modified to include states of health for those cohort members with normal liver transaminase levels and for those with known or unknown hepatitis C. Patients with unknown hepatitis C were assumed to have silent disease and did not incur any HCV-related health care costs until they developed hepatocellular carcinoma or decompensated liver disease.

Data

US population. The prevalence of disease was based on the NHANES III data, in which free-living civilians had household interviews and standardized physical examinations between 1988 and 1994.[18] NHANES III used a multistage probability sample design with oversampling of children younger than 5 years, persons aged 60 years or older, Mexican Americans, and non-Hispanic Blacks. The data were weighted for the different probabilities of selection and response to produce estimates representative of the national population. The analysis assumed a population distribution that matched the 1991 US population census estimates (the midpoint of the NHANES III study), which divided the 251 million Americans into 12 age groups.

We focused on antibody testing for HCV. Because none of the patients younger than 6 years were tested for HCV antibodies, the computer simulation considered 9 age groups (Table 1). The 30- to 39-year-old group had the highest prevalence of HCV antibody—3.9%, for an estimated 1.6 million HCV-infected individuals. Among those who were antibody positive, an estimated 2.7 million people (70% of those infected) had detectable serum HCV RNA.[6]

Table 2 presents the data used.[13,16,19–35] To make conservative assumptions (possibly underestimating the disease burden from hepatitis C), we assumed that 2 million of the 3.9 million who were antibody positive could develop progressive liver disease. We excluded 1.9 million by assuming a benign prognosis for 2 subgroups: (1) the 30% who had no detectable viral RNA and (2) the 25% of those remaining because they presumably had normal serum liver transaminase tests.[32] Although these patients are referred to as "healthy HCV carriers," only 13% of the liver biopsies in these patients were normal.[7] In sensitivity analysis, we varied the natural history of this group and allowed these patients to progress at half the rate of those with elevated transaminases.[36] We assumed that only 5% of the patients with hepatitis C have known disease.[33]

Although CDC data regarding the risk factors associated with acute HCV infection are available, the specific route of transmission (injection drug use or transfusion) for the hepatitis C cases found in the NHANES III survey is unknown. We therefore explored the effects of excess mortality (beyond that occurring in an age- and sex-matched sample from the general population) associated with the source of HCV infection: injection drug use[35] or the disease leading to transmission of hepatitis C by transfusion.[22,34] Depending on the available data, we used an additive or a multiplicative mortality model.[37] HCV-infected pa-

TABLE 1—NHANES III–Based Age-Related Prevalence of HCV Antibodies in the United States[18]

Age Group, y	No. of Persons	% With HCV	No. With HCV
6–11	18 772 358	0.166	31 093
12–19	25 786 732	0.392	101 141
20–29	36 812 463	1.571	578 264
30–39	40 139 198	3.897	1 564 346
40–49	32 018 127	3.031	970 369
50–59	21 042 877	1.414	297 584
60–69	18 778 678	0.865	162 444
70–79	12 312 104	0.942	115 923
≥80	4 622 441	1.158	53 509
Total	210 284 978	1.843	3 874 673

Note. NHANES = National Health and Nutrition Examination Survey; HCV = hepatitis C virus.

tients, who are more likely to die from other causes, will be less likely to live long enough to develop HCV-related liver complications. To make the model tractable, we did not consider co-infection with hepatitis B or HIV, which shortens life expectancy but which also may increase the likelihood of developing progressive liver disease.[38–40]

HCV-related mortality, decompensated cirrhosis, and compensated cirrhosis. In 1991, 25 429 deaths were attributed to chronic liver disease and cirrhosis.[41] From 1979 to 1988, 36% to 41% of the deaths related to chronic liver disease were attributable solely or partly to hepatitis C,[4] so 9154 to 10 426 of the deaths in 1991 were likely to be related to hepatitis C. To provide a conservative estimate, we assumed that 8000 deaths were related to hepatitis C–induced chronic liver disease in 1991.[1]

To estimate the likelihood of cirrhosis in each NHANES III age group, we performed a linear regression analysis (R^2=0.97) of 2235 patients who underwent liver biopsy and obtained their age at the time of biopsy (Table 2).[19] Because these patients were involved in treatment trials and subject to selection bias, we adjusted the proportion of patients with compensated and decompensated cirrhosis in each NHANES III age group until the predicted number of non-cancer-related deaths from HCV for 1991 was 8000, thereby perhaps correcting the selection bias inherent in this data set.[3] To estimate the likelihood of histologically moderate hepatitis for each age group, we assumed a 13.7-year lag time based on a 7.3% annual probability of developing cirrhosis with moderate hepatitis.[13]

Hepatocellular carcinoma. In 1991, the incidence of hepatobiliary cancers was 15 000.[42] Two thirds arise in the gallbladder or the intrahepatic or extrahepatic biliary ducts,[43] leaving 5000 primary hepatocellular carcinomas, of which one third, or 1667, may be related to HCV.[44,45] From the 5-year period 1986 to 1990 through 1991 to 1995, the age-adjusted incidence of hepatocellular carcinoma increased by about 26%,[46] so we reduced our baseline estimate for the annual probability of hepatocellular carcinoma until there were 4.8% more cases in 1992 than in 1991, or 1747 incident cases. We then applied this 0.5% annual probability of developing carcinoma for all subsequent years.

Orthotopic liver transplantation. From the United Network for Organ Sharing data, we determined that 4930 liver transplants for hepatitis C occurred between 1991 and 1997.[47] We adjusted the annual likelihood of liver transplantation so that our model predictions matched this estimate. We then applied this 1.5% annual probability of liver transplantation to all patients with decompensated cirrhosis. We compared the number of patients on the waiting list and the number receiving transplants who were younger than 65 with those who were 65 and older and found a close match for years 1988 to 1996, so we did not decrease the likelihood of transplant for those 65 and older. Presumably, this occurs because only those individuals who are healthier or physiologically younger are selected to be placed on the transplant waiting list.

Alcohol and hepatitis C. In the base case, we did not include any specific effect of alcohol on disease progression. In sensitivity analysis, we examined the effect of alcohol consumption on disease progression. From the NHANES III data, we determined that 17.6% of those with hepatitis C antibodies ingested more than 50 g/day of alcohol compared with 8.6% in the group without hepatitis C antibodies.[18] If the HCV-infected population is similar to that observed by Wiley et al.,[48] about half would ingest more than 50 g/day of alcohol. Because such intake doubles the progression rate and because 17.6% of the NHANES III HCV-infected population ingested that much alcohol,[19] the result would be a 1.28 relative increase in the annual probability of progression for all patients. Similarly, if alcohol intake could be eliminated from this population, the annual likelihood of progressive liver disease would be reduced by 15%.[18,19]

Normal liver transaminase levels. In the base case, we assumed that the 25% of the patients with chronic hepatitis C and persistently normal liver transaminase levels would not develop progressive liver disease. In sensitivity analysis, we examined the effect of assuming that 33% of the patients with chronic hepatitis C have persistently normal liver transaminase levels and would not develop progressive liver disease. We also examined the effect of assuming that individuals with normal transaminases might develop progressive liver disease, albeit at one half the rates in Table 2 of individuals with elevated transaminases (e.g., the annual likelihood of progression from mild to moderate hepatitis was 2.1%). This estimate was based on a comparison study of serial liver biopsies in patients with and without elevated transaminases.[36]

Mortality related to other causes. In the base case, we did not assume any additional non-HCV-related mortality risk compared with the general population. In additional analyses, we examined the effect of excess mortality associated with the source of the HCV infection, in particular, related to continued injection drug use or related to a disease that necessitated a blood transfusion (e.g., coronary bypass surgery). This excess mortality reduced future HCV-related liver complications by increasing deaths from other causes, thereby decreasing the proportion of the cohort that would survive to develop HCV-related complications. Although data exist on the etiology of hepatitis C for incident cases, no such data are available for the HCV-positive individuals in the NHANES III, because injection drug use was not asked about and could not be linked to hepatitis C antibody results, and history of transfusion was not available. To determine the maximum potential effect, we therefore assumed that this risk affected the entire population.

Costs. Direct medical care cost estimates were based on actual variable costs for patients with hepatitis C treated at a university hospital.[13] Variable costs refer to the cost to care for 1 additional patient with a particular medical problem and exclude fixed and indirect costs. The annual costs associated with each health state included medications, laboratory tests, office visits, and hospitalizations, based on their yearly frequency. The cost data were in 1995 dollars and were adjusted to 1999 dollars with the medical care component of the Consumer Price Index (Table 2).[49]

In a separate analysis, we estimated the additional indirect costs related to disability or mortality from hepatitis C. We used the computer simulation to determine the years of life spent by the cohort with decompensated cirrhosis or hepatocellular carcinoma. To estimate the years of life lost, we also compared life expectancy estimates for the

TABLE 2—Base-Case Data for Estimating Future HCV Morbidity, Mortality, and Costs

Predicted prevalence of different histologies[19a]

Age Group, y	Initial Probability, %, of Cirrhosis	Moderate Hepatitis	Mild Hepatitis
6–11	0	0	100
12–19	0	1	99
20–29	0	11	89
30–39	7	22	71
40–49	18	32	50
50–59	28	43	29
60–69	39	54	7
70–79	50	50	0
≥80	60	40	0

Initial Health State	Event	Annual Probability, %
Mild chronic hepatitis	Remission[20]	0.2
	Moderate chronic hepatitis[21–23]	4.1
Moderate chronic hepatitis	Cirrhosis[21–23]	7.3
	Hepatocellular carcinoma	0.1
Cirrhosis	Ascites[24]	2.5
	Variceal hemorrhage[24]	1.1
	Hepatic encephalopathy[24]	0.4
	Hepatocellular carcinoma[24]	0.5
Ascites	Refractory ascites[25]	6.7
	Death[25]	11
Refractory ascites	Death[25]	33
Variceal hemorrhage	Death (first year)[26]	40
	Death (subsequent year)[26]	13
Hepatic encephalopathy	Death (first year)[27]	68
	Death (subsequent year)[27]	40
Hepatocellular carcinoma	Death[28]	86
Liver transplantation	Death (first year)[29–31]	21
	Death (subsequent year)[29–31]	5.7

Probability of—	%
Normal transaminases in HCV-infected population[32]	25
Known disease[33]	5

Excess mortality risk	%
Transfusion-related disease (additive risk per year)[22,34]	0.15
Injection drug use (annual relative or multiplicative risk compared with general population)[35]	
Age < 21 y	14
Age 21–30 y	10
Age > 30 y	4

Annual cost for health state[13]	1999 $
Known mild, moderate hepatitis or compensated cirrhosis	110
Ascites	
Diuretic-sensitive	1855
Diuretic-refractory	18730
Variceal hemorrhage	
First year	19127
Subsequent years	3743
Hepatic encephalopathy	
First year	12278
Subsequent years	2845
Hepatocellular carcinoma	32995
Liver transplantation	
First year	108659
Subsequent years	18976

Note. HCV = hepatitis C virus.
[a]Probability of cirrhosis = age × 0.0107 − 0.2913 (SE = 0.0107 ± 0.0008 and −0.2913 ± 0.0436, $P < .0001$ for both). Probability of moderate hepatitis = (age + 13.7) × 0.0107 − 0.2913, assuming a 13.7-year lag from moderate hepatitis to compensated cirrhosis.

chronic hepatitis C population with those for an age- and sex-matched general population. To assign an economic indirect or time cost related to lost productivity due to death (mortality costs) or disability (morbidity costs), we applied the median weekly earnings of full-time wage and salary workers for the fourth quarter of 1999 ($568) or $29 536 annually for time lost.[50] These estimates calculated premature mortality and assumed permanent disability once patients developed decompensated cirrhosis or hepatocellular carcinoma but did not consider quality-of-life deficits or time lost for outpatient visits or hospitalizations.

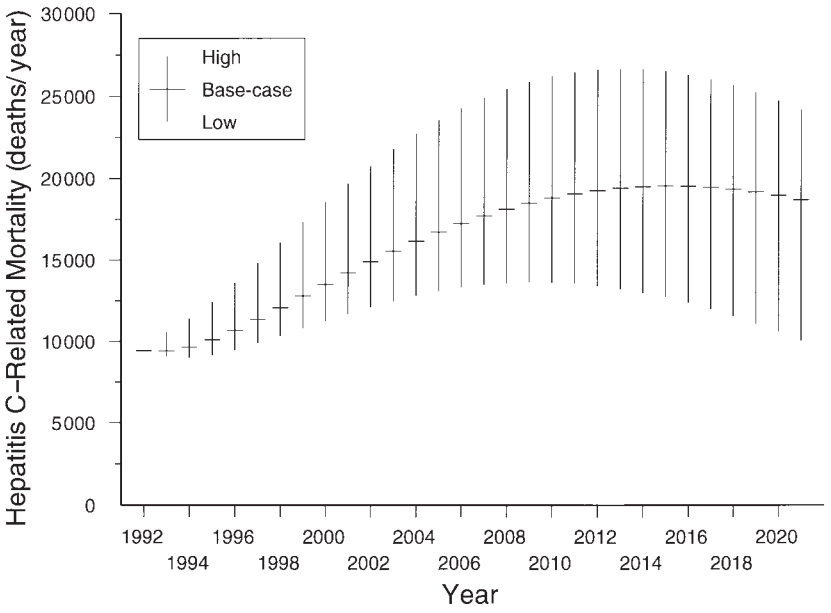
Results

Comparison With Published Studies

Because some parameters had changed from the previously published model, we sought to compare model predictions with published outcomes. Seeff et al.[51] followed up 568 patients with non-A, non-B hepatitis for 18 years and found a 51% mortality, with 3.3% of the deaths related to liver disease. Matching the age of this population and the 51% mortality after 18 years, our model estimated that 2.3% of the patients would die from liver disease, assuming that acute infection was resolved in 15% of the patients and that progressive liver disease might develop in the remaining 85%. If, however, 25% of the 85% whose infection did not acutely resolve had persistently normal transaminases and would not develop progressive liver disease, then our model predicted that only 1.7% of the patients would die from liver disease after 18 years.

Among 384 hepatitis C patients with compensated cirrhosis, Fattovich et al.[24] found that 18% developed decompensated cirrhosis, 8% developed hepatocellular carcinoma, and 13% died over 5 years of follow-up. Matching the age of this population, our model estimated that 18% of the patients would have developed decompensated cirrhosis, 2.3% would have developed hepatocellular carcinoma, and 12% would have died.

We also compared the predicted number of liver transplants from the model beyond 1997 with a regression-based prediction ($R^2 = 0.99$, details available from the authors) and found the numbers to be similar. Assuming that 20% to 30% of all future liver transplants would be for hepatitis C, the model predicted 1443 transplants in 2015 vs a regression-based prediction of 1377 to 2065 transplants. Thus, our model predictions are conservative but similar to published outcomes or to regression-based predictions.



Note. The higher estimates reflect alternative assumptions that chronically infected patients with persistently normal transaminases might develop progressive liver disease or that a higher proportion of patients ingested alcohol in excess of 50 g/day. The lower estimates reflect alternative assumptions regarding mortality from other causes, none of the infected patients drinking more than 50 g/day of alcohol, or 33% of the chronically infected patients having normal transaminases and never developing progressive liver disease. On the basis of existing cases of chronic hepatitis C in 1991, our analysis would suggest continued rising mortality over the next 10 years with a subsequent decline 10 to 20 years from now.

FIGURE 2—Projected annual deaths from hepatitis C–related chronic liver disease and hepatocellular carcinoma from 1992 to 2020.

Model Predictions

Based on the 2 million individuals who had detectable viral RNA for HCV and who presumably had elevated liver transaminases in 1991, our model predicted that annual HCV-related liver deaths for the years 2010 to 2019 would increase 2-fold when compared with the 8000 deaths in 1991 (Figure 2). HCV-related chronic liver disease mortality would be 181 300 over this 10-year period, with another 27 200 deaths from HCV-related hepatocellular carcinoma (Table 3). The highest proportion of deaths related to hepatitis C would occur 10 to 20 years from now, peaking in 2014. The need for liver transplants would rise until 2015. Because of the higher risk for decompensated liver disease and the relatively low risk of cancer assumed for this analysis, new cases of hepatocellular carcinoma would rise only until 2008 but would remain relatively stable throughout the next 20 years, varying by at most several hundred. Figure 3 shows the estimated annual direct medical care costs. For the 10-year period from 2010 to 2019, direct medical expenditures would be $10.7 billion.

Sensitivity Analysis

We examined the effects of varying particular assumptions of the model (Figures 2 and 3, Table 3). Increasing the proportion of individuals with known hepatitis C had little effect because antiviral treatment costs were not considered; thus, costs were mostly for treatment of hepatocellular carcinoma and decompensated liver disease as opposed to monitoring costs in the presymptomatic stages of the disease. To determine upper-bound estimates for future HCV-related mortality, we asked what would happen if patients with normal transaminase levels could progress and what would happen if half of this population ingested more than 50 g/day of alcohol.[48] In such scenarios, annual HCV-related deaths 10 to 20 years from now might be 2.2 to 2.9 times the number of deaths in 1991. HCV-related chronic liver disease deaths might reach as high as 225 800, with another 34 900 deaths from hepatocellular carcinoma and direct medical care costs reaching $14.1 billion over this 10-year period (Table 3).

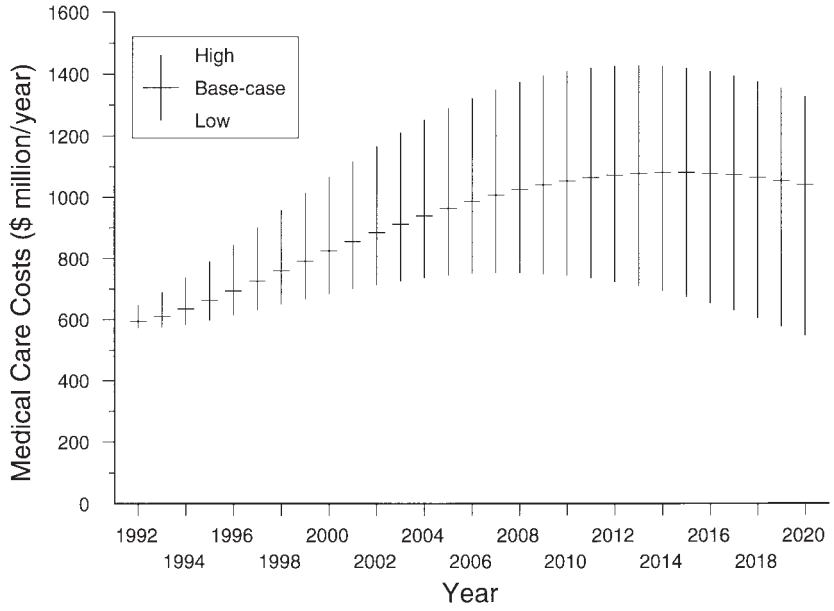
To determine lower-bound estimates, we introduced deaths from other causes related to the route of acquisition of hepatitis C (injection drug use or transfusion). Despite these additional forces of mortality, HCV-related deaths from chronic liver disease would still be 1.1 to 1.5 times the 8000 deaths in 1991 and would result in at least 105 700 deaths and another 17 700 deaths from hepatocellular carcinoma, with direct medical care costs exceeding $6.7 billion from 2010 through 2019 (Table 3).

Finally, we determined additional lower-bound estimates, assuming (1) that alcohol use

TABLE 3—Base-Case and Sensitivity Analysis Results for HCV Antibodies: United States, 2010–2019

	Chronic Liver Disease–Related Deaths	Hepatocellular Carcinoma Deaths	Costs, $ Million in 1999 Dollars
Base case	165 900	27 200	10 700
Hypothetical worst case			
Progressive HCV with normal transaminases	181 300	30 300	11 600
Excess alcohol in 50% of HCV population	225 800	35 000	14 100
Hypothetical best case			
Excess mortality from parenteral drug use	105 700	17 700	6 700
Excess mortality from transfusion	117 600	19 200	7 500
No excess alcohol in HCV population	132 700	22 500	8 900
Normal transaminases in 33% of HCV population	147 500	24 200	9 500

Note. HCV = hepatitis C virus.



Note. The higher estimates reflect alternative assumptions that chronically infected patients with persistently normal transaminases might develop progressive liver disease or that a higher proportion of patients ingested alcohol in excess of 50 g/day. The lower estimates reflect alternative assumptions regarding mortality from other causes, none of the infected patients drinking more than 50 g/day of alcohol, or 33% of the chronically infected patients having normal transaminases and never developing progressive liver disease. On the basis of existing cases of chronic hepatitis C in 1991, our analysis would suggest continued rising medical costs over the next 10 years with a subsequent decline 10 to 20 years from now.

FIGURE 3—Projected annual direct hepatitis C–related medical care costs from 1992 to 2020.

could be reduced so that no HCV-infected individuals drank more than 50 g/day of alcohol or (2) that one third (as opposed to one fourth) of the viral-positive individuals had normal transaminase levels[52] and would not develop progressive liver disease. With either scenario, annual HCV-related deaths from chronic liver disease would range from 1.6 to 1.9 times the number of deaths in 1991. HCV-related chronic liver disease and hepatocellular carcinoma would result in at least 132 700 and 22 400 deaths, respectively, with direct medical care costs exceeding $8.9 billion from 2010 through 2019.

Indirect Costs

From the year 2010 to 2019, our model projected 165 900 deaths from chronic liver disease and 27 200 deaths from hepatocellular carcinoma related to hepatitis C. When compared with an age-matched general population over these 10 years, the HCV-infected cohort would have 959 700 years of decompensated cirrhosis or hepatocellular carcinoma and the loss of 3.09 million years of life. Considering those younger than 65, hepatitis C may lead to 720 700 years of decompensated cirrhosis and hepatocellular carcinoma and to the loss of 1.83 million years of life. Over the 10 years from 2010 through 2019, the societal cost of premature mortality for those younger than 65 would be $54.2 billion, and the cost of morbidity from disability related to decompensated cirrhosis and hepatocellular carcinoma would be $21.3 billion.

Discussion

Hepatitis C was discovered just 10 years ago, but much progress has been made in detecting this disease, determining its incidence, and initiating treatment. However, uncertainty persists regarding its natural history and future health burden. In 1991, nearly 4 million Americans had antibody evidence of hepatitis C exposure. Based on only the estimated 2.0 million exposed individuals who were viremic and likely had elevated liver transaminases, our computer projections corroborated CDC predictions that mortality from HCV-related liver disease may increase 2- to 3-fold over the next 10 to 20 years. Our projections may have underestimated mortality because they excluded (1) the more than 200 000 cases of acute hepatitis C that have occurred over the past 7 years (85% of these patients are likely to have developed chronic hepatitis)[18] and (2) the 700 000 or so inmates in the United States with HCV infection[53] who were not included in the NHANES III. Also, our estimates did not consider the possibility of accelerated HCV progression in older individuals or those coinfected with hepatitis B or HIV, who are more likely to develop hepatic complications.[19] Corroborating our results, Davis et al.[54] predicted substantial future health burden related to hepatitis C, and Deuffic et al.[55] also predicted similar results for the hepatitis C epidemic in France.

If patients with normal transaminase levels can develop progressive liver disease (albeit slowly) or if a higher proportion of patients with hepatitis C ingest more than 50 g/day of alcohol, the future burden of HCV would increase. However, our results also showed that excess mortality related to the source of HCV transmission (e.g., injection drug use or blood transfusion) may limit the proportion of patients living long enough to develop HCV-related complications. Even so, HCV-related deaths still may exceed 105 700 from chronic liver disease and 17 700 from hepatocellular carcinoma from the year 2010 through 2019.

When only direct medical costs were considered, our model predicted that the cost to treat future HCV-related disease would range from $6.5 to $13.6 billion for the years 2010 through 2019. Our projections for hepatitis C likely underestimated the long-term costs because they did not include future expenses related to periodic liver biopsy, screening for hepatocellular carcinoma, and treatment costs. Moreover, our estimates applied variable costs (the additional cost to treat 1 more patient) and not charges (retail price) or total costs (including fixed costs or overhead).[56] The latter are typically 2 to 3 times higher. For example, in this analysis, liver transplantation cost $108 659 for the first year and $18 976 per year subsequently (in 1999 dollars), but other studies that used charge data reported transplantation costs of $200 000 or higher for the surgery and $25 000 per year for medications.[57,58] In addition to direct medical costs, our analysis suggested that the societal burden of indirect or time costs[59] related to premature mortality or disability from decompensated cirrhosis or hepatocellular carcinoma may add another $54.2 and $21.3 billion, respectively, in lost productivity, both of which exceed the $10.3 billion baseline direct medical costs of hepatitis C.

Our results suggested that despite the remarkable decline in the incidence of hepatitis C, mortality related to existing cases of hepatitis C in 1991 will likely continue to increase over the next 10 to 20 years, and our results confirmed that hepatitis C may be an

awakening giant.[60] Although screening tests and treatments are available, waiting times for new patient appointments to see a hepatologist for evaluation of hepatitis C in some parts of the United States have increased to several months, emphasizing the need to train clinicians in the management of hepatitis C. There is some urgency for action because hepatitis C is frequently asymptomatic until cirrhosis develops, at which time treatment is less effective. Once hepatic decompensation occurs, treatment is limited by the shortage of donor transplant organs. Additional research regarding the cost-effectiveness of screening for hepatitis C and indications for treatment should be pursued to help formulate public health policy in this area. Continued research on the natural history of hepatitis C and the development of new treatments should remain priorities for the nation's health. □

Contributors

J. B. Wong planned the study, analyzed the data, and wrote the paper. G. M. McQuillan and T. Poynard provided additional data and contributed to the writing of the paper. J. G. McHutchison contributed to the writing of the paper.

Acknowledgments

Supported in part by a grant from the Schering-Plough Corporation.

We thank Miriam J. Alter, PhD, for her helpful review and comments and investigators and institutions participating in the OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups.

United Network for Organ Sharing provided data, but we alone are responsible for the reporting and interpretation of these data.

References

1. Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR Morb Mortal Wkly Rep.* 1998;47:1–39.
2. Alter MJ, Mast EE. The epidemiology of viral hepatitis in the United States. *Gastroenterol Clin North Am*. 1994;23:437–455.
3. National Institutes of Health Consensus Development Conference Panel Statement. Management of hepatitis C. *Hepatology.* 1997;26(suppl 1):2S–10S.
4. Hurwitz ES, Neal JJ, Holman RC, et al. Chronic liver disease deaths associated with viral hepatitis in the United States [abstract]. In: *Program and Abstracts of the Seventh National Conference on Chronic Disease Prevention and Control, Salt Lake City, Utah, 1992.* Atlanta, Ga: Public Health Service; 1992:85.
5. McQuillan G, Alter M, Moyer L, Lambert S, Margolis H. A population based serologic study of hepatitis C in the United States. In: Abstracts of IX Triennial International Symposium on Viral Hepatitis and Liver Disease; April 21–25, 1996; Rome, Italy. Abstract 8.
6. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States: 1988 through 1994. *N Engl J Med.* 1999;341:556–562.
7. Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. *Hepatology.* 1997;26:15S–20S.
8. *Healthy People 2000: National Health Promotion and Disease Prevention Objectives.* Washington, DC: US Dept of Health and Human Services; 1991. DHHS publication PHS 91-50212.
9. National Center for Health Statistics. *Healthy People 2000 Review, 1994.* Hyattsville, Md: Public Health Service; 1995.
10. Hurwitz ES, Holman RC, Strine TW, Chorba TL. Chronic liver disease mortality in the United States, 1979 through 1989. *Am J Public Health.* 1995;85:1256–1260.
11. Ventura SJ, Anderson RN, Martin JA, Smith BL. Births and deaths: preliminary data for 1997. *Natl Vital Stat Rep.* 1998;47:1–25.
12. Wong JB. Interferon treatment for chronic hepatitis B or C infection: costs and effectiveness. *Acta Gastroenterol Belg.* 1998;61:238–242.
13. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med.* 1997;127:855–865.
14. Beck JR, Pauker SG. The Markov Process in medical prognosis. *Med Decis Making.* 1983;3: 419–458.
15. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993;13:322–338.
16. Wong JB, Bennett WG, Koff RS, Pauker SG. Pretreatment evaluation of chronic hepatitis C: risks, benefits and costs. *JAMA.* 1998;280:2088–2093.
17. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading, and staging. *Hepatology.* 1994;19:1513–1520.
18. National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–94. *Vital Health Stat 1.* 1994;32.
19. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C: the OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet.* 1997;349:825–832.
20. Yousuf M, Nakano Y, Sodeyama T, Kiyosawa K. Persistence of viremia in patients with type-C chronic hepatitis during long-term follow-up. *Scand J Gastroenterol.* 1992;27:812–816.
21. Mattsson L. *Chronic Non-A, Non-B Hepatitis* [dissertation]. Stockholm, Sweden: Karolinska Institute; 1989.
22. Tremolada F, Casarin C, Alberti A, et al. Long-term follow-up of non-A, non-B (type C) post-transfusion hepatitis. *J Hepatol.* 1992;16: 273–281.
23. Takahashi M, Yamada G, Miyamoto R, Doi T, Endo H, Tsuji T. Natural course of chronic hepatitis C. *Am J Gastroenterol.* 1993;88:240–243.
24. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology.* 1997;112:463–472.
25. Salerno F, Borroni G, Moser P, et al. Survival and prognostic factors of cirrhotic patients with ascites: a study of 134 outpatients. *Am J Gastroenterol.* 1993;88:514–519.
26. The Veterans Affairs Cooperative Variceal Sclerotherapy Group. Sclerotherapy for male alcoholic cirrhotic patients who have bled from esophageal varices: results of a randomized, multicenter clinical trial. *Hepatology.* 1994;20: 618–625.
27. Christensen E, Krintel JJ, Hansen SM, Johansen JK, Juhl E. Prognosis after the first episode of gastrointestinal bleeding or coma in cirrhosis: survival and prognostic factors. *Scand J Gastroenterol.* 1989;24:999–1006.
28. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment: study of 850 patients. *Cancer.* 1985;56:918–928.
29. Kilpe VE, Krakauer H, Wren RE. An analysis of liver transplant experience from 37 transplant centers as reported to Medicare. *Transplant.* 1993;56:554–561.
30. Ascher NL, Lake JR, Emond J, Roberts J. Liver transplantation for hepatitis C virus-related cirrhosis. *Hepatology.* 1994;20(suppl):24S–27S.
31. Detre KM, Belle SH, Lombarddero M. Liver transplantation for chronic viral hepatitis. *Viral Hepatol Rev.* 1996;2:219–228.
32. EASL International Consensus Conference on Hepatitis C. Paris, France, February 26–28, 1999, Consensus Statement. European Association for the Study of the Liver. *J Hepatol*. 1999;30: 956–961.
33. Koop CE. *Statement of C. Everett Koop, MD, ScD, Before the Subcommittee on Human Resources, Committee on Government Reform and Oversight, US House of Representatives.* Washington, DC: Congress of the United States; 1998:1–8.
34. Koretz RL, Abbey H, Coleman E, Gitnick G. Non-A, non-B post-transfusion hepatitis: looking back in the second decade. *Ann Intern Med.* 1993;119:110–115.
35. Joe GW, Lehman W, Simpson DD. Addict death rates during a four-year posttreatment follow-up. *Am J Public Health.* 1982;72:703–709.
36. Mathurin P, Moussalli J, Cadranel JF, et al. Slow progression rate of fibrosis in hepatitis C virus patients with persistently normal alanine transaminase activity. *Hepatology.* 1998;27:868–872.
37. Kuntz KM, Weinstein MC. Life expectancy biases in clinical decision modeling. *Med Decis Making.* 1995;15:158–169.
38. Benvegnu L, Fattovich G, Noventa F, et al. Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis: a prospective study. *Cancer.* 1994;74:2442–2448.
39. Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol.* 1997;26:1–5.
40. Zarski JP, Bohn B, Bastie A, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. *J Hepatol.* 1998;28:27–33.
41. National Center for Health Statistics. Supplements to the *Monthly Vital Statistics Report*: Advance Reports, 1991 and 1992. *Vital Health Stat 24.* 1996;7. DHHS publication PHS 96-1957.
42. Boring CC, Squires TS, Tong T. Cancer statistics, 1991. *CA Cancer J Clin.* 1991;41:19–36.
43. Lotze MT, Flickinger JC, Carr BI. Hepatobiliary neoplasms. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of*

Oncology. 4th ed. Philadelphia, Pa: JB Lippincott Co; 1993:883–914.
44. Yu MC, Yuan JM, Ross RK, Govindarajan S. Presence of antibodies to the hepatitis B surface antigen is associated with an excess risk for hepatocellular carcinoma among non-Asians in Los Angeles County, California. *Hepatology.* 1997; 25:226–228.
45. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. *Hepatology.* 1997;26(3 suppl 1): 34S–38S.
46. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma. *N Engl J Med.* 1999;340: 745–750.
47. Health Resources and Services Administration. *1997 Annual Report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant Data: 1988–1996.* Rockville, Md: United Network for Organ Sharing and Health Resources and Services Administration, Office of Special Programs, Division of Transplantation; 1997.
48. Wiley TE, McCarthy M, Breidi L, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology.* 1998;28:805–809.
49. Bureau of Labor Statistics. *Consumer Price Index for All Urban Consumers, US City Average, Medical Care, 1982–99.* Washington, DC: US Dept of Labor; 2000.
50. Bureau of Labor Statistics. *Usual Weekly Earnings of Wage and Salary Workers: Fourth Quarter 1999.* Washington, DC: US Dept of Labor; 2000.
51. Seeff LB, Buskell-Bales Z, Wright EC, et al. Long-term mortality after transfusion-associated non-A, non-B hepatitis. The National Heart, Lung, and Blood Institute Study Group. *N Engl J Med.* 1992;327:1906–1911.
52. Alter MJ. Occupational exposure to hepatitis C virus: a dilemma. *Infect Control.* 1994;15: 742–744.
53. Reindollar RW. Hepatitis C and the correctional population. *Am J Med.* 1999;107(suppl 6B): 100S–103S.
54. Davis GL, Albright JE, Cook S, Rosenberg D. Projecting the future healthcare burden from hepatitis C in the United States [abstract]. *Hepatology.* 1998;28:390A.
55. Deuffic D, Buffat L, Poynard T, Valleron AJ. Modeling the hepatitis C virus epidemic in France. *Hepatology.* 1999;29:1596–1601.
56. Finkler SA. The distinction between cost and charges. *Ann Intern Med.* 1982;96:102–109.
57. Wong LL, McFall P, Wong LM. The cost of dying of end-stage liver disease. *Arch Intern Med.* 1997; 157:1429–1432.
58. Congressional Research Service. *Hepatitis C: A Challenge to Public Health. Congressional Research Report for Congress.* Washington, DC: Library of Congress; 1998.
59. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine.* New York, NY: Oxford University Press; 1996.
60. Alter MJ. Hepatitis C: a sleeping giant? *Am J Med.* 1991;91:112S–115S.